計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

愛滋病防治整合型研究計畫—
愛滋病防治中心
The HIV/AIDS Control and Study Center

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院附設醫院

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研 究 經 費：新臺幣 820 萬元整

執 行 期 間：106 年 1 月 1 日至 106 年 12 月 31 日

目　錄

共 286 頁

中文摘要

研究目的：

愛滋病之防治、愛滋病患之照護與愛滋病學研究。

研究方法：

本年度延續 18 年來的工作，追蹤在台大醫院接受「高效抗反轉錄病毒療法」(Highly active antiretroviral therapies，HAART)治療的愛滋病患，包括其伺機性感染、臨床研究、及新病毒株的進行。本年計畫在人事穩定的基礎上，繼續活用本中心之軟、硬體，發揮本中心之特性，以臨床醫療服務為主軸，基礎研究及行為科學為輔，加強門診對病患之服務，改善併合療法及藥物副作用之研究。

依據聯合國愛滋病組織（UNAIDS）發表的最新報告顯示愛滋病毒(HIV) 感染人數逐年創新高，其中性行為與毒品是最主要的感染途徑，全球男女感染比率目前已趨近 1：1，因懷孕導致小孩垂直感染的案例日增，亦即可能有更多愛滋寶寶將由母親處感染到愛滋病毒。

在台灣，HIV/AIDS 的漫延稍晚，但其感染率仍然呈現逐年增加的趨勢，至 106 年 9 月底止，本國籍 HIV 感染通報人數共 35,414 人，已造成 5,417 人死亡。一直以來的愛滋病毒傳染途徑 90%係經由性行為傳染，毒品施用者因共用針具注射行為造成愛滋病毒感染長久以來為個位數，但自民國 92 年毒癮者感染人數首次突破十位數達 74 人，至 96 年 6 月已累積至 5,488 名，佔總感染人數 38.94%，顯示疫情逐漸飆升，面對此一新挑戰，幸賴行政院核定「愛滋病減害計畫」以因應毒癮愛滋個案的遽增，94 年 8 月由台北市、台北縣、桃園縣、台南縣進行「毒品病患愛滋減害試辦計畫」；並於 95 年 7 月起擴大辦理清潔針具計畫，全國 23 縣市共計設置清潔針具及愛滋衛教諮商輔導站 427 處；於 95 年 8 月擴大辦理替代療法計畫，全國 22 縣市設置替代療法醫療執行機構，使得毒品注射群體愛滋病盛行率顯著下降，但男同性戀族群間的愛滋病毒感染率仍然每年新增比例都超過 15%。再者，台灣與東南亞國家和中國大陸等高感染盛行率地區的交流頻繁，更加速 HIV 感染的擴散。

政府於 79 年 11 月 30 日經立法院三讀通過「後天免疫缺乏症候群防治條例」，同年 12 月 17 日由總統公布實施，中間歷經數次修訂施行細則以符合實際需求。90 年年底行政院衛生福利部(前衛生署)為有效推動愛滋病防治計畫，減少感染人口，維護國人健康

和確保青壯人口生產力，以防範愛滋病流行造成社會和經濟動盪，故凝聚各部會之力量共同推動，以統籌落實各項因應措施，特別設置了「愛滋病防治推動委員會」，將愛滋病防治提昇至中央跨部會之層級。為確保對愛滋病防治的重視，行政院承諾將愛滋病防治經費列為國家預算優先編列項目，加強跨部會協調與合作，盡一切努力，積極推動防治工作，全面對抗愛滋病漫延。台大醫院充分瞭解政府相關單位打擊愛滋病的決心，故結合本院與北區熱心同仁一起籌組「愛滋病防治中心」，以全體之力與政府共同對抗愛滋病帶來的挑戰。

台大醫院「愛滋病防治中心」於 86 年 6 月間成立以來，全體同仁積極參與防治與臨床工作，陣容愈來愈強化，不但責無旁貸地照護住院病患，亦主動且積極地派遣醫護人員前往各家醫療院所支援。本中心 20 年來在衛生福利部疾病管制署大力資助下已達到初期的成果，不論是臨床醫療服務或是研究工作皆成果豐碩，在人事訓練及佈局都已漸穩定，中心實驗室已稍具規模，將踏實地邁入繼往開來承先啟後的關鍵期。我們責無旁貸將繼續擔負起愛滋病防治與醫療的重要責任，所以向衛生福利部疾病管制署提出申請「愛滋病防治中心」第四期 3 年計畫，因為愛滋病毒的傳播涉及社會文化、性行為改變，實是一社會改造運動，而非單純醫療衛生問題，所以除了愛滋病醫療照護外，本中心將結合教育、文化、社會各體系共同合作推動防治計畫，尤其注重教育訓練，預定將以本中心及北區各個醫院之現有資源，開辦一系列衛教課程及研討會，因為普及防治教育和宣導，是打破 HIV 感染惡性循環的最佳方法。

我們體認到愛滋病不僅是致命疾病，更嚴重影響社會發展、減低生產力、讓外資怯步、降低人民生活水準，甚至削弱政府與社區力量。根據目前 HIV 感染增加率估算我國因愛滋感染之健保醫療累計支出將逐年增加，而薪資損失、社會福利等其他社會成本比健保支出更高數倍以上。若以實際 HIV 感染人數計算，其社會損失更為驚人。本中心的全體醫護同仁將提供愛滋病病患最適當的抗病毒藥物和伺機性感染藥物治療，每年更新用藥的準則，另外討論檢驗項目及間隔時間，訂定檢驗項目的原則，讓臨床醫師在照顧病患時有所遵循，並力行節約健保資源，研究更為經濟之治療方式來造福愛滋病患者，並強化照護系統，使病患、家人和其社區都能獲得適當的支持。

為提昇及結合全國愛滋病指定醫院醫療資源及感染者相關資料，進行全國性跨醫院之 HIV 臨床流行病學相關研究，協力從事包括了解國內感染者臨床特徵、伺機性感染治療與預防、就醫意願、高危險行為、治療之抗藥性及副作用等相關臨床流行病學研究，

以供後續治療與防治相關政策制定與修訂之參考。另「愛滋病防治中心」應扮演領導國內治療與防治相關角色，應有相當之資源規劃教育訓練及建置並執行 PP line 等項目。

「愛滋病防治中心」106 度計畫的實施重點如下列：

總計畫名稱：愛滋病防治整合型研究計畫—愛滋病防治中心

一、研究重點：本研究重點為愛滋高風險族群介入措施與其他預防策略，及提 升愛滋照護品質整合性策略二大研究方向，共含研究重點如下：

1. 我國暴露愛滋病毒前口服預防性投藥（Pre-exposure prophylaxis, PrEP）之自費病人臨床實證研究

2. 使用 nPEP 或 PrEP 且合併成癮藥物使用對象之戒治整合性照護服務研究。

3. 暴露愛滋病毒前後預防性投藥問題諮詢專線之成效

4. 成立愛滋病指定診所及其執行效益評估

5. 針對診斷即刻服藥個案之服藥成效評估

6. 接受抗病毒療法愛滋感染者之藥品動態學和基因學研究

7. 愛滋個案開始服藥前與服藥後之抗藥性發生率追蹤研究

8. 國內愛滋感染者老化與其他慢性病共病之相關研究

二、研究目標：

1. 瞭解愛滋預防性投藥及整合預防服務介入措施，對國內愛滋防治成效之影響。

2. 瞭解新治療、照護與個案追蹤模式，對感染者治療照護成效及防治愛滋感染之效益。

3. 瞭解藥物與個案治療結果之相關性，以提升個案治療品質效果和品質。

「愛滋病防治中心」106 年度已完成 6 個子計畫，發表 11 篇學術論文，參加 4 次國際會議。

關鍵字：愛滋病防治中心、高效抗反轉錄病毒療法、伺機性感染預防與治療、愛滋病毒體液暴露後預防性用藥、醫事人員愛滋病治療照護及全面性防護措施

Abstract

Research Objective:

To study practices in AIDS control, AIDS patient care and treatment, and AID related studies.

Research Methodology:

This year is a continuing work implemented during the Phase I, the five-year Phase II, and three-year Phase III programs, and we shall track conditions of AIDS patients that underwent the Highly Active Antiretroviral Therapies (HAART) at the National Taiwan University (NTU) Hospital; at the same time, we shall also study the related opportunistic infection, clinical researches, and new virus strains. The program of this year, based on the established human resource foundation, shall see to the continuous utilization of the software and hardware of the Control Center to further develop the Control Center's features, and to focus the work on clinical treatment services, which is to be supplemented by fundamental studies and behavioral science. The program shall also see to the enhancement of outpatient treatment service, improvement of the integrated therapy, and study on the pharmaceutical side effects.

Since the establishment of the HIV/AIDS Control and Study Center of the NTU Hospital in June 1997, every member of the staff dedicatedly applied themselves to the AIDS control and clinical operations of the center, and the Center has continued to build a formidable human resource. Under the strong support of the Center for Disease Control of the Ministry of Health and Welfare (before was DOH) in the past eighteen years, the NTU AIDS Control Center managed to achieve the astounding accomplishments for its initial period work in both clinical treatment service and fundamental research. The human resource training and distribution of the Control Center has reached a certain level of stability, and the Control Center lab operations have achieved a certain scale. We expect to see sound progress towards the key periods of the course of the program. The Control Center adheres to the serious responsibility in the campaign for AIDS control and treatment since the proliferation of AIDS is closely related to the social culture and the change of sexual practices. Hence, it is a true social reform. The AIDS problem could not be solved by mere medical treatment and public health policies. Hence, in addition to providing AIDS treatment and nursing care, the Control Center shall also implement the AIDS control campaign in cooperation with the educational, cultural, and social sectors. The campaign shall focus especially on health education. Moreover, a series of health education courses and seminars shall be held at the Control Center and the hospital facilities of the northern district for the popular dissemination of AIDS

control education. This would be the most effective means by which we may break the vicious HIV communication cycle.

In response to the harm reduction policy of the government, the Control Center, under the leadership of Dr. Hung Chien-Ching, a team of young doctors and nurses from the Infectious Disease Department of Yunlin Branch Hospital take turns in conducting the following procedures every Friday at the Yunlin First Prison, the Yunlin Second Prison, and the Chiayi Prison: 1. Examine the newly diagnosed AIDS infected inmates or newly admitted inmates. 2. Understand the risk factors and current health conditions of the inmates, inform inmates of the relevant important health information, and answer health-related questions of infected inmates. Furthermore, conduct CD4/CD8 and AIDS virus count, Hepatitis A, B, and C viruses, liver function, and other basic biochemical tests. 3. Track the changes in the CD4/CD8 and/or HIV virus count and changes in the liver function; determine the time when sufferers should start taking HIV antiretroviral medicine. 4. Evaluate the methadone maintenance therapy aggressively implemented by the Yunlin Branch Hospital.

In an effort to upgrade and consolidate the resources and AIDS sufferer related information of the various AIDS designated hospitals in the country, nation-wide cross-hospital studies on HIV clinical epidemiology had been conducted, and assistance had been provided to researchers conducting studies on clinical epidemiology related matters, such as, clinical symptoms of AIDS sufferers in Taiwan, treatment and control of opportunistic infection, inclination to seek medical treatment, high risk behaviors, drug resistance and side effects of therapies. Results obtained shall serve as reference for the future definition and subsequent amendment of AIDS therapy and control related policies. Moreover, the HIV/AIDS Control and Study Center takes on the key role in leading AIDS treatment and control related efforts in the country; hence, it should assume the responsibility of planning the HIV-related education and training of medical personnel in the country, as well as establishing and operating the PP line. Recently, under the lead of Dr. Sheng Wang-Hui, a unified HIV body fluid exposure incident treatment procedure had been established through the concerted efforts of the doctors, nurses, and medical technologists of the NTU Hospital HIV/AIDS Control and Study Center, with the help of the Branch for Communicable Disease Control of the Taipei City Hospitals (Kunming Branch) to aid sufferers exposed to the HIV body fluid. A 24-hour HIV screening and a hotline information and health education service had been established in an effort to reduce chances of HIV infection and to alleviate the fears and anxieties of persons seeking advices. Furthermore, a fast and single HIV test channel is provided to facilitate the diagnosis of any HIV infection within 24 hours. Once HIV infection is determined, free preventive medicine is provided to the patient within 24 to 36 hours, and notification is sent to the proper health authorities for the institution of effective epidemic

control. Essentials of the implementation of the 2017 annual program of the HIV/AIDS Control and Study Center are as follows:

Study Subject: Integrated Plan for the Control of HIV/AIDS

Focal Point of the Study: This research focuses on two major research streams; interventional processes and other preventive strategies in HIV/AIDS high-risk populations and integrated approaches to enhance HIV quality care, with a total of 10 priorities described as follows:

1. National clinical study on pre-exposure prophylaxis (PrEP) in self-pay subjects.
2. Research related to integrated care of patients with abuse substance undertaking drug replacement therapy using PrEP or non-occupational PEP (post-exposure prophylaxis).
3. Effectiveness of counseling line for pre- and post-exposure prophylaxis questions.
4. Assessment of the benefits of implementing designated clinics for adult HIV/AIDS.
5. Evaluation of the treatment effectiveness in cases treated immediately after diagnosis.
6. Pharmacodynamics and genetic study in HIV-infected patients receiving antiretroviral therapy.
7. Cohort study on resistance profile in HIV/AIDS clients before and after initiation of treatment.
8. Research related to ageing and other co-morbidities in Taiwanese HIV-infected subjects.

Research objectives:

1. To understand the effectiveness of HIV prophylaxis and integrated interventional preventive services, and its impact on the national HIV/AIDS prevention and control.
2. To understand the effectiveness of new therapies, care and case follow-up model in patient treatment care and HIV/AIDS disease prevention and control.
3. To understand the relationship between drug treatment and health outcomes in cases to improve patient treatment care and quality of life.

We have completed 6 sub-plans. There were 11 papers been published and participated in 4 international conferences.

Keywords: HIV, AIDS, The HIV / AIDS Control and Study Center, Highly active antiretroviral therapy, HAART, Post Exposure Prophylaxis line / PP line.

(一)前言

1997年12月李登輝總統公佈實施之新「後天免疫缺乏症候群防治條例」[(1)]，其中第四條明文規定:「中央衛生主管機關應設專責機構，辦理本條例有關事項及後天免疫缺乏症候群之防治與研究」。基於撙節人力、資源之原則，在專責機構正式成立之初，先於1997年6月間，由台大醫院與前台北市立性病防治所(現台北市立聯合醫院疾病管制院昆明院區)先行辦理「愛滋病防治中心」第一、二期5年計劃暨第三期3年計劃，進行相關防治與研究事宜。

根據衛生福利部疾病管制署截至2017年9月底最新統計資料顯示[(4)]，國內累計愛滋病毒感染人數已達36,515人（本國籍為35,414人），目前已發病人數本國籍是16,476例。歷年來MSM的感染人數幾乎是呈現逐年增加的趨勢，從1985年的1人，逐漸增加到2016年9月份的21,934人。1988-1991年MSM之性行為主要之傳染途徑；1992-1995年異性戀間性行為則躍居主要傳染途徑；1996-2003年MSM又回到第一位。2004-2006年毒癮者共用針具取而代之成為主要傳染途徑，但因2005年開始執行減害計畫，2008年毒癮愛滋感染者大幅下降，MSM又再度躍居第一名，且近兩年來MSM感染者增加率皆大於10%。在年齡層分布方面，感染愛滋的年齡層以25至49歲最多，佔69.34%，其次為15至24歲，佔23.81%，兩者共佔全體感染者的93.15％左右，顯見青壯年是感染愛滋病的最大族群，且〝危險性行為〞及〝毒品使用〞仍是最主要的傳染途徑。

本國人士得到愛滋病毒感染之人數近年來因注射靜脈毒品感染者在 2005 年突然劇增而快速成長，幸賴 2008 年因減害計劃推動而大幅減少。壞消息是若扣除毒癮之新感染者，2011 年新通報之男同志愛滋病毒感染者比起 2004 年數目增加 2 倍，異性間性行為而感染者亦增加有 1.5 倍之多，意即每年新發現毒癮以外之新個案數仍然持續增加中。因此除了繼續推動減害計劃外，對於安全性行為之加強推廣尚需努力。台灣過去因性行為而感染到的是 B 及 A/E 亞型，但從 2004 年起經由注射毒品而新感染者突然大增，靜脈毒癮者其亞型與大陸類似，以 CRF B/C 亞型最多；因毒癮患者之男女比例較為接近，且部分女毒癮患者有出賣靈肉之情形，因而可能影響性行為而來之病毒亞型分佈。因此台灣愛滋病毒亞型之監測是今後必須持續進行之長期流行病學工作。

由上述之感染趨勢，估計目前已登記但尚不需治療之感染者達到CD4<300/cmm應開始HAART治療時，約是3-4年後，屆時每年會有超過1,000人。在HAART的治療下，愛

滋病之伺機性感染與腫瘤發生機會微乎其微；但在現實世界裏，不是所有感染者均會聽從醫囑，部分病患根本不來定期檢驗，往往愛滋病發後方來就醫，此一情形在毒癮感染者極為常見。此外，一般認為真正已感染之人數往往是登記有案數目的兩倍以上，因此病發時才查到HIV抗體陽性者不在少數。這個現象反映在今年台大醫院因愛滋病病發(即伺機性感染或腫瘤)而住院者，竟有一半是病發後才被查出有愛滋病毒感染；這些病患可能因延誤而死亡，即使存活， 也是療程坎坷，社會成本與醫療成本更是浩大。未能及早治療成為愛滋病防治之一大隱憂。

為了使醫療界各機構對HIV/AIDS病患之處置與研究專責化、全面化，「愛滋病防治中心」必須更積極推展防治與研究工作，並擔負起統籌全國性HIV/AIDS防治、醫療與研究的重責大任[(2)]。

(二)材料與方法

實施期間為自民國 106 年 1 月 1 日起至 12 月 31 日止。本期最重要防治工作必須接續前 19 年的未完成工作，並擴大本中心之功能，其實施重點如下列：

106 度實施重點如下列：

總計畫名稱：愛滋病防治整合型研究計畫—愛滋病防治中心

一、研究重點：本研究重點為愛滋高風險族群介入措施與其他預防策略，及提升愛滋照護品質整合性策略二大研究方向，共含研究重點如下：

1.暴露愛滋病毒前口服預防性投藥（Pre-exposure prophylaxis, PrEP）之自費病人臨床實證研究

2.nPEP 或 PrEP 且合併成癮藥物使用對象之戒治整合性照護服務研究。

3.愛滋病毒前後預防性投藥問題諮詢專線之成效

4.愛滋病指定診所及其執行效益評估

5.診斷即刻服藥個案之服藥成效評估

6.抗病毒療法愛滋感染者之藥品動態學和基因學研究

7.個案開始服藥前與服藥後之抗藥性發生率追蹤研究

8.國內愛滋感染者老化與其他慢性病共病之相關研究

二、研究目標：

1.愛滋預防性投藥及整合預防服務介入措施，對國內愛滋防治成效之影響。

2.新治療、照護與個案追蹤模式，對感染者治療照護成效及防治愛滋感染之效益。

3.藥物與個案治療結果之相關性，以提升個案治療品質效果和品質。

配合以上重大主題之推展，故擬規劃執行以下 6 個子計畫，其工作內容分述如下：

(一)〝愛滋病毒感染者服用希寧起始劑量為半量的有效性及停用的比例〞之研究：

希寧此抗病毒藥物目前仍然是治療指引所建議的藥物之一，不僅服用簡便(一天一次)且藥物顆粒數少(一顆)，亦同時具有療效及安全性。若感染者有肺結核感染時此藥物同時也是與肺結核藥物(rifampicin)併用的首選處方。此藥物最常見的副作用為中樞神經副作用及皮膚疹，中樞神經的副作用症狀,包含頭暈、頭痛、注意力不集中、多夢、失眠、情緒不穩、情緒低落以及焦躁不安，這些

症狀可能發生的時間在服用希寧後沒多久，同時可能會讓感染者提早停止服用希寧。根據西班牙 Gutierrez-Valencia A 等人的研究結果發現，逐步增加希寧劑量可以減少此藥物引起的中樞神經學症狀而且也同時具有療效。在追蹤 24 週後，只有 6 位個案(5.3%)是病毒學上的失敗。此研究結果建議我們可以在從未接受治療過抗病毒藥物之感染者給予希寧減量的起始劑量。

我們將採觀察性研究，收集自 2012 年 6 月 1 日開始，從未接受治療過抗病毒藥物且開始服藥的個案。開始服藥的個案處方中包含希寧，採取的策略是依個案的決定分成兩組，一組是起始劑量為半量者(300mg)服用 7 天後，第 8 天改全量，另一組是起始劑量為全量者(600mg)。我們將使用標準紀錄格式來收集病患的基本資料包括年紀、性別、B 型肝炎、C 型肝炎以及梅毒。各種生化標記包含血脂肪(T-CHO、TG、LDL-C、HDL-C)，血糖、糖化血色素(HbA1c)。愛滋病毒量、CD4 淋巴球計數、血清梅毒標記(RPR) 亦同時記錄。

由台北市立聯合醫院昆明院區王建淳醫師擔任此計畫負責人執行，詳細研究成果參見附件一。

(二)從事〝愛滋個案開始服藥前與服藥後之抗藥性發生率追蹤及藥物組合治療效果評估研究〞：

高效能抗愛滋病毒治療（highly active antiretroviral therapy；HAART），俗稱「雞尾酒療法」，可有效控制人類免疫不全病毒(human immunodeficiency virus type 1；HIV-1)感染者的病毒量、提高 CD4 淋巴球數，大幅降低病患發生伺機性感染、腫瘤與死亡的風險。近年來，更發現普及性治療 HIV-1 HIV-1 感染患者可減少 HIV-1 病毒的傳播。根據衛生福利部疾病管制署的統計，截至民國一百零五年八月底為止，在台灣已累計有三萬三千六百五十八人遭到 HIV-1 的感染。目前，在台灣遭到人類免疫不全病毒感染的本國病患，皆可在愛滋病指定醫院接受由衛生福利部疾病管制署公務預算支應的三合一雞尾酒療法。但隨著感染者人數逐年增加，藥費的支出也持續成長，為了兼顧財政預算及感染者的醫療權益，疾病管制署自 2012 年 6 月 1 日起實施「抗人類免疫缺乏病毒藥品處方使用規範」方案，建議臨床醫師按照該規範，優先開立價廉同療效之處方；該方案甚至於今年六月推出以一天一劑的藥型做為第一線用藥。所以本計畫首先預定調查臺灣地區尚未使用抗人類免疫缺乏病毒藥物的一百位 HIV 患

者的原生性抗藥性病毒基因盛行率，希望了解在新規範實施後，對於病毒基因型抗藥性盛行率的改變，及其對於臨床治療效果的影響。預計將以 Stanford University“HIV drug resistance database” 分析抗藥性基因型，分析藥物將包含 Reverse Transcriptae Inhibitor (RTI)、Protease Inhibitor (PI) 及 Integrase Inhibitor (INI)等三大類藥物。第二，在這些個案接受雞尾酒治療後，我們將追蹤這些個案治療效果。針對治療失敗者(大於 1000 copies /mL)，我們將進行抗藥性基因檢測，分析其抗藥性病毒基因突變。我們也會將抗藥性基因檢測報告給臨床醫師，以幫助其選擇適當的藥物，及根據抗藥檢測結果所採取的藥物組合治療效果進行評估。第三，追蹤最新處方使用規範(2016/6/1)，即三種每日一次複方藥品舒發錠（Atripla）、康普萊（Complera）及三恩美（Triumeq），在國內實施後的治療效果。

由台大醫學院醫技系張淑媛教授擔任此計畫負責人執行，詳細研究成果參見附件二。

(三)進行〝合併 HIV 和 C 型肝炎病毒感染病患之照顧〞：

合併 HIV 和 C 型肝炎病毒感染病患有較高和肝臟相關的罹病率及死亡率。此外，和僅感染 C 型肝炎病毒病患相較，這類病人較不容易清除 C 型肝炎病毒病，且進展成肝硬化，肝衰竭，或肝癌的速度也較快。過去研究顯示，合併 HIV 和 C 型肝炎病毒感染病患使用抗 HIV 病毒藥物，可達到較佳的預後。本研究欲評估合併 HIV 和 C 型肝炎病毒感染病患血中可偵測到 C 型肝炎病毒的比例，基因型，及 C 型肝炎病毒感染途徑。這些病患發生急性肝炎，肝硬化，和肝癌的盛行率和發生率。其接受 C 型肝炎病毒治療的狀況及效果(即達到持續病毒反應的比例)，包括使用長效型干擾素合併雷巴威林或小分子抗 C 型肝炎病毒藥物。次外，這些病患在治癒 C 型肝炎病毒感染後，C 型肝炎病毒感染的復發狀況。

此計畫由台大醫院內科部感染科孫幸筠醫師負責主持，詳細研究成果參見附件三。

(四)實施〝HIV 感染者藥品動態學和基因學研究〞：

高效能抗愛滋病毒藥物（highly active antiretroviral therapy, HAART）的使用使愛滋病毒的感染受到良好的控制，減少後天免疫不全症候群（AIDS）的發生與死亡率。ART 中，核苷酸反轉錄酶抑制劑（nucleoside reverse transcriptase

inhibitor, NRTI）為治療骨幹；非核苷酸反轉錄酶抑制劑（non-nucleoside reverse transcriptase inhibitor, NNRTI）efavirenz 與 nevirapine、蛋白酶抑制劑（protease inhibitor, PI）lopinavir/ ritonavir、CCR5 抑制劑（chemokine receptor type 5 antagonist）maraviroc 等主要經由肝臟酵素 cytochrome P450（CYP 450）代謝；PI 類 atazanavir 與整合酶抑制劑（integrase strand transfer inhibitor）raltegravir、dolutegravir 主要經由肝臟尿苷二磷酸葡萄糖醛酸基轉移酶（UDP-glucuronosyltransferase, UGT1A1）進行葡萄糖醛酸反應（glucuronidation），上述酵素的活性影響 ART 的代謝速率，而酵素活性與單一核苷酸基因多形性（single nucleotide polymorphism, SNP）、生理病理狀況、藥品交互作用息息相關，因此每個人代謝藥品的速率可能差異極大，使藥品動態學（pharmacokinetics, PK）的特性相去甚遠。代謝快時血中濃度（serum concentration）降低，可能影響治療效果，甚至促使愛滋病毒產生抗藥性；代謝慢時，藥物之血中濃度提高，可能因此而增加療效、甚至增加劑量相關的毒性。不僅 ART 有這樣的特性，治療 AIDS 相關之伺機性感染（opportunistic infection）的抗生素如 rifabutin 與 trimethoprim/sulfamethoxazole (cotrimoxazole)亦然，使得監測藥物血中濃度極具臨床價值。目前國內也有多項 ART 學名藥（generic drug）上市，提供病人有效但價廉的選擇；監測藥物血中濃度可確保療效與安全性，在符合藥物經濟的原則下提供多一層把關。

文獻中多使用高效能液相層析儀（high performance liquid chromatography, HPLC）檢測藥物血中濃度，但並非每個醫療院所都能進行此種檢驗方式，因此有必要成立一個『藥品濃度監測中心』（PK laboratory），協助各地的醫療人員監測 ART 與其他抗生素的血中濃度，並檢測相關酵素或 P-glycoprotein 基因型。本研究目的是藉由前瞻性的觀察，追蹤血中濃度、基因多型性、療效與副作用等關係，以探索最適合國人的 ART 劑量、藥品交互作用時之劑量調整原則等課題，累積國內之本土經驗，與國外文獻、臨床經驗相比較，不僅可增進病人用藥安全、達到最大的經濟效益，也能以論文期刊的方式與世界各國分享我國的用藥經驗。

本實驗室近年來已建立監測 efavirenz、nevirapine、atazanavir、rifabutin 與 trimethoprim/ sulfamethoxazole (cotrimoxazole)血中濃度的 HPLC 方法，共檢測多

家醫院、超過千位服藥的愛滋病毒感染者；目前計畫繼續協助臨床醫師監測病人血中濃度，並開發核苷酸反轉錄酶抑制劑與整合酶抑制劑的血中濃度檢測方式。延續研究的結果不僅可確認國內成立 PK lab 的可行性、監測血中濃度的必要性及適當範圍，ART 與其他 HIV 患者常用之抗生素血中濃度的結果可提供臨床醫師調整劑量的參考資料，甚至做為衛生主管機關建議國人使用劑量時的重要參考。

此主題由台大醫學院臨床藥學研究所林淑文助理教授執行，詳細研究成果參見附件四。

(五)進行〝愛滋病毒感染之暴露前預防性投藥之前瞻性研究〞：

全世界每一年大約有兩百七十萬人新診斷為愛滋病毒（Human immunodeficiency virus; HIV）感染；性行為是傳染愛滋病毒的主要途徑。根據衛生福利部疾病管制署(以下簡稱疾管署)的通報資料，自從注射藥物者(Persons who inject drugs; PWID）感染愛滋病毒的疫情獲得控制可以後，2007 年到 2014 年臺灣每年新診斷的愛滋病毒感染者大約在 1,600 到 2,000 人，不安全性行為是愛滋病毒感染最主要的傳染途徑。

2010 年二個大型臨床試驗分別首度證實抗愛滋病毒藥物治療可有效降低異性戀正負相異伴侶（serodiscordant couples）92%感染愛滋病毒的機率及降低男男性行為者（men who have sex with men; MSM）44%感染機率。2010 年之後，許多研究評估在接觸愛滋病毒前使用暴露前預防性投藥（pre-exposure prophylaxis; PrEP），都發現在特定族群上具有顯著預防愛滋病毒感染的效果。2011 年世界衛生組織（World Health Organization; WHO）主張治療就是最好的預防。2012 年七月美國食品藥管理局（Food and Drug Association; FDA）正式核准 tenofovir + emtricitabine（TDF/FTC, Truvada）成為暴露前預防性投藥的首選藥物。2011 年美國疾病管制及預防中心（US Centers for Disease Control and Prevention）首先針對男男性行為者，制定暴露前預防性投藥暫時性的使用指引，隨後 2012 年針對性活躍的異性戀成人、2013 年針對注射藥物者推出暴露前預防性投藥暫時性的使用指引，並且於 2014 年正式公布暴露前預防性投藥臨床使用指引。WHO 於 2015 年建議暴露前預防性投藥作為全球愛滋病毒感染防治的防治的重要措施之一。

本計劃將針對愛滋病毒感染之高風險對象，並已經自費使用暴露前預防性投藥下，提供定期而免費的愛滋病毒抗原抗體定性及病毒量篩檢，性病(梅毒、淋病、披衣菌)篩檢及衛教諮詢，以期能藉由提供諮商和高敏感度的免費篩檢，促進高風險群定期檢驗與使用預防藥物的意願，同時了解高風險群對於愛滋病毒暴露前預防性投藥之使用方式與頻度，以及副作用和相關性病發生率。

此計畫由台大醫院內科部感染科洪健清醫師負責主持，詳細研究成果參見附件五。

(六)HIV 臨床流行病學相關研究，將有〝愛滋病毒感染者新陳代謝症候群與心血管疾病等慢性病之盛行率、發生率及相關因子調查〞：

愛滋病毒感染者因為高效能抗反轉錄療法 (highly active antitroviral therapy; HAART) 的廣泛使用而得以改善存活。根據台大醫院的研究調查顯示，年齡大於 50 歲的感染者相較於 40-49 歲的感染者有較多的共病症，包括糖尿病、高血壓、心血管疾病、高血脂。研究人員開始觀察到愛滋病毒感染者因年齡的增加與老化，相繼發生的代謝相關併發症, 包括: 葡萄糖耐受不良、糖尿病與脂質代謝異常，這些往往都是心血管疾病的危險因子之一。高效能抗反轉錄療法一方面雖然減少了愛滋病毒感染者造成愛滋病的發生率，但從另一方面看來，許多愛滋病毒感染相關、而非後天免疫不全症候群的情形(HIV-Associated Non-AIDS conditions, HANA)卻有越來越多的趨勢[5]。我們已知，長期接受治療愛滋病毒感染者會表現出許多類似老化的特徵，例如: 有許多共病症(包含糖尿病、高血壓、心臟血管疾病、高血脂、腎臟疾病、骨質疏鬆等)、多重藥物的使用、身體或認知方面的衰退、功能性下降、身體成分的改變，以及較容易受到壓力影響等等。

本研究將針對年齡大於 18 歲的感染者，分別使用 WHO FRAX equation 估算 10 年內發生骨折的機率，Framingham equation 估算 10 年內發生心血管疾病的風險及 D:A:D equation 估算 5 年內發生心血管疾病的風險，再從 FRAX equation 挑出年紀大於或等於 50 歲進行骨質密度檢查，及血清維他命 D 定量。我們將針對在 2003 年 1 月 1 日至 2014 年 12 月 31 日期間，新診斷且持續留在本院追蹤大於 6 個月之個案。進行基本資料收集並紀錄病患家族病史、抗愛滋病毒藥物種類、服用藥物的累積總時間、接受其他藥物治療、過去共病史(包含

梅毒、B 型肝炎、C 型肝炎)、糖尿病相關慢性併發症，血清中維他命 D 的含量、血脂肪、愛滋病毒量、CD4 淋巴球計數、RPR titer、骨質密度檢查。紀錄個案每年的之抽血數值變化包含飯前血糖(AC glucose)、糖化血色素(HbA1c)、基礎點的愛滋病毒量、CD4 淋巴球計數。糖尿病發生率、危險因子、10 年內發生骨折的機率、骨質密度檢查，及血清維他命 D 含量以及其他的慢性病(高血脂、冠狀動脈心臟病、高血壓)也會在此研究一併調查。

此計畫由台大醫院新竹分院內科部感染科黃于珊醫師負責主持，詳細研究成果參見附件六。

(三)結果

一、“愛滋病毒感染者服用希寧起始劑量為半量的有效性及停用的比例”之研究，詳細成果內容如附件一。

二、從事“愛滋個案開始服藥前與服藥後之抗藥性發生率追蹤及藥物組合治療效果評估研究”，詳細成果內容如附件二。

三、進行“合併HIV和C型肝炎病毒感染病患之照顧”，詳細成果內容如附件三。

四、實施“HIV 感染者藥品動態學和基因學研究”，詳細成果內容如附件四。

五、進行“愛滋病毒感染之暴露前預防性投藥之前瞻性研究”，詳細成果內容如附件五。

六、HIV臨床流行病學相關研究，將有“愛滋病毒感染者新陳代謝症候群與心血管疾病等慢性病之盛行率、發生率及相關因子調查”，詳細成果內容如附件六。

七、其他成果：

(A)、參與國際研討會、研究計畫或藥物試驗方面：

主持人洪健清醫師帶領同仁共參加以下四場國際會議：

(1) 2/13~16 日在美國西雅圖舉辦之 Conference on Retroviruses and Opportunistic Infections(CROI 2017)國際會議。進行學術交流討論並發表 2 篇海報論文。

1.Lin KY, Hsieh SM, Sun HY, Lo YC, Sheng WH, Chuang YC, Pan SC, Hung CC, Chang SC. Effectiveness of HAV vaccination among HIV-positive patients during an HAV outbreak. 22nd Conference on Retroviruses and Opportunistic Infections. Abstract no. 977. Seattle, WA, 13-16 Feb, 2017.

2. Llibre JM, Hung CC, Brinson C, Castelli F, Girard P, Kahl LP, Blair E, Wynne B, Vandermeulen K, Aboud M. Phase III SWORD 1 & 2: Switch to DTG+RPV maintains virologic suppression through 48 Wks. 22nd Conference on Retroviruses and Opportunistic Infections. Abstract no. 44LB. Seattle, WA, 13-16 Feb, 2017.

(2) 6/1~3 日在香港舉辦之 2st Asia Pacific AIDS & Co-infections Conference (APACC)會議進行學術交流討論。

(3) 10/4~8 日在美國聖地牙哥舉辦之 ID week (歐洲愛滋病學會)國際會議。進行學術交流討論並發表 1 篇海報論文。

1.Walmsley S, Richmond G, Bredeek F, Ramgopal M, Hung CC, Blair L, Kahl L,

Underwood M, Angelis K, Vandermeulen K, Wynne B, Aboud M. SWORD 1 & SWORD

2: Subgroup analysis of 48-Week results by age, race and gender. ID Week 2017.

(4) 10/25~27 日在義大利米蘭舉辦之 The 16th European AIDS Conference (美國感染症年會)國際會議。進行學術交流討論並發表 4 篇海報論文與 1 個專題演講。

1. Chen GJ, Sun HY, Lin KY, Cheng A, Huang YC, Hsieh SM, Sheng WH, Liu WC, Hung CC, Chang SC. Serological responses to revaccination with hepatitis A vaccines among HIV-positive individuals whose anti-HAV antibody waned after primary vaccination. 16th European AIDS Conference. Abstract no. Milan, 24-27 October, 2017. [oral presentation]
2. Sun HY, Liu WC, Su YC, Chen GJ,, Chang SY, Hung CC. Effectiveness of substitution of protease inhibitors with dolutegravir in combination with 2 NRTIs as maintenance antiretroviral therapy among HIV-positive patients. 16th European AIDS Conference. Abstract no. Milan, 24-27 October, 2017. [poster]
3. Wu PY, Zhang JY, Luo YZ, Yang SP, Chang HY Sun HY, Hung CC. Risk of cardiovascular disease among the HIV-infected patients in Taiwan. 16th European AIDS Conference. Abstract no. Milan, 24-27 October, 2017. [poster]
4. Su YC, Lin YT, Huang CW, Huang SH, Yang SP, Liu WC, Lin SW, Chang SY, Hung CC. Effectiveness of maintenance combination antiretroviral therapy using half-dose efavirenz plus 2 nucleoside reverse-transcriptase inhibitors with the guidance of therapeutic drug monitoring. 16th European AIDS Conference. Abstract no. Milan, 24-27 October, 2017. [poster]
5. Liu WC, Liu CH, Sun HY, Hung CC, Kao JH. Real-world effectiveness and safety of generic velpatasvir plus sofosbuvir for chronic hepatitis C in patients coinfected with human immunodeficiency virus. 16th European AIDS Conference. Abstract no. Milan, 24-27 October, 2017. [poster]

(B)、相關論文發表：

台大醫院「愛滋病防治中心」成立至今已屆 20 年，經由醫護、社工等工作人員的努力，合計照顧過數千位愛滋病病毒感染者，不僅提供臨床醫療服務，對於他們的社會、心理需求，亦盡心提供諮詢及協助。

對於愛滋病的各項研究工作，本中心一直不敢懈怠，各子計畫主持人及各

組研究人員雖經費拮据，仍一本初衷熱心投入各項研究，上半年已有豐碩的成果展現，有許多優秀的論文分別發表在國內外各大期刊中，明細如下：

1. Wu PY, Cheng CY, Liu CE, Lee YC, Yang CJ, Tsai MS, Cheng SH, Lin SP, Lin DY, Wang NC, Lee YC, Sun HY, Tang HJ, Hung CC. Multicenter study of hepatotoxicity and skin rash in antiretroviral-naïve HIV-positive patients initiating non-nucleoside reverse transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS One 2017;12:e0171596.
2. Cheng A, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, Wu PY, Hung CC*, Chang SC. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in HIV-positive adults on antiretroviral therapy. J Infect Dis 2017;215:606-13.
3. Chen GJ, Lin KY, Hung CC*, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. J Infect Dis 2017;215:1339-40. [Letter to the editor]
4. Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY, Chang SY, Liu CE*, Hung CC*. Hepatitis A virus infection and hepatitis A vaccination in HIV-positive patients: a review. World J Gastroenterol 2017;23:3589-606. [invited review]
5. Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Liu CE, Lee YT, Tang HJ, Wang NC, Lin TY, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Chang SH*, Hung CC*, for the Taiwan HIV Study Group. Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up. PLoS One 2017;12:e0179870.
6. Huang YS, Yang JJ, Lee NY, Chen GJ, Ko WC, Sun HY, Hung CC*. Treatment of Pneumocystis jirovecii pneumonia in HIV-infected patients: a review. Expert Rev Anti Infect Ther. 2017 Aug 21:1-20. doi: 10.1080/14787210.2017.1364991.
7. Lee YL, Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Tang HJ, Lin TY, Wang NC, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Cheng SH, Lee YT, Liu CE, Hung CC, for the Taiwan HIV Study Group. Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS One 2017;12: e0186338.

8. Lee YC, Chang SY, Lin KY, Chang LH, Liu WC, Wu CH, Sun HY*, Hung CC*, Chang SC. Attitudes towards preexposure exposure prophylaxis against HIV transmission among individuals seeking voluntary counseling and testing for HIV. BMJ Open 2017;7:e015142.
9. Huang YS, Chan CK, Tsai MS, Lee KY, Lin SW, Chang SY, Hung CC*, Chang SC. Kidney dysfunction associated with tenofovir exposure in HIV-1-infected Taiwanese patients. J Microbiol Immunol Infect 2017;50:595-603.
10. Chen GJ, Lin KY, Sun HY, Sheng WH, Hsieh SM, Huang YC, Cheng A, Liu WC, Hung CC*, Chang SC. Incidence of acute hepatitis A among HIV-positive patients during an ongoing outbreak among men who have sex with men in Taiwan: impact of hepatitis A virus vaccination. Liver Int 2017;37 (Dec):(in press)
11. Tsai MS, Chang SY, Kuo CH, Sun HY, Wu BR, Tang SY, Liu WC, Su YC, Lin SW, Hung CC*. Treatment response to switch regimens of unboosted atazanavir in combination with tenofovir and lamivudine in HIV-1-infected patients who had achieved virological suppression: a therapeutic drug monitoring and pharmacogenetic study. J Microbiol Immunol Infect 2017;50 (December): (in press)

(C)、有關經費使用方面：

在全體同仁的瞭解及共體時艱下，大家互相配合協調，發揮分工合作的精神，將有限的經費完全充分運用，本期最後之經費結餘為 0 元。其明細如下：

期　間	補助款實收	人事費	業務費	管理費	結　餘
106年1月~12月	8,200,000 元	6,227,149 元	1,872,851 元	100,000 元	$0

(四)對政策之具體建議

一、子計畫一對政策之具體建議:

疾管署在民國 106 年 9 月公告四種 Single Table Regimen 做為愛滋病毒感染者處方的第一線藥物，含有希寧 Efavirenz 成分之 Atripla 仍為其中之一，價格為四者藥物中最低。使用希寧的副作用雖然相對較多但以研究中發現病毒學治療失敗比率低，而且血中藥物濃度皆高於治療目標濃度，在台灣地區當病患需要並用抗結核藥物時預期藥物交互作用之產生，仍可考量使用 Atripla 而不需要調整藥物劑量。新藥物 Genvoya 大部分醫院尚未進用藥物，B 型肝炎個案當 HIV 病毒量超過 10 萬仍考量以 Atripla 做為治療藥物。起始半量使用雖然停用比例仍高但是仍可以舒緩病患開始用藥之不適，然而台灣地區希寧之原廠藥商已經停止供貨，目前僅有學名藥可以使用，是否可以相同方式起始半量使用有待研究。

二、子計畫二對政策之具體建議:

1. 因為非擬似核苷酸衍生物反轉錄酶抑制藥物的抗藥性盛行率有升高的趨勢，所以建議如果病人要服用以非擬似核苷酸衍生物反轉錄酶抑制藥物為基礎的一天一顆的第一線處方藥物時(例如 TDF/FTC/EFV 及 TDF/FTC/RPV)，應該在用藥前接受抗藥性基因檢測，以確保藥物治療的效果。
2. 抗藥性的病毒株主要分布在北部，對於這地區的持續性抗藥性監測是必須的，以確保抗藥性病毒株不會蔓延。

三、子計畫三對政策之具體建議:

1. 建議照護 HCV 抗體陰性的愛滋病毒感染的病患，至少每年進行一次 HCV 抗體檢測，或在其發生梅毒和無法解釋的肝功能異常時，給予 HCV 抗體檢測，以求早期診斷，早期治療。
2. 可考慮廣為推行小分子抗 C 型肝炎病毒學名藥物在合併 C 型肝炎病毒和愛滋病毒感染者的治療，以減少此類病患未來發生肝癌和肝硬化的狀況，甚至減少 C 型肝炎病毒的傳播。

四、子計畫四對政策之具體建議:

本研究結果顯示個體間的 ATV、EFV、cotrimoxazole 血中濃度差異極大，且與療效、副作用相關，應常規進行血中濃度監測，做為調整劑量的參考，進而提

昇醫療經濟效益。DTG 與 rifabutin 則有待納入病人樣本數以便進一步評估。

五、子計畫五對政策之具體建議:

本年度計畫最重要的研究成果在於進行了完整的 PrEP 追蹤並且給予 Daily 以及 On demand 的選擇，並初步顯示其有效預防 HIV 感染的成果。此初步成果將可作為防疫之參考，應持續於全國推行 PrEP，視為減害計畫 2.0 版本，並且持續宣導 PrEP 之觀念；此外，由於分析中顯示價格為影響 PrEP 意願的原因之一，應努力尋求或制定相關防疫政策，減少 PrEP 之個人花費，將可更快速增加願意接受 PrEP 之人數。

六、子計畫六對政策之具體建議:

根據本研究，愛滋病毒感染者年紀越大則心血管疾病風險越高，尤其在≧60 歲的患者，若以量表來估算心血管疾病發生的風險可高達 70%以上。而在糖尿病的世代觀察研究中，愛滋病毒感染者新發生糖尿病的風險與年長、高血壓、抗愛滋病毒藥物累積暴露時間、特定藥物如核苷酸*反轉錄酶抑制劑有*關。愛滋病毒感染者的骨密度調查則發現，年過 45 歲的患者有相當比例發生骨密度降低，且患者十年的骨質疏鬆與髖部骨折風險隨著年齡增加，特別是 50 歲以上並接受抗愛滋病毒藥物治療的感染者。體重過輕也是發生骨質疏鬆的風險因子之一。

隨著高效能反轉錄病毒藥物的廣泛使用，愛滋感染者壽命延長，將有更多患者步入中老年。建議針對中高齡的患者，特別是年紀大於 60 歲、長期服藥且合併高血壓的族群，定期進行心血管疾病風險評估如血脂肪、血糖檢驗，鼓勵戒菸，並制定年度監測指標。骨密度檢查的給付條件，則可考慮開放給高齡且長期接受抗愛滋病毒藥物治療或已合併臨床症狀的患者，以盡早評估並開始骨骼保健及骨折預防。同時也建議參與愛滋照護的醫師與個案管理師，皆能接受心血管與新陳代謝，包含骨密度監測與骨質疏鬆處置等主題的老年醫學學程訓練。

(五)參考文獻

1. 後天免疫缺乏症候群防治條例：第四條：1997 年 12 月。
2. 莊哲彥、張鴻仁、陳茂源、涂醒哲、林瑞宜，愛滋病防治中心五年計劃：1997:1-35。
3. 2014 年度台大同仁有關 HIV/AIDS 論文(詳表一及附錄論文影本)。
4. 衛生福利部疾病管制署：愛滋病統計報表 2017 年 9 月。
   https://www.syndriver.com/portal/#/sharing/6d82b78e2cc444438236bc9da9603d2e
5. Chang SY, Ko W, Chen MY, et al. Association between SNP3 and c.553G>T of APOA5 with hypertriglyceridemia after treatment with protease inhibitors in human immunodeficiency virus type 1 infected-individuals in Taiwan. Clin Infect Dis 2009;48:832-5.
6. Chang SY, Lin SW, Hung CC*. Do we still need lead-in dosing of nevirapine in HIV-Infected patients who are receiving rifampicin-containing antituberculous therapy? [Letter to the Editor] Clin Infect Dis 2009;49:1452-3.
7. Chen YM, Kuo SH. HIV-1 in Taiwan. Lancet 2007;369:623-5.
8. Hung CC, Chen MY, Hsieh SM, et al. Clinical spectrum, morbidity, and mortality of acquired immunodeficiency syndrome in Taiwan: a 5-year prospective study. J Acquir Immune Defic Syndr 2000;24:378-85.
9. Hung CC, Chang SY, Su CT, et al. A 5-year longitudinal follow-up study of serologic responses to 23-valent polysaccharide pneumococcal vaccination among patients with human immunodeficiency virus infection who received highly active antiretroviral therapy. HIV Med 2009 (in press).
10. Lo YC, Lauderdale TL, Chang SY, et al. Streptococcus pneumoniae colonization among HIV-1-infected patients who had received 23-valent polysaccharide pneumococcal vaccine. J Microbiol Immunol Infect 2009;42(3):234-42.
11. Lo YC, Chen MY, Sheng WH, et al. Risk factors of incident diabetes mellitus among HIV-Infected individuals receiving combination antiretroviral therapy in Taiwan: a case-control study. HIV Med 2009;10:302-9.
12. Lo YC, Chang SY, Sheng WH, et al. Association of pancreatic autoantibodies and human leukocyte antigen haplotypes with resolution of diabetes mellitus following therapy for hepatitis C virus infection in patients with human immunodeficiency virus infection: case report and review of the literature. Euro J Gastroenterol Hepatol 2009;21:478-81.
13. Sheng WH, Kao JH, Chen PJ, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. Clin Infect Dis 2007;45:1221-9.
14. Sheng WH, Hung CC, Liu CJ, et al. Management of hepatitis B virus and human immunodeficiency virus co-infection: Asian perspectives. (submitted)

15. Sheng WH, Hung CC, Huang HH, Liang SY, Cheng YJ, Ji DD, Chang SC: First case of granulomatous amebic encephalitis caused by Acanthamoeba in Taiwan. Am J Trop Med Hyg 2009;81:277-9.
16. Sun HY, Chen MY, Hsieh SM, et al. Changes in the clinical spectrum of opportunistic illnesses in persons with HIV infection in Taiwan in the era of highly active antiretroviral therapy. Jpn J Infect Dis 2006;59:311-6.
17. Sun HY, Ko WC, Tsai JJ, et al. Seroprevalence of chronic hepatitis B virus infection among Taiwanese human immunodeficiency virus type 1-infected persons in the era of nationwide hepatitis B vaccination. Am J Gastroenterol 2009;104:877-84.
18. Sun HY, Kung HC, Ho YC, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis 2009;13:e199-205.
19. Hung CC, Chang SY, Su CT, et al. A 5-year longitudinal follow-up study of serologic responses to 23-valent polysaccharide pneumococcal vaccination among patients with human immunodeficiency virus infection who received highly active antiretroviral therapy. HIV Med 2010;11:54-63.
20. Tan CK, Hung CC, Lai CC, et al. Diagnosis of active tuberculosis by enzyme-linked immunospot assay for interferon-γ in HIV-Infected patients. J AIDS 2010;53:546-7.
21. Chen SJ, Yang SP, Hung CC, Fung CP. Abacavir-induced agranulocytosis in two Taiwanese patients tested HLA*B5701 negative. AIDS 2010;24:1238-9.
22. Cheng CY, Chen MY, Hsieh SM, et al. Long-term risk of pneumocystosis after early discontinuation of prophylaxis among HIV-infected patients receiving highly active antiretroviral therapy. BMC Infect Dis 2010;10:126.
23. Yang YL, Hung CC, Wang AH, et al. Oropharyngeal colonization of HIV-infected outpatients by yeast pathogens in Taiwan. J Clin Microbiol 2010;48:2609-12.
24. Sun HY, Lee HC, Liu CE, et al. Factors associated with isolated anti-hepatitis B core antibody in HIV-positive patients: impact of compromised immunity. J Viral Hepatitis 2010;17:578-87.
25. Yang CJ, Chen MY, Hsieh SM, et al. Non-Hodgkin lymphomas in patients with human immunodeficiency virus infection in Taiwan. J Microbiol Immunol Infect 2010;43:278-84.
26. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of HIV epidemic: incidence and risk factors. Clin Infect Dis 2010;51:976-9.
27. Hung CC, Wu PY, SY Chang, et al. Amebiasis among persons who sought voluntary and testing for HIV infection: a case-control study. Am J Trop Med Hyg 2011;84:65-9.

28.Chang SY, Yang CL, Lin CY, et al. . Molecular epidemiology of hepatitis D virus infection among injecting drug users with and without HIV infection in Taiwan. J Clin Microbiol 2011;49:1083-9.
29.Yang SJ, Hung CC, Chang SY, et al. Immunoglobulin G and M antibodies to human parvovirus 4 (PARV4) are frequently detected in patients with HIV-1 infection. J Clin Virol 2011;51:64-7.
30.Lo YC, Wu PY, Hsieh CY, et al. Late diagnosis of HIV infection in the era of highly active antiretroviral therapy: role of socio-behavioral factors and medical encounters. J Formos Med Assoc 2011;110: 306-15.
31. Lu CL, Lin YH, Lin HH, et al. Outcomes of switch to atazanavir-containing combination antiretroviral therapy in HIV-1-infected patients with hyperlipidemia. J Microbiol Immunol Infect 2011;44:258-64.
32. Liu WL, Lai CC, Hsiao CH, et al. Bacteremic pneumonia caused by Nocardia veterana in an HIV-infected patient. Int J Infect Dis 2011;15:e430-2.
33. Chiang HH, Hung CC, Lee JM, et al. Admissions to the intensive care unit in HIV-infected patients in Taiwan: etiology and predictive factors of mortality. Crit Care 2011;15:R202.
34. Hung CC, Chang SY, Lee KY, et al. Risk and incidence of pulmonary diseases among HIV-infected patients in the era of combination antiretroviral therapy. Am J Resp Crit Care Med 2011;184:1086-7.
35.Hsieh SM, Chang SY, Hung CC, et al. Emerging HIV-1 resistance to tipranavir and darunavir in patients with virological failure to first-generation protease inhibitors in Taiwan. Int J STD AIDS 2011;22:617-20.
36. Sheng WH#, Hung CC#, Chang SY, Liu CJ, Chen MY, Hsieh SM, Kao JH, Chen PY, Chang SC. Differential clinical and virologic impact of hepatitis B virus genotypes B and C on HIV co-infected patients receiving lamivudine-containing highly active antiretroviral therapy. Clin Infect Dis 2012;54:548-55. [#equal contribution]
37. Sun HY, Chang SY, Yang ZY, Lu CL, Wu H, Yeh CC, Liu WC, Hsieh CY, Hung CC*, Chang SC. Recent hepatitis C virus infection in HIV-positive persons in Taiwan: incidence and associated factors. J Clin Microbiol 2012;50:781-7.
38. Sun HY, Chang SY, Sheng WH, Chen MY, Hsieh SM, Tseng YT, Lu CL,Yang CJ, Wu H, Liu WC, Wu PY, Hung CC*, Chang SC. Incidence of acute pancreatitis in human immunodeficiency virus-positive patients with extreme hypertriglyceridemia: is it really high? Pancreas 2012;41:283-9.
39. Lu CL, Hung CC*. Reversible cystic lesions of Pneumocystis jirovecii pneumonia. Am J Resp Crit Care Med 2012;185:e7-8.

40. Wu PY#, Hung CC#, Liu WC, Hsieh CY, Lu CL, Wu H, Chien KL. Metabolic syndrome among HIV-infected Taiwanese patients in the era of highly active antiretroviral therapy: prevalence and associated factors. J Antimicrob Chemother 2012;67:1001-9. [#equal contribution]
41. Lai CC, Hung CC, Chen MY, Sun HY, Lu CL, Tseng YT, Chang SF, Su YC, Liu WC, Hsieh CY, Wu PY, Chang SY, Chang SC. Trends of transmitted drug resistance of HIV-1 and its impact on treatment response to first-line antiretroviral therapy in Taiwan. J Antimicrob Chemother 2012;67:1254-60.
42. Hung CC, Chang SY, Ji DD. Amebiasis deaths in the United States. [Letter to the Editor] Am J Trop Med Hyg 2012;86:908. [Letter to the Editor]
43. Lu CL, Hung CC*, Chuang YC, Liu WC, Su CT, Hsiao CF, Tseng YT, Su C, Chang SF, Chang SY*, Chang SC. Comparison of serologic response to vaccination with one dose or two doses of 7-valent pneumococcal conjugate vaccine in HIV-infected adults. Vaccine 2012;30:3526-33.[*alternative corresponding author]
44. Huis In 't Veld D, Sun HY, Hung CC, Colebunders R. The immune reconstitution inflammatory syndrome related to HIV co-infections: a review. Eur J Clin Microbiol Infect Dis 2012;31:919-27.
45. Wu H, Chang SY, Lee NY, Huang WC, Wu BR, Yang CJ, Liang SH, Lee CH, Ko WC, Lin HH, Chen YH, Liu WC, Su YC, Hsieh CY, Wu PY, Hung CC*. Evaluation of macrolide resistance and enhanced molecular typing of Treponema pallidum in patients with syphilis in Taiwan: a prospective multicenter study. J Clin Microbiol 2012;50:2299-304.
46. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, Lu CL, Hsieh CY, Hung CC*. Seroprevalence of hepatitis virus infections among men who have sex with men aged between 18 to 40 years in Taiwan. J Formos Med Assoc 2012;111:431-8.
47. Lu CL, Chang SY, Sun HY, Liu WC, Sun HY, Tseng YT, Hsieh CY, Wu PY, Hung CC*, Chang SC. Impact of vaccination with 7-valent pneumococcal conjugate vaccine on virologic and immunologic outcomes among HIV-infected adult patients in the era of combination antiretroviral therapy. J Formos Med Assoc 2012;11:445-51.
48. Hung CC, Chang SY, Ji DD. Entamoeba histolytica infection in men who have sex with men. Lancet Infect Dis 2012;12:729-36.
49. Lee KY, Huang CH, Tang HJ, Yang CJ, Ko WC, Chen YH, Lee YC, Hung CC*. Acute psychosis related to use of trimethoprim/sulfamethoxazole in treatment of HIV-infected patients with Pneumocystis jirovecii pneumonia: a multicenter retrospective study. J Antimicrob Chemother 2012;67:2749-54.
50. Hung CC, Chang SY, Sun HY, Hsueh PR. Cavitary pneumonia due to Penicillium marneffei in an HIV-infected patient. Am J Resp Crit Care Med 2013;187:e3-4.

51. Lee YC, Lu CL, Lai CC, Tseng YT, Sun HY, Hung CC*. Mycobacterium avium complex infection-related immune reconstitution inflammatory syndrome of the central nervous system in an HIV-infected patient: case report and review of the literature. J Microbiol Immunol Infect 2013;46:68-72.
52. Lu CL, Hung CC*, Chuang YC, Liu WC, Su CT, Su YC, Chang SF, Chang SY*, Chang SC. Serologic response to primary vaccination with 7-valent pneumococcal conjugate vaccine is better than with 23-valent pneumococcal polysaccharide vaccine in HIV-infected patients in the era of combination antiretroviral therapy. Human Vacc Immunother 2013;9:398-404. 226.
53. Tseng YT, Chang SY, Liu WC, Sun HY, Wu CH, Wu PY, Lu CL, Hung CC*, Chang SC. Comparative effectiveness of 2 doses versus 3 doses of hepatitis A vaccine in HIV-infected men who have sex with men in the era of combination antiretroviral therapy. Hepatology 2013;57:1734-41.
54. Chang SY, Lin PH, Tsai CJ, Hung CC, Chang SC. The first case of H7N9 influenza in Taiwan. Lancet 2013;381:1621.
55. Hung CC, Zhao TL, Sun HY, Yang YF, Su YC, Chang SF, Liu WC, Wu CH, Chang SY, Chang SC. Seroepidemiology of novel influenza A (H1N1) infection among HIV-infected patients in the era of highly active antiretroviral therapy. J Microbiol Immunol Infect 2013;46:151-7.
56. Hsieh SM, Pan SC, Chang SY, Hung CC, Sheng WH, Chen MY, Chang SC. Differential impact of resistance-associated mutations to protease inhibitors and nonnucleoside reverse transcriptase inhibitors on HIV-1 replication capacity. AIDS Res Hum Retrovir 2013;29:1117-22.
57. Lu CL, Chang SY, Tseng YT, Wu BR, Liu WC, Sun HY, Hung CC. Immune reconstitution inflammatory syndrome of Kaposi's sarcoma in an HIV-infected patient. J Microbiol Immunol Infect 2013;46:309-12.
58. Tseng FC, Ko NY, Lee HC, Wu CJ, Hung CC, Ko WC. HIV risk profiles differed by gender and experience of men who have sex with men among attendees of anonymous voluntary counseling and testing in Taiwan. AIDS Care 2013;25:1092-101.
59. Tsai MS, Chang SY, Lo YC, Yang CJ, Sun HY, Liu WC, Wu PY, Hung CC*. Hepatitis B virus coinfection accelerates immunologic progression in patients with primary HIV infection in an area of hyperendemicity for hepatitis B virus infection. J Infect Dis 2013;208:1184-6.
60. Yang CJ, Li SY, Chang SY, Wu PY, Liao MH, Liu WC, Wu CH, Sun HY, Hung CC. Associated factors with and genotypes of Chlamydia trachomatis infection among clients seeking voluntary counseling and testing for HIV infection in Taiwan. J Microbiol

Immunol Infect. 2013 Dec 31. pii: S1684-1182(13)00202-8. doi: 10.1016/ j.jmii.2013.10.007. [Epub ahead of print] PubMed PMID: 24387885.

61. Chang YH, WC Liu, Chang SY, Wu BR, Wu PY, Tsai MS, Hung CC, Lew-Ting CY. Associated factors with syphilis among human immunodeficiency virus-infected men who have sex with men in Taiwan in the era of combination antiretroviral therapy. J Microbiol Immunol Infect. 2013 Dec 31. pii: S1684-1182 (13) 00207-7.doi: 10.1016/ j.jmii.2013.11.003. [Epub ahead of print] PubMed PMID: 24388575.
62. Lee KY, Lin SW, Sun HY, Kuo CH, Tsai MS, Tang SY, Wu BR, Liu WC, Chang SY, Hung CC*. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. PLoS One 2014;9:e88497.
63. Lu CL, Chang SY, Chuang YC, Liu WC, Su CT, Su YC, Chang SF, Hung CC*. Revaccination with 7-valent pneumococcal conjugate vaccine elicits better serological response than 23-valent pneumococcal polysaccharide vaccine in HIV-infected adult patients who have undergone primary vaccination with 23-valent pneumococcal polysaccharide vaccine in the era of combination an tiretroviral therapy. Vaccine 2014;32:1031-5.
64. Sun HY, Cheng CY, Lee NY, Yang CJ, Liang SH, Ko WC, Liu WC, Wu CH, Wu PY, Cheng SH, Lin HH*, Hung CC*. Seroprevalence of hepatitis B virus among persons at high risk for HIV transmission two decades after implementation of nationwide vaccination program in Taiwan. PLoS One 2014;9: e90194.
65. Tsai MS, Hung CC, Liu WC, Shen CC, Chen MY, Hsieh SM, Sheng WH, Sun HY, Shih TTF. Reduced bone mineral density in HIV-infected patients in Taiwan: prevalence and associated factors. J Microbiol Immunol Infect 2014;47:109-15.
66. Hung CC, Wu SM, Lin PH, Sheng WH, Yang ZY, Sun HY, Tsai MS, Lee KY, Su YC, Liu WC, Chang SY. Increasing incidence of recent hepatitis D virus infection in HIV-Infected patients in an area hyperendemic for hepatitis B virus infection. Clin Infect Dis 2014;58:1625-33.
67. Lin KY, Cheng CY, Yang CJ, Tsai MS, Hsieh SM, Sun HY, Sheng WH, Chen MY, Chang SY, Cheng SH*, Hung CC*. Skin rash related to once-daily boosted darunavir-containing antiretroviral therapy in HIV-infected Taiwanese: incidence and associated factor. J Infect Chemother 2014;20:465-70.
68. Tebas P, Sension M, Arribas J, Duiculescu D, Florence E, Hung CC, Wilkin T, Deckx H, Vanveggel S, Stevens M, on behalf of the ECHO and THRIVE study groups. Lipid levels and changes in body fat distribution in treatment-na"ive, HIV-1-infected adults treated with rilpivirine or efavirenz for 96 weeks in the ECHO and THRIVE trials. Clin Infect Dis 2014;59:425-34.

69. Wu PY, Chen MY, Hsieh SM, Sun HY, Tsai MS, Lee KY, Liu WC, Yang SP, Luo YZ, Zhan JY, Sheng WH*, Hung CC*. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. PLoS One 2014;9:e104945.
70. Tsai MS, Yang CJ, Lee NY, Hsieh SM, Lin YH, Sun HY, Sheng WH, Lee KY, Yang SP, Liu WC, Wu PY, Ko WC*, Hung CC*. Jarisch-Herxheimer reaction among HIV-positive patients with early syphilis: azithromycin vs benzathine penicillin G therapy. J Int AIDS Soc 2014;17: 18993.
71. Yang JJ, Huang CH, Liu CE, Tang HJ, Yang CJ, Lee YC, Lee KY, Tsai MS, Lin SW, Chen YH, Lu PL*, Hung CC*. Multicenter study of hepatotoxicity related to trimethoprim/sulfamethoxazole in treatment of HIV-infected patients with Pneumocystis jirovecii pneumonia: incidence and associated factors. PLoS One 2014;9:e106141. [Alternative corresponding author]
72. Yang CJ, Chen TC, Lee NY, Lin YH, Liang SH, Lu PL, Huang WC, Tang HJ, Lee CH, Lin HH, Chen YH, Ko WC, Hung CC*. One dose versus three doses of benzathine penicillin G for patients co-infected with HIV and early syphilis: a multicenter, prospective observational study. PLoS One 2014;9: e109667.
73. Lo YC, Ji DD, Hung CC*. Prevalent and incident HIV diagnoses among Entamoeba histolytica-infected adult males: a changing epidemiology associated with sexual transmission-Taiwan, 2006-2013. PLoS NTD 2014:8:e3222.
74. Tsai JC, Lin YH, Lu PL, Shen NC, Yang CJ, Lee NY, Tang HJ, Liu YM, Huang WC, Lee CH, Ko WC, Chen YH, Chen TC*, Hung CC*. Comparison of serological response to doxycycline versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients: a multi-center observational study. [Alternative corresponding author] PLoS One 2014;9:e109813.
75. Sun HY, Sheng WH, Tsai MS, Lee KY, Chang SY, Hung CC*. Hepatitis B virus infection and HIV coinfection: a review. World J Gastroenterol 2014;20:14598-614. [invited review]
76. Tseng YT, Yang CJ, Chang SY, Lin SW, Tsai MS, Liu WC, Wu PY, Lo YC, Yang SP, Hung CC*, Chang SC. Incidence and risk factors of skin rashes and hepatotoxicity in HIV-positive patients receiving nevirapine-containing combination antiretroviral therapy in Taiwan. Int J Infect Dis 2014;29:e12-7.
77. Yang CJ, Li SY, Chang SY, Wu PY, Liu WC, Wu BR, Lo YC, Hung CC*. Associated factors with and genotypes of Chlamydia trachomatis infection among clients seeking voluntary counseling and testing for HIV infection in Taiwan. J Microbiol Immunol Infect 2014;47:526-32.
78. Chang YH, Chang SY, Liu WC, Hsieh CY, Wu PY, Hung CC*, Liew-Ting CY. Associated factors with syphilis among HIV-infected men who have sex with men in Taiwan. J Microbiol Immunol Infect 2014;47:533-41.

79. Lo YC, Hung CC. Prevalence of HIV infection and risky sexual practices among adult males with travel-associated Entamoeba histolytica infection in Taiwan, 2006-2013. Travel Med Infect Dis 2015;13:104-5. [Letter to the Editor]
80. Yang CJ, Chen YH, Tsai MS, Hung CC*. Optimal dose of benzathine penicillin G for the treatment of early syphilis in HIV-infected patients in the era of combination antiretroviral therapy. Clin Infect Dis 2015;60:1433-4. [Letter to the Editor]
81. Sun HY, Hsueh PR, Liu WC, Su YC, Chang SY, Hung CC*, Chang SC. Risk of active tuberculosis in HIV-infected patients in Taiwan with free access to HIV care and a positive T-Spot.TB test. PLoS One 2015;10:e0125260.
82. Yang CJ, Chang SY, Wu BR, Yang SP, Liu WC, Wu PY, Zhang JY, Luo YZ, Hung CC*, Chang SC. Unexpectedly high prevalence of Treponema pallidum infection in the oral cavity of human immunodeficiency virus-infected patients with early syphilis who had engaged in unprotected sex practices. Clin Microbiol Infect 2015:21:787.e1-7.
83. Lee SS, Lin HH, Tsai HC, Su IJ, Yang CH, Sun HY, Hung CC, Sy CL, Wu KS, Chen JK, Chen YS, Fang CT. A clinical algorithm to identify HIV patients at high risk for incident active tuberculosis: a prospective 5-year cohort study. PLoS One 2015;10:e0135801.
84. Lin KY, Liao SH, Liu WC, Cheng A, Lin SW, Chang SY, Tsai MS, Kuo CH, Wu MR, Wang SP*, Hung CC*, Chang SC. Cholelithiasis and nephrolithiasis among HIV-infected patients in the era of combination antiretroviral therapy. PLoS One 2015;10:e0137660.
85. Lo YC, Tsai MS, Sun HY, Hung CC, Chuang JS. National trend and characteristics of acute hepatitis C among HIV-infected individuals: a case-control study-Taiwan, 2001-2014. PLoS One 2015;10: e0139687.
86. Tsai JC, Hung CC, Chang SY, Liu WC, Wu CH, Chang LH, Luo YZ, Wu PY, Su YC, Sun HY, Chang SC. Increasing incidences of recent hepatitis C infection among the clients seeking voluntary counseling and testing for HIV and sexually transmitted infections in Taiwan. BMJ Open 2015;5:e0406.
87. Lee YC, Lin SW, Chen MY, Chang SY, Sheng WH, Hsieh SM, Sun HY, Chang HY, Wu MR, Liu WC, Wu PY, Yang SP, Zhang JY, Su YC, Luo YZ, Hung CC. Presence of tablet remnants of nevirapine extended-release in stools and its impact on virological outcome in HIV-infected patients: a prospective cohort study. PLoS One 2015;10: e0140574.
88. Lin KY, Hung CC*. Clinical relevance of cross-reactivity between darunavir and trimethoprim-sulfamethoxazole in HIV-infected patients. AIDS 2015;29:2213-4. [Correspondence]
89. Wu PY, Cheng CY, Liu CE, Lee YC, Yang CJ, Tsai MS, Cheng SH, Lin SP, Lin DY, Wang NC, Lee YC, Sun HY, Tang HJ, Hung CC. Multicenter study of hepatotoxicity and skin rash in antiretroviral-naïve HIV-positive patients initiating non-nucleoside reverse transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS One 2017;12:e0171596.

90. Cheng A, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, Wu PY, Hung CC*, Chang SC. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in HIV-positive adults on antiretroviral therapy. J Infect Dis 2017;215:606-13.
91. Chen GJ, Lin KY, Hung CC*, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. J Infect Dis 2017;215:1339-40. [Letter to the editor]
92. Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY, Chang SY, Liu CE*, Hung CC*. Hepatitis A virus infection and hepatitis A vaccination in HIV-positive patients: a review. World J Gastroenterol 2017;23:3589-606. [invited review]
93. Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Liu CE, Lee YT, Tang HJ, Wang NC, Lin TY, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Chang SH*, Hung CC*, for the Taiwan HIV Study Group. Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up. PLoS One 2017;12:e0179870.
94. Huang YS, Yang JJ, Lee NY, Chen GJ, Ko WC, Sun HY, Hung CC*. Treatment of Pneumocystis jirovecii pneumonia in HIV-infected patients: a review. Expert Rev Anti Infect Ther. 2017 Aug 21:1-20. doi: 10.1080/14787210.2017.1364991.
95. Lee YL, Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Tang HJ, Lin TY, Wang NC, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Cheng SH, Lee YT, Liu CE, Hung CC, for the Taiwan HIV Study Group. Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS One 2017;12: e0186338.
96. Lee YC, Chang SY, Lin KY, Chang LH, Liu WC, Wu CH, Sun HY*, Hung CC*, Chang SC. Attitudes towards preexposure exposure prophylaxis against HIV transmission among individuals seeking voluntary counseling and testing for HIV. BMJ Open 2017;7:e015142.
97. Huang YS, Chan CK, Tsai MS, Lee KY, Lin SW, Chang SY, Hung CC*, Chang SC. Kidney dysfunction associated with tenofovir exposure in HIV-1-infected Taiwanese patients. J Microbiol Immunol Infect 2017;50:595-603.
98. Chen GJ, Lin KY, Sun HY, Sheng WH, Hsieh SM, Huang YC, Cheng A, Liu WC, Hung CC*, Chang SC. Incidence of acute hepatitis A among HIV-positive patients during an ongoing outbreak among men who have sex with men in Taiwan: impact of hepatitis A virus vaccination. Liver Int 2017;37 (Dec):(in press)
99. Tsai MS, Chang SY, Kuo CH, Sun HY, Wu BR, Tang SY, Liu WC, Su YC, Lin SW, Hung CC*. Treatment response to switch regimens of unboosted atazanavir in combination with tenofovir and lamivudine in HIV-1-infected patients who had achieved virological suppression: a therapeutic drug monitoring and pharmacogenetic study. J Microbiol Immunol Infect 2017;50 (December): (in press)

附表一

一〇六年度計畫著作一覽表

計畫名稱：愛滋病防治整合型研究計畫—愛滋病防治中心
主 持 人：洪健清
計畫編號：MOHW106-CDC-C-114-000107

序號	計 畫 產 出 名 稱	產出形式	SCI*
1	Wu PY, Cheng CY, Liu CE, Lee YC, Yang CJ, Tsai MS, Cheng SH, Lin SP, Lin DY, Wang NC, Lee YC, Sun HY, Tang HJ, Hung CC. Multicenter study of hepatotoxicity and skin rash in antiretroviral-na"ive HIV-positive patients initiating non-nucleoside reverse transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS One 2017;12:e0171596.	期刊	2.806
2	Cheng A, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, Wu PY, Hung CC, Chang SC. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in HIV-positive adults on antiretroviral therapy. J Infect Dis 2017;215:606-13.	期刊	6.273
3	Chen GJ, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. J Infect Dis 2017;215:1339-40. [Letter to the editor]	期刊	6.273
4	Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY, Chang SY, Liu CE, Hung CC. Hepatitis A virus infection and hepatitis A vaccination in HIV-positive patients: a review. World J Gastroenterol 2017;23:3589-606. [invited review]	期刊	3.365
5	Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Liu CE, Lee YT, Tang HJ, Wang NC, Lin TY, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Chang SH*, Hung CC*, for the Taiwan HIV Study Group. Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up. PLoS One 2017;12:e0179870.	期刊	2.806
6	Huang YS, Yang JJ, Lee NY, Chen GJ, Ko WC, Sun HY, Hung CC*. Treatment of Pneumocystis jirovecii pneumonia in HIV-infected patients: a review. Expert Rev Anti Infect Ther. 2017 Aug 21:1-20. doi: 10.1080/14787210.2017.1364991.	期刊	3.139
7	Lee YL, Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, Tang HJ, Lin TY, Wang NC, Lee YC, Lin SP, Huang YS, Zhang JY, Ko WC, Cheng SH, Lee YT, Liu CE, Hung CC, for the Taiwan HIV Study Group. Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS One 2017;12: e0186338.	期刊	2.806

8	Lee YC, Chang SY, Lin KY, Chang LH, Liu WC, Wu CH, Sun HY*, Hung CC*, Chang SC. Attitudes towards preexposure exposure prophylaxis against HIV transmission among individuals seeking voluntary counseling and testing for HIV. BMJ Open 2017;7:e015142.	期刊	2.369
9	Huang YS, Chan CK, Tsai MS, Lee KY, Lin SW, Chang SY, Hung CC*, Chang SC. Kidney dysfunction associated with tenofovir exposure in HIV-1-infected Taiwanese patients. J Microbiol Immunol Infect 2017;50:595-603.	期刊	2.973
10	Chen GJ, Lin KY, Sun HY, Sheng WH, Hsieh SM, Huang YC, Cheng A, Liu WC, Hung CC*, Chang SC. Incidence of acute hepatitis A among HIV-positive patients during an ongoing outbreak among men who have sex with men in Taiwan: impact of hepatitis A virus vaccination. Liver Int 2017;37 (Dec):(in press)	期刊	4.116
11	Tsai MS, Chang SY, Kuo CH, Sun HY, Wu BR, Tang SY, Liu WC, Su YC, Lin SW, Hung CC*. Treatment response to switch regimens of unboosted atazanavir in combination with tenofovir and lamivudine in HIV-1-infected patients who had achieved virological suppression: a therapeutic drug monitoring and pharmacogenetic study. J Microbiol Immunol Infect 2017;50 (December): (in press)	期刊	2.973

SCI: Science Citation Index，若發表之期刊為 SCI 所包含者，請打「∨」。

伍、附件

附件一

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

愛滋病毒感染者服用希寧起始劑量為半量的有效性及停用的比例

年 度 研 究 報 告

執行機構：國立台灣大學醫學院附設醫院

計畫主持人：王建淳

研 究 人 員：巫沛瑩

執 行 期 間：106 年 1 月 1 日至 106 年 12 月 31 日

目　　錄

共 12 頁

壹、中文摘要：

為了了解是否起始使用半顆希寧可以降低因為神經精神副作用停止用藥的比例，我們調查在 2014/1/1-2017/6/30 期間，在昆明院區接受起始半量希寧和兩種核苷酸反轉錄酶抑制劑治療的病患，因為前述副作用停藥的比例和治療效果。台北市立聯合醫院昆明院區希寧(efavirenz)起始劑量為半量之個案，回溯性分析病歷的研究收集 103 年 1 月 1 日開始至 106 年 6 月 30 日，總共收集個案數為 390 人。副作用所發生則是依照病歷上所記錄之資料進行分析，分類為紅疹(rash)、眩暈(dizziness)、多夢(dreams)與夢魘(nightmare)、睡眠障礙(sleep disturbance)、發熱感(heat sensation)。病人可能出現一種以上的副作用。390 個案中出現任何一種副作用有 279 人(71.5%)，因為任何副作用而停藥的病人有 141 人(36.2%)。最常出現的副作用為暈眩，病歷上有提到此副作用的患者有 155 人(39.7%)，因為眩暈而停用希寧有 50 人(12.8%)。出現紅疹的個案數有 92 個患者(23.6%)，因此停藥者有 51 人(13.1%)，出現紅疹的時間距離開始服用藥平均約 11 天。其他副作用如多夢與夢魘有 62 人、睡眠障礙有 46 人、有 12 個病人提到有發熱感。 停用希寧的時間最常發生在四周內有 73 (18.7%)人，而在一年內停用希寧的病人數有 135 人(34.6%)。但是因為希寧起始劑量半量因病毒學治療失敗而需停用和更換藥物的病人僅有 11 人(2.8%)。390 位個案服藥追蹤滿 48 週以上有 225 人，病毒量<40 copies/ml 者有 208 人(92.4%)，服藥滿 96 週以上有 139 人，病毒量<40 copies/ml 者有 133 人(95.7%)。

關於藥物濃度的監測，自今年四月一日起至今年七月三十一日止，在台大醫院一共有 77 男性在起始服用抗病藥物時是選用希寧藥物的個案，他們的平均年齡為 34 歲。基礎點的愛滋病病毒量平均值為 4.98 $\log_{10}$ copies/ml，CD4 免疫球的平均值為 271 cells/μl，98.7% 的個案所搭配的核甘酸反轉錄酶抑制劑為 Truvada。 剛開始服用的前兩週，其中有 41 位(53.2%)是選用全劑量的希寧，36 位(46.8%)是選用半劑量的希寧，在這些服用希寧的個案中有 10 位(13.0%)停止繼續服用此藥物，平均停用天數距離開始使用的時間為 18 天，停用原因最多的為皮疹佔了 70%。台大醫院的病患中一共有 19 位(24.7%)個案有檢驗服用全劑量 efavirenz 時的藥物濃度，藥物濃度的平均值為 2.29 ng/ml (IQR, 1.43-4.87 ng/ml) 。

關鍵詞：希寧、藥物濃度監測、愛滋病毒量、藥物副作用、高效能抗愛滋病毒藥物治療

貳、英文摘要：

To investigate the effectiveness and adverse effects of lead-in efavirenz (1/2# for the fist 7 days) plus 2 NRTIs in the treatment of ARV-naïve HIV-infected patients, we retrospectively observed 390 patients who initiated combination antiretroviral therapy consisting 2 NRTIs plus efavirenz at Taipei City Hospital Kunming Branch between January 2014 and June 2017. In total, 71.5% of the patients reported one or more adverse effects to the regimens and 33.7% of the patient's had to switch efavirenz/2NRTIs to other non-efavirenz-containing regimens. Of the adverse effects reported included dizziness (39.7%), skin rashes (23.6%), dreams and nightmares (15.9%), sleep disturbance (10.3%), and heat sensation (3.1%). While about one third of the patients had to change regimens due to side effect, virological failure was observed only in 2.8% (n=11) of the patients who continued efavirenz-containing regimens. Among those patients who continued to receive efavirenz-containing regimen more than 48 weeks, 92.4% were able to achieve PVL<40 copies/ml at week 48 and 95.7% at week 96.

Between April and July 2016, 77 HIV-infected patients initiated efavirenz-containing regimens at the National Taiwan University Hospital; 41 started at full dose of efvavirenz while 36 at lead-in dosing for 1 week followed by switch to full-dose efavirenz. 19 patients who started lead-in dosing of efavirenz underwent therapeutic drug monitoring when they were switched to efavirenz at 600 mg daily for 14 days or more. The mean plasma efavirenz concentration of these 19 patients was 2.29 ng/ml (IQR, 1.43-4.87).

We conclude that, while a substantial proportion of the patients taking efavirenz-containing regimens had to stop efavirenz, lead-in dosing of efavirenz within the first week of initiation of cART did not appear to compromise its long-term effectiveness in achieve durable viral suppression. Despite lead-in dosing in the first week of therapy, all patients achieved target plasma efavirenz concentrations (>1 ng/ml)

Keywords: efavirenz; therapeutic drug monitoring; plasma HIV RNA load; adverse effect; highly active antiretroviral therapy

參、本文：

（一）前言

含有 efavirenz, tenofovir disoproxil fumarate (TDF) 和 emtricitabine (FTC)組合性的抗愛滋病毒藥物組合，依然是在世界衛生組織和台灣國內的愛滋病毒感染成人的治療指引上優先首選建議.[1-4] 希寧(efavirenz)此藥物在單獨使用時的血漿中半衰期長達 52 小時，組合劑量的半衰期也有 40-55 小時[5]，希寧此藥物的顆粒數少及每天使用頻次少(一天一次，一次一顆)，同時許多過去的研究下也證實它的安全性及耐受性。[6,7] 同時, 當愛滋病毒感染者同時合併感染肺結核時在服用 rifampicin 抗結核病藥物時，所搭配的首選抗病毒藥物也是含有希寧的抗愛滋病毒藥物組合。[8,9]

與希寧有相關的不良事件，最顯著的為皮疹及中樞神經相關症狀的副作用。在服用希寧的患者中約有 25-70%的人會有中樞神經或是精神神經上的擾亂相關的副作用。[10-13] 這些症狀包含暈眩、頭痛、注意力不集中、多夢、失眠、悲傷、情緒改變、易怒等。這些症狀通常出現在剛開始服藥的前幾天，同時也可能因為這些症狀而影響感染者持續服藥的意願而造成感染者提早中斷藥物。[13]

希寧是由肝臟 CYP2B6 酵素系統代謝,它會受到希寧的使用活化,並且在使用後的第十四天達到最大活性。根據 Gutierrez-Valencia A 等人的隨機分派臨床試驗研究結果發現，逐步地將希寧藥物濃度調高 (前六天是 200 mg，7-13 天為 400 mg，第 14 天後增加為 600 mg)此做法會減少與希寧此藥物所造成的中樞神經或是精神神經上擾亂(efavirenz-related neuropsychiatric adverse events (NPAEs))相關副作用的強度，但仍然保持它的療效。[14] 在追蹤 24 週後只有 6 位個案(5.3%)是病毒學上的失敗。[14] 其次,根據我們自己的藥物監測的觀察研究,在 431 位接受全劑量希寧的愛滋病毒感染台灣人,第十二小時的血漿希寧濃度影 73%的受試者高於 2.0 ng/ml (Hung CC, EACS 2015, oral abstract)。這意味著愛滋病毒感染的國人服用全劑量的希寧,有相當高的比例可能濃度過高,可能導致的不良反應以至於停藥的比例過高。

在本研究中,我們將對於從未接受治療過抗愛滋病毒藥物之愛滋病毒感染者給予希寧減半量的起始劑量。我們預期可以同時減少藥物的副作用增加感染者持續服藥的信心，同時也可以保有抗病毒藥物的療效。

（二）材料與方法

執行期間： 2014 年 1 月 1 日迄 2017 年 6 月 30 日。

1. 研究設計及地點

此研究為單組的介入性研究，參與研究的兩家醫院分別為台灣大學醫學院附設醫院及台北市立聯合醫院昆明院區，包含各種抗愛滋病毒藥物提供，愛滋病病毒量及免疫力(CD4)及其他血液的監測。

2. 個案選取

年紀大於 20 歲的愛滋病毒感染者，從未接受過抗病毒藥物者，病毒經檢測並不對於 efavirenz, FTC, TDF 具有抗藥基因突變, 此次為初次服用抗病毒藥物者，初次服用的抗愛滋病毒藥物種類為希寧加上 TDF/FTC (coformulated as Truvada)。排除條件為同時使用 rifamycins 藥物之個案、懷孕婦女、曾經服用抗病毒藥物者(包含事後預防用藥(post-exposure prophylaxis)以及母子傳直感染預防用藥)。

3. 研究方法及追蹤流程

根據我們之前的研究結果發現 9，經由血清監測藥物濃度我們發現，我國感染者的希寧藥物在血清中的濃度有高比例高於國際上建議的濃度(1-4 ng/ml)。我們會經由臨床醫師及個案管理師向個案解釋藥物減半的策略(1-7 天服用 300 mg，第八天後開始服用 600 mg; 如果病患在第七天依然覺得無法耐受藥物的神經系統副作用, 病患可以繼續使用一星期的半顆的希寧加上全劑量的 TDF/FTC, 但是半量的希寧總使用時間不超過 14 日)。在個案服藥滿一個月後我們會檢測個案服藥後 12 小時的希寧濃度，同時我們會在第七天, 第十四天,第二十一天和第二十八天記錄個案服藥的不適症狀, 包含暈眩、頭痛、注意力不集中、多夢、失眠、悲傷、情緒改變、易怒等。

根據疾管署的規定，我們分別會在個案服藥前、服藥後滿 4 週、12-16 週、24-28 週、36-40 週和 48-52 週抽血檢測愛滋病病毒量、免疫球數值、生化數值(GOT/GPT/TG/T-CHO/LDL-C)。我們採用統一格式的 excel 檔案去收集並記錄個案基本資料(年齡、性別、身高、體重)、副作用記錄表單以及各項抽血數值。

為了了解是否起始使用半顆希寧可以降低因為神經精神副作用停止用藥

的比例，我們將調查在 2014/1/1-2017/6/30 期間接受半量希寧和兩種核甘酸反轉錄酶抑制劑治療的病患因為前述副作用停藥的比例。在這期間使用希寧的病患,除了藥物濃度監測以外,也都接受根據治療指引所提供相同的醫療照護和血液追蹤。同時，我們針對在 2016/4/1-2016/7/31 期間在台大醫院初始使用含 efavirenz 的藥物組合的病患,邀請他們接受藥物濃度監測。

（三）結果

本年度的報告，關於藥物副作用的觀察，先以昆明院區的回溯性資料收集為主。關於要濃度的監測，則以台大醫院收納個案為主。

台北市立聯合醫院昆明院區希寧(efavirenz)起始劑量為半量之個案，回溯性分析病歷的研究收集 103 年 1 月 1 日開始至 106 年 6 月 30 日，總共收集個案數為 390 人，個案的服用希寧時的年齡平均為 32.4 歲(18～71 歲) ，服用藥物時愛滋病毒感染的時間平均為 1.8 年，所有 390 個案中 387 人為男性，僅有 3 人為女性。病患感染的危險因子(risk factors)中大部分為男男間性行為(MSM, men who have sex with men)與雙性戀(bisexual)共有 370 人(94.9%)、HIV 感染者中合併 B 型肝炎帶原者有（HBsAg: positive）53 人(13.6%)，而 HIV 感染者合併有 C 型肝炎帶原者(Anti-HCV: positive)有 24 人(6.2%)。

在服用希寧(efavirenz)之前的實驗室檢驗，免疫力 CD4 T lymphocyte 平均值為 263.3(4.8-842)，CD4<200 有 142 人(36.4%)。而 HIV viral load 平均值為 251624 (167～5854000)，plasma HIV RNA load $>10^5$ copies/ml 的個案有 202 人（51.8 %），390 人中有 2 人缺 baseline CD4 數值，有 2 人缺 baseline HIV viral load 數值。

副作用所發生則是依照病歷上所記錄之資料進行分析，分類為紅疹(rash)、眩暈(dizziness)、多夢(dreams)與夢魘(nightmare)、睡眠障礙(sleep disturbance)、發熱感(heat sensation)。病人可能出現一種以上的副作用。390 個案中出現任何一種副作用有 279 人(71.5%)，因為任何副作用而停藥的病人有 141 人(36.2%)。最常出現的副作用為暈眩，病歷上有提到此副作用的患者有 155 人(39.7%)，因為眩暈而停用希寧有 50 人(12.8%)。出現紅疹的個案數有 92 個患者(23.6%)，因此停藥者有 51 人(13.1%)，出現紅疹的時間距離開始服用藥平均約 11 天。其他副作用如多夢與夢魘有 62 人、睡眠障礙有 46 人、有 12 個病人提到有發熱感。

患者使用的抗病毒藥物組合除了希寧之外的核苷酸反轉錄酶抑制劑(NRTI)，使用 Combivir 者有 205 個病患，停用希寧 104 人(50.7%)。使用 tenofovir disoproxil fumarate (TDF) + lamivudine 組合者有 107 人，停用藥物 35 人 (32.7%)。使用 Truvada (TDF/FTC) 有 69 位患者，停用藥物 21 人(30.4%)。此外有 8 位病人使用 Kivexa，停用藥物 5 人 (62.5%)。

停用希寧的時間最常發生在四周內有 73 (18.7%)人，而在一年內停用希寧的病人數有 135 人(34.2%)。但是因為希寧起始劑量半量因病毒學治療失敗而需停用和更換藥物的病人僅有 11 人(2.8%)。

390 位個案目前服藥滿 48 週以上有 225 人，病毒量<40 copies/ml 者有 208 人(92.4%)，服藥滿 96 週以上有 139 人，病毒量<40 copies/ml 者有 133 人(95.7%)。

關於藥物濃度的監測，自今年四月一日起至今年七月三十一日止，在台大醫院一共有 77 男性在起始服用抗病藥物時是選用希寧藥物的個案，他們的平均年齡為 34 歲。基礎點的愛滋病病毒量平均值為 4.98 $\log_{10}$ copies/ml，CD4 免疫球的平均值為 271 cells/μl，98.7%的個案所搭配的核甘酸反轉錄酶抑制劑為 Truvada。　　剛開始服用的前兩週，其中有 41 位(53.2%)是選用全劑量的希寧，36 位(46.8%)是選用半劑量的希寧，在這些服用希寧的個案中有 10 位(13.0%)停止繼續服用此藥物，平均停用天數距離開始使用的時間為 18 天，停用原因最多的為皮疹佔了 70%。台大醫院的病患中一共有 19 位(24.7%)一開始使用半量 efavirenz 的個案在更換到全劑量的兩週後有檢驗服用全劑量 efavirenz 時的藥物濃度，藥物濃度的平均值為 2.29 ng/ml (IQR, 1.43-4.87 ng/ml)。

（四）討論

希寧依然是世界衛生組織和國內建議治療愛滋病毒感染的首選藥物之一。但是其副作用，如同本研究發現,儘管使用半顆 lead-in，再轉換成整顆之際，依然還是有很高的比例病患因為無法耐受這些神經精神和皮疹等副作用必須更換藥物。

昆明院區此回溯性希寧半量為起始劑量的抗病毒藥物治療的研究，和台灣絕大多數的醫院一樣，雖然沒有服用藥物前的抗藥性基因檢測報告，病毒治療失敗人數僅有 11 人(2.8%)，以北台灣地區的非核苷酸反轉錄酶抑制劑(NNRTI)抗藥性盛行率(大約 6-8%)相比較，以希寧半量為起始劑量之治療仍然為可靠之治療，並不會因為初始使用半顆而

增加治療失敗的風險。這是因為我國人使用整顆的希寧時藥物濃度有 3/4 會超過 2 ng/ml，因此在初始階段服用希寧後誘發代謝自己的 CYP2B6 的反應需要二週的時間才達到最高峰。

副作用的比例偏高，以神經、精神系統的副作用為最常見，而因為副作用而停用希寧的原因，則是以藥物引起紅疹為最多。眩暈引起停用藥物的比例約 10%，神經、精神系統之副作用較為主觀且嚴重度因人而異，大部分服用一段時期後病患可以耐受。然而，因同類藥理作用新藥物的引進，也可能因臨床醫師使用新藥物而使得觀察的停用藥物比例偏高。藥物停用最常的時間點為服用藥的四週內。

至於初始使用半量的 efavirenz 一週後再改為全劑量，接受藥物濃度監測的 19 位病患中，其血中藥物濃度都能達到高於 1 ng/ml 的治療目標。

（五）結論

針對台灣的病患使用希寧半量加上兩種核甘酸反轉錄酶抑制劑做為初始第一線治療愛滋病毒，在臨床上的治療規劃是可行的，但是儘管半量的開始，轉換成全量希寧之後，依然有高比例的病患因為副作用停用希寧。初始使用半量並不會影響後續全劑量後達到標的血中藥物濃度。

（六）建議

疾管署在民國 106 年 9 月公告四種 Single Table Regimen 做為愛滋病毒感染者處方的第一線藥物，含有希寧 Efavirenz 成分之 Atripla 仍為其中之一，價格為四者藥物中最低。使用希寧的副作用雖然相對較多但以研究中發現病毒學治療失敗比率低，而且血中藥物濃度皆高於治療目標濃度，在台灣地區當病患需要並用抗結核藥物時預期藥物交互作用之產生，仍可考量使用 Atripla 而不需要調整藥物劑量。新藥物 Genvoya 大部分醫院尚未進用藥物，B 型肝炎個案當 HIV 病毒量超過 10 萬仍考量以 Atripla 做為治療藥物。起始半量使用雖然停用比例仍高但是仍可以舒緩病患開始用藥之不適，然而台灣地區希寧之原廠藥商已經停止供貨，目前僅有學名藥可以使用，是否可以相同方式起始半量使用有待研究。

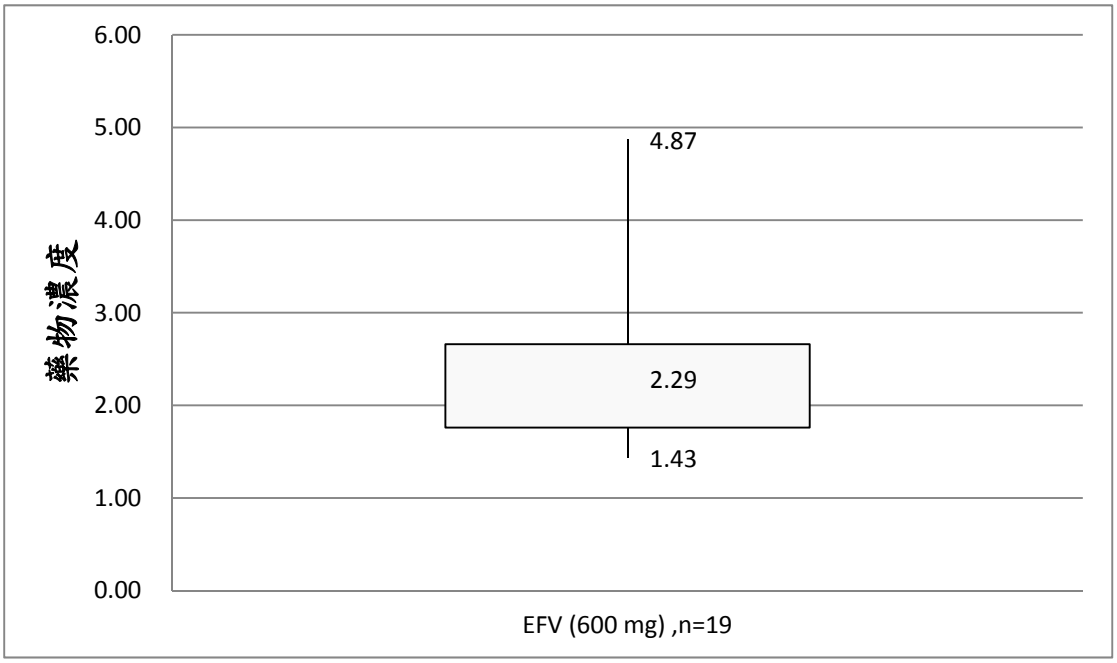
（七）參考文獻

1. DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2014; http://aidsinfo.nih.gov/guidelines.
2. WHO. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. July 2014; http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf? ua=1&ua=1.
3. EACS. Guidelines ART of HIV-positive Persons. [Initial Combination Regimen for ART-naive Adult HIV-positive Persons]. November 2014; http://www.eacsociety.org/files/guidelines_english_71_141204.pdf.
4. Writing G, Williams I, Churchill D, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV medicine. Jan 2014;15 Suppl 1:1-85.
5. Molina JM, Peytavin G, Perusat S, et al. Pharmacokinetics of emtricitabine, didanosine and efavirenz administered once-daily for the treatment of HIV-infected adults (pharmacokinetic substudy of the ANRS 091 trial). HIV medicine. Mar 2004;5(2):99-104.
6. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. The New England journal of medicine. Jan 19 2006;354(3):251-260.
7. Molina JM, Ferchal F, Rancinan C, et al. Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients. The Journal of infectious diseases. Aug 2000;182(2):599-602.
8. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. The Journal of antimicrobial chemotherapy. Dec 2006;58(6):1299-1302.
9. Lee KY, Lin SW, Sun HY, et al. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. PloS one. 2014;9(2):e88497.
10. Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. Journal of acquired immune deficiency syndromes. Mar 1 2002;29(3):244-253.

11. Hawkins T, Geist C, Young B, et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV clinical trials. Jul-Aug 2005;6(4):187-196.
12. Perez-Molina JA. Safety and tolerance of efavirenz in different antiretroviral regimens: results from a national multicenter prospective study in 1,033 HIV-infected patients. HIV clinical trials. Jul-Aug 2002;3(4):279-286.
13. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. AIDS reviews. Apr-Jun 2009;11(2):103-109.
14. Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Annals of internal medicine. Aug 4 2009;151(3):149-156.

（八）圖表

十九位病患初始使用半量的 efavirenz 一週後增加至全劑量至少兩週後檢測的血中藥物濃度



附件二

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

愛滋個案開始服藥前與服藥後之抗藥性發生率追蹤及藥物組合治療效果評估研究

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院醫學檢驗暨生物技術學系

計畫主持人：張淑媛

研 究 人 員：洪健清、張淑芳、蘇意青

執 行 期 間：106 年 01 月 01 日至 106 年 12 月 31 日

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目　　錄

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壹、中文摘要：

本計畫主要探討台灣地區未接受組合式抗愛滋病毒療法病的人，其病毒抗藥性的基因型盛行率及追蹤其接受第一線治療後的治療成果。過去一月到十月，我們根據疾病管制署的建議到各縣市收集未接受抗愛滋病毒藥物治療的病人檢體。在這十個月當中, 我們已經收納 456 位尚未接受抗愛滋病毒藥物治療患者的檢體，進行原生性 HIV-1 病毒基因型抗藥性分析。這些患者對於任一類藥物具有抗藥性的比例為 17.1%；其中針對蛋白酶抑制劑 (protease inhibitor)、核苷酸反轉錄酶抑制劑 (nucleoside or nucleotide reverse-transcriptase inhibitors, NRTIs)、非核苷酸反轉錄酶抑制劑 (non-nucleoside reverse-transcriptase inhibitors, nNRTIs)藥物的抗藥性基因型盛行率分別為 0.7%、6.1%、及 12.5%。對於兩類以上藥物具抗藥性的抗藥性基因型盛行率是 2.2%。相較於去年的抗藥性盛行率調查， nNRTI 抗藥性盛行率有顯著的上升(8.4% v.s. 12.5%)(P=0.05)與 PI 抗藥性盛行率則有顯著的下降(2.5% v.s. 0.7%)(P=0.03) 。根據我們的研究成果, 我們建議如果病人要服用以非核苷酸反轉錄酶抑制劑為基礎的一天一顆的第一線處方藥物時(例如 TDF/FTC/EFV 及 TDF/FTC/RPV)，應該在用藥前接受抗藥性基因檢測，以確保藥物治療的效果。

關鍵詞：人類免疫不全病毒(HIV-1)、病毒抗藥性分析、蛋白酶、反轉錄酶、嵌合酶

貳、英文摘要：

This study aimed to determine the prevalence of transmitted drug resistance among antiretroviral-naive HIV-1-infected patients in Taiwan. From January to October, 2017, we have completed analyses of 456 specimens. The prevalence of transmitted drug resistance to any class of antiretroviral agents among antiretroviral--naive HIV-1 infected patients was 17.1%. The prevalence of resistance to protease inhibitors, nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs), and non-nucleoside reverse-transcriptase inhibitors, (nNRTIs) was 0.7%、6.1% and 12.5%, respectively. The prevalence of resistance to more than two classes of drugs was 2.2%. Compared to the survey conducted in 2016, the prevalence of antiretroviral resistance to nNRTI has significantly increased from 8.4% to 12.5% (P=0.05) and that to PI has decreased from 2.5% to 0.7% (P=0.03). Based on the findings of our surveys, we suggest that patients who are to initiate nNRTI-based single-tablet regimens such as TDF/FTC/EFV (Atripla) and TDF/FTC/RPV (Complera) as the first-line regimen should submit blood specimens for determinations of antiretroviral resistance to ensure the efficacy of antiretroviral therapy.

