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衛生福利部疾病管制署 105 年委託科技研究計畫

愛滋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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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 105 年 9 月底止，本國籍 HIV 感染通報人數共 32,817 人，已造成 5,397 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 19 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」105 年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

研究重點：愛滋病防治之相關措施及治療照護與專業醫療人力培訓應用研究

研究目標：藉由調查及實驗室分析不同之易感族群之醫療利用特性，結合全國愛滋病指定醫院協力從事愛滋病防治相關流行病學與臨床治療研究、監測、專業人員培訓及感染者預防計畫，以發展更佳之醫療照護及防治之介入模式，提供健全愛滋病醫療照護及防治策略之建議。

研究內容：

主題 1.愛滋病毒體液暴露後預防性用藥（Post-exposure Prophylaxis）：提供衛教諮詢、檢驗、預防性投藥與追蹤等服務，並評估其治療成效以及於高風險族群進一步推廣之效益與可行方案。

主題 2.研究國內 HIV 感染者的臨床病徵、藥物治療成效、副作用、伺機性感染處置、就醫行為與高風險行為等長期臨床研究與監測。

主題 3.分析不同易感族群接受 HAART 治療、預防性投藥或保險套使用等預防感染措施之相關因素，改善相關醫療照護模式及發展有效之預防介入措施。

主題 4.蒐集並監測愛滋病毒感染者合併感染症、抗藥性、基因亞型等相關流行病學與 HAART 血中濃度等臨床檢驗資料。

主題 5.辦理醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練課程至少 2 場、專題研討會至少 15 場。

「愛滋病防治中心」105 年度已完成 12 個子計畫，主辦 4場次大型在職教育訓練課程及研討會、2 場次 workshop、3 場次中小型研討會，發表 9 篇學術論文，參加 4 次國際會議發表 7 篇論文。

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 2016 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: Applied Research of HIV/AIDS Control Measures, Treatment & Care, and Professional Human Resource Training Courses

Study Objectives: To develop better medical care and interventional methods for disease control by conducting surveys and analyzing laboratory data of at-risk groups, by performing nation-wide cross-hospital epidemiological studies and treatment /monitoring studies with support of AIDS designated hospitals in the country, by providing training to medical personnel, preventive planning for infected subjects, in order to, ultimately, provide recommendations on integrated HIV care and preventive strategies.

Topic 1: Post-exposure Prophylaxis: provide services (such as health education consultation, testing, prophylaxis treatment, follow-up, etc…) and evaluate effectiveness of therapy and promote effective and practical plans for high-risk groups.

Topic 2:Conduct domestic research of HIV population: long-term clinical research and monitoring of HIV infected subjects including their clinical characteristics, drug therapy efficacy, side effects, management of opportunistic infections, inclination to seek medical treatment and high-risk behaviors.

Topic 3:Analyze HAART drug therapy, prophylaxis, factors related to preventive methods, such as use of condoms among different infected populations in order to improve medical care and develop effective interventional preventive programs.

Topic 4:Collect and monitor epidemiology data of HIV infected subjects: co-infections, drug resistance, genetic subtypes, etc… and clinical laboratory data, such as HAART drug blood concentrations. Report resistance surveillance data to Center for Disease

Control on a regular basis.

Topic 5:Conduct a series of HIV training programs for medical personnel: health education courses (at least 2 courses) and seminars (at least 15 courses) related to HIV care and universal precautions.

We have completed 12 sub-plans. There were 4 large-scale education and training in this year. There were 9 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2016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38,850人（本國籍為32,817人），目前已發病人數本國籍是15,085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19,589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69.42%，其次為15至24歲，佔23.62%，兩者共佔全體感染者的93.04％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 105 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 18 年的未完成工作，並擴大本中心之功能，其實施重點如下列：

105 年度實施重點如下列：

總計畫名稱：愛滋病防治整合型研究計畫—愛滋病防治中心

研究重點：愛滋病防治之相關措施及治療照護與專業醫療人力培訓應用研究

研究目標：藉由調查及實驗室分析不同之易感族群之醫療利用特性，結合全國愛滋病指定醫院協力從事愛滋病防治相關流行病學與臨床治療研究、監測、專業人員培訓及感染者預防計畫，以發展更佳之醫療照護及防治之介入模式，提供健全愛滋病醫療照護及防治策略之建議。

研究內容：

主題 1.愛滋病毒體液暴露後預防性用藥（Post-exposure Prophylaxis）：提供衛教諮詢、檢驗、預防性投藥與追蹤等服務，並評估其治療成效以及於高風險族群進一步推廣之效益與可行方案。

主題 2.研究國內 HIV 感染者的臨床病徵、藥物治療成效、副作用、伺機性感染處置、就醫行為與高風險行為等長期臨床研究與監測。

主題 3.分析不同易感族群接受 HAART 治療、預防性投藥或保險套使用等預防感染措施之相關因素，改善相關醫療照護模式及發展有效之預防介入措施。

主題 4.蒐集並監測愛滋病毒感染者合併感染症、抗藥性、基因亞型等相關流行病學與 HAART 血中濃度等臨床檢驗資料。

主題 5.辦理醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練課程至少 2 場、專題研討會至少 15 場。

為配合以上重大主題之推展，故擬規劃執行以下 12 個子計畫，其工作內容分述如下：

一、〝醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練〞之實施：

為配合疾病管制局關於 HIV 指定醫事機構的指定原則文中第三條規定：醫療人員、藥師及個管師需有愛滋病學相關教育學分 8~10 小時，故規劃及執行各科醫事人員針對

愛滋感染者照護之相關在職訓練，分北區、南區舉辦「醫事人員愛滋病治療之相關在職訓練課程」，此教育訓練課程將有初階及進階等不同的課程內容，參加對象為對於照護愛滋病患有興趣之醫療人員，並與疾病管制局合作宣導及鼓勵其他科別的醫師來參加訓練，籌劃跨科整合的訓練課程，擬包含感染科、婦產科、兒科、家庭醫學科、精神科、內科、外科、牙科、藥師等醫護人員及社工人員等，同時申請臺灣醫學會、台灣感染症醫學會、台灣婦產科醫學會、台灣兒科醫學會、台灣愛滋病學會、內科醫學會、台灣家庭醫學會等相關醫學會持續教育學分認證，以提高學員之參加意願，全程參加者結業時並頒發授課證明。105 年度擬定期於北區及中區舉辦 HIV 感染者病例個案討論會，由各區之指定醫療院所輪流提出各院診療之有意義及特殊的病例，和與會者一起討論。

此主題由台大醫院內科部感染科洪健清醫師執行，詳細研究成果參見附件一。

二、從事〝台灣地區原生性抗愛滋病毒藥物抗藥性的調查研究〞：

第一型人類免疫不全病毒(HIV-1)病毒感染會降低宿主的免疫力，增加伺機性感染的機會，進而造成患者死亡。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 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 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，截至民國一百零四年八月底為止，在台灣已累計有三萬一千二百三十人遭到 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，疾管署自 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。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三百位 HIV 患者的原生性抗藥性病毒基因盛行率，希望了解在該規範實施後，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。第二，由於接受雞尾酒治療的病人仍有一定比例的病人會有治療失敗的情形，為了幫助病人得到較好的醫療效果及避免醫療資源浪費，我們也將提供一百個免費的抗藥性病毒基因檢測給治療失敗的病人，希望其報告結果可以幫助臨床醫師選擇適當的藥物，可以在最短的時間內將病人的病毒量抑制到可接受的範圍。由於目前許多新型的藥物已不斷地推出，我們除

了分析蛋白酶(protease)及反轉錄酶(reverse transcriptase, RT)的基因變異，也將納入嵌合酶(integrase)及共受體選擇性(cell tropism)分析，以求提供臨床醫師全方位的藥物選擇。

由台大醫學院醫技系張淑媛教授擔任此計畫負責人，詳細研究成果參見附件二。

三、進行〝再次接種兩劑或三劑A型肝炎疫苗於人類後天免疫不全病毒感染之感染者保護力評估〞：

1.對於沒有A型肝炎抗體的人類免疫不全病毒感染者（不願意施打疫苗者、施打後對疫苗反應不佳且不願意再次施打者）進行追蹤，以瞭解每年其A型肝炎血清學陽轉的比率，和臨床上A型肝炎感染的影響程度。

2.對於曾經接種過A型肝炎疫苗而沒有產生抗體反應的人類免疫不全病毒感染者，進行隨機分派實驗，將其分為重新接受傳統兩劑正常劑量的疫苗接種（於第0及第6個月接種）以及接受三劑正常劑量的疫苗接種（於第 0、1、6 個月施打）；以觀察此兩組病人是否有機會再接種完的四周產生具有保護力的抗體反應，並且比較這兩組不同的接種方式所產生的抗體反應是否有所差異。

綜合上述兩項研究之結果，對於人類免疫不全病毒的感染者接種A型肝炎疫苗做出更為完整的建議。

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三。

四、實施〝出生於全國B型肝炎預防注射年代的人類免疫不全病毒感染患者追加施打B型肝炎疫苗之劑量研究〞：

研究針對出生於全國 B 型肝炎預防注射年代的人類免疫不全病毒感染患者對於施打B型肝炎疫苗後產生不反應性後追加施打之劑量對血清保護率的影響;探討出生於全國 B 型肝炎預防注射年代的人類免疫不全病毒感染患者及非出生於全國 B 型肝炎預防注射年代的患者對B肝炎疫苗產生不反應後追加施打之反應性比較。

此計畫由中山醫學院附設醫院內科部感染科李原地醫師負責主持，詳細研究成果參見附件四。

五、HIV臨床流行病學相關研究，將有〝愛滋病毒感染患者延遲使用抗愛滋病毒組合療法時機之趨勢及其預後〞：

本研究旨在探討台灣的愛滋病毒感染患者，開始使用抗愛滋病毒藥物時的 CD4 數目趨勢、延遲開始使用的預測因子、以及治療預後。此研究將 2012 至 2016 年間，於本院新診斷並開始使用抗愛滋病毒藥物之愛滋病毒感染患者。藉由整合病人相關臨床資料、開始使用抗愛滋病毒藥物時間及其 CD4 數值、發生愛滋病相關死亡、病毒治療失敗、以及換藥的情形，以分析開始使用抗愛滋病毒藥物之趨勢及預後。本研究將分為三個部分進行：1. 調查開始使用抗愛滋病毒藥物時的 CD4 數目趨勢，以及延遲開始使用抗愛滋病毒藥物的比例。2. 分析延遲開始使用抗愛滋病毒藥物的預測因子。3. 評估延遲開始使用抗愛滋病毒藥物的治療預後。

此計畫由台北市立醫院昆明防治中心兼任主治醫師林冠吟醫師負責主持，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〝急性愛滋病毒感染臨床表徵、病毒特性與宿主免疫系統之研究〞：

近幾年來政府、醫院和許多民間團體提供各種匿名或者具名的篩檢，加上臨床醫療人員的診斷愛滋病毒感染的能力持續改善，因此臨床端診斷發現急性愛滋病毒感染的案例，有逐漸增加的趨勢。及早診斷急性愛滋病毒感染，從臨床和公共衛生防治愛滋病毒感染的角度，非常重要。我們有機會提供早期治療，減少繼續傳播愛滋病毒的機會，同時可以提早減緩感染者免疫系統的破壞。 本計畫主要探討急性病毒感染者臨床表現、病毒學特性與宿主免疫系統的影響。

預計完成下列項目:

1.急性病毒感染者感染症狀及出現的頻率之分析

2.急性病毒感染者共病疾病分析、有無合併 B.C 型肝炎

3.急性病毒感染者使用抗病毒藥物分析

4.急性病毒感染者病毒基因鑑定及抗藥性位點分析

5.急性病毒感染者宿主免疫系統凋亡相關分析

6.急性病毒感染者宿主免疫系統變化的相關因素

本計畫如完成後可探討急性病毒感染後臨床表徵及相關預後不良因子的原因分析

，可以做為疾管署防疫政策制定的參考。

此計畫由三軍總醫院內科部感染科林德宇醫師負責主持，詳細研究成果參見附件六。

七、擬進行〝抗人類免疫缺乏病毒藥品處方使用規範效果分析〞：

我國自 1988 年起，政府預算提供感染者免費藥物治療，1998 年起則由健保局依重大傷病給付，2006 年起愛滋感染者的治療及藥費，改由衛生福利部疾病管制署每年編列公務預算支應。依據中央健保局統計，2000 年愛滋感染者醫療費用為四億五千多萬元，2010 年全年愛滋經費支出增加至 22 億，2012 年政府支出約 30 億元，其中藥費約 25.8 億元。衛生福利部疾病管制署訂定「抗人類免疫缺乏病毒藥品處方使用規範」，自 2012 年 6 月 1 日起實施，以同療效但價格相對較低的處方作為優先選擇，目的希望能有效控制藥費支出。成本效益分析的結果，部份決定於所鍵入的參數，如藥物費用、副作用發生率、抗藥性的比率、更動藥物的比率、治療失敗的發生率及勞動成本等眾多因素，台灣的醫療成本、藥物規範、副作用發生率、抗藥性的型態與其他地區均有差異，國外的成本效益分析未必適用於台灣，本研究欲延續過去一年的資料，持續提供實施「抗人類免疫缺乏病毒藥品處方使用規範」後首次服藥病患的臨床資料，作為未來分析的依據。

由亞東醫院內科部感染科蔡茂松醫師主持此研究，詳細研究成果參見附件七。

八、追蹤進行〝台灣、日本與香港男同志間新發 C 型肝炎病毒分子流行病學研究〞：

近二十年來在歐洲、北美和澳洲等國家紛紛發現急性或者近期的 C 型肝炎病毒傳染的發生率增加，特別是在男同性戀族群。經由分子流行病學的研究，發現有不少群聚感染的現象。台灣在過去十多年間也出現這樣現象。在 2012 年台大醫院的研究人員發現，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。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。 同一個期間，日本和香港也都陸續注意到這現象。在與香港中文大學李瑞山教授和日本國立感染症研究所愛滋病中心主任 Sinichi Oka 教授討論後，我們一致認為因為亞洲地區因為旅遊的熱潮,，C 型肝炎病毒極有可能在三地的男同性戀者間，出現群聚感染的現象。因此，我們此次研究打算利用三地所收集到的 C 型肝病毒株進行亞型分型和分子流病學研究，藉

以檢視是否此現象在亞洲地區發生，以做為臨床衛教和公共衛生政策參考。

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八。

九、探討〝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〞計畫：

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。

此主題由台北市立醫院昆明防治中心王建淳醫師執行，詳細研究成果參見附件九。

十、執行〝危險性行為後愛滋病毒感染之非職業性暴露後預防性投藥效果之前瞻性研究〞計畫：

愛滋病從 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，已逾二萬三千名以上被診斷和通報，由於感染人數持續增加，而且年齡層逐漸下降，早已經是衛生署傳染病防治工作的重要課題之一。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大多是經由性行為，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。根據衛生署的統計資料顯示，平均每 2~3 個小時發現 1 名新感染者，因此提供一個可信賴的 HIV 體液暴露者篩檢與專業心理諮詢的管道，應是杜絕愛滋病傳播最重要而且有效的方法，並可讓感染者有及早接受治療的機會。此外，目前已有多項國外觀察性研究顯示，體液暴露後預防性投藥可減低愛滋病毒感染的風險，因此，我們還可針對特定高危險族群(如男同志)在發生性行為發生體液暴露後，除了提供諮商以外，我們還可以提供相關性病的檢驗和治療，並且進一步評估是否有需要建議使用暴露後預防性投藥以降低愛滋病毒傳染的風險。

本計畫將針對特定高風險族群等非職業性高危險愛滋病毒體液暴露者建立完整且統一的愛滋病毒體液暴露事件處理流程。提供愛滋病毒篩檢及專線諮詢與衛教服務，以降低愛滋病毒感染的機會及減輕諮詢者其不安及焦慮。此外, 於適當評估體液暴露感染之風險並提供愛滋病毒之快速篩檢, 確定為非愛滋病毒感染者後, 於 48 至 72 小時內給予及時之自費預防藥物, 以發揮有效之防疫功能。收集反覆尋求暴露後預防性投藥之個案, 徵詢進一步轉為暴露前預防性投藥之意願, 以評估暴露前預防性投藥之可能。

此主題由亞東醫院內科部感染科楊家瑞醫師執行，詳細研究成果參見附件十。

十一、觀察分析〝HIV-1感染者在第一線抗病毒藥物失敗後的抗藥性和臨床結果分析〞：

三合一高效能抗病毒治療藥物比使用單一病毒抑制劑更能有效地抑制病毒的感染，但是，在服用藥物過程中，可能因為病毒快速產生變異及病人不依醫師指示定時服藥等因素，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。它會使得患者體內的病毒無法被完全地抑制，更嚴重的是這些抗藥性病毒株的產生，會造成原生抗藥性病毒株的流行。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，並進一步節省醫療資源。這些抗藥性病毒株的傳播與感染，將會影響藥物治療的效果，繼而造成醫療資源的浪費。因此，本調查將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，並提高個案的有效治療。此外期望患者接受新藥物治療後可以減少伺機性感染或細菌感染的風險。本研究為一年性

研究，105年度預期完成之工作項目如下：

倍者進行抗藥性測試，分析抗藥性基因和帶有抗藥性病毒的危險因子，並給予最佳治療藥物和進一步觀察病人臨床表現，是否有增加伺機性感染或細菌感染的風險，研究期間為 105 年 1 月至 105 年 12 月。

此主題由署立桃園醫院感染科鄭健禹醫師執行，詳細研究成果參見附件十一。

十二、深入探討〝HIV 感染者藥品動態學和基因學研究〞：

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;目前計畫繼續開發核苷酸反轉錄酶抑制劑(nucleoside reverse transcriptase inhibitor, NRTI）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十二。

(三)結果

一、〝醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練〞之實施：

愛滋病毒感染相關的知識日新月異，新藥物與治療的研發蓬勃發展，面對這些醫療新知的獲取，對照護愛滋病患的醫事人員而言格外重要且迫切，故愛滋病防治中心扮演傳播及教育國內治療與防治相關知識的角色，積極且定期規劃及執行各科醫事人員「愛滋病治療照護及全面性防護措施等相關在職訓練」課程。

(1)、105 年 5 月 7 日於台北舉辦「愛滋治療與共病風險評估研討會」邀請 Prof. Jens D. Lundgren 來台演講,衛生署指定醫療院所照護愛滋病毒感染者之專責醫師及個管師共 35 位參與。

(2)、協助財團法人器官捐贈移植登錄中心舉辦『105 年度器官捐贈移植醫療臨床實務研討會』(北區) 6/29 日亞東紀念醫院約有 250 人參加、(中區) 8/5 日台中榮民總醫院約有 200 人參加、(南區) 7/22 日高雄醫學大學附設醫院約有 210 人參加、(東區) 8/26 日花蓮慈濟醫院約有 120 人參加；負責兩個重要愛滋防護講題如下:(A)國際愛滋病毒感染者接受器官移植現況與醫事人員污染體液暴露後處置介紹；(B)國內愛滋病毒感染者之護理照護及個案管理經驗。

(3)、為配合衛生福利部疾病管制署對於指定醫療院所照護 HIV/AIDS 醫護人員之在職訓練要求，105 年 5 月 28 日於財團法人張榮發基金會國際會議中心 801 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」，任職後天免疫缺乏症候群指定醫療院所的藥師，參與減害計畫指定醫院或藥房之藥師，其他對於愛滋病治療有興趣的藥師參會者共有 87 位藥師。

(4)、為提昇國內指定醫師院所現職愛滋病毒感染個案管理師臨床專業能力及參與力，特別開立此教育訓練研習班。參加對象：國內指定醫師院所現職之臨床愛滋病毒感染個案管理師。舉辦日期：7 月 30、31 日。共有 61 位個管師參與。

(5)、105年9月9~10日於台北喜來登酒店與成大醫院共同舉辦「105年度台灣HIV研究平台會議 Taiwan HIV/AIDS Research Meeting」會中並邀請研究HAV及HBV疫苗之法國專家Dr. Odile Launay專題演講，並與國內專家學者共同討論，計有86位專家學者參與。

(6)、9/24、25 日(共 1.5 天) 於公務人力發展中心福華國際文教會館舉辦「感染症醫師

愛滋病治療專業能力教育訓練研習班」目前有 64 位醫師參加。

(7)、協助學會舉辦北中南三場次「暴露愛滋病毒前預防性投藥(Pre- exposure Prophylaxis, PrEP）教育訓練」，南區舉辦日期：105 年 7 月 2 日 (六) 國立成功大學醫學院（成杏校區）護理系三樓 309 教室共有 52 位參加。中區舉辦日期：105 年 8 月 6 日 (六) 於中山醫學大學正心樓 0212 教室共有 50 位參加。北區舉辦日期：105 年 8 月 13 日 (六)於台大醫學院 101 講堂共有 102 位。

(8)、105 年 11 月 19 日於台北舉辦「Post-HIV Drug Therapy Conference」，分享 11/23~26 日在英國舉辦的「The HIV Drug Therapy Glasgow」國際會議的成果，約有 70~80 位醫療人員參加參加。

(9)、105 年 11 月 9 日、12 月 2 日、12 月 16 日三場次在台北、台中、高雄舉辦「HIV/AIDS 病患 HAART 藥物治療個案討論會」，總計各場次約有 70~80 位醫療人員參加。

(10)、105 年 12 月 17 日 (星期六) (共 0.5 天) 財團法人張榮發基金會國際會議中心 1002 講堂「愛滋病相關伺機性感染治療進展研討會」隨著 ART 的發展，有部分伺機性感染出現的情形也漸漸有減少的趨勢，然而， 每年仍然還是會有一部分的感染者延遲到伺機性感染出現才被診斷而住院；針對各項不同病原所造成的伺機性感染，學會特別舉辦此研討會，針對個別病原所造成疾病的處置之最新進展做深入的探討，並預計於明年進行國內指引的修正。預計有 60~80 位醫護同仁參加。

(11)、本中心延續以往的愛滋病研討會在綜合病房研討室舉行，本年度聘請了各方面的專家來進行全方位的研討，其內容包括有臨床醫學、病毒學、免疫學、流行病學、護理學、精神科醫學、個案研究、研究成果發表及新抗病毒藥物之介紹等；參加成員亦日益踴躍，包括有各科各級醫師、護理人員、檢驗人員、助理人員、社工人員、各基礎學科教師，踴躍參與，以期大家能各憑專業集思廣益。上半年1~11月初已進行33場。(詳細成果內容如附件一)

二、從事〝台灣地區原生性抗愛滋病毒藥物抗藥性的調查研究〞：

自今年一月一日起至今年十月三十一日止，自未接受過三合一雞尾酒療法的 HIV 感染者，我們一共收到 480 件血液檢體進行基因型抗藥性檢測，目前已完成 405 件檢體的 HIV-1 病毒基因型抗藥性分析。自三合一雞尾酒療法治療失敗的 HIV 感染者，我們一共收到 299 件血液檢體進行基因型抗藥性檢測，目前已完成 244 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，其中 91.5% (713 件)來自北部醫院，0.8% (6 件)來自中部醫院，4.0% (31 件)來自南部醫院，3.7% (29 件)來自東部醫院。

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 13.1%，對反轉錄酶抑制藥物(nucleoside reverse transcriptase inhibitors, NRTIs)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(non-nucleoside reverse transcriptase inhibitors, nNRTIs) 及蛋白酶抑制劑 (protease inhibitor)的抗藥性病毒株的比例分別為 4.0%、8.4%、及 2.5%。對兩種以上藥物具抗藥性的比例為 1.5%。

在抗反轉錄藥物治療失敗病人檢體中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 57.0%。對反轉錄酶抑制藥物、非擬似核苷酸衍生物的反轉錄酶抑制藥物及蛋白酶抑制劑的抗藥性病毒株的比例分別為 38.9%、46.3%、及 7.8%。對兩種以上藥物具抗藥性的比例為 33.2%。

由於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 13.1%，相較於之前我們去年的調查，其抗藥性的比例有些微下降的趨勢(13.1% v.s. 14.1%,)(P=0.64)，主要升高的抗藥性藥物種類是擬似核苷酸衍生物的反轉錄酶抑制藥物(4.0% v.s. 2.9%)(P=0.38)；非擬似核苷酸衍生物的反轉錄酶抑制藥物的抗藥性盛行率是大約持平(8.4% v.s. 8.4%)(P=0.99)，而蛋白酶抑制劑的抗藥性盛行率是下降(2.5% v.s. 4.2%)(P=0.14)。

在接受抗反轉錄藥物治療失敗的病人中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 57.0%，相較於之前我們去年的調查，其抗藥性的比例有些微升高的趨勢(57.0% v.s. 55.8%)(P=0.78)。蛋白酶抑制劑(7.8% v.s. 6.3%)(P=0.52)、擬似核苷酸衍生物的反轉錄酶抑制藥物(38.9% v.s. 37.9%)(P=0.81)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(46.3% v.s. 45.4%)(P=0.83)及多重抗藥性病毒株的盛行率(33.2% v.s. 32.3%)(P=0.84)都有升高的趨勢。

至於嵌合胺抑制劑的抗藥性檢測，今年共做了 148 件檢體；其中 42 件是未接受抗反轉錄藥物治療的病人，106 件是接受抗反轉錄藥物治療失敗的病人。42 件未接受抗反轉錄藥物治療的病人檢體中沒有一件是帶有對嵌合胺抑制劑具抗藥性的病毒株。106 件接受抗反轉錄藥物治療失敗的病人檢體中有 13 件(12.3%)是帶有對嵌合胺抑制劑具抗藥性的病毒株；其中八件在 H148 的位點有突變，兩件在 N155 的位點有突變，三件在 Y143 的位點有突變。需注意的是 13 件檢體中已有八件對於第二代的嵌合胺抑制劑

Dolutegravir 具有抗藥性。其中三件對於第二代的嵌合胺抑制劑 Dolutegravir 具有高度抗藥性(Q148H/R/K 突變加上 2-3 個 G140A/C/S、L74I、E138A/K/T 突變)；四件對於第二代的嵌合胺抑制劑 Dolutegravir 具有中度抗藥性(Q148H/R/K 突變加上 1 個 G140A/C/S、L74I、E138A/K/T 突變)；一件對於第二代的嵌合胺抑制劑 Dolutegravir 具有低度抗藥性(Q148H/R/K 突變)。(詳細成果內容如附件二)

三、進行〝再次接種兩劑或三劑A型肝炎疫苗於人類後天免疫不全病毒感染之感染者保護力評估〞：

自 2015 年 6 月至 2016 年 9 月，已納入 1597 位 A 型肝炎病毒抗體為陰性之愛滋病毒感染者；其平均年齡為 35 歲、94.7%為透過男男間性行為感染愛滋病毒、分別有約 10%及 8%合併 B 型及 C 型肝炎感染、92 位先前有接受過 A 型肝炎病毒疫苗接種。此次注射常規疫苗時，95.0%之愛滋病毒感染者有接受抗愛滋病毒組合療法，且其基礎 CD4 中位數為 567 cells/mm^3、基礎愛滋病毒量為偵測不到。

統計至 2016 年 9 月，有 1053 位(65.9%)至少已接種一劑 A 型肝炎病毒疫苗，324 位(20.3%)已完成兩劑疫苗接種(圖一)。於接種第一劑與第二劑疫苗之間，其整體抗體陽轉率為 32.9%；而於接種第一劑後之 4 周內、5-8 周、9-16 周、17-24 周之抗體陽轉率分別為 16.0%、26.7%、50.0%、49.8%。而於接種第二劑疫苗後，其抗體陽轉率上升至 94.6%(圖二)。影響抗體陽轉之相關因子為疫苗種類(VAQTA®; adjusted odd ratio [AOR], 2.4; 95% confidence interval [CI], 1.6-3.6)、追蹤抗體之間隔時間(AOR, per 1-week increase, 1.1; 95% CI, 1.1-1.2)、先前有接受過 A 型肝炎病毒疫苗者(AOR, 30.0; 95% CI, 11.8-76.5)。

於 92 位先前有接受過 A 型肝炎病毒疫苗接種者，其中有 79 位追加接種 A 型肝炎病毒疫苗。於追加接種第一劑及第二劑疫苗後，其抗體陽轉率分別為 86.1%及 100%，相較於 974 位初次接受 A 型肝炎病毒疫苗者顯著增加。

於臺灣急性 A 型肝炎疫情下，有接受及沒接受 A 型肝炎病毒疫苗之愛滋病毒感染者之急性 A 型肝炎發生率分別 0.7 per 100 person-years of follow-up 及 11.0 per 100 person-years of follow-up；因此接種 A 型肝炎病毒疫苗所產生預防急性 A 型肝炎之效力為 93.8%。發生急性 A 型肝炎的病患皆為男男性行為者，且於研究期間前皆未接受過 A 型肝炎疫苗；其他預測因子包含研究期間未接種疫苗(adjusted hazard ratio [AHR], 12.5; 95% CI, 3.8-50.0)及近期梅毒感染(AHR, 4.6; 95% CI, 2.6-8.3)。(詳細成果內容如附件三)

四、實施〝出生於全國 B 型肝炎預防注射年代的人類免疫不全病毒感染患者追加施打 B 型肝炎疫苗之劑量研究〞：

在我們的研究中，同時探討了這個族群的B型肝炎、C型肝炎、及梅毒的發生率。在1,526人年的追蹤中，有14個新發生的B型肝炎感染(9.1/1000PYFU)。B型肝炎抗原或抗體皆為陰性的患者中，B型肝炎的發生率為6.6/1000PYFU。C型肝炎及梅毒的發生率相當高，分別是20/1000PYFU及100/1000PYFU。在接受B型肝炎疫追加施打的患者中，不反應者B型肝炎的發生率高於反應者:分別為13.4/1000PYF及9.6/1000PYFU。(詳細成果內容如附件四)

五、HIV 臨床流行病學相關研究，將有〝愛滋病毒感染患者延遲使用抗愛滋病毒組合療法時機之趨勢及其預後〞：

於 2012 至 2016 年此四年研究期間，於北區幾家愛滋病毒感染照護指定醫院(台大醫院、亞東醫院、三軍總醫院、衛生福利部桃園醫院、台大醫院新竹分院)所收納的病患總數為 2593 人，其 95.4%為男性，年齡中位數為 31 歲，76.9%透過男男性行為傳染愛滋病毒；而合併 B 型及 C 型肝炎感染則約有 10%及 20%。整體而言，開始使用抗愛滋病毒組合療法時的基礎 CD4 中位數值為 270 cells/mm^3；如果以每半年為切點，則 CD4 中位數值由 2012 後半年的 207 cells/mm^3 逐漸顯著上升至 2016 前半年的 298 cells/mm^3。若進一步將開始使用抗愛滋病毒藥物時的基礎 CD4 中位數值細分為大於或等於 500 cells/mm^3、350-499 cells/mm^3、200-349 cells/mm^3、以及小於 200 cells/mm^3 四個分層，可觀察到基礎 CD4 數值的增加主要來自於大於或等於 500 cells/mm^3 及 350-499 cells/mm^3 這兩個分層，隨之而減少的是 200-349 cells/mm^3 及小於 200 cells/mm^3 這兩個分層。然而直至 2016 前半年，仍有 30%的病患開始使用抗愛滋病毒組合療法的基礎 CD4 中位數值低於 200 cells/mm^3。若再進一步分析延遲開始使用抗愛滋病毒組合療法的比例，則由 2012 後半年的 49.1%逐漸顯著下降至 2016 前半年的 29.0%；其中合併愛滋相關疾病的比例，則由 2012 後半年的 14.4%至 2016 前半年的 6.5%，並無顯著改變。

與延遲開始使用抗愛滋病毒組合療法的相關因子包含年齡較大(勝算比, 1.05; 95%信賴區間, 1.04-1.06)、B 型肝炎病毒表面抗原陽性(勝算比, 1.31; 95%信賴區間, 1.05-1.64)、以及較早期開始使用抗愛滋病毒組合療法。較不易延遲開始使用抗愛滋病毒組合療法的相關因子則包含靜脈注射毒癮者(勝算比, 0.54; 95%信賴區間, 0.37-0.79)及 C 型肝炎抗

體陽性(勝算比, 0.69; 95%信賴區間, 0.49-0.97) 。延遲開始使用抗愛滋病毒組合療法對於治療預後有所影響。在愛滋相關疾病所造成的死亡上，延遲開始使用抗愛滋病毒組合療法者的比例(1.7%)較高於非延遲開始使用抗愛滋病毒組合療法者(0.3%)，風險比值(hazard ratio)為 6.86 (95%信賴區間為 2.78-16.91)；其他增加愛滋相關死亡的因子還包含年齡較大。在病毒治療失敗上(定義為治療六個月後愛滋病毒量仍大於 200 cells/mm^3)，延遲開始使用抗愛滋病毒組合療法者的比例(16.0%)較高於非延遲開始使用抗愛滋病毒組合療法者(8.3%)，風險比值為 2.09 (95%信賴區間為 1.70-2.58)。在更換抗愛滋病毒藥物使用上，延遲開始使用抗愛滋病毒組合療法者的比例(44.4%)與非延遲開始使用抗愛滋病毒組合療法者的比例(41.3%)並未達統計上差異，風險比值為 1.10 (95%信賴區間為 0.99-1.22)。但如果細分更換抗愛滋病毒藥物使用的原因，則因為藥物副作用而換藥部分，延遲開始使用抗愛滋病毒組合療法者的比例(33.0%)與非延遲開始使用抗愛滋病毒組合療法者的比例(35.1%)並未達統計上差異；因為抗藥性或病毒治療失敗而換藥部分，延遲開始使用抗愛滋病毒組合療法者的比例(7.1%)較高於非延遲開始使用抗愛滋病毒組合療法者的比例(2.6%)，風險比值為 2.82 (95%信賴區間為 2.04-3.90)。(詳細成果內容如附件五)

六、HIV 臨床流行病學相關研究有〝急性愛滋病毒感染臨床表徵、病毒特性與宿主免疫系統之研究〞：

研究結果顯示三個年代急性病毒感染治療前病毒量平均為 1000000copies/ml，治療後病毒量均可下降，CD4 數值在 2008 年前為 945，相較 2009~2012 及 2013~2016 兩組初始 CD4 數值 228 及 271 來的高，不過 2008 年前病患只有四位，樣本數較少是否有臨床上的差異有待更多的資料分析。在 24 週控制較差組中一開始病毒量較高(log PVL 6.48 vs 6.15; p=0.033)，在控制較差組中使用蛋白酶抑制劑人數較多(5 vs 1 人)。多變項的分析結果顯示治療後 4 週血紅素較高者 24 週仍測得到病毒量的機會較低(p=0.035)。另外我們嘗試使用不同模式(病毒量大於 500000 對比病毒量小於 500000)，24 週測不到病毒量的比率趨近一致，使用 CD4 數值大於 350 對比小於 350 進行分析，24 週測不到病毒量的比率趨近一致，分析臨床上會影響血紅素的抗愛滋病毒藥物主要為含有 Zidovudine 類藥物如 Combivir，在我們的分析中顯示如使用藥物避開影響血紅素有較高的機會於 24 週讓病毒量降到 0，控制會較好。(詳細成果內容如附件六)

七、進行〝抗人類免疫缺乏病毒藥品處方使用規範效果分析〞：

自 2012 年 6 月實施抗人類免疫缺乏病毒藥品處方使用規範後，目前總共陸續收集 1,125 位 HIV 病毒感染者開始使用抗人類免疫缺乏病毒藥物，其中 97.2%為男性，年齡中位數[median (IQR)]為 31.0(26.4-37.6)歲，開始接受抗病毒藥物治療前，平均 CD4 淋巴球數[median (IQR)]為 288.8 (146.9-399.1) cells/ul，平均病毒量[median (IQR)]為 4.84 (4.41-5.27) log10 copies/mL。

1,125 位使用抗病毒藥物病患中 31.6%(356)使用第一類處方，62.1%(699)使用第二類處方，2.8%(31)使用第三類處方，3.5%(39)需使用第四類處方，於 2016/6/1 後起始治療有 31 人，27 人使用第二類處方，1 人使用第三類，3 人使用第四類。

1,125 位使用抗病毒藥物病患中 65.2%(677)會至少更動一次處方，開始使用到更動處方時間間隔為[median (IQR)] 38(14-209)天，其中 20.8%(139)是因為臨床懷疑是藥物過敏相關的皮疹，13.4%(90)因為抗病毒藥物相關神經精神副作用而換藥，8.5%(57)產生無法忍受的腸胃道不適而更替藥物，10.5%(70)的病患因為血紅素下降/白血球低下而換藥，值得注意的是 10.5% (70)因為治療效果不如預期或是藥物的抗藥性(genotypic resistance)而改變處方，35.0%(236)則因為服藥方便性(藥物顆粒數和服藥次數)更替處方。

使用卡貝茲(combivir, zidovudine+ lamivudine)超過 28 天的病患，平均血紅素相較於基礎值下降 1.5 g/dL (95% CI. 0.9~2.1)達統計學上的意義。扣除單純因為服藥方便性而更動藥物者有 441 人，起始處方的選擇與之後持續處方具有統計的相關性，治療後的一年內使用第一類處方作為起始處方之後有 54.8%需要更動處方，使用第二類處方作為起始處方之後有 27.9%需要更動處方，使用非第三類處方作為起始處方之後有 58.0%需要更動處方，使用第四類處方作為起始處方之後有 37.1%需要至少更動一次處方，四組之間有統計學上顯著的差異(Log-Rank p <0.001)。(詳細成果內容如附件七)

八、追蹤進行〝台灣、日本與香港男同志間新發 C 型肝炎病毒分子流行病學研究〞：

自 2011 年 1 月至 2015 年 12 月，共計 3,483 位 15 歲以上的愛滋病毒感染者至台大醫院就診，排除 29 位沒有基礎點 C 型肝炎病毒抗體報告、240 位 2011 年後無追蹤 C 型肝炎病毒抗體報告、369 位於 2011 年前 C 型肝炎病毒抗體陽性及 316 位感染途徑為靜脈毒癮者或不清楚，納入 2,529 位基礎點 C 型肝炎病毒抗體陰性且有至少一次的抗體追蹤檢測者進入研究。

研究期間發現 123 位 C 型肝炎病毒抗體陰轉陽，其中 90 位為近期或急性 C 型肝炎感染者，發生率為每 1,000 人年 10.8，各年發生率為 2011 年 5.46、2012 年 10.36、2013 年 11.48、2014 年 10.17、2015 年 11.85。

與 2,406 位無合併 C 型肝炎感染者比較，90 位近期或急性 C 型肝炎感染者均為男性且年齡較輕（平均值 31.6 vs 35.8 years, P=0.0002），以同性間性行為傳染途徑居多（97.8% vs. 88.3%, P 值 0.0021），而且近期（在最後觀察時間點前 6 個月或 3 個月內）曾梅毒指數上升 4 倍或接受梅毒藥物治療的機率較高（67.8% vs. 11.3%, P 值<0.0001），但兩組在是否有 B 型肝炎帶原與是否使用 HARRT 的比例並無統計顯著。另外在其它檢驗數據中可看出，90 位近期或急性 C 型肝炎感染者，曾經肝功能上升的比例居高，其中 90%的感染者曾 ALT＞41 U/liter（平均值 333±366）。

90 位近期或急性 C 型肝炎感染者中，基礎點的 C 型肝炎病毒量平均值為 5.5 $\log_{10}$ IU/mL，其中有 10 位基礎點 C 型肝炎病毒量為< 3 $\log_{10}$ IU/mL。在病毒基因型中，以 2a 型最多（44%, 24/51）、其次為 1b（38%,21/51）。在藥物治療上，仍以傳統干擾素配合口服藥物為主，目前仍有 10 位尚在治療中，38 位已完成治療，有 28 位於停止治療後半年血中 HCV 病毒量持續陰性(SVR)，但有 3 位感染者於 SVR 後病毒量再度被偵測到。(詳細成果內容如附件八)

九、探討〝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〞計畫：

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 105 年 6 月 30 日，總共收集個案數為 350 人，個案的服用希寧時的年齡平均為 32.7 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 350 個案中 347 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 335 人(95.7%)、HIV 感染者中合併 B 型肝炎帶原者有（HBSAg: positive）47 人(13.4%)，而 HIV 感染者合併有 C 型肝炎帶原者(Anti-HCV: positive)有 23 人(6.6%)。

在服用希寧(efavirenz)之前的實驗室檢驗，免疫力 CD4 T lymphocyte 平均值為 263.7(4.8-842)，CD4<200 有 128 人(36.6%)。而 HIV viral load 平均值為 237467 (501～

5854000)，plasma HIV RNA load $>10^5$ 的個案有 185 人（52.9 %），350 人中有一人缺 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。350 個案中出現任何一種副作用有 246 人(70.3%)，因為任何副作用而停藥的病人有 118 人。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 138 人(39.4%)，因為眩暈而停用希寧有 35 人(10%)。出現紅疹的個案數有 87 個患者(24.9%)，因此停藥者有 44 人(12.8%)，出現紅疹的時間距離開始服用藥平均約 10 天。其他副作用如多夢與夢魘有 53 人、睡眠障礙有 37 人、有 11 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 202 個病患，停用希寧 87 人(43.1%)。使用 tenofovir disoproxil fumarate (TDF) + lamivudine 組合者有 104 人，停用藥物 32 人(30.8%)。使用 Truvada (TDF/FTC) 有 35 位患者，停用藥物 6 人(17.1%)。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 66 (18.9%)人，而在一年內停用希寧的病人數有 123 人(35.1%)。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 9 人(2.6%)。

350 位個案目前追蹤滿 48 週以上有 113 人，病毒量<40 copies/ml 者有 111 人(97.4%)，追蹤滿 96 週以上有 42 人，病毒量<40 copies/ml 者有 41 人(97.6%)。

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)。(詳細成果內容如附件九)

十、執行〝危險性行為後愛滋病毒感染之非職業性暴露後預防性投藥效果之前瞻性研究〞計畫：

由於本次前瞻性研究之 IRB 於 2015 年 05 月 05 日通過可正式收案, 因此自 2015 年 05 月 05 日至 2015 年 10 月 31 日止，共有 50 人次至板橋亞東醫院接受暴露後預防性投藥，全部的人均在 72 小時之內投藥，完成 28 天投藥的比例為 100%。對於處方之藥物主要是以 TDF/FTC (或少數為 TDF+3TC) +RAL 為主，其次則為 TDF/FTC (或極少數為 TDF+3TC) +LPV/r，追蹤至 2016 年 10 月底，並無血清陽轉出現 HIV 感染者，於追蹤過程中，亦無出現急性 C 型肝炎者。此外，有一位個案自 2011 年至 2015 年底共接受過 4 次 nPEP，已經過諮商轉介為暴露前預防性投藥，服藥情形良好。

由 Table 1 顯示，尋求預防性投藥者絕大多數為男性，但男男間性行為者約佔所有人的 73.4%, 有 68.8%的人是透過網路尋求一夜情對象，另外則有 28.1%是找性工作者; 92.1%的人學歷在大學以上，有 75.0%的人在過去三個月內至少有過兩個以上的性伴侶, 而這些高危險族群中有 54.7%曾經做過 HIV 篩檢；此外，有 56.2%在過去三個月內戴保險套的比例低於 50%, 29.7%的個案曾經使用娛樂性用藥助性。由於 nPEP 已推行數年，因此有 15.6%的個案過去曾經接受過預防性投藥。

比較 backbone 為 Zidovudine (AZT) based regimen 和 Tenofovir (TDF) based regimen 耐受性的差異，可以看到在 Nausea/vomiting, dizziness 或是 general malaise 的部分都是以 AZT-based regimen 顯著較多。比較以 ralteravir (RAL)搭配或是其他藥物搭配 backbone NRTI 的耐受性差異，可以看到除了 skin rash 沒有之外，其餘各項常見的副作用均以 RAL-based regimen 顯著較少。(詳細成果內容如附件十)

十一、分析〝HIV-1感染者在第一線抗病毒藥物失敗後的抗藥性和臨床結果分析〞：

在這段研究期間,共有 1,642 為初感染者接受了含有非核苷酸反轉錄酶抑制劑的第一線處方，而 454 位(27.4%)有更換處方的經驗，其中因為副作用換藥的有 323 位(19.7%)，依治療前的抗藥序列換藥的有 41 位(2.5%)，而因為治療失敗而換藥的有 83 位(5.1%)。對衛滋(nevirapine)、希寧(efavirenz)及恩臨(rilpivirine)產生抗葯的比率分別為 9.7% (41/422)、4.2% (40/946)和 0.7% (2/277)。其中 68 位(3.8%)有產生抗藥性突變點，42 位(62.7%)對核苷酸反轉錄酶抑制劑產生抗藥突變點，而對非核苷酸反轉錄酶抑制劑、蛋白酶抑制劑及任何一種藥物有抗藥性突變點的機率分別為 28 位 (41.2%)，1 位和 48 位

(71.6%)，此外有 21 位(31.3%)帶有多重抗藥性。最常見的抗藥突變點分別為 K65R (25%)、M184I (10.3%)、M184V (36.8%)、V90I (5.9%)、K101E (5.9%)、K103N (19.1%)、V108I (7.4%)、Y181C (11.8%)、G190A (5.9%)。再次分組分析中發現受試者 HIV 病毒量高於 10 萬 copies/mL 者治療失敗而產生抗藥性的比率在衛滋及希寧的組別分別有 16.4%和 7.8%，而對 HIV 病毒量低於 10 萬 copies/mL 的受試者在衛滋、希寧及恩臨抗藥性的比率分別為4.9%、1.9% 及0.7%。在使用衛滋治療失敗最常產生的抗藥點有Y181C (12.2%), K101E (7.3%) and V108I (7.3%)，而對希寧最長的抗藥點是 K103N (27.5%)。(詳細成果內容如附件十一)

十二、探討〝HIV 感染者藥品動態學和基因學研究〞：

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。監測 ART 血中濃度的結果可提供臨床醫師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。

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 ATV、EFV、rifabutin 與 cotrimoxazole 血中濃度的服務、嘗試開發以 HPLC 方法測定 dolutegravir 與其他 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。(詳細成果內容如附件十二)

十三、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. 2/22~25 日在美國波士頓舉辦之 Conference on Retroviruses and Pooprtunistic infections(CROI 2016)國際會議。進行學術交流討論。
2. 5/17~19 日在香港舉辦之 1st Asia Pacific AIDS & Co-infections Conference (APACC)會議進行學術交流討論。

3. 6/21-22 日香港中文大學舉辦的第十三屆新興傳染病研討會 The 13th Annual Scientific Meeting of CEID 並發表四篇海報論文與一個專題演講。

(1). Short-term effectiveness of hepatitis A vaccination in HIV-positive men who have sex with men during a hepatitis A outbreak Taiwan. Kuan-Yin Lin, Wen-Chun Liu, Hsin-Yun Sun, Chien-Ching Hung.

(2). Seroepidemiology of hepatitis B virus infection among HIV-positive persons who were born after 1986. Yi-Chia Huang, Hsin-Yun Sun, Shang-Ping Yang, Chien-Ching Hung, Shan-Chwen Chang.

(3). Seroepidemiology of hepatitis A virus infection among HIV-positive men who have sex with men in the era of combination antiretroviral therapy. Guan-Jhou Chen, Hsin-Yun Sun, Wang-Huei Sheng, Szu-Min Hsieh, Yu-Chung Chuang, Chien-Ching Hung, Shan-Chwen Chang.

(4). The incidence of recent hepatitis C virus infections continued to increase among HIV-positive men who have sex with men in Taiwan. Wen-Chun Liu, Yi-Ching Su, Li-Hsin Su, Hsin-Yun Sun, Sui-Yuan Chang, Chien-Ching Hung.

4. 10/23-26 日於英國 Glasgow 舉辦之 HIV Drug Therapy Glasgow 國際會議並發表 10 篇海報論文等。

(1). Effectiveness of hepatitis A vaccination in HIV-positive men who have sex with men during an ongoing hepatitis A outbreak in Taiwan. Kuan-Yin Lin[1], Pei-Ying Wu[2], Wen-Chun Liu[1], et al.

(2).Outcome of antiretroviral regimens prescribed by following the regulations on combination antiretroviral therapy by Taiwan Centers for Disease Control. Mao-Song Tsai[1], Chia-Jui Yang[1], Jun-Yu Zhang[2], et al.

(3). Continued increase of recent hepatitis C virus infections among HIV-positive patients in Taiwan.Wen-Chun Liu[1], Li-Hsin Su[1], Cheng-Hsin Wu[1], et al.

(4). Patterns of emergent resistance-associated mutations after initiation of non-nucleoside reverse-transcriptase inhibitor-containing regimens in Taiwan: a multicenter cohort study. Chien-Yu Cheng[1] , Yi-Ching Su[2], Mao-Song Tsai[3], et al.

(5). Decreasing incidence of diabetes mellitus in HIV-positive Taiwanese patients on combination antiretroviral therapy from 2004 to 2013. Pei-Ying Wu[1], Shang-Ping Yang[1], Yu-Zhen Lou[1], et al.

(6).Comparison of early serologic response of early syphilis to treatment with a single-dose benzathine penicillin G between HIV-positive and HIV-negative patients: a cohort study. Yi-Ching Su[1], Lan-Shin Chang[1], Wen-Chun Liu[1], et al.

(7).Seroepidemiology of hepatitis B virus (HBV) infection among HIV-positive men who have sex with men born in the era of nationwide neonatal HBV vaccination in Taiwan. Yi-Chia Huang[1], Shang-Ping Yang[2], Wen-Chun Liu, et al.

(8).Seroepidemiology of hepatitis A virus among HIV-positive patients in Taiwan in the setting of acute hepatitis A outbreak in 2015-2016. Guan-Jhou Chen, Kuan-Yin Lin, Hsin-Yun Sun, et al.

(9).Attitudes towards pre-exposure prophylaxis against HIV infection among individuals seeking voluntary counseling and testing for HIV in Taiwan. Lan-Hsin Chang[1], Wen-Chun Liu[1], Cheng-Hsin Wu[1], et al.

(10). Short-term safety and tolerability of switch of backbone antiretroviral agents to coformulated tenofovir disoproxil fumarate/emtricitabine in HIV-positive Taiwanese patients. Hsi-Yen Chang[1], Pei-Ying Wu[1], Jun-Yu Zhang[1], et al.

6/19-6/24 日張淑媛老師受邀前往荷蘭參訪多家知名病毒實驗室，並且討論加入歐洲愛滋病毒抗藥監測計畫 (SPREAD) 。

6/16~6/20 日林淑文藥師參加 American Society of Microbiology (ASM) Microbe 2016, Boston, MA, USA ，並發表海報論文:Chien TL, Wang CY, Hung CC, Chang SY, Yang JH, Kuo CH, Lin YT, Liu WC, Lin SW. Genetic polymorphism relating to the concentration and adverse drug reactions of sulfamethoxazole-trimethoprim and metabolite (SUNDAY-502). In: Abstract of American Society of Microbiology (ASM) Microbe 2016, Boston, MA, USA, June 16-20, 2016.