關鍵詞：HIV-1; drug resistance; protease inhibitor; reverse transcriptase; integrase

參、本文：

（一）前言

藥物治療對於受人類免疫不全病毒感染的患者已有很大的成效，不僅可以延長病人的壽命，並可進一步幫助恢復部分受損的免疫系統功能。目前，絕大多數的抗病毒治療藥物，都是藉由抑制人類免疫不全病毒的*pol*基因上與病毒活性或複製相關的病毒酵素，來達到抑制病毒複製的效果。依照藥物抑制的病毒基因與機制, 抗愛滋病毒藥物可分為三大類。第一類主要是抑制病毒蛋白酶的活性(Protease inhibitor,PI)。第二類是以擬似核苷酸衍生物的方式，來抑制反轉錄腖的活性(nucleoside or nucleotide reverse-transcriptase inhibitors, NRTIs)。第三類是以非擬似核苷酸衍生物的形式，來抑制反轉錄酶的活性(non-nucleoside reverse-transcriptase inhibitors, nNRTIs)。由於組合式抗愛滋病毒藥物治療比使用單一病毒抑制劑更能有效而長期地抑制病毒的複製，使用兩種或者三種不同類別的抗愛滋病毒藥物治療病人已經是臨床的常規。但是，在服用藥物過程中，可能因為病毒快速產生變異、病人沒有定時定量服藥或者因為藥物交互作用等因素，病毒會在患者體內衍生出抗藥性病毒株。這些抗藥性病毒株的產生，已知與病人體內的病毒量快速增加，有極高的相關性[1, 2], 它會使得患者體內的病毒無法被完全地抑制，進而嚴重地影響到治療的效果與治療所需的時間 [3, 4]。更嚴重的是, 這些抗藥性病毒株的產生後，會因為繼續傳播造成原生抗藥性病毒株的流行。根據最近歐美的研究指出，在北美及歐洲分別有 1-11%及 9-21%的患者，是被原生抗藥性病毒株所感染[5-10]。而這些被原生抗藥性病毒株所感染的病人，其接受藥物療法的成效，比被一般無抗藥性病毒株所感染的病人為差。例如，被原生抗藥性病毒株所感染的病人，經藥物治療後，其體內病毒量降至 500 copies/ml 以下所需的時間平均為十二週。遠較被一般病毒株感染病人的五週為長 [11]。因此，了解原生抗藥性病毒株的盛行率及其所抗藥的藥物種類，將可作為臨床醫師在做藥物選擇上的參考，並且可以進一步節省使用後線藥物組合和追蹤檢測所需的醫療資源。因此，本調查將藉由分析蛋白酶酶及反轉錄酶這些基因上與抗藥性相關的基因變異，了解台灣地區原生抗藥性人類免疫不全病毒的盛行率。希望研究成果未來能幫助節省醫療成本，並提高病患的有效治療成功率。

（二）材料與方法

執行期間： 2017 年 1 月 1 日迄 2017 年 12 月 31 日。

研究方法

1. 受試者：

在 2017 年 1 月到 2017 年 12 月期間，年滿 20 歲的愛滋病毒感染者只要未曾接受過組合式抗愛滋病毒藥物治療，我們會分析其血液檢體中病毒抗藥性基因型，並分析盛行率的趨勢以提供臨床醫師將來選擇治療藥物的參考；同時我們藉由電腦程式 PHYLIP 將被用來作基因系統樹分析(phylogenetic analysis)，以決定抗藥性病毒株之間的相關性。本研究業經台大醫院及相關參與醫院的倫委會同意通過後執行，受試者必須填寫受試者同意書後方可以參加試驗。

2. 實驗室檢驗

我們自病人血漿中萃取病毒顆粒中的 RNA，經由反轉錄酶反應將 RNA 轉換為 cDNA，再以 PCR 反應來放大病毒的 *gag-RT* 可轉錄區域。這些 PCR 產物經由洋膠電泳純化後，將直接作核酸定序，以為進一步病毒基因序列的相關分析。有關抗藥性相關的基因變異，我們主要依據國際愛滋病學會與美國之抗藥突變小組委員會 (International AIDS Society-USA Mutations Panel) 所訂定，與人類免疫不全病毒抗藥性相關的基因變異[15, 16] (http://www.iasusa.org/) 以及參考 the Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu)、Geno2pheno (http://www.genafor.org/index.php) 的抗藥性基因型分析。分析結果我們會以一標準報告格式，以電子郵件寄給送件的臨床醫師，以為治療時藥物選擇或更換的參考。

3. 統計分析

所有的統計分析將利用 SPSS software; version 11.0 (SPSS)進行。類別變數將由$\chi 2$ 或是費雪精確度檢定(Fisher's exact test)分析；連續變數將由 2-sample *t* 分析。非類別變數將由 Wilcoxon rank sum test 分析。 *P* 值小於 0.05 將被認為有統計學上的意義。

（三）結果

自今年一月一日起至今年十月二十七日止，自未接受過三合一雞尾酒療法的 HIV 感染者，我們一共收到 547 件血液檢體進行基因型抗藥性檢測，目前已完成 456 件檢體的 HIV-1 病毒基因型抗藥性分析。這些檢體來自全台各家醫院，其分布如圖一，其中 87.7% (400 件)來自北部醫院，4.4% (20 件)來自中部醫院，5.5% (25 件)來自南部醫院，2.4% (11 件)來自東部醫院。因為本計畫實際收案的檢體分布跟當初疾病管制署所希望的樣本數有些落差(如圖二)，所以研究結果就依實際收案的檢體數及經由隨機取樣的樣本數來分析及呈現。

依實際收案的檢體數，在未接受抗反轉錄藥物治療的病人中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 17.1%，對反轉錄酶抑制藥物(NRTIs)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(nNRTIs) 及蛋白酶抑制劑 (PIs)的抗藥性病毒株的比例分別為 6.1%、12.5%、及 0.7%。對兩種以上藥物具抗藥性的比例為 2.2% (圖三)。就縣市的分布來看，台北市、新北市及基隆市、及桃園市對任一類藥物具有抗藥性的病毒株其總體盛行率為 15%以上，新竹縣及苗栗縣也有 10.5%。其它地區則分布較不均，彰化縣、高雄市、及花蓮縣、台東縣及離島地區分別有 20%、12. 5%、及 27. 3%。相較於我們去年的調查，其整體抗藥性的比例有些微上升(17.1% v.s. 13.1%,)(*P*=0.10) (圖四及五)，主要升高的抗藥性藥物種類是 NRTI 的藥物(4.0% v.s. 6.1%)(*P*=0.15)及 nNRTI 的藥物(8.4% v.s. 12.5%) (*P*=0.05)，而 PI 的抗藥性盛行率是下降(2.5% v.s. 0.7%) (*P*=0.03) (圖二)；其中 nNRTI 抗藥性盛行率的上升與 PI 抗藥性盛行率的下降是達到統計學有意義的差異。

經由隨機取樣的樣本數，在未接受抗反轉錄藥物治療的病人中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 17.6%，對反轉錄酶抑制藥物(NRTIs)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(nNRTIs) 及蛋白酶抑制劑 (PIs)的抗藥性病毒株的比例分別為 6.7%、 12.7%、及 0.6%。對兩種以上藥物具抗藥性的比例為 2.4% (圖六)。依地區分類的原生性抗藥性盛行率(圖七)與圖四(依實際收案的檢體數)沒有太多的不同。抗藥性趨勢的分析也與依實際收案的檢體數的分析結果一樣，即 nNRTI 抗藥性盛行率的上升與 PI 抗藥性盛行率的下降都是具有統計學有意義的差異。

圖八分別就全台、台北市、新北市及基隆市、及桃園市的原生性抗藥性盛行率就實際收案的檢體數及經由隨機取樣的樣本數來比較。在全台的原生性抗藥性盛行率部分(圖八 A)沒有差異。台北市的 NRTIs (11.8% v.s. 7.8%)及多重抗藥性(2.9% v.s. 1.0%)原生

性抗藥性盛行率在隨機取樣的樣本數比較高，而 nNRTIs 原生性抗藥性盛行率(13.6% v.s. 11.8%)則是在實際收案的檢體數分析中比較高(圖八 B)。新北市及基隆市的 NRTIs s(14.3% v.s. 10.1%)及 nNRTI (14.3% v.s. 12.8%)原生性抗藥性盛行率在隨機取樣的樣本數比較高，多重抗藥性原生性抗藥性盛行率(13.6% v.s. 11.8%)則是在實際收案的檢體數分析中為零(圖八 C)。桃園市的 nNRTIs (19.0% v.s. 11.8%)及多重抗藥性(4.8% v.s. 2.4%)原生性抗藥性盛行率在隨機取樣的樣本數比較高，PI 原生性抗藥性盛行率(13.6% v.s. 11.8%)則是在實際收案的檢體數分析中比較高(1.8% v.s. 0.0%) (圖八 D)。

就收案的患者中，目前回傳已使用藥物的個案有 387 人。其中使用的第一線藥物種類如表一。其中以使用 abacavir/lamivudine/dolutegravir (Triumeq)人數最多，占 50.1%；其次為 TDF/FTC/rilpivirine (Complera) 的 23.3%及 TDF/FTC/efavirenz (Atripla)的 17.1%。這 387 人中，有 348 個個案有做服藥後第一次的病毒量偵測，時間分布為服藥後 6-204 天。這些個案大多數的治療效果都很好，有 98%的病人(147/150)在治療後第四週有大於十倍的血漿病毒量的下降；62.4% (217/348)的病人在治療後中位數 31 天(分布為 7-204 天)，病毒量已降到 20 copies/mL 或以下。我們會持續追蹤這些患者在治療後第 12-15 個月及第 24 個月的治療效果。

（四）討論

我們收到的檢體其分布如圖一，其中 87.7% (400 件)來自北部醫院，4.4% (20 件)來自中部醫院，5.5% (25 件)來自南部醫院，2.4% (11 件)來自東部醫院。實際收案的檢體分布跟當初疾病管制署所希望的樣本數有些落差(圖二)。經分析，可能的原因如下: 第一，北部醫院因為之前合作比較頻繁，對於送件流程比較熟悉，所以送件的意願比較強烈；因此實際收件數比原先預定的樣本數多出三倍(400 件 v.s. 100 件)。第二，因為抗藥性基因檢測沒有列在 HIV 照護的常規檢查裡，一些醫院必須在自家醫院提出倫理委員會的申請才能送件，所以會降低臨床醫院送檢的意願。有些有意願的醫院在提出申請後，也是最近才取得醫院倫委會的同意，例如成大醫院及奇美醫院；所以這兩家醫院目前的送檢數比較少。第三，有些配合的臨床醫院因為新診斷個案比較少，所以送檢數也會受影響。如彰化基督教醫院及屏東基督教醫院。這些我們都會再持續與之溝通，並開發新的醫療院所來共同參與研究。

今年的追蹤研究發現，在未接受抗反轉錄藥物治療的病人中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 17.1%，相較於之前我們去年的調查，其整體抗藥性的比例有些微上升的趨勢(17.1% v.s. 13.1%; *P*=0.10) (圖四及五)，主要升高的抗藥性藥物種類來自於對 NRTIs 的抗藥 (4.0% v.s. 6.1%; *P*=0.15)及 nNRTI 的抗藥 (8.4% v.s. 12.5%; *P*=0.05)，而 PI 的抗藥性盛行率是下降 (2.5% v.s. 0.7%; *P*=0.03) (圖二)；其中 nNRTI 抗藥性盛行率的上升與 PI 抗藥性盛行率的下降是具有統計學意義的差異。因為台灣衛生福利部疾病管制署於今年九月一日起推動一天一顆的處方藥物為第一線的治療選擇；其中兩種藥物是以兩個擬似核苷酸衍生物的反轉錄酶抑制藥物搭配一個非擬似核苷酸衍生物的反轉錄酶抑制藥物 (TDF/FTC/EFV 及 TDF/FTC/RPV)，我們建議目前如果要接受包含非擬似核苷酸衍生物反轉錄酶抑制藥物的抗反轉錄病毒藥物治療前，應進行抗藥性檢測以確定病人沒有帶有非擬似核苷酸衍生物反轉錄酶抑制藥物的基因突變，而影響藥物治療效果。

（五）結論

對政策之具體建議:

1. 因為非擬似核苷酸衍生物反轉錄酶抑制藥物的抗藥性盛行率有升高的趨勢，所以建議如果病人要服用以非擬似核苷酸衍生物反轉錄酶抑制藥物為基礎的一天一顆的第一線處方藥物時(例如 TDF/FTC/EFV 及 TDF/FTC/RPV)，應該在用藥前接受抗藥性基因檢測，以確保藥物治療的效果。
2. 抗藥性的病毒株主要分布在北部，對於這地區的持續性抗藥性監測是必須的，以確保抗藥性病毒株不會蔓延。

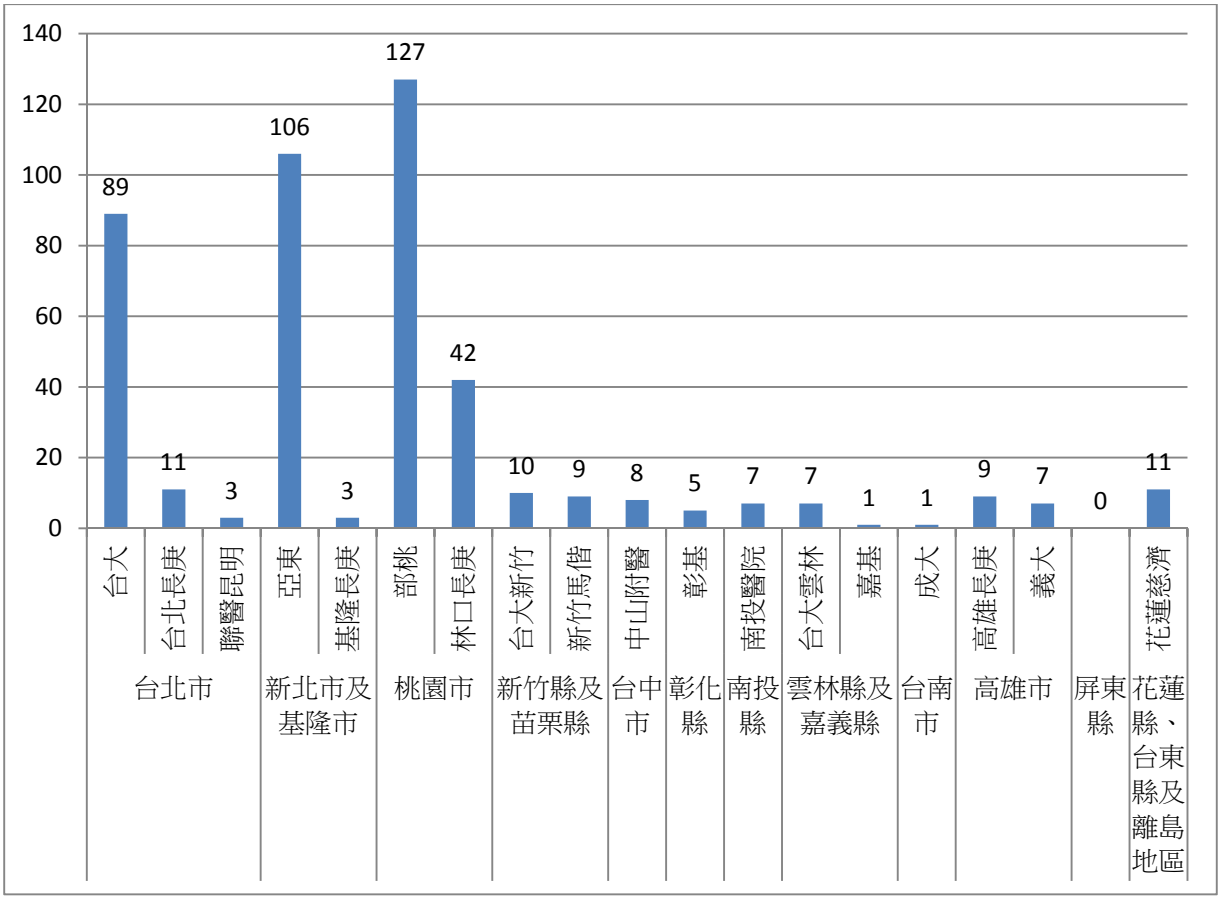
（六）參考文獻

1. Schuurman, R., et al., *Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC).* J Infect Dis, 1995. **171**(6): p. 1411-9.
2. Eastman, P.S., et al., *Genotypic changes in human immunodeficiency virus type 1 associated with loss of suppression of plasma viral RNA levels in subjects treated with ritonavir (Norvir) monotherapy.* J Virol, 1998. **72**(6): p. 5154-64.
3. Coombs, R.W., et al., *Association of plasma human immunodeficiency virus type 1 RNA level with risk of clinical progression in patients with advanced infection. AIDS Clinical Trials Group (ACTG) 116B/117 Study Team. ACTG Virology Committee Resistance and HIV-1 RNA Working Groups.* J Infect Dis, 1996. **174**(4): p. 704-12.
4. O'Brien, W.A., et al., *Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS.* N Engl J Med, 1996. **334**(7): p. 426-31.
5. Little, S.J., et al., *Reduced antiretroviral drug susceptibility among patients with primary HIV infection.* Jama, 1999. **282**(12): p. 1142-9.
6. Boden, D., et al., *HIV-1 drug resistance in newly infected individuals.* Jama, 1999. **282**(12): p. 1135-41.
7. Salomon, H., et al., *Prevalence of HIV-1 resistant to antiretroviral drugs in 81 individuals newly infected by sexual contact or injecting drug use. Investigators of the Quebec Primary Infection Study.* Aids, 2000. **14**(2): p. F17-23.
8. Yerly, S., et al., *Transmission of antiretroviral-drug-resistant HIV-1 variants.* Lancet, 1999. **354**(9180): p. 729-33.
9. Balotta, C., et al., *Prevalence of transmitted nucleoside analogue-resistant HIV-1 strains and pre-existing mutations in pol reverse transcriptase and protease region: outcome after treatment in recently infected individuals.* Antivir Ther, 2000. **5**(1): p. 7-14.
10. *Analysis of prevalence of HIV-1 drug resistance in primary infections in the United Kingdom.* Bmj, 2001. **322**(7294): p. 1087-8.
11. Grant, R.M., et al., *Time trends in primary HIV-1 drug resistance among recently infected persons.* Jama, 2002. **288**(2): p. 181-8.
12. Doyon, L., et al., *Second locus involved in human immunodeficiency virus type 1 resistance to protease inhibitors.* J Virol, 1996. **70**(6): p. 3763-9.
13. Cote, H.C., Z.L. Brumme, and P.R. Harrigan, *Human immunodeficiency virus type 1 protease cleavage site mutations associated with protease inhibitor cross-resistance selected by indinavir, ritonavir, and/or saquinavir.* J Virol, 2001. **75**(2): p. 589-94.

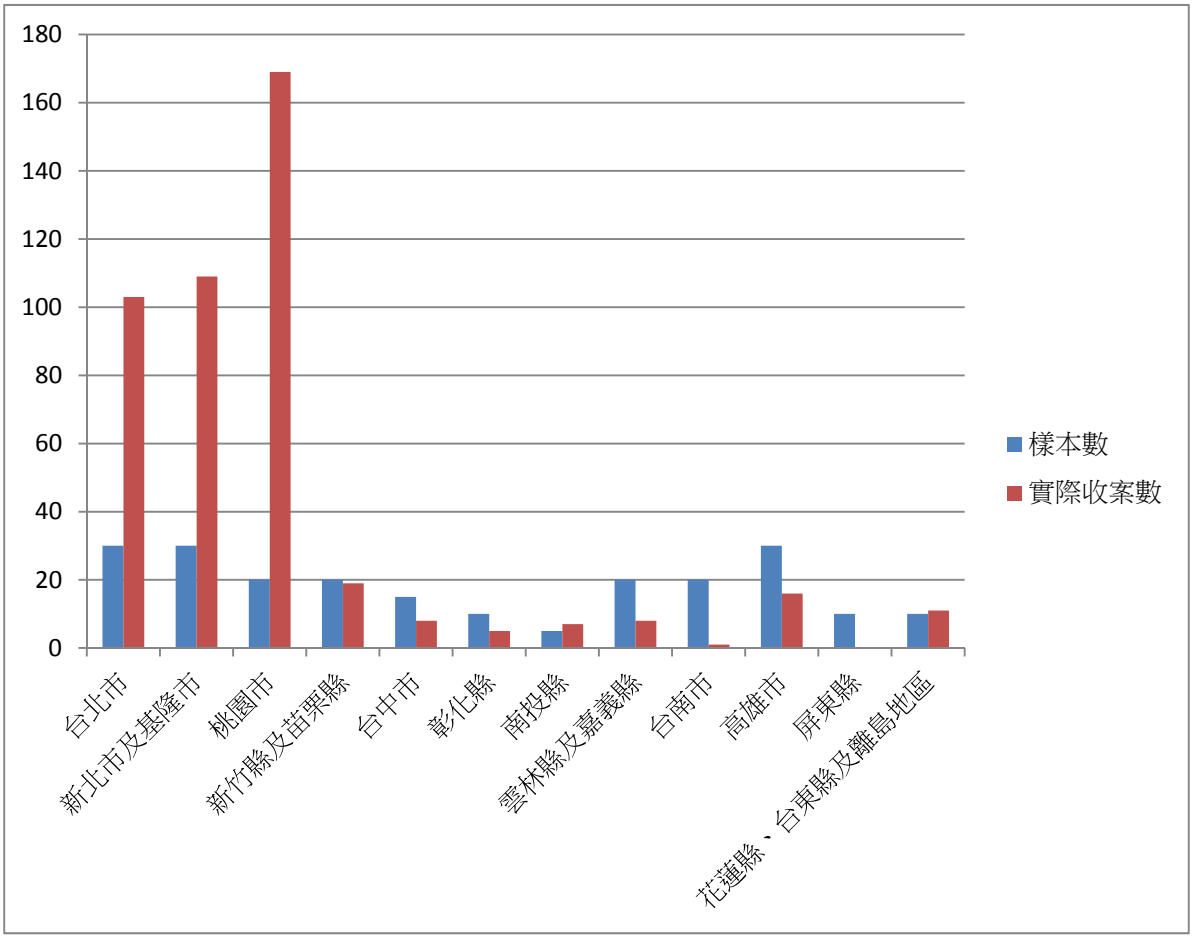
14. Gatanaga, H., et al., *Amino acid substitutions in Gag protein at non-cleavage sites are indispensable for the development of a high multitude of HIV-1 resistance against protease inhibitors.* J Biol Chem, 2002. **277**(8): p. 5952-61.
15. Hanna, G.J. and R.T. D'Aquila, *Antiretroviral Drug Resistance in HIV-1.* Curr Infect Dis Rep, 1999. **1**(3): p. 289-297.
16. Hirsch, M.S., et al., *Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel.* Jama, 2000. **283**(18): p. 2417-26.
17. Lai, C.C., et al., *Trends of transmitted drug resistance of HIV-1 and its impact on treatment response to first-line antiretroviral therapy in Taiwan.* J Antimicrob Chemother. **67**(5): p. 1254-60.
18. Wittkop, L., et al., *Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study.* Lancet Infect Dis, 2011. **11**(5): p. 363-371.

（七）圖表

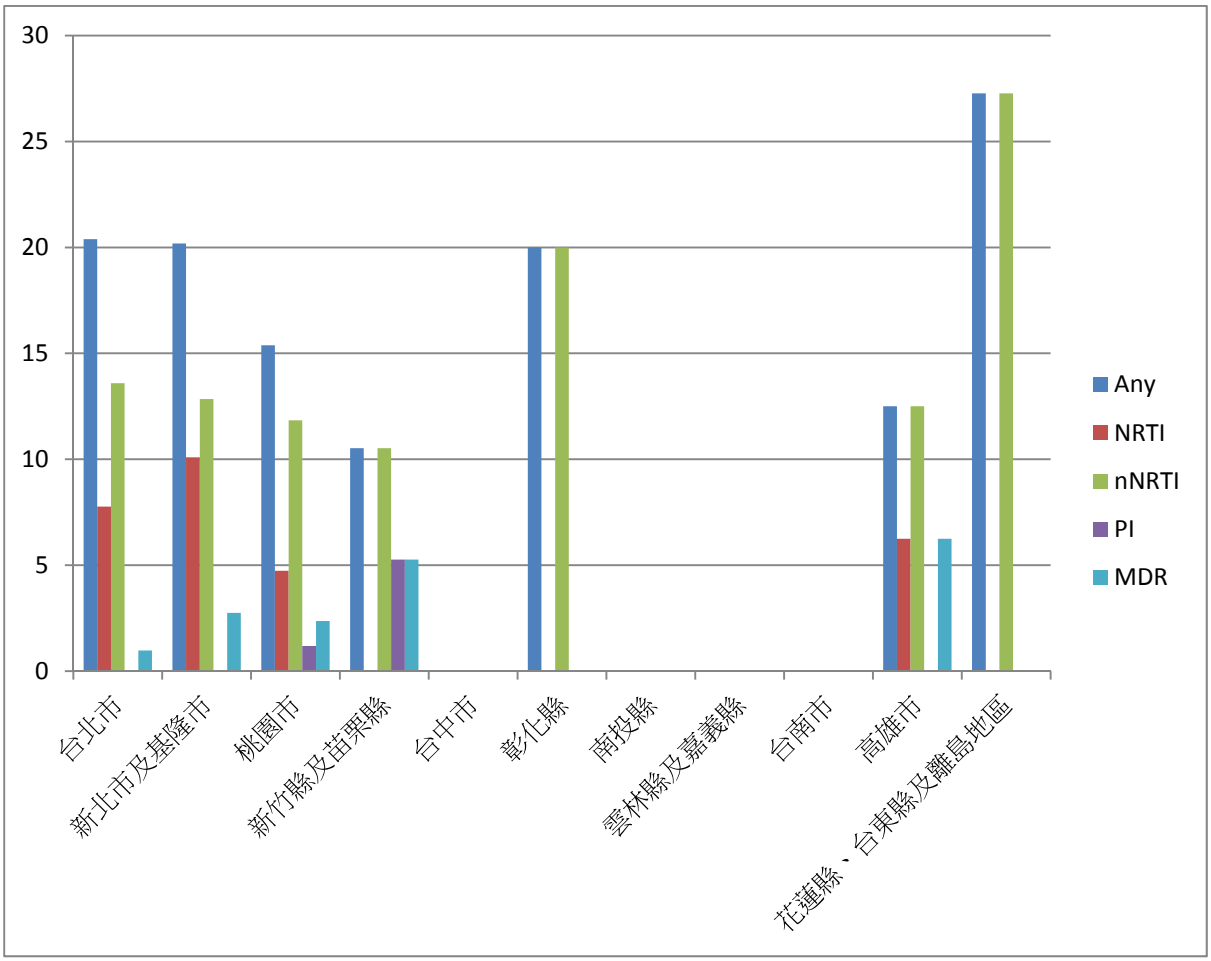
圖一、檢體來源分布圖



圖二、檢體樣本數與實際收案數比較



圖三、原生性抗藥性的盛行率(全部檢體，依縣市分類)



註一：台北市(N=103)包括國立臺灣大學醫學院附設醫院(N=89)、台北長庚紀念醫院(N=11)、及台北市立聯合醫院昆明院區(N=3)。

註二：新北市及基隆市(N=109)包括亞東紀念醫院(N=106)及基隆長庚紀念醫院(N=3)。

註三：桃園市(N=169)包括衛生福利部桃園醫院(N=127)及林口長庚紀念醫院(N=42)。

註四：新竹縣及苗栗縣(N=19)包括台大新竹分院(N=10)及新竹馬偕醫院(N=9)。

註五：台中市(N=20)為中山醫學大學附設醫院(N=8)。

註六：彰化縣為彰化基督教醫院(N=5)。

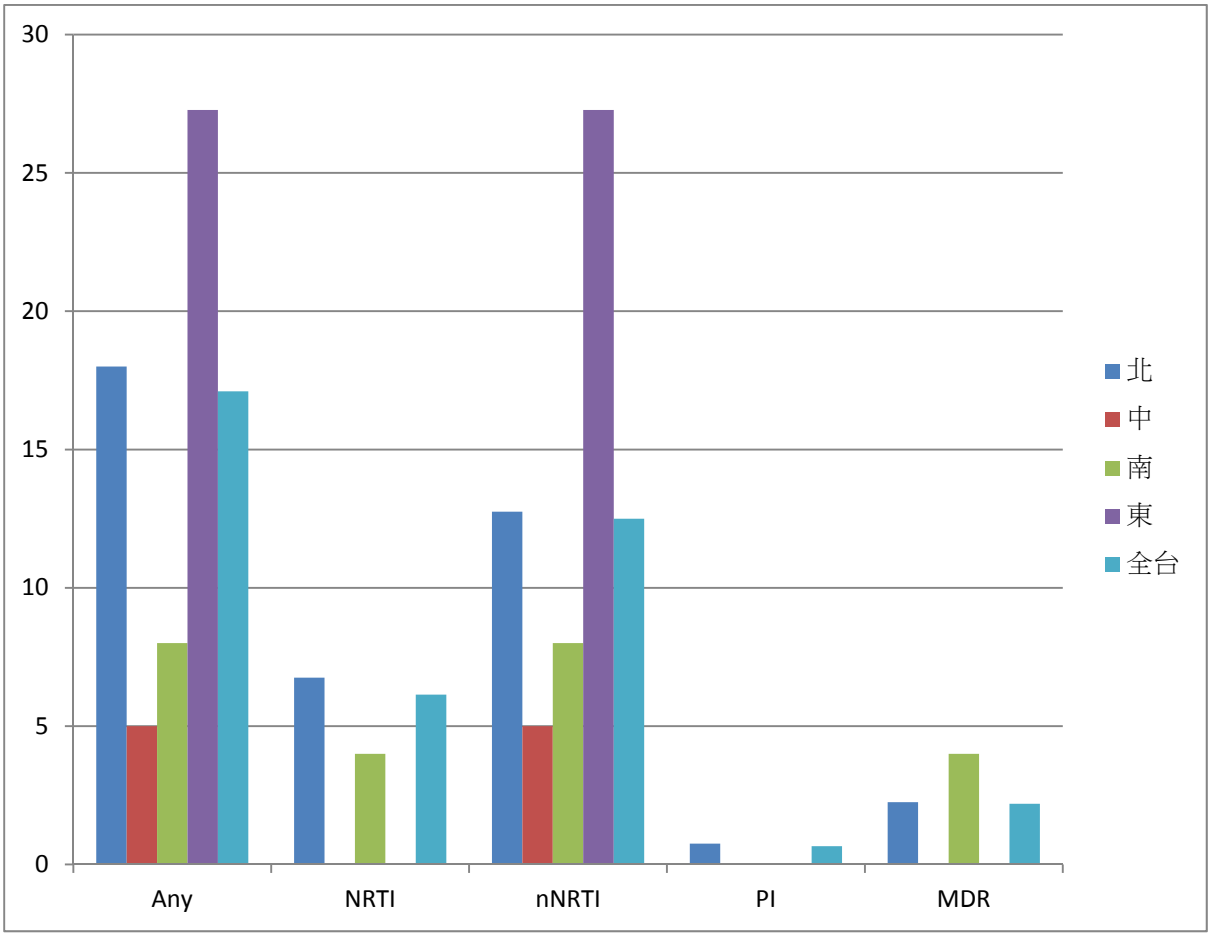
註七：南投縣為衛生福利部南投醫院(N=7)。

註八：雲林縣及嘉義縣(N=8)包括台大雲林分院(N=7)及戴德森醫療嘉義基督教醫院(N=1)。

註九：高雄市(N=16)包括高雄長庚紀念醫院(N=9)、財團法人義大醫院(N=7)。

註十：東部為花蓮慈濟醫院(N=11)。

圖四、原生性抗藥性的盛行率(全部檢體，依地區分類)



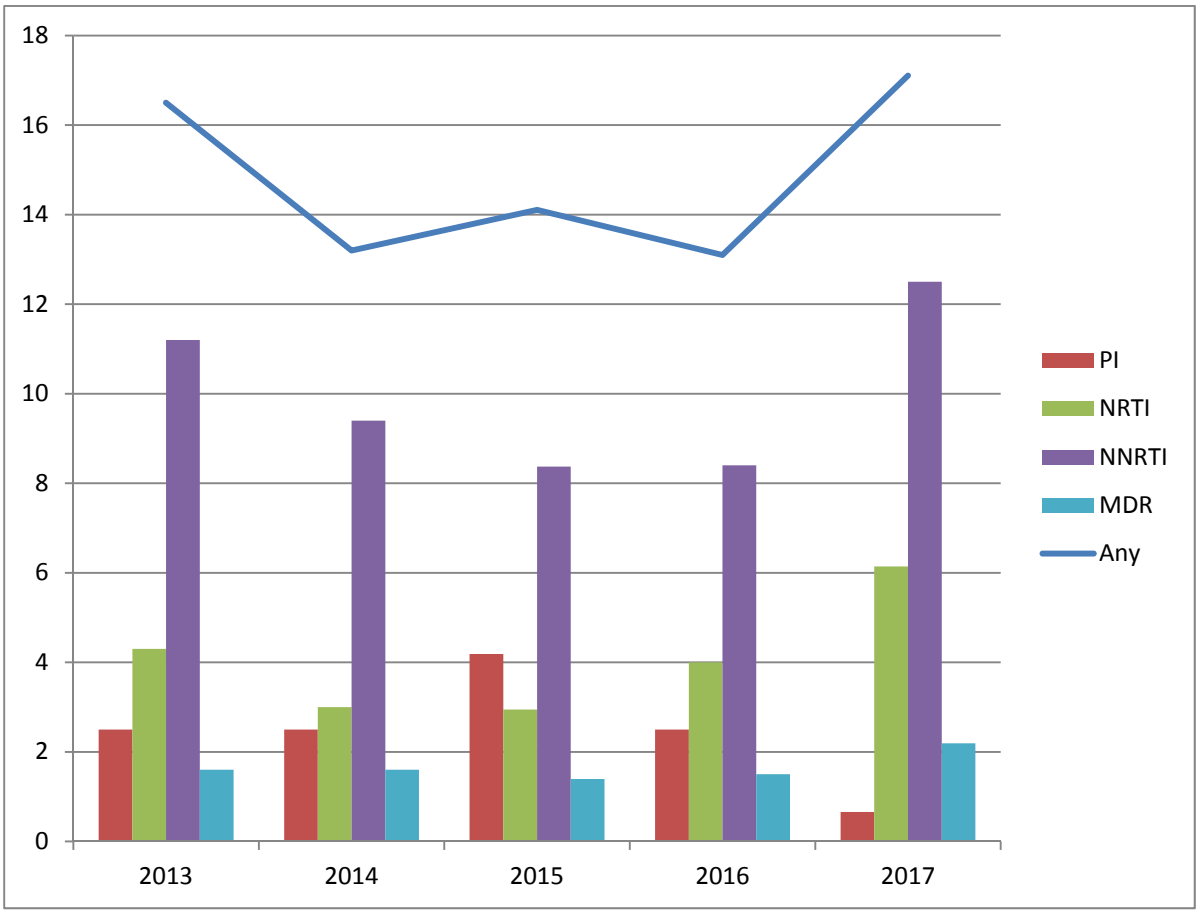
註一：北部(N=400)包括國立臺灣大學醫學院附設醫院(N=89)、台北長庚紀念醫院(N=11)、台北市立聯合醫院昆明院區(N=3)、亞東紀念醫院(N=106)、基隆長庚紀念醫院(N=3)、衛生福利部桃園醫院(N=127)、林口長庚紀念醫院(N=42)、台大新竹分院(N=10)、及新竹馬偕醫院(N=9)。

註二：中部(N=20)包括中山醫學大學附設醫院(N=8)、彰化基督教醫院(N=5) 、衛生福利部南投醫院(N=7)。

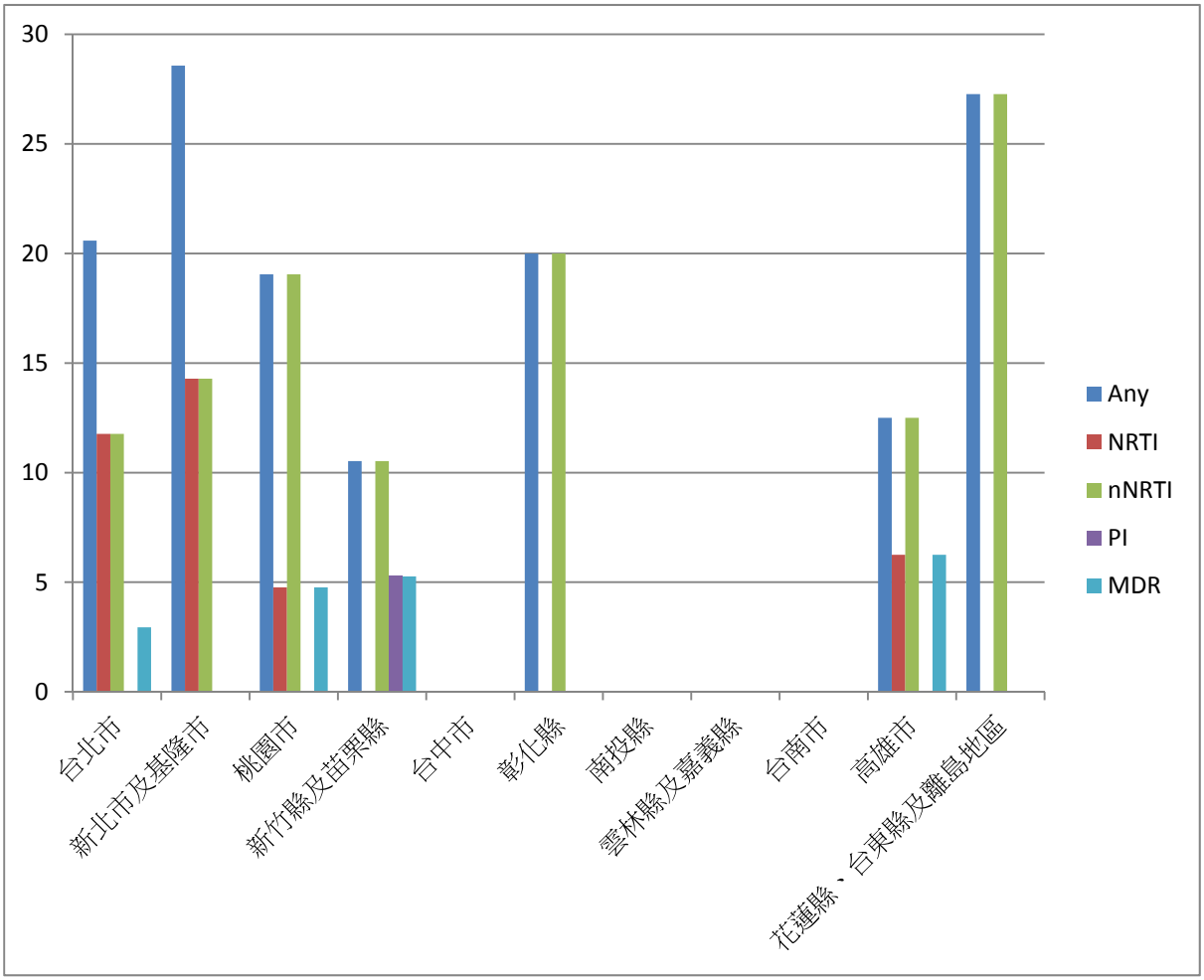
註三：南部(N=25)包括台大雲林分院(N=7)、戴德森醫療嘉義基督教醫院(N=1)、成大醫院(N=1)、高雄長庚紀念醫院(N=9)、財團法人義大醫院(N=7)。

註四：東部為花蓮慈濟醫院(N=11)。

圖五、原生性抗藥性盛行率的趨勢圖



圖六、原生性抗藥性的盛行率(依樣本數比例，依縣市分類)



註一：台北市(N=34)包括國立臺灣大學醫學院附設醫院(N=30)、台北長庚紀念醫院(N=3)、及台北市立聯合醫院昆明院區(N=1)。

註二：新北市及基隆市(N=35)包括亞東紀念醫院(N=35)。

註三：桃園市(N=21)包括衛生福利部桃園醫院(N=13)及林口長庚紀念醫院(N=8)。

註四：新竹縣及苗栗縣(N=19)包括台大新竹分院(N=10)及新竹馬偕醫院(N=9)。

註五：台中市(N=20)為中山醫學大學附設醫院(N=8)。

註六：彰化縣為彰化基督教醫院(N=5)。

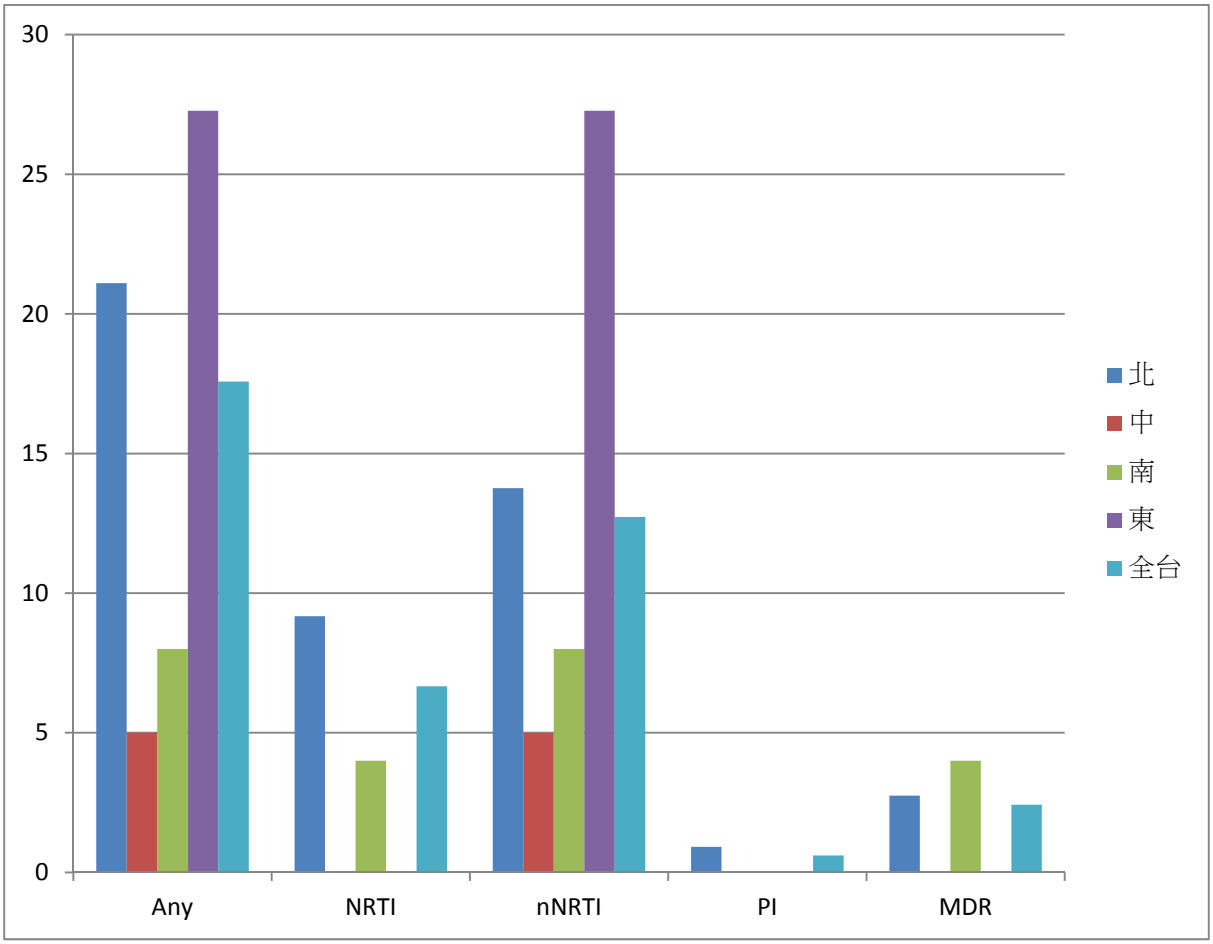
註七：南投縣為衛生福利部南投醫院(N=7)。

註八：雲林縣及嘉義縣(N=8)包括台大雲林分院(N=7)及戴德森醫療嘉義基督教醫院(N=1)。

註九：高雄市(N=16)包括高雄長庚紀念醫院(N=9)、財團法人義大醫院(N=7)。

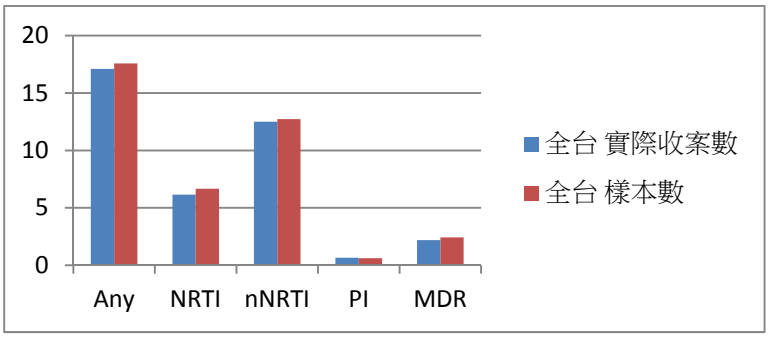
註十：東部為花蓮慈濟醫院(N=11)。

圖七、原生性抗藥性的盛行率(依樣本數比例，依地區分類)

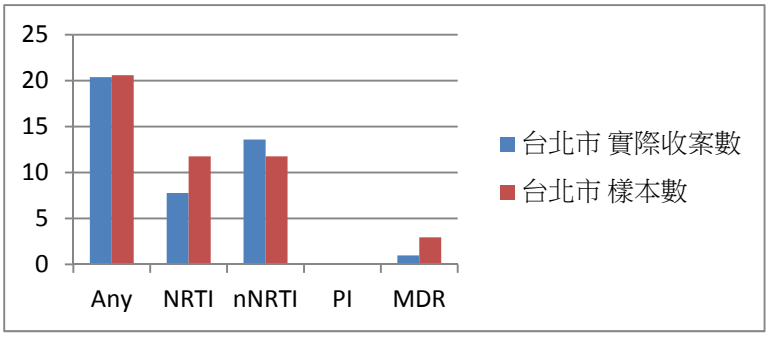


圖八、原生性抗藥性的盛行率的比較

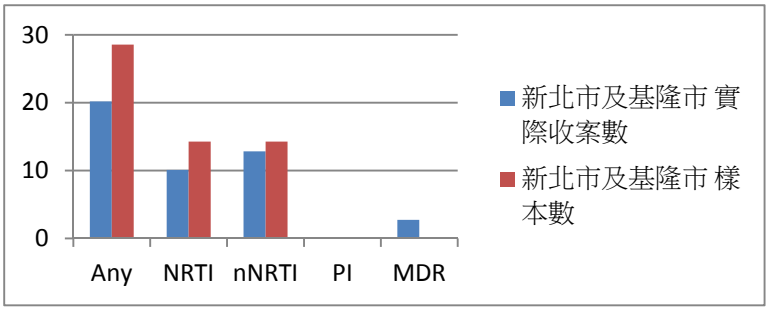
(A)



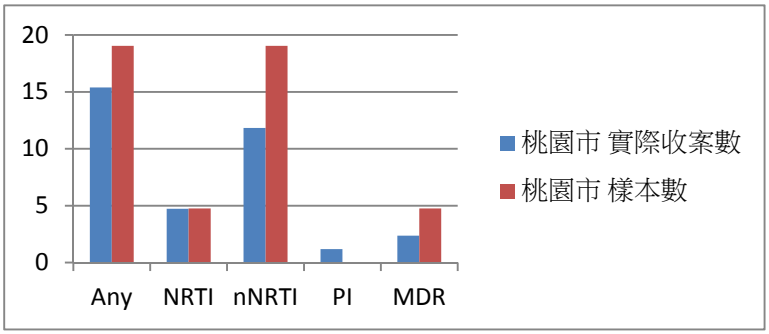
(B)



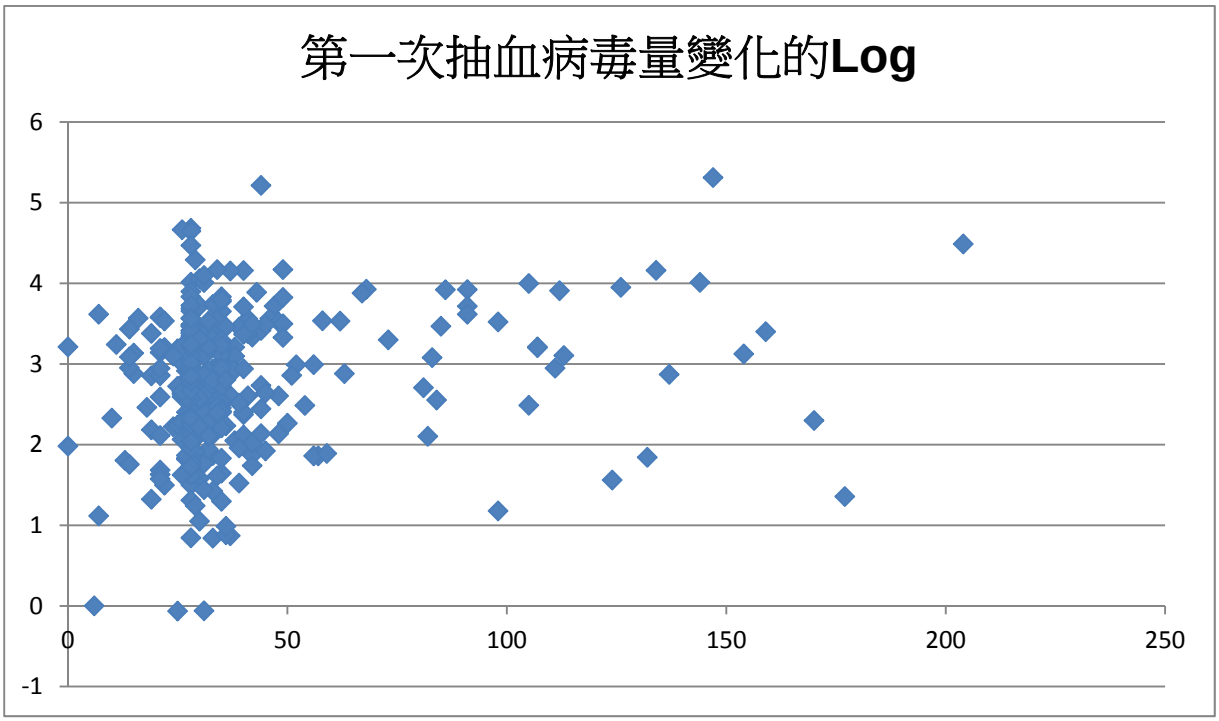
(C)



(D)



圖八、收案病患服藥後的第一次病毒量變化



註: 第一次抽血病毒量變化的 Log= Log(服藥後第一次病毒量/服藥前最後一次病毒量)

表一 收件個案使用第一線藥物的種類

藥物種類	個案數
Atripla	66
AZT/3TC+DTG	1
Combivir+Kaletra	1
Complera	90
DTG study	7
Duovir+LPVr	1
Triumeq	194
Truvada+EFV	26
Truvada+RAL	1

附件三

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

合併 HIV 和 C 型肝炎病毒感染病患之照顧

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院附設醫院

計畫主持人：孫幸筠

執 行 期 間：106 年 01 月 01 日至 106 年 12 月 31 日

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目　　錄

壹、中文摘要：

關鍵詞：C 型肝炎病毒感染，HIV 病毒感染，梅毒

目的：我們過去研究中觀察到我們過去研究中觀察到，在台大醫院就醫 HCV 抗體陰性的愛滋病毒感染者，近期急性 C 型肝炎感染的發生率有增加的趨勢(西元 1994-2000 為 0 每 1000 追蹤人年，西元 2001-2005 為 2.29 每 1000 追蹤人年，西元 2006-2010 為 10.13 每 1000 追蹤人年)。故本研究欲探討，是否近年來，此發生率仍在上升當中。

研究方法：自西元 2011 年一月一日至 2015 年十二月三十一日，在台大醫院就醫 HCV 抗體陰性的愛滋病毒感染者，接受每年至少一次 HCV 抗體檢測，或在其發生梅毒和無法解釋的肝功能異常時，給予 HCV 抗體檢測。近期急性 C 型肝炎感染的近期急性 C 型肝炎感染的定義為病患在一年內，原本 HCV 抗體陰性者發生 HCV 抗體陽轉。所有病患皆追蹤至自西元 2016 年四月三十日。

結果：自西元 2011 年一月一日至 2015 年十二月三十一日，3,483 位年紀大於等於 15 歲的病患曾至台大醫院就醫。排除 29 位未曾在一開始就醫時檢測過 HCV 抗體，和 371 位在一開始就醫時即 HCV 抗體陽性，3,080 位在一開始就醫時即 HCV 抗體陰性者接受前瞻性地追蹤。在追蹤 9900.51 人年的過程中，共 136 位(4.4%)發生近期急性 C 型肝炎感染，即整體近期急性 C 型肝炎感染發生率為 13.74 每 1000 人年追蹤。此急性 C 型肝炎感染發生率在 2011, 2012, 2013, 2014, 2015 各年度分別為 12.64, 13.81, 13.76, 10.87, 和 17.23 每 1000 追蹤人年。相較於 2,699 位沒有發生近期急性 C 型肝炎感染的患者，發生近期急性 C 型肝炎感染的病患皆為男性(100% vs. 96.2，P=0.009)，年紀較輕(平均年齡為 32.4 vs. 35.6 歲，P=0.0004)，大多為男同志(85.7% vs. 78.4%，P=0.0065)，且曾發生近期梅毒感染(64.7% vs. 11.2%, P<0.0001)。平均血中 C 型肝炎病毒的平均病毒量為每 cc，5.39 $\log_{10}$。在 84 株檢測到的 C 型肝炎病毒中，基因型 1 和 2 個佔 45%和 35%。

54 位合併 C 型肝炎病毒感染的愛滋病毒感染者再在追蹤的過程中，接受 12 週小分子抗 C 型肝炎病毒學名藥物治療(velpatasvir/sofosbuvir [VEL/SOF])。治療

過程中，至少發生一項副作用的比例在合併感染者和單獨感染者分別為 70.3% 和 68.5%，但大多為輕微的副作用，且症狀在未經藥物治療下消失。停藥 12 週後，C 型肝炎病毒病毒量測不到的比例(sustained virolgic response at week 12, SVR_{12})在合併感染者和單獨感染者分別為 96.3% (52/54) vs. 98.4% (122/124)。

結論：本研究結果顯示，在 2011 至 2015 年在本醫學中心就醫的 HIV 病毒感染病患中，近期急性 C 型肝炎感染的發生率仍在增加。除使用上相當安全外，在合併 C 型肝炎病毒和愛滋病毒感染者的治療效果，相當於單獨 C 型肝炎病毒感染者的治療效果。

貳、英文摘要：

keywords：Hepatitis C virus infection, HIV infection, Syphilis

Background: We previously have shown that the rate of recent hepatitis C virus (HCV) infection in HIV-positive patients seeking HIV care at the National Taiwan University Hospital (NTUH), Taipei, had increased from 0 in 1994 to 2000 and 2.29 in 2001 to 2005 to 10.13 per 1,000 person-years of follow-up [PYFU] in 2006 to 2010. This study aimed to investigate whether the increasing trend of recent HCV infection continued between 2011 and 2015.

Materials and Methods: Between January, 2011 and December, 2015, HIV-positive patients seeking care at the NTUH were prospectively observed and serologic tests for HCV were provided at baseline during their first visit and subsequently on an annual basis or to those who acquired syphilis or had elevated aminotransferases according to the national HIV treatment guidelines. Antibodies to HCV were determined with a third-generation enzyme immunoassay (Ax SYM HCV III; Abbott Laboratories, North Chicago, IL). HCV RNA load was determined and HCV was genotyped. Recent HCV seroconversion was defined as the first positive anti-HCV detected within 1 year after the last negative anti-HCV. The date of seroconversion was assigned as the midpoint between the date of the last negative and that of the first positive anti-HCV result. All patients were followed until 30 April, 2016.

Results: During the 5-year study period, 3,483 HIV-positive patients aged 15 years or older sought HIV care at NTUH. After excluding 29 patients without anti-HCV data at baseline and 371 testing positive for HCV (prevalent HCV infections), 3,083 were included for prospective follow-up. A total of 136 (4.4%) had recent HCV infection (incident HCV infections) during a total observation duration of 9900.51 PYFU, giving an overall incidence rate of 14.14 per 1000 PYFU. The rate was 12.64, 13.81, 13.76, 10.87, and 17.23per 1000 PYFU in 2011, 2012, 2013, 2014, and 2015, respectively. Compared with 2,699 patients without HCV seroconversion, patients with recent HCV seroconversion were more likely to be

male (100.0% vs 96.2%, P=0.009), younger (mean age, 32.4 vs 35.6 years, P=0.0004), and men who have sex with men (85.7% vs 78.4%, P=0.0065) and to have recent syphilis (64.7% vs 11.2%, P<0.0001). The mean plasma HCV RNA load was 5.39 $\log_{10}$ copies/ml. Of the 84HCV strains submitted for genotyping, genotypes 1 and 2 accounted for 45% and 35%, respectively. Additionally, 54 HIV/HCV-coinfected and 124 HCV-monoinfected patients receiving generic VEL/SOF-based therapies (ribavirin-free for compensated liver disease and weight-based ribavirin for decompensated cirrhosis) for 12 weeks. The sustained virologic response at week 12 off-therapy (SVR_{12}) was achieved in 52 of 54 HIV/HCV-coinfected patients (96.3%; 95% CI, 87.5%-99.0%) and in 122 of 124 HCV-monoinfected patients (98.4%; 95% CI, 94.3-99.6%). All HIV/HCV-coinfected patients completed 12 weeks of treatment without interruption. Thirty-eight (70.3%) HIV/HCV-coinfected and 85 (68.5%) HCV-monoinfected patients had at least one AE. However, most of them were mild in grade and resolved without medications.

Conclusions: The increasing trend of recent HCV infection continued in HIV-positive patients seeking HIV care at the university hospital in Taiwan from 2011 to 2015. Generic VEL/SOF-based therapies for 12 weeks provided excellent effectiveness and safety profiles for HCV in patients with HIV coinfection.

參、本文：

(一)、前言

C 型肝炎病毒和 HIV 病毒經由一樣的路徑傳播，故 HIV 感染者亦容易同時有 C 型肝炎病毒感染。以往 C 型肝炎病毒主要經由使用靜脈注射藥物傳播。西元 2003-2006 年，國內經使用靜脈注射藥物感染 HIV 患者有 88.9%-98.62%的病患同時感染 C 型肝炎病毒，且最常見的基因型為 1a, 6a 和 3a [1]。自西元 2000 年來，在歐洲、北美和澳洲等國家紛紛發現急性或者近期的 C 型肝炎病毒(acute or recent hepatitis C virus, HCV)感染的發生率增加, 尤其是在男同性戀的族群 [2-7]。流行病學的調查顯示，粗暴的性行為、性病、使用娛樂性用藥等，和這波急性或近期 C 型肝炎病毒感染相關。同時，經由分子流行病學的研究,研究人員發現，從病毒親緣的關係推測，有不少 C 型肝炎病毒藉由男同性戀者之間的不安全性行為，發生跨國際群聚傳播的現象 [8]。

這樣的現象，在 2012 年台大醫院孫醫師等人研究發現，在台大醫院接受追蹤治療的愛滋病毒感染者，近期 C 型肝炎病毒(recent HCV infection)感染，從 1994-2000 間沒有任何案例發生，到 2001-2005 發生率每一千人年有 2.29 案例，持續增加到 2006-2010 間發生率為每一千人年有 10.13 案例 [9]。疾管署的羅一鈞醫師利用資料庫分析也發現急遽增加的 C 型肝炎病毒通報案例，其中絕大部分是男同性戀者和併有愛滋病毒感染 [10]。這兩個研究,都同時發現近期或急性 C 肝病毒感染在統計學上和梅毒發生相關。這些研究發現意涵著不安全性行為的發生同時造成梅毒和 C 型肝炎病毒的傳播,或者因為梅毒造成的生殖器，口腔或者肛門潰瘍或黏膜的傷害增加了 C 肝病毒的傳染力。

合併 HIV 和 C 型肝炎病毒感染病患有較高和肝臟相關的罹病率及死亡率 [11, 12]。此外，和僅感染 C 型肝炎病毒病患相較之下，這類病人較不容易清除 C 型肝炎病毒病，且進展成肝硬化，肝衰竭，或肝癌的速度也較快。過去研究顯示，合併 HIV 和 C 型肝炎病毒感染病患使用抗 HIV 病毒藥物，可達到較佳的預後。

過去在使用干擾素治療 C 型肝炎病毒的年代，不少研究顯示合併 HIV 病毒和 C 型肝炎病毒感染病患達到持續病毒反應(sustapined viral response, SVR, 即停用治療 C 型肝炎病毒的藥物後，仍持續偵測不到 C 型肝炎病毒)的比例，遠低於僅 C 型肝炎病毒感染病患 [13-15]。再者，和僅感染 C 型肝炎病毒病患相較之下，合併 HIV 病毒和 C 型肝炎病毒感染病患治療 C 型肝炎病毒的過程中，副作用的發生比例高，且耐受性

低，故僅有少數患者可達到持續病毒反應的狀況 [15]。台大醫院劉醫師等人研究發現，國內 HIV 病毒感染病患使用長效型干擾素合併雷巴威林治療急性或慢性 C 型肝炎病毒感染，達到續病毒反應的比例為 83%及 72% [16]。

近年來小分子抗 C 型肝炎病毒藥物大幅改善病患達到持續病毒反應的比例 (90-100%) [17]。相同情況亦可適用於合併 HIV 病毒和 C 型肝炎病毒感染病患。目前相關研究有 PHOTON-1, PHOTON-2, ION-4, ALLY-2, C-EDGE COINFECTION, C-WORTHY, ERADICATE, TURQUOISE-I 等 [18]。這些研究中，因研究族群，C 型肝炎病毒基因型，治療藥物組合及治療藥物組合及時間的不同，導致結果不盡相同，但不管如何，病患達到持續病毒反應皆大幅提升至 80-100% [18]。

C 型肝炎病毒感染病患達到持續病毒反應(SVR)後，算是治癒 C 型肝炎病毒感染，但 C 型肝炎病毒的復發，是接下來要面對的挑戰。一系統整合分析及文獻回顧的文章分析 C 型肝炎病毒感染病患達到持續病毒反應(SVR)後，C 型肝炎病毒的覆發狀況 [19]。其研究結果顯示，僅感染 C 型肝炎病毒的低風險病患達到持續病毒反應(SVR)後，5 年復發(定義為再次偵測到 C 型肝炎病毒)的風險為 0.95%，僅感染 C 型肝炎病毒的高風險(定義為使用靜脈注射藥物或受刑者)病患達到持續病毒反應(SVR)後，5 年覆發的風險為 10.67%，而合併 HIV 病毒和 C 型肝炎病毒感染病患達到持續病毒反應(SVR)後，5 年覆發的風險高達 15.02%，且主要是再感染到新的 C 型肝炎病毒，而非原來的 C 型肝炎病毒復發 [19]。

(二)、材料與方法

本研究為前瞻性世代觀察性研究。在台大醫院就醫 HCV 抗體陰性的愛滋病毒感染者，接受每年至少一次 HCV 抗體檢測，或在其發生梅毒和無法解釋的肝功能異常時，再給予 HCV 抗體檢測。近期急性 C 型肝炎感染的近期急性 C 型肝炎感染的定義，為病患在一年內，原本 HCV 抗體陰性者發生 HCV 抗體陽轉。所有病患皆追蹤至自西元 2016 年四月三十日。另外，所有於 2011 年 1 月 1 日至 2015 年 12 月 31 日，在台大醫院就診同時感染 HIV 和 C 型肝炎病毒的病患，皆納入此研究，作為觀察對象直至 2016 年 4 月 30 日。HIV 感染病患同時感染 C 型肝炎病毒的狀況(即陽性 C 型肝炎病毒抗體[anti-HCV]的比例)，開始使用抗 HIV 病毒藥物的狀況 (用藥處方，開始時間，當時之 CD4 數和病毒量數)。將以高敏感度方法測定血清中 C 型肝炎病毒之病毒量(Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, limit of detection: 15 IU/mL)。若病患於 C 型肝炎病毒治癒後，追蹤時發現有陽性病毒反應時，會將治療前以及後續病毒陽性之檢體先行測定病毒基因型及基因亞型以確定親子關係 (Abbott RealTime HCV Genotype II, Abbott Diagnostics, IL)。若此項檢體測定為同一病毒基因型及基因亞型則進一步使用 5'UTR, core gene, and NS5B gene sequencing 再以樹狀分析圖分析親子關係 Phylogeny Inference Package (PHYLIP)以確定為再次感染或是遲發性復發之狀態。

(三)、結果

自西元 2011 年一月一日至 2015 年十二月三十一日，3,483 位年紀大於等於 15 歲的病患曾至台大醫院就醫。排除 29 位未曾在一開始就醫時檢測過 HCV 抗體，和 371 位在一開始就醫時即 HCV 抗體陽性，3,080 位在一開始就醫時即 HCV 抗體陰性者接受前瞻性地追蹤。在追蹤 9900.51 人年的過程中，共 136 位(4.4%)發生近期急性 C 型肝炎感染(如圖一所示)，即整體近期急性 C 型肝炎感染發生率為 13.74 每 1000 人年追蹤。近期急性 C 型肝炎感染發生時，96.32%(131/136)的病患使用抗 HIV 病毒藥物，其中 77.86%(102/131)的病患 HIV 病毒小於 200 copies/mL。此急性 C 型肝炎感染發生率在 2011, 2012, 2013, 2014, 2015 各年度分別為 12.64, 13.81, 13.76, 10.87, 和 17.23 每 1000 追蹤人年(如圖二所示)。

相較於 2,699 位沒有發生近期急性 C 型肝炎感染的患者，發生近期急性 C 型肝炎感染的病患皆為男性(100% vs. 96.2，P=0.009)，年紀較輕(平均年齡為 32.4 vs. 35.6 歲，P=0.0004)，大多為男同志(85.7% vs. 78.4%，P=0.0065)，且曾發生近期梅毒感染(64.7% vs. 11.2%, P<0.0001)(如表一所示)。平均血中 C 型肝炎病毒的平均病毒量為每 cc，5.39 $\log_{10}$。在 84 株檢測到的 C 型肝炎病毒中，基因型 1 和 2 個佔 45%和 35%。

54 位(14.6%, 54/371)合併 C 型肝炎病毒感染的愛滋病毒感染者在追蹤的過程中，接受 12 週小分子抗 C 型肝炎病毒學名藥物治療(velpatasvir/sofosbuvir [VEL/SOF])。相較於 124 位亦接受相同 C 型肝炎病毒學名藥治療的單獨感染 C 型肝炎病毒患者，合併 C 型肝炎病毒和愛滋病毒感染者年紀較輕，主要為男性，有較高的 C 型肝炎病毒量，較少的嚴重肝硬化(如表二所示)。抗 C 型肝炎病毒藥物治療下，兩組病患。停藥 12 週後，C 型肝炎病毒病毒量測不到的比例(sustained virolgic response at week 12, SVR_{12})在合併感染者和單獨感染者分別為 96.3% (52/54) vs. 98.4% (122/124) (如表三所示)。所有 54 位合併 C 型肝炎病毒和愛滋病毒感染者皆完成 12 週的治療。治療過程中，至少發生一項副作用的比例在合併感染者和單獨感染者分別為 70.3%和 68.5%，但大多為輕微的副作用，且症狀在未經藥物治療下消失。在治療失敗的病患中，兩組各有一位發生基因型 1a 的復發。其他兩位在治療後失聯在治療後失聯，故認定為治療失敗。

(四)、討論

本研究結果顯示，在 2011 至 2015 年在本醫學中心就醫的 HIV 病毒感染病患中，近期急性 C 型肝炎感染的發生率仍持續在增加。小分子抗 C 型肝炎病毒學名藥物治療 (velpatasvir/sofosbuvir [VEL/SOF])，除使用上相當安全外，在合併 C 型肝炎病毒和愛滋病毒感染者的治療效果，相當於單獨 C 型肝炎病毒感染者的治療效果。和之前的研究觀察類似，近期急性 C 型肝炎感染的發生和近期梅毒感染相關[9, 10]。荷蘭一研究發現，早期治療近期急性 C 型肝炎感染者，可降低近期急性 C 型肝炎感染的發生率。原本 2014 年，荷蘭 HIV 病毒感染病患近期急性 C 型肝炎感染的發生率為 11.2 每 1000 人年，且歷年來一直是上升的趨勢。自 2016 年開始，荷蘭開始有政策免費提供 HIV 病毒感染合併急性 C 型肝炎感染病患，小分子抗 C 型肝炎病毒藥物治療。至 2016 年底，自近期急性 C 型肝炎感染開始流行，有史來第一次近期急性 C 型肝炎感染的發生率開始下降至 5.5 每 1000 人年。[20] 國內小分子抗 C 型肝炎病毒藥物治療，HIV 病毒感染病患並非優先接受治療的族群。有鑒於在合併 C 型肝炎病毒和愛滋病毒感染者容易進展成肝硬化，肝衰竭，或肝癌，且速度較快。我們和腸胃科劉振驊醫師合作，透過管道讓病患自費 5-7 萬買到小分子抗 C 型肝炎病毒學名藥物(velpatasvir/sofosbuvir [VEL/SOF])，以進行 C 型肝炎病毒治療，目前看來成效相當不錯。SVR_{12} 可達到 96.3%(52/54)，和單獨 C 型肝炎病毒感染者的效果相當(98.4%, 122/124)。

(五)、結論與建議

本研究結果顯示，在 2011 至 2015 年在本醫學中心就醫的 HIV 病毒感染病患中，近期急性 C 型肝炎感染的發生率仍在增加。小分子抗 C 型肝炎病毒學名藥物治療在合併 C 型肝炎病毒和愛滋病毒感染者的治療效果和安全性表現相當優異。

對政策之具體建議：

1. 建議照護 HCV 抗體陰性的愛滋病毒感染的病患，至少每年進行一次 HCV 抗體檢測，或在其發生梅毒和無法解釋的肝功能異常時，給予 HCV 抗體檢測，以求早期診斷，早期治療。
2. 可考慮廣為推行小分子抗 C 型肝炎病毒學名藥物在合併 C 型肝炎病毒和愛滋病毒感染者的治療，以減少此類病患未來發生肝癌和肝硬化的狀況，甚至減少 C 型肝炎病毒的傳播。

(六)、參考文獻

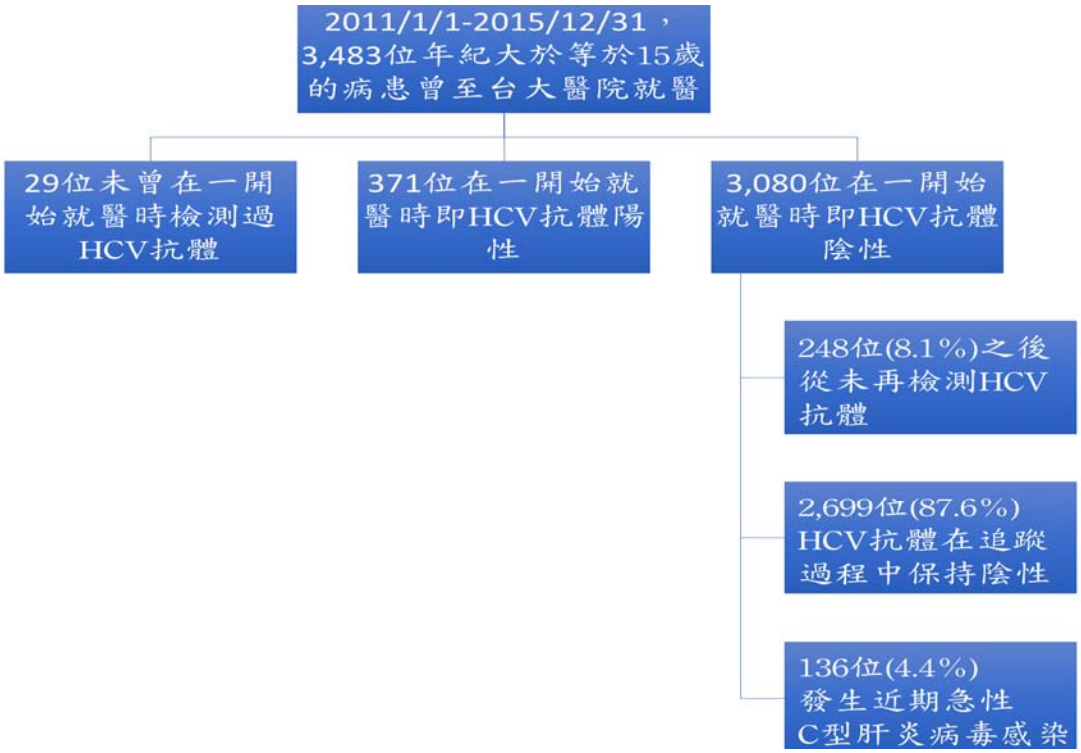
1. Liu JY, Lin HH, Liu YC, Lee SS, Chen YL, Hung CC, et al. Extremely high prevalence and genetic diversity of hepatitis C virus infection among HIV-infected injection drug users in Taiwan. Clin Infect Dis. 2008;46(11):1761-8. doi: 10.1086/587992. PubMed PMID: 18433337.
2. Browne R, Asboe D, Gilleece Y, Atkins M, Mandalia S, Gazzard B, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? Sexually transmitted infections. 2004;80(4):326-7. doi: 10.1136/sti.2003.008532. PubMed PMID: 15295139; PubMed Central PMCID: PMC1744861.
3. Gambotti L, Batisse D, Colin-de-Verdiere N, Delaroque-Astagneau E, Desenclos JC, Dominguez S, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2005;10(5):115-7. PubMed PMID: 16077209.
4. van de Laar TJ, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. The Journal of infectious diseases. 2007;196(2):230-8. doi: 10.1086/518796. PubMed PMID: 17570110.
5. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. Aids. 2007;21(8):983-91. doi: 10.1097/QAD.0b013e3281053a0c. PubMed PMID: 17457092.
6. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HB, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. Aids. 2005;19(9):969-74. PubMed PMID: 15905679.
7. Serpaggi J, Chaix ML, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. Aids. 2006;20(2):233-40. doi: 10.1097/01.aids.0000200541.40633.56. PubMed PMID: 16511416.
8. van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of

a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology. 2009;136(5):1609-17. PubMed PMID: 19422083; PubMed Central PMCID: PMCPMC4260925.

9. Sun HY, Chang SY, Yang ZY, Lu CL, Wu H, Yeh CC, et al. Recent hepatitis C virus infections in HIV-infected patients in Taiwan: incidence and risk factors. J Clin Microbiol. 2012;50(3):781-7. doi: 10.1128/JCM.06014-11. PubMed PMID: 22189113; PubMed Central PMCID: PMCPMC3295121.
10. Lo YC, Tsai MS, Sun HY, Hung CC, Chuang JH. National Trend and Characteristics of Acute Hepatitis C among HIV-Infected Individuals: A Matched Case-Control Study-Taiwan, 2001-2014. PLoS One. 2015;10(10):e0139687. doi: 10.1371/journal.pone.0139687. PubMed PMID: 26439381; PubMed Central PMCID: PMCPMC4595084.
11. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;32(3):492-7. doi: 10.1086/318501. PubMed PMID: 11170959.
12. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006;166(15):1632-41. doi: 10.1001/archinte.166.15.1632. PubMed PMID: 16908797.
13. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351(5):451-9. doi: 10.1056/NEJMoa032653. PubMed PMID: 15282352; PubMed Central PMCID: PMCPMC4113392.
14. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351(5):438-50. doi: 10.1056/NEJMoa040842. PubMed PMID: 15282351.
15. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347(13):975-82. doi: 10.1056/NEJMoa020047. PubMed PMID: 12324553.

16. Liu CH, Sheng WH, Sun HY, Hsieh SM, Lo YC, Liu CJ, et al. Peginterferon plus Ribavirin for HIV-infected Patients with Treatment-Naive Acute or Chronic HCV Infection in Taiwan: A Prospective Cohort Study. Sci Rep. 2015;5:17410. doi: 10.1038/srep17410. PubMed PMID: 26616669; PubMed Central PMCID: PMCPMC4663763.
17. Zopf S, Kremer AE, Neurath MF, Siebler J. Advances in hepatitis C therapy: What is the current state - what come's next? World J Hepatol. 2016;8(3):139-47. doi: 10.4254/wjh.v8.i3.139. PubMed PMID: 26839638; PubMed Central PMCID: PMCPMC4724577.
18. Wyles DL, Sulkowski MS, Dieterich D. Management of Hepatitis C/HIV Coinfection in the Era of Highly Effective Hepatitis C Virus Direct-Acting Antiviral Therapy. Clin Infect Dis. 2016;63 Suppl 1:S3-S11. doi: 10.1093/cid/ciw219. PubMed PMID: 27363438; PubMed Central PMCID: PMCPMC4928450.
19. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016;62(6):683-94. doi: 10.1093/cid/civ948. PubMed PMID: 26787172; PubMed Central PMCID: PMCPMC4772843.
20. Boerekamps A, van den Berk G, Lauw F, Leyten E, Arends J, Kasteren M, et al. SUBSTANTIAL DECLINE IN ACUTE HCV INFECTIONS AMONG DUTCH HIV+MSM AFTER DAA ROLL OUT. 137LB. Conference on Retroviruses and Opportunistic Infections; Feb 13-16; Seattle, Washington2017.

圖一、 研究病患收納流程圖



圖二、 歷年(1994-2015) 近期急性 C 型肝炎感染的發生率變化

表一、 近期 C 型肝炎感染者和非近期 C 型肝炎感染者之特徵比較

特徵	近期 C 型肝炎感染者	非近期 C 型肝炎感染者	P 值
病患數	136	2699	
男性, 個案數 (%)	136 (100.0)	2,595 (96.2)	0.0090
研究開始的年紀，平均值 (標準差), 歲	32.4 (8.1)	35.6 (10.6)	0.0004
HIV 感染風險, 個案數 (%)			0.0065
男同志/雙性戀	117 (86.0)	2,116 (78.4)	
異性戀	5 (3.7)	282 (10.5)	
靜脈毒癮藥物使用者	2 (1.5)	8 (0.3)	
其他	12 (8.8)	293 (10.9)	
HBsAg 陽性, 個案數 (%)	19 (14.0)	379 (14.0)	0.6626
曾使用過抗病毒藥物, 個案數 (%)	133 (97.8)	2,514 (93.2)	0.0335
近期梅毒感染, 個案數 (%)	88 (64.7)	301 (11.2)	<0.001

表二、 合併 HIV/HCV 感染者和 HCV 單獨感染者之比較

特徵	合併 HIV/HCV 感染者	HCV 單獨感染者	P 值
病患數	54	124	
年紀, 平均值 (標準差), 歲	40 (11)	61 (11)	< 0.001
年紀 ≥ 50 歲, 個案數 (%)	9 (16.7)	103 (83.1)	< 0.001
男性, 個案數 (%)	52 (96.3)	55 (44.4)	< 0.001
曾經接受治療, 個案數 (%)	9 (16.7)	35 (28.2)	0.13
HBsAg 陽性, 個案數 (%)	8 (14.8)	7 (5.6)	0.07
補償不全肝硬化, 個案數 (%)	2 (3.7)	6 (4.8)	1.00
HIV 病毒量 < 50 copies/mL, 個案數 (%)	51 (94.4)	-	-
CD4 數, 平均值 (標準差), 10^9 cells/L	0.6 (0.2)	-	-
HIV 感染風險, 個案數 (%)			
靜脈毒癮藥物使用者	4 (7.4)	-	-
男同志	48 (88.9)	-	-
血友病患者	2 (3.7)	-	-
BMI, 平均值 (標準差), kg/m^2	22.2 (2.2)	24.4 (3.4)	< 0.001
Hemoglobin, 平均值 (標準差), g/dL	14.8 (1.5)	13.8 (1.8)	0.001
白血球, 平均值 (標準差), 10^9 cells/L	5.4 (1.4)	5.4 (2.0)	0.81
血小板, 平均值 (標準差), 10^9 cells/L	224 (69)	170 (70)	< 0.001
INR, 平均值 (標準差)	0.99 (0.54)	0.99 (0.91)	0.99
白蛋白, g/dL, mean (SD)	4.5 (0.3)	4.2 (0.4)	< 0.001
總膽紅素, 平均值 (標準差), mg/dL	1.0 (0.9)	0.9 (0.5)	0.31
直接膽紅素, 平均值 (標準差), mg/dL	0.3 (0.2)	0.3 (0.2)	0.86
AST, 平均值 (標準差)	1.8 (1.2)	1.8 (1.5)	0.90
ALT, 平均值 (標準差)	2.8 (2.5)	1.9 (1.5)	0.002
Creatinine, 平均值 (標準差), mg/dL	0.9 (0.2)	0.9 (0.3)	0.54
eGFR, 平均值 (標準差), $mL/min/1.73m^2$	105 (24)	88 (31)	0.001
eGFR < 60 $mL/min/1.73m^2$, 個案數 (%)	2 (3.7)	27 (21.8)	0.002
HCV 病毒量, log_{10} IU/mL, 平均值 (標準差)	6.3 (0.6)	5.9 (1.0)	0.004
HCV 基因型, 個案數 (%)			< 0.001
1a	8 (14.8)	9 (7.3)	
1b	19 (35.2)	59 (47.6)	

2	12 (22.2)	52 (41.9)	
3	5 (9.3)	1 (0.8)	
4	2 (3.7)	0 (0)	
6	8 (14.8)	3 (2.4)	
HCV 病毒量 > 2M IU/mL, 個案數 (%)	28 (51.9)	45 (36.3)	0.068
HCV 病毒量 > 6M IU/mL, 個案數 (%)	16 (29.6)	17 (13.7)	0.02
纖維化時期, 個案數 (%)			0.028
F0-1	27 (50.0)	46 (37.1)	
F2	16 (29.6)	25 (20.2)	
F3	5 (9.3)	15 (12.1)	
F4	6 (11.1)	38 (30.6)	

表三、小分子抗 C 型肝炎病毒學名藥物(velpatasvir/sofosbuvir [VEL/SOF])治療成效

HCV 病毒量< 25 IU/mL	合併 HIV/HCV 感染者 (病患數= 54)		HCV 單毒感染者 (病患數=124)	
	個案數(%)	95% 信賴區間	個案數 (%)	95% 信賴區間
治療當中				
Week 1	2 (3.7)	1.0-12.5	21 (16.9)	11.4-24.5
Week 2	20 (37.0)	25.4-50.4	58 (46.8)	38.2-55.5
Week 4	46 (85.2)	73.4-92.3	113 (91.1)	84.8-95.0
Week 6	54 (100)	93.4-100	123 (99.2)	95.6-99.9
Week 8	54 (100)	93.4-100	124 (100)	97.0-100
Week 12	54 (100)	93.4-100	123 (99.2)	95.6-99.9
治療停止後				
Week 4 (SVR_4)	54 (100)	93.4-100	122 (98.4)	94.3-99.6
Week 8 (SVR_8)	54 (100)	93.4-100	122 (98.4)	94.3-99.6
Week 12 (SVR_{12})	52 (96.3)	87.5-99.0	122 (98.4)	94.3-99.6
治療失敗的原因， 個案數				
復發	1		1	
失聯	1		1	

附件四

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

台灣地區 HIV 感染者藥品動態學和基因學研究

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院附設醫院

計畫主持人：林淑文

研 究 人 員：洪健清、張淑媛、蔡茂松、李官燁、林亞葶、劉玟君、唐新亞、鄭芷寧

執 行 期 間：106 年 1 月 1 日至 106 年 12 月 31 日

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目錄

壹、中文摘要：

抗愛滋病毒藥物 (ART) 中，NNRTI 與 PI 等主要經由肝臟酵素 cytochrome P450 (CYP 450) 代謝、integrase strand transfer inhibitor 則由 phase II 酵素 UGT1A1 代謝。代謝酵素的活性與單一核苷酸基因多形性 (single nucleotide polymorphism, SNP)、生理病理狀況、藥品交互作用息息相關，因此每個人代謝藥品的速率可能差異極大，可能影響治療效果、或增加劑量相關的毒性。因此監測藥物血中濃度極具臨床價值。治療 AIDS 相關之伺機性感染(opportunistic infection) 的抗生素如 rifabutin 與 trimethoprim/ sulfamethoxazole (cotrimoxazole) 亦有這樣的特性。

本研究藉由前瞻性的觀察，以高效能液相層析儀（HPLC）追蹤血中濃度、基因多型性、療效與副作用等關係，以探索最適合國人的 ART 劑量、藥品交互作用時之劑量調整原則等課題，累積國內之本土經驗，增進病人用藥安全、達到最大的經濟效益。迄今已為 891 位服用 EFV、549 位服用 ATV、3 位服用 dolutegravir、108 位使用 cotrimoxazole 與 1 位服用 rifabutin 的病人進行分析。

服用 EFV 者的藥物血中濃度差異性相當大，絕大部分濃度高於治療指引建議的 1 μg/mL，因此針對使用 EFV 達 6 個月以上、血中濃度高於 2 μg/mL、病毒量低於 200 copies/mL 者，我們近來嘗試將其 EFV 劑量減半、密切追蹤血中濃度與臨床療效與副作用。雖然 ATV 的血中濃度可能受 tenofovir (TDF)影響而降低，但本研究發現併用者的血中濃度未較低，療效也良好。多數病人 SMX-TMP 血中濃度達到文獻建議的治療範圍之內；SMX 代謝物與原型藥藥物血中濃度比值在不良反應的發生上有統計顯著差異；而電解質不平衡和 TMP 藥物濃度與使用劑量之間也有顯著關係。Dolutegravir 與 rifabutin 只有個位數的病人檢測，血中濃度在正常範圍內。

在本研究室將繼續現行模式，除了提供全國各醫療院所常規監測 ART 與抗生素血中濃度的服務、嘗試開發以 HPLC 方法測定其他 ART，在進行臨床相關研究的同時，亦提供臨床醫師重要的藥品濃度訊息。

關鍵詞：抗愛滋病毒藥物、基因多型性、atazanavir、efavirenz, cotrimoxazole, rifabutin, dolutegravir

貳、英文摘要：

Highly active antiretroviral therapy (HAART) uses combination therapy of multiple antiretroviral agents. It dramatically improves the clinical responses in patients infected with human immunodeficiency virus (HIV), and decreases the mortality and morbidity of acquired immunodeficiency syndrome (AIDS). Efavirenz (non-nucleoside reverse transcriptase inhibitors, NNRTI), lopinavir/ ritonavir (protease inhibitor, PI), and maraviroc (chemokine receptor type 5 antagonist, CCR5 antagonist) are metabolized by cytochrome P450 (CYP 450) enzymes. Atazanavir (PI) and dolutegravir (integrase strand transfer inhibitor) are metabolized via UDP-glucuronosyltransferase (UGT1A1) in the liver. The activities of abovementioned enzymes affect the metabolic rates of ART, and their activities are determined by the single nucleotide polymorphism (SNP), pathophysiological state, and drug interactions. Each individual may metabolize ART in different rates, which causes the variability in pharmacokinetic (PK) parameters. Serum drug concentration may decreases in extensive metabolizes, which leads to treatment failure or drug resistance. On the other hand, serum concentration may be elevated in slow metabolizers and result in better treatment outcomes and/or more dose-related toxicity. This phenomenon also applys to antibiotics in the treatment of opportunistic infections in AIDS patients, such as rifabutin and trimethoprim/sulfamethoxazole (cotrimoxazole). Therefore, it is clinically valuable to measure the plasma concentration of these medications. Furthermore, generic ART have been available recently.

Measurement of plasma concentration would provide a security net to ensure effectiveness of safety of treatment. Previous studies used high performance liquid chromatography (HPLC) to quantify the plasma concentration of ART and other antibiotics in HIV patients. Unfortunately, the assay is not feasible to all hospitals in Taiwan. A “PK laboratory” for plasma concentration and SNP may be beneficial for our medical care. The purpose of this prospective clinical study is to evaluate the relationship between drug plasma concentration, SNP, and effectiveness and adverse event of ARTs. Results of this study will serve as guidance for dosing adjustment in clinical use of ARTs and for management of drug interactions in patients with HIV. We will share our observations and experiences at the National Taiwan University Hospital domestically and internationally through our publications in the future.

Our laboratory has established assay methods with HPLC for plasma concentrations of efavirenz, atazanavir, co-trimoxazole and rifabutin in the past, and dolutegravir this year. We have monitored 891, 549, 108, 1 and 3 patient in this year prospectively. There is a significant inter-individual variation of plasma concentration of ARTs and antimicrobial agents for opportunistic infections. Therefore, measurement of plasma concentration should be emphasized in clinical practice in Taiwan. The continuous study in the next year may assure the availability of the PK lab, provide the data for clinicians as a reference for ART regimen adjustment, and crucial information for health authority for decision making.

參、本文：

（1）前言

自從台灣地區診斷第一例愛滋病毒感染迄今已超過二十年，抗愛滋病毒藥物（antiretroviral therapy, 簡稱 ART）問世後，愛滋病毒的感染受到良好的控制；由多種 ART 組合而成的高效能抗愛滋病毒療法(highly active antiretroviral therapy, 簡稱 HAART）更使治療效果大增，減少後天免疫不全症候群（AIDS）的發生與死亡率[1-3]。ART 中，非核苷酸反轉錄酶抑制劑（non-nucleoside reverse transcriptase inhibitor, NNRTI）、蛋白酶抑制劑（protease inhibitor, PI）、CCR5 抑制劑（chemokine receptor type 5 antagonist）等主要經由肝臟酵素 cytochrome P450（CYP 450）代謝；整合酶抑制劑（integrase strand transfer inhibitor, INSTI）主要經由肝臟尿苷二磷酸葡萄糖醛酸基轉移酶（UDP-glucuronosyltransferase, UGT1A1）進行葡萄糖醛酸反應（glucuronidation），上述酵素的活性影響 ART 的代謝速率，而酵素活性與單一核苷酸基因多形性（single nucleotide polymorphism, SNP）、生理病理狀況、藥品交互作用息息相關，因此每個人代謝藥品的速率可能差異極大，使藥物動力學（pharmacokinetics, PK）的特性相去甚遠。病人本身代謝快或酵素活性被其他藥物誘導（induction）時，藥物半衰期（half-life）減短、血中濃度（serum concentration）降低，可能影響治療效果，甚至促使愛滋病毒產生抗藥性；若代謝慢或酵素活性被抑制時，藥物之血中濃度及目標作用部位（targeted site of action）的濃度將提高，可能因此而增加療效、甚至增加劑量相關（exposure-related）的毒性。為確保療效，應密切追蹤 CD4 淋巴球數與血漿愛滋病毒量，甚至考慮進行藥物血中濃度監測及/或調整 ART 劑量，維持 ART 的最低血中濃度在特定數值之上以確保療效。美國國家衛生研究院的衛生署(Department of Health and Human Services, DHHS）愛滋病的治療指引中建議 ART 最低血中濃度應維持在特定數值之上以確保療效[4]，例如：

- Efavirenz (EFV): ≥ 1 μg/mL
- Nevirapine (NVP): ≥ 3 μg/mL
- Amprenavir 或 fosamprenavir: ≥ 0.4 μg/mL
- Atazanavir (ATV): ≥ 0.15 μg/mL
- Indinavir: ≥ 0.1 μg/mL
- Lopinavir/ritonavir: ≥ 1 μg/mL

- Nelfinavir: ≥ 0.8 μg/mL
- Saquinavir: ≥ 0.1-0.25 μg/mL
- Tipranavir: ≥ 20.5 μg/mL

一般而言，ART 雖療效佳，但副作用卻難以避免，可能導致高膽紅素血症、糖尿病、血脂肪過高、骨質疏鬆等問題。加上病患壽命越漸增長，身體器官功能異常或老化相關的疾病也愈容易在感染者身上出現。因此，在病患照顧上，不僅應追蹤藥效與存活，監測生化值變化與觀察上述副作用以確保用藥安全亦是醫療照護的重點。特定 ART 的某些副作用與血中濃度有關，例如 EFV (商品名 Stocrit，希寧，NNRTI 類) 及 ATV（商品名 Reyataz，瑞塔滋，PI 類）即是。EFV 加上兩種核苷酸反轉錄酶抑制劑（tenofovir + emtricitabine）之三合一複合錠是現今國內外愛滋病毒感染治療建議中的首選[1]，可以確保藥物長期使用的遵囑性（adherence）。但若血中濃度超過 4 μg/mL 的病患，發生中樞神經副作用的比例為血中濃度在 1-4 μg/mL 病患的 3 倍[2]。EFV 係由 CYP3A 和 CYP2B 酵素系統代謝，CYP2B (516 位點)的 SNP 會造成 EFV 在體內的代謝速度有差異[3]。ATV 約自 95 年正式在臺灣上市使用，與其他 PI 相較，ATV 較少發生代謝方面如高血脂症及脂肪分佈異常（lipodystrophy)等併發症；但臨床使用時，由於 ATV 和膽紅素同樣經過 UGT1A1 代謝，互相競爭的情況下，國內約有一半的患者在服用 ATV 一個月後，膽紅素會上升，5%左右的患者更會產生明顯的黃疸症狀。國外的案例報告發現 ATV 的血中濃度是影響高膽紅素血症的重要原因之一。由於目前已知 UGT1A1 有基因多形性（genetic polymorphism）的現象，酵素活性差（慢代謝，UGT1A1*28）者可能較傾向產生嚴重的高膽紅素血症。由於國人中約有 56%為正常代謝者，其餘為異質接合（heterozygous）或同質接合（homozygous），可能增加高膽紅素血症的發生率。因此，以往的研究強調監測血中濃度的重要性，避免 EFV 濃度高於 4 μg/mL 或 ATV 濃度高於 0.85 μg/mL[3]。

另一方面，ATV 雖然一天只需服用一次，但需要酸性環境以促進胃腸道的吸收，因此建議盡量與食物一起吃、或飯後立即服用，而且要避免與制酸劑或其他胃藥合併服用[3]。但國人服藥時常習慣與胃藥併服，因此 ATV 血中濃度是否有達到美國 DHHS 治療指引中建議的 0.15 μg/mL 以上，亟需確認。再者，ATV 主要經由肝臟酵素 CYP3A4 代謝，可能受許多藥品或食品的影響而改變代謝速率，國內臨床使用 ATV 時，似乎不必加上

ritonavir (RTV, boosted PI) 也能達到很好的療效，因此監測 ATV 血中濃度實屬必要。某些西方研究建議適當的血中濃度範圍為 0.15 - 0.85 μg/mL，以免因藥物濃度過低、使愛滋病毒產生抗藥性；或因濃度過高、增加高膽紅素血症的產生。

如同 ATV，PI 類的 lopinavir/ritonavir 也都經由 CYP 3A4 代謝，RTV 可強效抑制 CYP3A4 與 2D6 的活性、卻能提高 UGT1A1 的活性。CYP3A4 的活性可能受許多藥品或食品的影響而改變代謝速率，國內臨床常使用 lopinavir/ritonavir，因此監測血中濃度實屬必要[4]。

治療愛滋病毒感染者的 TB 時，EFV 雖因不受 rifampin 影響而成為首選藥物[29]，但對妊娠第一期的孕婦、無法忍受 EFV 副作用者、或感染抗藥性的病毒時，NVP 應是合適的替代藥品。但 NVP 與 rifampin 併用時，NVP 血中濃度會下降 37~58%，且兩者都有皮膚過敏與肝毒性的副作用，雖然小型研究並未證實 NVP 與 rifampin 的交互作用會影響臨床療效，但南非的大型世代追蹤研究、泰國的隨機分配臨床試驗與印度的臨床試驗卻發現 nevirapine 與 rifampin 併用的治療效果不佳，比起 EFV 與 rifampin 併用之病毒學反應較差、死亡率也較高，血中濃度偏低可能是導致臨床反應不良的主因之一[12-15]。此外，長期併用 NVP 與 rifampin 的安全性有待研究，也不清楚是否會增加肝毒性。泰國比較 TB 患者開始服用 NVP 標準劑量（最初兩週每日 200 mg、接著每日 400 mg）或提高劑量（最初兩週每日 400 mg、接著每日 600 mg）後的血中濃度，發現 80%接受標準劑量的血中濃度過低，但接受較高劑量者易發生 NVP 過敏反應。因此建議亞洲人若已在服用 rifampin，由於 CYP3A4 與 CYP2B6 活性已被誘導，加入 NVP 之最初兩週不需要以低劑量開始，之後也不需要因藥動學特性而特別提高劑量，使用標準劑量即可[16-19]。

與 EFV 相似，NVP 除了經由 CYP3A4 代謝外，CYP2B6 也佔了重要的地位，而 CYP2B6 的單一核苷酸基因多形性使每個人代謝藥品的速率差異極大，日本人中約有 20%的人代謝較其他人慢[20]，而國人的比例不詳。若 CYP2B6 代謝能力差，藥物可能經由其他途徑例如 CYP3A4 代謝，而具有 SNP 的基因如 CYP3A4*1B、CYP3A5*3 及 MDR1 (multidrug resistance protein 1)也可能會造成代謝速度差異[21-22]，

新藥 dolutegravir （DTG）為愛滋病毒的整合酶抑制劑（integrase strand transfer inhibitor），主要經由肝臟 UGT1A1 進行葡萄糖醛酸反應（glucuronidation）而代謝，因此 UGT1A1 的誘導物（如 rifampin）會顯著降低 dolutegravir 的血中濃度，使 AUC 下降

40%，trough 濃度下降 61%，因此需將服藥頻率由一般的每日一次增加為每日兩次，並密切監測愛滋病毒量。若同時併用藥會顯著提高 UGT1A1 的活性，臨床上應盡量避免此類的併用，以其他藥品取代使用。UGT1A1 的誘導物包括 rifampin、rifabutin、EFV、含 ritonavir 的 tipranavir；若治療反應不如預期，需考慮交互作用可能導致的影響。如前所述，UGT1A1 有基因多形性，代謝慢（UGT1A1*28）的愛滋病毒感染者是否較可能因血中濃度過高而產生副作用有待密切追蹤[3]。

新藥 maraviroc（MVC）是 CCR5 抑制劑（chemokine receptor type 5 antagonist）中唯一上市的藥品，經由 CYP 3A4 及 CYP 3A5 代謝，同時亦為 P-glycoprotein 的受質；但本身不影響 CYP 3A4 及 P-glycoprotein（P-gp）的活性。併用其他的 CYP 3A4 抑制物（如 ritonavir 及其他 PI）或誘導物（EFV、etravirine、rifampin）時，MVC 的代謝速率會被影響，應盡量避免此種合併使用，但若有臨床治療需要時，必須視併用藥品的特性調整 MVC 的劑量，以維持血中濃度在 50 ng/mL 以上。仿單建議 MVC 與強效 CYP 3A4 誘導物（例如 rifampin）併用時，MVC 的 AUC 可能下降 64%，只要同時間未使用任何 CYP 3A4 抑制藥品，劑量就需加倍為每次 600 mg；若同時也併用強效的 CYP 3A4 抑制藥品，劑量則維持每次 300 mg。與抑制 CYP 3A4 效果較弱 rifabutin 併用時，只要沒有同時使用其他的 CYP 3A4 抑制物或誘導物，仍可用 MVC 的正常劑量每次 300 mg；若同時也併用強效的 CYP 3A4 抑制藥品，劑量則維持每次 150 mg；不論劑量如何改變，服藥頻率都維持為一天二次。由於 MVC 為新藥、且只適用於已產生抗藥性的愛滋病毒感染，文獻中缺乏國內病人依上述建議調整劑量後的治療效果與副作用，亟待以追蹤藥品交互作用、血中濃度、療效與副作用確認。此外，雖然 MVC 經由 CYP 3A4 代謝的比例是 CYP 3A5 的 25 倍，但由於 CYP 3A5 具基因多型性，且同質合子的 SNP 6986G (*3)在白人占 90%、黑人占 30%，而中國人占 73%；國內發現在 42 位健康受試者中有 39 人（93%）帶有 CYP 3A5*3 基因型，SNP 如何影響 MVC 的 PK 性質仍不得而知。而 P-gp 的生成是由 multidrug resistance-1 (MDR1)基因調控，但目前 MDR1 的 SNP 仍在發展中，初步研究顯示國人的 SNP 型態與比例和其他種族、甚至中國大陸或新加坡的華人均不太相同，因此 MVC 的 PK 與 SNP 相當值得探索[3]。但本院目前尚無病人使用。

文獻中多使用高效能液相層析儀（high performance liquid chromatography, HPLC）檢測 ART 血中濃度[3]，但並非每個醫療院所都能進行此種檢驗方式，因此有必要成立一個『藥品濃度監測中心』（PK laboratory），協助各地的醫療人員監測 ART 血中濃度。並

藉由追蹤血中濃度、基因多型性、療效與副作用等關係，探索最適合國人的 ART 劑量、藥品交互作用時之劑量調整原則等課題，累積國內之本土經驗，與國外文獻、臨床經驗相比較，不僅可增進病人用藥安全、達到最大的經濟效益，也能以論文期刊的方式與世界各國分享我國的用藥經驗。

本研究目的是藉由前瞻性的觀察，監測 ART 血中最低濃度（trough），紀錄服藥期間的治療效果（血漿愛滋病毒量、CD4 淋巴球數變化）與療效、副作用的發生率與嚴重度，藉以探索其相關性，不僅可確認國內成立 PK lab 的可行性、監測血中濃度的必要性及適當範圍，ART 血中濃度的結果可提供臨床醫師調整劑量的參考資料。此外，本研究將詢問患者是否併用 ritonavir、任何胃藥、影響 CYP3A4 的藥品/食品/中草藥等，以觀察藥品—藥品或藥品—食品交互作用對 ART 血中濃度的影響。

（2）材料與方法

執行期間： 2017 年 1 月 1 日迄 2017 年 12 月 31 日。

研究方法：

病患收納條件

一、十八歲以上感染愛滋病毒患者，即將開始接受ATV、EFV、DTG等ART或cotrimoxazole, rifabutin治療的愛滋病毒感染者，在填妥同意書後可以加入本研究；

二、病患願意在未來服用抗結核藥物的九到十二個月中繼續在本院持續追蹤治療者。

排除條件

一、已知對於將使用之上述ART過敏或無法耐受者

二、曾經接受過上述ART並且產生抗藥性者

三、臨床醫師判斷患者病況嚴重，無法存活一個月以上

研究步驟

一、針對即將開始接受上述ART治療者，檢測服藥前CD4淋巴球數、血漿愛滋病毒量、肝腎功能指數、血液相檢查、凝血功能檢查。並記錄所有用藥及劑量。

二、開始服用ATV後，一週時檢測血中最低濃度（trough concentration, C24 concentration）或服藥後血中第12 ± 1小時濃度（C12 concentration）；使用EFV者，兩週後檢測服藥後血中第12 ± 1小時濃度（C12 concentration）；開始服用DTG後，一週時檢測血中最低濃度（trough concentration, C24 concentration）。

三、服用四週後，依尋常愛滋病患的醫療，追蹤CD4淋巴球數、血漿愛滋病毒量、肝腎功能、血液相檢查、凝血功能檢查、空腹血醣檢查、血脂肪（三酸甘油脂、LDL、HDL）檢查；相同檢查在後續追蹤當中每十二個星期執行一次，一直到服用抗病毒藥物四十八週為止。

四、住院中每星期接受肝腎功能與血液相、凝血功能檢查。

五、若生化檢驗值顯示異常，將依尋常愛滋病患的醫療，安排相關檢查，並再次檢測ART血中最低濃度。

六、紀錄患者是否併用任何胃藥、影響CYP3A4的藥品/食品/中草藥等。

研究地點

台大醫院愛滋病防治中心專屬愛滋病房及/或門診

ART 血中濃度檢測：

ATV 血中濃度檢測

本研究使用HPLC檢測ATV血中濃度。方法詳述如下：

一、HPLC 系統

a. 儀器：包含自動注射器（autosampler）、梯度幫浦（gradient pump）、層析管柱恆溫箱、紫外線偵測器（UV detector）、電腦設備及分析軟體。

b. 管柱（column）：Mightsil RP-18 GP，with 5 μm beads，4.6 mm-25 cm，並附有相容的保護管柱（guard column）。

c. 移動相（mobile phase）：10 mM 磷酸鹽緩衝溶液(pH=2.5)與 acetonitrile (ACN)比例為 58:42 (v/v)。

d. 紫外線偵測波長：249 nm。

e. 流速：1 mL/min

f. 注射體積：30 μL

g. 滯留時間（retention time）：ATV 為 13.83 分鐘，diazepam (internal standard)為 17.23 分鐘。

二、標準品之製備

將 ATV 與 diazepam 溶於 methanol 中，製成 1 mg/mL 的標準品貯液，存放於-20°C；再以 methanol 稀釋成 1.5、5、10、25、50、75、100 μg/mL 的 ATV 工作液與 10 μg/mL 的 diazepam 工作液，存放於 4°C。將工作液加入健康受試者之血漿，使血漿標準檢品中 ATV 濃度分別為 0.15、0.5、1、 2.5、5、7.5、10 ng/mL。

三、血漿檢品前處理

在配製好的血漿標準檢品及病人之待測檢品（各 400 μL）中分別加入 25 μL 的 diazepam、400 μL 2M sodium carbonate 及 800 μL ethyl acetate-n-hexane (50：50 v/v)，經由 vortex 混合均勻，利用高速離心機（轉速為 17900 g）離心，於-80°C 冷凍 30 分鐘，再取出所有有機層溶液，最後以氮氣將有機層溶液吹乾。加入 200 μL methanol 以溶解管內剩餘乾燥物，以孔徑 0.22 μm 的 PVDF filter 過濾，取出其中 30 μL、打入 HPLC 中分析。

四、分析方法之確效

a. 準確度（accuracy）及線性（linearity）

分析一系列的 ATV 血漿標準檢品，濃度由 0.15 到 10 μg/mL。連續 6 天檢測這些血漿標準品，以評估一日內（intra-day）與異日之間（inter-day）濃度檢測變異性。實驗結果顯示濃度自 0.15 到 10 μg/mL 間皆呈線性，準確度為 90.9% ~ 97.8%。

b. 精確度（precision）

將連續 3 天檢測 3 種濃度的 ATV 血漿標準檢品（0.15, 5, 10 μg/mL）以分析精確度。實驗結果顯示精確度為 1.90% ~ 2.55%。

c. 回收率（recovery）

將 ATV 加入無藥（drug-free）血漿中調成 3 種不同濃度的（0.15, 5, 10 μg/mL）、加入 internal standard。ATV 自血漿檢品中的回收率百分比是比較 methanol 萃取前後 peak height ratio 的差異，共執行 3 次。實驗結果顯示回收率為 95%。

d. 選擇性（selectivity）

過去的文獻已評估過一般常與 ATV 併用的藥品並不會干擾本研究將採用的 HPLC 分析方法，包括抗愛滋病毒藥 efavirenz, nevirapine, zidovudine, didanosine, stavudine, lamivudine, indinavir, nelfinavir；抗結核病藥 rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin；及其他常見併用藥品 ofloxacin, acetazolamide, loperamide, prednisolone, phenytoin, amitriptyline, cotrimoxazole, fluconazole。

e. 定量極限（limit of quantification；LOQ）及偵測極限（limit of detection；LOD）

LOQ：將健康人血漿檢品逐步稀釋至其訊號與雜訊的比值（S/N）等於 10，則此血漿標準品濃度為本分析方法之定量極限。

LOD：將健康人血漿檢品逐步稀釋至其訊號與雜訊的比值（S/N）等於 3，則此血漿標準品濃度為本分析方法之偵測極限。實驗結果顯示 LOQ 為 0.15 μg/mL，LOD 為 0.1 μg/mL。

f. 安定性（stability）

根據過去的文獻，ATV 的血漿溶液可在室溫下保存 4 天、-20°C 下保存一年不變質。

五、病人檢體收集（samples）

由於 ATV 膠囊應與正餐一起服用以提高口服吸收率，病人可能習慣早餐或晚餐時服用，但一般抽血時間大多排定為早晨，因此視病人服藥習慣，待開始治療後的第 8 天之後，於前一天服藥後 12 ± 1 小時或 24 ± 1 小時抽取 7 c.c.的血液分別測定 C12 或最低血中濃度(C24)。血液樣品使用含足夠抗凝血劑 K2EDTA 的小管收集，運送過程中以 4˚C 保存。病人全血利用高速離心機 2500 g 在室溫下離心十分鐘，將上清液（血漿）分裝於冷凍小管。取 400 μL 血漿以最適化條件分析病人血中 ATV 的濃度。剩餘之血漿置於-80˚C 下保存。

EFV 血中濃度檢測

本研究使用HPLC檢測EFV血中濃度。方法詳述如下：

一、HPLC 系統

a. 儀器：包含自動注射器（autosampler）、梯度幫浦（gradient pump）、層析管柱恆溫箱、紫外線偵測器（UV detector）、電腦設備及分析軟體。
b. 管柱（column）：Mightsil RP-18 GP，with 5 μm beads，4.6 mm-25 cm，並附有相容的保護管柱（guard column）。
c. 移動相（mobile phase）：10 mM 磷酸鹽緩衝溶液(pH=4)與 acetonitrile (ACN) 比例為 57:43 (v/v)。
d. 紫外線偵測波長：245 nm。
e. 流速：1 mL/min
f. 注射體積：20 μL
g. 滯留時間（retention time）：EFV 為 13.43 分鐘。

二、標準品之製備

將 EFV 溶於 methanol 中，製成 1 mg/mL 的標準品貯液，存放於 4°C；再以 methanol 稀釋成 100 μg/mL 的 EFV 工作液並加入健康受試者之血漿，使血漿標準檢品中 EFV 濃度分別為 0.5、2.5、5.0、7.5、10.0 μg/mL，以建立定量線。

三、血漿檢品前處理

在配製好的血漿標準檢品及病人之待測檢品（各 300 μL）中分別加入 300

μL 的 acetonitrile 進行去蛋白步驟，經由 vortex 混合均勻，利用高速離心機（轉速為 17900 g）離心，再取出 400 μL 的上清液，在 40℃下以氮氣將上清液吹乾。最後加入 200 μL 動相以溶解管內乾燥物，以孔徑 0.22 μm 的 PVDF filter 過濾取出其中 20 μL、打入 HPLC 管柱。

四、 分析方法之確效

a. 準確度（accuracy）及線性（linearity）

分析一系列的 EFV 血漿標準檢品，濃度由 0.5 到 10 μg/mL。連續 3 天檢測這些血漿標準品，以評估一日內（intra-day）與異日之間（inter-day）濃度檢測變異性。實驗結果顯示濃度自 0.5 到 10 μg/mL 間皆呈線性，準確度為 97.7% ~ 101.6%。

b. 精確度（precision）

將連續 3 天檢測 3 種濃度的 EFV 血漿標準檢品（0.5, 5.0, 10.0 μg/mL）以分析精確度。實驗結果顯示精確度為 1.15% ~ 1.93%。

c. 回收率（recovery）

將 EFV 加入無藥（drug-free）血漿中調成 3 種不同濃度的（0.5, 5.0, 10.0 μg/mL）標準檢品，比較樣品前處理前後 peak area 的差異，共執行 3 次。實驗結果顯示回收率為 101%。

d. 選擇性（selectivity）

需評估一般常與 EFV 併用的藥品是否會干擾本研究將採用的 HPLC 分析方法，包括抗愛滋病毒藥 atazanavir, nevirapine, zidovudine, didanosine, stavudine, lamivudine, indinavir, nelfinavir；抗結核病藥 rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin；及其他常見併用藥品 ofloxacin, acetazolamide, loperamide, prednisolone, phenytoin, amitriptyline, cotrimoxazole, fluconazole。

e. 定量極限（limit of quantification；LOQ）及偵測極限（limit of detection；LOD）

實驗結果顯示 LOQ 為 0.5 μg/mL，LOD 為 0.2 μg/mL。

五、 病人檢體收集（samples）

由於 EFV 可能導致病人頭暈或精神狀況不佳，因此一般通常建議病人在睡前服用。待開始治療後的第 15 天早晨，於前一天服藥後 12 ± 1 小時抽取 7 c.c. 的血液測定最低血中濃度。血液樣品使用含足夠抗凝血劑 K2EDTA 的小管收集，

運送過程中以4˚C保存。病人全血利用高速離心機2500 g在室溫下離心十分鐘，將上清液（血漿）分裝於冷凍小管。取500 μL血漿以最適化條件分析病人血中EFV的濃度。剩餘之血漿置於-80˚C下保存。

測定 cotrimoxozale 血中濃度

本研究使用 HPLC 檢測 cotrimoxozale 血中濃度。方法詳述如下：以含有抗凝血劑（K2EDTA）收集受試者病人血液約 5-7 mL，使用 2500 rcf 離心 10 分鐘以取得血漿，並存放在-80℃冰箱保存。

將病人血漿檢體 200 μL 加入 200 μL 7% 過氯酸（perchloric acid），以去除血漿中蛋白部分，接著利用高速離心機 15000 g 離心 5 分鐘，取出上清液後，以 0.22 μm 濾膜過濾，最後再以高效能液相層析儀（high-performance liquid chromatography, HPLC）分析 SMX-TMP 濃度。

HPLC 使用管柱為 Luna C18 column, 250x4.6 mm, 5 μm （Phenomenex, Torrance, CA, USA），在室溫下操作。分析條件為：移動相（mobile phase）為氰甲烷（acetonitrile）與 7 mM 磷酸二氫鉀（KH2PO4）以體積比 20:80 所組成。7 mM 磷酸二氫鉀（KH2PO4）使用 10 M 氫氧化鈉（NaOH）調整酸鹼值至 pH=6.5。流速設定為 1 mL/min，最後之沖提液以 UV 230 nm 波長吸收偵測。不須內標準品。SMX 和 TMP 的滯留時間分別為 6.98 分鐘及 9.03 分鐘。

分析方法確效之檢量線（calibration curve）方面，SMX 以 5, 10, 25, 50, 100, 200 μg/mL、TMP 以 0.5, 1, 2.5, 5, 10, 20 μg/mL 六點濃度所建立，分別得迴歸式 Y=26186X + 4101.3，相關係數（correlation coefficient，r2）為 0.9998，及 Y= 56858X － 9193.7，相關係數為 0.9996。兩藥物的偵測極限（lower limit of detection, LOD）為 0.5 g/mL，SMX 和 TMP 之定量極限（lower limit of quantification, LOQ）分別為 5 g/mL 及 1 g/mL。每次濃度測量結果將檢測準確度（accuracy），將控制在 10% 誤差範圍之內；精確度（precision）則進行一日內重複性（repeatability；intra-day precision）及異日間之再現性（inter-day precision；between-run repeatability），分別控制相對標準差（relative standard deviation，RSD）小於 2%及 5%。

DTG 血中濃度檢測

本研究使用HPLC檢測DTG血中濃度。方法詳述如下：

一、HPLC 系統

a. 儀器：包含自動注射器（autosampler）、梯度幫浦（gradient pump）、層析管柱恆溫箱、紫外線偵測器（UV detector）、電腦設備及分析軟體。

b. 管柱（column）：Luna RP-18, GP, 250x4.6 mm, 5 μm (Kanto chemical Co. Inc., Japan)，並附有相容的保護管柱（guard column）。

c. 移動相（mobile phase）：10 mM 磷酸鹽緩衝溶液(pH=4)與 acetonitrile (ACN) 比例為 57:43 (v/v)。

d. 紫外線偵測波長：245 nm。

e. 流速：1 mL/min

f. 注射體積：20 μL

g. 滯留時間（retention time）：11.02 分鐘。

二、標準品之製備

將 DTG 溶於 methanol 中，製成 1 mg/L 的標準品貯液，存放於 4°C；再以 methanol 稀釋成 100 mcg/mL 的 DTG 工作液並加入健康受試者之血漿，使血漿標準檢品中 DTG 濃度分別為 0.2、0.5、1.0、2.5、5.0、8.0、10.0 mcg/mL，以建立定量線。

三、血漿檢品前處理

在配製好的血漿標準檢品及病人之待測檢品（各 300 μL）中分別加入 300 μL 的 acetonitrile 進行去蛋白步驟，經由 vortex 混合均勻，利用高速離心機（轉速為 17900 g）離心，再取出 400 μL 的上清液，在 40℃下以氮氣將上清液吹乾。最後加入 200 μL 動相以溶解管內乾燥物，以孔徑 0.22 μm 的 PVDF filter 過濾取出其中 20 μL、打入 HPLC 管柱。

四、分析方法之確效

a.準確度（accuracy）及線性（linearity）

分析一系列的 DTG 血漿標準檢品，濃度由 0.2 到 10 μg/mL。連續 3 天檢測這些血漿標準品，以評估一日內（intra-day）與異日之間（inter-day）濃度檢測變異性。

b.精確度（precision）

將連續 3 天檢測 3 種濃度的 DTG 血漿標準檢品（0.2, 5.0, 10.0 μg/mL）以分析精確度。

c.回收率（recovery）

將 DTG 加入無藥(drug-free)血漿中調成 3 種不同濃度的(0.2, 5.0, 10.0 μg/mL）標準檢品，比較樣品前處理前後 peak area 的差異，共執行 3 次。

d.選擇性（selectivity）

需評估一般常與 DTG 併用的藥品是否會干擾本研究將採用的 HPLC 分析方法，包括抗愛滋病毒藥 atazanavir, efavirenz, nevirapine, zidovudine, didanosine, stavudine, lamivudine, indinavir, nelfinavir；抗結核病藥 rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin；及其他常見併用藥品 ofloxacin, acetazolamide, loperamide, prednisolone, phenytoin, amitriptyline, cotrimoxazole, fluconazole。

e.定量極限（limit of quantification；LOQ）及偵測極限（limit of detection；LOD）

五、病人檢體收集（samples）

預計收納服用 DTG 的病人。每位病人均於早餐後服用。待開始治療後的第 5-7 天早晨，於前一天服藥後 24 ± 1 小時抽取 7 c.c.的血液測定最低血中濃度。血液樣品使用含足夠抗凝血劑 K2EDTA 的小管收集，運送過程中以 4˚C 保存。病人全血利用高速離心機 2500 g 在室溫下離心十分鐘，將上清液（血漿）分裝於冷凍小管。取 500 μl 血漿以最適化條件分析病人血中 DTG 的濃度。剩餘之血漿置於-80˚C 下保存。

（3）結果

以 HPLC 檢測 ART 與 cotrimoxazole (SMX-TMP)、rifabutin 血中濃度方法的開發與確效已在往年的結果報告中呈現，因此不再此贅述。此類分析方法之準確度、一日內跟異日間之藥物精確度（precision）都符合標準。將藥物在低、中、高三種濃度於血漿中做三次冷凍（-80℃）解凍（3-cycled freeze-thaw）之安定性試驗，均有良好的準確度（< 10%）及精確度（< 5%）。

由於今年已開發出 Dolutegravir 的血中濃度分析方法；以下將呈現 HPLC 確效的結果。檢量線的結果顯示濃度自 0.2 到 10 μg/mL 之間皆呈線性，而 LOQ 及 LOD 分別為 0.45、0.15 μg/mL。在 Dolutegravir 低、中、高濃度（0.2, 5, 10 μg/mL）有分別進行準確度（accuracy，用 bias%表示）、精確度（precision）的測試，另外也有進行安定性測試。

本分析方法之準確度不論在低、中、高濃度均小於 FDA 規定之 15%以內，且大多均落在 5%以內，顯示本分析方法有好的準確度。一日內跟異日間之藥物精確度（precision），以一日內重複性和異日間之再現性表示。DTG 不論在低、中、高濃度都符合標準：一日內之濃度變化均<2%，異日間之濃度變化均<5%；詳見表 1。

將 0.5 ppm 及 2.5 ppm DTG 在室溫及 4℃冰箱下於全血中之 0、1、2、4、6、8、12、24、48、72 小時之安定性測試。一開始時 DTG 在全血中濃度變化是由低往高，再慢慢降低，很可能隨著血球逐漸破壞釋出 DTG 於血漿之中，導致分析結果時回收率有大於 100%情形發生。在室溫下，72 小時過後不論濃度 DTG 仍在 90%以上；然而在 4℃冰箱下，24 小時過後 DTG 可能會掉到 90%以下，極有可能是因為 dolutegravir 本身在低溫溶解率不佳；可能的解決方法是將全血回溫到室溫不用急著離心，減少低溫 DTG 結晶時隨著離心而損失，詳見圖 1、2。

本年度之研究計畫專注執行 EFV、ATV 的藥物血中濃度與代謝酵素基因型、治療預後的初步分析；繼續協助臨床醫師監測藥物血中濃度，迄今已為 891 位服用 EFV、549 位服用 ATV 與 3 位服用 DTG 的病人分析藥物血中濃度與代謝酵素基因型、療效、副作用的相關性。

服用 EFV 者的藥物血中濃度差異性相當大，其中分析 891 位服用 EFV 的愛滋病毒感染者的血液檢體，絕大部分的濃度高於治療指引建議的 1 μg/mL，藥物血中濃度平均

值為 2.39 ± 1.25 mcg/mL（0～12.84 μg/mL），但有 4 人完全測不到血中濃度、而 1 人的血中濃度高達 12.84 mcg/mL，遠高於臨床研究與治療指引建議的 1~4 mcg/mL 範圍。

EFV 主要經由肝臟酵素 CYP 2B6 代謝，本研究觀察到 CYP 2B6 為異質接合（G516T）者、同型合子慢代謝者的濃度中位數分別高達 3.47 μg/mL 與 8.78 μg/mL，比正常功能的 CYP 2B6 者的 2.50 μg/mL 高。後續追蹤 456 位病人，以多變項回歸分析發現基因型與體重會顯著影響 EFV 濃度，目前文稿正由期刊審閱中 [23]。

由於絕大多數病人的 EFV 血中濃度高於治療指引建議的 1 μg/mL，因此針對使用 EFV 達 6 個月以上、血中濃度高於 2 μg/mL、病毒量低於 200 copies/mL 者，我們近來嘗試將 105 位病人的 EFV 劑量減半、密切追蹤血中濃度與臨床療效與副作用。減半前的 EFV 血中濃度平均為 3.69 mcg/mL（Q1-Q3=2.63-4.36 mcg/mL）、減半後追蹤的 64 病人的血中濃度為 1.96 mcg/mL（Q1-Q3=1.53-2.33 mcg/mL），濃度下降 51.6%（範圍 26-80.6%）。36 位病人有病毒量的追蹤，皆為<20 copies/mL。本研究將持續追蹤成效，若未來愛滋病毒感染者若沒有使用 rifampin，也許 EFV 的劑量可以略降，一方面可以替國家節省醫療費用，一方面可以降低愛滋病毒感染者長期接受抗病毒藥物副作用的發生率。

ATV 血中濃度方面，目前已追蹤的 549 位病人中，全數完成測定 ATV 血中濃度。由於 ATV 只需一天服用一次、食物可增進 ATV 胃腸吸收，建議在正餐後服用，為配合病人回診抽血時間，因此抽血點共有 2 種：C12 (12 hr)濃度，共計 316 人 (57.6%)；C24 (24 hr, trough)濃度，共計 196 人 (35.7%)；抽血或服藥時間不詳 37 人。

文獻建議 C12 濃度應維持在 0.23 mg/L 以上、C24 濃度應維持在 0.15 mg/L 以上；雖然本研究中 C12 濃度平均值為 1.00 mg/L、C12 濃度平均值為 0.73 mg/L，均高於目標值。但 C12 組中濃度達到目標者只有 85.5%，C24 組更降至 37.6%，只有 64.5%病人的藥物血中濃度高於目標值。由於抽血時間多在清晨，因此應鼓勵病人盡量於晚餐後服用 ATV，以增進胃腸吸收，維持療效並避免產生抗藥性。

ATV 主要經由肝臟酵素 UGT1A1 代謝，分析 492 位服用 ATV 病人的 SNP，帶有變異基因 UGT1A1*28 者共 98 人（19.9%），其中只有 2 位帶有雙股 SNP，其他均為 heterozygous 者。

HPLC 分析方法方面，ATV 的定量極限原為 0.1 mg/L，極接近藥品血中濃度的目標值，經過多次測試，成功將最小檢驗濃度（lower limit of quantification, LOQ）自 0.15 mg/L

降低為 0.1 mg/L，增加分析之靈敏度。由於 ATV 的血中濃度可能受 tenofovir (TDF)影響而降低，因此若未使用 ritonavir (RTV)的狀況下，國外文獻中不建議 ATV 與 TDF 同時併用，以免影響療效。故本研究分析無使用 RTV、且病毒量小於 200 copies/mL 的病人中，比較 128 位併用 TDF/lamivudine (TDF-based)與 186 位併用其他 NRTI 類(non-TDF-based)達 6 個月以上的病人，發現有 83.5%的病人雖使用 TDF-based 治療，ATV 血中濃度仍達到目標值；而使用 non-TDF-based 治療的病人，只有 64.9%的 ATV 血中濃度可達到目標值。追蹤 96 週後，各有 14.9%的 TDF-based 病人與 18.3%的 non-TDF-based 病人發生治療失敗（viroloical failure, *P*=0.6）。原就有較高的病毒量（40-200 copies/mL）與缺乏 ATV 血中濃度監測者較易治療失敗。而 MDR1 (positions 2677 and 3435)、PXR genotypes (position 63396)、UGT1A1*28 在兩組無顯著差異。此結果已在今年被 Journal of Microbiology, Immunology and Infection 接受刊登[3]。詳見圖 3 與表 2。

Cotrimoxazole 方面，於 2014 年 1 月 19 日至 2017 年 8 月 31 日間，前瞻性收案量測血中最低濃度（trough concentration）與最高濃度（peak concentration）。108 位被納入分析的病人中，年齡中位數為 45 歲（範圍 23-87 歲），82.9%是男性，共有 98 位為治療肺囊蟲肺炎的案例。目前各有 63 人與 68 人進行 NAT1、NAT2 基因型與藥品血中濃度。不論是 SMX 或者 TMP，血中最高濃度及最低濃度均有良好的線性關係(r>0.9)、而 SMX 與 TMP 之最高濃度中位數分別為 117.8 μg/mL (range: 40.2-279.1) and 4.6 μg/mL (1.1-10.1)，有 64.9%與 70.2%的比例在建議寫中濃度範圍內。治療期間，AST 及 ALT grade1-3 上升者分別佔總人數之 17.3%，這些病人相較於沒有發生 AST、ALT 上升者有較高的 SMX 血中最高及最低濃度（p<0.05）；發生高血鉀（發生率 26.9%）及低血鈉（發生率 5.8%）不良反應的病人有較高的 TMP 血中濃度。另外，發生高血鉀不良反應之病人使用較高的劑量（14.1 vs. 12.3 mg/kg/day, p=0.0302）。

Rifabutin 仍只有一位病人檢測，血中濃度在正常範圍內。Dolutegravir HPLC 分析方法目前已完成並開始收納病人，目前只有三位病人，藥物血中濃度平均值為 1.09 ± 0.04 mcg/mL（1.06～1.13 μg/mL），個體間濃度變異不大，與臨床試驗之藥動學資料相似，也接近日本文獻中的濃度（1.06 μg/mL），因基因型尚未檢測，待收到更多病人後可進行更詳細的分析。

本研究發現 EFV、ATV 與 cotrimoxazole 的個體間濃度差異性大、且部分病人的藥物血中濃度在建議值之外，有需要進行常規的血中濃度監測；針對 ATV 濃度過低者，

應考慮加上 ritonavir 併用以提高 ATV 血中濃度、確保療效，但需密集監測總膽紅素數值，以避免副作用。而 EFV 劑量若依血中濃度修改，可避免副作用並達到較佳的經濟學效益。

本研究室之現行模式，除了提供全國各醫療院所常規監測 ATV、EFV、DTG、rifabutin 與 cotrimoxazole 血中濃度的服務，亦嘗試開發以 HPLC 方法測定其他 ART。在進行臨床相關研究的同時，可提供臨床醫師藥品濃度訊息做為調整劑量或換藥的重要參考資料，研究成果不僅可用以確認國內成立 PK lab 的可行性、監測血中濃度的必要性，甚至做為衛生主管機關建議國人使用 ART 劑量時的重要依據。

（4）討論

本研究延續前年度之研究成果，預定於本年度繼續協助臨床醫師監測 ART 血中濃度，並大量收納使用 EFV、ATV、rifabutin 與 cotrimoxazole 的病人，加上新開發之 DTG 分析方法，著手進行藥品血中濃度與代謝酵素基因型、治療預後、副作用的分析。

ATV 臨床使用時，雖比其他蛋白酶抑制劑較少發生代謝方面的併發症，但因經由肝臟酵素 CYP 3A4 代謝，可能因藥品交互作用而影響藥效；另一肝臟酵素 UGT 1A1 負責 ATV 的排除，ATV 與膽紅素競爭的結果可能造成高膽紅素血症，5%左右的病人更會產生明顯的黃疸症狀。國外研究者發現 ATV 的血中濃度是影響高膽紅素血症的重要原因之一，因此建議血中濃度維持在 0.15 - 0.85 μg/mL 之間。[3] 另一方面，ATV 時需飯後立即服用、避免與制酸劑或其他胃藥併服。加上目前初步分析發現過高的 ATV 血中濃度與嚴重總膽紅素血症相關，與其他國外文獻的結論相符，因此監測 ATV 血中濃度與避免藥品交互作用實屬必要。

EFV 一般的給藥劑量通常是 600 mg 睡前服用，以避免中樞神經相關的副作用。我們監測EFV的血中濃度顯示絕大多數病人的數值均高於HIV治療指引建議的1 μg/mL，且四分之三的人用藥時可兼顧療效達成與副作用的避免。

EFV 主要經由肝臟酵素 CYP 2B6 代謝，其基因多型性在歐美、泰國、日本、印度的研究結果均顯示會顯著影響 EFV 的血中濃度，而本研究觀察國人的追蹤結果也印證了這一點。為避免不良反應的產生，目前在極少數療效佳、EFV 濃度高的病人中，已嘗試將劑量降低成每日 300 mg（半顆）、密切追蹤病毒量與 EFV 血中濃度，觀察是否具有藥物經濟學上的優勢。

今年已將 DTG 的分析條件開發完成，並收納 3 位病人，濃度皆在 1.0 μg/mL 左右。根據最近發表的日本文獻提到，發生神經精神相關副作用的病人，DTG 最低血中濃度顯著高於未發生者（1.31 μg/mL vs. 1.01 μg/mL, p value = 0.0013）；此外，同篇研究也指出若病人帶有 UGT1A1*6 或 UGT1A1*28 跟較高的濃度以及發生神經精神副作用相關，因此在臨床上定期監測 DTG 血中濃度可能有其必要性，至於基因多型性與濃度及副作用的關係有待未來進一步探討。

（5）結論與建議

ATV 與 EFV 主要經由酵素 CYP 450 代謝，而酵素活性與 SNP、生理病理狀況、藥品交互作用息息相關，因此每個人的藥物血中濃度變動可能影響療效與副作用。國外文獻中多使用 HPLC 檢測 ART 血中濃度，本計畫藉由前瞻性地以 HPLC 測定 ATV、EFV 血中濃度、檢測相關酵素基因型、追蹤療效與副作用，嘗試以 PK lab 的方式，協助各地的醫療人員監測 ART 血中濃度，同時進行臨床研究。

目前追蹤了 891 位服用 EFV、549 位服用 ATV，研究結果顯示個體間的藥物血中濃度差異極大，有需要進行常規的血中濃度監測。併用 TDF 似乎並未對 ATV 血中濃度造成顯著影響。而過高的 ATV 血中濃度則會使總膽紅素數值異常增高。

雖然絕大多數病人有 EFV 血中濃度在文獻建議的 1～4 μg/mL 之間，但個體間差異大，主要代謝酵素 CYP 2B6 若異質接合（G516T）者，血中濃度接近建議值的上線，此類病人可考慮調降每日劑量為一般建議劑量的一半，以避免副作用並達到較佳的經濟學效益，目前此研究正在進行中。

本研究雖發現住院的成人使用 SMX-TMP 的劑量低於仿單建議劑量，但大多數病人可達文獻建議之 TMP 治療濃度，因此推測成人可能不需依照仿單建議的使用劑量即可達到理想濃度。肝毒性和 SMX 濃度有顯著關係；電解質不平衡和藥物濃度與使用劑量之間也有顯著關係。病人血中濃度個體間變異性大，因此，監測藥物血中濃度將有助於避免副作用。由於兩藥之血中最高濃度及最低濃度有良好的線性關係，可利用臨床上較易取得之血中最低濃度去預測最高濃度。Rifabutin 及 DTG 分別只有一位及三位病人檢測，血中濃度均在正常範圍內。

以上研究結果不僅可確認國內成立 PK lab 的可行性、監測血中濃度的必要性，ART 血中濃度的結果可提供臨床醫師調整劑量的參考資料，甚至做為衛生主管機關建議國人使用 ART 劑量時的重要依據。本研究室將繼續現行模式，提供全國各醫療院所常規監測 ATV、EFV、DTG 血中濃度的服務；並嘗試開發檢測其他 ART 的 HPLC 方法，追蹤病人的藥物血中濃度與肝臟酵素及 P-gp 的基因型、評估臨床療效與副作用，以期達到最佳療效並確保用藥安全。

（6）重要研究成果及具體建議

本研究結果顯示個體間的 ATV、EFV、cotrimoxazole 血中濃度差異極大，且與療效、副作用相關，應常規進行血中濃度監測，做為調整劑量的參考，進而提昇醫療經濟效益。DTG 與 rifabutin 則有待納入病人樣本數以便進一步評估。

（7）參考文獻

1. Hung CC, Chen MY, Hsieh SM, Sheng WH, Chang SC: Clinical spectrum, morbidity and mortality of acquired immunodeficiency syndrome in Taiwan: a 5-year prospective study. J Acquir Immune Defic Syndr 2000;24:378-85.
2. Hung CC, Hsiao CF, Chen MY, Hsieh SM, Chang SY, Sheng WH, Sun HY, Chang SC: Improved survival of persons with human immunodeficiency virus Type 1 infection in the era of highly active antiretroviral therapy in Taiwan. Jpn J Infect Dis 2006;59:222-8.
3. Mocroft A, Phillips AN, Gatell J, Ledergerber B, Fisher M, Clumeck N, Losso M, Lazzarin A, Fatkenheuer G, Lundgren JD, for the EuroSIDA Study Group. Normalization of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. Lancet 2007;370:407-13.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 8,2015; 1-161. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf . Accessed on April 8, 2015.
5. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001 Jan 5;15(1):71-5.
6. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004 Dec 3;18(18):2391-400.
7. Fellay J, Marzolini C, Meaden ER, et al. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. Lancet 2002 Jan 5;359(9300):30-6.

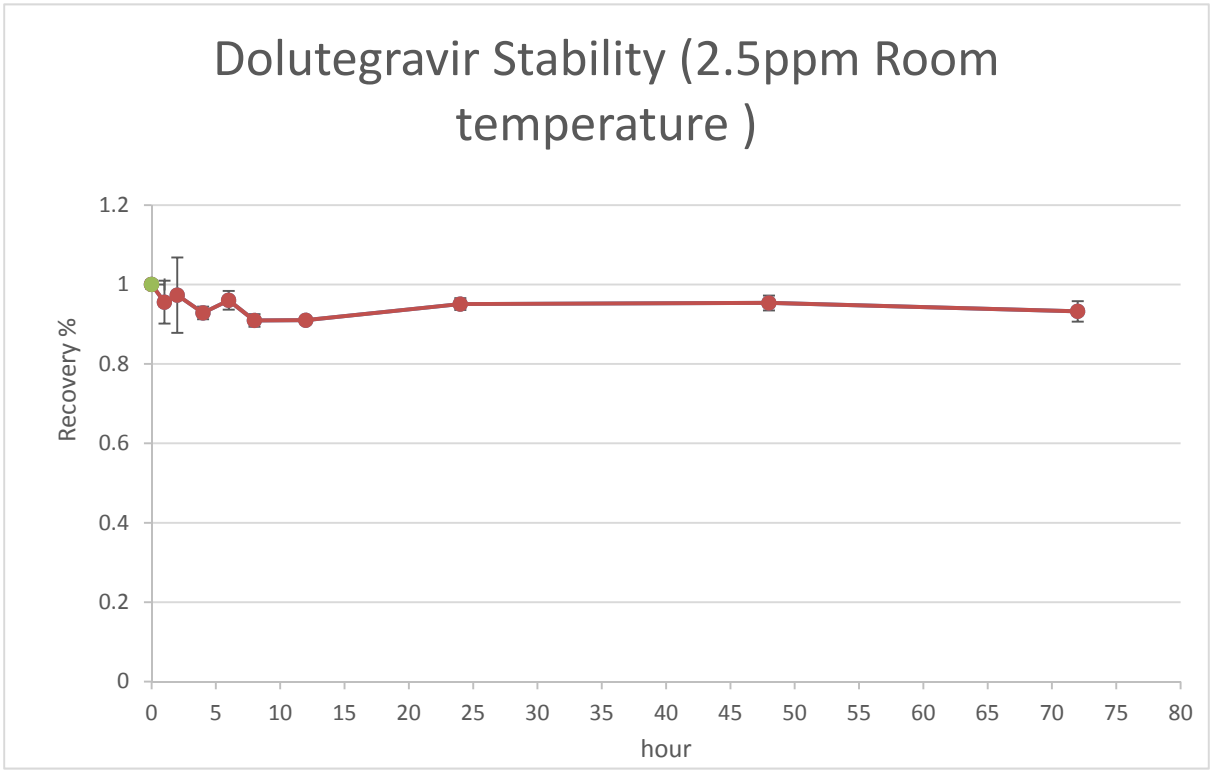
8. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: the price of success. JAMA 2006;296:844-54.
9. Cleijsen RM, van de Ende ME, Kroon FP, et al. Therapeutic drug monitoring of the HIV protease inhibitor atazanavir in clinical practice. J Antimicrob Chemother. 2007 Oct;60(4):897-900.
10. Müller AC, Kanfer I. An efficient HPLC method for the quantitative determination of atazanavir in human plasma suitable for bioequivalence and pharmacokinetic studies in healthy human subjects. J Pharm Biomed Anal. 2010 Sep 21;53(1):113-8.
11. Uglietti A, Novati S, Gulminetti R, et al. Correlations between atazanavir C(trough)and hyperbilirubinemia: a case report. J Med Case Reports. 2009 Dec 1;3:9307.
12. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA 2008;300:530-39.
13. Manosuthi W, Sungkanuparph S, Tantanathip P., et al., A Randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: The N(2)R study. Clin Infect Dis 2009;48:1752-60.
14. Oliva J, Moreno S, Sanz J et al. Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis. AIDS 2003;17: 637-42.
15. Swaminathan S, Padmapriyadarsini C, Venkatesan, et al. Once-daily nevirapine vs efavirenz in the treatment of HIV-infected patients with TB: a randomized clinical trial [abstract 35]. In: Program and abstracts of the 16th Annual Conference on Retroviruses and Opportunistic Infections (Montreal). Alexandria, VA: Foundation for Retrovirology and Human Health, 2009.
16. Manosuthi W, Sungkanuparph S, Thakkinstian A, et al. Plasma nevirapine levels and 24-week efficacy in HIV-infected patients receiving nevirapine- based highly active antiretroviral therapy with or without rifampicin. Clin Infect Dis 2006; 43:253-5.
17. Manosuthi W, Ruxrungtham K, Likanonsakul S, et al. Nevirapine levels after discontinuation of rifampicin therapy and 60-week efficacy of nevirapine-based antiretroviral therapy in HIVinfected patients with tuberculosis. Clin Infect Dis 2007; 44:141-4.

18. Avihingsanon A, Manosuthi W, Kantipong P, et al. Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis coinfection receiving rifampicin. Antivir Ther 2008;13:529–36.
19. Chang SY, Lin SW,Hung CC. Do we still need lead‐in dosing of nevirapine in HIV‐infected patients who are receiving rifampicin‐containing antituberculous therapy? Clin Infect Dis 2009;49:1452-3.
20. Gatanaga H, Hayashida T, Tsuchiya K. Successful Efavirenz Dose Reduction in HIV Type 1–Infected Individuals with Cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007;45:1230-1237.
21. Haas DW, Ribaudo HJ, Kim RB, et al., Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004;18:2391-400.
22. Fellay J, Marzolini C, Meaden ER, et al., Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. Lancet 2002;359:30-6.
23. CDC: Managing drug interactions in the treatment of HIV-related tuberculosis [online]. 2007 Available from URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm.
24. Cattaneo D, Maggiolo F, Ripamonti D, et al. Determination of atazanavir in human plasma by high-performance liquid chromatography with UV detection. J Chromatogr Sci. 2008 Jul;46(6):485-9.
25. Notari S, Tommasi C, Nicastri E, et al. Simultaneous determination of maraviroc and raltegravir in himan plasma by HPLC-UV. IUBMB Life 2009;61(4):470-5.
26. Colombo S, Beguin A, Marzolini C, et al. Determination of the novel non-peptide HIV-protease inhibitor tipranavir by HPLC-UV after solid-phase extraction. J of Chromatogr B 2006;832:138-43.
27. Droste JAH, Verweij-van Wissen CPWGM, Burger DM. Simultaneous determination of the HIV grugs indinavir, amprenavir, sequinavir, ritonavir, lopinavir, nelfinavir, the nelfinavir hydroxymetabolite M8, and nevirapine in human plasma by reverse-phase high-performance liquid chromatography. The Ther Drug Monit 2003;25 (3):393-9.
28. Bennetto CJ, King JR, Turner ML, et al. Effects of concentration and temperature on the stability of nevirapine in whole blood and serum. Clinical Chemistry

2004;50:209-211.

29. Lee KY, Lin SW, Sun HY, Kuo CH, Tsai MS, Wu BR, Tang SY, Liu WC, Chang SY, Hung CC. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. Plos One 2014;9(2):e88497.
30. Tsai MS, Chang SY, Lin SW, Kuo CH, Sun HY, Wu BR, Tang SY, Liu WC, Su YC, Hung CC, Chang SC. Treatment response to unboosted atazanavir in combination with tenofovir disoproxil fumarate and lamivudine in human immunodeficiency virus-1-infected patients who have achieved virological suppression: A therapeutic drug monitoring and pharmacogenetic study. J Microbiol Immunol Infect. 2016 Jan 11. [Epub ahead of print]
31. Yagura H, Watanabe D, Kushida H, et al. Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse events in Japanese individuals infected with HIV-1. BMC Infect Dis. 2017;17(1):622.
32. Huang SH, Lin SW, Chang SY, Lin YT, et al. Prediction of plasma efavirenz concentrations among HIV-positive patients taking efavirenz-containing combination antiretroviral therapy (under reviewed)

（8）圖表



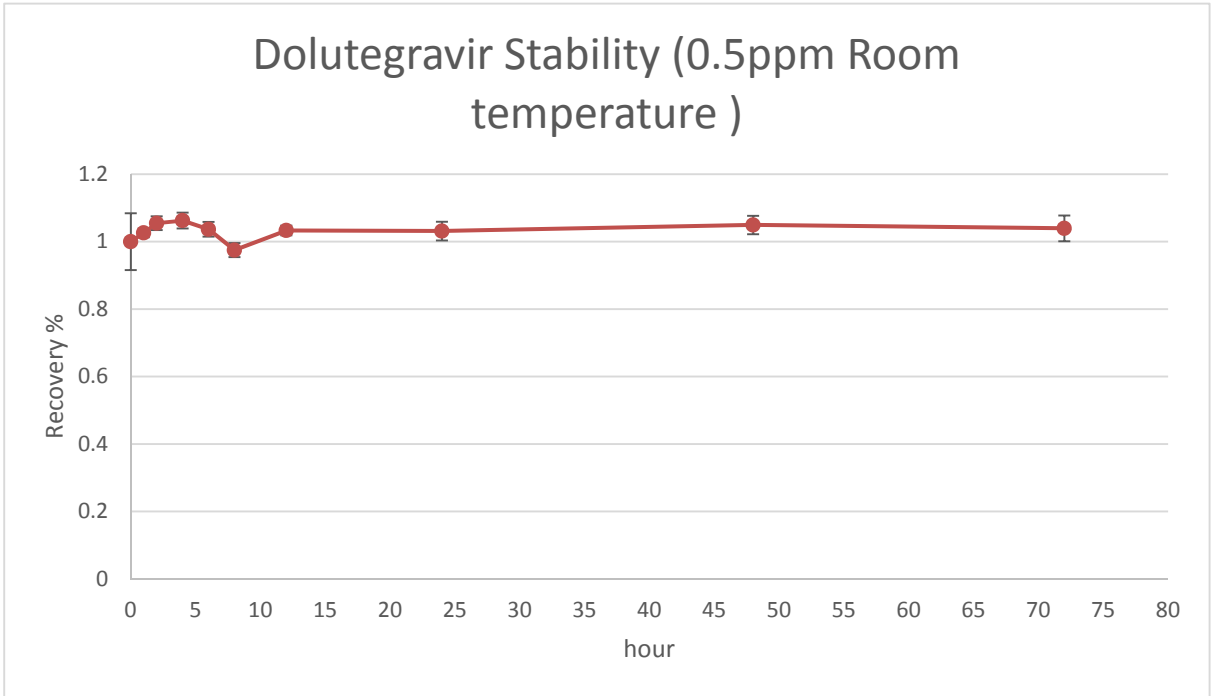
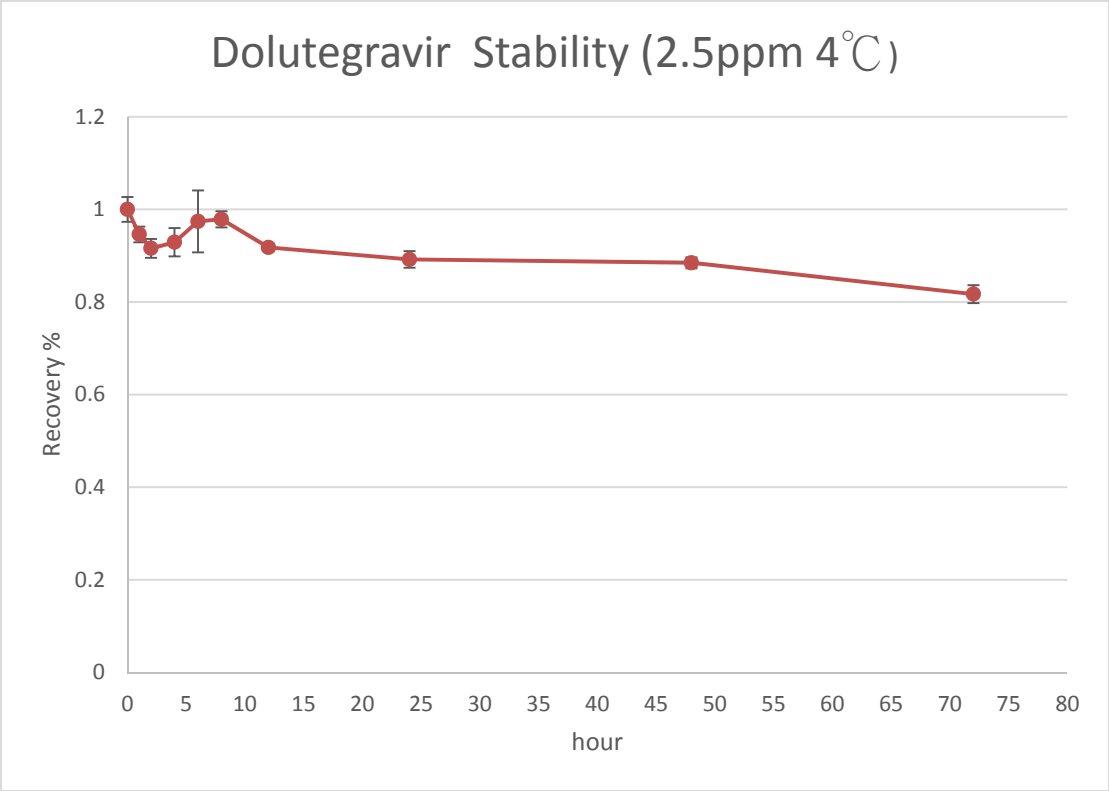


圖 1、Trend of 72 hours dolutegravir concentrations (2.5, 0.5 ppm) in room temperature



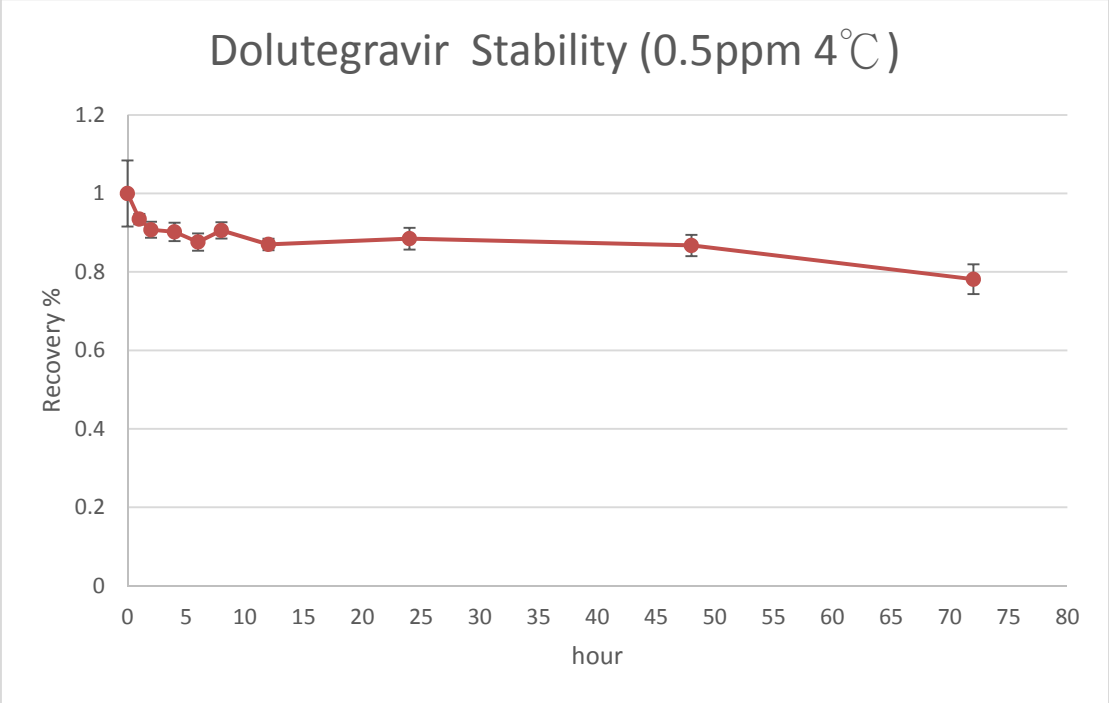


圖 2、Trend of 72 hours dolutegravir concentrations (2.5, 0.5 ppm) in 4˚C

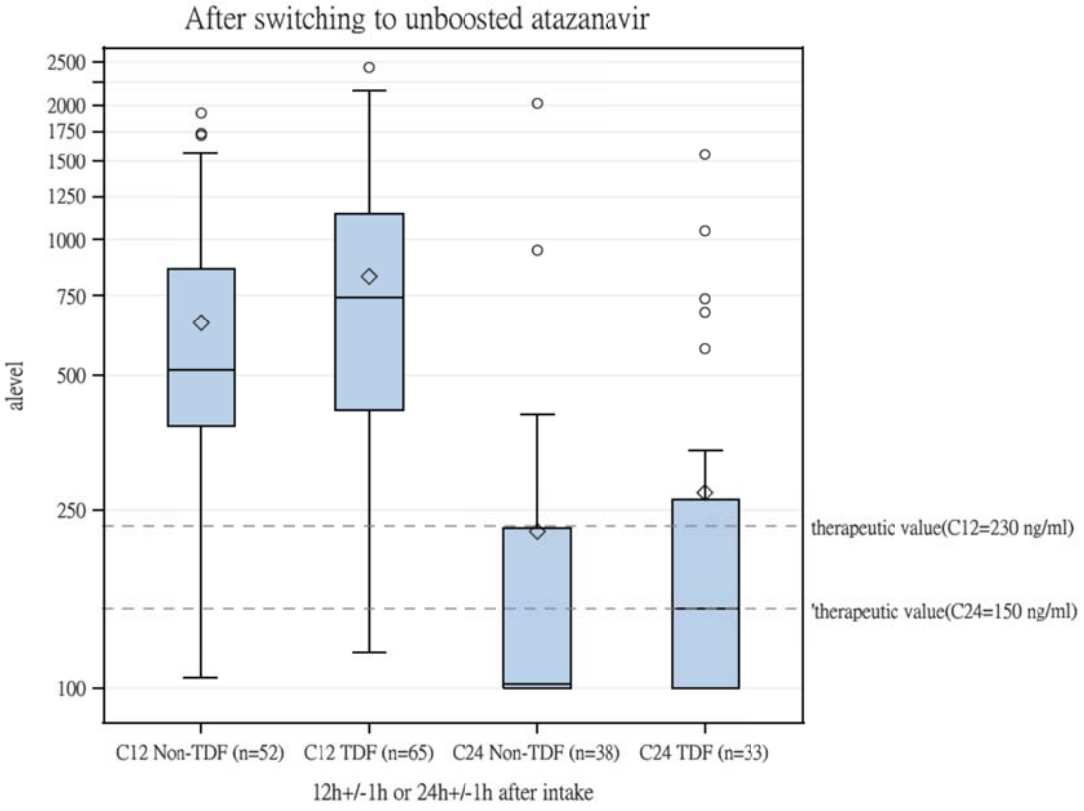


圖 3、Plasma atazanavir concentrations in patients receiving tenofovir, lamivudine plus unboosted atazanavir and those receiving abacavir or zidovudine, lamivudine plus unboosted atazanavir

表 1、Precision test of dolutegravir (intra-day and inter-day)

Precision (intra-day)	0.5 ppm	5.0 ppm	10.0 ppm
	16301	174321	327249
	16817	174318	332436
	16574	174389	333920
	16890	177857	325413
	16900	177463	325646
	16761	177016	324723
average	16707.2	175894.0	328231.2
STD	231.6	1720.3	3948.2
CV %	1.39%	0.98%	1.20%

Precision (inter-day)	0.5 ppm	5.0 ppm	10.0 ppm
2017/05/22	16301	174321	327249
	16817	174318	332436
	16574	174389	333920
	16890	177857	325413
	16900	177463	325646
	16761	177016	324723
2017/05/24	16875	178815	334912
	16509	179788	333772
	16787	179234	333462
2017/05/25	16575	177999	335180
	16818	178454	335142
	16774	178568	334198
average	16715.1	177351.8	331337.8
STD	184.8	1960.5	4226.
CV %	1.11%	1.11%	1.28%

表 2、Univariate and multivariate analysis for factors associated with virological failure in 200 patients

Variables	Reference	Univariate			Multivariate		
		HR	95% CI	P-value	HR	95% CI	P-value
Tenofovir-based	**Non- tenofovir-based**	1.31	0.63-2.72	0.49	1.62	0.72-3.66	0.24
Age, years	**per 1-year increase**	0.99	0.96-1.03	0.71	1.00	0.96-1.04	0.96
HBsAg-positive	**HBsAg-negative**	1.37	0.65-2.86	0.41	1.05	0.48-2.31	0.91
Anti-HCV-positive	**Anti-HCV- negative**	1.14	0.27-4.75	0.86	1.09	0.26-4.64	0.90
Baseline plasma HIV RNA load (RNA, 40-200 copies/mL)	**RNA <40 copies/mL**	2.70	1.27-5.88	0.01	2.33	1.03-5.26	0.04
Without therapeutic drug monitoring	**With therapeutic drug monitoring**	2.46	1.22-4.98	0.01	2.48	1.18-5.19	0.02

Notes: HRs and 95% CIs were calculated using Cox regression analysis.

Abbreviations: HBsAg, hepatitis B virus surfacce antigen; HCV, hepatitis C virus; HR, hazard ratio; CI, confidence interval

附件五

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

愛滋病毒感染之暴露前預防性投藥之前瞻性研究

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院附設醫院

計畫主持人：洪健清

研 究 人 員：

執 行 期 間：106 年 1 月 1 日至 106 年 12 月 31 日

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目　　錄

壹、中文摘要：

研究目的：針對愛滋病毒感染之高風險對象，並已經自費使用暴露前預防性投藥下，提供定期而免費的愛滋病毒病毒量篩檢，性病(梅毒、淋病、披衣菌)篩檢及衛教諮詢，以期能藉由提供諮商和高敏感度的免費篩檢，促進高風險群定期檢驗與使用預防藥物的意願，同時了解高風險群對於愛滋病毒暴露前預防性投藥之使用方式與頻度，以及副作用和相關性病發生率。

研究方法：凡對象為年齡在 20 歲以上，排除急性 HIV 感染與懷孕之可能，且具備同性間或異性間性行為可能感染 HIV 之風險者，納入暴露前預防性投藥，在門診或匿名篩檢站進行問卷評估後，並由個案確定採取每日服用或是需要時服用(On demand)之方式開立處方簽由患者自費領藥，並且同時進行檢驗，後續定期追蹤 HIV 使否陽轉以及各項性病是否感染。

主要發現：至 2016 年 10 月 31 日止，共有 37 人接受暴露前預防性投藥，其中僅一人為異性間性行為者，餘 36 人皆為同性間性行為者；此外，共有 33 人(89.2%)選用需要時服用之方式，均為同性間性行為者。完成 12 個月，9 個月以及 6 個月追蹤者分別各有 1, 4, 6 人，無任何一人出現 HIV 陽轉；此外，在追蹤過程中，僅有 1 人感染淋病， 1 人感染梅毒需治療。在副作用部分，未出現腎功能之影響，僅 2.7%有頭痛，16.2%有輕微腹瀉，但未有因副作用而無法進行者。

結論：暴露前預防性投藥可作為整體 HIV 預防措施之一，並可達到良好的成效，在本計劃中並無 HIV 陽轉者，且無嚴重之副作用出現，性病之發生率亦不高。

關鍵詞：愛滋病毒感染、暴露前預防性投藥、愛滋病毒檢驗、抗愛滋病毒藥物

貳、英文摘要：

Aims of Study: We aimed to enhance the adherence to and willing of using PrEP and participating in regular screening in the high-risk populations by providing consultation and free screening tests.

Study design: Individuals who were aged above 20 years and had unprotected sex an initiated PrEP were included after exclusion of acute HIV infection or pregnancy. After completing questionnaire interviews at the outpatient clinics or voluntary counseling and testing (VCT) services, daily PrEP or on-demand PrEP were begun. The prescription will be paid by the clients. Baseline examinations including HIV PCR, sexually transmitted diseases (STDs), hepatitis markers were performed. After taking PrEP, the clients were followed regularly.

Results: During the 10-month study period, 37 persons were enrolled. Only one of them was a heterosexual female and all the others were male homosexuals. Most of them decided to use On-demand PrEP (33/37, 89.2%) and they were all homosexuals. The case numbers of those who completed 6-month, 9-month, and 12-month were 6, 4, and 1, respectively. During follow-up, no HIV seroconversion was detected. One male had gonorrhea while another one had syphilis during the follow up. No renal impairment developed while only 2.7% of them reported headache and 16.2% diarrhea. No individuals stopped PrEP because of adverse effects.

Conclusions: In this study, no HIV seroconversion was detected among the 37 patients initiating PrEP; and there were no severe adverse effects. As far, the incidence rate of STDs was low.

Key words: HIV infection; Pre-exposure prophylaxis; PrEP, antiretroviral drug; HIV examination

參、本文：

（一）前言

後天免疫缺乏症候群（愛滋病，Acquired Immunodeficiency Syndrome, AIDS），自從 1981 年在美國發現以來，已成為全世界二十一世紀最重要的公共衛生問題，國內自 1984 年首例迄今，已逾三萬名以上，是疾管署傳染病防治工作的重要課題。愛滋病是由人類免疫缺乏病毒(human Immunodeficiency Virus, HIV)透過血液或體液接觸而所傳染，全球各地主要之流行途徑多是經由性行為，因此亦為性病之一，防治之法無他，即倡導安全性行為之重要性，以及教導高危險群定期檢驗追蹤；已被感染者若能及早發現，一方面需要追蹤治療，另一方面藉由 100%之安全性行為，防堵已感染者將愛滋病毒進一步傳播。因此呼籲經常無保護措施性行為者、且性伴侶眾多者接受篩檢與專業心理諮詢，是非常重要的。而根據統計，2007 年到 2015 年臺灣每年新診斷的愛滋病毒感染者大約在 1,600 到 2,200 人，不安全性行為是愛滋病毒感染最主要的傳染途徑。

隨著抗 HIV 藥物的發展及高效性抗愛滋病毒治療方法（highly active antiretroviral therapy，HAART）的問世，感染愛滋病毒的病患已能藉之而獲得病情的控制。近期幾個重要的研究都提供及早治療是預防愛滋病毒傳播的重要的公共衛生的手段之一的臨床證據。在加拿大溫哥華的觀察研究顯示，整體社區病毒量越低，愛滋病毒新發案例越少。在異性戀為主的 HPTN-052 研究中，研究人員發現及早治療愛滋病毒感染者，可以顯著降低性伴侶的傳染。在 START 研究中，研究人員發現及早治療也可以降低病發伺機性感染和腫瘤的發生風險。雖然如此，多先進國家依然看到愛滋病毒感染持續發生，尤其是在男同性戀族群中，新感染人數並未降低。因此除了鼓勵篩檢提早診斷和治療愛滋病毒感染以外，還需一些新的預防感染的措施才能真正達到減少新案的發生。

2010 年大型臨床試驗首度證實抗愛滋病毒藥物治療可有效降低男男性行為者（men who have sex with men; MSM）44%感染機率。2010 年之後，後續許多研究評估在接觸愛滋病毒前使用暴露前預防性投藥（Preexposure prophylaxis; PrEP）對於預防愛滋病毒感染的成效，在特定族群上具有顯著預防愛滋病毒感染的效果。2011 年世界衛生組織（World Health Organization; WHO）主張治療就是最好的預防。2012 年七月美國食品藥管理局（Food and Drug Association; FDA）正式核准 tenofovir + emtricitabine（TDF/FTC, Truvada）成為暴露前預防性投藥的首選藥物。2011 年美國疾病管制及預防中心（The

Centers for Disease Control and Prevention in Untied States）首先針對男男性行為者，制定暴露前預防性投藥暫時性的使用指引，隨後 2012 年針對性活躍的異性戀成人、2013 年針對注射藥物者推出暴露前預防性投藥暫時性的使用指引，並且於 2014 年正式公布暴露前預防性投藥臨床使用指引。WHO 於 2015 年建議暴露前預防性投藥作為全球愛滋病防治的防治的重要措施之一。

本計劃將針對愛滋病毒感染之高風險對象, 並已經自費使用暴露前預防性投藥下，提供定期而免費的愛滋病毒病毒量篩檢，性病(梅毒、淋病、披衣菌)篩檢及衛教諮詢，以期能藉由提供諮商和高敏感度的免費篩檢，促進高風險群定期檢驗與使用預防藥物的意願，同時了解高風險群對於愛滋病毒暴露前預防性投藥之使用方式與頻度，以及副作用和相關性病發生率。在執行此計畫之前，我們已經利用前來接受匿名篩檢的高風險群進行對於預防投藥的知識與態度調查，我們發現在 1010 位接受問卷調查的受試者，其中有 48%願意開始使用預防性投藥，而且在有意願開始使用預防性投藥的人當中，87%選擇使用 on-demand 的方式，同時知道預防性投藥的訊息的人遠較不知道這訊息的人更有意願開始使用預防性投藥。因此，我們未來的研究期待可以發現在高風險群自費使用預防性投藥過程中，是否能持續維持定期服藥與追蹤，可能出現的問題，這些計畫成果將可提供政府制定防治愛滋病毒感染的公共衛生政策參考之用。

（二）材料與方法

執行期間：2017 年 1 月 1 日迄 2017 年 12 月 31 日。

1.研究方法：

為三年期之計畫，預計每年納入 100 人次，三年共 300 人次

(1)本試驗為臨床之觀察性研究，預計納入之對象為年齡在 20 歲以上，排除急性 HIV 感染與懷孕之可能，且具備以下之風險者，納入暴露前預防性投藥：

a) 男男間性行為者 (MSM)：過去 6 個月內有過無套肛交，或過去 6 個月內曾經感染過性病，或伴侶為 HIV 感染者，或發生性行為時合併使用娛樂性藥物，或是過去一年內使用兩次以上的非職業性暴露後預防性投藥

b) 異性戀者：伴侶為 HIV 感染者，或本身為性工作者，或具有多重性伴侶且非常規使用保險套進行性行為

(2)於門診或匿名篩檢站進行評估後，符合納入條件，並由個案確定採取每日服用或是需要時服用(On demand)之方式開立處方簽由患者自費領藥，並且同時進行檢驗，檢驗項目根據投藥之時程如下：

服藥前基本評估	HIV PCR (定性) 腎功能 (eGFR) 尿液分析 Urinalysis 性傳染病檢驗 (TPPA/RPR, PCR for 淋病/披衣菌) 懷孕檢查 HBsAg, anti-HBs, anti-HCV
服藥後四周	HIV Ag/Ab combo test
服藥後每三個月	HIV Ag/Ab combo test 性傳染病檢驗 (RPR, PCR for 淋病/披衣菌) 懷孕檢查
服藥後每半年	尿液分析 Urinalysis; 腎功能 (eGFR)
服藥後一年	HBsAg, anti-HBs, anti-HCV

a) 定期回門診或是匿名篩檢站接受評估，檢驗與衛教諮詢；由藥物使用情形評估服用順從性，並記錄服用後是否有副作用；諮詢中若個案有使用娛樂性藥物則協助轉介至精神科進行藥物戒斷，並定期紀錄成效。

b) 發現為愛滋病毒感染個案時，血液檢體將盡快轉送張淑媛老師接續進行抗藥檢測；同時將聯繫個案管理師接續門診的照護，即刻開始抗愛滋病毒治療

2.資料收集：

以固定之 Case record form 紀錄追蹤日期, 檢驗結果, 副作用與 HIV 陽轉情形

3.分析方法：

利用 SPSS 或是 SAS 統計軟體分析 HIV 陽轉發生率, 性病發生率以及副作用情形

（三）結果

本計畫因涉及匿名採集檢體，本院倫理委員會考量維護受試者權益，須重新設計試驗說明書並須經過一般審查，延至本年度 4 月底方才通過。截至 10 月底，收納 23 名受試者。為鼓勵服藥持續性及增加本計畫個案數，我們亦邀請 5 月前已開始服用或打算開始服用藥物之受試者，總計 37 位。

Table 1 顯示了這 37 位的基本資料，僅有一位是女性，在受試者中有 33 位選擇了需要時服用(On demand)的方式，而 4 位選擇每日服用一顆；男性受試者均為 MSM/Bisexual, 在年齡層的部分，選用 On demand 的組別較為年輕一些(31.9±3.8 vs. 33.8±6.3)；受試者的平均月收入僅 40.5%在 5 萬以上。圖一則為轉介暴露前預防性投藥的管道，絕大部分來自於匿名篩檢處。

Table 2 則為受試者加入時 baseline 以及後續追蹤之檢驗狀況和問卷調查之情形。目前完成 3, 6, 9, 12 個月追蹤的人數分別為 8, 6, 4, 以及 1 人，在追蹤的過程中，沒有任何一人出現 anti-HIV 陽性；僅 1 人在第 3 個月追蹤時看到有梅毒新感染，1 人在第 9 個月時 urine PCR 檢出淋病感染，因此 STD 發生比率僅 5.4%。在性行為模式調查方面，發現使用 On demand 或是 daily PrEP 的人三個月內的性伴侶數大部分為 1-5 人(88.5%, 50%)，僅在 On demand 族群中，有 15.4%明確知道過去一年內的性伴侶為 HIV 或是性病感染者；在兩組中共將近 50%的人表示過去三個月內保險套使用的比例達到 100%，而開始進行 PrEP 後是否保險套使用比例有下降則需等到大部分人追蹤滿一人後方才能比較；在 On demand 組中，曾使用成癮性藥物的比例偏高，約 42.3%；在 PrEPr 進行的過程中，僅少數人有 nausea 或是 diarrhea 之狀況。

Table 3 為2017年台大醫院匿篩諮詢處調查PrEP意願之結果,在有無意願進行PrEP中的單變項分析，發現有意願進行 PrEP 的人年齡較輕 [28.9 (±6.9) vs. 30.4 (±6.9)，

p<0.001]，主要是 MSM，利用網路或 app 約炮 (66% vs. 56.7%, p=0.0049)，過去三個月有性伴侶數較多者，過去一年內比較少發生無套肛交者 (30.7% vs. 43.8%, p<0.001)，過去一年內曾經使用娛樂性藥物助性 (9.6% vs. 3.2%, p<0.0001)，有常規篩檢 HIV 者 (64.9% vs. 51.6%, p<0.001)，知道有 HIV PEP 者 (70.1% vs. 53.4%, p<0.0001)，曾經使用過 HIV PEP 者 (4.4% vs. 1.2%, p=0.0039)，較不知道有 HIV PrEP 者。多變項分析的結果則列在 table 4 中，願意使用 PrEP 的因子為曾經使用網路或 app 約炮者 (AOR 1.028, 95% CI: 1.008-1.049), 過去一年曾使用娛樂性用藥助性者 (AOR 2.626, 95% CI: 1.442-4.782)，知道有 HIV PEP 者 (AOR 2.629, 95% CI: 1.840-3.758)，以及曾經使用 HIV PEP (AOR 2.695, 95% CI: 1.074-6.763) 。

針對不願意進行 PrEP 的原因進行分析，相較於 2016 年同期的問卷調查進行比較，圖二顯示 2017 年有意願進行 PrEP 的比例下降，其可能影響的因素列在 Table 5，主要和過去 2016 年所做的調查差別在於個人沒有需求(15.1%)，覺得貴(23.6%)以及沒有辦法預期何時發生性行為(4.9%)的比例增加，然而，其他較為負面可能影響 PrEP 的因素比例反而下降。Table 6 則針對 2017 年的問卷調查無意願進行 PrEP 再分成是否曾聽過或是清楚 PrEP 兩組進行比較，聽過 PrEP 的人不願意進行 PrEP 較多的可能在於覺得藥物取得麻煩(10.2%)，沒有辦法預期何時發生性行為(9.5%)，沒有想過這問題(10.6%)以及覺得貴(27.4%)。

（四）討論

從目前初步的結果可以看出，PrEP 在進行時大部分的人會選擇 On demand 的方式，而這部分的人有將近 90%左右使用 PrEP 前三個月內的性伴侶人數在 1~5 人，與 2017 年 7 月 International AIDS Conference 法國 IPERGAY 的進一步分析符合, On demand 的使用方式比較適合性行為相對比較不頻繁的族群；此外，在進行中，雖然追蹤滿 12 個月的人數目前較少，然而沒有任何一位受試者出現 HIV 陽轉的情形，顯示 PrEP 如同目前世界上主要的實行結果一樣，是預防 HIV 感染的有效做法之一。

目前反對 PrEP 的聲音中，有一部分阻力來自於認為使用 PrEP 後會減少保險套使用並且增加性病感染的機會，相較於英國 PROUD study 以及法國 IPERGAY study 中興並發生比例大約 25~35%，我們所看到新發生的淋病， 梅毒或是披衣菌尿道炎的比例僅有 5.4%，明顯比國外來得低, 一方面或許台灣的性病盛行率較國外低, 一方面也可能來自於多重性伴侶的情形比國外要少。因此，在台灣似乎是更適合推行 PrEP 的地方。而且，在我們的研究中並發現，吃 PrEP 的過程中，副作用比例極低。

再進一步從匿篩的問卷分析，可以看到覺得貴很可能仍然是無意願使用 PrEP 的因素，並且清楚了解或聽過 PrEP 的人當中，更會覺得價格是令人卻步的因素之一，因此，實際在進行時，大多數人會選擇 On demand 的方式，或許會較為經濟，也比較能夠負擔得起; 但若是以月收入的高低比較，卻看不出統計學上有差異的狀況。

在有意願進行 PrEP 的分析當中，我們發現意使用 PrEP 的因子為曾經使用網路或 app 約炮者 (AOR 1.028, 95% CI: 1.008-1.049)，過去一年曾使用娛樂性用藥助性者 (AOR 2.626, 95% CI: 1.442-4.782), 知道有 HIV PEP 者 (AOR 2.629, 95% CI: 1.840-3.758)，以及曾經使用 HIV PEP (AOR 2.695, 95% CI: 1.074-6.763)，顯示在過去推行 PEP 的政策可作為進一步結合 PrEP 的有效防治措施，此外，也表示網路約炮或是藥物助性者漸漸地也都認知到自己有潛在 HIV 感染的可能，因此也較有意願要進行 PrEP。

本研究目前仍然存在一些限制，主要是樣本數的不足以及完成較長期追蹤的人數太少，進而影響適當的分析，也可能造成對於 PrEP 中後續發生性病的解讀產生偏差，因此，本研究將持續進行收案，已納入更多個案進行分析。

（五）結論

就目前的結果而言，PrEP 在預防 HIV 感染的成效如預期般沒有陽轉個案，且副作用少，後續發生性病比例也低，應持續進行納入更多有可能感染風險的人，將能看出在公共衛生上防疫的成效。

（六）重要研究成果及政策具體建議

本年度計畫最重要的研究成果在於進行了完整的 PrEP 追蹤並且給予 Daily 以及 On demand 的選擇, 並初步顯示其有效預防 HIV 感染的成果。此初步成果將可作為防疫之參考, 應持續於全國推行 PrEP, 視為減害計畫 2.0 版本, 並且持續宣導 PrEP 之觀念; 此外, 由於分析中顯示價格為影響 PrEP 意願的原因之一, 應努力尋求或制定相關防疫政策, 減少 PrEP 之個人花費, 將可更快速增加願意接受 PrEP 之人數。

（七）參考文獻

1. Hung CC, Chang HJ, Chen MY, et al: The current state of human immunodeficiency virus infection and antiretroviral care in Taiwan. AIDS 2000;14:1669-71.
2. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. Jan 21 2005;54(RR-2):1-20.
3. Böttiger D, Johansson N-G, Samuelsson B, et al: Prevention of simian immunodeficiency virus, SIV_{sm} or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. AIDS 1997;11:157-62.
4. Martin LN, Murphey-Corb M, Soike KF, et al: Effects of initiation of 3'-azido, 3'-deoxythymidine (zidovudine) treatment at different times after infection of rhesus monkeys with simian immunodeficiency virus. J infect Dis 1993;168:825-35.
5. Tsai C-C, Follis KE, Sabo A, et al: Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. Science 1995;270:1197-9.

6. LaFon SW, Mooney BD, McMullen JP, et al: A double-blind, placebo-controlled study of the safety and efficacy of retrovir® (zidovudine, ZDV) as a chemoprophylactic agent in health care workers sxposed to HIV [abstract 489]. In: Program and abstracts of the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy. Atlanta, GA: American Society For Microbiology 1990;167.
7. Connor EM, Sperling RS, Gelber R, et al: Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:173-80.
8. Garner JS: Guideline for isolation precaution in hospitals. Infect Control Hosp Epidemiol 1996;17:54-73.
9. J. D. Post-exposure prophylaxis in raped women. IV International Conference on HIV infection in women and children. Rio de Janeiro2002.
10. Katzenstein TL, Dickmeiss E, Aladdin H, et al. Failure to develop HIV infection after receipt of HIV-contaminated blood and postexposure prophylaxis. Annals of internal medicine. Jul 4 2000;133(1):31-34.
11. Bloch M, Carr A, Vasak E, Cunningham P, Smith D. The use of human immunodeficiency virus postexposure prophylaxis after successful artificial insemination. American journal of obstetrics and gynecology. Sep 1999;181(3):760-761.
12. Centers for Diseases Control and Prevention, U.S. Updated guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV-United States, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65 (17): 458
13. Durand-Zaleski I, Mutuon P, Charreau I et al. Costs and benefits of On-Demand HIV Pre-Exposure Prophylaxis in Men Who Have Sex with Men Analysis of the ANRS IPERGAY study with a one-year follow-up. AIDS. 2017; [Epub ahead]
14. Molina JM, Capitant C, Spire B, Pialoux G et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015; 373: 2237-46

(八) 圖、表。

Table 1. Basic characteristics among cases using on demand or daily PrEP

	On demand	daily
	N=33 (89.2%)	N=4 (10.8%)
Gender, n (%)		
Male	33 (100.0)	3 (75.0)
Female	0 (0.0)	1 (25.0)
Age(mean±SD), yr	31.9±3.8	33.8±6.3
Risk, n (%)		
MSM/Bi-sexual	33 (100.0)	3 (75.0)
Heterosexual	0 (0.0)	1 (25.0)
Others	0 (0.0)	0 (0.0)
Highest level of education, n (%)		
More than college	11 (33.3)	1 (25.0)
College or less	22 (66.7)	3 (75.0)
Current employment status, n (%)		
Full-time	20 (60.6)	2 (50.0)
Others	13 (39.4)	2 (50.0)
Current monthly income status, n (%), NTDs		
< 50,000	21 (63.6)	1 (25.0)
≥50,000	12 (36.40	3 (75.0)
Regular screening for HIV infection, n (%)	24 (72.7)	4 (100.0)

Table 2 Baseline and follow-up data between on demand or daily PrEP

	Baseline		3 mo		6 mo		9 mo		12 mo	
	On demand	daily	On demand	daily	On demand	daily	event-driven	daily	event-driven	daily
	N=33 (89.2%)	N=4 (10.8%)	N=6 (75.0)	N=2 (25.0)	N=5 (83.3)	N=1 (16.7)	N=3 (75.0)	N=1 (25.0)	N=1 (100.0)	N= 0 (0.0)
目前已經開始使用 PrEP	21/33 (63.6)	4/4 (100.0)	-	-	-	-				
Lab results										
Anti-HIV, n/N (%)	0/31 (0.0)	0/4 (0.0)	0/6 (0.0)	0/1 (0.0)	0/5 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
RPR≧4, n/N (%)	3/31 (9.7)	1/4 (25.0)	-	-	-	-	-	-	-	-
RPR≧4X 上升, n/N (%)	-	-	1/6 (16.7)	0/1 (0.0)	0/5 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
HBsAg, n/N (%)	1/29 (3.4)	1/3 (33.3)	-	-	-	-	-	-	0/1 (0.0)	-
Anti-HBs, n/N (%)	23/29 (79.3)	2/3 (66.6)	-	-	-	-	-	-	1/1 (100.0)	-
Anti-HAV, n/N (%)	7/29 (24.1)	1/3 (33.3)	-	-	-	-	-	-	0/1 (0.0)	-
Anti-HCV, n/N (%)	1/29 (3.4)	0/3 (0.0)	-	-	-	-	-	-	0/1 (0.0)	-
HPV-DNA on any site, n/N (%)	3/29 (10.3)	0/3 (0.0)	-	-	0/3 (0.0)	0/1 (0.0)	-	-	0/1 (0.0)	-
CT-PCR, n/N (%)	0/27 (0.0)	1/3 (33.3)	0/4 (0.0)	0/1 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
NG-PCR, n/N (%)	0/27 (0.0)	0/3 (0.0)	0/4 (0.0)	0/1 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	1/1 (100.0)	0/1 (0.0)	-
Abnormal eGFR (<90 ml/min/1.73 m^2), n/N (%)	9/25 (36.0)	1/2 (50.0)	-	-	1/4 (25.0)	0/1 (0.0)	-	-	0/1 (0.0)	-
Risk behaviors										
性交易	0/26 (0.0)	1/4 (25.0)	1/6 (16.7)	1/2 (50.0)	2/4 (50.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
透過網站或交友軟體認識朋友，並與其發生性行為	16/26 (61.5)	1/4 (25.0)	3/6 (50.0)	1/2 (50.0)	3/4 (75.0)	1/1 (100.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
在三溫暖、PUB、健身房等認識，並與其發生性行為	3/26 (11.5)	2/4 (50.0)	0/6 (0.0)	0/2 (0.0)	1/4 (25.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
一夜情	9/26 (34.6)	0/4 (0.0)	2/6 (33.3)	0/2 (0.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
過去三個月內性伴侶數										-
0	0/26 (0.0)	0/4 (0.0)	1/6 (16.7)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
1~5	23/26 (88.5)	2/4 (50.0)	2/6 (33.3)	0/2 (0.0)	1/4 (25.0)	1/1 (100.0)	2/2 (100.00	0/1 (0.0)	1/1 (100.0)	-
6~10	3/26 (11.5)	1/4 (25.0)	3/6 (50.0)	1/2 (50.0)	3/4 (75.0)	0/1 (0.0)	0/2 (0.0)	1/1 (100.0)	0/1 (0.0)	-
>10	0/26 (0.0)	1/4 (25.0)	0/6 (0.0)	1/2 (50.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
最近一年內有性伴侶是 HIV 感染者或性病感染者	4/26 (15.4)	0/4 (0.0)	2/6 (33.3)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
最近三個月肛交時使用保險套的比例										-
100%	12/26 (46.2)	2/4 (50.0)	2/6 (33.3)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	1/1 (100.0)	-
75%	5/26 (19.2)	1/4 (25.0)	1/6 (16.7)	1/2 (50.0)	2/4 (50.0)	1/1 (100.0)	0/2 (0.0)	1/1 (100.0)	0/1 (0.0)	-
50%	2/26 (7.7)	0/4 (0.0)	2/6 (33.3)	0/2 (0.0)	1/4 (25.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
25%	0/26 (0.0)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
0%	3/26 (11.5)	0/4 (0.0)	1/6 (16.7)	0/2 (0.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
無肛交行為	4/26 (15.4)	1/4 (25.0)	0/6 (0.0)	1/2 (50.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
最近三個月口交時使用保險套的比例										-
100%	1/26 (3.8)	1/4 (25.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
75%	2/26 (7.7)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
50%	3/26 (11.5)	1/4 (25.0)	1/6 (16.7)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
25%	1/26 (3.8)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
0%	16/26 (61.5)	2/4 (50.0)	5/6 (83.3)	2/2 (100.0)	4/4 (100.0)	1/1 (100.0)	2/2 (100.00	1/1 (100.0)	1/1 (100.0)	-
無口交行為	3/26 (11.5)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
最近三個月陰道交時使用保險套的比例										-
100%	0/26 (0.0)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
75%	0/26 (0.0)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
50%	0/26 (0.0)	0/4 (0.0)	0/6 (0.0)	1/2 (50.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
25%	0/26 (0.0)	1/4 (25.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
0%	0/26 (0.0)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
無陰道交行為	26/26 (100.0)	3/4 (75.0)	6/6 (100.0)	1/2 (50.0)	4/4 (100.0)	1/1 (100.0)	2/2 (100.00	1/1 (100.0)	1/1 (100.0)	-
最近一年內曾使用過成癮藥物	11/26 (42.3)	0/4 (0.0)	4/6 (66.7)	0/2 (0.0)	2/4 (50.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
使用 2 種以上	2/26 (7.7)	0/4 (0.0)	0/6 (0.0)	0/2 (0.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
現在仍在使用	6/26 (23.1)	0/4 (0.0)	4/6 (66.7)	0/2 (0.0)	2/4 (50.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
STD after medicine within 3mo, n/N (%)	2/26 (7.7)	0/4 (0.0)	1/6 (16.7)	0/2(0.0)	1/5 (20.0)	0/1 (0.0)	0/2 (0.0)	1/1 (100.0)	0/1 (0.0)	-
副作用 (多重選項)										-
Nil			3/6 (50.0)	0/2 (0.0)	3/4 (75.0)	1/1 (100.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)	-
naussea			0/6 (0.0)	1/2 (50.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
headcahe			2/6 (33.3)	1/2 (50.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-
diarrhea			1/6 (16.7)	2/2 (100.0)	0/4 (0.0)	0/1 (0.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)	-
others			1/6 (16.7)	1/2 (50.0)	0/4 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	-

Table 3.Comparison of characteristics between 2016 and 2017 regarding wiling or unwilling to use PrEP

Variables	2016 Apr-Sep				2017 Apr-Sep			
	All individuals	Individuals willing to use PrEP	Individuals unwilling to use PrEP	Statistics P value*	All individuals	Individuals willing to use PrEP	Individuals unwilling to use PrEP	Statistics P value
Patient number, n (%)	1,173 (100.0)	546 (46.5)	627 (53.5)		933 (100.0)	365 (39.1)	568 (60.9)	
Age, mean (± SD), years	29.7 (±7.9)	29.7 (±7.2)	29.8 (±8.6)	0.2643	29.6 (±6.9)	28.9 (±6.9)	30.4 (±6.9)	<.0001
Gender, % (n/N)								
Male	88.2 (1,035/1,173)	93.4 (510/546)	83.7 (525/627)	<.0001	87.4 (815/933)	89.6 (327/365)	85.9 (488/568)	0.2067
Female	11.8 (138/1,173)	6.6 (36/546)	16.3 (102/627)		12.5 (117/933)	10.4 (38/365)	13.9 (79/568)	
Transgender	0.0 (0/1,173)	0.0 (0/546)	0.0 (0/627)		0.1 (1/933)	0.0 (0/365)	0.2 (1/568)	
Highest level of education, % (n/N)								
More than high school	88.3 (1,036/1,173)	89.1 (486/546)	87.7 (550/627)	0.5241	92.4 (862/933)	92.9 (339/365)	92.1 (523/568)	0.7054
High school or less	11.7 (137/1,173)	11.0 (60/546)	12.3 (77/627)		7.6 (71/933)	7.1 (26/365)	7.9 (45/568)	
Current employment status, % (n/N)								
Full-time	61.6 (719/1,167)	66.5 (356/543)	58.2 (363/624)	0.0112	64.6 (603/933)	67.4 (246/365)	62.9 (357/568)	0.1612
Others	38.4 (448/1,167)	34.4 (187/543)	41.8 (261/624)		35.4 (330/933)	32.6 (119/365)	37.2 (211/568)	
Current monthly income status, % (n/N), NTDs								
< 30,000	42.8 (497/1,161)	39.1 (210/537)	46.0 (287/624)	0.0203	40.3 (376/933)	38.1 (139/365)	41.7 (237/568)	0.2747
≥30,000	57.2 (664/1,161)	60.9 (327/537)	54.0 (337/624)		59.7 (557/933)	61.9 (226/365)	58.3 (331/568)	
Sexual partners, % (n/N)								
Non-MSM male	20.9 (245/1,173)	17.6 (96/546)	23.8 (149/627)		17.4 (162/933)	11.8 (43/365)	21.0 (119/568))	
MSM or bisexual male	67.4 (790/1,173)	75.8 (414/546)	60.0 (376/627)	<.0001	70.1 (654/933)	77.8 (284/365)	65.1 (370/568)	<.0001
Female	11.8 (138/1,173)	6.6 (36/546)	16.3 (102/627)		12.5 (117/933)	10.4 (38/365)	13.9 (79/568)	
Activities engaged in, % (n/N)								
Sex work (provider or consumer)	10.1 (119/1,173)	9.5 (52/546)	10.7 (67/627)	0.5611	9.7 (90/933)	8.2 (20/365)	10.6 (60/568)	0.2571
Having sex with someone dating online or from apps	57.5 (674/1,173)	61.5 (336/546)	53.9 (338/627)	0.0092	60.3 (563/933)	66.0 (241/365)	56.7 (322/568)	0.0049
Having sex with someone dating at places, like a pub, bathhouse, or gym	9.5 (112/1,173)	11.5 (63/546)	7.8 (49/627)	0.0362	11.4 (106/933)	13.7 (50/365)	9.9 (56/568)	0.0733
One night stand	27.5 (323/1,173)	32.6 (178/546)	23.1 (145/627)	<.0001	20.7 (193/933)	23.3 (85/365)	19.0 (108/568)	0.1167
Risk behaviors								
Number of sex partners within 3 months								
0	16.9 (198/1,169)	13.8 (75/543)	19.7 (123/626)	0.0295	10.9 (102/933)	10.4 (38/365)	11.3 (64/568)	0.0071
1-5	79.7 (932/1,169)	82.7 (449/543)	77.2 (483/626)		82.9 (773/933)	80.3 (293/365)	84.5 (480/568)	
> 5	3.3 (39/1,169)	3.5 (19/543)	3.2 (20/626)		6.2 (58/933)	9.3 (34/365)	4.2 (24/568)	
Having a committed sexual partner within 3 months	45.2 (530/1,173)	47.6 (260/546)	43.1 (270/627)	0.1263	39.9 (372/933)	37.3 (136/365)	41.6 (236/568)	0.1940
Condomless anal sex in the past 1 year	38.3 (449/1,173)	46.2 (252/546)	31.4 (197/627)	<.0001	38.7 (361/933)	30.7 (112/365)	43.8 (249/568)	<.0001
Partner infected with HIV or other STIs	11.1 (130/1,173)	12.6 (69/546)	9.7 (61/627)	0.1355	4.9 (46/933)**	6.0 (22/365)	4.2 (24/568)	0.219
Ever having STIs in the past 1 year	6.8 (80/1,173)	8.2 (45/546)	5.6 (35/627)	0.0815	8.9 (83/933)	11.0 (40/365)	7.6 (43/568)	0.0784
Ever using recreational drugs before or during sexual activity or attending drug party in the past 1 year	7.5 (88/1,173)	11.7 (64/546)	3.8 (24/627)	<.0001	5.7 (53/933)	9.6 (35/365)	3.2 (18/568)	<.0001
Knowledge on prevention								
Regular screening for HIV infection	52.9 (620/1,173)	60.3 (329/546)	46.4 (291/627)	<.0001	56.8 (530/933)	64.9 (237/365)	51.6 (293/568)	<.0001
Knew of HIV PEP	67.2 (788/1,173)	73.1 (399/546)	62.0 (389/627)	<.0001	59.9 (559/933)	70.1 (256/365)	53.4 (303/568)	<.0001
HIV PEP used	-	-	-	-	2.5 (23/933)	4.4 (16/365)	1.2 (7/568)	0.0039
Knew of HIV PrEP	40.2 (471/1,173)	48.0 (262/546)	33.3 (209/627)	<.0001	45.2 (422/933)	34.8 (127/365)	51.9 (195/568)	<.0001
Diagnosis of STDs by current VCT								
Syphilis	2.9 (34/1,173)	3.7 (20/546)	2.2 (14/627)	0.1644	4.6 (43/933)	5.3 (19/365)	4.2 (24/568)	0.5237
HIV	3.4 (40/1,173)	5.7 (31/546)	1.4 (9/627)	<.0001	3.0 (28/933)	4.1 (15/365)	2.3 (13/568)	0.1194

Table 4. Multivariate analysis for factors associated with the willingness to use pre-exposure prophylaxis against HIV infection in individuals seeking for voluntary counseling and testing for HIV from April to June 2017

Variables	References	OR (95% CI)	*P* value
age		1.028 (1.008-1.049)	0.0055
Having sex with someone dating online or from apps	nil	1.494 (1.124-1.985)	0.0056
Ever using recreational drugs in the past 1 year	nil	2.626 (1.442-4.782)	0.0016
Knew of HIV PEP	unknown	2.629 (1.840-3.758)	<.0001
Ever using HIV PEP	nil	2.695 (1.074-6.763)	0.0347

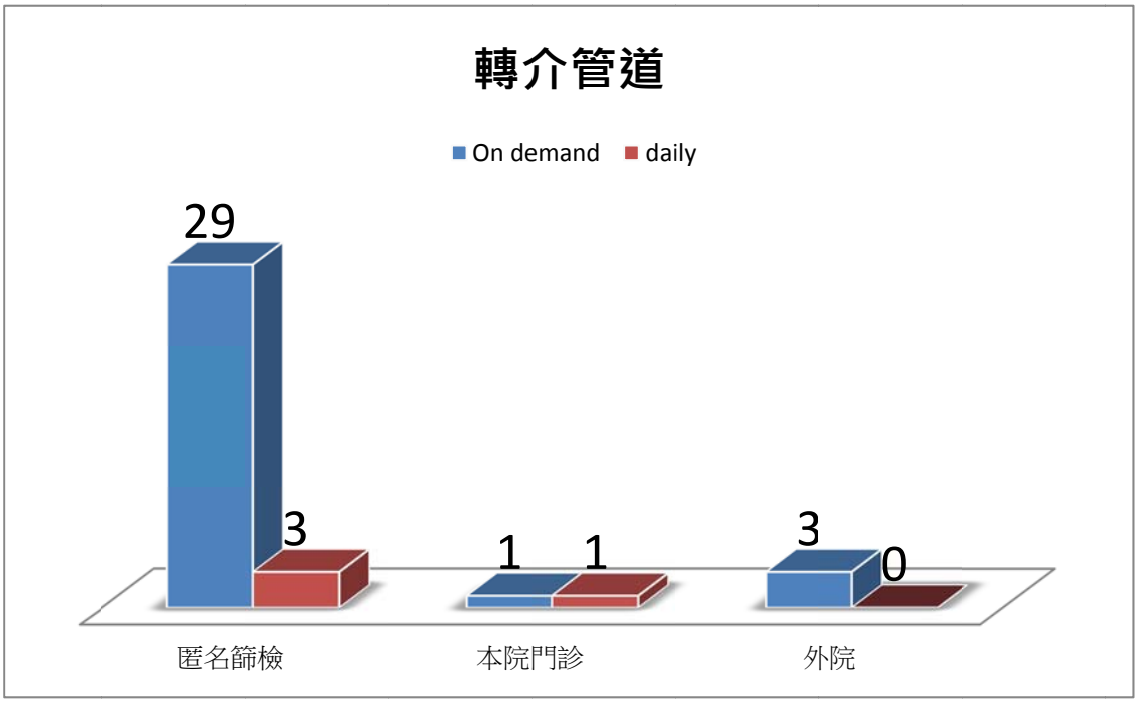
Table 5. Comparisons of the barriers among those who do not want to receive PrEP between 2016 and 2017

	2016 Apr-Sep	2017 Apr-Sep
no Consider Characteristics	N=627	N=568
僅與固定伴侶發生關係, n（%）	268 (42.7)	120 (21.1)
會進行安全性行為	322 (51.4)	183 (32.2)
不常有性行為	57 (9.1)	45 (7.9)
個人沒這個需求	53 (8.5)	86 (15.1)
沒有想過這問題	-	31 (5.5)
覺得貴	116 (18.5)	134 (23.6)
每顆 元(mean)	138	139
覺得麻煩	-	4 (0.7)
藥物取得地點麻煩	54 (8.6)	31 (5.5)
擔心藥物有副作用	73 (11.6)	15 (2.6)
不想吃藥	28 (4.5)	15 (2.6)
討厭吃任何藥物	27 (4.3)	2 (0.4)
怕忘記吃藥	-	1 (0.2)
覺得這樣是在鼓勵不安全性行為	44 (7.0)	9 (1.6)
如果百分之百有效就會吃	2 (0.3)	1 (0.2)
沒有辦法預期何時發生性行為	1 (0.1)	28 (4.9)

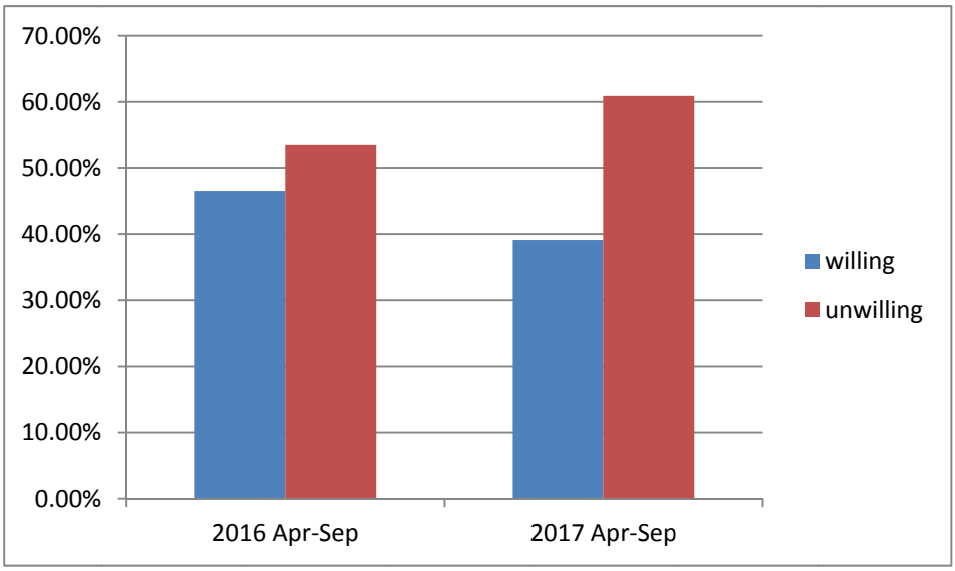
Table 6. Comparison among those who had heard or known PrEP and those who had never known PrEP in 2017

2017 Apr-June	曾聽過或清楚 PrEP	未曾聽過或不清楚 *PrEP*
no Consider Characteristics	N=274	N=294
僅與固定伴侶發生關係	58 (21.2)	62 (21.1)
會進行安全性行為	91 (33.2)	92 (31.3)
個人沒這個需求	39 (14.2)	47 (16.0)
藥物取得麻煩	28 (10.2)	3 (1.0)
覺得貴	75 (27.4)	59 (20.1)
每顆　　元	143	136
沒有辦法預期何時發生性行為	26 (9.5)	2 (0.7)
沒有想過這問題	29 (10.6)	2 (0.7)
不常有性行為	3 (1.1)	42 (14.3)
覺得麻煩	3 (1.1)	1 (0.3)
怕忘記吃藥	1 (0.4)	-
擔心藥物有副作用	2 (0.7)	13 (4.4)
不想吃藥	-	15 (5.1)
討厭吃任何藥物	-	2 (0.7)
覺得這樣是在鼓勵不安全性行為	-	9 (3.1)

圖一 PrEP 個案的轉介來源



圖二 2016 年和 2017 年使用 PrEP 意願的變化



附件六

計畫編號：MOHW106-CDC-C-114-000107

衛生福利部疾病管制署 106 年委託科技研究計畫

愛滋病毒感染者新陳代謝症候群與心血管疾病等慢性病之盛行率、發生率及相關因子調查

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院附設醫院

計畫主持人：黃于珊

研 究 人 員：巫沛瑩、張君俞

執 行 期 間：106 年 1 月 1 日至 106 年 12 月 31 日

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目　　錄

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壹、中文摘要：

針對年紀在四十歲或以上的愛滋病毒感染者心血管疾病風險的調查，我們從 2017 年 3 月 21 日至 2017 年 9 月 7 日為止，在這五個多月當中，一共收集了 2,808 份問卷，受訪人平均年齡為 40 歲，年齡大於或等於 40 歲的感染者有 1,251 人，其中有完整資料可以分析資料的感染者一共有 926 人。在這 926 位受訪者當中, 864 位(93.3%)為男性，他們的身體質量指數 (body-mass index) 的平均值為 23.9 kg/m^2，297 位(32.1%)仍持續抽菸。在抽血的數值中，CD4 的平均值為 622 cells/μL，愛滋病毒量平均值為 1.42 log_{10} copies/mL。在其他共病症的部分，其中 114 (12.3%)人有高血壓、73 (7.9%)有糖尿病。我們進一步使用三種不同的量表來估算這 926 位受訪者心血管疾病發生的風險，在 Framingham equation (FRS)估算中，未來 10 年內發生心血管疾病風險≧10%的感染者有 281 人 (30.3%); 使用 D:A:D (R) 風險評估在未來 5 年內發生心血管疾病風險≧10%的受訪者有 37 人(4.0%)人；而使用(ASCVD) 風險評估未來 10 年內發生動脈粥狀硬化心血管疾病 ≧7.5%的個案有 208 人 (22.5%)人, ≧10%的個案有 129 人(13.9%)。在不同年齡層我們可以看到, 受訪者如果能成功在戒菸心血管疾病的風險≧10%的比例都會明顯下降，FRS 量表中在 40-44 歲中從 5.8%下降至 0%, ≧60 歲中從 75%下降至 60.0%，ASCVD 量表中在 40-44 歲中從 1.8%下降至 0.3%, ≧60 歲中從 71%下降至 66.0%。

在糖尿病的世代研究中，我們從 2003 年 1 月 1 日收案至 2014 年 12 月 31 日，符合收案的未曾接受過抗病毒藥物治療的感染者一共有 2,130 位，總追蹤時間為 10,971 人年，共發現 36 位新發生糖尿病之個案，糖尿病的發生率為 3.28/1000 人年。新發生的糖尿病個案與年紀較長 (aHR: 1.079, 95% CI:1.044-1.116,P<0.001)、高血壓 (aHR: 4.903, 95% CI:1.965-12.235,P<0.001)有關，抗病毒藥物累積暴露時間越長糖尿病的發生率越高，<12 個月為 0/1000 人年、12-36 個月為 2.8/1000 人年、36-72 個月為 4.7/1000 人年、≧72 個月為 3.5/1000 人年；在 NRTI 類藥物 zidovudine/lamivudine，<12 個月為 1.8/1000 人年、12-24 個月為 1.7/1000 人年、24-36 個月為 3.1/1000 人年、≧36 個月為 3.8/1000 人年。

愛滋病毒感染者之骨質疏鬆疾病風險評估研究中，我們採用 WHO FRAX equation 預估未來 10 年內發生骨折的風險。自 2016 年 5 月 4 日至 2017 年 5 月 23 日共收集了 2,404 份問卷，受訪者平均年齡為 40 歲，身體質量指數的平均值為 22.9 kg/m^2，當中有 2,325 (96.7%)位受訪者有服用抗病毒藥物。FRAX 問卷分析結果顯示，針對 10 年內發生主要

骨鬆性骨折的風險，98.7%的受訪者屬低度骨折風險 (≦10%)、1.2%受訪者屬中度骨折風險 (10-20%)、0.08%受訪者屬高度骨折風險(≧20%)。 10 年內發生髖骨骨折的風險，95.8%受訪者屬低度骨折風險、2%受訪者屬中度骨折風險、2.2%受訪者屬高度骨折風險。研究中我們安排年齡大於或等於 45 歲的感染者進行骨密度檢查(Hologic)，其中有完整資料可分析者為 336 人，其股骨頸和髖骨骨密度檢查的平均值為 0.82/0.89 g/cm^2，腰椎骨密度檢查的平均值 1.06 g/cm^2; 股骨頸和髖骨骨密度低下(48.2%)或者已經到骨質疏鬆(14%)的比例高達 62%; 腰椎骨密度低下(38.5%)或者已經到骨質疏鬆(5.5%)的比例高達 44%。這些受試者抽血檢驗 25-OH 維他命 D 的平均值 23.7 ng/ml，有 258 位(76.8%) 25-OH 維他命 D 小於 30 ng/ml。在骨密度降低與骨質疏鬆的相關因子多變項分析中，年齡每增加一歲則骨密度降低風險增加 1.155 倍(95%信賴區間 0.993-1.342; P=0.03)。

關鍵詞：共病症、抗愛滋病毒藥物、糖尿病、心肌梗塞、心血管疾病、戒菸、骨折、骨質疏鬆

貳、英文摘要：

A cross-sectional questionnaire interview was performed to collect information on the demographic and clinical characteristics at the HIV clinics of the National Taiwan University Hospital between March and September, 2017. In the 5-month study period, 2,808 patients were enrolled and 1251 were aged ≧40 years, of whom 926 patients had complete data for the assessment of their CVD risk. The participants, who were predominately male with a mean age of 49.5 years, 32.1% had current smoking, 12.3% had hypertension and 15.1% used antihypertensive medications. However, if those aged 40 years or more who were current smokers had stopped smoking, FRS and ASCVD CVD risk ≧ 10% was reduced from 75.0% and 71.0% to 60.0% and 66.0%, respectively, in those aged≧60 years.

Between 2004 and 2014, 2130 ART-naïve HIV-positive patients without DM initiated cART at the National Taiwan University Hospital. All patients were followed until the date when DM was diagnosed, 31 December, 2015, loss to follow-up, or death, whichever occurred first. Incident DM was defined as fasting glucose≧126 mg/dl or HbA1C≧6.5%. Over a total observation of 10,866 person-years of follow up (PYFU), DM was diagnosed in 36 patients, with an overall incidence rate of 3.3 per 1,000 PYFU. While the rate increased with cumulative exposure to cART, from 0 per 1000 PYFU in patients with cumulative exposure to cART of <12 months to 3.5 per 1000 PYFU in those with cumulative exposure of ≧72 months, the overall rate decreased from 3.7 per 1,000 PYFU in 2004-2008 to 1.6 per 1,000 PYFU (p=0.04). The occurrence of DM was associated with an older age (adjusted hazard ratio [aHR], 1.079; 95% CI, 1.044-1.116), hypertension (aHR: 4.903, 95% CI:1.965-12.235, P<0.001), exposure to darunavir (aHR: 3.157, 95% CI:1.130-8.815,P=0.03), duration of exposure to antiretroviral therapy (<12 months, 0/1000 person-years of follow-up [PYFU]; 12-36 months, 2.8/1000 PYFU, 36-72 months, 4.7/1000 PYFU and ≧72 months, 3.5/1000 PYFU.

Between 2016 and 2017, 2404 HIV-positive patients were enrolled and evaluated by WHO FRAX equation to assess the fracture probability. The average age of the patients was 40 years old, and their average body mass index was 22.9 kg/m^2**.** 2325 (96.7%) patients had received ART. Using FRAX equation, the percentage of patients with low (≤10%), moderate (10-20%) and high (≥20%) 10 year probability of a major osteoporotic fracture was 98.7%,

1.2%, and 0.08%, respectively. The percentage of patients with low, moderate, and high 10 year probability of a hip fracture was 95.8%, 2%, and 2.2%, respectively. 336 patients underwent bone mineral density (BMD) examination. The average BMD of the femoral neck/hip was 0.82/0.89 g/cm^2, and the average BMD of the lumbar spine was 1.06 g/cm^2. Their average serum 25-OH Vitamin D level was 23.7 ng/ml. 258 of 336 (76.8%) patients had a 25-OH Vitamin D level <30 ng/ml. In multivariate analysis, factors associated with reduced BMD were older age and lower body weight.

Key words: diabetes mellitus, antiretroviral therapy, Framingham Heart Study (FRS) risk scores, D:A:D risk equation, ASCVD, cardiovascular disease, smoking cessation, fracture, osteoporosis

參、本文：

（一）前言

愛滋病毒感染者因為高效能抗反轉錄療法 (highly active antiretroviral therapy; HAART) 的廣泛使用而得以改善存活。根據統計，美國愛滋病毒感染者 50 歲以上所占比例，已經從 2001 年的 17%上升到 2008 年的 31%。並且估計到了 2015 年，甚至會超過一半以上的比例 [11]。根據台大醫院的研究調查顯示，年齡大於 50 歲的感染者相較於 40-49 歲的感染者有較多的共病症，包括糖尿病、高血壓、心血管疾病、高血脂 [1]。在其他的國家研究人員開始觀察到愛滋病毒感染者因年齡的增加與老化，相繼發生的代謝相關併發症包括葡萄糖耐受不良、糖尿病與脂質代謝異常，這些往往都是心血管疾病的危險因子之一 [2-4]。

高效能抗反轉錄療法一方面雖然減少了愛滋病毒感染者的併發愛滋病，但從另一方面看來，許多愛滋病毒感染相關、而非後天免疫不全症候群的情形(HIV-Associated Non-AIDS conditions, HANA)卻有越來越多的趨勢 [5]。這些情況舉凡有：代謝疾病、糖尿病 [12]、心血管疾病、肺部疾病、感染或非感染相關之癌症、愛滋病毒感染相關的神經認知疾病、骨質缺乏/骨質疏鬆 [13-15]、肝硬化，以及腎臟病等等。目前而言，在一些研究裡也發現四分之一接受治療的病患有代謝症候群的情形 [16,17]，感染者有骨質疏鬆的盛行率是非感染者的三倍，尤其是在有服用抗愛滋病毒藥物者 [18]。我們已知，長期愛滋病毒感染會表現出許多類似老化的特徵，例如：有許多共病症(包含糖尿病、高血壓、心臟血管疾病、高血脂、腎臟疾病、骨質疏鬆等) [6-10]、多重藥物的使用、身體或認知方面的衰退、功能性下降、身體成分的改變，以及較容易受到壓力影響等等。長期下來，這些的慢性病會逐漸成為照護者、公共衛生的負擔，也是我們應該要開始持續關注的議題，所以我們必須更深入且持續研究有關老化、愛滋病毒感染、其他共病症，以及其他共存治療之間的關係。

本研究的目的是將針對到指定醫院接受愛滋病毒照護的病患，進行追蹤，了解病患發生新陳代謝、骨折、骨密度降低、心血管疾病、糖尿病等的風險。

(二）材料與方法

1. 研究設計: 世代追蹤型研究

2. 研究對象:

(1)持續在本院醫院追蹤的個案中，我們以問卷調查分別調查骨折及心血管疾病的分險，問卷分別為 (WHO FRAX equation) 10 年內發生骨折的風險，在心血管疾病的風險中我們分別以三種不同的評估量表，分別為以下三個：1.Framingham equation (FRS) 估算 10 年內發生心血管疾病的風險、2.D:A:D (R)風險評估來估算五年內發生心血管疾病的風險、3. Atherosclerotic Cardiovascular Disease risk score (ASCVD) 動脈粥狀硬化心血管疾病風險評估。再針對年紀大於或等於 45 歲的病患進行骨質密度檢查，及血清維他命 D 定量(族群一)，以及 Framingham equation 風險評估後≧10% 以及(ASCVD) ≧7.5% 的個案，建議做心電圖檢查。

(2) 2003 年 1 月 1 日至 2014 年 12 月 31 日，新診斷之個案且持續留在本院追蹤大於 6 個月之個案 (族群二)

(3)納入條件：大於 18 歲以上於感染科門診追蹤之愛滋病毒感染患者

(4)排除條件：進入研究前 12 個月曾有使用過類固醇藥物、伺機性感染、或腫瘤病史 (族群一)、進入研究前已經診斷糖尿病、追蹤時間小於 6 個月 (包含死亡及失聯) 族群二。

3. 資料收集

(1) 資料收集時間：族群一：2015 年 1 月 1 日至 2017 年 12 月 31 日。
族群二：2003 年 1 月 1 日至 2014 年 12 月 31 日，之後再追蹤 1 年。

(2) 基本資料收集 (性別、年紀、危險因子、身高、體重、身體質量指數(BMI)、抽菸、喝酒狀況)詢問並紀錄病患家族病史(糖尿病、高血壓)、抗愛滋病毒藥物、接受其他藥物治療(包括降血壓藥物、降血脂藥物等)或使用其他藥品或物質、過去共病史(包含梅毒、B 型肝炎、C 型肝炎)、糖尿病相關慢性併發症(族群一、二)

(3) 血清中維他命 D 的含量檢測、血脂肪(TG、T-CHO、HDL、LDL)、愛滋病毒量、CD4 淋巴球計數、RPR titer、骨質密度檢查(族群一)，心電圖檢查結果。紀錄個案每年的之抽血數值變化包含飯前血糖(AC sugar)、糖化血色素(HbA1c)、基礎點的愛滋病毒量、CD4 淋巴球計數(族群二)。

(4) 收集每位個案服用抗病毒藥物的種類、服用藥物的累積總時間(族群一、二)

(5) 分析的資料的方法，單變項統計，變項是連續變數使用 t-test，變項非連續變數則使用 x^2 tests，多變項統計的方法則是使用羅吉斯回歸檢定方法，$P<0.05$ 才會考慮統計上是具有顯著意義，我們所有的統計都是使用 SAS (Version 9.3)。

(6) 計算發生率的方面，我們是以人年(person-year)來計算並呈現追蹤的資料，比較有無發生糖尿病與其他因子之間的關係，我們會使用存活率分析方法(Cox proportional hazards model) 分析哪些因子與糖尿病發生率有相關。

（三）結果

1、心血管疾病風險研究

在心血管疾病風險的研究中，我們從 2017 年 3 月 1 日至 2017 年 9 月 7 日，五個月當中，一共有 2,808 受訪者參加問卷調查，他們的平均年齡為 40 歲，其中有 2,698 位(96.1%)為生理男性，身體質量指數的平均值為 23.3 kg/m^2，885 位 (32.5%)是目前仍在持續抽菸的個案，2,738 位(97.5%)受訪時持續服用抗病毒藥物。在這其中我們挑選出年齡大於或等於 40 歲的受訪者進一步分析資料。收案流程如圖一。

年齡大於或等於 40 歲的受訪者一共有 1,251 人,其中具有完整資料可以分析資料者為 926 人，基本資料如表一。其中, 864 位(93.3%)為男性，平均年齡為 50 歲，身體質量指數的平均值為 23.9 kg/m^2，297 位 (32.1%)仍持續抽菸。在抽血的數值中，CD4 的平均值為 622 cells/μL，愛滋病的病毒量平均值為 1.42 log_{10} copies/mL，142 位 (19.2%)帶有慢性 B 型肝炎，103 位(12.9%)的 C 型肝炎抗體呈現陽性。在共病症的部分，114 位(12.3%)有高血壓、73 位 (7.9%)有糖尿病，在合併使用其他藥物中，140 位 (15.1%)併服降血壓藥物、98 位(10.6%)併服降血脂藥物。

我們進一步使用三種不同的量表來估算心血管疾病發生的風險，在 Framingham equation (FRS)估算中，未來 10 年內發生心血管疾病風險，其中≧10%的受訪者有 281 人 (30.3%)、D:A:D (R)風險評估在未來 5 年內發生心血管疾病風險，其中≧10%的受訪者有 37 人 (4.0%)、ASCVD 風險評估未來 10 年內發生動脈粥狀硬化心血管疾病，其中≧7.5%的受訪者有 208 人 (22.5%)、≧10%的受訪者有 129 人(13.9%)。

以年齡分層來看三種不同量表的風險≧10%分別各佔之比例，如圖二。從 40-44 歲至≧

60 歲在不同的量表中，風險≧10%的受訪者比例都有隨著年齡而逐漸上升趨勢，FRS 量表中在≧10%的受訪者比例從 5.8% (40-44 歲)上升至 75.0% (≧60 歲)、D:A:D(R) 在≧10%的受訪者比例從 0.3% (40-44 歲)上升 21.0% (≧60 歲)、ASCVD 在≧10%的受訪者比例從 1.8% (40-44 歲)上升 71.0% (≧60 歲)。

同時，我們也估算若受訪者能成功戒菸，以年齡分層來看兩種不同量表的風險≧10%可以各自降多少比例，如圖三。在不同年齡層可以看到受試者在戒菸後心血管疾病的風險≧10%的受訪者比例都會下降，FRS 量表中在 40-44 歲受訪者中從 5.8%下降至 0%，≧60 歲受訪者中從 75%下降至 60.0%，ASCVD 量表中在 40-44 歲受訪者中從 1.8%下降至 0.3%、≧60 歲受訪者中從 71%下降至 66.0%。

2、糖尿病的世代研究

在糖尿病的世代研究中，我們從 2003 年 1 月 1 日收案至 2014 年 12 月 31 日，在本院新通報之感染者有 2,514 人，失聯個案有 582 人，死亡 125 人，其中分別排除追蹤時間少於 6 個月 274 (失聯)及 74 人 (死亡)，新通報個案同時有糖尿病時的感染者為 36 人，最後符合收案追蹤之感染者為 2,130 人，這 2,130 位感染者在同時追蹤至 2015 年 10 月 31 日為止。收案流程如圖四

在 2,130 位個案中，總追蹤時間為 10,971 人年，我們一共發現 36 位新發生糖尿病之個案，整體糖尿病的發生率為 3.28/1000 人年，總追蹤平均時間為 5.1 年。在單變項的分析中發現，有發生糖尿病的個案相較於沒有糖尿病的個案，診斷愛滋病毒感染的年紀較長 (40.3 vs. 32.4 歲)、有較高比例的高血壓 (40.6 vs. 3.3%)、基礎點的 CD4 數值較低 (173 vs.301 cells/μL)、基礎點的飯前血糖數值較高 (96 vs. 88 mg/dl)。他們的基本資料如表二

在多變項的分析中，我們的研究結果顯示新發生的糖尿病個案與年紀較長 (aHR: 1.079, 95% CI:1.044-1.116, P<0.001)、高血壓 (aHR: 4.903, 95% CI:1.965-12.235, P<0.001)、曾經服用過 darunavir 藥物 (aHR: 3.157, 95% CI:1.130-8.815, P=0.03)有關。(表三)

同時，我們將服用抗病毒藥物的累積天數(月)分成四組分別為：<12 個月、12-36 個月、36-72 個月、≧72 個月，分別來看糖尿病的發生率。(圖五) 我們發現抗病毒藥物累積暴露時間越長糖尿病的累積發生率越高，<12 個月為 0/1000 人年、12-36 個月為 2.8/1000 人年、36-72 個月為 4.7/1000 人年、≧72 個月為 3.5/1000 人年。如果我們只單

看藥物 zidovudine/lamivudine，我們也發現此藥物累積暴露時間越長糖尿病的發生率越高，<12 個月為 1.8/1000 人年、12-24 個月為 1.7/1000 人年、24-36 個月為 3.1/1000 人年、≧36 個月為 3.8/1000 人年。(圖五)

3、骨質疏鬆疾病的研究

骨質疏鬆疾病風險評估的研究中，主要是以世界衛生組織 10 年骨折風險評估問卷(WHO FRAX equation)預估未來 10 年內發生骨折的風險，收案自 2016 年 5 月 4 日至 2017 年 5 月 23 日共收集有 2,404 份問卷，受訪者平均年齡為 40 歲，其中男性 2310 位，佔 96.1%，CD4 的平均值為 609 cells/μL，愛滋病毒的病毒量平均值為 1.5 $\log_{10}$ copies/mL，其中有 2110 位(87.8%)的愛滋病毒量小於 50 copies/mL。受訪者身體質量指數的平均值為 22.9 kg/m^2 ，有 321 位(13.9%)為 B 型肝炎表面抗原反應陽性，235 位(10.1%)的 C 型肝炎抗體呈現陽性。159 人(6.6%)每日補充鈣片，776 人(32.3%)每日補充綜合維他命。在家族病史的部分，有 113 位(4.7%)受訪者的父母親曾發生髖骨骨折，662 位(27.5%)受訪者的父母親有糖尿病，1089 位(45.3%)受訪者的父母親有高血壓。藥物及物質使用的部分，目前仍持續吸菸者為 257 人(31.5%)，每日飲用酒精 3 單位或以上為 88 人(3.7%)，服用類固醇個案 49 人(2.1%)，確診有類風濕性關節炎 35 人(1.5%)，有續發性骨質疏鬆症 17 人(0.7%) (表四)。

在 2,404 份收案問卷之中，2,325 位 (96.7%)有服用抗病毒藥物，有共病症為 928 人(38.6%)，其中 106 位(11.4%)有糖尿病，高血壓有 227 人(24.5%)，高血脂有 352 人(37.9%)。在合併使用其他藥物的調查中，89 人(9.6%)併服降血糖藥物、187 人(20.2%)併服降血壓藥物、134 人(14.4%)併服降血脂藥物、106 人(11.4%)接受治療 C 型肝炎感染。FRAX 問卷分析結果，針對 10 年內發生主要骨鬆性骨折的風險，98.7%的受訪者屬低度骨折風險(≦10%)、1.2%受訪者屬中度骨折風險 (10-20%)、0. 08%受訪者屬高度骨折風險(≧20%)。若是 10 年內發生髖骨骨折的風險，95.8%受訪者屬低度骨折風險、2%受訪者屬中度骨折風險、2. 2%受訪者屬高度骨折風險。

進一步將年齡大於或等於 45 歲感染者安排做骨密度檢查(Hologic)，其中有完整資料可以分析為 336 人，男性有 327 位(92.1%)，平均年齡為 54 歲，有服用 tenofovir disoproxil fumarate (TDF)抗病毒藥物者有 327 人(92.1%)，服用 protease inhibitors (PI)者有 163 人(45.9%)，服用同時含 tenofovir disoproxil fumarate (TDF)與 protease inhibitors (PI)之抗病

毒藥物處方者有 152 人(42.8%)，其結果股骨頸/髖骨骨密度檢查的平均值 0.82/0.89 g/cm^2，腰椎骨密度檢查的平均值 1.06 g/cm^2。股骨頸和髖骨骨密度低下(48.2%)或者已經到骨質疏鬆(14%)的比例高達 62%; 腰椎骨密度低下(38.5%)或者已經到骨質疏鬆(5.5%)的比例高達 44%。抽血檢驗 25-OH 維他命 D 的平均值 23.7 ng/ml，有 258 位的個案其 25-OH 維他命 D 小於 30 ng/ml(表五)。

骨密度降低與骨質疏鬆的風險因子多變項分析中，骨密度降低的相關因子為年齡每增加一歲則骨密度降低風險增加 1.155 倍(95%信賴區間 0.993-1.342 ;P 值 0.0311)，而體重每增加一公斤則風險降為 0.870 (95%信賴區間 0.783- 0.966;P 值 0.0091)，骨質疏鬆的風險因子分析亦有相似發現(表六、七)。

（四）討論

在心血管疾病風險的研究中，FRS 量表估算中，在未來 10 年內發生心血管疾病風險≧10%的受訪者有 281 人(30.3%)、D:A:D (R)風險評估在未來 5 年內發生心血管疾病風險≧10%的受訪者有 37 人(4.0%)、(ASCVD) 風險評估未來 10 年內發生動脈粥狀硬化心血管疾病≧7.5%的受訪者有 208 人 (22.5%)、≧10%的個案有 129 人(13.9%)。

以年齡分層來看三種不同量表的風險≧10%分別各佔之比例，從 40-44 歲至≧60 歲在不同的量表中，風險≧10%的比例都有隨著年齡而逐漸上升趨勢。這些的研究結果也與其他研究結果相似，年紀越大者的心血管疾病風險就越大 [19.20]。另外，在巴西的回溯性世代研究結果發現，年紀大於 40 歲的個受訪者與心血管疾病的發生率有相關 ($p<0.05$)[21]，所以年紀是影響心血疾病的重要因素之一。同時我們也發現在共病症中以高血壓(12.3%)佔多數。

若受訪者能夠成功戒菸，以年齡分層來看兩種不同量表，在不同年齡層可以看到受訪者在戒菸後心血管疾病的風險≧10%的比例都會明顯下降。在其他的研究結果也顯示出戒菸後所帶來的好處，也就是未來 10 年內發生心血管的風險會減少 [22.23]。根據一個 D:A:D 的研究結果發現，當個案戒菸後心血管疾病的發生率比(IRR)會下降，從追蹤的第一年 3.32 下降至追蹤第三年的 1.49 [23]。

在糖尿病的世代研究中，我們一共收案 2,130 位個案，共追蹤了 10,971 人年，36 位感染者發生糖尿病，整體糖尿病的發生率為 3.28/1000 人年。我們的研究結果與以下研究

結果相近，分別為瑞士的愛滋病世代研究 (4.4/1000 人年)[24]、泰國的研究 (5.0/1000 人年)[25] 以及 D:A:D 的研究 (4.2/1000 人年)[26]，但相較於其他研究較低, 分別為法國的世代研究 (14.1/1000 人年)[27]，美國的世代研究（11.35/1000 人年)[28] 以及台灣羅一鈞醫師在十年前利用台大醫院的研究（13.1/1000 人年)[12]。我們的研究結果發生率較低的可能原因是我們的研究族群中有較多的男性（96.01%)，年齡也相較其他研究族群較輕(診斷愛滋病的平均年齡為 32.5 歲)。

在服用抗病毒藥物與糖尿病的發生率之相關性研究則是有許多的意見不一致，我們研究結果顯示糖尿病的發生率隨著藥物暴露時間越長有越高的趨勢(0-3.5/1000 人年)。在一些研究結果也顯示核苷酸反轉錄酶抑制劑(NRTI)與糖尿病有高度相關性[12、24、27]，與我們的研究結果相似，我們研究結果顯示暴露於 zidovudine/lamivudine 藥物時間越長，糖尿病的發生率越高(1.8-3.8/1000 人年)。

在愛滋病毒感染者骨密度與骨折的流行病學研究中已發現，不論年紀，感染者骨質流失的盛行率都較於同年齡的非感染者為高，也較早發生[29, 30]。在我們的骨質疏鬆風險評估研究中，根據 WHO FRAX 問卷分析結果，10 年內發生主要骨鬆性骨折的風險，98.7%的受訪者屬低度骨折風險 (≦10%)、1.2%受訪者屬中度骨折風險 (10-20%)、0.08%受訪者屬高度骨折風險(≧20%)。若是 10 年內發生髖骨骨折的風險，95.8%受訪者屬低度骨折風險、2%受訪者屬中度骨折風險、2.2%受訪者屬高度骨折風險，大部分的愛滋病毒感染者屬低度骨折風險。文獻中亦曾以 FRAX equation 評估愛滋病毒感染者的骨折風險，如義大利的研究曾報告 50 位愛滋病毒感染者發生主要骨折的平均風險為 5.2 ± 2.6%[31]，而來自美國的研究收納了 7064 位愛滋病毒感染者，其發生主要骨鬆性骨折的風險為 2.9±1.5%[32]。若以年齡分層來探討未來 10 年內發主要骨鬆性骨折及髖骨骨折的風險機率，研究資料結果發現，年齡越大的患者面臨主要骨鬆性骨折及髖骨骨折的機率也越大，尤其是年紀超過 60 歲的患者 (圖七、圖八)。骨密度降低與骨質疏鬆的相關因子多變項分析中，也發現年齡增加與低體重是顯著的危險因子，此兩項因子皆為傳統認知會造成骨密度降低的因素，在文獻中，某些抗愛滋病毒藥物的使用如 tenofovir[33]、efavirenz、蛋白酶抑制劑[34]也被報告過可能與骨質流失有關，其機轉包括影響腎小管功能或 vitamin D 代謝有關，但在我們的調查中並未看到特定抗病毒藥物對骨密度有統計上顯著影響。

（五）結論

FRS 量表中在≧10%的比例從 5.8% (40-44 歲)上升至 75.0% (≧60 歲)、D:A:D(R) 在≧10%的比例從 0.3% (40-44 歲)上升 21.0% (≧60 歲)、ASCVD 在≧10%的比例從 1.8% (40-44 歲)上升 71.0% (≧60 歲)。個案在戒菸後心血管疾病的風險≧10%的比例都會下降，FRS 量表中在 40-44 歲中從 5.8%下降至 0%，≧60 歲中從 75%下降至 60.0%，ASCVD 量表中在 40-44 歲中從 1.8%下降至 0.3%、≧60 歲中從 71%下降至 66.0%。在糖尿病的世代研究中，糖尿病的發生率為 3.28/1000 人年，糖尿病個案與年紀較長有關 (aHR: 1.079, 95% CI:1.044-1.116,P<0.001)，抗病毒藥物累積暴露時間越長糖尿病的發生率越高，<12 個月為 0/1000 人年、12-36 個月為 2.8/1000 人年、36-72 個月為 4.7/1000 人年、≧72 個月為 3.5/1000 人年。

骨質疏鬆疾病的風險評估研究，以 WHO FRAX equation 預估未來 10 年內發生骨折的風險，顯示 10 年內發生主要骨鬆性骨折的風險評估中，98.7%的受訪者屬低度骨折風險 (≦10%)、1.2%受訪者屬中度骨折風險 (10-20%)、0.08%受訪者屬高度骨折風險(≧20%)。若是 10 年內發生髖骨骨折的風險，95.8%受訪者屬低度骨折風險、2%受訪者屬中度骨折風險、2.2%受訪者屬高度骨折風險。年齡大於或等於 45 歲的愛滋病毒感染者接受骨密度檢查(Hologic)，其結果股骨頸/髖骨骨密度檢查的平均值為 0.82/0.89 g/cm^2，腰椎骨密度檢查的平均值 1.06 g/cm^2，抽血檢驗 25-OH 維他命 D 的平均值 23.7 ng/ml，有 258 位(76.8%)的個案之 25-OH 維他命 D 小於 30 ng/ml。骨密度降低與骨質疏鬆的相關因子多變項分析中，年齡增加為顯著的危險因子。

（六）對政策之具體建議

根據本研究，愛滋病毒感染者年紀越大則心血管疾病風險越高，尤其在≧60 歲的患者，若以量表來估算心血管疾病發生的風險可高達 70%以上。而在糖尿病的世代觀察研究中，愛滋病毒感染者新發生糖尿病的風險與年長、高血壓、抗愛滋病毒藥物累積暴露時間、特定藥物如核苷酸反轉錄酶抑制劑有關。愛滋病毒感染者的骨密度調查則發現，年過 45 歲的患者有相當比例發生骨密度降低，且患者十年的骨質疏鬆與髖部骨折風險隨著年齡增加，特別是 50 歲以上並接受抗愛滋病毒藥物治療的感染者。體重過輕也是發生骨質疏鬆的風險因子之一。

隨著高效能反轉錄病毒藥物的廣泛使用，愛滋感染者壽命延長，將有更多患者步入中老年。建議針對中高齡的患者，特別是年紀大於 60 歲、長期服藥且合併高血壓的族群，定期進行心血管疾病風險評估如血脂肪、血糖檢驗，鼓勵戒菸，並制定年度監測指標。骨密度檢查的給付條件，則可考慮開放給高齡且長期接受抗愛滋病毒藥物治療或已合併臨床症狀的患者，以盡早評估並開始骨骼保健及骨折預防。同時也建議參與愛滋照護的醫師與個案管理師，皆能接受心血管與新陳代謝，包含骨密度監測與骨質疏鬆處置等主題的老年醫學學程訓練。

（七）參考文獻

1. Wu PY, Chen MY, Hsieh SM, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PloS one.* 2014;9(8):e104945.
2. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jan 2001;32(1):130-139.
3. Yarasheski KE, Tebas P, Sigmund C, et al. Insulin resistance in HIV protease inhibitor-associated diabetes. *Journal of acquired immune deficiency syndromes.* Jul 1 1999;21(3):209-216.
4. Group DADS, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *The New England journal of medicine.* Apr 26 2007;356(17):1723-1735.
5. Erlandson KM, Allshouse AA, Duong S, MaWhinney S, Kohrt WM, Campbell TB. HIV, aging, and advance care planning: are we successfully planning for the future? *Journal of palliative medicine.* Oct 2012;15(10):1124-1129.
6. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Dec 2011;53(11):1130-1139.
7. Vance DE, Mugavero M, Willig J, Raper JL, Saag MS. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *The Journal of the Association of Nurses in AIDS Care : JANAC.* Jan-Feb 2011;22(1):17-25.
8. Oursler KK, Goulet JL, Crystal S, et al. Association of age and comorbidity with physical function in HIV-infected and uninfected patients: results from the Veterans Aging Cohort Study. *AIDS patient care and STDs.* Jan 2011;25(1):13-20.
9. Manrique L, Aziz M, Adeyemi OM. Successful immunologic and virologic outcomes in elderly HIV-infected patients. *Journal of acquired immune deficiency syndromes.* Jul 2010;54(3):332-333.
10. Ibrahim F, Hamzah L, Jones R, et al. Comparison of CKD-EPI and MDRD to estimate baseline renal function in HIV-positive patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* Jun 2012;27(6):2291-2297.
11. Aberg JA. Aging, inflammation, and HIV infection. *Topics in antiviral medicine.* Aug-Sep 2012;20(3):101-105.
12. Lo YC, Chen MY, Sheng WH, et al. Risk factors for incident diabetes mellitus among HIV-infected patients receiving combination antiretroviral therapy in Taiwan: a case-control study. *HIV medicine.* May 2009;10(5):302-309.