(B)、相關論文發表：

台大醫院「愛滋病防治中心」成立至今已屆 19 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. Lai CC, Liu WC, Fang CT, Yang JY, Chang LH, Wu PY, Luo YZ, Chang SF, Su YC, Chang SY, Hung CC*. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. J Antimicrob Chemother 2016;71:226-34.
2. Cheng A, Chang SY, Tsai MS, Su YC, Liu WC, Sun HY, Hung CC*. 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.
3. Yang CJ, Tang HJ, Chang SY, Hsieh SM, Lee KY, Lee YT, Sheng WH, Yang SP, Hung CC*, Chang SC. Comparison of serological response to 2-gram single-dose azithromycin versus benzathine penicillin G for early syphilis in HIV-infected patients. J Antimicrob Chemother 2016;71:775-82.
4. Chou YJ, Lin HW, Yang CJ, Chen MY, Sheng WH, Liu WC, Chang SY, Hung CC*, Hsueh PR, Chang SC. Risk of recurrent nontyphoid Salmonella bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy. J Microbiol Immunol Infect 2016;49:760-7.
5. 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 2015;xx:1-9.
6. 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 2016;xx:1-9.
7. Lee YC, Hung CC, Zhang JY, Wu PY, Yang SP, Lou YZ, Chang HY, Liu WC, Liu WC, Sun HY, Chang SC. Incidence and risk factors of herpes zoster in HIV-positive patients initiating combination antiretroviral therapy in Taiwan. J Microbiol Immunol Infect 2016;xx:1-7.
8. Chan D, Sun HY, Wong H, Hung CC*, Lee SS. Sexually transmitted hepatitis C virus infection in the Asia-Pacific region: a review. Int J Infect Dis (accepted)
9. Lee YC, Hung CC, Cheng A, Liu WC, Wu PY, Yang SP, Zhang JY, Lou YZ, Chang HY, Sun HY, Chang SC. Willingness of HIV-positive patients to donate their organs for transplantation in Taiwan. Transplant Infect Dis (accepted)

(C)、整合台灣地區 HIV/AIDS 多中心研究合作平台：

本中心為整合國內 HIV/AIDS 相關之研究，特別於 105 年度召開多次的「台灣地區 HIV/AIDS 多中心研究合作平台討論會」，105 年 9 月 9~10 日於台北喜來登酒店與成大醫院共同舉辦「105 年度台灣 HIV 研究平台會議 Taiwan HIV/AIDS Research Meeting」會中並邀請研究 HAV 及 HBV 疫苗之法國專家 Dr. Odile Launay 專題演講，並與國內專家學者共同討論，計有 86 位專家學者參與。

(D)、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
105年1月~12月	9,000,000 元	6,622,339 元	2,277,661 元	100,000 元	$0

(四)討論

一、〝醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練〞之實施：

本計畫在 105 年已舉辦 4場次大型在職教育訓練課程及研討會、6 場次 workshop、3 場次中小型研討會，各場次皆有醫療人員約 50~102 人次參與，對國內愛滋病防治之醫療教育貢獻良多。為提昇國內 HIV/AIDS 臨床及學術研究，105 年度舉辦 1 場「台灣地區 HIV/AIDS 多中心研究合作平台討論會」。有醫師及研究人員 86 名參加，會中互相討論做成許多共識與結論。明年度擬繼續舉辦。每週一次的愛滋病防治中心研討會，本年度繼續聘請各界的專家來進行全方位的研討，內容包括臨床醫學、藥學、病毒學、免疫學、流行病學、護理學、精神科醫學、個案研究、研究成果發表及新抗病毒藥物之介紹等；以後將加強個案討論，以期大家能各憑專業集思廣益互相交流。明年度擬繼續定期舉辦。(詳細成果報告詳附件一)

二、從事〝台灣地區原生性抗愛滋病毒藥物抗藥性的調查研究〞：

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 13.1%，相較於之前我們去年的調查，其抗藥性的比例有些許下降的趨勢(13.1% v.s. 14.1%,)(P=0.64)。進一步的分析發現，具原生性人類免疫不全病毒(HIV-1)抗藥性基因盛行率的下降主要是因為蛋白酶抑制劑的抗藥性盛行率是下降(2.5% v.s. 4.2%)(P=0.14)。而非擬似核苷酸衍生物的反轉錄酶抑制藥物的抗藥性盛行率是雖然與去年相較變動不大(8.4% v.s. 8.4%)(P=0.99)，但是 8.4%的抗藥性盛行率仍不容小覷。特別是，台灣衛生福利部疾病管制署於今年六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)，一種是兩個擬似核苷酸衍生物的反轉錄酶抑制藥物搭配一個嵌合胺抑制劑(ABC/3TC/DTG)。根據前人的研究及本計畫的研究結果，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。此外，值得注意的是，雖然在 42 件未接受抗反轉錄藥物治療的病人檢體中沒有一件是帶有對嵌合胺抑制劑具抗藥性的病毒株，但是在 106 件接受抗反轉錄藥物治療

失敗的病人檢體中有 13 件(12.3%)是帶有對嵌合胺抑制劑具抗藥性的病毒株，其中有八件甚至對於第二代的嵌合胺抑制劑 Dolutegravir，即目前第一線治療藥物(ABC/3TC/DTG)的成分具有抗藥性。所以我們建議要持續監測這些對嵌合胺抑制劑具抗藥性的病毒株是否會傳入未接受抗反轉錄藥物治療的病人族群中。(詳細成果報告如附件二)

三、進行〝再次接種兩劑或三劑A型肝炎疫苗於人類後天免疫不全病毒感染之感染者保護力評估〞：

此研究與過去的文獻類似，顯示 A 型肝炎病毒疫苗的保護力在愛滋病毒感染者無法達到與非愛滋病毒感染者一樣好的保護力。於此研究中，我們可以觀察到 A 型肝炎病毒抗體陽轉率會隨著追蹤時間間隔拉長而逐漸增加的現象，但在接種第二劑疫苗前，仍只能達到約 50%的抗體陽轉率。唯有在接種第二劑疫苗後，才能提高抗體陽轉率至 94.6%。這種疫苗抗體隨追蹤時間及劑量逐漸成熟增加的現象，也能在其他免疫不全的患者身上觀察到。過去的文獻普遍指出，施打 A 型肝炎病毒疫苗後抗體陽轉的相關因子包含 CD4 較高及愛滋病毒量較低。但於此研究中，由於使用抗愛滋病毒組合療法的病患比例增加，施打 A 型肝炎病毒疫苗前之基礎 CD4 較高且愛滋病毒量較低，因此並無法觀察到如同過去文獻所指出的相關因子。此研究特別發現的相關因子為，先前有接受過 A 型肝炎病毒疫苗者，追加接受 A 型肝炎病毒疫苗接種，能產生較佳的抗體血清反應。這意指對於接種A型肝炎病毒疫苗後，沒有產生足夠的免疫反應的愛滋病毒感染者，追加接種疫苗可以提供足夠的免疫力。但進一步關於何種追加接種疫苗的劑數，對免疫反應較為有利；是常規的兩劑疫苗，還是減少或增加疫苗劑數，仍需後續研究釐清。我們將會納入此研究中未能產生足夠免疫反應的愛滋病毒感染者，進入後續追加接種疫苗的劑數研究。

本研究中所發生的急性 A 型肝炎個案，符合台灣疾病管制署的疫情調查結果；透過男男間性行為以及近期感染梅毒者，為急性 A 型肝炎的預測因子。而有接受過 A 型肝炎病毒疫苗，則為顯著的保護因子，其效果高達 93.8%。因此，儘管 A 型肝炎病毒疫苗於愛滋病毒感染者之抗體血清學反應較差，在疫情下仍能提供顯著的預防效果。 (詳細成果報告如附件三)

四、實施〝出生於全國 B 型肝炎預防注射年代的人類免疫不全病毒感染患者追加施打 B 型肝炎疫苗之劑量研究〞：

雖然大部分台灣針對HIV患者治療指引建議針對不具B型肝炎抗體保護效價的患者進行追加施打，但患者需要自費約 1,000 元來購買三劑的疫苗。在我們的研究當中，不到一半的患者接受追加施打。部分的患者在接受兩劑疫苗注射後即產生很高的抗體效價(>100 mIU/ml)，因而沒有接受第三劑的疫苗注射。只有四分之一的患者接受完整的三劑疫苗注射。整體的疫苗反應率為 62% (以 ntention-to-treat 分析)及 67%(有接受完整施打之分析)。過去我們認為追加施打能產生的效果往往比初次施打來的好，在我們研究中得到這樣的結果暗示了 HIV 感染對於本來具有的免疫能力及後續反應的免疫反應都有所影響。此外在接種疫苗後的長期反應也是相當令人失望的(52%)。在疫苗不反應者中，不到一半的患者願意接受第二次追加施打，然而其反應卻是更差。過去許多研究探討了針對這些病人是否可以用雙倍劑量的疫苗施打。在我們的研究中有 2 位接受了雙倍劑量之第二次追加施打，其中有一位產生了很高效價的抗體反應但另一位仍為不反應者。由於樣本數太少，無法進行劑量與反應結果的分析。在台灣背影盛行率仍為 3%之下，我們的研究中 B 型肝炎的發生率(6.6/1000PYFU)已接近一般定義低盛行國家之發生率(美國 0.27%, 荷蘭 0.2%,日本 1%)。這個結果說明了新生兒 B 型肝炎疫苗在免疫不全之病人仍有長期的效果。由於在我們的研究當中，C 型肝炎及梅毒的發生率相當高，因此安全的性行為仍然是需要再三加強宣導的。(詳細成果報告如附件四)

五、HIV 臨床流行病學相關研究，將有〝愛滋病毒感染患者延遲使用抗愛滋病毒組合療法時機之趨勢及其預後〞：

此研究顯示台灣開始使用抗愛滋病毒組合療法時的基礎 CD4 中位數值雖逐年上升，但歷年之整體基礎 CD4 中位數值皆低於 2012 年台灣愛滋指引所建議的 350 cells/mm^3。此外，延遲開始使用抗愛滋病毒組合療法的比例雖逐年降低，但仍佔有不少比例。因此，台灣開始使用抗愛滋病毒組合療法的時機仍有進步的空間，尤其延遲開始使用抗愛滋病毒組合療法者，是最急需要改善的族群。過去的文獻指出，提早開始使用抗愛滋病毒組合療法後，主要造成延遲開始使用抗愛滋病毒組合療法的原因，來自於延遲診斷愛滋病毒感染；而若要提早診斷愛滋病毒感染，則有賴於減少社會歧視與增加篩檢率。而年齡較大者容易較晚才診斷愛滋感染及接受治療，有可能是因為較年長者對於保護性性

行為與愛滋病毒感染的資訊較欠缺，或就醫時較不容易被納入愛滋病毒感染的鑑別診斷。合併B型肝炎感染可能對免疫造成負面影響，而使得基礎CD4中位數值較低。合併 C 型肝炎感染較易提早接受抗愛滋病毒組合療法治療，有可能和較多合併 C 型肝炎感染者之傳染途徑為靜脈注射毒癮，而其因為入監受刑，較易有機會接受愛滋相關醫療照顧有關係。較早期的年代除了因為社會端或醫療端因素，較有可能延遲診斷愛滋感染之外，對於開始使用抗愛滋病毒組合療法的時機，也有 CD4 數值上的限制，因此較易延遲開始使用抗愛滋病毒組合療法。本研究也發現，延遲開始使用抗愛滋病毒組合療法會造成治療預後不佳。除了愛滋相關死亡會受延遲開始使用抗愛滋病毒組合療法影響之外，其他增加愛滋相關死亡的因子還包含年齡較大。近年來的研究顯示，年齡較大者(45 至 65 歲)相較於年齡較小者，更容易因為延遲開始使用抗愛滋病毒藥物，而增加未來 10 年死亡率。綜合以上結果，年齡較大者不但較易延遲開始使用抗愛滋病毒組合療法，而且其治療預後較差。因此，年齡較大之愛滋病毒感染者，是較需要改善開始使用抗愛滋病毒組合療法時機的族群。(詳細成果報告如附件五)

六、HIV 臨床流行病學相關研究有〝急性愛滋病毒感染臨床表徵、病毒特性與宿主免疫系統之研究〞：

之前急性病毒感染是否需立即治療有些爭論，有些學者建議立即治療，另外一些學者建議可再觀察一段時間後再治療，不過近一、二年的治療指引均建議立即治療，我們研究的分析結果顯示治療後 4 週血紅素較高者 24 週仍測得到病毒量的機會較低(p=0.035)。(詳細成果報告如附件六)

七、進行〝抗人類免疫缺乏病毒藥品處方使用規範效果分析〞：

研究結果顯示，使用含有卡貝茲的起始處方，有超過一半的病人需要更動處方，考慮治療效果、藥物副作用發生率與嚴重程度、抗藥性的型態，舊有規範對於病人的用藥安全效果、臨床治療效果、符合病患服藥的方便性及順從性等議題需要有其他更好的調整，唯因醫院採購及進藥程序，至 2016/9 始備齊第一線處方，此研究尚無法瞭解新規範對於治療效果的影響。

2015 年 HIV 患者的醫療費用約為 35 億新台幣，其中大部分費用歸咎於抗病毒藥物。為了控制醫療成本的上升，2011 年起，疾管署開始了多項醫療費用控制對策，包括

藥物處方管理(drug formulary management)，價格談判(price negotiation)和批量採購(bulk purchasing)。費用增長率從 2014 年的 2.2%降至 2015 年的 0.5%，而同時治療人數增加 15%此規範為 2012 年中開始實施，WHO 於 2013 年更改愛滋病治療指引，而近年來有越來越多的研究開始考慮簡化藥物的方式，除了藥物的可能副作用外，減少藥物種類的另一項好處是減少藥物的費用，而未來的 1-2 年內許多藥物的專利期即將終止，在學名藥的競爭，藥物的價格可望大幅下降，我國未來的治療指引，在治療選擇與藥物價格的抉擇中，將更具彈性。(詳細成果報告如附件七)

八、追蹤進行〝台灣、日本與香港男同志間新發 C 型肝炎病毒分子流行病學研究〞：

目前研究成果與 2012 年孫醫師研究相似，從圖二中可看出非靜脈毒癮的愛滋病毒感染者，在確診後再感染 C 型肝炎仍持續發生，且自 2001 年後可看到發生率為增加的趨勢，至 2015 年更達每 1,000 人年 11.85；相關因子仍以同性間性行為者與近期有梅毒的感染為顯著因子，顯示目前近期或急性 C 型肝炎的愛滋病毒感染者，以不安全性行為為主要感染途徑，且疫情並無減緩的現象。

而比較 1994-2010 及 2011-2015 年兩階段近期或急性 C 型肝炎感染者臨床資料上的差別，可看到後者發現 C 型肝炎感染時年齡較輕（32 vs.42），且較多因為肝功能指數升高進而檢測出 C 型肝炎抗體，目前在疾管署檢驗指引建議愛滋病毒感染者每年定期檢驗一次 C 型肝炎抗體，但至本院就醫的愛滋病毒感染者仍有 7%僅有基礎點甚至從未檢測過，而研究顯示愛滋病毒感染者合併 C 型肝炎感染進展為肝硬化的時間較非滋病毒感染者快，因此應除鼓勵感染者接受定期檢驗外，如發生危險性行為後有肝功能指數上升或感染其他性病時，亦應主動告知照護醫護人員進行 C 型肝炎抗體檢測，以期提早發現。

在兩階段的病毒基因型中，均以 2a 基因型較多，目前健保給付仍以長效型干擾素及雷巴威林治療為主，若是第二型及第三型基因型 48 週治療的 SVR 有較高比例成功，而愛滋病毒感染者建議在 CD4>200 cells/μl 時治療，在我們的觀察中，有 73.6%的感染者達到 SVR，成功機率算是頗高，但仍可看到有 3 位感染者於治療後 C 型肝炎病毒量再度升高，推測應是再度感染。而是否藉由同性間的不安全性行為，發生群聚傳播的現象，甚至透過旅遊是否造成本國與日本、香港這些地區有群聚感染，研究目前仍由各地研究人員進行分析，待日後資料彙整後，檢視是否此現象在亞洲地區發生，以做為臨床衛教和公共衛生政策參考。(詳細成果報告如附件八)

九、探討〝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〞計畫：

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九人(2.57%)，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(12.6%)。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，因為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。(詳細成果報告如附件九)

十、執行〝危險性行為後愛滋病毒感染之非職業性暴露後預防性投藥效果之前瞻性研究〞計畫：

就初步的結果而言，暴露後預防性投藥有其效果，但絕非單一之預防方式，而應整合將個案連結進入衛教諮詢的系統，方可在 HIV 防疫上收到好的成效；針對難以抑制慾望而反覆發生高風險行為者，可考慮建議轉為暴露前預防性投藥。此外，TDF/FTC 和 RAL 為主的處方耐受性較佳，有助於患者順利完成投藥期程。國內應以此為基礎，修正先前的指引中建議的用藥提供臨床醫師參考。(詳細成果報告如附件十)

十一、分析〝HIV-1感染者在第一線抗病毒藥物失敗後的抗藥性和臨床結果分析〞：

在本研究中發現接受非核苷酸反轉錄脢為第一線抗病毒治療的受試者中，多數人

都能維持第一線抗病毒藥物，而換藥最常見的原因是藥物的副作用(27.4%)，其次是因為抗藥性突變點的產生而治療失敗和換藥(5.1%)。衛滋(nevirapine)是治療高病毒量的受試者有較高失敗率的藥物(16.4%)，而 Y181C 是最常見的抗藥突變點；希寧(efavirenz)對高病毒量的受試者失敗率為 7.8%，而 K103N 為最常見的抗藥突變點。這些發現跟歐美等國的文獻相似，因為都是抗病毒藥物較普及的國家,但跟東南亞和其他第三世界國家的發現有些不同之處。針對核苷酸反轉錄酶抑制劑藥物的使用後產生的抗藥點的分析中，已使用惠立妥(tenofovir)較普及的地區會有較高比率的 M184V 和 K65R 等抗藥突變點的產生，在我們的研究中發現 M184V/I 和 K65R 在治療失敗者的發生機率分別為 47.1%和 25%。但如果在使用卡貝茲(zidovudine/lamivudine)較普及的地區較常見的抗藥突變點為 M41L、D67N、T215Y..等。然而在我們的研究中確比較少發現這些抗藥突變點的出現，可能跟藥物副作用有關,因為有 27.4%的受試者因藥物副作用換藥，他們少了這些藥物的暴露，因而減少了產生這些突變點的機會。根據這個研究的結果，我們建議病人要接受非核苷酸反轉錄酶抑制劑的抗病毒藥物前，應進行抗藥性檢測，而如果治療失敗也應該立即進行第二次或第三次的抗藥性檢測。同時先把藥物調整為其他類的抗病毒藥，如蛋白酶抑制劑或是嵌入酶抑制劑。(詳細成果報告如附件十一)

十二、探討〝HIV 感染者藥品動態學和基因學研究〞：

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，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。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。(詳細成果報告如附件十二)

(五)結論與建議

一、106 年度擬定期於北區及中區舉辦 HIV 感染者病例個案討論會，由各區之指定醫療院所輪流提出各院診療之有意義及特殊的病例，和與會者一起討論。明年度希望加強定期舉辦各次專科及藥師相關愛滋病毒感染的繼續教育研討會，藉以增進其他次專科及藥師對於愛滋病毒感染的認知。持續舉辦「暴露愛滋病毒前預防性投藥(Pre-exposure Prophylaxis, PrEP）」相關教育訓練。根據當年度 HIV 病患之新興感染疾病(例如近年來的 HAV 及腸胃道感染)舉辦 workshop。根據本中心研究發現定期向國內相關醫事人員報告 HIV 病患之各種疫苗接種相關問題。有關新藥品的相關問題 workshop。繼續與器捐中心合作舉辦有關「HIV 病患器官捐贈移植醫療臨床實務」相關問題教育訓練。

二、對政策之具體建議:

1. 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，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. 持續監測對第二代嵌合胺抑制劑具抗藥性的病毒株是否會傳入未接受抗反轉錄藥物治療的病人族群中。

三、對政策之具體建議: 對於愛滋病毒感染者，提供二劑常規 A 型肝炎病毒疫苗，是對於預防急性 A 型肝炎必要的措施。

四、新生兒 B 型肝炎疫苗已改變了台灣 B 型肝炎的疾病結構，即使在 HIV 患者中也能見到盛行率及發生率的顯著下降。由於疫苗產生的抗體會隨著時間衰減，不論患者最初是否具有針對 B 型肝炎之抗體保護，規則的追蹤並針對不足的患者施打是重要的。HIV 患者還是需要更好的疫苗施打計畫來增加反應率。

五、對政策之具體建議: 必須藉由減少社會歧視、提早篩檢診斷、提早提供感染者抗愛滋病毒組合療法等方式，改善台灣開始使用抗愛滋病毒組合療法之時機，減少死亡以及病毒治療失敗的風險。年齡較大的感染者，由於有較高的死亡風險，因此我們更應該在此族群積極實施改善措施。

六、對政策之具體建議:在急性病毒感染時選擇抗病毒藥物建議避開會影響骨髓造血功能的藥物，會有較好的治療效果。

七、病患對於藥物組合的臨床耐受性有所不同，參考 WHO 於 2013 年的治療建議及 2015

訂定的治療目標，Combivir 做為國內的治療選擇必須配合臨床工作人員注意相關的副作用，而一日兩次的服藥對於病患的服藥順從性是一大考驗，新的治療規範已有大幅度的修改，有待日後更長時間追蹤及更多的病患納入分析。重要研究成果及具體建議:發表海報論文於 14th European AIDS Clinical Society, Brussels, 16-19 Oct 2013 HIV Glasgow, 23-26 October 2016。2016 年 6 月實施修正後的「愛滋藥品使用規範」，期待新的處方規範能提高台灣愛滋病毒感染者的醫療品質，在未來持續觀察臨床反應能及時回饋已達到 90-90-90 的目標。

八、對政策之具體建議: 對於愛滋病毒感染者，提供定期 C 型肝炎抗體及其他性病檢驗，及及時提供 C 型肝炎及 HARRT 治療，是對於預防感染者進展為肝硬化或肝癌必要的措施。

九、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。

十、本年度最重要的研究成果在於建立起完整 nPEP 的流程後，近一年多來納入的個案均能順利完成預防性投藥，且確實無個案有 HIV 陽轉的狀況，確立 nPEP 的成效並可提供其他指定醫院參考，建議各參與醫院可提供自己醫院專門的聯絡窗口協助諮詢以及安排個案接受投藥與後續的追蹤；此外，也確立較適合的處方藥物組合確實如同國外陸續修正的指引，建議以 TDF/FTC + RAL 為主要的選擇，下一步國內應以此為基礎, 修正先前的指引中建議的用藥提供臨床醫師參考。

十一、研究多數更換含有非核苷酸反轉錄胺抑制劑第一線處方的初感染者是因為藥物副作用，因抗藥性而治療失敗的比率相對較少。此外，多數藥物治療失敗的處方中含有惠立妥(tenofovir disoproxil fumarate)、速汰滋(lamivudine)、衛滋(nevirapine)及希寧(efavirenz)。

十二、藥品動態學的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 只有一位病人檢測，血中濃度在正常範圍內。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 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。

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94..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 (in press)

附表一

一〇五年度計畫著作一覽表

計畫名稱：愛滋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：MOHW105-CDC-C-114-000104

序號	計 畫 產 出 名 稱	產出形式	SCI*
1	Lai CC, Liu WC, Fang CT, Yang JY, Chang LH, Wu PY, Luo YZ, Chang SF, Su YC, Chang SY, Hung CC*. Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan. J Antimicrob Chemother 2016;71:226-34.	期刊	4.919
2	Cheng A, Chang SY, Tsai MS, Su YC, Liu WC, Sun HY, Hung CC*. 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.	期刊	6.256
3	Yang CJ, Tang HJ, Chang SY, Hsieh SM, Lee KY, Lee YT, Sheng WH, Yang SP, Hung CC*, Chang SC. Comparison of serological response to 2-gram single-dose azithromycin versus benzathine penicillin G for early syphilis in HIV-infected patients. J Antimicrob Chemother 2016;71:775-82.	期刊	4.919
4	Chou YJ, Lin HW, Yang CJ, Chen MY, Sheng WH, Liu WC, Chang SY, Hung CC*, Hsueh PR, Chang SC. Risk of recurrent nontyphoid Salmonella bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy. J Microbiol Immunol Infect 2016;49:760-7.	期刊	2.955
5	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 2015;xx:1-9.	期刊	2.955
6	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 2016;xx:1-9.	期刊	2.955

7	Lee YC, Hung CC, Zhang JY, Wu PY, Yang SP, Lou YZ, Chang HY, Liu WC, Liu WC, Sun HY, Chang SC. Incidence and risk factors of herpes zoster in HIV-positive patients initiating combination antiretroviral therapy in Taiwan. J Microbiol Immunol Infect2016;xx:1-7.	期刊	2.959
8	Chan D, Sun HY, Wong H, Hung CC*, Lee SS. Sexually transmitted hepatitis C virus infection in the Asia-Pacific region: a review. Int J Infect Dis (accepted)	期刊	2.229
9	Lee YC, Hung CC, Cheng A, Liu WC, Wu PY, Yang SP, Zhang JY, Lou YZ, Chang HY, Sun HY, Chang SC. Willingness of HIV-positive patients to donate their organs for transplantation in Taiwan. Transplant Infect Dis (accepted)	期刊	1.459

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：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練課程

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：王素華、張乃慈

執 行 期 間：105 年 1 月 1 日至 105 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

中文摘要

依據聯合國愛滋病組織（Joint United Nations Programme on HIV/AIDS；UNAIDS）的統計資料顯示，至 2010 年中，全球感染愛滋病人數已達三千三百四十萬人；其中成人約為三千三百萬人；且整體全球感染人數比 2000 年多了 20%；而亞洲感染人數約為四百七十萬人。在亞洲地區，愛滋病的盛行率在性工作者中為 3.4~18%，亞洲地區很多性工作者同時也有使用毒品，所以感染途徑與靜脈毒癮會有重疊的情況。在異性間性行為部分，在亞洲地區有些男性經由性交易感染愛滋病毒之後，又與其性伴侶發生不安全的性行為，讓以往低危險性的異性戀感染率上升。靜脈毒癮者的愛滋病毒盛行率為 6.7~52%，男同性間的愛滋病發生率為 5.2~32.8%。

台灣於民國 75 年年初，第一例本國籍同性戀者死於 AIDS，新感染的個案數即不斷地增加，94 年間國內毒品注射群體爆發一波疫情的成長，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。國內累計愛滋病毒感染人數至 99 年 10 月達 2 萬人以上，105 年 9 月底已達 33,850 人（本國籍為 32,817 人）。在愛滋感染者年齡層方面，仍以 25~49 歲為主要族群，但 15~24 歲感染人數卻也逐年增多，大家千萬不能掉以輕心，因此醫療人員在從業的過程中有很大的機會接觸到愛滋病毒感染者，故應該定期接受愛滋病治療照護及全面性防護措施等相關在職訓練。

另一方面為配合疾病管制署關於 HIV 指定醫事機構的指定原則文中第三條規定：醫療人員、藥師及個管師每年需有愛滋病學相關教育學分 8~10 小時，故規劃及執行各科醫事人員針對愛滋病毒感染者照護之相關在職訓練，分北區、南區舉辦「醫事人員愛滋病治療之相關在職訓練課程」，此教育訓練課程有初階及進階等不同的課程內容，參加對象為對於照護愛滋病患有興趣之醫療人員，並與疾病管制署合作宣導及鼓勵其他科別的醫師來參加訓練，籌劃跨科整合的訓練課程，包含感染科、婦產科、兒科、家庭醫學科、精神科、內科、外科、牙科、藥師等醫護人員及社工人員等，同時申請臺灣醫學會、

台灣感染症醫學會、台灣婦產科醫學會、台灣兒科醫學會、台灣愛滋病學會、內科醫學會、台灣家庭醫學會等相關醫學會持續教育學分認證，以提高學員之參加意願，全程參加者結業時並頒發授課證明。

暴露前預防性投藥(HIV Pre-exposure prophylaxis, PrEP)是近年來愛滋病預防的新方法，世界衛生組織預估在男男間性行為者間使用PrEP，能降低20-25%的HIV發生率，10年能避免100萬個HIV新感染個案的發生。在現實世界的情況中要如何執行才能有效降低愛滋病傳染的風險，尤其是針對高風險族群(例如：男男間性行為者)，是全球關注的議題，顯示暴露愛滋病毒前預防性投藥是防治愛滋病的重要手段之一。由於高風險民眾可視個人需求，由診療醫師開立處方，自費購買使用因國內愛滋病診療醫師為民眾進行相關醫療服務之主要諮詢對象，亦為愛滋病預防、診斷及治療的第一線把關者，為促使本項服務之普及性與提升服務意願，並加強診療醫師對暴露愛滋病毒前預防性投藥之適用性、投藥實務、治療及防治等專業知能，特別與愛滋病學會分北中南區三場次開立「暴露愛滋病毒前預防性投藥（Pre- exposure Prophylaxis, PrEP）教育訓練」，在評估個案接觸HIV前給予預防性投藥的流程，對於其使用時機、對象、安全性、衛教、諮詢提供完整的評估及處置流程。

關鍵詞：愛滋病、滋病毒感染、抗病毒藥物、毒品病患愛滋減害計畫、愛滋病減害計畫醫事人員愛滋病治療之相關在職訓練課程、暴露愛滋病毒前預防性投藥教育訓練

英文摘要

According to the statistics of the Joint United Nations Programme on HIV/AIDS (UNAIDS), 34 million people were living with HIV/AIDS, and among which 23.5 million people are in sub-Saharan Africa. Some 14.8 million people require medical treatment, but only 8 million people have availed of proper treatment. Moreover, the HIV-infected population in the world is 20% higher than that posted in year 2000. In Asia, the HIV-infected population is estimated at 4.7 million people. In the Asian region, the prevalence rate of HIV/AIDS among people plying the sex trade ranges between 3.4% and 18%. Since many sex workers in Asian region are also prohibited substance users, intravenous drug users are likely to come in contact with the infection route of the virus. On the other hand, heterosexual males in the Asian region tend to continue engaging in unsafe sex with their regular sex partners even after being infected with HIV/AIDS through sex trade, thereby resulting in a rise in the infection rate among the previously identified as low-risk heterosexual groups. The HIV/AIDS prevalence rate among the intravenous drug dependents ranges between 6.7% and 52%; whereas, HIV/AIDS prevalence rate among male homosexuals ranges between 5.2 and 32.8%.

In Taiwan, the first reported case of homosexual AIDS sufferer died of the disease in the early period of 1986; thereafter, cases of new HIV infections continue to sprout. In 2005, HIV infection reached an explosive growth rate among the intravenous drug using clusters; consequently, the Executive Yuan ratified the AIDS Harm Reduction Program to cope with the drastic rise of HIV infection among the drug dependent population. In August of 2005, Taipei City, Taipei County, Taoyuan County, and Tainan County organized the AIDS Harm Reduction Program for Drug Dependents; thereafter, a clean syringe campaign was launched in July 2006. There were 427 syringe sterilization and AIDS health information and counseling stations established throughout the 23 cities and counties of Taiwan. In the massive campaign for the use of alternative therapy launched in August 2006, the alternative therapy program implementing facilities established throughout the 22 cities and counties of Taiwan resulted in the significant decrease of AIDS prevalence rate among intravenous drug users; unfortunately, the ratio of new HIV infections reported annually remained to post 15% and above among the male heterosexuals. Furthermore, exchanges between Taiwan and Southeast Asian countries and China having high HIV prevalence rates are quite common, a factor that further hastened the spread of HIV infection. In Taiwan, the total HIV infected

population as of end of Sep. 2016 has reached 33,850 (local nationals comprised 32,817), or an average of 6 persons being infected per day. A more daunting factor is that statistics showed a lowering in the age of HIV-infected persons. Although the 25-49 age group remains to be the primary cluster (70.10%) of people with HIV/AIDS, the ratio of infected people in the 15-24 age group is posting a gradually annual growth, a matter that should not be taken lightly. Since there is a high probability for medical workers to come in contact with people with HIV in their line of duty, it is imperative that they receive regular job training on the matter of AIDS treatment and care and AIDS-related universal precautions.

Moreover, in coordination with Article 3 of the General Designation Principles of the HIV Medical Facilities stipulated by the Centers for Disease Control (CDC) of the Ministry of Health and Welfare, the medical workers, pharmacists, and case managers are required to annually receive the AIDS medicine related education program for 8 to 10 hours; hence, in the future, job training courses on the medical care of people with HIV/AIDS shall be planned and implemented for medical workers of the respect. AIDS treatment related job training courses for medical workers are conducted in the northern and southern regions of Taiwan annually. These education and training courses are classified into beginning and advance courses. Participants are generally medical workers interested in the provision of medical care to people with AIDS. Furthermore, joint campaigns with the CDC will be conducted to disseminate information and to encourage medical practitioners of other fields to join the training program. Cross-disciplinary training programs are being planned for the training of medical workers in the fields of infectious diseases, obstetrics & gynecology, pediatrics, family medicine, psychiatry, internal medicine, surgery, dentistry, and pharmacology, and also social workers. In addition, requests will be forwarded to the medical associations, such as, Formosan Medical Association, Infectious Diseases Society of Taiwan, Taiwan Association of Obstetrics and Gynecology, Taiwan Pediatric Association, Taiwan AIDS Society, Taiwan Society of Internal Medicine, and Taiwan Association of Family Medicine for the accreditation of continuing education credit hours to enhance the participation inclination of medical workers. The course completion certificates are awarded to participants who have satisfactorily completed the entire training courses.

Keywords: HIV, AIDS, HAART, Antiviral drug, Universal precautions. Pre-exposure Prophylaxis, PrEP

一、前言

台灣於民國 73 年年底，因一名患有 AIDS 之美籍同性戀者過境台北，一時造成國人的熱烈討論；衛生福利部(前衛生署)遂於 74 年春成立愛滋病防治小組。75 年初第一例本國籍同性戀者死於 AIDS，新感染的個案數即不斷地逐年增加。94 年國內爆發毒癮族群的愛滋病毒感染，當年度的通報感染者人數 3,445 人比 93 年的 1,568 人成長了 119%，為防範藥癮者因共用針具、稀釋液或稀釋容器而感染愛滋病毒，衛生福利部(前衛生署)於 95 年擴大辦理「藥癮愛滋減害計畫」，國內幸賴各相關單位積極參與「藥癮愛滋減害計畫」使得 95 年年底通報人數降為 2,979 人，96 年更降為 1,976 人，但與 92 年以前都只有 3 位數的通報人數相較，仍然有許多防疫上需要努力的地方。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，更加速國內 HIV 感染的擴散。目前累計愛滋病毒感染人數至 105 年 9 月底已達 33,850 人（本國籍為 32,817 人）。在愛滋病毒感染者年齡層方面，感染愛滋病毒的年齡層以 25 至 49 歲最多，佔 70.1%，其次為 15 至 24 歲，佔 24.23%，顯示我國愛滋病毒感染者幾乎集中在生產力旺盛的青壯族群，大家千萬不能掉以輕心。

有鑑於醫護人員在從業的過程中有很大的機會接觸到愛滋病毒感染者，所以對於醫護人員的愛滋病毒感染相關知識教育及在職訓練非常重要並有其迫切性。故本計劃規劃及執行各科醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練，每年分別在北區、南區舉辦「醫事人員愛滋病治療照護及全面性防護措施等相關在職訓練課程」，此教育訓練課程有初階及進階等不同的課程內容，參加對象為對於照護愛滋病患有興趣之醫療人員，並與疾病管制署合作宣導及鼓勵其他科別的醫師來參加，籌劃跨科整合的訓練課程，擬包含感染科、婦產科、兒科、家庭醫學科、精神科、內科、外科、藥師等醫護人員及社工人員等，同時申請臺灣醫學會、台灣感染症醫學會、台灣婦產科醫學會、台灣兒科醫學會、台灣愛滋病學會、內科醫學會、台灣家庭醫學會等相關醫學會持續教育學分認證，以提高學員之參加意願，全程參加者結業時並將頒發授課證明。

「愛滋病防治中心」成立 19 年來，業已完成階段性的任務，包括專職人員的訓練招募、醫療設備更新、研究人員的招攬等，但是，儘管感染者的生命存活大為延長之際，新增感染者卻仍持續增加中，這個現象反映出預防工作上的缺失。再者，新的藥物不斷地開發引進台灣，藥物治療的複雜和長期副作用往往不明，長期而言，可能對於感染者

產生早發性心血管病變、骨質缺乏、新陳代謝等病變。但是目前國內臨床醫師對於這些副作用的處理或認知，仍處於渾沌不清的時期；而大量抗病毒藥物的使用，可能導致抗藥性病毒株產生，並進而造成傳播，導致新近感染者治療上的困擾；而病毒株分型的改變，也可能影響到未來疫苗的研發等。在伺機性感染方面，國內仍缺乏長期性、多中心、系統性的研究等，諸如上述問題的解決，都有賴「愛滋病防治中心」繼續運作，並擴大其防治功能，協調各相關醫院的臨床和基礎研究人員，一起研究方能事半功倍。

二、材料與方法

定期分區舉辦「醫事人員愛滋病治療之相關在職訓練課程」，加強醫護人員、臨床醫師對愛滋病的認知。以及每年舉辦一次「全國提昇愛滋病患臨床醫療照顧品質研討會」，及其他科醫療人員之愛滋病研習會，實施方法及進行步驟如下：

（一）初階教育課程，課程內容包括：

1. 台灣愛滋病政策與法令及流行病學介紹
2. HIV 之基因與分子流行病學
3. HIV 感染之檢驗、診斷及臨床表徵
4. 抗愛滋病毒藥物治療指引
5. 愛滋病毒之伺機性感染及治療
6. HIV 門診時之相關醫師衛教
7. 母子垂直感染防治政策及成果
8. 懷孕婦女之抗病毒治療與預防
9. 台灣嬰幼兒愛滋病感染之現況與抗病毒治療
10. HIV 檢驗前後之諮商及家屬衛生教育指導
11. 醫療環境防護措施及人員針扎事件之處理原則
12. HIV/AIDS 之護理照顧
13. 暴露愛滋病毒前預防性投藥（Pre- exposure Prophylaxis, PrEP）教育訓練

（二）進階教育課程，課程內容包括：

1. HIV/AIDS 抗病毒藥物治療之副作用與交互作用
2. 愛滋病毒之伺機性感染個論

3. HIV/AIDS 之慢性 B 型和 C 型肝炎處置

4. 愛滋病毒感染者之糖尿病

5. 愛滋病毒感染者之心血管疾病與高血脂症之處置

6. 愛滋病毒感染者之糖尿病

7. 愛滋病毒感染者之腸胃疾病

8. 愛滋病毒感染者之腫瘤

9. 愛滋病毒感染者之神經系統疾病

10. 愛滋病毒感染者之性病

11. 愛滋病毒感染者之骨科疾病

12. 抗藥性病毒株之監測及處理

13. HAART 治療失敗病人的處理

14. 器官捐贈移植醫療臨床實務研討會

（三）靜脈毒癮 HIV 感染者相關之教育訓練課程，課程內容包括：

1. 台灣 HIV 感染及靜脈毒癮 HIV 感染者之流行病學介紹

2. 台灣 HIV 感染及靜脈毒癮 HIV 感染者之分子流行病學介紹

3. HIV/AIDS 毒癮者之治療經驗

4. HIV/AIDS 毒癮者之一般性感染與處置

5. HIV/AIDS 毒癮者之慢性 B 型和 C 型肝炎處置

6. HIV/AIDS 毒癮者之精神疾病與處置

7. HIV/AIDS 毒癮者之護理照護經驗

8. 「減少傷害 Harm Reduction」之相關工作坊及訓練課程

（四）參加對象：對於照護愛滋病患有興趣之醫事人員，包含感染科、婦產科、兒科、家庭醫學科、精神科、內科、外科、藥師等醫護人員及社工人員。

（五）申請臺灣醫學會、台灣感染症醫學會、台灣婦產科醫學會、台灣兒科醫學會、台灣愛滋病學會、內科醫學會、台灣家庭醫學會等相關醫學會持續教育學分認證，以提高學員之參加意願。

（六）全程參加者結業時頒發授課證明。

（七）進行課程評量，瞭解學員之需求及意見，以做為辦理下屆訓練課程之參考。

三、結果

愛滋病毒感染相關的知識日新月異，新藥物與治療的研發蓬勃發展，面對這些醫療新知的獲取，對照護愛滋病患的醫事人員而言格外重要且迫切，故愛滋病防治中心扮演傳播及教育國內治療與防治相關知識的角色，積極且定期規劃及執行各科醫事人員「愛滋病治療照護及全面性防護措施等相關在職訓練」課程。

(1)、105 年 5 月 7 日於台北舉辦「愛滋治療與共病風險評估研討會」邀請 Prof. Jens D. Lundgren 來台演講，衛生署指定醫療院所照護愛滋病毒感染者之專責醫師及個管師共 35 位參與。研討會內容：

❖

Time	Topic	Speaker	Moderator
12:30-13:50	報到	All	
13:50-14:00	Opening	Prof. Jens D. Lundgren	林錫勳醫師
14:00-14:40	“START” early “START” now		
14:40-14:50	Q&A		
14:50-15:00	中場休息	All	
15:00-15:25 Workshop 1	Introduce CVD risk prediction model in HIV-positive patients	Prof. Jens D. Lundgren	洪健清醫師
15:25~15:40	CVD84 8 案例討論	楊家瑞 醫師 顧文瑋 醫師	盛望徽醫師 王永衛醫師
15:40-16:00	綜合討論	Prof. Jens D. Lundgren	洪健清醫師
16:00-16:25 Workshop 2	Introduce CKD risk score model in HIV-positive patients	Prof. Jens D. Lundgren	洪健清醫師
16:25-16:40	CKD 案例討論 1	鄭健禹 醫師	鄭舒倖醫師
Parallel	CKD 案例討論 2	林德宇 醫師	王甯祺醫師
16:40-17:00	綜合討論	Prof. Jens D. Lundgren	洪健清醫師
17:00-17:10	Closing Remark	Prof. Jens D. Lundgren	林錫勳醫師

(2)、協助財團法人器官捐贈移植登錄中心舉辦『105年度器官捐贈移植醫療臨床實務研討會』（北區）6/29日亞東紀念醫院約有250人參加、（中區）8/5日台中榮民總醫院約有200人參加、（南區）7/22日高雄醫學大學附設醫院約有210人參加、（東區）8/26日花蓮慈濟醫院約有120人參加；負責兩個重要愛滋防護講題如下：(A)國際愛滋病毒感染者接受器官移植現況與醫事人員污染體液暴露後處置介紹；(B)國內愛滋病毒感染者之護理照護及個案管理經驗。研討會內容：

時　間	105 課 程 主 題	講　師
8:40~9:00	報　　到	
8:50~9:00	致　　詞	器捐登錄中心
9:00~10:30	A.【器官移植感染議題】 器官移植手術前後常見感染之處置	北區/三總王竇祺醫師 中區/台大孫幸筠醫師 南區/台大孫幸筠醫師 東區/慈濟李明哲醫師
10:30~10:40	休　　息	
10:40~12:10	B、C 肝炎病人在器官移植手術前後之評估與治療	北區/台大劉振驊醫師 中區/台大劉振驊醫師 南區/高長林志哲醫師 東區/慈濟李明哲主任
12:10~13:30	午 餐 時 間	
13:30~14:20	B.【愛滋防護議題】 國際愛滋病毒感染者接受器官移植現況與醫事人員污染體液暴露後處置介紹	北區/台大洪健清醫師 中區/中榮林育蕙醫師 南區/高榮吳冠陞醫師 東區/台大洪健清醫師
14:20~14:30	休　　息	
14:30~15;20	國內愛滋病毒感染者之護理照護及個案管理經驗	北區/台大李慶玟護理長 中區/中榮謝佳吟個管師 南區/成大柯乃熒教授 東區/台大李慶玟護理長
15:20~	賦　　歸	

(3)、為配合衛生福利部疾病管制署對於指定醫療院所照護 HIV/AIDS 醫護人員之在職訓練要求，105 年 5 月 28 日於財團法人張榮發基金會國際會議中心 801 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」,任職後天免疫缺乏症候群指定醫療院所的藥師，參與減害計畫指定醫院或藥房之藥師，其他對於愛滋病治療有興趣的藥師參會者共有 87 位藥師。課後評量統計表詳見附件一~1。課程內容：

時　　間	題　　目	演講者	主持人
08:00~08:30	Registration		
08:30~08:40	Welcome address		林慧玲常務理事 盛望徽常務理事
08:40~09:30	愛滋病毒感染的藥物治療與順從性評估	顧文瑋醫師	盛望徽 醫師
09:30~10:10	Presentation of Cases-1	王建淳醫師	盛望徽 醫師
10:10~10:30	Coffee Break		
10:30~11:20	愛滋病毒感染長期治療的併發症	楊家瑞醫師	鄭舒倖 醫師
11:20~12:00	Presentation of Cases-2	鄭健禹醫師	鄭舒倖 醫師
12:00~12:20	Panel Discussion		鄭舒倖 醫師
12:20~13:30	Lunch		
13:30~14:20	愛滋病毒感染相關伺機性感染的治療與預防	蔡茂松醫師	林育蕙 醫師
14:20~15:00	Presentation of Cases-3	林德宇醫師	林育蕙 醫師
15:00~15:20	Coffee Break		
15:20~16:10	愛滋病毒感染藥物治療的交互作用	林淑文藥師	王甯祺 醫師
16:10~16:50	Presentation of Cases-4	劉佳穎醫師	王甯祺 醫師
16:50~17:20	Discussion & Closing		林育蕙 醫師 王甯祺 醫師

(4)、為提昇國內指定醫師院所現職愛滋病毒感染個案管理師臨床專業能力及參與力，特別開立此教育訓練研習班。參加對象：國內指定醫師院所現職之臨床愛滋病毒感染個案管理師。舉辦日期：7 月 30、31 日。共有 61 位個管師參與。課後評量統計表詳見附件一~2。課程內容如下：

7/30 日(六)	題 目		演講者	主持人
09:40-10:00	報 到			
10:00-10:10	歡 迎			林錫勳理事長
10:10-10:50	性病(含新興傳染疾病)評估與處置		鄔豪欣 醫師	林錫勳理事長
10:50-11:40	HAART 藥物副作用之評估與處理(含 STR 使用)		洪健清 醫師	林錫勳理事長
11:40-12:00	討 論			林錫勳理事長
12:00-13:00	午 餐			林錫勳理事長
13:00-13:30	個案管理實務綜論(含考生分享)		莊苹 常務理事 郭乙錡	柯乃熒理事
13:30-17:30	分組討論	危險性行為的解決策略(併使用娛樂性藥物成癮藥物者)	A 組(柯乃熒老師)北部個管	莊苹常務理事
		服藥順從性提升策略(併使用娛樂性藥物成癮藥物者)	B 組(孫娜俐個管師) 中部個管	
		未預期懷孕的因應	C 組(賴怡因個管師)北部個管	
		初感染者的評估與因應(併使用娛樂性藥物成癮藥物者)	D 組(李幸娟個管師)南部個管	
17:30-18:00	討論與回饋			莊苹常務理事

7/31 日(日)	題 目	演講者	主持人
09:00-09:50	接觸者追蹤策略	邱飄逸 老師	盛望徽常務理事
09:50-10:40	困難個案諮商技巧 (含娛樂性藥物使用文化)	李夢萍 老師	盛望徽常務理事
10:40-10:50	茶 敘		
10:50-11:40	感染者侵權之評估與處置	林宜慧 秘書長	王永衛常務理事
11:40-12:30	(即將)旅外感染者照護 (含就醫資訊取得)	顧文瑋 醫師	王永衛常務理事
12:30-13:00	綜合討論		盛望徽常務理事 王永衛常務理事

(5)、105 年 9 月 9~10 日於台北喜來登酒店與成大醫院共同舉辦「105 年度台灣 HIV 研究平台會議 Taiwan HIV/AIDS Research Meeting」會中並邀請研究 HAV 及 HBV 疫苗之法國專家 Dr. Odile Launay 專題演講，並與國內專家學者共同討論，計有 86 位專家學者參與。

	9 月 9 日 TOPIC	Speaker	Moderator
19:00-19:05	OPENING	His-Hsun Lin 林錫勳　理事長	
19:05-19:30	Prevalence of anal squamous intraepithelial lesions in HIV-positive and HIV-negative men who have sex with men in northern Taiwan	Wen-Wei Ku 顧文瑋　醫師	Shu-Hsing Cheng 鄭舒倖 主任
19:30-19:55	Epidemiology of human papillomavirus infection in a community cohort of adult men who have sex with men in Southern Taiwan: Preliminary findings	Carol Strong 莊佳蓉 助理教授	Shu-Hsing Cheng
19:55-20:20	Comparison of early serological response to benzathine penicillin between HIV-positive and HIV-negative patients	Chia-Jui Yang 楊家瑞　主任	Shu-Hsing Cheng
20:20-20:45	Shigellosis outbreak among HIV-positive MSM in Taiwan: association with immunosuppression and antimicrobial resistance	Hao-Hsin Wu 鄔豪欣　醫師	Po-Liang Lu 盧伯樑 主任
20:45-21:10	High daily doses of trimethoprim/sulfamethoxazole are an independent risk factor for adverse reactions in patients with pneumocystis pneumonia and AIDS	Hui-Min Chang 張惠敏　藥師	Po-Liang Lu
21:10-21:20	DISCUSSION		Po-Liang Lu

	9 月 10 日 TOPIC	Speaker	Moderator
9:00-9:05	OPENING	Wen-Chien Ko 柯文謙主任	
9:05-10:00	Plenary: HAV and HBV vaccination in HIV-infected patients	Dr. Odile Launay	Yi-Chun Lo 羅一鈞 主任
10:00-10:25	Outbreak of acute HAV infection among MSM in Taiwan, 2015-2016	Wan-Ching Chen 陳婉青　醫師	Yi-Chun Lo
10:25-10:50	Serologic response to HAV vaccination among HIV-positive patients in a setting of an ongoing HAV outbreak	Kuan-Yin Lin 林冠吟　醫師	Yi-Chun Lo
10:50-11:00	DISCUSSION		
11:00-11:10	BREAK		
11:10-11:35	Durability of HAV vaccination in HIV-positive patients receiving 2 or 3 doses of HAV vaccine	Chien-Ching Hung 洪健清　醫師	Sui-Yuan Chang 張淑媛 教授
11:35-12:00	HBV seroepidemiology and vaccination effectiveness of HIV-positive patients born in the era of nationwide HBV vaccination	Yi-Chia Huang 黃怡嘉　醫師	Sui-Yuan Chang
12:00-12:25	Long-term virologic response to TDF-containing regimens in HIV/HBV-coinfected patients	Yu-Shang Huang 黃于珊　醫師	Sui-Yuan Chang
12:25-13:30	LUNCH		
13:30-13:55	Prevalence of resistance mutations from ARV-naïve HIV-positive patients in Taiwan	Ya-Wei Wong 翁雅為　醫師	Hung-Chin Tsai 蔡宏津 主任
13:55-14:20	Patterns of resistance mutations in HIV-positive patients failing nNRTI-containing regimens	Chien-Yu Cheng 鄭建禹　醫師	Hung-Chin Tsai
14:20-14:45	Survey of fracture risk using FRAX among HIV-positive patients in Taiwan	Jun-Yu Zhang 張君俞 個管師	Hung-Chin Tsai
14:45-14:55	DISCUSSION		
14:55-15:05	BREAK		

15:05-15:30	Reasons of changing antiretroviral regimens prescribed according to Taiwan CDC regulations	Mao-Song Tsai 蔡茂松　醫師	Hung-Jen Tang 湯宏仁　主任
15:30-15:55	Risk of diabetes mellitus in HIV-positive patients receiving highly active antiretroviral therapy: a nationwide population-base study	Shi-Ping Lin 林詩萍　醫師	Hung-Jen Tang
15:55-16:20	Trends of and associated factors with diabetes mellitus in HIV-positive patients seeking HIV care at a university hospital	Pei-Ying Wu 巫沛瑩 個管師	Hung-Jen Tang
16:20-16:45	PrEP: Can it eliminate HIV epidemic and its cost-effectiveness in Taiwan?	Hui-Jen Wu 吳慧娟　碩士	Nai-Ying Ko 柯乃熒 教授
16:45-17:10	Survey of intention to start pre-exposure prophylaxis (PrEP) against HIV transmission among VCT clients in Taipei	Yi-Chieh Lee 李怡頡　醫師	Nai-Ying Ko
17:10-17:20	DISCUSSION		Nai-Ying Ko
17:20-17:25	CLOSING	Chien-Ching Hung Wen-Chien Ko	

(6)、9/24、25 日(共 1.5 天) 於公務人力發展中心福華國際文教會館舉辦「感染症醫師愛滋病治療專業能力教育訓練研習班」目前有 64 位醫師參加。課後評量統計表詳見附件一~3。課程內容：

Sep. 24 (六)	Topic	講師	主持人
08:30-09:00	Registration		
09:00-09:10	Opening		顏慕庸 院長
09:10-09:50	Update on HIV virology: diagnosis and monitoring	張淑媛 教授	顏慕庸 院長
09:50-10:30	Update of the management of hepatitis co-infection among people living with HIV	孫幸筠 醫師	顏慕庸 院長
10:30-10:50	Break		
10:50-11:30	Management of common sexually transmitted infections	王建淳 醫師	洪健清 醫師
11:30-12:10	Update on combination antiretroviral therapy and current guidelines	吳冠陞 醫師	洪健清 醫師
12:10-14:00	Lunch		
14:00-14:40	Metabolic syndrome and cardiovascular disease among people living with HIV	蔡茂松 醫師	莊銀清理事長
14:40-15:20	Update of management of Pre- and post-exposure prophylaxis in occupation and non-occupational settings	楊家瑞 醫師	莊銀清理事長
15:20-15:40	Break		
15:40-16:20	Management and prophylaxis of opportunistic infections and malignancy: respiratory and central nervous systems (1)	鄭健禹 醫師	林錫勳理事長
16:20-16:50	Case demonstration (1)– respiratory and central nervous system	林詩萍 醫師	林錫勳理事長
16:50-17:20	Q&A		林錫勳理事長
17:30-19:30	Dinner		

Sep. 25 (日)	Topic	講師	主持人
09:00-09:40	Recreational drug use among people living with HIV	顧文瑋 醫師	王永衛 醫師
09:40-10:20	Update on management of opportunistic infections and malignancy: gastrointestinal, mucocutaneous and others (2)	林冠吟 醫師	王永衛 醫師
10:20-10:40	Break		
10:40-11:10	Case demonstration (2)–gastrointestinal and others	李佳雯 醫師	盧柏樑 醫師
11:10-11:50	Vaccination strategy among people living with HIV	李育霖 醫師	盧柏樑 醫師
11:50-12:00	Q&A		盧柏樑 醫師

(7)、協助學會舉辦北中南三場次「暴露愛滋病毒前預防性投藥(Pre- exposure Prophylaxis, PrEP）教育訓練」，南區舉辦日期：105年7月2日 (六) 國立成功大學醫學院（成杏校區）護理系三樓309教室共有52位參加。中區舉辦日期：105年8月6日 (六) 於中山醫學大學正心樓0212教室共有50位參加。北區舉辦日期：105年8月13日 (六) 於台大醫學院101講堂共有102位參加。課程內容：

時　　間	題　　目	演講者	主持人
13:30~14:00	Registration		
14:00~14:10	Welcome address		南區: 賴俊麟科長 中區: 林明誠主任 北區: 劉瀞鎂科長 南區:林錫勳醫師 中區:林育蕙醫師 北區:王永衛醫師
14:10~15:00	What’s the Evidence of PrEP in Clinical Trials	南區:李佳雯醫師 中區:林詩萍醫師 北區:蔡茂松醫師	南區:林錫勳醫師 中區:林育蕙醫師 北區:王永衛醫師
15:00~15:50	From Clinical Trial to Real-life Implementation	南區:吳冠陞醫師 中區:顧文瑋醫師 北區:楊家瑞醫師	南區:柯乃熒教授 中區:李原地醫師 北區:謝思民醫師
15:50~16:10	Coffee Break		
16:10~16:40	Cases Wrap-up	南區:吳冠陞醫師 南區:李佳雯醫師 中區:林詩萍醫師 中區:顧文瑋醫師 北區:蔡茂松醫師 北區:楊家瑞醫師	南區:柯乃熒教授 中區:李原地醫師 北區:謝思民醫師
16:40~17:00	Question and Feedback	南區:吳冠陞 醫師 南區:李佳雯 醫師 中區:林詩萍醫師 中區:顧文瑋醫師 北區:蔡茂松醫師 北區:楊家瑞醫師	南區:林錫勳醫師 南區:柯乃熒教授 中區:林育蕙醫師 中區:李原地醫師 北區:王永衛醫師 北區:謝思民醫師

(8)、105年11月19日於台北舉辦「Post-HIV Drug Therapy Conference」，分享11/23~26日在英國舉辦的「The HIV Drug Therapy Glasgow」國際會議的成果，約有70~80位醫療人員參加，議程如下：

Time	Topic	Presenter	Moderator
14:00-14:10	Opening	蘇世強 醫師 新竹馬偕	
14:00-14:50	Treatment strategies: simplification, dual therapy, and switching studies	蔡茂松 醫師 亞東醫院	林育蕙 醫師 台中榮總
14:50-15:40	Co-morbidities and HIV management	陳冠州 醫師 臺大醫院	洪健清 醫師 臺大醫院
15:40-15:50	Discussion	洪健清 醫師	
15:50-16:10	Coffee break		
16:10-17:00	PrEP: evidence for effectiveness and implementation strategies	楊家瑞 醫師 亞東醫院	蔡宏津 醫師 高雄榮總
17:00-17:50	Antiretroviral strategies: Current progress and remaining challenges of ART efficacy and side effects and future new drugs	林冠吟 醫師 臺大醫院	林錫勳 醫師 義大醫院
17:50-18:20	Recap and closing	洪健清 醫師	

(9)、105年11月9日、12月2日、12月16日三場次在台北、台中、高雄舉辦「HIV/AIDS病患HAART藥物治療個案討論會」，總計各場次約有70~80位醫療人員參加，議程如下：

11/9 日	Presentation of Case	Presenter	Moderator
18:20-18:30	Opening	洪健清醫師	
18:30-19:00	A 24-year-old homosexual man presented with a 5-day history of progressive bilateral upper/lower limb weakness	陳志昊醫師 亞東醫院	蔡茂松醫師 亞東醫院
19:00-19:30	Emerging HIV-1 drug resistance after post-exposure prophylaxis	鄭健禹醫師 桃園醫院	鄭舒倖主任 桃園醫院
19:30-20:00	A 25 year-old man with intermittent fever and sore throat for 10 days	黃馨慧醫師 台北市立聯合醫院忠孝院區	王登鶴主任 台北市立聯合醫院忠孝院區
20:00-20:30	Mental Health among HIV sero-discordant couples	衛漢庭醫師 台北市立聯合醫院昆明院區	王建淳主任 台北市立聯合醫院昆明院區
21:10-21:30	Recap and closing	洪健清醫師	

12/2 日	Presentation of Case	Presenter	Moderator
18:30-18:40	Opening	何茂旺主任	
18:40-19:20	Dual therapy in treatment naïve patient	陳正斌醫師 中榮嘉義分院	林育蕙醫師 台中榮總
19:20-20:00	ART Choice in HIV/HBV co-infection Patient	林伯昌醫師 中國附醫	何茂旺主任 中國附醫
20:00-20:40	A young man with fever and dizziness for 4 days-Diagnosis of HIV Acute Infection	劉元孟醫師 彰化基督教醫院	劉尊榮主任 彰化基督教醫院
20:40-21:20	84 y/o Man Acute Kidney Injury with Hyperkalemia and Hyponatremia	李鑒峯醫師 中山附醫	李原地主任 中山附醫
21:20-21:30	Recap and closing	李原地主任	

12/16 日	Presentation of Case	Presenter	Moderator
18:30-18:40	Opening	林錫勳理事長	
18:40-19:20	Management of HIV & HAV coinfection	翁雅為醫師 高雄榮總	蔡宏津醫師 高雄榮總
19:20-20:00	Toxoplasmosis in HIV Patient	謝旻翰醫師 大同醫院	陳惇杰主任 大同醫院
20:00-20:40	Management of opportunistic infections	梁修豪醫師 義大醫院	林錫勳理事長 義大醫院
20:40-21:20	Primary mediastinal large B-cell lymphoma in HIV: report of two cases	黃文琦醫師 高雄長庚	李楨祥醫師 高雄長庚
21:20-21:30	Recap and closing	林錫勳理事長	

(10)、105 年 12 月 17 日 (星期六) (共 0.5 天) 財團法人張榮發基金會國際會議中心 1002 講堂「愛滋病相關伺機性感染治療進展研討會」隨著 ART 的發展，有部分伺機性感染出現的情形也漸漸有減少的趨勢，然而， 每年仍然還是會有一部分的感染者延遲到伺機性感染出現才被診斷而住院；針對各項不同病原所造成的伺機性感染，學會特別舉辦此研討會，針對個別病原所造成疾病的處置之最新進展做深入的探討，並預計於明年進行國內指引的修正。預計有 60~80 位醫護同仁參加。課程內容：