13. Jones S, Restrepo D, Kasowitz A, et al. Risk factors for decreased bone density and effects of HIV on bone in the elderly. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Jul 2008;19(7):913-918.
14. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *Aids.* Mar 12 2007;21(5):617-623.
15. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *Aids.* Mar 10 2000;14(4):F63-67.
16. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *Journal of acquired immune deficiency syndromes.* Jul 1 2012;60 Suppl 1:S1-18.
17. Wu PY, Hung CC, Liu WC, et al. Metabolic syndrome among HIV-infected Taiwanese patients in the era of highly active antiretroviral therapy: prevalence and associated factors. *The Journal of antimicrobial chemotherapy.* Apr 2012;67(4):1001-1009.
18. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *Aids.* Nov 14 2006;20(17):2165-2174.
19. Law MG, Friis-Moller N, El-Sadr WM, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV medicine.* May 2006;7(4):218-230.
20. Parra S, Coll B, Aragones G, et al. Nonconcordance between subclinical atherosclerosis and the calculated Framingham risk score in HIV-infected patients: relationships with serum markers of oxidation and inflammation. *HIV medicine.* Apr 2010;11(4):225-231.
21. Diaz CM, Segura ER, Luz PM, et al. Traditional and HIV-specific risk factors for cardiovascular morbidity and mortality among HIV-infected adults in Brazil: a retrospective cohort study. *BMC infectious diseases.* Aug 08 2016;16:376.
22. Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* May 01 2015;60(9):1415-1423.
23. Petoumenos K, Worm S, Reiss P, et al. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*). *HIV medicine.* Aug 2011;12(7):412-421.
24. Ledergerber B, Furrer H, Rickenbach M, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study.

Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jul 1 2007;45(1):111-119

25. Riyaten P, Salvadori N, Traisathit P, et al. New-Onset Diabetes and Antiretroviral reatments in HIV-Infected Adults in Thailand. *Journal of acquired immune deficiency yndromes.* Aug 1 2015;69(4):453-459.
26. Petoumenos K, Worm SW, Fontas E, et al. Predicting the short-term risk of diabetes in HIV-positive patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Journal of the International AIDS Society.* 2012;15(2):17426. 2012;15(2):17426.
27. Capeau J, Bouteloup V, Katlama C, et al. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *Aids.* Jan 28 2012;26(3):303-314.
28. Tripathi A, Liese AD, Jerrell JM, et al. Incidence of diabetes mellitus in a population-based cohort of HIV-infected and non-HIV-infected persons: the impact of clinical and therapeutic factors over time. *Diabetic medicine : a journal of the British Diabetic Association.* Oct 2014;31(10):1185-1193.
29. Bruera D, Luna N, David DO, et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 2003;17:1917-23.
30. Gonciulea A1, Wang R, Althoff KN, et al. An increased rate of fracture occurs a decade earlier in HIV+ compared with HIV- men. AIDS. 2017 Jun 19;31(10):1435-1443.
31. Pepe J, Isidori AM, Falciano M, et al. The combination of FRAX and Ageing Male Symptoms scale better identifies treated HIV males at risk for major fracture. Clin Endocrinol. 2012 Nov;77(5):672-8.
32. Yin MT, Shiau S, Rimland D, et al. Fracture Prediction With Modified-FRAX in Older HIV-Infected and Uninfected Men. Journal of acquired immune deficiency syndromes. 2016 Aug 15;72(5):513-20.
33. Stellbrink HJ, Orkin C, Arribas JR et al. Comparison ofchanges in bone density and turnover with abacavir-lamivu-dine versus tenofovir-emtricitabine in HIV-infected adults:48-week results from the ASSERT study. Clin Infect Dis 2010;51: 963–72.
34. Brown TT, McComsey GA. Association between initiation ofantiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. Antivir Ther 2010; 15: 425–9.

（八）圖表

表一 、心血管疾病風險評估量表之個案基本資料

Characteristic	N=926
Male, n (%)	864 (93.3)
Age, mean (SD), year	49.5 (7.7)
Body mass index, mean (SD), kg/m^2	23.9 (3.5)
Systolic blood pressure, mean (SD), mmHg	127 (17.1)
Diastolic blood pressure, mean (SD), mmHg,	79 (11.8)
Positive anti-HCV, n (%) N=797	103 (12.9)
Positive HBsAg, n (%) N=739	142 (19.2)
Positivity anti-HAV, n (%) N=863	751 (87.0)
Smoking status, n (%)	
Never	422 (45.6)
Past	207 (22.4)
Current	297 (32.1)
Family history of Diabetes mellitus, n (%)	296 (31.9)
Family history of Hypertension, n (%)	526 (56.8)
Family history of CAD, n (%)	153 (16.5)
HIV viral load, median (SD),log 10 copies/ml	1.42 (0.52)
CD4, mean (SD), cells/μl,	622 (289)
TG, mean (SD), mg/dl,	158 (126)
T-cholesterol, mean(SD),	172 (35)
HDL, mean(SD), mg/dl	44 (11)
Comorbidities, n (%)	
CAD	19 (2.1)
Diabetes mellitus	73 (7.9)
Hypertension	114 (12.3)
Concurrent medications, n (%)	
Lipid-lowering	98 (10.6)
Hypoglycemics	71 (7.6)
Anti-hypertensives	140 (15.1)

表二 、糖尿病研究之個案基本資料

variable	DM(+), n=36	DM(-), n=2094	all, N= 2130	p
Sex, male, n (%)	35 (97.22)	2010 (95.99)	2045 (96.01)	0.7077
Age at HIV diagnosis,years	40.28 (10.88)	32.40 (9.34)	32.53 (9.42)	<.0001
HBsAg-Positive, n (%)	7 (20.00)	257 (12.69)	264 (12.82)	0.1997
Anti-HCV Positive, n (%)	1 (2.94)	187 (9.27)	188 (9.16)	0.2048
Hypertension, n (%)	13 (40.63)	62 (3.29)	75 (3.91)	<.0001
CAD, n (%)	2 (6.25)	13 (0.69)	15 (0.78)	0.0004
Baseline CD4 count mean (SD), cells/μl (N=27,1581)	173.2 (207.5)	301.8 (246.4)	299.6 (246.3)	0.0071
Baseline HIV RNA, mean (SD),log 10 copies/ml (N=33,1844)	4.99 (0.81)	4.80 (0.93)	4.80 (0.93)	0.2420
Baseline AC sugar, mean (SD), mg/dl	96.1 (18.5)	88.3 (10.1)	88.49 (10.39)	0.0416
Baseline Hb, mean (SD), g/dL	12.89 (2.72)	13.65 (2.22)	13.64 (2.23)	0.0518
Baseline MCV, mean (SD),fL	86.3 (12.5)	86.5 (8.13)	86.51 (8.23)	0.9222
Duration of follow up, mean (SD),year	5.11 (2.45)	5.10 (3.01)	5.10 (3.00)	0.9847
ART, n (%)	36 (100.00)	1889 (90.21)	1925 (90.21)	0.0483
ART duration, mean (SD), month	54.16 (54.16)	48.99 (34.29)	49.09 (34.13)	0.2254

表三 、糖尿病研究之多變項分析

Variable	aHR	95% CI	P
Age	1.079	1.044 - 1.116	<.0001
Sex	1.562	0.194- 12.599	0.6757
Hypertension	4.903	1.965- 12.235	0.0007
CAD	3.882	0.823- 18.310	0.0866
Baseline PVL	1.290	0.720- 2.309	0.3921
Baseline CD4	0.998	0.995- 1.000	0.0655
ART duration	0.954	0.941- 0.969	<.0001
Tenofovir, TDF	0.173	0.059- 0.509	0.0014
Darunavir, DRV	3.157	1.130- 8.815	0.0282
Cumulative duration of exposure to Abacavir	0.980	0.957- 1.003	0.0896
Cumulative duration of exposure to Atazanavir	0.981	0.957- 1.005	0.1207

表四、骨質疏鬆疾病風險評估之個案基本資料

Variable	N=2404
Male, n (%)	2310 (96.1)
Age, mean (SD), year	40.0 (11.0)
18-29 years, n (%)	410 (17.0)
30-39	898 (37.4)
40-49	680 (28.3)
50-59	290 (12.1)
>60	126 (5.2)
CD4 count, mean (SD), cells/μl	609 (271)
Plasma HIV RNA load, mean (SD), $\log_{10}$ copies/ml	1.5 (0.7)
Plasma HIV RNA load ≦50 copies/ml, n (%)	2110 (87.8)
BH, mean (SD), cm	171.1 (6.4)
BW, mean (SD), Kg	67.3 (11.2)
Body mass index, mean (SD), kg/m^2	22.9 (3.4)
HBsAg-positive, n (%)	321 (13.9)
Anti-HCV-positive, n (%)	235 (10.1)
Route of HIV transmission, n (%)	
MSM/bisexual	2125 (88.4)
Heterosexual	216 (9.0)
IDU	42 (1.7)
Other	21 (0.9)
Daily calcium supplement, n (%)	159 (6.6)
Daily multi-vitamin, n (%)	776 (32.3)
Previous fracture, n (%)	350 (14.6)
Parents with fractured hip, n (%)	113 (4.7)
Mother	83 (73.5)
Father	40(35.4)
Mother and father	11 (9.7)
Family history of diabetes, n (%)	662 (27.5)
Mother	351 (53.0)
Father	392 (59.2)
Mother and father	81 (12.2)
Family history of hypertension, n (%)	1089 (45.3)
Mother	647 (59.4)
Father	698 (64.1)
Mother and father	256 (23.5)
Current smoker, n (%)	757 (31.5)
Use of glucocorticoids, n (%)	49 (2.1)
Rheumatoid arthritis, n (%)	35 (1.5)
Secondary osteoporosis, n (%)	17 (0.7)
Alcohol consumption, 3 or more units/day, n (%)	88 (3.7)

表五、骨密度檢查資料分析

Variable	N=355
Male, n (%)	327 (92.1)
Age, mean (SD), year	54 (8)
On tenofovir disoproxil fumarate (TDF), n (%)	327 (92.1)
On protease inhibitors (PI)	163 (45.9)
BMD of femoral neck/hip , mean (SD), g/cm^2	0.82/0.89 (0.14)
Lumbar spine (L1-L4), mean (SD), g/cm^2	1.06 (0.17)
25-OH Vitamin D, mean (SD), ng/ml	23.7 (9.1)
25-OH Vitamin D <30 ng/ml, n (%)	258/336 (76.8)

表六、骨密度降低相關因子之多變項分析

Variable*	**Adjusted OR**	**95% CI**	**P**
Male gender, n (%)	7.533	1.119-50.717	0.0380
Age, per 1-year increase	1.085	1.007-1.168	0.0311
Body mass index, per 1-kg/m^2 increase	1.143	0.852-1.535	0.3726
Body weight, per 1-kg increase	0.870	0.783- 0.966	0.0091
25-OH Vitamin D, per 1-ng/ml increase	1.007	0.956-1.060	0.7874
Tenofovir disoproxil fumarate (TDF)	6.158	0.933-40.668	0.0591
Protease inhibitors (PI)	5.748	0.320-103.245	0.2353

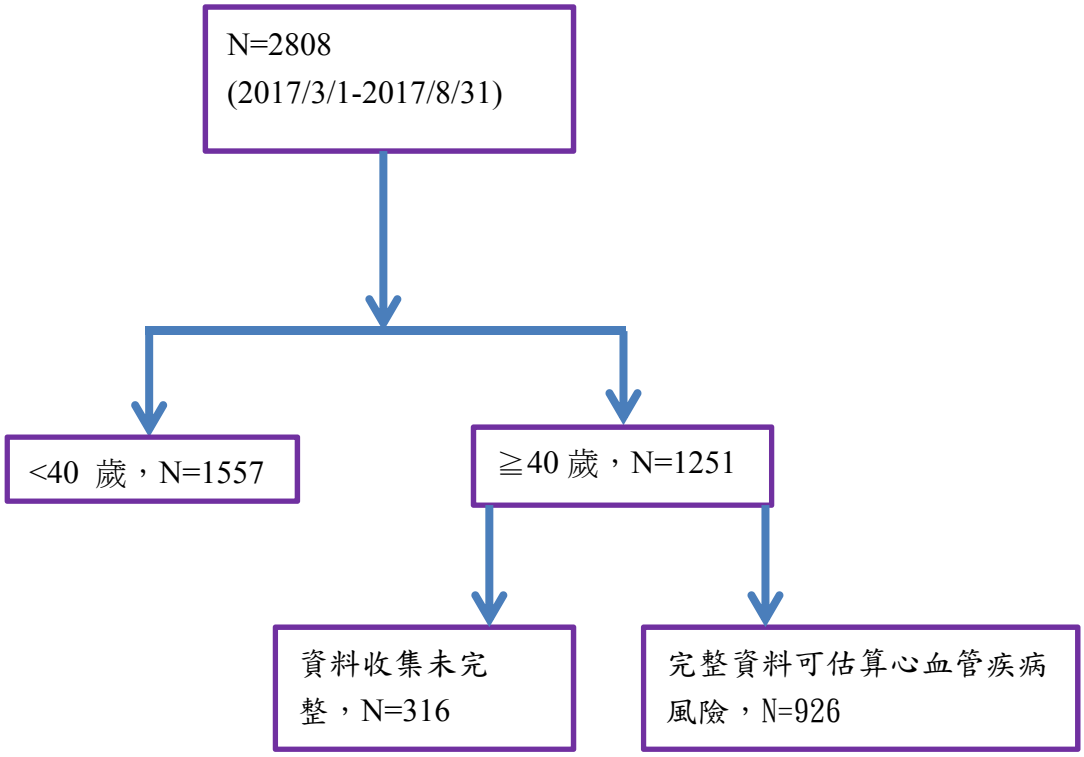
*Variables with P<0.05 and ART were entered into logistic regression analysis

表七、骨質疏鬆風險因子之多變項分析

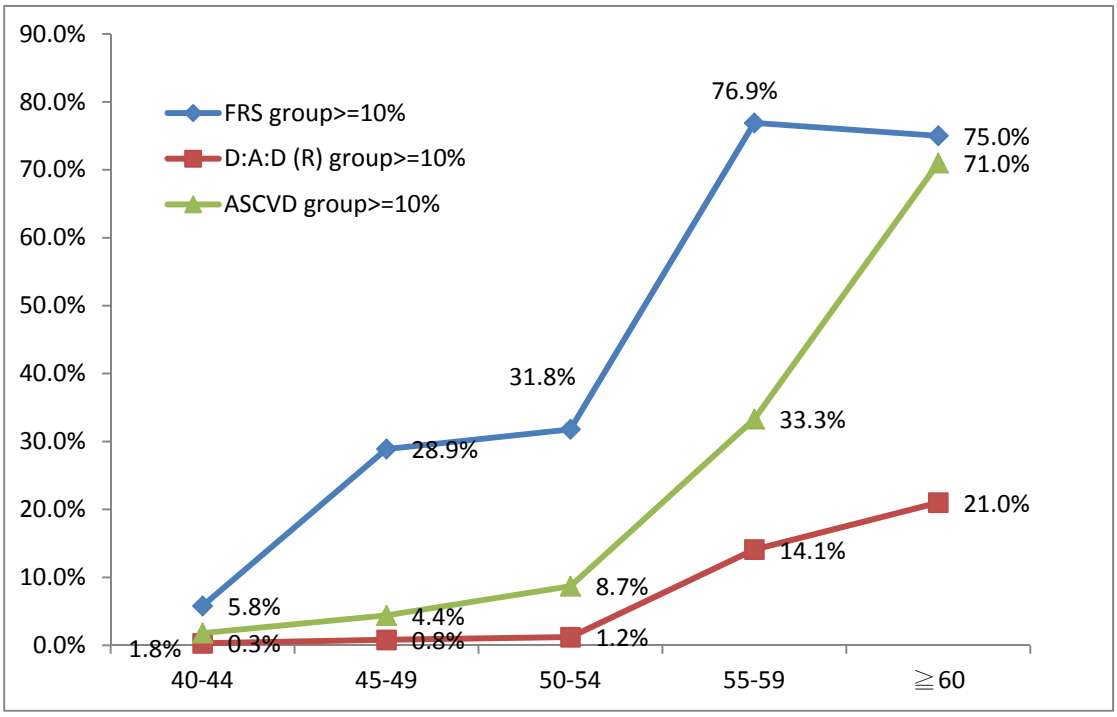
Variable*	Adjusted OR	95% CI	P
Male gender, n (%)	16.218	0.392-671.806	0.1425
Age, per 1-year increase	1.155	0.993-1.342	0.0611
Body mass index, per 1-kg/m^2 increase	1.603	0.683-3.760	0.2779
Body weight, per 1-kg increase	0.645	0.450-0.924	0.0168
25-OH Vitamin D, per 1-ng/ml increase	1.093	0.986-1.211	0.0922
Tenofovir disoproxil fumarate (TDF)	3.789	0.149-96.192	0.4195
Protease inhibitors (PI)	3.263	0.090-117.963	0.5183

*Variables with P<0.05 and ART were entered into logistic regression analysis

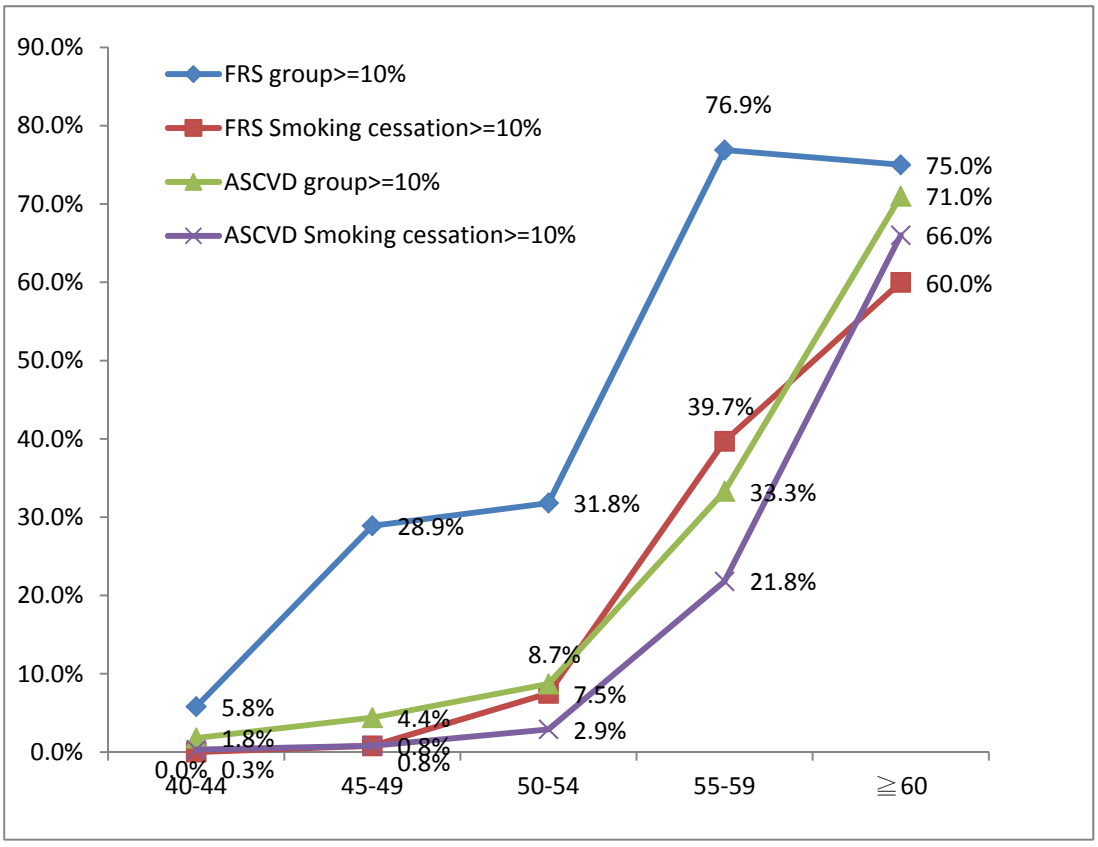
圖一、 收案流程圖 (CVD)



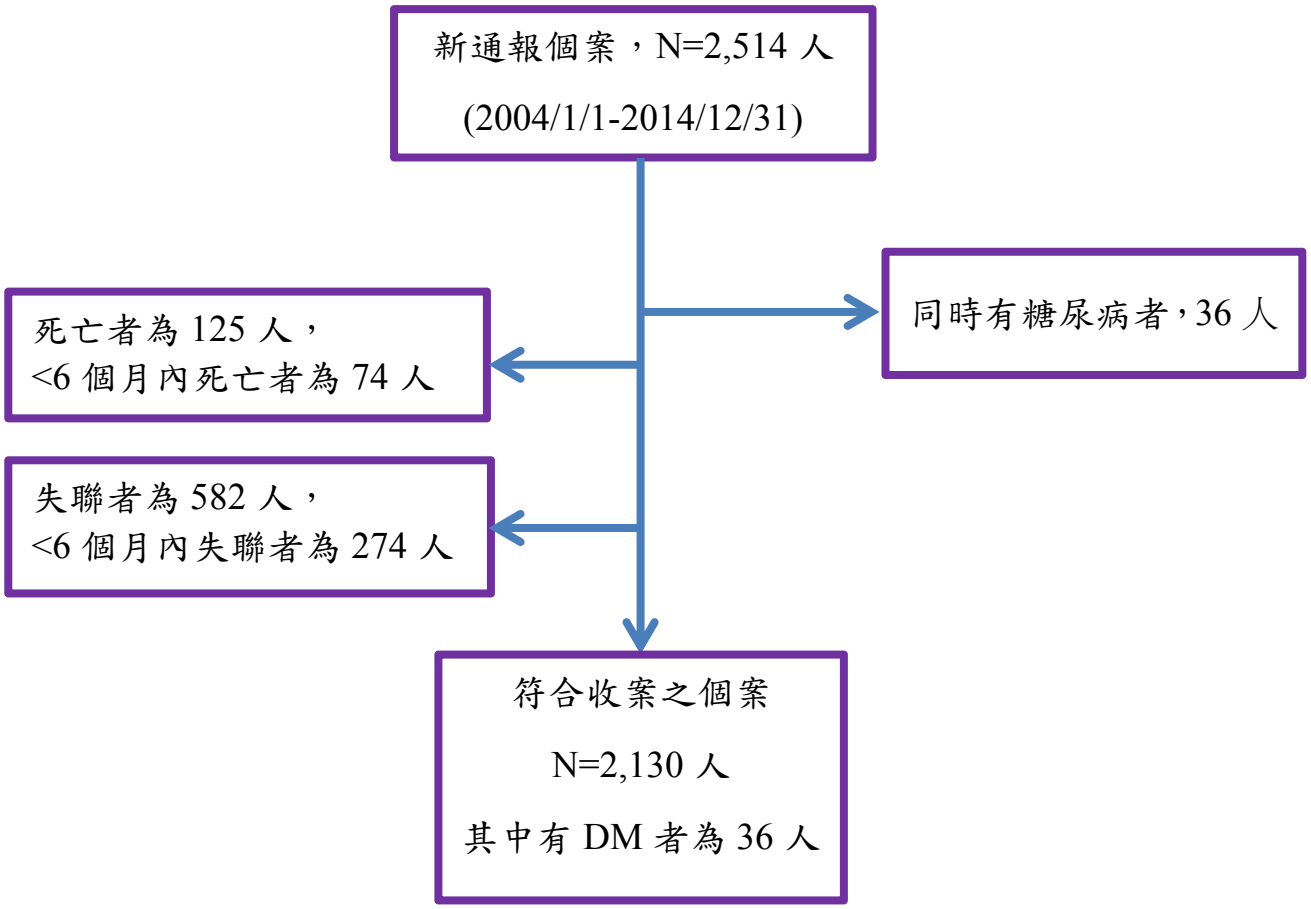
圖二、不同年齡層的三種風險評估量表≧10%之百分比圖



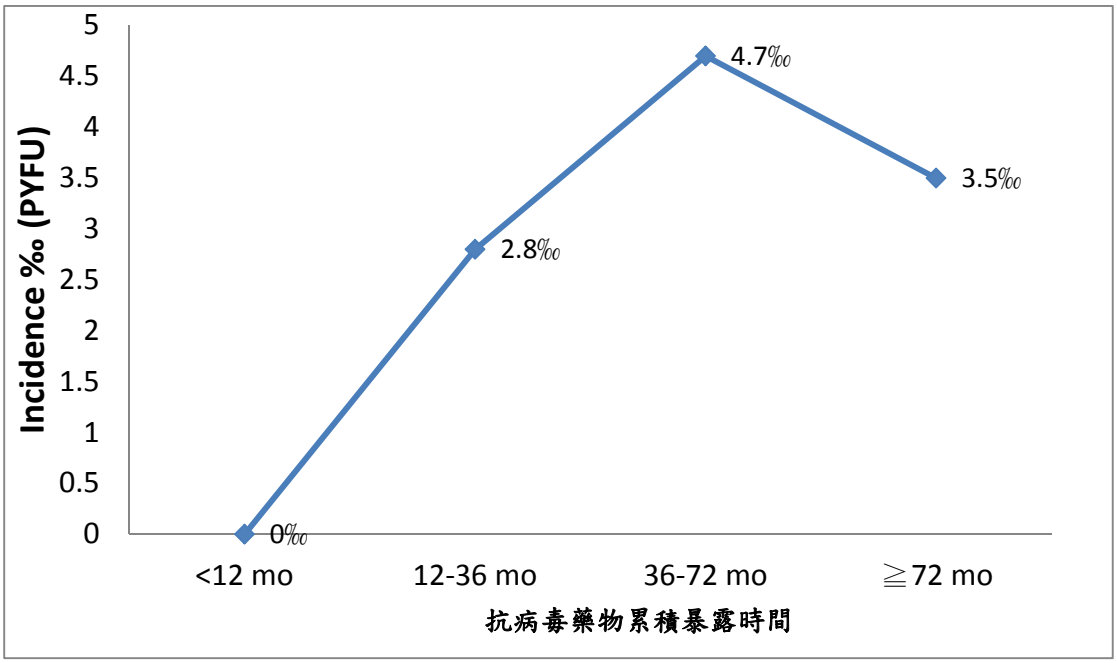
圖三、不同年齡層的兩種風險評估量表≧10%的比例之個案在戒菸後的風險圖



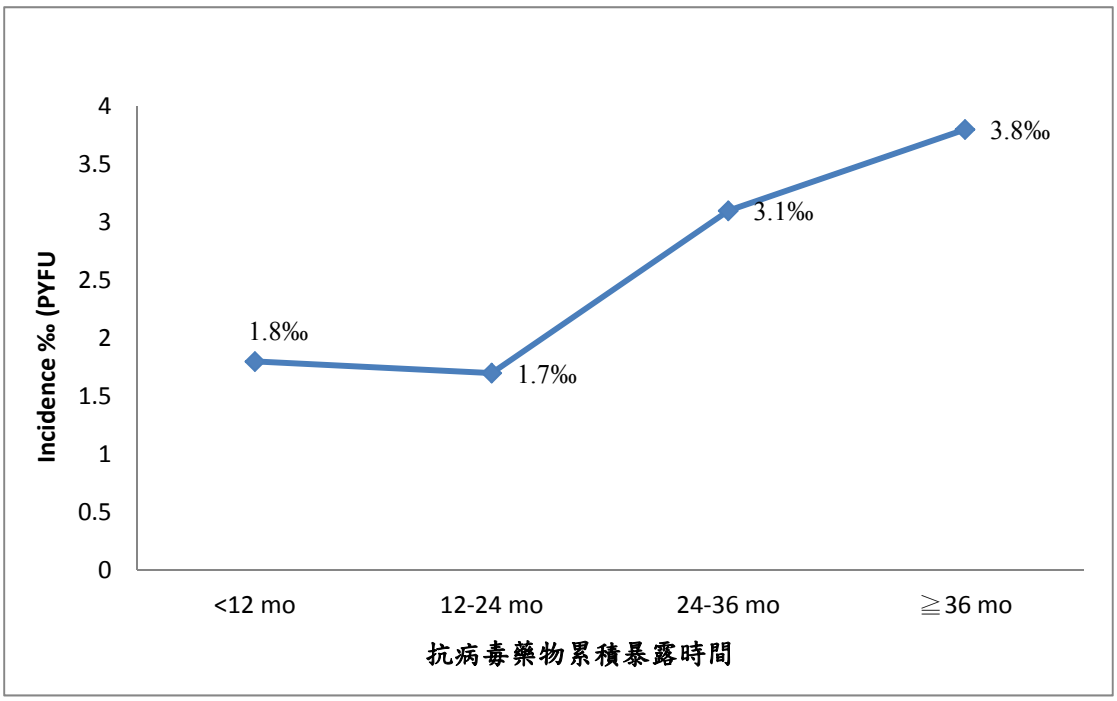
圖四、 收案流程 (DM)


新通報個案，N=2,514 人
(2004/1/1-2014/12/31)
同時有糖尿病者，36 人
死亡者為 125 人，
<6 個月內死亡者為 74 人
失聯者為 582 人，
<6 個月內失聯者為 274 人
符合收案之個案
N=2,130 人
其中有 DM 者為 36 人

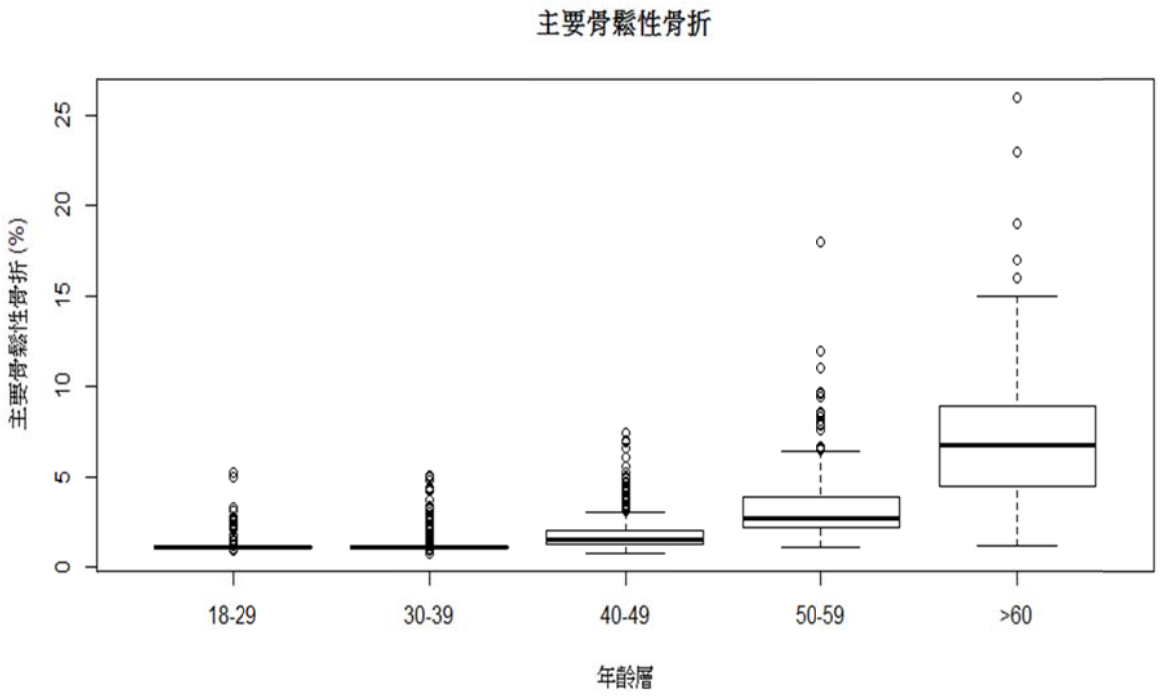
圖五、糖尿病的發生率與抗病毒藥物累積暴露時間與風險圖



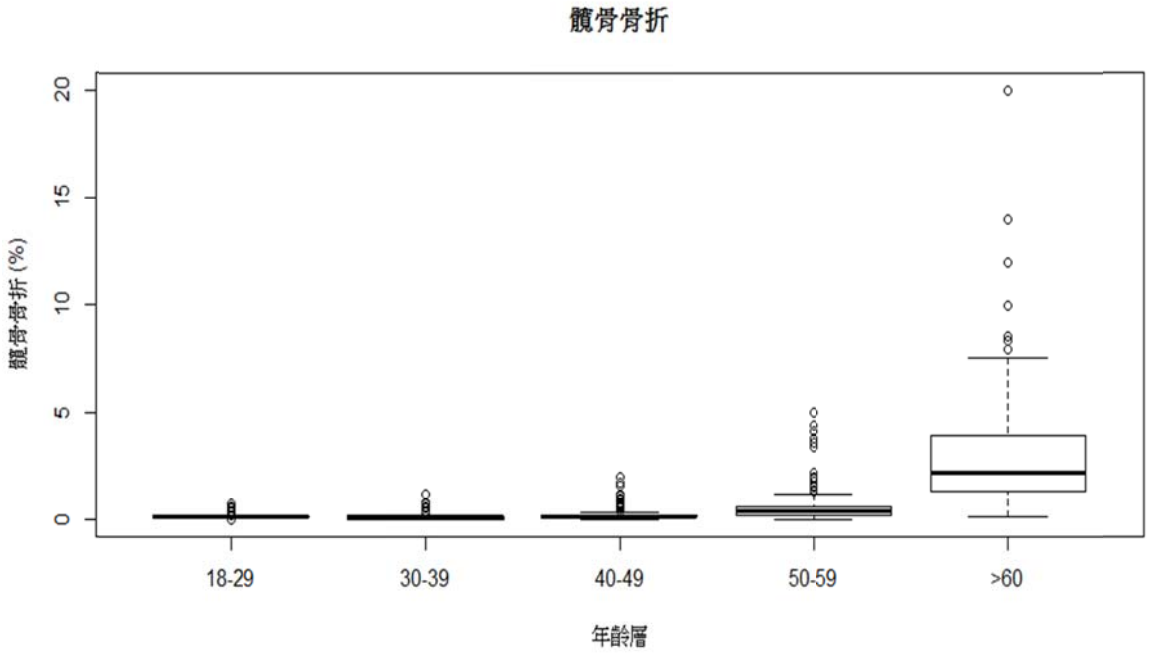
圖六、糖尿病的發生率與 zidovudine/lamivudine 藥物累積暴露時間與風險圖



圖七、主要骨鬆性骨折在各年齡層分布



圖八、髖骨骨折在各年齡層分布



陸、附錄

105年度中英文論文影本

PLOS ONE

RESEARCH ARTICLE

Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naïve HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan

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OPEN ACCESS

Citation: Wu P-Y, Cheng C-Y, Liu C-E, Lee Y-C, Yang C-J, Tsai M-S, et al. (2017) Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naïve HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS ONE 12(2): e0171596. doi:10.1371/journal.pone.0171596

Editor: Luis Menéndez-Arias, Universidad Autonoma de Madrid Centro de Biologia Molecular Severo Ochoa, SPAIN

Received: September 28, 2016

Accepted: January 23, 2017

Published: February 21, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by grants from the Centers for Disease Control, Taiwan (MOHW104-CDC-C-114-000301 to C.H.).

Competing interests: The authors have declared that no competing interests exist.

Abstract

Objectives

Two nucleos(*t*)ide reverse-transcriptase inhibitors (NRTIs) plus 1 non-NRTI (nNRTI) remain the preferred or alternative combination antiretroviral therapy (cART) for antiretroviral-naive HIV-positive patients in Taiwan. The three most commonly used nNRTIs are nevirapine (NVP), efavirenz (EFV) and rilpivirine (RPV). This study aimed to determine the incidences of hepatotoxicity and skin rashes within 4 weeks of initiation of cART containing 1 nNRTI plus 2 NRTIs.

Methods

Between June, 2012 and November, 2015, all antiretroviral-naive HIV-positive adult patients initiating nNRTI-containing cART at 8 designated hospitals for HIV care were included in this retrospective observational study. According to the national HIV treatment guidelines, patients were assessed at baseline, 2 and 4 weeks of cART initiation, and subsequently every 8 to 12 weeks. Plasma HIV RNA load, CD4 cell count and aminotransferases were determined. The toxicity grading scale of the Division of AIDS (DAIDS) 2014 was used for reporting clinical and laboratory adverse events.

Results

During the 3.5-year study period, 2,341 patients initiated nNRTI-containing cART: NVP in 629 patients, EFV 1,363 patients, and RPV 349 patients. Rash of any grade occurred in 14.1% (n = 331) of the patients. In multiple logistic regression analysis, baseline CD4 cell counts (per 100-cell/μl increase, adjusted odds ratio [AOR], 1.125; 95% confidence interval [95% CI], 1.031–1.228) and use of NVP (AOR, 2.443; 95% CI, 1.816–3.286) (compared with efavirenz) were independently associated with the development of skin rashes. Among the 1,455 patients (62.2%) with aminotransferase data both at baseline and week 4, 72 (4.9%) developed grade 2 or greater hepatotoxicity. In multiple logistic regression analysis, presence of antibody for hepatitis C virus (HCV) (AOR, 2.865; 95% CI, 1.439–5.704) or hepatitis B surface antigen (AOR, 2.397; 95% CI, 1.150–4.997), and development of skin rashes (AOR, 2.811; 95% CI, 1.051–7.521) were independently associated with the development of hepatotoxicity.

Conclusions

The baseline CD4 cell counts and use of NVP were associated with increased risk of skin rashes, while hepatotoxicity was independently associated with HCV or hepatitis B virus coinfection, and development of skin rashes in antiretroviral-naïve HIV-positive Taiwanese patients within 4 weeks of initiation of nNRTI-containing regimens.

Introduction

In recent practice guidelines of first-line antiretroviral treatment of HIV infection, the preferred or alternative combination antiretroviral therapy (cART) regimens include a combination of two nucleo(*t*)side reverse-transcriptase inhibitors (NRTIs) (tenofovir disoproxil fumarate [TDF] and emtricitabine or lamivudine) plus an active drug from one of the following classes: integrase strand transfer inhibitor (INSTI), ritonavir-boosted protease inhibitor (PI) [1–3], non-nucleoside reverse transcriptase inhibitor (nNRTI) (efavirenz [EFV] [2] or rilpivirine [RPV])[3]. The World Health Organization (WHO) Guidelines 2015 recommend either nevirapine (NVP) or EFV as a part of first-line antiretroviral therapy [4]. Other than efficacy, the choice of first-line therapy is determined based on various considerations, which include safety, drug tolerability, transmission of drug-resistant HIV-1 in the untreated population, coinfections, such as tuberculosis [5] and viral hepatitis, pregnancy, comorbidities, concurrent medications, or availability of antiretroviral agents. The cost of antiretroviral therapy is also an important factor to consider, especially in countries with limited resources [6].

The antiretroviral regimens containing the first-generation nNRTIs, EFV and NVP, have been shown to be efficacious and safety in different populations [7, 8]. In patients co-infected with HIV infection and tuberculosis, EFV remains the preferred nNRTI to be combined with rifampicin-containing anti-tuberculous therapy [5, 9]; however, neuropsychiatric symptoms are common adverse effects of EFV [10, 11]. In contrast, NVP is the preferred nNRTI in the first-line antiretroviral regiments in pregnancy because of substantial clinical experience in pregnant women and its proven efficacy in reducing mother-to-child transmission [12, 13]; however, higher incidences of rash, Stevens-Johnson syndrome, and hepatotoxicity have been associated with NVP than EFV [7, 14–17].

The frequency of elevation of liver enzymes in patients on EFV-containing regimens ranges from 1 to 8% [7, 8, 18–20], whereas in patients treated with NVP-containing regimens, it ranges from 4 to 18% [8, 16, 18–22]. NVP-related hepatotoxicity occurs almost exclusively during the first 6 weeks of treatment, which is more likely to develop in women with CD4 cell counts >250 cells/μl and in men with CD4 cell counts >400 cells/μl [23, 24], In previous studies, the associated factors with EFV-related hepatotoxicity were hepatitis C virus (HCV) coinfection and excessive alcohol use [25, 26]; moreover, skin rash has been reported to be associated with symptomatic hepatitis [23].

The second-generation nNRTIs, RPV, has demonstrated antiviral efficacy similar to that of EFV in antiretroviral-naïve adults with baseline plasma HIV RNA load (PVL) ≦100,000 copies/ml over 96 weeks in phase 3 clinical trials (ECHO and THRIVE) [27–29]. Compared with EFV, RPV was associated with a significantly lower incidence of skin rash (4% vs. 9%) and treatment-emergent elevation of aminotransferase levels (6% vs. 10–11%) [28].

In Taiwan, the three most commonly used nNRTIs among antiretroviral-naive patients are NVP, EFV, and RPV. A higher prevalence of chronic viral hepatitis B or C among HIV-positive patients in Taiwan [30, 31] and pharmacokinetics of antiretroviral therapy [32] has raised our concerns about the potential risks of hepatotoxicity and skin rashes related to the use of nNRTIs as the first-line antiretroviral therapy [33]. This multicenter, retrospective observational study aimed to investigate the incidences of skin rashes and hepatotoxicity within the first 4 weeks of initiation of nNRTI-containing antiretroviral therapy in HIV-1-infected adult patients in Taiwan.

Methods

Study population and setting

This retrospective observational study was conducted at 8 designated hospitals for HIV care around Taiwan (National Taiwan University Hospital, Tri-Service General Hospital, Far Eastern Memorial Hospital, Taoyuan General Hospital, Taichung Veterans General Hospital, Changhua Christian Hospital, Chia-Yi Christian Hospital and Chi Mei Hospital). We included all HIV-positive patients aged 20 years or greater who were antiretroviral-naive and initiated nNRTI-containing cART between 1 June, 2012 and 31 November 2015. All patients were followed until 31 January, 2016, death or loss to follow-up, whichever occurred first. The study was approved by the research ethics committee of each participating hospital and informed consent was waived.

HIV care, including cART and monitoring of CD4 cell count and PVL, has been provided free-of-charge since cART became available in Taiwan in April 1997. Due to financial constraints on the provision of free-of-charge access to cART, the Centers of Disease Controls (CDC) in Taiwan implemented regulations on the prescription of cART to antiretroviral-naive HIV-positive patients who received their first-line cART on 1 June 2012. Four categories of cART were defined: the first category consisted of NVP, RPV or EFV plus zidovudine/lamivudine (coformulated); the second category, NVP or EFV plus abacavir/lamivudine (coformulated); or TDF/emtricitabine (coformulated) or TDF and lamivudine; the third category, zidovudine/lamivudine plus protease inhibitors (PIs) or raltegravir; and the fourth category, TDF/emtricitabine, TDF and lamivudine, or abacavir/lamivudine plus PIs or raltegravir. Patients could start antiretroviral regimens in the first three categories, but initiation of regimens in the fourth category required approval before prescription. Raltegravir was not available in clinical use for antiretroviral-experienced patients until 2009; and in 2012, it was available for antiretroviral-naïve patients to be combined with 2 NRTIs. RPV was not available until January 2014. In patients with chronic HBV infection, TDF-containing regimens were recommended and RPV was recommended only for patients with baseline PVL <100,000 copies/ml.

Laboratory investigations

Before initiation of cART, baseline assessment included hemogram, CD4 count, PVL, serologic markers of syphilis and hepatitis A, B, and C viruses, urinalysis, and serum biochemistry, including total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lipid profiles. Transmitted drug resistance mutations of HIV-1 to NRTIs, nNRTIs, PIs, and INSTIs were not routinely determined before cART was initiated; genotypic resistance testing was only performed retrospectively for the purposes of surveillance [34, 35].

After initiation of cART, patients were mandatorily enrolled in case management program implemented by Taiwan CDC and patients were usually seen 2 weeks after initiation of cART to assess the adverse effects and tolerability of the regimens prescribed. Aminotransferases and hemogram were determined. Patients returned for reassessment of virological and immunological responses and adverse effects at week 4 of cART, and subsequently every 8 to 12 weeks. At these visits, physical examination was performed and PVL, CD4 cell count, serum chemistries, including total bilirubin, AST, ALT, and lipid profiles, were determined to assess the clinical and laboratory adverse events. A standardized case record form was used to collect information on demographic and clinical characteristics and immunological and virological responses.

Definitions

We assessed the incidence of skin rashes within 4 weeks of cART initiation. Hepatotoxicity grading was based on ALT and AST levels, which was defined in accordance with the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) [36], in the following manner: grade 1, 1.25–2.4 times the upper limit of normal (ULN) (upper normal values, 31–41 U/L for AST and 41–44 U/L for ALT, depending on the ULN values of each participating hospital); grade 2, 2.5–4.9 × ULN; grade 3, 5.0–9.9 × ULN; and grade 4, ≧10 × ULN, for those patients with normal aminotransferase levels at baseline. For patients with abnormal aminotransferase levels at baseline, hepatotoxicity was defined as a 2-fold or greater increase from baseline levels [33]. The skin rashes was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) [36].

HCV infection was defined as presence of antibodies for HCV, while hepatitis B virus (HBV) infection was defined as presence of HBV surface antigen (HBsAg).

Statistical analysis

Categorical variables were analyzed by using X^2 test and continuous variables were compared using Student's *t* test. A *P*-value of <0.05 was considered statistically significant. All *P* values were two-tailed. Variables with $P<0.10$ or those of biological significance in the univariate analyses were entered into a multivariate logistic analyses. Association between hepatotoxicity and skin rash and clinical characteristics were assessed in logistic regression analysis. Variables included in these analyses were age, gender, HIV risk group, baseline CD4 cell count, baseline PVL, and baseline AST and ALT. Statistical analyses were performed using SAS software (Version 9.3).

Results

Clinical characteristics of the patients

A total of 2,341 antiretroviral-naïve patients started cART between June 2012 and November 2015; 629 patients received NVP plus 2 NRTIs, 1,363 patients EFV plus 2 NRTIs, and 349

patients RPV plus 2 NRTIs. Their baseline demographic and clinical characteristics are shown in Table 1. Overall, the great majority (95.8%) of the patients were male, with a mean age of 33 years, and men who have sex with men and injection drug users accounted for 77.7% and 16.7% of the patients, respectively. While the mean PVL was 4.7 $\log_{10}$ copies/mL, most of the patients initiated cART late with a mean CD4 count 279 cells/μl and only 29.8% initiated cART with a baseline CD4 count of 350 cells/μl or greater (data not shown). HBsAg was determined in 2,291 patients (97.9%) with 275 (12.0%) testing positive, while anti-HCV antibody was determined in 2,286 patients (97.7%) with 437 (19.1%) testing positive.

Not unexpectedly, clinical characteristics differed significantly among the patients initiating cART with 3 different regimens consisting of nNRTIs plus 2 NRTIs because of the regulations on prescription of the first-line antiretroviral therapy in antiretroviral-naïve patients, a higher prevalence of chronic HBV infection that required cART containing TDF, and injection drug users who often had low PVL and higher CD4 counts at baseline than other risk groups owing to infections with defective HIV-1 subtype CRF 07_BC in Taiwan [37]. Therefore, a higher proportion of patients who initiated RPV plus 2NRTIs were injection drug users than those who initiated EFV or NVP plus 2 NRTIs (24.3% vs 15.3% and 15.2%, respectively) (Table 1). Compared with patients initiating EFV or NVP plus 2 NRTIs, patients initiating RPV plus 2 NRTIs had a lower mean PVL (4.3 vs 4.8 $\log_{10}$ copies/ml) and higher CD4 count (388 vs 281 and 214 cells/μl, respectively).

Within the first 4 weeks of cART, the percentage of patients who discontinued nNRTIs due to any adverse events was 55.4%. Of the patients discontinuing nNRTIs, 67.1% were due to

Table 1. Clinical characteristics of the patients initiating non-nucleoside reverse-transcriptase inhibitor-containing regimens.

Variable	ALL	NVP group	EFV group	RPV group	P*
Case number, n (%)	2341	629	1363	349	-
Age, mean (SD), years	33 (9.3)	33 (10)	33 (9.3)	33 (8.6)	0.7905
Male sex, n (%)	2242 (95.8)	597 (94.9)	1314 (96.4)	331 (94.8)	0.1979
Risk behavior for HIV transmission, n (%)					0.0025
MSM	1818 (77.7)	493 (78.4)	1080 (79.2)	245 (70.2)	
IDU	390 (16.7)	96 (15.2)	209 (15.3)	85 (24.3)	
Others	133 (5.7)	40 (6.4)	74 (5.4)	19 (5.4)	
HBsAg positivity, n (%)	275/2291 (12.0)	56/617 (9.1)	202/1333 (15.2)	17/341 (5.0)	< .0001
Anti-HCV positivity, n (%)	437/2286 (19.1)	99/618 (16.0)	243/1331(18.3)	95/337 (28.2)	< .0001
CD4 count at baseline, mean (SD), cells/μl	279 (183)	214 (127)	281 (189)	388 (194)	< .0001
Plasma HIV RNA load at baseline, mean (SD), $\log_{10}$ copies/ml	4.7 (0.8)	4.8 (0.8)	4.8 (0.8)	4.3 (0.6)	< .0001
Baseline AST, mean (SD), IU/L	42 (84)	38 (98)	45 (86)	37 (38)	0.0398
Baseline ALT, mean (SD), IU/L	43 (97)	35 (43)	46 (120)	42 (59)	0.0010
NRTIs, n (%)					
ZDV/3TC	1219 (52.1)	355 (56.4)	537 (39.4)	327 (93.7)	< .0001
ABC/3TC	130 (5.6)	45 (7.2)	82 (6.0)	3 (0.9)	0.0001
TDF/3TC or TDF/FTC	986 (42.1)	224 (35.6)	743 (54.5)	19 (5.4)	< .0001
CD4 count at 1 month, mean (SD), cells/μl,	398 (222)	333 (177)	401 (224)	491 (241)	< .0001
Plasma HIV RNA load at 1 month, mean (SD), $\log_{10}$ copies/ml,	2.5 (0.8)	2.7 (0.9)	2.5 (0.8)	2.2 (0.7)	< .0001

*P value was calculated for the differences among the three groups. Continuous variables were analyzed with nonparametric statistics, Kruskal-Wallis H test, while categorical variables with chi-square test.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EFV, efavirenz; FTC, emtricitabine; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IDU, injection drug users; MSM, men who have sex with men; NVP, nevirapine; RPV, rilpivirine; SD, standard deviation; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

doi:10.1371/journal.pone.0171596.t001

skin rash, 23.2% due to neuropsychiatric symptoms, 5.6% due to gastrointestinal upset, 5.3% due to hepatitis, and 1.1% due to depression.

Skin rashes: Incidence and associated factors

Within 4 weeks of cART, rash of any grade occurred in 331 (14.1%) of the patients: 149 (23.7%) in NVP group, 180 (13.2%) in EFV group, and 2 (0.6%) in RPV group. The mean interval between initiation of cART and development of skin rashes was longer for the NVP group than EFV group (22 vs 16 days, $P = 0002$). Of the 149 patients who received NVP with skin rash, the proportions of HBV coinfection did not differ between those who discontinued and those who continued NVP (10.6% vs. 14.3%, p = 0.756), and neither did the proportions of HCV coinfection (19.2% vs. 14.3%, P = 0.749). Likewise, of the 180 patients who received EFV with rash, the proportions of HBV coinfection did not differ between those who discontinued and those who continued EFV (10.6% vs. 25.0%, p = 0.131), and neither did the proportions of HCV coinfection (14.2% vs. 25.0%, P = 0.311) (data not shown).

Table 2 shows the results of univariate analyses of factors associated with skin rash for all patients after initiation of nNRTI-containing regimens within the first 4 weeks. In univariate analysis, patients who initiated NVP plus 2 NRTIs had a higher risk of developing skin rashes ($P<0.0001$), while those who initiated RPV plus 2 NRTIs had a lower risk. In multiple logistic regression analysis among patients who received NVP or EFV, we found a higher baseline CD4 cell counts (per 100-cell/μl increase, adjusted odds ratio [AOR], 1.125; 95% confidence interval [95% CI], 1.031–1.228) and use of NVP plus 2 NRTIs (AOR, 2.443; 95% CI, 1.816–3.286) were independently associated with the development of skin rashes (Table 3).

For each of nNRTI-containing regimen, the results of multivariate analysis of associated factors with skin rashes are shown in S1 Table. In NVP group, we found that baseline CD4 cell count ($P = 0.05$) and age ($P = 0.04$) were associated with developing skin rashes in univariate analysis (data not shown), while in multiple logistic regression analysis, we were not able to identify any factor statistically significantly associated with developing skin rashes. In EFV

Table 2. Univariate analyses for factors associated with skin rash after initiation of nNRTI-containing regimens within the first 4 weeks.

Variable	Skin rash	No skin rash	All	P
	n = 331	n = 2010	n = 2341	
Age, mean (SD), years	33.21 (9.55)	33.36 (9.27)	33.34 (9.31)	0.7805
Gender, male, n (%)	314 (94.86)	1928 (95.92)	2242 (95.77)	0.3762
Baseline CD4, mean (SD), cells/μl	274.6 (177.3)	279.5 (184.5)	278.8 (183.5)	0.6503
Baseline CD4 ≥200 cells/μl, n (%)	218 (66.67)	1304 (66.06)	1522 (66.15)	0.8296
Baseline CD4 ≥250	176 (53.82)	1080 (54.71)	1256 (54.58)	0.7650
Baseline CD4 ≥350	97 (29.66)	591 (29.94)	688 (29.90)	0.9197
Baseline PVL, mean (SD), $\log_{10}$ copies/ml	4.80 (0.83)	4.73 (0.78)	4.74 (0.78)	0.1630
HBsAg-positive, n (%), [n = 2291]	36 (11.11)	239 (12.15)	275 (12.00)	0.5938
Anti-HCV-positive, n (%), [n = 2286]	54 (16.67)	383 (19.52)	437 (19.12)	0.2261
Baseline AST, mean (SD), IU/L,	39.7 (59.6)	42.4 (87.9)	41.9 (84.3)	0.5175
Baseline ALT, mean (SD), IU/L,	41.4 (67.3)	43.1 (101.3)	42.8 (97.1)	0.7229
NVP, n (%)	149 (45.02)	480 (23.88)	629 (26.87)	< .0001
EFV, n (%)	180 (54.38)	1183 (58.86)	1363 (58.22)	0.1261
RPV, n (%)	2 (0.60)	347 (17.26)	349 (14.91)	< .0001

Abbreviations: 95% CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; nNRTI, non-nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; RPV, rilpivirine; SD, standard deviation.

doi:10.1371/journal.pone.0171596.t002

Table 3. Multivariate analyses for factors associated with skin rash after initiation of nNRTI-containing regimens within the first 4 weeks (patients receiving rilpivirine were excluded).

Variable	OR*	95%CI*
Age	1.004	0.988–1.020
Male gender	0.691	0.359–1.329
Baseline CD4 cells/μl, per 100-cell/μl increase	1.125	1.031–1.228
Baseline PVL $\log_{10}$ copies/m	1.083	0.893–1.315
HBsAg-positive	0.949	0.626–1.438
Anti-HCV-positive	0.842	0.568–1.247
Baseline AST, per 1-IU/L increase	0.999	0.997–1.002
Baseline ALT, per 1-IU/L increase	1.000	0.998–1.002
NVP (vs EFV)	2.443	1.816–3.286

* These analyses were conducted in 1992 patients.

Abbreviations: 95% CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EFV, efavirenz.

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; nNRTI, non-nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PVL, plasma HIV RNA load.

doi:10.1371/journal.pone.0171596.t003

group, developing skin rashes was associated with older age ($P = 0.02$) and baseline CD4 cell count≧350 cells/μl ($P = 0.004$) in univariate analysis (data not shown). In multiple logistic regression analysis, only baseline CD4 cell count ≧350 cells/μl (AOR, 2.326; 95% CI, 1.211–4.466) was independently associated with the development of skin rashes.

Hepatotoxicity: Incidence and associated factors

Baseline aminotransferase levels available for patients initiating EFV-, NVP-, and RPV-containing regimens are shown in Table 1. Among the 1,455 patients (62.2%) with both baseline and follow-up data of aminotransferases at week 4, 72 (4.9%) patients developed hepatotoxicity of grade 2 or greater: 37 (4.4%) in EFV group, 24 (6.9%) in NVP group and 11 (4.1%) in RPV group. In patients with treatment-emergent hepatic laboratory abnormalities, there was a higher incidence of grade 2 or more AST and ALT elevation in the patients with normal baseline levels of aminotransferase in the NVP group than in the EFV and RPV groups at week 4 (Fig 1).

Of the 24 patients who received NVP with hepatotoxicity, the proportions of HBV coinfection did not differ between those who discontinued and those who continued NVP (7.7% vs. 36.4%, p = 0.084), and neither did the proportions of HCV coinfection (23.1% vs. 45.5%, P = 0.247). Of the 37 patients who received EFV with hepatotoxicity, the proportions of HBV coinfection did not differ between those who discontinued and those who continued EFV (27.3% vs. 34.8%, p = 0.662), and neither did the proportions of HCV coinfection (36.4% vs. 36.0%, P = 0.983) (data not shown).

Univariate analyses of factors associated with hepatotoxicity for all patients are shown in Table 4. We found that older age ($P = 0.0038$), anti-HCV positivity ($P<0.0001$), HBsAg positivity ($P = 0.0007$), and development of skin rashes within 4 weeks of cART ($P = 0.0008$) were associated with hepatotoxicity of grade 2 or greater. In multiple logistic regression analysis, anti-HCV positivity (AOR, 2.865; 95% CI, 1.439–5.704), the development of skin rash (AOR, 2.811; 95% CI, 1.051–7.521) and HBsAg positivity (AOR, 2.397; 95% CI, 1.150–4.997) were independently associated with the development of hepatotoxicity (Tables 5 and 6). Other variables analyzed such as male gender, HIV transmission category, baseline CD4 count and baseline PVL were not statistically significantly associated with hepatotoxicity.

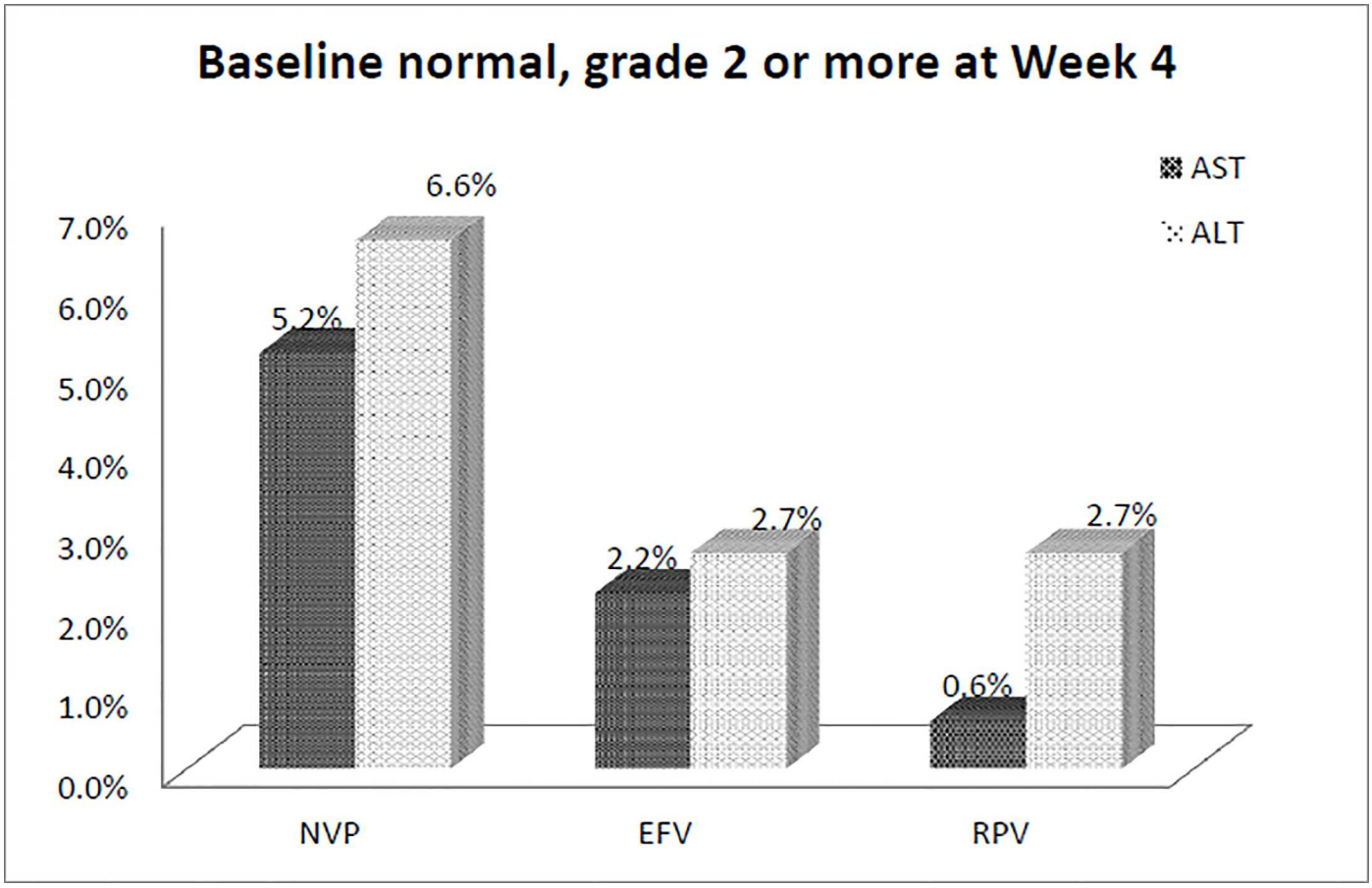

Fig 1. Percentages of grade 2 or higher hepatotoxicity at week 4 in patients with normal aminotransferase levels at baseline (NVP, nevirapine; EFV, efavirenz; RPV, rilpivirine).

doi:10.1371/journal.pone.0171596.g001

The results of multivariate analysis for each nNRTI-containing regimen are shown in S2 Table. In univariate analysis in NVP group (data not shown), we found that baseline CD4 cell count ($P = 0.002$), HBsAg positivity ($P = 0.04$) and development of skin rash within 4 weeks of cART ($P<0.001$) were associated with hepatotoxicity of grade 2 or greater. In multiple logistic regression analysis, a higher baseline CD4 cell count (per 100-cell/μl increase, AOR, 1.705; 95% CI, 1.187–2.449) and development of skin rashes (AOR, 4.704; 95% CI, 1.537–14.394) were independently associated with the development of hepatotoxicity.

In univariate analysis in EFV group (data not shown), we found that that older age ($P = 0.02$), anti-HCV-positivity ($P = 0.02$), and HBsAg positivity ($P = 0.02$) were associated with hepatotoxicity of grade 2 or greater. In multiple logistic regression analysis (S2 Table), anti-HCV positivity (AOR, 5.342; 95% CI, 1.865–15.302) and HBsAg positivity (AOR, 3.598; 95% CI, 1.353–9.570) were independently associated with the development of hepatotoxicity. For the patients in RPV group, we were not able to identify any factor statistically significantly associated with hepatotoxicity in either univariate analysis or multiple logistic regression analysis.

Discussion

In this study conducted in a country where cART comprising 1 nNRTI plus 2 NRTIs remains the preferred regimen for antiretroviral-naïve HIV-positive patients, we found that the overall

Table 4. Univariate analyses for factors associated with hepatotoxicity after initiation of nNRTI-containing regimens within the first 4 weeks.

Variable	With hepatotoxicity	Without hepatotoxicity	ALL	P
	n = 72	n = 1383	n = 1455	
Age, mean (SD), years	36.66 (10.17)	33.46 (9.05)	33.62 (9.13)	0.0038
Male gender, n (%)	70 (97.22)	1320 (95.44)	1390 (95.53)	0.4766
Baseline CD4, mean (SD), cells/μl	262 (157.8)	284 (189.4)	283 (188.0)	0.2616
Baseline CD4 >200 cells/μl, n (%)	48 (67.61)	906 (65.84)	954 (65.93)	0.7599
Baseline plasma HIV RNA load, mean (SD), log_{10} copies/ml	4.71 (0.75)	4.72 (0.75)	4.72 (0.75)	0.889
HIV mono-infected, n (%) [n = 1432]	31 (44.93)	945 (69.33)	976 (68.16)	< .0001
HIV/HBV co-infected, n (%) [n = 1165]	16 (34.04)	173 (15.47)	189 (16.22)	0.0007
HIV/HCV co-infected, n (%) [n = 1298]	27 (46.55)	295 (23.79)	322 (24.81)	< .0001
Development of skin rashes, n (%)	8 (11.11)	47 (3.40)	55 (3.78)	0.0008
Baseline AST, mean (SD), IU/L	39 (23.5)	43 (96.3)	42 (94.0)	0.3726
Baseline ALT, mean (SD), IU/L	43 (29.9)	44 (112.5)	44 (109.7)	0.7984
NVP, n (%)	24 (33.33)	323 (23.36)	347 (23.85)	0.0527
EFV, n (%)	37 (51.39)	801 (57.92)	838 (57.59)	0.2744
RPV, n (%)	11 (15.28)	259 (18.73)	270 (18.56)	0.4629

Abbreviations: 95% CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EFV, efavirenz; HBV, hepatitis B virus; HCV, hepatitis C virus; nNRTI, non-nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; RPV, rilpivirine; SD, standard deviation.

doi:10.1371/journal.pone.0171596.t004

incidence of hepatotoxicity and skin rashes within 4 weeks of initiation was 4.9% and 14.1%, respectively. HCV coinfection and development of skin rash were independently associated with hepatotoxicity of grade 2 or greater. On the other hand, a higher baseline CD4 cell count and use of NVP plus 2 NRTIs were independently associated with the development of skin rashes.

The rate of skin rashes among HIV-positive patients receiving regimens containing first-generation nNRTIs ranges from 3.8 to 21.6% [7, 17, 28, 33, 38, 39]. In our study, the overall incidence of skin rashes in patients initiating nNRTI-containing regimens was 14.1% (331/2341), which was significantly higher in patients starting NVP-containing regimens (23.7%)

Table 5. Multivariate analyses for factors associated with hepatotoxicity after initiation of nNRTI-containing regimens within the first 4 weeks (HBV/HIV co-infected vs HIV mono-infected).

Variable	Odds Ratio*	95% CI*
Age, per 1-year older	1.025	0.993–1.059
Male gender	-	-
Baseline CD4 count, per 100-cell/μl increase	0.936	0.758–1.155
Baseline PVL, per 1-log_{10} copies/ml increase	1.133	0.695–1.847
HBsAg-positive (vs HIV mono-infected)	2.397	1.150–4.997
Development of skin rashes	2.919	0.976–8.732
Baseline AST, per 1-IU/L increase	0.997	0.985–1.010
Baseline ALT, per 1-IU/L increase	1.000	0.990–1.010
NVP	1.423	0.454–4.453
EFV	0.733	0.251–2.139

* These analyses were conducted in 1455 patients.

Abbreviations: 95% CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase

EFV, efavirenz; HBsAg, hepatitis B surface antigen; NVP, nevirapine; PVL, plasma HIV RNA load.

doi:10.1371/journal.pone.0171596.t005

Table 6. Multivariate analyses for factors associated with hepatotoxicity after initiation of nNRTI-containing regimens within the first 4 weeks (HCV/HIV co-infected vs. HIV mono-infected).

Variable	Odds Ratio*	95% CI*
Age, per 1-year older	1.008	0.975–1.042
Male gender	2.209	0.502–9.713
Baseline CD4 count, per 100-cell/μl increase	1.041	0.865–1.253
Baseline PVL, per 1-$\log_{10}$ copies/ml increase	1.135	0.754–1.707
Anti-HCV-positive (vs HIV mono-infected)	2.865	1.439–5.704
Development of skin rashes	2.811	1.051–7.521
Baseline AST, per 1-IU/L increase	0.998	0.987–1.009
Baseline ALT, per 1-IU/L increase	1.000	0.990–1.010
NVP	1.717	0.710–4.152
EFV	0.861	0.387–1.917

* These analyses were conducted in 1455 patients.

Abbreviations: 95% CI, 95% confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; EFV, efavirenz

HCV, hepatitis C virus; NVP, nevirapine PVL, plasma HIV RNA load.

doi:10.1371/journal.pone.0171596.t006

than that in those starting EFV-containing regimens (13.2%) and RPV-containing regimens (0.6%). In addition, a higher baseline CD4 count and use of NVP were associated with the development of skin rashes. According to the systematic review and meta-analysis by Shubber et al [10], severe skin rash was more likely to develop among patients on NVP than those on EFV (OR 3.9; 95% CI, 2.5–5.4). In contrast, skin rash was rare in patients receiving RPV in our study, which was similar to the findings observed in the ECHO and THRIVE studies [28]. The mechanism of NVP-associated hypersensitivity is unclear, but several HLA alleles have been found to be associated with NVP hypersensitivity [40, 41]. In our study, the mean onset time of rashes was 18 days among nNRTI users and 22 days among NVP users, which are also consistent with what have been described in the previous reports (8–13 days among nNRTI users [15, 38] and 14–30 days among NVP users) [33, 39].

Hepatotoxicity is observed in 1.1–25.5% of HIV-positive patients treated with cART [7, 14–16, 20–22, 33, 39, 42]. The wide range of hepatotoxicity rates among patients receiving cART may be related to different study designs and populations (age, gender, races, and body weight), prevalence of HBV or HCV coinfection, definitions of hepatotoxicity used, follow-up duration, CD4 counts (particularly in pregnant patients with CD4 >250 cell/μl receiving nevirapine for the prevention of mother-to-children transmission) [43], and antiretroviral regimens initiated. For example, the overall rate of hepatotoxicity, defined as grade 4, was 7.9% in a retrospective cohort study of 560 HIV-positive patients in the Netherlands [42] while the rate of severe hepatotoxicity, defined as grade 3, was 5% in another prospective cohort study of 820 HIV-positive women in 3 countries [39].

The findings that patients on NVP are more likely to develop hepatotoxicity than those on EFV in our study are consistent with those in several studies [10, 14, 15, 18, 25]. Our study also found the baseline CD4 counts and the development of rashes were associated with hepatotoxicity among the patients starting NVP-containing regimens. Likewise, a review of 17 randomized clinical trials of NVP shows rash and other possibly immune-mediated events (most often fever) occurred concurrently with hepatic events in 2.2% of NVP-treated patients, and approximately 46% of symptomatic hepatic events were associated with rash [23]. The key risk factors of this unique rash-associated hepatotoxicity were treatment with NVP, almost exclusively within the first 6 weeks of NVP, and higher baseline CD4 cell counts [23]. Additionally, a

2-fold or greater increase of aminotransferases from the ULN levels was associated with developing rashes in Taiwanese patients receiving NVP-containing regimens [33]. Thus, baseline assessment of liver function is needed in patients who are scheduled to initiate NVP-containing regimens. It is prudent to carefully monitor when NVP-containing regimens is chosen or avoid use of NVP in those who have elevated aminotransferases at baseline.

Higher baseline levels of AST/ALT have been shown to be associated with cART-associated hepatotoxicity [21, 23, 39]. We also found the rate of hepatotoxicity at week 4 was higher in patients with abnormal baseline levels of AST/ALT than that in those with normal baseline levels of AST/ALT (AST, 5.3 vs. 2.6%; ALT, 7.2 vs.3.7%) (data not shown). Chronic viral hepatitis, particularly HCV coinfection, has been recognized a risk factor for hepatotoxicity [16, 18, 21, 23, 25, 26]. Our findings in HIV-positive Taiwanese are in line with the findings of these studies. The mechanism of increased antiretroviral-associated hepatotoxicity in patients with chronic viral hepatitis is not clearly known, but is more likely to be multifactorial. While initiation of antiretroviral therapy containing lamivudine with or without TDF could suppress replication of HBV, previous studies have suggested that hepatic injury may be caused by enhanced HCV replication and cytotoxic T-cell activity during cART-associated immune reconstitution [18, 44, 45]. However, our findings of similar increases of CD4 count within 4 weeks of cART may not support this hypothesis of immune reconstitution-related hepatotoxicity (data not shown).

Our findings may have clinical implications in the management of HIV infection in patients who start cART containing nNRTIs. Monitoring of AST/ALT levels every 2 weeks during the first month of therapy may identify early, and potentially reversible, drug-induced hepatotoxicity, particularly in patients with chronic HCV infection. The appearance of a rash, nausea, or fever during the first 4 weeks of therapy should prompt closer monitoring and assessment.

There are several limitations in this study and interpretation of our findings should be cautious. First, the patients were not randomly assigned to any of the regimens in this cohort and primary care physicians might take into consideration risk behaviors for HIV transmission, baseline liver function, hepatitis coinfection, and immunological as well as virological status of the patients before prescribing any of the 3 nNRTI-containing regimens on an individual basis, which may introduce significant bias or confounding factors. For example, other than the CD4 count cut-offs that are associated with risks for hepatotoxicity related of NVP, we previously found that elevated aminotransferase values at baseline were associated with NVP-associated skin rashes in HIV-positive patients in Taiwan [33]. Clinicians might tend not to prescribe NVP to patients with chronic viral hepatitis or patients who were injection drug users; instead, RPV plus 2 NRTIs was more likely to be used in such populations given the findings that RPV plus 2 NRTIs was associated with lower incidence of hepatotoxicity than EFV in ECHO/THRIVE trials.

Second, we did not have data on exposure to other hepatotoxins (e.g. alcohol and chronic aflatoxin exposure) or agents that might cause hepatotoxicity or skin rashes (e.g. anti-tuberculous agents, fluconazole, trimethoprim/sulfamethoxazole) [46]. Third, because of concerns about the long-term impact of other chronic viral hepatitis, fatty liver and other medications, we limited the observation duration to 4 weeks with an attempt to assess the short-term tolerability of the nNRTI-containing regimens. Such a short observation duration may have underestimated the overall incidence of hepatic and dermatologic complications related to cART in our patients and precluded us from identifying factors associated with chronic elevations of transaminase, such as ongoing exposure to regimens containing ddI, d4T and TDF and short-term exposure to NVP, EFV, FTC and ATV [47]. Fourth, the data regarding the percentages of HBsAg-positive patients with HBeAg-positive and/or detectable HBV DNA and these of HCV-positive patients with detectable HCV RNA were not available. These data might be

essential to understanding the role of active replication of HBV or HCV as an underlying cause of hepatotoxicity. Lastly, the case number of patients receive RPV plus 2 NRTIs was much smaller than that of the other two groups (349 patients receiving RPV; 1363 receiving EFV; 629 receiving NVP)

In conclusion, our study among a large treatment-naive HIV-positive population receving nNRTI- containing regimens in Taiwan reveals that the overall rate of hepatotoxicity within 4 weeks of cART initiation was low (4.9%). HCV or HBV coinfection and development of skin rash were independently associated with the development of hepatotoxicity, whereas higher baseline CD4 counts and use of NVP were independently associated with skin rashes within 4 weeks of cART initiation.

Supporting information

S1 Table. Multivariate analyses for factors associated with skin rash after initiation of nNRTI-containing regimens within the first 4 weeks.
(DOCX)

S2 Table. Multivariate analyses for factors associated with hepatotoxicity after initiation of nNRTI-containing regimens within the first 4 weeks.
(DOCX)

S1 Data. The minimal data set of the patients in this study.
(XLSX)

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References

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services (DHHS); 2015.

2. European Guidelines for treatment of HIV-infected adults in Europe. European AIDS Clinical Society (EACS)October 2015.
3. British HIV association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. British HIV association (BHIVA) 2015.
4. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. World health organization; November 2015.
5. Luetkemeyer AF, Rosenkranz SL, Lu D, Marzan F, Ive P, Hogg E, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2013; 57(4):586–93. PubMed Central PMCID: PMC3719885.
6. Bendavid E, Grant P, Talbot A, Owens DK, Zolopa A. Cost-effectiveness of antiretroviral regimens in the World Health Organization's treatment guidelines: a South African analysis. Aids. 2011; 25(2):211–20. PubMed Central PMCID: PMC3071983. doi: 10.1097/QAD.0b013e328340fdf8 PMID: 21124202
7. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet. 2004; 363(9417):1253–63. doi: 10.1016/S0140-6736(04)15997-7 PMID: 15094269
8. Manfredi R, Calza L, Chiodo F. Efavirenz versus nevirapine in current clinical practice: a prospective, open-label observational study. Journal of acquired immune deficiency syndromes. 2004; 35(5):492–502. PMID: 15021314
9. Lee KY, Lin SW, Sun HY, Kuo CH, Tsai MS, Wu BR, et al. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. PloS one. 2014; 9(2):e88497. PubMed Central PMCID: PMC3925114. doi: 10.1371/journal.pone.0088497 PMID: 24551111
10. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Thery F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. Aids. 2013; 27(9):1403–12. doi: 10.1097/QAD.0b013e32835f1db0 PMID: 23343913
11. Gazzard B, Balkin A, Hill A. Analysis of neuropsychiatric adverse events during clinical trials of efavirenz in antiretroviral-naive patients: a systematic review. AIDS reviews. 2010; 12(2):67–75. PMID: 20571601
12. Moodley D, Moodley J, Coovadia H, Gray G, McIntyre J, Hofmyer J, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. The Journal of infectious diseases. 2003; 187(5):725–35. doi: 10.1086/367898 PMID: 12599045
13. McKoy JM, Bennett CL, Scheetz MH, Differding V, Chandler KL, Scarsi KK, et al. Hepatotoxicity associated with long- versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug events And Reports (RADAR) project. Drug safety. 2009; 32(2):147–58. PubMed Central PMCID: PMC2768573. doi: 10.2165/00002018-200932020-00007 PMID: 19236121
14. Rivero A, Mira JA, Pineda JA. Liver toxicity induced by non-nucleoside reverse transcriptase inhibitors. The Journal of antimicrobial chemotherapy. 2007; 59(3):342–6. doi: 10.1093/jac/dkl524 PMID: 17255142
15. Sanne I, Mommeja-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. The Journal of infectious diseases. 2005; 191(6):825–9. doi: 10.1086/428093 PMID: 15717255
16. Law WP, Dore GJ, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996–2001. Aids. 2003; 17(15):2191–9. doi: 10.1097/01.aids.0000076348.42412.3a PMID: 14523276
17. Sarfo FS, Sarfo MA, Norman B, Phillips R, Chadwick D. Incidence and determinants of nevirapine and efavirenz-related skin rashes in West Africans: nevirapine's epitaph? PloS one. 2014; 9(4):e94854. PubMed Central PMCID: PMC3984248. doi: 10.1371/journal.pone.0094854 PMID: 24728406
18. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002; 35(1):182–9. doi: 10.1053/jhep.2002.30319 PMID: 11786975
19. Martin-Carbonero L, Nunez M, Gonzalez-Lahoz J, Soriano V. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. HIV clinical trials. 2003; 4(2):115–20. doi: 10.1310/N4VT-3E9U-4BKN-CRPW PMID: 12671779
20. Martinez E, Arnaiz JA, Podzamczer D, Dalmau D, Ribera E, Domingo P, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus

infection. The New England journal of medicine. 2003; 349(11):1036–46. doi: 10.1056/NEJMoa021589 PMID: 12968087

21. Martinez E, Blanco JL, Arnaiz JA, Perez-Cuevas JB, Mocroft A, Cruceta A, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. Aids. 2001; 15(10):1261–8. PMID: 11426070

22. Chu KM, Boulle AM, Ford N, Goemaere E, Asselman V, Van Cutsem G. Nevirapine-associated early hepatotoxicity: incidence, risk factors, and associated mortality in a primary care ART programme in South Africa. PloS one. 2010; 5(2):e9183. PubMed Central PMCID: PMC2822855. doi: 10.1371/journal.pone.0009183 PMID: 20174653

23. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of non-nucleoside reverse-transcriptase inhibitors. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2004; 38 Suppl 2:S80–9.

24. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. Journal of acquired immune deficiency syndromes. 2003; 34 Suppl 1:S21–33.

25. Ena J, Amador C, Benito C, Fenoll V, Pasquau F. Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients. International journal of STD & AIDS. 2003; 14(11):776–81.

26. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. Journal of acquired immune deficiency syndromes. 2001; 27(5):426–31. PMID: 11511818

27. Molina JM, Clumeck N, Orkin C, Rimsky LT, Vanveggel S, Stevens M, et al. Week 96 analysis of rilpivirine or efavirenz in HIV-1-infected patients with baseline viral load </ = 100 000 copies/mL in the pooled ECHO and THRIVE phase 3, randomized, double-blind trials. HIV medicine. 2014; 15(1):57–62. doi: 10.1111/hiv.12071 PMID: 23980523

28. Cohen CJ, Molina JM, Cassetti I, Chetchotisakd P, Lazzarin A, Orkin C, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. Aids. 2013; 27 (6):939–50. doi: 10.1097/QAD.0b013e32835cee6e PMID: 23211772

29. Nelson M, Amaya G, Clumeck N, Arns da Cunha C, Jayaweera D, Junod P, et al. Efficacy and safety of rilpivirine in treatment-naive, HIV-1-infected patients with hepatitis B virus/hepatitis C virus coinfection enrolled in the Phase III randomized, double-blind ECHO and THRIVE trials. The Journal of antimicrobial chemotherapy. 2012; 67(8):2020–8. PubMed Central PMCID: PMC4643643. doi: 10.1093/jac/dks130 PMID: 22532465

30. Sun HY, Ko WC, Tsai JJ, Lee HC, Liu CE, Wong WW, et al. Seroprevalence of chronic hepatitis B virus infection among taiwanese human immunodeficiency virus type 1-positive persons in the era of nationwide hepatitis B vaccination. The American journal of gastroenterology. 2009; 104(4):877–84. doi: 10.1038/ajg.2008.159 PMID: 19259078

31. Sun HY, Cheng CY, Lee NY, Yang CJ, Liang SH, Tsai MS, et al. Seroprevalence of hepatitis B virus among adults at high risk for HIV transmission two decades after implementation of nationwide hepatitis B virus vaccination program in Taiwan. PloS one. 2014; 9(2):e90194. PubMed Central PMCID: PMC3935970. doi: 10.1371/journal.pone.0090194 PMID: 24587275

32. Lee YC, Lin SW, Chen MY, Chang SY, Kuo CH, Sheng WH, et al. Presence of Tablet Remnants of Nevirapine Extended-Release in Stools and Its Impact on Virological Outcome in HIV-1-Infected Patients: A Prospective Cohort Study. PloS one. 2015; 10(10):e0140574. PubMed Central PMCID: PMC4605833. doi: 10.1371/journal.pone.0140574 PMID: 26465325

33. Tseng YT, Yang CJ, Chang SY, Lin SW, Tsai MS, Liu WC, et al. Incidence and risk factors of skin rashes and hepatotoxicity in HIV-infected patients receiving nevirapine-containing combination antiretroviral therapy in Taiwan. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2014; 29:12–7.

34. Lai CC, Liu WC, Fang CT, Yang JY, Chang LH, Wu PY, et al. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. The Journal of antimicrobial chemotherapy. 2016; 71(1):226–34. doi: 10.1093/jac/dkv284 PMID: 26404079

35. Lai CC, Hung CC, Chen MY, Sun HY, Lu CL, Tseng YT, et al. Trends of transmitted drug resistance of HIV-1 and its impact on treatment response to first-line antiretroviral therapy in Taiwan. The Journal of antimicrobial chemotherapy. 2012; 67(5):1254–60. doi: 10.1093/jac/dkr601 PMID: 22302562

36. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. National Institutes of Health. 2014.

37. Lin PH, Lai CC, Yang JL, Huang HL, Huang MS, Tsai MS, et al. Slow immunological progression in HIV-1 CRF07_BC-infected injecting drug users. Emerging microbes & infections. 2013; 2(12):e83. PubMed Central PMCID: PMC3880871.

38. Manosuthi W, Thongyen S, Chumpathat N, Muangchana K, Sungkanuparph S. Incidence and risk factors of rash associated with efavirenz in HIV-infected patients with preceding nevirapine-associated rash. HIV medicine. 2006; 7(6):378–82. doi: 10.1111/j.1468-1293.2006.00396.x PMID: 16903982

39. Peters PJ, Stringer J, McConnell MS, Kiarie J, Ratanasuwan W, Intalapaporn P, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count >/ = 250 cells/muL among women in Zambia, Thailand and Kenya. HIV medicine. 2010; 11(10):650–60. doi: 10.1111/j.1468-1293.2010.00873.x PMID: 20659176

40. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, Manosuthi W, et al. HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenetics and genomics. 2009; 19(2):139–46. doi: 10.1097/FPC.0b013e32831d0faf PMID: 19104471

41. Likanonsakul S, Rattanatham T, Feangvad S, Uttayamakul S, Prasithsirikul W, Tunthanathip P, et al. HLA-Cw*04 allele associated with nevirapine-induced rash in HIV-infected Thai patients. AIDS research and therapy. 2009; 6:22. PubMed Central PMCID: PMC2774340. doi: 10.1186/1742-6405-6-22 PMID: 19845952

42. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. The Journal of infectious diseases. 2002; 186(1):23–31. doi: 10.1086/341084 PMID: 12089658

43. Ford N, Calmy A, Andrieux-Meyer I, Hargreaves S, Mills EJ, Shubber Z. Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis. Aids. 2013; 27(7):1135–43. doi: 10.1097/QAD.0b013e32835e0752 PMID: 23299174

44. John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? Aids. 1998; 12 (17):2289–93. PMID: 9863871

45. Ragni MV, Bontempo FA. Increase in hepatitis C virus load in hemophiliacs during treatment with highly active antiretroviral therapy. The Journal of infectious diseases. 1999; 180(6):2027–9. doi: 10.1086/315143 PMID: 10558963

46. Yang JJ, Huang CH, Liu CE, Tang HJ, Yang CJ, Lee YC, et al. Multicenter study of trimethoprim/sulfamethoxazole-related hepatotoxicity: incidence and associated factors among HIV-infected patients treated for Pneumocystis jirovecii pneumonia. PloS one. 2014; 9(9):e106141. PubMed Central PMCID: PMC4153565. doi: 10.1371/journal.pone.0106141 PMID: 25184238

47. Kovari H, Sabin CA, Ledergerber B, Ryom L, Reiss P, Law M, et al. Antiretroviral Drugs and Risk of Chronic Alanine Aminotransferase Elevation in Human Immunodeficiency Virus (HIV)-Monoinfected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Open forum infectious diseases. 2016; 3(1):ofw009. PubMed Central PMCID: PMC4767274. doi: 10.1093/ofid/ofw009 PMID: 26925429

The Journal of Infectious Diseases
MAJOR ARTICLE

Long-term Durability of Responses to 2 or 3 Doses of Hepatitis A Vaccination in Human Immunodeficiency Virus–Positive Adults on Antiretroviral Therapy

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Background. Previous studies have shown that the durability of serological response is impaired in successfully vaccinated human immunodeficiency virus–1 (HIV-1) positive subjects after receiving 2 doses of inactivated hepatitis A virus (HAV) vaccine. We evaluated whether 3 doses compared with 2 doses of HAV vaccine could improve the long-term seroprotection for this susceptible group.

Methods. Antibody persistence among HIV-positive men who have sex with men aged 18–40 years who had received 2 or 3 doses of HAV vaccine according to a 0–6- or a 0–1–6-month schedule was evaluated biannually for 5 consecutive years in this prospective, nonrandomized cohort study.

Results. At the end of 5 years, seroprotection persisted in 79% (146/185) versus 76% (85/110) and 94% (146/155) versus 88% (84/95) of the 3- versus 2-dose primary responders by intention-to-treat and per-protocol analyses, respectively ($P > .05$). Throughout the 5 years, the geometric mean concentrations of anti-HAV immunoglobulin G (IgG) were significantly higher for the 3-dose than the 2-dose group. In the multivariable analysis, a 3-dose regimen compared with a 2-dose regimen (odds ratio = 3.36; 95% confidence interval = 1.14–9.93) was independently associated with sustained seroprotection.

Conclusions. Three doses versus 2 doses of HAV vaccine improve the durability of immune responses in terms of higher concentrations of specific IgG, which take longer to decay to subthreshold levels.

Keywords. long-term antibody persistence; hepatitis A vaccine; immunogenicity; seroresponsiveness; seroprotection.

Hepatitis A virus (HAV) infection is the most common form of acute viral hepatitis worldwide [1]. Approximately 1.4 million clinical cases and tens of millions of HAV infections occur every year, although these figures are likely to underestimate the high proportion of asymptomatic cases [1]. The case fatality rate is low, however, ranging from 0.1% in children aged <15 years to 2.1% in adults aged >40 years [1, 2]. Improved sanitation in many parts of the world, including Taiwan, has resulted in a greater proportion of the population remaining susceptible to the disease, which is more severe in adulthood [2–6].

Among persons living with human immunodeficiency virus (HIV), men who have sex with men (MSM) are more susceptible to HAV infection. Among such individuals, HAV infection is approximately 1.5–3 times more prevalent than among the general population [7, 8] and causes more episodes of severe disease, partly due to the higher burden of chronic liver disease [9–11]. Moreover, HIV-positive individuals have higher peak HAV loads and prolonged duration of viremia, with important public health consequences for transmission within the community [12]. Although routine vaccination of HIV-positive adults is not widely accepted, the World Health Organization, the US Advisory Committee on Immunization Practices guidelines, the British HIV Association (BHIVA) guidelines for the immunization of HIV-positive adults, and the European AIDS Clinical Society all recommend vaccinating HIV-positive persons if other risk-conferring lifestyle or medical conditions concur [13–16]. Men who have sex with men and injection drug users are considered at higher risks of acquiring HAV [8, 17, 18]. For these at-risk HIV-positive persons, the most widely recommended vaccination schedule is 2 doses of formaldehyde-inactivated vaccine separated by 6–12 months [1].

Compared with healthy controls, the immune response to the HAV vaccine is impaired in HIV-positive patients, with seroconversion rates after 2 doses of vaccine ranging 48.5%–93.9% [1]. Moreover, the duration of protection is impaired in successfully vaccinated HIV-positive patients [19] such that the BHIVA recommends a booster vaccine dose every

Received 7 June 2016; editorial decision 1 December 2016; accepted 7 December 2016; published online December 23, 2016.

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The Journal of Infectious Diseases® 2017;215:606–13

DOI:10.1093/infdis/jiw605

5 years [16, 20]. However, few studies have assessed the duration of protection provided by HAV vaccination in HIV-positive adults, and none have assessed the duration of protection provided by >2 doses of HAV vaccination beyond the 4th year [20, 21]. Although previously Launay et al and our group have demonstrated that addition of a 3rd dose can augment both the proportion of primary responders and the absolute concentrations of HAV antibodies shortly after vaccination, the aim of this study was to determine whether the dose–response persists in the long-term with implications on how many doses to be delivered in the primary series and the timing of booster doses for this vulnerable population [22, 23].

METHODS

Study Population and Settings

This prospective cohort study of HIV-positive males aged 18–40 years who were HAV vaccine-naive and seronegative for anti-HAV immunoglobulin G (IgG) at baseline was conducted at the National Taiwan University Hospital. Subjects were vaccinated with 2 or 3 doses of HAV vaccine (HAVRIX 1440) between June 2009 and December 2010 according to a 0–6-month schedule (2 doses) or 0–1–6-month schedule (3 doses) as previously described [23]. All participants were then followed for 5 years, and serum samples were obtained biannually at months 12, 18, 24, 30, 36, 42, 48, 54, and 60 for determination of anti-HAV antibody titers.

Before and throughout the study period, participants had free access to regular outpatient HIV care including combination antiretroviral therapy (cART) and monitoring of CD4 cell count and plasma HIV RNA load as part of the public health program of Taiwan Centers for Disease Control for HIV infection and AIDS. cART was defined as the use of at least 3 agents from at least 2 classes of antiretroviral agents according to the local treatment guidelines. The study was approved by the Research Ethics Committee of the hospital, and the participants gave written informed consent (registration no. 200903063M).

Laboratory Methods

The anti-HAV antibody titers were determined with the use of a commercially available enzyme-linked immunosorbent assay method (ETI-AB-HAVK PLUS; DiaSorin, Saluggia, Italy) [23]. The laboratory staff was unaware of the doses of HAV vaccine the subjects had received. Plasma HIV RNA load was quantified using the Cobas Amplicor HIV-1 Monitor test with a lower detection limit of 20 copies/mL, and CD4 count was determined using FACFlow (BD FACS Calibur, Becton Dickinson, CA). The CD4 counts and plasma HIV RNA load were monitored 1 month after initiation of cART in antiretroviral-naive participants or after a change of regimens for virological failure and every 3–6 months thereafter.

Definitions

Seroconversion was defined by anti-HAV antibody concentrations of ≥20 mIU/mL. Participants were classified as primary responders if they had documented seroconversion at month 12 (ie, 6 months after the last vaccine dose and before month 18). Those lacking seroconversion at month 12 and before month 18 were classified as primary nonresponders. Primary responders were followed for the persistence of antibody responses for the next 4 years at 6-month intervals and were considered to have lost seroprotection (be seroreverters) if their anti-HAV IgG levels dropped to <20 mIU/mL during follow-up and remained <20 mIU/mL. Vaccinees with a one-off IgG level <20 mIU/mL that recovered to ≥20 mIU/mL at the next testing without meeting the definition of a natural booster event were considered technical blips and not seroreverters. In the per-protocol analysis of the persistence of the antibody responses to vaccination, vaccinees with missing serological data were excluded. In the intention-to-treat analysis, vaccinees with missing serological data were considered as seroreverters.

Natural booster events among primary responders by exposure to circulating HAV were defined by any sustained secondary rises of ≥2-fold magnitude above the preceding anti-HAV IgG titers after an initial decline in IgG titers that was otherwise unexplained by additional booster dose(s) of HAV vaccines. A crude incidence rate of HAV acquisition was calculated from the number of natural booster events.

Late seroconversion occurring after month 18 among the primary nonresponders were classified as (1) late effects of vaccination and immune restoration when subthreshold titers increase gradually from 1–19 to ≥20 mIU/mL and were sustained for at least 6 months or as (2) responses following natural HAV infection if anti-HAV IgG increased suddenly from below the level of detection (ie, 0 mIU/mL) to ≥2-fold the threshold value of protection (ie, >40 mIU/mL) at any point during follow-up and was sustained for at least 6 months in the absence of additional vaccination(s).

Statistical Analysis

The analyses were conducted using the statistical package SAS 9.2. Chi-square tests or, if necessary, Fisher's exact tests were used for categorical variables. Student's *t* and Mann–Whitney *U* tests were used for numerical variables. Because observations were made over time periods, generalized estimating equations to account for the interdependence among observations were used to compare mean response rates to different HAV vaccine doses, with adjustments made for time-updated variables, including the patient's age at time of vaccination and at each testing, the CD4 cell counts >350 cells/μL at baseline and CD4 gains at each testing (in increments of 50 cells/μL), suppressed plasma HIV RNA load to <20 copies/mL at baseline and each testing, receipt of cART at time of vaccination and at each testing, baseline hepatitis B coinfection defined by the presence of

hepatitis B surface antigen at time of vaccination, hepatitis C virus (HCV) infection defined by the seroconversion of anti-HCV antibody, or syphilis defined as an acute 4-fold increase in rapid plasma reagin titers combined with clinical findings compatible with early syphilis (primary, secondary, or early latent syphilis) or confirmed by the *Treponema pallidum* hemagglutination assay during the study period. A stepwise model comparison and selection were used to determine the final model. We used the SAS PROC GENMOD procedure to fit generalized estimating equation models. Odds ratios (ORs) for each prognostic factor and 95% confidence intervals (CIs) were also calculated. All statistical tests were 2-tailed, and P values <.05 were considered significant.

RESULTS

The study cohort comprised 365 HIV-positive MSM with a mean age of 30 (standard deviation [SD] = 5.2) years and CD4 count of 485 (SD = 215) cells/μL. Of 365 vaccinees, 334 had their anti-HAV titers determined at month 12 and could be classified as primary responders or nonresponders. There were 110 (87.3%) primary responders and 16 (12.7%) nonresponders among the 126 vaccinees who received 2 doses of HAV vaccine, and 185 (88.9%) primary responders and 23 (11.1%) nonresponders among the 208 vaccinees who received 3 doses and were followed beyond month 12 (Figure 1). The clinical characteristics of the overall cohort and these 4 subgroups are shown in Table 1.

At baseline, there were significant differences between the 2-dose and 3-dose primary responders, with the former having higher baseline CD4 counts (560 vs 470 cells/μL), lower plasma HIV RNA load (2.5 vs 2.9 $\log_{10}$ copies/mL), and higher cART coverage (70.0% vs 58.9%). With regards to viral hepatitis and syphilis coinfections, the proportions of patients with chronic viral hepatitis were comparable between the 2 groups, although prior syphilis was more frequent among the 2-dose versus the 3-dose responders (24.7% vs 14.2%; P = .03). Despite these differences, the crude primary response rates of the 3-dose group with more advanced HIV disease were noninferior to the 2-dose group (88.9% vs 87.3%; P = .65). After matching baseline immunologic and virologic characteristics, the primary response of the 3-dose group by per-protocol analysis was in fact higher than the 2-dose group (91.7% vs 81.6%; P = .04; data not shown because it was previously reported in our earlier study [23]).

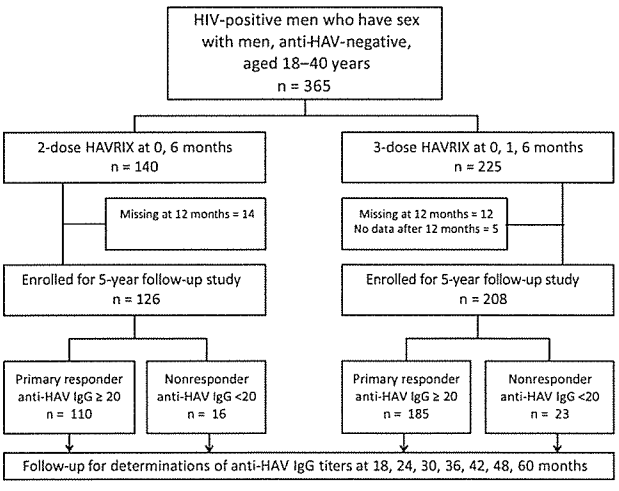

Figure 1. Study flow of human immunodeficiency virus–positive men who have sex with men who received 2 or 3 doses of inactivated hepatitis A vaccine (HAVRIX). Abbreviations: HAV, hepatitis A virus; IgG, immunoglobulin G.

Within dosing groups, there were marked differences in the surrogate markers of baseline immune status between primary responders and nonresponders, particularly for the 3-dose group, with nonresponders having, as expected, lower mean CD4 counts than responders (415 vs 560 cells/μL, P = .02 for the 2-dose group; 315 vs 470 cells/μL, P = .001 for the 3-dose group). There were also significantly fewer subjects with undetectable plasma HIV RNA load at the time of vaccination among those who did not seroconvert compared with those who seroconverted after 3 doses of vaccination (21.7% vs 43.8%; P = .046).

At the end of the 5-year study, the overall mean CD4 counts and the proportions of viral suppression and subjects taking cART had increased from 485 (SD = 215) at baseline to 635 (SD = 252) cells/μL, from 44.1% to 80.2%, and from 61.6% to 91.2%, respectively. Because of universal access to HIV care, there were no longer any significant differences in the CD4 counts, plasma HIV RNA load, and treatment status between the subgroups at the end of the 5 years of follow-up.

Persistence of Serological Responses Among Primary Responders

The percentages of persistent responders classified by anti-HAV IgG titers of ≥20 mIU/mL by intention-to-treat and per-protocol analyses in the following years are shown in Figure 2 (and the Supplementary Table). The proportion of vaccinees with persistent seroprotection waned over time from 87.0% and 90.0% at 18 months to 76.4% and 78.9% after 60 months for the 2-dose and 3-dose groups, respectively, by intention-to-treat and from 93.4% and 94.7% at 18 months to 88.4% and 94.2% after 60 months for the 2-dose and 3-dose groups, respectively, by per-protocol analysis. However, persistent seroprotection was more consistently observed for the 3-dose vaccinees compared with the 2-dose vaccinees, although the difference between the 2 groups was only statistically significant in the per-protocol analysis in the 2nd–4th years after vaccination. The Kaplan-Meier curves also show a nonsignificant trend toward better maintained levels of seroprotection for the 3-dose versus 2-dose group (Figure 3), whereas the geometric mean concentrations of specific anti-HAV IgG were consistently maintained at a higher level for the 3-dose group compared with the 2-dose group throughout the 5 years of follow-up (Figure 4).

Table 1. Baseline and End-of-Study Characteristics of Human Immunodeficiency Virus–positive Men Who Have Sex With Men After 2 or 3 Doses of Hepatitis A Vaccine (HAVRIX) Who Were Followed for 5 Years After Vaccination Classified by Initial Seroconversion Status

Characteristic	All vaccinees n = 365	Two-dose primary responders n = 110	Three-dose primary responders n = 185	Two-dose nonresponders n = 16	Three-dose nonresponders n = 23	Significant *P* only for groups */**
Age at vaccination, years, mean (SD)	30.2 (5.2)	31.0 (5.6)	29.8 (5.1)	31.2 (4.4)	30.9 (4.9)	…
Baseline CD4, cells/μL, mean (SD)	485 (215)	560 (232)*	470 (195)*	415 (169)	315 (152)	<.001
Baseline CD4 < 200 cells/μL, % (n)	7.1 (26)	1.8 (2)*	7.0 (13)*	6.3 (1)**	34.8 (8)**	.05/.06
Baseline CD4 > 500 cells/μL, % (n)	43.4 (158)	57.8 (63)*	41.6 (77)*	12.5 (2)	13.0 (3)	.01
Baseline PVL, log_{10}, copies/mL, mean (SD)	2.8 (1.3)	2.5 (1.2)*	2.9 (1.4)*	2.8 (1.3)	3.3 (1.2)	.01
Baseline undetected PVL, % (n)	44.1 (161)	53.6 (59)	43.8 (81)	37.5 (6)	21.7 (5)	…
Baseline cART, % (n)	61.6 (225)	70.0 (77)*	58.9 (109)*	56.3 (9)	62.5 (15)	.06
Chronic hepatitis B, % (n)	13.9 (50/359)	14.5 (16)	12.6 (25)	6.3 (1)	26.1 (6)	…
Chronic hepatitis C, % (n)	5.5 (20/363)	5.5 (6)	5.4 (10)	6.3 (1)	4.3 (1)	…
Syphilis history, % (n)	20.3 (60/296)	24.7 (24)*	14.2 (23)*	21.4 (3/11)	31.6 (6/19)	.03
Smoking, % (n)	43.2 (144/333)	45.7 (48/105)	42.0 (71/169)	62.5 (10/16)*	27.3 (6/22)*	.03
End-of-study CD4, cells/μL, mean (SD)	635 (252)	653 (221)	642 (264)	668 (275)	531 (200)	…
End-of-study CD4 < 200 cells/μL, % (n)	1.4 (4/284)	0 (0/96)	1.3 (2/155)	6.3 (1/16)	5.6 (1/18)	…
End-of-study CD4 > 500 cells/μL, % (n)	74.6 (212/284)	88.6 (77/96)	73.5 (114/155)	66.8 (11/16)	55.6 (10/18)	…
End-of-study PVL, log_{10}, copies/mL, mean (SD)	1.6 (0.9)	1.7 (1.0)	1.6 (0.9)	1.6 (0.9)	1.4 (0.2)	…
End-of-study undetected PVL, % (n)	80.2 (243/303)	78.9 (75/95)	84.5 (131/155)	81.3 (13/16)	76.5 (13/19)	…
End-of-study cART, % (n)	91.2 (279/306)	87.6 (85)	91.7 (144)	93.8 (15)	100.0 (19/19)	…

Abbreviations: cART, combination antiretroviral therapy; PVL, plasma HIV RNA load; SD, standard deviation.

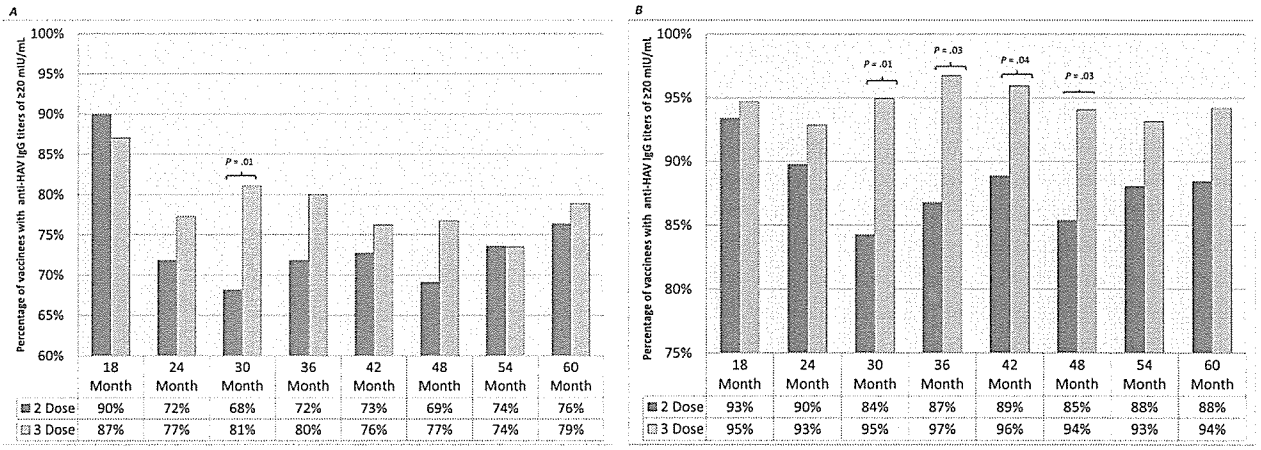

Figure 2. Percentage of persistent responders classified by anti–hepatitis A virus (HAV) immunoglobulin G (IgG) titers of ≥20 mIU/mL by intention-to-treat (*A*) and per-protocol analysis (*B*) in the 5 years following vaccination with 2 or 3 doses of hepatitis A vaccine.

Multivariable Analysis for Factors Associated With Persistent Seroprotection

Because of the differences in surrogate markers of immune status and risk behavior between the 2 dosing groups at baseline, a multivariable analysis was conducted to identify the factors associated with persistent seroprotection, as shown in Table 2. One additional dose of HAV vaccine in this study was associated with long-term persistence of seroprotection (adjusted OR [aOR] = 3.36; 95% CI = 1.14–9.93; P = .03), as was acquisition of syphilis during the follow-up period (aOR = 3.73; 95% CI = 1.00–13.9; P = .05). In contrast, acute HCV seroconversion during the follow-up was associated with loss of seroprotective responses (aOR = 0.08; 95% CI = .01–.48; P = .01).

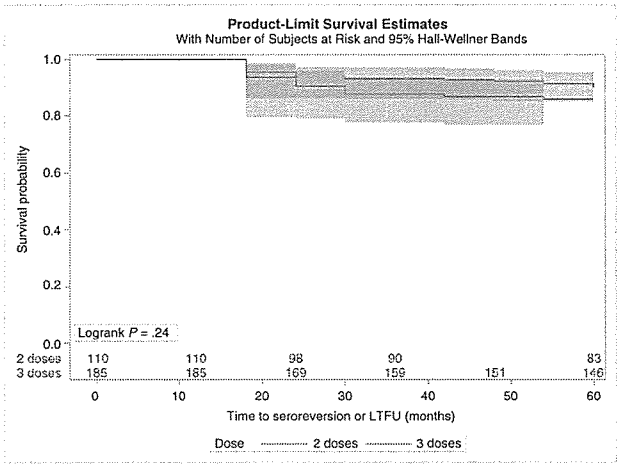

Figure 3. Kaplan-Meier curves plotting the time to seroreversion (in months) stratified by dosing groups. The shaded areas indicate the 95% confidence intervals, and the numbers above the X-axis indicate the pointwise numbers at risk. Abbreviations: LTFU – loss-to-follow up.

Natural Boosters Among Primary Responders

Only 45.1% (133/295) of the primary responders had anti-HAV IgG concentrations that peaked at 12 months after vaccination and decayed gradually in a stepwise manner from the start of the study to the end of the follow-up period. The remainder (54.9%; 162/295) had either late peaking of anti-HAV IgG concentrations or sustained secondary rises of anti-HAV IgG after an initial decline during the following 4 years. When the secondary rises were of ≥2-fold magnitude above the previous anti-HAV IgG and sustained for 6 months, these were classified as natural booster events from exposure to circulating wild-type HAV. According to this definition, the overall crude incidence rate of HAV exposure among the primary responders was 19.6 per 1000 person-years of follow-up (PYFU), with a slightly higher incidence rate among 2-dose versus 3-dose vaccinees (21.9 vs 18.2 per 1000 PYFU). These episodes were asymptomatic, and only 3 were associated with modest elevations of either total serum bilirubin (to 3.76 mg/dL) or hepatic transaminases (within 3 times the upper limit of normal).

Late Seroconversion of Primary Nonresponders

Of the 16 nonresponders after 2 doses of HAV vaccination, 6 (37.5%) subsequently seroconverted, whereas of the 23 nonresponders after 3 doses of HAV vaccination, 11 (47.8%) subsequently seroconverted. Of these late seroconverters, the majority were classified as late effects of vaccination (5 in the 2-dose group and 9 in the 3-dose group). Only 1 late seroconversion in the 2-dose group and 2 seroconversions in the 3-dose group were classified as possibly due to asymptomatic HAV acquisition.

DISCUSSION

In this prospective long-term study of the durability of seroprotection conferred by vaccination with 2 or 3 doses of inactivated

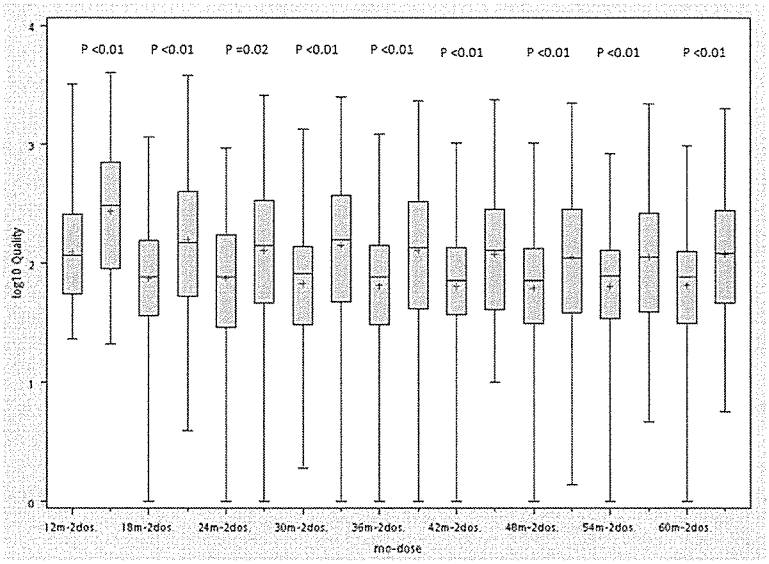

Figure 4. The sequential geometric mean concentrations of serum anti–hepatitis A virus (HAV) immunoglobulin G (IgG) were significantly higher for human immunodeficiency virus (HIV)–positive males receiving 3 vs 2 doses of HAV vaccine throughout the 5 years of follow-up.