12 月 17 日	Topic	講師	主持人
13:00-13:20	Registration		
13:20-13:30	Opening	林錫勳 理事長	
13:30-14:20	Fungal infections	孫幸筠 醫師	王甯祺 主任
14:20-15:10	Bacterial Infections	楊家瑞 醫師	盛望徽 主任
15:10-15:20	Discussion	盛望徽 主任	
15:20-15:40	Coffee break		
15:40-16:30	Virus Infections	李育霖 醫師	盧伯樑 主任
16:30-17:20	Tuberculosis	楊佳鈴 醫師	李欣蓉 主任
17:20-18:10	Non-tuberculous mycobacterial infections	吳冠陞 醫師	洪健清 主任
18:10-18:30	Panel discussion and closing	洪健清 主任	
18:30~	dinner		

(11)、本中心延續以往的愛滋病研討會在綜合病房研討室舉行，本年度聘請了各方面的專家來進行全方位的研討，其內容包括有臨床醫學、病毒學、免疫學、流行病學、護理學、精神科醫學、個案研究、研究成果發表及新抗病毒藥物之介紹等；參加成員亦日益踴躍，包括有各科各級醫師、護理人員、檢驗人員、助理人員、社工人員、各基礎學科教師，踴躍參與，以期大家能各憑專業集思廣益。上半年1~11月初已進行33場。題目及演講者如附件一-4。

四、結論與建議

本計畫已達成之目標、結論與建議如下：

一、本計畫在 105 年已舉辦 4場次大型在職教育訓練課程及研討會、6 場次 workshop、3 場次中小型研討會，各場次皆有醫療人員約 50~102 人次參與，對國內愛滋病防治之醫療教育貢獻良多。

二、為提昇國內 HIV/AIDS 臨床及學術研究，105 年度舉辦 1 場「台灣地區 HIV/AIDS 多中心研究合作平台討論會」。有醫師及研究人員 86 名參加，會中互相討論做成許多共識與結論。明年度擬繼續舉辦。

三、每週一次的愛滋病防治中心研討會，本年度繼續聘請各界的專家來進行全方位的研討，內容包括臨床醫學、藥學、病毒學、免疫學、流行病學、護理學、精神科醫學、個案研究、研究成果發表及新抗病毒藥物之介紹等；以後將加強個案討論，以期大家能各憑專業集思廣益互相交流。明年度擬繼續定期舉辦。

四、106 年度擬定期於北區及中區舉辦 HIV 感染者病例個案討論會，由各區之指定醫療院所輪流提出各院診療之有意義及特殊的病例，和與會者一起討論。

五、明年度希望加強定期舉辦各次專科及藥師相關愛滋病毒感染的繼續教育研討會，藉以增進其他次專科及藥師對於愛滋病毒感染的認知。

六、暴露愛滋病毒前預防性投藥(Pre- exposure Prophylaxis, PrEP）相關教育訓練。

七、根據當年度 HIV 病患之新興感染疾病(例如近年來的 HAV 及腸胃道感染)舉辦 workshop。

八、 根據本中心研究發現定期向國內相關醫事人員報告 HIV 病患之各種疫苗接種相關問 題。

九、有關新藥品的相關問題 workshop。

十、有關「HIV 病患器官捐贈移植醫療臨床實務」相關問題教育訓練。

五、參考文獻

1. 92 年 2 月 22~23 日屏東舉辦「全國提昇愛滋病患臨床醫療照顧品質研討會」。
2. 92 年 8 月 16 日台北、9/13 日台中、9/20 日高雄，各一場「抗 HIV 藥物繼續教育課程 2003」。
3. 92 年 11 月 1~2 日台北舉辦「2003 Updated Management of HIV Infections in Taiwan-Working to Success」。
4. 93 年 4 月 10 日台南舉辦「2004 全國提昇愛滋病臨床醫療照顧品質研討會」。
5. 93 年 4 月 17 日北區舉辦教育訓練課程—台灣地區愛滋病診斷與治療之最新進展。
6. 93 年 10 月 16 日台北舉辦「2004 愛滋病毒感染者之相關伺機性感染研討會」。
7. 93 年 11 月 20 日舉辦「校園愛滋病防治教育研習會（北區）」。
8. 93 年 12 月 18 日台大醫院第七講堂舉辦「2004 HIV/AIDS 醫護人員的新挑戰研討會」。
9. 94 年 3 月 5 日舉辦「2005 全國提昇愛滋病患臨床醫療照顧品質研討會」。
10. 94 年 6 月 6~10 日舉辦「指定藥癮治療業務醫療機構之醫事人員照護毒癮愛滋個案藥癮戒治和愛滋病治療專業能力之培訓和教育訓練案」課程。
11. 94 年 8 月 13 日假台南成大舉辦「2005 HIV/AIDS 醫護人員的新挑戰研討會」。
12. 94 年 8 月 15 日在台大醫院景福館舉辦「改變藥癮行為的階段性治療模式工作坊」。
13. 95 年 4 月 29 日在台大醫學院第 101 講堂，舉辦「2006 全國提昇愛滋病患臨床醫療照顧　　品質研討會」。
14. 95 年 6 月 8~9 日美國臨床心理師 Patt Denning 博士舉辦為期 2 天之「減少傷害心理治療 模式訓練工作坊」。
15. 95 年 7 月 8 日在台大公衛學院 101 講堂舉辦「醫療人員愛滋病治療專業能力初階教育訓練課程」。
16. 95 年 11 月 18 日在衛生署彰化醫院合辦「愛滋病感染管制教育訓練課程」。
17. 95 年 11 月 25 日在台大醫院國際會議舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」。
18. 95 年 12 月 11 日財團法人羅東博愛醫院舉辦「台灣地區愛滋病診斷與治療之最新進展」研討會。
19. 96 年 4 月 14~15 日於羅東舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」。

20. 96 年 6 月 2 日於台北舉辦「Update management of HIV: Workshop for HIV co-infection disease」。
21. 96 年 6 月 23 日台大醫院國際會議舉辦「愛滋病毒感染治療藥物新進展介紹」。
22. 96 年 9 月 29 日在台北市舉辦本年度的 HIV/AIDS Workshop for Drug Resistance and Treatment Options。
23. 96 年 10 月 13、14、20、21 日大同大學尚志教育館一樓 106 會議室及 103 電腦教室舉行「感染症專科醫師藥品臨床研究設計及執行研習班」。
24. 96 年 11 月 3 日台北市徐州路 2 號台大醫院國際會議中心 101 講堂舉辦「愛滋病毒感染者之新陳代謝相關問題研討會」。
25. 96 年 12 月 15 日台北市仁愛路一段 1 號台大醫學院 101 講堂舉辦「醫療人員 HIV 體液暴露後之諮詢、檢驗、診斷及治療相關研討會」教育訓練課程。
26. 97 年 5 月 3 日高雄市左營區蓮潭國際文教中心講堂舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」。
27. 97 年 6 月 28 日台南成大醫院舉辦「醫療人員 HIV 體液暴露後之諮詢、檢驗、診斷及治療相關研討會」。
28. 97 年 9 月 25 日台中地方法院檢察署第二辦公大樓六樓會議室舉辦「監所受刑人回歸社區之愛滋病/性病/肝炎防治工作坊」。
29. 97 年 10 月 4 日羅東博愛醫院 5 樓大禮堂舉辦「醫療人員愛滋病治療專業能力初階教育訓練課程」。
30. 97 年 11 月 1 日台大醫學院 101 講堂舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」邀請美國 Buffalo University 蕭秋彬博士主講「HIV 感染者之治療新展望」。
31. 97 年 12 月 7 日署立台北醫院 8 樓大禮堂舉辦「牙科醫療人員愛滋病治療專業能力初階教育訓練課程」。
32. 98 年 3 月 7 日台大醫院國際會議中心 401 室舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」。
33. 98 年 5 月 3 日台中裕元花園酒店舉辦「監所及看守所毒癮愛滋病毒感染受刑人相關問題座談會」。
34. 98 年 6 月 20 日台大醫學院 101 講堂、104 講堂舉辦「醫療人員愛滋病治療專業能力初階教育訓練課程」。

35. 98 年 8 月 6 日台灣大學醫學院 102 講堂舉辦「98 年北部地區 HIV 篩檢前後諮詢人員訓練」。
36. 98 年 8 月 15 日台灣大學醫學院 102 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」。
37. 98 年 9 月 5 日 桃園縣南方莊園舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」。
38. 98 年 9 月 19 日台南市遠東國際大飯店舉辦「愛滋個案管理計畫相關醫師及個管師座談會」。
39. 98 年 10 月 31 日舉辦「愛滋病個案管理師訓練」(北區 10/31~11/1 日)、(中區 11/20~21 日)、(南區 11/6~7 日) 」。
40. 99 年 3 月 6~7 日交通部國際會議中心 3 樓講堂舉辦北區「愛滋病治療專業能力教育訓練課程」。
41. 99 年 3 月 13~14 日彰化基督教醫院教學研究大樓 12 樓蘭大衛國際會議廳舉辦中區「愛滋病治療專業能力教育訓練課程」。
42. 99 年 3 月 20~21 日高雄榮民總醫院第二會議室舉辦南區「愛滋病治療專業能力教育訓練課程」。
43. 99 年 5 月 16 日台中亞緻大飯店會議廳舉辦「愛滋病毒匿名篩檢計畫座談會」。
44. 99 年 5 月 30 日台中日華金典酒店舉辦「2010 提昇愛滋病患臨床醫療照顧品質研討會—HIV 合併 HBV 之相關問題」。
45. 99 年 8 月 17 日及 8 月 20 日 Conference of Immune Reconstitution Disease (高雄場及台北場)。
46. 99 年 8 月 21~22 日台北縣深坑福容大飯店與台灣感染症醫學會、台灣愛滋病學會合辦「感染症專科醫師愛滋病治療專業能力教育訓練研習班」。
47. 99 年 11 月 20 日舉辦「2010 年全國 HIV 及 TB 治療指引研討會」。
48. 99 年 12 月 5 日署立台北醫院 8 樓大禮堂舉辦「牙科醫療人員愛滋病治療專業能力初階教育訓練課程」。
49. 100 年 3 月 12 日台大醫學院 101 講堂舉辦「2011 醫療人員 HIV/AIDS 治療座談會」。
50. 100 年 5 月 22 日台中亞緻大飯店會議廳舉辦「2011 愛滋病毒匿名篩檢及個案管理計畫座談會」。

51. 100 年 6 月 11 日高雄市蓮潭會館 1 樓講堂協辦「愛滋病最新進展國際研討會」。
52. 100 年 7 月 8 日舉辦「2011 年度愛滋病防治中心期中研究成果討論會」。
53. 100 年 9 月 17~18 日公務人力發展中心福華國際文教會館舉辦「感染症專科醫師愛滋病治療專業能力教育訓練研習班」。
54. 100 年 12 月 10 日台大醫學院 101 講堂召開「2011 醫療人員 HIV/AIDS 治療座談會」。
55. 100 年 12 月 10 日召開「台灣地區 HIV/AIDS 多中心研究合作平台討論會」。
56. 100 年 12 月 15 日舉辦「2011 年度愛滋病防治中心研究成果討論會」。
57. 101 年 2 月 17 日舉辦「101 年度台灣地區 HIV/AIDS 多中心研究合作平台討論會 I」。
58. 101 年 5 月 26 日國立成功大學醫學院護理學系 3 樓 309 教室舉辦「101 年度進階愛滋個管工作坊」。
59. 101 年 6 月 16 日台大國際會議中心 401 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」。
60. 101 年 9 月 15~16 日舉辦「感染症專科醫師愛滋病治療專業能力教育訓練研習班」。
61. 101 年 12 月 8 日台大醫學院 102 講堂再度召開「2012 醫療人員 HIV/AIDS 治療座談會」。
62. 102 年 1 月 12 日(六)舉辦「102 年度台灣地區 HIV/AIDS 多中心研究合作平台—梅毒研究討論會 I」。
63. 102 年 5 月 5 日(星期日)於高雄榮民總醫院會議中心第二會議室舉辦「藥師愛滋病治療專業能力教育訓練課程」。
64. 102 年 5 月 31 日(五)舉辦「102 年度台灣地區 HIV/AIDS 多中心研究合作平台—愛滋病毒抗藥性監測計劃討論會」。
65. 102 年 6 月 15 日(六)於台大國際會議中心 4 樓 402 室舉辦「Streptococcus pneumoniae infection and pneumococcal vaccination among HIV-infected adults in the era of combination antiretroviral therapy」研討會。
66. 102 年 9 月 28~29 日公務人力發展中心福華國際文教會館舉辦「感染症專科醫師愛滋病治療專業能力教育訓練研習班」。
67. 103 年 5 月 3 日(星期六)於台大國際會議中心 402 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」。
68. 103 年 8 月 30、31 日 (1.5 日)於台北舉辦「103 年度台灣地區 HIV/AIDS 多中心研究

合作平台學術研討會」。

69. 103 年 7 月 12~13 日(1.5 日)於公務人力發展中心福華國際文教會「HIV 個案管理師教育訓練研習班」。

70. 103 年 9 月 20~21 日(1.5 日)於公務人力發展中心福華國際文教會館舉辦「感染症專科醫師愛滋病治療專業能力教育訓練研習班」。

71. 104 年 3 月 14 日於台北舉辦「2015 醫療人員 Post-CROI 研討會」

72. 104 年 3 月 28 日舉辦「愛滋病毒跨院教育與研究」共集結國內臨床醫療及研究學者專家共 35 位一起討論有關「臨床照護教育及研究平台」。

73. 104 年 4 月 29 日舉辦「台灣急性愛滋病毒感染研究討論會」

74. 104 年 6 月 7 日於成大舉辦「藥師愛滋病治療專業能力教育訓練課程」

75. 104 年 9 月 4 日梅毒比利時專家 Dr. Chris Kenyon 舉辦「HIV/AIDS Research Meeting」(9/4~9/5 日在台南)，「Symposium of Management of Sexually Transmitted Diseases」(9/7 日在台北)。

76. 104 年 9 月 12~13 日於台北舉辦「感染症醫師愛滋病治療專業能力教育訓練研習班」。77. 104 年 8 月 22 日(六)、11/17 日(六)系列性的 HIV Resistance(抗藥性) Workshop。

78. 105 年 5 月 7 日「愛滋治療與共病風險評估研討會」邀請 Prof. Jens D. Lundgren 來台演講。

79. 協助財團法人器官捐贈移植登錄中心舉辦『105 年度器官捐贈移植醫療臨床實務研討會』。

80. 105 年 5 月 28 日財團法人張榮發基金會國際會議中心 801 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」。

81. 105 年 7 月 30~31 日財團法人張榮發基金會國際會議中心 801 講堂舉辦「藥師愛滋病治療專業能力教育訓練課程」。

82. 105 年 9 月 9~10 日於台北喜來登酒店與成大醫院共同舉辦「105 年度台灣 HIV 研究平台會議 Taiwan HIV/AIDS Research Meeting」邀請研究 HAV 及 HBV 疫苗之法國專家 Dr. Odile Launay 演講。

83. 105 年 9 月 24~25 日於台北舉辦「感染症醫師愛滋病治療專業能力教育訓練研習班」。

84. 105 年 7 月 2 日、8 月 6 日、8 月 13 日南中北區「暴露愛滋病毒前預防性投藥(Pre-exposure Prophylaxis, PrEP）教育訓練」。

85. 105 年 12 月 17 日於台北舉辦「愛滋病相關伺機性感染治療進展研討會」。

附件一~1

105年度藥師愛滋病治療專業能力教育訓練課程

課程評量統計表(日期:105年5月28日)

	非常滿意 5	滿意 4	普通 3	不滿意 2	差 1
課程					
1.時間安排控制	61.5%	37.2%	1.3%	0	0
2.講義教材	62.8%	34.6%	2.6%	0	0
3.課程內容的結構性	67.9%	30.8%	1.3%	0	0
場地餐食					
1.場地設施、空間的滿意程度	75.6%	23.1%	1.3%	0	0
2.您對餐點(量與質)的滿意程度	66.7%	28.2%	5.1%	0	0
講題內容對 您目前工作的幫助程度					
講題一：愛滋病毒感染的藥物治療與順從性評估	70.5%	28.2%	1.3%	0	0
Presentation of Cases-1	70.5%	28.2%	1.3%	0	0
講題二：愛滋病毒感染長期治療的併發症	64.1%	34.6%	1.3%	0	0
Presentation of Cases-2	64.1%	32.1%	3.8%	0	0
講題三：愛滋病毒感染相關伺機性感染的治療與預防	56.4%	39.7%	3.8%	0	0
Presentation of Cases-3	62.8%	34.6%	2.6%	0	0
講題四：愛滋病毒感染藥物治療的交互作用	70.5%	26.9%	2.6%	0	0
Presentation of Cases-4	71.8%	26.9%	1.3%	0	0
總評					
1.您對本課程整體收獲的滿意程度	70.5%	28.2%	1.3%	0	0

2.本次課程需改進的地方：

教材講義部份：

講題三的講義編排和課堂上的差異較大，學員在做筆記時比較有困難、講題三蔡醫師的slides 與課本相差頗大,容易讓思緒與講者演講脫鉤、很好、good!、盡可能與final presentation一致、希望是彩色版，報名費可以高點沒關係、覺得很棒 :)、希望能提供電子檔、有重疊的圖、文字在PPT (因動畫設計的關係)、Good、完整

內容結構部份：

銜接度高，收穫豐富、很好、搭配case 印象深刻，good!、覺得很棒 :)、Good、貼近

講師教學部份：

臨床實務臨床實戰經驗豐富、很好、good!、可以邀請羅一鈞醫師來講、Great、Good、簡易明瞭

其他建議事項：

這類課程對從事HIV照顧的藥師幫助很多，謝謝學會，希望往後能有固定的課程、謝謝愛滋病學會舉辦這麼棒的課程、可以有更多臨床實例、場地很好，希望以後都能在這上課。、希望有熱茶、HIV感染者與其他慢性病共存的case分享，例如精神分裂...、八點準時到卻發現簽到處尚未準備好，請準時、飲料熱的品項可以多一些，因場內冷氣冷、希望除了課堂上課之外可以利用工作坊增加實務經驗，可以多辦幾次，或者可分初、中、高階、新藥多（包括Combo drug) 希望每次有drug review

1. 下一次課程您最希望聽到的議題為：

案例、藥物、1. HIV & Hepatitis A/B/C 2. 今天藥的部分是較簡單的，著重於SE的差異，日後若有深入討論比較亦很令人期待、老化的HIV預後照顧 positive 與醫療人員互動、HIV的藥物選擇方向、CCR5 inhibitor and Fusion inhibitor的使用經驗、藥物或愛滋發展歷史、藥師如何在愛滋病團隊展現專業能力、臨床上HIV藥物如何選擇及劑量調整，新藥物如Isentress如何搭配、各國治療用藥規範、伺機性感染、case 分享、case 議題收穫多，謝謝！、藥物--> 癌症藥物與HAART藥間需注意之處、cases, drug

2. 下一次課程您最希望聽到那一位講師的演講：

林育蕙 (X2)、劉佳穎(x3)、羅一鈞、林淑文藥師(x3)、顧文瑋(x5)、王建淳(x2)、台大洪健清、林德宇醫師、鄭舒倖、楊家瑞、王甯祺

附件一~2

愛滋病毒感染個案管理師教育訓練研習班

105年度課程評量統計表(105年7月30~31日)

	非常滿意 5	滿意 4	普通 3	不滿意 2	差 1
課程					
1. 時間安排控制	68%	28%	4%	0%	0%
2. 講義教材	66%	32%	2%	0%	0%
3. 課程內容的結構性	72%	26%	2%	0%	0%
講題內容對 您目前工作的幫助程度					
講題一：HAART 藥物副作用之評估與處理(洪健清)	77%	21%	2%	0%	0%
講題二：性病(含新興傳染疾病)評估與處置(鄔豪欣)	77%	19%	4%	0%	0%
講題三：接觸者追蹤策略(邱飄逸)	81%	15%	4%	0%	0%
講題四：困難個案諮商技巧(李夢萍)	81%	17%	2%	0%	0%
講題五：感染者侵權之評估與處置(林宜慧)	66%	19%	15%	0%	0%
講題六：(即將)旅外感染者照護(顧文瑋)	72%	26%	2%	0%	0%
講題七：個案管理實務綜論(莊苹、郭乙錡)	72%	26%	2%	0%	0%
總評					
1. 您對本課程整體收獲的滿意程度	81%	17%	2%	0%	0%

2. 本次課程需改進的地方：

教材講義部份：Dr顧無講義，不易做筆記，但講述內容很好。Ok。

內容結構部份：權益、接觸者時間過短。

講師教學部份：教師選擇很棒，課程規劃很好。

其他建議事項：這一次分組討論的課程安排很棒，可以學習到不同的溝通及會談的技巧!感恩主辦單位及各位工作人員。報名的資格限制要控管一下，非個管應不要核准。

謝謝學會及講師們，辛苦了。 個管師教育應篩檢學員來源，避免不明理的人員對個管師的角色與業務有誤解。本研習會 主要是for個管師的考前集訓班，是否應有報名的條件限制，畢竟有太多非個管經驗的人員搞不清楚狀況也很難投入課程內容，也影響其他學員。

附件一~3

感染症醫師愛滋病治療專業能力教育訓練研習班

105年度課程評量統計表(105年9月24~25日)

	非常滿意 5	滿意 4	普通 3	不滿意 2	差 1
課程					
4. 時間安排控制	67.4%	32.6%	0	0	0
5. 講義教材	55.8%	44.2%	0	0	0
6. 課程內容的結構性	62.8%	37.2%	0	0	0

講題內容對 您目前工作的幫助程度

(9 月 24 日)

講題一：Update on HIV virology: diagnosis and monitoring. (張淑媛教授)	62.8%	34.9%	2.3%	0	0
講題二：Update of the management of hepatitis co-infection among people living with HIV. (孫幸筠醫師)	34.9%	51.2%	13.9%	0	0
講題三：Management of common sexually transmitted infections. (王建淳醫師)	60.5%	39.5%	0	0	0
講題四：Update on combination antiretroviral therapy and current guidelines.(吳冠陞醫師)	74.4%	25.6%	0	0	0
講題五：Metabolic syndrome and cardiovascular disease among people living with HIV.(蔡茂松醫師)	37.2%	41.9%	20.9%	0	0
講題六：Update of management of Pre- and post-exposure prophylaxis in occupation and non-occupational settings. (楊家瑞醫師)	58.1%	39.5%	2.3%	0	0
講題七：Management and prophylaxis of opportunistic infections and malignancy: respiratory and central nervous systems (1). (鄭健禹醫師)	53.5%	34.9%	11.6%	0	0
講題八：Case demonstration (1)– respiratory and central nervous system. (林詩萍醫師)	51.2%	39.5%	9.3%	0	0

(9 月 25 日)

講題九：Recreational drug use among people living with HIV. (顧文瑋醫師)	55.8%	41.9%	2.3%	0	0
講題十：Update on management of opportunistic infections and malignancy: gastrointestinal, mucocutaneous and others (2). (林冠吟醫師)	48.8%	51.2%	0	0	0
講題十一：Case demonstration (2)–gastrointestinal and others. (李佳雯醫師)	72.1%	27.9%	0	0	0
講題十二：Vaccination strategy among people living with HIV. (李育霖醫師)	58.1%	37.2%	4.7%	0	0

總評

3. 您對本課程整體收獲的滿意程度	62.8%	37.2%	0	0	0

4. 本次課程需改進的地方:

教材講義部份:
希望提供講義電子檔，可節省資源。Good。有幾堂課slide與講義不同，比較不方便(孫醫師與蔡醫師)。希望各講師投影片皆有附上。講義字很大，很棒。

內容結構部份: Good。很好。

講師教學部份:
很棒的師資!希望有機會上到羅一鈞醫師的課程，感謝接待及行政人員。HBV,HCV等建議找好Dr上課。Good。很好。

其他建議事項:
建議可增加母子垂直感染預防及疑似愛滋寶寶的檢驗，追蹤及疫苗施打。
謝謝學會安排此課程，收穫非常豐富。這次有增加 HIV patient 建議施打 HPV vaccination 之介紹。地點與時間掌控很好，秘書很細心!感謝! Update on HIV virology: diagnosis and monitoring.可再拆分為二堂課。

附表一~4、台大醫院內科部「愛滋病防治中心」105 年度 HIV/AIDS 專題研討會

序號	日期	演講者	題目	職稱
1	1/5 日	陳南伃	HIV-1 capsid is required for post-nuclear entry steps	長庚主治醫師
2	1/12 日	楊家瑞	Early serologic response after treatment of early syphilis among HIV-infected and HIV-uninfected patients	亞東主治醫師
3	1/19 日	黃于珊	Virological response to TDF in HIV-infected patients with 3TC resistant HBV co-infection in an area hyperendemic for HBV infection	台大新竹分院主治醫師
4	1/27 日	Dr. Corklin Steinhart	Inhibiting integrase in HIV treatment – why is it important?	
5	3/1 日	林冠吟	Clinical development of antiretroviral therapy	台大研究助理
6	3/8 日	陳婉青	HAV outbreak among MSM in Taiwan	CDC 防疫醫師
7	3/15 日	劉玟君	Seroincidence of HIV and prevalence of transmitted drug resistance of HIV-1 strains among persons seeking VCT in Taiwan.	本案研究助理
8	3/22 日	林武甫	Management of gonorrhea and chlamydia infection among MSM	台大總醫師
9	3/29 日	施鐘卿	HIV 婦女產後照護	台大個管師
10	4/12 日	孫幸筠	Analyses of treatment outcome of ARV-naïve patients who failed the first-line regimens	台大主治醫師
11	4/19 日	楊佳鈴	CART in patients with active tuberculosis	台大主治醫師
12	4/26 日	張君俞	Bone mineral density study among HIV infection patients.	台大個管師
13	5/3 日	李官燁	Update on anti-HCV therap	禾利行研究醫師
14	5/10 日	林俊宏	醣分子於 HIV 感染的角色與疫苗開發，以及於幽門螺旋桿菌的相關研究	中研院研究員
15	5/17 日	廖敏伶	愛滋孕婦照護案例分享	台大個管師
16	5/24 日	李原地	To be determined	中山醫學大學附設醫院主治醫師
17	5/31 日	林詩萍	DM among HIV-infected patients in the HAART era: incidence and risk factor	台中榮總主治醫師
18	6/7 日	楊佳鈴	CART in patients with active tuberculosis (Part 2)	台大主治醫師
19	6/14 日	Dr. Riaz	Not all STRs are the same	GSK 藥廠
20	6/28 日	李昭慧	Topical therapy (Veregen) of genital warts	杏輝藥廠
21	7/5 日	謝郁俐	溫哥華參與高風險群外展防治計畫經驗	台大個管師

22	7/12 日	鄭健禹	Patterns of emergent resistanc-associated mutations in HIV-positive patients who developed virologica failure to first-line cART	署立桃園醫院主治醫師
23	7/19 日	楊上平	個案分享	台大個管師
24	7/26 日	張藍心	Survey of pre-exposure prophylaxis against HIV infection using truvada among clients seeking voluntary counseling and testing	台大內科部助理
25	9/20 日	吳慧娟	Elimination of HIV Epidemic in Taiwan:Mathematical Modeling and Cost-effectiveness of PrEP Intervention	國立成功大學醫學院護理系研究助理員
26	10/4 日	羅玉珍	個案分享	台大個管師
27	10/11 日	李育霖	Diagnosis of acute HIV infection in patients receiving PEP or PrEP	彰化基督教醫院內科部感染科主治醫師
28	10/18 日	陳冠州	Journal reading: Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis	台大住院醫師
29	11/1 日	黃怡嘉	Post-HIV Drug Therapy, Glasgow (1): Epidemiology and management of coinfections	台大總醫師
30	11/8 日	陳冠州	Post-HIV Drug Therapy, Glasgow (2): Epidemiology and management of opportunistic illnesses	台大住院醫師
31	11/15 日	楊鎮嘉	Management of reduced bone mineal density	台大老年醫學部主治醫師
32	11/22 日	蔡茂松	Bone health and HIV infection	亞東主治醫師
33	11/29 日	張喜雁	Case management (2)	台大個管師

地點：台大醫院西址綜合病房討論室(舊五東病房三樓，由萊爾富便利商店上樓)
演講時間：週二上午 8：00~9：00

附件二

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

台灣地區原生性抗愛滋病毒藥物抗藥性的調查研究

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：105 年 01 月 01 日至 105 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

頁碼

共 (12) 頁

壹、中文摘要

本計畫主要探討台灣地區未接受三合一雞尾酒療法病人，其病毒抗藥性的基因型盛行率。過去十個月，我們已經收納 480 位尚未接受三合一雞尾酒療法患者的檢體，進行原生性 HIV-1 病毒基因型抗藥性分析；其中 405 位愛滋病毒感染者的 HIV-1 病毒基因型抗藥性分析已完成。這些患者對於任一類藥物具有抗藥性的比例為 13.1%；其中針對蛋白酶抑制劑 (protease inhibitor)、核苷酸類似物的反轉錄酶抑制劑 (nucleoside-analogue reverse transcriptase inhibitors, NRTIs)、非核苷酸類似物的反轉錄酶抑制劑 (non-nucleoside-analogue reverse transcriptase inhibitors, NNRTIs)藥物的抗藥性基因型盛行率分別為 2.5%、4.0%、及 8.4%。對於兩種以上藥物具抗藥性的抗藥性基因型盛行率是 1.5%。在分析同時，我們也收到 299 位接受三合一雞尾酒療法失敗患者的檢體，我們進行一般性 HIV-1 病毒基因型抗藥性分析；其中 244 位愛滋病毒感染者的 HIV-1 病毒基因型抗藥性分析已完成。這些病人中有 139 位(57.0%)對於任一類藥物具有抗藥性基因突變；其中針對蛋白酶抑制劑、核苷酸類似物的反轉錄酶抑制劑、非核苷酸類似物的反轉錄酶抑制劑藥物的抗藥性基因型盛行率分別為 7.8%、38.9%、46.3%；而同時具有兩種以上抗病毒藥物的抗藥性基因突變的比例為 33.2%。

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 was aimed to determine the prevalence of transmitted drug resistance among treatment-naive HIV-1 infected patients in Taiwan. In the past ten months, we have received 480 specimens for analysis and among those, we have completed analysis of 405 specimens. The prevalence of transmitted drug resistance to any class of drugs among treatment-naive HIV-1 infected patients is 13.1%. The prevalence of resistance to protease inhibitor class, nucleoside-analogue reverse transcriptase inhibitors (NRTIs) class, and non-nucleoside-analogue reverse transcriptase inhibitors, (nNRTIs) are 2.5%、4.0% and 8.4%. The prevalence of resistance to more than two classes of drugs is 1.4%. In the mean time, we have received 299 specimens from treatment-experienced patients and among those, we have completed analysis of 244 specimens. The prevalence of transmitted drug resistance to any class of drugs among treatment-experienced HIV-1 infected patients is 57.0%. The prevalence of resistance to protease inhibitor class, nucleoside-analogue reverse transcriptase inhibitors (NRTIs) class, and non-nucleoside-analogue reverse transcriptase inhibitors, (nNRTIs) are 7.8%、38.9% and 46.3% . The prevalence of resistance to more than two classes of drugs is 33.2%.

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影響的免疫系統功能。目前，絕大多數的病毒抑制劑，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　制病毒生長的效果。依藥物抑制的病毒基因與機制可分為三大類。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，來抑制反轉錄腶的活性(nucleoside 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)。近年來，由於三合一雞尾酒療法比使用單一病毒抑制劑更能有效地抑制病毒的感染，許多醫師開始使用兩種或者三種不同類別的病毒抑制劑來治療病人。但是，在服用藥物過程中，可能因為病毒快速產生變異及病人不依醫師指示定時服藥等因素，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，會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百分之一至十一及百分之九至二十一的患者，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，並進一步節省醫療資源。因此，本調查將藉由分析蛋白酶、反轉錄酶、嵌合酶及副受器這些基因上與抗藥性相關的基因變異，來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，並提高個案的有效治療。

（二）材料與方法

執行期間： 2016 年 1 月 1 日迄 2016 年 12 月 31 日。

研究方法

1. 受試者：

在 2016 年 1 月到 2016 年 12 月期間，年滿 20 歲的愛滋病毒感染者只要未曾接受過三合一雞尾酒療法。我們會分析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；並藉由電腦程式 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。。針對收集個案病患之基本資料，如性別、年齡、HIV 感染危險因子、HIV 感染時間、伺機性感染或腫瘤、接受治療之時間、CD4 淋巴球之變化、血清 HIV 病毒量之變化、合併伺機性感染之有無、是否死亡等等作資料整理登錄。最後我們會分析那些可能的危險因子，如性別、感染途徑、及病毒亞型等，與抗藥性基因型具有相關性。本研究業經台大醫院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協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。此外，一些新近鑑定的基因變異也會陸續地被列入研究分析中。分析結果我們會以一標準格式，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三十一日止，自未接受過三合一雞尾酒療法的 HIV 感染者，我們一共收到 480 件血液檢體進行基因型抗藥性檢測，目前已完成 405 件檢體的 HIV-1 病毒基因型抗藥性分析。自三合一雞尾酒療法治療失敗的 HIV 感染者，我們一共收到 299 件血液檢體進行基因型抗藥性檢測，目前已完成 244 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(圖一)，其中 91.5% (713 件)來自北部醫院，0.8% (6 件)來自中部醫院，4.0% (31 件)來自南部醫院，3.7% (29 件)來自東部醫院。

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 13.1%，對反轉錄酶抑制藥物(nucleoside reverse transcriptase inhibitors, NRTIs)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(non-nucleoside reverse transcriptase inhibitors, nNRTIs) 及蛋白酶抑制劑 (protease inhibitor)的抗藥性病毒株的比例分別為 4.0%、 8.4%、及 2.5%。對兩種以上藥物具抗藥性的比例為 1.5%。

在抗反轉錄藥物治療失敗病人檢體中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 57.0%。對反轉錄酶抑制藥物、非擬似核苷酸衍生物的反轉錄酶抑制藥物及蛋白酶抑制劑的抗藥性病毒株的比例分別為 38.9%、46.3%、及 7.8%。對兩種以上藥物具抗藥性的比例為 33.2%。

由於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 13.1%，相較於之前我們去年的調查，其抗藥性的比例有些微下降的趨勢(13.1% v.s. 14.1%,)(*P*=0.64) (圖二)，主要升高的抗藥性藥物種類是擬似核苷酸衍生物的反轉錄酶抑制藥物(4.0% v.s. 2.9%)(*P*=0.38)；非擬似核苷酸衍生物的反轉錄酶抑制藥物的抗藥性盛行率是大約持平(8.4% v.s. 8.4%)(*P*=0.99)，而蛋白酶抑制劑的抗藥性盛行率是下降(2.5% v.s. 4.2%)(*P*=0.14) (圖二)。

在接受抗反轉錄藥物治療失敗的病人中，對任一類藥物具有抗藥性的病毒株其總體盛行率為 57.0%，相較於之前我們去年的調查，其抗藥性的比例有些微升高的趨勢(57.0% v.s. 55.8%)(*P*=0.78) (圖三)。蛋白酶抑制劑(7.8% v.s. 6.3%)(*P*=0.52)、擬似核苷酸衍生物的

反轉錄酶抑制藥物(38.9% v.s. 37.9%)(*P*=0.81)、非擬似核苷酸衍生物的反轉錄酶抑制藥物(46.3% v.s. 45.4%)(*P*=0.83)及多重抗藥性病毒株的盛行率(33.2% v.s. 32.3%)(*P*=0.84)都有升高的趨勢(圖三)。

至於嵌合胺抑制劑的抗藥性檢測，今年共做了 148 件檢體；其中 42 件是未接受抗反轉錄藥物治療的病人，106 件是接受抗反轉錄藥物治療失敗的病人。42 件未接受抗反轉錄藥物治療的病人檢體中沒有一件是帶有對嵌合胺抑制劑具抗藥性的病毒株。106 件接受抗反轉錄藥物治療失敗的病人檢體中有 13 件(12.3%)是帶有對嵌合胺抑制劑具抗藥性的病毒株；其中八件在 H148 的位點有突變，兩件在 N155 的位點有突變，三件在 Y143 的位點有突變(表一)。需注意的是 13 件檢體中已有八件對於第二代的嵌合胺抑制劑 Dolutegravir 具有抗藥性。其中三件對於第二代的嵌合胺抑制劑 Dolutegravir 具有高度抗藥性(Q148H/R/K 突變加上 2-3 個 G140A/C/S、L74I、E138A/K/T 突變)；四件對於第二代的嵌合胺抑制劑 Dolutegravir 具有中度抗藥性(Q148H/R/K 突變加上 1 個 G140A/C/S、L74I、E138A/K/T 突變)；一件對於第二代的嵌合胺抑制劑 Dolutegravir 具有低度抗藥性(Q148H/R/K 突變)。

（四）討論

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 13.1%，相較於之前我們去年的調查，其抗藥性的比例有些許下降的趨勢(13.1% v.s. 14.1%,)(*P*=0.64)。進一步的分析發現，具原生性人類免疫不全病毒(HIV-1)抗藥性基因盛行率的下降主要是因為蛋白酶抑制劑的抗藥性盛行率是下降(2.5% v.s. 4.2%)(*P*=0.14) (圖二)。而非擬似核苷酸衍生物的反轉錄酶抑制藥物的抗藥性盛行率是雖然與去年相較變動不大(8.4% v.s. 8.4%)(*P*=0.99)，但是 8.4%的抗藥性盛行率仍不容小覷。特別是，台灣衛生福利部疾病管制署於今年六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)，一種是兩個擬似核苷酸衍生物的反轉錄酶抑制藥物搭配一個嵌合胺抑制劑(ABC/3TC/DTG)。根據前人的研究及本計畫的研究結果，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。此外，值得注意的是，雖然在 42 件未接受抗反轉錄藥物治療的病人檢體中沒有一件是帶有對嵌合胺抑制劑具抗藥性的病毒株，但是在 106 件接受抗反轉錄藥物治療失敗的病人檢體中有 13 件(12.3%)是帶有對嵌合胺抑制劑具抗藥性的病毒株，其中有八件甚至對於第二代的嵌合胺抑制劑 Dolutegravir，即目前第一線治療藥物(ABC/3TC/DTG)的成分具有抗藥性。所以我們建議要持續監測這些對嵌合胺抑制劑具抗藥性的病毒株是否會傳入未接受抗反轉錄藥物治療的病人族群中。

（五）結論

對政策之具體建議:

1. 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，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. 持續監測對第二代嵌合胺抑制劑具抗藥性的病毒株是否會傳入未接受抗反轉錄藥物治療的病人族群中。

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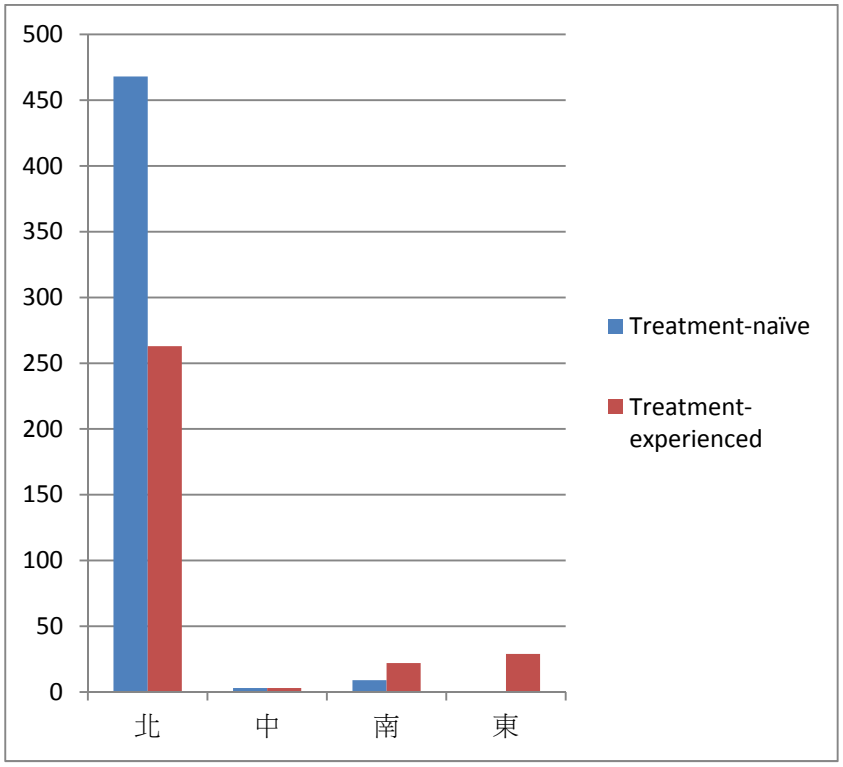
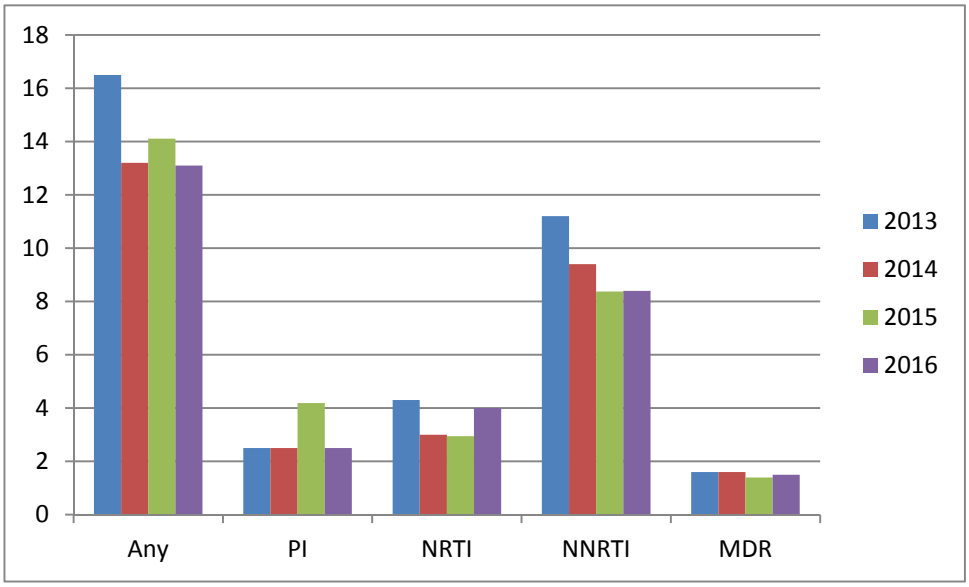
（七）圖表

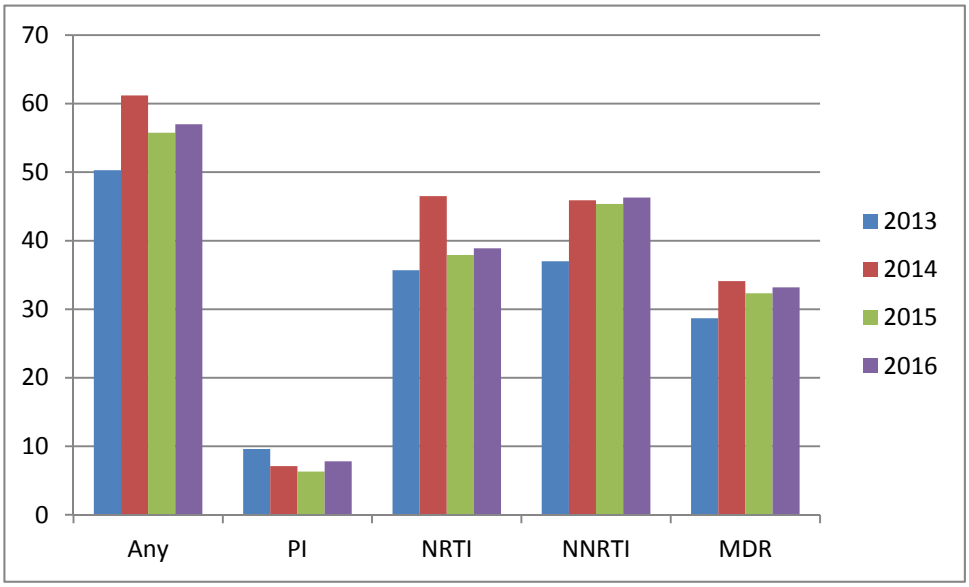
圖一、檢體來源分布圖



圖二、原生性抗藥性盛行率的趨勢圖



圖三、治療失敗患者抗藥性盛行率的趨勢圖



表一、嵌合胸抗藥性的基因突變位點分析

	位點	個數
主要突變位點	Q148HRK	8
	N155H	2
	Y143CR	3
次要突變位點	L74I	2
	L74M	2
	T97A	3
	E138A	1
	G140S	7
	V151I	2
	G163RK	2
	S230R	1

附件三

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

再次接種兩劑或三劑 A 型肝炎疫苗於人類後天免疫不全病毒感染之感染者保護力評估

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、林邑璁

研 究 人 員：陳冠州、黃怡嘉、吳政信

執 行 期 間：105 年 1 月 1 日至 105 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

頁碼

共 (14) 頁

壹、中文摘要

目的：自 2015 年 6 月起，在臺灣透過男男間性行為發生急性 A 型肝炎病毒群聚感染。此研究旨在於疫情下，觀察愛滋病毒感染者接種A型肝炎疫苗後的效果。

方法：自 2015 年 6 月起，於台大醫院針對大於 20 歲的愛滋病毒感染者，檢驗血中A型肝炎病毒抗體。對於抗體為陰性者，建議其接種兩劑常規A型肝炎疫苗；並追蹤其抗體血清學反應及發生急性A型肝炎情形。對於接種兩劑疫苗後仍未有抗體產生者，後續將進一步提供追加疫苗接種。

結果：自 2015 年 6 月至 2016 年 9 月，已納入 1597 位 A 型肝炎病毒抗體為陰性之愛滋病毒感染者，其中有 1053 位(65.9%)已接種一劑 A 型肝炎病毒疫苗，324 位(20.3%)已完成兩劑疫苗接種。於接種第一劑與第二劑疫苗之間，其整體抗體陽轉率為 32.9%；而於接種第一劑後之4周內、5-8周、9-16周、17-24周之抗體陽轉率分別為16.0%、26.7%、50.0%、 49.8%。於接種第二劑疫苗後，其抗體陽轉率上升至 94.6%。影響抗體陽轉之相關因子為疫苗種類(VAQTA®)、追蹤抗體之間隔時間、先前有接受過 A 型肝炎病毒疫苗者。其中有 79 位先前有接受過 A 型肝炎病毒疫苗者，其於再次接種第一劑及第二劑疫苗後，其抗體陽轉率分別為 86.1%及 100%。接種疫苗所產生預防急性 A 型肝炎之效力為 93.8%；而發生急性 A 型肝炎的預測因子為未接種疫苗及近期梅毒感染。

結論：儘管 A 型肝炎病毒疫苗於愛滋病毒感染者之抗體血清學反應較差，在疫情下仍能提供顯著的預防效果。先前有接受過 A 型肝炎病毒疫苗者，再次接受追加疫苗接種之抗體血清學反應較佳。

關鍵詞：A型肝炎、人類後天免疫不全病毒、疫苗

貳、英文摘要

Objectives: An ongoing outbreak of acute hepatitis A virus (HAV) infection has been occurring among men who have sex with men (MSM) in Taiwan since June 2015. This study aimed to evaluate the effectiveness of HAV vaccination in HIV-positive patients in an outbreak setting.

Methods: We performed a seroepidemiological survey of HAV in HIV-positive patients since June 2015. The HAV-seronegative patients were offered HAV vaccine. The serologic outcomes were assessed after the first and last doses of HAV vaccine. The clinical outcome was acute HAV infection. For those who who failed to achieve serologic response in the primary vaccination, we will provide them with booster HAV vaccine.

Results: A total of 1597 HAV-seronegative patients with 94.7% being MSM and a median CD4 count of 567 cells/mm^3 were included for analysis. Among them, 1053 patients (65.9%) had received at least one dose of HAV vaccine, and 324 (20.3%) had completed the 2-dose vaccine series. The overall seroconversion rate before the administration of the second dose of HAV vaccine was 32.9%. The seroconversion rates within 4 weeks, at weeks 5-8, weeks 9-16, and weeks 17-24 were 16.0%, 26.7%, 50.0%, and 49.8%, respectively. One month after the last dose, the seroconversion rate increased to 94.6%. The factors associated with seroconversion between the first and last doses of HAV vaccination were receiving VAQTA® (AOR, 2.4; 95% CI, 1.6-3.6), time to anti-HAV IgG testing (AOR, per 1-week increase, 1.1; 95% CI, 1.1-1.2) and previous HAV vaccination (AOR, 30.0; 95% CI, 11.8-76.5). As for 79 patients who had received previous HAV vaccination, the seroconversion rate after receiving the first and second doses of booster HAV vaccine was 86.1% and 100%, respectively. The incidence rate of acute HAV infection in patients without receiving HAV vaccine and those receiving at least 1 dose of HAV vaccine was 11.0 and 0.7 per 100 person-years of follow-up (PYFU), respectively, resulting in vaccine effectiveness of 93.8%. The factors associated with acquisition of acute HAV infection included having not received HAV vaccine (AHR, 12.5; 95% CI, 3.8-50.0) and recent syphilis (AHR, 4.6; 95% CI, 2.6-8.3).

Conclusions: Despite the delayed serologic response to HAV vaccination in HIV-positive MSM, the risk of acute HAV infection was significantly reduced by HAV vaccination during the outbreak setting. Patients with previous HAV vaccination had a higher seroconversion rate after receiving booster HAV vaccine.

關鍵詞：hepatitis A, human immunodeficiency virus infection, vaccination

參、本文

（一）前言

A 型肝炎是公共衛生的一個重要議題，其感染盛行率和發生率是環境衛生的指標之一。雖然 A 型肝炎病毒感染致死率並不高，但根據國內外已發表的文獻發現，成人、年長者與既有慢性病毒性肝炎的患者發生急性 A 型肝炎病毒感染時的臨床症狀及死亡率較高。如國人常見的慢性 B 型或 C 型肝炎的感染者，當感染 A 型肝炎時，會有較高的機會發生猛爆性肝炎[1-4]。但根據衛生署統計資料顯示，由於社會的進步與衛生條件改善，台灣居民曾感染而對 A 型肝炎病毒有免疫力的比例已較往年下降，這也表示 A 型肝炎潛在性的易感受群人數增加。由於 A 型肝炎病毒是藉由飲食感染，因此當衛生環境和飲食衛生條件惡化時，可能有機會發生 A 型肝炎大規模的流行。目前研究也發現，愛滋病毒感染者在感染 A 型肝炎病毒時會有較長時間的病毒血症和腸道排泄病毒，使傳染給他人的機會增加[5]；而男同志族群因為有口對肛門的性行為方式，更容易在密切接觸的性伴侶間造成腸道疾病傳播，歐洲地區已有許多在男同志族群中的 A 型肝炎群聚感染的報告[6,7]。近年來台灣愛滋病毒感染者之數目持續增加，其中超過 50%是因為男同性間性行為傳播相關，綜上所述，可知這些愛滋病毒感染者由於過去未感染過 A 型肝炎而具備 A 型肝炎的感受性，同時又有高風險的行為，而且在感染之後有更高的機會傳染給其他親密接觸者，這使得 A 型肝炎自 2015 年 6 月起於愛滋病毒感染者發生群突發的現象。目前美國及台灣成人疫苗接種諮詢委員會針對愛滋病毒感染者及男同性戀等高危險群，建議接種 A 型肝炎疫苗[8]。

然而，目前的資料顯示，A 型肝炎疫苗的保護力在愛滋病毒感染者無法達到與非感染者一樣好(接近 100%)的保護力。在一般的常規兩劑疫苗(Havrix®, 1.0 ml=1440 Elisa unit，於第 0 及第 6 個月施打)之下，產生有效抗體的比例及濃度遠不及沒有感染愛滋病毒的族群[9,10]。自 1993 年後，先後由義大利、德國、及英國的臨床研究顯示，以常規成人一半劑量(Havrix®, 0.5ml=720 Elisa unit)做三次的施打(第 0、1、6 個月施打)，雖然結果顯示此方式是十分安全的，但並未提高產生有效 A 型抗體的比率。法國的研究團隊於 2008 年率先發表大規模的臨床研究，以成人的常規劑量 A 型肝炎疫苗(Havrix®, 1ml = 1440 ELISA units)做三次的施打(第 0、1、6 個月施打)，除了安全無虞之外，結果接受三劑疫苗注射的受試者其產生抗體的比率有增加的趨勢，但在統計上無法達到顯著。到了

第十八個月時，接受兩劑及三劑疫苗施打的受試者間的抗體陽轉率差異性又再次拉近(兩劑 vs.三劑: 61.2% vs. 78.3%, P=0.07)，意即沒有證據顯示多施打一劑疫苗在第十八個月以後的保護性會比常規兩劑來得更好[15]。

為証實此一現象與了解在台灣愛滋感染的患者是否也會面臨一樣的問題，我們在2009 年至 2010 年的研究，納入了 582 位男同志，含愛滋病毒感染者與非感染者，提供 A 型肝炎疫苗的施打。我們也發現多給予一劑 A 型肝炎疫苗並無法顯示在產生有效抗體的比率會優於傳統兩劑疫苗的施打。在初次接種後第 48 週的追蹤時間發現在不論是兩劑組或三劑組都有約 20～25%的病人沒有產生有效的 A 型肝炎抗體[16]。換句話說，目前所研究的不同接種方式和劑量，都無法解決約有 20～25%的愛滋病毒感染者在接種後無法產生足夠的抗體保護力的問題。

對於這些已經接受過兩劑或三劑 A 型肝炎疫苗，卻依舊未產生有效保護性抗體的愛滋病毒感染者，目前並沒有很好的研究可以提供參考該如何保護這群患者。因此我們希望透過此次臺灣 A 型肝炎疫情，建議愛滋病毒感染者接種常規A型肝炎疫苗並追蹤其抗體血清學反應；並進一步針對接種A型肝炎疫苗後仍未產生抗體反應者，再度給予追加A型肝炎疫苗接種，以觀察愛滋病毒感染者在追加疫苗之後的反應。

（二）材料與方法

對於愛滋病毒感染者接種疫苗的流程，首先會檢查其血液中是否有A型肝炎的抗體，抗體陽性者則是已經有免疫力的患者。對於A型肝炎抗體為陰性的病人，依照目前的建議應該接種兩劑常規劑量的A型肝炎疫苗(分別在第 0 及第 6 個月)；這些接種後的愛滋病毒感染者則會持續追蹤其抗體血清學反應及發生急性 A 型肝炎之情形，對於疫苗有反應者則視為已獲得免疫力。

對疫苗沒有反應者，是研究接續所鎖定的對象，願意進入試驗的病人，會建議再次接受兩劑常規劑量的接種(VAQTA®，於第 0 及第 6 個月施打)或是三劑A型肝炎疫苗的接種(VAQTA®, 於第 0、1、6 個月施打)。在接種的過程中，我們會追蹤患者血液中的A型肝炎抗體的血清學反應，來進行兩組間的比較。患者如果不願意參與研究，我們會依照常規持續追蹤，以了解血液中A型肝炎抗體是否有自動陽轉的情形(可能是自然感染造成)。

研究中追蹤血液A型肝炎抗體的時間點如下：

（一） 接種兩劑的受試者：接種第一劑疫苗前（baseline）、接種第一劑疫苗之後四周（week 4）、接種第二劑疫苗前（week 24）、以及接種第二劑疫苗後四周 （week 28）。

（二）接種三劑的受試者：接種第一劑疫苗前（baseline）、接種第二劑疫苗前（week 4）、接種第三劑疫苗前（week 24）、以及接種第三劑疫苗後四周（week 28）。

（三）抗體陰性且不願意接種疫苗者（包含不願意接種疫苗者，以及對疫苗沒有反應但不願意參與研究者）：每 6-12 個月追蹤一次A型肝炎抗體，以了解在病程中發生自然感染後血清學陽轉的機會。

除了接種疫苗後產生的抗體血清學反應之外，我們也會分析年齡、性別、感染途徑、初始病毒量、CD4 細胞數、是否同時有其他病毒型肝炎感染等變項，作為兩組樣本在比較中的參考。

（三）結果

自 2015 年 6 月至 2016 年 9 月，已納入 1597 位 A 型肝炎病毒抗體為陰性之愛滋病毒感染者；其平均年齡為 35 歲、94.7%為透過男男間性行為感染愛滋病毒、分別有約 10%及 8%合併 B 型及 C 型肝炎感染、92 位先前有接受過 A 型肝炎病毒疫苗接種。此次注射常規疫苗時，95.0%之愛滋病毒感染者有接受抗愛滋病毒組合療法，且其基礎 CD4 中位數為 567 cells/mm^3、基礎愛滋病毒量為偵測不到。

統計至 2016 年 9 月，有 1053 位(65.9%)至少已接種一劑 A 型肝炎病毒疫苗，324 位(20.3%)已完成兩劑疫苗接種(圖一)。於接種第一劑與第二劑疫苗之間，其整體抗體陽轉率為 32.9%；而於接種第一劑後之 4 周內、5-8 周、9-16 周、17-24 周之抗體陽轉率分別為 16.0%、26.7%、50.0%、49.8%。而於接種第二劑疫苗後，其抗體陽轉率上升至 94.6%(圖二)。影響抗體陽轉之相關因子為疫苗種類(VAQTA®; adjusted odd ratio [AOR], 2.4; 95% confidence interval [CI], 1.6-3.6)、追蹤抗體之間隔時間(AOR, per 1-week increase, 1.1; 95% CI, 1.1-1.2)、先前有接受過 A 型肝炎病毒疫苗者(AOR, 30.0; 95% CI, 11.8-76.5)(表一)。

於 92 位先前有接受過 A 型肝炎病毒疫苗接種者，其中有 79 位追加接種 A 型肝炎病毒疫苗。於追加接種第一劑及第二劑疫苗後，其抗體陽轉率分別為 86.1%及 100%，相較於 974 位初次接受 A 型肝炎病毒疫苗者顯著增加(圖三)。

於臺灣急性 A 型肝炎疫情下，有接受及沒接受 A 型肝炎病毒疫苗之愛滋病毒感染者之急性 A 型肝炎發生率分別 0.7 per 100 person-years of follow-up 及 11.0 per 100 person-years of follow-up；因此接種 A 型肝炎病毒疫苗所產生預防急性 A 型肝炎之效力為 93.8%(圖四)。發生急性 A 型肝炎的病患皆為男男性行為者，且於研究期間前皆未接受過 A 型肝炎疫苗；其他預測因子包含研究期間未接種疫苗(adjusted hazard ratio [AHR], 12.5; 95% CI, 3.8-50.0)及近期梅毒感染(AHR, 4.6; 95% CI, 2.6-8.3) 。

（四）討論

此研究與過去的文獻類似，顯示 A 型肝炎病毒疫苗的保護力在愛滋病毒感染者無法達到與非愛滋病毒感染者一樣好的保護力[17]。於此研究中，我們可以觀察到 A 型肝炎病毒抗體陽轉率會隨著追蹤時間間隔拉長而逐漸增加的現象，但在接種第二劑疫苗前，仍只能達到約 50%的抗體陽轉率。唯有在接種第二劑疫苗後，才能提高抗體陽轉率至 94.6%。這種疫苗抗體隨追蹤時間及劑量逐漸成熟增加的現象，也能在其他免疫不全的患者身上觀察到[18]。過去的文獻普遍指出，施打 A 型肝炎病毒疫苗後抗體陽轉的相關因子包含 CD4 較高及愛滋病毒量較低[17]。但於此研究中，由於使用抗愛滋病毒組合療法的病患比例增加，施打 A 型肝炎病毒疫苗前之基礎 CD4 較高且愛滋病毒量較低，因此並無法觀察到如同過去文獻所指出的相關因子。此研究特別發現的相關因子為，先前有接受過 A 型肝炎病毒疫苗者，追加接受 A 型肝炎病毒疫苗接種，能產生較佳的抗體血清反應。這意指對於接種A型肝炎病毒疫苗後，沒有產生足夠的免疫反應的愛滋病毒感染者，追加接種疫苗可以提供足夠的免疫力。但進一步關於何種追加接種疫苗的劑數，對免疫反應較為有利；是常規的兩劑疫苗，還是減少或增加疫苗劑數，仍需後續研究釐清。我們將會納入此研究中未能產生足夠免疫反應的愛滋病毒感染者，進入後續追加接種疫苗的劑數研究。

本研究中所發生的急性 A 型肝炎個案，符合台灣疾病管制署的疫情調查結果；透過男男間性行為以及近期感染梅毒者，為急性 A 型肝炎的預測因子。而有接受過 A 型肝炎病毒疫苗，則為顯著的保護因子，其效果高達 93.8%。因此，儘管 A 型肝炎病毒疫苗於愛滋病毒感染者之抗體血清學反應較差，在疫情下仍能提供顯著的預防效果。

（五）結論

對政策之具體建議: 對於愛滋病毒感染者，提供二劑常規 A 型肝炎病毒疫苗，是對於預防急性 A 型肝炎必要的措施。

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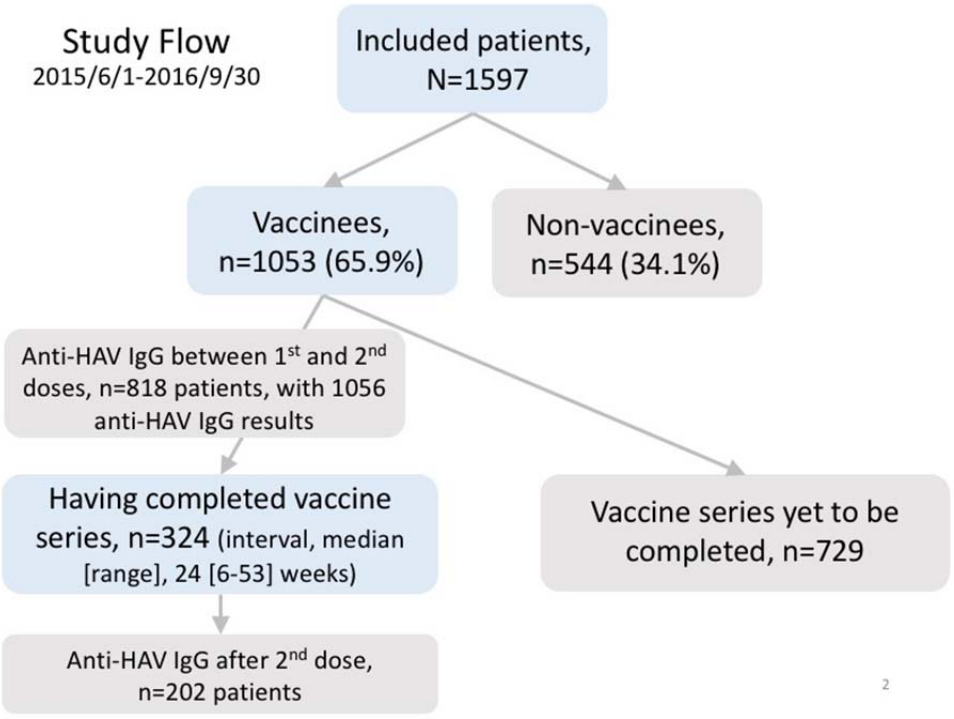
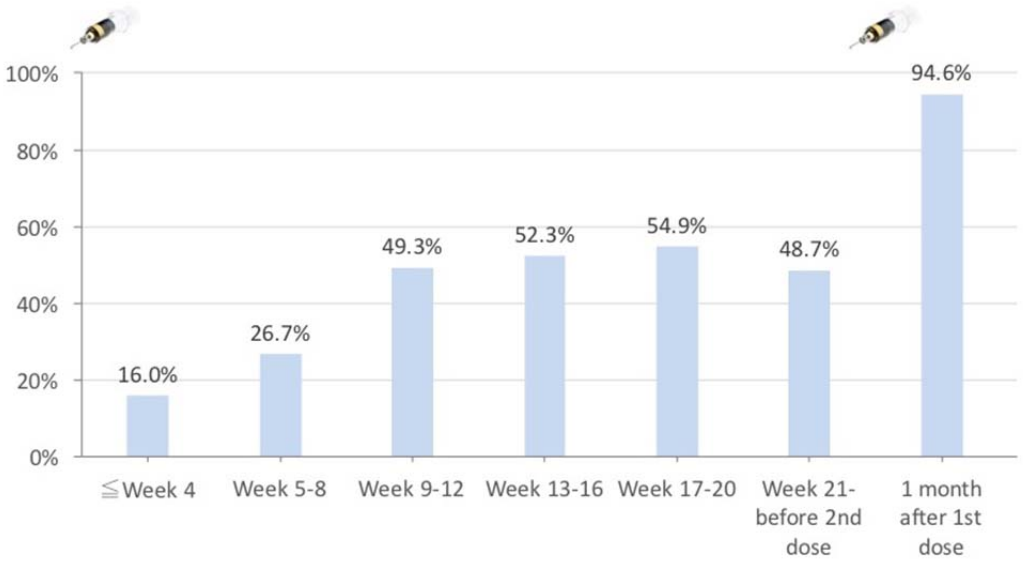
（七）圖表

圖一、研究收案流程圖



圖二、接種 A 型肝炎病毒疫苗後之抗體陽轉率變化

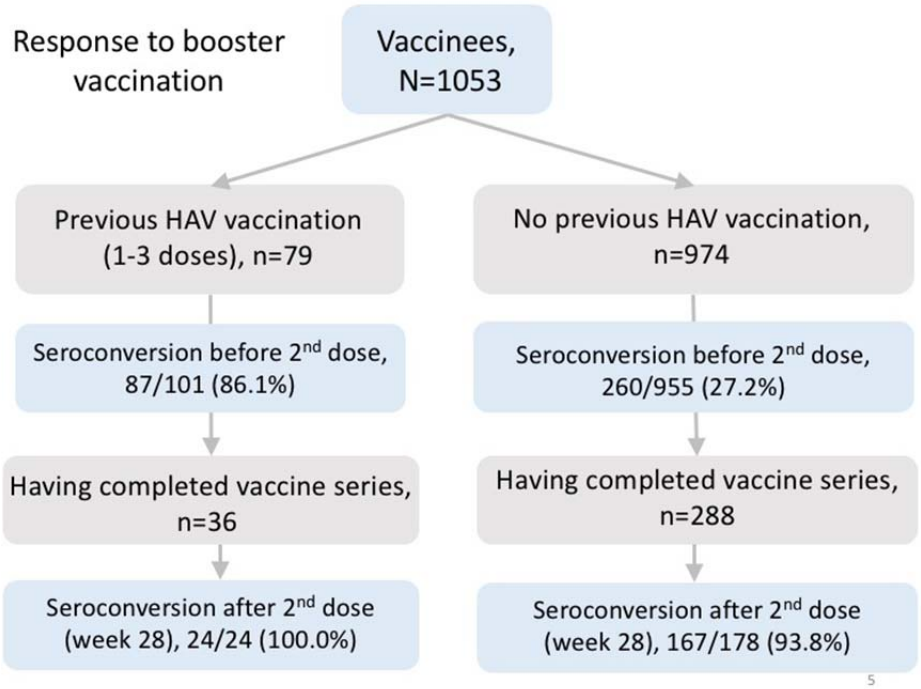


表一、接種 A 型肝炎病毒疫苗後之抗體陽轉的相關因子

Multivariable GEE analysis	AOR (95% CI)	*p*
Age, per 1-year increase	0.99 (0.96-1.01)	0.390
Male sex	1.44 (0.26-7.84)	0.675
Risk behavior, MSM	1.26 (0.50-3.18)	0.624
Weight, per 1-kg increase	1.00 (0.99-1.02)	0.914
Smoking	1.09 (0.73-1.63)	0.689
HBsAg positivity	0.57 (0.32-1.02)	0.059
Anti-HCV positivity	0.99 (0.39-2.50)	0.987
Nadir CD4, , per 1-cells/μL increase	1.001 (1.000-1.002)	0.250
CD4 count at vaccination, per 1-cells/μL increase	1.001 (1.000-1.001)	0.113
PVL at vaccination, per 1-$\log_{10}$ copies/mL increase	0.95 (0.77-1.18)	0.657
Vaccine type, Vaqta vs. Havrix	2.43 (1.63-3.62)	0.0001
Time to anti-HAV follow-up, per 1-week increase	1.12 (1.09-1.14)	0.0001
Previous HAV vaccination	29.99 (11.76-76.47)	0.0001

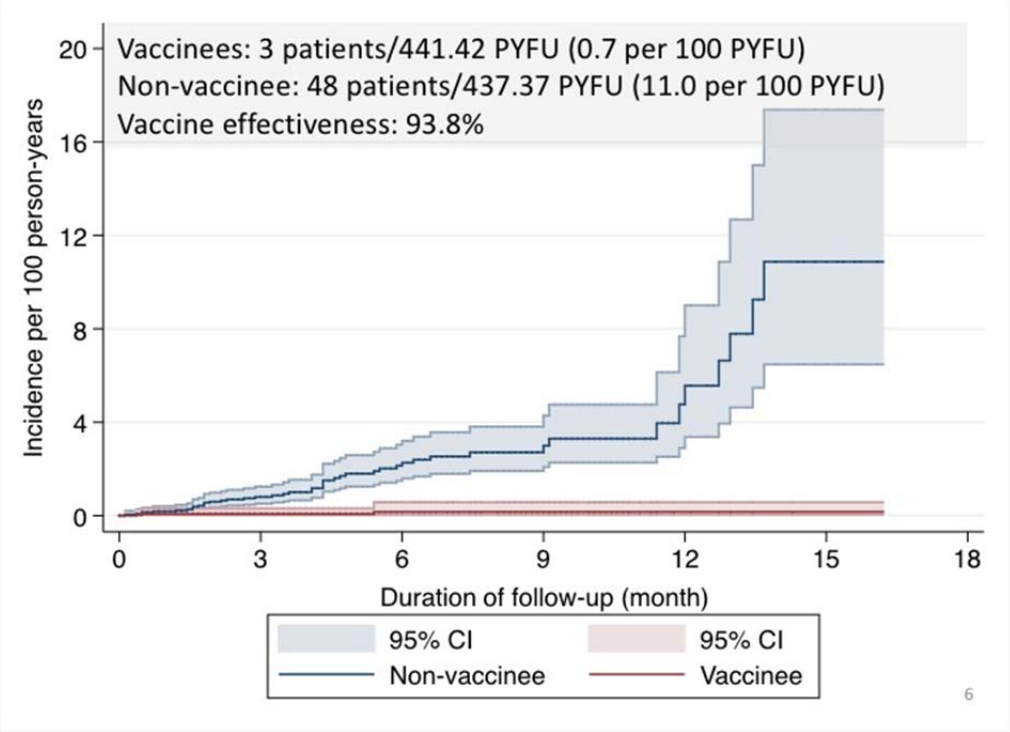
4

圖三、再次與初次接受常規 A 型肝炎病毒疫苗接種之抗體陽轉率比較



5

圖四、有接受及沒接受 A 型肝炎病毒疫苗接種之急性 A 型肝炎發生率



附件四

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

出生於全國 B 型肝炎預防注射年代的人類免疫不全病毒感染患者追加施打 B 型肝炎疫苗之劑量研究

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、李原地

研 究 人 員：黃怡嘉

執 行 期 間：105 年 1 月 1 日至 105 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

台灣自西元一九八六年起全面實施新生兒全面接種 B 型肝炎疫苗後，大幅降低國人 B 型肝炎帶原率。在一九八六年後出生之人類免疫不全病毒感染患者也同樣受到新生兒時期所接種的B肝炎疫苗保護，因而有較低的表面抗原血清轉換率。然而在接種多年後，可能因為 B 型肝炎表面抗體效價降低或消失而對 B 型肝炎不具保護力。 人類免疫不全病毒感染患者即使重新接受完整的 B 型肝炎疫苗施打，仍有較高的比例無法產生足夠之 B 型肝炎表面抗體。因此本研究試圖調查不同的疫苗追加劑量對於原本不反應的人類免疫不全病毒及 B 型肝炎感染患者產生之保護效果。我們回顧在 2000-2016 年之間在台大醫院就醫的 651 位出生於 1986 年全面疫苗接種世代的病患中，B 型肝炎病毒帶原率大約 3.2%。287 為病患已經喪失保護性抗體濃度(<10 mIU/ml)。在後續的追蹤當中，一共有 151 為病患至少接受一劑或以上的 B 型肝炎疫苗接種,而 92 位(62%)病患產生保護性抗體。這其中的 72 位在 52 周時有再度進行抗體檢測,其中 37 位(51%)仍然保有足量的保護性抗體。至於已經喪失保護性抗體的病患其中七位發生 B 型肝炎病毒感染（出現核心抗體或者表面抗原),整體發生率大約是每一千人年的觀察中有 8.4 案例。

關鍵詞： B 型肝炎疫苗， 不反應性， 追加施打，人類免疫不全病毒感染患者

貳、英文摘要

Objectives: Previous studies have demonstrated a waning immunity against hepatitis B virus (HBV) 15 years after vaccination in individuals born after 1986 when nationwide HBV vaccination program was implemented in Taiwan, where the prevalence of chronic HBV infection was 15-20% among those born before 1984. We aimed to assess the HBV seroepidemiology and serologic response to booster vaccination for HBV among HIV-positive men who have sex with men (MSM) born after 1986.

Methods: Medical records of HIV-positive MSM who were born after 1986 and sought HIV care at the NTUH between 2000 and 2016 were reviewed and information on clinical characteristics and antiretroviral therapy containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or lamivudine (3TC) were collected.

Results: During the 16-year study period, 651 HIV-positive MSM were included, with a mean age of 23.7 years. About 83% were receiving cART containing TDF plus FTC or 3TC. 22 patients (3.4%) had anti-HCV antibody and 195 (30.0%) had syphilis at baseline. 46 patients (7.1%) were excluded from analysis due to lack of the result of anti-HBc antibody at baseline. Among 651 patients, 25 (3.2%) had chronic HBV infection, and 287 (44.1%) had lost HBV seroprotection (anti-HBs <10 mIU/ml). During the follow-up, 151 patients received at least 1 dose of HBV vaccine and 92 patients (62%) with follow-up of serologic response after vaccination achieved anti-HBs titers >10 mIU/ml. Among the vaccine-responders, 72 had repeat testing at week 52 of booster vaccination and 37 (51%) had a sustained serologic response. For those who had lost HBV seroprotection at the beginning of this study, 7 incident cases of HBV infection occurred after 837 person-years of follow-up (PYFU), accounting for an incidence rate of 8.4 per 1000 PYFU.

Conclusions: The neonatal hepatitis B vaccination has changed the seroepidemiology of hepatitis B. For patients who were susceptible to HBV infection, re-vaccination should be recommended and the serological response should be confirmed. HIV-infected patients need a better re-vaccination regimen for a higher response and more sustained seroprotection.

關鍵詞： hepatitis B vaccine, non-responder, booster, re-vaccination, HIV

參、本文

（一）前言

慢性 B 型肝炎由於與 HIV 有類似的感染途徑，因而在 HIV 族群當中相當常見[1]。由於較快速的病程，慢性 B 型肝炎與併發症往往在 HIV 患者有造成較高的死亡率或重大疾病。台灣過去是 B 型肝炎的盛行國家，在數十年前其盛行率估計可達 15%。自西元一九八六年起全面實施新生兒全面接種 B 型肝炎疫苗後，大幅降低國人 B 型肝炎帶原率[4]。即使是在一九八六年後出生之人類免疫不全病毒感染患者也同樣受到新生兒時期所接種的 B 肝炎疫苗保護，因而有較低的表面抗原血清轉換率。在一九八四年前出生之人類免疫不全病毒感染患者，B 型肝炎帶原率為 14%；而在一九八六年後出生之人類免疫不全病毒感染患者，B 型肝炎帶原率僅有４%[5]。

然而在接種多年後，可能因為 B 型肝炎表面抗體效價降低或消失而對 B 型肝炎不具保護力[6,7]。對於成年後感染人類免疫不全病毒的患者來說，是否對 B 型肝炎仍具有保護力是個重要的議題。在我們過去的研究中，一九八六年後出生之人類免疫不全病毒感染患者約有 35%仍具有足夠之 B 型肝炎表面抗體而 40%已失去抗體[8]。雖然追加施打的效果在人類免疫不全病毒感染患者較差，大部分國際治療指引建議針對這些患者進行追加施打[9]。值得注意的是，目前仍未有報告討論在出生時即接受過第一次施打後，在成人時期得到ＨＩＶ感染後接受 B 型肝炎疫苗追加施打的效果。因此本研究試圖調查疫苗追加劑量施打對於原本不反應的人類免疫不全病毒及 B 型肝炎感染患者產生之保護效果。

（二）材料與方法

我們收集了台大醫院由2000年至2016年之間所有接受HIV照護的患者，回顧病歷及用藥:其中包含B 型肝炎及C型肝炎血清學資料與梅毒檢驗資料。檢驗的時間點包含納入研究的起始狀態、接受疫苗注射前後、以及後續追蹤結果。疫苗的施打以標準劑量進行第一次追加施打(三劑)。於最後一劑施打後四週進行B 型肝炎表面抗體檢測，並定義表面抗體效價大於等於10 mIU/ml者為有反應者、抗體效價小於10 mIU/ml為不反應者。針對不反應者給予第二次追加施打三劑，劑量分別給予標準劑量或雙倍劑量。

（三）結果

在十六年病歷回顧中，我們收集了台大醫院由2000年至2016年之間共651位出生於一九八六年後接受HIV照護的患者，平均年齡為23.7歲。其中約83%有接受愛滋病雞尾酒療法，而有98%接受含有TDF之治療。30%的患者在納入研究之初即有梅毒感染而有3%的患者有C型肝炎。在我們的研究對象中，僅3.2%有慢性B 型肝炎; 過去曾感染過佔了9.8%; 有35.8%為施打過疫苗的血清學結果; 而有44.1%的患者的B 型肝炎抗原或抗體皆為陰性 (表1). 在每個年齡層中，B型肝炎抗原或抗體皆為陰性的狀況占了40-50%不等(圖1)。

針對297位B型肝炎抗原及抗體皆為陰性的患者，我們都建議追加施打標準劑量共三劑疫苗。但由於經濟或過低的CD4，僅有148(49.8%)的患者接受至少一劑施打、120(40.4%)的患者接受至少兩劑、80(26.9%)的患者接受完整三劑施打。我們在最後一劑疫苗施打後的四週後進行B 型肝炎表面抗體檢測。整體的疫苗反應率為62% (以intention-to-treat分析)及 67%(有接受完整施打之分析)。在92位有反應者當中, 72位在第一劑疫苗注射之52週後有接受表面抗體追蹤:其中有51.4% 仍保有足夠抗體效價(表2)。針對不反應者，有25位接受了給予第二次追加施打三劑，其中25位接受了標準劑量而2位接受了雙倍劑量之第二次追加施打。以第二次追加施打來分析，疫苗反應率為52% (以intention-to-treat分析)及 40%(有接受完整施打之分析)。

在我們的研究中，同時探討了這個族群的B型肝炎、C型肝炎、及梅毒的發生率。 在1526人年的追蹤中，有14個新發生的B型肝炎感染(9.1/1000PYFU)。B型肝炎抗原或抗體皆為陰性的患者中，B型肝炎的發生率為6.6/1000PYFU(表3)。C型肝炎及梅毒的發生率相當高，分別是20/1000PYFU及100/1000PYFU。在接受B型肝炎疫追加施打的患者中，不反應者B 型肝炎的發生率高於反應者:分別為13.4/1000PYF及9.6/1000PYFU。

（四）討論

雖然大部分台灣針對HIV患者治療指引建議針對不具B型肝炎抗體保護效價的患者進行追加施打[9], 但患者需要自費約1000元來購買三劑的疫苗。在我們的研究當中，不到一半的患者接受追加施打。部分的患者在接受兩劑疫苗注射後即產生很高的抗體效價(>100 mIU/ml)，因而沒有接受第三劑的疫苗注射。只有四分之一的患者接受完整的三劑疫苗注射。整體的疫苗反應率為62% (以intention-to-treat分析)及 67%(有接受完整施打之分析)。過去我們認為追加施打能產生的效果往往比初次施打來的好，在我們研究中得到這樣的結果暗示了HIV感染對於本來具有的免疫能力及後續反應的免疫反應都有所影響。此外在接種疫苗後的長期反應也是相當令人失望的(52%)。在疫苗不反應者中，不到一半的患者願意接受第二次追加施打，然而其反應卻是更差。過去許多研究探討了針對這些病人是否可以用雙倍劑量的疫苗施打[12-14]。在我們的研究中有2位接受了雙倍劑量之第二次追加施打，其中有一位產生了很高效價的抗體反應但另一位仍為不反應者。由於樣本數太少，無法進行劑量與反應結果的分析。

在台灣背影盛行率仍為3%之下，我們的研究中B型肝炎的發生率(6.6/1000PYFU)已接近一般定義低盛行國家之發生率(美國0.27%[15], 荷蘭0.2% [16],日本1%[17])。這個結果說明了新生兒B型肝炎疫苗在免疫不全之病人仍有長期的效果。由於在我們的研究當中，C型肝炎及梅毒的發生率相當高，因此安全的性行為仍然是需要再三加強宣導的。

（五）結論

新生兒 B 型肝炎疫苗已改變了台灣 B 型肝炎的疾病結構，即使在 HIV 患者中也能見到盛行率及發生率的顯著下降。由於疫苗產生的抗體會隨著時間衰減，不論患者最初是否具有針對 B 型肝炎之抗體保護，規則的追蹤並針對不足的患者施打是重要的。HIV 患者還是需要更好的疫苗施打計畫來增加反應率。

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（七）圖表

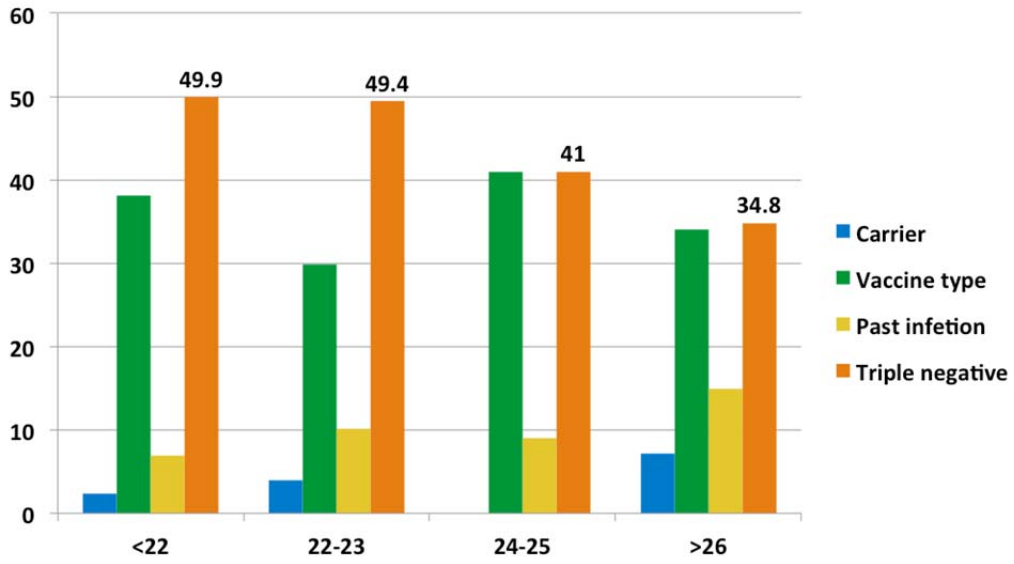
表1. Patient characteristics at baseline

Mean age (year)	23.7 (SD 2.7)	
CD4 count (cells/μl)	N=	%
<200	92	14.1
200-350	173	26.6
350-500	160	24.6
>500	226	34.7
On ART	540	83.0
On TDF and 3TC or FTC-containing cART	532	81 98 (532/540) among on ART
Syphilis *	195	30.0
HCV infection	22	3.4

表 2. HBV serology category at baseline

	HBV carrier	Past infection	Vaccine type	Triple-negative
HBsAg	+	-	-	-
Anti-HBs	+/-	+/-	+	-
Anti-HBc	+/-	+	-	-
Patient number	21 (3.2%)	64 (9.8%)	233 (35.8%)	287 (44.1%)
Mean age	25	24.5	23.8	23.2
on ART %	81.0%	85.9%	81.6%	84.5%

圖 1. Proportion of serology categories in each age group



表三 3. Incidence rates of HBV, syphilis, and HCV In each patient category

Category	Patient number	Total FU duration	Mean FU duration	HBV cases	HBV rate (1000PY)	Syphilis rate (1000PY)	HCV Rate (1000PY)
Vaccine type At baseline	223	699	3.13	7	**10**	100	22.9
Triple-negative - No vaccination	146	301	2.06	2	**6.6**	119.3	19.9
Responder	92	312	3.39	2	**6.4**	64.2	9.6
Non-responder	56	224	4.00	3	**13.4**	75.9	13.4

附件五

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

愛滋病毒感染患者延遲使用抗愛滋病毒組合療法時機之趨勢及其預後

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：林冠吟、楊家瑞、鄭健禹、林邑璁、林德宇、王建淳

研 究 人 員：愛滋病防治中心專任研究助理

執 行 期 間：105 年 1 月 1 日至 105 年 12 月 31 日

目　　錄

頁碼

共　13　頁

壹、中文摘要

目的：近來愛滋病毒感染治療準則皆逐步支持擴大抗愛滋病毒組合療法的治療對象，本研究旨在評估台灣延遲開始使用抗愛滋病毒組合療法的趨勢以及治療預後。

方法；於 2012 至 2016 年間，於台灣北區愛滋病毒感染照護指定醫院納入新診斷並開始使用抗愛滋病毒組合療法的愛滋病毒感染患者。延遲開始使用抗愛滋病毒組合療法定義為 CD4 <200 cells/mm^3 或患有愛滋相關疾病。

結果：研究期間共納入 2593 位愛滋病毒感染者。整體來說，開始使用抗愛滋病毒組合療法的 CD4 數目中位數為 270 cells/mm^3；由 2012 年之 207 cells/mm^3 上升至 2016 年之 298 cells/mm^3。延遲開始使用抗愛滋病毒組合療法之比例由 2012 年之 49.1%下降至 2016 年之 29.0%。延遲開始使用抗愛滋病毒組合療法的相關因子分別為年紀較大、B 型肝炎病毒表面抗原陽性、較早期開始使用抗愛滋病毒組合療法；靜脈注射毒癮者及 C 型肝炎抗體陽性則較不易延遲開始使用抗愛滋病毒組合療法。相較於非延遲開始使用抗愛滋病毒組合療法，延遲開始使用抗愛滋病毒組合療法有較高的愛滋病相關死亡率(1.7% vs. 0.3%)、病毒治療失敗(16.0% vs. 8.3%)、因治療失敗更換抗愛滋病毒藥物(7.1% vs. 2.6%)。愛滋病相關死亡的預測因子為延遲開始使用抗愛滋病毒組合療法及年紀較大。

結論：此研究顯示台灣延遲開始使用抗愛滋病毒組合療法的比例雖逐年降低，但仍佔有不少比例。延遲開始使用抗愛滋病毒組合療法會造成較差預後，因此我們必須改善台灣診斷愛滋病毒感染及開始使用抗愛滋病毒組合療法之時機。年齡較大的愛滋病毒感染者 更應積極實施改善措施。

關鍵詞：延遲開始服藥、病毒治療失敗、愛滋病相關死亡、亞洲

貳、英文摘要

Objectives: The latest HIV treatment guidelines have stressed the intensive focus on scaling up access to combination antiretroviral therapy (cART). We aimed to assess the trends and treatment outcomes of late initiation of cART in Taiwan.

Methods: Between 2012 and 2016, we retrospectively included antiretroviral-naive HIV-positive adults who initiated cART at major designated hospitals for HIV care in Northern Taiwan. Late cART initiation was defined as a CD4 count <200 cells/mm3 or experiencing AIDS-defining illness before cART initiation. The treatment outcomes, including AIDS-related death, virological failure, and regimen modification, were assessed up to 6 months after starting cART.

Results: During the 4-year study period, 2593 HIV-positive patients were included. 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 overall median CD4 count was 270 cells/mm^3, which increased from 207 cells/mm^3 in 2012 to 298 cells/mm^3 in 2016. The overall proportion of late cART initiation decreased from 49.1% in 2012 to 29.0% in 2016 (both *P* for trend <0.001). The independent factors associated with late initiation were older age (adjusted odds ratio [AOR], 1.05; 95% CI, 1.04-1.06), HBsAg seropositivity (AOR, 1.31; 95% CI, 1.05-1.64), initiating cART in the earlier year, intravenous drug use (AOR, 0.54; 95% CI, 0.37-0.79), and negative hepatitis C serostatus (AOR, 0.69; 95% CI, 0.49-0.97). Compared with non-late cART initiators, more late initiators had AIDS-related death (1.7% vs. 0.3%), virological failure (16.0% vs. 8.3%), and regimen modification due to treatment failure (7.1% vs. 2.6%) (all P<0.05). The predicting factors of AIDS-related death 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 in the era of treatment scale-up. The late initiators had higher risk for mortality, virological failure, and regimen modification due to treatment failure. The need for strategies to improving early detection of HIV infection and expediting cART initiation should be highlighted, especially among the older population.

關鍵詞：late initiation; virological failure; AIDS-related death; Asia

參、本文

（一）前言

擴大抗愛滋病毒組合療法的治療對象有助於減少愛滋病相關死亡、降低愛滋病毒新感染者人數、以及縮減醫療照護支出。全球及地區性的愛滋病毒感染治療準則及照護計畫皆逐步支持擴大抗愛滋病毒組合療法的治療對象。如 DHHS 治療準則，自 2012 年即建議不論 CD4 數值多寡，所有愛滋病毒感染患者皆可接受抗愛滋病毒組合療法[1]。最近的 START 雙盲性試驗也進一步提供，不論 CD4 數值，所有愛滋病毒感染患者立即接受抗愛滋病毒組合療法的有力證據[2]。WHO/UNAIDS 則在 2015 年後推行 90-90-90 的目標; 藉由擴大治療所有的愛滋病毒感染患者，而達到 90%的愛滋病毒感染患者獲得抗愛滋病毒組合療法治療的目標[3]。然而統計到 2013 年底，全球只有 37%的愛滋病毒感染患者接受抗愛滋病毒組合療法治療[3]。雖然亞洲許多國家已經藉由地區性的愛滋病毒感染治療準則及照護計畫，使得接受抗愛滋病毒藥物的人數增加，但是治療的涵蓋率仍低於全球涵蓋率[4]。亞洲地區的研究顯示開始使用抗愛滋病毒組合療法的 CD4 數目有逐年增加的趨勢，但數值仍然落在 200 cells/mm^3; 其原因可能包含延遲診斷愛滋病毒感染、延遲開始愛滋病毒感染醫療照護、以及延遲開始使用抗愛滋病毒藥物[5]。

然而這些亞洲整體的研究結果並無法完全推論到個別地區，且評估個別地區的愛滋病毒感染照護計畫成果需要倚靠各地區的研究。台灣是高收入的亞洲國家，愛滋病毒感染的相關醫療照護及藥物由政府免費提供; 根據 2013 年台灣愛滋病毒感染治療指引，建議 CD4≦500 cells/mm3 的愛滋病毒感染患者應接受抗愛滋病毒組合療法[6]。本研究評估 2012 至 2016 年間，在台灣北區愛滋病毒感染照護指定醫院接受照護的愛滋病毒感染患者，開始使用抗愛滋病毒組合療法時的 CD4 數目趨勢、延遲開始使用抗愛滋病毒組合療法的相關因子、以及治療預後。期望此研究成果能夠進一步提供臨床醫師以及公衛防疫人員，目前台灣愛滋病毒感染照護計畫的成果以及未來努力的目標。

（二）材料與方法

由研究主持人和研究人員，追蹤 2012 至 2016 年間於北區幾家愛滋病毒感染照護指定醫院新診斷的愛滋病毒感染者；使用制式的 Excel 檔案記錄病歷中病患的基本資料(如年齡、性別、身高、體重)、愛滋病症的相關資料(如感染愛滋病毒途徑、同時感染 B 型肝炎及 C 型肝炎、抗藥性分析結果)、開始使用抗愛滋病毒藥物之時間及其 CD4 數值、使用的抗愛滋病毒藥物、開始服藥 6 個月內的預後(發生愛滋病相關死亡、病毒治療失敗、更換藥物)。由上述結果可了解開始使用抗愛滋病毒組合療法之 CD4 數目趨勢變化、延遲開始使用抗愛滋病毒藥物的比例及預後; 再藉由觀察及統計上述結果，分析各項變因以找出延遲開始使用藥物的相關因子以及影響預後的預測因子。

以下針對各實施方法進行細項及步驟之說明:

1.受試者納入及排除條件

納入 2012 至 2016 年所有於北區幾家愛滋病毒感染照護指定醫院新診斷並開始使用抗愛滋病毒組合療法的愛滋病毒感染者，且年齡必需大於 20 歲。排除條件為缺乏開始使用抗愛滋病毒組合療法之 CD4 數值者。

2.資料之蒐集處理評估

研究主持人和研究人員採用制式的 Excel 紀錄病人資料。資料紀錄完成後，再加以進行統計分析工作。

3.統計分析方法

所有的統計分析將利用 Stata software version 12.0。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 Wilcoxon rank sum test 分析。P 值小於 0.05 將被認為有統計學上的意義。並使用邏輯性迴歸分析出各項變因以找出延遲開始使用藥物的相關因子及影響預後的預測因子。

（三）結果

於 2012 至 2016 年此四年研究期間，於北區幾家愛滋病毒感染照護指定醫院(台大醫院、亞東醫院、三軍總醫院、衛生福利部桃園醫院、台大醫院新竹分院)所收納的病患總數為 2593 人，其 95.4%為男性，年齡中位數為 31 歲，76.9%透過男男性行為傳染愛滋病毒；而合併 B 型及 C 型肝炎感染則約有 10%及 20%。整體而言，開始使用抗愛滋病毒組合療法時的基礎 CD4 中位數值為 270 cells/mm^3；如果以每半年為切點，則 CD4 中位數值由 2012 後半年的 207 cells/mm^3 逐漸顯著上升至 2016 前半年的 298 cells/mm^3 (圖一)。若進一步將開始使用抗愛滋病毒藥物時的基礎 CD4 中位數值細分為大於或等於 500 cells/mm^3、350-499 cells/mm^3、200-349 cells/mm^3、以及小於 200 cells/mm^3 四個分層，可觀察到基礎 CD4 數值的增加主要來自於大於或等於 500 cells/mm^3 及 350-499 cells/mm^3 這兩個分層，隨之而減少的是 200-349 cells/mm^3 及小於 200 cells/mm^3 這兩個分層。然而直至 2016 前半年，仍有 30%的病患開始使用抗愛滋病毒組合療法的基礎 CD4 中位數值低於 200 cells/mm^3 (圖一)。若再進一步分析延遲開始使用抗愛滋病毒組合療法的比例，則由 2012 後半年的 49.1%逐漸顯著下降至 2016 前半年的 29.0%；其中合併愛滋相關疾病的比例，則由 2012 後半年的 14.4%至 2016 前半年的 6.5%，並無顯著改變 (圖二)。

與延遲開始使用抗愛滋病毒組合療法的相關因子包含年齡較大(勝算比, 1.05; 95%信賴區間, 1.04-1.06)、B 型肝炎病毒表面抗原陽性(勝算比, 1.31; 95%信賴區間, 1.05-1.64)、以及較早期開始使用抗愛滋病毒組合療法。較不易延遲開始使用抗愛滋病毒組合療法的相關因子則包含靜脈注射毒癮者(勝算比, 0.54; 95%信賴區間, 0.37-0.79)及 C 型肝炎抗體陽性(勝算比, 0.69; 95%信賴區間, 0.49-0.97) (表一)。

延遲開始使用抗愛滋病毒組合療法對於治療預後有所影響 (表二)。在愛滋相關疾病所造成的死亡上，延遲開始使用抗愛滋病毒組合療法者的比例(1.7%)較高於非延遲開始使用抗愛滋病毒組合療法者(0.3%)，風險比值(hazard ratio)為 6.86 (95%信賴區間為 2.78-16.91)；其他增加愛滋相關死亡的因子還包含年齡較大。在病毒治療失敗上(定義為治療六個月後愛滋病毒量仍大於 200 cells/mm^3)，延遲開始使用抗愛滋病毒組合療法者的比例(16.0%)較高於非延遲開始使用抗愛滋病毒組合療法者(8.3%)，風險比值為 2.09 (95%信賴區間為 1.70-2.58)。在更換抗愛滋病毒藥物使用上，延遲開始使用抗愛滋病毒組合療法者的比例(44.4%)與非延遲開始使用抗愛滋病毒組合療法者的比例(41.3%)並未

達統計上差異，風險比值為 1.10 (95%信賴區間為 0.99-1.22)。但如果細分更換抗愛滋病毒藥物使用的原因，則因為藥物副作用而換藥部分，延遲開始使用抗愛滋病毒組合療法者的比例(33.0%)與非延遲開始使用抗愛滋病毒組合療法者的比例(35.1%)並未達統計上差異；因為抗藥性或病毒治療失敗而換藥部分，延遲開始使用抗愛滋病毒組合療法者的比例(7.1%)較高於非延遲開始使用抗愛滋病毒組合療法者的比例(2.6%)，風險比值為 2.82 (95%信賴區間為 2.04-3.90)。

（四）討論

此研究顯示台灣開始使用抗愛滋病毒組合療法時的基礎 CD4 中位數值雖逐年上升，但歷年之整體基礎 CD4 中位數值皆低於 2012 年台灣愛滋指引所建議的 350 cells/mm^3。此外，延遲開始使用抗愛滋病毒組合療法的比例雖逐年降低，但仍佔有不少比例。因此，台灣開始使用抗愛滋病毒組合療法的時機仍有進步的空間，尤其延遲開始使用抗愛滋病毒組合療法者，是最急需要改善的族群。過去的文獻指出，提早開始使用抗愛滋病毒組合療法後，主要造成延遲開始使用抗愛滋病毒組合療法的原因，來自於延遲診斷愛滋病毒感染；而若要提早診斷愛滋病毒感染，則有賴於減少社會歧視與增加篩檢率[7]。而年齡較大者容易較晚才診斷愛滋感染及接受治療，有可能是因為較年長者對於保護性性行為與愛滋病毒感染的資訊較欠缺，或就醫時較不容易被納入愛滋病毒感染的鑑別診斷[8]。合併 B 型肝炎感染可能對免疫造成負面影響，而使得基礎 CD4 中位數值較低[9]。合併 C 型肝炎感染較易提早接受抗愛滋病毒組合療法治療，有可能和較多合併 C 型肝炎感染者之傳染途徑為靜脈注射毒癮，而其因為入監受刑，較易有機會接受愛滋相關醫療照顧有關係[10]。較早期的年代除了因為社會端或醫療端因素，較有可能延遲診斷愛滋感染之外，對於開始使用抗愛滋病毒組合療法的時機，也有 CD4 數值上的限制，因此較易延遲開始使用抗愛滋病毒組合療法。

本研究也發現，延遲開始使用抗愛滋病毒組合療法會造成治療預後不佳。除了愛滋相關死亡會受延遲開始使用抗愛滋病毒組合療法影響之外，其他增加愛滋相關死亡的因子還包含年齡較大。近年來的研究顯示，年齡較大者(45 至 65 歲)相較於年齡較小者，更容易因為延遲開始使用抗愛滋病毒藥物，而增加未來 10 年死亡率[11]。綜合以上結果，

年齡較大者不但較易延遲開始使用抗愛滋病毒組合療法，而且其治療預後較差。因此，年齡較大之愛滋病毒感染者，是較需要改善開始使用抗愛滋病毒組合療法時機的族群。

（五）結論

對政策之具體建議: 必須藉由減少社會歧視、提早篩檢診斷、提早提供感染者抗愛滋病毒組合療法等方式，改善台灣開始使用抗愛滋病毒組合療法之時機，減少死亡以及病毒治療失敗的風險。年齡較大的感染者，由於有較高的死亡風險，因此我們更應該在此族群積極實施改善措施。

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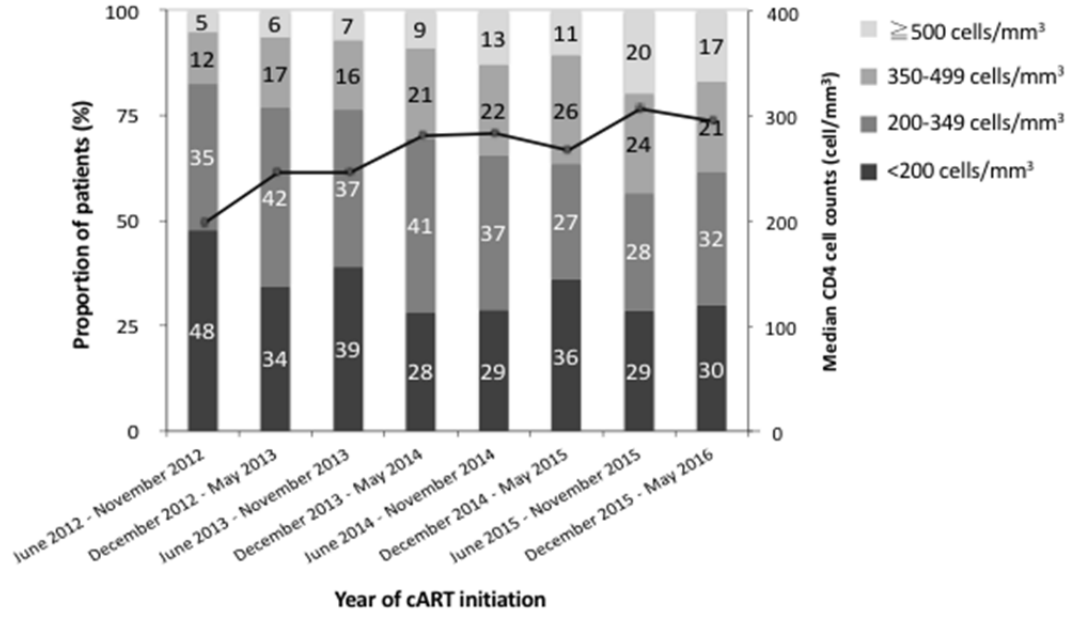
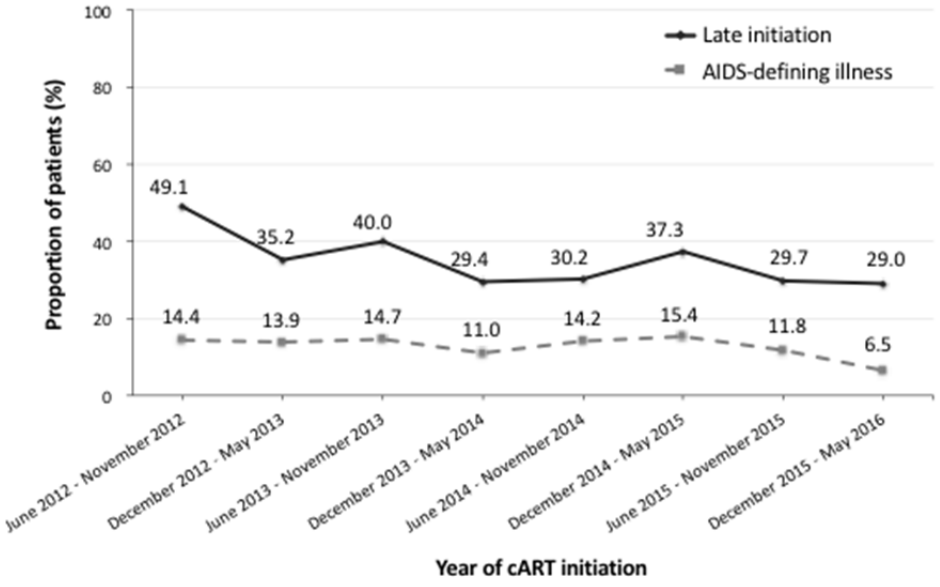
（七）圖表

圖一、開始使用抗愛滋病毒組合療法時的基礎 CD4 中位數值趨勢



圖二、延遲開始使用抗愛滋病毒組合療法之比例趨勢



表一、延遲開始使用抗愛滋病毒組合療法之相關因子

Variables	Univariate analysis		Multivariable analysis	
	OR (95% CI)	***P***	**OR (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	1.03 (0.70-1.53)	0.864
Mode of HIV exposure				
Homosexual sex	1.00 (reference)		1.00 (reference)	
Heterosexual sex	1.81 (1.38-2.39)	<0.001	1.17 (0.84-1.62)	0.346
Intravenous drug use	0.70 (0.57-0.85)	<0.001	0.54 (0.37-0.79)	0.002
HBsAg seropositivity	1.54 (1.25-1.91)	<0.001	1.31 (1.05-1.64)	0.018
HCV antibody seropositivity	0.67 (0.56-0.81)	<0.001	0.69 (0.49-0.97)	0.035
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)	0.007
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	0.61 (0.49-0.75)	<0.001

Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; OR, odds ratio.

表二、延遲與非延遲開始使用抗愛滋病毒組合療法之預後比較

Outcomes	Patients with late initiation (n=1278)	Patients with non-late initiation (n=2377)	HR or OR (95% CI)	*P*
AIDS-related death, n (%)	22 (1.7)	6 (0.3)	6.86 (2.78-16.91)	<0.001
Virological failure, n (%)	204 (16.0)	198 (8.3)	2.09 (1.70-2.58)	<0.001
Regimen modification, n (%)	568 (44.4)	981 (41.3)	1.10 (0.99-1.22)	0.068
Adverse event	422 (33.0)	834 (35.1)	0.94 (0.83-1.05)	0.264
Treatment failure	91 (7.1)	62 (2.6)	2.82 (2.04-3.90)	<0.001
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; OR, odds ratio.

附件六

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

急性愛滋病毒感染臨床表徵、病毒特性與宿主免疫系統之研究

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：林德宇

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執 行 期 間： 105 年 1 月 1 日至 105 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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中文摘要

近幾年來政府、醫院和許多民間團體提供各種匿名或者具名的篩檢，加上臨床醫療人員的診斷愛滋病毒感染的能力持續改善，因此臨床端診斷發現急性愛滋病毒感染的案例，有逐漸增加的趨勢。及早診斷急性愛滋病毒感染，從臨床和公共衛生防治愛滋病毒感染的角度，非常重要。我們有機會提供早期治療，減少繼續傳播愛滋病毒的機會，同時可以提早減緩感染者免疫系統的破壞。我們收集指定醫院急性感染病例121位，依據診斷的年代區分為2008年以前(n=4)、2009~2012 (n=26)及2013~2016 (n=91)三組，log病毒量趨勢如圖一，CD4數值變化趨勢如圖二。依據急性病毒感染者24週log病毒量為0或不為0分成兩組，臨床表徵如附表一，在24週控制較差組中一開始病毒量較高(log PVL 6.48 vs 6.15; p=0.033)，在控制較差組中使用蛋白酶抑制劑人數較多(5 vs 1人)。兩組藥物治療後4週、16週、24週、36週、48週病毒量變化及CD4數值統計如表三。兩組藥物治療前及治療後4週、16週、24週、36週、48週白血球、血紅素、血小板、肝指數、尿素氮、肌酸酐及血脂數值統計如表四。單變項的分析結果如表五之一所顯示。我們發現年紀較大、治療前log病毒量數值及合併肌肉痠痛症狀者有較高的比例24週仍測得到病毒量，如治療後4週血紅素較高者24週仍測得到病毒量的機會較低，多變項的分析結果如表五之二所顯示。治療後4週血紅素較高者24週仍測得到病毒量的機會較低(p=0.035)。

關鍵字： 抗愛滋病毒療法; 急性病毒感染;

摘要 (英文)

The incidence of human immunodeficiency virus (HIV) infection with acute retroviral syndrome appears to be increasing on account of multiple screening methods provided by government, hospital and non-government organizations. Early diagnosis of HIV infection with acute retroviral syndrome is very important in the part of prevention strategy of HIV infection. We could provide early highly active antiretroviral therapy to prevent further transmission and minimize the impact of immunosuppression in patients. In this study, we were able to include a total of 121 patients with acute retroviral syndrome. We classified the patients to three groups according to the year when the diagnosis was made: the year before 2008 (n=4), 2009~2012 (n=26) and 2013~2016 (n=91). The trends of plasma HIV RNA loads was shown as Figure 1. The trends of CD4 counts are shown as Figure 2. The patients were also categorized into two groups: well-controlled vs poorly-controlled according to plasma HIV RNA load at the end of weeks 24 of treatment. The clinical characteristics of these two groups are shown as Table 1. The mean value of plasma HIV RNA load before treatment of poorly-controlled group was higher than that of well-controlled group (6.48 vs 6.15 $\log_{10}$ copies/ml, p=0.033). PVL and CD4 counts in the two groups were measured at baseline, week 4, week 16, week 24, week 36 and week 48 (Table 3). The results of other laboratory tests of the two groups at baseline. week 4, week 16, week 24, week 36 and week 48 are shown in Table 4. Univariate analysis revealed old age, higher plasma HIV RNA load before treatment and myalgia symptom were related factors to predict poor virological response. On the contrary, a higher hemoglobin level measured at week 4 was associated with viral suppression (p=0.035).