HAV vaccine (HAVRIX 1440) among HIV-positive MSM, we documented that anti-HAV IgG titers ≥20 mIU/mL were maintained by 88.4% and 94.2% of primary responders in the 2- and 3-dose groups, respectively. The 3-dose schedule appeared to achieve the durability of immune responses generated by a 2-dose schedule in healthy individuals, in whom protective antibody levels have been shown to persist beyond 10 years and underlying immune memory has been shown to provide protection far beyond the duration of anti-HAV antibodies [24]. Our findings suggest that, given immune reconstitution with cART and a primary 3-dose vaccine series, booster vaccinations after 5 years as recommended by the BHIVA may not be necessary in HIV-positive individuals in the same way that boosters are not recommended in healthy individuals.

Table 2. Multivariable Analysis of Factors Associated With Persistent Seroprotective Responses Defined by Anti–Hepatitis A Virus Immunoglobulin G Levels of ≥20 mIU/mL 5 Years After Vaccination With 2 or 3 Doses of Inactivated Hepatitis A Vaccine in Human Immunodeficiency Virus–Positive Men Who Have Sex With Men

Variable	aOR	95% CI	*P* value
3 doses vs 2 doses	3.36	1.14–9.93	.03
Age at vaccination >30 vs < 30 years	0.93	.32–2.69	.89
Baseline combination ART vs treatment naive	1.63	.62–4.30	.33
Baseline CD4 >350 vs < 350 cells/μL	1.36	.50–3.71	.55
Time-updated CD4 counts (per 50-cell/μL increase)	0.98	.95–1.01	.18
Undetectable plasma HIV RNA level at every test	0.99	.52–1.90	.98
Baseline positive HBsAg vs negative HBsAg	1.21	.27–5.36	.80
Baseline positive anti-HCV vs negative anti-HCV	0.76	.08–7.29	.81
cART treatment status at every test	0.49	.15–1.56	.23
Syphilis during follow-up	3.73	1.00–13.90	.05
HCV seroconversion during follow-up	0.08	.01–0.48	.01
Smoker vs non-smoker	2.30	.82–6.44	.11

Smokers were defined as those who reported to have smoked at least 100 cigarettes in their lifetime. Those who reported never having smoked 100 cigarettes were defined as never smoker.

Abbreviations: aOR, adjusted odds ratio; cART, combination antiretroviral therapy; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

In addition, we confirm that the geometric mean concentrations of anti-HAV IgG were higher following 3 doses rather than 2 doses of HAV vaccination, rendering these titers more robust to rapid decline to subthreshold levels, despite the baseline lower CD4 counts, higher plasma HIV RNA load, and lower cART coverage of the 3-dose group. Furthermore, more late seroconversions, possibly as a delayed effect of cART, were observed among the primary nonresponders following 3 doses rather than 2 doses of vaccination (47.8% vs 37.5%). The multivariable analysis confirmed that the addition of a vaccine dose sandwiched at week 4 between the 0- and 6-month doses was an independent predictor of durable protection after 5 years (aOR = 3.36; $P = .03$). This dose–response sustainability has also been observed following vaccination with 7-valent pneumococcal conjugate vaccine and recombinant hepatitis B vaccine in HIV-positive persons receiving cART [25, 26].

The multivariable analysis also identified recent episodes of syphilis during the follow-up period to be associated with persistent responses (aOR = 3.73; $P = .05$). Given the shared routes of transmission (through oral–anogenital sexual transmission) between syphilis [27] and HAV, it is possible that acute syphilis is associated with natural booster events by wild-type circulating HAV, which appears not to be uncommon in our relatively young cohort of sexually active MSM [28]. Because there is a

lack of serological marker of natural HAV infection, unlike that represented by the antibody against the hepatitis B core antigen for hepatitis B infection, we used the arbitrary definition of an otherwise unexplained sustained ≥2-fold rise in anti-HAV IgG following an initial decline. Overall, 26 of the primary responders (11 in the 2-dose group and 15 in the 3-dose group) met the criteria for asymptomatic HAV acquisition, giving rise to a crude incidence rate of 19.6 per 1000 PYFU.

On the other hand, acute HCV infection in the follow-up period was a risk factor for loss of protective levels of anti-HAV IgG. Although HCV is also sexually acquired [29], it is known to suppress the host immune response [30] by infecting immune cells, such as macrophages, B cells, and T cells, as well as interfering with host immune responses through the endogenous interferon system [31], T cell function [32], and possibly also dendritic cell function [33]. Hence, it is possible that the immunomodulatory effects of HCV infection predominate and lead to loss of sustained antibody production.

Neither the CD4 cell count nor suppression of HIV replication at time of vaccination was predictive of the development of anti-HAV in our regression analysis in contrast with other published studies [21, 34, 35]. This may be because of the relatively low proportion of patients in our study with very low CD4 cell counts, but notably, only 1 other study, which had 26 patients with long-term follow-up data, has vaccinated patients with >2 vaccine doses [21]. Our data imply that the addition of a 3rd dose of HAV vaccine can ameliorate the degree of immune impairment at baseline, although individuals with more advanced HIV disease may need more time to develop immunity consistent with data from other studies of HAV vaccination among immunocompromised populations [20].

There are several limitations to this study, and interpretation of our findings should be cautious. First, this was not a randomized controlled trial. Therefore, 3 doses may not outperform 2 in the long run because the proportions of primary responders with persistent seroprotection at 5 years were not statistically different between the 2 dosing groups. However the 3-dose group had significantly lower CD4 cell counts at baseline. Hence, whether subsets of HIV-positive persons with initial low CD4 counts or risk factors such as viral hepatitis would benefit from a 3-dose schedule deserves further study. In addition, any potential benefits of adding a 3rd dose should be weighed against the additional costs incurred. Second, no clinical endpoints to determine vaccine efficacy were studied. Third, our population was comprised entirely of young MSM in an area of low to intermediate HAV endemicity [2]. Hence whether the findings are generalizable to injecting drug users, women or children coinfected with HIV, or individuals residing in areas of higher HAV endemicity remains to be proven.

In conclusion, in this prospective, nonrandomized longitudinal study, the 3-dose group with lower baseline CD4 counts and higher plasma HIV RNA load compared with the 2-dose group maintained higher antibody concentrations but similar seroprotection rates after 5 years. Therefore, 3 doses may overcome the poor responses observed for those with more advanced immunosuppression and render these responses longer lasting because higher titers take longer to serorevert. However, given concurrent cART and subtle immunosuppression, 2 standard doses also achieved highly durable seroprotection (>75%), rendering additional doses or booster vaccinations of questionable relevance for this population.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We would like to thank the patients and their family for participation in this study and Taiwan Centers for Disease Control for research grant support. A. C., S.-Y. C., C.-C. H., and S.-C. C conceived and designed the experiments. S.-Y. C., W.-C. L., Y.-C. S., and P.-Y. W. performed the experiments. A. C., S.-Y. C., H.-Y. S., M.-S. T., and C.-C. H. analyzed the data. A. C., H.-Y. S., M.-S. T., C.-C. H., and S.-C. C wrote the paper.

Financial support. This study was supported by grants from the Centers for Disease Control, Taiwan (grant nos. DOH102-DC-1401 and MOHW103-CDC-C-114-000405 to C.-C. H.). The funding source had no role in study design and conduct; data collection, analysis, or interpretation; or in the writing of the manuscript or the decision to submit it for publication.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Mena G, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: a review. Hum Vaccin Immunother **2015**; 11:2582–98.
2. Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. Curr Opin Infect Dis **2015**; 28:488–96.
3. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine **2010**; 28:6653–7.
4. Chen JY, Chiang JC, Lu SN, et al. Changing prevalence of anti-hepatitis A virus in adolescents in a rural township in Taiwan. Chang Gung Med J **2010**; 33:321–6.
5. Forbes A, Williams R. Increasing age—an important adverse prognostic factor in hepatitis A virus infection. J R Coll Physicians Lond **1988**; 22:237–9.
6. Tseng YT, Sun HY, Chang SY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18–40 years in Taiwan. J Formos Med Assoc **2012**; 111:431–8.
7. Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. N Engl J Med **1980**; 302:435–8.
8. Sun HY, Kung HC, Ho YC, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis **2009**; 13:e199–205.
9. Sung JJ. Epidemiology of hepatitis A in Asia and experience with the HAV vaccine in Hong Kong. J Viral Hepat **2000**; 7:27–8.
10. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med **1998**; 338:286–90.
11. Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med **1998**; 128:111–4.
12. Ida S, Tachikawa N, Nakajima A, et al. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. Clin Infect Dis **2002**; 34:379–85.

13. WHO position paper on hepatitis A vaccines—June 2012. Wkly Epidemiol Rec **2012**;87:261–76.
14. Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for use of hepatitis A vaccine in close contacts of newly arriving international adoptees. MMWR Morb Mortal Wkly Rep **2009**; 58:1006–7.
15. European AIDS Clinical Society (EACS). European Guidelines for treatment of HIV-infected adults in Europe. Version 7.1. 2014:55.
16. Geretti AM, Brook G, Cameron C, et al. British HIV Association guidelines for immunization of HIV-infected adults 2008. HIV Med **2008**; 9:795–848.
17. Villano SA, Nelson KE, Vlahov D, Purcell RH, Saah AJ, Thomas DL. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. Clin Infect Dis **1997**; 25:726–8.
18. Chan PC. Reemerging threat of hepatitis A among men who have sex with men in Taiwan. J Formos Med Assoc **2014**; 113:985–6.
19. Kernéis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boëlle PY. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. Clin Infect Dis **2014**; 58:1130–9.
20. Garcia Garrido HM, Wieten RW, Grobusch MP, Goorhuis A. Response to hepatitis A vaccination in immunocompromised travelers. J Infect Dis **2015**; 212:378–85.
21. Kernéis S, Desaint C, Brichler S, et al. Long-term persistence of humoral immunity after hepatitis A vaccination in HIV-infected adults. J Acquir Immune Defic Syndr **2011**; 57:e63–6.
22. Launay O, Grabar S, Gordien E, et al. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC study. J Acquir Immune Defic Syndr **2008**; 49:272–5.
23. Tseng YT, Chang SY, Liu WC, et al. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. Hepatology **2013**; 57:1734–41.
24. Van Damme P, Banatvala J, Fay O, et al. Hepatitis A booster vaccination: is there a need? Lancet **2003**; 362:1065–71.
25. Cheng A, Chang SY, Tsai MS, et al. Long-term immune responses and comparative effectiveness of one or two doses of 7-valent pneumococcal conjugate vaccine (PCV7) in HIV-positive adults in the era of combination antiretroviral therapy. J Int AIDS Soc **2016**; 19:20631.
26. Launay O, Rosenberg AR, Rey D, et al. Long-term immune response to hepatitis B virus vaccination regimens in adults with human immunodeficiency virus 1: secondary analysis of a randomized clinical trial. JAMA Intern Med **2016**; 176:603–10.
27. Yang CJ, Chang SY, Wu BR, et al. Unexpectedly high prevalence of *Treponema pallidum* infection in the oral cavity of human immunodeficiency virus-infected patients with early syphilis who had engaged in unprotected sex practices. Clin Microbiol Infect **2015**; 21:787.e781–7.
28. Chang YH, Liu WC, Chang SY, et al. Associated factors with syphilis among human immunodeficiency virus-infected men who have sex with men in Taiwan in the era of combination antiretroviral therapy. J Microbiol Immunol Infect **2014**; 47:533–41.
29. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. Int J Infect Dis **2016**; 49:47–58.
30. Soguero C, Joo M, Chianese-Bullock KA, Nguyen DT, Tung K, Hahn YS. Hepatitis C virus core protein leads to immune suppression and liver damage in a transgenic murine model. J Virol **2002**; 76:9345–54.
31. Foy E, Li K, Wang C, et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science **2003**; 300:1145–8.
32. Large MK, Kittlesen DJ, Hahn YS. Suppression of host immune response by the core protein of hepatitis C virus: possible implications for hepatitis C virus persistence. J Immunol **1999**; 162:931–8.
33. Bain C, Fatmi A, Zoulim F, Zarski JP, Trépo C, Inchauspé G. Impaired allostimulatory function of dendritic cells in chronic hepatitis C infection. Gastroenterology **2001**; 120:512–24.
34. Weissman S, Feucht C, Moore BA. Response to hepatitis A vaccine in HIV-positive patients. J Viral Hepat **2006**; 13:81–6.
35. Overton ET, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. J Viral Hepat **2007**; 14:189–93.

The Journal of Infectious Diseases
CORRESPONDENCE

Hepatitis A Outbreak Among Men Who Have Sex With Men in a Country of Low Endemicity of Hepatitis A Infection

To the Editor—We read with interest the recent article by Manor et al [1] on an outbreak of hepatitis A virus (HAV) infection originating among injecting drug users and homeless adults in Tel Aviv, and subsequently spreading to the general population in Tel Aviv metropolitan region. From analyses of clinical and sewage samples, Manor et al presented phylogenetic evidence to suggest that HAV had continued to circulate endemically in Israel despite the universal toddlers' vaccination (UTV) program in place since 1999, and finally resulted in the outbreak in Tel Aviv in 2012–2013.

In the United States [2], Australia [3], and Korea [4], reports have also demonstrated an increase of the seroprevalence of anti-HAV immunoglobulin G (IgG) and a decrease of acute hepatitis A incidence with the implementation of large-scale vaccination programs. In Israel, the seroprevalence of anti-HAV IgG is 80%–90% in children who are covered by the UTV program; in contrast, the seropositivity is only ≤57% in adult populations who are not included in the UTV program. Furthermore, compliance with HAV vaccines was generally low in at-risk groups, such as men who have sex with men (MSM) or injection drug users [5], which may increase the risk of subsequent HAV outbreaks.

Before 1980, Taiwan was a country of high HAV endemicity. However, recent surveys suggest that seropositivity has declined significantly among Taiwanese children, with the improvement of sanitation and implementation of HAV vaccination for toddlers in townships with a high incidence of acute hepatitis A after 1995. In a survey conducted in central Taiwan in 2010, the seroprevalence of anti-HAV antibody was only 2.3% among schoolchildren aged <15 years [6]. The incidence of acute hepatitis A declined significantly in both vaccine-covered townships and non-vaccine-covered townships [7].

The seropositivity in young, high-risk populations was also low in Taiwan. The seroprevalence among human immunodeficiency virus (HIV)–infected MSM aged <40 years was 27.5% in a survey between 2004 and 2007 [8]. In another survey conducted among young HIV-infected and HIV-uninfected MSM aged 18–40 years between 2009 and 2010, the overall HAV seroprevalence further decreased to 10.4% [9]. Although HAV vaccination is recommended for high-risk populations by the Adult Committee on Immunization Practices (ACIP) of Taiwan's Centers for Disease Control (CDC), compliance has been low.

Since June 2015, 2 indigenous cases of acute hepatitis A in patients coinfected with HIV were reported to the Taiwan CDC; the number of indigenous cases of acute hepatitis A increased thereafter, with >1000 indigenous cases reported in 2016 (Figure 1), and >70% of the cases concentrated in northern Taiwan [10]. At least 70% of the cases were in MSM; 60% had HIV infection and >60% had syphilis, gonorrhea, or shigellosis; and subgenotype IA was identified as the strain causing the outbreak (Taiwan CDC, unpublished data). In response to this unprecedented outbreak of acute

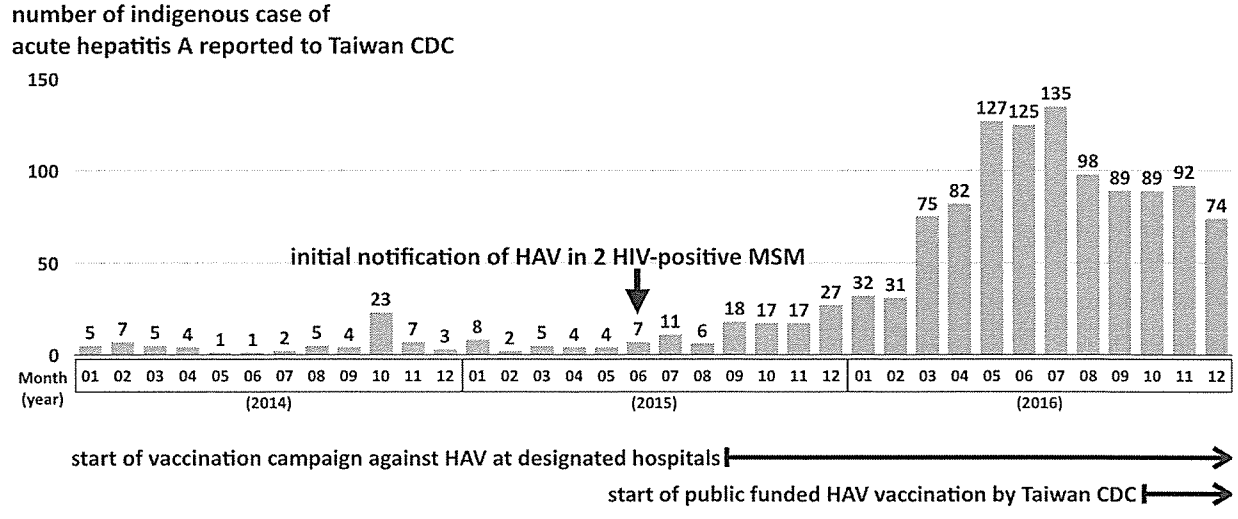

Figure 1. Number of indigenous cases of acute hepatitis A virus (HAV) reported to the Taiwan Centers for Disease Control (CDC) between 2014 and 2016, including among men who have sex with men (MSM). Black arrowhead marks the start of the ongoing outbreak of acute hepatitis A.

hepatitis A among at-risk populations, a vaccination campaign against HAV was launched in September 2015 at designated hospitals for HIV care, and the Taiwan CDC has, since October 2016, provided free HAV vaccine to HIV-infected patients and those individuals who sought medical attention because of sexually transmitted diseases; this has been associated with gradually decreasing trends of acute hepatitis A (Figure 1).

Both data from Israel and Taiwan demonstrate that outbreaks of acute hepatitis A among high-risk populations may occur even though the incidence of HAV infection is low in the general population. While universal coverage of HAV vaccines decreases the burden of acute hepatitis A in the general population, this benefit may not extend to high-risk groups when vaccination practices are neglected. Awareness of, and adherence to, the recommendations of HAV vaccination should be promoted among the healthcare providers and at-risk populations.

Note

Potential conflicts of interest. All authors: No potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References

1. Manor Y, Lewis M, Ram D, et al. Evidence for hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. J Infect Dis **2017**; 215: 574–80.
2. Kruszon-Moran D, Klevens RM, McQuillan GM. Change in hepatitis A seroprevalence among U.S. children and adolescents: results from the National Health and Nutrition Examination Survey 2003–2006 and 2007–2010. Vaccines **2013**; 1:105–19.
3. Heywood AE, Newall AT, Gao Z, et al. Changes in seroprevalence to hepatitis A in Victoria, Australia: a comparison of three time points. Vaccine **2012**; 30:6020–6.
4. Chung SJ, Kim TY, Kim SM, et al. Changes in the seroprevalence of IgG anti-hepatitis A virus between 2001 and 2013: experience at a single center in Korea. Clin Mol Hepato **2014**; 20:162–7.
5. Hoover KW, Butler M, Workowski KA, et al; Evaluation Group for Adherence to STD and Hepatitis Screening. Low rates of hepatitis screening and vaccination of HIV-infected MSM in HIV clinics. Sex Transm Dis **2012**; 39:349–53.
6. Tsai CF, Lin DB, Chen SC, Chang YH, Chen CY, Lin JB. Seroepidemiology of hepatitis A virus infection among schoolchildren in Taiwan. J Med Virol **2011**; 83:196–200.
7. Tsou TP, Liu CC, Huang JJ, Tsai KJ, Chang HF. Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995–2008. Vaccine **2011**; 29:2956–61.
8. Sun HY, Kung HC, Ho YC, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis **2009**; 13:e199–205.
9. Tseng YT, Sun HY, Chang SY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. J Formos Med Assoc **2012**; 111:431–8.
10. Taiwan Centers for Disease Control. Taiwan National Infectious Disease Statistics System. Available at: http://nidss.cdc.gov.tw/en/. Accessed 6 January 2017.

Received 8 January 2017; editorial decision 6 March 2017; accepted 8 March 2017; published online March 15, 2017.

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The Journal of Infectious Diseases® 2017;215:1339–40

DOI: 10.1093/infdis/jix123

Hepatitis E Virus–Associated Neurological Injury in China

To the Editor—We read with interest the article by Zhou et al [1] as hepatitis E virus (HEV)–associated neurological injury is of general interest and arouses attention worldwide [2]. The authors found that HEV can infect neurons and the virus RNA and that proteins can be detected in the brains of infected mice and macaques [1]. In their study, both mice and macaques were infected with HEV genotype 4 (HEV-4); however, the human patients they presented were all enrolled in countries where HEV-3 is predominant. Few studies have reported HEV-4–induced neurological injury in patients. China is endemic for HEV and the predominated subtype is HEV-4 [3]. Thus, we have investigated the prevalence of HEV in patients with neurological injury in China.

Our study cohort was composed of 69 patients with Guillain-Barré syndrome (GBS) and 21 patients with encephalitis who were recruited at Peking University First Hospital, Beijing, China, from January 2014 to December 2015. All patients were diagnosed according to international criteria [4, 5]. Paired serum and cerebrospinal fluid (CSF) samples from all patients were obtained. This study was approved by the Ethics Committee of Peking University Health Science Center. All patients gave informed consent for testing of clinical samples.

The ages of GBS patients ranged from 9 to 80 years (median, 48 years) and of encephalitis patients from 1 to 71 years (median, 29 years). A large majority of the recruited GBS (46/69 [66.7%]) and encephalitis (16/21 [76.2%]) patients were male. Anti-HEV immunoglobulin M (IgM) (Wantai, Beijing, China) was demonstrated in 1 (1/69 [1.4%]) of the GBS patients but none of the encephalitis patients. This anti-HEV IgM-positive patient was also anti-HEV immunoglobulin G (IgG) positive (Wantai, Beijing, China). Of the 69 GBS patients and the 21 encephalitis patients, 18 (26.1%) and 9 (42.9%) tested positive for anti-HEV IgG, respectively. HEV RNA was tested in paired serum and CSF samples from all patients by a nested reverse transcription polymerase chain reaction, which has been described previously [3]. No HEV RNA was detected (Table 1).

Thus, 1 of 69 (1%) GBS patients had a possible acute HEV infection. However no HEV RNA was detected. Two previous reports conducted in the Netherlands and Bangladesh, where HEV-3 and HEV-1 predominates, respectively, found that 5% [6] and 11% [7] of patients with GBS had positive anti-HEV IgM. More recently, a study conducted in Belgium [8] found

World Journal of Gastroenterology

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World J Gastroenterol 2017 May 28; 23(20): 3589-3606

DOI: 10.3748/wjg.v23.i20.3589

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: A review

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Author contributions: Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY and Chang SY performed the literature search and review, and wrote the paper; Liu CE and Hung CC edited and revised the manuscript.

Supported by Centers for Disease Control, Taiwan, No. JH105022.

Conflict-of-interest statement: Chien-Ching Hung has received research support from Janssen, Abbvie, Bristol-Myers Squibb, Merck, and ViiV and speaker honoraria from Gilead Sciences, and served on the advisory boards for Gilead Sciences, ViiV, Abbvie, and Janssen. Other authors report no potential conflict of interest.

Manuscript source: Invited manuscript

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Received: February 12, 2017
Peer-review started: February 14, 2017
First decision: March 16, 2017
Revised: March 31, 2017
Accepted: May 4, 2017
Article in press: May 4, 2017
Published online: May 28, 2017

Abstract

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis worldwide. The virus is known to be transmitted fecal-orally, resulting in symptoms ranging from asymptomatic infection to fulminant hepatitis. HAV can also be transmitted through oral-anal sex. Residents from regions of low endemicity for HAV infection often remain susceptible in their adulthood. Therefore, clustered HAV infections or outbreaks of acute hepatitis A among men who have sex with men and injecting drug users have been reported in countries of low endemicity for HAV infection. The

duration of HAV viremia and stool shedding of HAV may be longer in human immunodeficiency virus (HIV)-positive individuals compared to HIV-negative individuals with acute hepatitis A. Current guidelines recommend HAV vaccination for individuals with increased risks of exposure to HAV (such as from injecting drug use, oral-anal sex, travel to or residence in endemic areas, frequent clotting factor or blood transfusions) or with increased risks of fulminant disease (such as those with chronic hepatitis). The seroconversion rates following the recommended standard adult dosing schedule (2 doses of HAVRIX 1440 U or VAQTA 50 U administered 6-12 mo apart) are lower among HIV-positive individuals compared to HIV-negative individuals. While the response rates may be augmented by adding a booster dose at week 4 sandwiched between the first dose and the 6-mo dose, the need of booster vaccination remain less clear among HIV-positive individuals who have lost anti-HAV antibodies.

Key words: Epidemiology; Viral hepatitis; Acute hepatitis; Fecal-oral transmission; Oral-anal sex; Men who have sex with men; Injecting drug use; Immunosuppression; Immunization

Core tip: We provide an updated review of hepatitis A virus (HAV) coinfection among human immunodeficiency virus (HIV)-positive individuals, focusing on the epidemiology, clinical manifestations, and prevention for HAV infection. The reported outbreaks of acute hepatitis A among men who have sex with men and injecting drug users are summarized. Updated vaccination guidelines for prevention of HIV-positive individuals against HAV infection are presented. We also review the published data of effectiveness or efficacy of HAV vaccination studies and the different approaches to improvement of the serological responses to conventional HAV vaccines among HIV-positive individuals.

Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY, Chang SY, Liu CE, Hung CC. Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: A review. *World J Gastroenterol* 2017; 23(20): 3589-3606 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i20/3589.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i20.3589

INTRODUCTION

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis worldwide. According to the WHO estimates, HAV resulted in 13.7 million illnesses and 28000 deaths in 2010[1]. HAV is primarily transmitted fecal-orally *via* contaminated food or water, or through close contact with an infected person. With improved sanitation and provision of HAV vaccination, areas or populations with high HAV endemicity show patterns of declining endemicity, according to their socioeconomic backgrounds[2]. Based on the different age-specific HAV seroprevalence profiles, the world can be divided into countries of high, intermediate, low, and very low HAV endemicity[3]. In countries of high endemicity, most people acquire HAV in their early childhood and are immune to the virus. On the contrary, adults from low endemic areas are first exposed to HAV during travel to or residence in endemic areas, or being engaged in risky behaviors, such as contact with infected persons, being men who have sex with men (MSM), or using illicit drugs[2,4].

Several outbreaks of acute HAV infection among the MSM and injecting drug users' (IDUs') communities have been reported in several developed countries of low endemicity for HAV infection. The duration of HAV viremia and stool shedding of HAV may be longer in HIV-positive individuals, increasing the window of opportunity for wider transmission of HAV to those engaged in risk behaviors. HAV vaccination is the most efficient approach to prevention of acquiring HAV infection. However, the seroconversion rates following the recommended standard 2-dose HAV vaccination schedule are lower among HIV-positive individuals compared to HIV-negative individuals, and the vaccination effectiveness among HIV-positive individuals is rarely investigated in the outbreak setting[5]. In this article, we review the epidemiology and clinical manifestations of acute HAV infection and HAV vaccination among HIV-positive individuals in the era of combination antiretroviral therapy (cART).

HAV VIROLOGY

HAV, first identified by Feinstone *et al*[6] in 1973, belongs to the *Hepatovirus* genus of the family *Picornaviridae*. The genome of HAV is a positive-strand RNA (range, 7470 to 7478 nucleotides) and encodes only a single open reading frame, which is translated into a polyprotein. The polyprotein is then cleaved by the virus-encoded protease ($3C^{pro}$) to yield 8 viral proteins, including VP0, VP3, VP1-2A, 2B, 2C, 3AB, $3C^{pro}$, and RNA-dependent RNA polymerase (RDRP, $3D^{pol}$). The virus particle is composed of 3 proteins, VP0, VP1-2A, and VP3. During the assembly of the virus capsid, 2A will be removed from the VP1-2A by cellular protease or $3C^{pro}$, and at the final stage of maturation, VP0 will be cleaved into VP2 and VP4. Five copies of each protein will be assembled to form a pentamer, and 12 copies of the pentamer will form a virus capsid. Despite that there are some amino acid variations between different HAV strains, the detection of anti-HAV antibody is not as complicated as other RNA viruses due to the fact that HAV exists as a single serotype. Due to the advances of molecular technology, 7 unique genotypes (Ⅰ to Ⅶ) of HAV are defined by analysis of a 168-base region, located

between the C terminus of VP1 and N terminus of P2A[7]. These 7 genotypes exhibit less than 85% of sequence identity between genotypes and no more than 15% of divergence within a genotype, a criterion used for polioviruses, another member of the family *Picornaviridae*. However, further detailed analyses of other viral regions reveal that the genotypes Ⅱ and Ⅶ should be reclassified as subtypes A and B of genotype Ⅱ[8], and genotypes Ⅰ and Ⅲ could also be divided into subgenotypes A and B[9]. Four genotypes (Ⅰ, Ⅱ, Ⅲ, and Ⅶ) are of human origin, and 3 (Ⅳ, Ⅴ, Ⅵ) are of simian origin. Genotypes Ⅰ and Ⅲ are the most prevalent genotypes identified in humans. Subgenotypes IA and IB are often found in North and South Americas, Europe, China, and Japan[7]. Clusters within genotypes predominant in certain geographic regions have been reported, such as a group of subgenotype IA strains from the United States[10], and genotype Ⅱ in the Netherlands, France, and Sierra Leone[7,11]. However, in other regions, the presence of variant genotypes was reported in Europe and Japan, likely representing international spread from the endemic regions.

EPIDEMIOLOGY OF HAV INFECTION AMONG HIV-POSITIVE PATIENTS

HAV seroprevalence among HIV-positive patients

Previous studies have shown higher seroprevalence and incidence of HAV infection among MSM compared to the general population[12-14], which were associated with oral-anal sex and the number of sexual contacts and partners[12,15-20]. The HAV seroprevalence also increases with age, indicating the cohort effect[2,12,19,21]. Unlike MSM, heterosexual men with risky sexual behaviors has been inconsistently associated with higher HAV seroprevalence. While a few studies reported a lower seroprevalence and incidence among heterosexual men with sexually transmitted diseases (STDs) compared to MSM[15,16], others indicated that the risks for HAV infection among heterosexual men with STDs and MSM were similar[12,19,21]. IDUs also had a higher HAV seroprevalence than the general population[13,14,22,23]. However, the high seroprevalence might not be solely attributable to needle contamination, since some reported similar elevation of the HAV seroprevalence between IDUs and non-injecting illicit drug users[22,23].

Although the direct evidence on the correlation between contracting HIV and HAV was scarce, observational data suggested that HIV-positive individuals, especially MSM and IDUs, are at increased risk of acquiring HAV[24]. In addition, one small study including 15 HIV-positive individuals demonstrated that the duration of HAV viremia in HIV-positive individuals with acute hepatitis A was prolonged compared to that in HIV-negative individuals with acute hepatitis A, which may increase the probability of HAV transmission to others[25]. Several studies have reported the HAV seroprevalence among HIV-positive individuals and at-risk persons in areas of different HAV endemicities and vaccine coverage (Table 1)[12-23,26-42]. In these studies, the HAV seroprevalence among HIV-positive individuals ranged from 15.1% in Taiwan to 96.3% in Iran[31,35]. While studies conducted in countries of high HAV endemicity showed no differences in the HAV seroprevalence between HIV-positive and HIV-negative individuals[27], the seroprevalence in countries of low endemicity was higher among HIV-positive individuals compared to HIV-negative individuals[26,30]. Among HIV-positive individuals, older age and injecting drug use were identified as the independent factors associated with seropositivity for HAV; the HAV seroprevalence was lower in HIV-positive MSM despite the at-risk sexual behaviors[29,30,33-36].

Hepatitis A outbreaks in the MSM population

In countries of low HAV endemicity, the majority of HAV-seronegative adults remain susceptible to acute HAV infection. Outbreaks of acute hepatitis A are often caused by introduction of HAV through contaminated foods and person-to-person transmission[2]. Numerous outbreaks of acute hepatitis A have been reported in the MSM population through sexual contacts, which are summarized in Table 2[43-70]. Since the early 1980s, outbreaks of acute hepatitis A among MSM have been described in Denmark[43], Sweden[44], the United Kingdom[45], and the United States[61,62]. The incidence of acute HAV infection among MSM peaked in the 1990s, and the affected countries included the United Kingdom[46,47,49,51], the Netherlands[48], Norway[50], the United States[63,65,66], Canada[64] and Australia[67-70]. One of the largest epidemics of acute hepatitis A occurred in Sydney, Australia, where 2 outbreaks affected 323 and 186 MSM during 1991-1992 and 1995-1996, respectively[69]. Since 2015, Taiwan reported a large outbreak involving more than 1000 indigenous cases, with more than 70% of the affected individuals being MSM[71]. While the HAV vaccine was licensed and recommended for MSM since the mid-1990s[47], the emergence of HAV infection continued to pose a health threat to MSM in several developed European countries during the 2000s, including Italy[52,54,55,60], Denmark[53], Spain[56,58], Poland[57], and the United Kingdom[59].

The duration of outbreaks of acute hepatitis A among MSM were mostly curtailed at 2 years; however, the outbreak in Canada extended from December 1994 to February 1998[64]. The cyclical outbreaks were noted in Australia during 1991-1996[69] and in Spain during 1989-2010[56], which might be facilitated by the continuous circulation of particular HAV strains in the MSM population[50,55,60]. The predominant circulating HAV strains among MSM belonged to genotype IA[50,55,59,60,72]. The patients contracting HAV during the outbreaks were mostly young adults with a mean or median age of 28-36 years[55,57]. HAV was recognized

Table 1 Seroprevalence of hepatitis A virus infection among human immunodeficiency virus-positive patients and at-risk populations

Ref.	Location	Study period	Study population	Age (yr)	HIV-positive population	Other populations	Associated factors[1] and comments
HIV-positive population							
Nandwani *et al*[26]	London, United Kingdom	1993	255 men attending genitourinary clinics	32	41.3%	MSM, 32.4% Heterosexuals, 30.0% Unknown HIV status, 26.4%	No difference between homosexual and heterosexual men
Fainboim *et al*[27]	Buenos Aires, Argentina	1994-1995	484 HIV-positive patients	29	84.0%	HIV-positive MSM, 83.3% HIV-positive heterosexuals, 86.3% HIV-positive IDUs, 85.7% Blood donors, 82.4%	High seroprevalence without difference between HIV-positive and HIV-negative individuals
Aloise *et al*[28]	Rio de Janeiro, Brazil	1988-2004	581 HIV-positive patients	35	79.8%	NA	Older age and lower educational level
Lee *et al*[29]	Tainan, Taiwan	2000-2005	484 patients with recent diagnosed HIV infection	36	65.8%	HIV-positive MSM, 40.0%; HIV-positive heterosexuals, 85.2% HIV-positive IDUs, 70.1%	Seroprevalence increased with age and among heterosexuals
Sun *et al*[30]	Taiwan	2004-2007	1580 HIV-positive patients	39	60.9%	HIV-positive MSM, 50.5% HIV-positive heterosexuals, 79.3% HIV-positive IDUs, 62.0% HIV-negative individuals, 48.0%	Older age and injecting drug use Higher seroprevalence in HIV-positive individuals
Davoudi *et al*[31]	Tehran, Iran	2005-2006	247 HIV-positive patients	36	96.3%	NA	
Hoover *et al*[32]	6 major cities[2], United States	2004-2007	627 HIV-positive MSM	41	16.1%[3]	NA	Low HAV screening and vaccination rates (28.5%)
Linkins *et al*[33]	Bangkok, Thailand	2006-2008	1291 MSM	27	32.4%[3]	HIV-negative MSM, 25.5%	Older age and lower education level
Baek *et al*[34]	Seoul, South Korea	2008-2010	188 HIV-positive patients	39	62.8%	HIV-positive MSM, 57.1% HIV-positive heterosexuals, 65.8%	Older age
Tseng *et al*[35]	Taipei, Taiwan	2009-2010	1128 MSM	18-40	15.1%[3]	HIV-negative MSM, 7.4%	Older age No difference between HIV-positive and HIV-negative individuals
Kourkounti *et al*[36]	Athens, Greece	2007-2011	897 HIV-positive MSM	41	35.7%[3]	NA	Older age and being foreigners
At-risk populations (MSM and IDUs)							
Corey *et al*[15]	Seattle, United States	1977-1979	159 patients from STD clinics	31	NA	MSM, 30.4% (annual incidence, 22%) Heterosexuals, 12.3% (annual incidence, 0%)	Oral-anal sexual contact Higher seroprevalence and incidence in MSM
McFarlane *et al*[12]	Nova Scotia, Canada	1977-1978	421 patients from STD clinics	25	NA	MSM, 42.4% Heterosexuals, 39.2% Blood donors, 12.6% Student nurses, 13.2%	Higher number of sex partners and older age
Kryger *et al*[16]	Copenhagen, Denmark	1979	269 men with previous syphilis	33	NA	MSM, 36.0%; Heterosexual, 20.0%	More episodes of syphilis in younger MSM
Coutinho *et al*[17]	Amsterdam, the Netherlands	1980-1982	689 MSM	31	NA	MSM, 42.0% (incidence, 14.0%)	Longer duration of homosexual activity
Crofts *et al*[22]	Victoria, Australia	1990-1992	2175 prison entrants 293 IDUs	30	NA	IDU, 43.7% Prison entrants, 60.1% Blood donors, 30.0%	History of incarceration
Katz *et al*[18]	San Francisco and Berkeley, United States	1992-1993	411 MSM	21	NA	MSM, 28.0%	Sexual and drug-using behaviors

Villano *et al*[13]	Baltimore, United States	1993-1994	294 MSM 292 IDUs	NA	NA	MSM, 32.3% IDU, 66.4% Blood donors, 13.7%	Increased risk for HAV infection in MSM and IDUs
Corona *et al*[19]	Rome, Italy	1997	432 male patients from STD clinics	NA	NA	MSM, 60.3% Heterosexual, 62.2%	Older age and more sexual partner
Ochnio *et al*[14]	Vancouver, Canada	1998	494 individuals from street outreach clinics	32	NA	MSM, 25.5% IDU, 42.6% Street youth, 6.3%	Increased risk for HAV infection in MSM and IDUs
Ross *et al*[21]	Birmingham, United Kingdom	2000	210 men attending genitourinary clinics	NA	NA	MSM, 23.0%; Heterosexual men, 32.0%	Ethnicity, older age, and history of sex in a sauna
Diamond *et al*[37]	Washington, United States	1997-2000	833 MSM	15-29	NA	MSM, 21.0%	Ethnicity, IDU, HBV and HIV infection Vaccination rate, 21%
Bialek *et al*[20]	7 major cities[4], United States	1994-2000	2708 MSM	15-29	NA	MSM, 18.4%	More male sex partners and unprotected anal sex
O'Riordan *et al*[38]	London, United Kingdom	2004	395 MSM attending genitourinary clinics	NA	NA	MSM, 49.9%	
Van Rijckevorsel *et al*[39]	Amsterdam, the Netherlands	1992-2006	1697 hepatitis A patients	NA	NA	Incidence, 0.97/1000 MSM	Clustered transmission in social MSM networks
Removille *et al*[23]	Luxembourg	2005	368 problem drug users	NA	NA	IDUs, 57.1% nIDUs, 65.9%	
Bozicevic *et al*[40]	Zagreb, Croatia	2006	360 MSM	27	NA	MSM, 14.2%	
Weerakoon *et al*[41]	Melbourne, Australia	2002-2011	3055 MSM	33	NA	MSM, 39.0%	Vaccination levels over 40%-50% to prevent outbreaks
Ali *et al*[42]	Sydney, Australia	1996-2012	14799 MSM	30	NA	MSM, 31.9% in 1996 to 63.8% in 2012	Vaccination rate, 9.8% in 1996 to 45.2% in 2012

[1]Factors associated with HAV seropositivity were identified by bivariate or multivariable logistic regression analysis; [2]The 6 major cities included Atlanta, Chicago, Los Angeles, Miami, New York City, and San Francisco; [3]Only HIV-positive MSM were included; [4]The 7 major cities included Baltimore, Dallas, Los Angeles, Miami, New York City, San Francisco, and Seattle. HAV: Hepatitis A virus; IDUs: Injecting drug users; MSM: Men who have sex with men; NA: Not available; nIDUs: Non-injecting drug users; STD: Sexually transmitted disease.

as being transmitted among MSM through sexual contacts[73], and case-control studies have identified several associated factors such as having anonymous sex partners, group sex, oral-anal and digital-rectal intercourse[63], contact with patients with acute hepatitis A[66], having sex in gay saunas[51,53], and visiting saunas and darkrooms[48]. In light of the risky sexual behavior, the largest HAV vaccination campaign for MSM was launched in Montréal, in which 9500-15000 first doses of HAV vaccine were administered to achieve a coverage rate between 20% and 41%. However, the decrease in the incidence of acute hepatitis A shortly after the vaccination campaign might indicate the relatively late implementation of HAV vaccination and the natural decline after herd immunity was established at the end of the outbreak[64]. The vaccination campaigns targeting MSM in Atlanta and Barcelona recruited 3,000 persons, which resulted in a 16% decrease of reported acute hepatitis A cases[56,65].

Coinfections with HAV and HIV were identified during the 2000s in Italy[52,54,55], Spain[56], and Poland[57]. Most HAV/HIV-coinfected individuals were males with known HIV status, while others were found to be HIV-positive concomitantly with acute HAV infections[52,54-57]. Among all male patients who received a diagnosis of acute hepatitis A during 2002-2008 in Italy, 15.2% (56/368) were HIV-positive[54]. After excluding those without available HIV serology, the HIV seroprevalence among was 27.6%[54]. The high proportion of HAV/HIV coinfection in the areas of low HAV endemicity highlights the importance of routine HIV testing in patients with acute hepatitis A[54].

Hepatitis A outbreak in the IDU population

Outbreaks of acute hepatitis A in the IDU population have been reported since 1970s as the numbers of IDUs increased[74]. The studies of outbreaks of acute hepatitis A among IDUs are summarized in Table 3[74-88]. During 1970-1979, the cyclic occurrence of outbreaks of acute hepatitis A in Sweden suggested a continuously increasing pool of susceptible young IDUs in the closed communities[74]. The outbreaks were mostly described in Europe[75-78] and the United States[82,83,85] in the 1980s and 1990s, but were seldom described after the early 2000s[79-81,86]. Up to 492 IDUs were infected with HAV in Norway between 1995 and 1996[77]. In Terni, Italy; 47 cases of acute hepatitis A were reported during 2002-2003, among which included 35 IDUs and 2 HIV-positive individuals. The most recent outbreak of acute HAV infection among IDUs was described in Israel during 2012-2013, which occurred in IDUs and homeless adults with subsequent spread to the general population in Tel Aviv, despite the nation-wide implementation of universal toddler's vaccination in 1999[88].

The outbreaks of acute hepatitis A among IDUs mainly lasted between 1 and 2 years, and young patients with a mean or median age of 20-34 years were predominantly affected[74,81]. HAV could be transmitted fecal-orally through poor personal hygiene

Table 2 Outbreaks of acute hepatitis A in the men who have sex with men population

Ref.	Location	Study period	Case number	Male	MSM	HIV-positive patients	Age (yr)	Risk factors[1] and comments
	Europe							
Høybye *et al*[43]	Copenhagen, Denmark	1977-1978	45	45	21	NA	29	
Christenson *et al*[44]	Stockholm, Sweden	1979-1980	145	145	145	NA	NA	Multiple partners and oral-anal sexual contact
Mindel *et al*[45]	London, United Kingdom	1980	24	NA	23	NA	NA	HAV infection was associated with homosexual activity
Kani *et al*[46]	London, United Kingdom	1989-1990	7000	NA	41	NA	NA	Oral-anal sexual contact
Atkins *et al*[47]	London, United Kingdom	1989-1992	206	121	65	NA	NA	Oral-anal sexual contact and sexual promiscuity
Leentvaar-Kuijpers *et al*[48]	Amsterdam, the Netherlands	1992-1993	293	NA	39	NA	NA	Visiting saunas and darkrooms
Walsh *et al*[49]	Thames region, United Kingdom	1995	481	NA	58	NA	NA	Oral-anal and digital-rectal intercourse
Stene-Johansen *et al*[50]	Oslo, Norway	1995-1998	26	26	26	NA	NA	
Bell *et al*[51]	London and East Sussex, United Kingdom	1997	48	NA	41	NA	NA	Eating shellfish and sex in gay saunas
Manfredi *et al*[52]	Bologna, Italy	1999-2004	122	104	81	11	28	Unprotected sexual contact
Mazick *et al*[53]	Copenhagen, Denmark	2004	18	18	18	NA	NA	Casual sex and sex in gay saunas
Girardi *et al*[54]	Rome, Italy	2002-2008	473	368	115	57	25-64	Same gender sex Routine HIV test in HAV-infected patients should be considered
Bordi *et al*[55]	Rome, Italy	2008-2010	162	143	34	14	36	Monophyletic HAV strain sustained the outbreak
Tortajada *et al*[56]	Barcelona, Spain	2002	48	47	NA	28%	31	
		2003-2004	60	60	NA	24%	32	
		2008-2009	189	185	NA	21%	33	
Dabrowska *et al*[57]	Warsaw, Poland	2007-2008	860	NA	50	6	28	No difference in disease severity between HIV-positive and HIV-negative individuals
Tortajada *et al*[58]	Barcelona, Spain	2008-2009	150	126	87	NA	33	
Sfetcu *et al*[59]	Northern Ireland, United Kingdom	2008-2009	38	36	26	NA	29	The outbreak strain was indistinguishable from that in Czech Republic
Taffon *et al*[60]	Tuscany, Italy	2008	240	NA	32%	NA	NA	A unique circulating HAV strain
	North America							
Kosatsky *et al*[61]	Anchorage, Alaska	1982-1983	17	17	17	NA	19-31	
Desenclos *et al*[62]	Florida, United States	1988-1989	311	69	26	NA	NA	
Henning *et al*[63]	New York, United States	1991	180	180	62	NA	20-49	Anonymous sex partner, group sex, oral-anal and digital-rectal intercourse
Allard *et al*[64]	Montréal, Canada	1996-1997	376	376	376	NA	33	Vaccination campaign achieving 20%-41% coverage in MSM decreased incidence rapidly
Finton *et al*[65]	Atlanta, United States	1996	222	NA	75%	NA	NA	Vaccination campaign in MSM decreased reported cases
Cotter *et al*[66]	Ohio, United States	1998-1999	136	118	47	NA	33	Contact with hepatitis A cases
	Asia-Pacific region							
Stewart *et al*[67]	Melbourne, Australia	1991	495	407	210	NA	NA	Sexual and social contact
Stokes *et al*[68]	Sydney, Australia	1991-1992	570	515	330	NA	31	Sexual contact was the most reported contact type
Ferson *et al*[69]	Sydney, Australia	1991-1996	1138	991	587	NA	30	Household or sexual contact
Delpech *et al*[70]	Sydney, Australia	1997-1999	354	265	139	NA	32	
Chen *et al*[71]	Taiwan	2015-2016	> 1000	NA	> 70%	> 60%	NA	A total of 1296 cases reported as of February, 2017

[1]Risk factors of acquiring HAV infection were identified by case-control studies. HAV: Hepatitis A virus; MSM: Men who have sex with men; NA: Not available.

and living conditions, or percutaneously through contamination of illicit drugs or injecting equipment by fecal materials or blood[81]. Three case-control studies identified not washing hands after using the toilet or before preparing food, not washing hands prior to preparing drugs, sharing of needles or syringes, use of contaminated illicit drugs, and contact with jaundiced persons to be factors associated with acute hepatitis A in IDUs[80,81,85]. To curb the epidemic of acute hepatitis A, HAV vaccination programs were implemented in

Table 3 Outbreaks of acute hepatitis A in the injecting drug user population

Ref.	Location	Study period	Total patients	IDU	HIV-positive individuals	Age (yr)	Risk factors[1] and comments
	Europe						
Widell *et al*[74]	Malmo, Sweden	1970-1979	323	188	NA	NA	
Sundkvist *et al*[75]	Helsingborg, Sweden	1983-1984	36	32	NA	18-35	The outbreak was associated with intrarectal transportation of illicit drugs
Leino *et al*[76]	Helsinki, Finland	1994-1995	238	131	NA	31	The outbreak was associated with intrarectal transportation of illicit drugs
Stene-Johansen *et al*[77]	Oslo, Norway	1995-1996	621	492	NA	NA	The outbreak was associated with needle sharing
O'Donovan *et al*[78]	United Kingdom	1998-1999	27	14	NA	25	
Syed *et al*[79]	Bristol, United Kingdom	2000	123	69	NA	25	The outbreak was associated with parenteral transmission from contaminated illicit drugs; HAV vaccination of IDUs decreased the reported cases
Roy *et al*[80]	Aberdeen, Scotland	2000-2002	106	74	NA	NA	Not washing hands after using the toilet, or before preparing food or drugs, sharing needles/syringes, and injecting contact with jaundiced persons
Spada *et al*[81]	Terni, Italy	2002-2003	47	35	2	34	Contact with jaundiced persons, but not related to injecting practices; HAV vaccination of IDUs decreased the reported cases
	North America						
Harkess *et al*[82]	Oklahoma, United States	1984-1987	79	42	NA	23-27	
Jenkerson *et al*[83]	New York, United States	1986-1987	256	70	NA	NA	
Jin *et al*[84]	Canada	1987-1989	65	59	NA	NA	
Hutin *et al*[85]	Iowa, United States	1996-1997	158	9.7%	NA	NA	Methamphetamine injection, sharing methamphetamine use, using brown methamphetamine, and needle sharing
Vong *et al*[86]	Florida, United States	2001-2002	403	11%	NA	32	HAV vaccination in jail decreased the reported cases
	Asia-Pacific region						
Shaw *et al*[87]	Queensland, Australia	1997	875	118	NA	NA	Sharing of instruments for smoking marijuana
Manor *et al*[88]	Tel-Aviv, Israel	2012-2013	75	9	NA	33	

[1]Risk factors of acquiring HAV infection were identified by case-control studies. HAV: Hepatitis A virus; HIV: Human immunodeficiency virus; IDU: Injecting drug user; NA: Not available.

Table 4 Clinical symptoms and signs of patients with acute hepatitis A infection[92-96]

Symptoms	Frequency
Asymptomatic	14%
Fever	48%-87%
Nausea/vomiting	56%-88%
Anorexia	66%-96%
Fatigue/malaise	49%-80%
Upper abdominal pain	42.5%-82%
Diarrhea	8%-23%
Signs	
Jaundice	24%-99%
Hepatomegaly	7%-78%
Splenomegaly	18%-30%

the United Kigndom[79], Norway[89] and Italy[81], and harm reduction program by providing clean injecting equipment was implemented in Switzerland[90].

CLINICAL MANIFESTATIONS OF ACUTE HAV INFECTION

The incubation period of acute HAV infection is 2.5 to 5 wk[91]. The typical symptoms of acute hepatitis A include fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. The frequencies of symptoms or signs of acute hepatitis A are listed in Table 4[92-96]. While most of acute HAV infections are self-limited, the severity of the symptoms may vary with age and concurrent comorbidities, particularly chronic viral hepatitis. Acute HAV infection is usually silent or subclinical in children, but approximately 30% of the infected patients older than 6 years have symptoms including hepatitis, jaundice, and abdominal pain[97]. Less than 25% of the patients have diarrhea though HAV is transmitted through fecal-oral route[98]. The data on the symptoms of acute hepatitis A

Table 5 Comparison of clinical manifestations of hepatitis A virus between human immunodeficiency virus-positive patients or human immunodeficiency virus-negative patients with acute hepatitis A

	HIV-positive patients	HIV-negative patients
Natural course of acute HAV infection		
Incubation period (wk)	NA	2.5-5[91]
Duration of stool shedding (d)	NA	25 (HAV antigen)[105] 81 (HAV RNA)[106]
Duration of viremia (d)	53 (10-89)[25]	22-95[25,106-108]
Laboratory findings		
Peak T-bilirubin (mg/dL)	5.1-5.9[25]	5.7-8.7[25,92,93,95,98,99]
Peak AST (IU/L)	929-1339[25,57]	1231-2271[25,92,93,99]
Peak ALT (IU/L)	1995-2368[25,57]	1079-3442[25,92,93,99,100]
Duration of elevated AST/ALT (d)	63 ± 38[109]	51[92]
Peak ALP (IU/L)	807[25,57]	228-396[25,92]

HIV: Human immunodeficiency virus; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HAV: Hepatitis A virus; NA: Not available.

among HIV-positive individuals are limited, and the study by Ida *et al*[25] of 15 HIV-positive and 15 HIV-negative individuals with acute hepatitis A suggested no differences in the frequency and severity of clinical symptoms of acute hepatitis A between the two groups.

Patients with acute hepatitis A usually have significantly elevated levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. In previous studies, the average peak levels of total bilirubin were 7-8 mg/dL and the levels of AST and ALT were higher than 1000 IU/L[25,92,93,98-100]. Alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GT) are also elevated in patients with acute hepatitis A. Resolution of the abnormal biochemical tests generally occurs within 1 to 6 wk after the onset of the illness[99]. Approximately 85% of the patients who are infected with HAV have full clinical and biochemical recovery within 3 mo and nearly all have a complete recovery by 6 mo[92]. The study by Ida *et al*[25] reported lower elevations in total bilirubin, AST, and ALT in HIV-positive individuals during acute hepatitis A than HIV-negative individuals, which were considered to be related to the weaker immune responses in HIV-positive patients or clonal spreading of a specific HAV strain that was able to escape from immunity in the study. Regulatory T cells (Tregs) normally suppress the T-cell responses directed against hepatitis viruses and down-regulate the immune reaction that is responsible for liver damage in viral hepatitis[101]. The study by Choi *et al*[102] suggested a decrease in Tregs leading to a severe liver injury during acute hepatitis A. HIV-positive individuals however are known to have high Tregs, compared to their HIV-negative counterparts, hence they may experience less severe injury during acute hepatitis A[103]. On the other hand, Ida *et al*[25] reported higher levels of ALP and γ-GT during acute hepatitis A in HIV-positive individuals than HIV-negative patients. Biliary tract is not the primary target of HAV infection. Lymphocytic cholangitis is rarely seen with acute HAV infection[104]. However, HIV-related cholangitis or cholangiography is a well-recognized late complication of acquired immunodeficiency syndrome (AIDS). Opportunistic infections such as cytomegalovirus infection or cryptosporidiosis may also cause cholangitis. HIV is also able to cause direct cytopathic effects on the biliary tract mucosa. Hence, the higher levels of ALP and γ-GT observed in HIV-positive patients with acute hepatitis A may be explained by multiple factors other than the liver injury caused by HAV itself.

In the general population, stool shedding of HAV antigen can be detected 19 d before the peak elevation of ALT levels and continue for at least 25 d[105] and even up to 80 d[106]. The duration of viremia is estimated to last around 20 to 40 d[25,106,107] and even longer than 3 mo[108]. In the study by Ida *et al*[25], the median duration of HAV viremia in HIV-positive individuals with acute hepatitis A was 53 d, which was longer than that of HIV-negative individuals. A longer duration of HAV viremia may be related to impaired host immunity[100]. Besides, the relationship between duration of viremia and specific HAV genotypes is still inconclusive[106,107]. The comparisons of clinical manifestations of acute hepatitis A between HIV-positive and HIV-negative individuals are summarized in Table 5[25,57,91-93,95,98-100,105-109].

Other atypical presentations of acute hepatitis A include renal insufficiency and relapsing hepatitis[93], which are usually present in children. Some individuals experienced a prolonged hepatitis (5.8%)[93] or cholestasis (6.8%), especially in the presence of hepatitis B virus[94]. Severe hepatic failure is rare and occurs more commonly in patients with underlying diseases or advanced age. Reported case fatality rates were 0.1% in infants and children, 0.45% in those aged 15 to 39 years, and 1.1% in those aged > 40 years. Patients with chronic hepatitis C virus (HCV) infection have a substantial risk of fulminant hepatitis and death associated with HAV superinfection[110]. HIV-positive individuals acquire HAV infection mostly in their adulthood and often have other underlying liver disease[25,57], which may increase the risk of hepatic failure and fatality caused by HAV. Therefore, prevention by HAV vaccination is important, especially for the HIV/HCV-coinfected individuals.

HAV VACCINATION AND FACTORS ASSOCIATED WITH IMMUNOGENICITY AND PERSISTENT PROTECTION

Vaccine immunogenicity and factors associated with immunogenicity

HAV vaccination is not universally recommended for HIV-positive individuals but specifically for those with

Table 6 Hepatitis A virus vaccination recommendations by the British human immunodeficiency virus Association, the European AIDS Clinical Society, the US Advisory Committee for Immunization Practices and the World Health Organization

Health Authority	Target candidates	Dosing Schedule	Comments
BHIVA[111]	Household and sexual contacts of infected persons Travellers MSM Injecting and non-injecting drug users Individuals at risk of infection during outbreaks Those with occupational exposure to HAV (*e.g.*, laboratory workers, sewage workers) Hemophiliacs Residents of care institutions, and their care givers	Monovalent HAV vaccine recommended Patients with CD4 counts > 350 cells/mm^3 should be offered 2 vaccine doses at 0 and 6 mo Patients with CD4 counts < 350 cells/mm^3 should receive 3 vaccine doses at 0, 1, and 6 mo Patients at continued risk of exposure receive a boosting vaccine dose every 10 yr Following a significant exposure, HIV-positive contacts who are HAV-seronegative receive post-exposure prophylaxis with the HAV vaccine, with the first dose given as soon as possible and within 14 d of exposure; if the CD4 count is < 200 cells/mm^3, they should also receive human normal immunoglobulin	We support the BHIVA's recommendations of targeted vaccination during outbreaks and of stratifying dosing schedule by CD4 counts, particularly administering a 3-dose schedule for those with lower CD4 counts. Despite waning antibody levels, we could not find evidence to justify routine boosters every 10 yr for those at risk. It may be preferable to follow antibody titers and revaccinate seroreverters
EACS[112]	Travellers MSM IDUs Active hepatitis B or C infection	Vaccinate if seronegative. Did not specify how	Shorter list of at risk candidates for vaccination. Our review supports their recommendation to check antibody titers in individuals with risk profile to guide the need for primary or booster vaccinations
ACIP[113]	MSM Injection or non-injection illicit drugs users Persons working with HAV-infected primates or with HAV in a research laboratory setting Persons with chronic liver disease Persons who receive clotting factor concentrates Travellers Close personal contact (*e.g.*, household or regular babysitting) with an international adoptee during the first 60 d after arrival in the United States from a country with high or intermediate endemicity	Monovalent vaccine formulations should be administered in a 2-dose schedule at either 0 and 6-12 mo (Havrix), or 0 and 6-18 mo (Vaqta) If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 mo; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21-30 followed by a booster dose at 12 mo	Unlike BHIVA, in addition to the monovalent vaccine formulations, ACIP also recommends the combined hepatitis A and B vaccine No mention of the need to follow antibody titers or booster vaccines or the application of immunization during outbreaks
WHO[114]	Travellers Immunosuppressed patients Patients with chronic liver disease	Inactivated vaccine: 2 doses, the second dose normally 6 mo after the first. If needed, this interval may be extended to 18-36 mo	Does not specify whether all HIV-positive persons should be considered as immunosuppressed patients although evidence from Table 5 suggests that except for the duration of viremia acute HAV is not more severe in HIV-positive compared to HIV-negative patients

HAV: Hepatitis A virus; HIV: Human immunodeficiency virus; IDUs: Injecting drug users.

increased risks of exposure (such as from injecting drug use, oral-anal sex, travel to or residence in endemic areas, frequent clotting factor or blood transfusions) or with increased risks of fulminant disease (such as those with chronic hepatitis) (Table 6)[111-114]. Of the two types of HAV vaccines that are currently available internationally, the live attenuated vaccine (based on H2 or LA-1 HAV strains and manufactured as well as mainly used in China or India) and the inactivated HAV vaccine (based on clinical trials since 1991 and licensed in the United States since 1995), only the latter is recommended for HIV-positive individuals. There are 3 formulations of inactivated HAV vaccines that have been assessed in HIV-positive individuals with varying degrees of immunodeficiency as shown in Table 7[115-129]. Although different specific anti-HAV IgG titers have been used to define seroconversion (10, 18, 20, or 33 mIU/mL), the majority of these studies have adopted 20 mIU/mL as the surrogate titer for seroprotection.

The earliest studies of HAV vaccination in moderately to severely immunodeficient HIV-positive individuals preceded the licensure of the adult formulation of HAVRIX 1440 U wherein a triple-mini dosing scheme (3 pediatric doses of HAVRIX 720 U administered at 0, 1, and 6 mo) was applied to hemophiliac patients and MSM with or without HIV[127-129]. The seroconversion rates among such HIV-positive hemophiliacs and MSM at month 7 were consistently between 76.0%-76.9% and lower than their HIV-negative counterparts at 100%[127-129]. Later studies of HIV-positive individuals without hemophilia but with other risk factors such as MSM confirmed that the seroconversion rates following the recommended standard adult dosing schedule (2 doses of HAVRIX 1440 U or VAQTA 50 U administered 6-12 mo apart) were lower among HIV-positive adults

Table 7 Primary response rates and predictors of seroconversion after hepatitis A virus vaccination in human immunodeficiency virus-positive patients

Ref.	Dates	Design/ Country	No. of patient[1]	HAV/ dosing schedules (mo)	CD4, cells/ mm^3	PVL, log_{10}, copies/ mL	ART	Timing of response[2], mo/cut-off[3], mIU/mL/assay	Response rate (%): ITT/PP	Predictors and comments[4]
Tseng *et al*[115]	2009-2010	Prospective, Taiwan	Standard 2-dose All 126; CD4 matched, 114	HAVRIX 1440 U/ 2 doses (0, 6)	Mean, 538	Mean, 2.5	67.1%	12, 18/20, a. CIA (ARCHITECT HAVAb-IgG) b. ELISA (ETIAB-HAVK PLUS)	12 m (CIA): 75.7/81.7 12 m (ELISA): NA/88.6 18 m (ELISA): NA/86.6	MSM only study; Higher baseline CD4 and suppressed PVL; 3 doses over 2 doses
			3-dose All, 213; CD4 matched, 114	HAVRIX 1440/ 3 doses (0, 1, 6)	Mean, 452	Mean, 3	58.2%		12 m (CIA): 77.8/81.8 12 m (ELISA): NA/89.2 18 m (ELISA): NA/86.9	
			Standard 2-dose HIV-negative, 193	HAVRIX 1440/ 2 doses (0, 6)	NA	NA	NA		12 m (CIA): 88.5/97.9 12 m (ELISA): NA/100 18 m (ELISA): NA/100	
Mena *et al*[116]	1997-2009	Retrospective, Spain	Standard 2-dose, 241	HAVRIX 1440/ (0, 6-12)	Median, 531	55.3%[5]	61.4%	10-16/20, CIA (Advia Centaur)	NA/80.7	Higher CD4/CD8 ratio; 2 or more doses compared to 1 dose only; female; no HCV infection
			Accelerated, 41	TWINRIX 720/ (0, 7, 21 d, 6-12)	Median, 543	73.2%	80.5%	5/20, CIA (Advia Centaur)	NA/70.7	
Jimenez *et al*[117]	2002-2008	Retrospective, United States	Standard 2-dose, 125	HAVRIX 1440/ (0, 6-12)	Median, 410	Median, 3.1	70.0%	Variable/< 0.8 signal relative to cut-off, CIA (Vitros ECi)	NA/54	Higher baseline CD4 count and suppressed PVL
			101	TWINRIX 720/ (0, 1, 6-12)					NA/53	
Kourkounti *et al*[118]		Retrospective, Greece	cART-experienced, 63	HAVRIX 1440 or Vaqta 50/ (0, 6-12)	628	< 1.7	100.0%	7-13/20, ELFA (VIDAS)	NA/78	Higher baseline CD4 count
			cART-naïve, 50		472	3.9	0.0%		NA/76	
Weinberg *et al*[119]	1994-2010	Prospective observational, United States	Hormone oral contraceptive, 13 No contraceptive, 149	2 doses (0, 6) or 3 doses (0, 2, 6)	478	47%[5]	78.0%	NA/20, ELISA (Mediagnost)	NA/62 NA/51	Women only study; Higher baseline CD4 count and suppressed PVL
Launay *et al*[120]	2003-2005	Randomized controlled trial, France	Standard 2-dose, 49	HAVRIX 1440/ (0, 6)	Median, 355	Median, < 1.7	78.0%	6-18/20, ELISA (ETIAB-HAVK PLUS)	6 m: 44.9/46.8 7 m: 69.4/72.3 18 m: 61.2/69.8	Absence of tobacco smoking
			3-dose, 46	HAVRIX 1440/ (0, 1, 6)	Median, 351	Median, < 1.7	83.0%		6 m: 69.6/74.4 7 m: 82.6/88.4 18 m: 78.3/85.7	
Overton *et al*[121]	1997-2004	Retrospective, United States	1 or 2-dose, 268	HAVRIX 1440/ NA (1 or 2 doses)	Mean, 447	Mean, 2.9	67.5%	NA/NA ELISA (Not specified)	NA/49.6	Male; PVL < 1000 copies/mL
Weissman *et al*[122]	2001-2003	Retrospective, United States	Standard 2-dose, 138	HAVRIX 1440/ (0, 6-12)	Mean, 424	NA	81.9%	6-13/18, EIA (Abbot IMx HAV Ab)	48.6 (67/138)	Female; CD4 count at vaccination > 200 cells/mm^3
Wallace *et al*[123]	1997-1998	Randomized controlled trial, United States	Standard 2-dose, HIV-positive, 55	Vaqta 50/ (0, 6)	Mean, 457.5	4.52	76.0%	1, 6, 7, 12/10, Quantitative modified HAVAb assay (NA)	1 m: NA/61, CD4 < 300/ 300+, 48/74 7 m: NA/94, CD4 < 300/ 300+, 87/100 12 m: NA/90, CD4 < 300/ 300+, 80/100	100% of subjects with CD4 counts ⩾ 300 cells/mm^3 seroconverted
			Standard 2-dose, HIV-negative, 72	Vaqta 50/ (0, 6)	NA	NA	NA		1 m: NA/90 7 m: NA/100 13 m: NA/90	

Kemper *et al*[124]	1995-1997	Double-blind, placebo-controlled trial, United States	Standard 2-dose, HIV-positive, 48	HAVRIX 1440/ (0, 6)	376	3.29	91.0%	1, 6, 7, 9/33, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/11 CD4 < 200/ 200+, 0/16 6 m: NA/9 CD4 < 200/ 200+, 0/13 7 m: NA/49, CD4 < 200/ 200+, 11/62 9 m: NA/52, CD4 < 200/ 200+, 9/67	Subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers
Neilsen *et al*[125]	Pre-1996	Randomized controlled trial, Australia	Accelerated 2-dose, HIV-positive, 48	HAVRIX 1440/ (0, 1)	Mean 569	NA	NA	1, 3/20, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/80.0 7 m: NA/93.2 CD4 ⩽ 200, 64	MSM only study; subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers; Vaccine schedule did not affect response; HIV-negative subjects had higher seroconversion rates and GMTs
			Standard 2-dose, HIV-positive, 42	HAVRIX 1440/ (0, 6)	Mean 454	NA	NA	1, 7/20, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/75.6 7 m: NA/81.3 CD4 ⩽ 200, 64	
			Standard 2-dose, HIV-negative, 46	HAVRIX 1440/ (0, 6)	NA	NA	NA	1, 7/20, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/90.2 7 m: NA/100	
Wilde *et al*[126]	Pre-1995	Prospective, United Kingdom	Three mini-dose, HIV-positive hemophiliacs, 31	HAVRIX 720/ (0, 1, 6)	Median 450 (IgG positive after 2 doses) Median 335 (IgG positive after 3 doses)	NA	0	1, 2, 7/20, EIA (SORIN Biomedica INCstar, Italy)	2 m: NA/29 7 m: NA/55	Hemophiliacs only (all anti-HCV positive); no patients with CD4 counts < 170 cells/mm^3 seroconverted
Tilzey *et al*[127]	Pre-1995	Prospective, United Kingdom	Three mini-dose, HIV-positive hemophiliacs, 25	HAVRIX 720/ (0, 1, 6)	NA	NA	NA	1, 2, 6, 7/20, ELISA (Boehringer-Mannheim)	1 m: NA/26 2 m: NA/50 6 m: NA/47 7 m: NA/76	Men only study; After 3 doses, all HIV-positive hemophiliacs with anti-HAV titers of < 50 mIU/mL had CD4 counts < 100 cells/mm^3. HAVRIX 1440 was given as a 4th booster dose to the 4 HIV vaccinees with anti-HAV < 50 mIU/mL after 3 doses; only 1 subsequently developed anti-HAV > 50 mIU/mL
			Three mini-dose, HIV-negative hemophiliacs, 8	HAVRIX 720/ (0, 1, 6)	NA	NA	NA		1 m: NA/57 2 m: NA/86 6 m: NA/100 7 m: NA/100	
			Three mini-dose, HIV-negative healthy controls, 25	HAVRIX 720/ (0, 1, 6)	NA	NA	NA		1 m: NA/100 2 m: NA/100 6 m: NA/100 7 m: NA/100	
Hess *et al*[128]	Pre-1994	Prospective, controlled, Germany	Three mini-dose, HIV-positive MSM, 26	HAVRIX 720/ (0, 1, 6)	495	NA	NA	1, 2, 6, 7/20, ELISA (SB Biologicals)	2 m: NA/78.6 7 m: NA/76.9	MSM only study; Seroconversion rates were independent of CD4 counts
			Three mini-dose, HIV-negative MSM, 20	HAVRIX 720/ (0, 1, 6)	NA	NA	NA		2 m: NA/100 7 m: NA/100	
Santagostino *et al*[129]	Pre-1994	NA, Italy	Three mini-dose, HIV-positive hemophiliacs, 47	HAVRIX 720 (0, 1, 6)	NA	NA	NA	1, 2, 7, 12/20	12 m: NA/76.6	Hemophiliacs; Seroconversion rates were dependent on stage of HIV disease
			Three mini-dose, HIV-negative hemophiliacs, 66	HAVRIX 720 (0, 1, 6)	NA	NA	NA	NA	12 m: NA/100	

[1]Number of HIV-positive individuals with baseline negative anti-HAV and data available; [2]Duration specified after the first dose when primary serological response was assayed; [3]Cut-off value of specific anti-HAV IgG used to define serological response; [4]Factors identified by multivariate analysis in HIV-positive individuals unless specified; [5]Percentage of patients with undetectable plasma HIV RNA load. cART: Combination of antiretroviral therapy; CIA: Chemiluminescence immunoassay; EIA: Enzyme immunoassay; ELISA: Enzyme linked immunosorbent assay; HAV: Hepatitis A virus; HCV: Hepatitis C virus; ITT: Intention-to-treat; NA: Not available; PVL: Plasma HIV RNA load; PP: Per-protocol.

compared to HIV-negative healthy adults, ranging from 48.6%-94.0%[122-125]. In a meta-analysis including 8 studies, combining a total of 458 HIV-positive patients, the overall rate of serological response to HAV vaccination was 64%[130]. In addition, the geometric mean titers (GMTs) of specific antibodies were also lower among HIV-positive individuals compared to the healthy population[115,123,127].

Overall, factors that correlated best with the poor response to HAV vaccination among HIV-positive individuals were surrogates of immune status such as low CD4 cell counts and high plasma HIV RNA loads at the time of vaccination as shown in Table 7[115-129]. Other factors identified with low rates of seroconversion were HCV coinfection and tobacco smoking[116,120]. Both male and female genders have been associated with seroconversion[121,122].

While the vaccination effectiveness among HIV-positive individuals was mostly evaluated by seroconversion rates in the countries of low endemicities, the serological and clinical responses to HAV vaccination were rarely investigated in the outbreak setting. In a recent prospective observational study during the outbreak of acute hepatitis A among MSM in Taiwan, the overall seroconversion rate among HIV-positive MSM was 39.7% and 93.4% after receiving 1 dose and completing 2-dose series of HAV vaccination, respectively. Despite the delayed serological response, HAV vaccination had led to a 93% reduction in the risk of acute HAV infection among HIV-positive MSM during the outbreak setting. Higher CD4 cell counts were consistently correlated with higher seroconversion rates[131].

Studies published after the meta-analysis in 2006 made various attempts to augment the immune response to the inactivated HAV vaccine despite the aforementioned non-modifiable adverse factors. One attempt was by using a virosome-formulated HAV vaccine (Epaxal1, Berna Biotech Ltd.) to enhance the immune responses of 14 HIV-positive individuals compared to 64 healthy adults[132]. After a primary dose at day 1 and a booster dose 12 mo later, the seroconversion rates (anti-HAV IgG > 20 mIU/mL) at month 13 were 91.7% and 100% in HIV-positive adults and in healthy adults, respectively. The GMTs of anti-HAV increased from 25.5 mIU/mL after the primary immunization to 659.2 mIU/mL after the booster dose in HIV-positive adults[132].

Other attempts were by increasing the number of doses of vaccine administered[115,120,121]. Two doses over 1 dose of HIV vaccine increased seroconversion rates in HIV-positive individuals[121,123,124]. There is less convincing evidence to show that 3 doses over 2 doses further increased seroconversion rates, possibly due to the smaller margin of benefit and the relatively larger sample size of adequate power needed to demonstrate the benefit. However, 2 studies showed trends of augmented responses in terms of seroconversion rates and GMTs by adding a booster dose at week 4 sandwiched between the first dose and the second dose at week 24[115,120]. In the intention-to-treat (ITT) analysis, seroconversion at week 28 was observed in 82.6% *vs* 69.4% (P = 0.13) and at week 48 in 84.2% *vs* 78.1% (P = 0.23) in the 3-dose *vs* the 2-dose group for the French and Taiwanese studies, respectively.

When multiple doses have been used, the timing of the second and third dose did not affect immunogenicity in persons with limited immunodeficiency[125]. Hence, in the outbreak settings, an accelerated schedule, *i.e.*, delivering the second or third booster dose at an interval of less than 3 mo from the first dose may be preferable although more studies are needed[131]. However, in HIV-positive individuals with more advanced immunodeficiency (CD4 < 300 cells/mm^3 or AIDS status), it may be preferable to wait for the CD4 count to recover before delivering the booster doses[123,127]. In the most primitive example, of the 2 HIV-positive hemophiliacs with CD4 counts below 100 cells/mm^3 who, after the third dose of HAVRIX 720 U, went on to receive a fourth booster dose of HAVRIX 1440 U, neither seroconverted[127].

To our knowledge, there is limited experience with using HAV vaccination as post-exposure prophylaxis in HIV-positive individuals. Although in healthy individuals, HAV vaccine has been demonstrated to be capable of protecting susceptible contacts with benefits of long-term protection when compared to passive immunization by immunoglobulins[133].

Durability of seroprotection and factors associated with persistent seroprotection

In healthy adults following a primary 2-dose schedule, mathematical models indicate that anti-HAV antibodies may persist in > 90% of vaccinees for 40 years or more[134]. In HIV-positive individuals, a slight decrease was observed over time; 88.6%-100% of responders were still seroprotected after 1 year[115,120], 86.8%-90% after 3 years[135,136], 85%-85.4% after 4 years[136,137], and 75.5%-88.4% after 5 years[135,136,138]. Percentages of seroprotection at the end of 5 years of follow-up were 78.9% *vs* 76.4% by ITT analysis (P = 0.61) (Table 8)[135-138]. GMTs were significantly higher throughout each consecutive year with the 3-dose schedule as compared to the standard 2-dose schedule[136]. Factors associated with persistent seroprotection include virologic suppression at vaccination and maintained lower levels of HIV viremia as denoted by time-updated plasma HIV RNA load[135,137], 3-dose compared to 2-dose schedule (adjusted odds ratio 3.36; 95%CI: 1.14-9.93), acute syphilis and absence of acute hepatitis C[136,138].

Given the lower initial antibody levels, the apparent waning of antibody levels and the increasing life expectancy of HIV-positive individuals, post-vaccination booster doses may be necessary to maintain anti-

Table 8 Long-term response rates and predictors of sustained seroprotection after hepatitis A virus vaccination in human immunodeficiency virus-positive patients

Ref.	Dates	Design/ Country	No. of patient[1]	HAV/ dosing schedules (mo)	CD4, cells/ mm^3	PVL, $\log_{10}$, copies/mL	ART (%)	Timing of assay[2], yr/cut-off[3], mIU/ mL/Assay	Response rate (%): ITT/PP	Predictors of persistent response and comments[4]
Cheng *et al*[136]	2010-2015	Prospective, Taiwan	Primary responders: 2 doses, 110 3 doses, 185 Non-responders: 2 doses, 16 3 doses, 23	HAVRIX 1440 U/ 2 doses (0, 6) 3 doses (0, 1, 6)	560/415 470/315	2.5/2.8 2.9/3.3	70/56 59/63	2, 3, 4, 5/20 ELISA (ETIAB-HAVK PLUS)	At 1.5 yr: 2 doses: 90.0/93.4 3 doses: 87.0/94.7 At 5 yr: 2 doses: 76.4/88.4 3 doses: 78.9/94.2	MSM only study; 3-doses over 2-dose, syphilis, lack of acute HCV
Kernéis *et al*[137]	2006-2009	Prospective, France	Primary responders: 71 (52)	HAVRIX 1440/ 2 doses (0, 6) 3 doses (0, 1, 6)	362	62%[5]	NA	7, 43/20 ELISA (ETIAB-HAVK PLUS)	At 3.7 yr: Overall: 61.9/84.6	PVL < 50 copies/mL at time of last vaccine dose and a short duration of HIV infection
Jablonowska *et al*[138]	2004	Prospective, Poland	Primary responders: 66	HAVRIX 1440 (0, 6)	450	NA	37	1.5, 5/20 CIA (Cobas, Roche)	At 1.5 yr: 75.8/81.9 At 5 yr: 56.1/75.5	Lack of co-infection with HCV
Crum-Cianflone *et al*[135]	1996-2003	Retrospective, United States	116	Vaqta 50 or HAVRIX 1440 (0, 6-18)	Median, 467	50%[5]	62	3, 6-10/10	At 3 yr: 90 At 6-10 yr: 85	Lower PVL; PVL < 400 copies/mL

[1]Number of vaccinees with primary seroconversion after the last dose of vaccine; (figure in parentheses is the number of vaccinees with primary conversion and subsequent sera for follow-up of antibody persistence); [2]Duration specified after the first dose when primary serological response was assayed; [3]Cut-off value of specific anti-HAV IgG used to define serological response; [4]Factors identified by multivariate analysis in HIV-positive individuals unless specified; [5]Percentage of patients with undetectable plasma HIV RNA load. ART: Antiretroviral therapy; CIA: Chemiluminescence immunoassay; ELISA: Enzyme linked immunosorbent assay; HAV: Hepatitis A virus; HCV: Hepatitis C virus; ITT: Intention-to-treat; MSM: Men who have sex with men; NA: Not available; PVL: Plasma HIV RNA load; PP: Per-protocol.

HAV levels after 10 years in HIV-positive individuals in the absence of virologic suppression[111]. Currently, only the British HIV Association (BHIVA) recommends delivering booster vaccination every 10 years whilst other health authorities recommend regular monitoring of anti-HAV IgG and booster vaccinations only if at continued risk after seroconversion (Table 6)[111-114]. However, among immunocompetent hosts, memory responses to HAV may exist even in the absence of detectable antibodies[139], and in the era of cART, the same may apply to HIV-positive patients with immune reconstitution[131]. Nevertheless, the strategies of booster HAV vaccination to those with waning immunity or non-responders need more studies to confirm the effectiveness.

Vaccine safety

Serious adverse events following HAV vaccination in HIV-positive individuals are rare and not more common among HIV-positive individuals compared to HIV-negative vaccinees. HAV vaccination does not have a significant impact on plasma HIV RNA load, progression to AIDS, or CD4 cell count[123,124,130].

CONCLUSION

In this review, we have found that, in developed countries of low HAV endemicity, HIV-positive individuals remain susceptible to HAV infection because of low adherence to recommended HAV vaccination, at-risk sexual behaviors, and injecting drug use, as demonstrated by the recent outbreaks of acute HAV infections among MSM and IDUs in Taiwan and Israel, respectively[71,88], despite the implementation of HAV vaccination programs in children. Serological response rates to the recommended 2-dose HAV vaccination are lower in HIV-positive individuals than HIV-negative individuals; an additional dose of HAV vaccine may improve serological responses and durability of seroprotection in HIV-positive individuals with initial low CD4 cell counts. While clinical trials are warranted to confirm the HAV vaccine efficacy in the outbreak

setting of acute HAV infection, the recent observational study suggested that implementation of the 2-dose HAV vaccination was effective in preventing acute HAV infection among MSM. With ongoing improvements in survival and quality of life with modern cART, the importance of awareness of and adherence to HAV vaccination recommendations cannot be overemphasized among health care providers as well as at-risk populations.

REFERENCES

1 **Havelaar AH**, Kirk MD, Torgerson PR, Gibb HJ, Hald T, Lake RJ, Praet N, Bellinger DC, de Silva NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, Devleesschauwer B. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Med* 2015; **12**: e1001923 [PMID: 26633896 DOI: 10.1371/journal.pmed.1001923]

2 **Aggarwal R**, Goel A. Hepatitis A: epidemiology in resource-poor countries. *Curr Opin Infect Dis* 2015; **28**: 488-496 [PMID: 26203853 DOI: 10.1097/qco.0000000000000188]

3 **Jacobsen KH**, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 2010; **28**: 6653-6657 [PMID: 20723630 DOI: 10.1016/j.vaccine.2010.08.037]

4 **Nelson NP**, Murphy TV. Hepatitis A: The changing epidemiology of hepatitis A. *Clin Liver Dis* (Hoboken) 2013; **2**: 227-230 [PMID: 26566433 DOI: 10.1002/cld.230]

5 **Mena G**, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: A review. *Hum Vaccin Immunother* 2015; **11**: 2582-2598 [PMID: 26208678 DOI: 10.1080/21645515.2015.1055424]

6 **Feinstone SM**, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. *Science* 1973; **182**: 1026-1028 [PMID: 4356028]

7 **Robertson BH**, Jansen RW, Khanna B, Totsuka A, Nainan OV, Siegl G, Widell A, Margolis HS, Isomura S, Ito K. Genetic relatedness of hepatitis A virus strains recovered from different geographical regions. *J Gen Virol* 1992; **73** (Pt 6): 1365-1377 [PMID: 1318940 DOI: 10.1099/0022-1317-73-6-1365]

8 **Costa-Mattioli M**, Cristina J, Romero H, Perez-Bercof R, Casane D, Colina R, Garcia L, Vega I, Glikman G, Romanowsky V, Castello A, Nicand E, Gassin M, Billaudel S, Ferré V. Molecular evolution of hepatitis A virus: a new classification based on the complete VP1 protein. *J Virol* 2002; **76**: 9516-9525 [PMID: 12186933]

9 **Lu L**, Ching KZ, de Paula VS, Nakano T, Siegl G, Weitz M, Robertson BH. Characterization of the complete genomic sequence of genotype II hepatitis A virus (CF53/Berne isolate). *J Gen Virol* 2004; **85**: 2943-2952 [PMID: 15448357 DOI: 10.1099/vir.0.80304-0]

10 **Nainan OV**, Armstrong GL, Han XH, Williams I, Bell BP, Margolis HS. Hepatitis a molecular epidemiology in the United States, 1996-1997: sources of infection and implications of vaccination policy. *J Infect Dis* 2005; **191**: 957-963 [PMID: 15717272 DOI: 10.1086/427992]

11 **Tjon GM**, Wijkmans CJ, Coutinho RA, Koek AG, van den Hoek JA, Leenders AC, Schneeberger PM, Bruisten SM. Molecular epidemiology of hepatitis A in Noord-Brabant, The Netherlands. *J Clin Virol* 2005; **32**: 128-136 [PMID: 15653415 DOI: 10.1016/j.jcv.2004.03.008]

12 **McFarlane ES**, Embil JA, Manuel FR, Thiébaux HJ. Antibodies to hepatitis A antigen in relation to the number of lifetime sexual partners in patients attending an STD clinic. *Br J Vener Dis* 1981; **57**: 58-61 [PMID: 6258702]

13 **Villano SA**, Nelson KE, Vlahov D, Purcell RH, Saah AJ, Thomas DL. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. *Clin Infect Dis* 1997; **25**: 726-728 [PMID: 9314468]

14 **Ochnio JJ**, Patrick D, Ho M, Talling DN, Dobson SR. Past infection with hepatitis A virus among Vancouver street youth, injection drug users and men who have sex with men: implications for vaccination programs. *CMAJ* 2001; **165**: 293-297 [PMID: 11517645]

15 **Corey L**, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. *N Engl J Med* 1980; **302**: 435-438 [PMID: 6243391 DOI: 10.1056/nejm198002213020804]

16 **Kryger P**, Pedersen NS, Mathiesen L, Nielsen JO. Increased risk of infection with hepatitis A and B viruses in men with a history of syphilis: relation to sexual contacts. *J Infect Dis* 1982; **145**: 23-26 [PMID: 6274966]

17 **Coutinho RA**, Albrecht-van Lent P, Lelie N, Nagelkerke N, Kuipers H, Rijsdijk T. Prevalence and incidence of hepatitis A among male homosexuals. *Br Med J* (Clin Res Ed) 1983; **287**: 1743-1745 [PMID: 6416573]

18 **Katz MH**, Hsu L, Wong E, Liska S, Anderson L, Janssen RS. Seroprevalence of and risk factors for hepatitis A infection among young homosexual and bisexual men. *J Infect Dis* 1997; **175**: 1225-1229 [PMID: 9129091]

19 **Corona R**, Stroffolini T, Giglio A, Cotichini R, Tosti ME, Prignano G, Di Carlo A, Maini A, Mele A. Lack of evidence for increased risk of hepatitis A infection in homosexual men. *Epidemiol Infect* 1999; **123**: 89-93 [PMID: 10487644]

20 **Bialek SR**, Barry V, Bell BP, Valleroy LA, Behel S, Mackellar DA, Secura G, Thiede H, McFarland W, Ford WL, Bingham TA, Shehan DA, Celentano DD. Seroprevalence and correlates of hepatitis a among HIV-negative American men who have sex with men. *Sex Health* 2011; **8**: 343-348 [PMID: 21851774 DOI: 10.1071/sh10162]

21 **Ross JD**, Ghanem M, Tariq A, Gilleran G, Winter AJ. Seroprevalence of hepatitis A immunity in male genitourinary medicine clinic attenders: a case control study of heterosexual and homosexual men. *Sex Transm Infect* 2002; **78**: 174-179 [PMID: 12238647]

22 **Crofts N**, Cooper G, Stewart T, Kiely P, Coghlan P, Hearne P, Hocking J. Exposure to hepatitis A virus among blood donors, injecting drug users and prison entrants in Victoria. *J Viral Hepat* 1997; **4**: 333-338 [PMID: 9310932]

23 **Removille N**, Origer A, Couffignal S, Vaillant M, Schmit JC, Lair ML. A hepatitis A, B, C and HIV prevalence and risk factor study in ever injecting and non-injecting drug users in Luxembourg associated with HAV and HBV immunisations. *BMC Public Health* 2011; **11**: 351 [PMID: 21595969 DOI: 10.1186/1471-2458-11-351]

24 **Franco E**, Giambi C, Ialacci R, Coppola RC, Zanetti AR. Risk groups for hepatitis A virus infection. *Vaccine* 2003; **21**: 2224-2233 [PMID: 12744847]

25 **Ida S**, Tachikawa N, Nakajima A, Daikoku M, Yano M, Kikuchi Y, Yasuoka A, Kimura S, Oka S. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. *Clin Infect Dis* 2002; **34**: 379-385 [PMID: 11774086 DOI: 10.1086/338152]

26 **Nandwani R**, Caswell S, Boag F, Lawrence AG, Coleman JC. Hepatitis A seroprevalence in homosexual and heterosexual men. *Genitourin Med* 1994; **70**: 325-328 [PMID: 8001944]

27 **Fainboim H**, González J, Fassio E, Martínez A, Otegui L, Eposto M, Cahn P, Marino R, Landeira G, Suaya G, Gancedo E, Castro R, Brajterman L, Laplumé H. Prevalence of hepatitis viruses in an anti-human immunodeficiency virus-positive population from Argentina. A multicentre study. *J Viral Hepat* 1999; **6**: 53-57 [PMID: 10847130]

28 **Aloise R**, de Almeida AJ, Sion FS, Morais-de-Sá CA, Gaspar AM, de Paula VS. Changes in hepatitis A virus seroepidemiology in HIV-infected Brazilian patients. *Int J STD AIDS* 2008; **19**: 321-326 [PMID: 18482962 DOI: 10.1258/ijsa.2007.007100]

29 **Lee HC**, Ko NY, Lee NY, Chang CM, Ko WC. Seroprevalence of viral hepatitis and sexually transmitted disease among adults with recently diagnosed HIV infection in Southern Taiwan, 2000-2005: upsurge in hepatitis C virus infections among injection drug users.

J Formos Med Assoc 2008; **107**: 404-411 [PMID: 18492625 DOI: 10.1016/s0929-6646(08)60106-0]
30 **Sun HY**, Kung HC, Ho YC, Chien YF, Chen MY, Sheng WH, Hsieh SM, Wu CH, Liu WC, Hung CC, Chang SC. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. *Int J Infect Dis* 2009; **13**: e199-e205 [PMID: 19208490 DOI: 10.1016/j.ijid.2008.12.009]
31 **Davoudi S**, Rasoolinejad M, Jafari S, Erfanzadeh M, Foroughi M, Hajiabdolbaghi M, Mohraz M. Prevalence of hepatitis A virus infection in a HIV positive community. *Acta Med Iran* 2010; **48**: 192-195 [PMID: 21137657]
32 **Hoover KW**, Butler M, Workowski KA, Follansbee S, Gratzer B, Hare CB, Johnston B, Theodore JL, Tao G, Smith BD, Chorba T, Kent CK. Low rates of hepatitis screening and vaccination of HIV-infected MSM in HIV clinics. *Sex Transm Dis* 2012; **39**: 349-353 [PMID: 22504597 DOI: 10.1097/OLQ.0b013e318244a923]
33 **Linkins RW**, Chonwattana W, Holtz TH, Wasinrapee P, Chaikummao S, Varangrat A, Tongtoyai J, Mock PA, Curlin ME, Sirivongrangson P, van Griensven F, McNicholl JM. Hepatitis A and hepatitis B infection prevalence and associated risk factors in men who have sex with men, Bangkok, 2006-2008. *J Med Virol* 2013; **85**: 1499-1505 [PMID: 23797893 DOI: 10.1002/jmv.23637]
34 **Baek JH**, Kim CO, Park JY, Jeong SJ, Koo NS, Kim HW, Han SH, Choi JY, Song YG, Kim JM. Clinical factors associated with hepatitis A virus seropositivity in HIV-infected adults living in a country with an epidemiologic shift for hepatitis A virus infection. *J Korean Med Sci* 2012; **27**: 969-971 [PMID: 22876069 DOI: 10.3346/jkms.2012.27.8.969]
35 **Tseng YT**, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, Lu CL, Hsieh CY, Hung CC. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. *J Formos Med Assoc* 2012; **111**: 431-438 [PMID: 22939661 DOI: 10.1016/j.jfma.2011.06.022]
36 **Kourkounti S**, Paparizos V, Leuow K, Kyriakis K, Antoniou C. Prevalence and titre of antibodies against Hepatitis A virus in HIV-infected men having sex with men in Greece. *Infez Med* 2014; **22**: 206-212 [PMID: 25269962]
37 **Diamond C**, Thiede H, Perdue T, Secura GM, Valleroy L, Mackellar D, Corey L. Viral hepatitis among young men who have sex with men: prevalence of infection, risk behaviors, and vaccination. *Sex Transm Dis* 2003; **30**: 425-432 [PMID: 12916134]
38 **O'Riordan M**, Goh L, Lamba H. Increasing hepatitis A IgG prevalence rate in men who have sex with men attending a sexual health clinic in London: implications for immunization policy. *Int J STD AIDS* 2007; **18**: 707-710 [PMID: 17945051 DOI: 10.1258/095646207782193902]
39 **Van Rijckevorsel GG**, Sonder GJ, Bovée LP, Thiesbrummel HF, Geskus RB, Van Den Hoek A. Trends in hepatitis A, B, and shigellosis compared with gonorrhea and syphilis in men who have sex with men in Amsterdam, 1992-2006. *Sex Transm Dis* 2008; **35**: 930-934 [PMID: 18685550 DOI: 10.1097/OLQ.0b013e3181812cdf]
40 **Bozicevic I**, Rode OD, Lepej SZ, Johnston LG, Stulhofer A, Dominkovic Z, Bacak V, Lukas D, Begovac J. Prevalence of sexually transmitted infections among men who have sex with men in Zagreb, Croatia. *AIDS Behav* 2009; **13**: 303-309 [PMID: 18690533 DOI: 10.1007/s10461-008-9436-7]
41 **Weerakoon AP**, Chen MY, Read TR, Bradshaw C, Fairley CK. Immunity to hepatitis A when outbreaks of infection in men who have sex with men (MSM) are rare. *Vaccine* 2012; **30**: 3430-3434 [PMID: 22449421 DOI: 10.1016/j.vaccine.2012.03.024]
42 **Ali H**, Regan DG, Guy RJ, Robertson P, Watchirs-Smith L, McNulty AM, Donovan B. Increasing hepatitis A immunity in men who have sex with men in Sydney, 1996-2012. *Vaccine* 2015; **33**: 4745-4747 [PMID: 25720793 DOI: 10.1016/j.vaccine.2015.01.090]
43 **Høybye G**, Skinhøj P, Hentzer B, Faber V, Mathiesen L. An epidemic of acute viral hepatitis in male homosexuals. Etiology and clinical characteristics. *Scand J Infect Dis* 1980; **12**: 241-244 [PMID: 7006056]
44 **Christenson B**, Broström C, Böttiger M, Hermanson J, Weiland O, Ryd G, Berg JV, Sjöblom R. An epidemic outbreak of hepatitis A among homosexual men in Stockholm. Hepatitis A, a special hazard for the male homosexual subpopulation in Sweden. *Am J Epidemiol* 1982; **116**: 599-607 [PMID: 7137147]
45 **Mindel A**, Tedder R. Hepatitis A in homosexuals. *Br Med J* (Clin Res Ed) 1981; **282**: 1666 [PMID: 6786425]
46 **Kani J**, Nandwani R, Gilson RJ, Johnson AM, Maguire HC, Tedder RS. Hepatitis A virus infection among homosexual men. *BMJ* 1991; **302**: 1399 [PMID: 2059724]
47 **Atkins M**, Zambon M, Watkins P. Hepatitis A virus infection. Should susceptible homosexual men be offered immunization. *BMJ* 1993; **307**: 562 [PMID: 8400990]
48 **Leentvaar-Kuijpers A**, Kool JL, Veugelers PJ, Coutinho RA, van Griensven GJ. An outbreak of hepatitis A among homosexual men in Amsterdam, 1991-1993. *Int J Epidemiol* 1995; **24**: 218-222 [PMID: 7797346]
49 **Walsh B**, Sundkvist T, Maguire H, Young Y, Heathcock R, Iverson A. Rise in hepatitis A among gay men in the Thames regions 1995 and 1996. *Genitourin Med* 1996; **72**: 449-450 [PMID: 9038651]
50 **Stene-Johansen K**, Jenum PA, Hoel T, Blystad H, Sunde H, Skaug K. An outbreak of hepatitis A among homosexuals linked to a family outbreak. *Epidemiol Infect* 2002; **129**: 113-117 [PMID: 12211577]
51 **Bell A**, Ncube F, Hansell A, Davison KL, Young Y, Gilson R, Macdonald N, Heathcock R, Warburton F, Maguire H. An outbreak of hepatitis A among young men associated with having sex in public venues. *Commun Dis Public Health* 2001; **4**: 163-170 [PMID: 11732354]
52 **Manfredi R**, Calza L, Chiodo F. Changing epidemiology of hepatitis A in the Bologna metropolitan area, northern Italy: importance of counselling and prophylactic measures for the male homo/bisexual population. *Clin Microbiol Infect* 2005; **11**: 845-848 [PMID: 16153262 DOI: 10.1111/j.1469-0691.2005.01219.x]
53 **Mazick A**, Howitz M, Rex S, Jensen IP, Weis N, Katzenstein TL, Haff J, Molbak K. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill* 2005; **10**: 111-114 [PMID: 16077208]
54 **Girardi E**, Scognamiglio P, Sciarrone MR, Loffredo M, Gnesivo C, Noto P, Antonucci G, Capobianchi MR, Ippolito G. High HIV prevalence in male patients with acute hepatitis A in the Rome metropolitan area, Italy 2002-2008. *J Hepatol* 2011; **54**: 1102-1106 [PMID: 21145799 DOI: 10.1016/j.jhep.2010.09.024]
55 **Bordi L**, Rozera G, Scognamiglio P, Minosse C, Loffredo M, Antinori A, Narciso P, Ippolito G, Girardi E, Capobianchi MR. Monophyletic outbreak of Hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008-2009. *J Clin Virol* 2012; **54**: 26-29 [PMID: 22341552 DOI: 10.1016/j.jcv.2012.01.009]
56 **Tortajada C**, de Olalla PG, Diez E, Pinto RM, Bosch A, Perez U, Sanz M, Caylà JA. Hepatitis A among men who have sex with men in Barcelona, 1989-2010: insufficient control and need for new approaches. *BMC Infect Dis* 2012; **12**: 11 [PMID: 22264382 DOI: 10.1186/1471-2334-12-11]
57 **Dabrowska MM**, Nazzal K, Wiercinska-Drapalo A. Hepatitis A and hepatitis A virus/HIV coinfection in men who have sex with men, Warsaw, Poland, September 2008 to September 2009. *Euro Surveill* 2011; **16**: [PMID: 21903035]
58 **Tortajada C**, de Olalla PG, Pinto RM, Bosch A, Caylà J. Outbreak of hepatitis A among men who have sex with men in Barcelona, Spain, September 2008-March 2009. *Euro Surveill* 2009; **14**: [PMID: 19371516]
59 **Sfetcu O**, Irvine N, Ngui SL, Emerson C, McCaughey C, Donaghy P. Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009. *Euro Surveill* 2011; **16**: [PMID: 21392487]
60 **Taffon S**, Bidini G, Vichi F, Corti G, Genovese D, Kondili LA, Bindi R, Armellini F, Leoncini F, Bartoloni A, Mazzotta F, Rapicetta M. A unique HAV strain circulated in patients with acute HAV infection with different risk exposures in Tuscany, Italy. *J*

Clin Virol 2011; **50**: 142-147 [PMID: 21094625 DOI: 10.1016/j.jcv.2010.10.011]
61 **Kosatsky T**, Middaugh JP. Linked outbreaks of hepatitis A in homosexual men and in food service patrons and employees. *West J Med* 1986; **144**: 307-310 [PMID: 3962292]
62 **Desenclos JC**, MacLafferty L. Community wide outbreak of hepatitis A linked to children in day care centres and with increased transmission in young adult men in Florida 1988-9. *J Epidemiol Community Health* 1993; **47**: 269-273 [PMID: 8228760]
63 **Henning KJ**, Bell E, Braun J, Barker ND. A community-wide outbreak of hepatitis A: risk factors for infection among homosexual and bisexual men. *Am J Med* 1995; **99**: 132-136 [PMID: 7625417]
64 **Allard R**, Beauchemin J, Bédard L, Dion R, Tremblay M, Carsley J. Hepatitis A vaccination during an outbreak among gay men in Montréal, Canada, 1995-1997. *J Epidemiol Community Health* 2001; **55**: 251-256 [PMID: 11238580]
65 **Centers for Disease Control and Prevention (CDC)**. Hepatitis A vaccination of men who have sex with men--Atlanta, Georgia, 1996-1997. *MMWR Morb Mortal Wkly Rep* 1998; **47**: 708-711 [PMID: 9746398]
66 **Cotter SM**, Sansom S, Long T, Koch E, Kellerman S, Smith F, Averhoff F, Bell BP. Outbreak of hepatitis A among men who have sex with men: implications for hepatitis A vaccination strategies. *J Infect Dis* 2003; **187**: 1235-1240 [PMID: 12696002 DOI: 10.1086/374057]
67 **Stewart T**, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. *Med J Aust* 1993; **158**: 519-521 [PMID: 8387627]
68 **Stokes ML**, Ferson MJ, Young LC. Outbreak of hepatitis A among homosexual men in Sydney. *Am J Public Health* 1997; **87**: 2039-2041 [PMID: 9431300]
69 **Ferson MJ**, Young LC, Stokes ML. Changing epidemiology of hepatitis A in the 1990s in Sydney, Australia. *Epidemiol Infect* 1998; **121**: 631-636 [PMID: 10030713]
70 **Delpech VC**, Thackway SV, Young L, Pontivivo G, Smedley E, Morgan K, Ferson MJ. Hepatitis A in south-eastern Sydney 1997-1999: continuing concerns for gay men and an outbreak among illicit drug users. *Commun Dis Intell* 2000; **24**: 203-206 [PMID: 10981351]
71 **Chen GJ**, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. *J Infect Dis* 2017; **215**: 1339-1340 [PMID: 28329351 DOI: 10.1093/infdis/jix123]
72 **Stene-Johansen K**, Tjon G, Schreier E, Bremer V, Bruisten S, Ngui SL, King M, Pinto RM, Aragonès L, Mazick A, Corbet S, Sundqvist L, Blystad H, Norder H, Skaug K. Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe. *J Med Virol* 2007; **79**: 356-365 [PMID: 17311331 DOI: 10.1002/jmv.20781]
73 **Urbanus AT**, van Houdt R, van de Laar TJ, Coutinho RA. Viral hepatitis among men who have sex with men, epidemiology and public health consequences. *Euro Surveill* 2009; **14**: [PMID: 19941800]
74 **Widell A**, Hansson BG, Moestrup T, Serléus Z, Mathiesen LR, Johnsson T. Acute hepatitis A, B and non-A, non-B in a Swedish community studied over a ten-year period. *Scand J Infect Dis* 1982; **14**: 253-259 [PMID: 6819637]
75 **Sundkvist T**, Johansson B, Widell A. Rectum carried drugs may spread hepatitis A among drug addicts. *Scand J Infect Dis* 1985; **17**: 1-4 [PMID: 3992196]
76 **Leino T**, Leinikki P, Hyypiä T, Ristola M, Suni J, Sutinen J, Holopainen A, Haikala O, Valle M, Rostila T. Hepatitis A outbreak amongst intravenous amphetamine abusers in Finland. *Scand J Infect Dis* 1997; **29**: 213-216 [PMID: 9255876]
77 **Stene-Johansen K**, Skaug K, Blystad H, Grinde B. A unique hepatitis A virus strain caused an epidemic in Norway associated with intravenous drug abuse. The Hepatitis A Study Group. *Scand J Infect Dis* 1998; **30**: 35-38 [PMID: 9670356]
78 **O'Donovan D**, Cooke RP, Joce R, Eastbury A, Waite J, Stene-Johansen K. An outbreak of hepatitis A amongst injecting drug users. *Epidemiol Infect* 2001; **127**: 469-473 [PMID: 11811880]
79 **Syed NA**, Hearing SD, Shaw IS, Probert CS, Brooklyn TN, Caul EO, Barry RE, Sarangi J. Outbreak of hepatitis A in the injecting drug user and homeless populations in Bristol: control by a targeted vaccination programme and possible parenteral transmission. *Eur J Gastroenterol Hepatol* 2003; **15**: 901-906 [PMID: 12867801]
80 **Roy K**, Howie H, Sweeney C, Parry J, Molyneaux P, Goldberg D, Taylor A. Hepatitis A virus and injecting drug misuse in Aberdeen, Scotland: a case-control study. *J Viral Hepat* 2004; **11**: 277-282 [PMID: 15117332 DOI: 10.1111/j.1365-2893.2004.00503.x]
81 **Spada E**, Genovese D, Tosti ME, Mariano A, Cuccuini M, Proietti L, Giuli CD, Lavagna A, Crapa GE, Morace G, Taffon S, Mele A, Rezza G, Rapicetta M. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. *J Hepatol* 2005; **43**: 958-964 [PMID: 16143420 DOI: 10.1016/j.jhep.2005.06.012]
82 **Harkess J**, Gildon B, Istre GR. Outbreaks of hepatitis A among illicit drug users, Oklahoma, 1984-87. *Am J Public Health* 1989; **79**: 463-466 [PMID: 2929804]
83 **Centers for Disease Control (CDC)**. Hepatitis A among drug abusers. *MMWR Morb Mortal Wkly Rep* 1988; **37**: 297-300, 305 [PMID: 3130560]
84 **Jin A**, Bardsley J. Intravenous drug use and hepatitis A: an investigation of an outbreak. *Can J Public Health* 1990; **81**: 79-81 [PMID: 2311058]
85 **Hutin YJ**, Sabin KM, Hutwagner LC, Schaben L, Shipp GM, Lord DM, Conner JS, Quinlisk MP, Shapiro CN, Bell BP. Multiple modes of hepatitis A virus transmission among methamphetamine users. *Am J Epidemiol* 2000; **152**: 186-192 [PMID: 10909956]
86 **Vong S**, Fiore AE, Haight DO, Li J, Borgsmiller N, Kuhnert W, Pinero F, Boaz K, Badsgard T, Mancini C, Nainan OV, Wiersma S, Bell BP. Vaccination in the county jail as a strategy to reach high risk adults during a community-based hepatitis A outbreak among methamphetamine drug users. *Vaccine* 2005; **23**: 1021-1028 [PMID: 15620475 DOI: 10.1016/j.vaccine.2004.07.038]
87 **Shaw DD**, Whiteman DC, Merritt AD, el-Saadi DM, Stafford RJ, Heel K, Smith GA. Hepatitis A outbreaks among illicit drug users and their contacts in Queensland, 1997. *Med J Aust* 1999; **170**: 584-587 [PMID: 10416427]
88 **Manor Y**, Lewis M, Ram D, Daudi N, Mor O, Savion M, Kra-Oz Z, Shemer Avni Y, Sheffer R, Shouval D, Mendelson E. Evidence for Hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. *J Infect Dis* 2016; Epub ahead of print [PMID: 28013247 DOI: 10.1093/infdis/jiw611]
89 **Grinde B**, Stene-Johansen K, Sharma B, Hoel T, Jensenius M, Skaug K. Characterisation of an epidemic of hepatitis A virus involving intravenous drug abusers--infection by needle sharing? *J Med Virol* 1997; **53**: 69-75 [PMID: 9298735]
90 **Naef MR**, Bucher HC, Erb P, Gyr N, Bassetti S, Battegay M. Reduced infections with HIV and hepatitis A during a Swiss intravenous opiate maintenance program. *J Acquir Immune Defic Syndr* 1999; **21**: 349-351 [PMID: 10428117]
91 **Istre GR**, Hopkins RS. An outbreak of foodborne hepatitis A showing a relationship between dose and incubation period. *Am J Public Health* 1985; **75**: 280-281 [PMID: 2983576]
92 **Tong MJ**, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. *J Infect Dis* 1995; **171** Suppl 1: S15-S18 [PMID: 7876641]
93 **Lee EJ**, Kwon SY, Seo TH, Yun HS, Cho HS, Kim BK, Choe WH, Lee CH, Kim JN, Yim HJ. [Clinical features of acute hepatitis A in recent two years]. *Korean J Gastroenterol* 2008; **52**: 298-303 [PMID: 19077476]
94 **Tekin R**, Yolbas I, Dal T, Demirpençe Ö, Kaya S, Bozkurt F, Deveci Ö, Çelen MK, Tekin A. Evaluation of adults with acute viral hepatitis a and review of the literature. *Clin Ter* 2013; **164**: 537-541 [PMID: 24424220 DOI: 10.7417/ct.2013.1634]
95 **Dahanayaka NJ**, Kiyohara T, Agampodi SB, Samaraweera PK, Kulasooriya GK, Ranasinghe JC, Semage SN, Yoshizaki S, Wakita

T, Ishii K. Clinical features and transmission pattern of hepatitis A: An experience from a hepatitis A outbreak caused by two cocirculating genotypes in Sri Lanka. *Am J Trop Med Hyg* 2016; **95**: 908-914 [PMID: 27382079 DOI: 10.4269/ajtmh.16-0221]

96 **Routenberg JA**, Dienstag JL, Harrison WO, Kilpatrick ME, Hooper RR, Chisari FV, Purcell RH, Fornes MF. Foodborne outbreak of hepatitis A: clinical and laboratory features of acute and protracted illness. *Am J Med Sci* 1979; **278**: 123-137 [PMID: 517565]

97 **Ford JC**. Infective Hepatitis. 300 Cases in an Outer London Borough. *Lancet* 1943; **241**: 675-678

98 **Hyun JJ**, Seo YS, An H, Yim SY, Seo MH, Kim HS, Kim CH, Kim JH, Keum B, Kim YS, Yim HJ, Lee HS, Um SH, Kim CD, Ryu HS. Optimal time for repeating the IgM anti-hepatitis A virus antibody test in acute hepatitis A patients with a negative initial test. *Korean J Hepatol* 2012; **18**: 56-62 [PMID: 22511904 DOI: 10.3350/kjhep.2012.18.1.56]

99 **Su CW**, Wu JC, Huang YS, Huo TI, Huang YH, Lin CC, Chang FY, Lee SD. Comparison of clinical manifestations and epidemiology between acute hepatitis A and acute hepatitis E in Taiwan. *J Gastroenterol Hepatol* 2002; **17**: 1187-1191 [PMID: 12453278]

100 **Hussain Z**, Das BC, Husain SA, Polipalli SK, Ahmed T, Begum N, Medhi S, Verghese A, Raish M, Theamboonlers A, Poovorawan Y, Kar P. Virological course of hepatitis A virus as determined by real time RT-PCR: Correlation with biochemical, immunological and genotypic profiles. *World J Gastroenterol* 2006; **12**: 4683-4688 [PMID: 16937439 DOI: 10.3748/wjg.v12.i29.4683]

101 **Alatrakchi N**, Koziel M. Regulatory T cells and viral liver disease. *J Viral Hepat* 2009; **16**: 223-229 [PMID: 19222744 DOI: 10.1111/j.1365-2893.2009.01081.x]

102 **Choi YS**, Lee J, Lee HW, Chang DY, Sung PS, Jung MK, Park JY, Kim JK, Lee JI, Park H, Cheong JY, Suh KS, Kim HJ, Lee JS, Kim KA, Shin EC. Liver injury in acute hepatitis A is associated with decreased frequency of regulatory T cells caused by Fas-mediated apoptosis. *Gut* 2015; **64**: 1303-1313 [PMID: 25007815 DOI: 10.1136/gutjnl-2013-306213]

103 **Chevalier MF**, Weiss L. The split personality of regulatory T cells in HIV infection. *Blood* 2013; **121**: 29-37 [PMID: 23043072 DOI: 10.1182/blood-2012-07-409755]

104 **Gupta E**, Chakravarti A. Viral infections of the biliary tract. *Saudi J Gastroenterol* 2008; **14**: 158-160 [PMID: 19568530 DOI: 10.4103/1319-3767.41740]

105 **Mao JS**, Yu PH, Ding ZS, Chen NL, Huang BZ, Xie RY, Chai SA. Patterns of shedding of hepatitis A virus antigen in feces and of antibody responses in patients with naturally acquired type A hepatitis. *J Infect Dis* 1980; **142**: 654-659 [PMID: 6257794]

106 **Tjon GM**, Coutinho RA, van den Hoek A, Esman S, Wijkmans CJ, Hoebe CJ, Wolters B, Swaan C, Geskus RB, Dukers N, Bruisten SM. High and persistent excretion of hepatitis A virus in immunocompetent patients. *J Med Virol* 2006; **78**: 1398-1405 [PMID: 16998883 DOI: 10.1002/jmv.20711]

107 **Kwon OS**, Byun KS, Yeon JE, Park SH, Kim JS, Kim JH, Bak YT, Kim JH, Lee CH. Detection of hepatitis A viral RNA in sera of patients with acute hepatitis A. *J Gastroenterol Hepatol* 2000; **15**: 1043-1047 [PMID: 11059935]

108 **Bower WA**, Nainan OV, Han X, Margolis HS. Duration of viremia in hepatitis A virus infection. *J Infect Dis* 2000; **182**: 12-17 [PMID: 10882576 DOI: 10.1086/315701]

109 **Arteaga-Rodríguez A**, Carrasco-Garrido P, de Andrés AL, de Miguel AG, Santos J, Jiménez-García R. Changes in the epidemiology of hepatitis A in Spain (2005-2008): trends of acute hepatitis A hospitalizations, comorbidities, and costs associated with the hospitalization. *Eur J Gastroenterol Hepatol* 2010; **22**: 1284-1289 [PMID: 20964258]

110 **Vento S**, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, Concia E. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; **338**: 286-290 [PMID: 9445408 DOI: 10.1056/nejm199801293380503]

111 **British HIV Association**. BHIVA guidelines on the use of vaccines in HIV-positive adults. 2015. Available from: URL: http://www.bhiva.org/documents/Guidelines/Vaccination/2015-Vaccination-Guidelines.pdf

112 **European AIDS Clinical Society**. EACS Treatment Guidelines updated. 2016. Available from: URL: http://www.eacsociety.org/files/guidelines_8.2-english.pdf

113 **Advisory Committee for Immunization Practices**. Hepatitis A ACIP Vaccine Recommendations. 2017. Available from: URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm

114 **World Health Organization**. Hepatitis A. 2017. Available from: URL: http://www.who.int/ith/vaccines/hepatitisA/en/

115 **Tseng YT**, Chang SY, Liu WC, Sun HY, Wu CH, Wu PY, Lu CL, Hung CC, Chang SC. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. *Hepatology* 2013; **57**: 1734-1741 [PMID: 23258666 DOI: 10.1002/hep.26210]

116 **Mena G**, García-Basteiro AL, Llupià A, Díez C, Costa J, Gatell JM, García F, Bayas JM. Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients in the era of highly active antiretroviral therapy. *Vaccine* 2013; **31**: 3668-3674 [PMID: 23777950 DOI: 10.1016/j.vaccine.2013.06.012]

117 **Jimenez HR**, Hallit RR, Debari VA, Slim J. Hepatitis A vaccine response in HIV-infected patients: are TWINRIX and HAVRIX interchangeable? *Vaccine* 2013; **31**: 1328-1333 [PMID: 23277097 DOI: 10.1016/j.vaccine.2012.12.045]

118 **Kourkounti S**, Mavrianou N, Paparizos VA, Kyriakis K, Hatzivassiliou M, Kordosis T, Katsambas A. Immune response to hepatitis A vaccination in HIV-infected men in Greece. *Int J STD AIDS* 2012; **23**: 464-467 [PMID: 22843998 DOI: 10.1258/ijsa.2011.011297]

119 **Weinberg A**, Allshouse AA, Mawhinney S, Canniff J, Benning L, Wentz EL, Minkoff H, Young M, Nowicki M, Greenblatt R, Cohen MH, Golub ET. Responses to hepatitis A virus vaccine in HIV-infected women: effect of hormonal contraceptives and HIV disease characteristics. *J Acquir Immune Defic Syndr* 2012; **60**: e15-e18 [PMID: 22517417 DOI: 10.1097/QAI.0b013e31824d30bd]

120 **Launay O**, Grabar S, Gordien E, Desaint C, Jegou D, Abad S, Girard PM, Bélarbi L, Guérin C, Dimet J, Williams V, Krivine A, Salmon D, Lortholary O, Rey D. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC study. *J Acquir Immune Defic Syndr* 2008; **49**: 272-275 [PMID: 18845961 DOI: 10.1097/QAI.0b013e318183a9c0]

121 **Overton ET**, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. *J Viral Hepat* 2007; **14**: 189-193 [PMID: 17305885 DOI: 10.1111/j.1365-2893.2006.00822.x]

122 **Weissman S**, Feucht C, Moore BA. Response to hepatitis A vaccine in HIV-positive patients. *J Viral Hepat* 2006; **13**: 81-86 [PMID: 16436125 DOI: 10.1111/j.1365-2893.2005.00658.x]

123 **Wallace MR**, Brandt CJ, Earhart KC, Kuter BJ, Grosso AD, Lakkis H, Tasker SA. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis* 2004; **39**: 1207-1213 [PMID: 15486846 DOI: 10.1086/424666]

124 **Kemper CA**, Haubrich R, Frank I, Dubin G, Buscarino C, McCutchan JA, Deresinski SC. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis* 2003; **187**: 1327-1331 [PMID: 12696015 DOI: 10.1086/374562]

125 **Neilsen GA**, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. *J Infect Dis* 1997; **176**: 1064-1067 [PMID: 9333168]

126 **Wilde JT**, Rymes N, Skidmoe S, Swann M, Linin J. Hepatitis A immunization in HIV-infected haemophilic patients. *Haemophilia* 1995; **1**: 196-199 [PMID: 27214540 DOI: 10.1111/j.1365-2516.1995.tb00068.x]

127 **Tilzey AJ**, Palmer SJ, Harrington C, O'Doherty MJ. Hepatitis

A vaccine responses in HIV-positive persons with haemophilia. *Vaccine* 1996; **14**: 1039-1041 [PMID: 8879099]

128 **Hess G**, Clemens R, Bienzle U, Schönfeld C, Schunck B, Bock HL. Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. *J Med Virol* 1995; **46**: 40-42 [PMID: 7623005]

129 **Santagostino E**, Gringeri A, Rocino A, Zanetti A, de Biasi R, Mannucci PM. Patterns of immunogenicity of an inactivated hepatitis A vaccine in anti-HIV positive and negative hemophilic patients. *Thromb Haemost* 1994; **72**: 508-510 [PMID: 7878624]

130 **Shire NJ**, Welge JA, Sherman KE. Efficacy of inactivated hepatitis A vaccine in HIV-infected patients: a hierarchical bayesian meta-analysis. *Vaccine* 2006; **24**: 272-279 [PMID: 16139398 DOI: 10.1016/j.vaccine.2005.07.102]

131 **Lin KY**, Hsieh SM, Sun HY, Lo YC, Sheng WH, Chuang YC, Pan SC, Hung CC, Chang SC. Effectiveness of HAV vaccination among HIV-positive patients during an acute hepatitis A outbreak. the 22th Conference of Retroviruses and Opportunistic Infections Abstract no 582. Seattle, WA, 2017

132 **Loutan L**, Bovier P, Herzog C. Immunogenicity and safety of a virosomal hepatitis A vaccine in HIV-positive patients. *Vaccine* 2007; **25**: 6310-6312 [PMID: 17640777 DOI: 10.1016/j.vaccine.2007.06.013]

133 **Victor JC**, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med* 2007; **357**: 1685-1694 [PMID: 17947390 DOI: 10.1056/NEJMoa070546]

134 **Theeten H**, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. *Vaccine* 2015; **33**: 5723-5727 [PMID: 26190091 DOI: 10.1016/j.vaccine.2015.07.008]

135 **Crum-Cianflone NF**, Wilkins K, Lee AW, Grosso A, Landrum ML, Weintrob A, Ganesan A, Maguire J, Klopfer S, Brandt C, Bradley WP, Wallace MR, Agan BK, Infectious Disease Clinical Research Program HIVWG. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. *J Infect Dis* 2011; **203**: 1815-1823 [PMID: 21606540 DOI: 10.1093/infdis/jir180]

136 **Cheng A**, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, Wu PY, Hung CC, Chang SC. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in human immunodeficiency virus-positive adults on antiretroviral therapy. *J Infect Dis* 2017; **215**: 606-613 [PMID: 28011921 DOI: 10.1093/infdis/jiw605]

137 **Kernéis S**, Desaint C, Brichler S, Rey D, Belarbi L, Gordien E, Pacanowski J, Lortholary O, Abgrall S, Boëlle PY, Grabar S, Launay O. Long-term persistence of humoral immunity after hepatitis A vaccination in HIV-infected adults. *J Acquir Immune Defic Syndr* 2011; **57**: e63-e66 [PMID: 21860353 DOI: 10.1097/QAI.0b013e31821fdec3]

138 **Jabłonowska E**, Kuydowicz J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: a 5-year observation. *Int J STD AIDS* 2014; **25**: 745-750 [PMID: 24452731 DOI: 10.1177/0956462413518902]

139 **Iwarson S**. Are we giving too many doses of hepatitis A and B vaccines? *Vaccine* 2002; **20**: 2017-2018 [PMID: 11972968]

P- Reviewer: Castiella A, Otsuka M **S- Editor**: Ma YJ **L- Editor**: A
E- Editor: Wang CH

Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327

PLOS ONE

RESEARCH ARTICLE

Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up

Kuan-Yin Lin[1], Chien-Yu Cheng[2,3], Chia-Wen Li[4,5], Chia-Jui Yang[6,7], Mao-Song Tsai[6], Chun-Eng Liu[8], Yuan-Ti Lee[9,10], Hung-Jen Tang[11,12], Ning-Chi Wang[13], Te-Yu Lin[13], Yi-Chien Lee[14], Shih-Ping Lin[15], Yu-Shan Huang[16], Jun-Yu Zhang[17], Wen-Chien Ko[4,5], Shu-Hsing Cheng[2,18]*, Chien-Ching Hung[19,20,21,22]*, for the Taiwan HIV Study Group¶

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¶ Membership of the Taiwan HIV Study Group is provided in the Acknowledgments.
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OPEN ACCESS

Citation: Lin K-Y, Cheng C-Y, Li C-W, Yang C-J, Tsai M-S, Liu C-E, et al. (2017) Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up. PLoS ONE 12(6): e0179870. https://doi.org/10.1371/journal.pone.0179870

Editor: Giuseppe Vittorio De Socio, Azienda Ospedaliera Universitaria di Perugia, ITALY

Received: January 20, 2017

Accepted: June 6, 2017

Published: June 30, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors would like to thank Taiwan Centers for Disease Control for research grant support (grant number MOHW103-CDC-C-114-000405 to C.-C. H.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Objectives

The international and national HIV treatment guidelines in 2016 have focused on scaling up access to combination antiretroviral therapy (cART). We aimed to assess the trends and treatment outcomes of late cART initiation in Taiwan.