Keywords: antiretroviral therapy; acute retroviral infection

一、前言

自從愛滋病毒發現後，愛滋病是人類安全中健康安全最重要議題，且其嚴重性已威脅到國家安全,聯合國安全理事會通過第1308號決議案表示:愛滋病可能對國家穩定與安全產生威脅。這是聯合國首次將一個疾病列為安全威脅，其嚴重性也成為全球安全的新焦點。依據世界衛生組織全球愛滋病流行統計資料(2014 AIDS epidemic update，WH0、UNAIDS)(1) ，自1981 年發現第一例愛滋病毒成染者以來，截至2013年7月，全球存活之愛滋病毒成染者已達3930萬人，其中2012年新感染人數為230萬人，愛滋病相關死亡人數約為160 萬人。在2013 年一年間,全球平均每天約新增7000名成染者,其中1000 名為15 歲以下的兒童，而每天新增之6000 名15 歲以上成染者中，約51% 為女性、41% 為15 至24 歲之年輕族群。另全球疾病負擔(Global Burden of Disease, GBD) 研究結果，2004 年全球有200 萬人死於愛滋病，造成失能調整人年(Disability Adjusted Life Years, DALY s) 原因的第五位，顯示，愛滋病所造成的問題，值得全球關注。依地區別而言，以非洲撒哈拉沙漠以南的地區疫情最為嚴重，而亞洲存活愛滋病毒成染人數約487 萬人，占全球存活成染者的15% ，其疫情嚴峻程度，僅次於非洲撒哈拉沙漠以南地區，近年亞洲國家愛滋疫情均漸趨穩定，亞洲各國成人愛滋盛行率均小於1% '雖然其盛行率相對較低，若不重視與強化國家整體防治作為，預估至西元 2020年將迫使亞洲增加6百萬的瀕臨貧窮家庭，並造成國家經濟重大影響。為因應全球疫情變化，各國紛紛提高國家因應層紋，如美國總統歐巴馬提出多項愛滋防治策略計畫，並以全面普及預防、治療、照護支持作為策略主軸，由於流行趨勢與主要傳染模式會隨時間演變，各國除應參考疫情變化及國情特性擬定策略外，亦有證據顯示，不論疫情處於何種狀態，都必須將性工作者、注射藥癮者及男男問性行為者三類對象納入國家整體防治計畫之內容，以期在2020年能夠達到遏止愛滋病持續蔓延之發展目標。

我國自1984 年發現第一例愛滋病毒感染者以來，截至2014年底，本國籍愛滋病毒感染者共28,710人，4,651人死亡；主要傳染途徑以男同性間不安全性行為最多，其次為異性間不安全性行為，透過不安全性行為感染者超過9成。以愛滋病疫情近年發展的趨勢看來，極有可能成為我國最大的敵人，耗損國力甚鉅。因為我國愛滋成染者以年輕男性為主體，成人染者中93.9%為男性，加強年輕男性的愛滋病防治觀念並指導其採取正確的預防措施是刻不容緩的工作

在2014年,疾管署利用世衛(WHO)的公式估計,台灣約有33500位愛滋病毒感染者。

因為近幾年來政府、醫院和許多民間團體提供各種匿名或者具名的篩檢，加上臨床醫療人員的診斷愛滋病毒感染的能力持續改善，因此臨床端診斷發現急性愛滋病毒感染的案例，有逐漸增加的趨勢。及早診斷急性愛滋病毒感染，從臨床和公共衛生防治愛滋病毒感染的角度，非常重要。我們有機會提供早期治療，減少繼續傳播愛滋病毒的機會，同時可以提早減緩感染者免疫系統的破壞。近期，許多國內關心和照護愛滋病毒感染患者的醫療同仁都陸續分享，發現急性愛滋病毒感染病情很嚴重的案例，似乎意味著國內流傳的病毒株對於免疫系統變得更具破壞力。

最早探討急性病毒感染的文獻可回溯至1985年，Cooper學者在雪梨調查約1000位男同志，發現12位急性病毒感染(2)，Schacker等人發現急性病毒感染的症狀有發燒.全身倦怠.肌肉痠痛.體重減輕.盜汗.腹瀉(3)，Simon及Cohen發現這些病患感染病毒後平均需25天體內才會出現抗愛滋病毒抗體(4-5)，Todd等人發現急性病毒感染後尚未使用抗病毒藥物時非洲人存活率不輸歐美先進國家，泰國人似乎預後較差(6)，Wandel等人發現抗愛滋病毒藥物的適用性比起之前專家學者計算的模式較久(7)，Crum-Cianflone N等人發現美國的新近感染者的CD4數值比之前明顯的偏低，這可能暗示著人類免疫缺乏病毒逐漸適應人類宿主環境進而產生嚴重的感染(8)，上述都是國外的文獻報告，國內則有蔡茂松醫師及洪健清醫師統計台大醫院約300多個急性病毒感染的個案，發現合併B型肝炎感染.CD4數值較低者及不是CCR5受器者可做為這些個案免疫功能的預測因子(9)。

Quinn發現在異性戀決定感染的因素主要為血中病毒量，如血中病毒量小1500copies/ml則傳染給別人的機會降低許多(10)，Attia等人使用系統性分析資料後發現如異性戀如有一方感染，一方未感染使用抗病毒藥物治療使病毒量降至400copies/ml未有新感染事件發生(11) 。

隨著時代的演變，人類免疫缺乏病毒的篩檢試劑已進展成第四代，可同時偵測抗原及抗體，Fiebig將實驗室偵測病毒的方法將急性病毒感染分成六個階段(12)，至於急性病毒感染是否需要治療早期仍有爭議，不過較新的共識建議及早開始治療(13)，Matthew和Buzon等人發現如在急性病毒感染時期早期使用抗病毒藥物可降低細胞中病毒儲存的數量(14-15)，Ananworanich發現在感染後數週內使用抗病毒藥物的效果最佳(16)，Whitney發現在老鼠的模式中病毒感染後很快就會於宿主細胞內繁殖與儲存(17)，所以如能早期使用抗病毒藥物，有機會減少宿主細胞內病毒的儲存。

本研究選取符合收案條件的病患，收集病患(性別.年齡.內外科疾病史.門診住院病程

記錄.血液常規檢驗.生化數值檢驗) 等資料加以統計分析，建立國內資料庫，探討急性愛滋病毒感染症狀及出現的頻率、使用抗愛滋病毒藥物的種類，定期追蹤病毒量及CD4數值的變化，並注意有無任何伺機性感染及是否產生免疫重建症候群的現象，持續觀察病患的臨床表徵及治療效果。

二、材料與方法

1.受試者納入條件

收集國內指定醫院符合急性感染定義病患，Fiebig stageI~IV 病患。

2.資料之蒐集處理評估

研究主持人和協同主持人採用制式的 Excel 紀錄病人資料。這些資料包括性別.年齡.內外科疾病史.門診住院病程記錄.血液常規檢驗.生化數值檢驗。我們使用 SPSS software; version 11.0 (SPSS)進行。類別變數將由χ2 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

1. 自今年一月一日起至今年十月三十一日止，我們收集指定醫院急性感染病例121位，依據診斷的年代區分為2008年以前(n=4)、2009~2012(n=26)及2013~2016(n=91)三組，log病毒量趨勢如圖一，CD4數值變化趨勢如圖二。
2. 依據急性病毒感染者24週log病毒量為0或不為0分成兩組，臨床表徵如附表一，在24週控制較差組中一開始病毒量較高(log PVL 6.48 vs 6.15; p=0.033)，在控制較差組中使用蛋白酶抑制劑人數較多(5 vs 1人)。兩組藥物治療後4週、16週、24週、36週、48週病毒量變化及CD4數值統計如表三。
4. 兩組藥物治療前及治療後4週、16週、24週、36週、48週白血球、血紅素、血小板、肝指數、尿素氮、肌酸酐及血脂數值統計如表四。
5. 單變項的分析結果如表五之一所顯示。我們發現年紀較大、治療前log病毒量數值及合併肌肉痠痛症狀者有較高的比例24週仍測得到病毒量，如治療後4週血紅素較高者24週仍測得到病毒量的機會較低，多變項的分析結果如表五之二所顯示。治療後4週血紅素較高者24週仍測得到病毒量的機會較低(p=0.035)。

四、討論

研究結果顯示三個年代急性病毒感染治療前病毒量平均為1000000 copies/ml，治療後病毒量均可下降，CD4數值在2008年前為945，相較2009~2012及2013~2016兩組初始CD4數值228及271來的高，不過2008年前病患只有四位，樣本數較少是否有臨床上的差異有待更多的資料分析。在24週控制較差組中一開始病毒量較高(log PVL 6.48 vs 6.15; p=0.033)，在控制較差組中使用蛋白酶抑制劑人數較多(5 vs 1人)。多變項的分析結果顯示治療後4週血紅素較高者24週仍測得到病毒量的機會較低(p=0.035)。另外我們嘗試使用不同模式(病毒量大於500000對比病毒量小於500000) ，24週測不到病毒量的比率趨近一致，使用CD4數值大於350對比小於350進行分析，24週測不到病毒量的比率趨近一致，分析臨床上會影響血紅素的抗愛滋病毒藥物主要為含有Zidovudine類藥物如Combivir，在我們的分析中顯示如使用藥物避開影響血紅素有較高的機會於24週讓病毒量降到0，控制會較好。

五、重要研究成果及具體建議

之前急性病毒感染是否需立即治療有些爭論，有些學者建議立即治療，另外一些學者建議可再觀察一段時間後再治療，不過近一、二年的治療指引均建議立即治療，我們研究的分析結果顯示治療後4週血紅素較高者24週仍測得到病毒量的機會較低(p=0.035) 。

對政策之具體建議:在急性病毒感染時選擇抗病毒藥物建議避開會影響骨髓造血功能的藥物，會有較好的治療效果。

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圖表

Table 1. Demographic and clinical characteristics (week 24 logPVL > 0 comparison)

	Poor-controlled (week 24 logPVL > 0) (n =22)	**Well-controlled (week 24 logPVL = 0) (n = 99)**	***p* value**
	n (% or IQR)		
Age, median (IQR)	30.9 ± 10.0	26.5 ± 6.0	0.060
Male, n(%)	22 (100.0)	99 (100.0)	—
MSM/bisexual, n(%)	21 (95.5)	89 (89.9)	0.825
Heterosexual, n(%)	1 (4.6)	7(7.1)	0.825
HBsAg(+)	2 (9.1)	3 (3.2)	0.955
Anti-HCV(+)	0 (0.0)	3 (3.2)	0.535
Anti-HAV(+)	1 (25.0)	2 (9.1)	0.360
Baseline CD4, median (IQR)	258 (158-405)	273 (181-411)	0.607
Baseline PVL, median (IQR)	6.48 (6.18-7.00)	6.15 (5.79-6.71)	0.033
Feibig stage			0.107
stage I	0 (0.0)	4 (5.7)	
stage II	2 (10.5)	3 (4.2)	
stage III	5 (26.3)	11 (15.3)	
stage IV	11 (57.9)	54 (75.0)	
stage V	1 (5.3)	0 (0.0)	
HAART			
NRTI+NNRTI	14 (63.6)	54 (54.6)	0.437
NRTI+PI	5 (22.7)	1 (1.0)	<.0001
NRTI+II	1 (4.6)	5 (5.1)	1.000

Table 2. Clinical Symptoms (week 24 logPVL > 0 comparison)

	Poor-controlled (week 24 logPVL > 0) (n =22)	Well-controlled (week 24 logPVL = 0) (n = 99)	*p* value
	n (%)		
Fever	21 (95.5)	83 (83.8)	0.156
Skin rash	7 (31.8)	36 (36.4)	0.687
Pharyngitis	16 (72.7)	56 (56.6)	0.163
Lymphadenopathy	7 (31.8)	16 (16.2)	0.091
Myalgia	13 (59.1)	35 (35.4)	0.040
Headache	6 (27.3)	26 (26.3)	0.923
Diarrhea	4 (18.2)	26 (26.3)	0.427
Arthralgia	2 (9.1)	4 (4.0)	0.324
Cough	4 (18.2)	17 (17.2)	0.910
Nausea	5 (22.7)	22 (22.2)	0.959
Fatigue	11 (50.0)	46 (46.5)	0.764
Vomiting	1 (4.6)	13 (13.1)	0.255
Weight loss	5 (22.7)	9 (9.1)	0.071
Genital ulcer	0 (0.0)	0 (0.0)	—
Oral ulcers	4 (18.2)	11 (11.1)	0.363
Aseptic meningitis	2 (9.1)	7 (7.1)	0.744
Night sweat	0 (0.0)	0 (0.0)	—
Syphilis	6 (27.3)	17 (17.2)	0.275
Gonorrhea	1 (4.6)	0 (0.0)	0.182
Chlamydia	0 (0.0)	0 (0.0)	—
Genital herpes	0 (0.0)	0 (0.0)	—
Condyloma	0 (0.0)	1 (1.0)	1.000

Table 3. Treatment outcomes (week 24 logPVL > 0 comparison)

	Poor-controlled (week 24 logPVL > 0) (n =22)	Well-controlled (week 24 logPVL = 0) (n = 99)	*p* value
	Median, (IQR)		
Log PVL			
Baseline	6.48 (6.18-7.00)	6.15 (5.79-6.71)	0.033
Week 4	3.56 (3.00-4.03)	3.12 (2.34-3.57)	0.018
Week 16	2.36 (1.81-2.75)	1.32 (0.00-2.09)	0.001
Week 24	2.00 (1.46-3.96)	0.0 (0.0-0.0)	<0.001
Week 36	1.69 (1.46-3.77)	0.0 (0.0-0.0)	<0.001
Week 48	0.0 (0.0-1.66)	0.0 (0.0-0.0)	—
CD4			
Baseline	258 (158-405)	273 (181-411)	0.607
Week 4	523 (356-653)	564 (443-669)	0.425
Week 16	606 (474-782)	609 (453-798)	0.906
Week 24	562 (397-773)	607 (467-726)	0.471
Week 36	665 (508-780)	688 (474-812)	0.871
Week 48	647(520-812)	605 (469-837)	0.928

Table 4-1. (week 24 logPVL > 0 comparison)

	Poor-controlled (week 24 logPVL > 0) (n =22)	Well-controlled (week 24 logPVL = 0) (n = 99)	*p* value
	Median, (IQR)		
Baseline	n=22	n=91	
WBC	4.36 (2.58-6.62)	4.83 (3.30-6.98)	0.374
Hb	13.8 (12.9-14.8)	14.2 (13.2-15.2)	0.361
PLT	185K (114K-280K)	175K (127K-244K)	0.604
Lymphocyte	37.0 (33.9-55.0)	30.1 (23.0-42.5)	0.090
T. Bililubin	0.7 (0.5-0.8)	0.6 (0.5-0.8)	0.973
AST	61 (33-101)	60 (27-134)	0.767
ALT	70 (44-98)	59 (28-141)	0.398
BUN	8.6 (7.0-9.0)	10.4 (8.5-13.0)	0.028
Cr	0.9 (0.7-1.0)	0.9 (0.8-1.0)	0.632
T.Cholesterol	148 (134-155)	130 (111-150)	0.394
TG	115 (111-276)	104 (67-131)	0.198
Week 4	n=6	n=17	
WBC	4.99 (4.55-6.30)	5.87 (4.84-6.51)	0.649
Hb	12.3 (11.2-13.1)	14.6 (14.1-15.2)	0.001
PLT	250K (234K-265K)	212K (205K-252K)	0.161
Lymphocyte	56.1 (38.6-66.4)	39.8 (31.4-44.5)	0.107
AST	24 (19-39)	16 (14-20)	0.285
ALT	37 (22-84)	19 (13-35)	0.285

Table 4-2.

	Poor-controlled (week 24 logPVL > 0) (n =22)	**Well-controlled (week 24 logPVL = 0) (n = 99)**	***p* value**
	Median, (IQR)		
Week 16	n=6	n=12	
WBC	6.95 (5.94-7.30)	5.73 (4.67-6.51)	0.160
Hb	14.5 (12.7-15.4)	15.2 (14.1-16.3)	0.260
PLT	237K (212K-286K)	227K (174K-261K)	0.454
Lymphocyte	37.7 (34.0-41.8)	38.1 (33.2-49.2)	0.574
T. Bililubin	0.5 (0.3-0.6)	0.5 (0.4-0.8)	0.664
AST	16 (15-19)	22 (19-23)	0.177
ALT	13 (12-19)	19 (16-26)	0.240
BUN	10.5 (9.5-12.0)	10 (9-13)	0.938
Cr	0.8 (0.7-1.2)	0.9 (0.8-0.9)	0.683
Week 24	n=7	n=10	
WBC	5.32 (4.75-7.20)	5.65 (4.58-6.61)	0.626
Hb	14.5 (13.8-15.4)	15.1 (14.7-16.1)	0.071
PLT	221K (154K-239K)	250K (206K-269K)	0.205
Lymphocyte	42.4 (35.8-51.5)	34.2 (27.8-39.0)	0.143
T. Bililubin	0.6 (0.4-0.7)	0.5 (0.3-0.5)	0.453
AST	17 (15-22)	20 (15-25)	0.769
ALT	20 (15-23)	24 (15-35)	0.590
BUN	14 (13-16)	12 (11-14)	0.083
Cr	0.9 (0.8-1.0)	0.9 (0.8-0.9)	0.338
T.Cholesterol	159 (116-201)	182 (180-206)	0.439
TG	121 (77-164)	111 (101-140)	1.000

Table 4-3.

	Poor-controlled (week 24 logPVL > 0) (n =22)	**Well-controlled (week 24 logPVL = 0) (n = 99)**	***p* value**
	Median, (IQR)		
Week 36	n=5	n=5	
WBC	6.71 (6.07-6.99)	5.44(4.51-6.71)	0.530
Hb	15.3 (13.5-16.0)	15.5 (15.4-15.8)	0.530
PLT	240K (222K-268K)	233K (191K-241K)	0.602
Lymphocyte	39.6 (38.5-46.3)	40.6 (40.6-48.6)	0.346
T. Bililubin	0.5 (0.4-0.7)	0.6 (0.4-0.8)	0.666
AST	17 (13-18)	20 (19-21)	0.128
ALT	14 (12-15)	20 (17-24)	0.120
BUN	14 (14-18)	12 (10-13)	0.254
Cr	0.8 (0.6-0.9)	0.9 (0.9-0.9)	0.833
T.Cholesterol	140 (127-169)	154 (147-176)	0.289
TG	194 (52-233)	67 (61-136)	0.724
Week 48	n=6	n=5	
WBC	6.38 (6.25-6.96)	5.62 (4.33-5.87)	0.144
Hb	15.2 (13.6-16.0)	14.7 (14.4-15.3)	0.715
PLT	238K (191K-264K)	253K (178K-281K)	1.000
Lymphocyte	37.8 (35.8-41.4)	34.7 (22.7-41.4)	0.522
T. Bililubin	0.6 (0.6-0.8)	0.4 (0.3-0.5)	0.766
AST	17 (16-19)	21 (19-23)	0.228
ALT	17 (12-17)	21 (14-51)	0.219
BUN	12 (12-15)	14 (12-16)	0.902
Cr	0.8 (0.8-0.9)	0.9 (0.8-0.9)	0.796
T.Cholesterol	174 (144-204)	166 (146-231)	1.000
TG	74 (64-84)	91 (73-380)	0.355

Table 5-1. Logistic Regression (Poor-controlled : week 24 logPVL > 0)

	Univariate Regression Crude-OR	*p* value
	Odds Ratio (95% CI)	
Age	1.08 (1.02-1.15)	0.013
HBsAg(+)	3.07 (0.48-19.6)	0.236
Baseline CD4	0.96 (0.84-1.11)	0.561
Baseline logPVL	2.32 (1.06-5.82)	0.035
Baseline BUN	0.84 (0.69-1.02)	0.080
Week 4 Hb	0.15 (0.03-0.71)	0.017
Myalgia	2.64 (1.03-6.79)	0.044

Table 5-2. Multivariate Logistic Regression (Poor-controlled : week 24 logPVL > 0)

	Univariate Regression Crude-OR	*p* value	Multivariate Regression Adjusted-OR	*p* value
	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Age	1.08 (1.02-1.15)	0.013		
HBsAg(+)	3.07 (0.48-19.6)	0.236		
Baseline CD4	0.96 (0.84-1.11)	0.561		
Baseline logPVL	2.32 (1.06-5.82)	0.035		
Baseline BUN	0.84 (0.69-1.02)	0.080		
Week 4 Hb	0.15 (0.03-0.71)	0.017	0.22 (0.05-0.90)	0.035
Myalgia	2.64 (1.03-6.79)	0.044		

Figure 1. logPVL trends of each HIV-diagnosed Year Groups

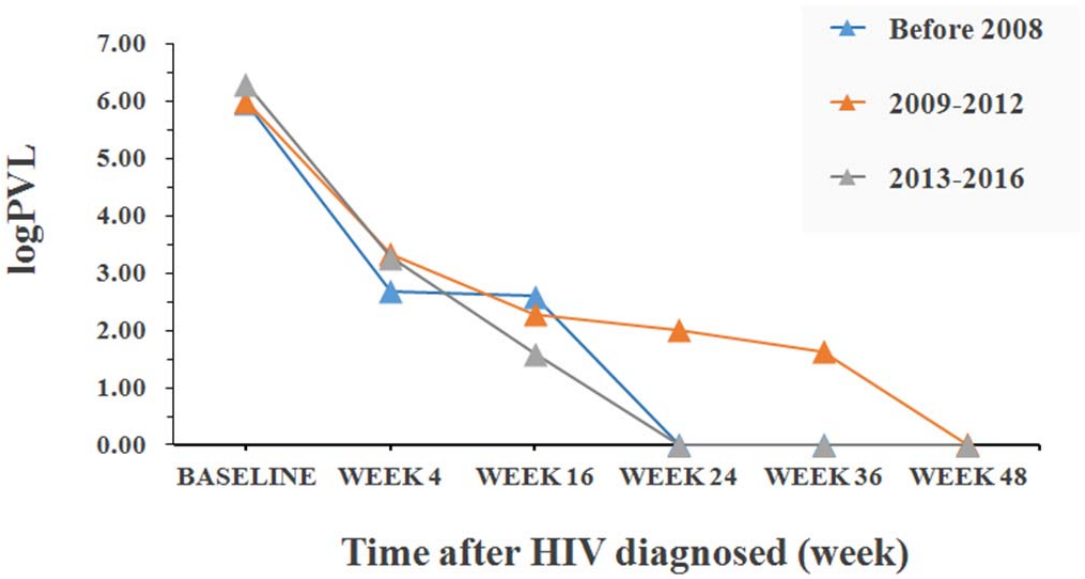
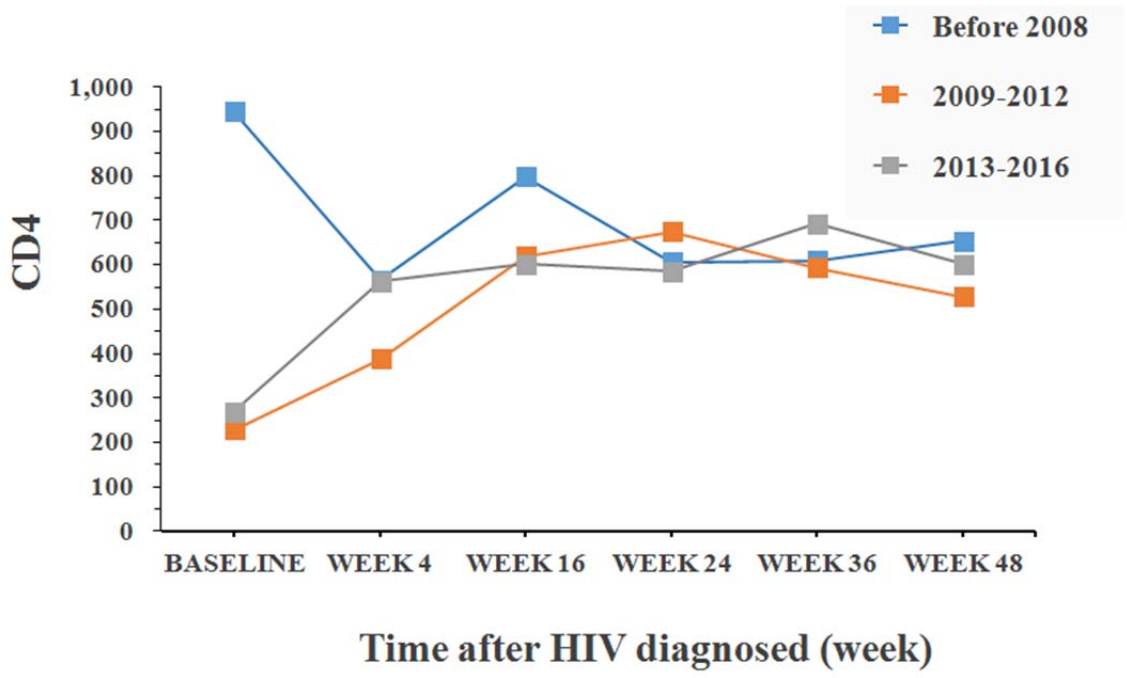


Figure 2. CD4 trends of each HIV-diagnosed Year Groups



附件七

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

抗人類免疫缺乏病毒藥品處方使用規範效果分析

年 度 研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：蔡茂松、張君俞、巫沛瑩、
劉玟君、楊上平、廖敏伶

執行期間： 105 年 1 月 1 日至 105 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: 抗愛滋病毒藥物、副作用、成效分析

後天免疫缺乏症候群自從 1981 年在美國發現以來，已成為二十一世紀重要的公共衛生問題，我國衛生署的統計資料顯示，截至 2012 年八月全台灣本國籍 HIV 累積感染人數已經達到 23,474 人，存活者有 19,817 人，感染者存活時間延長使得累積存活人數增加，其中有效的雞尾酒療法(combination antiretroviral therapy, cART)更是其中的關鍵因素，藥物治療大幅地降低了病患發生伺機性感染（opportunistic infections）和腫瘤的機會與致死的風險。

我國自 1988 年起，政府預算提供感染者免費藥物治療， 1998 年起則由健保局依重大傷病給付，2006 年起愛滋感染者的治療及藥費，改由衛生署疾病管制局每年編列公務預算支應。依據中央健保局統計，2000 年愛滋感染者醫療費用為四億五千多萬元，2010 年全年愛滋經費支出大幅增加至 22 億。

因此，疾病管制局訂定「抗人類免疫缺乏病毒藥品處方使用規範」，並公告自 101 年 6 月 1 日起實施，以同療效但價格相對較低的處方作為優先選擇，對於 101 年 6 月 1 日後首次服藥病患，應優先開立第一類處方；若個案因生理因素不適用第一類處方者，才選擇第二或第三類處方。第二類處方或第三類處方之使用。若需使用每月藥價超過 20,500 元之第四類處方者，則必須向疾病管制局申請事前審查。

然而過去四年(2012/6~2016/8)的時間納入 1,087 位首次服藥病患，針對藥物副作用發生率與嚴重程度、抗藥性的型態有初步的分析，發現起始處方的選擇與之後更動處方存在相關性，使用第一類處方（59%）與第三類處方（64%），含卡貝茲的組合，有較高的機會需要更動處方，使用第二類（29%）及第四類處方（25%）作為起始處方者，有較低的比例需要更動處方，達統計學上顯著的差異。

考慮治療效果、藥物副作用發生率與嚴重程度、抗藥性的型態，過去規範對於病人用藥安全及耐受性有其侷限。然而最新處方使用規範自 2016/6/1 起實施，根據實證醫學，將三種每日一次安全且有效複方藥品舒發錠（Atripla）、康普萊（Complera）及三恩美（Triumeq）列為第一線推薦處方，隨著各指定醫院採購及進藥，新規範效果值得繼續追蹤。

貳、英文摘要：請摘述本計畫之目的與實施方法及關鍵詞

keywords：Antiretroviral therapy, Adverse effect, Cost and effectiveness

To curb the increasing medical cost for HIV care, Taiwan Centers for Disease Control (CDC) implemented regulations on combination antiretroviral therapy (cART) according to the monthly cost for each regimen on 1 June 2012. By following the regulations, many individuals commence thymidine analogue (TA)-based regimens. Prior authorization is needed for the regimens containing protease inhibitors (PIs), integrase inhibitors (IIs), or rilpivirine (RPV) plus non-thymidine analogue backbones [abacavir/lamivudine (ABC/3TC); tenofovir disoproxil fumarate /emtricitabine (TDF/ or TDF plus 3TC].

During the 48-month study period, 1,087 patients with baseline median CD4 count of 282 cells/μL and plasma HIV RNA load (PVL) 4.85 log10 copies/ml initiated cART. Overall, 61% had to change the initial regimens at a median interval of 41 days (range, 1 to 1140). The rates of regimens modification for drug-related adverse reactions were 59%, 29%, 64% and 25% in patients on the first, second, third, and fourth category of regimens, respectively.

A significant proportion of patients on cART regimens, especially the regimens containing TA backbone that were prescribed by following the regulations of Taiwan CDC had to be changed due to toxicities, transmitted drug resistance, or unsatisfactory virological response.

After 1 June 2016, Taiwan CDC decalred the major revision of drug formulary management. Three less toxic, more convenient and simplified once-daily fixed-dose combinations, TDF/FTC/EFV, TDF/FTC/RPV, and ABC/3TC/Dolutegravir (DTG) are the preferred first-line ART regimens while the regimens containing PIs or IIs, plus thymidine analogue backbones, ABC/3TC plus EFV, and TDF/FTC (+3TC) plus NVP are alternative first-line ARV regimens. Prior authorization is needed for the regimens with higher cost as second-line regimens.

The regimens recommended by Taiwan CDC this year are better and more tolerable formulations to support successful treatment and are suitable for a larger proportion of patients. We aimed to describe the outcome of the regimens prescribed by following the revised regulations in Taiwan.

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，依據聯合國愛滋病組織(Joint United Nations Programme on HIV/AIDS; UNAIDS)的資料發現雖然新增愛滋病毒(human immunodeficiency virus, HIV)感染人數似乎有緩慢下降的趨勢，愛滋病死亡的人數在 2005 年達到高峰亦逐漸下降，然而愛滋病毒感染者的存活人數正逐年增加中，2010 年估算約有 3,400 萬人存活，相較於 2001 年的統計增加了 17%，根據我國衛生署的統計資料顯示，截至 2012 年八月全台灣本國籍 HIV 累積感染人數已經達到 23,474 人，存活者有 19,817 人，感染者存活時間延長是導致累積存活人數快速增加的主因，有效的雞尾酒療法(combination antiretroviral therapy, cART)更是其中的關鍵因素，藥物治療大幅地降低了病患發生伺機性感染（opportunistic infections）和腫瘤的機會與致死的風險[1, 2]。

我國自 1988 年起，政府預算提供感染者免費藥物治療，1997 年 4 月開始提供感染者免費雞尾酒療法，1998 年起則由健保局依重大傷病給付，2006 年起愛滋感染者的治療及藥費，改由衛生署疾病管制局每年編列公務預算支應，愛滋病毒感染對於接受治療的病患來說，已不是 20 世紀的黑死病，目前長則二十幾年的存活時間使得愛滋病儼然為一慢性疾病。 依據中央健保局統計，2000 年愛滋感染者醫療費用為四億五千多萬元，每位感染者平均花掉一年 35 萬元藥費，為一般民眾醫療花費的 100 倍，在 2010 年全年愛滋經費支出更大幅增加至 22 億。

由於公務預算有限且醫療費用呈現嚴重赤字，為以有限的公務預算讓所有的感染者都能得到最基本的醫療照顧的權益，疾病管制局訂定「抗人類免疫缺乏病毒藥品處方使用規範」，並公告自 101 年 6 月 1 日起實施，以同療效但價格相對較低的處方作為優先選擇，對於 101 年 6 月 1 日後首次服藥病患，應優先開立第一類處方；若個案因生理因素不適用第一類處方者，才選擇第二(例如不宜使用 zidovudine 者）或第三類處方(例如不宜使用非核苷酸反轉錄酶抑制劑者)。第二類處方或第三類處方之使用。若前三類處方均不適用，而需使用每月藥價超過 20,500 元之第四類處方者，則必須向疾病管制局申請事前審查 (表一)。

在英國已經有研究證實比較不同種類的藥物搭配做為第一線治療，核苷酸反轉錄酶抑制劑加上非核苷酸反轉錄酶抑制劑相較於核苷酸反轉錄酶抑制劑加上蛋白質酶抑制劑，的確能達到降低醫療支出的目的[3]；但也有研究指出在考慮抗藥性及治療失敗因素下，使用較昂貴的核苷酸反轉錄酶抑制劑 tenofovir 相較於舊藥 zidovudine 做為第一線其實是較合乎成本效益的治療選擇[4]；在南非的成本效益研究認為在選擇核苷酸反轉錄酶抑制劑上，應避免 starvudine，至於 tenofovir 與 zidovudine 的比較，雖然治療效果上 tenofovir 優於 zidovudine，但費用上以 zidovudine 較為低廉[5]；美國的研究發現，以成本效益的觀點 abacavir 的第一線治療上可以作為 tenofovir 的替代選擇[6]。

然而，過去四年(2012/6~2016/5)的觀察，納入 1,087 位首次服藥病患，針對藥物副作用發生率與嚴重程度、抗藥性的型態的分析，61%的病患因為副作用(過敏，貧血，肝炎或腸胃道不適)及抗藥性需要更動至少一次的處方，發現起始處方的選擇與之後更動處方存在相關性，使用第一類處方（59%）與第三類處方（64%），含卡貝茲的組合，有較高的機會需要更動處方，使用第二類（29%）及第四類處方（25%）作為起始處方者，有較低的比例需要更動處方，達統計學上顯著的差異。

抗病毒藥物費用在疾病管制署的努力下價格均有不同程度的下降，特別是卡貝茲降幅逾 70%，但臨床的方便性及耐受性卻不如其他不含卡貝茲的組合（第二類及第四類處方）。

因應世界衛生組織(WHO)發布最新愛滋治療指引，疾病管制署參考 WHO、美國及歐盟建議，重新修訂「抗人類免疫缺乏病毒藥品處方使用規範」(表二)，兼顧費用及藥物特性，將處方分類且正名為[第一線推薦處方]、[第一線替代處方]及[第二線處方]，於 2016 年 6 月 1 日起生效。新版處方使用規範將每日一次且副作用低的三種三合一複方藥品列為「第一線推薦處方」，若無使用禁忌優先使用，預期此規範有助於提升服藥順從性。

本研究欲延續過去的資料，持續提供實施 2016 年版「抗人類免疫缺乏病毒藥品處方使用規範」後首次服藥病患的臨床資料，作為未來分析的依據。

（二）材料與方法

1. 研究設計: 多中心觀察性研究
2. 研究對象: 101 年 6 月 1 日後首次服藥病患
   a. 納入條件: 大於十八歲以上於感染科門診追蹤之 HIV 感染患者
   b. 排除條件: 已知懷孕或即將懷孕的婦女、肝硬化、癌症、慢性腎臟病患、多發性硬化患者、懷孕女性、使用類固醇或免疫抑制劑之患者及過去曾經因為任何原因使用雞尾酒藥物者
   c. 資料收集
      (1) 詢問並紀錄病患系統性疾病病史、因任何疾病住院治療、疫苗注射史、抽菸、飲酒習慣、接受其他藥物治療或使用其他藥品或物質
      (2) 我們也會調閱病患的病歷資料
      (3) 病患將依據國內外治療指引，建議於基礎值、用藥後兩周、四到六周與之後每三到六個月接受抽血檢驗，建議檢驗項目如下表

建議血液檢查及時程

	基礎值	二周	四到六周	八周	三個月	六個月
genotypic drug resistance testing	V					
CD4	V		V		V	V
Complete blood count with differential	V	V	V	V	V	V
Plasma viral load	V		V		V	V
Serum liver enzymes: AST ALT	V	V	V		V	V
Blood urea nitrogen/creatinine	V	V			V	V
Serologic tests for syphilis: VDRL/RPR, TPHA	V				V	V
Anti-HAV	V					
HBsAg, anti-HBs, HBc	V					
HCV antibody test (e.g., EIA/ELISA)	V					V
Lipid profile	V					V

(1) 紀錄病患抽血檢查的結果

(2) 紀錄病患使用雞尾酒藥物發生過敏反應的時間與嚴重程度

(3) 紀錄病患使用雞尾酒藥物發生肝炎的時間與嚴重程度

(4) 紀錄病患發生雞尾酒藥物其他相關副作用的時間與嚴重程度

(5) 紀錄病患因各種原因需更換初始雞尾酒藥物的時間及更換後的藥物種類

d. 資料分析

所有的資料收集後，以 Excel 應用程式彙整完成後，以統計軟體 SAS 9.4 版本，先以描述性統計方法分析樣本的基本資料。之後進行卡方檢定(Chi-square)分析，比較不同藥物組合下，影響的各樣結果的因子，採雙尾檢定 p 值＜0.05 為具有統計學上的意義，以多元迴歸邏輯(multiple logistic regression)中逐步回歸的方法找出有顯著差異的變項，並以統計方法中的殘差分析、影響力分析、以及多元共線性分析去檢定統計結果的正確性。

（三）結果

自 2012 年 6 月(實施抗人類免疫缺乏病毒藥品處方使用規範)後，目前總共陸續收集 1,125 位 HIV 病毒感染者開始使用抗人類免疫缺乏病毒藥物，其中 97.2%為男性，年齡中位數[median (IQR)]為 31.0(26.4-37.6)歲，開始接受抗病毒藥物治療前，平均 CD4 淋巴球數[median (IQR)]為 288.8 (146.9-399.1) cells/ul，平均病毒量[median (IQR)]為 4.84 (4.41-5.27) log10 copies/mL。

1,125 位使用抗病毒藥物病患中 31.6%(356)使用第一類處方，62.1%(699)使用第二類處方，2.8%(31)使用第三類處方，3.5%(39)需使用第四類處方，於 2016/6/1 後起始治療有 31 人，27 人使用第二類處方，1 人使用第三類，3 人使用第四類。

1,125 位使用抗病毒藥物病患中 65.2%(677)會至少更動一次處方，開始使用到更動處方時間間隔為[median (IQR)] 38(14-209)天，其中 20.8%(139)是因為臨床懷疑是藥物過敏相關的皮疹，13.4%(90)因為抗病毒藥物相關神經精神副作用而換藥，8.5%(57)產生無法忍受的腸胃道不適而更替藥物，10.5%(70)的病患因為血紅素下降/白血球低下而換藥，值得注意的是 10.5% (70)因為治療效果不如預期或是藥物的抗藥性(genotypic resistance)而改變處方，35.0%(236)則因為服藥方便性(藥物顆粒數和服藥次數)更替處方。

使用卡貝茲(combivir, zidovudine+ lamivudine)超過 28 天的病患，平均血紅素相較於基礎值下降 1.5 g/dL (95% CI. 0.9~2.1)達統計學上的意義。

扣除單純因為服藥方便性而更動藥物者有 441 人，起始處方的選擇與之後持續處方具有統計的相關性，治療後的一年內使用第一類處方作為起始處方之後有 54.8%需要更動處方，使用第二類處方作為起始處方之後有 27.9%需要更動處方，使用非第三類處方作為起始處方之後有 58.0%需要更動處方，使用第四類處方作為起始處方之後有 37.1%需要至少更動一次處方，四組之間有統計學上顯著的差異(Log-Rank p <0.001)。

（四）討論

研究結果顯示，使用含有卡貝茲的起始處方，有超過一半的病人需要更動處方，考慮治療效果、藥物副作用發生率與嚴重程度、抗藥性的型態，舊有規範對於病人的用藥安全效果、臨床治療效果、符合病患服藥的方便性及順從性等議題需要有其他更好的調整，唯因醫院採購及進藥程序，至 2016/9 始備齊第一線處方，此研究尚無法瞭解新規範對於治療效果的影響。

2015 年 HIV 患者的醫療費用約為 35 億新台幣，其中大部分費用歸咎於抗病毒藥物。為了控制醫療成本的上升，2011 年起，疾管署開始了多項醫療費用控制對策，包括藥物處方管理(drug formulary management)，價格談判(price negotiation)和批量採購(bulk purchasing)。費用增長率從 2014 年的 2.2%降至 2015 年的 0.5%，而同時治療人數增加 15%

此規範為 2012 年中開始實施，WHO 於 2013 年更改愛滋病治療指引，而近年來有越來越多的研究開始考慮簡化藥物的方式，除了藥物的可能副作用外，減少藥物種類的另一項好處是減少藥物的費用，而未來的 1-2 年內許多藥物的專利期即將終止，在學名藥的競爭，藥物的價格可望大幅下降，我國未來的治療指引，在治療選擇與藥物價格的抉擇中，將更具彈性。

(1) 結論與建議

病患對於藥物組合的臨床耐受性有所不同，參考 WHO 於 2013 年的治療建議及 2015 訂定的治療目標，Combivir 做為國內的治療選擇必須配合臨床工作人員注意相關的副作用，而一日兩次的服藥對於病患的服藥順從性是一大考驗，新的治療規範已有大幅度的修改，有待日後更長時間追蹤及更多的病患納入分析。

（五）重要研究成果及具體建議

Poster 14th European AIDS Clinical Society, Brussels, 16-19 Oct 2013

Poster HIV Glasgow, 23-26 October 2016

2016 年 6 月實施修正後的「愛滋藥品使用規範」，期待新的處方規範能提高台灣愛滋病毒感染者的醫療品質，在未來持續觀察臨床反應能及時回饋已達到 90-90-90 的目標。

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（柒）圖表

表一、各類處方之使用規範詳如下表：101 年 6 月 1 日公告

類別	處方(藥物品項)	每月藥價	使用規範
一	Combivir+NVP	15,324	無藥物禁忌症之首次服藥病患優先處方。
	Combivir+EFV	16,992	
二	Viread＋3TC＋NVP	17,262	醫師應於病歷記載使用該類處方之適應症或不宜使用 AZT 之原因。
	Viread ＋3TC＋EFV	18,564	
	Kivexa＋NVP	18,930	
	Kivexa＋EFV	20,232	
三	Combivir+Kaletra	19,550	醫師應於病歷記載使用該類處方之適應症或不宜使用 NNRTI 之原因。
	Combivir+Prezista/r	19,551	
	Combivir+ATV(300)/r	19,551	
	Combivir+ATV(400)	19,554	
四	常見之每月超過 20,500 元之處方如下：		須事前審查。（公告日前已使用該類處方者，需提報備查；公告日後之新使用者，需經審查通過才能使用。）
	Viread+3TC+Kaletra	21,488	
	Viread+3TC+Prezista/r	21,489	
	Viread+3TC+ATV(300)/r	21,489	
	Viread+3TC+ATV(400) 【註 4】	21,492	
	Combivir+Isentress	22,212	
	Kivexa+kaletra	22,790	
	Kivexa+Prezista/r	22,791	
	Kivexa+ATV(300)/r	22,791	
	Kivexa+ATV(400)	22,794	
	Viread+3TC+Isentress	24,150	
	Kivexa+Isentress	25,452	

表二、修正「愛滋藥品使用規範」，自 2016 年 06 月 01 日實施

第一線推薦處方(Recommended First Line)
TDF/FTC/EFV TDF/FTC/RPV ABC/3TC/DTG(自取得健保代辦核定藥品價格日起生效)
第一線替代處方(Alternative First Line)
AZT/3TC+EFV AZT/3TC/NVP or AZT/3TC+NVP[IR or XR] AZT/3TC+RPV AZT/3TC+LPV/r AZT/3TC+ATV(300)+r AZT/3TC+DRV(800)+r AZT/3TC+RAL AZT/3TC+DTG(50) AZT/3TC+MVC ABC/3TC+EFV TDF/FTC+NVP[IR] TDF+3TC+NVP[IR]
注意事項： 一、本規範將依預算核給、藥品上市及藥價調整情形適時檢討。 二、斜線/表示複方，(數字)表示每日劑量。各藥品成分簡稱、學名及商品名之對照表後附。 三、若無醫療相關使用禁忌，優先使用「第一線推薦處方」。第一線推薦處方須為(含)方、每日服用一次、WHO/DHHS/EACS 優先推薦且藥價在 13,999 元/月以下者。 四、本規範中「第一線替代處方」僅列出常用處方組合，其他藥價在 15,500 元/月以之處方組合，使用前皆無須事前審查。 五、「第二線處方」為藥價 15,500 元/月以上之處方組合，使用前皆須事前審查（請參「第二線抗人類免疫缺乏病毒藥品事前審查作業」)。 六、疾病管制署不給付 CCR5 趨性試驗之檢驗及相關費用。 七、個別藥物之適用狀況，請參考專業學會建議。

附件八

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

台灣、日本與香港男同志間新發 C 型肝炎病毒分子流行病學研究

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：洪健清

研 究 人 員：張淑媛、孫幸筠、劉玟君

執 行 期 間：105 年 1 月 1 日至 105 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

頁碼

共 (15) 頁

壹、中文摘要

目的：本研究指在藉以分子生物學方式,針對香港日本和台灣三地，針對近期或急性 C 型感染的男同性戀族群所收集到的 HCV 病毒株，進行 HCV 亞型分型和檢視這些病毒株間的親緣關係。

方法：研究人員回溯本院 2011-2015 年間合併發生近期或急性 C 型肝炎感染之愛滋感染者資料,近期或急性 C 型肝炎感染定義為 C 型肝炎抗體在一年內陰性轉陽性結果，而定義陰轉陽時間點為最後一次 C 型肝炎抗體陰性時間點與第一次 C 型肝炎抗體陽性時間點的平均時間點，進而可計算出每年近期或急性 C 型肝炎在愛滋感染者中的發生率。本研究中僅納 15 歲以上感染者，且感染途徑為異性間性行為或同性間性行為者，排除靜脈毒癮感染者或不清楚感染途徑者。收案期間從 2011/1/1 起，因考慮檢驗空窗期，每位受試者觀察至 2016/4/30 止。除了 C 型肝炎的抗體血清學反應之外，我們也會分析年齡、性別、感染途徑、是否使用 HARRT、是否同時有其他病毒型肝炎感染或近期內是否有梅毒感染等變項，作為樣本在比較中的參考。合併近期或急性 C 型肝炎感染的感染者，我們並紀錄其 C 型肝炎病毒量、基因型種類、是否正服用 HARRT、基礎點 HIV 病毒量、CD4 數量及有無肝功能指數異常等。針對在 2010-2015 年間新進發生 C 型肝炎病毒傳染的男同性戀者，進行病毒亞型的分型和針對病毒的 NS5B 進行基因定序，將三地這些結果彙整，進行病毒間親緣關係分析。

結果：自 2011 年 1 月至 2015 年 12 月，發現 123 位 C 型肝炎病毒抗體陰轉陽，其中 90 位為近期或急性 C 型肝炎感染者,發生率為每 1,000 人年 10.8,各年發生率為 2011 年 5.46、2012 年 10.36、2013 年 11.48、2014 年 10.17、2015 年 11.85。與 2,406 位無合併 C 型肝炎感染者比較，90 位近期或急性 C 型肝炎感染者均為男性且年齡較輕（平均值 31.6 vs 35.8 years, P=0.0002），以同性間性行為傳染途徑居多（97.8% vs. 88.3%, P 值 0.0021），而且近期（在最後觀察時間點前 6 個月或 3 個月內）曾梅毒指數上升 4 倍或接受梅毒藥物治療的機率較高（67.8% vs. 11.3%, P 值<0.0001），但兩組在是否有 B 型肝炎帶原與是否使用 HARRT 的比例並無統計顯著。另外 90 位近期或急性 C 型肝炎感染者，曾經肝功能上升的比例居高,其中 90%的感染者曾 ALT ＞41 U/liter(平均值 333±366)。其基礎點的 C 型肝炎病毒量平均值為 5.5 $\log_{10}$ IU/mL，其中有 10 位基礎點 C 型肝炎病

毒量為< 3 $\log_{10}$ IU/mL。在病毒基因型中，以 2a 型最多（44%, 24/51）、其次為 1b（38%,21/51）。在藥物治療上，仍以傳統干擾素配合口服藥物為主，目前仍有 10 位尚在治療中，38 位已完成治療，有 28 位於停止治療後半年血中 HCV 病毒量持續陰性（SVR），但有 3 位感染者於 SVR 後病毒量再度被偵測到。

結論：於愛滋病毒感染者，提供定期 C 型肝炎抗體及其他性病檢驗，及及時提供 C 型肝炎及 HARRT 治療，是對於預防感染者進展為肝硬化或肝癌必要的措施。

關鍵詞：急性 C 型肝炎; 性病; 同性間性行為; 分子流行病學

貳、英文摘要

Objectives: 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.

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 Apr, 2016. The present study excluded HIV-infected injecting drug users (IDUs).

Results: During the 4-year study period, HCV seroconversion was diagnosed in 123 patients, including 90 fulfilling the diagnosis of recent or acute HCV infection, resulting in an incidence rate of 10.8 per 1000 person-years of follow-up. The incidence rate increased from 5.46 per 1000 PYFU in 2011, 10.36 per 1000 PYFU in 2012, 11.48 per 1000 PYFU in 2013, 10.17 per 1000 PYFU in 2014 to 11.85 per 1000 PYFU. Compared with 2046 HIV-positive patients who did not seroconvert for HCV, those 90 patients with recent or acute HCV seroconversions were significantly younger (31.6 years vs 35.8 years), more likely to be MSM (97.8% vs 88.3%), and recent syphilis (67.8% vs 11.3%). The mean baseline plasma HCV RNA load of the 90 patients was 5.5 $\log_{10}$ copies/ml. Genotypes 2a (44%, n=24), genotype 2b (38%, n=21) were the most common genotypes of the 51 strains available for genotyping.

Conclusions: The incidence of recent or acute HCV infection continued to increase over

the past 4 years, which occurred predominantly among MSM and was associated with recent syphilis. Genotypes 2a and 2b remained the most common genotypes in HIV-positive patients with acute or recent HCV infection.

關鍵詞：hepatitis C virus infection; sexually transmitted infection; men who have sex with men; molecular epidemiology

參、本文

（一）前言

近二十年來在歐洲，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(hepatitis C virus， HCV)傳染的發生率增加，特別是在男同性戀族群。流行病學的調查顯示粗暴的性行為、性病、娛樂性用藥等等似乎和 C 型肝炎病毒的傳播相關。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，發生群聚傳播的現象 [1-9]。

這樣的現象，在過去十多年間。在 2012 年台大醫院孫醫師等人發現，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[10]。 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 [11]。 台大醫院孫醫師等人進一步利用匿名篩檢的個案檢體檢測 C 型肝炎病毒，他們也發現在非愛滋病毒感染的匿名篩檢受檢者，自從 2006 到 2013 年間，C 型肝炎病毒感染從 2006-2009 年間每 1000 人年的 2.28 案例（95%CI，0.05-4.51）逐漸增加到 2010-2011 年間的每 1000 人年的 3.33 案例（95%CI，0.86-5.80）和 2012-2013 年間的每 1000 人年的 4.94 案例（95%CI，0.99-8.99）[12]。台大醫院的兩個研究，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。

同一個期間，日本和香港也都陸續注意到這現象。日本的研究顯示娛樂性用藥可能和 C 型肝炎病毒傳播相關[13]。 因此在多此次的國際會議中，我等與香港中文大學李瑞山教授和日本國立感染症研究所愛滋病中心主任 Sinichi Oka 教授討論後，我們一致認為，因為亞洲地區旅遊的熱潮，C 型肝炎病毒極有可能在三地的男同性戀者間，出現群聚感染的現象。因此，我們此次研究打算利用三地所收集到的 C 型肝病毒株進行亞型分型和分子流病學研究，藉以檢視是否此現象在亞洲地區發生，以做為臨床衛教和公共衛生政策參考。

（二）材料與方法

研究人員回溯本院2011-2015年間合併發生近期或急性C型肝炎感染之愛滋感染者資料，近期或急性 C 型肝炎感染定義為 C 型肝炎抗體在一年內陰性轉陽性結果，而定義陰轉陽時間點為最後一次 C 型肝炎抗體陰性時間點與第一次 C 型肝炎抗體陽性時間點的平均時間點，進而可計算出每年近期或急性C型肝炎在愛滋感染者中的發生率。本研究中僅納 15 歲以上感染者，且感染途徑為異性間性行為或同性間性行為者，排除靜脈毒癮感染者或不清楚感染途徑者。收案期間從 2011/1/1 起，因考慮檢驗空窗期，每位受試者觀察至 2016/4/30 止。除了 C 型肝炎的抗體血清學反應之外，我們也會分析年齡、性別、感染途徑、是否使用 HARRT、是否同時有其他病毒型肝炎感染或近期內是否有梅毒感染等變項，作為樣本在比較中的參考。合併近期或急性 C 型肝炎感染的感染者，我們並紀錄其 C 型肝炎病毒量、基因型種類、是否正服用 HARRT、基礎點 HIV 病毒量、CD4 數量及有無肝功能指數異常等。

另外將與本院肝膽腸胃科劉振驊醫師合作，在取得本院倫理委員會同意後，針對在2010-2015年間新進發生C型肝炎病毒傳染的男同性戀者，進一步收集劉振驊醫師另一研究案之剩餘檢體，進行病毒亞型的分型和針對病毒的NS5B進行基因定序，定序方式如下：

I. A 336-bp fragment covering partial HCV NS5B (nucleotides [nt] 8294 to 8629 relative to HCV reference strain H77) was amplified by PCR. The PCR conditions are briefly described below.

   The first primer pair used was NS5B_513 (5' -CCA ATW SMCACN ACC ATC ATG GC-3') and aNS5B_1200 (5'-GAN ACR TTK GAK GAR CAW GAT GT-3').

   The amplification conditions were 30 cycles of 94°C for 30 seconds, 55°C for 1 minute, and 72°C for 2 minutes and a final extension at 72°C for 7 minutes.

   A 1-l aliquot of the first-round PCR product was used for the second-round PCR under conditions that were the same as those used for the first round.

   The second primer pair used was NS5B_755 (5 '-TAT GAY ACC CGC TGY TTT GAC TC-3') and aNS5B_1121 (5' -GCN GAR TAY CTV GTC ATA GCC TC-3').

II. The PCR results were sequenced. The study and reference sequences were aligned using the Clustal W program with minor manual adjustment.

III. The tree was constructed by the neighbor-joining method based on the Kimura 2-parameter distance matrix listed in MEGA software (version 3.0)

由三地各自所收集到的C型肝病毒株進行亞型分型和分子流病學研究，最後將這些結果彙整，進行病毒間親緣關係分析，藉以檢視是否此現象在亞洲地區發生。

（三）結果

自 2011 年 1 月至 2015 年 12 月，共計 3,483 位 15 歲以上的愛滋病毒感染者至台大醫院就診，排除 29 位沒有基礎點 C 型肝炎病毒抗體報告、240 位 2011 年後無追蹤 C 型肝炎病毒抗體報告、369 位於 2011 年前 C 型肝炎病毒抗體陽性及 316 位感染途徑為靜脈毒癮者或不清楚，納入 2,529 位基礎點 C 型肝炎病毒抗體陰性且有至少一次的抗體追蹤檢測者進入研究（圖一）。

研究期間發現 123 位 C 型肝炎病毒抗體陰轉陽，其中 90 位為近期或急性 C 型肝炎感染者，發生率為每 1,000 人年 10.8，各年發生率為 2011 年 5.46、2012 年 10.36、2013 年 11.48、2014 年 10.17、2015 年 11.85（圖二）。

與 2,406 位無合併 C 型肝炎感染者比較，90 位近期或急性 C 型肝炎感染者均為男性且年齡較輕（平均值 31.6 vs 35.8 years, P=0.0002），以同性間性行為傳染途徑居多（97.8% vs. 88.3%, P 值 0.0021），而且近期（在最後觀察時間點前 6 個月或 3 個月內）曾梅毒指數上升 4 倍或接受梅毒藥物治療的機率較高（67.8% vs. 11.3%, P 值<0.0001），但兩組在是否有 B 型肝炎帶原與是否使用 HARRT 的比例並無統計顯著（表一）。另外在其它檢驗數據中可看出（表二），90 位近期或急性 C 型肝炎感染者，曾經肝功能上升的比例居高，其中 90%的感染者曾 ALT ＞41 U/liter（平均值 333±366）。

90 位近期或急性 C 型肝炎感染者中，基礎點的 C 型肝炎病毒量平均值為 5.5 $\log_{10}$ IU/mL，其中有 10 位基礎點 C 型肝炎病毒量為< 3 $\log_{10}$ IU/mL。在病毒基因型中，以 2a 型最多（44%, 24/51）、其次為 1b（38%,21/51）（圖三）。在藥物治療上，仍以傳統干擾素配合口服藥物為主，目前仍有 10 位尚在治療中，38 位已完成治療，有 28 位於停止治療後半年血中 HCV 病毒量持續陰性（SVR），但有 3 位感染者於 SVR 後病毒量再度被偵測到。

（四）討論

目前研究成果與 2012 年孫醫師研究相似，從圖二中可看出非靜脈毒癮的愛滋病毒感染者，在確診後再感染 C 型肝炎仍持續發生，且自 2001 年後可看到發生率為增加的趨勢，至 2015 年更達每 1,000 人年 11.85；相關因子仍以同性間性行為者與近期有梅毒的感染為顯著因子，顯示目前近期或急性 C 型肝炎的愛滋病毒感染者，以不安全性行為為主要感染途徑，且疫情並無減緩的現象。

而比較 1994-2010 及 2011-2015 年兩階段近期或急性 C 型肝炎感染者臨床資料上的差別，可看到後者發現 C 型肝炎感染時年齡較輕（32 vs.42），且較多因為肝功能指數升高進而檢測出 C 型肝炎抗體，目前在疾管署檢驗指引建議愛滋病毒感染者每年定期檢驗一次 C 型肝炎抗體，但至本院就醫的愛滋病毒感染者仍有 7%僅有基礎點甚至從未檢測過，而研究顯示愛滋病毒感染者合併 C 型肝炎感染進展為肝硬化的時間較非滋病毒感染者快，因此應除鼓勵感染者接受定期檢驗外，如發生危險性行為後有肝功能指數上升或感染其他性病時，亦應主動告知照護醫護人員進行 C 型肝炎抗體檢測，以期提早發現。

在兩階段的病毒基因型中（圖三），均以 2a 基因型較多，目前健保給付仍以長效型干擾素及雷巴威林治療為主，若是第二型及第三型基因型 48 週治療的 SVR 有較高比例成功，而愛滋病毒感染者建議在 CD4>200 cells/μl 時治療，在我們的觀察中，有 73.6%的感染者達到 SVR，成功機率算是頗高，但仍可看到有 3 位感染者於治療後 C 型肝炎病毒量再度升高，推測應是再度感染。而是否藉由同性間的不安全性行為，發生群聚傳播的現象，甚至透過旅遊是否造成本國與日本、香港這些地區有群聚感染，研究目前仍由各地研究人員進行分析，待日後資料彙整後，檢視是否此現象在亞洲地區發生，以做為臨床衛教和公共衛生政策參考。

（五）結論

對政策之具體建議: 對於愛滋病毒感染者，提供定期 C 型肝炎抗體及其他性病檢驗，及及時提供 C 型肝炎及 HARRT 治療，是對於預防感染者進展為肝硬化或肝癌必要的措施。

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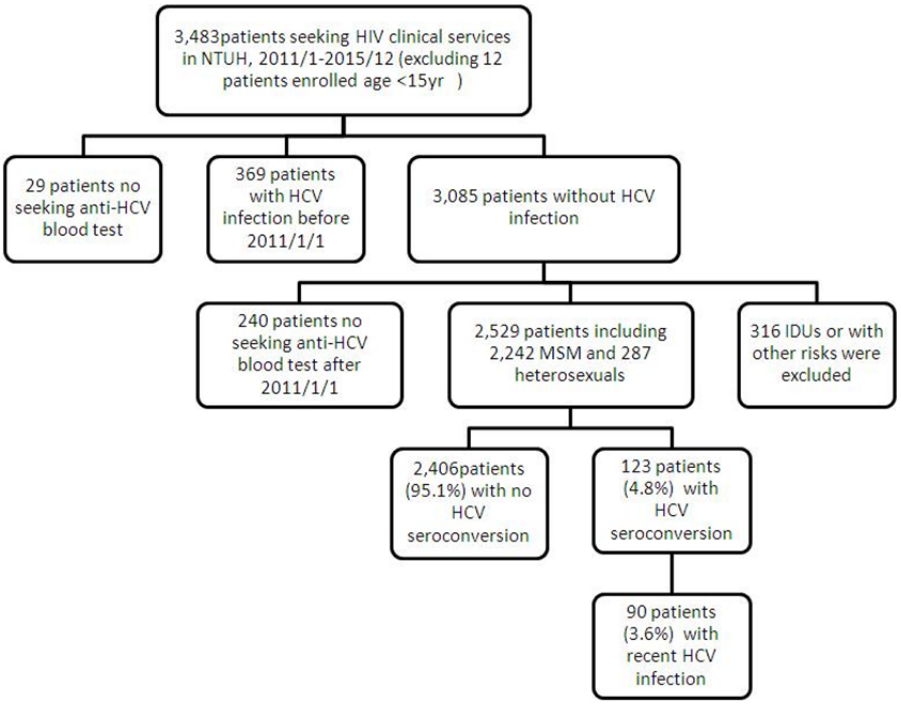
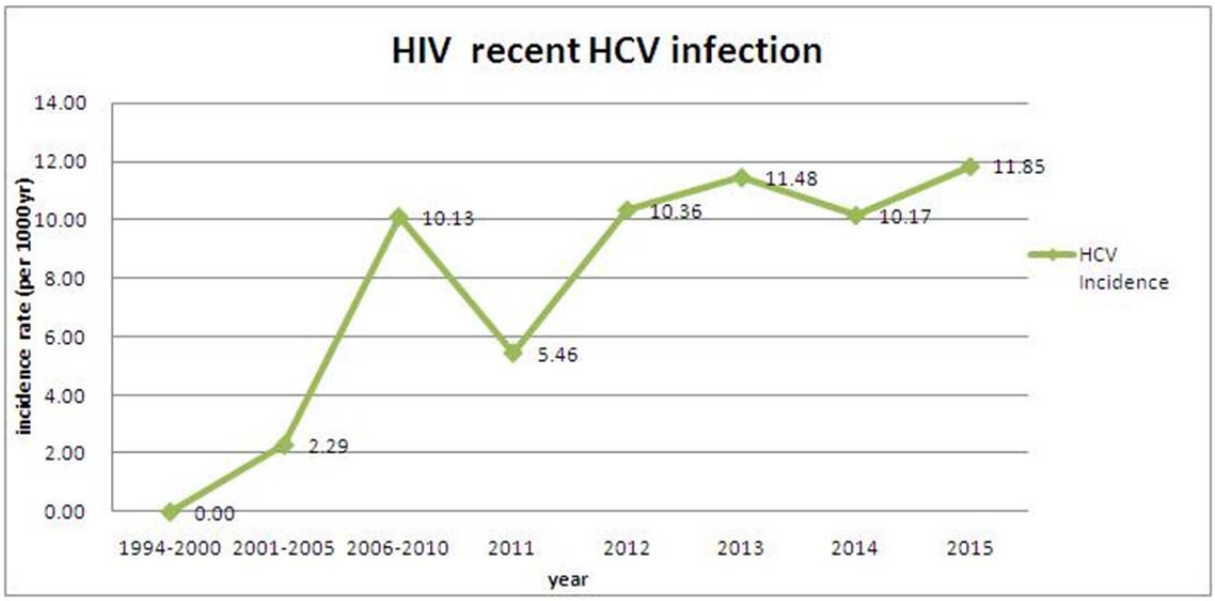
（七）圖表

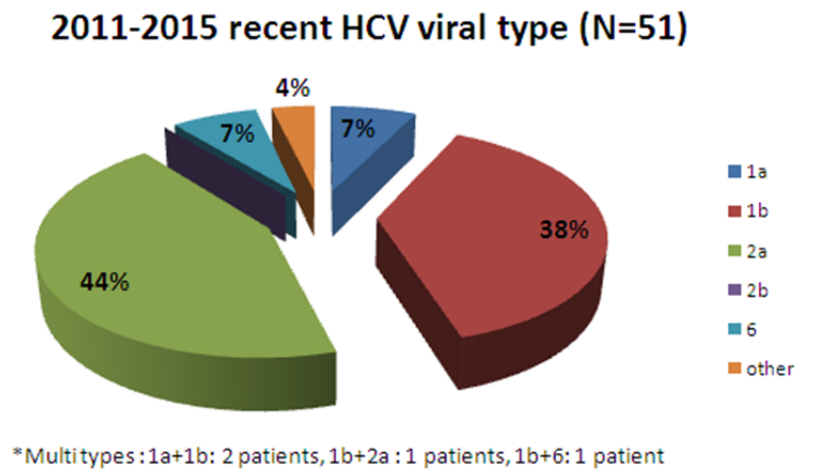
圖一、研究收案流程圖



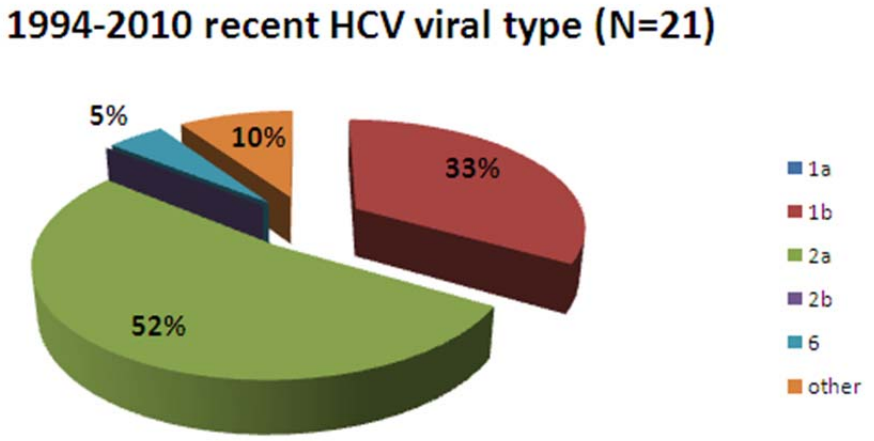
圖二、愛滋病毒感染者近期或急性 C 型肝炎逐年發生率



圖三、愛滋病毒感染者近期或急性 C 型肝炎基因型分佈



*Multitypes:1a+1b: 2 patients, 1b+2a : 1 patients, 1b+6: 1 patient



表一、比較近期或急性 C 型肝炎之愛滋病毒感染的相關因子

Characteristics	recent HCV infection	No recent HCV infection	p Value
	N=90	N=2,406	
Male, n (%)	90 (100.0)	2,313 (96.1)	0.0091*
Age at the study started (mean±SD),yr	31.6 (±7.1)	35.8 (±10.7)	0.0002*
Risk, n (%)			0.0021*
MSM/Bisexual	88 (97.8)	2,124 (88.3)	
Heterosexual	2 (2.2)	282 (11.7)	
HBsAg positive, n (%)	13 (14.4)	345 (14.3)	0.9951
On HARRT, n (%)	88 (97.8)	2,281 (94.8)	0.0869
prior syphilis occurred (before last visit or seroconversion 6 mo and after 3mo), n (%)	61 (67.8)	272 (11.3)	<.0001*

表二、比較 1994-2010 與 2011-2015 近期或急性 C 型肝炎愛滋病毒感染者

Characteristics	1994-2010	2011-2015
HCV seroconversion, N	30	90
Mean age at HCV seroconversion (SD)	42 (10)	32 (7)
% male (n)	100 (30)	100 (90)
% risk (n)		
MSM	93.3 (28)	97.8 (88)
Heterosexuals	6.7 (2)	2.2 (2)
% positive HBsAg (no. of patients with indicated result/total no. of patients)	10.3 (3/29)	14.9 (13/87)
% of patients with recent syphilis acquisition at last follow-up (no. of patients with indicated result/total no. of patients)	45.8 (11/24)	67.8 (61/90)
Liver function tests at last follow-up		
Mean AST level in U/liter (SD) (no. of patients with data available)	113 (179) (24)	150 (156) (70)
% of patients with AST ＞37 U/liter (no. of patients with indicated result/ total no. of patients)	75 (18/24)	77 (54/70)
Mean ALT level in U/liter (SD) (no. of patients with data available)	194 (212) (20)	333 (366) (73)
% of patients with ALT ＞41 U/liter (no. of patients with indicated result/ total no. of patients)	85 (17/20)	90 (66/73)
Mean total bilirubin level in mg/dl (SD) (no. of patients with data available)	1.20 (0.87) (20)	1.41 (1.29) (49)
% of patients with total bilirubin levels ＞1.2 mg/dl (no. of patients with indicated result/total no. of patients)	35 (7/20)	39 (19/49)
Use of antiretroviral therapy at last follow-up	76.7 (23)	97.8 (88)
Mean baseline CD4 cells/μl (SD)	477 (214)	597 (270)
% of patients with ＜200 CD4 cells/μl (no. of patients with indicated result/ total no. of patients)	10.0 (3)	5.6 (5)
Mean baseline log10 PVL copies/ml (SD)	2.30 (1.10)	2.02 (1.1)
% of patients with ＞5 log10 PVL copies/ml (no. of patients with indicated result/total no. of patients)	3.3 (1)	3.3 (3)

附件九

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 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：105 年 1 月 1 日至 105 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

頁碼

共 (11) 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 2014/1/1-2016/6/30 期間，在昆明院區接受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 105 年 6 月 30 日，總共收集個案數為 350 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。350 個案中出現任何一種副作用有 246 人(70.3%)，因為任何副作用而停藥的病人有 118 人(33.7%)。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 138 人(39.4%)，因為眩暈而停用希寧有 35 人(10%)。出現紅疹的個案數有 87 個患者(24.9%)，因此停藥者有 44 人(12.8%)，出現紅疹的時間距離開始服用藥平均約 10 天。其他副作用如多夢與夢魘有 53 人、睡眠障礙有 37 人、有 11 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 66 (18.9%)人，而在一年內停用希寧的病人數有 123 人(35.1%)。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 9 人(2.6%)。350 位個案目前追蹤滿 48 週以上有 113 人，病毒量<40 copies/ml 者有 111 人(97.4%)，追蹤滿 96 週以上有 42 人，病毒量<40 copies/ml 者有 41 人(97.6%)。

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 plus 2 NRTIs in the treatment of ARV-naïve HIV-infected patients, we retrospectively observed 350 patients who initiated combination antiretroviral therapy consisting 2 NRTIs plus efavirenz at Taipei Venereal Disease Clinic between January 2014 and June 2016. In total, 70.3% of the patients reported one or more adverse effects to the regimens and 33.7% had to switch efavirenz/2NRTIs to other non-efavirenz- containing regimens. Of the adverse effects reported included dizziness (39.4%), skin rashes (24.9%), dreams and nightmares (15.1%), sleep disturbance (10.6%), and heat sensation (3.1%). While one third of the patients had to change regimens (treatment failure), virological failure was observed only in 2.6% (n=9) of the patients. Among those patients who continued to receive efavirenz-containing regimen for >48 weeks, 97.4% were able to achieve PVL<40 copies/ml at week 48 and 97.6% 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 2016 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 2014/1/1-2016/6/30 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 105 年 6 月 30 日，總共收集個案數為 350 人，個案的服用希寧時的年齡平均為 32.7 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 350 個案中 347 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 335 人(95.7%)、HIV 感染者中合併 B 型肝炎帶原者有（HBSAg: positive）47 人(13.4%)，而 HIV 感染者合併有 C 型肝炎帶原者(Anti-HCV: positive)有 23 人(6.6%)。

在服用希寧(efavirenz)之前的實驗室檢驗，免疫力 CD4 T lymphocyte 平均值為 263.7(4.8-842)，CD4<200 有 128 人(36.6%)。而 HIV viral load 平均值為 237467 (501～5854000)，plasma HIV RNA load $>10^5$ 的個案有 185 人（52.9 %），350 人中有一人缺 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。350 個案中出現任何一種副作用有 246 人(70.3%)，因為任何副作用而停藥的病人有 118 人。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 138 人(39.4%)，因為眩暈而停用希寧有 35 人(10%)。出現紅疹的個案數有 87 個患者(24.9%)，因此停藥者有 44 人(12.8%)，出現紅疹的時間距離開始服用藥平均約 10 天。其他副作用如多夢與夢魘有 53 人、睡眠障礙有 37 人、有 11 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 202 個病患，停用希寧 87 人(43.1%)。使用 tenofovir disoproxil fumarate (TDF) + lamivudine 組合者有 104 人，停用藥物 32 人 (30.8%)。使用 Truvada (TDF/FTC) 有 35 位患者，停用藥物 6 人(17.1%)。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 66 (18.9%)人，而在一年內停用希寧的病人數有 123 人(35.1%)。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 9 人(2.6%)。

350 位個案目前追蹤滿 48 週以上有 113 人，病毒量<40 copies/ml 者有 111 人(97.4%)，追蹤滿 96 週以上有 42 人，病毒量<40 copies/ml 者有 41 人(97.6%)。

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九人(2.57%)，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(12.6%)。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，因為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。

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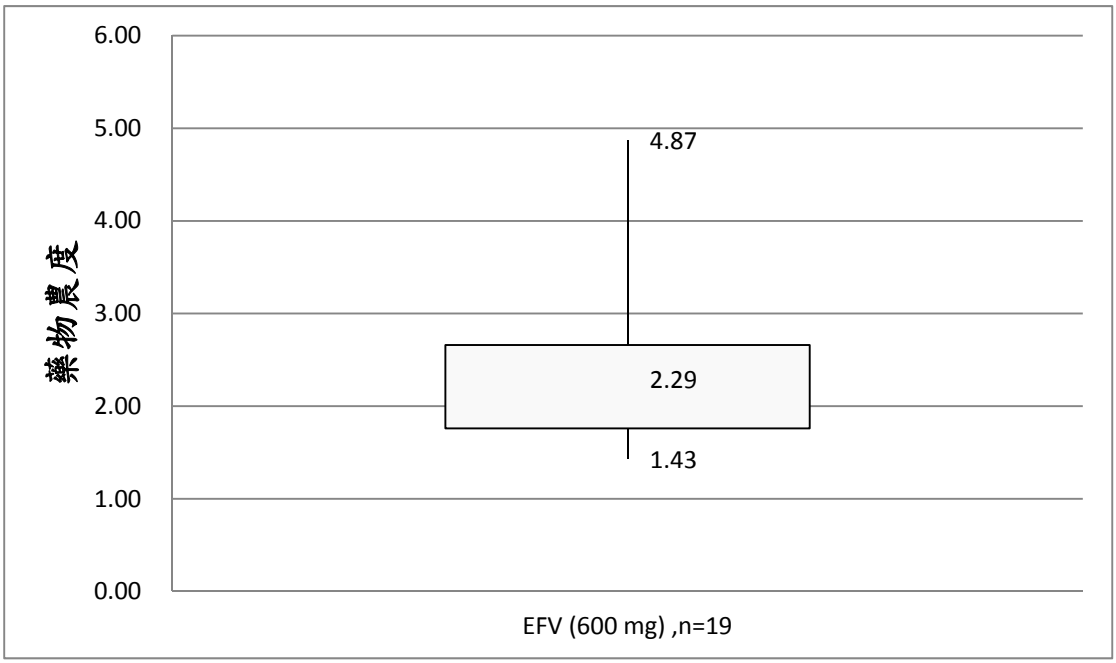
（七）圖表

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



附件十

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

危險性行為後愛滋病毒感染之非職業性暴露後預防性投藥效果之前瞻性研究

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：楊家瑞

研 究 人 員：李幸娟

執 行 期 間：105 年 1 月 1 日至 105 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：愛滋病毒感染在台灣目前新增加的感染者仍然尚未得到良好之控制，本計劃的目的在於針對特定高風險族群等非職業性高危險愛滋病毒體液暴露者，提供愛滋病毒篩檢，諮詢以及衛教服務，並且於 48 至 72 小時內給予預防藥物，評估後續愛滋病毒感染之風險以及預防性藥物不同處方之耐受性。

研究方法：自 2014 年 05 月開始, 建立專線電話接受諮詢並協助安排至感染科門診接受完整之問診以及風險評估，並提供檢驗包含 HIV 篩檢，B 型肝炎，C 型肝炎以及梅毒，在快速 HIV 篩檢結果為陰性後，提供預防病毒感染之藥物組合。門診給藥時程為 7 天，7 天，以及 14 天；並於暴露時間點後 6 週，12 週以及 24 週安排後續之追蹤檢驗，並以制式之個案記錄表登記個案之資料。

主要發現：自 2015 年 05 月 05 日至 2015 年 10 月 31 日止，共有 128 人次至板橋亞東醫院接受暴露後預防性投藥，全部的人均在 72 小時之內投藥，完成 28 天投藥的比例為 100%。對於處方之藥物主要是以 TDF/FTC (或少數為 TDF+3TC) +RAL 為主，其次則為 TDF/FTC (或極少數為 TDF+3TC) +LPV/r，追蹤至 2016 年 10 月底，並無血清陽轉出現 HIV 感染者。而在所使用的處方中，以 TDF/FTC 和 RAL 為使用藥物的組合耐受度較佳。

結論：暴露後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。此外，TDF/FTC 和 RAL 為主的處方耐受性較佳，有助於患者順利完成投藥期程。國內應以此為基礎, 修正先前的指引中建議的用藥提供臨床醫師參考。

關鍵詞：愛滋病毒感染、暴露後預防性投藥、愛滋病毒檢驗、抗愛滋病毒藥物

貳、英文摘要：

Aim of Study: Newly diagnosed HIV-infected patients annually are not under controlled yet. We aim to provide anti-HIV screening, HIV counselling and HIV post-exposure prophylaxis within 48 to 72 hours after risky behavior for subjects who underwent unprotective sexual behavior and sought for medical help. The seroconversion rate of HIV and tolerability of different regimens will be evaluated.

Study design: We set a special phone number to receive counselling by a trained consultant and the consultant will arrange further medical evaluation in our outpatient clinics of Infection specialist. We offer the baseline examination of HIV screening, hepatitis B, hepatitis C and screening of syphilis. After negative result from rapid test for HIV, medication as post-exposure prophylaxis will be given for 7 days, 7 days followed by 14 days which is total 28 days course. The subject will be followed after sexual exposure in 6-week, 12-week and 24-week. The data will be record with a standard form.

Rsults: From May, 2015 to 31st, October, 2016, There were 128 subjects received non-occupational post-exposure prophylaxis (nPEP). All the subjects received nPEP within 72 hours and the completion of 28 days course was 100%. The major regimens were TDF/FTC + RAL and TDF/FTC + LPV/r. Among the subjects, 88 of them had completed 24-week follow up and no HIV seroconversion was found. In addition, prophylactic regimen with TDF/FTC + RAL demonstrated better tolerability.

Conclusion: NPEP had good efficacy in the prevention of HIV infection and could be used as one of the bundle strategies of HIV prevention. Prophylactic regimen with TDF/FTC + RAL demonstrated better tolerability and we should modify the previous nPEP guideline of Taiwan.

Key words: postexposure prophylaxis, HIV, antiretroviral drugs

參、本文：

（1）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，已逾二萬三千名以上被診斷和通報，由於感染人數持續增加，而且年齡層逐漸下降，早已經是衛生署傳染病防治工作的重要課題之一。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大多是經由性行為，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。根據衛生署的統計資料顯示，平均每 2~3 個小時發現 1 名新感染者，因此提供一個可信賴的 HIV 體液暴露者篩檢與專業心理諮詢的管道,應是杜絕愛滋病傳播最重要而且有效的方法，並可讓感染者有及早接受治療的機會。此外，目前已有多項國外觀察性研究顯示，體液暴露後預防性投藥可減低愛滋病毒感染的風險，因此，我們還可針對特定高危險族群(如男同志)在發生性行為發生體液暴露後，除了提供諮商以外，我們還可以提供相關性病的檢驗和治療，並且進一步評估是否有需要建議使用暴露後預防性投藥以降低愛滋病毒傳染的風險。

本計畫將針對特定高風險族群等非職業性高危險愛滋病毒體液暴露者建立完整且統一的愛滋病毒體液暴露事件處理流程。提供欲至亞東醫院尋求協助的個案專線諮詢與衛教服務，並適當評估體液暴露感染之風險並提供愛滋病毒之快速篩檢, 確定為非愛滋病毒感染者後, 於 48 至 72 小時內給予及時之自費預防藥物, 以發揮有效之防疫功能。

（2）材料與方法

執行期間： 2016 年 1 月 1 日迄 2016 年 12 月 31 日。

研究方法：

實施方式：

1. 利用國內外資訊管道蒐集各種相關文獻，並彙集其他國家對於疑似愛滋病毒體液暴露後事件處理流程等資料。成立「愛滋病毒體液暴露諮詢及篩檢」專線。提供問題解決的管道，透過諮詢過程加強對傳染病防治的認識，積極採取預防措施，降低感染率。安排相關人員接受訓練及在職教育，加強電話中處理方法及程序的一致性。
2. 加強高風險族群愛滋病毒防治之宣傳。印製愛滋病毒感染服藥相關衛教之資料提供暴露個案參考。內容包括服務時間、愛滋病疑問、如何預防及檢驗等。提供快速且正確的檢驗、診斷及治療，降低感染的機會。
3. 提供篩檢前之諮詢服務：將進行工作人員訓練，使其具有諮詢服務之能力。諮詢服務之內容：清楚解釋「愛滋病」及「愛滋病毒檢驗」、空窗期與潛伏期的意義、愛滋病的主要傳染途徑、愛滋病的預防方法、「全程」使用保險套的「安全性行為」及「比較安全性行為」觀念、愛滋病病毒檢驗的功能、限制以及如何獲知檢驗結果。電話先由護理師予以回答，依其嚴重性決定是否轉介給醫師。若有必要時可立即諮詢醫師在門診時間內予診斷及治療。
4. 檢驗方法：以酵素免疫反應法及顆粒凝集法(Particle Agglutination, PA)進行初步篩檢，呈陽性反應者，再採檢體並重複酵素免疫反應法與西方墨點法，皆為陽性者為確認個案。。檢驗結果由醫師給予必要的檢驗後諮商。陽性反應者請回院門診，並填報「傳染病個案報告單」。
5. 針對 HIV 體液暴露後之高風險族群，提供自費之藥物預防，並追蹤血清之變化諮詢記錄及處理追蹤結果可作為相關單位及學術機構研究發展之用，作為爾後政策擬定之參考。追蹤之期程為暴露後 6 周, 3 個月及 6 個月。同時於第一次檢驗時, 檢查其他性病如梅毒, 並送驗尿液檢體至疾病管制局檢驗淋病及披衣菌尿道炎。進行流程如附表二

6. 教育及資料更新：提供對 HIV 指定照顧醫院對 HIV 體液暴露之諮詢教育，且參考國內外文獻及指引更新 HIV 體液暴露預防流程及藥物，定期舉辦研討會提供 HIV 體液暴露處理相關資訊。

表二 暴露後血液檢查及時程

	基礎值	暴露後 二周	暴露後 六周	暴露後 三個月	暴露後 六個月
HIV1/2 antibody (EIA)$	V		V	V	V
Complete blood count with differential	V	V			
Serum liver enzymes: AST ALT	V	V			
Urine PCR for chlamydia and gonorrhea	V				
Serologic tests for syphilis: VDRL/RPR, TPHA	V	V	V		
HBsAg, anti-HBs#	V		V	V	
HCV antibody test (e.g., EIA/ELISA)*	V			V	V
Pregnancy test (urine and blood)	V	V	V		

（3）結果

由於本次前瞻性研究之 IRB 於 2015 年 05 月 05 日通過可正式收案, 因此自 2015 年 05 月 05 日至 2015 年 10 月 31 日止, 共有 50 人次至板橋亞東醫院接受暴露後預防性投藥, 全部的人均在 72 小時之內投藥, 完成 28 天投藥的比例為 100%。對於處方之藥物主要是以 TDF/FTC (或少數為 TDF+3TC) +RAL 為主, 其次則為 TDF/FTC (或極少數為 TDF+3TC) +LPV/r, 追蹤至 2016 年 10 月底, 並無血清陽轉出現 HIV 感染者, 於追蹤過程中, 亦無出現急性 C 型肝炎者。此外, 有一位個案自 2011 年至 2015 年底共接受過 4 次 nPEP, 已經過諮商轉介為暴露前預防性投藥, 服藥情形良好。

由 Table 1 顯示, 尋求預防性投藥者絕大多數為男性, 但男男間性行為者約佔所有人的 73.4%, 有 68.8%的人是透過網路尋求一夜情對象, 另外則有 28.1%是找性工作者; 92.1%的人學歷在大學以上, 有 75.0%的人在過去三個月內至少有過兩個以上的性伴侶, 而這些高危險族群中有 54.7%曾經做過 HIV 篩檢; 此外, 有 56.2%在過去三個月內戴保險套的比例低於 50%, 29.7%的個案曾經使用娛樂性用藥助性。由於 nPEP 已推行數年, 因此有 15.6%的個案過去曾經接受過預防性投藥。

在 Table 2 中是比較 backbone 為 Zidovudine (AZT) based regimen 和 Tenofovir (TDF) based regimen 耐受性的差異, 可以看到在 Nausea/vomiting, dizziness 或是 general malaise 的部分都是以 AZT-based regimen 顯著較多。而 Table 3 中是比較以 ralteravir (RAL)搭配或是其他藥物搭配 backbone NRTI 的耐受性差異, 可以看到除了 skin rash 沒有之外, 其餘各項常見的副作用均以 RAL-based regimen 顯著較少。

（4）討論

從目前初步的結果可以看出,暴露後預防性投藥在高風險族群中,具有一定的成效，就如同國外多項觀察性研究一樣。到目前為止，無個案出現真正的 HIV 陽轉。一部份的原因可能是藥物本身的預防成效，但另一方面則也有可能是因單次性行為其實感染率就文獻統計而言並不高，再加上來源個案的感染狀態絕大多數不明，因此沒有 HIV 感染。然而，我們已經觀察到，重複接受 nPEP 的比例有 15.6%, 顯示我們仍需仰賴針對這一些個案的衛教諮詢, 加強他們對於安全性行為的概念，方能在預防上達到最好的成效，更進一步可結合目前國際上推行的暴露前預防性投藥，提供給予反覆尋求 nPEP 的人。

此外，如何針對網路一夜情進行宣導，減少高風險性行為的比例, 將是未來在防疫上重要的一環。在今年度的研究和以往比起來，使用娛樂性用藥的比例開始增加，顯示如何針對藥物助性(Chemsex)的行為加以宣導或尋求精神科協助戒癮，亦將會是未來的重要項目。

另外，美國 CDC 針對 nPEP 的指引也終於在今年度更新，更新的重點及在於建議處方的改變，改為以 TDF/FTC+RAL 或是 DTG 為優先首選的建議， 我們的研究和國外大致上是相符合，從 Table 2 和 Table 3 可以看出 TDF/FTC 結合 RAL 在目前具有最佳的耐受性，因此，我們可能也應該要考慮修正國內的 nPEP 指引中的用藥了。

（5）結論

就初步的結果而言，暴露後預防性投藥有其效果，但絕非單一之預防方式，而應整合將個案連結進入衛教諮詢的系統，方可在 HIV 防疫上收到好的成效；針對難以抑制慾望而反覆發生高風險行為者，可考慮建議轉為暴露前預防性投藥。此外，TDF/FTC 和 RAL 為主的處方耐受性較佳, 有助於患者順利完成投藥期程。國內應以此為基礎, 修正先前的指引中建議的用藥提供臨床醫師參考。

（6）重要研究成果及具體建議

本年度計畫最重要的研究成果在於建立起完整 nPEP 的流程後, 近一年多來納入的個案均能順利完成預防性投藥，且確實無個案有 HIV 陽轉的狀況，確立 nPEP 的成效並可提供其他指定醫院參考，建議各參與醫院可提供自己醫院專門的聯絡窗口協助諮詢以及安排個案接受投藥與後續的追蹤; 此外，也確立較適合的處方藥物組合確實如同國外陸續修正的指引，建議以 TDF/FTC + RAL 為主要的選擇，下一步國內應以此為基礎, 修正先前的指引中建議的用藥提供臨床醫師參考。

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(8) 圖、表。

Table 1. Baseline characteristics of the cases who sought for nPEP of HIV

Characteristics	Numbers (%)
Sex	
Male	119 (93.0)
Female	9 (7.0)
Risky behavior	
MSM	94 (73.4)
non-MSM	34 (26.6)
Source cases	
Internet	88 (68.8)
Sex workers	36 (28.1)
Others	4 (3.1)
Education: college or higher	118 (92.1)
Marriage	
Yes	12 (6.3)
No	116 (93.7)
History of STDs	30 (23.4)
Illicit drug use	38 (29.7)
Sex partners in the past 3 months	
Partner ≤1	
Partners: 2-5	32 (25.0)
Partners >5	86 (67.2)
	10 (7.8)
History of nPEP	20 (15.6)
History of HIV screening	70 (54.7)
Condom use in the past 3 months: <50%	72 (56.2)
Completion of nPEP for 28 days	128 (100)
nPEP regimen	
TDF+3TC/FTC+LPV/r	20 (15.6)
TDF+3TC/FTC+RAL	92 (71.9)
AZT+3TC+RAL	14 (10.9)
AZT+3TC+EFV	2 (1.6)

Table 2. Tolerability of AZT-based regimen and TDF-based regimen

	AZT-based regimen (n=16)	TDF-based regimen (n=112)	P-value
Nausea/vomiting, n (%)	5 (31.2)	4 (3.6)	<0.001
Dizziness, n (%)	5 (31.2)	1 (0.9)	<0.001
General malaise, n (%)	4 (25.0)	2 (1.8)	<0.001
Diarrhea, n (%)	1 (6.3)	14 (12.5)	0.23
Skin rash, n (%)	0 (0)	0 (0)	-
Complete 28 days course, n (%)	16 (100)	112 (100)	1.00

Table 3. Tolerability of RAL-based regimen and other regimens

	RAL-based regimen (n=106)	other regimens (n=22)	P-value
Nausea/vomiting, n (%)	5 (4.7)	4 (18.2)	0.004
Dizziness, n (%)	3 (2.8)	3 (13.6)	0.02
General malaise, n (%)	3 (2.8)	3 (13.6)	0.02
Diarrhea, n (%)	1 (0.9)	14 (63.6)	<0.001
Skin rash, n (%)	0 (0)	0 (0)	-
Complete 28 days course, n (%)	106 (100)	22 (100)	1.00

附件十一

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 年委託科技研究計畫

HIV-1 感染者在第一線抗病毒藥物失敗後的抗藥性和臨床結果分析

年 度 研 究 報 告

執 行 機 構：國立台灣大學醫學院內科部

計畫主持人：鄭健禹

研 究 人 員：洪健清、孫幸葯、鄭健禹、蔡茂松

執 行 期 間：105 年 01 月 01 日至 105 年 12 月 31 日

目　　錄

頁碼

共 (13) 頁

壹、中文摘要

含有非核苷酸反轉錄酶抑制劑的抗病毒藥在世界多數國家仍是被推薦治療人費免疫不全病毒感染的第一線處方。然而非核苷酸反轉錄酶抑制劑相關抗藥突變點的增加卻造成資源不足國家的困境。在這一多中心的研究中我們目的在調查使用含有非核苷酸反轉錄酶抑制劑的第一線處方後新增相關抗藥突變點的發生機率, 及進而造成治療失敗的風險值。從2012年6月至2016年3月, 使用含有非核苷酸反轉錄酶抑制劑第一線處方得初感染者我們檢驗治療前、治療後4-6周及之後的每12至16周的人類免疫不全病毒的病毒量。治療失敗的定義是在使用抗病毒藥物六個月後病毒量仍高於200 copies/ml, 或病毒量從原本測不到(<50 copies/ml)到高於200 copies/ml。這些檢體將進行抗藥性檢測, 而抗藥點的判斷標準是根據IAS-USA 2015的指引。在這段研究期間,共有1642為初感染者接受了含有非核苷酸反轉錄酶抑制劑的第一線處方,而454位(27.4%)有更換處方的經驗, 其中因為副作用換藥的有323位(19.7%), 依治療前的抗藥序列換藥的有41位(2.5%),而因為治療失敗而換藥的有83位(5.1%)。對衛滋(nevirapine)、希寧(efavirenz)及恩臨(rilpivirine)產生抗葯的比率分別為9.7% (41/422), 4.2% (40/946)和0.7% (2/277)。其中68位(3.8%)有產生抗藥性突變點, 42位(62.7%)對核苷酸反轉錄酶抑制劑產生抗藥突變點, 而對非核苷酸反轉錄酶抑制劑、蛋白酶抑制劑及任何一種藥物有抗藥性突變點的機率分別為28位(41.2%), 1位和48位(71.6%), 此外有21位(31.3%)帶有多重抗藥性。最常見的抗藥突變點分別為K65R (25%)、M184I (10.3%)、M184V (36.8%)、V90I (5.9%)、K101E (5.9%)、K103N (19.1%)、V108I (7.4%)、Y181C (11.8%)、G190A (5.9%)。在研究的中心中多數更換含有非核苷酸反轉錄酶抑制劑第一線處方的初感染者是因為藥物副作用,因抗藥性而治療失敗的比率相對較少。此外, 多數藥物治療失敗的處方中含有惠立妥(tenofovir disoproxil fumarate)、速汰滋(lamivudine)、衛滋(nevirapine)及希寧(efavirenz)。

關鍵詞：非核苷酸反轉錄酶抑制劑、相關抗藥突變點(RAMs)、第一線處方

貳、英文摘要

Non-nucleoside reverse-transcriptase inhibitor (NNRTI)-containing antiretroviral therapy (ART) remains the recommended first-line regimens for adults infected with HIV. Increasing trends of resistance-associated mutations (RAMs) to nNRTIs have caused concerns about the effectiveness of the regimens in national programs in resource-limited regions. In this multicenter study, we aimed to investigate the incidence of emergent RAMs of HIV-1 to antiretrovirals (ARVs) in HIV-positive adults who developed virological failure to first-line nNRTI-containing ART in Taiwan. Between June 2012 and March 2016, ARV-naïve HIV-positive adults who initiated 2 NRTIs plus nNRTI at participating hospitals were included for analysis. Plasma HIV RNA load (PVL) was determined at baseline, and week 4-6 and subsequently every 12 to 16 weeks after ART initiation. Virological failure was defined as PVL ≥200 copies/ml at 6 months of ART initiation or confirmed HIV RNA ≥ 200 copies/ml after virologic suppression (PVL<50 copies/ml). Population sequencing was used to detect RAMs. Detection of RAMs at baseline was performed retrospectively. RAMs were interpreted using the IAS-USA 2015 mutations list. During the 3.5-year study period, 1642 patients initiated nNRTI-containing regimens, and 454 (27.4%) had to switch first-line ART because of adverse effects or intolerance (323, 19.7%), subsequent detection of RAMs at baseline (41, 2.5%) and virological failure (83, 5.1%). Virological failure to NRTIs plus nevirapine, efavirenz, and rilpivirine was 9.7% (41/422), 4.2% (40/946), and 0.7% (2/277), respectively. In 68 patients (3.8%) emergent RAMs were identified: 42 (62.7%) NRTI RAMs; 28 (41.2%), 1 and 48 patients (71.6%) nNRTI, protease inhibitors (PI) and any ART RAMs, respectively and 21 (31.3%) multi-drug resistance. The common emergent RAMs to NRTIs were K65R (25%), M184I (10.3%), and M184V (36.8%), and RAMs to nNRTIs are V90I (5.9%), K101E (5.9%), K103N (19.1%), V108I (7.4%), Y181C (11.8%), and G190A (5.9%). While a substantial proportion of the patients discontinued first-line NNRTI-containing regimens due to adverse effects, virological response to nNRTI-containing regimens remained good in patients who were able to tolerate the regimens in Taiwan. Most common RAMs in those with virological failure were related to exposure to tenofovir disoproxil fumarate, lamivudine, nevirapine, and efavirenz.

關鍵詞：nNRTI、resistance-associated mutations (RAMs)、first-line regimens

參、本文

（一）前言

世界衛生組織對後天免疫不全病毒感染者的建議第一線抗病毒藥物為核苷酸反轉錄酶抑制劑及非核苷酸反轉錄酶抑制劑，蛋白酶抑制劑通常為第二線用藥 [1]。台灣自 1994 年四月起免費提供抗病毒藥物給感染者，而 2016 年六月前建議的抗病毒藥物為卡貝滋(zidovudine/lamivudine),克惟滋(abacavir/lamivudine)或惠立妥(tenofovir 併 lamivudine)併用希寧、衛滋或卡貝茲併恩臨(病毒量小於 100, 000 copies/ml)為第一線使用藥。自抗病毒藥物大規模使用於治療感染者後，死亡率、母子垂直感染率及人類免疫不全病毒傳染率都大幅改善[1, 2]。然而隨之而來的是抗藥性病毒株的產生,一方面是因為服藥順從性不佳或是藥物的交互作用,最終導致抗藥性菌株的傳播而造成一大威脅[3, 4]。非核苷酸反轉錄酶抑制劑是一類低抗藥門檻的抗病毒藥，因此較常引起反轉錄酶相關的抗藥性突變，最終造成治療失敗[5-7]。而這個機率約為 53-95%,此外甚至有高達 38-64%的病人會產生多重抗藥病毒株[8-11]。抗藥性測試對於抗藥性突變點的偵測不管在初感染者或是福抗病毒藥治療失敗者都是相當重要的檢查，這可以避免帶有抗藥性菌株的傳播和保留新的抗病毒藥物的選擇。然而，例行性的抗藥性測試在台灣大多數的醫療院所卻無法進行檢測。截至 2016 年七月底，共有 32,427 位 HIV 感染者，且有超過半數已經在服用抗病毒藥物[12]。從 2006 至 2014 初步估計有 11.1%的初感染者帶有至少一個抗藥突變點,核苷酸反轉錄酶抑制劑及蛋白酶抑制劑的抗藥性比率都在下降,但非核苷酸反轉錄酶抑制劑的抗藥性問題卻在惡化中,且高於 5%[13, 14]。因此這個多中心研究的目的在調查使用含有非核苷酸反轉錄酶抑制劑的第一線處方後新增相關抗藥突變點的發生機率，及進而造成治療失敗的風險值。

（二）材料與方法

執行期間： 2016 年 1 月 1 日迄 2016 年 12 月 31 日。

研究方法

1. 受試者：

這是個前瞻性的臨床試驗在分析使用含有非核苷酸反轉錄酶抑制劑的第一線處方的初感染者在治療失敗後產生哪些常見的抗藥性突變點。自 2012 年六月起在台灣第一線建議的抗病毒藥物為卡貝滋(zidovudine/lamivudine), 克惟滋(abacavir/lamivudine)或惠立妥(tenofovir 併 lamivudine)併用希寧、衛滋或卡貝茲併恩臨(病毒量小於 100, 000 copies/ml)。在參與研究的中心抗藥性測試會提供給初感染者及治療失敗者,但台灣的治療指引只提供給治療失敗且服藥滿六個月而病毒量仍高於 1000 copies/ml 的感染者。針對這些個案我們將蒐集基本資料，如性別、年齡、HIV 感染危險因子、HIV 感染時間、伺機性感染或腫瘤、接受治療之時間、CD4 淋巴球之變化、血清 HIV 病毒量之變化、合併伺機性感染之有無、是否死亡和抗病毒藥物紀錄(包含第一線及第二線)等等作資料整理登錄。本研究業經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協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。此外，一些新近鑑定的基因變異也會陸續地被列入研究分析中。分析結果我們會以一標準格式，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

我們會使用 SPSS 19.0 統計軟體進行所有統計分析。

（三）結果

研究受試者

在這三年半的研究期間共有 1642 為受試者接受了含有非核苷酸反轉錄酶抑制劑的第一線處方,而基本資料如下：(1)平均年齡為 33.5 ± 9.0 歲 (2)95.5%為男性 (3)曾有男男性行為者有 77.7%, 而靜脈毒癮者有 18.5% (4)B 型肝炎及 C 型肝炎帶原者有 12.0%和 20.0% (5)CD4 淋巴球平均為 298 ± 189 cells/μL (5)HIV 病毒量高於 10 萬 copies/mL 有 564 位(34.3%) (6)HIV 病毒為 B 型亞型佔大多數(75.4%)。

抗藥性報告及第一線處方

共有 1168 位受試者接收了服藥前的抗藥性測試,其中 150 位(12.8%)帶有抗藥性突變點,而對核苷酸反轉錄酶抑制劑、非核苷酸反轉錄酶抑制劑及蛋白酶抑制劑的抗藥性比率分別為 3.9%, 7.9%和 1.7%。此外,在第一線抗病毒藥物中使用卡貝滋(zidovudine/lamivudine)有 49.0%,惠立妥(tenofovir 併 lamivudine)有 48.1%,而克惟滋(abacavir/lamivudine)有 2.9%。而非核苷酸反轉錄酶抑制劑中使用衛滋(nevirapine)、希寧(efavirenz)及恩臨(rilpivirine)分別有 57.5%, 25.7%和 16.8%。

新增抗藥性突變點 (resistance-associated mutations)

在這段研究期間,共有 1642 為初感染者接受了含有非核苷酸反轉錄酶抑制劑的第一線處方,而 454 位(27.4%)有更換處方的經驗, 其中因為副作用換藥的有 323 位(19.7%), 依治療前的抗藥序列換藥的有 41 位(2.5%),而因為治療失敗而換藥的有 83 位(5.1%)。對衛滋(nevirapine)、希寧(efavirenz)及恩臨(rilpivirine)產生抗葯的比率分別為 9.7% (41/422), 4.2% (40/946)和 0.7% (2/277)。其中 68 位(3.8%)有產生抗藥性突變點, 42 位(62.7%)對核苷酸反轉錄酶抑制劑產生抗藥突變點, 而對非核苷酸反轉錄酶抑制劑、蛋白酶抑制劑及任何一種藥物有抗藥性突變點的機率分別為 28 位 (41.2%), 1 位和 48 位(71.6%), 此外有 21 位(31.3%)帶有多重抗藥性。最常見的抗藥突變點分別為 K65R (25%)、M184I (10.3%)、M184V (36.8%)、V90I (5.9%)、K101E (5.9%)、K103N (19.1%)、V108I (7.4%)、Y181C (11.8%)、G190A (5.9%)。（圖一、圖二）再次分組分析中發現受試者 HIV 病毒量高於 10 萬 copies/mL 者治療失敗而產生抗藥性的比率在衛滋及希寧的組別分別有 16.4%和 7.8%, 而對 HIV 病毒量低於 10 萬 copies/mL 的受試者在衛滋、希寧及恩臨抗藥性的比率分別為 4.9%、1.9% 及 0.7%。（圖三）在使用衛滋治療失敗最常產生的抗藥點有 Y181C (12.2%), K101E (7.3%) and V108I (7.3%), 而對希寧最長的抗藥點是 K103N (27.5%)。（圖四）

(四)討論

在本研究中發現接受非核苷酸反轉錄酶為第一線抗病毒治療的受試者中，多數人都能維持第一線抗病毒藥物，而換藥最常見的原因是藥物的副作用(27.4%)，其次是因為抗藥性突變點的產生而治療失敗和換藥(5.1%)。衛滋(nevirapine)是治療高病毒量的受試者有較高失敗率的藥物(16.4%),而 Y181C 是最常見的抗藥突變點；希寧(efavirenz)對高病毒量的受試者失敗率為 7.8%，而 K103N 為最常見的抗藥突變點。這些發現跟歐美等國的文獻相似,因為都是抗病毒藥物較普及的國家,但跟東南亞和其他第三世界國家的發現有些不同之處。針對核苷酸反轉錄酶抑制劑藥物的使用後產生的抗藥點的分析中,已使用惠立妥(tenofovir)較普及的地區會有較高比率的 M184V 和 K65R 等抗藥突變點的產生,在我們的研究中發現 M184V/I 和 K65R 在治療失敗者的發生機率分別為 47.1%和 25%。但如果在使用卡貝茲(zidovudine/lamivudine)較普及的地區較常見的抗藥突變點為 M41L、D67N、T215Y..等。然而在我們的研究中確比較少發現這些抗藥突變點的出現,可能跟藥物副作用有關,因為有 27.4%的受試者因藥物副作用換藥,他們少了這些藥物的暴露,因而減少了產生這些突變點的機會。根據這個研究的結果,我們建議病人要接受非核苷酸反轉錄酶抑制劑的抗病毒藥物前,應進行抗藥性檢測,而如果治療失敗也應該立即進行第二次或第三次的抗藥性檢測。同時先把藥物調整為其他類的抗病毒藥,如蛋白酶抑制劑或是嵌入酶抑制劑。

(五) 結論

在研究的中心中多數更換含有非核苷酸反轉錄酶抑制劑第一線處方的初感染者是因為藥物副作用,因抗藥性而治療失敗的比率相對較少。此外，多數藥物治療失敗的處方中含有惠立妥(tenofovir disoproxil fumarate)、速汰滋(lamivudine)、衛滋(nevirapine)及希寧(efavirenz)。

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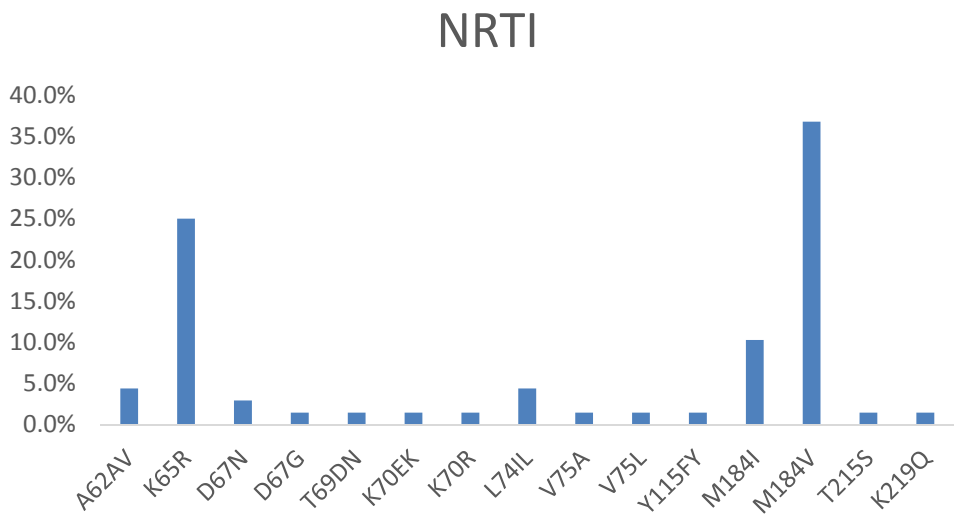
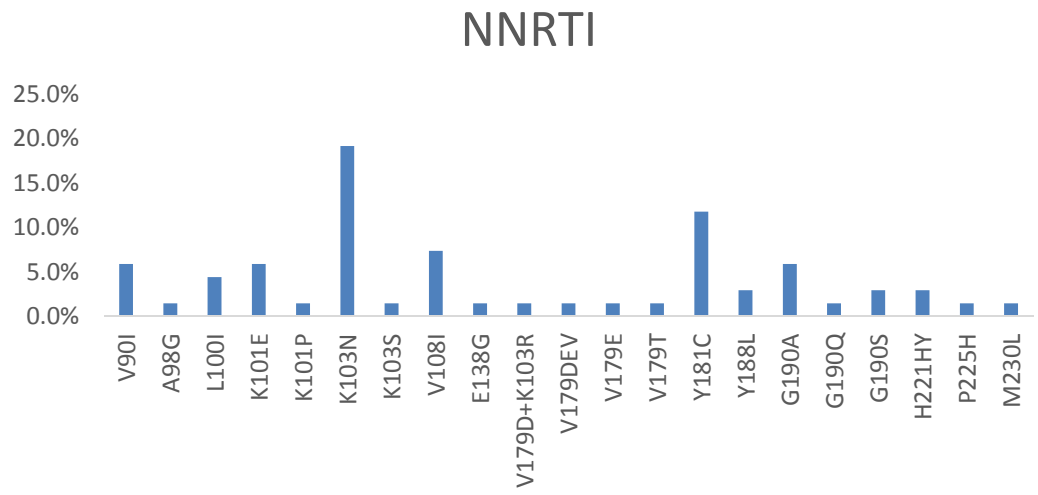
（七）圖表

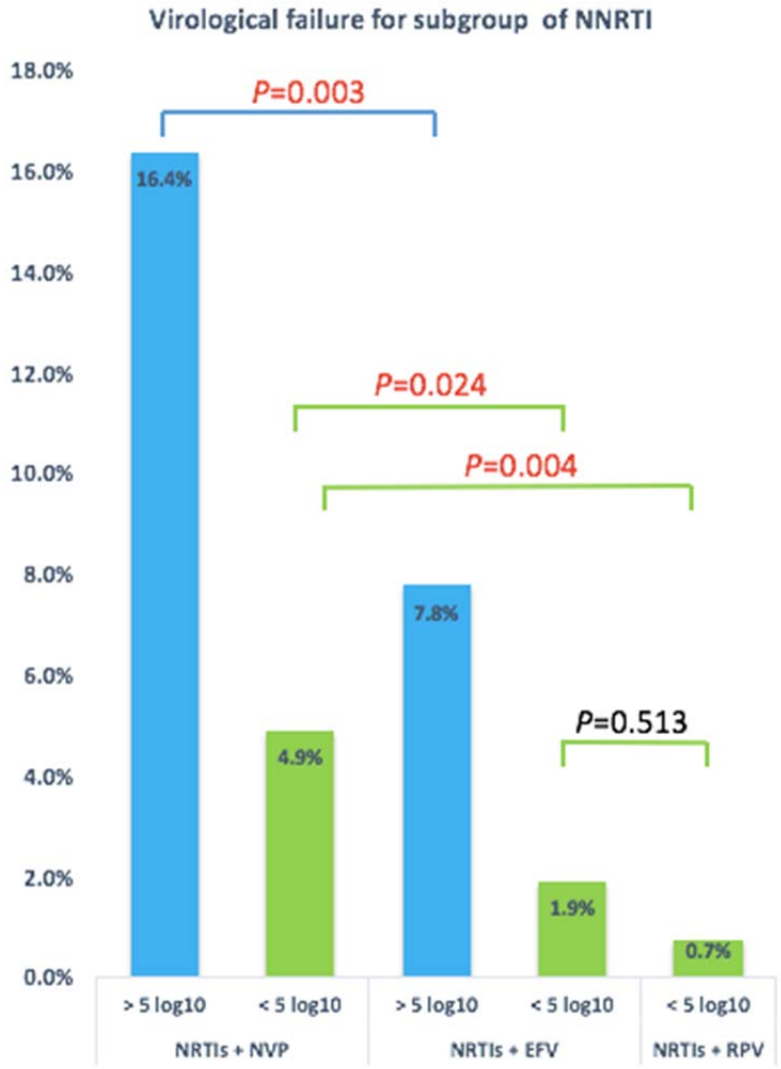
圖一、核苷酸反轉錄酶抑制劑常見的抗藥突變點



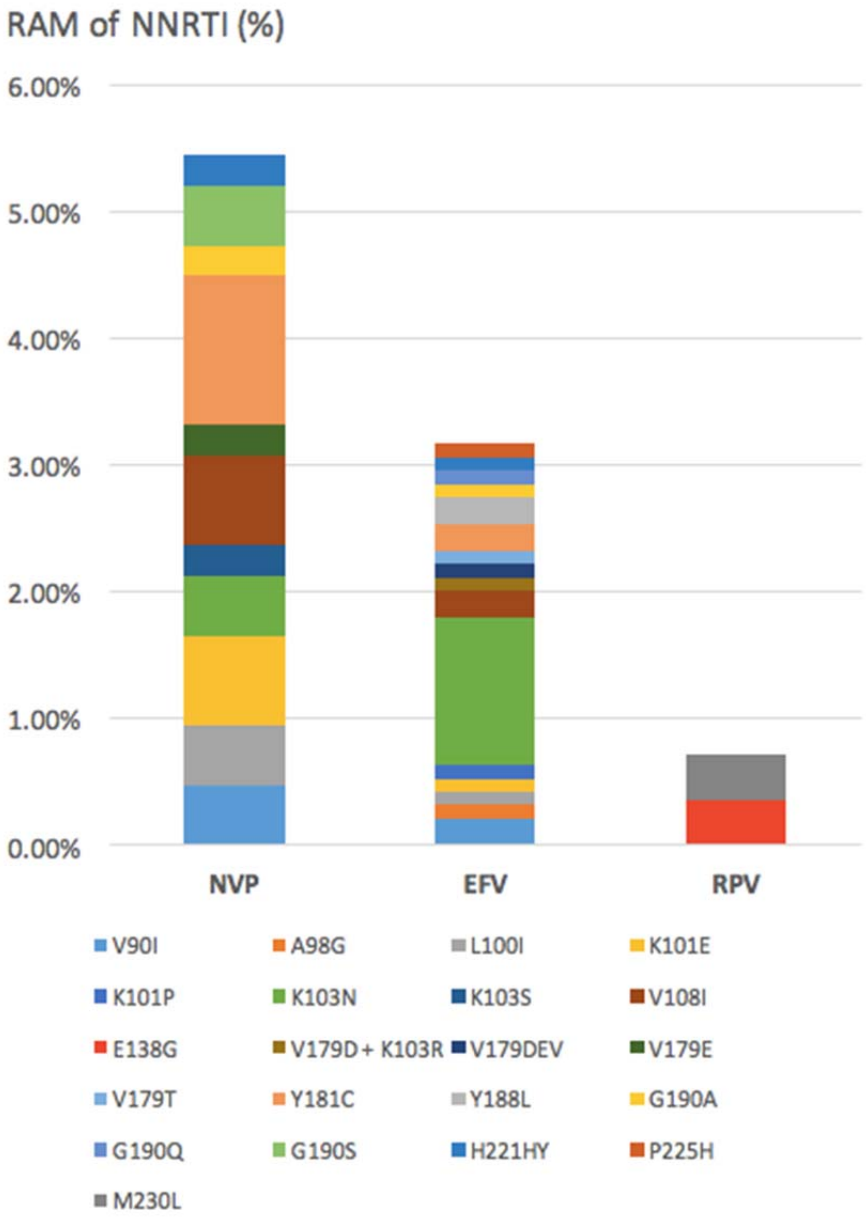
圖二、非核苷酸反轉錄酶抑制劑常見的抗藥突變點



圖三、非核苷酸反轉錄酶抑制劑不同藥物間藥物治療失敗的比率



圖四、非核苷酸反轉錄酶抑制劑不同藥物間藥物治療失敗後常見的抗藥突變點



附件十二

計畫編號：MOHW105-CDC-C-114-000104

衛生福利部疾病管制署 105 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

執 行 期 間：105 年 1 月 1 日至 105 年 12 月 31 日

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 870 位服用 EFV、547 位服用 ATV、108 位使用 cotrimoxazole 與 1 位服用 rifabutin 的病人進行分析；dolutegravir 分析方法開發中，預期可與 EFV 同時測定血中濃度。

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。由於 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。Rifabutin 只有一位病人檢測，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

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. We have monitored 870, 547, 108, and 1 patient in this year prospectively. Assay method of olutegravir is under investigation. 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.