Methods

Between June 2012 and May 2016, we retrospectively included antiretroviral-naive HIV-positive adults who initiated cART. Late initiation was defined as when cART was initiated in patients with a CD4 count <200 cells/mm^3 or having experienced AIDS-defining illnesses. The treatment outcomes were assessed up to 6 months after starting cART.

Competing interests: One of the authors, Hung CC, has the following competing interests: research support from Janssen, Merck, Bristol-Myers Squibb, and ViiV, speaker honoraria from Abbvie, Bristol-Myers Squibb, Gilead Sciences, and ViiV, and serving on advisory boards for Gilead Sciences, Janssen, ViiV, and Abbvie. The other authors have no competing interest to disclose. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Abbreviations: cART, combination antiretroviral therapy.

Results

We included 3655 HIV-positive patients, and the majority of the patients were male (95.4%) with a median age of 31 years and initiated non-nucleoside reverse-transcriptase inhibitor-containing regimens (87.0%). The median CD4 count at cART initiation increased from 207 cells/mm^3 in 2012 to 298 cells/mm^3 in 2016, and the overall proportion of late cART initiation decreased from 49.1% in 2012 to 29.0% in 2016 (*P* for trend <0.001). Late cART initiation mainly resulted from late presentation for HIV care and was associated with older age (per 1-year increase, adjusted odds ratio [AOR], 1.05; 95% CI, 1.04–1.06), HBsAg seropositivity (AOR, 1.31; 95% CI, 1.04–1.64), HIV care in central and southern Taiwan, initiating cART in earlier year, non-intravenous drug users (AOR, 1.96; 95% CI, 1.33–2.86), and negative hepatitis C serostatus (AOR, 1.47; 95% CI, 1.04–2.08). Compared with non-late initiators, late initiators had a higher rate of all-cause mortality (1.7% vs. 0.3%) and regimen modification due to virological failure (7.1% vs. 2.6%). The predicting factors of all-cause mortality were late cART initiation (adjusted hazard ratio [AHR], 5.40; 95% CI, 2.14–13.65) and older age (AHR, 1.06; 95% CI, 1.03–1.10).

Conclusions

While the proportion of late cART initiation decreased over time in Taiwan, late initiation remained in a substantial proportion of HIV-positive patients. The late initiators had higher risk for poor outcomes. The need for strategies to earlier detection of HIV infection and expediting cART initiation should be highlighted, especially among the older population.

Introduction

The scale-up combination antiretroviral therapy (cART) helps reduce AIDS-related deaths and new HIV infections, as well as decrease further expenses for medical services [1]. The global and national HIV treatment guidelines and programs support and facilitate the scale-up of cART. The US Department of Health and Human Services (DHHS) guidelines have recommended cART for all HIV-positive patients regardless of CD4 cell count since 2012 [2]. Further results from randomized trials also confirmed the benefits of immediate initiation of cART in all HIV-positive patients [3, 4]. The global target set by World Health Organization and the Joint United Nations Programme on HIV/AIDS (WHO/UNAIDS) in 2015 aimed to provide cART to 90% of all people with diagnosed HIV infection by expanding the use of cART to all HIV-positive patients [5]. At the end of 2015, 46% of people living with HIV worldwide were receiving cART [6].

Many countries in the Asia-Pacific region have made great strides in accessing cART through their HIV treatment guidelines and programs, and the region's treatment coverage rate has increased from 19% in 2010 to 41% in 2015; however, the coverage rate still lagged behind the global coverage rate [6–8]. While studies conducted in Asia have demonstrated the increasing trends of CD4 cell count at cART initiation, the median CD4 cell count remained at around 200 cells/mm^3 in 2011 [9]. The low median CD4 cell count at cART initiation suggests that late HIV diagnosis, delayed linkage to HIV care, and late cART initiation despite timely entry into care remain prevalent in this region [9].

These previous findings may not be generalized across all Asia-Pacific countries, however; whether the national HIV treatment programs get HIV-positive patients treated earlier may

rely on regional studies. In Taiwan, a high-income country according to the World Bank classification [10], HIV-related medical services are provided free-of-charge. In response to expanding antiretroviral therapy through the national HIV treatment guidelines [11], assessing the trends and predictors of late cART initiation can improve engagement strategies in HIV care. In this study, we aimed to investigate the CD4 cell counts at cART initiation, to characterize the temporal trends of late cART initiation, and to evaluate the associated factors with late cART initiation and its impact on treatment outcomes in Taiwan.

Patients and methods

Study population and setting

We conducted a retrospective cohort study at 11 major designated hospitals for HIV care that participated in the Taiwan HIV Study Group. We included all HIV-positive patients aged 20 years or greater who were antiretroviral-naïve and initiated cART between 1 June 2012 and 31 May 2016. Patients without baseline CD4 cell count before cART initiation were excluded. Data was collected locally at each participating hospital, and then pooled and analyzed at the National Taiwan University Hospital. The study was approved by the Research Ethics Committee of National Taiwan University Hospital, Research Ethics Review Committee of Far Eastern Memorial Hospital, Medical Ethics and Institutional Review Board of Taoyuan General Hospital, and Institutional Review Boards (Tri-Service General Hospital, National Taiwan University Hospital Hsin-Chu Branch, Taichung Veterans General Hospital, Chung Shan Medical University Hospital, Changhua Christian Hospital, Chia-Yi Christian Hospital, National Cheng Kung University Hospital, and Chi Mei Medical Center). The informed consent was waived.

The Taiwan Centers for Disease Control (CDC) has provided HIV-positive patients with free-of-charge medical services, including cART, management of opportunistic illnesses, and laboratory testing, including monitoring of CD4 cell count and plasma HIV RNA load (PVL). Genotypic resistance assays were neither offered free-of-charge or routinely determined before cART initiation, although surveillance data suggested that the prevalence of transmitted drug resistance of HIV-1 to at least one antiretroviral was in the range of 10–15%; instead, the assays were performed at Taiwan CDC or a few designated hospitals for patients with virological failure and PVL >1000 copies/mL [12–14].The national HIV treatment guidelines had increased the CD4 cell count threshold for cART initiation from 350 to 500 cells/mm^3 in September 2013 [11], which was further revised to treat all HIV-positive patients irrespective of CD4 cell count in June 2016. In light of increasing medical expenditure and budgetary constraints, Taiwan CDC has implemented regulations on the regimens of cART to be initiated in antiretroviral-naive patients since 1 June 2012. Between 1 June 2012 and 31 May 2016, antiretroviral-naive patients had been recommended to start cART with the preferred regimens of non-nucleoside reverse-transcriptase inhibitor (nNRTI)-containing regimens [15]. After 1 June 2016, the preferred regimens have been changed to 3 single-tablet regimens, including coformulated efavirenz/emtricitabine/tenofovir, rilpivirine/emtricitabine/tenofovir, and dolutegravir/abacavir/lamivudine. Rilpivirine and coformulated emtricitabine/tenofovir were not available in Taiwan until early 2014 and 2015, respectively. The study period was selected based on the date when major changes were made to the national HIV treatment guidelines.

Data collection and definitions

We collected the information on demographics and clinical characteristics, such as age, sex, mode of HIV exposure, hepatitis B virus (HBV) surface antigen (HBsAg), hepatitis C virus (HCV) antibody, baseline CD4 cell count and PVL at cART initiation and serial follow-up

visits, AIDS-defining illnesses before cART initiation, dates of cART initiation and loss to follow-up, and initial and switched antiretroviral regimens. The baseline CD4 cell count and PVL were defined as the data prior to and nearest to the date of cART initiation. Late initiation of cART was defined as when cART was initiated in patients with a baseline CD4 cell count <200 cells/mm^3 or having experienced AIDS-defining illnesses before cART initiation [9, 16].

The treatment outcomes were assessed at 6 months and comparisons were made between HIV-positive patients with and without late cART initiation, and those initiating cART at CD4 cell count <500 versus ≧500 cells/mm^3, or PVL <100,000 versus ≧100,000 copies/mL. Within 6 months after initiating cART, patients returned for assessment of virological, immunological, and clinical responses at week 4, and subsequently every 8 to 12 weeks [15]. The treatment outcomes assessed included all-cause mortality and regimen modification. Regimen modification, which was defined as the removal, addition or switch of at least one antiretroviral drug from the initial cART regimen within 6 months after cART initiation, and loss to follow-up. The reasons for modifying cART regimen were further categorized into 4 groups, including adverse event, treatment failure (e.g. virological failure, loss to follow-up, or cART interruption), simplification, and other reasons (e.g. drug-drug interaction, patient's choice, or unknown cause). Virological failure was defined as a PVL >200 copies/mL at least 6 months after starting cART.

Statistical analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test if the expected values were <10. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. The trend analyses were evaluated by the generalized linear model and Cochran-Armitage trend test for continuous and categorical variables, respectively. The factors associated with late cART initiation were identified by logistic regression model. The predictors of all-cause mortality and regimen modification were determined by Kaplan-Meier survival estimations and Cox proportional hazards model. All variables in univariate analyses were selected for subsequent multivariable analyses. Ninety-five percent confidence intervals (CIs) of odds ratios (ORs) or hazard ratios (HRs) were computed to estimate the effects of each variable. All tests were two-tailed and P <0.05 was considered statistically significant. Statistical analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX).

Results

Characteristics of study population

During the 4-year study period, 3655 HIV-positive Taiwanese patients initiating cART were included. The demographics and clinical characteristics of all included patients are summarized in **Table 1**. Most patients were male (95.4%) with a median age of 31 years and men who have sex with men (76.9%) and received HIV care at designated hospitals in northern Taiwan (70.9%). Approximately 10% and 20% of the patients were HBsAg-positive and anti-HCV-positive at cART initiation, respectively. The overall median baseline CD4 cell count was 270 cells/mm^3 (interquartile range [IQR], 148–381 cells/mm^3), and 13.2% of the patients had experienced AIDS-defining illnesses before cART initiation. Half (50.6%) of the patients initiated cART before the first half year of 2014, and approximately 87.0% started nNRTI-containing regimens.

Among those 3655 included patients, the dates of and CD4 cell counts at HIV diagnosis were available in 953 patients (26.1%), in whom 340 (35.7%) presented for HIV care with CD4 cell counts <200 cells/mm^3. The median duration between HIV diagnosis and cART initiation

Table 1. Patients' characteristics at initiation of combination antiretroviral therapy (cART) stratified by late and non-late initiation of cART.

Characteristics	All patients (n = 3655)	Patients with late initiation (n = 1278)	Patients with non-late initiation (n = 2377)	*P**
Age, median (IQR), years	31 (26–38)	33 (28–41)	30 (25–37)	<0.001
Sex, male, n (%)	3487 (95.4)	1219 (95.4)	2268 (95.4)	0.966
Mode of HIV exposure, n (%)				<0.001
Homosexual sex	2810 (76.9)	987 (77.2)	1823 (76.7)	
Heterosexual sex	220 (6.0)	109 (8.5)	111 (4.7)	
Intravenous drug use	591 (16.2)	162 (12.7)	429 (18.0)	
Others**	34 (0.9)	20 (1.6)	14 (0.6)	
Region of HIV care, n (%)***				<0.001
Northern Taiwan	2593 (70.9)	819 (31.6)	1774 (68.4)	
Central Taiwan	509 (13.9)	222 (43.6)	287 (56.4)	
Southern Taiwan	553 (15.1)	237 (42.9)	316 (57.1)	
HBsAg seropositivity, n (%)	390 (10.7)	172 (13.5)	218 (9.2)	<0.001
HCV seropositivity, n (%)	665 (18.2)	185 (14.5)	480 (20.2)	<0.001
Baseline CD4 cell count, median (IQR), cells/mm^3	270 (148–381)	89 (34–156)	339 (272–442)	<0.001
Baseline PVL, median (IQR), $\log_{10}$ copies/mL	4.8 (4.3–5.2)	5.2 (4.8–5.6)	4.6 (4.2–5.0)	<0.001
AIDS-defining illness, n (%)	483 (13.2)	483 (37.8)	0 (0.0)	<0.001
Year of cART initiation, n (%)				<0.001
June 2012—May 2013	793 (21.7)	331 (25.9)	462 (19.4)	
June 2013—May 2014	1057 (28.9)	365 (28.6)	692 (29.1)	
June 2014—May 2015	1045 (28.6)	353 (27.6)	692 (29.1)	
June 2015—May 2016	760 (20.8)	229 (17.9)	531 (22.3)	
Type of cART, n (%)				0.640
NRTIs plus nNRTI	3180 (87.0)	1108 (86.7)	2072 (87.2)	
NRTIs plus PI	368 (10.1)	128 (10.0)	240 (10.1)	
NRTIs plus INSTI	107 (2.9)	42 (3.3)	65 (2.7)	

Abbreviations: CART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NRTI, nucleoside reverse-transcriptase inhibitor; nNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PVL, plasma HIV RNA load.

*The statistical significance was tested for the differences between patients with late and non-late cART initiation.

**Others included patients with exposure to blood products and unknown exposures.

***Five hospitals located in northern Taiwan (National Taiwan University Hospital, Tri-Service General Hospital, Far Eastern Memorial Hospital, Taoyuan General Hospital, and National Taiwan University Hospital Hsin-Chu Branch); 3 hospitals in central Taiwan (Taichung Veterans General Hospital, Chung Shan Medical University Hospital, and Changhua Christian Hospital) and 3 hospitals in southern Taiwan (Chia-Yi Christian Hospital, National Cheng Kung University Hospital, and Chi Mei Medical Center).

https://doi.org/10.1371/journal.pone.0179870.t001

was 1.6 months (range, 0–182.3 months) in these patients. The interval between HIV diagnosis and cART initiation according to the year of HIV diagnosis decreased from 3.5 months in 2012 to 0.5 months in 2016.

Trends of CD4 cell count at cART initiation

The trends of median CD4 cell counts at cART initiation that were assessed over each 6-month study period are shown in Fig 1. The median CD4 cell count significantly increased from 207 cells/mm^3 for the patients initiating cART in the second half year of 2012 to 298 cells/mm^3 for those in the first half year of 2016 (P for trend <0.001). The CD4 cell counts

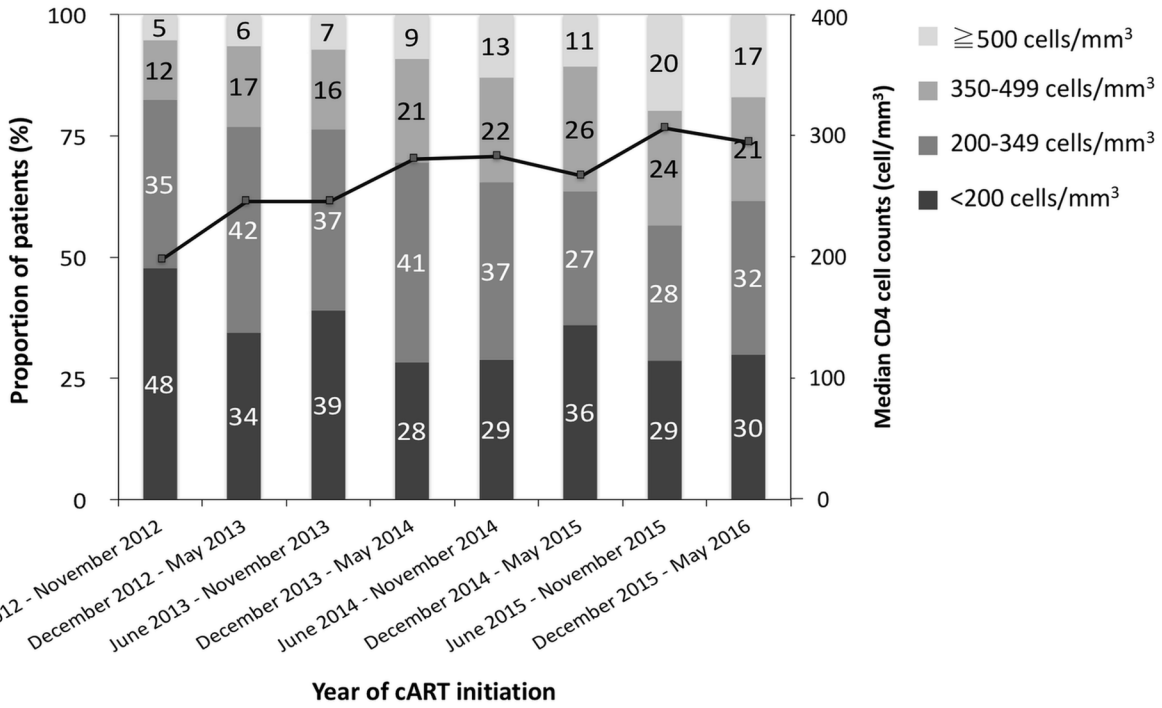

Fig 1. Trends in median and distribution of CD4 cell counts at initiation of combination antiretroviral therapy (cART) from 1 June 2012 to 31 May 2016.

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were classified into 4 groups: <200 cells/mm^3, 200–349 cells/mm^3, 350–499 cells/mm^3, and ≧500 cells/mm^3. In the second half year of 2012, the majority of the patients (47.7%) initiated cART with a CD4 cell count <200 cells/mm^3; in contrast, more than one-third of the patients (38.4%) started cART with a CD4 cell count ≧350 cells/mm^3 in the first half year of 2016. While the proportions of baseline CD4 cell counts between 350–499 cells/mm^3 and ≧500 cells/mm^3 from 2013 onwards were significantly higher than those in 2012, the proportions of CD4 cell counts between 200–349 cells/mm^3 and <200 cells/mm^3 decreased over time (*P* for trend <0.001). However, there were still 30% of the patients who initiated cART late with CD4 cell counts <200 cells/mm^3 in the most recent study year. In addition, the median CD4 cell counts had no significant change among patients aged 50 years or greater, among whom the median CD4 cell count was 130 cells/mm^3 in the second half year of 2012 and 165 cells/mm^3 in the first half year of 2016.

Trends and associated factors with late cART initiation

Among the 3655 patients, 1278 (35.0%) initiated cART late and 2377 (65.0%) did not. In Fig 2, the proportion of the patients with late cART initiation had significantly declined from 49.1% in the second half year of 2012 to 29.0% in the first half year of 2016 (*P* for trend <0.001). However, the percentage of the patients having AIDS-defining illnesses prior to cART initiation remained at more than 10% till the first half year of 2016, without statistically significant difference compared with those of previous study years (*P* for trend = 0.082).

The demographics and clinical characteristics of the patients stratified by late and non-late cART initiation are shown in Table 1. The patients with late cART initiation were older and more likely to be heterosexual, seropositive for HBsAg, and seronegative for HCV antibody, and to receive HIV care at hospitals in central and southern Taiwan. They also tended to have

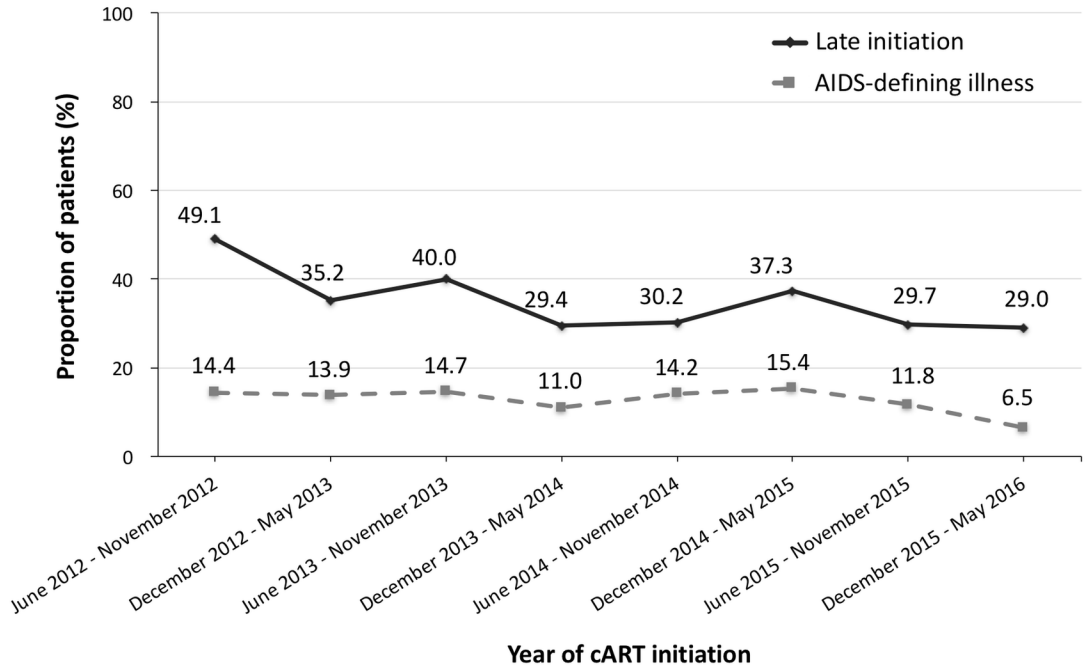

Fig 2. Changes over time in proportion of patients with late initiation of combination antiretroviral therapy (cART) and AIDS-defining illnesses from 1 June 2012 to 31 May 2016.

https://doi.org/10.1371/journal.pone.0179870.g002

lower baseline CD4 cell counts and higher PVL, and started cART in the earlier years (all $P < 0.05$). In multivariable analysis, the factors associated with late cART initiation were older age (per 1-year increase, adjusted OR [AOR], 1.05; 95% CI, 1.04–1.06), receiving HIV care at hospitals in central and southern Taiwan (AOR, 1.78; 95% CI, 1.45–2.19 and 1.65; 95% CI, 1.35–2.00, respectively), and HBsAg seropositivity (AOR, 1.31; 95% CI, 1.04–1.64). Late cART initiators were more likely to be non-intravenous drug users (IDUs) (AOR, 1.96; 95% CI, 1.33–2.86) and to test negative for anti-HCV (AOR, 1.47; 95% CI, 1.04–2.08). In line with the aforementioned trend analysis for baseline CD4 cell count, there was a statistically significant association between non-late cART initiation and initiating cART in later years, which strengthened over time during the study period (Table 2).

Treatment outcomes and predicting factors

The comparisons of treatment outcomes between late and non-late initiation are shown in Table 3, while the comparisons between patients initiating cART at CD4 cell counts <500 versus ≧500 cells/mm^3 are shown in S1 Table. All-cause mortality occurred in 22 (1.7%) and 6 (0.3%) patients in the late initiation and non-late initiation groups, respectively. The estimated HR for all-cause mortality in the late initiation group was 6.86 (95% CI, 2.78–16.91) compared with the non-late initiation group in univariate analysis (Fig 3A). However, the difference in all-cause mortality between the patients initiating cART at CD4 cell counts <500 and those at CD4 cell counts ≧500 cells/mm^3 did not reach statistical significance (HR, 3.37; 95% CI, 0.46–24.78) (Fig 3B). In multivariable analysis, late cART initiation remained statistically significantly associated with all-cause mortality. The other independent predictor of all-cause mortality was older age (per 1-year increase, adjusted HR [AHR], 1.06; 95% CI, 1.03–1.10) (Table 4).

Within 6 months after cART initiation, more than 40% of the patients had to modify their first antiretroviral regimens; the major reason for modification was cART-associated adverse events,

Table 2. Logistic analysis to identify the factors associated with late initiation of combination antiretroviral therapy.

Variables	Univariate analysis		Multivariable analysis*	
	OR (95% CI)	*P*	AOR (95% CI)	*P*
Age, per 1-year increase	1.04 (1.03–1.04)	<0.001	1.05 (1.04–1.06)	<0.001
Male sex	0.99 (0.72–1.37)	0.966	0.95 (0.64–1.40)	0.784
Mode of HIV exposure				
Homosexual sex	1.00 (reference)		1.00 (reference)	
Heterosexual sex	1.81 (1.38–2.39)	<0.001	0.99 (0.71–1.39)	0.970
Intravenous drug use	0.70 (0.57–0.85)	<0.001	0.51 (0.35–0.75)	0.001
Region of HIV care				
Northern Taiwan	1.00 (reference)		1.00 (reference)	
Central Taiwan	1.68 (1.38–2.03)	<0.001	1.78 (1.45–2.19)	<0.001
Southern Taiwan	1.62 (1.35–1.96)	<0.001	1.65 (1.35–2.00)	<0.001
HBsAg seropositivity	1.54 (1.25–1.91)	<0.001	1.31 (1.04–1.64)	0.020
HCV seropositivity	0.67 (0.56–0.81)	<0.001	0.68 (0.48–0.96)	0.030
Year of cART initiation				
June 2012—May 2013	1.00 (reference)		1.00 (reference)	
June 2013—May 2014	0.74 (0.61–0.89)	0.002	0.77 (0.63–0.93)	0.008
June 2014—May 2015	0.71 (0.59–0.86)	<0.001	0.72 (0.59–0.88)	0.001
June 2015—May 2016	0.60 (0.49–0.74)	<0.001	0.65 (0.52–0.81)	<0.001

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; OR, odds ratio.
*All variables in univariate analyses were selected for subsequent multivariable analyses.

https://doi.org/10.1371/journal.pone.0179870.t002

followed by treatment failure and simplification (Table 3). The percentages of overall regimen modification, regimen modification due to adverse events, and simplification were all similar when the comparisons were stratified by late cART initiation (Fig 3C) or initiating cART at CD4

Table 3. Comparisons of treatment outcomes in patients with late and non-late combination antiretroviral therapy initiation.

Outcomes	Patients with late initiation (n = 1278)	Patients with non-late initiation (n = 2377)	HR (95% CI)	*P*
All-cause mortality, n (%)	22 (1.7)	6 (0.3)	6.86 (2.78–16.91)	<0.001
Regimen modification, n (%)*	598 (46.8)	1041 (43.8)	1.10 (0.99–1.21)	0.077
Adverse event	422 (33.0)	834 (35.1)	0.94 (0.83–1.05)	0.264
Treatment failure**	120 (9.4)	120 (5.1)	2.02 (1.56–2.61)	<0.001
Virological failure	91 (7.1)	62 (2.6)	2.82 (2.04–3.90)	<0.001
Baseline PVL ≥100,000	69 (5.4)	24 (1.0)	2.04 (1.28–3.25)	0.003
copies/mL				
Baseline PVL <100,000	22 (1.7)	38 (1.6)	2.27 (1.34–3.84)	0.002
copies/mL				
Loss to follow-up or	29 (2.3)	58 (2.4)	1.03 (0.64–1.64)	0.911
interruption				
Simplification	47 (3.7)	70 (2.9)	1.23 (0.85–1.78)	0.281
Others	14 (1.1)	20 (0.8)	1.21 (0.60–2.43)	0.591

Abbreviations: CI, confidence interval; HR, hazard ratio; PVL, plasma HIV RNA load.
*Regimen modification included the removal, addition, and switch of at least one antiretroviral drug from the initial cART regimen, and loss to follow-up within 6 months after starting cART.
**The causes of treatment failure included virological failure, loss to follow-up, and cART interruption. Virological failure was defined as a PVL >200 copies/mL at least 6 months after starting cART.

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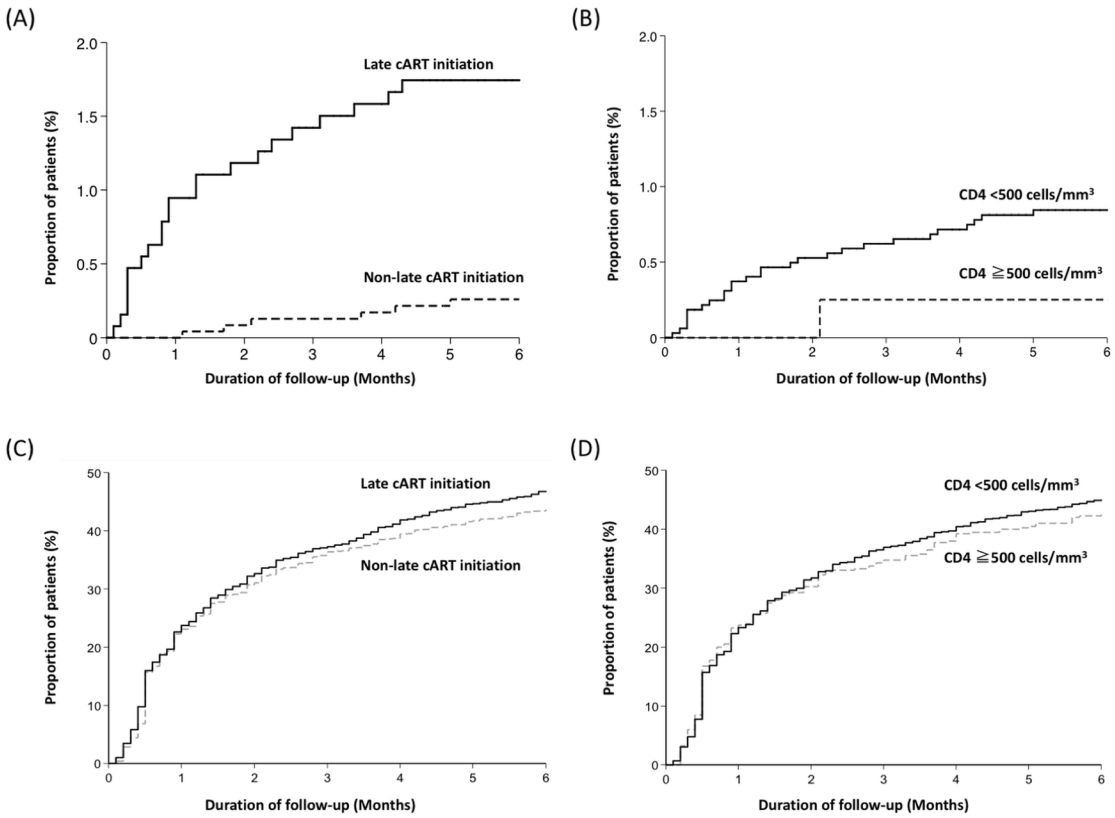

Fig 3. Kaplan-Meier estimates of the cumulative proportion of patients with treatment outcomes. All-cause mortality stratified by late initiation and non-late initiation (A), All-cause mortality stratified by baseline CD4 cell counts <500 and ≧500 cells/mm^3 (B), Regimen modification stratified by late initiation and non-late initiation (C), and Regimen modification stratified by baseline CD4 cell counts <500 and ≧500 cells/mm^3 (D).

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cell counts <500 cells/mm^3 (Fig 3D). Patients initiating cART late and at CD4 cell counts <500 cells/mm^3 were more likely to modify cART for virological failure, with the estimated HR of 2.82

Table 4. Cox-regression hazards model for factors predicting all-cause mortality.

Variables	Univariate analysis		Multivariable analysis*	
	HR (95% CI)	*P*	AHR (95% CI)	*P*
Late initiation	6.86 (2.78–16.91)	<0.001	5.40 (2.14–13.65)	<0.001
Age, per 1-year increase	1.07 (1.05–1.10)	<0.001	1.06 (1.03–1.10)	<0.001
Male sex	1.31 (0.18–9.64)	0.791	1.97 (0.26–14.82)	0.508
HBsAg seropositivity	1.39 (0.48–4.02)	0.539	0.84 (0.29–2.43)	0.742
HCV seropositivity	1.25 (0.51–3.07)	0.633	0.96 (0.38–2.43)	0.933
Year of cART initiation				
June 2012—May 2013	1.00 (reference)		1.00 (reference)	
June 2013 –May 2014	1.89 (0.59–6.02)	0.283	2.37 (0.74–7.57)	0.147
June 2014 –May 2015	1.93 (0.60–6.15)	0.267	2.42 (0.75–7.75)	0.138
June 2015 –May 2016	1.04 (0.26–4.17)	0.953	1.37 (0.34–5.51)	0.654

Abbreviations: AHR, adjusted hazard ratio; cART, antiretroviral therapy; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HR, hazard ratio.

*All variables in univariate analyses were selected for subsequent multivariable analyses.

https://doi.org/10.1371/journal.pone.0179870.t004

(95% CI, 2.04–3.90) and 2.58 (95% CI, 1.21–5.52) in univariate analysis, respectively. The negative impact of late cART initiation on virological response was observed not only in the patients initiating cART at PVL <100,000 but also those at PVL ≧100,000 copies/mL (Table 3).

Discussion

Despite the substantial number of studies on the trends of CD4 cell count at cART initiation before 2013, this study aimed to evaluate the temporal changes and outcomes of late cART initiation during the period of rapid treatment scale-up based on recent guidelines [17–19]. Our study demonstrates declining proportions of late initiation over the 4-year study period. Initiating cART late was mainly driven by late presentation for care, which had significant impact on all-cause mortality and regimen modification due to virological failure.

The trends of CD4 cell count at cART initiation provide valuable insight into how well HIV programs are implemented in response to HIV epidemic [20]. Since initiating cART at a higher CD4 cell count prevents HIV-associated illnesses, averts new infections, and saves money to achieve the target of ending the AIDS epidemic [5], current HIV treatment guidelines have evolved to recommend initiating cART regardless of CD4 cell counts [2, 21]. Both the WHO and Taiwanese HIV treatment guidelines had increased the CD4 threshold from 350 cells/mm^3 to 500 cells/mm^3 in 2013 [11, 19]. In our study, the overall median baseline CD4 cell count remained below 300 cells/mm^3 and less than half of the patients started cART at a CD4 cell count >350 cells/mm^3. In addition, the proportion of late cART initiators was substantial, with 29% in the first half year of 2016. Nearly half of late cART initiators had prior AIDS-defining illnesses, for which no statistically significant temporal declines were found. The percentage of late cART initiation remained high because it was the consequence of late presentation for HIV care. The findings of our study and the previous studies all suggest that HIV-positive patients still accessed HIV care and treatment late worldwide. According to the meta-regression from Western developed countries, the mean CD4 cell count at presentation for HIV care increased minimally by 1.5 cells/mm^3 per year, from 307 cells/mm^3 in 1992 to 336 cells/mm^3 in 2011 [17]. A large multi-national cohort study in Asia, which recruited patients in all categories of country income, reported temporal trends similar to our study [9], in which the median CD4 cell count at cART initiation increased from 115 cells/mm^3 in 2008 to 302 cells/mm^3 after 2011, and proportion of late cART initiation decreased from 81.7% to 36.3%.

The factors associated with late cART initiation identified in our study were partly consistent with previous studies, which reported that male sex, older age, earlier year of cART initiation, heterosexual sex as the HIV exposure category, marital status, and higher education level were associated with a greater likelihood of late cART initiation [9, 22, 23]. The older HIV-positive patients, especially those aged 50 years or greater, had lower CD4 cell counts at cART initiation without statistically significant trends compared with all included HIV-positive patients. Entry into HIV care at an advanced age is not only associated with higher mortality in both the natural and treated history of HIV infection but with adverse consequences of delayed cART initiation [24, 25]. The contributing factors to the findings that older HIV-positive patients were diagnosed and treated at a more advanced stage may include limited sexual health information targeting older adults, poor awareness of the risk of HIV infection, and failure of physicians to consider the possibility of HIV infection [26, 27]. The Taiwanese national surveillance data also reported the similar epidemiological picture; the percentages of newly diagnosed HIV infection and AIDS in patients between the age of 40 and 64 years were 15.3% and 28.7%, respectively [28].

The differences in the timing of cART initiation across geographical regions may reflect diverse socioeconomic status of the patients and the clinical practices of physicians. People

living in central and southern Taiwan have lower accessibility of medical resources and educational status, which may hamper scale-up of HIV treatment [23, 29, 30]. The finding of lower baseline CD4 cell count among HIV/HBV co-infected patients when cART was initiated may be related to the adverse impact of HBV on immunologic progression, especially in patients with positive hepatitis B e-antigen and a high HBV DNA load [31, 32]. Therefore, the recommendation of immediate cART initiation in HBV co-infected patients should be reinforced [2]. In contrast, HIV/HCV co-infection was inversely related with late cART initiation. The previous outbreak of HIV infection among Taiwanese IDUs had led to the high prevalence of HIV/HCV co-infection among the IDUs in our study (82.3%) [33]. Given that fact that HIV screening is mandatory for inmates and persons on entry into correctional facilities, who also receive free-of-charge HIV care under the national HIV treatment program in Taiwan, it is not surprising that linkage to HIV care and cART initiation during the incarceration periods is much easier for IDUs with HCV infection than other risk groups [33].

The large Asian observational cohort with the similar mortality rate also reported that late cART initiation was associated with mortality [9]. The meta-analysis of clinical trials has demonstrated that late cART initiation was consistently associated with poorer CD4 cell count recovery, which was not modulated by the individual cART regimen [34]. In our study, we did not observe the impact of late cART initiation on reasons of regimen modification other than due to virological failure. The absence of difference in the overall percentage of regimen modification between patients with and those without late cART initiation was also observed in an Australian cohort study [35]. The relationship between initiating cART at a CD4 cell count <500 cells/mm^3 and regimen modification due to virological failure also supported the recommendation of universal access to cART [2, 21].

Our study has several limitations. First, the lack of information on other patient-level characteristics, such as education, marital status and socioeconomic status, may preclude us from identifying the association between those patient-level characteristics with late cART initiation. The association between seeking HIV care in different regions in Taiwan and late cART initiation probably reflects the impact of patient-level characteristics. Second, though almost every Taiwanese is covered by the National Health Insurance and HIV care is free of charge in Taiwan, the extent to which the late cART initiation in our study was driven by late HIV diagnosis, delayed linkage into HIV care, and late cART initiation was unclear. The substantial proportion of patients presenting for HIV care with CD4 cell counts less than 200 cells/mm^3 suggested late diagnosis may play an important role in late cART initiation. Finally, genotypic resistance assays were not routinely determined in Taiwanese treatment-naïve HIV-positive patients and thus the impact of transmitted drug resistance of HIV-1 on the short-term treatment outcomes was unclear.

In conclusion, the median CD4 cell count at cART initiation increased and the proportion of late initiation decreased over time among HIV-positive Taiwanese patients in the era of treatment scale-up. However, the median CD4 cell count remained lower than the recommended threshold of cART initiation and the percentage of late initiators was still substantial. The late initiators had increased probability of all-cause mortality and regimen modification due to virological failure. The strategies to facilitating earlier diagnosis of HIV infection and access to cART are urgently needed, especially among the older population.

Supporting information

S1 Table. Compared treatment outcomes in patients with combination antiretroviral therapy initiation at CD4 cell counts ≧500 cells/mm3 and <500 cells/mm3.
(DOCX)

S1 Data. The minimal data set of the patients in this study.
(XLSX)

Acknowledgments

The authors would like to thank Taiwan Centers for Disease Control for research grant support (grant number MOHW103-CDC-C-114-000405 to C.-C. H.). The funding source played no role in study design and conduct, data collection, analysis or interpretation, writing of the manuscript, or the decision to submit it for publication. The authors also thank all study members participating in the Taiwan HIV Study Group: Hsin-Yun Sun, Sui-Yuan Chang, Pei-Ying Wu, Jun-Yu Zhang, Hsi-Yen Chang, Wen-Chun Liu, Yi-Ching Su, and Chien-Ching Hung[$], National Taiwan University Hospital, Taipei; Ning-Chi Wang and Te-Yu Lin, Tri-Service General Hospital and National Defense Medical Center, Taipei; Kuan-Yin Lin, National Taiwan University Hospital Jin-Shan Branch, New Taipei City; Chia-Jui Yang, and Mao-Song Tsai, Far Eastern Memorial Hospital, New Taipei City; Yi-Chieh Lee, Lotung Poh-Ai Hospital, Lo-Hsu Foundation, I-Lan; Chien-Yu Cheng and Shu-Hsing Cheng, Tao-Yuan General Hospital, Ministry of Health and Welfare, Tao-Yuan; Yu-Shan Huang, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu; Yuan-Ti Lee and Chia-Chun Lin, Chung Shan Medical University Hospital, Taichung; Shih-Ping Lin, Chia-Yin Hsieh, and Hsiu-Wen Wang, Taichung Veterans General Hospital, Taichung; Mao-Wang Ho, China Medical University Hospital, Taichung; Chun-Eng Liu and Yu-Lin Lee, Changhua Christian Hospital, Changhua; Yi-Chien Lee, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi; Hung-Jen Tang and Huei-Chun Ku, Chi Mei Medical Center, Tainan; Chia-Wen Li, Nan-Yao Lee, and Wen-Chien Ko, National Cheng Kung University Hospital, Tainan; Po-Liang Lu and Yen-Hsu Chen, Kaohsiung Medical University Hospital, Kaohsiung; Hsi-Hsun Lin, E-Da Hospital, Kaohsiung; Wen-Chi Huang and Chen-Hsiang Lee, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung; Tun-Chieh Chen, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung.

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References

1. UNAIDS/WHO. Report on the global AIDS epidemic. 2013. Available from: http://www.unaids.org/en/resources/documents/2013/20130923_UNAIDS_Global_Report_2013. Cited 10 May 2017.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. Available from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Cited 10 May 2017.
3. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. The New England journal of medicine. 2015; 373(9):808–22. https://doi.org/10.1056/NEJMoa1507198 PMID: 26193126
4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. The New England journal of medicine. 2016; 375 (9):830–9. https://doi.org/10.1056/NEJMoa1600693 PMID: 27424812
5. UNAIDS/WHO. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. 2014. Available from: http://www.unaids.org/en/resources/documents/2014/90-90-90. Cited 10 May 2017.
6. UNAIDS/WHO. Global AIDS update. 2016. Available from: http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016. Cited 10 May 2017.
7. UNAIDS/WHO. HIV in Asia and the Pacific. 2013. Available from: http://www.unaids.org/en/resources/documents/2013/20131119_HIV-Asia-Pacific. Cited 10 May 2017.
8. UNAIDS/WHO. Antiretroviral therapy for HIV infection in adults and adolescents. 2010. Available from: http://www.who.int/hiv/pub/arv/adult2010/en/. Cited 10 May 2017.
9. Kiertiburanakul S, Boettiger D, Lee MP, Omar SF, Tanuma J, Ng OT, et al. Trends of CD4 cell count levels at the initiation of antiretroviral therapy over time and factors associated with late initiation of antiretroviral therapy among Asian HIV-positive patients. Journal of the International AIDS Society. 2014; 17:18804. https://doi.org/10.7448/IAS.17.1.18804 PMID: 24598459
10. The World Bank. Country and Lending Groups. 2016. Available from: http://data.worldbank.org/about/country-and-lending-groups-High_income. Cited 10 May 2017.
11. Centers for Disease Control, R.O.C. (Taiwan). Guidelines for diagnosis and treatment of HIV/AIDS. 2013. Available from: http://www.cdc.gov.tw/uploads/files/201310/1e64c227-32fc-49ab-8bfc-9484ec50c4f3.pdf. Cited 10 May 2017.
12. Lai CC, Hung CC, Chen MY, Sun HY, Lu CL, Tseng YT, et al. Trends of transmitted drug resistance of HIV-1 and its impact on treatment response to first-line antiretroviral therapy in Taiwan. The Journal of antimicrobial chemotherapy. 2012; 67(5):1254–60. https://doi.org/10.1093/jac/dkr601 PMID: 22302562
13. Lai CC, Liu WC, Fang CT, Yang JY, Chang LH, Wu PY, et al. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. The Journal of antimicrobial chemotherapy. 2016; 71(1):226–34. https://doi.org/10.1093/jac/dkv284 PMID: 26404079
14. Chang SY, Lin PH, Cheng CL, Chen MY, Sun HY, Hsieh SM, et al. Prevalence of integrase strand transfer inhibitors (INSTI) resistance mutations in Taiwan. Scientific reports. 2016; 6:35779. https://doi.org/10.1038/srep35779 PMID: 27779200
15. Wu PY, Cheng CY, Liu CE, Lee YC, Yang CJ, Tsai MS, et al. Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naive HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLOS ONE. 2017; 12(2):e0171596. https://doi.org/10.1371/journal.pone.0171596 PMID: 28222098
16. Lourenco L, Samji H, Nohpal A, Chau W, Colley G, Lepik K, et al. Declines in highly active antiretroviral therapy initiation at CD4 cell counts $\leq$ 200 cells/uL and the contribution of diagnosis of HIV at CD4 cell counts $\leq$ 200 cells/uL in British Columbia, Canada. HIV medicine. 2015; 16(6):337–45. https://doi.org/10.1111/hiv.12212 PMID: 25721157
17. Lesko CR, Cole SR, Zinski A, Poole C, Mugavero MJ. A systematic review and meta-regression of temporal trends in adult CD4(+) cell count at presentation to HIV care, 1992–2011. Clinical infectious diseases. 2013; 57(7):1027–37. https://doi.org/10.1093/cid/cit421 PMID: 23921882
18. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: a meta-analysis. Clinical infectious diseases. 2015; 60(7):1120–7. https://doi.org/10.1093/cid/ciu1137 PMID: 25516189
19. UNAIDS/WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/download/en/. Cited 10 May 2017.
20. Ford N, Mills EJ, Egger M. Editorial commentary: immunodeficiency at start of antiretroviral therapy: the persistent problem of late presentation to care. Clinical infectious diseases. 2015; 60(7):1128–30. https://doi.org/10.1093/cid/ciu1138 PMID: 25516184

21. UNAIDS/WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/. Cited 10 May 2017.
22. Lahuerta M, Lima J, Nuwagaba-Biribonwoha H, Okamura M, Alvim MF, Fernandes R, et al. Factors associated with late antiretroviral therapy initiation among adults in Mozambique. PLOS ONE. 2012; 7 (5):e37125. https://doi.org/10.1371/journal.pone.0037125 PMID: 22615917
23. Mutimura E, Addison D, Anastos K, Hoover D, Dusingize JC, Karenzie B, et al. Trends in and correlates of CD4+ cell count at antiretroviral therapy initiation after changes in national ART guidelines in Rwanda. AIDS. 2015; 29(1):67–76. https://doi.org/10.1097/QAD.0000000000000520 PMID: 25562492
24. Edwards JK, Cole SR, Westreich D, Mugavero MJ, Eron JJ, Moore RD, et al. Age at entry into care, timing of antiretroviral therapy initiation, and 10-year mortality among HIV-seropositive adults in the United States. Clinical infectious diseases. 2015; 61(7):1189–95. https://doi.org/10.1093/cid/civ463 PMID: 26082505
25. Bunting E, Rajkumar C, Fisher M. The human immunodeficiency virus and ageing. Age and ageing. 2014; 43(3):308–10. https://doi.org/10.1093/ageing/afu016 PMID: 24622488
26. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over. AIDS. 2010; 24(13):2109–15. https://doi.org/10.1097/QAD.0b013e32833c7b9c PMID: 20616697
27. Grabar S, Weiss L, Costagliola D. HIV infection in older patients in the HAART era. The Journal of antimicrobial chemotherapy. 2006; 57(1):4–7. https://doi.org/10.1093/jac/dki411 PMID: 16284223
28. Centers for Disease Control, R.O.C. (Taiwan). Statistics of Communicable Diseases and Surveillance Report. 2014. Available from: http://www.cdc.gov.tw/professional/infectionreportinfo.aspx?treeid=56ca56252a0fa705&nowtreeid=CA20FC0DAB36F820&tid=15B0DEB6406CAF71. Cited 10 May 2017.
29. Ministry of Health and Welfare, R.O.C. (Taiwan). Density of Medical Resources in Taiwan. 2008. Available from: http://www.mohw.gov.tw/cht/DOS/DisplayStatisticFile.aspx?d=4002. Cited 10 May 2017.
30. Ministry of the Interior, R.O.C. (Taiwan). Educational level Table in Taiwan. 2016. Available from: http://statis.moi.gov.tw/micst/stmain.jsp?sys=100. Cited 10 May 2017.
31. Huang SM, Cai WP, Hu FY, Lan Y, Liao BL, Chen YP, et al. Epidemiological and clinical characteristics of hepatitis B virus in HIV-infected patients in Guangdong, China. International journal of STD & AIDS. 2016; 27(10):890–7. https://doi.org/10.1177/0956462415600570 PMID: 26384940
32. Tsai MS, Chang SY, Lo YC, Yang CJ, Sun HY, Liu WC, et al. Hepatitis B virus (HBV) coinfection accelerates immunologic progression in patients with primary HIV infection in an area of hyperendemicity for HBV infection. The Journal of infectious diseases. 2013; 208(7):1184–6. https://doi.org/10.1093/infdis/jit299 PMID: 23840045
33. Liu JY, Lin HH, Liu YC, Lee SS, Chen YL, Hung CC, et al. Extremely high prevalence and genetic diversity of hepatitis C virus infection among HIV-infected injection drug users in Taiwan. Clinical infectious diseases. 2008; 46(11):1761–8. https://doi.org/10.1086/587992 PMID: 18433337
34. Perez-Molina JA, Diaz-Menendez M, Plana MN, Zamora J, Lopez-Velez R, Moreno S. Very late initiation of HAART impairs treatment response at 48 and 96 weeks: results from a meta-analysis of randomized clinical trials. The Journal of antimicrobial chemotherapy. 2012; 67(2):312–21. https://doi.org/10.1093/jac/dkr478 PMID: 22127587
35. Wright ST, Law MG, Cooper DA, Keen P, McDonald A, Middleton M, et al. Temporal trends of time to antiretroviral treatment initiation, interruption and modification: examination of patients diagnosed with advanced HIV in Australia. Journal of the International AIDS Society. 2015; 18:19463. https://doi.org/10.7448/IAS.18.1.19463 PMID: 25865372

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2017
VOL. 15, NO. 9, 873–892
https://doi.org/10.1080/14787210.2017.1364991

Taylor & Francis
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REVIEW

Treatment of *Pneumocystis jirovecii* pneumonia in HIV-infected patients: a review

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ABSTRACT

Introduction: *Pneumocystis* pneumonia is a potentially life-threatening pulmonary infection that occurs in immunocompromised individuals and HIV-infected patients with a low CD4 cell count. Trimethoprim-sulfamethoxazole has been used as the first-line agent for treatment, but mutations within dihydropteroate synthase gene render potential resistance to sulfamide. Despite advances of combination antiretroviral therapy (cART), *Pneumocystis* pneumonia continues to occur in HIV-infected patients with late presentation for cART or virological and immunological failure after receiving cART.

Areas covered: This review summarizes the diagnosis and first-line and alternative treatment and prophylaxis for *Pneumocystis* pneumonia in HIV-infected patients. Articles for this review were identified through searching PubMed. Search terms included: '*Pneumocystis* pneumonia', '*Pneumocystis jirovecii* pneumonia', '*Pneumocystis carinii pneumonia*', 'trimethoprim-sulfamethoxazole', 'primaquine', 'trimetrexate', 'dapsone', 'pentamidine', 'atovaquone', 'echinocandins', 'human immunodeficiency virus infection', 'acquired immunodeficiency syndrome', 'resistance to sulfamide' and combinations of these terms. We limited the search to English language papers that were published between 1981 and March 2017. We screened all identified articles and cross-referenced studies from retrieved articles.

Expert commentary: Trimethoprim-sulfamethoxazole will continue to be the first-line agent for *Pneumocystis* pneumonia given its cost, availability of both oral and parenteral formulations, and effectiveness or efficacy in both treatment and prophylaxis. Whether resistance due to mutations within dihydropteroate synthase gene compromises treatment effectiveness remains controversial. Continued search for effective alternatives with better safety profiles for *Pneumocystis* pneumonia is warranted.

ARTICLE HISTORY
Received 15 April 2017
Accepted 4 August 2017

KEYWORDS
Interstitial pneumonitis; trimethoprim-sulfamethoxazole; alternative therapy; prophylaxis; combination antiretroviral therapy

1. Introduction

With the advances of combination antiretroviral therapy (cART), the incidence of *Pneumocystis* pneumonia in HIV-infected population has significantly decreased worldwide [1–4]. In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the incidence rate of *Pneumocystis* pneumonia declined from 0.92 cases during 2000–2003 to 0.39 cases during 2008–2010 per 100 person-years of observation [1]. Nevertheless, *Pneumocystis* pneumonia continues to draw our attention because it still occurs in HIV-infected patients who are not aware of their HIV infection and present with late-stage disease [5,6], those who are aware of their infection but not linked to HIV care [6,7], and those with poor adherence to cART or infected with multidrug-resistant HIV [8,9] with virological and immunological nonresponse despite cART [10]. Although the life expectancy has significantly increased among HIV-infected patients in the cART era [11], *Pneumocystis* pneumonia remains an important cause of pulmonary infections [12,13], hospitalization [14,15], and death [16–20] in the HIV-infected populations.

Pneumocystis pneumonia is a potentially life-threatening pulmonary infection that occurs among HIV-infected patients with a low CD4 count [21,22]. It is formerly known as *Pneumocystis carinii* pneumonia (PCP), but DNA analysis showed *Pneumocystis* organisms from different host species have very different DNA sequences [23]. The organism causing human PCP is now named *Pneumocystis jirovecii* [24]. The acronym PCP can still be used despite the name change because it can be read '*P*neumo*c*ystis *p*neumonia' [23]. Patients with *Pneumocystis* pneumonia classically present with fever, nonproductive or minimally productive cough, dyspnea (clinical triad), and malaise, which, however, are not specific to *Pneumocystis* pneumonia [21,22,25]. The average duration of pulmonary symptoms is about 3 weeks before presentation for medical attention. Extrapulmonary manifestations of *Pneumocystis* infection are rare, however [26]. In the present review, we aim to review the preferred and alternative antimicrobial agents for the treatment of and prophylaxis for *Pneumocystis* pneumonia in HIV-infected adult patients.

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2. Diagnosis of *Pneumocystis* pneumonia

The diagnosis of *Pneumocystis* pneumonia may be difficult owing to nonspecific symptoms and signs, and should be considered in patients at risk for *Pneumocystis* pneumonia who present with consistent radiographic findings [21,27]. Imaging studies are an essential companion to microbiological testing for the diagnosis of *Pneumocystis* pneumonia [28]. The chest radiographic findings may be normal in patients with early mild disease. Diffuse bilateral infiltrates extending from the perihilar region are visible in most patients with *Pneumocystis* pneumonia. Given an equivocal chest radiography, high-resolution computed tomography (HRCT) of the lungs yields a high sensitivity for *Pneumocystis* pneumonia in HIV-infected patients [29]. The most frequent HRCT findings are bilateral, ground-glass changes with apical predominance and peripheral sparing with a background of interlobular septal thickening [28]. Nuclear imaging modalities such as 18F fludeoxyglucose-positron emission tomography have been used as an adjunct to plain radiography or CT [30,31].

Because *Pneumocystis* cannot be readily cultured in the routine laboratory, the golden standard for the diagnosis of *Pneumocystis* pneumonia is the direct visualization of the organisms in the respiratory specimens, such as induced sputum, bronchoalveolar lavage (BAL) fluid, or lung biopsy specimens [21,32,33]. In the 1960s and 1970s, the identification of the organism was made by staining with Gomori-methenamine silver, cresyl violet, toluidine blue O, or calcofluor white, and in 1986, monoclonal antibodies for *Pneumocystis* were developed [25,34]. In recent years, the diagnosis can be made by identification of *Pneumocystis* DNA in a clinically relevant sample [27,35]. Studies on the use of molecular diagnosis have largely been based on BAL specimens in HIV-uninfected immunocompromised patients [30,36], but experience with HIV-infected patients is limited [37–39]. *Pneumocystis* colonization is easily detectable in individuals with HIV infection [40]. The range of colonization prevalence varies from 20% to 69% based on DNA detection with PCR-based methods [41]. This variability likely results from differences in the patient populations studied, the samples collected, and the detection methods used. Quantitative real-time PCR assays may become useful in distinguishing colonization from active infection [42,43] and monitoring therapeutic effectiveness [44], but these assays are not yet available for routine clinical use. Messenger RNA is much less stable than DNA, and its identification may serve as a surrogate for organism viability [35]. The use of serum testing to diagnose *Pneumocystis* pneumonia [35], such as (1–3)-β-D-glucan (BDG), Krebs von den Lungen-6 antigen, and S-adenosyl methionine also gains great interests [45]. BDG is a cell wall component of many fungi, including *Candida, Aspergillus*, and *Pneumocystis* but not the *Zygomycetes* [35]. A cost-effectiveness analysis showed that BDG was found to be the most reliable serologic biomarker for the diagnosis of *Pneumocystis* pneumonia [45]. Elevated BDG levels can also be observed in patients infected with other fungi, however, and false positives can be seen as a result of other clinical variables. Therefore, potential confounding factors must be considered when interpreting the results of this test [46].

3. Treatment of *Pneumocystis pneumonia*

3.1. *Trimethoprim-sulfamethoxazole: the drug of choice*

Over the past several decades, trimethoprim-sulfamethoxazole (TMP-SMX) remains the drug of choice for all forms of *Pneumocystis* pneumonia. TMP and SMX act synergistically to block folic acid synthesis by inhibiting dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), respectively [47,48]. A fixed combination of TMP-SMX in the ratio of 1:5 of weight could achieve a 1:20 concentration ratio *in vivo*, at which the maximum inhibition of susceptible organism occurs [49]. Patients with folate deficiency or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should avoid this agent, however.

Before TMP-SMX was well accepted as the first-line therapy, treatment of *Pneumocystis* pneumonia was limited to the use of pentamidine. TMP-SMX was initially found to be highly effective for *Pneumocystis* pneumonia in rat model [50]. Subsequent trials in humans demonstrated that TMP-SMX was either equally effective or superior to pentamidine as therapy for *Pneumocystis* pneumonia in both pediatric and adult patients [51–54]. In a study including 70 AIDS patients, oxygenation improved 8 days earlier, and survival was greater by up to 25% (95% confidence interval [CI], 5–45%, $p = 0.03$) in subjects receiving TMP-SMX than those receiving pentamidine [54].

The dose, efficacy, and potential side effects of TMP-SMX are summarized in Table 1. TMP-SMX has the advantage of good efficacy and availability in both oral and parenteral forms, but adverse effects are common [66]. The recommended daily dose for *Pneumocystis* pneumonia is TMP 15–20 mg/kg plus SMX 75–100 mg/kg. This dose was established by Hughes et al. from the experience that TMP 20 mg/kg/day plus SMX 100 mg/kg/day was more effective than TMP 4–7 mg/kg/day plus SMX 20–35 mg/kg/day in the pediatric cancer patients [67]. Owing to frequently encountered side effects, treatment with a lower dose of TMP-SMX was reinvestigated. Thomas et al. reported an overall survival rate of 93% (and 81% in patients with severe disease) among 73 HIV-infected patients treated with TMP 10 mg/kg/day plus SMX 50 mg/kg/day [68]. A step-down strategy from intermediate-dose TMP-SMX (TMP 10–15 mg/kg/day) to low-dose TMP-SMX (TMP 4–6 mg/kg/day) in selective patients was also shown to be successful [69]. The efficacy of a lower dose of TMP-SMX (<15 mg/kg/day of TMP) needs further confirmation, however. Several prospective studies evaluated the role of therapeutic drug monitoring in conjunction with TMP-SMX therapy [70–73]. A target SMX peak serum level of 100–150 μg/ml was proposed to maximize the therapeutic efficacy [51]. However, association between peak SMX levels and rates of adverse events and the utility of therapeutic drug monitoring during TMP-SMX therapy for *Pneumocystis* pneumonia remain uncertain [74,75]. The optimal treatment duration of *Pneumocystis* pneumonia has not been well studied, but it is generally recommended to treat HIV-infected patients for 21 days and HIV-uninfected patients for at least 14 days [76,77].

Mutations in the DHFR and DHPS gene of *P. jirovecii* with resistance to TMP and SMX, respectively, have been reported, and the prevalence seems increasing [78,79]. Kazanjian et al. reported that DHPS gene mutations were detected in 76% of the specimens from patients exposed to sulfa or sulfone prophylaxis compared with 23% of the specimens from patients not exposed [80]. The mutations in the DHFR or DHPS gene have been linked to prophylactic failure, but published reports [81–87] regarding whether the mutations increased the rates of death or treatment failure remain controversial due to different definitions for treatment success or failure and evaluation of death at different time points [78]. In the study using different definitions of prophylaxis and mortality endpoints among 301 HIV-infected patients with *Pneumocystis* pneumonia to analyze the association between prophylaxis, DHPS mutant subtypes, and treatment outcomes [88], Yoon et al. revealed that prophylaxis increased the risk of infection with pure DHPS mutant, irrespective of definitions used. Nevertheless, infection with mutant DHPS was not associated with increased mortality [88].

Adjunctive corticosteroid therapy is beneficial for HIV-infected patients with moderate to severe *Pneumocystis* pneumonia, defined by arterial oxygen pressure less than 70 mmHg or an alveolar-arterial oxygen gradient greater than 35 mmHg while breathing ambient air [89]. It was observed that concomitant use of corticosteroids attenuated the inflammatory responses following degradation of *P. jirovecii* [90]. A randomized study including 251 HIV-infected patients with *Pneumocystis* pneumonia demonstrated that treatment with corticosteroids had led to a lower cumulative risk of respiratory failure and death at 31 days, as well as a lower risk of death within 84 days [89]. Another study also found that adjunctive corticosteroids given with antibiotics for less than 72 h in patients with AIDS and severe *Pneumocystis* pneumonia could significantly improve survival (corticosteroids recipients 75% vs. placebo recipients 18%, $p < 0.008$) [91]. In a meta-analysis, HIV-infected patients with *Pneumocystis* pneumonia who were treated with adjunctive corticosteroids had a significantly decreased risk of mortality (relative risk, 0.55; $p < 0.05$) as compared to those without corticosteroids [92,93]. The recommended protocol is an initial dose of 40 mg of oral prednisone twice daily on day 1 through 5, and 40 mg of prednisone daily on day 6 through 10, and 20 mg of prednisone daily on day 11 through 21 [94]. For HIV-uninfected patients with moderate to severe *Pneumocystis* pneumonia, data on the efficacy of adjunctive corticosteroids are limited, and it is unclear how to treat patients with prior or ongoing use of corticosteroids [77,95,96]. Although the role of adjunctive corticosteroids is not well studied, many experts still suggest the use of corticosteroids in this population given the high mortality of the disease.

3.2. Alternative therapies for *pneumocystis* pneumonia

Owing to the high rate of intolerance of first-line TMP-SMX [66], several antimicrobials have been used as alternative or rescue therapy for HIV-infected patients with *Pneumocystis* pneumonia. The clinically available alternative therapies for *Pneumocystis* pneumonia are summarized in Table 1.

Table 1. Summary of available therapies to treat *Pneumocystis* pneumonia and reported adverse effects.

Regimens and dose	Route	Severity of disease	Reported treatment success rate	Treatment-limiting ADRs	Reported ADRs
Therapy of choice: TMP-SMX					
TMP 15–20 mg/kg plus SMX 75–100 mg/kg	IV/PO	Mild-to-moderate[a] Moderate-to-severe[b]	67–93% [53–61]	17–40% [53,56,59–61]	Fever, hypersensitivity, skin rash, SJS/TEN, hemolytic anemia, leukopenia, thrombocytopenia, nausea/vomiting, diarrhea, glossitis, hepatitis, pancreatitis, hyperkalemia, hyponatremia, AKI, psychosis, tremor
Alternative therapies					
Pentamidine 4 mg/kg/day	IV	Moderate-to-severe[b]	40–74% [53,54,59,62]	36% [62]	Hypotension, azotemia, neutropenia, cardiac arrhythmias, dysglycemia,
Clindamycin 2400 mg/day plus Primaquine 30 mg/day	IV	Moderate-to-severe[b]	64–76% [58,63]	20–33% [60,61]	**Clindamycin**: fever, rash, erythema multiforme, anaphylaxis, nausea, hepatitis, renal injury, reversible neutropenia/thrombocytopenia and eosinophilia, diarrhea, *Clostridium difficile* colitis
Clindamycin 1800 mg/day plus Primaquine 30 mg/day	PO	Mild-to-moderate[a]	85–100% [59,60,64]	20–33% [60,61]	**Primaquine**: methemoglobinemia, nausea/vomiting if taken on empty stomach
Atovaquone 750 mg twice to thrice per day	PO	Mild-to-moderate[a]	57–80% [61,62]	4–7% [61,62]	Fever, rash, nausea, hepatitis
Dapsone 100 mg/day plus TMP 20 mg/kg/day	PO	Mild-to-moderate[a]	88–93% [60,65]	23% [60]	**Trimethoprim**: fever, rash, hyperkalemia **Dapsone**: methemoglobinemia, gastrointestinal discomfort, DHS

ADR: adverse drug reaction; AKI: acute kidney injury; DHS: dapsone hypersensitivity syndrome; IV: intravenously; PO: orally; SJS: Stevens-Johnson syndrome SJS; TMP-SMX: trimethoprim-sulfamethoxazole; TEN: toxic epidermal necrolysis.
[a]Arterial $pO_2 > 70$ mmHg while breathing ambient air and alveolar-arterial O_2 gradient <35 mmHg.
[b]Arterial $pO_2 < 70$ mmHg while breathing ambient air or alveolar-arterial O_2 gradient >35 mmHg.

Alternative therapies for *Pneumocystis* pneumonia are generally classified according to the severity of disease (Table 1). For patients with moderate-to-severe *Pneumocystis* pneumonia, intravenous pentamidine has been used as the first-line therapy before introduction of TMP-SMX and remains as an alternative therapy to TMP-SMX [97]. When compared with TMP-SMX in clinical trials, intravenous pentamidine was associated with similar or slightly inferior clinical outcome [53–55]. However, the use of systemically administered pentamidine is generally limited by its toxicities. Some studies also reported using a reduced dose of intravenous pentamidine (3 mg/kg/day) for the treatment of HIV-infected patients with mild-to-moderate *Pneumocystis* pneumonia, with less adverse effects and similar clinical efficacy [98,99]. Use of aerosolized pentamidine was also evaluated as salvage therapy for patients who could not tolerate TMP-SMX and intravenous pentamidine; however, most patients included in these clinical trials had only mild-to-moderate *Pneumocystis* pneumonia and the clinical effectiveness was inferior to systemic therapies [56,100]. Trimetrexate, a potent DHFR inhibitor that demonstrated up to 1500-fold higher *in vitro* activity compared to TMP, has been used to treat *Pneumocystis* pneumonia in combination with calcium folinate to reduce adverse effects [101]. In a head-to-head comparison study of treating moderate-to-severe *Pneumocystis* pneumonia in HIV-infected patients with trimetrexate vs. TMP-SMX, the efficacy of trimetrexate appeared to be inferior to TMP-SMX with higher rates of 21-day mortality and treatment failure [57]. Despite being inferior to TMP-SMX, intravenous trimetrexate still demonstrated a treatment success rate of 62–71% in clinical studies [57,102].

Another medication that had been used in the past is eflornithine, an irreversible inhibitor of ornithine decarboxylase [103]. In two cohorts reporting compassionate use of eflornithine as salvage therapy for HIV-infected patients with *Pneumocystis* pneumonia who failed to respond to or were intolerant of TMP-SMX and intravenous pentamidine, the treatment success rate was 45.5% (15/33) and 87.0% (27/31) [103,104]. However, both trimetrexate and eflornithine are not available for treatment of *Pneumocystis* pneumonia globally.

Clindamycin and primaquine in combination is also recommended by clinical guidelines as alternative treatment [97], although clinical trials demonstrating its efficacy in patients with moderate-to-severe *Pneumocystis* pneumonia are scarce. In a clinical trial comparing clindamycin and primaquine in combination vs. TMP-SMX, which included 44 patients with moderate-to-severe *Pneumocystis* pneumonia who presented with initial PaO_2 between 50 and 70 mmHg, the clinical success rate was similar with either drug combination [58]. Retrospective studies also demonstrated clindamycin and primaquine in combination as an effective alternative when patients had clinical failure or progression during the therapy with TMP-SMX [59,60,63]. However, in a retrospective study including HIV-uninfected patients who developed *Pneumocystis* pneumonia after renal transplantation, the clinical efficacy of clindamycin-primaquine seemed to be inferior to TMP-SMX in patients with severe pneumonia [105].

For HIV-infected patients with mild-to-moderate *Pneumocystis* pneumonia, the alternative therapies most commonly used include clindamycin-primaquine, atovaquone, as well as dapsone-TMP. Combination of clindamycin and primaquine has been proved to be both effective and tolerable in patients with mild-to-moderate *Pneumocystis* pneumonia. When compared with TMP-SMX in prospective and retrospective cohorts, treatment with clindamycin and primaquine was associated with similar treatment success and 3-month mortality rates and fewer adverse effects [58–60,64,106]. The clinical efficacy of clindamycin and primaquine was also compared with other salvage therapies. In a meta-analysis conducted in 2001 that included 497 patients in need of salvage therapy with microbiologically confirmed *Pneumocystis* pneumonia from 27 published studies, combination of clindamycin with primaquine seemed to be associated with the highest treatment success rate among all of the alternative regimens assessed [107]. Compared with intravenous pentamidine, clindamycin combined with primaquine was also associated with higher treatment success rates in patients with mild-to-moderate *Pneumocystis* pneumonia [59,63].

For patients who could tolerate oral medications, atovaquone was another alternative to TMP-SMX in patients with mild-to-moderate *Pneumocystis* pneumonia. However, in a double-blinded randomized trial, atovaquone appears to be less efficacious than TMP-SMX and was associated with a higher treatment failure rate (20% vs. 7%) and mortality rate (7% vs. 0.6%)[61]. In contrast, atovaquone was better tolerated with less treatment-limiting adverse effects than TMP-SMX (7% vs. 20%) and intravenous pentamidine (4% vs. 36%) [61,62]. Treatment success with atovaquone was positively associated with serum level of atovaqoune, as patients with serum levels higher than 15 μg/ml had a treatment success rate of greater than 95% [61]. To ensure adequate serum concentration, the medication should be taken with food containing moderate fat to increase its bioavailability [108]. On the other hand, the efficacy of atovaquone would be reduced if patients have diarrhea or other illness interfering the absorption of atovaquone [61]. Furthermore, atovaquone should not be coadministered with rifampicin, rifabutin, boosted atazanavir, and efavirenz because these medications are known to decrease the serum level of atovaquone. An advantage of atovaquone is the safety when treating patients with G-6-PD deficiency, for whom primaquine, SMX, and dapsone are contraindicated.

Dapsone, coadministrated with TMP, is another alternative to treat mild-to-moderate *Pneumocystis* pneumonia. In prospective trials conducted in the 1990s, dapsone combined with TMP demonstrated similar clinical success rates to TMP-SMX with less treatment-limiting toxicity [60,65]. However, the use of this combination is largely limited by the availability of single-formulated TMP.

Echinocandins are a new class of antifungal medication by inhibition of the synthesis of BDG, an important component of fungal cell. The cyst form of *P. jirovecii* also contains BDG and might be susceptible to echinocandins, while the trophic form does not synthesize the molecule and is not susceptible to echinocandins. In an animal study with *P. murina*-infected mice, treatment with echinocandins significantly reduced the cyst burden within the lung tissue, while the reduction of trophic burden was suboptimal [109]. Three commercially available echinocandins (caspofungin, micafungin, and anidulafungin) were compared in the animal study at different

doses. All three agents displayed similar effects in reducing the cyst burden of the infected lung tissue when given at a high dose, though micafungin appeared to be less efficacious than the other two agents when given at a lower dose [109]. In another animal study involving immunocompromised rats with *Pneumocystis* infection, treatment with either caspofungin or TMP-SMX had similar rat survival and reduction of cyst burden in the lung tissue [110]. Other investigators also demonstrated additive effects when combining caspofungin with TMP-SMX to treat *P. murina*-infected mice [111]. Despite the success in animal studies, experience of treating *Pneumocystis* pneumonia with echinocandins in the HIV-infected patients remains very limited. All reported cases of *Pneumocystis* pneumonia treated with echinocandins, including HIV-infected and HIV-uninfected patients, are summarized in Table 2. In a retrospective cohort, Armstrong-James et al. reported their experience with combination of caspofungin with other second-line medications, including clindamycin-primaquine, TMP-SMX, or intravenous pentamidine, as salvage therapy for *Pneumocystis* pneumonia in HIV-infected patients. In this single center cohort study, the treatment success rate of patients with microbiologically confirmed *Pneumocystis* pneumonia was as high as 90% [124]. In another small retrospective study, anidulafungin was used as the only alternative agent for seven HIV-infected patients with *Pneumocystis* pneumonia intolerant of TMP-SMX, and two patients died of non-*Pneumocystis* pneumonia-related causes during follow-up [125]. In HIV-uninfected, immunocompromised patients who were diagnosed with *Pneumocystis* pneumonia, the reported effectiveness of echinocandins was inconsistent, however (Table 2). To the best of our knowledge, echinocandin monotherapy for HIV-infected patients with *Pneumocystis* pneumonia has not been evaluated in clinical trials and should only be used very carefully as salvage therapy when other medications are unavailable or cause intolerable adverse effects.

4. Prevention of *Pneumocystis* pneumonia

Guidelines have been published for prophylaxis against *Pneumocystis* pneumonia in patients with HIV infection, hematologic malignancies, or organ transplantation [76,77,126,127]. However, controversies remain on the use of prophylaxis in many immunocompromised populations, such as patients receiving corticosteroids for pulmonary diseases or immunosuppressive agents for rheumatologic diseases.

For asymptomatic HIV-infected patients, guidelines recommend that patients with CD4 counts less than 200 cells/μl start primary prophylaxis for *Pneumocystis* pneumonia. This recommendation is based on the observation of a large-scale study of 1665 HIV-infected patients, in which the risk of *Pneumocystis* pneumonia greatly increased in participants with a CD4 count less than 200 cells/μl (relative risk, 4.9; 95% CI, 3.1–8.0) [128]. Other proposed criteria for primary prophylaxis include oropharyngeal candidiasis, CD4 cell percentage less than 14%, or a history of AIDS-defining illness [128,129]. With the use of antimicrobial prophylaxis, the risk of developing *Pneumocystis* pneumonia decreased by ninefold [130]. Once the CD4 count increases to 200 cells/μl or more for greater than 3 months in response to cART, primary prophylaxis may be discontinued. Using the above criteria, a randomized trial showed no episodes of *Pneumocystis* pneumonia occurred in patients off primary and secondary prophylaxis after a median follow-up for 20 and 12 months, respectively [131]. Lately, a lower CD4 threshold for discontinuing prophylaxis in patients on effective cART was examined. Observational data from 23,412 patients revealed that prophylaxis significantly reduced the incidence of *Pneumocystis* pneumonia among patients with CD4 counts less than 100 cells/μl, but not those with CD4 counts of 101–200 cells/μl [132]. The pooled analyses suggested that the primary prophylaxis for *Pneumocystis* pneumonia might be withdrawn safely in patients with a suppressed HIV replication and a CD4 count of 101–200 cells/μl [133,134]. However, more data are needed to support this conclusion, and the sustained adherence and response to cART should be taken into consideration before the decision to discontinue prophylaxis is to be made.

HIV-infected patients who have been successfully treated for *Pneumocystis* pneumonia should be given secondary prophylaxis until the CD4 counts increase to 200 cells/μl or more for greater than 3 months after the initiation of ART [135]. Both primary and secondary prophylaxis should be reintroduced if the CD4 count decreases to less than 200 cells/μl again [136].

4.1. Agents for prophylaxis against *Pneumocystis* pneumonia

TMP-SMX is the preferred prophylactic agent for *Pneumocystis* pneumonia, which can simultaneously provide protection against toxoplasmosis and several bacterial infections. TMP-SMX has been shown to be superior to alternative regimens in a meta-analysis of 6583 patients on prophylaxis for *Pneumocystis* pneumonia [137]. The recommended dose of TMP-SMX is one double-strength (DS; TMP-SMX dose of 160 mg/800 mg) tablet or one single-strength (SS; TMP-SMX dose of 80 mg/400 mg) tablet daily. In a multicenter trial, none of the 260 HIV-infected patients receiving DS or SS TMP-SMX developed *Pneumocystis* pneumonia, but adverse reactions were seen more frequently in the DS group [138]. In another study comparing the efficacy of once-daily vs. thrice-weekly DS TMP-SMX for prophylaxis for *Pneumocystis* pneumonia in 2625 HIV-infected patients, the estimates of efficacy endpoints favored daily DS TMP-SMX for *Pneumocystis* pneumonia, death, and bacterial pneumonia, though the rates of intolerance were also higher [139]. The dose of one DS TMP-SMX daily is suggested in patients with a lower CD4 count (less than 100 cells/μl) since it confers better protection against toxoplasmosis than low-dose TMP-SMX [140].

For patients intolerant of TMP-SMX, dapsone [141], atovaquone [142,143], aerosolized pentamidine [144], and a combined regimen with dapsone, pyrimethamine plus leucovorin [145,146] are alternative prophylactic agents. The regimen of dapsone, pyrimethamine plus leucovorin is favored if prophylaxis against toxoplasmosis is indicated. Table 3 summarizes the results of the studies evaluating the prophylactic regimens of *Pneumocystis* pneumonia in HIV-infected patients. A recent study suggested that CD101 is a novel long-acting echinocandin and inhibits the formation of asci which is critical for

Table 2. Summary of reported cases of *Pneumocystis* pneumonia in immunocompromised patients who were treated with echinocandins.

Age/sex	Underlying	Initial PaO_2/clinical status	Initial regimens	Days before switch	Reason for switch/intolerance	Second-line regimens	Treatment duration, days	Outcome	Reference
45/M	HSCT conditioning	N/A	TMP-SMX	11	Clinical progression	CAS + TMP-SMX	45	Improved	[112]
5/M	ALL, chemotherapy	SpO_2 80%	–	0	N/A	CAS + TMP-SMX	N/A	Improved	[113]
43/F	ATLL, chemotherapy	N/A	TMP-SMX	13	Clinical progression	MFG + others	30	Failed	[114]
13/M	CML s/p HSCT	N/A	–	0	N/A	CAS + Pentamidine	9	Failed	[114]
57/M	Kidney transplantation	56 mmHg	–	0	N/A	CAS + TMP-SMX	14	Improved	[115]
28/M	Kidney transplantation	51 mmHg	TMP-SMX	7	Clinical progression	CAS + TMP-SMX	16	Improved	[115]
59/M	Heart transplantation	59 mmHg	TMP-SMX	6	Clinical progression	CAS + TMP-SMX	7	Improved	[115]
58/M	Heart transplantation	55 mmHg	–	0	N/A	CAS + TMP-SMX	14	Improved	[115]
60/M	GPA, steroid	N/A	–	0	N/A	CAS	21	Improved	[116]
39/M	HIV/AIDS	MV	TMP-SMX	28	Clinical progression	CAS + TMP-SMX	N/A	Improved	[117]
44/M	HIV/AIDS	53 mmHg	–	0	History of allergy	CAS + clindamycin	13	Failed	[118]
1/M	SCID	<60 mmHg	TMP-SMX	25	Clinical progression	CAS + various	25	Failed	[119]
63/M	Liver transplantation	<60 mmHg	TMP-SMX	9	Clinical progression	CAS + TMP-SMX	4	Failed	[119]
57/M	Kidney transplantation	<60 mmHg	TMP-SMX	17	Clinical progression	CAS + TMP-SMX	11	Failed	[119]
46/M	Liver transplantation	<60 mmHg	TMP-SMX	5	Clinical progression	CAS + clindamycin-primaquine	7	Improved	[119]
61/M	Kidney transplantation	NPPV	TMP-SMX	NA	Hepatic injury	CAS + low dose TMP-SMX	14	Improved	[120]
35/M	Kidney transplantation	59 mmHg	TMP-SMX	10	Leukopenia	CAS + low dose TMP-SMX	14	Improved	[120]
43/M	Kidney transplantation	NPPV	–	0	N/A	CAS + low dose TMP-SMX	14	Improved	[120]
46/M	IgA nephropathy	NPPV	TMP-SMX	7	Drug allergy	CAS + clindamycin	21	Improved	[121]
46/M	DLBCL, Rituximab	N/A	–	0	History of allergy	CAS	N/A	Improved	[122]
46/M	AIDS	N/A	TMP-SMX	7	Drug allergy	CAS	14	Improved	[123]
–	12 AIDS patients	N/A	TMP-SMX	N/A	Clinical failure (10) Drug toxicity (2)	CAS + clindamycin-primaquine (6) CAS + TMP-SMX (4) CAS + pentamidine (2)	N/A	Improved (10/12)	[124]

AIDS: acquired immunodeficiency syndrome; ALL: acute lymphoblastic leukemia; ATLL: adult T-cell leukemia/lymphoma; CAS: caspofungin; CML: chronic myelogenous leukemia; DLBCL: diffuse large B-cell lymphoma; GPA: granulomatosis with polyangiitis; HIV: human immunodeficiency virus; HSCT: hematopoietic stem cell transplantation; MFG: micafungin; MV: mechanical ventilation; N/A: not available; NPPV: noninvasive positive-pressure ventilation; SCID: severe combined immunodeficiency; TMP-SMX: trimethoprim-sulfamethoxazole

Table 3. Clinical trials of prophylaxis for *Pneumocystis* pneumonia in HIV-infected patients.

Regimen	Study design	Case no.	Outcomes	Comments
TMP-SMX				
TMP-SMX DS twice per day vs. no prophylaxis [147]	RCT	30 vs. 30	*Pneumocystis* pneumonia: 0 in TMP-SMX vs. 16 in no prophylaxis group	• Primary prophylaxis • Toxoplasmosis: 1 in TMP-SMX
TMP-SMX SS daily vs. DS daily [138]	RCT	131 vs. 129	None developed *Pneumocystis* pneumonia	• Primary prophylaxis
TMP-SMX DS daily vs. thrice-weekly [139]	RCT	1312 vs. 1313	*Pneumocystis* pneumonia rate: daily vs. thrice-weekly, 3.5 vs. 4.1 per 100 person-years (RR 0.82, $p = 0.16$)	• Primary and secondary prophylaxis • Toxoplasmosis: 1.8/100 person-years in each group
TMP-SMX DS thrice-weekly [148]	Prospective	104	*Pneumocystis* pneumonia rate: 2.9% or 1/413 person-months in primary prophylaxis group; 7.4% or 1/167 person-months in secondary prophylaxis group	• Primary and secondary prophylaxis
Dapsone				
Dapsone 50 or 100 mg/day [149]	Retrospective	20 vs. 10	Relapse in 1 patient with dapsone at a dose of 50 mg/day	• Primary and secondary prophylaxis
Dapsone 100 mg twice weekly [150]	Prospective	55	*Pneumocystis* pneumonia rate per year: 6.79%	• Primary prophylaxis
Dapsone 100 mg vs. TMP-SMX DS daily [151]	RCT	47 vs. 39	*Pneumocystis* pneumonia: dapsone 1/862 person-months vs. TMP-SMX 1/776 person-months	• Primary prophylaxis
Dapsone-pyrimethamine 100/25 mg weekly vs. TMP-SMX DS thrice-weekly [152]	RCT	85 vs. 81	*Pneumocystis* pneumonia: dapsone-pyrimethamine 13/85 (15.2%) vs. TMP-SMX 3/81 (3.7%) ($p = 0.01$)	• Primary prophylaxis • Toxoplasmosis: dapsone-pyrimethamine group, 3; TMP-SMX, 2 (no significant difference)
Dapsone-pyrimethamine 100/50 mg twice weekly vs. TMP-SMX DS thrice-weekly [145]	RCT	115 vs. 115	*Pneumocystis* pneumonia: dapsone-pyrimethamine 6/96 (6.3%) vs. TMP-SMX 0/104 (0%) ($p < 0.0001$)	• Primary prophylaxis • Toxoplasmosis: dapsone-pyrimethamine group, 2; TMP-SMX, 1 (no significant difference)
Dapsone 100 mg twice weekly vs. aerosolized pentamidine 400 mg monthly [153]	RCT	50 vs. 46	*Pneumocystis* pneumonia: dapsone 9/50 (18%) vs. pentamidine 8/46 (17%)	• Primary and secondary prophylaxis
Dapsone 100 mg twice weekly vs. aerosolized pentamidine 100 mg every 2 weeks [154]	RCT	126 vs. 152	*Pneumocystis* pneumonia: 15 (18%) in dapsone group vs. to 15 (14%) in pentamidine group ($p = 0.4$)	• Primary prophylaxis • Toxoplasmic encephalitis: 6 in pentamidine group; 0 in dapsone group ($p = 0.01$)
Dapsone 50 mg/day vs. aerosolized pentamidine 300 mg monthly [155]	RCT	93 vs. 103	Mortality rates at 18 months: dapsone 53.1% vs. pentamidine 24.6% ($p < 0.003$, log-rank test)	• Secondary prophylaxis
Dapsone 50 mg/day-pyrimethamine 50mg/week vs. aerosolized pentamidine 300 mg monthly [156]	RCT	173 vs. 176	*Pneumocystis* pneumonia: 10 cases in each group ($p = 0.79$)	• Primary prophylaxis • Toxoplasmosis: dapsone-pyrimethamine group, 19/173; pentamidine group 32/176 ($p = 0.02$)

(*Continued*)

Table 3. (Continued).

Regimen	Study design	Case no.	Outcomes	Comments
Dapsone-pyrimethamine 200/75 mg weekly vs. aerosolized pentamidine monthly [157]	RCT	291 vs. 242	*Pneumocystis* pneumonia: 12 cases in dapsone-pyrimethamine group vs. 13 cases in pentamidine group	• Primary prophylaxis • Toxoplasmic encephalitis: 14 in dapsone-pyrimethamine group; 20 in pentamidine group ($p = 0.1$)
Atovaquone				
Atovaquone 1500 mg vs. dapsone 100 mg [142]	RCT	536 vs. 521	Atovaquone 15.7 cases per 100 person-years vs. dapsone 18.4 cases per 100 person-years (RR 0.85, $p = 0.20$)	• Primary and secondary prophylaxis • Toxoplasmosis: 4 in atovaquone group, 3 in dapsone group; RR 1.18, $p = 0.83$)
Atovaquone 750 mg/day, 1500 mg/day vs. aerosolized pentamidine 300 mg monthly [143]	RCT	188 vs. 175 vs. 186	*Pneumocystis* pneumonia rate: 26%, 22%, and 17%, respectively (no statistically significant differences)	• Primary & secondary prophylaxis
Pentamidine				
Aerosolized pentamidine [158]	Retrospective	232	*Pneumocystis* pneumonia: 11 patients (4.7%).	• Primary prophylaxis
Aerosolized pentamidine 300 mg monthly [159]	Retrospective	29	*Pneumocystis* pneumonia: 2/16 (12.5%) with primary prophylaxis; 4/13 (30.8%) with secondary prophylaxis	• Primary and secondary prophylaxis
Aerosolized pentamidine 60 mg biweekly vs. no prophylaxis [160]	RCT	105 vs. 104	*Pneumocystis* pneumonia cumulative incidence by 18 months: 13% in the pentamidine group and 30% in the control; $p = 0.002$).	• Primary prophylaxis
Aerosolized pentamidine 60 mg biweekly vs. IV pentamidine 200–300mg biweekly [161]	Retrospective	78 vs. 42	*Pneumocystis* pneumonia-free rates in survivors at 12 months: 0.83 and 0.77, respectively	• Secondary prophylaxis
Aerosolized pentamidine 300 mg monthly vs. TMP-SMX SS daily [162]	RCT	106 vs. 108	*Pneumocystis* pneumonia rate per year: pentamidine group 3.1% vs. TMP-SMX group 1.3% ($p > 0.05$)	• Primary prophylaxis • 19 episodes of cerebral toxoplasmosis: pentamidine 18, TMP-SMX 1
Aerosolized pentamidine 300 mg monthly vs. TMP-SMX DS daily [163]	RCT	156 vs. 154	Recurrence rate at 18 months: pentamidine group 27.6% vs. TMP-SMX group 11.4% ($p < 0.001$)	• Secondary prophylaxis • Toxoplasmosis: pentamidine group, 6; TMP-SMX group, 4 • Bacterial infection: pentamidine group, 38; TMP-SMX group, 19 ($p = 0.017$)
Comparison of 3 anti-*Pneumocystis* agents				
TMP-SMX vs. aerosolized pentamidine vs. dapsone-pyrimethamine [164]	RCT	107 vs. 108 vs. 116	*Pneumocystis* pneumonia: 3% in TMP-SMX, 5.6% in pentamidine, and 8.3% in dapsone-pyrimethamine group ($p > 0.05$)	• Primary prophylaxis • Neither TMP-SMX alone nor pyrimethamine with dapsone or TMP-SMX prevented initial episodes of toxoplasmosis
TMP-SMX vs. aerosolized pentamidine vs. dapsone-pyrimethamine [165]	RCT	66 vs. 68 vs. 63	*Pneumocystis* pneumonia: 2.0 per 100 person-years in the TMP-SMX, 10.2 in the pentamidine, and 32.1 in the dapsone-pyrimethamine group (RR of dapsone-pyrimethamine vs. TMP-SMX: 17.5; $p = 0.007$)	• Primary prophylaxis • Toxoplasmic encephalitis rate: 8.9 per 100 person-years in TMP-SMX, 25.6 per 100 person-years in pentamidine, and 9.4 per 100 person-years in dapsone-pyrimethamine group.
TMP-SMX vs. aerosolized pentamidine vs. dapsone [166]	RCT	276 vs. 278 vs. 288	Estimated 36-month cumulative risks of *Pneumocystis* pneumonia: 18% in TMP-SMX, 21% in pentamidine, and 17% in dapsone group ($p = 0.22$)	• Primary prophylaxis • 24 episodes of toxoplasmosis: TMP-SMX group, 9; pentamidine group, 9; dapsone group, 6
TMP-SMX vs. aerosolized pentamidine vs. dapsone [167]	Retrospective	172 vs. 28 vs. 91	1 in 1110 person-months of TMP-SMX, 6 in 418 person-months of dapsone, and 3 in 164 person-months of pentamidine group	• Primary and secondary prophylaxis

DS: double-strength; IV: intravenous; RCT: randomized controlled trial; RR: relative risk; SS: single-strength; TMP-SMX: trimethoprim-sulfamethoxazole.

replication of *Pneumocystis* [168]. Compared with no treatment, both CD101 and TMP-SMX significantly reduced nuclei levels (trophic forms) and asci levels in C3H/HeN mice infected with *P. murina* [168].

Dapsone is the commonly used alternative prophylactic agent [149]. A comparative trial of dapsone vs. TMP-SMX as primary prophylaxis revealed only one episode of *Pneumocystis* pneumonia in each group during the 1638 person-months of observation [151]. Bozzette et al. compared the effectiveness among TMP-SMX, dapsone, and aerosolized pentamidine for primary prophylaxis for *Pneumocystis* pneumonia, and the estimated 36-month cumulative risk of *Pneumocystis* pneumonia was 18%, 17%, and 21%, respectively ($p = 0.22$) [166]. Additionally, failure of prophylaxis was more commonly observed with 50 mg of dapsone than with 100 mg. In another randomized trial comparing TMP-SMX, dapsone plus pyrimethamine, and aerosolized pentamidine as primary prophylaxis, the annual rate of *Pneumocystis* pneumonia was 3.0%, 8.3%, and 5.6%, respectively ($p > 0.05$) [164]. The effect of dapsone as an alternative prophylactic agent was also observed in HIV-uninfected patients [169]. However, clinicians should be aware of the organisms not covered by dapsone monotherapy, such as *Toxoplasma* or *Nocardia* [170].

Atovaquone has a comparable efficacy to dapsone and aerosolized pentamidine, and it is also active against *Toxoplasma*. In a trial of 1057 patients on prophylaxis for *Pneumocystis* pneumonia, the relative risk of developing *Pneumocystis* pneumonia for atovaquone group vs. dapsone group was 0.85 (95% CI, 0.67–1.09; $p = 0.2$) [142]. One study comparing atovaquone 750 or 1500 mg daily with aerosolized pentamidine revealed no statistically significant difference in the incidence of *Pneumocystis* pneumonia [143]. Aerosolized pentamidine, given at a dose of 300 mg monthly, was inferior to TMP-SMX but resulted in less treatment-associated side effects [144]. However, aerosolized pentamidine lacks the activity against *Toxoplasma*.

5. Adverse effects of anti-*Pneumocystis* treatments

The common and some rare but severe adverse effects of the first-line and alternative treatment regimens of *Pneumocystis* pneumonia are summarized in Table 1.

5.1. Trimethoprim-sulfamethoxazole

Two mechanisms have been postulated to explain the TMP-SMX-induced toxicities [171]. Hypersensitivity to TMP-SMX is possibly mediated by glutathione metabolism [48,172]. Single-nucleotide polymorphism rs761142 in the glutamate cysteine ligase catalytic (GCLC) subunit was found to be associated with reduced GCLC mRNA expression. By catalyzing a critical step in glutathione biosynthesis, it is associated with SMX-induced hypersensitivity in HIV-infected patients. The hepatic N-acetyltransferase plays a role in transforming TMP-SMX to nontoxic metabolites, and the rate of acetylation may contribute to the risks of TMP-SMX-related toxicity. A previous study has shown that HIV-infected patients with slow acetylation phenotypes had a higher incidence of adverse reactions to TMP-SMX [173]. The alternative pathway of TMP-SMX metabolism is via the cytochrome protein 450 (CYP) 2C9 pathway, wherein SMX is metabolized to hydroxylamine by the CYP 2C9 pathway. Hydroxylamine plays an important role in TMP-SMX-related toxicity [174]. The frequency of poor metabolizers for CYP 2C9 may vary among persons of different ethnicities; for example, in the Taiwanese population the frequency is around 8.2%, which is significantly lower than that in Caucasians (about 20%) [175]. Therefore, the likelihood of TMP-SMX being metabolized rapidly to hydroxylamine will be higher among Taiwanese, which may contribute to the higher incidence of hepatotoxicity observed in a previous multicenter study [66].

5.1.1. Constitutional

TMP-SMX-related drug fever could occur immediately only a few hours after taking the medications, and it could also have a delayed onset up to the eighth day of treatment [176]. Hypersensitivity reactions, such as fever, rash, and hypotension, could develop immediately after the administration of TMP-SMX. The presence, absence, or characteristics of prior adverse reactions to TMP-SMX does not predict the subsequent severe reactions. Although the mechanism of hypersensitivity remains unknown, this reaction has features of both IgE-mediated anaphylaxis and cytokine (tumor necrosis factor)-mediated effects [177]. Oral desensitization procedure may help the patients with AIDS tolerate TMP-SMX well, and the success rate could be as high as 80–100% [178,179].

5.1.2. Dermatologic

Cutaneous reactions to TMP-SMX develop in 8–47% of the AIDS patients with *Pneumocystis* pneumonia. This rash generally occurs 4 days after the initiation of therapy (1–9 days), mainly with presentations of maculopapular cutaneous eruptions [180].

5.1.3. Hematologic

TMP-SMX-induced thrombocytopenia occurs 1–2 weeks after initiation of the medications. Severe cases of thrombocytopenia have been reported, which usually resolves within a week of discontinuation of TMP-SMX. A decrease in platelets with or without purpura is one of the most frequently reported severe adverse events in the elderly patients. Thrombocytopenia is often associated with megaloblastic anemia; therefore, use of TMP-SMX should be cautious in patients with megaloblastic anemia until more data become available. Monitoring of hemogram during the course of TMP-SMX therapy is advised [181]. AIDS patients treated for *Pneumocystis* pneumonia may experience a higher rate of leukopenia with an incidence of 21.8–47%. Leucovorin (folinic acid) could lower the incidence of neutropenia. However, the incidences of treatment failure (15%) and death (11%) were significantly higher in the group that received leucovorin [66,182]. Therefore, leucovorin should not be routinely used and could be considered for selective patients who develop severe neutropenia.

5.1.4. Gastrointestinal

TMP-SMX is associated with upper gastrointestinal upset, such as nausea or vomiting, which may occur in 3.4–24.9% of the patients and appears to be higher among females than males. Glossitis is infrequently reported, occurring in 0.4% of the patients. Occurring in 0.6% of the patients, diarrhea is a relatively uncommon reaction to TMP-SMX use [66,183]. In the study by Yang et al., about 16.4% of the patients who received TMP-SMX for *Pneumocystis* pneumonia developed TMP-SMX-related hepatotoxicity; of the hepatotoxicity events, 89.4% were classified as hepatocellular type, 2.1% cholestatic type, and the other 8.5% mixed type; and 42.6% of the cases were of grade 3 to 4 hepatotoxicity, and 6.4% of the patients developed jaundice. The interval between initiation of TMP-SMX and development of hepatotoxicity ranged from 2 to 24 days (median, 11 days) [66]. Furthermore, 87.2% of the patients had normalization of liver-function profiles after dose reduction or discontinuation of TMP-SMX; however, 42.6% had to discontinue TMP-SMX and change to other regimens (clindamycin plus primaquine or dapsone), and 34% had to reduce the dose of TMP-SMX [66].

Fluconazole is an inhibitor for CYP2C9 activity [184]. In a previous pharmacokinetic study in healthy volunteers who concurrently received fluconazole and TMP-SMX, the use of fluconazole decreased the area-under-the-curve of hydroxylamine by 37% [185]. Therefore, the observation that the risk of TMP-SMX-related hepatotoxicity was reduced in association with concomitant use of fluconazole may be explained by reduced formation of hydroxylamine by fluconazole [66]. Pancreatitis has been linked to TMP-SMX use in several case reports. If evidence of pancreatic involvement occurs during sulfonamide therapy, the medication should be discontinued immediately [186].

5.1.5. Electrolyte disturbance and renal impairment

TMP is structurally similar to the potassium-sparing diuretics, such as amiloride and triamterene. It has been postulated that hyperkalemia is caused by the inhibition of sodium channels in the distal tubules [48]. The risk factors of developing hyperkalemia include renal insufficiency, having underlying disorders of potassium metabolism, and receiving concomitant hyperkalemia-inducing drugs [187,188]. The serum potassium concentration increases by an average of 1.1 mM after 7–10 days of treatment. The incidence of TMP-SMX-related hyperkalemia was about 21–28% in patients under the treatment for *Pneumocystis* pneumonia [189]. The serum potassium level would decrease after discontinuing TMP-SMX [189]. The incidence of hyponatremia may be as high as 70% in AIDS patients [66,190]. Hyponatremia has been attributed to a large volume of fluid required for intravenous infusion and diuretic action causing natriuresis. Acute kidney injury could develop in about 11% of the patients who received TMP-SMX for *Pneumocystis* pneumonia [191]. Acute kidney injury resolved promptly with discontinuation of therapy in almost all patients, but in some sporadic cases, dialysis was needed. Patients with hypertension and diabetes mellitus have increased risk for renal insufficiency, especially if these conditions are poorly controlled. The treatment dose, duration, or age is not associated with increased risk of acute kidney injury. Renal function would return to baseline in more than 90% of the patients within a mean of 9.1 ± 9.4 days (median, 5.5 days) after discontinuation of the medication [66,191].

5.1.6. Neuropsychiatric disorder

A multicenter, retrospective study demonstrated that the incidence of acute psychosis was estimated 11.9% in HIV-infected patients who received TMP-SMX for *Pneumocystis* pneumonia after a median duration of 5 days of treatment (range, 3–11 days) [192]. The incidence increased from 0% in patients who received a daily trimethoprim dose of ≤12 mg/kg to 23.5% in those who received a daily dose of >18 mg/kg. The risk significantly increased with a higher daily dose of TMP-SMX and use of adjunctive corticosteroids for *Pneumocystis* pneumonia. Tremor has been temporally related to TMP-SMX in AIDS patients being treated for *Pneumocystis* pneumonia. The onset of tremors usually occurred within 3–6 days after the initiation of treatment, and the symptoms resolved 2–3 days after TMP-SMX was discontinued or the dose was reduced [193,194].