叁、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[4]，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[5]。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[6,7]。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[8-11]。

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[4]。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[4,23]。

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[4,23]。

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[24-27]，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： 2016 年 1 月 1 日迄 2016 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）。

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, 10.0μg/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%。

（3）結果

以 HPLC 檢測 ART 與 cotrimoxazole (SMX-TMP)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%）。

近幾年來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；本年度仍繼續協助臨床醫師監測藥物血中濃度，迄今已為 870 位服用 EFV 與 547 位服用 ATV 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，期中分析 870 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 2.43 ± 1.32 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。

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 547 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 314 人 (57.4%)；C24

(24 hr, trough)濃度，共計 196 人 (35.8%)；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。另外，dolutegravir HPLC 分析方法正在開發中，預估可以與 efavirenz (EFV)同時上機檢測，有助於加速研究進度。

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 101 年 9 月的 Interscience Conference on Antimicrobial Agents and chemotherapy (ICAAC)以壁報發表，manuscript 也於今年被 Journal of Microbiology, Immunology and Infection 接受刊登[30]。詳見圖 1 與表 2。

Cotrimoxazole 方面，於 2014 年 1 月 19 日至 2016 年 05 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, $p=0.0302$）。初步結果以壁報方式在 ASM Microbe 年會發表。

Rifabutin 仍只有一位病人檢測，血中濃度在正常範圍內。

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。監測 ART 血中濃度的結果可提供臨床醫師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。

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 ATV、EFV、rifabutin 與 cotrimoxazole 血中濃度的服務、嘗試開發以 HPLC 方法測定 dolutegravir 與其他 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。

（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，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。[8-11]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。

（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 870 位服用 EFV、547 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 只有一位病人檢測，血中濃度在正常範圍內。

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 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。

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（8）圖表

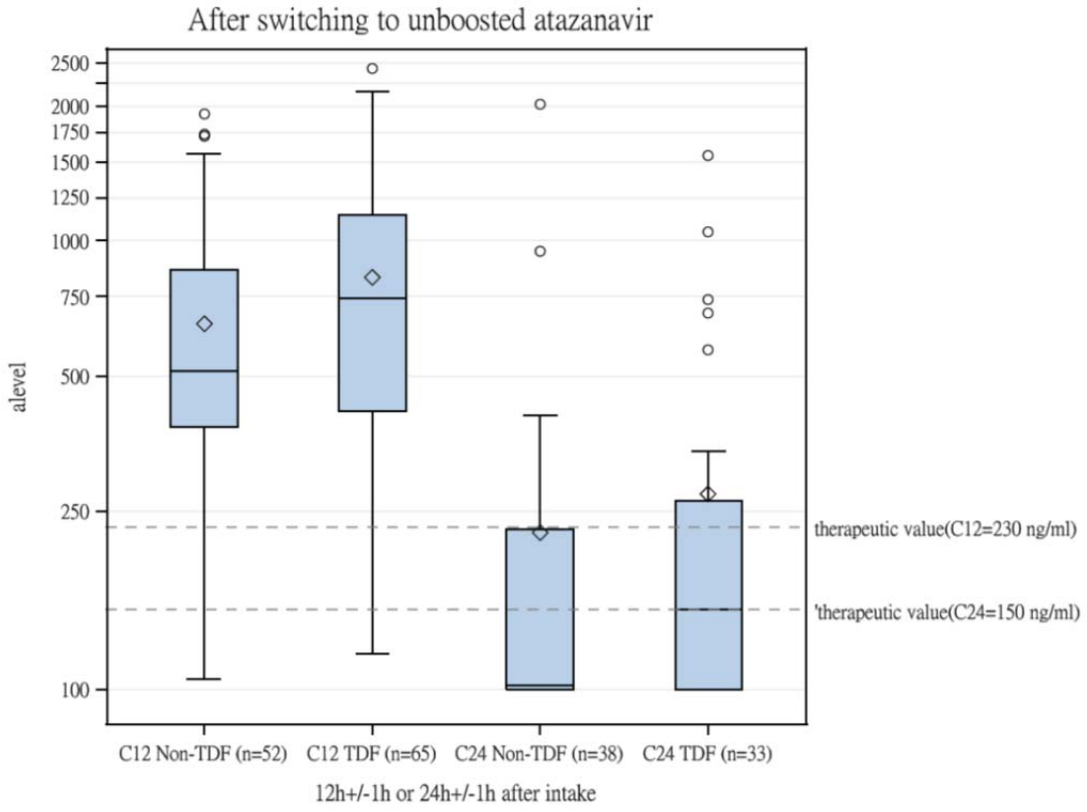

圖 1、Plasma atazanavir concentrations in patients receiving tenofovir, lamivudine plus unboosted atazanavir and those receiving abacavir or zidovudine, lamivudine plus unboosted atazanavir

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

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Transmitted drug resistance of HIV-1 strains among individuals attending voluntary counselling and testing in Taiwan

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Background: Genotypic drug resistance testing for HIV-1 has been integrated into voluntary counselling and testing (VCT) programmes to investigate the trends of transmitted drug resistance (TDR), including integrase mutations, among individuals with recent or chronic HIV infections in Taiwan.

Methods: Between 2006 and 2014, 745 of 21 886 subjects (3.4%) tested HIV positive in the VCT service. The BED assay was used to identify recent HIV infections. Genotypic resistance mutations were interpreted using the WHO 2009 list. Integrase resistance mutations were analysed using the Stanford HIV Drug Resistance Database.

Results: Three-hundred-and-sixty (48.3%) patients were recently infected with HIV-1. Of 440 patients linked to HIV care with analysable reverse transcriptase and protease genes, 49 (11.1%) were infected with HIV-1 harbouring at least one resistance-associated mutation (RAM). The prevalence of TDR to NRTIs, NNRTIs and PIs was 4.1%, 6.4% and 2.3%, respectively. TDR prevalence did not change significantly during the study period. CD4 counts $\leq$500 cells/mm^3 and hepatitis B surface antigen positivity were independent factors associated with acquiring drug-resistant HIV. The prevalence of integrase mutations was 3.2%. Among the seven major integrase mutations (T66I, E92Q, G140S, Y143C/H/R, S147G, Q148H/K/R and N155H), only one strain harbouring the Q148R mutation was detected. We found no statistically significant difference between patients with chronic infection and those with recent infection in the prevalence of drug-resistant mutations to any of the four classes of antiretroviral agents.

Conclusions: The prevalence of TDR of HIV-1 strains to available antiretroviral agents is moderately high, but transmission of HIV-1 with drug-resistant mutations remains stable in Taiwan.

Introduction

The emergence and spread of HIV with drug resistance seems to be inevitable as coverage of ART continues to grow, despite adequate ART options and optimal adherence.[1] This has posed a serious threat to public health globally with the rapid scale-up of ART in low- and middle-income countries, where infrastructures for frequent virological monitoring and testing for drug resistance are lacking.[2]

Transmitted drug resistance (TDR), which occurs when previously uninfected individuals are infected with a drug-resistant HIV strain, is of particular concern because it will jeopardize the success of first-line combination ART (cART).[3–5] The burdens of TDR vary substantially across geographical regions and temporal changes in TDR have been inconsistent in different parts of the world.[6–12] Current data from WHO surveys suggest there is an association between higher levels of ART coverage and a higher prevalence of TDR to NNRTIs.[1] Regular population-based

surveillance of transmission of drug-resistant strains is critical to ensure sustained effectiveness of ART and to provide the basis for selecting first-line regimens, especially in resource-limited countries where routine HIV drug resistance testing prior to ART initiation is not generally available due to cost constraints.

Conventionally, standard genotypic resistance testing involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes, and surveillance of TDR is limited to NRTIs, NNRTIs and PIs. However, among the five recommended regimens for ART-naive patients in the recently revised guidelines, four are integrase strand transfer inhibitor (INSTI) based.[13] Currently, transmission of INSTI-resistant virus has rarely been reported among ART-naive patients with HIV infection.[14–16] In addition, integrase resistance mutations may have negative impacts on viral fitness.[17,18] Therefore, routine testing for INSTI resistance is not recommended at present.[13] However, as the use of INSTIs will increase following physician adherence to the guidelines, the potential for transmission of these HIV-1 strains with resistance to INSTIs may also increase. Data on pre-treatment resistance to INSTIs remain scarce among ART-naive patients, especially outside Europe and the USA.[19]

Previous studies on trends of TDR prevalence of HIV-1 in Taiwan showed an increased rate during 2003–06 and a decline during 2007–10, with the use of the HIVdb programme of the Stanford University HIV Drug Resistance Database.[5,20] However, many patients included in prior studies were probably chronically infected, and the prevalence of TDR may be underestimated because drug-resistant strains might revert to WT virus over time in the absence of ART.[21] Anonymous voluntary counselling and testing (VCT) has been demonstrated to reach the target populations most at risk of HIV infection, and patients diagnosed with HIV infection via VCT are more likely to be in an early stage of HIV infection.[22,23] In this study, we evaluated the prevalences of TDR to NRTIs, NNRTIs, PIs and INSTIs among VCT subjects testing positive for HIV, including patients with laboratory-confirmed recent infection.

Methods

Setting of the voluntary counselling and testing programme

The National Taiwan University Hospital (NTUH), the largest hospital providing free-of-charge HIV care in Taiwan, has provided VCT services since 1999, which was expanded in 2006. The number of attendees of the VCT programme at NTUH accounted for ~14% of the total number in Taiwan in recent years. A standardized anonymous, self-administered questionnaire interview (available as Supplementary data at *JAC* Online) designed by the Taiwan CDC has been performed to obtain the information on the demographics, sexual practices, risk behaviours, history of sexually transmitted infections (STIs), number of sexual partners, HIV serostatus of sexual partners, condom use and use of illicit drugs.[22] After interview and counselling by trained counsellors, an 8–10 mL blood sample was collected from each individual for serological tests of HIV infection and other STIs. The results were given to the subjects by mobile phone, using a unique testing code consisting of the first alphabetic character and the last three digits of the national identification card, sex and birth year for identification. Those testing positive would be linked to a clinical care and case management programme that was implemented in 2006. Other details have been described previously.[22] The study was approved by the research ethics committee of the hospital and the patients who were linked to HIV care at the hospital gave written informed consent for determination of TDR and the BED-CEIA (capture enzyme immunoassay).

Setting of HIV care in Taiwan

HIV-infected Taiwanese patients receive HIV care according to the national treatment guidelines at designated hospitals around Taiwan. Medical costs related to HIV care, including cART, quantification of CD4 lymphocyte counts and plasma HIV RNA load (PVL), and management for opportunistic illnesses are totally reimbursed by the Taiwan CDC. Drug resistance testing, however, was not routinely available and restricted to patients experiencing treatment failure and to pregnant women. The Taiwan CDC has implemented nationwide regulations on the use of first-line regimens since March 2011 due to substantial financial pressure in providing HIV care, and NNRTI-based regimens have been the preferred cART. Regimens with higher costs require pre-prescription approval by the Taiwan CDC. Since then, use of NNRTIs has increased markedly. Furthermore, generic versions of antiretroviral agents have been introduced since December 2012.

Determination of recent HIV infections, subtypes and coinfections

Anti-HIV antibody was tested using particle agglutination (SFD HIV 1/2 PA; Bio-Rad FUJIREBIO, Japan) and HIV infection was confirmed using western blotting (MP Diagnostics HIV BLOT 2.2; MP Biomedicals Asia Pacific Pte Ltd, Singapore). Hepatitis B surface antigen (HBsAg), anti-HBs antibody and hepatitis B core antibody (anti-HBc antibody) were determined with the use of enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Antibodies to hepatitis C virus were determined with the use of a third-generation enzyme immunoassay (Ax SYM HCV III; Abbott Laboratories, North Chicago, IL, USA).

The BED assay was performed in the residual samples. The BED-CEIA (Calypte, MD, USA) determines the proportion of anti-HIV-1-specific IgG in relation to total IgG, based on the observation that the ratio of anti-HIV IgG to total IgG increases with time shortly after HIV infection.[24] If a specimen is reactive in the standard sensitive enzyme immunoassay and has a normalized optical density of <0.8 in the BED assay, the source patient is considered recently infected. The window period of recent infection is 153 days (95% CI 145–166 days). In addition, we also used age <25 years as an indicator of recent infection, according to WHO TDR survey methods, to validate the classification based on the BED assay.[6] The HIV-1 subtypes were determined as described previously.[25]

Determination of drug resistance mutations

For those with confirmed HIV infection and linked to clinical care at NTUH, genotypic resistance assays were performed retrospectively as described previously.[5,20] Resistance-associated mutations (RAMs) were defined by the presence of at least one mutation included in the 2009 WHO surveillance drug resistance mutation list.[26] To determine genotypic resistant mutations related to INSTIs, an 884 bp fragment of integrase coding regions was PCR amplified. The PCR primer pair used was *pol*2950A (5′-TCA KCA CCT GCC ATC TGT TTT CC-3′)/2064A (5′-AYA ARG GRA TTG GAG GAA ATG AAC A-3′). The amplification condition was 35 cycles of 94°C for 15 s, 55°C for 1 min and 72°C for 2 min, and a final extension at 72°C for 7 min. The sequences were submitted to the Stanford HIVdb (http://hivdb.stanford.edu) to determine the mutation pattern and susceptibility.[27] Mutations causing low-level resistance or above were considered clinically relevant.

PVL and CD4 lymphocyte count were quantified by the Cobas Amplicor HIV-1 Monitor™ Test, version 1.5 (Roche Diagnostics Corporation, Indianapolis, USA) and FACSFlow (Becton Dickinson), respectively.

Statistical analysis

Data were analysed using SAS 9.2 (SAS Institute, NC, USA). Categorical data were analysed using the χ^2 or Fisher's exact test, as appropriate, and continuous variables were compared using the Wilcoxon test. All tests were two-tailed and a P value <0.05 was considered significant.

Results

Characteristics of the study population

From April 2006 to December 2014, 21 886 VCT subjects had HIV tests at NTUH (Figure 1). MSM and heterosexuals accounted for 13 325 (60.9%) and 8434 (38.5%) of the attendance, respectively. Almost 60% (n=12 978; 59.3%) of VCT subjects were aged 20–29 years. Overall, 745 individuals were newly diagnosed with HIV-1 infection, with an overall HIV seroprevalence of 3.4% (95% CI 3.2%–3.7%) (Figure 1). Among the 745 HIV-positive persons, 360 (48.3%) were considered as having recent infections and 376 (50.5%) long-standing infections based on the BED assay. Three-quarters (n=557; 74.8%) of those infected with HIV-1 were linked to HIV care at NTUH, including 264 (47.4%) classified as having recent infections and 286 (51.3%) chronic infections. The characteristics of these two groups of patients are shown in Table 1. In multivariate analysis, age ≤25 years (OR 2.50; 95% CI 1.62–3.86, P<0.001), transactional sex behaviours (OR 2.93; 95% CI 1.23–6.98, P=0.02), oral sex practices (OR 2.14; 95% CI 1.16–3.96, P=0.02) and having CD4 lymphocyte counts >500 cells/mm^3 (OR 1.82; 95% CI 1.16–2.86, P<0.01) and PVL >5 $\log_{10}$ copies/mL (OR 2.41; 95% CI 1.55–3.76, P<0.001) were associated with recent infections.

Approximately 95% of HIV-infected patients were MSM. Overall, 197 (92.9%) of patients with recent infections and 201 (89.7%) of those with chronic infections were infected with HIV-1 subtype B. The second most common subtype was CRF01_AE, which accounted for 3.3% of those with recent infections and 5.8% of those with chronic infections.

TDR to NRTIs, NNRTIs and PIs

Among the 557 HIV-positive patients linked to HIV care at NTUH, 534 (95.9%) had blood specimens available for genotypic resistance tests, and the PR and RT genes were successfully sequenced in 440 of them (82.4%). Patients with analysable RT/PR sequences had significantly higher baseline PVL (4.66 versus 4.46 $\log_{10}$ copies/mL, P=0.02) compared with those without analysable RT/PR sequences, and other baseline demographic and clinical characteristics were generally similar (Table S1, available as Supplementary data at *JAC* Online).

Forty-nine HIV-1 strains (11.1%) harboured at least one PR or RT mutation. The overall prevalence of transmitted RAMs to NRTIs, NNRTIs and PIs was 4.1%, 6.4% and 2.3%, respectively (Figure 1). The prevalence of transmitted RAM to any class of antiretroviral agents (NRTIs, NNRTIs or PIs) was 9.0% and 13.4% (P=0.19) for HIV-1 strains from patients with recent infections and those with

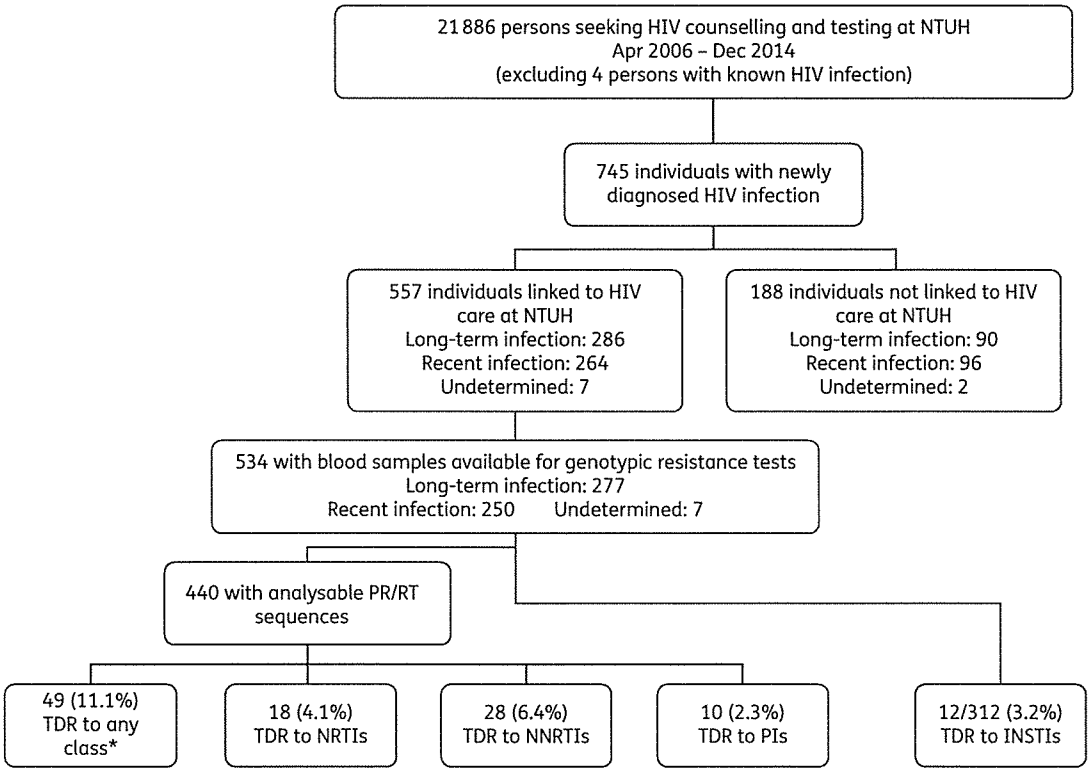

Figure 1. Flow chart of this study. *Any class refers to NRTIs, NNRTIs or PIs.

Table 1. Comparisons of characteristics between VCT subjects with recent and those with long-term HIV infections who were linked to HIV care

Characteristic	All patients,[a] $N=557$	Recent infections, $N=264$	Long-term infections, $N=286$	P
Male, *n* (%)	543 (97.5)	262 (99.2)	274 (95.8)	0.01*
Age (years), mean ± SD	29.5 ± 7.2	27.5 ± 5.8	31.3 (±7.8)	<0.001*
≤25 years, *n* (%)	163 (29.3)	101 (38.3)	60 (21.0)	<0.001*
Risk, *n* (%)				0.10
MSM	527 (94.6)	255 (96.6)	267 (93.4)	
heterosexual	26 (4.7)	7 (2.7)	18 (6.3)	
IDU with needle sharing	4 (0.7)	2 (0.8)	1 (0.4)	
Reasons for screening, *n* (%)				
having confirmed HIV-infected sexual partners	102 (18.3)	34 (12.9)	67 (23.4)	0.001*
having an IDU partner	2 (0.4)	2 (0.8)	0 (0.0)	0.23
ever having an STI	132 (23.7)	60 (22.7)	71 (24.8)	0.62
having transactional sex	30 (5.4)	21 (8.0)	9 (3.2)	0.01*
having a one-night stand	246 (44.2)	132 (50.0)	110 (38.5)	0.01*
having anal sex	438 (78.6)	231 (87.5)	202 (70.6)	<0.001*
having oral sex	432 (77.6)	225 (85.2)	201 (70.3)	<0.001*
illicit drug use	147 (26.4)	75 (28.4)	70 (24.5)	0.33
Baseline laboratory results				
RPR ≥4, *n* (%)	70 (12.6)	27 (10.2)	42 (14.7)	0.12
western blot for HIV-1, *n* (%)				<0.001*
positive	510 (91.6)	222 (84.1)	283 (99.0)	
indeterminate	37 (6.6)	35 (13.3)	0 (0.0)	
PVL (log_{10} copies/mL), mean ± SD	4.60 ± 0.76	4.75 ± 0.82	4.47 (±0.66)	<0.001*
>5 log_{10} copies/mL, *n* (%)	157 (28.2)	98 (37.1)	56 (19.6)	<0.001*
CD4 cell count (cells/mm^3), mean ± SD	388.4 ± 209.5	436.8 ± 220.7	345.8 (±187.5)	<0.001*
>500 cells/mm^3, *n* (%)	138 (24.8)	83 (31.4)	52 (18.2)	<0.001*
HBsAg positivity, *n* (%)	53 (9.5)	20 (7.6)	32 (11.2)	0.19
anti-HCV positivity, *n* (%)	18 (3.2)	5 (1.9)	11 (3.8)	0.21
available genotypic resistance results, *n* (%)	440 (79.0)	212 (80.3)	224 (78.3)	0.52

HCV, hepatitis C virus; IDU, injecting drug users; RPR, rapid plasma reagin.
*$P<0.05$.
[a]Including seven patients with undetermined duration of HIV-1 infection by the BED assay.

chronic infections, respectively. The prevalence of TDR to each class was not statistically significantly different between patients with recent and those with chronic infections, based on the BED assay (Figure 2a). If we used age <25 years as the only criterion of recent infection, the TDR prevalence of patients with recent and those with chronic infections remained comparable (12.6% versus 10.5%, $P=0.65$) (data not shown).

The overall prevalence of TDR to any antiretroviral agent (NRTIs, NNRTIs or PIs) was 13.9%, 11.5% and 9.8% during 2006–08, 2009–11 and 2012–14, respectively (Figure 2b). The numerically declining trends of TDR to any class of antiretroviral agents did not reach statistical significance. Specific RAMs to NRTIs, NNRTIs and PIs are shown in Figure 3(a). Only K101E/P and K103N/S mutations in RT were observed in >1% of the HIV-1 strains.

Comparisons between patients infected with HIV-1 strains harbouring drug-resistant mutations and those without are shown in Table 2. All HIV strains with transmitted RAMs came from MSM, and all but one were subtype B. CD4 lymphocyte counts ≤500 cells/mm^3 and HBsAg positivity were independent predictors of acquiring drug-resistant HIV in the multivariate model.

TDR-associated mutations to INSTIs

Among 312 HIV-positive patients with genotypic resistance testing of the HIV-1 integrase gene, 216 (69.2%) were enrolled during the period 2012–14. Overall, 10 (3.2%) HIV-1 strains harboured integrase RAMs (Figure 1). The prevalence was 4.3% (1/23) during 2006–08, before the introduction of INSTIs in Taiwan (Figure 2b). The frequencies of individual RAMs are shown in Figure 3(b). If we limited RAMs to major INSTI mutations (T66I, E92Q, G140S, Y143C/H/R, S147G, Q148H/K/R, N155H),[14] only one strain harbouring the Q148R mutation was detected, however.

Discussion

Our study, conducted among VCT subjects testing positive for HIV-1 in Taiwan during 2006–14, showed that 11.1% of the patients were infected with HIV-1 strains harbouring at least

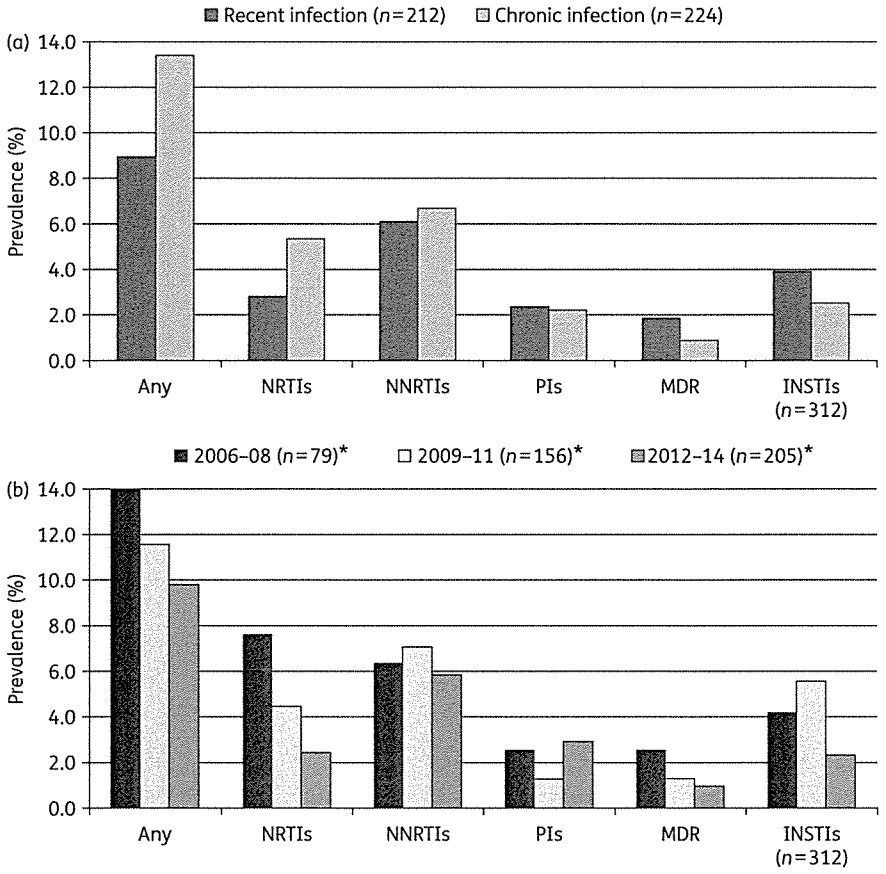

Figure 2. Prevalence of HIV-1 TDR by recent infections (a) and by study periods (b). Any class refers to NRTIs, NNRTIs or PIs. *These numbers did not include genotypic resistance testing of integrase gene.

one PR or RT RAM. Consequently, the prevalence of TDR of HIV-1 in Taiwan was estimated as moderate (5%–15%) according to the WHO categorization method. The prevalence of TDR seemed to be stable throughout the 9 years of the study. We also identified transmission of HIV strains with RAMs to INSTIs for the first time in Taiwan, at a prevalence of 3.2%. In only one patient, a major mutation (Q148R) conferring high-level resistance to two INSTIs in clinical use (raltegravir and elvitegravir) was found.

Our prior surveillance in Taiwan during 2000–10 showed that the overall prevalence of RAMs was 8.0%, and many patients were probably chronically infected due to their low CD4 lymphocyte counts.[5,20] Since transmitted RAMs are more likely to be detected in persons with recent infection compared with those with established infection,[28] it is not surprising that the prevalence in this study seems to be slightly higher. Our HIV-infected patients in the current study were predominately MSM with subtype B, and nearly half of them had recently acquired HIV (within the past 153 days) according to the BED assay. Therefore, this study may be more accurate in estimating the current rate of transmission of RAMs when access to VCT services have been further improved to detect HIV infection early. However, no statistically significant difference was found between chronic and recent infections in the prevalence of one or more drug resistance mutations. In our study, even patients with chronic infections beyond the 153 day window had relatively high CD4 lymphocyte counts (mean 346 cells/mm^3) at baseline, which suggests that the interval between infection and testing was not too extended. Our findings were consistent with a similar surveillance among VCT subjects in southern Taiwan, which reported a 10.6% prevalence of TDR.[29] This prevalence is also in line with those reported in Australia, Europe and North America, in the range of 8%–17%.[8,9,12,23]

To ameliorate the surging costs of antiretroviral drugs, Taiwan CDC, which started to provide free-of-charge ART in the 1990s, has implemented regulations for the prescription of more expensive INSTI- or PI-based regimens. These measures have raised concerns about the emergence of drug resistance, particularly in the absence of routine baseline genotypic resistance testing before cART initiation. In this surveillance, we did not detect any rising trends of TDR to any of the three classes of antiretroviral agents (NRTIs, NNRTIs and PIs). However, mutations conferring resistance to NNRTIs were most common (6.4%), accounting for more than half of the RAMs found. This finding is worrisome, as NNRTI-based regimens are the preferred first-line cART in Taiwan. Vigilant national monitoring in the following years is needed to determine the long-term impacts of the ART policy on the transmission of RAMs and its clinical implications.

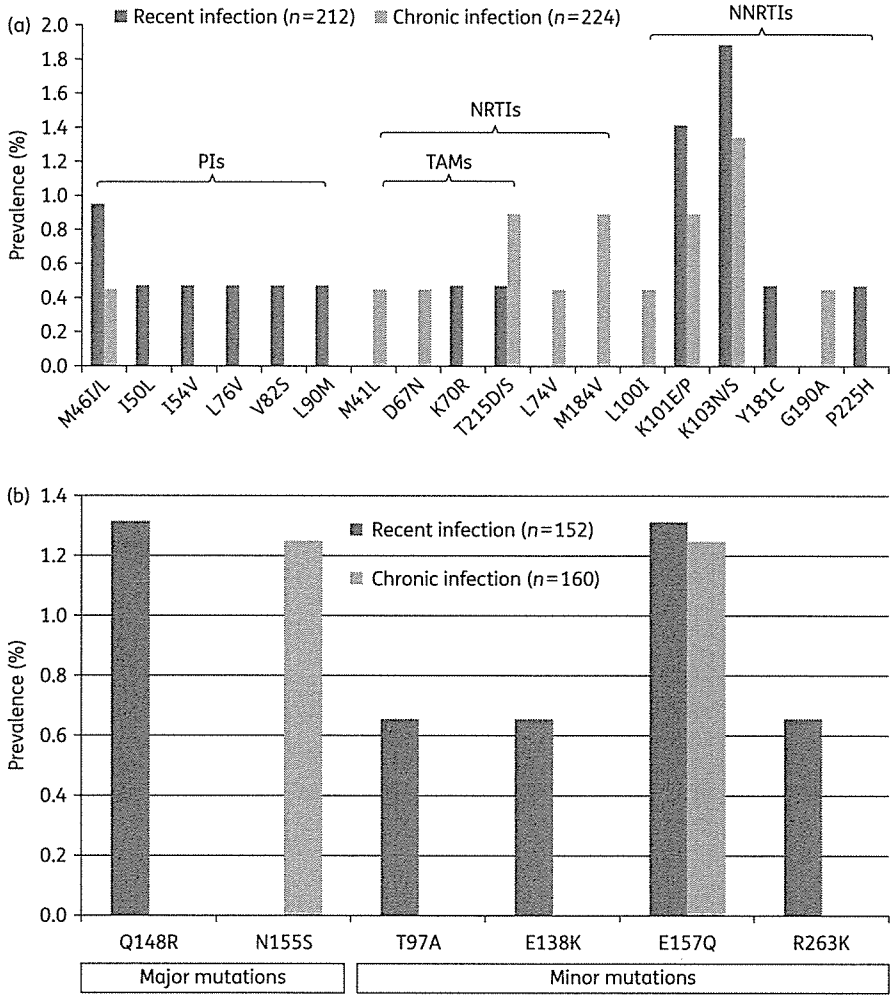

Figure 3. Frequencies of TDR mutations to NRTIs, NNRTIs and PIs (a) and to INSTIs (b). TAM, thymidine analogue mutation.

In this study, CD4 lymphocyte counts ≤500 cells/mm^3 and positive HBsAg were independent predictors of acquisition of HIV with RAMs. To our knowledge, hepatitis B virus (HBV) infection has not been reported to be associated with TDR acquisition. Many of our patients were born after 1986, when universal neonatal HBV vaccination and catch-up vaccination were implemented in Taiwan.[30] In the era of nationwide HBV vaccination for newborns, HBsAg positivity has also been identified to be significantly associated with syphilis and hepatitis C virus antibody (anti-hepatitis C virus) positivity, which implies that HBV might still be transmitted through high-risk sexual behaviours when immunity against HBV wanes and booster vaccination may not be administered.[30] An outbreak of HBV infection with transmission of drug resistance via sexual contacts among HIV-infected patients has also been reported.[31] One possibility of our finding is that drug-resistant HIV might be co-transmitted with HBV through high-risk behaviours. However, this point may not be supported due to similarly high-risk behaviours between patients with and without TDR. Another explanation is HBV/HIV-coinfected patients might be exposed to lamivudine as HBV treatment before HIV diagnosis. Indeed, in our study, two HBsAg-positive patients had received lamivudine monotherapy for HBV before, with their HIV-1 strains harbouring the M184V mutation (data not shown). However, among 18 patients acquiring NRTI-resistant strains, the frequencies of the M184V mutation in HBsAg-positive and HBsAg-negative patients were not significantly different [2/5 (40%) versus 3/13 (23.1%), $P=0.53$] (data not shown). Further studies are needed to elucidate the correlation of HBV coinfection and TDR.

INSTI resistance is potentially influenced by exposure to antiretroviral drugs and HIV-1 subtypes. In clinical trials of ART-naive patients, rates of virological failure with INSTI resistance were low, ranging from 0% to 3%.[17] Raltegravir has been licensed in Taiwan since 2009 and remains the only INSTI in the Taiwanese market. Despite its established efficacy and safety, raltegravir is reserved for patients for whom NNRTI-based regimens are not indicated because of tolerance or resistance issues according to the Taiwanese regulations on cART. In this setting, a prevalence of 3.2% RAMs in integrase, though low, is a point

Table 2. Comparison of characteristics between patients with resistant strains and those without RAMs

Characteristic	With RAMs, $N=49$	Without RAMs, $N=391$	P	Multivariate analysis	
				OR (95% CI)	P
Year of sampling, *n* (%)			0.59		
2006–08	11 (22.5)	68 (17.4)		1	
2009–11	18 (36.7)	138 (35.3)		1.04 (0.39–2.76)	0.94
2012–14	20 (40.8)	185 (47.3)		0.88 (0.33–2.33)	0.80
Male, *n* (%)	49 (100.0)	380 (97.2)	0.62		0.99
Age (years), mean ± SD	29.2 ± 6.3	29.5 ± 7.1	0.75		
≤25 years, *n* (%)	16 (32.7)	111 (28.4)	0.62	1.65 (0.77–3.57)	0.20
MSM, *n* (%)	49 (100.0)	366 (93.6)	0.10		0.98
Recent HIV infections, *n* (%)	19 (38.8)	193 (49.4)	0.17	0.64 (0.31–1.31)	0.22
Reasons for screening, *n* (%)					
having confirmed HIV-infected sexual partners	9 (18.4)	69 (17.7)	0.84		
having an IDU partner	0 (0.0)	2 (0.5)	>0.99		
ever having an STI	8 (16.3)	97 (24.8)	0.22		
having transactional sex	1 (2.0)	23 (5.9)	0.50		
having a one-night stand	21 (42.9)	176 (45.0)	0.88		
having anal sex	38 (77.6)	312 (79.8)	0.71		
having oral sex	38 (77.6)	312 (79.8)	0.71		
having unsafe oral sex once[a]	33 (86.8)	300 (96.2)	0.05	0.22 (0.02–2.62)	0.23
illicit drug use	9 (18.4)	107 (27.4)	0.23		
Baseline laboratory results					
RPR ≥4, *n* (%)	8 (16.3)	51 (13.0)	0.51		
western blot for HIV-1, *n* (%)			0.23		
positive	46 (93.9)	356 (91.0)			
indeterminate	1 (2.0)	29 (7.4)			
PVL (log_{10} copies/mL), mean ± SD	4.52 ± 0.68	4.68 ± 0.74	0.17		
>5 log_{10} copies/mL, *n* (%)	12 (24.5)	120 (30.7)	0.41	0.62 (0.28–1.37)	0.23
CD4 cell count (cells/mm^3), mean ± SD	336.9 ± 173.5	387.6 ± 201.7	0.09		
>500 cells/mm^3, *n* (%)	5 (10.2)	97 (24.8)	0.02*	0.33 (0.11–0.98)	0.05*
HBsAg positivity, *n* (%)	10 (20.4)	29 (7.4)	0.01*	4.82 (1.94–11.9)	<0.001*
anti-HCV positivity, *n* (%)	0 (0.0)	14 (3.6)	0.38		
subtype B	48 (98.0)	354 (90.5)	0.10	3.08 (0.39–24.11)	0.28

HCV, hepatitis C virus; IDU, injecting drug user; RPR, rapid plasma reagin.
*$P<0.05$.
[a]The denominators were patients having oral sex for each category.

of concern. Among the INSTI-related major mutations we detected, Q148R can cause 30- to 100-fold reduction of drug susceptibility,[32] while N155S is a rare non-polymorphic mutation which was selected *in vitro* and can reduce raltegravir efficacy less efficiently than N155H.[33] Among the four minor mutations detected in this study, T97A and E157Q are polymorphic accessory mutations that can be selected in patients receiving raltegravir,[34] while E138K and R263K are non-polymorphic INSTI-resistance mutations selected in patients receiving INSTIs.[35] At present, none of these minor mutations occurs in combination with INSTI-related major mutations in our study subjects. Further investigations are needed to determine to what extent these RAMs impact the clinical effectiveness of INSTIs. Moreover, additional research is required to determine the source of these mutations. Continuous monitoring is warranted to prevent the spread of strains resistant to INSTIs in the community.

Some questions about INSTI resistance remain unanswered, however. Major INSTI resistance mutations listed in the 2014 edition of the IAS-USA panel and the Stanford University HIV Drug Resistance database are different.[36] Some minor integrase mutations do not reduce susceptibility to INSTIs on their own, but require the presence of other mutations, and minor RAMs have been observed in up to 22.5% of INSTI-naive patients.[27]

The findings of this study should be interpreted with the necessary caution. First, the study was based on data from persons seeking VCT at only one hospital, although this site provides the largest VCT programme and HIV care in Taiwan. Second, the number of cases included in this study was small. Third, our

participants were predominately MSM infected with subtype B. While MSM account for >85% of HIV infections reported to Taiwan CDC annually after 2008, when the HIV outbreak among injecting drug users was brought under control, this sampling bias precludes generalization of our findings to injecting drug users and heterosexuals. Furthermore, it has been recognized that TDR is most prevalent among MSM worldwide.[12] Thus, TDR epidemics in Taiwan in at-risk populations other than MSM or in subtypes other than B remain to be investigated.

In conclusion, the prevalence of TDR-associated mutations among persons seeking VCT services in Taiwan remains stable and is comparable to the range found in high-income countries. Consequently, baseline genotypic resistance testing should be considered for routine use in newly diagnosed HIV-infected individuals according to the treatment guidelines.[13]

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Author contributions

Conceived and designed the experiments: C.-C. L., W.-C. L., C.-T. F., J.-Y. Y., C.-C. H. and S.-Y. C. Performed the experiments: W.-C. L., J.-Y. Y., L.-H. C., P.-Y. W., Y.-Z. L., S.-F. C., Y.-C. S. and S.-Y. C. Analysed the data: C.-C. L., W.-C. L., C.-T. F., J.-Y. Y., C.-C. H. and S.-Y. C. Wrote the paper: C.-C. L., W.-C. L., C.-C. H. and S.-Y. C.

Supplementary data

The standardized anonymous, self-administered questionnaire interview and Table S1 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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Research article

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

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Abstract

Introduction: HIV infection impairs maintenance of immunological memory, yet few studies of HIV-positive adults receiving 7-valent pneumococcal conjugate vaccine (PCV7) have followed them beyond the first year. We determined and compared the durability of serological responses and the clinical outcomes of HIV-positive adults annually for five years following vaccination with one or two doses of PCV7.

Methods: In this non-randomized clinical trial, 221 pneumococcal vaccine-naïve HIV-positive adults receiving one ($n = 109$) or two doses four weeks apart ($n = 112$) of PCV7 between 2008 and 2010 were longitudinally followed for evaluation of significant serological response and for episodes of pneumonia and invasive pneumococcal disease.

Results: At the time of vaccination, the two groups were well matched for age, risk factors, combination antiretroviral therapy (cART) coverage, CD4 count and plasma HIV RNA load (PVL). At the end of five years, the CD4 counts for the one- and two-dose groups had increased from 407 and 406 to 550 and 592 cells/μL, respectively, and 82.4 and 81.6% of the participants had fully suppressed PVL. Significant immune responses to ≥ 2 serotypes persisted for 67.9 vs 78.6%, 64.2 vs 71.4%, 66.1 vs 71.4%, 57.8 vs 69.6% in the second, third, fourth and fifth years after one and two doses of PCV7 in the intention-to-treat analysis, respectively. In multivariate analysis, immunization with two doses of PCV7 (odds ratio (OR) 1.71, 95% confidence interval (CI) 1.10 to 2.65, $p = 0.016$), concurrent cART (OR 2.16, 95% CI 1.16 to 4.00, $p = 0.015$) and CD4 proliferation (OR 1.12, 95% CI 1.01 to 1.27, $p = 0.031$) were predictive of persistent serological responses in the fifth year. Only one patient in the one-dose group had documented pneumococcal pneumonia (non-bacteraemic) and none had invasive pneumococcal disease in the 6.5 years of follow-up.

Conclusions: One or two doses of PCV7 achieve durable seroprotective responses in HIV-treated participants; however, two doses may be more robust than one dose in a larger study population or in real-world populations with less cART coverage.

Keywords: serological response; anti-capsular antibody; immunogenicity; *Streptococcus pneumoniae*; invasive pneumococcal disease.

To access the supplementary material to this article please see Supplementary Files under Article Tools online.

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Introduction

Adults infected with the human immunodeficiency virus (HIV) are at significantly higher risk of invasive and recurrent pneumococcal infections despite combination antiretroviral therapy (cART) [1–3]. This risk may be related to HIV-related accelerated senescence of immune repertoire and loss of memory B cells prior to viral suppression and the relative dysregulation of the reconstituted but incompletely restored immune system following antiretroviral therapy [4–8]. Consequently most authorities, including the Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention, the World Health Organization (WHO), the European AIDS Clinical Society and the British HIV Association, recommend pneumococcal vaccination for all HIV-positive adults regardless of immune status [9–13].

Strategies to optimize vaccine efficacy and effectiveness at the individual and public health levels vary from country to country. However, of the two different vaccines that have been developed (pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV)), current guidelines recommend the latter, which elicits a T-cell-dependent response and memory B and T cells, as the initial vaccine for

HIV-positive adults and children [10,11,14,15]. The 23-valent PPV may be administered subsequently to broaden serotype coverage [16]. Given the improved survival of HIV-positive persons on cART, when and how many doses should be administered as revaccination over the lifetime of HIV-positive persons following priming with vaccination with PCVs become important clinical issues [9].

Unfortunately, there is a dearth of data on the long-term immunogenicity of PCVs in HIV-positive adults, although we know that following PPV antibody concentrations drop below the cutoff values for most serotypes after five years; hence revaccination after five years is recommended [17–21]. Whether the same paradigm applies following PCV remains unanswered. We previously showed that HIV-positive adults on cART who received two doses of 7-valent PCV (PCV7) achieved better serological responses than those who received one dose during and at the end of 48 weeks of follow-up [22]. Here we followed this cohort longitudinally and investigated the durability and superiority of two doses over one dose of PCV7 during the five consecutive years of follow-up.

Methods

Study population and setting

HIV-positive adults aged ≥ 20 years who had no history of pneumococcal vaccination were recruited from infectious disease clinics at the National Taiwan University Hospital, the largest designated hospital for inpatient and outpatient HIV care in Taiwan, from October 2008 to June 2010. HIV infection was confirmed by Western blot. Participants with the following conditions were excluded: current pregnancy, use of immunomodulating agents within the past three months or use of cytoreductive chemotherapy within the last six months [22]. The study was approved by the Research Ethics Committee of the hospital and the participants gave written informed consent.

In Taiwan, HIV-positive patients have free access to HIV care that includes cART and monitoring of CD4 cell counts, plasma HIV RNA load (PVL) and biochemistry following the local HIV treatment guidelines. CART was defined as the combination of at least three antiretroviral agents that contained two nucleoside reverse-transcriptase inhibitors plus boosted or unboosted protease inhibitors or one non-nucleoside reverse-transcriptase inhibitor or integrase inhibitor or alternatively three nucleoside reverse-transcriptase inhibitors.

Vaccine administration

All eligible participants were consecutively enrolled to receive one or two doses of vaccine four weeks apart administered by study nurses via intramuscular deltoid injections. This dosing schedule was used in the only efficacy trial of PCV7 in HIV-positive adults as well as earlier PCV7 immunogenicity trials [23,24]. Each 0.5-ml dose of PCV7 vaccine (Prevenar/Prevnar®, Wyeth-Lederle, New York, USA) contained 2 μg of capsular polysaccharide from each of six serotypes (4, 9V, 14, 18C, 19F and 23F) and 4 μg of capsular polysaccharide from serotype 6B, linked to 20 to 25 μg of CRM_{197}. After vaccination, participants were prospectively followed and blood samples were collected every 12 weeks during the first 48-week follow-up period and annually for the subsequent four years of follow-up. Subjects in the two groups selected for final analysis were matched by CD4 count and PVL at vaccination.

Laboratory investigations

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 copies/mL, and CD4 count was determined using FACFlow (BD FACS Calibur, Becton Dickinson, San Jose, CA, USA). The CD4 counts and PVL were monitored one month after initiation of cART in antiretroviral-naïve participants or after a change of regimen due to virological failure and every three to six months thereafter according to the local HIV treatment guidelines.

Determinations of anti-capsular antibody levels

Serum samples were separated from clotted blood samples by centrifugation and stored at -70°C. Anti-capsular antibody concentrations to the four most prevalent pneumococcal serotypes (serotypes 6B, 14, 23F and 19F) in Taiwan [25] were determined in serially collected blood specimens using ELISA as previously described [26]. The antibody responses between the second and fifth years were determined using the new human pneumococcal standard reference serum, 007sp, and dual adsorption with cell-wall polysaccharide and pneumococcal polysaccharide 22F as specified in the WHO standard [27]. In previous years (4-week to 48-week ELISA responses), the concentration of immunoglobulin (IgG) used the original WHO-approved reference standard 89F, which did not specify the use of pneumococcal polysaccharide 22F [28]. However, since the reference standard 89F was exhausted and bridged to the 007sp serum, we used the new standard reference serum with dual adsorption. Comparison of the two methods revealed similar results for methods, especially at antibody levels of >1 μg/mL [29].

Primary and secondary end points

The primary end point of the study was durable significant antibody responses, defined as a twofold or greater increase in specific IgG against two or more serotypes after five years [17,22,24]. Serological secondary end points included the geometric mean titres (GMTs), proportion of participants with sustained specific IgG concentrations above ≥ 1 μg/mL and the proportion of participants with persistent seroprotective responses, defined as a twofold or greater increase plus titres ≥ 1 μg/mL to at least two of four serotypes studied [24,30]. Antibody response rates were estimated by both intention-to-treat (ITT) analysis, in which participants with missing data were considered non-responders, and per-protocol (PP) analysis, in which participants with missing data were excluded from analysis. Clinical secondary end points included pneumonia, pneumococcal pneumonia and invasive pneumococcal disease (IPD) episodes. Pneumonia was defined by clinical presentation and radiographic findings consistent with community-acquired pneumonia. A diagnosis of probable pneumococcal pneumonia was made if a sputum smear with a Quality score of 3 yielded Gram-positive cocci in chains in the absence of another identifiable aetiology; the diagnosis was confirmed if, additionally, the sputum culture yielded *Streptococcus pneumoniae* or if the urinary pneumococcal antigen test was positive [31]. IPD was defined by the isolation

of *S. pneumoniae* from a normally sterile site (i.e. blood, cerebrospinal or pleural fluid) [31]. The laboratory researchers who quantified the antibody responses were blinded to the identity, clinical and vaccination status of the participants. The radiologists who reported the radiographic findings were also blinded to the vaccination status of the participants.

Statistical analyses

The analyses were conducted using the statistical package SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Chi-square tests or, if necessary, Fisher's exact tests were used for categorical variables. Student's *t*-tests and Mann-Whitney U tests were used for numerical variables. Since observations were made over time periods, generalized estimating equations (GEEs) accounting for the interdependence among observations were used to compare mean response rates to different PCV doses, with adjustments made for time-updated variables including the patient's age at time of vaccination; at the second, third, fourth and fifth years; the CD4 counts at baseline, at nadir and at the second, third, fourth and fifth years (in increments of 100 cells/μL); PVL at baseline, peak PVL and suppressed PVL <20 copies/mL at the second, third, fourth and fifth years; co-infection with hepatitis B and hepatitis C virus (HCV) as defined by the presence of hepatitis B surface antigen (HBsAg) and anti-HCV antibody, respectively, at time of vaccination; and receipt of cART at time of vaccination and at the second, third, fourth and fifth years. A stepwise model comparison and selection were used to determine the final model of multiple variable analysis [32]. We used the SAS PROC GENMOD procedure to fit the GEE models. Odds ratios for each prognostic factor and 95% confidence intervals (CIs) were also calculated. All statistical tests were two-tailed, and p values <0.05 were considered significant.

Results

The study flow is shown in Figure 1. Serological responses beyond the first year were evaluated in 221 participants by ITT analysis, 112 of whom had received two doses of PCV7 and 109 one dose only. Their baseline clinical characteristics are shown in Table 1. The cohort comprised mainly male adults who had acquired HIV via sexual intercourse. At the time of vaccination, over 70% of the cohort were receiving cART but less than half had undetectable PVL. After five years of follow-up, the percentages of participants receiving cART and achieving undetectable PVL had increased to above 90% and 80%, respectively. The one- and two-dose groups were well matched for age, cART coverage, CD4 count and co-morbidities both at baseline and at the end of five years of follow-up. With the exception of the peak PVL, which was higher in the two-dose group compared to the one-dose group (5.8 $\log_{10}$ copies/mL vs 4.9 $\log_{10}$ copies/mL, $p = 0.025$), the PVL at time of vaccination and at the end of follow-up were similar between groups.

Overall serological responses

Significant serological responses characterized by a twofold or greater increase in antibody levels to two or more serotypes by ITT and PP analyses are represented in Table 2 and Figure 2. Throughout the five years of follow-up, serological responses were maintained by 57.6 to 67.9% and 69.6 to 78.6% of the vaccinees in the one- and two-dose groups by ITT analysis,

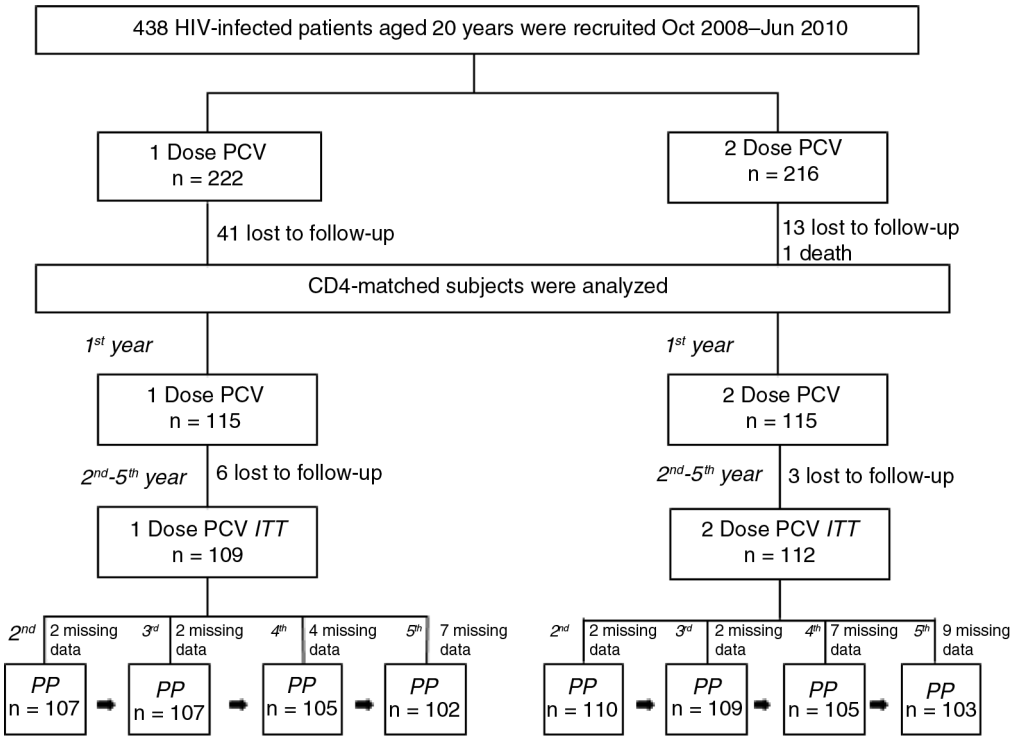

Figure 1. Study flow of HIV-positive adult participants receiving one or two doses of 7-valent pneumococcal conjugate vaccine followed for five consecutive years.