5.2. TMP plus dapsone

Dapsone (diaminodiphenyl sulfone or DDS) is a sulfone-derived medication that was initially used as an antibacterial agent to treat leprosy in the 1940s, and it was later also used for *Pneumocystis* pneumonia and toxoplasmosis. The adverse effects of dapsone could be classified into two types: (1) dose-dependent (pharmacological) adverse effects that include hemolytic anemia and methemoglobinemia; and (2) dose-independent (idiosyncratic) adverse effects that include dapsone hypersensitivity syndrome [195]. Dapsone is metabolized by the liver through the oxidation reactions of N-acetylation and N-hydroxylation [196]. Hydroxylated amine metabolites produced during the oxidation reactions are potent oxidants that have been suspected to cause dapsone's hematologic effects, including hemolytic anemia and methemoglobinemia [197]. The initial treatment for patients with methemoglobinemia involves ventilator support and removing the offending agent. A previous study suggested that a patient with dyspnea or a methemoglobin level of more than 30% should receive methylene blue intravenously at 1–2 mg per kilogram of body weight over a 5-min period [198]. Methylene blue is oxidized into leucomethylene blue by accepting an electron from nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of NADPH-methemoglobin reductase. Leukomethylene blue plays as an artificial electron acceptor to methemoglobin, resulting in its conversion back to hemoglobin [199]. Dapsone hypersensitivity syndrome is a severe, multiorgan reaction to dapsone that includes fever, rash, jaundice, splenomegaly, lymphadenopathy, and pedal edema. Hemolytic anemia, atypical lymphocytosis, and hepatitis are other associated findings. Dapsone hypersensitivity syndrome is now considered to be one kind of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which is a special pattern of drug hypersensitivity. Only withdrawal of dapsone is usually not enough, and prolonged high-dose

corticosteroid therapy may be needed [200]. The incidence of dapsone hypersensitivity syndrome among Chinese patients was estimated 1.5%, with a case fatality rate of 9.6%. Early withdrawal of dapsone and appropriate treatment reduce the fatality rate. Most importantly, the HLA-B 13:01 allele has been found to be a useful genetic marker for screening for dapsone hypersensitivity syndrome among high-risk populations [201].

5.3. Atovaquone

Atovaquone has been shown to be effective for the treatment of *Pneumocystis* pneumonia in HIV-infected patients who were intolerant of TMP-SMX or dapsone, especially those with G-6-PD deficiency [61,62]. About 2–4% of the patients who took atovaquone would develop adverse effects, such as rash or liver dysfunction, and fewer than 2% of the patients developed pruritus, nausea, vomiting, or fever [61,202]. Atovaquone is generally well tolerated to most of the treated patients.

5.4. Primaquine plus clindamycin

Primaquine has been known to undergo N-dealkylation in humans to generate 6-methoxy-8-aminoquinoline (6-MAQ). N-dealkylation of primaquine followed by N-oxidation of 6-MAQ may be a contributing pathway for the expression of primaquine homological toxicity, such as hemolysis [203]. Hemolysis can occur among the G-6-PD deficient individuals [204]. The second important side effect is an increase in the level of serum methemoglobin, which is mild and generally well tolerated unless the patient has an inborn deficiency of the methemoglobin reductase metabolic pathway [205]. Finally, the abdominal discomfort is the most common adverse effect of primaquine. Primaquine can result in dose-dependent gastrointestinal discomfort when taken on an empty stomach, and it is well tolerated when taken with food [206].

The common side effects of systemic clindamycin treatment are diarrhea, nausea, vomiting, abdominal pain, and metallic taste. Hepatotoxicity is a rare adverse effect of clindamycin. While hepatotoxicity occurs, it is usually a transient elevation of transaminases. There are only a few cases of acute idiosyncratic liver injury after receiving systemic clindamycin therapy [207]. Clindamycin-induced acute liver injury is mediated by apoptotic mechanisms that result in cell death [208]. Fever, pruritus, and rash could occur during the treatment of clindamycin. Some rare serious dermatological events, such as acute generalized exanthematous pustulosis [209] and DRESS, have also been observed [210]. Furthermore, HLA-B*51:01 is a risk allele for clindamycin-related cutaneous adverse effects in Han Chinese, especially when clindamycin is administered via intravenous route [211].

It has been known that adverse hematological effects, such as anemia, neutropenia, and thrombocytopenia, could occur when receiving clindamycin, alone or in combination. Neutropenia may be caused by direct damage to the neutrophils or their precursors, inhibition of granulocyte colony-stimulating factor (G-CSF) activity, or an idiosyncratic reaction [212,213]. Thrombocytopenia could be caused by the immune-related destruction of platelets or caused by an idiosyncratic reaction [214]. A case report revealed that the pancytopenia was established by injury of the hematopoietic tissue [215].

Clindamycin could cause acute kidney injury, which can present so severe that temporary hemodialysis is needed. Clindamycin-related acute kidney injury is largely reversible and is associated with episodes of gross hematuria [216]. Clindamycin can lead to the development of *Clostridium difficile*-associated colitis, now described as *C. difficile* infection (CDI) [217]. The risk of having colitis on clindamycin treatment is similar to the risks with treatment with expanded-spectrum cephalosporins and broad-spectrum penicillins, and the incidence of colitis is reportedly 5% among the hospitalized patients [218]. The most important risk factors for the disease include hospitalization, comorbid conditions, old age, and the duration of treatment [219]. CDI is not common in patients taking clindamycin for 3 days or less [220]. If clindamycin is discontinued immediately after the occurrence of diarrhea, the disease is often self-limited [221]. However, recent emergence of BI/NAP1/027 strain has significantly changed the importance of CDI in that some previous effective treatment regimen, such as metronidazole, faces a higher risk of treatment failure [222].

5.5. Pentamidine

Pentamidine must be given intravenously over at least 1 h to avoid possible lethal hypotension. The adverse effects can be severe and irreversible and include renal injury, hyperkalemia, dysglycemia (life-threatening hypoglycemia that can occur days or weeks after initial infusion and could be followed by hyperglycemia), neutropenia, and torsades de pointes [223]. Therefore, 5% glucose solution should be used to dissolve pentamidine. Local pain or sterile abscess formation at an intramuscular injection site can also occur [224]. Nephrotoxicity occurs in at least 25% of patients with *Pneumocystis* pneumonia receiving parenteral pentamidine. Pentamidine-induced nephrotoxicity can be manifested by an increase in serum creatinine concentration and/or blood urea nitrogen that usually develops gradually and appears during the second week of therapy. Renal insufficiency is usually mild to moderate in severity and reversible following discontinuation of pentamidine; however, acute renal failure (e.g. serum creatinine concentration greater than 6 mg/dl) or severe renal insufficiency requiring discontinuation of the drug may occur occasionally [225,226]. Urinary luminal pentamidine inhibits distal nephron reabsorption of sodium ion by blocking apical sodium channels in a manner similar to 'potassium-sparing' diuretics. This causes a decrease in the electrochemical gradients that drives secretion of distal nephron potassium ion. This renal tubular effect is responsible for pentamidine-induced hyperkalemia [227]. Pentamidine-induced dysglycemia are primarily due to inappropriate insulin release and toxicity to the islet beta-cells. Drug accumulation due to an excessive dosage, prolonged courses, and renal impairment is the determining risk factor [228]. Pentamidine administration could occasionally result in acute pancreatitis, and, therefore, serum amylase concentrations should be

monitored during the treatment process [229]. Inhalational pentamidine could result in respiratory irritation, and it should be avoided in patients with active or a prior history of asthma. Patients with possibility of pulmonary tuberculosis should be excluded from inhalational pentamidine therapy. Bronchodilators could be used before the usage of inhalational pentamidine, and it can reduce the unwanted respiratory irritations [230].

5.6. Caspofungin

Fever, thrombophlebitis, headache, and liver enzyme elevations are well-known drug-related side effects of caspofungin noted in clinical trials [231]. The most-common drug-related adverse events in the patients receiving caspofungin were phlebitis (2–3.8%), and increased alkaline phosphatase level (2–6.9%) and aspartate transaminase level (2–4%) [232]. Diarrhea and nausea were also observed. Hypokalemia could develop during the treatment in 11.8% of the patients [233].

6. Timing of antiretroviral therapy initiation

Most HIV-infected patients presenting with *Pneumocystis* pneumonia are antiretroviral therapy (ART)-naïve. Early initiation of cART following treatment of *Pneumocystis* pneumonia has been shown to result in better outcomes in a randomized trial that compared early (median, 12 days after initiation of therapy for opportunistic infection) vs. deferred initiation of cART (median, 45 days) in 282 patients with acute opportunistic infections other than tuberculosis (63% of patients with *Pneumocystis* pneumonia). Lower risks of AIDS progression and death were also observed in the early-ART group [234]. Thus, the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America recommend that cART be initiated within 2 weeks of diagnosis of *Pneumocystis* pneumonia [76]. Nevertheless, several experts believe that the initiation of cART can be delayed until acute treatment is completed in the guidelines by the German and Austrian AIDS societies [235]. Furthermore, a study has shown that improved survival for HIV-infected patients with severe *Pneumocystis* pneumonia was independent of timing of cART [236].

Early initiation of cART may raise concerns about the risk of immune reconstitution inflammatory syndrome (IRIS). In the above mentioned study by Zolopa et al., IRIS was confirmed in 20 patients, and 13 were patients with *Pneumocystis* pneumonia [234]. However, unlike cryptococcosis-[237] and tuberculosis-related IRIS [238], use of uniform IRIS definitions for all opportunistic infections in the trial is questionable. Although early ART did not increase the risk for IRIS than deferred ART (odds ratio = 0.06; 95% confidence interval 0.24–1.4, $p = 0.35$) [239], life-threating IRIS after *Pneumocystis* pneumonia has been reported [240]. It remains difficult to distinguish *Pneumocystis* pneumonia-related IRIS from clinical deterioration after the treatment of *Pneumocystis* pneumonia and cART due to disease relapse [241], concurrent infections, drug resistance, or toxicity.

In the study of tuberculosis-related IRIS, additional illnesses other than tuberculosis (72%), such as new AIDS-defining illness, bacterial infections, gastroenteritis, and drug toxicity to cART, are the most frequent causes for clinical deterioration during antitubercular treatment in HIV-infected patients [242]. Therefore, in the setting of clinical deterioration in HIV-infected patients with *Pneumocystis* pneumonia who initiate cART, every effort should be made to rule out other illness than *Pneumocystis* pneumonia while keeping the entity of *Pneumocystis* pneumonia-related IRIS in mind.

7. Conclusions

With the widespread, early initiation of effective cART and use prophylactic TMP-SMX, *Pneumocystis* pneumonia could be prevented in HIV-infected populations. However, HIV-infected patients unaware of their HIV infection or aware of HIV infection but with poor adherence to cART with virological and immunological failure continue to suffer significant morbidities and mortality by *Pneumocystis* pneumonia. Current molecular and serum diagnostic modalities have improved the diagnosis of *Pneumocystis* pneumonia in vulnerable hosts with compatible symptoms. TMP-SMX and several alternative therapies have proven effective in the treatment of and prophylaxis for *Pneumocystis* pneumonia in HIV-infected patients in the pre-cART as well as post-cART era; however, the treatment options remain associated with significant side effects. Additionally, emerging resistance associated with DHPS mutations may potentially compromise the efficacy of prophylaxis. Health-care providers treating HIV-infected patients with *Pneumocystis* pneumonia should be vigilant for any adverse reactions during the course of treatment and prophylaxis.

8. Expert commentary

With the early diagnosis of HIV infection through testing and widespread use of cART, HIV-infected patients developing *Pneumocystis* pneumonia will continue to decrease, but it will not disappear given the fact that late diagnosis of HIV infection, poor compliance, and emergence or transmission of multiple-drug resistant HIV may continue to occur in some HIV-infected patients. Furthermore, *Pneumocystis* pneumonia has become an emerging challenge to HIV-uninfected patients receiving cytoreductive chemotherapy or immunosuppressives [243,244]. Given the declining incidence of *Pneumocystis* pneumonia among HIV-infected patients, primary care or infectious diseases physicians will become less familiar with this disease and its management when dealing with HIV-infected patients at risk; and late diagnosis and inappropriate management may cause significant morbidities and mortalities.

The diagnosis of *Pneumocystis* pneumonia remains problematic due to the nonspecific symptoms and signs of the disease and the inability to evaluate treatment response by the currently available diagnostic methods in the setting of clinical deterioration when the differential diagnosis includes additional illness, such as cytomegalovirus pneumonitis, treatment failure, and IRIS. Since there is no *in vitro* culture system

for *Pneumocystis*, the identification of the organisms in the respiratory specimens remains the gold standard. With the improved sensitivity, molecular diagnosis and serum BDG testing through less invasive diagnostic procedures will become popular in the diagnosis and evaluation of treatment response of *Pneumocystis* pneumonia. Nevertheless, how to distinguish colonization from active disease by molecular diagnosis or serum testing will become challenging.

With the effectiveness and long-term clinical experience of TMP-SMX for *Pneumocystis* pneumonia, TMP-SMX will continue to be the first-line agent for *Pneumocystis* pneumonia since it is available in both oral and parenteral formulations, effective in both treatment and prophylaxis for *Pneumocystis* pneumonia and infections caused by several other bacteria or protozoa, and with great cost-effectiveness in resource-limited regions. Whether emergence of TMP-SMX-resistant *Pneumocystis* impacts the clinical outcomes deserves further investigation by standardized definitions for clinical outcome assessment.

Although many alternative agents could be considered in the setting of intolerance of TMP-SMX for *Pneumocystis* pneumonia, their unavailability and common adverse reactions still preclude their use in clinical practice. Given the safety profiles and demonstrated effectiveness against cyst form in rodent model of *Pneumocystis* pneumonia, more clinical studies are warranted to examine the effectiveness or efficacy of echinocandins as an alternative agent or in combination for patients with *Pneumocystis* pneumonia who are intolerance of TMP-SMX since the clinical data on the effectiveness of echinocandins remain limited.

9. Five-year view

Pneumocystis pneumonia will remain an important cause of morbidity and mortality in HIV-infected patients with late HIV diagnosis and failure to respond to cART. Future diagnosis of *Pneumocystis* pneumonia will rely on molecular diagnosis. Despite its numerous adverse reactions, TMP-SMX will continue to be the first-line treatment and prophylaxis for *Pneumocystis* pneumonia. Given the limited access to other alternative agents and their associated side effects, echinocandins will become increasingly used as an alternative agent for *Pneumocystis* pneumonia.

Key issues

- The incidence of *Pneumocystis* pneumonia has decreased dramatically in HIV-infected patients in the era of combination antiretroviral therapy (cART). However, *Pneumocystis* pneumonia still poses a great threat to HIV-infected patients presenting with late-stage disease, poor adherence, or failure to respond to cART.
- Identification of *P. jirovecii* in the respiratory specimens by direct visualization or staining methods remains the gold standard for diagnosis of *Pneumocystis* pneumonia, though detection of *Pneumocystis* DNA has gained increasing interest and clinical experience.
- Trimethoprim-sulfamethoxazole (TMP-SMX, TMP 15–20 mg/kg plus SMX 75–100 mg/kg for 21 days) is the most effective therapy for all forms of *Pneumocystis* pneumonia. For HIV-infected patients with moderate to severe disease, adjunctive corticosteroid therapy significantly reduces the mortality.
- Early initiation of cART following treatment of *Pneumocystis* pneumonia in cART-naïve HIV-infected patients is associated with better outcomes. Clinicians should be aware of paradoxical immune reconstitution inflammatory syndrome (IRIS) when there is clinical deterioration after initiation of cART.
- Alternative therapies for *Pneumocystis* pneumonia include intravenous pentamidine, clindamycin plus primaquine, atovaquone, and dapsone plus TMP. Trimetrexate and eflornithine have been shown to be effective for *Pneumocystis* pneumonia, but both agents are not globally available. All alternative regimens are less efficacious than TMP-SMX.
- Echinocandins exert its activity against *Pneumocystis* pneumonia by inhibiting beta-1,3-D-glucan of the cyst form of *P. jirovecii*. Case reports and retrospective studies have demonstrated their potential role as alternative therapy for *Pneumocystis* pneumonia in HIV-infected patients.
- Primary prophylaxis against *Pneumocystis* pneumonia should be started in HIV-infected patients whose CD4 counts less than 200 cells/μL. A lower CD4 threshold (less than 100 cells/μL) for prophylaxis has been proposed for patients with suppressed HIV replication and good adherence to cART.
- TMP-SMX is the preferred prophylactic agent for *Pneumocystis* pneumonia, and it can prevent toxoplasmosis simultaneously. The alternative agents are dapsone, atovaquone, and aerosolized pentamidine with comparable efficacy to each other, but all are inferior to TMP-SMX.
- TMP-SMX therapy is often associated with significant side effects. Genetic difference in the enzymes participating the metabolic pathway of TMP-SMX is related to the frequency and severity of TMP-SMX-related adverse effects.

Funding

The study was supported by grants from the Ministry of Science and Technology, Taiwan (Grant number:103-2314-B-0020176-MY3).

Declaration of interest

CC Hung has received research support from Janssen, AbbVie, Bristol-Myers Squibb, Merck, ViiV and speaker honoraria from Gilead Sciences, and served on the advisory boards for Gilead Sciences, ViiV, AbbVie and Janssen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000–2010. J Infect Dis. 2016;214:862–872.

•• **A study nicely described the declining rates of the first opportunistic infections of all kinds during 2000–2010 in a large and diverse cohort of HIV-infected patients in North America in the contemporary cART era with predominance of *Pneumocystis* pneumonia and esophageal candidiasis.**

2. Schwarcz L, Chen MJ, Vittinghoff E, et al. Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. AIDS. 2013;27:597–605.
3. Mocroft A, Sabin CA, Youle M, et al. Changes in AIDS-defining illnesses in a London Clinic, 1987–1998. J Acquir Immune Defic Syndr. 1999;21:401–407.
4. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994–98: the EuroSIDA study. Lancet. 2000;356:291–296.
5. Fei MW, Sant CA, Kim EJ, et al. Severity and outcomes of Pneumocystis pneumonia in patients newly diagnosed with HIV infection: an observational cohort study. Scand J Infect Dis. 2009;41:672–678.
6. Lin KY, Cheng CY, Li CW, et al. Trends and outcomes of late initiation of combination antiretroviral therapy driven by late presentation among HIV-positive Taiwanese patients in the era of treatment scale-up. PLoS One. 2017;12:e0179870.
7. Lanoy E, Lewden C, Lievre L, et al. How does loss to follow-up influence cohort findings on HIV infection? A joint analysis of the French hospital database on HIV, Mortalite 2000 survey and death certificates. HIV Med. 2009;10:236–245.
8. Lundberg BE, Davidson AJ, Burman WJ. Epidemiology of *Pneumocystis carinii* pneumonia in an era of effective prophylaxis: the relative contribution of non-adherence and drug failure. AIDS. 2000;14:2559–2566.
9. Chow JY, Alsan M, Armstrong W, et al. Risk factors for AIDS-defining illnesses among a population of poorly adherent people living with HIV/AIDS in Atlanta, Georgia. AIDS Care. 2015;27:844–848.
10. Lapadula G, Cozzi-Lepri A, Marchetti G, et al. Risk of clinical progression among patients with immunological nonresponse despite virological suppression after combination antiretroviral treatment. AIDS. 2013;27:769–779.
11. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013;8:e81355.
12. Lee KY, Ho CC, Ji DD, et al. Etiology of pulmonary complications of human immunodeficiency virus-1-infected patients in Taiwan in the era of combination antiretroviral therapy: a prospective observational study. J Microbiol Immunol Infect. 2013;46:433–440.
13. Wolff AJ, O'Donnell AE. HIV-related pulmonary infections: a review of the recent literature. Curr Opin Pulm Med. 2003;9:210–214.
14. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994–2005. AIDS. 2008;22:1345–1354.
15. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. J Acquir Immune Defic Syndr. 2005;40:609–616.
16. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014;384:241–248.
17. Palella FJ Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006;43:27–34.
18. Hooshyar D, Hanson DL, Wolfe M, et al. Trends in perimortal conditions and mortality rates among HIV-infected patients. AIDS. 2007;21:2093–2100.
19. Mocroft A, Sterne JA, et al.; Antiretroviral Therapy Cohort C. Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. Clin Infect Dis. 2009;48:1138–1151.
20. Neuhaus J, Angus B, Kowalska JD, et al. Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. AIDS. 2010;24:697–706.
21. Thomas CF Jr., Limper AH. Pneumocystis pneumonia. N Engl J Med. 2004;350:2487–2498.
22. Thomas CF Jr., Limper AH. Current insights into the biology and pathogenesis of Pneumocystis pneumonia. Nat Rev Microbiol. 2007;5:298–308.
23. Stringer JR, Beard CB, Miller RF, et al. A new name (*Pneumocystis jiroveci*) for Pneumocystis from humans. Emerg Infect Dis. 2002;8:891–896.
24. Frenkel JK. Pneumocystis pneumonia, an immunodeficiency-dependent disease (IDD): a critical historical overview. J Eukaryot Microbiol. 1999;46:89S–92S.
25. Tasaka S, Tokuda H. Recent advances in the diagnosis of *Pneumocystis jirovecii* pneumonia in HIV-infected adults. Expert Opin Med Diagn. 2013;7:85–97.
26. Cohen OJ, Stoeckle MY. Extrapulmonary *Pneumocystis carinii* infections in the acquired immunodeficiency syndrome. Arch Intern Med. 1991;151:1205–1214.
27. Calderon EJ, Gutierrez-Rivero S, Durand-Joly I, et al. Pneumocystis infection in humans: diagnosis and treatment. Expert Rev Anti Infect Ther. 2010;8:683–701.
28. Vogel MN, Vatlach M, Weissgerber P, et al. HRCT-features of *Pneumocystis jiroveci* pneumonia and their evolution before and after treatment in non-HIV immunocompromised patients. Eur J Radiol. 2012;81:1315–1320.
29. Kanne JP, Yandow DR, Meyer CA. *Pneumocystis jiroveci* pneumonia: high-resolution CT findings in patients with and without HIV infection. AJR Am J Roentgenol. 2012;198:W555–61.
30. Cooley L, Dendle C, Wolf J, et al. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J. 2014;44:1350–1363.
31. Reid AB, Chen SC, Worth LJ. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. Curr Opin Infect Dis. 2011;24:534–544.
32. Catherinot E, Lanternier F, Bougnoux ME, et al. *Pneumocystis jirovecii* pneumonia. Infect Dis Clin North Am. 2010;24:107–138.
33. Huang L, Cattamanchi A, Davis JL, et al. HIV-associated Pneumocystis pneumonia. Proc Am Thorac Soc. 2011;8:294–300.
34. Kovacs JA, Ng VL, Masur H, et al. Diagnosis of *Pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. N Engl J Med. 1988;318:589–593.
35. Krajicek BJ, Limper AH, Thomas CF Jr. Advances in the biology, pathogenesis and identification of Pneumocystis pneumonia. Curr Opin Pulm Med. 2008;14:228–234.
36. Alanio A, Hauser PM, Lagrou K, et al. ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71:2386–2396.
37. Kovacs JA, Gill VJ, Meshnick S, et al. New insights into transmission, diagnosis, and drug treatment of *Pneumocystis carinii* pneumonia. JAMA. 2001;286:2450–2460.
38. Fischer S, Gill VJ, Kovacs J, et al. The use of oral washes to diagnose *Pneumocystis carinii* pneumonia: a blinded prospective study using a polymerase chain reaction-based detection system. J Infect Dis. 2001;184:1485–1488.
39. Lu Y, Ling G, Qiang C, et al. PCR diagnosis of Pneumocystis pneumonia: a bivariate meta-analysis. J Clin Microbiol. 2011;49:4361–4363.
40. Calderon EJ. Epidemiology of Pneumocystis infection in human. Congr Soc Med Mycol. 2008;19:270–275.
41. Morris A, Norris KA. Colonization by *Pneumocystis jirovecii* and its role in disease. Clin Microbiol Rev. 2012;25:297–317.
42. Alanio A, Desoubeaux G, Sarfati C, et al. Real-time PCR assay-based strategy for differentiation between active *Pneumocystis jirovecii* pneumonia and colonization in immunocompromised patients. Clin Microbiol Infect. 2011;17:1531–1537.
43. Fauchier T, Hasseine L, Gari-Toussaint M, et al. Detection of *Pneumocystis jirovecii* by quantitative PCR to differentiate

colonization and pneumonia in immunocompromised HIV-positive and HIV-negative patients. J Clin Microbiol. 2016;54:1487–1495.
44. Tsolaki AG, Miller RF, Wakefield AE. Oropharyngeal samples for genotyping and monitoring response to treatment in AIDS patients with *Pneumocystis carinii* pneumonia. J Med Microbiol. 1999;48:897–905.
45. Esteves F, Cale SS, Badura R, et al. Diagnosis of Pneumocystis pneumonia: evaluation of four serologic biomarkers. Clin Microbiol Infect. 2015;21:379 e1–10.
46. Arvanitis M, Anagnostou T, Fuchs BB, et al. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev. 2014;27:490–526.
47. Volpe F, Ballantine SP, Delves CJ. The multifunctional folic acid synthesis fas gene of *Pneumocystis carinii* encodes dihydroneopterin aldolase, hydroxymethyldihydropterin pyrophosphokinase and dihydropteroate synthase. Eur J Biochem. 1993;216:449–458.
48. Masters PA, O'Bryan TA, Zurlo J, et al. Trimethoprim-sulfamethoxazole revisited. Arch Intern Med. 2003;163:402–410.
49. Castro JG, Morrison-Bryant M. Management of *Pneumocystis jirovecii* pneumonia in HIV infected patients: current options, challenges and future directions. HIV AIDS (Auckl). 2010;2:123–134.
50. Hughes WT, McNabb PC, Makres TD, et al. Efficacy of trimethoprim and sulfamethoxazole in the prevention and treatment of *Pneumocystis carinii* pneumonitis. Antimicrob Agents Chemother. 1974;5:289–293.
51. Hughes WT, Feldman S, Chaudhary SC, et al. Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. J Pediatr. 1978;92:285–291.
52. Dennis, T. Trimethoprim-sulfamethoxazole or pentamidine for Pneumocystispneumonia in the acquired immunodeficiency syndrome. Ann Intern Med. 1986;105:629–630.
53. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. AIDS. 1992;6:301–305.
54. Sattler FR, Cowan R, Nielsen DM, et al. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective, noncrossover study. Ann Intern Med. 1988;105:629–630.
- **The authors compared the efficacy between TMP-SMX and pentamidine for treatment of *Pneumocystis* pneumonia. TMP-SMX was shown to improve oxygenation more quickly and patient survival was better with TMP-SMX than pentamidine.**
55. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. Ann Intern Med. 1986;105:37–44.
56. Montgomery AB, Feigal DW Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for *Pneumocystis carinii* in acquired immune deficiency syndrome. Am J Respir Crit Care Med. 1995;151:1068–1074.
57. Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. J Infect Dis. 1994;170:165–172.
58. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). CTN-PCP study group. Clin Infect Dis. 1998;27:524–530.
59. Helweg-Larsen J, Benfield T, Atzori C, et al. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. J Antimicrob Chemother. 2009;64:1282–1290.
60. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. Ann Intern Med. 1996;124:792–802.
61. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. N Engl J Med. 1993;328:1521–1527.
62. Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for *Pneumocystis carinii* pneumonia in patients with AIDS. Atovaquone Study Group. Ann Intern Med. 1994;121:174–180.
63. Kim T, Kim SH, Park KH, et al. Clindamycin-primaquine versus pentamidine for the second-line treatment of pneumocystis pneumonia. J Infect Chemother. 2009;15:343–346.
64. Ruf B, Rohde I, Pohle HD. Efficacy of clindamycin/primaquine versus trimethoprim/sulfamethoxazole in primary treatment of *Pneumocystis carinii* pneumonia. Eur J Clin Microbiol Infect Dis. 1991;10:207–210.
65. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. N Engl J Med. 1990;323:776–782.
66. Yang JJ, Huang CH, Liu CE, et al. Multicenter study of trimethoprim/sulfamethoxazole-related hepatotoxicity: incidence and associated factors among HIV-infected patients treated for *Pneumocystis jirovecii* pneumonia. PLoS One. 2014;9:e106141.
- **The authors conducted a multicenter study to collect the data on the adverse effects of TMP-SMX during the treatment of *Pneumocystis* pneumonia, with a large case number. The association between use of fluconazole and the decreased rate of TMP-SMX-related hepatotoxicity deserves more studies.**
67. Hughes WT, Feldman S, Sanyal SK. Treatment of *Pneumocystis carinii* pneumonitis with trimethoprim-sulfamethoxazole. Can Med Assoc J. 1975;112:47–50.
68. Thomas M, Rupali P, Woodhouse A, et al. Good outcome with trimethoprim 10 mg/kg/day-sulfamethoxazole 50 mg/kg/day for *Pneumocystis jirovecii* pneumonia in HIV infected patients. Scand J Infect Dis. 2009;41:862–868.
69. Creemers-Schild D, Kroon FP, Kuijper EJ, et al. Treatment of Pneumocystis pneumonia with intermediate-dose and step-down to low-dose trimethoprim-sulfamethoxazole: lessons from an observational cohort study. Infection. 2016;44:291–299.
70. Klinker H, Langmann P, Zilly M, et al. Drug monitoring during the treatment of AIDS-associated *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole. J Clin Pharm Ther. 1998;23:149–154.
71. Joos B, Blaser J, Opravil M, et al. Monitoring of co-trimoxazole concentrations in serum during treatment of *Pneumocystis carinii* pneumonia. Antimicrob Agents Chemother. 1995;39:2661–2666.
72. Hughes WT, LaFon SW, Scott JD, et al. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related Pneumocystis carinii pneumonia. J Infect Dis. 1995;171:1295–1301.
73. Chin TW, Vandenbroucke A, Fong IW. Pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients. Antimicrob Agents Chemother. 1995;39:28–33.
74. Silverman M, Kearney P. Diagnosis and treatment of Pneumocystis carinii pneumonia. Arch Dis Child. 1978;53:87–88.
75. Dao BD, Barreto JN, Wolf RC, et al. Serum peak sulfamethoxazole concentrations demonstrate difficulty in achieving a target range: a retrospective cohort study. Curr Ther Res Clin Exp. 2014;76:104–109.
76. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2017. [cited 2017 Apr 24]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.)

77. Maschmeyer G, Helweg-Larsen J, Pagano L, et al. ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients. J Antimicrob Chemoth. 2016;71:2405–2413.
78. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in Pneumocystis and sulfa resistance. Emerg Infect Dis. 2004;10:1721–1728.
•• **The authors comprehensively reviewed the studies of mutations in *P. jirovecii*, assessed the association between dihydropteroate synthase gene mutations and important clinical outcomes in published studies, and emphasized the importance of further investigations.**
79. Queener SF, Cody V, Pace J, et al. Trimethoprim resistance of dihydrofolate reductase variants from clinical isolates of *Pneumocystis jirovecii*. Antimicrob Agents Chemother. 2013;57:4990–4998.
80. Kazanjian P, Armstrong W, Hossler PA, et al. *Pneumocystis carinii* mutations are associated with duration of sulfa or sulfone prophylaxis exposure in AIDS patients. J Infect Dis. 2000;182:551–557.
81. Alvarez-Martinez MJ, Moreno A, Miro JM, et al. *Pneumocystis jirovecii* pneumonia in Spanish HIV-infected patients in the combined antiretroviral therapy era: prevalence of dihydropteroate synthase mutations and prognostic factors of mortality. Diagn Microbiol Infec Dis. 2008;62:34–43.
82. Navin TR, Beard CB, Huang L, et al. Effect of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of *P carinii* pneumonia in patients with HIV-1: a prospective study. Lancet. 2001;358:545–549.
83. Ponce CA, Chabe M, George C, et al. High prevalence of *Pneumocystis jirovecii* dihydropteroate synthase gene mutations in patients with a first episode of pneumocystis pneumonia in Santiago, Chile, and clinical response to trimethoprim-sulfamethoxazole therapy. Antimicrob Agents Chemother. 2017;61(2):e01290-16.
84. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, et al. Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated P. *carinii* pneumonia. Lancet. 1999;354:1347–1351.
85. Visconti E, Ortona E, Mencarini P, et al. Mutations in dihydropteroate synthase gene of *Pneumocystis carinii* in HIV patients with *Pneumocystis carinii* pneumonia. Int J Antimicrob Agents. 2001;18:547–551.
86. Ma L, Kovacs JA, Cargnel A, et al. Mutations in the dihydropteroate synthase gene of human-derived *Pneumocystis carinii* isolates from Italy are infrequent but correlate with prior sulfa prophylaxis. J Infect Dis. 2002;185:1530–1532.
87. Takahashi T, Hosoya N, Endo T, et al. Relationship between mutations in dihydropteroate synthase of *Pneumocystis carinii* f. sp. hominis isolates in Japan and resistance to sulfonamide therapy. J Clin Microbiol. 2000;38:3161–3164.
88. Yoon C, Subramanian A, Chi A, et al. Dihydropteroate synthase mutations in Pneumocystis pneumonia: impact of applying different definitions of prophylaxis, mortality endpoints and mutant in a single cohort. Med Mycol. 2013;51:568–575.
89. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1990;323:1451–1457..
•• **The authors demonstrated the survival benefit of early adjunctive corticosteroids in HIV-infected patients with moderate-to-severe *Pneumocystis* pneumonia. The dosing regimen of corticosteroids in this study has become a standard in current practice**
90. Huang ZB, Eden E. Effect of corticosteroids on IL1 beta and TNF alpha release by alveolar macrophages from patients with AIDS and *Pneumocystis carinii* pneumonia. Chest. 1993;104:751–755.
91. Gagnon S, Boota AM, Fischl MA, et al. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome - a double-blind, placebo-controlled trial. N Engl J Med. 1990;323:1444–1450.
92. Ewald H, Raatz H, Boscacci R, et al. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection. Cochrane Database Syst Rev. 2015;(4):CD006150.
93. Wang LI, Liang H, Ye LI, et al. Adjunctive corticosteroids for the treatment of *Pneumocystis jiroveci* pneumonia in patients with HIV: a meta-analysis. Exp Ther Med. 2016;11:683–687.
94. Pneumonia NIoH-UoCEPfCaATfP; The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. N Engl J Med. 1990;323:1500–1504.
95. Lemiale V, Debrumetz A, Delannoy A, et al. Adjunctive steroid in HIV-negative patients with severe Pneumocystis pneumonia. Respir Res. 2013;14:87. doi: 10.1186/1465-9921-14-87.
96. Fujikura Y, Manabe T, Kawana A, et al. Adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: a systematic review and meta-analysis of observational studies. Arch Bronconeumol. 2017;53:55–61.
97. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recommendations and reports: Morbidity and Mortality Weekly Report Recommendations and Reports 2009;58:1–207; quiz CE1–4.
98. Conte JE Jr., Hollander H, Golden JA. Inhaled or reduced-dose intravenous pentamidine for *Pneumocystis carinii* pneumonia. A pilot study. Ann Intern Med. 1987;107:495–498.
99. Conte JE Jr., Chernoff D, Feigal DW Jr., et al. Intravenous or inhaled pentamidine for treating *Pneumocystis carinii* pneumonia in AIDS. A randomized trial. Ann Intern Med. 1990;113:203–209.
100. Montgomery AB, Debs RJ, Luce JM, et al. Aerosolized pentamidine as second line therapy in patients with AIDS and *Pneumocystis carinii* pneumonia. Chest. 1989;95:747–750.
101. Fulton B, Wagstaff AJ, McTavish D. Trimetrexate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of *Pneumocystis carinii* pneumonia. Drugs. 1995;49:563–576.
102. Allegra CJ, Chabner BA, Tuazon CU, et al. Trimetrexate for the treatment of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. N Engl J Med. 1987;317:978–985.
103. Paulson YJ, Gilman TM, Heseltine PN, et al. Eflornithine treatment of refractory *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Chest. 1992;101:67–74.
104. Smith D, Davies S, Nelson M, et al. *Pneumocystis carinii* pneumonia treated with eflornithine in AIDS patients resistant to conventional therapy. AIDS. 1990;4:1019–1021.
105. Nickel P, Schurmann M, Albrecht H, et al. Clindamycin-primaquine for *Pneumocystis jiroveci* pneumonia in renal transplant patients. Infection. 2014;42:981–989.
106. Noskin GA, Murphy RL, Black JR, et al. Salvage therapy with clindamycin/primaquine for *Pneumocystis carinii* pneumonia. Clin Infect Dis. 1992;14:183–188.
107. Smego RA Jr., Nagar S, Maloba B, et al. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. Arch Intern Med. 2001;161:1529–1533.
108. Freeman CD, Klutman NE, Lamp KC, et al. Relative bioavailability of atovaquone suspension when administered with an enteral nutrition supplement. Ann Pharmacother. 1998;32:1004–1007.
109. Cushion MT, Linke MJ, Ashbaugh A, et al. Echinocandin treatment of pneumocystis pneumonia in rodent models depletes cysts leaving trophic burdens that cannot transmit the infection. PLoS One. 2010;5:e8524.
110. Sun P, Tong Z. Efficacy of caspofungin, a 1,3-beta-D-glucan synthase inhibitor, on Pneumocystis carinii pneumonia in rats. Med Mycology. 2014;52:798–803.

111. Lobo ML, Esteves F, De Sousa B, et al. Therapeutic potential of caspofungin combined with trimethoprim-sulfamethoxazole for pneumocystis pneumonia: a pilot study in mice. PLoS One. 2013;8:e70619.
112. Annaloro C, Della Volpe A, Usardi P, et al. Caspofungin treatment of Pneumocystis pneumonia during conditioning for bone marrow transplantation. Eur J Clin Microbiol Infect Dis. 2006;25:52–54.
113. Beltz K, Kramm CM, Laws HJ, et al. Combined trimethoprim and caspofungin treatment for severe *Pneumocystis jiroveci* pneumonia in a five year old boy with acute lymphoblastic leukemia. Klin Padiatr. 2006;218:177–179.
114. Kamboj M, Weinstock D, Sepkowitz KA. Progression of *Pneumocystis jiroveci* pneumonia in patients receiving echinocandin therapy. Clin Infect Dis. 2006;43:e92–4.
115. Utili R, Durante-Mangoni E, Basilico C, et al. Efficacy of caspofungin addition to trimethoprim-sulfamethoxazole treatment for severe pneumocystis pneumonia in solid organ transplant recipients. Transplantation. 2007;84:685–688.
116. Hof H, Schnulle P. *Pneumocystis jiroveci* pneumonia in a patient with Wegener's granulomatosis treated efficiently with caspofungin. Mycoses. 2008;51(Suppl 1):65–67.
117. Ceballos ME, Ortega M, Andresen M, et al. Successful treatment with echinocandin in an HIV-infected individual failing first-line therapy for *Pneumocystis jirovecii* pneumonia. AIDS. 2011;25:2192–2193.
118. Yao Z, Hua Z, Jun X, et al. Lack of response in severe pneumocystis pneumonia to combined caspofungin and clindamycin treatment: a case report. Chin Med Sci J. 2011;26:246–248.
119. Kim T, Hong HL, Lee YM, et al. Is caspofungin really an effective treatment for *Pneumocystis jirovecii* pneumonia in immunocompromised patients without human immunodeficiency virus infection? Experiences at a single center and a literature review. Scand J Infect Dis. 2013;45:484–488.
120. Tu GW, Ju MJ, Xu M, et al. Combination of caspofungin and low-dose trimethoprim/sulfamethoxazole for the treatment of severe *Pneumocystis jirovecii* pneumonia in renal transplant recipients. Nephrology (Carlton, Vic). 2013;18:736–742.
121. Li H, Huang H, He H. Successful treatment of severe Pneumocystis pneumonia in an immunosuppressed patient using caspofungin combined with clindamycin: a case report and literature review. BMC Pulm Med. 2016;16:144.
122. Jiang XQ, Fang L, Mei XD, et al. *Pneumocystis jiroveci* pneumonia in patients with non-Hodgkin's lymphoma after rituximab-containing regimen: two cases of report and literature review. J Thorac Dis. 2013;5:E162–6.
123. Lee WS, Hsueh PR, Hsieh TC, et al. Caspofungin salvage therapy in *Pneumocystis jirovecii* pneumonia. J Microbiol Immunol Infect. 2016 Mar 28. pii: S1684-1182(16)30029-9. doi: 10.1016/j.jmii.2016.03.008. [Epub ahead of print].
124. Armstrong-James D, Stebbing J, John L, et al. A trial of caspofungin salvage treatment in PCP pneumonia. Thorax. 2011;66:537–538.
• **The largest case series of using caspofungin as alternative or salvage therapy among HIV-infected patients who were diagnosed with *Pneumocystis* pneumonia.**
125. Sun HY, Cheng A, Huang SH, et al. Anidulafungin for patients with *Pneumocystis carinii* pneumonia, an alternative option? Poster no. M-1297. Interscience Conference on Antimicrobial Agents and Chemotherapy; San Diego; 2015.
126. Maertens J, Cesaro S, Maschmeyer G, et al. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71:2397–2404.
127. Practice ASTIDCo, Martin SI, Fishman JA. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):272–279.
128. Phair J, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. N Engl J Med. 1990;322:161–165.
•• **This large cohort study provided the evidence that the risk of *Pneumocystis* pneumonia significantly increased in HIV-1-infected patients when their CD4 counts decreased to 200 cells/μl or less. This cut-off value is now the threshold for initiating prophylaxis for *P. jirovecii*.**
129. Kaplan JE, Hanson DL, Navin TR, et al. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. J Infect Dis. 1998;178:1126–1132.
130. Stansell JD, Osmond DH, Charlebois E, et al. Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Am J Respir Crit Care Med. 1997;155:60–66.
131. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al.; Grupo de Estudio del SIDA 04/98. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. N Engl J Med. 2001;344:159–167.
132. Mocroft A, Reiss P, Kirk O, et al.; Opportunistic Infections Project Team of the Collaboration of Observational HIVERiE. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? Clin Infect Dis. 2010;51:611–619.
133. Sidhu VK, Foisy MM, Hughes CA. Discontinuing *Pneumocystis jirovecii* pneumonia prophylaxis in HIV-infected patients with a CD4 cell count <200 cells/mm^3. Ann Pharmacother. 2015;49:1343–1348.
134. Costiniuk CT, Fergusson DA, Doucette S, et al. Discontinuation of *Pneumocystis jirovecii* pneumonia prophylaxis with CD4 count <200 cells/microL and virologic suppression: a systematic review. PLoS One. 2011;6:e28570.
135. Zellweger C, Opravil M, Bernasconi E, et al. Long-term safety of discontinuation of secondary prophylaxis against *Pneumocystis pneumonia*: prospective multicentre study. AIDS. 2004;18:2047–2053.
136. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2017. [cited 2017 Apr 24]. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
137. Ioannidis JPA, Capelleri JC, Skolnik PR, et al. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. Arch Intern Med. 1996;156:177–188.
138. Schneider MM, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. Dutch AIDS Treatment Group. J Infect Dis. 1995;171:1632–1636.
139. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Clin Infect Dis. 1999;29:775–783.
140. Ribera E, Fernandez-Sola A, Juste C, et al. Comparison of high and low doses of trimethoprim-sulfamethoxazole for primary prevention of toxoplasmic encephalitis in human immunodeficiency virus-infected patients. Clin Infect Dis. 1999;29:1461–1466.
141. Hughes WT. Use of dapsone in the prevention and treatment of *Pneumocystis carinii* pneumonia: a review. Clin Infect Dis. 1998;27:191–204.
142. El-Sadr WM, Murphy RL, Yurik RM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med. 1998;339:1889–1895.
143. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis. 1999;180:369–376.

144. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. N Engl J Med. 1992;327:1836–1841.
145. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis pneumonia* and toxoplasmosis in patients infected with HIV. Ann Intern Med. 1995;122:755–761.
146. Coker RJ, Nieman R, Mcbride M, et al. Cotrimoxazole versus dapsone-pyrimethamine for prevention of *Pneumocystis carinii* pneumonia. Lancet. 1992;340:1099.
147. Fischl MA, Dickinson GM, Lavoie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. JAMA-J Am Med Assoc. 1988;259:1185–1189.
148. Stein DS, Stevens RC, Terry D, et al. Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother. 1991;35:1705–1709.
149. Kemper CA, Tucker RM, Lang OS, et al. Low-dose dapsone prophylaxis of *Pneumocystis carinii* pneumonia in AIDS and AIDS-related complex. AIDS. 1990;4:1145–1148.
150. Cruciani M, Bertazzoni Minelli E, Mirandola M, et al. Twice-weekly dapsone for primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1 infection: efficacy, safety and pharmacokinetic data. Clin Microbiol Infect. 1996;2:30–35.
151. Blum RN, Miller LA, Gaggini LC, et al. Comparative trial of dapsone versus trimethoprim/sulfamethoxazole for primary prophylaxis of *Pneumocystis carinii* pneumonia. J Acquir Immune Defic Syndr. 1992;5:341–347.
152. Podzamczer D, Santin M, Jimenez J, et al. Thrice-weekly cotrimoxazole is better than weekly dapsone-pyrimethamine for the primary prevention of *Pneumocystis carinii* pneumonia in HIV-infected patients. AIDS. 1993;7:501–506.
153. Slavin MA, Hoy JF, Stewart K, et al. Oral dapsone versus nebulized pentamidine for *Pneumocystis carinii* pneumonia prophylaxis: an open randomized prospective trial to assess efficacy and haematological toxicity. AIDS. 1992;6:1169–1174.
154. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. Am J Med. 1993;95:573–583.
155. Salmon-Ceron D, Fontbonne A, Saba J, et al. Lower survival in AIDS patients receiving dapsone compared with aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia. Study Group. J Infect Dis. 1995;172:656–664.
156. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. N Engl J Med. 1993;328:1514–1520.
157. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. Clin Infect Dis. 1995;20:531–541.
158. Pretet S, Salmon D, Rousseau F, et al. Long-term results of monthly inhaled pentamidine as primary prophylaxis of *Pneumocystis carinii* pneumonia in HIV-infected patients. Am J Med. 1993;94:35–40.
159. Konishi M, Yoshimoto E, Takahashi K, et al. Aerosolized pentamidine prophylaxis against AIDS-related *Pneumocystis carinii* pneumonia and its short- and long-term effects on pulmonary function in the Japanese. J Infect Chemother. 2003;9:178–182.
160. Jensen BN, Nielsen TL, Backer V, et al. Aerosolized pentamidine for primary prophylaxis of *Pneumocystis carinii* pneumonia: a controlled, randomized trial. J Acquir Immune Defic Syndr. 1993;6:472–477.
161. Lidman C, Tynell E, Berglund O, et al. Aerosolized pentamidine versus i.v. pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia. Infection. 1993;21:146–149.
162. May T, Beuscart C, Reynes J, et al. Trimethoprim-sulfamethoxazole versus aerosolized pentamidine for primary prophylaxis of *Pneumocystis carinii* pneumonia: a prospective, randomized, controlled clinical trial. LFPMI study group. Ligue Francaise de Prevention des Maladies Infectieuses. J Acquir Immune Defic Syndr. 1994;7:457–462.
163. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome - AIDS Clinical-Trials Group Protocol-021. N Engl J Med. 1992;327:1842–1848.
164. Mallolas J, Zamora L, Gatell JM, et al. Primary prophylaxis for *Pneumocystis carinii* pneumonia: a randomized trial comparing cotrimoxazole, aerosolized pentamidine and dapsone plus pyrimethamine. AIDS. 1993;7:59–64.
165. Antinori A, Murri R, Ammassari A, et al. Aerosolized pentamidine, cotrimoxazole and dapsone-pyrimethamine for primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. AIDS. 1995;9:1343–1350.
166. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of 3 antipneumocystis agents in patients with advanced human-immunodeficiency-virus infection. N Engl J Med. 1995;332:693–699.
167. Warnock AC, Rimland D. Comparison of trimethoprim-sulfamethoxazole, dapsone, and pentamidine in the prophylaxis of *Pneumocystis carinii* pneumonia. Pharmacotherapy. 1996;16:1030–1038.
168. Cushion MT, Ashbaugh A, Lynch K, et al. Prevention of Pneumocystis pneumonia (PCP) by the novel echinocandin, Cd101. Interscience Conference on Antimicrobial Agents and Chemotherapy; Boston; 2016.
169. Nazir HF, Elshinawy M, AlRawas A, et al. Efficacy and safety of dapsone versus trimethoprim/sulfamethoxazol for *Pneumocystis jiroveci* prophylaxis in children with acute lymphoblastic leukemia with a background of ethnic neutropenia. J Pediatr Hematol Oncol. 2017;39:203–208.
170. Wuerz TC, Bow EJ, Seftel MD. Potential consequences of essential drug shortages in Canada: brain abscess due to *Nocardia farcinica* associated with dapsone prophylaxis for *Pneumocystis jirovecii* pneumonia. Can J Infect Dis Med Microbiol. 2013;24:159–161.
171. Vyas PM, Roychowdhury S, Khan FD, et al. Enzyme-mediated protein haptenation of dapsone and sulfamethoxazole in human keratinocytes: I. Expression and role of cytochromes P450. J Pharm Exp Ther. 2006;319:488–496.
172. Berg PA, Daniel PT. Co-trimoxazole-induced hepatic injury–an analysis of cases with hypersensitivity-like reactions. Infection. 1987;15 (Suppl 5):S259–S264.
173. Smith CL, Brown I, Torraca BM. Acetylator status and tolerance of high-dose trimethoprim-sulfamethoxazole therapy among patients infected with human immunodeficiency virus. Clin Infect Dis. 1997;25:1477–1478.
174. Lee BL, Delahunty T, Safrin S. The hydroxylamine of sulfamethoxazole and adverse reactions in patients with acquired immunodeficiency syndrome. Clin Pharmacol Ther. 1994;56:184–189.
175. Schwarz UI. Clinical relevance of genetic polymorphisms in the human CYP2C9 gene. Eur J Clin Invest. 2003;33(Suppl 2):23–30.
176. Boyce TG, Smidt RG, Edmonson MB. Fever as an adverse reaction to oral trimethoprim-sulfamethoxazole therapy. Pediatr Infect Dis J. 1992;11:772–773.
177. Kelly JW, Dooley DP, Lattuada CP, et al. A severe, unusual reaction to trimethoprim-sulfamethoxazole in patients infected with human immunodeficiency virus. Clin Infect Dis. 1992;14:1034–1039.
178. Kalanadhabhatta V, Muppidi D, Sahni H, et al. Successful oral desensitization to trimethoprim-sulfamethoxazole in acquired immune deficiency syndrome. Ann Allergy Asthma Immunol. 1996;77:394–400.

179. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. J Allergy Clin Immunol. 1994;93:1001–1005.
180. Mitsuyasu R, Groopman J, Volberding P. Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. N Engl J Med. 1983;308:1535–1536.
181. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematology Am Soc Hematol Educ Program. 2009;1:153–158.
182. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. J Infect Dis. 1994;170:912–917.
183. Lawson DH, Paice BJ. Adverse reactions to trimethoprim-sulfamethoxazole. Rev Infect Dis. 1982;4:429–433.
184. Hellden A, Bergman U, Engstrom Hellgren K, et al. Fluconazole-induced intoxication with phenytoin in a patient with ultra-high activity of CYP2C9. Eur J Clin Pharmacol. 2010;66:791–795.
185. Mitra AK, Thummel KE, Kalhorn TF, et al. Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. Clin Pharmacol Ther. 1996;59:332–340.
186. Bartels RH, van der Spek JA, Oosten HR. Acute pancreatitis due to sulfamethoxazole-trimethoprim. South Med J. 1992;85:1006–1007.
187. Takaichi K, Takemoto F, Ubara Y, et al. Analysis of factors causing hyperkalemia. Intern Med. 2007;46:823–829.
188. Perazella MA, Mahnensmith RL. Trimethoprim-sulfamethoxazole: hyperkalemia is an important complication regardless of dose. Clin Nephrol. 1996;46:187–192.
189. Greenberg S, Reiser IW, Chou SY, et al. Trimethoprim-sulfamethoxazole induces reversible hyperkalemia. Ann Intern Med. 1993;119:291–295.
190. Ahn YH, Goldman JM. Trimethoprim-sulfamethoxazole and hyponatremia. Ann Intern Med. 1985;103:161–162.
191. Fraser TN, Avellaneda AA, Graviss EA, et al. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012;67:1271–1277.
192. Lee KY, Huang CH, Tang HJ, et al. Acute psychosis related to use of trimethoprim/sulfamethoxazole in the treatment of HIV-infected patients with *Pneumocystis jirovecii* pneumonia: a multicentre, retrospective study. J Antimicrob Chemother. 2012;67:2749–2754.
• **The first multicenter study that revealed a dose-response association with acute psychosis related to the use of TMP-SMX.**
193. Patterson RG, Couchenour RL. Trimethoprim-sulfamethoxazole-induced tremor in an immunocompetent patients. Pharmacotherapy. 1999;19:1456–1458.
194. Slavik RS, Rybak MJ, Lerner SA. Trimethoprim/sulfamethoxazole-induced tremor in a patient with AIDS. Ann Pharmacother. 1998;32:189–192.
195. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. J Dermatol. 2005;32:883–889.
196. Tingle MD, Coleman MD, Park BK. An investigation of the role of metabolism in dapsone-induced methaemoglobinaemia using a two compartment in vitro test system. Br J Clin Pharmacol. 1990;30:829–838.
197. Ashurst JV, Wasson MN, Hauger W, et al. Pathophysiologic mechanisms, diagnosis, and management of dapsone-induced methemoglobinemia. J Am Osteopath Assoc. 2010;110:16–20.
198. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia. Treatment issues. Drug Saf. 1996;14:394–405.
199. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med. 1999;34:646–656.
200. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124:588–597.
201. Wang N, Parimi L, Liu H, et al. A review on dapsone hypersensitivity syndrome among Chinese patients with an emphasis on preventing adverse drug reactions with genetic testing. Am J Trop Med Hyg. 2017.
202. Rosenberg DM, McCarthy W, Slavinsky J, et al. Atovaquone suspension for treatment of *Pneumocystis carinii* pneumonia in HIV-infected patients. AIDS. 2001;15:211–214.
203. Bolchoz LJ, Budinsky RA, McMillan DC, et al. Primaquine-induced hemolytic anemia: formation and hemotoxicity of the arylhydroxylamine metabolite 6-methoxy-8-hydroxylaminoquinoline. J Pharmacol Exp Ther. 2001;297:509–515.
204. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf. 2010;33:713–726.
205. Fryauff DJ, Baird JK, Basri H, et al. Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. Lancet. 1995;346:1190–1193.
206. Clayman CB, Arnold J, Hockwald RS, et al. Toxicity of primaquine in Caucasians. J Am Med Assoc. 1952;149:1563–1568.
207. Moole H, Ahmed Z, Saxena N, et al. Oral clindamycin causing acute cholestatic hepatitis without ductopenia: a brief review of idiosyncratic drug-induced liver injury and a case report. J Community Hosp Intern Med Perspect. 2015;5:28746.
208. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354:731–739.
209. Smeets TJ, Jessurun N, Harmark L, et al. Clindamycin-induced acute generalised exanthematous pustulosis: five cases and a review of the literature. Neth J Med. 2016;74:421–428.
210. Miller Quidley A, Bookstaver PB, Gainey AB, et al. Fatal clindamycin-induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Pharmacotherapy. 2012;32:e387–92.
211. Yang Y, Chen S, Yang F, et al. HLA-B*51:01 is strongly associated with clindamycin-related cutaneous adverse drug reactions. Pharmacogenomics J. 2016 Aug 16. doi: 10.1038/tpj.2016.61. [Epub ahead of print].
212. Andres E, Maloisel F. Groupe d'Etude des agranulocytoses medicamenteuses des Hopitaux Universitaires de S. [Idiosyncratic drug-induced agranulocytosis]. Rev Med Interne. 2006;27:209–214.
213. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007;146:657–665.
214. Reese JA, Li X, Hauben M, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood. 2010;116:2127–2133.
215. Morales MP, Carvallo AP, Espinosa KA, et al. A young man with myelosuppression caused by clindamycin: a case report. J Med Case Rep. 2014;8:7.
216. Wan H, Hu Z, Wang J, et al. Clindamycin-induced kidney diseases: a retrospective analysis of 50 patients. Intern Med. 2016;55:1433–1437.
217. Wistrom J, Norrby SR, Myhre EB, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother. 2001;47:43–50.
218. Bartlett JG. *Clostridium difficile*: clinical considerations. Rev Infect Dis. 1990;12(Suppl 2):S243–51.
219. Anand A, Bashey B, Mir T, et al. Epidemiology, clinical manifestations, and outcome of *Clostridium difficile*-associated diarrhea. Am J Gastroenterol. 1994;89:519–523.
220. Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. Ann Intern Med. 1974;81:429–433.
221. Kyne L, Hamel MB, Polavaram R, et al. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis. 2002;34:346–353.
222. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431–455.
223. Sands M, Kron MA, Brown RB. Pentamidine: a review. Rev Infect Dis. 1985;7:625–634.
224. Bolognia JL. Cutaneous ulceration: an unusual complication of intravenous pentamidine therapy. Dermatologica. 1991;183:221–224.

225. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. DICP. 1991;25:1171–1174.
226. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. Am J Med. 1989;87:260–263.
227. Kleyman TR, Roberts C, Ling BN. A mechanism for pentamidine-induced hyperkalemia: inhibition of distal nephron sodium transport. Ann Intern Med. 1995;122:103–106.
228. Assan R, Perronne C, Assan D, et al. Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. Diabetes Care. 1995;18:47–55.
229. Murphey SA, Josephs AS. Acute pancreatitis associated with pentamidine therapy. Arch Intern Med. 1981;141:56–58.
230. Harrison KS, Laube BL. Bronchodilator pretreatment improves aerosol deposition uniformity in HIV-positive patients who cough while inhaling aerosolized pentamidine. Chest. 1994;106:421–426.
231. Stone EA, Fung HB, Kirschenbaum HL. Caspofungin: an echinocandin antifungal agent. Clin Ther. 2002;24:351–77.
232. Betts RF, Nucci M, Talwar D, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis. 2009;48:1676–1684.
233. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. Drugs. 2011;71:11–41.
234. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One. 2009;4:e5575.
•• **A multicenter randomized trial evaluated optimal timing of cART initiation in patients with AIDS-related opportunistic infections, and the authors concluded that early cART led to less AIDS progression/death with no increase in adverse events or loss of virology responses than deferred cART.**
235. Thoden J, Potthoff A, Bogner JR, et al. Therapy and prophylaxis of opportunistic infections in HIV-infected patients: a guideline by the German and Austrian AIDS societies (DAIG/OAG) (AWMF 055/066). Infection. 2013;41(Suppl 2):S91–115.
236. Miller RF, Allen E, Copas A, et al. Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. Thorax. 2006;61:716–721.
237. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 2010;10:791–802.
238. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8:516–523.
239. Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. PLoS One. 2010;5:e11416.
240. Jagannathan P, Davis E, Jacobson M, et al. Life-threatening immune reconstitution inflammatory syndrome after *Pneumocystis pneumonia*: a cautionary case series. AIDS. 2009;23:1794–1796.
241. Kolditz M, Halank M, Bandt D, et al. Early recurrence of *Pneumocystis jiroveci* pneumonia in two HIV-infected patients: linking infection relapse and immune reconstitution syndrome. Respirology. 2009;14:910–912.
242. Pepper DJ, Rebe K, Morroni C, et al. Clinical deterioration during antitubercular treatment at a district hospital in South Africa: the importance of drug resistance and AIDS defining illnesses. PLoS One. 2009;4:e4520.
243. Avino LJ, Naylor SM, Roecker AM. *Pneumocystis jirovecii* pneumonia in the non-HIV-infected population. Ann Pharmacother. 2016;50:673–679.
244. Bienvenu AL, Traore K, Plekhanova I, et al. Pneumocystis pneumonia suspected cases in 604 non-HIV and HIV patients. Int J Infect Dis. 2016;46:11–17.

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RESEARCH ARTICLE

Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan

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¶ Membership of the Taiwan HIV Study Group is provided in the Acknowledgments.
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OPEN ACCESS

Citation: Lee Y-L, Lin K-Y, Cheng C-Y, Li C-W, Yang C-J, Tsai M-S, et al. (2017) Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS ONE 12(10): e0186338. https://doi.org/10.1371/journal.pone.0186338

Editor: Yury E Khudyakov, Centers for Disease Control and Prevention, UNITED STATES

Received: June 11, 2017

Accepted: October 1, 2017

Published: October 16, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: Taiwan Centers for Disease Control (Award Number: MOHW103-CDC-C-114-000405), Recipient: Chien-Ching Hung. The funding source played no role in study design and conduct, data collection, analysis or interpretation, writing of the manuscript, or the decision to submit it for publication.

Abstract

Objectives

The study aimed to describe the seroprevalence of hepatitis A virus (HAV) in HIV-positive adult patients in Taiwan between 2012 and 2016 and to examine the evolution of HAV seroprevalence between 2004–2007 and 2012–2016.

Methods

Clinical information and data of anti-HAV antibody results were collected from 2,860 antiretroviral-naïve HIV-positive Taiwanese aged 18 years or older who initiated combination antiretroviral therapy at 11 hospitals around Taiwan between 2012 and 2016 (2012–2016 cohort). A multivariate logistic regression model was applied to identify independent variables associated with HAV seropositivity. Comparisons of HAV seroprevalences and associated clinical characteristics were made between this 2012–2016 cohort and a previous cohort of 1580 HIV-positive patients in 2004–2007 (2004–2007 cohort).

Competing interests: The authors have declared that no competing interests exist.

Results

Of the 2,860 HIV-positive patients between 2012 and 2016, the overall HAV seropositivity rate was 21.2% (605/2860), which was independently associated with an older age (adjusted odds ratio [AOR], per 1-year increase, 1.13; 95% confidence interval [95% CI], 1.11–1.15) and co-infection with hepatitis B virus (AOR 1.44; 95% CI, 1.08–1.93). Residence in southern Taiwan (AOR 0.49; 95% CI, 0.34–0.72) was inversely associated with HAV seropositivity. The overall HAV seroprevalence in the 2012–2016 cohort was significantly lower than that in the 2004–2007 cohort (21.2% vs 60.9%, p<0.01). The decreases of HAV seropositivity rate were observed in nearly every age-matched group, which suggested the cohort effect on HAV seroepidemiology. However, among individuals aged 25 years or younger, the HAV seropositivity rate increased from 3.8% (2/52) in the 2004–2007 cohort to 8.5% (50/587) in the 2012–2016 cohort, with 95.4% (560/587) being MSM in this age group of the latter cohort.

Conclusions

HAV seroprevalence has decreased with time among HIV-positive adults in Taiwan. The cohort effect has increased the number of young HIV-positive patients that are susceptible to HAV infection in a country without nationwide childhood vaccination program against HAV.

Introduction

Hepatitis A virus (HAV) is transmitted through the fecal-oral route either by direct contact with an infectious person or by ingestion of contaminated food or water [1]. According to the World Health Organization (WHO) estimation, HAV infection caused 3.7 million illnesses and 28,000 deaths in 2010 with differences observed in regions of different endemicities around the world [2]. In the developing countries in Asia, Africa, Central and South Americas, and Oceania, most HAV infections occur in childhood and the seroprevalence before teenage ranges from 63% to 94% [3, 4]. In contrast, the overall HAV seroprevalence is less than 15% among the adolescents in the North America, Europe, and Australia [5].

The correlation between the HIV and HAV infection varies according to the local HIV and HAV epidemiology [6]. In the countries of high HAV endemicity, no significant difference of HAV seroprevalence was observed between HIV-positive and HIV-negative individuals [7]. In contrast, HIV-positive patients usually have a higher HAV seroprevalence than their HIV-negative counterparts in the developed countries of low HAV endemicity [8, 9]. Certain sexual behaviors associated with risk groups for HIV transmission may also increase the risk for HAV transmission, including oral-anal sex [10] and percutaneous exposure to contaminated illicit drugs or injecting equipment [11]. Those risky behaviors may facilitate the emergence of acute hepatitis A outbreaks in countries of low HAV endemicity because of an increasing number of susceptible hosts. For example, injecting drug users (IDUs) in countries with better health and hygiene conditions usually have higher HAV seroprevalence than the general population [12–15], and acute HAV infection among IDUs may be associated with a higher fatality rate due to co-infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) [11]. On the other hand, outbreaks of acute HAV infection among men who have sex with men (MSM) emerged in recent years across several European countries and the UK [16–18]. The outbreaks were linked to risky sexual contacts and increased international travel and susceptible hosts, especially in young adults with low adherence to recommended HAV vaccination [6, 17].

Taiwan used to be endemic for HAV infection; seroepidemiologic studies in the 1980s revealed that more than 90% of Taiwanese became HAV-seropositive by the age of 20 years and the rates increased with age [19–21]. With the improvement of sanitation and hygiene and implementation of vaccination program for children in counties of high endemicity for HAV infection, HAV seroprevalence has significantly declined and less than 10% of teenagers were positive for anti-HAV antibodies in 1998 [22]. Among the HIV-positive patients, a study by Sun et al between 2004 and 2007, when an outbreak of HIV infection was occurring among IDUs in Taiwan, revealed a higher HAV seroprevalence (60.9%) among HIV-positive patients than HIV-negative individuals seeking health check-ups (48.0%); and injection drug use and age were identified as the independent factors associated with HAV seropositivity [9].

However, the HIV epidemic has significantly changed in recent years in Taiwan. The proportion of IDUs among the newly diagnosed HIV-positive patients declined rapidly with the successful, sustained implementation of harm reduction program since 2004–2005 [23–25]; instead, the number of young HIV-positive MSM increased steadily and MSM has again become the major risk group for HIV transmission. The increasing number of susceptible host who have a low adherence to the recommendations of HAV vaccination has laid the fertile ground for an outbreak of acute hepatitis A to occur in Taiwan in June 2015 [26–28]. Furthermore, the outbreak strain in Taiwan appeared to be genetically linked to the strain that caused the recent outbreak of acute hepatitis A in Europe [17].

In this study, we aimed to examine the evolution of HAV seroepidemiology and identify the associated factors with HAV infection among HIV-positive Taiwanese patients in recent years to help inform the HAV vaccination policy.

Patients and methods

Study setting and population

This retrospective cohort study was conducted at 11 major designated hospitals for HIV care around Taiwan, where HIV care including combination antiretroviral therapy (cART) and monitoring of CD4 and plasma HIV RNA load (PVL) has been provided free-of-charge [29]. Between 1 June, 2012 and 31 May, 2016, all patients who were aged 18 years or greater and initiated cART were included in this study (2012–2016 cohort). A case record form was used to collect information on the demographic and clinical characteristics of the patients at baseline and during follow-up, which included birth date, sex, route of HIV transmission, serologies of viral hepatitis and syphilis, CD4, and PVL. Patients were divided into four risk groups according to the routes of HIV transmission including MSM, IDUs, heterosexual contact, and unknown status. The study was approved by the Research Ethics Committee of National Taiwan University Hospital [201003112R] and Far Eastern Memorial Hospital [105040-F], Medical Ethics and Institutional Review Board of Taoyuan General Hospital [TYGH103011], and Institutional Review Boards of Tri-Service General Hospital [1-105-05-057], National Taiwan University Hospital Hsin-Chu Branch [105-017-F], Taichung Veterans General Hospital [CF16114B], Chung Shan Medical University Hospital [CS14034], Changhua Christian Hospital [160408], Chia-Yi Christian Hospital [105034], National Cheng Kung University Hospital [B-BR-105-038], and Chi Mei Medical Center [10505–002]. The informed consent was waived.

HAV vaccination was not included in routine vaccination schedule for toddlers in Taiwan. Since 1995, HAV vaccination was only provided to children in 30 indigenous townships and 19 non-indigenous townships in order to control HAV infection in counties of high endemicities of HAV infection in Taiwan. However, the vaccination program covered only 2% of the total population in Taiwan. The study sites participating in this study did not include hospitals

located in those townships that were covered by the HAV vaccination program. It was only until one year after the onset of the recent outbreak of acute hepatitis A that Taiwan Centers for Disease Control (CDC) started to implement free-of-charge 1-dose HAV vaccination program in October 2016 that aimed to target those testing negative for anti-HAV antibody who were aged 40 years or less, those who had close contacts with individuals receiving the diagnosis of acute hepatitis A, and those who had sexually transmitted infections.

A previous retrospective cohort study conducted at two designated hospitals for HIV care by Sun et al was compared to examine the evolution of HAV seroprevalence among HIV-positive patients in Taiwan [9]. The previous cohort study was performed between 2004 and 2007 (2004–2007 cohort), which included 1580 HIV-positive persons seeking HIV care and 2581 HIV-negative controls seeking health check-up at the National Taiwan University Hospital, Taipei (northern Taiwan) and National Taiwan University Hospital Yun-Lin Branch (central Taiwan). In this 2004–2007 cohort, the HIV-positive patients included 658 (41.6%) MSM, 304 (19.2%) heterosexuals, and 577 (36.5%) IDU.

Laboratory investigations

Testing for anti-HIV antibodies, Western blot for confirmation of HIV infection, CD4 count and PVL and antibodies for HBV and HCV were performed by each participating hospital with the use of certified diagnostic kits [29]. Data on baseline CD4 count and PVL, and baseline anti-HAV antibody, anti-HCV antibody, hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs antibody), anti-hepatitis B core antibody (anti-HBc antibody), and the rapid plasma reagin (RPR) for syphilis were collected locally at each participating hospital, which were then pooled and analyzed at the National Taiwan University Hospital, Taipei. HBV infection was defined as patients to have positive result of either HBsAg or anti-HBc antibody or both.

Statistical analysis

All statistical analyses were performed with the use of SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the Chi-square or Fisher's exact test, whereas non-categorical variables were compared using the Mann-Whitney U-test. The variables with p-value <0.2 in univariate analysis were allowed to enter into multiple logistic regression model. A multiple logistic regression model was built to identify independent variables associated with anti-HAV seropositivity. All tests were two tailed and a p-value of <0.05 was considered significant.

Results

In the 2012–2016 cohort, a total of 2,860 HIV-positive patients were included for analysis, which included 2,229 (77.9%) MSM, 437 (15.3%) IDUs, 166 (5.8%) heterosexuals, and 28 (1.0%) others (Table 1). MSM (mean age, 30.5 ± 7.7 years) were significantly younger than heterosexuals (40.0 ± 12.5 years) and IDUs (41.8 ± 7.7 years) (both comparisons, $p<0.001$). With regard to specific age groups, 54.9% of MSM were aged less than 30 years, while only 24.1% of heterosexuals and 2.8% of IDUs were aged less than 30 years (both comparisons, $p<0.001$). The overall HAV seroprevalence was 21.2% and the rate was significantly lower among MSM (16.7%) than heterosexuals (37.3%) and IDU (37.1%) (both comparisons, $p<0.001$). In our study, most of the included patients lived in northern Taiwan (70.4%), and the composition of risk groups for HIV infection, including MSM, heterosexuals and IDUs, was different across the different regions in Taiwan. For example, less MSM (154/316, 48.7%) and more IDUs (123/316, 38.9%) were included in central Taiwan than northern Taiwan (MSM, 81.8% [1647/

Table 1. Demographic and clinical characteristics of HIV-positive patients with different routes of HIV transmission, 2012–2016.

	All HIV-positive persons	Men who have sex with men	Heterosexuals	Injecting drug users
Number, n =	2860	2229	166	437
Male sex, n (%)	2730 (95.5)	2229 (100)	107 (64.5)	368 (84.2)
Age, mean ± SD, years[a]	32.9 ± 9.3	30.5 ± 7.7	40.0 ± 12.5[c]	41.8 ± 7.7[c]
Age group, years[a]				
18–20, n (%)	78 (2.7)	75 (3.4)	3 (1.8)	0 (0.0)
21–25	509 (17.8)	485 (21.8)	16 (9.6)	2 (0.5)
26–30	696 (24.3)	661 (29.7)	21 (12.7)	10 (2.3)
31–35	606 (21.2)	497 (22.3)	29 (17.5)	75 (17.2)
36–40	382 (13.4)	229 (10.3)	24 (14.5)	124 (28.4)
41–45	255 (8.9)	153 (6.9)	12 (7.2)	88 (20.1)
46–50	173 (6.0)	84 (3.8)	24 (14.5)	64 (14.6)
51–55	86 (3.0)	25 (1.1)	14 (8.4)	46 (10.5)
56–60	55 (1.9)	15 (0.7)	11 (6.6)	26 (5.9)
>60	20 (0.7)	5 (0.2)	12 (7.2)	2 (0.5)
Residence in Taiwan[a], n (%)				
Northern	2013 (70.4)	1647 (73.9)	75 (45.2)	276 (63.2)
Central	316 (11.0)	154 (6.9)	29 (17.5)	123 (28.1)
Southern	531 (18.6)	428 (19.2)	62 (37.3)	38 (8.7)
Cohort				
Diagnosed before 2015/5/31	2118 (74.1)	1642 (73.7)	128 (77.1)	327 (74.8)
Diagnosed after 2015/6/1	742 (25.9)	587 (26.3)	38 (22.9)	110 (25.2)
Median CD4,[a] (range), cells/μl	272 (0–2217)	275 (0–2217)	216 (1–1085)[c]	287 (0–917)
Median plasma HIV RNA load,[a] (range), log10, copies/ml	4.8 (1.3–7.6)	4.8 (1.43–7.6)	4.7 (1.6–6.6)	4.4 (1.3–6.7)[c]
Positive anti-HAV antibody, n (%)	605 (21.2)	372 (16.7)	62 (37.3)[c]	162 (37.1)[c]
Positive HBsAg, n/N[b] (%)	309/2851 (10.8)	200/2221 (9.0)	24/165 (14.5)[c]	82/437 (18.8)[c]
Positive anti-HBs antibody, n/N[b] (%)	1083/2051 (52.8)	927/1720 (53.9)	64/135 (47.4)	86/179 (48.0)
Positive anti-HBc antibody, n/N[b] (%)	603/1937 (31.1)	430/1629 (26.4)	50/123 (40.7)[c]	119/170 (70.0)[c]
Positive anti-HCV antibody, n/N[b] (%)	511/2849 (17.9)	78/2219 (3.5)	20/166 (12.0)[c]	412/436 (94.5)[c]

Abbreviations: anti-HAV, anti-hepatitis A virus; anti-HBs, anti-hepatitis B surface; anti-HBc, anti-hepatitis B core; anti-HCV, anti-hepatitis C virus; HBsAg, hepatitis B surface antigen

[a] $p<0.001$ for comparisons among men who have sex with men (MSM), heterosexuals, and injecting drug users (IDUs); between MSM and heterosexuals; between MSM and IDUs; and between heterosexuals and IDUs.

[b] n/N = number of patients with positive test results/number of patients with test results.

[c] Compared with MSM, $p<0.05$.

https://doi.org/10.1371/journal.pone.0186338.t001

2013]; and IDUs, 13.7% [276/2013]) and southern Taiwan (MSM, 80.6% [428/531]; and IDUs 7.1% [38/531]) (both comparisons, $p<0.001$, Table 1).

For co-infections with other viral hepatitis, MSM had statistically significantly lower seropositive rates of HBsAg (9.0%) and anti-HBc antibody (26.4%) than heterosexuals and IDUs, and higher percentages of positive anti-HBs antibodies than non-MSM groups (53.9% vs 47.7%, $p = 0.053$). In contrast, IDUs had the highest rate of HCV seropositivity (94.5%), compared with heterosexuals (12.0%) and MSM (3.5%) (Table 1).

In the univariate analysis (Table 2), factors associated with anti-HAV positivity in the 2012–2016 cohort included an older age, female sex, higher PVL, residence in regions other than southern Taiwan, non-MSM, HBV infection as indicated by presence of either HBsAg,

Table 2. Factors associated with positive anti-HAV antibody in the 2012–2016 cohort.

	Anti-HAV antibody		Univariate			Multivariate		
	Negative(n = 2255)	Positive(n = 605)	OR	95% CI	p	OR	95% CI	P
Age, mean ± SD, years	31.1 ± 8.0	39.3 ± 10.8	-	-	<0.01	1.13	1.11–1.15	<0.01
Male sex, n (%)	2171 (96.3)	559 (92.4)	0.47	0.32–0.68	<0.01	0.59	0.28–1.23	0.29
CD4, mean ± SD, cells/μl	287.1 ± 188.0	277.6 ± 199.5	-	-	0.28	-	-	-
Plasma HIV RNA load, mean ± SD, log_{10} copies/ml	4.8 ± 0.8	4.7 ± 0.8	-	-	0.01	0.95	0.83–1.09	0.46
Residence in Taiwan, n (%)					<0.01			
Northern	1579 (70.0)	434 (71.7)	Referent			Referent		
Central	216 (9.6)	100 (16.5)	1.68	1.30–2.18	<0.01	0.75	0.48–1.16	0.19
Southern	460 (20.4)	71 (11.7)	0.56	0.43–0.74	<0.01	0.49	0.34–0.72	<0.01
Risk group, n (%)					<0.01			
MSM	1857 (82.3)	372 (61.5)	Referent			Referent		
Heterosexuals	104 (4.6)	62 (10.2)	2.94	2.35–3.68	<0.01	1.49	0.83–2.66	0.18
IDUs	275 (12.2)	162 (26.8)	2.98	2.13–4.15	<0.01	1.44	0.75–2.75	0.27
Others	19 (0.8)	9 (1.5)	2.37	1.06–5.27	0.03	2.861	0.76–10.85	0.12
HBV infection[a], n (%)	427/1559 (27.4)	220/371 (59.3)	3.86	3.05–4.89	<0.01	1.44	1.08–1.93	0.01
Anti-HBs-positive, n (%)	864/1652 (52.3)	219/399 (54.9)	1.11	0.89–1.38	0.35	-	-	-
Anti-HCV-positive, n (%)	325/2249 (14.5)	186/600 (31.0)	2.66	2.16–3.28	<0.01	1.523	0.90–2.59	0.12
RPR-positive, n (%)	404/1622 (24.9)	87/391 (22.3)	0.86	0.66–1.12	0.27	-	-	-

Abbreviations: 95% CI, 95% confidence interval; anti-HAV, anti-hepatitis A virus; anti-HBs, anti-hepatitis B surface; anti-HBc, anti-hepatitis B core; anti-HCV, anti-hepatitis C virus; HBsAg, hepatitis B surface antigen; IDUs, injecting drug users; MSM, men who have sex with men; OR, odds ratio; RPR, rapid plasma reagin; SD, standard deviation.

[a]HBV infection indicates presence of either HBsAg, anti-HBc or both.

https://doi.org/10.1371/journal.pone.0186338.t002

anti-HBc or both) and HCV infection (Table 2, all $p<0.05$). No correlation was found between the results of anti-HBs antibody and RPR with anti-HAV positivity.

In the multivariate analysis (Table 2), an older age (adjusted odds ratio [AOR], per 1-year increase, 1.13; 95% confidence interval [95% CI], 1.11–1.15) and HBV infection (AOR 1.40; 95% CI, 1.03–1.90) were independently associated with HAV seropositivity. On the other hand, residents in southern Taiwan were less likely to have positive anti-HAV antibody than those in northern Taiwan (AOR 0.49; 95% CI, 0.34–0.72). To explore the association between HAV seropositivity and HBV infection, we performed a subgroup analysis by dividing our cohort into two groups including the sexually-transmitted group (heterosexuals and MSMs) (S1 Table) and the percutaneous exposure (IDUs) group (S2 Table). In the multivariate analysis, the statistically significant association between HAV and HBV infection was still noted in the sexually-transmitted group (AOR 1.38; 95% CI, 1.06–1.78), but not in the percutaneous exposure group (AOR 1.43; 95% CI, 0.62–3.30).

We further examined the impact of geographic region and risk group for HIV transmission on the HAV seroprevalence in different age groups. We found that patients in central Taiwan after the age of 40–45 years and those in northern Taiwan before the age of 30–35 years had higher HAV seroprevalence than the other two regions (Fig 1). HAV seroprevalence among IDUs in central and southern Taiwan was 48.7% and 52.6%, respectively, which was significantly higher than that of northern Taiwan (29.7%). Heterosexuals in central Taiwan had higher HAV seroprevalence (55.2%) than those in northern Taiwan (34.7%) and southern Taiwan (32.3%). Conversely, MSM in northern Taiwan (19.6%) had the highest HAV seroprevalence followed by those in central Taiwan (12.3%) and those in southern Taiwan (7.2%). The higher HAV seroprevalence in the young cohort in northern Taiwan was attributed to higher

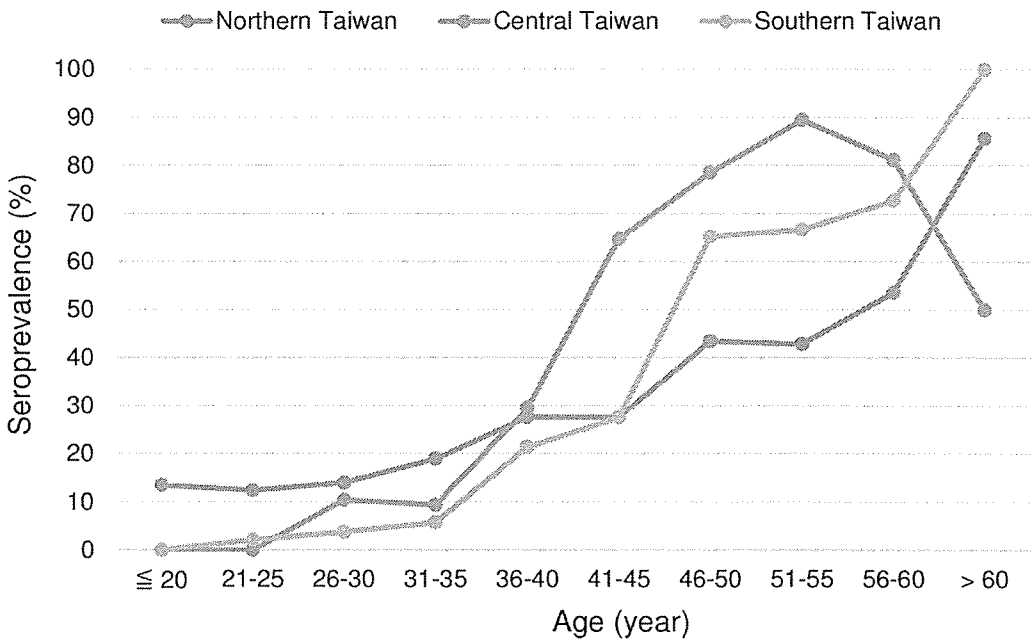

Fig 1. Comparisons of hepatitis A virus seroprevalence according to different regions in Taiwan.

https://doi.org/10.1371/journal.pone.0186338.g001

HAV seroprevalence among MSM (S1 Fig). In contrast, the higher HAV seroprevalence in central Taiwan was related to higher HAV seropositivity among the older IDUs and heterosexuals (S2 and S3 Figs).

In order to investigate the evolution of HAV seroprevalence, we compared the current 2012–2016 cohort to the 2004–2007 cohort [9]. HIV-positive patients in the 2012–2016 cohort were significantly younger than those in the 2004–2007 cohort (mean age, 32.9 vs. 40.7 years, $p<0.05$). The proportion of patients aged less than 25 years increased from 3.3% (52/1580) in the 2004–2007 cohort to 20.5% (587/2860) in the 2012–2016 cohort. Most (95.4%, 560/587) of the young patients in the 2012–2016 cohort were MSM (Table 1). In contrast, the proportion of IDUs declined from 36.5% (577/1580) in the 2004–2007 cohort to 15.3% (437/2860) in the 2012–2016 cohort.

Although the HAV seroprevalence increased with age in both cohorts, the overall HAV seroprevalence of the 2012–2016 cohort (21.5%) was significantly lower than that of the 2004–2007 cohort (60.9%, $p<0.05$). Two diverse trends, however, were observed for the evolution of age-specific seroprevalence. Patients aged less than 25 years had a higher HAV seroprevalence in the 2012–2016 cohort than those in the 2004–2007 cohort; in the rest of specific age groups, a parallel decline of HAV seroprevalence was observed from the 2004–2007 cohort to the 2012–2016 cohort (all comparisons between the age-matched groups, $p<0.001$, Fig 2). For subgroup analysis of patients in different risk groups for HIV transmission, two different trends of HAV seroprevalence were also found in MSM and heterosexuals (S4 and S5 Figs). There were only 2 HIV-positive IDUs aged less than 25 years in the 2012–2016 cohort and the number was too small for comparison (S6 Fig). When the 2012–2016 cohort was divided into two groups including those before or after the recent outbreak of acute hepatitis A in mid-2015, a higher HAV seroprevalence was found among the individuals aged 30 years or younger who were included after June 2015 (Fig 3). Different from the findings in the 2004–2007 cohort [9], young MSM was the most at-risk population for HAV infection in the recent outbreak in Taiwan.

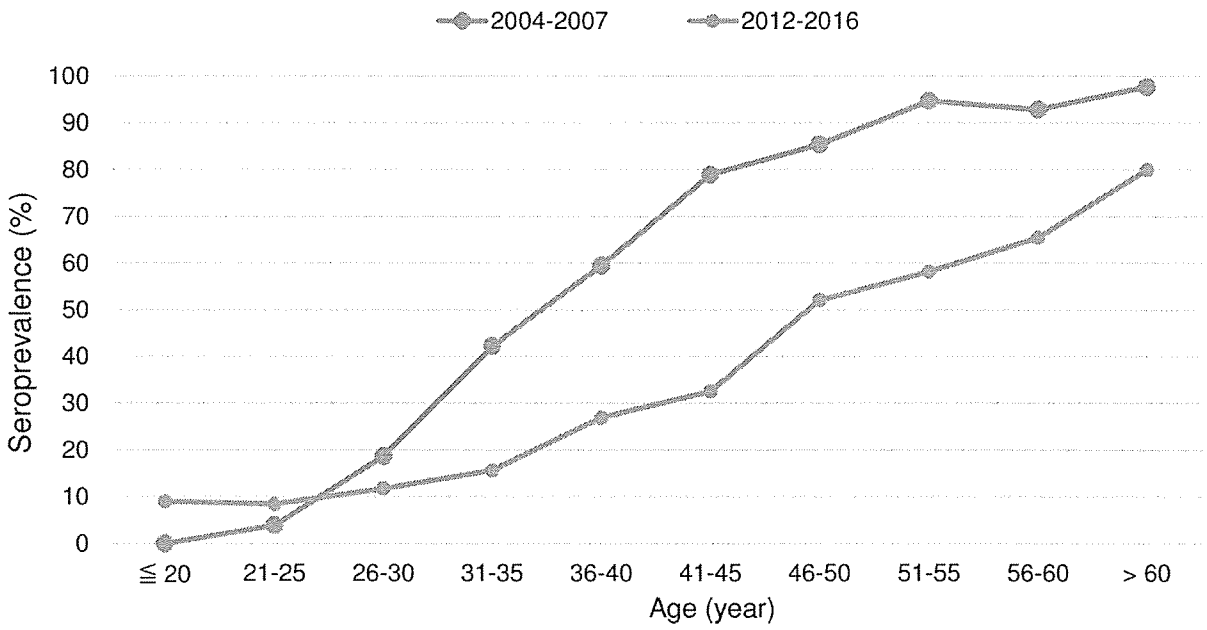

Fig 2. Comparisons of hepatitis A virus seroprevalence according to age-specific groups between the 2004–2007 cohort and the 2012–2016 cohort.

https://doi.org/10.1371/journal.pone.0186338.g002

Comparing the HAV seroprevalence by year of birth may provide a more precise description of the cohort effect (Table 3). Persons born before 1980 who were included in the 2012–2016 cohort had a lower HAV seroprevalence than those in the 2004–2007 cohort. However,

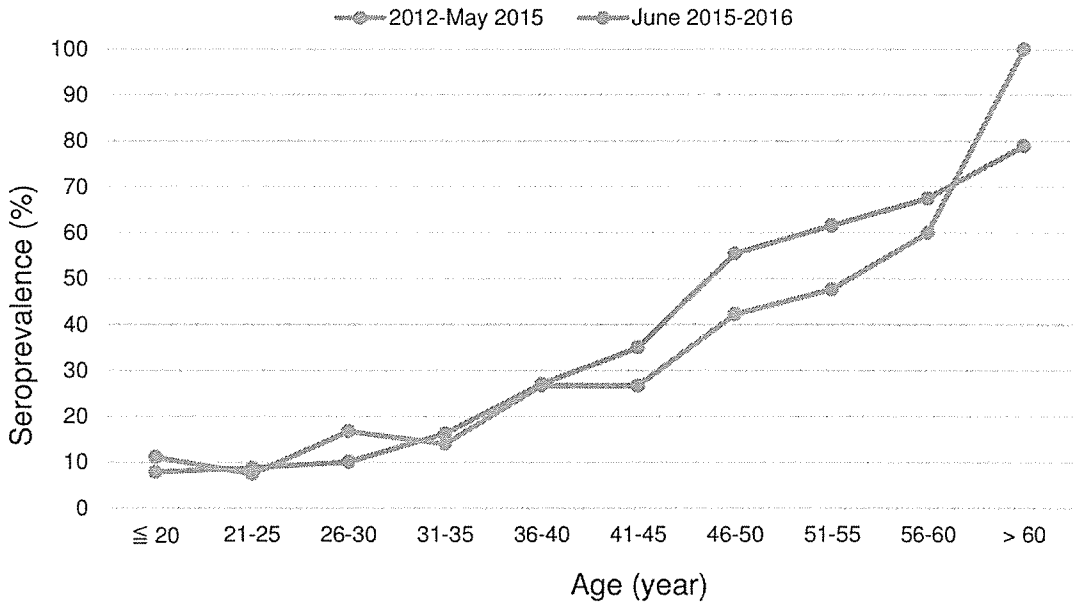

Fig 3. Comparisons of hepatitis A virus seroprevalence according to age-specific groups in the 2012–2016 cohort during the non-epidemic (2012—May 2015) and epidemic (June 2015–2016) period.

https://doi.org/10.1371/journal.pone.0186338.g003

Table 3. Comparisons of hepatitis A seroprevalence by age and birth year between the 2004–2007 cohort and the 2012–2016 cohort.

Study cohort	Sun et al.[9] (2004–2007 cohort)			Current study (2012–2016 cohort)		
Overall						
Age, years	Year of birth	Case/total	Rate, %	Year of birth	Case/total	Rate, %
18–20	After 1988	0/1	0	After 1996	6/35	17.1
20–28	1980–1988	11/159	6.9	1988–1996	75/786	9.5
28–36	1972–1980	182/460	39.6	1980–1988	141/1027	13.7
36–44	1964–1972	334/483	69.2	1972–1980	153/580	26.4
44–52	1956–1964	240/272	88.2	1964–1972	133/279	47.7
52–60	1948–1956	108/116	93.1	1956–1964	73/123	59.3
60–68	1940–1948	53/54	98.1	1948–1956	18/23	78.3
>68	Before 1940	34/35	97.1	Before 1948	6/7	85.7
Men who have sex with men						
18–20 years	After 1988	0/0	-	After 1996	6/31	19.4
20–28	1980–1988	2/46	4.3	1988–1996	71/753	9.4
28–36	1972–1980	41/186	22.0	1980–1988	114/898	12.7
36–44	1964–1972	121/217	55.8	1972–1980	82/357	23.0
44–52	1956–1964	85/106	80.2	1964–1972	71/149	47.7
52–60	1948–1956	28/30	93.3	1956–1964	21/33	63.6
60–68	1940–1948	8/8	100	1948–1956	6/7	85.7
>68	Before 1940	4/4	100	Before 1948	1/1	100

https://doi.org/10.1371/journal.pone.0186338.t003

the HAV seroprevalence increased in patients born between 1980 and 1988 from 6.9% (11/159) in the 2004–2007 cohort to 13.7% (141/1027) in the 2012–2016 cohort. Moreover, the proportion of HIV-positive patients born after 1988 had significantly increased and most of the young HIV-positive patients were MSM (784/821, 95.5%) and their HAV seroprevalence was 9.9% (81/821) (Table 3).

Discussion

The present study demonstrated the evolution of HAV seroprevalence due to cohort effect related to the changes of HIV epidemiology in Taiwan. There were two diverse trends of HAV seroprevalence between specific age groups of HIV-positive patients in Taiwan. We observed a parallel decline of HAV seropositivity in each age-matched group older than 25 years between the two cohorts with an interval of 8 years (Fig 2). However, in the young cohort (less than 25 years) mainly consisting of MSM, HAV seroprevalence increased than before. The findings may demonstrate the impact of the changing HIV epidemiology on HAV seroepidemiology in Taiwan in recent years [23, 24], when the average age of individuals acquiring HIV has been decreasing and MSM account for the majority of the patients newly diagnosed with HIV infection.

Taiwan used to be endemic for HAV infection before 1980s [30]. HAV seroprevalence was 81.3% in the age group 20 to 24 years in 1979 in Taipei area and nearly 100% among subjects in southern Taiwan in 1981 [19–21]. With the improvement of sanitation, people born after 1982 had significant declines of HAV seroprevalence [30]; only 0.96% (2/209) among individuals born between 1984 and 1985 tested positive for anti-HAV antibodies in the adolescents [31]. The cohort effect was also observed in the HIV-positive patients. In this study, we found that the age of 50% HAV seropositivity among HIV-positive patients had shifted from 35–40 years to 45–50 years between the two cohorts with 8 years apart (Fig 2). The decreasing

immunity against HAV has created a huge number of susceptible host to acquisition of HAV, especially in the young cohort. As a result, the surveillance data from Taiwan CDC revealed that the majority of the HIV-positive patients acquiring acute hepatitis A in the recent outbreak since June 2015 were men aged between 18 and 39 years who contracted HIV through unsafe sex [32].

Although HAV infection is a vaccine-preventable disease, cases of acute hepatitis A continue to occur worldwide because of low awareness of and adherence to HAV vaccination [27, 33]. A recent outbreak of acute hepatitis A in the Netherlands between July 2016 and February 2017 was linked to an international event to celebrate equality rights of the lesbian, gay, bisexual and transgender community called "EuroPride" that took place in Amsterdam in 2016 [17]. According to the phylogenic analysis of HAV sequencing, the EuroPride strain RIV-M-HAV16-090 was 99.57% identical to the previous strain submitted by Japan in 2001 and the strain responsible for the recent outbreak of acute hepatitis A in Taiwan [34, 35]. In addition, the strain also caused several HAV outbreaks in the United Kingdom, Germany, Italy, and Spain since late 2016. The worldwide outbreaks have two features in common: all of the affected countries were of low endemicity for HAV infection, and most of the patients in the outbreaks were young MSM [16–18]. The international travel and unprotected sexual contacts among MSM populations, including oral-anal sex or digital-anal sex, might have played an important role in the transmission of HAV.

In our 2012–2016 cohort, the association between injecting drug use and higher HAV prevalence was no longer observed. In Taiwan, with the implementation of harm reduction program since 2004–2005 [25, 36] comes with the significant decreases of IDUs acquiring HIV in recent years. The IDUs accounted for 15.3% of all HIV-positive patients in the 2012–2016 cohort, which was significantly lower than that (36.5%) in the 2004–2007 cohort [9]; moreover, the HAV seroprevalence among IDUs also decreased from 62.0% to 37.1% despite the average age increased from 35.7 years to 41.8 years. We postulate that the harm reduction program that included expanded access to counseling, screening, clean needles and syringes, and methadone maintenance treatment [25] might have not only changed the HIV epidemiology but decreased HAV transmission among IDUs in Taiwan.

An association between HBV and HAV infection was noted among MSM and heterosexuals, but not IDUs in our multivariate analysis. In previous studies on MSM, several factors such as the number of sexual partners, group sex, oral-anal and digital-rectal intercourse were associated with both HAV and HBV infection [6, 37]. The findings in our subgroup analysis also suggested the intimate contact such as sex exposure may increase both of the risks of HAV and HBV transmission. While the factors such as poor personal hygiene, oral ingestion of faecally-contaminated drugs and parenteral transmission have been identified to facilitate HAV transmission among IDUs [38], HBV and HCV have higher infectivity through parenteral routes than HAV. Most of our IDUs were born in the era without vaccination coverage [9, 37] and the rate of HBV infection had been high regardless of the positive result of anti-HAV antibody (50.0%) or not (46.0%). Similar to previous study, as high as 94.5% of IDUs had HCV infection in out cohort [9]. The high infection rates of HBV and HCV infection among the IDUs may preclude us from identifying the association between HAV seropositivity and HCV or HBV infection.

HAV vaccination is the most effective strategy in preventing HAV infection [39, 40]. Many countries including Israel, U.S.A., Argentina and Chile have introduced universal HAV vaccination in routine childhood immunizations and have achieved great reduction of HAV infection in the general population [41–44]. Besides, the cost-effective analysis for universal childhood HAV vaccination also demonstrated both health and economic benefits [45–47]. The previous vaccination policy in Taiwan covered only 2% of the total population, however

[48]. Given the fact that a mathematical model suggested an immune threshold of 70% to prevent HAV outbreaks [49], Taiwan is at high risk of outbreaks of acute HAV infection because of increasing numbers of susceptible hosts and frequency of international travel. The adherence to recommendations of HAV vaccination was low among the HIV-positive MSM in recent surveys [27, 28], and implementation of nationwide HAV vaccination program is urgently needed to control and prevent the HAV outbreaks.

There are several limitations of our study. First, the included patients came from different areas in these two cohorts used to examine the evolution of HAV seroprevalence. The present 2012–2016 cohort included HIV-positive patients from 11 designated hospitals for HIV care around Taiwan while the previous 2004–2007 cohort included patients from only two hospitals located in northern and central Taiwan. To minimize the interference of geographic variation on the HAV seroprevalence, we performed a sensitivity analysis by comparing only patients from northern and central Taiwan. The evolution of HAV seroprevalence was still noted (S7 Fig). Second, the information on personal hygiene, living environment, socioeconomic status, sexual behaviors, and illicit drug-taking behavior was lacking in our study. Those factors may confound the findings of changing HAV prevalence. Third, we were not able to collect the history of HAV vaccination in this retrospective study. Some of our patients might have been vaccinated and presence of anti-HAV antibody could not be used to differentiate natural infection from vaccination, though a recent survey suggested that the rate of HAV vaccination was low before the recent outbreak of acute hepatitis A among MSM in Taiwan [27].

In conclusion, the HAV seroepidemiology in HIV-positive patients is changing in Taiwan. The cohort effect has created a huge number of susceptible host to HAV infection, which may have contributed to the outbreak of acute hepatitis A among young HIV-positive MSM in Taiwan in recent years. Information, education and communication to increase the HAV vaccination coverage are urgently needed among the susceptible individuals.

Supporting information

S1 Fig. Comparisons of hepatitis A virus seroprevalence among men who have sex with men (MSM) according to geographic regions in Taiwan.
(TIF)

S2 Fig. Comparisons of hepatitis A virus seroprevalence among injecting drug users (IDUs) according to geographic regions in Taiwan.
(TIF)

S3 Fig. Comparisons of hepatitis A virus seroprevalence among heterosexuals according to geographic regions in Taiwan.
(TIF)

S4 Fig. Comparisons of hepatitis A virus seroprevalence according to age-specific groups among men who have sex with men between the 2004–2007 cohort and the 2012–2016 cohort.
(TIF)

S5 Fig. Comparisons of hepatitis A virus seroprevalence according to age-specific groups among heterosexuals between the 2004–2007 cohort and the 2012–2016 cohort.
(TIF)

S6 Fig. Comparisons of hepatitis A virus seroprevalence according to age-specific groups among injecting drug users between the 2004–2007 cohort and the 2012–2016 cohort.
(TIF)

S7 Fig. Sensitivity analysis of comparing hepatitis A seroprevalence according to age-specific groups between the 2004–2007 cohort and the 2012–2016 cohort including only patients from northern and central Taiwan.
(TIF)

S1 Table. Factors associated with positive anti-HAV antibody among men who have sex with men (MSM) and heterosexuals.
(DOCX)

S2 Table. Factors associated with positive anti-HAV antibody among injecting drug users (IDUs).
(DOCX)

S3 Table. Comparisons of hepatitis A virus seroprevalence by age and birth year among heterosexuals in the two cohorts.
(DOCX)

S4 Table. Comparison of hepatitis A virus seroprevalence by age and birth year among injecting drug users (IDUs) in the two cohorts.
(DOCX)

S1 Data. The minimal data set of the patients in this study.
(XLSX)

Acknowledgments

The authors also thank all study members participating in the Taiwan HIV Study Group: Hsin-Yun Sun, Sui-Yuan Chang, Pei-Ying Wu, Jun-Yu Zhang, Hsi-Yen Chang, Wen-Chun Liu, Yi-Ching Su, and Chien-Ching Hung, National Taiwan University Hospital, Taipei; Ning-Chi Wang and Te-Yu Lin, Tri-Service General Hospital and National Defense Medical Center, Taipei; Kuan-Yin Lin, National Taiwan University Hospital Jin-Shan Branch, New Taipei City; Chia-Jui Yang and Mao-Song Tsai, Far Eastern Memorial Hospital, New Taipei City; Yi-Chieh Lee, Lotung Poh-Ai Hospital, Lo-Hsu Foundation, I-Lan; Chien-Yu Cheng and Shu-Hsing Cheng, Tao-Yuan General Hospital, Ministry of Health and Welfare, Tao-Yuan; Yu-Shan Huang, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu; Yuan-Ti Lee and Chia-Chun Lin, Chung Shan Medical University Hospital, Taichung; Shih-Ping Lin, Chia-Yin Hsieh, and Hsiu-Wen Wang, Taichung Veterans General Hospital, Taichung; Mao-Wang Ho, China Medical University Hospital, Taichung; Chung-Eng Liu and Yu-Lin Lee, Changhua Christian Hospital, Changhua; Yi-Chien Lee, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi; Hung-Jen Tang and Huei-Chun Ku, Chi Mei Medical Center, Tainan; Chia-Wen Li, Nan-Yao Lee, and Wen-Chien Ko, National Cheng Kung University Hospital, Tainan; Po-Liang Lu and Yen-Hsu Chen, Kaohsiung Medical University Hospital, Kaohsiung; Hsi-Hsun Lin, E-Da Hospital, Kaohsiung; Wen-Chi Huang and Chen-Hsiang Lee, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung; Tun-Chieh Chen, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung.

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References

1. Cuthbert JA. Hepatitis A: old and new. Clin Microbiol Rev. 2001; 14(1):38–58. https://doi.org/10.1128/CMR.14.1.38-58.2001 PMID: 11148002
2. Havelaar AH, Kirk MD, Torgerson PR, Gibb HJ, Hald T, Lake RJ, et al. World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. PLoS Med. 2015; 12(12):e1001923. doi: 10.1371/journal.pmed.1001923. eCollection 2015 Dec. PMID: 26633896
3. Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect. 2004; 132(6):1005–22. PMID: 15635957
4. Neffatti H, Lebraud P, Hottelet C, Gharbi J, Challouf T, Roque-Afonso AM. Southern Tunisia: A still high endemicity area for hepatitis A. PLoS One. 2017; 12(4):e0175887. doi: 10.1371/journal.pone.0175887. eCollection 2017. PMID: 28426700
5. Wu D, Guo CY. Epidemiology and prevention of hepatitis A in travelers. J Travel Med. 2013; 20(6):394–9. doi: 10.1111/jtm.12058. Epub 2013 Jul 29. PMID: 24165384
6. Lin KY, Chen GJ, Lee YL, Huang YC, Cheng A, Sun HY, et al. Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: A review. World J Gastroenterology. 2017; 23(20):3589–606.
7. Fainboim H, Gonzalez J, Fassio E, Martinez A, Otegui L, Eposto M, et al. Prevalence of hepatitis viruses in an anti-human immunodeficiency virus-positive population from Argentina. A multicentre study. J Viral Hepat. 1999; 6(1):53–7. PMID: 10847130
8. Nandwani R, Caswell S, Boag F, Lawrence AG, Coleman JC. Hepatitis A seroprevalence in homosexual and heterosexual men. Genitourin Med. 1994; 70(5):325–8. PMID: 8001944
9. Sun HY, Kung HC, Ho YC, Chien YF, Chen MY, Sheng WH, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis. 2009; 13(5):e199–205. doi: 10.1016/j.ijid.2008.12.009. Epub 9 Feb 8. PMID: 19208490
10. Ishida T, Nakamura T, Ajisawa A, Negishi M, Kashiyama T, Takechi A, et al. Outbreak of hepatitis A virus infection among HIV-1 seropositive men who had sex with men. Jpn J Infect Dis. 1999; 52(3):131–2. PMID: 10507997
11. Spada E, Genovese D, Tosti ME, Mariano A, Cuccuini M, Proietti L, et al. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. J Hepatol. 2005; 43(6):958–64. Epub 2005 Jul 11. https://doi.org/10.1016/j.jhep.2005.06.012 PMID: 16143420
12. Villano SA, Nelson KE, Vlahov D, Purcell RH, Saah AJ, Thomas DL. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. Clin Infect Dis. 1997; 25(3):726–8. PMID: 9314468
13. Collier MG, Drobeniuc J, Cuevas-Mota J, Garfein RS, Kamili S, Teshale EH. Hepatitis A and B among young persons who inject drugs—vaccination, past, and present infection. Vaccine. 2015; 33(24):2808–12. doi: 10.1016/j.vaccine.2015.04.019. Epub Apr 15. PMID: 25889161
14. Lugoboni F, Pajusco B, Albiero A, Quaglio G. Hepatitis A Virus among Drug Users and the Role of Vaccination: A Review. Front Psychiatry. 2011; 2:79. doi: 10.3389/fpsyt.2011.00079. eCollection 2011. PMID: 22347865
15. Syed NA, Hearing SD, Shaw IS, Probert CS, Brooklyn TN, Caul EO, et al. Outbreak of hepatitis A in the injecting drug user and homeless populations in Bristol: control by a targeted vaccination programme

and possible parenteral transmission. Eur J Gastroenterol Hepatol. 2003; 15(8):901–6. PMID: 12867801

16. Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveill. 2017; 22(5).(pii):30454. doi: 10.2807/1560-7917.ES.2017.22.5.
17. Freidl GS, Sonder GJ, Bovee LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill. 2017; 22(8).(pii):30468. doi: 10.2807/1560-7917.ES.2017.22.8.
18. Werber D, Michaelis K, Hausner M, Sissolak D, Wenzel J, Bitzegeio J, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017—linked to other German cities and European countries. Euro Surveill. 2017; 22(5).(pii):30457. doi: 10.2807/1560-7917.ES.2017.22.5.
19. Hwang LY, Beasley RP, Yang CS, Hsu LC, Chen KP. Incidence of hepatitis A virus infection in children in Taipei, Taiwan. Intervirology. 1983; 20(2–3):149–54. PMID: 6313545
20. Sung JL, Chen DS, Yu JU, Wang TH, Lay MY, Wang CY, et al. Hepatitis A virus infection in Taiwan. A hospital-based study. Trop Geogr Med. 1980; 32(4):324–8. PMID: 6259786
21. Wu JS, Chen CH, Chiang YH, Lee YC, Lee MH, Ko YC, et al. Hepatitis A virus infection in Taiwan. Taiwan Yi Xue Hui Za Zhi. 1980; 79(8):694–9. PMID: 6934257
22. Wang SM, Liu CC, Huang YS, Yang YJ, Lei HY. Change in hepatitis A virus seroepidemiology in southern Taiwan: a large percentage of the population lack protective antibody. J Med Virol. 2001; 64 (2):104–8. PMID: 11360241
23. Chen KT, Chang HL, Chen CT, Chen YA. The changing face of the HIV epidemic in Taiwan: a new challenge for public health policy strategies. AIDS Patient Care STDS. 2009; 23(3):195–201. https://doi.org/10.1089/apc.2008.0047 PMID: 19866537
24. Hsieh YH, Lin PC. Current Trends and Future Projection of HIV/AIDS Epidemic in Taiwan: A Modeling Analysis. Curr HIV Res. 2016; 14(2):138–47. PMID: 26487305
25. Chen JS. Harm reduction policy in Taiwan: toward a comprehensive understanding of its making and effects. Harm Reduct J. 2016; 13:11. https://doi.org/10.1186/s12954-016-0101-6 PMID: 27044357
26. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18–40 years in Taiwan. J Formos Med Assoc. 2012; 111 (8):431–8. doi: 10.1016/j.jfma.2011.06.022. Epub 2 Mar 8. PMID: 22939661
27. Chen GJ, Lin KY, Sun HY, Sheng WH, Hsieh SM, Huang YC, et al. Incidence of acute hepatitis A among HIV-positive patients during an outbreak among MSM in Taiwan: Impact of HAV vaccination. Liver Int. 2017; 8(10):13468.
28. Chen GJ, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. J Infect Dis. 2017;15(10).
29. Wu PY, Cheng CY, Liu CE, Lee YC, Yang CJ, Tsai MS, et al. Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naive HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS One. 2017; 12(2):e0171596. doi: 10.1371/journal.pone.0171596. eCollection 2017. PMID: 28222098
30. Su SB, Lin CY, Sheu MJ, Kan WC, Wang HY, Guo HR. Decrease in seroprevalence of hepatitis A after the implementation of nationwide disposable tableware use in Taiwan. BMC Public Health. 2010; 10:719. https://doi.org/10.1186/1471-2458-10-719 PMID: 21092247
31. Chen JY, Chiang JC, Lu SN, Hung SF, Kao JT, Yen YH, et al. Changing prevalence of anti-hepatitis A virus in adolescents in a rural township in Taiwan. Chang Gung Med J. 2010; 33(3):321–6. PMID: 20584510
32. Centers for Disease Control, R.O.C (Taiwan). Press release. Available from: http://www.cdc.gov.tw/english/info.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=557BA6C13262600C. 2016. Cited 7 July 2017.
33. Liu SJ, Sharapov U, Klevens M. Patient awareness of need for hepatitis a vaccination (prophylaxis) before international travel. J Travel Med. 2015; 22(3):174–8. doi: 10.1111/jtm.12186. Epub 2015 Jan 24. PMID: 25619557
34. Hsieh Y-J, Huang AS, Chiu C-M, Chou Y-M, Yang C-H. A Vaccination Program to Control an Outbreak of Acute Hepatitis A among MSM in Taiwan, 2016. World Academy of Science, Engineering and Technology. 2017; 4(2).
35. Ishii K, Kiyohara T, Yoshizaki S, Kawabata K, Kanayama A, Yahata Y, et al. Epidemiological and genetic analysis of a 2014 outbreak of hepatitis A in Japan. Vaccine. 2015; 33(45):6029–36. doi: 10.1016/j.vaccine.2015.04.061. Epub May 6. PMID: 25957664

36. Chen JS. Education as networking: Rethinking the success of the harm reduction policy of Taiwan. Health (London). 2015; 19(3):280–93. doi: 10.1177/1363459314545697. Epub 2014 Aug 18. PMID: 25139870

37. Sun HY, Sheng WH, Tsai MS, Lee KY, Chang SY, Hung CC. Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: a review. World J Gastroenterol. 2014; 20(40):14598–614. doi: 10.3748/wjg.v20.i40.14598. PMID: 25356024

38. Stewart T, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. Med J Aust. 1993; 158(8):519–21. PMID: 8387627

39. Song YJ, Lim J, Park WS, Sohn H, Lee MS, Shin DH, et al. Seropositivity among Korean Young Adults Approximately 2 Years after a Single-Dose Vaccination against Hepatitis A Virus. PLoS One. 2015; 10 (11):e0142297. doi: 10.1371/journal.pone.0142297. eCollection 2015. PMID: 26540392

40. Kim KA, Lee A, Ki M, Jeong SH. Nationwide Seropositivity of Hepatitis A in Republic of Korea from 2005 to 2014, before and after the Outbreak Peak in 2009. PLoS One. 2017; 12(1):e0170432. doi: 10.1371/journal.pone.0170432. eCollection 2017. PMID: 28099530

41. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005; 294(2):194–201. https://doi.org/10.1001/jama.294.2.194 PMID: 16014593

42. Quezada A, Baron-Papillon F, Coudeville L, Maggi L. Universal vaccination of children against hepatitis A in Chile: a cost-effectiveness study. Rev Panam Salud Publica. 2008; 23(5):303–12. PMID: 18510790

43. Levine H, Kopel E, Anis E, Givon-Lavi N, Dagan R. The impact of a national routine immunisation programme initiated in 1999 on Hepatitis A incidence in Israel, 1993 to 2012. Euro Surveill. 2015; 20(7):3–10. PMID: 25719962

44. Mor Z, Srur S, Dagan R, Rishpon S. Hepatitis A disease following the implementation of universal vaccination: who is at risk? J Viral Hepat. 2010; 17(4):293–7. doi: 10.1111/j.1365-2893.2009.01176.x. Epub 2009 Aug 18. PMID: 19691457

45. Zhuang GH, Pan XJ, Wang XL. A cost-effectiveness analysis of universal childhood hepatitis A vaccination in China. Vaccine. 2008; 26(35):4608–16. doi: 10.1016/j.vaccine.2008.05.086. Epub Jun 13. PMID: 18597903

46. Valenzuela MT, Jacobs RJ, Arteaga O, Navarrete MS, Meyerhoff AS, Innis BL. Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. Vaccine. 2005; 23(32):4110–9. Epub 2005 Apr 12. https://doi.org/10.1016/j.vaccine.2005.03.021 PMID: 15964479

47. Lopez E, Debbag R, Coudeville L, Baron-Papillon F, Armoni J. The cost-effectiveness of universal vaccination of children against hepatitis A in Argentina: results of a dynamic health-economic analysis. J Gastroenterol. 2007; 42(2):152–60. Epub 2007 Mar 12. https://doi.org/10.1007/s00535-006-1984-x PMID: 17351805

48. Tsou TP, Liu CC, Huang JJ, Tsai KJ, Chang HF. Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995–2008. Vaccine. 2011; 29(16):2956–61. doi: 10.1016/j.vaccine.2011.02.001. Epub Feb 15. PMID: 21329774

49. Regan DG, Wood JG, Benevent C, Ali H, Smith LW, Robertson PW, et al. Estimating the critical immunity threshold for preventing hepatitis A outbreaks in men who have sex with men. Epidemiol Infect. 2016; 144(7):1528–37. doi: 10.1017/S0950268815002605. Epub 2015 Nov 13. PMID: 26566273

BMJ Open

Awareness and willingness towards pre-exposure prophylaxis against HIV infection among individuals seeking voluntary counselling and testing for HIV in Taiwan: a cross-sectional questionnaire survey

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To cite: Lee Y-C, Chang S-Y, Lin K-Y, *et al*. Awareness and willingness towards pre-exposure prophylaxis against HIV infection among individuals seeking voluntary counselling and testing for HIV in Taiwan: a cross-sectional questionnaire survey. *BMJ Open* 2017;**7**:e015142. doi:10.1136/bmjopen-2016-015142

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-015142).

Received 12 November 2016
Revised 31 July 2017
Accepted 1 August 2017

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ABSTRACT

Objectives We aimed to investigate the awareness and willingness towards pre-exposure prophylaxis (PrEP) among individuals seeking voluntary counselling and testing (VCT) for HIV in Taiwan, where PrEP is currently not reimbursed by the insurance.

Methods Between April and October 2016, a questionnaire interview was conducted among VCT clients to inquire about the attitudes towards PrEP against HIV infection. Multivariate logistic regression analysis was performed to identify the associated factors with willingness to initiate PrEP.

Results During the 6-month period, 1173 VCT clients (99.8%) completed the interviews, with 67.4% being homosexual or bisexual male. While 67.2% of the clients knew of postexposure prophylaxis, 40.2% heard of PrEP. Overall, 546 clients (46.5%) were willing to initiate PrEP and 89.5% of them would choose event-driven PrEP. In multivariate analysis, male gender (OR 1.796; 95% CI 1.165 to 2.768), full-time job (OR 1.354; 95% CI 1.052 to 1.742), one-night stand (OR 1.374; 95% CI 1.043 to 1.810), having casual sex partners within 3 months (OR 1.329; 95% CI 1.031 to 1.714), condomless anal sex (OR 1.405; 95% CI 1.122 to 1.878) and ever having chemsex or attending a drug party in the past 1 year (OR 2.571; 95% CI 1.541 to 4.287), regular screening for HIV infection (OR 1.321; 95% CI 1.021 to 1.711) and knowledge of PrEP (OR 1.504; 95% CI, 1.159 to 1.953) were associated with willingness to initiate PrEP.

Conclusions Understanding the willingness to initiate PrEP against HIV among the VCT clients in Taiwan, which was associated with male gender, risky sexual behaviours and awareness of PrEP, will help inform the implementation of PrEP programme.

Strengths and limitations of this study

- This is the first study in the Asia-Pacific region to investigate the willingness of initiating pre-exposure prophylaxis (PrEP) among individuals, particularly men who have sex with men (MSM), who sought voluntary counselling and testing (VCT) for HIV.
- This study provides important information on factors and barriers associated with the willingness to start PrEP, which may inform the implementation of PrEP among individuals at risk for HIV infection in the Asia-Pacific region, where PrEP is not reimbursed by the national health insurance in most of the countries.
- Information and recall bias may limit the interpretation of the data that were obtained using questionnaire interviews from the clients.
- The findings in this single-centre study with an HIV incidence rate of 5.5 per 100 person-years among the VCT clients who are MSM may not be generalised to other settings, risk groups, centres or countries.

INTRODUCTION

Pre-exposure prophylaxis (PrEP), with the use of antiretroviral agents by HIV-negative individuals before potential exposure to HIV to prevent transmission, has been proven to be efficacious in the reduction of HIV transmission in clinical trials in certain populations, such as men who have sex with men (MSM), heterosexual men and women and injection drug users.[1–4] The efficacy of PrEP in preventing HIV transmission depends on the adherence to daily doses of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC),[5] which could be greater than 90% if the adherence is high (taking four tablets or more per week).[5] The US Food and Drug Administration (FDA) has approved daily use of coformulated TDF/FTC as PrEP in July 2012.[6] The US Centers for Disease Control and Prevention published a comprehensive

clinical practice guideline of PrEP for the prevention of HIV infection in May 2014.[7] Furthermore, the Pre-exposure Option for reducing HIV in the UK: immediate or Deferred (PROUD) study supported the addition of PrEP to the standard prevention strategies for MSM who were at risk of HIV infection in England, refuting the concerns of risk compensation,[8] and the results of the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) trial has provided another efficacious prevention strategy using on-demand PrEP in MSM against HIV infection in France.[9]

Although the results of the clinical trials of PrEP are promising and a significantly increasing trend in the utilisation of TDF/FTC for PrEP among commercially insured persons in the USA between 2010 and 2014,[10] successful implementation of PrEP among high-risk populations needs an understanding of sociocultural relationship, knowledge and acceptability of the intervention and appropriate risk assessment. Several studies have explored the awareness and willingness of PrEP in different high-risk populations.[11–13] The percentage of willingness and acceptability of PrEP ranged from 49.9% to 60.8% in these studies, which was associated with lower levels of education, regular gay scene attendance, high-risk unprotected anal intercourse (defined as having two or more partners, casual partners and/or unknown/discordant partners in the previous 12 months) and testing for HIV or sexually transmitted infections (STIs) in the previous 12 months.[12]

In Asia-Pacific region, PrEP using TDF/FTC has not been widely implemented or reimbursed by the health insurance, except in Australia and Thailand.[14] In Taiwan, 34 479 cases of HIV infection have been reported to Taiwan Centers for Disease Control (CDC) between 1984 and 2016, with an estimated HIV prevalence of 1465 per 100 000 populations. The annual cases of HIV infection continues to increase over the past decade and MSM remain the leading risk group of HIV infection, accounting for 60.4% of reported cases of HIV infection.[15] HIV care, including combination antiretroviral therapy and monitoring of plasma HIV RNA load and CD4 count, is provided free-of-charge at designated hospitals around Taiwan. However, the National Health Insurance does not reimburse the cost related to PrEP, though Taiwan CDC and Taiwan AIDS Society have issued PrEP guidelines in May 2016.[16]

Understanding how PrEP is perceived by individuals at risk for HIV transmission is important before implementation of PrEP as one of the HIV prevention strategies. This cross-sectional questionnaire survey aimed to investigate the awareness and willingness toward PrEP among individuals seeking confidential voluntary counselling and testing (VCT) services for HIV in Taiwan.

METHODS

Setting of the VCT services

VCT services for HIV and syphilis have been offered free-of-charge in Taiwan, with grant support from the Taiwan CDC.[17] The National Taiwan University Hospital (NTUH) has provided VCT services since 1999, which was expanded in 2006. The number of attendees of the VCT programme at NTUH accounted for approximately 14% of the total number in Taiwan in recent years.[18 19] Each client seeking VCT services has a unique identification code for test results and has to complete a standardised, confidential, self-administered questionnaire interview prepared in Chinese (the English translated version available as online supplementary data at *BMJ Open* Online), designed by Taiwan CDC. After completion of counselling by trained counsellors, a blood sample was obtained for testing for HIV, syphilis and other STIs. This study was approved by the Research Ethics Committee of the hospital (registration number, 200904084R), and the VCT clients gave written informed consent with the use of the unique code before participating in this survey.

Among the VCT clients, the overall prevalence and incidence rate was 3.5% and 3.4 per 100 person-years (PY) for HIV infection, 2.2% and 1.6 per 100 PY for syphilis and 0.3% and 0.34 per 100 PY for HCV infection, respectively, and the prevalence was 4.2% to 4.7% for chlamydia, 1.0% for amoebiasis and 0.7% for gonorrhoea.[17 19 20] Among the MSM population, the incidence rate of HIV infection (5.5 per 100 PY) was 10-fold higher than that of heterosexuals.[21]

Self-administered questionnaire interview of PrEP

The content of the questionnaire for VCT and PrEP comprised of four parts: first, the general and basic data of age, gender, level of education, current employment status and current monthly income status; second, frequency of seeking VCT services for HIV and activities clients engaged in, for example, one-night stand sex (defined as a single sexual encounter without an expectation of further relationship); third, risk assessment, which included the number of sexual partners in the past 3 months and condomless anal intercourse and use of recreational drugs in the past 1 year and fourth, the knowledge of HIV postexposure prophylaxis (PEP) and PrEP, willingness to use PrEP, concerns about using PrEP and reasons of no intention to use PrEP. PrEP was briefly described and information on the two current PrEP strategies was provided: oral PrEP with TDF/FTC administered on a once-daily basis and with TDF/FTC on an on-demand (event-driven) basis, especially on the differences of medication instruction and cost.[8 9] During the study period, TDF/FTC had not yet obtained its approval for PrEP from Taiwan FDA. All antiretrovirals were only available at the designated hospitals for HIV care around Taiwan.

The pilot questionnaire interview was conducted among the first 66 VCT clients to identify the validity and comprehensibility of the questionnaire from 9 March to 7 April 2016. After modification of the questionnaire, 44 clients piloted questionnaire interview from 8 to 13 April 2016 and no changes were made to the questionnaire thereafter.

Statistical analysis

Statistical analyses were performed using SAS software V.9.2 (SAS, North Carolina, USA). Continuous variables were reported as mean±SD, analysed with non-parametric statistics and compared with Kruskal-Wallis tests. Categorical variables were expressed as percentage of the total number of clients analysed and compared with χ^2 test. To identify factors associated with willingness of initiating PrEP, the variables with a p value less than 0.05 in univariate analysis were entered into the multivariate logistic regression analysis. Model selection were conducted using a backward elimination technique based on two criteria (ie, Akaike Information Criteria (AIC) and Type III p values) until the final model reached the optimum (minimum) AIC.[22] A p value of less than 0.05 was considered statistically significant. Missing data were excluded for analysis.

RESULTS

From 8 April to 8 October 2016, a total of 1175 clients sought VCT services at NTUH and 1173 of them (99.8%) agreed to participate in this study and completed questionnaire interviews. The demographic and clinical characteristics of the participants are shown in table 1. The participants had a mean age of 29.7 years (SD, 7.9 years), 88.2% were of male gender, 67.4% were homosexual or bisexual male, 88.3% had diploma more than high school, 61.6% had full-time job and 57.2% had monthly income more than 30 000 New Taiwan Dollars (NTDs) (approximately US$950).

Regarding the activities that VCT clients were engaged in, 57.5% of the clients reported having sex with someone online from apps and 27.5% had one-night stand sex. Up to 80% of the clients (79.7%) reported having 1–5 sexual partners in the past 3 months; 38.3% had condomless anal sex within the past 1 year and 11.1% had partners with HIV infection or other STIs. Sixty-nine percent of the clients had a casual sexual partner. Around 8.0% of the clients (7.5%) admitted to use of recreational drug during sexual activity or attending a drug party within 3 months before this survey.

With respect to knowledge on HIV testing and prevention, 52.9% of the clients had used to attend regular screening for HIV. About two-thirds of the clients (67.2%) knew of PEP while 40.2% heard of PrEP before this survey. While 3.4% of the clients tested positive for HIV, 2.9% tested positive for syphilis in the survey during the study period.

Overall, 546 VCT clients (46.5%) expressed their willingness to use PrEP, if TDF/FTC was approved for PrEP in Taiwan. Comparisons of the baseline data and characteristics between the clients with and without willingness to use PrEP are shown in table 1. Compared with individuals unwilling to use PrEP, individuals willing to use PrEP were more likely to be male (93.4% vs 83.7%, p<0.0001) and homosexual and bisexual male (75.8% vs 60.0%, p<0.0001), to have full-time job (66.5% vs 58.2%, p=0.0112) and current monthly income more than 30 000 NTDs (60.9% vs 54.0%, p=0.0203), to be engaged in sex with someone online from apps (61.5% vs 53.9%, p=0.0092) and with someone by dating at places like a pub, bathhouse or gym (11.5% vs 7.8%, p=0.0362) and to have one-night stand sex (32.6% vs 23.1%, p<0.0001).

When the risk behaviours were concerned, not having any sexual partners (13.8% vs 19.7%, p=0.0295) and having a casual partner (53.7% vs 65.6%, p<0.0001) were negatively associated with willingness to use PrEP. On the other hand, having condomless anal intercourse in the past 1 year (46.2% vs 31.4%, p<0.0001) and ever using recreational drug during sexual activity or attending a drug party in the past 1 year (11.7% vs 3.8%, p<0.0001) were associated with willingness to use PrEP.

Regarding the knowledge of HIV testing and prevention, regular screening for HIV (60.3% vs 46.4%, p<0.0001), and being aware of PEP (73.1% vs 62.0%, p<0.0001) and PrEP (48.0% vs 33.3%, p<0.0001) were more common in clients with willingness to use PrEP than those without. Compared with clients without willingness to use PrEP, clients with willingness to use PrEP were more likely to test positive for HIV during the current VCT visits (5.7% vs 1.4%, p<0.0001).

In multivariate analysis, factors associated with willingness to use PrEP are shown in table 2. Independent factors associated with willingness to start PrEP included male gender (OR 1.796; 95% CI 1.165 to 2.768), having full-time job (OR 1.354; 95% CI 1.052 to 1.742), one-night stand sex (OR 1.374; 95% CI 1.043 to 1.810), casual sex partners within 3 months (OR 1.329; 95% CI 1.031 to 1.714) and condomless anal sex in the past 1 year (OR 1.405; 95% CI 1.122 to 1.878), ever using recreational drugs during sexual activity or attending a drug party in the past 1 year (OR 2.571; 95% CI 1.541 to 4.287) and having regular screening for HIV infection (OR 1.321; 95% CI 1.021 to 1.711) and knowledge of PrEP (OR 1.504; 95% CI 1.159 to 1.953).

Of the 546 clients who reported willingness to use PrEP, 89.5% preferred to use TDF/FTC on an on-demand (event-driven) basis. However, the concerns raised about PrEP included higher cost of medications (41.0%), potential side effects (33.5%) and inconvenient access to acquisition of TDF/FTC (28.7%). The reasons for not considering PrEP for the 627 clients included having adopted protective measures during sex (78.5%) and concerns about higher cost of medications (18.5%), potential side effects (11.6%) and inconvenient access to acquisition of TDF/FTC (8.6%).

DISCUSSION

This is the first study to report on awareness of using TDF/FTC as PrEP against HIV and willingness to use PrEP among individuals seeking for VCT in the Asia-Pacific region in recent years. We found that, while PrEP was not reimbursed by the National Health Insurance in Taiwan, 46.5% of VCT clients were willing to use PrEP and 89.5%

Table 1 Univariate analysis of factors associated with the willingness to use PrEP among 1173 individuals seeking voluntary counselling testing for HIV in Taiwan

Variables	All individuals	Individuals willing to use PrEP	Individuals unwilling to use PrEP	Statistics p value*
Patient number, N (%)	1173 (100.0)	546 (46.5)	627 (53.5)	
Age, mean (SD), years	29.7 (7.9)	29.7 (7.2)	29.8 (8.6)	0.2643
Gender, %				
Male	88.2	93.4	83.7	<0.0001
Female	11.8	6.6	16.3	
Transgender	0.0	0.0	0.0	
Highest level of education, %	100.0	100.0	100.0	
More than high school	88.3	89.1	87.7	0.5241
High school or less	11.7	11.0	12.3	
Current employment status, % (n/N)	99.5	99.5	99.5	
Full time	61.6 (719/1167)	66.5 (356/543)	58.2 (363/624)	0.0112
Others	38.4 (448/1167)	34.4 (187/543)	41.8 (261/624)	
Current monthly income status, % (n/N)				
<30 000 NTDs	42.8 (497/1161)	39.1 (210/537)	46.0 (287/624)	0.0203
≥30 000 NTDs	57.2 (664/1161)	60.9 (327/537)	54.0 (337/624)	
Sexual partners, %				
Non-MSM male	20.9	17.6	23.8	<0.0001
MSM or bisexual male	67.4	75.8	60.0	
Female	11.8	6.6	16.3	
Activities engaged in, %				
Sex work (provider or consumer)	10.1	9.5	10.7	0.5611
Having sex with someone dating online or from apps	57.5	61.5	53.9	0.0092
Having sex with someone dating at places, like a pub, bathhouse or gym	9.5	11.5	7.8	0.0362
Attending a sex party	0.5	0.7	0.3	0.4255
One-night stand sex	27.5	32.6	23.1	<0.0001
Risk behaviours, % (n/N)				
Number of sex partners within 3 months				
0	16.9 (198/1169)	13.8 (75/543)	19.7 (123/626)	0.0295
1–5	79.7 (932/1169)	82.7 (449/543)	77.2 (483/626)	
>5	3.3 (39/1169)	3.5 (19/543)	3.2 (20/626)	
Having a committed sexual partner within 3 months	45.2 (530/1173)	47.6 (260/546)	43.1 (270/627)	0.1263
Having a casual sex partner within 3 months	60.0 (704/1173)	53.7 (293/546)	65.6 (411/627)	<0.0001
Condomless anal sex in the past 1 year	38.3 (449/1173)	46.2 (252/546)	31.4 (197/627)	<0.0001
Partner infected with HIV or other STIs	11.1 (130/1173)	12.6 (69/546)	9.7 (61/627)	0.1355
Ever having STIs in the past 1 year	6.8 (80/1173)	8.2 (45/546)	5.6 (35/627)	0.0815
Alcohol consumption before or during sexual activity	17.3 (203/1173)	17.0 (93/546)	17.5 (110/627)	0.8771
Ever using recreational drugs before or during sexual activity or attending drug party in the past 1 year	7.5 (88/1173)	11.7 (64/546)	3.8 (24/627)	<0.0001

Continued

Table 1 Continued

Variables	All individuals	Individuals willing to use PrEP	Individuals unwilling to use PrEP	Statistics p value*
Knowledge on prevention, %				
Regular screening for HIV infection	52.9	60.3	46.4	<0.0001
Knew of HIV PEP	67.2	73.1	62.0	<0.0001
Knew of HIV PrEP	40.2	48.0	33.3	<0.0001
Diagnosis of STIs by current VCT visit				
Syphilis	2.9 (34/1173)	3.7 (20/546)	2.2 (14/627)	0.1644
HIV	3.4 (40/1173)	5.7 (31/546)	1.4 (9/627)	<0.0001

*p Value was calculated for the differences among the two groups. Continuous variables were analysed with non-parametric statistics, Kruskal-Wallis test, while categorical variables with χ^2 test.
MSM, men who have sex with men; NTD, New Taiwan Dollar; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; VCT, voluntary counselling testing.

of them preferred to use PrEP on an event-driven basis. VCT clients who were male with full-time job, regular screening for HIV infection and knowledge of PrEP and engaged in one-night stand sex, having casual sex partners and condomless anal sex and using recreational drugs before or during sex were more likely to report willingness of initiation of PrEP. Given the demonstrated efficacy of PrEP in preventing HIV infection among MSM who were engaged in risky behaviours,[8 9] these findings suggest that there is a substantial unmet need for a new prevention strategy against HIV transmission among individuals who perceived themselves at risk for HIV and STIs and sought VCT in Taiwan.

In this study, the risky behaviours that we identified to be associated with willingness to use PrEP, particularly condomless anal sex, were similar to those reported in other studies,[12 23–27] which implies that engagement in risky sexual behaviours may potentiate the willingness to use PrEP. However, ever using recreational drugs before or during sexual activity has only been identified in a recent study that revealed the association between use of amyl nitrate and having sex outside the relationship.[28] Recreational drug use before or during sex, also termed 'chemsex', was associated with increased odds of unprotected anal intercourse by encounter-level analysis,[29 30] which has been found to be a risk factor for acquisition of HIV infection.[31 32] Therefore, the published guidelines also identify those persons having chemsex as potential candidates to initiate PrEP.[7]

Regarding the awareness of HIV prevention, we found that prior knowledge of PrEP was associated with willingness to uptake PrEP. Goedel and colleagues also identified the correlation between awareness with willingness to use PrEP in gay, bisexuals and other MSM in New York City.[33] In Spain, MSM who had heard of PrEP were more forceful in their options on the willingness to use PrEP.[34] Therefore, with the increased awareness of PrEP, the population at risk will be more likely to accept and initiate PrEP. To effectively implement PrEP programme, information, education and counselling of PrEP should be delivered to the populations at risk for HIV infection.

Among VCT clients with willingness to use PrEP, almost 90% of them preferred event-driven strategy to prevention against HIV infection in our study. However, the VCT clients were concerned about inconvenient access to acquisition of TDF/FTC (28.7%), higher cost of the medications (41.0%) and their potential side effects (33.5%). In the Dutch study, Bil and colleagues found that

Table 2 Multivariate analysis for factors associated with the willingness to use pre-exposure prophylaxis (PrEP) against HIV infection in individuals seeking voluntary counselling and testing for HIV

Variables	Reference	OR (95% CI)	p Value
Male	Female	1.796 (1.165 to 2.768)	0.0081
Full-time job	Other types	1.354 (1.052 to 1.742)	0.0187
One-night stand sex	Nil	1.374 (1.043 to 1.810)	0.0240
Having a casual sex partner within 3 months	Nil	1.329 (1.031 to 1.714)	0.0283
Condomless anal sex in the past 1 year	No	1.405 (1.122 to 1.878)	0.0046
Ever using recreational drugs before or during sexual activity or attending drug party in the past 1 year	No	2.571 (1.541 to 4.287)	0.0003
Regular screening for HIV infection	No	1.321 (1.021 to 1.711)	0.0344
Knew of HIV PrEP	Not knowing of PrEP	1.504 (1.159 to 1.953)	0.0022

NTD, New Taiwan Dollar; PEP, postexposure prophylaxis.

compared with daily PrEP use, the benefits of intermittent PrEP use included the lower cost and potential risk of side effects and lower threshold to start PrEP, while the barriers to PrEP included the perceived need to plan their sex life and adherence to multiple prevention strategies among MSM.[35] Another qualitative research identified preference of on-demand PrEP over daily PrEP, injectable PrEP and free or standardised access through community organisations or government hospitals among MSM in India.[36] The greatest consensus regarding more acceptable PrEP attributes has been in the mode of delivery and its cost.[37] Therefore, provision of information on PrEP efficacy and potential side effects, a convenient access to PrEP service and reimbursement of PrEP are necessary to make implementation of PrEP more successful among the populations at risk.

The cost of PrEP medications has been a major concern and barrier to wide implementation of PrEP among persons at risk for HIV infection. Several mathematical models investigated the cost-effectiveness or impact of PrEP on the HIV epidemic among MSM in North America,[38–41] Australia,[42] the UK[43] and the Netherlands.[44] All these studies demonstrated that targeting PrEP to MSM at high risk of HIV infection was cost-effective. The variability of cost-effectiveness among the different studies could be due to the differences in the HIV epidemic among MSM, direct and indirect costs and the percentage of MSM targeted for intervention. Therefore, the demonstration of the cost-effectiveness of PrEP and the potential impact on HIV epidemic when PrEP is used along with other HIV treatment and prevention programmes should be able to provide evidence and rationale for the policymakers to commit to the implementation of affordable PrEP for persons at risk for HIV infection.[37 38]

Compared with other studies about willingness to use PrEP, our study had a large sample size (1173 participants) and high participation rate of questionnaire interview (99.8% of 1175 VCT clients approached). However, several limitations should be considered. First, the study was conducted using confidential questionnaire interview to collect information on sexual risk behaviours and all data were self-reported; therefore, it is difficult to avoid recall bias and we were not able to verify the information provided. Second, the willingness of PrEP use might be overestimated because of the hypothetical questions in questionnaire interview. Given the barriers to initiation of PrEP using TDF/FTC, it remains to be seen whether action will be taken by the individuals with risky behaviours when TDF/FTC was approved for PrEP in Taiwan. Third, this is a single-centre study including VCT clients who were mainly MSM with an HIV incidence rate of 5.5 per 100 PY and all the study participants are of Asia ethnicity. Therefore, our findings may not be generalised to participants of other ethnicities and countries.

CONCLUSIONS

Among the individuals seeking VCT services in Taiwan, a substantial portion (46.5%) of the participants had willingness to initiate PrEP against HIV infection, which were independently associated with having risky sexual behaviours and awareness of PrEP. The barriers to PrEP included cost, potential adverse effects and accessibility issues. The implementation of PrEP in Taiwan could be facilitated through dissemination of the information on PrEP and provision of PrEP that is affordable and easy to access.

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Acknowledgements We would like to thank the VCT clients for their participation in this survey and Taiwan Centers for Disease Control for the research grant support.

Contributors YCL, SYC, HYS, and CCH designed the study; KYL, LSC, WCL and CHW performed the questionnaire interview and data collection; YCL, HYS, KYL and WCL contributed to data analysis and SCC oversaw the study. First draft was written by YCL with substantive revisions and input from all authors. All authors have read and approved the final manuscript.

Funding This study was supported by grants from Taiwan Centers for Disease Control (MOHW105-CDC-C-114-000104 to CCH). The funding source played no role in study design and conduct, data collection, analysis or interpretation, writing of the manuscript or the decision to submit it for publication.

Competing interests CCH has received research support from Janssen, Merck, Bristol-Myers Squibb and ViiV; speaker honoraria from ViiV, Abbvie and Gilead and served on advisory boards for Gilead, Janssen, ViiV and Abbvie. Other authors, none to declare.

Ethics approval Research Ethics Committee of National Taiwan University Hospital

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Grant RM, Lama JR, Anderson PL, *et al*. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587–99.
2. Baeten JM, Donnell D, Ndase P, *et al*. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367:399–410.

3. Thigpen MC, Kebaabetswe PM, Paxton LA, *et al*. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012;367:423–34.
4. Choopanya K, Martin M, Suntharasamai P, *et al*. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013;381:2083–90.
5. Grant RM, Anderson PL, McMahan V, *et al*. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014;14:820–9.
6. United States Food and Drug Administration. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm (accessed 10 Aug 2016).
7. United States Public Health Service. Preexposure prophylaxis for the prevention of HIV in the United States—2014: a clinical practice guideline. http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf (accessed 10 Aug 2016).
8. McCormack S, Dunn DT, Desai M, *et al*. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016;387:53–60.
9. Molina JM, Capitant C, Spire B, *et al*. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015;373:2237–46.
10. Wu H, Mendoza MC, Huang YA, *et al*. Uptake of HIV preexposure prophylaxis among commercially insured persons – United States, 2010–2014. *Clin Infect Dis* 2017;64:144–9.
11. Hoots BE, Finlayson T, Nerlander L, *et al*. Willingness to take, use of, and indications for pre-exposure prophylaxis among men who have sex with men – 20 US Cities, 2014. *Clin Infect Dis* 2016;63:672–7.
12. Young I, Li J, McDaid L. Awareness and willingness to use HIV pre-exposure prophylaxis amongst gay and bisexual men in Scotland: implications for biomedical HIV prevention. *PLoS One* 2013;8:e64038.
13. Hoff CC, Chakravarty D, Bircher AE, *et al*. Attitudes towards PrEP and anticipated condom use among concordant HIV-negative and HIV-discordant male couples. *AIDS Patient Care STDS* 2015;29:408–17.
14. Zablotska I, Grulich AE, Phanuphak N, *et al*. PrEP implementation in the Asia-Pacific region: opportunities, implementation and barriers. *J Int AIDS Soc* 2016;19:21119.
15. Taiwan CDC. Statistics of HIV/AIDS. 2016 http://www.cdc.gov.tw/downloadfile.aspx?fid=CF697A305BCC94CF (accessed 1 May 2017).
16. Taiwan AIDS society. Guideline for the use of pre-exposure oral prophylaxis (PrEP) in Taiwan. 2016 http://www.aids-care.org.tw/%E8%87%BA%E7%81%A3%E6%9A%B4%E9%9C%B2%E5%89%8D%E5%8F%A3%E6%9C%8D%E9%A0%90%E9%98%B2%E6%80%A7%E6%8A%95%E8%97%A5%E4%BD%BF%E7%94%A8%E6%8C%87%E5%BC%95(%E5%85%AC%E5%91%8A%E7%89%8820160502).pdf (accessed 17 May 2017).
17. Wu H, Wu PY, Li SY, Py W, Sy L, *et al*. Maximising the potential of voluntary counselling and testing for HIV: sexually transmitted infections and HIV epidemiology in a population testing for HIV and its implications for practice. *Sex Transm Infect* 2012;88:612–6.
18. Lai CC, Liu WC, Fang CT, *et al*. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. *J Antimicrob Chemother* 2016;71:226–34.
19. Tsai JC, Hung CC, Chang SY, *et al*. Increasing incidence of recent hepatitis C virus infection among persons seeking voluntary counselling and testing for HIV and sexual transmitted infections in Taiwan. *BMJ Open* 2015;13:e008406.
20. Yang CJ, Li SY, Chang SY, *et al*. Associated factors with and genotypes of *Chlamydia trachomatis* infection among clients seeking voluntary counseling and testing for HIV infection in Taiwan. *J Microbiol Immunol Infect* 2014;47:526–32.
21. Liu WC, Chang LH, Wu PY, Py W, *et al*. Seroincidence of HIV and prevalence of transmitted drug resistance of HIV-1 strains among persons seeking voluntary counselling and testing in Taiwan. *J Int AIDS Soc* 2014;17:19758.
22. Lima VD, Geller J, Bangsberg DR, *et al*. The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007;21:1175–83.
23. Saberi P, Gamarel KE, Neilands TB, *et al*. Ambiguity, ambivalence, and apprehensions of taking HIV-1 pre-exposure prophylaxis among male couples in San Francisco: a mixed methods study. *PLoS One* 2012;7:e50061.
24. Krakower DS, Mimiaga MJ, Rosenberger JG, *et al*. Limited awareness and low immediate uptake of pre-exposure prophylaxis among men who have sex with men using an internet social networking site. *PLoS One* 2012;7:e33119.
25. Grov C, Whitfield TH, Rendina HJ, *et al*. Willingness to take PrEP and potential for risk compensation among highly sexually active gay and bisexual men. *AIDS Behav* 2015;19:2234–44.
26. Hoagland B, De Boni RB, Moreira RI, *et al*. Awareness and willingness to use pre-exposure prophylaxis (PrEP) among men who have sex with men and transgender women in Brazil. *AIDS Behav* 2017;21:1278–87.
27. Holt M, Lea T, Schmidt HM, *et al*. Willingness to use and have sex with men taking HIV pre-exposure prophylaxis (PrEP): results of online surveys of Australian gay and bisexual men, 2011-2015. *Sex Transm Infect* 2017;93::438–44.
28. Mitchell JW, Stephenson R. HIV-negative partnered men's willingness to use pre-exposure prophylaxis and associated factors among an internet sample of U.S. HIV-negative and HIV-discordant male couples. *LGBT Health* 2015;2:35–40.
29. Boone MR, Cook SH, Wilson P. Substance use and sexual risk behavior in HIV-positive men who have sex with men: an episode-level analysis. *AIDS Behav* 2013;17:1883–7.
30. Melendez-Torres GJ, Hickson F, Reid D, *et al*. Nested event-level case-control study of drug use and sexual outcomes in multipartner encounters reported by Men who have sex with men. *AIDS Behav* 2016;20:646–54.
31. Plankey MW, Ostrow DG, Stall R, *et al*. The relationship between methamphetamine and popper use and risk of HIV seroconversion in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr* 2007;45:85–92.
32. Chen X, Li X, Zheng J, *et al*. Club drugs and HIV/STD infection: an exploratory analysis among men who have sex with men in Changsha, China. *PLoS One* 2015;10:e0126320.
33. Goedel WC, Halkitis PN, Greene RE, *et al*. Correlates of awareness and willingness to use pre-exposure prophylaxis (PrEP) in gay, bisexual, and other men who have sex with men who use geosocial-networking smartphone applications in New York City. *AIDS Behav* 2016;20:1435–42.
34. Ferrer L, Folch C, Fernandez-Davila P, *et al*. Awareness of pre-exposure prophylaxis for HIV, willingness to use it and potential barriers or facilitators to uptake among men who have sex with men in Spain. *AIDS Behav* 2016;20:1423–33.
35. Bil JP, van der Veldt WM, Prins M, *et al*. Motives of Dutch men who have sex with men for daily and intermittent HIV pre-exposure prophylaxis usage and preferences for implementation: a qualitative study. *Medicine* 2016;95:e4910.
36. Chakrapani V, Newman PA, Shunmugam M, *et al*. Acceptability of HIV pre-exposure prophylaxis (PrEP) and implementation challenges among men who have sex with men in India: a qualitative investigation. *AIDS Patient Care STDS* 2015;29:569–77.
37. Kessler J, Myers JE, Nucifora KA, *et al*. Evaluating the impact of prioritization of antiretroviral pre-exposure prophylaxis in New York. *AIDS* 2014;28:2683–91.
38. Koppenhaver RT, Sorensen SW, Farnham PG, *et al*. The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model. *J Acquir Immune Defic Syndr* 2011;58:e51–e52.
39. Ross EL, Cinti SK, Hutton DW, *et al*. clinically actionale strategy for targeting HIV preexposure prophylaxis to high risk men who have sex with men. *J Acquir Immune Defic Syndr* 2016;72:e61–7.
40. Juusola JL, Brandeau ML, Owens DK, *et al*. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012;156:541–50.
41. MacFadden DR, Tan DH, Mishra S. Optimizing HIV pre-exposure prophylaxis implementation among men who have sex with men in a large urban centre: a dynamic modelling study. *J Int AIDS Soc* 2016;23:20791.
42. Schneider K, Gray RT, Wilson DP. A cost-effectiveness analysis of HIV preexposure prophylaxis for men who have sex with men in Australia. *Clin Infect Dis* 2014;58:1027–34.
43. Cambiano V, Miners A, Dunn DT, *et al*. Is PrEP for HIV prevention cost-effective in MSM in the UK? BASHH Spring Conference, Glasgow, UK. 2015. *Sex Transm Infect* 2015;91:A1.
44. Nichols BE, Boucher CAB, van der Valk M, *et al*. Cost-effectiveness analysis of pre-exposure prophylaxis for HIV-1 prevention in the Netherlands: a mathematical modelling study. *Lancet Infect Dis* 2016;16:1423–9.

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Awareness and willingness towards pre-exposure prophylaxis against HIV infection among individuals seeking voluntary counselling and testing for HIV in Taiwan: a cross-sectional questionnaire survey

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BMJ Open 2017 7:
doi: 10.1136/bmjopen-2016-015142

Notes

Journal of Microbiology, Immunology and Infection (2017) 50, 595–603

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients

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Received 25 June 2015; received in revised form 24 August 2015; accepted 27 August 2015
Available online 9 September 2015

KEYWORDS
antiretroviral therapy;
kidney dysfunction;

Abstract *Background/Purpose:* Tenofovir disoproxil fumarate (TDF) is associated with kidney tubular dysfunction, for which the risk may vary among patients of different ethnicities. Data are limited, however, on the association between renal function changes and TDF exposure in human immunodeficiency virus (HIV)-infected Taiwanese patients.

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http://dx.doi.org/10.1016/j.jmii.2015.08.019

nucleotide reverse-transcriptase inhibitor;
proximal renal tubulopathy;
tenofovir

Methods: Medical records of HIV-infected Taiwanese patients seeking HIV care at a university hospital from 2011 to 2014 were reviewed. The change of estimated glomerular filtration rate (eGFR) was compared between patients not receiving combination antiretroviral therapy (cART) and those starting cART with or without TDF. The determinants of annual eGFR changes and factors associated with greater annual eGFR decline in TDF-exposed patients were explored.
Results: A total of 775 patients were included: 140 were cART-naïve, 393 received TDF-containing cART, and 242 received cART without TDF. Compared with cART-naïve patients, the annual eGFR decline was greater in TDF-exposed patients (0.57 ± 8.6 mL/min/1.73 m^2 and 2.7 ± 8.9 mL/min/1.73 m^2, $p = 0.012$). The annual eGFR decline between patients receiving cART with or without TDF was similar (2.7 ± 8.9 mL/min/1.73 m^2 and 1.8 ± 8.3 mL/min/1.73 m^2, $p = 0.567$). Diabetes was associated with worsening eGFR decline in all studied patients. TDF exposure correlated with an additional annual eGFR decline of 2.73 mL/min/1.73 m^2 (95% confidence interval 0.139—5.326, $p = 0.039$) in patients with CD4 count < 350 cells/μL. Among TDF-exposed patients, the factors associated with annual eGFR decline of > 3 mL/min/1.73 m^2 were higher baseline eGFR and lower CD4 counts.
Conclusion: Among HIV-infected Taiwanese patients, cART exposure correlated with the decline of renal function. However, TDF-exposed patients are more likely to have prominent eGFR decline, especially those with higher baseline eGFR, advanced HIV disease, and diabetes.

Introduction

Tenofovir disoproxil fumarate (TDF) is a widely used nucleotide reverse-transcriptase inhibitor, and is an important component of combination antiretroviral therapy (cART) for patients with human immunodeficiency virus (HIV) infection.[1,2] With the introduction of cART, survival of HIV-infected patients has significantly improved. However, aging, multiple comorbidities, complex medications, and prolonged cART may increase the risk of kidney injury. In recent years, kidney dysfunction has become a clinically relevant and important issue.[3—5]

Since its introduction for clinical use, TDF has been found to be associated with an increased risk of kidney tubular dysfunction including Fanconi syndrome, diabetes insipidus, or osteomalacia.[6,7] Decline in renal function was also reported in patients with exposure to TDF, experiencing either acute or chronic kidney injury, or merely a decrease of estimated glomerular filtration rate (eGFR) when compared with baseline values.[8]

The magnitude and clinical impact of TDF on renal function are still being debated. Variable degrees of eGFR loss have been reported, ranging from < 5 mL/min/1.73 m^2 to $>$ 10 mL/min/1.73 m^2 annually.[8—10] In a 10-year longitudinal prospective follow-up study, there was only a mild decline of eGFR that was attributable to TDF.[11] By contrast, a study on a cohort of Japanese patients showed that the loss of eGFR increased continuously for up to 5 years.[12] Moreover, increased frequency of proteinuria has been observed in patients receiving TDF-containing cART.[13,14] Because proteinuria may often precede GFR loss, measurements of biomarkers, such as urine β-2-microglobulin, have been proposed for early detection of renal tubular dysfunction.[15]

Previous studies have shown different incidences and profiles of adverse effects of cART in Asian populations compared with those reported in Western countries.[16,17] The predictive factors of TDF-related kidney injury have been recognized, which vary among patients of different ethnicities. For Asian people, a lower weight[18,19] and certain genetic variability[20] may contribute to the development of kidney injury. A few studies have reported on the change in renal function in TDF-exposed Asians,[19,21—24] however, most of the studies had short observation periods. This study aimed to assess the eGFR changes and to identify the risk factors for decline of renal function associated with TDF exposure in HIV-1-infected Taiwanese patients.

Methods

Patient population

This retrospective cohort study was conducted between January 2011 and December 2014 at a university hospital that is the largest designated hospital for HIV care in Taiwan. Because TDF was not introduced into clinical use in Taiwan until 2011, the study population included all HIV-infected patients who regularly sought HIV care at the hospital since 2011. Three groups of patients were defined according to their treatment status: those not receiving cART, those receiving TDF-containing cART, and those receiving cART not containing TDF.

Patients were included if they were aged ≥ 20 years with at least two serum creatinine measurements with an interval of 90 days or more. The exclusion criteria included receipt of ART < 90 days, intermittent or unknown duration of ART exposure, and end-stage renal disease on dialysis. ART was initiated and prescribed according to the national treatment guidelines for HIV infection proposed by the Taiwan Centers for Disease Control.[25] The decision to

switch or stop cART was at the discretion of the HIV-treating physicians. The study was approved by the Research Ethics Committee of National Taiwan University Hospital (registration number NTUH-201301041RIND). The data were analyzed anonymously, and written or oral informed consent was waived.

Data collection and evaluation of renal function

We used a standardized case record form to collect the information on the demographics, sexual preference, weight and height, comorbidity, treatment history of cART, plasma HIV RNA load, CD4 lymphocyte count, concomitant medications, and serum creatinine at the start of the study from the medical records of the patients. Chronic kidney disease was defined as an eGFR $<$ 60 mL/min/1.73 m^2. Dyslipidemia was defined by regular use of lipid-lowering agents, or a total cholesterol of $\geq$ 240 mg/dL, or a triglycerides level of $\geq$ 200 mg/dL. Serum creatinine measurements were performed every 6–12 months until the study ended. All patients underwent annual proteinuria screening. If the patients discontinued TDF due to renal dysfunction, serum creatinine levels and urinalysis results were monitored and followed up until the end of study (December 31, 2014).

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, incorporating serum creatinine, age, sex, and race as four parameters to estimate GFR. The CKD-EPI equation was shown to be more accurate than the Modification of Diet in Renal Disease (MDRD) equation in the subgroup with GFR $>$ 60 mL/min/1.73 m^2.[26] Such populations include patients without kidney disease and young patients, which are very much similar to our study population. Guidelines published by the Kidney Disease Improving Global Outcomes organization, managed by the National Kidney Foundation of the United States, recommends the CKD-EPI equation for patients with higher GFR.[27] Proteinuria, detected using spot urine sample, was defined as $>$ 1+ (i.e., urine protein level $\geq$ 30 mg/dL).

Our primary outcome of interest was the change of GFR for each group of patients. The secondary objective was to identify the risk factors associated with GFR decline in patients with TDF exposure.

Statistical analysis

Patients' demographics and basic characteristics were evaluated by descriptive statistics. Data were presented as mean (standard deviation) or count (percent). Categorical variables were compared using chi-square test or Fisher exact test. Continuous variables were compared using the Kruskal–Wallis one-way analysis of variance or Mann–Whitney *U* test. For data from two related samples, variables were compared using paired *t* test. A two-tailed *p* value $<$ 0.05 was considered statistically significant. Factors associated with annual eGFR change in all patients were identified using multivariate linear regression model. Factors associated with annual eGFR decline by $>$ 3 mL/min/1.73 m^2 in patients exposed to TDF were explored using the multivariate logistic regression model. Variables were entered into the model with a backward stepwise linear or logistic regression approach with p value $<$ 0.1 as a requirement for acceptance. Data were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of patients

During the 4-year study period, a total of 775 HIV-infected patients with available serial serum creatinine data over a 90-day interval were included for analysis: 140 were not receiving cART, 393 had exposure to TDF-containing cART (TDF-exposed group), and 242 received cART not containing TDF (non-TDF-exposed group). The baseline characteristics of the patients are shown in Table 1. Overall, most patients were middle-aged homosexual men. The average weight of patients was 66.6 kg. One fourth of the patients in the TDF-exposed group had chronic hepatitis B virus infection. More patients in the non-TDF-exposed group had diabetes mellitus, hypertension, dyslipidemia, and longer duration of cART exposure with 80% of the regimens containing protease inhibitor(s). The mean follow-up duration of the patients was 672 days (standard deviation 292 days).

Renal function change of HIV patients exposed or unexposed to tenofovir

The trends of changes in eGFR in each group of patients are demonstrated chronologically by the timing of serum creatinine tests in Figure 1. In the 4-year study period, patients not starting cART had stable eGFR at around 110 mL/min/1.73 m^2. By contrast, patients receiving cART had significant decline of eGFR: a decline from 105.6 mL/min/1.73 m^2 to 97.6 mL/min/1.73 m^2 in the TDF-exposed group, and from 99.4 mL/min/1.73 m^2 to 92.7 mL/min/1.73 m^2 in the non-TDF-exposed group (Figure 1).

In Table 2, we compared the changes between the first and the last eGFR among the three groups. Both groups of patients receiving cART with or without TDF had significantly lower eGFR in the last measurements, compared with their respective first eGFR measurements (105.6 $\pm$ 16.4 mL/min/1.73 m^2 and 100.5 $\pm$ 17.1 mL/min/1.73 m^2; 99.4 $\pm$ 17.6 mL/min/1.73 m^2 and 96.4 $\pm$ 18.1 mL/min/1.73 m^2, respectively; both $p < 0.001$), however, patients not receiving cART had similar levels (110.1 $\pm$ 14.4 mL/min/1.73 m^2 and 109.8 $\pm$ 13.4 mL/min/1.73 m^2; $p = 0.387$). Compared with patients not receiving cART, the annual decline of eGFR was greater in the TDF-exposed group (0.57 $\pm$ 8.6 mL/min/1.73 m^2 and 2.7 $\pm$ 8.9 mL/min/1.73 m^2; $p = 0.012$). However, the annual declines of eGFR between the TDF-exposed group and the non-TDF-exposed group were not statistically significantly different (2.7 $\pm$ 8.9 mL/min/1.73 m^2 and 1.8 $\pm$ 8.3 mL/min/1.73 m^2; $p = 0.567$). The annual percentage of decline in eGFR was 0.1 $\pm$ 8.1% for the patients not receiving cART, which was significantly lower than that for the TDF-exposed group (2.3 $\pm$ 8.6%, $p = 0.032$) or the non-TDF-exposed group (1.3 $\pm$ 10.3%, $p = 0.035$). A urine specimen tested positive for proteinuria (protein level $\geq$ 30 mg/dL) in 23.2% of the patients not receiving cART, 13.9% of the patients in the TDF-exposed group, and 14.0% of the patients in the non-TDF-exposed group. The

Table 1 Baseline characteristics of the HIV-infected patients with different treatment status.

	Not on cART (n = 140)	cART experienced, TDF exposed (n = 393)	cART experienced, non-TDF exposed (n = 242)	P
Age (y)	31.5 ± 7.3	38.2 ± 10.0	43.4 ± 12.3	<0.001
Male sex	131 (93.6)	379 (96.4)	230 (95.0)	0.345
MSM	115 (82.1)	330 (84.0)	172 (71.1)	<0.001
Injecting drug user	15 (10.7)	6 (1.5)	5 (2.1)	<0.001
Weight (kg)	67.8 ± 14.1	65.9 ± 10.7	67.0 ± 11.4	0.63
BMI (kg/m^2)	23.0 ± 4.1	22.6 ± 3.4	23.4 ± 3.4	0.038
Comorbidity				
HBsAg positive	12 (8.6)	100 (25.4)	30 (12.4)	<0.001
Anti-HCV positive	28 (20)	37 (9.4)	10 (4.1)	<0.001
Hypertension	6 (4.3)	37 (9.4)	40 (16.5)	<0.001
Diabetes mellitus	5 (3.6)	15 (3.8)	21 (8.7)	0.018
CKD [a]	0 (0)	2 (0.5)	11 (4.5)	<0.001
Malignancy	1 (0.7)	28 (7.1)	15 (6.2)	0.554
Heart failure	0 (0)	2 (0.5)	2 (0.8)	0.017
Years since HIV diagnosis	5.5 ± 2.5	7.0 ± 4.8	9.9 ± 4.9	<0.001
Duration of ART (y)	0 ± 0	5.9 ± 4.6	9.1 ± 4.9	<0.001
CD4 count (cells/μL)	541 ± 173	374 ± 291	547 ± 258	<0.001
Plasma HIV RNA load ($\log_{10}$ copies/mL)	3.96 ± 0.8	3.3 ± 1.9	1.70 ± 0.9	<0.001
Exposed to PI	0 (0)	140 (35.6)	197 (81.4)	<0.001
ACEI or ARB use	3 (2.1)	14 (3.6)	17 (7.0)	0.042
Dyslipidemia	2 (1.4)	18 (4.6)	49 (20.2)	<0.001
Follow-up duration (d)	549 ± 267	797 ± 316	541 ± 137	<0.001

[a] Defined as eGFR < 60 mL/min/1.73 m^2.

Results are presented as n (%) or mean ± standard deviation.

ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; cART = combination antiretroviral therapy; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MSM = men who have sex with men; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate.

prevalence of proteinuria was significantly higher in the patients not receiving cART than the TDF-exposed and non-TDF-exposed groups (23.2% vs. 13.9%, $p = 0.032$; 23.2% vs. 14.0%, $p = 0.035$, respectively), but it was similar between the TDF-exposed and the non-TDF-exposed groups (13.9% vs. 14.0%, $p = 0.524$).

The factors influencing annual change of eGFR in HIV-infected patients were explored by multivariate linear regression (Table 3). The analysis indicated that presence of diabetes mellitus and dyslipidemia would lead to greater eGFR decrement annually at a rate of 5.01 mL/min/1.73 m^2 [95% confidence interval (CI), 1.539−7.128, $p = 0.002$] and 2.46 mL/min/1.73 m^2 (95% CI, 0.838−6.177, $p = 0.010$), respectively. On the contrary, chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2) and every additional CD4 cell count increase would lessen the annual decrement of eGFR. TDF exposure had no significant influence on annual eGFR change.

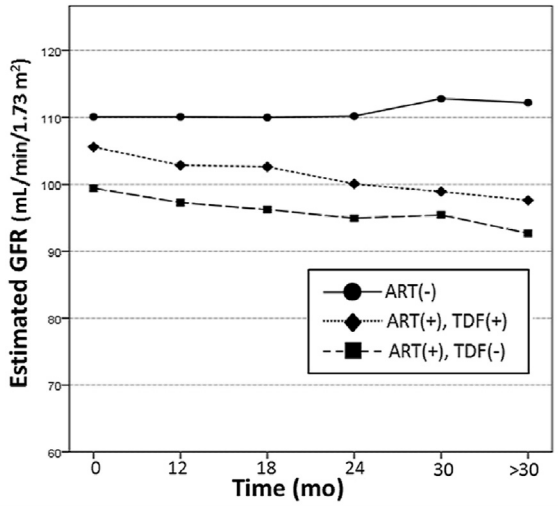
In the subgroup analysis, we investigated the influence of TDF exposure on the annual eGFR change in patients with different CD4 levels using linear regression. In 277 patients with CD4 count < 350 cells/μL, those exposed to TDF had an additional 2.73-mL/min/1.73 m^2 eGFR decrement annually (95% CI 0.139−5.326; $p = 0.039$). Diabetes mellitus continued to have a significant impact on eGFR decline in this analysis (Table 3, Analysis 2).

Factors associated with renal function decline in patients with TDF exposure

Analysis of the risk factors associated with annual eGFR loss >3 mL/min/1.73 m^2 in 393 TDF-exposed patients is shown in Table 4. In univariate analysis, factors associated with annual eGFR loss >3 mL/min/1.73 m^2 were increased plasma HIV RNA load and higher baseline eGFR. Patients with higher CD4 counts and longer TDF exposure appeared to have a lower rate of annual eGFR loss >3 mL/min/1.73 m^2. In multivariate logistic regression, higher baseline eGFR levels were associated with an increased risk of annual eGFR loss > 3 mL/min/1.73 m^2 [for every 10 mL/min/1.73 m^2 increase, odds ratio (OR) 1.292; 95% CI 1.123−1.486; $p < 0.001$], and higher CD4 counts were protective against HIV RNA (for every 1 cell/μL increase, OR 0.999; 95% CI 0.998−1.000; $p = 0.008$).

Outcomes of patients with TDF-related renal failure

During the study period, 11 of 393 (2.8%) patients discontinued TDF. Six patients switched to other cART regimens due to emergence of antiretroviral resistance, and five (1.3%) patients withdrew TDF due to increased serum



Months	0	12	18	24	30	>30
ART(-), *N*	140	77	66	53	21	12
ART(+),TDF(+), *N*	393	257	284	298	289	238
ART(+),TDF(-), *N*	242	220	217	95	12	4

Figure 1. Trends of changes in estimated glomerular filtration rate (eGFR) in HIV-infected patients with three different status of combination antiretroviral therapy (cART). The three groups were as follows: patients not receiving cART [ART (−)], patients receiving TDF-containing cART [ART (+), TDF (+)], and patients receiving cART not containing TDF [ART (+), TDF (−)]. The maximal follow-up duration was 48 months. TDF = tenofovir disoproxil fumarate.

creatinine levels. The details of these five patients are shown in Table 5. Their average eGFR at baseline was 74 mL/min/1.73 m^2. At TDF discontinuation, the average loss of eGFR was 32 mL/min/1.73 m^2, and the average increase of serum creatinine levels was 0.67 mg/dL. Three patients had pre-existing hypertension or diabetes mellitus. The other two patients had no chronic illness, but their body mass indices were < 20 kg/m^2. The serum creatinine level of four patients recovered partially after TDF discontinuation (median follow-up duration 161 days). The only one patient with worsening renal function despite discontinuation of TDF was the oldest, with poorly controlled diabetes mellitus.

Discussion

In this Taiwanese cohort, the average annual decline of eGFR in TDF-exposed patients was 2.7 mL/min/1.73 m^2. In multivariate analysis, TDF exposure was correlated with an additional annual eGFR decrement of 2.73 mL/min/1.73 m^2 in patients with CD4 count < 350 cells/μL. For patients receiving TDF, the factors associated with annual eGFR decrement > 3 mL/min/1.73 m^2 were lower CD4 counts and higher baseline eGFR in multivariate analysis. The prevalence of proteinuria was higher in patients not receiving cART, but similar between patients receiving TDF- or non-TDF-containing cART. During the 4-year study period, five (1.3%) patients withdrew TDF due to deteriorating renal function.

The first study in HIV-infected Asians to evaluate change of creatinine clearance after TDF initiation was performed in Thai patients.[21] Using the Cockcroft—Gault formula and MDRD formula, the authors concluded that creatinine clearance remained stable after a median of 21 weeks of TDF exposure. Later studies in HIV-infected Japanese,[12,18,23] Chinese,[22] and Vietnamese[28] patients all suggested a harmful effect of TDF on renal function, yet expressed the result in different ways, such as TDF exposure shown to increase the risk of eGFR < 60 mL/min/1.73 m^2, eGFR > 10 mL/min/1.73 m^2 or a 25% decline of eGFR from baseline, or presence of urine markers for proximal renal tubulopathy. Overall, these studies suggested a higher risk for TDF-related renal dysfunction among Asians than the patients in Western countries.

Few studies in Asian people calculated the eGFR changes over time. Cao et al[22] reported an 8.8-mL/min/1.73 m^2 decline in eGFR at Week 48 in patients receiving both TDF and protease inhibitors.[22] Kinai and Hanabusa[23] reported a 17-mL/min/1.73 m^2 loss of eGFR at Week 96 in TDF-treated patients. The degrees of eGFR decline in these two studies are much greater compared with our observation. This could be due to the difference in observation duration. Several reports have found that eGFR of TDF-treated patients tends to decline rapidly within the first few months of TDF exposure, and then stabilizes.[22,29,30] It has been suggested that changes in eGFR may be due to inhibition of creatinine secretion of the proximal tubule due to TDF exposure rather than due to actual damages to glomerular functions.[31] When patients are followed up for longer periods, the average annual decline in eGFR would be smaller. Another factor leading to discrepancies in eGFR levels among the different studies is the equation used to estimate GFR. In HIV-infected patients with eGFR > 120 mL/min/1.73 m^2, MDRD may give higher mean eGFR estimates than CKD-EPI.[32]

Advanced HIV disease, characterized by a low CD4 count and high plasma HIV RNA load, had been recognized as a predictor of TDF-related renal function decline.[10] Current guidelines suggest initiating cART in HIV-infected individuals with a CD4 count < 500 cells/μL, and as the priority, for patients who have a CD4 count < 350 cells/μL.[1] In our study, TDF exposure was associated with a 2.73-mL/min/1.73 m^2 eGFR decline annually in patients with CD4 count < 350 cells/μL. Our results suggest that more frequent monitoring of renal function is needed in patients with advanced HIV disease preparing for initiation of TDF-based regimens. Among the factors that would increase the risk of renal dysfunction in TDF-exposed patients, a lower body weight is frequently mentioned in Asian populations.[18,28,33] The hypothesis is that a lower weight would lead to a higher TDF plasma concentration, which increases the risk of nephrotoxicity. A recent study measuring TDF plasma concentration revealed that overexposure to TDF was associated with a time-dependent decrease in eGFR.[34] In multivariate analysis, we did not find a statistically significant association between a lower weight and kidney dysfunction. However, two of the five patients with no comorbidity who discontinued TDF due to worsening renal function in our study did have a low body mass index.

Our analyses showed TDF-exposed patients with higher eGFR at baseline tend to have more prominent eGFR loss.

Table 2 Renal function change and incidence of proteinuria of HIV-infected patients with different treatment status.

	Not on cART (n = 140)	cART experienced, TDF exposed (n = 393)	cART experienced, TDF unexposed (n = 242)	Three groups p	Not on cART vs. TDF exposed	Not on cART vs. TDF unexposed	cART experienced, TDF vs. non-TDF
					p		
First serum Cr (mg/dL)	0.89 ± 0.14	0.89 ± 0.18	0.91 ± 0.18				
Last serum Cr (mg/dL)	0.88 ± 0.13	0.93 ± 0.19	0.94 ± 0.22				
First eGFR [a] (mL/min/1.73 m^2)	110.1 ± 14.4	105.6 ± 16.4	99.4 ± 17.6				
Last eGFR (mL/min/1.73 m^2)	109.8 ± 13.4	100.5 ± 17.1	96.4 ± 18.1				
Annual eGFR change (mL/min/1.73 m^2)	−0.57 ± 8.6	−2.7 ± 8.9	−1.8 ± 8.3	0.057	0.012	0.12	0.567
Annual eGFR change (%)	−0.1 ± 8.1	−2.3 ± 8.6	−1.3 ± 10.3	0.059	0.032	0.035	0.524
Proteinuria (≥ 30 mg/dL)	23.2% (16/69)	13.9% (47/338)	14.0% (32/235)	0.115	0.052	0.055	0.922

[a] eGFR was calculated by CKD-EPI equation.
Results are n (%), or mean ± standard deviation.
cART = combination antiretroviral therapy; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; Cr = creatinine; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; TDF = tenofovir disoproxil fumarate.

Similar findings have also been reported previously.[18,35,36] Horberg et al[35] demonstrated that TDF-exposed patients with a baseline eGFR > 80 mL/min/1.73 m^2 had a more pronounced eGFR loss than those with baseline eGFR between 50 mL/min/1.73 m^2 and 79 mL/min/1.73 m^2. A later study from Japan found that high eGFR levels at baseline was a risk factor for a decline in eGFR by > 25%.[18] CKD patients were expected to have faster decline of renal function after initiating a nephrotoxic drug treatment. The exact reason for these conflicting data is unclear. One possible explanation is that by using the MDRD or CKD-EPI formula, patients with high eGFR had greater eGFR change than those with low eGFR in response to a same level of serum creatinine elevation. To avoid this phenomenon, methods that evaluate renal function directly, such as ^{51}Cr-EDTA clearance, might be more accurate.

Proteinuria was observed in a higher percentage of patients not receiving cART compared with the patients

Table 3 Determinants of annual change of eGFR in HIV-infected patients using multivariate linear regression.

Variable	Univariate analysis		Multivariate analysis	
	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
Analysis 1: All patients [a] (N = 775)				
Male sex	−3.574 (−6.493 to −0.600)	0.018		
Diabetes mellitus	−3.969 (−6.698 to −1.241)	0.004	−5.011 (−7.768 to −2.254)	<0.001
Chronic kidney disease	7.747 (2.997−12.497)	0.001	10.149 (5.403−14.895)	<0.001
Dyslipidemia	−1.986 (−4.138 to 0.165)	0.070	−2.455 (−4.610 to −0.301)	0.026
CD4 count (cells/μL)	0.004 (0.002−0.007)	<0.001	0.005 (0.003−0.007)	<0.001
Tenofovir exposure	−1.376 (−2.600 to −0.151)	0.028		
ACEI or ARB use	−2.616 (−5.608 to 0.377)	0.087		
Analysis 2: Patients with CD4 < 350 (cells/μL)[b] (N = 277)				
Diabetes mellitus	−13.862 (−20.757 to −6.967)	<0.001	−14.507 (−21.389 to −7.625)	<0.001
Tenofovir exposure	−2.246 (−4.905 to 0.412)	0.097	−2.733 (−5.326 to −0.139)	0.039

[a] In analysis 1, univariate linear regression showed no significant contribution (p > 0.1) of age, injective drug user, body weight, HBsAg-positivity, Anti-HCV-positivity, hypertension, congestive heart failure, duration of cART, plasma HIV RNA load, exposure to protease inhibitor, and follow-up duration on eGFR (not listed in the table).
[b] In analysis 2, univariate linear regression showed no significant contribution (p > 0.1) of age, injective drug user, body weight, HBsAg-positivity, Anti-HCV-positivity, chronic kidney disease, hypertension, congestive heart failure, dyslipidemia, ACEI or ARB use, duration of ART, plasma HIV RNA load, exposure to protease inhibitor, and follow-up duration on eGFR (not listed in the table).
ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; cART = combination antiretroviral therapy; CI = confidence interval; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Table 4 Determinants of annual decline of eGFR by ≥ 3 mL/min/1.73 m^2 in HIV-infected patients treated with tenofovir.

	Annual decline of eGFR		Univariate analysis		Multivariate analysis	
	≥ 3 mL/min/1.73 m^2 (n = 146)	< 3 mL/min/1.73 m^2 (n = 247)	OR (95% CI)	p	OR (95% CI)	p
Age (Y) [a]	38.8 ± 11.1	37.8 ± 9.3	1.009 (0.989–1.030)	0.363		
Male sex	143 (97.9)	236 (95.5)	2.222 (0.61–8.099)	0.226		
Weight < 50 kg	11 (7.5)	13 (5.5)	1.423 (0.62–3.268)	0.406		
HBsAg-positive	32 (21.9)	68 (27.5)	0.739 (0.457–1.196)	0.218		
Anti-HCV-positive	11 (7.5)	26 (10.5)	0.693 (0.332–1.447)	0.328		
Hypertension	17 (11.6)	20 (8.1)	1.496 (0.756–2.957)	0.247		
Diabetes mellitus	8 (5.5)	7 (2.8)	1.988 (0.706–5.600)	0.194		
Malignancy	11 (7.5)	17 (6.9)	1.102 (0.502–2.423)	0.808		
Congestive heart failure	1 (0.7)	1 (0.4)	1.697 (0.105–27.33)	0.709		
Dyslipidemia	5 (3.4)	13(5.3)	0.638 (0.223–1.828)	0.403		
CD4 count (cells/μL) [a]	308 ± 294	412 ± 282	0.999 (0.998–0.999)	0.004	0.999 (0.998–1.000)	0.008
HIV PVL (log_{10} copies/mL) [a]	3.6 ± 1.9	3.1 ± 1.8	1.156 (1.035–1.291)	0.010		
Exposure to PI	54 (37.0)	86 (34.8)	1.099 (0.718–1.682)	0.665		
ACEI or ARB use	6 (4.1)	8 (3.2)	1.280 (0.435–3.766)	0.653		
Tenofovir exposure (d) [a]	736 ± 178	833 ± 332	0.999 (0.998–1.000)	0.003	1.000 (0.999–1.000)	0.186
Baseline eGFR (mL/min/1.73 m^2) [a]	110.2 ± 16.4	102.9 ± 15.9	1.342 (1.168–1.542)	<0.001	1.292 (1.123–1.486)	<0.001

[a] For continuous variable in logistic regression, the odds ratios are shown for each 1-year increase in age, for each 1-cell/μL increase of CD4 count, for each 1 log_{10} copy/mL increase of PVL, for each 1-day increase of TDF exposure, and for each 10-mL/min/1.73 m^2 increase of baseline eGFR.

ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OR = odds ratio; PI = protease inhibitor; PVL = plasma HIV RNA load; TDF = tenofovir disoproxil fumarate.

receiving cART in our study. This is not unexpected because with the introduction of cART, there has been a decreasing incidence of HIV-associated nephropathy. A previous study also showed that cART initiation was associated with improvement in proteinuria.[37] Being a simple laboratory test, urine dipstick test is recommended for screening proteinuria in TDF-treated patients.[38] One study that included 10,841 HIV-infected patients reported that 1 additional year of TDF exposure was associated with 34% increased risk of proteinuria.[39] Limited by the small sample size of our study, we did not find a statistically significant difference in the prevalence of proteinuria between the TDF-exposed and non-TDF-exposed groups.

Five (1.3%) patients withdrew TDF due to increased serum creatinine levels during the study period. The average increase in serum creatinine levels was 0.67 mg/dL at TDF discontinuation. In a cohort study of 10,343 HIV-infected patients receiving TDF-containing cART, 2.2% of patients had an increase in serum creatinine levels of ≥ 0.5 mg/dL, and 0.5% experienced a serious renal adverse event of any type.[40] A more recent study in Thailand reported that 41 of 1204 (3.4%) TDF-treated patients had an increase in serum creatinine level of ≥ 0.5 mg/dL from baseline.[41] Published guidelines suggest obtaining measurements of serum creatinine levels consistently for TDF-treated patients.[38] However, there is no consensus on the optimal timing to discontinue TDF in patients whose kidney function declines progressively, and the best marker for TDF-related kidney injury has yet to be defined. After discontinuation of TDF, four of the five patients in this study had their eGFR partially recovered, which is in line with the previous studies showing that the loss of renal function may not be fully reversible with TDF withdrawal.[42]

There are several limitations of our study and our results should be interpreted with caution. First, this is a retrospective study. Patients included in our study might not have a uniform schedule of blood sampling, and their adherence to cART might be incomplete. Second, although we provided a relatively longer observation period than previous studies in Asia,[21,22] the duration of TDF exposure was no more than 4 years. Because the pattern of eGFR decline may not be linear, the changes of renal function in the short-term observation period may not predict the long-term clinical effect. Third, we did not examine other parameters representing renal tubular dysfunction, such as glycosuria, urine phosphate, or urinary β2-microglobulin. Likewise, we assessed proteinuria only qualitatively. Measurement of microalbuminuria or urine protein-to-creatinine ratio would more precisely reflect the urine protein loss. Finally, HIV-infected women and patients with a low eGFR comprised only a small proportion of our study populations. Whether our findings can be generalized to these patients warrants further investigations.

In conclusion, cART exposure correlated with the decline of renal function among HIV-infected Taiwanese patients. However, TDF-exposed patients are more likely to have

Table 5 Details of the patients who discontinued tenofovir due to worsening renal dysfunction.

Patient No.	Age/Sex	Weight (kg)/BMI (kg/m^2)	Comorbidity	Concomitant ART	CD4 (cells/μL)	TDF duration (d)	Baseline		Maximal		Protein in urinalysis (mg/dL)	After TDF withdrawal	
							Cr (mg/dL)	eGFR (mL/min/1.73 m^2)	Cr	eGFR		Cr	eGFR
1	40/M	55/18.2	Nil	3TC/LPVr	242	663	0.9	106	1.6	53	30 (1+)	1.3	67
2	43/M	67/22.3	HTN	3TC/EFV	497	869	1.5	53	1.9	42	Negative	1.5	55
3	50/M	73/26.1	HTN, DM	3TC/NVP	15	530	1.2	70	1.8	42	100 (2+)	1.7	45
4	54/M	60/19.2	Nil	3TC/RAL	13	311	1.1	76	1.9	39	30 (1+)	1.8	41
5	75/M	62/24.2	HTN, DM	3TC/LPVr	410	738	1.1	65	1.9	33	50 (1+)	2.2	28

3TC = lamivudine; ART = antiretroviral therapy; BMI = body mass index; Cr = creatinine; DM = diabetes mellitus; EFV = efavirenz; eGFR = estimated glomerular filtration rate; HTN = hypertension; LPVr = lopinavir/ritonavir; M = male; NVP = nevirapine; RAL = raltegravir; TDF = tenofovir disoproxil fumarate.

prominent eGFR decline, especially those with advanced HIV disease (lower CD4 and high HIV RNA), diabetes mellitus, and higher baseline eGFR levels. Our results highlight the importance of renal function monitoring when starting TDF in patients initiating cART. As the survival rates of HIV-infected patients are approaching that of the general population in the cART era, the impact of prolonged TDF exposure on renal function should be carefully monitored.

Conflicts of interest

C.-C. H. has received research support from Janssen and speaker honoraria from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and ViiV, and served on advisory boards for Gilead Sciences and AbbVie. All other authors have no conflicts of interest to declare.

Acknowledgments

We would like to thank Taiwan Centers for Disease Control for the research grant support. This study was supported by grants from the Centers for Disease Control, Taiwan (Grant Nos. DOH102-DC-1401 and MOHW103-CDC-C-114-000405 to C.-C. H.). The funding source played no role in study design and conduct, data collection, analysis or interpretation, writing of the manuscript, or the decision to submit it for publication.

References

1. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland: World Health Organization; 2013.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf [Last accessed June 24, 2015].
3. Wu PY, Chen MY, Hsieh SM, Sun HY, Tsai MS, Lee KY, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PLoS One* 2014;**9**:e104945.
4. Hsieh MH, Lu PL, Kuo MC, Lin WR, Lin CY, Lai CC, et al. Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan. *J Microbiol Immunol Infect* 2015;**48**:256—62.
5. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. *AIDS Res Treat* 2011;**2011**, Article id 562790.
6. Haverkort ME, van der Spek BW, Lips P, Slieker WA, ter Heine R, Huitema AD, et al. Tenofovir-induced Fanconi syndrome and osteomalacia in two HIV-infected patients: role of intracellular tenofovir diphosphate levels and review of the literature. *Scand J Infect Dis* 2011;**43**:821—6.
7. Rollot F, Nazal EM, Chauvelot-Moachon L, Kélaïdi C, Daniel N, Saba M, et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir-ritonavir-didanosine. *Clin Infect Dis* 2003;**37**:e174—6.
8. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? *J Am Soc Nephrol* 2013;**24**:1519—27.
9. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir

disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;**51**:496—505.
10. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Niño MD, Izquierdo MC, Poveda J, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat* 2011;**2011**, Article id 354908.
11. Laprise C, Baril JG, Dufresne S, Trottier H. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. *Clin Infect Dis* 2013;**56**:567—75.
12. Nishijima T, Kawasaki Y, Tanaka N, Mizushima D, Aoki T, Watanabe K, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS* 2014;**28**:1903—10.
13. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis* 2011;**57**:773—80.
14. Kelly MD, Gibson A, Bartlett H, Rowling D, Patten J. Tenofovir-associated proteinuria. *AIDS* 2013;**27**:479—81.
15. Nishijima T, Shimbo T, Komatsu H, Takano M, Tanuma J, Tsukada K, et al. Urinary beta-2 microglobulin and alpha-1 microglobulin are useful screening markers for tenofovir-induced kidney tubulopathy in patients with HIV-1 infection: a diagnostic accuracy study. *J Infect Chemother* 2013;**19**:850—7.
16. Sun HY, Hung CC, Lin PH, Chang SF, Yang CY, Chang SY, et al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *J Antimicrob Chemother* 2007;**60**:599—604.
17. Lin KY, Cheng CY, Yang CJ, Tsai MS, Hsieh SM, Sun HY, et al. Skin rash related to once-daily boosted darunavir-containing antiretroviral therapy in HIV-infected Taiwanese: incidence and associated factor. *J Infect Chemother* 2014;**20**:465—70.
18. Nishijima T, Komatsu H, Gatanaga H, Aoki T, Watanabe K, Kinai E, et al. Impact of small body weight on tenofovir-associated renal dysfunction in HIV-infected patients: a retrospective cohort study of Japanese patients. *PLoS One* 2011;**6**:e22661.
19. Mizushima D, Tanuma J, Kanaya F, Nishijima T, Gatanaga H, Lam NT, et al. WHO antiretroviral therapy guidelines 2010 and impact of tenofovir on chronic kidney disease in Vietnamese HIV-infected patients. *PLoS One* 2013;**8**:e79885.
20. Nishijima T, Komatsu H, Higasa K, Takano M, Tsuchiya K, Hayashida T, et al. Single nucleotide polymorphisms in ABCC2 associate with tenofovir-induced kidney tubular dysfunction in Japanese patients with HIV-1 infection: a pharmacogenetic study. *Clin Infect Dis* 2012;**55**:1558—67.
21. Gayet-Ageron A, Ananworanich J, Jupimai T, Chetchotisakd P, Prasithsirikul W, Ubolyam S, et al. No change in calculated creatinine clearance after tenofovir initiation among Thai patients. *J Antimicrob Chemother* 2007;**59**:1034—7.
22. Cao Y, Han Y, Xie J, Cui Q, Zhang L, Li Y, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. *BMC Infect Dis* 2013;**13**:301.
23. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. *AIDS Res Hum Retroviruses* 2009;**25**:387—94.
24. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Endo T, Horiba M, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. *PLoS One* 2013;**8**:e73639.
25. Centers for Disease Control, ROC, Taiwan. Guidelines for diagnosis and treatment of HIV/AIDS. Available from: http://www.cdc.gov.tw/uploads/files/201310/1e64c227-32fc-49ab-8bfc-9484ec50c4f3.pdf [Last accessed June 24, 2015].
26. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med* 2012;**156**:785—95.
27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1—150.
28. Mizushima D, Tanuma J, Dung NT, Dung NH, Trung NV, Lam NT, et al. Low body weight and tenofovir use are risk factors for renal dysfunction in Vietnamese HIV-infected patients. A prospective 18-month observation study. *J Infect Chemother* 2014;**20**:784—8.
29. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;**40**:1194—8.
30. Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008;**197**:102—8.
31. Hall AM. Update on tenofovir toxicity in the kidney. *Pediatr Nephrol* 2013;**28**:1011—23.
32. Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA, et al. Comparison of CKD-EPI and MDRD to estimate baseline renal function in HIV-positive patients. *Nephrol Dial Transplant* 2012;**27**:2291—7.
33. Chaisiri K, Bowonwatanuwong C, Kasettratat N, Kiertiburanakul S. Incidence and risk factors for tenofovir-associated renal function decline among Thai HIV-infected patients with low-body weight. *Curr HIV Res* 2010;**8**:504—9.
34. Lê MP, Landman R, Koulla-Shiro S, Charpentier C, Sow PS, Diallo MB, et al. Tenofovir plasma concentrations related to estimated glomerular filtration rate changes in first-line regimens in African HIV-infected patients: ANRS 12115 DAYANA substudy. *J Antimicrob Chemother* 2015;**70**:1517—21.
35. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. *J Acquir Immune Defic Syndr* 2010;**53**:62—9.
36. Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med* 2005;**6**:284—90.
37. Wyatt CM, Kitch D, Gupta SK, Tierney C, Daar ES, Sax PE, et al. Changes in proteinuria and albuminuria with initiation of antiretroviral therapy: data from a randomized trial comparing tenofovir disoproxil fumarate/emtricitabine versus abacavir/lamivudine. *J Acquir Immune Defic Syndr* 2014;**67**:36—44.
38. Gupta SK, Eustace JA, Winston JA, Boydstun II , Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;**40**:1559—85.
39. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2012;**26**:867—75.
40. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 2007;**21**:1273—81.
41. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Gvetadze RJ, et al. Renal function of participants in the Bangkok tenofovir study—Thailand, 2005—2012. *Clin Infect Dis* 2014;**59**:716—24.
42. Jose S, Hamzah L, Campbell LJ, Hill T, Fisher M, Leen C, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. *J Infect Dis* 2014;**210**:363—73.

Received: 4 February 2017 | Accepted: 28 April 2017

DOI: 10.1111/liv.13468

ORIGINAL ARTICLE

WILEY Liver INTERNATIONAL

Incidence of acute hepatitis A among HIV-positive patients during an outbreak among MSM in Taiwan: Impact of HAV vaccination

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Funding Information
The study was sponsored by the Centers for Disease Control, Taiwan (No. JH105022)

Handling Editor: Chun-Jen Liu

Abstract

Background: An unprecedented outbreak of acute hepatitis A has occurred among MSM in Taiwan since June 2015. We aimed to describe the seroepidemiology of HAV infection and to investigate the relationship between HAV vaccination and the incidence of acute hepatitis A among HIV-positive patients at the largest designated hospital for HIV care during the outbreak.

Methods: Between 2012 and 2016, the HAV serostatus, vaccination history and clinical characteristics of HIV-positive patients were retrospectively reviewed. A case-control study was performed to identify the factors associated with acute hepatitis A. The trends of HAV vaccination rate and incidence of acute hepatitis A among HAV-seronegative patients were examined during the outbreak.

Results: During the 4.5-year period, 2088 HIV-positive patients with a mean age of 37.7 years and 90.2% being MSM were included. The overall HAV seroprevalence was 34.3%, which was significantly higher in older and non-MSM patients. The estimated incidence rate of acute hepatitis A was 52.6 cases per 1000 person-years of follow-up during the outbreak. The associated factors with acquiring acute hepatitis A were recent syphilis and having not received HAV vaccines. The HAV vaccination rate during the outbreak increased from 4.7% to 70.6% and the incidence rate of acute hepatitis A declined when up to 65% of the patients were immunized or tested positive for HAV.

Conclusions: The seroprevalence of HAV infection was low in the younger HIV-positive individuals. Prevention of acute hepatitis A was achieved among HIV-positive, HAV-seronegative patients through HAV vaccination and increased herd immunity during the ongoing outbreak.

KEYWORDS
faecal-oral transmission, immunization, immunosuppression, sexually transmitted disease

Abbreviations: 95% CI, 95% confidence interval; ACIP, Adult Committee on Immunization Practices; AOR, adjusted odds ratio; cART, combination antiretroviral therapy; CDC, Centers for Disease Control; HAV, hepatitis A virus; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; IgM, immunoglobulin M; MSM, men who have sex with men; NTUH, National Taiwan University Hospital; PCR, polymerase-chain reaction; PVL, plasma HIV RNA load; PYFU, person-years of follow-up; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

1 | INTRODUCTION

Hepatitis A virus (HAV) is one of the most common infectious aetiologies of acute hepatitis worldwide, with an estimated 1.37 million cases in 2010.[1] The virus is transmitted faecal-orally, resulting in symptoms ranging from asymptomatic infection to fulminant hepatitis. In countries with a high endemicity for HAV, most individuals are exposed to HAV during childhood and develop long-standing protective immunity thereafter.[2] In contrast, residents from regions of low endemicity for HAV infection often remain susceptible in their adulthood; and clustered HAV infections or outbreaks have been reported in these regions. Other than being labelled as a food-borne infection, HAV can also be transmitted faecal-orally through oral-anal sex among men who have sex with men (MSM).[3,4] In developed countries, outbreaks among the MSM community have been reported and resulted in significant economic losses.[5-7]

HAV infection is a vaccine-preventable disease, and current guidelines recommend HAV vaccination for high-risk groups such as MSM.[8,9] HAV vaccination not only provides protection to vaccinated individuals, but generates herd immunity against outbreaks of acute hepatitis A in the MSM community when a high HAV vaccine coverage is achieved.[10,11] HAV vaccines, with or without HAV immune globulin, are also recommended by international guidelines for post-exposure prophylaxis.[8,9] Recently, Parron et al.[12] reported using HAV vaccination as post-exposure prophylaxis during outbreaks for patients exposed to index cases of acute hepatitis A, with an estimated efficacy of 97.6%. However, it is not clear whether the results could be generalized to HIV-positive individuals who have suboptimal responses to HAV vaccination.[13] Furthermore, the effectiveness of implementing HAV vaccination in the setting of an ongoing outbreak of acute hepatitis A has rarely been evaluated. In this retrospective cohort study, we aimed to investigate the seroepidemiology of HAV and the correlation between HAV vaccine coverage and the incidence of acute hepatitis A among HIV-positive patients seeking HIV care at a designated university hospital during an ongoing acute hepatitis A outbreak in Taiwan between mid-2015 and 2016.[14]

Key Points

- While the HAV seroprevalence was low among young HIV-positive MSM in Taiwan, poor adherence to HAV vaccination recommended was observed before the outbreak of acute hepatitis A.
- During the outbreak of acute hepatitis A in Taiwan, recent syphilis was identified as the associated factor among HIV-positive MSM in the case-control study.
- During the ongoing outbreak, HAV vaccination for HIV-positive individuals reduced the risk of acute hepatitis A.
- In the setting of an outbreak of acute hepatitis A, a herd immunity exceeding 65% of the entire cohort reduced further transmission of HAV.

2 | METHODS

2.1 | Study setting

Acute hepatitis A is a notifiable disease in Taiwan, and an average of 83 indigenous cases were reported to Taiwan's Centers for Disease Control (CDC) annually during 2010 to 2014.[15] Since June 2015, an ongoing acute hepatitis A outbreak has been occurring in Taiwan,[14] and a total of 1053 indigenous cases were reported in 2016, with 65% of the cases concentrating in four cities in the greater Taipei area (Taipei City, Keelung City, New Taipei City and Taoyuan City).[15] High rates of HIV co-infection and MSM characterized this outbreak. Further virological investigations revealed that HAV genotype 1A was responsible for this outbreak (Taiwan CDC, unpublished data). Before this outbreak, the rate of HAV vaccination had been low among HIV-positive patients, despite the recommendations by the Adult Committee on Immunization Practices (ACIP) of Taiwan CDC. In response to the outbreak, a campaign of 2-dose HAV vaccination, given at 6-12 months apart, was launched at the designated hospitals for HIV care around Taiwan since September 2015. In the campaign, Taiwan CDC announced the outbreak in the mass media and distributed alert letters to medical societies concerned and specialists of infectious diseases to promote HAV screening and vaccination among the at-risk populations. Afterwards, since 1st October 2016, the Taiwan CDC started to provide free-of-charge HAV vaccines to patients with HIV infection and those with newly diagnosed syphilis or gonorrhoea who were aged 40 years or less. In our cohort, all HIV-positive patients were encouraged to receive HAV vaccines regardless of their CD4 cell count, plasma HIV RNA load (PVL), or use of combination antiretroviral therapy (cART).

2.2 | Study population

HIV-positive patients aged 18 years or greater who sought HIV care at least once at the National Taiwan University Hospital (NTUH) between 1st January 2012 and 30th June 2016 were included in this study. HIV-positive individuals who had never been tested for anti-HAV antibodies were excluded from further analysis. HIV-positive patients who were lost to follow-up before 1st June 2015 were also excluded since their information on contracting acute hepatitis A was not available during the outbreak.

We reviewed the medical records of the patients from 1st January 2012 to 30th November 2016 to collect information on demographics and clinical characteristics, which included age, sex, risk group for HIV transmission, use of antiretroviral therapy, CD4 cell count and PVL at baseline, and serologies of HAV, hepatitis B virus (HBV), hepatitis C virus (HCV) and syphilis at baseline and during follow-up, and dates of HAV vaccination and acute hepatitis A.

Most of the included patients were followed every 3-6 months as part of routine HIV care in our clinics according to the national HIV treatment guidelines. All patients were followed until time of death, loss to follow-up, or to end of this study on 30th November, 2016,

whichever occurred first. The study was approved by the National Taiwan University Hospital Research Ethics Committee (registration no., 201003112R) and informed consent was waived.

2.3 | Laboratory investigations

During the study period, the determinations of anti-HAV immunoglobulin G (IgG) were performed using chemiluminescence immunoassay (ARCHITECT HAVAb-IgG, Abbott Diagnostics, Wiesbaden, Germany). In patients with acute hepatitis A during the study period, anti-HAV immunoglobulin M (IgM) was determined with the use of the Architect HAVAb-IgM assay (Abbott Diagnostics, Wiesbaden, Germany). Anti-HCV antibody and HBV surface antigen (HBsAg) were also detected by chemiluminescent micro-particle immunoassays. PVL was quantified using the Cobas Amplicor HIV-1 Monitor test (Cobas Amplicor version 1.5, Roche Diagnostics, Indianapolis, IN, USA) with a lower detection limit of 20 (1.3 $\log_{10}$) copies/mL. CD4 count was determined using FACFlow (BD FACS Calibur, Becton Dickinson, San Jose, CA, USA). Serological tests for syphilis included the rapid plasma regain (RPR) test (BD Macro-VueTMRPR Card tests, USA) and *Treponema pallidum* particle agglutination (TPPA) test (FTI-SERODIA-TPPA. Fujirebio Taiwan Inc., Taoyuan, Taiwan).

2.4 | Case definitions

Acute hepatitis A was defined by the presence of clinical symptoms, elevated aminotransferases and positive anti-HAV IgM. Stool specimens were obtained from those who were diagnosed with acute hepatitis A for polymerase-chain reaction (PCR) assays to detect HAV at the Taiwan CDC. The baseline HAV serology was defined as the first available anti-HAV IgG test results between 1st January 2012 and 30th June 2016. Baseline clinical characteristics and laboratory findings were those collected at the time of baseline HAV serological testing. Patients who tested positive for anti-HAV IgG at baseline were defined as "HAV-seropositive" and considered to be immune to new HAV infection; in contrast, patients who tested negative for anti-HAV IgG were defined as "HAV-seronegative" and considered susceptible to acute HAV infection before HAV vaccination was administered.

Patients who had consistent clinical symptoms, new RPR seroreactivity in the presence of positive TPPA test, or a four-fold increase in RPR titres were considered to have early syphilis that included primary, secondary, or early latent syphilis.

2.5 | Case-control study

After identifying the cases of acute hepatitis A in our cohort during the study period, we conducted a 1:3 matched case-control study to examine the associated factors with acute hepatitis A. Controls were those HAV-seronegative, HIV-positive patients in our cohort who did not acquire acute hepatitis A during the same period. Controls were matched to cases by age (±3 years), sex, route of HIV transmission and duration of follow-up (±3 months). If more than three controls were available for matching, three controls were selected randomly by the EXCEL software, version 15.29 (Microsoft Corporation, Albuquerque, New Mexico, the United States).

2.6 | Incidence of acute hepatitis A and vaccine coverage

To better understand the relationship between the incidence of acute hepatitis A and HAV vaccine coverage, we calculated the duration of follow-up and incidence of acute hepatitis A among unvaccinated, HAV-seronegative patients every 6 months before and every 2 months after the detection of acute hepatitis A outbreak in Taiwan. For each unvaccinated, HAV-seronegative patient included, the at-risk duration was defined as the interval between the date of the first available HAV serology or beginning of the designated follow-up period, whichever occurred first, and the date of death, loss to follow-up, administration of the first dose of HAV vaccines or the end of designated study period, whichever occurred first. Confirmed cases of acute hepatitis A were recorded within each designated period and the incidence was calculated accordingly. The observation of the study ended on 30 November, 2016.

It has been hypothesized that a substantial proportion of immunity to HAV in the high-risk population could confer herd immunity and prevent outbreaks from taking place.[11] To better describe the relationship between the incidence rate of acute hepatitis A and the level of HAV herd immunity during this outbreak, we classified patients as being "protected against HAV" for those who were HAV-seropositive at baseline, had received at least one dose of HAV vaccine, or had recovered from acute hepatitis A during the study period. In our previous HAV vaccination study, we have found that HAV-seropositive patients following vaccination might lose their anti-HAV IgG during the 5-year longitudinal follow-up;[16,17] those patients with sero-reversion would be considered susceptible to new HAV infections and HAV booster vaccination was recommended if they tested negative for anti-HAV during the study period.

The proportion of patients who were "protected against HAV" and the incidence rate of acute hepatitis A were calculated at the beginning of and during each designated follow-up period. Total reported cases of acute hepatitis A in the greater Taipei region were also recorded for comparison.

2.7 | Statistical analysis

We used descriptive statistics to describe the seroprevalence of HAV infection among the HIV-positive patients. To understand the relationship between the level of herd immunity and the incidence of acute hepatitis A, we depicted the proportion of patients immune to HAV and the incidence rate of acute hepatitis A every 2 months during the outbreak. Comparisons of demographic and clinical characteristics were made between HAV-seropositive and HAV-seronegative patients. The non-categorical variables were compared using Student's *t* test or Mann-Whitney *U* test and categorical variables were compared using Chi-square test. In the case-control study, a multivariable logistic regression analysis was used to determine the adjusted odds ratio

of each variable for acquiring acute hepatitis A. The statistical analyses were performed using STATA software, version 14.0 S/E (Stata Corporation, College Station, Austin, TX). All *P* values are two-sided.

3 | RESULTS

3.1 | HAV seroprevalence and baseline characteristics

During the 54-month study period, 2859 HIV-positive patients sought HIV care at NTUH; 771 patients (27.0%) who had never been tested for HAV serologies were excluded from further analysis. Of the 2088 patients with available baseline anti-HAV IgG data, 34.3% (n=717) were seropositive and 65.7% (n=1371) were seronegative. The HAV seroprevalences in different age groups are shown in Figure 1. Of note, the HAV seropositivity was 19.6% (247/1262) among those who were MSM and aged 40 years or less.

The demographic and clinical characteristics of HAV-seropositive and HAV-seronegative patients are shown in Table 1. In multivariable logistic regression analysis, factors that remained statistically significantly associated with HAV seropositivity were age (per 1-year increase, adjusted odds ratio [AOR], 1.09; 95% confidence [95% CI], 1.08-1.11), previous HAV vaccination (AOR, 5.25; 95% CI, 4.05-6.82) and not acquiring HIV via MSM risk behaviour (AOR, 1.95; 95% CI, 1.17-3.24; data not shown).

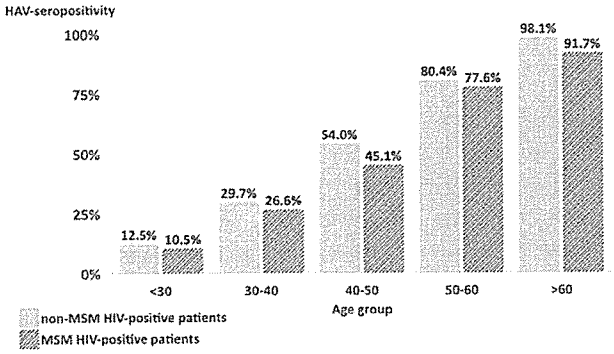


FIGURE 1 HAV seroprevalence by age and risk groups of HIV transmission

3.2 | Case-control study

Forty-six cases of acute hepatitis A were diagnosed during the follow-up period. All of the patients contracting acute hepatitis A were MSM. Of these 46 patients, four developed acute hepatitis A after receiving HAV vaccines; two developed acute hepatitis A within 2 weeks after HAV vaccination and the other two developed acute hepatitis A 3 and 6 months after the first dose of HAV vaccination, respectively.

The comparisons made between the 46 case patients and 138 controls are shown in Table 2. In multivariable logistic regression model, case patients with acute hepatitis A were more likely to have early syphilis within 3 months (AOR, 9.41; 95% CI, 3.23-27.40), less likely to have received HAV vaccines during the study period (AOR, 0.10; 95% CI 0.10-0.35), and had lower baseline PVL (AOR per 1-log increase, 0.77; 95% CI 0.63-0.94) when compared to controls (data not shown). There were no statistically significant differences in other clinical characteristics, including baseline CD4 cell count, presence of anti-HCV antibody and HBsAg at baseline and recent acquisition of HCV.

3.3 | HAV vaccine coverage and acute HAV infection

During the study period, a total of 944 of 1371 HAV-seronegative patients (68.9%) received at least one dose of HAV vaccine. Most of the vaccinated patients (919/944, 97.4%) received vaccination only after the outbreak was taking place. Early in the outbreak, the coverage rate of vaccination was as low as 4.7% among HAV-seronegative patients (3.8% of our entire cohort) despite our vaccination campaign,

TABLE 1 The demographic and clinical characteristics of HAV-seropositive and HAV-seronegative HIV-positive patients

Variables	Baseline serostatus			
	All patients N=2088	HAV-seropositive N=717	HAV-seronegative N=1371	*P*-value
Age, mean (SD), y	37.7 (10.9)	45.1 (11.7)	33.9 (8.2)	<.001
Male sex, n (%)	2019 (96.7)	679 (94.7)	1340 (97.7)	<.001
MSM, n (%)	1884 (90.2)	592 (81.6)	1299 (94.7)	<.001
cART use, n (%)	2019 (96.7)	701 (97.8)	1318 (96.1)	.046
HBsAg positivity, n (%)	258/1952 (13.2)	122/690 (17.7)	136/1262 (10.8)	<.001
Anti-HCV positivity, n (%)	92/1851 (5.0)	40/664 (6.0)	52/1187 (4.4)	.12
Baseline PVL, median (IQR), $\log_{10}$ copies/mL[a,b]	1.3 (1.3-4.5)	1.3 (1.3-2.7)	2.3 (1.3-4.7)	<.001
Baseline CD4 cell count, median (IQR), cells/μL[b]	484 (325-666)	519 (362-702)	468 (304-652)	<.001
Previous HAV vaccination before the outbreak, n (%)	573 (27.4)	408 (56.9)	165 (12.0)	<.001

CART, combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; PVL, plasma HIV RNA load.

[a]Patients with undetectable PVL were arbitrarily assigned as having 19 copies/mL.

[b]Baseline data of CD4 and PVL were obtained within 3–6 mo of inclusion into the study.

TABLE 2 Case-control analysis of factors associated with acute hepatitis A

	Case N=46	Control N=138	*P*-value
Age, mean (SD), y	30.2 (5.9)	30.3 (5.7)	.93
Male sex, n (%)	46 (100)	138 (100)	–
MSM, n (%)	46 (100)	138 (100)	–
HBsAg positivity at baseline, n (%)	4/40 (10)	7/110 (6.3)	.39
Anti-HCV positivity at baseline, n (%)	5/44 (11.3)	6/130 (4.3)	.11
HCV seroconversion[a]	1/29 (2.2)	1/79 (0.7)	.46
cART use, n (%)	44/46 (95.7)	135/138 (97.8)	.60
Baseline CD4 cell count, median (IQR), cells/μL[c]	420 (310-666)	432 (258-595)	.82
Baseline PVL, median (IQR), $\log_{10}$ copies/mL[b,c]	3.9 (1.3-4.9)	4.5 (3.6-5.1)	.04
Duration of follow-up, median (IQR), mo	18.3 (18.3-31.8)	19 (14.5-31.8)	.82
Recent syphilis within ±3 mo of acute hepatitis A, n (%)	18/46 (12.3)	9/136 (6.6)	<.001
Previous HAV vaccination before date of acute hepatitis A, n (%)[d]	4/46 (8.7)	58/138 (42.0)	<.001

CART, combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; PVL, plasma HIV RNA load; IQR, interquartile range; MSM, men who have sex with men; SD, standard deviation.

[a]Patients who had HCV seroconversion during the study period.

[b]Patients with undetectable PVL were arbitrarily assigned as having 19 copies/mL.

[c]Baseline data of CD4 and PVL were obtained within 3–6 mo of inclusion into the study.

[d]For the control patients, we considered them to be "vaccinated before the date of acute hepatitis A" if they were vaccinated before their matched case patients were diagnosed with acute hepatitis A.

which increased to reach 70.6% of the HAV-seronegative patients at the end of the study, when the acute hepatitis A outbreak continued around Taiwan.

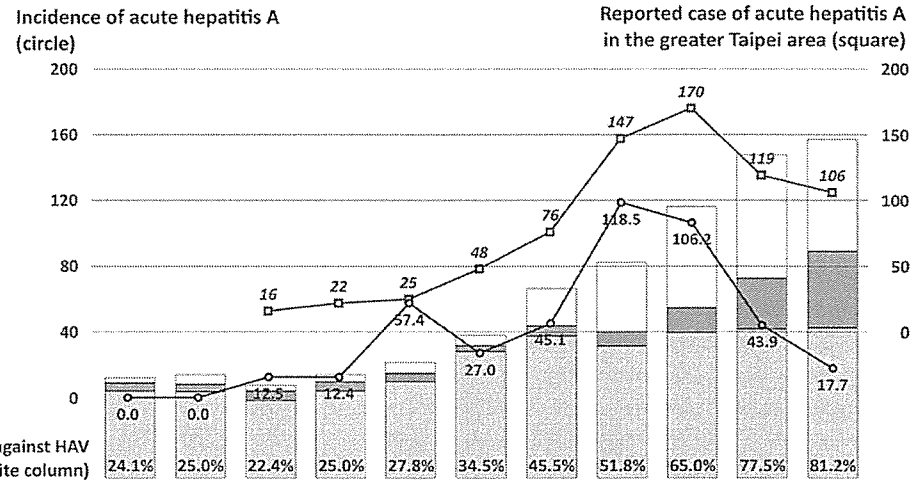
The total follow-up duration of unvaccinated, HAV-seronegative patients was 798.66 person-years. The overall incidence rate of acute hepatitis A was 52.6 cases per 1000 person-years of follow-up (PYFU) during the outbreak period (from 1st June 2015 to 30th November 2016).

The trends of the proportions of patients who were "protected against HAV" (ie, patients who were vaccinated or tested positive for HAV), and the incidence rates of acute hepatitis A are demonstrated in Figure 2. After the detection of the acute hepatitis A outbreak, the incidence rate of acute hepatitis A in our cohort continued to increase with time, peaking in April-May 2016, with an incidence rate of 118.5 cases per 1000 PYFU. Meanwhile, the proportions of patients who were protected against HAV also increased simultaneously. Although the proportion of HAV-seropositive patients remained stable at around 20%-30%, the proportion of HAV-seronegative patients who received HAV vaccines continued to increase during the ongoing outbreak. In June, 2015, when the first several cases of acute hepatitis A were reported, only 4.7% of HAV-seronegative patients in our cohort had ever been vaccinated and 2.8% of HAV-seronegative patients had completed two doses of HAV vaccination. As of October, 2016, the proportion of HAV-seronegative patients who received one dose and two doses had increased to 70.6% and 28.8% respectively. After the proportion of patients who were vaccinated or tested positive for HAV exceeded 65% of the entire cohort, the incidence rate of acute hepatitis A started to decrease in our hospital and a similar trend, albeit to a lesser extent and delayed, was observed within the greater Taipei area (Figure 2).

4 | DISCUSSION

In this cohort study conducted in Taiwan, we found that the overall seroprevalence of HAV was low in HIV-positive patients, particularly in MSM aged less than 40 years (19.6%), which may facilitate the development of outbreaks of acute hepatitis A, along with risky sexual behaviours and low adherence to the recommended HAV vaccination. In the setting of the acute hepatitis A outbreak in Taiwan, we found that the overall incidence rate of acute hepatitis A was 52.6 cases per 1000 PYFU among the HAV-seronegative, HIV-positive patients seeking HIV care at our university hospital. The incidence rate declined only after the level of herd immunity exceeded 65% of our entire cohort in the setting of the ongoing outbreak. By the time when the incidence of acute hepatitis A started to decline, 46.4% of HAV-seronegative patients had been vaccinated against HAV but only 9.1% had completed two doses of HAV vaccines (Figure 2).

Although serological responses after HAV vaccination were not determined, one dose of HAV vaccine seemed to provide high level of protection against new HAV infection in our cohort in the setting of ongoing outbreak of acute hepatitis A, as only four vaccinees developed



Patients received 1 HAV vaccine (white column)	1.2%	2.3%	1.5%	1.9%	2.6%	2.6%	9.0%	16.7%	24.3%	29.5%	26.8%
Patients received 2 HAV vaccines (deep grey column)	2.0%	1.8%	2.3%	2.2%	2.1%	1.5%	2.4%	3.5%	5.9%	12.1%	18.4%
Proportion of HAV-seropositivity (pale grey column)	20.9%	20.8%	18.6%	20.9%	23.1%	30.3%	34.1%	31.6%	34.9%	35.8%	36.0%
Incidence of acute hepatitis A within cohort (○)	0.0	0.0	12.5	12.4	57.4	27.0	45.1	118.5	106.2	43.9	17.7
Reported acute hepatitis A in the greater Taipei area (□)	—	—	16	22	25	48	76	147	170	119	106

FIGURE 2 The relationship between HAV vaccine coverage and incidence rate of acute hepatitis A in our cohort, and reported cases of acute hepatitis A in the greater Taipei area

acute hepatitis A after their first dose of HAV vaccine. It is well known that serological responses to HAV vaccines among HIV-positive individuals are inferior to HIV-negative individuals,[13,17] and the serological responses are positively associated with higher CD4 cell counts and suppression of HIV replication.[17,18] In our cohort, 96.7% of patients were on cART and had a high CD4 cell count (median, 484 cells/μl), which might contribute to the high level of protection observed in our cohort after the first dose of HAV vaccination.

In recent years, the seroprevalence of HAV had declined significantly in Taiwan.[19,20] In our previous survey in 2009-2010, the HAV seroprevalence of HIV-positive MSM aged 40 year or less was 15.1%,[21] which was similar to the proportion (19.6%) observed in this study. Despite the recommendations by the ACIP of Taiwan CDC, the adherence to HAV vaccination in this immunocompromised remained low; only 12% of HIV-positive patients had received HAV vaccines before 2012 in our cohort and only 4.7% of HAV-seronegative patients underwent vaccination early in the outbreak. The low adherence to the vaccination recommendation may be explained by the fact that HAV infection is often overlooked by physicians and patients because of its self-limited disease course. In a study enrolling 1329 HIV-positive MSM in the United States who were regularly followed at HIV clinics, only 47.2% were screened for HAV serologies and only 28.5% of HAV-seronegative patients were vaccinated.[22]

In our cohort, acute hepatitis A was statistically significantly associated with early syphilis within 3 months. In many studies, syphilis was used as a surrogate of risky sexual behaviours that increased transmission of other sexually transmitted diseases. In HIV-positive patients, recent syphilis had been linked to seroconversion of sexually transmitted HCV.[23,24] A similar association was also observed in faecal-orally transmitted infections such as shigellosis.[25] Outbreaks of sexually transmitted HAV had been reported in the past decades worldwide.[5,6,13] In an outbreak of acute hepatitis A affecting 25 MSM in New York in 1995, the transmission of HAV was associated with recent oral-anal or digital-rectal intercourse.[26] In Denmark, an outbreak of acute hepatitis A was also linked to casual sex in gay saunas.[27] These findings highlight that safe sex practices and adherence to vaccination recommendations for vaccine-preventable diseases cannot be overemphasized in the high-risk populations such as MSM.

The effectiveness of HAV vaccination in the outbreak setting has rarely been evaluated in high-risk populations before. In a retrospective study focusing on post-exposure prophylaxis for individuals who had exposure to index HAV cases during an outbreak, Parron et al.[12] found that HAV vaccination resulted in a 97.6% reduction of secondary cases. In our case-control study, timely HAV vaccination was protective against acquiring acute hepatitis A (AOR 0.10, 95% CI 0.03-0.35). We also demonstrated herd immunity whereby the incidence rate of acute hepatitis A declined as the proportion of patients who were "protected against HAV" in our cohort expanded (Figure 2). Beginning from the onset of the outbreak in June 2015, the incidence rate of acute hepatitis A continued to increase every 2 months with a peak observed in April-May 2016. The proportion of patients "protected against HAV" also increased as more and more patients received HAV vaccine in our cohort. The incidence rate of HAV declined significantly when the level of herd immunity exceeded 65%. Meanwhile, the reported cases of acute hepatitis A within greater Taipei area did not decrease as drastically as that in our cohort.

Like other infectious diseases, it has been hypothesized that herd immunity against HAV might serve to prevent outbreaks from taking place. In an observational cohort study from Australia, the authors concluded that HAV outbreaks were rare when the HAV seroprevalence exceeded 40%-50% at the population level.[10] Using the epidemiological data collected during the 1991-1992 outbreaks in Sydney, Regan et al.[11] estimated the range of basic reproduction number (R_0) of HAV among an MSM population to be 1.71-3.67. Based on this estimation, they also suggested a critical immunity threshold of 70% to prevent future outbreaks.

The study has several limitations and interpretation of our findings should be cautious. Firstly, while our data were collected retrospectively from the largest medical centre for HIV care in northern Taiwan where the epidemic concentrated, most patients received cART and had achieved good control of HIV. Our findings might not be generalizable to other parts of world or cohorts of HIV-positive patients not receiving cART or with more advanced immunosuppression. Secondly, not all HIV-positive patients in our cohort were tested for anti-HAV IgG and we were not able to have a precise estimation of the serological responses to HAV vaccination and seropositivity throughout the study duration. Thirdly, in the case-control study, potential factors associated with risky sexual behaviours, such as recreational drug use or unprotected oral-genital or oral-anal sex and consistency of condom use, were not recorded. Fourthly, in the analysis of vaccine coverage rate and incidence of acute hepatitis A in our cohort, we were not able to determine the impact of vaccine coverage rate in the community. Also, our study only focused on symptomatic acute hepatitis A and might have underestimated the true incidence of HAV acquisition since asymptomatic seroconversion could not be estimated in our cohort.

In conclusion, we identified that the incidence of acute hepatitis A in the setting of a prolonged outbreak started to decline when the level of herd immunity for HAV reached 65% among HIV-positive patients in Taiwan, where the contemporary HAV seroprevalence remained low in the young MSM population. Provision of information, education and communication with respect to safe sex practices and HAV vaccination are important to prevent future outbreaks among such susceptible persons.

CONFLICT OF INTEREST

Chien-Ching Hung has received research support from Janssen, Abbvie, Bristol-Myers Squibb, Merck, and ViiV and speaker honoraria from Gilead Sciences, and served on the advisory boards for Gilead Sciences, ViiV, Abbvie and Janssen. Other authors report no potential conflict of interest.

REFERENCES

1. Havelaar AH, Kirk MD, Torgerson PR, et al. World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. *PLoS Med*. 2015;12:e1001923.
2. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine*. 2010;28:6653-6657.
3. Franco E, Giambi C, Ialacci R, Coppola RC, Zanetti AR. Risk groups for hepatitis A virus infection. *Vaccine*. 2003;21:2224-2233.
4. Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. *N Engl J Med*. 1980;302:435-438.
5. Tortajada C, de Olalla PG, Pinto RM, Bosch A, Cayla J. Outbreak of hepatitis A among men who have sex with men in Barcelona, Spain, September 2008-March 2009. *Euro Surveill*. 2009;14:19175.
6. Bordi L, Rozera G, Scognamiglio P, et al. Monophyletic outbreak of Hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008-2009. *J Clin Virol*. 2012;54:26-29.
7. Sansom SL, Cotter SM, Smith F, et al. Costs of a hepatitis A outbreak affecting homosexual men: Franklin County, Ohio, 1999. *Am J Prev Med*. 2003;25:343-346.
8. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55:1-23.
9. Geretti AM, Brook G, Cameron C, et al. British HIV Association Guidelines on the Use of Vaccines in HIV-Positive Adults 2015. *HIV Med*. 2016;17(Suppl. 3):s2-s81.
10. Weerakoon AP, Chen MY, Read TR, Bradshaw C, Fairley CK. Immunity to hepatitis A when outbreaks of infection in men who have sex with men (MSM) are rare. *Vaccine*. 2012;30:3430-3434.
11. Regan DG, Wood JG, Benevent C, et al. Estimating the critical immunity threshold for preventing hepatitis A outbreaks in men who have sex with men. *Epidemiol Infect*. 2016;144:1528-1537.
12. Parron I, Planas C, Godoy P, et al. Effectiveness of hepatitis A vaccination as post-exposure prophylaxis. *Hum Vaccin Immunother*. 2017;13:423-427.
13. Lin KY, Chen GJ, Lee YL, et al. Hepatitis A virus infection and hepatitis A vaccination in HIV-positive patients: a review. *World J Gastroenterol*. 2017;23:3589-3606.
14. Chen GJ, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. *J Infect Dis*. 2017;215:1339-1340.
15. http://nidss.cdc.gov.tw/en/. Accessed January 6, 2017.
16. Cheng A, Chang SY, Sun HY, et al. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in HIV-positive adults on antiretroviral therapy. *J Infect Dis*. 2017;215:606-613.
17. Tseng YT, Chang SY, Liu WC, et al. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. *Hepatology*. 2013;57:1734-1741.
18. Kemper CA, Haubrich R, Frank I, et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis*. 2003;187:1327-1331.
19. Tsai CF, Lin DB, Chen SC, Chang YH, Chen CY, Lin JB. Seroepidemiology of hepatitis A virus infection among schoolchildren in Taiwan. *J Med Virol*. 2011;83:196-200.
20. Tsou TP, Liu CC, Huang JJ, Tsai KJ, Chang HF. Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995-2008. *Vaccine*. 2011;29:2956-2961.
21. Tseng YT, Sun HY, Chang SY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. *J Formos Med Assoc*. 2012;111:431-438.
22. Hoover KW, Butler M, Workowski KA, et al. Low rates of hepatitis screening and vaccination of HIV-infected MSM in HIV clinics. *Sex Transm Dis*. 2012;39:349-353.
23. Sun HY, Chang SY, Yang ZY, et al. Recent hepatitis C virus infections in HIV-infected patients in Taiwan: incidence and risk factors. *J Clin Microbiol*. 2012;50:781-787.
24. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. *Int J Infect Dis*. 2016;49:47-58.

25. Chiou CS, Izumiya H, Kawamura M, et al. The worldwide spread of ciprofloxacin-resistant Shigella sonnei among HIV-infected men who have sex with men, Taiwan. *Clin Microbiol Infect*. 2016;22:383.e11-6.
26. Henning KJ, Bell E, Braun J, Barker ND. A community-wide outbreak of hepatitis A: risk factors for infection among homosexual and bisexual men. *Am J Med*. 1995;99:132-136.
27. Mazick A, Howitz M, Rex S, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill*. 2005;10:111-114.

How to cite this article: Chen G-J, Lin K-Y, Sun H-Y, et al. Incidence of acute hepatitis A among HIV-positive patients during an outbreak among MSM in Taiwan: Impact of HAV vaccination. *Liver Int*. 2017;00:1–8. https://doi.org/10.1111/liv.13468