Table 1. Characteristics of HIV-positive adults receiving primary vaccination with one or two doses of PCV7 at baseline and at the end of the five years of follow-up

	One dose ($n = 109$)	Two doses ($n = 112$)	*p*
Age, mean (SD), years	35.8 (10.1)	36.1 (10.8)	0.789
Male, *n* (%)	104 (95.4)	108 (96.4)	0.746
Risk factor, *n* (%)			0.520
Homosexual/bisexual male	93 (86.1)	87 (80.6)	
Heterosexual	13 (12.0)	17 (15.7)	
Injecting drug user	2 (1.9)	4 (3.7)	
Treatment status, *n* (%)			
On cART at baseline	77 (70.6)	81 (72.3)	0.782
On cART at end of five years	94 (92.2)	95 (92.2)	0.984
CD4 lymphocyte count, cells/μL, median (IQR)			
Nadir CD4	240 (79 to 387)	229 (51 to 450)	0.737
Baseline CD4	407 (244 to 583)	446 (252 to 591)	0.543
< 200, *n* (%)	13 (11.9)	15 (13.4)	0.743
200 to 349, *n* (%)	25 (22.9)	26 (23.2)	0.961
350 to 499, *n* (%)	31 (28.4)	26 (23.2)	0.375
≥ 500, *n* (%)	40 (36.7)	45 (40.2)	0.595
End of five-year CD4	550 (426 to 735)	592 (433 to 749)	0.476
< 200, *n* (%)	6 (5.6)	11 (10.0)	0.229
200 to 349, *n* (%)	21 (19.6)	14 (12.7)	0.167
350 to 499, *n* (%)	32 (29.9)	26 (23.6)	0.297
≥ 500, *n* (%)	46 (43.0)	59 (53.6)	0.117
Plasma HIV RNA load (PVL), $\log_{10}$ copies/mL			
Peak PVL, median (IQR)	4.9 (4.3 to 5.4)	5.8 (4.4 to 5.6)	0.025
Baseline PVL, median (IQR)	2.2 (1.6 to 4.0)	1.7 (1.6 to 3.9)	0.314
End of five-year PVL, median (IQR)	1.3 (1.3 to 1.3)	1.3 (1.3 to 1.3)	0.974
Undetectable PVL at baseline, *n* (%)	48 (44.0)	52 (46.4)	0.721
Undetectable PVL at five years, *n* (%)	84 (82.4)	84 (81.6)	0.882
Co-morbidities prevaccination, *n* (%)			
Chronic HBV co-infection	20 (19.0)	20 (17.9)	0.821
Chronic HCV co-infection	6 (5.6)	5 (4.5)	0.710
Isolated anti-HBc	48 (47.5)	45 (42.5)	0.463
Chronic pulmonary disease	1 (0.9)	6 (5.4)	0.119
Congestive heart failure	1 (0.9)	3 (2.7)	0.622
Diabetes mellitus	4 (3.7)	2 (1.8)	0.441

cART, combination antiretroviral therapy; HBV, hepatitis B virus; anti-HBc, hepatitis B core antibody; HCV, hepatitis C virus; IQR, interquartile ratio; PCV7, 7-valent pneumococcal conjugate vaccine; SD, standard deviation.

respectively. At the end of five years of follow-up, more participants in the two-dose group had persistent serological responses compared to the one-dose group, but this difference was only statistically significant by PP analysis: 68.6 vs 57.8% ($p = 0.067$) by ITT and 61.8 vs 76% ($p = 0.026$) by PP. Adding the arbitrary cutoff of antibody concentrations ≥ 1 μg/mL to the primary end point yielded similar results (Table 3).

Serological responses to individual serotypes

The antibody responses to individual serotypes are shown in Supplementary Figures 1 and 2. Individual response rates were highest to serotype 14, followed by 23F, 6B and 19F. Sequential GMTs of specific anti-capsular IgG antibodies to serotypes 6B, 14, 19F and 23F are shown in Table 4, and the proportions of participants with persistent absolute IgG concentrations > 1 μg/mL are shown in Table 5. Both groups maintained increased specific antibody levels above baseline throughout the five years, gradually decreasing thereafter.

Factors associated with persistent serological response

Table 6 summarizes the results of linear regression with the GEE approach to define the factors associated with persistent serological response between the second and fifth years of follow-up. Two doses versus one dose of PCV7 (adjusted odds ratio (AOR) 1.71, 95% CI 1.10 to 2.65, $p = 0.016$), concurrent cART (OR 2.16, 95% CI 1.16 to 4.00, $p = 0.015$) and CD4 lymphocyte recovery (AOR 1.12, per 100 cells/μL gained,

Table 2. Percentage of HIV-positive adults with persistent immune responses defined by a twofold or more IgG rise to at least two *Streptococcus pneumoniae* serotypes in the second, third, fourth and fifth years following one or two doses of PCV7 by intention-to-treat (ITT) and per-protocol (PP) analyses (primary end point)

	One dose	Two doses	*p*
ITT			
Year 2	67.9	78.6	0.072
Year 3	64.2	71.4	0.251
Year 4	66.1	71.4	0.388
Year 5	57.8	69.6	0.067
PP			
Year 2	67.4	78.2	0.079
Year 3	61.7	73.3	0.084
Year 4	66.3	76.3	0.128
Year 5	61.8	76.0	0.026

IgG, immunoglobulin; PCV7, 7-valent pneumococcal conjugate vaccine.

95% CI 1.01 to 1.27, $p = 0.031$) were significantly associated with persistent serological responses in the fifth year following vaccination. We repeated the GEE model to incorporate time-updated values for CD4 count and PVL. However, this measure did not change the fact that two doses over one dose and cART were predictive of persistent responses in the fifth year. Time-updated CD4 counts were predictive of persistent responses only in the fifth year (AOR 1.131, 95% CI 1.021 to 1.265, $p = 0.031$).

Pneumonia and invasive pneumococcal disease

Fifteen episodes of pneumonia occurred in 11 vaccinated subjects, seven of whom had received one dose of PCV and four of whom had received two doses over a median follow-up duration of 6.5 years (range: 5.8 to 6.8 years) post-vaccination. Only one patient in the one-dose group received a confirmed diagnosis of *S. pneumoniae* pneumonia, 4.2 years after vaccination, on the basis of right lobar pneumonia by chest radiography, sputum smear showing Gram-positive cocci in chains and a positive test for urine pneumococcal antigen. This patient had persistent serological responses to three of four serotypes throughout the five years of follow-up. Two other vaccinees (one in each dosing group) had a probable diagnosis of pneumococcal pneumonia with lobar consolidation and sputum smear showing Gram-positive cocci in chains, sputum cultures yielding ''mixed flora'' and no other alternative aetiological agent by serological or antigen testing. The patient in the one-dose group was a primary non-responder and the patient in the two-dose group had twofold or greater serological responses to at least two serotypes until the third year but was not tested in the fourth and fifth years of follow-up. No vaccinated subjects had a documented episode of IPD.

Adverse events

Self-limited injection-related adverse events occurred in 34.3% of our participants, with the most common being injection site soreness ($n = 95$). None of the patients who received two doses of PCV reported worsening or new adverse events after receipt of the second dose. There was no statistically significant difference in occurrences of adverse events between patients receiving one or two doses of PCV7 [33].

Discussion

This study documents durable antibody responses in 58 to 70% of HIV-positive adults who received cART five years after vaccination with PCV7. Our data show that the antibody concentrations post-vaccination remained significantly elevated from baseline and declined very gradually in the subsequent five years, similar to the long-lasting (5- to 10-year) responses elicited against most but not all of the serotypes in children and adolescents post-PCV series in infancy [34–36]. Slow decay of anti-pneumococcal-specific IgG post-PCV in contrast to the more rapid decay post-PPV suggests that the generation of memory B cells via a T-cell-dependent response and natural boosting contributed to antibody persistence [35,37–39]. The levels of antibody persistence are a novel finding for this population, since no prior studies have been conducted in HIV-positive adults with good disease control or in adults with a high incidence of pneumococcal carriage as evidenced by the high prevaccination GMTs with baseline titres greater than 1 μg/mL for two of the four serotypes in our cohort. These high baseline GMTs are in line with the high prevaccination GMTs exceeding 1 μg/mL for all tested serotypes of past or present HIV cohorts in the United States and Spain due to the high pre-PCV incidence of pneumococcal disease and colonization among HIV-positive individuals [40–42]. However, to our knowledge, the present study is the first to examine the long-term (longer than three years) immunogenicity of PCVs in adults, and specifically in those living with HIV (Supplementary Table 1 [24,30,40,43–52]).

Persistent immune responses were more likely to be observed for HIV-positive adults who had received two primary doses administered four weeks apart rather than one dose and among those on cART with CD4 expansion as a surrogate marker for immune reconstitution. In addition, clinical episodes of pneumonia were less frequent for the two-dose than the one-dose group. Only one confirmed case of pneumococcal pneumonia occurred in the one-dose group, and no cases of IPD occurred in the vaccinated cohort in the follow-up period of 6.5 years. Hence, perhaps with a larger sample size, the statistical trend of 57.8 vs 68.6% ($p = 0.067$) by ITT analysis between the single- and double-dosing strategies will prove to be a real difference.

Although long-term data for HIV-positive adults receiving PCVs are not available for comparison, there are a few long-term (4- to 5-year) immunogenicity studies of HIV-positive children [53,54] and midterm (1.5- to 3-year) studies of HIV-negative adults [51,55,56]. Of HIV-positive children who received three doses of 9-valent PCV at infancy, 36 to 77% harboured persistent immune responses (defined as ≥ 0.35 μg/mL of serotype-specific antibody) at five years against serotypes 6B, 14, 19F and 23F [54]. Of older (aged 2 to 18 years) HIV-positive children who received two doses of PCV7 plus one dose of PPV23, 82% had persistent immune responses (≥ 0.5 μg/mL) at five years against serotypes 6B and 14 [53]. Of our cohort, 68 to 100% had persistent

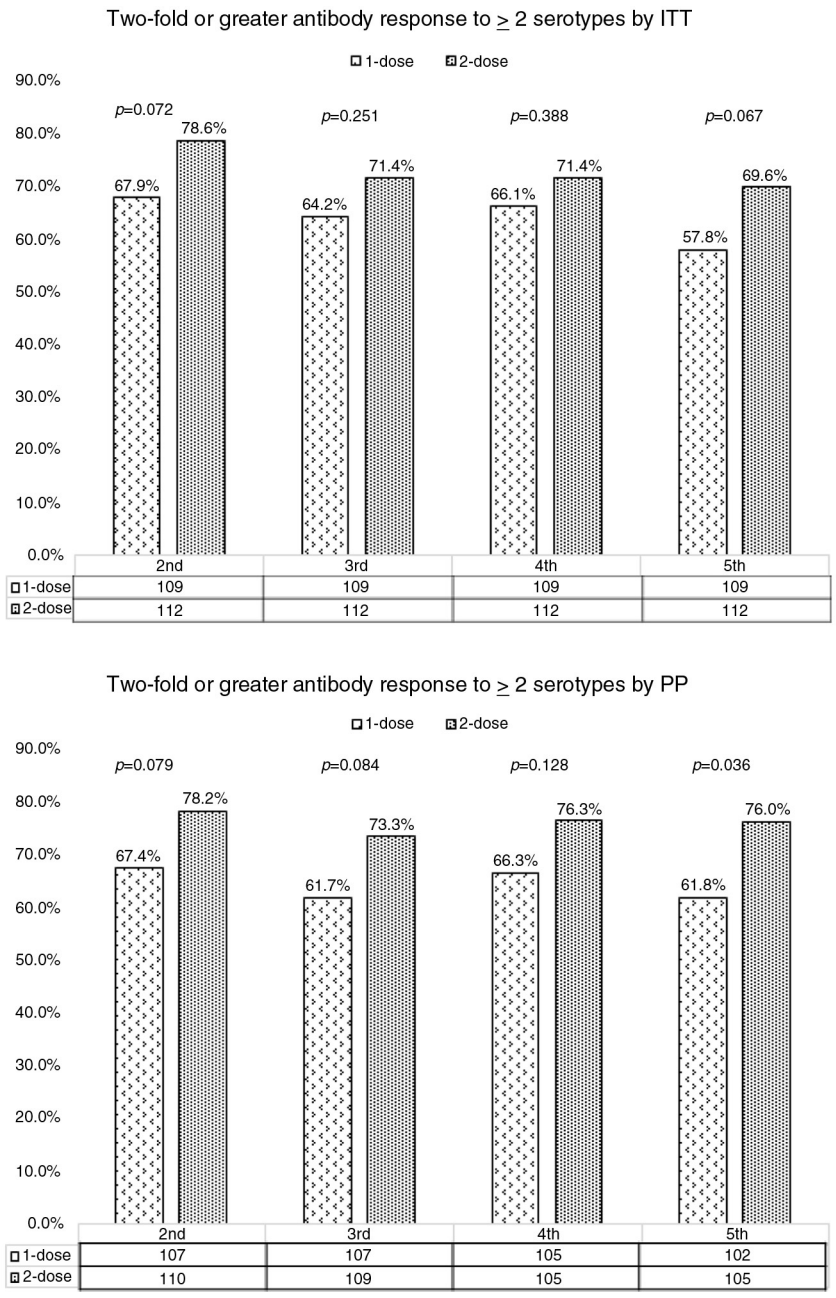

Figure 2. Persistent immune responses defined by a twofold or more immunoglobulin rise to at least two *Streptococcus pneumoniae* serotypes among 221 HIV-positive adult participants in the second, third, fourth and fifth years following vaccination with one or two doses of 7-valent pneumococcal conjugate vaccine by intention-to-treat and per-protocol analyses.

immune responses (using the threshold of 1 μg/mL adopted for adults as a measure of seroprotection [9,57]) at five years against serotypes 6B, 14, 19F and 23F. The percentage of persistent responders ($\geq$1 μg/mL) to the two vaccine serotypes with generally the lowest responses (6B and 23F) for rheumatoid participants after one dose at 1.5 years was remarkably lower (21%) than our one-dose HIV-positive vaccinees (72%) at two years [51].

Despite the different definitions for durability, serotype-differences in durability were similar across diverse populations. The most durable response following PCV7 was observed for serotype 14 in our HIV-positive adults at five years, adults with chronic pulmonary obstructive disease at two years and adults post-renal transplantation at three years [56,58]. Similarly, the greatest decay in serotype-specific antibody was observed for serotype 23F for HIV-positive children and adults with rheumatic diseases, as well as our HIV-positive adults [51,53,54]. However, this does not predict an increased risk of IPD by serotype 23F. A recent study showed serotype-specific correlates of protection in healthy children were lower than 0.35 μg/mL for serotypes 6B and 23F and higher than 0.35 μg/mL for 19F, supporting the notion that there may

Table 3. Percentage of HIV-positive participants with persistent immune responses defined by a twofold or more IgG rise plus an absolute IgG titre >1 μg/mL to at least two *Streptococcus pneumoniae* serotypes in the second, third, fourth and fifth years following one or two doses of PCV7 by intention-to-treat (ITT) and per-protocol (PP) analyses (secondary end point)

	One dose	Two doses	*p*
ITT			
Year 2	67.9	77.7	0.102
Year 3	64.2	70.5	0.317
Year 4	66.1	70.5	0.474
Year 5	57.8	67.9	0.122
PP			
Year 2	69.2	79.1	0.095
Year 3	65.4	72.5	0.262
Year 4	68.6	75.2	0.282
Year 5	61.8	73.8	0.065

IgG, immunoglobulin; PCV7, 7-valent pneumococcal conjugate vaccine.

Table 4. Sequential geometric mean titres (95% confidence interval) of specific anti-capsular immunoglobulin (IgG) antibodies to *Streptococcus pneumoniae* serotypes 6B, 14, 19F and 23F in the second to fifth years following vaccination with one or two doses of PCV7 (secondary end point)

	One dose	Two doses	*p*
Anti-6B serotype IgG levels, μg/mL			
Baseline	0.855 (0.743 to 0.985)	0.774 (0.643 to 0.843)	0.131
Year 2	2.023 (1.780 to 2.300)	1.943 (1.691 to 2.231)	0.670
Year 3	1.896 (2.149 to 1.747)	1.747 (1.537 to 1.987)	0.367
Year 4	1.948 (1.714 to 2.214)	1.760 (1.544 to 2.006)	0.272
Year 5	1.790 (1.571 to 2.040)	1.734 (1.519 to 1.979)	0.734
Anti-14 serotype IgG levels, μg/mL			
Baseline	1.992 (1.656 to 2.397)	1.905 (1.574 to 2.308)	0.739
Year 2	8.493 (7.037 to 10.253)	9.816 (8.182 to 11.776)	0.274
Year 3	7.706 (6.359 to 9.337)	8.696 (7.725 to 10.439)	0.366
Year 4	7.704 (6.355 to 9.338)	8.803 (7.345 to 10.549)	0.317
Year 5	6.980 (5.704 to 8.543)	8.216 (6.760 to 9.985)	0.250
Anti-19F serotype IgG levels, μg/mL			
Baseline	1.917 (1.648 to 2.230)	1.608 (1.354 to 1.910)	0.130
Year 2	3.254 (2.847 to 3.719)	3.265 (2.855 to 3.734)	0.973
Year 3	3.021 (2.649 to 3.446)	2.986 (2.633 to 3.387)	0.899
Year 4	3.277 (2.862 to 3.753)	3.020 (2.646 to 3.446)	0.392
Year 5	3.049 (2.682 to 3.477)	2.892 (2.537 to 3.295)	0.566
Anti-23F serotype IgG levels, μg/mL			
Baseline	0.734 (0.643 to 0.843)	0.644 (0.548 to 0.757)	0.020
Year 2	1.840 (1.554 to 2.180)	1.862 (1.574 to 2.202)	0.924
Year 3	1.709 (1.454 to 2.009)	1.624 (1.385 to 1.904)	0.654
Year 4	1.711 (1.444 to 2.028)	1.567 (1.343 to 1.829)	0.448
Year 5	1.555 (1.315 to 1.839)	1.502 (1.287 to 1.752)	0.760

P values compare IgG levels between one- and two-dose groups; IgG, immunoglobulin; PCV7, 7-valent pneumococcal conjugate vaccine.

be variability in the threshold of antibody concentrations required for protection against invasive disease for different serotypes [59]. An epidemiological survey from 2000 to 2012 showed that serotypes 14 and 23F were the two most common serotypes causing IPD in adults in Taiwan [33].

For this reason, and to adjust for the high prevaccination concentrations of antibodies to common serotypes among adults with many years of exposure to pneumococci [58], the primary end point in our study used only the fold increase in antibody concentrations to denote immunogenicity. Using a twofold increase in IgG titres, only 13 to 39% of adult renal transplant recipients compared to 40 to 78% of our HIV-positive participants maintained responses three years after one dose of PCV7 [56].

Double dosing (1 ml) or multiple sequential doses have been administered to improve primary immune responses and also to extend durability of these responses [49,52,60,61]. Previously, we demonstrated superiority of two doses of PCV7 over one dose for HIV-positive adults up to 48 weeks post-vaccination [22]. Here, we show that the dose-response persists after five years. However, in the only clinical efficacy trial of PCV7 in HIV-positive adults receiving two doses one month apart (matching dosing schedule), vaccine efficacy dropped dramatically from 85 to 25% after the first year [23]. Hence, two doses of PCV7 may not be sufficient to prevent recurrent IPD in the less immunocompetent (13% cART coverage and median CD4 212 cells/μL), more at risk (recent IPD on average 19 days earlier) HIV-positive participants in the African study compared to our participants. Yet, a study of HIV-treated adults given three doses of PCV13 administered at six-month intervals failed to demonstrate the value added by the second and third doses in terms of geometric fold rises [61]. The lack of dose-response may be related to the fact that PCV13 was being used as booster vaccinations in individuals previously vaccinated with PPV23 in the study by Glesby and colleagues and not in vaccine-naïve subjects as in our study. Moreover in the PCV13 study, antibody responses beyond one month after each vaccination were not evaluated and, therefore, the long-lasting value of multiple doses could not be evaluated. Current guidelines recommending only a single dose of PCV for HIV-positive adults do not take into account the durability of antibody responses due to the lack of long-term data [11,41].

Like the long-term studies of HIV-positive children, our data show a significant positive association between persistent antibody responses, receipt of cART and duration of cART [53]. In our multivariate analysis, we show that receipt of cART becomes a significant predictor of significant immune responses in the fourth and fifth years but not in the second and third years; that is, cART takes time to have an effect. This finding is consistent with studies showing persistent defects in pneumococcal antigen specific immunity by IFN-gamma ELI-Spot, T-cell proliferation, CD154 expression and intracellular cytokine assays despite 12 months of cART and persistently higher *S. pneumoniae* carriage rates despite 18 months of cART [6,8]. As the extent of immune recovery at 12 months was greater than at three or six months after cART, the capacity for ongoing reconstitution over time and subsequent effect thereof on immunogenicity and induced-immunological

Table 5. Proportions of HIV-positive adults with serotype-specific antibody concentrations of ≥1 μg/mL before and after vaccination with PCV7 between the following two to five years (secondary end point)

	Baseline	Year 2	Year 3	Year 4	Year 5
6B					
One dose	37.6% (41/109)	84.1% (90/107)	86.9% (93/107)	84.8% (89/105)	83.3% (85/102)
Two doses	33.9% (33/112)	82.7% (91/110)	77.1% (84/109)	81.0% (85/105)	79.6% (82/103)
14					
One dose	69.7% (76/109)	100% (107/107)	100% (107/107)	100% (105/105)	100% (102/102)
Two doses	69.6% (78/112)	100% (110/110)	100% (109/109)	100% (105/105)	100% (104/103)
19F					
One dose	81.7% (89/109)	98.1% (105/107)	98.1% (102/107)	97.1% (102/105)	99.0% (101/102)
Two doses	74.1% (83/112)	96.4% (106/110)	95.4% (104/109)	96.2% (101/105)	94.3% (97/103)
23F					
One dose	33.0% (36/109)	74.8% (80/107)	71.0% (76/107)	74.3% (78/105)	67.6% (69/102)
Two doses	30.4% (34/112)	77.3% (85/110)	75.2% (82/109)	75.2% (79/105)	73.8% (76/103)

All p values >0.05 when comparing the one-dose and two-dose groups; PCV7, 7-valent pneumococcal conjugate vaccine.

memory of PCV is implied [8]. The late effects of cART could also be inferred from the similar responses found for immunologically AIDS patients immunized immediately compared to those who had received cART for 6 to 12 months before vaccination [62]. The lack of benefit from delaying vaccination and our findings showing that baseline CD4 counts and PVL were not predictive of long-lasting immune responses support the current recommendations of vaccinating all individuals at the time of HIV diagnosis [12,14].

Widespread PCV vaccination of children contributing to herd immunity may decrease the burden of pneumococcal disease in adults [39,63]. However, given the high pre-PCV incidence of IPD in the HIV-positive population, herd effect is unlikely to negate the importance of targeted PCV vaccination [63]. In addition, the incidence of IPD among HIV-positive injecting drug users remains unchanged even in the post-PCV, post-HAART era [64]. For the underprivileged individuals and communities bereft of the benefits of pneumococcal childhood immunization, the role of targeted PCV vaccination of HIV-positive adults continues to be highly relevant.

The 13-valent PCV (PCV13, Prevnar 13), licensed by the US Food and Drug Administration in 2010 for prevention of IPD and otitis media among young children, has now superseded PCV7 [65]. PCV13 contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) and six additional serotypes (serotypes 1, 3, 5, 6A, 7F and 19A). PCV13

Table 6. Adjusted odds ratio (AOR) for persistent significant antibody responses, defined as a twofold or greater increase in specific IgG to two or more serotypes from baseline in the second to fifth years following vaccination with PCV7

	Second year				Third year				Fourth year				Fifth year			
	AOR	95% CI		p	AOR	95% CI		p	AOR	95% CI		p	AOR	95% CI		p
Age (continuous)	0.986	0.962	1.011	0.259	0.981	0.957	1.006	0.133	0.984	0.961	1.008	0.190	0.984	0.960	1.008	0.195
Two doses vs one dose	**1.786**	**1.123**	**2.840**	**0.014**	**1.623**	**1.027**	**2.566**	**0.038**	**1.604**	**1.024**	**2.513**	**0.039**	**1.711**	**1.104**	**2.652**	**0.016**
On cART vs untreated	1.260	0.621	2.556	0.522	1.763	0.897	3.466	0.100	**1.793**	**0.950**	**3.384**	**0.071**	**2.156**	**1.162**	**4.000**	**0.015**
HBsAg-positive	1.001	0.510	1.965	0.999	1.031	0.528	2.017	0.928	0.896	0.469	1.714	0.741	0.860	0.459	1.611	0.637
Anti-HCV-positive	1.368	0.535	3.497	0.513	1.729	0.647	4.616	0.275	1.602	0.703	3.650	0.262	1.270	0.566	2.849	0.563
Baseline PVL $>10^5$ copies/mL	1.909	0.628	5.809	0.255	2.196	0.808	5.970	0.123	1.718	0.673	4.382	0.258	1.713	0.643	4.560	0.281
Time-updated PVL <20 copies/ml	1.022	0.492	2.125	0.954	0.939	0.491	1.796	0.848	0.802	0.421	1.530	0.504	0.766	0.363	1.618	0.485
Nadir CD4 count <200 cells/μL	1.251	0.691	2.266	0.459	1.205	0.669	2.171	0.534	1.268	0.716	2.246	0.416	1.424	0.805	2.518	0.225
Time-updated CD4 counts	1.084	0.937	1.253	0.277	0.993	0.880	1.120	0.908	1.105	0.986	1.239	0.085	**1.131**	**1.012**	**1.265**	**0.031**

cART, combination antiretroviral therapy; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IgG, immunoglobulin; PCV7, 7-valent pneumococcal conjugate vaccine; PVL, plasma HIV RNA load. Bold indicates the variables where p is significant <0.05.

has comparable immunogenicity to the serotypes common with PCV7 and a comparable adverse reaction profile to PCV7 [66]. Hence, it may be possible to extrapolate the findings of our study to PCV13.

Data on the PCVs are too preliminary to suggest the optimal timing of booster vaccination in adults [43–48,50,57]. Our study addresses this gap, although it was not designed to answer questions on dosing schedules. Given cART, the implications for HIV-positive adults receiving a single or a double 0.5-ml dose of PCV are that they are less likely to require a booster after five years than HIV-positive adults receiving PPV initially. In our study, although two doses were associated with persistent immune responses in the fifth year, in terms of cost-effectiveness, one dose may be sufficient given cART.

There are several limitations to be acknowledged. First, our study was not a randomized trial and no subjects received placebo; however, we performed matched pair analyses to minimize potential confounding factors. Second, we did not compare serological responses to vaccination with PCV vs PPV; further studies are needed to compare the long-term benefits of boosting with PCV or PPV. Third, we did not perform opsonophagocytic assays (OPAs) since OPA titres $\geq$8 were not necessarily predictive of IPD in children [59] and OPA results appear to correlate well with antibody concentrations even in immunocompromised hosts [54,67]. Fourth, our findings may not apply to women. Lastly, a larger sample size may be necessary to render the long-term dose-effect statistically significant.

We conclude that primary vaccination with one or two 0.5-ml doses of PCV7 achieved durable serological responses in HIV-treated adults throughout the five years of follow-up. This remarkable persistence of antibody responses in contrast to the more rapid decline seen in other immunocompromised populations is sustained by long-term antiretroviral therapy and immune reconstitution.

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Competing interests
None of the authors declare any competing interests.

Authors' contributions
HC was responsible for the study design. YS, HS, WL and SC collected the data and were responsible for laboratory methods and subject recruitment. AC, MT and HC analyzed the data. AC, SC and HC wrote, reviewed and edited the manuscript. All authors have read and approved the final draft.

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Comparison of serological responses to single-dose azithromycin (2 g) versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients in an area of low prevalence of macrolide-resistant *Treponema pallidum* infection

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Objectives: Effectiveness of single-dose azithromycin (2 g) in the treatment of early syphilis among HIV-infected patients has rarely been evaluated in the era of combination ART.

Methods: Consecutive HIV-infected patients with early syphilis, who received 2 g single-dose azithromycin or 2.4 MU benzathine penicillin G, between 2007 and 2014, were prospectively observed. Genotypic resistance to macrolides was determined in *Treponema pallidum* isolates identified from clinical specimens using PCR assays. Rapid plasma reagin (RPR) titres were determined at baseline and every 3 months after treatment. Primary outcome was a decline of RPR titre by ≥4-fold at 12 months after treatment.

Results: During the study period, 162 HIV-infected patients with early syphilis received benzathine penicillin G and 237 patients received azithromycin. At 12 months follow-up, the serological response rate for penicillin and azithromycin groups was 61.1% and 56.5% ($P=0.41$), respectively; respective response rate was 61.1% and 65.9% ($P=0.49$) if we only included patients infected with *T. pallidum* not harbouring macrolide resistance in the azithromycin group. In multivariate analysis, RPR titres ≥1:32 (OR 2.56; 95% CI 1.55–4.21) and prior syphilis (OR 0.54; 95% CI 0.35–0.81) were predictors of serological response. Most common adverse effects of azithromycin included diarrhoea (52.7%), nausea (22.4%), abdominal pain (18.6%), bloating (17.7%) and lassitude/somnolence (27.4%).

Conclusions: In the setting of a low prevalence of macrolide-resistant *T. pallidum*, 2 g single-dose azithromycin achieved a similar serological response to benzathine penicillin G in HIV-infected patients with early syphilis. Major adverse effects of azithromycin were gastrointestinal symptoms and lassitude/somnolence.

Introduction

The global incidence of syphilis has been increasing in developed as well as developing countries in recent years, particularly among MSM.[1–4] Other than behaviour modification, effective antibiotic treatment is a key component for the control of syphilis. According to current treatment guidelines in Canada, Europe and the USA, the standard treatment for early syphilis (primary, secondary and early latent syphilis) is single-dose (2.4 MU) benzathine penicillin G, although whether multiple doses of benzathine penicillin G are

needed for the management of early syphilis in HIV-infected patients remains controversial.[5-9] In the presence of penicillin allergy and benzathine penicillin G shortages that have occurred in several countries such as Japan and Taiwan,[10] ceftriaxone, doxycycline and azithromycin could be alternative agents for early syphilis, given the caveat that clinical studies assessing the effectiveness of these alternative treatments are limited.[6,7,11]

Azithromycin has been considered an alternative for treatment of early syphilis when *in vitro* and animal studies have demonstrated its effectiveness against *Treponema pallidum*.[12-14] Several clinical trials have demonstrated comparable clinical efficacy of single-dose azithromycin versus benzathine penicillin G, with the serological response rate ranging from 56% to 98%.[12,15,16] In HIV-negative patients, Hook and colleagues[17] have demonstrated the equivalent efficacy of 2 g single-dose azithromycin to single-dose benzathine penicillin G in a randomized controlled trial. As an alternative treatment option, azithromycin is more cost-effective, has a favourable adverse event profile[18,19] and causes much less frequent Jarisch-Herxheimer reaction when compared with benzathine penicillin G;[20] moreover, partner treatment, directly observed therapy and treatment of several other concurrent sexually transmitted diseases (STDs) can be conducted with the use of azithromycin.[7]

Despite the documented clinical efficacy of azithromycin, treatment failures among patients with primary and secondary syphilis have been noted since 2002.[19,21,22] Point mutations (A2058G and A2059G) of treponemal DNA have been shown associated with macrolide resistance and treatment failures.[22,23] The prevalence of macrolide resistance in *T. pallidum* is highly variable around the world; however, it reportedly ranges from 0% to 100% in different regions studied, and MSM have been identified as a risk group of infection with macrolide-resistant *T. pallidum* in the USA.[19,22,24-27] A significantly higher prevalence of *T. pallidum* harbouring A2058G mutation was detected in the isolates from MSM than from men who have sex with women (prevalence ratio 5.7; 95% CI, 2.9-10.8), particularly in the west region of the USA. In addition, higher prevalences of macrolide resistance in *T. pallidum* among MSM have also been reported in other studies.[19,25] Therefore, azithromycin, as an alternative agent for early syphilis, is not recommended for pregnant women and MSM according to the current Sexually Transmitted Diseases Treatment Guidelines of the CDC.[6,7]

In Taiwan, our multicentre surveillance study has demonstrated a low prevalence of macrolide resistance (0.7%) among the *T. pallidum* isolates in patients with syphilis who were predominantly HIV-infected MSM.[24,28] In this study, we aimed to compare the serological response of early syphilis to 2 g single-dose azithromycin versus single-dose benzathine penicillin G and to evaluate the tolerability of azithromycin among HIV-infected patients with access to combination ART (cART).

Methods

Study population and setting

This multicentre, prospective observational study was conducted between January 2007 and April 2014 at five hospitals designated for HIV care in northern (three hospitals), central (one) and southern (one) Taiwan where inpatient or outpatient HIV care, including cART and monitoring of CD4 cell counts and plasma HIV RNA load (PVL) are provided free-of-charge. According to the national guidelines for HIV care in Taiwan, non-treponemal serological tests for syphilis are recommended at least once yearly and on an as-needed basis as dictated by the clinical presentations and every 3-6 months over a period of 2 years for those who receive treatment for syphilis. The patients who receive stable cART are usually followed as outpatients every 3 months and monitoring of immunological and virological status is performed every 3-6 months. During the study period, the treatment regimens for syphilis were prescribed according to the STDs Treatment Guidelines of the CDC in 2006 and 2010.[7,29]

HIV-infected patients aged 20 years or over who presented with early syphilis and received single-dose benzathine penicillin G (2.4 MU) at the participating hospitals from January 2007 to April 2014 were included in this observational study. The methods were described previously.[8] From 2012 to 2013, there was a shortage of benzathine penicillin G in Taiwan and azithromycin or doxycycline became the treatment options instead of benzathine penicillin G.[11] Azithromycin was considered an alternative option to benzathine penicillin G because our previous surveillance study between 2009 and 2014 has shown that the prevalence of *T. pallidum* harbouring macrolide resistance mutations remained low (0.7%).[24,28] Patients receiving azithromycin who had completed follow-up for 12 months between 2012 and 2014 were included in this observational study using the same inclusion criteria with those who received benzathine penicillin G.[8]

Patients were excluded from analysis if antibiotics were concurrently given that were treatment options for syphilis such as ceftriaxone or doxycycline when early syphilis was diagnosed, or if those antibiotics were used for treatment of diseases other than syphilis during the 12 months of follow-up after azithromycin or benzathine penicillin G treatment was administered. Patients with rapid plasma reagin (RPR) titres <1:4 were not included because of concerns about increased risk of biological false-positive serology of syphilis (RPR titre of 1:1 or 1:2). Patients with symptomatic neurosyphilis or tertiary syphilis were also excluded. CSF examination was not routinely performed if there were no neurological symptoms. The study was approved by the Research Ethics Committees of the participating hospitals and patients gave written informed consent for detection of macrolide-resistant *T. pallidum* before receiving azithromycin (registration number, 201003110R).

Data collection

A standardized case record form was used to collect information on demographic characteristics, risk behaviour for HIV transmission, PVL and CD4 counts at baseline and during follow-up, cART, stage of syphilis, RPR titres before treatment and during the first 3 and 6 months of follow-up, and the first episode of recurrent syphilis and its stage. Azithromycin was taken under the direct observation of HIV case managers. To alleviate the gastrointestinal adverse effects, patients were advised to take a light meal before taking azithromycin. Cell phone calls were made to inquire about any adverse effects, including Jarisch-Herxheimer reactions, by case managers 24 and 48 h after azithromycin was administered using a standardized case record form.[20]

Laboratory investigations

Serological tests for syphilis were performed with the use of rapid RPR test (BD Macro-VueTMRPR Card tests, USA) and *Treponema pallidum* haemagglutination test (FTI-SERODIA-TPPA. Fujirebio Taiwan Inc., Taoyuan, Taiwan) at the participating hospitals. PVL and CD4 lymphocyte count were quantified by the Cobas Amplicor HIV-1 Monitor™ Test, version 1.5 (Roche Diagnostics Corporation, Indianapolis, IN, USA) and FACSFlow (Becton Dickinson), respectively.

Treponemal DNA was extracted from clinical specimens using the Qiagen DNA minikit (Qiagen, Gmbh, Hildens, Germany) according to the manufacturer's protocol. The presence of *T. pallidum* was determined by amplification of the polymerase I gene (*polA*) as previously.[30] The detection of macrolide resistance mutations (A2058G or A2059G) in the 23S rRNA gene was performed using PCR-RFLP.[22]

Urine was collected to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* concomitantly from patients with early syphilis who received

azithromycin. The detection of *C. trachomatis* and *N. gonorrhoeae* was performed with the use of a multiplex real-time PCR assay on an automated system (m2000; Abbott Molecular Diagnostics, Des Plaines, IL, USA).[31] Results were reported as positive or negative.

Definitions

Early syphilis that includes primary, secondary and early latent syphilis was defined according to STDs Treatment Guidelines of the CDC in 2010.[7] Patients were diagnosed as having primary syphilis if they had ulcers or chancres at the infection site; secondary syphilis if they developed skin rash, mucocutaneous lesions or lymphadenopathy in the presence of seroreactivity for *T. pallidum*; and early latent syphilis if seroconversion was documented within the past 12 months in the absence of clinical symptoms. Serological response was defined as a decline of an RPR titre by ≥4-fold from the baseline value at 12 months of azithromycin or benzathine penicillin G treatment.[17] Non-responders were those who received another course of treatment regardless of serological response during the follow-up; or those who failed to achieve a decline of RPR titres by ≥4-fold at 12 months following treatment. In addition, serofast was defined as either no change in RPR titres or ≤2-fold decrease or increase of RPR titres from baseline.[32]

Statistical analysis

All statistical analyses were performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 or Fisher's exact test whereas non-categorical variables were compared using Student's *t*-test or Mann–Whitney *U*-test. All tests were two-tailed and $P<0.05$ was considered significant. Multiple logistic regression method was used to identify factors associated with serological response at 6 months of treatment. We included the variables with a $P<0.2$ in the univariate analysis or variables that were of biological significance such as antibiotic administered (benzathine penicillin G versus azithromycin) in the multivariate logistic regression models.

Results

During the study period, a total of 238 HIV-infected patients received 2 g single-dose azithromycin for treatment of early syphilis, among whom 85 patients had *T. pallidum* (identified with the use of PCR assays from clinical specimens) that did not harbour macrolide resistance mutations and 1 patient was excluded because of infection with *T. pallidum* harbouring macrolide resistance mutation (A2058G) (azithromycin group, $n=237$); and 162 HIV-infected patients with early syphilis received single-dose benzathine penicillin G (penicillin group) (Table 1). Table S1 (available as Supplementary data at *JAC* Online) shows the comparisons of baseline characteristics between 152 patients from whom *T. pallidum* was not identified in the clinical specimens collected and 85 patients infected with *T. pallidum* without harbouring macrolide resistance mutations. There were no differences in terms of age, risk for HIV transmission, RPR titres ≥1:32, CD4 count stratification, mean $\log_{10}$ PVL, PVL <400 copies/mL, concomitant chlamydial infection or receipt of cART. However, patients infected with *T. pallidum* without harbouring macrolide resistance mutations had a higher percentage of secondary syphilis, a lower percentage of early latent syphilis and prior syphilis, and a lower mean CD4 count than those who did not have *T. pallidum* identified.

All patients in the azithromycin group and penicillin group had follow-up RPR titres at 3, 6 and 12 months after treatment. The

Table 1. Clinical characteristics of patients receiving single-dose benzathine penicillin G (2.4 MU) or 2 g single-dose azithromycin for treatment of early syphilis

	Single-dose benzathine penicillin G ($n=162$)	2 g azithromycin ($n=237$)	*P* value
Age, mean (SD), years	32.0 (7.6)	33.1 (7.6)	0.26
Sexual preference, *n* (%)			
MSM	161 (99.4)	235 (99.2)	1.00
non-MSM	1 (0.6)	2 (0.8)	
Syphilis stage, *n* (%)			
primary	13 (8.0)	33 (13.9)	0.08
secondary	82 (50.6)	84 (35.4)	0.003
early latent	67 (41.4)	120 (50.6)	0.08
RPR titre, median (IQR)	64 (32–128)	64 (32–128)	0.72
RPR titre ≥1:32, *n* (%)	136 (84.0)	180 (75.9)	0.06
CD4 count, mean (SD), cells/mm^3	463 (240)	546 (237)	0.73
CD4 <200, *n* (%)	17 (10.5)	10 (4.2)	0.02
200 ≤ CD4 ≤ 350, *n* (%)	37 (22.8)	41 (17.3)	0.20
CD4 >350, *n* (%)	108 (66.1)	186 (78.5)	0.01
PVL, mean (SD), $\log_{10}$ copies/mL	2.98 (1.54)	2.22 (1.41)	<0.001
PVL <400 copies/mL, *n* (%)	89 (54.9)	174 (73.4)	<0.001
Prior history of syphilis, *n* (%)	57 (35.2)	161 (67.9)	<0.001
cART, *n* (%)	112 (69.1)	195 (82.3)	0.003

cART, combination ART; IQR, interquartile range; PVL, plasma HIV RNA load; RPR, rapid plasma reagin; SD, standard deviation.

clinical characteristics of patients in the azithromycin group and penicillin group are shown in Table 1. All except one patient in the penicillin group and two patients in azithromycin group were MSM. Compared with the patients in the penicillin group, patients in the azithromycin group had a lower percentage of secondary syphilis (35.4% versus 50.6%, $P=0.003$), CD4 count <200 cells/mm^3 (4.2% versus 10.5%, $P=0.02$), but had a higher percentage of CD4 count >350 cells/mm^3 (78.5% versus 66.1%, $P=0.01$), PVL <400 copies/mL (73.4% versus 54.9%, $P<0.001$), prior syphilis (67.9% versus 35.2%, $P<0.001$), taking cART (82.3% versus 69.1%, $P=0.003$) and lower mean $\log_{10}$ PVL (2.22 ± 1.41 versus 2.98 ± 1.54 copies/mL, $P<0.001$).

The serological response rates to single-dose benzathine penicillin G or azithromycin at 12 months are illustrated in Figure 1. Similar serological response rates were observed between the penicillin and azithromycin groups (61.1% versus 56.5%, $P=0.41$). If we only included those 85 patients confirmed to be infected with *T. pallidum* and not harbouring macrolide resistance mutations by PCR assays (Figure 1), we found that there were no statistically significant differences in the serological response rates between the penicillin group and azithromycin group at 12 months of follow-up (61.1% versus 65.9%, $P=0.49$).

In univariate analysis, factors associated with achieving serological response at 12 months in patients receiving benzathine penicillin G or azithromycin are shown in Table 2. More patients with higher RPR titres (RPR ≥1:32) achieved serological response than those with lower RPR titres (85.8% versus 69.9%, $P<0.001$), while patients with early latent syphilis (42.1% versus 53.6%, $P=0.03$) and a prior history of syphilis (48.1% versus 63.9%, $P=0.002$) were less likely to achieve serological response. In addition, there was no relationship between the stratifications of CD4 cell counts, $\log_{10}$ PVL, cART or treatment regimen administered for syphilis and serological response. In multivariate analysis using logistic regression (Table 2), patients with higher RPR titres (RPR ≥1:32) were more likely to achieve serological response with an adjusted odds ratio (AOR) of 2.56 (95% CI 1.55–4.21) while patients with a prior history of syphilis was less likely to achieve serological response (AOR 0.54; 95% CI 0.35–0.81). Patients receiving single-dose benzathine penicillin G appeared to have a similar serological response rate compared with those receiving 2 g single-dose azithromycin at 12 months of follow-up in multivariate analysis (AOR 0.94; 95% CI 0.59–1.47, $P=0.77$).

The tolerability of 2 g single-dose azithromycin was assessed among all 237 patients who took azithromycin under the direct observation of case managers (Table 3). The most common adverse effects included gastrointestinal discomfort such as diarrhoea (52.7%), loose stool passage (6.3%), abdominal pain (18.6%), nausea (22.4%) and abdominal bloating (17.7%). Other adverse effects such as vertigo, headache or dizziness were noted in a few patients but lassitude/somnolence was more commonly seen (27.4%). In addition, 14.8% of the patients receiving azithromycin with early syphilis experienced Jarisch–Herxheimer reactions.

There was no statistically significant difference between the patients with or without taking cART in terms of the frequency of adverse effects. Among the 195 patients who were taking cART, 52.8% ($n=103$) were taking PI-based regimens while the others were taking NNRTI-based regimens (Table S2). Patients who were taking PI-based regimens tended to have a higher percentage of

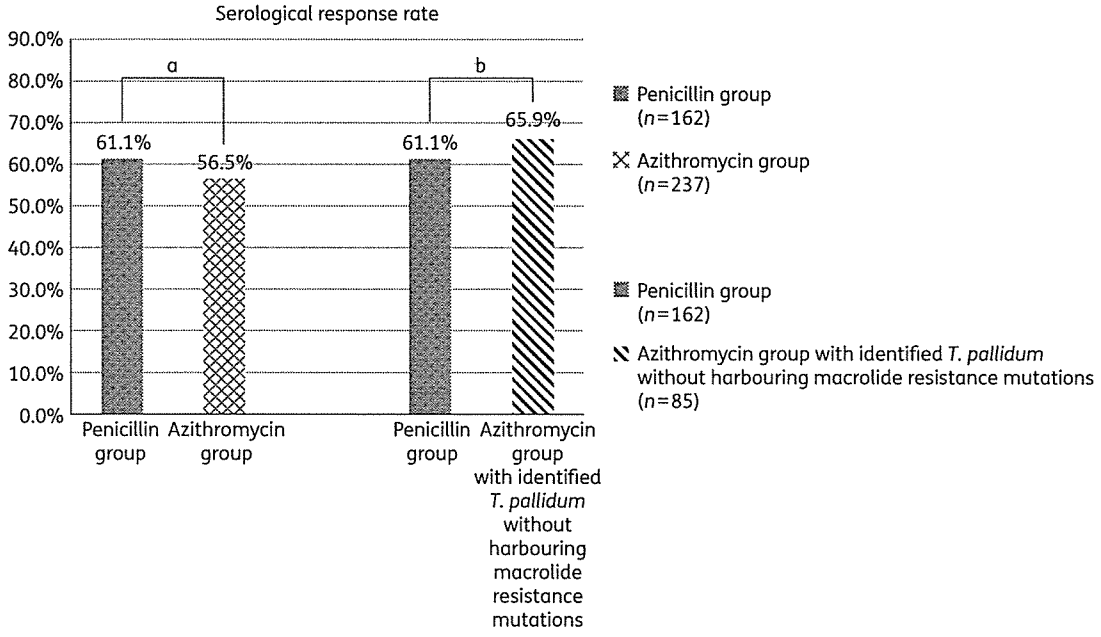

Figure 1. Serological response rates to single-dose benzathine penicillin G and 2 g single-dose azithromycin at 12 months of treatment. (a) All patients in the penicillin group and all 237 patients in azithromycin group (risk difference: −4.6%, 95% CI: −14.4 to 5.2, $P=0.41$). (b) All patients in the penicillin group and 85 patients with identified *T. pallidum* without harbouring macrolide resistance mutations in the azithromycin group (risk difference: 4.8%, 95% CI: −7.8 to 17.3, $P=0.49$).

Table 2. Factors associated with serological response to single-dose benzathine penicillin G or 2 g single-dose azithromycin at 12 months of follow-up in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	Responders (n=233)	Non-responders (n=166)	P value	AOR	95% CI	P value
Age, mean (SD), years	32.7 (8.1)	32.7 (6.9)	0.35	1.03	0.99–1.05	0.11
Risk, *n* (%)						
MSM	232 (99.6)	164 (98.8)	0.57	—	—	—
non-MSM	1 (0.4)	2 (1.2)		—	—	—
Syphilis stage, *n* (%)						
primary	29 (12.4)	17 (10.2)	0.53	1	—	—
secondary	106 (45.5)	60 (36.1)	0.07	1.38	0.70–2.74	0.35
early latent	98 (42.1)	89 (53.6)	0.03	1.16	0.72–1.88	0.55
RPR titre, median (IQR)	1:64 (32–128)	1:64 (16–128)	0.001			
RPR titre ≥1:32, *n* (%)	200 (85.8)	116 (69.9)	<0.001	2.56	1.55–4.21	<0.001
CD4 count, mean (SD), cells/mm^3	500 (220)	529 (267)	0.11			
CD4<200, *n* (%)	18 (7.7)	9 (5.4)	0.42	1	—	—
200≤CD4≤350, *n* (%)	39 (16.7)	39 (23.5)	0.10	1.12	0.49–2.76	0.72
CD4>350, *n* (%)	176 (75.5)	118 (71.1)	0.36	0.63	0.37–1.06	0.08
PVL, mean (SD), $\log_{10}$ copies/mL	2.59 (1.54)	2.44 (1.46)	0.08			
PVL<400 copies/mL, *n* (%)	150 (64.4)	113 (68.8)	0.46	1.26	0.59–2.70	0.55
Prior history of syphilis, *n* (%)	112 (48.1)	106 (63.9)	0.002	0.54	0.35–0.81	0.003
cART, *n* (%)	178 (76.4)	129 (77.7)	0.81	1.30	0.58–2.93	0.52
Single-dose benzathine penicillin G, *n* (%)	99 (42.5)	63 (40.0)	0.41	0.94	0.59–1.47	0.77

BPG, benzathine penicillin G; cART, combination ART; IQR, interquartile range; PVL, plasma HIV RNA load; RPR, rapid plasma reagin; SD, standard deviation.

Table 3. Adverse effects in patients taking or not taking cART who received azithromycin for treatment of early syphilis

Symptom, *n* (%)	All patients (n=237)	Patients with cART (n=195)	Patients without cART (n=42)	P value
Diarrhoea	125 (52.7)	103 (52.8)	22 (52.4)	>0.99
Loose stool	15 (6.3)	12 (6.2)	3 (7.1)	0.73
Abdominal pain	44 (18.6)	36 (18.5)	8 (19.0)	>0.99
Nausea	53 (22.4)	42 (21.5)	11 (26.2)	0.54
Vomiting	3 (1.3)	3 (1.5)	0 (0)	>0.99
Abdominal bloating	42 (17.7)	34 (17.4)	8 (19.0)	0.82
Dizziness	41 (17.3)	33 (16.9)	8 (19.0)	0.82
Headache	9 (3.8)	8 (4.1)	1 (2.4)	>0.99
Vertigo	7 (3.0)	5 (2.6)	2 (4.8)	0.61
Lassitude/somnolence	65 (27.4)	53 (27.2)	12 (28.6)	0.85
Palpitation	0 (0)	0 (0)	0 (0)	—
Jarisch-Herxheimer reaction	35 (14.8)	28 (14.4)	7 (16.7)	0.64

cART, combination ART.

diarrhoea than those who were taking non-PI-based regimens (56.3% versus 48.9%, P=0.36), and patients taking non-PI-based regimens had a significantly higher frequency of lassitude/somnolence (34.8% versus 20.4%, P=0.02).

Discussion

In this multicentre, prospective observational study of HIV-infected patients who were predominantly MSM, we demonstrate that patients receiving 2 g single dose azithromycin achieved similar serological response rates to those receiving single-dose benzathine penicillin G for early syphilis, regardless of detection of *T. pallidum* without macrolide resistance mutations by PCR assays in the clinical specimens. A high RPR titre (RPR ≥1:32) was an independent predictor of achieving serological response (AOR, 2.56; 95% CI, 1.55–4.21), while a prior history of syphilis was associated with poor serological response after treatment (AOR, 0.54; 95% CI, 0.35–0.81).

Whether azithromycin can be used as an effective alternative to benzathine penicillin G depends on the prevalence of *T. pallidum* with macrolide resistance mutations in areas studied. During 2007–09, a surveillance study to detect 23S rRNA A2058G point mutation in *T. pallidum* strains was conducted across the USA, and the prevalence of macrolide-resistant *T. pallidum* differed from the West region to the Midwest and South regions.[33] In Taiwan, our surveillance study revealed that the prevalence of macrolide resistance of *T. pallidum* remained low.[24,28] While the study population in our study consisted mostly of MSM and HIV-infected patients, our surveillance study suggests that azithromycin could be an alternative option to benzathine penicillin G in the treatment of early syphilis among HIV-infected MSM in Taiwan.

Since 2002, several clinical trials have shown the clinical efficacy of azithromycin for early syphilis (Table S3).[12,15–17] However, the participants enrolled in those studies comprised a higher percentage of female patients (38%–68%) and a lower percentage of subjects with HIV infection (0%–52.1%); moreover, HIV-infected patients had limited access to cART in these reported studies. Therefore, the study results cannot inform the clinical decision in the treatment of early syphilis using azithromycin in HIV-infected MSM when shortage of benzathine penicillin G occurs. While our study demonstrated similar serological response rates between patients in the azithromycin and penicillin groups at 12 months of treatment, the response rates to benzathine penicillin G (61.1%) and azithromycin (56.5% for overall cases and 65.9% for cases of macrolide-susceptible *T. pallidum* infection) are lower compared with those reported in the randomized clinical trial comparing 2 g single-dose azithromycin and benzathine penicillin G in an HIV-negative population.[17] Because the PCR assays used in this study may not be of sufficient sensitivity in the detection of *T. pallidum*, those patients without *T. pallidum* being detected could be cases of macrolide-resistant *T. pallidum* infection. Other causes for non-response encountered in both treatment groups are shown in Table S4. Cases of reinfection indicated by the appearance of new chancres or ≥4-fold increases of RPR titres after initial achievement of serological response increased at 12 months follow-up (56.3%). Similar to our previous report,[8] the lower response rates for the two treatment groups were likely because of higher rates of reinfections with syphilis in HIV-infected MSM.[34,35]

Treatment with azithromycin for early syphilis has several benefits. First, as an alternative oral agent, azithromycin could be administered under supervision in the setting of outpatient clinics. Second, azithromycin is also an effective treatment agent for non-gonococcal urethritis and gonococcal infection, though it is not recommended as routine use for the latter because of concerns about evolving resistance.[7,36] In Taiwan, previous studies have shown *in vitro* activity of azithromycin for *N. gonorrhoeae*.[37,38] Among the 85 patients in our study, 1 had concomitant gonococcal urethritis and 7 chlamydial urethritis who were successfully treated with azithromycin (Table S1). Third, treatment with azithromycin was recently shown to be associated with a significantly lower risk of Jarisch–Herxheimer reactions than that with benzathine penicillin G (14.1% versus 56.3%) and a delayed onset of Jarisch–Herxheimer reactions (8 h versus 4 h).[20]

In our study, gastrointestinal symptoms and lassitude/somnolence were the main adverse effects encountered in patients receiving azithromycin, which appears to be more frequent than those reported in previous clinical trials, in which gastrointestinal symptoms and lassitude/somnolence occurred in 10%–24.4% and 6.7% of the subjects, respectively.[12,17] We postulate that concurrent use of cART and phone calls to actively obtain information on adverse effects might play a role. However, the higher percentage of diarrhoea distributed nearly equally among patients with or without concurrent cART in our study (52.8% versus 52.4%, $P > 0.99$). Limited by the sample size, we were not able to find a statistically significant difference in terms of frequency of diarrhoea between patients who were taking PI-based regimens and those taking non-PI-based regimens in a further analysis of patients taking cART and azithromycin. The association between non-PI-based regimens and a higher frequency of lassitude/somnolence may be attributed to the fact that NNRTI such as efavirenz causes more CNS symptoms than PIs.[39]

There are several limitations in our study and interpretation of our results should be cautious. First, our study is not a randomized controlled trial and the two groups of patients had significant differences in several baseline characteristics for which we were not able to avoid confounding in the analyses. Second, the two groups of patients were included in different periods because of the shortage of benzathine penicillin G in Taiwan; most patients who received azithromycin were enrolled mainly in 2012–13 while most of the patients in the penicillin group was enrolled between 2007 and 2012, although the follow-up schedules for RPR titres were the same for the two treatment groups. Third, our cohort study comprised convenience samples of consecutive patients seeking syphilis treatment and was not powered to demonstrate non-inferiority of azithromycin to benzathine penicillin G. Assuming the lower boundary of the two-sided 95% CI (one-sided $\alpha = 0.025$) for the difference of the serological response rate between the two groups set at −0.1 (i.e. the non-inferiority margin was set to 10%) with serological response rate of 75% for penicillin group, at least 232 patients will be needed for each group to confirm the non-inferiority of azithromycin to benzathine penicillin G with a power of 80%.[8] Lastly, our study was conducted in an area of low prevalence of *T. pallidum* with macrolide resistance and the results may not be generalized to areas of higher prevalence of *T. pallidum* with macrolide resistance.

In conclusion, our study suggests that, in the settings of a low prevalence of macrolide-resistant *T. pallidum*, azithromycin had a similar serological response rate to that of benzathine penicillin G in HIV-infected MSM. The major adverse effects of azithromycin are gastrointestinal symptoms and lassitude/somnolence in those individuals concurrently taking cART.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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ORIGINAL ARTICLE

Risk of recurrent nontyphoid *Salmonella* bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy

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Abstract *Background/Purpose:* Nontyphoid *Salmonella* (NTS) bacteremia causes high mortality and recurrence rates in human immunodeficiency virus (HIV)-infected patients. This study aimed to investigate the risk of recurrent NTS bacteremia in the era of combination antiretroviral therapy (cART).
Methods: The medical records of consecutive HIV-infected patients with NTS bacteremia from January 2006 to June 2014 were reviewed. The patients were divided into two groups: patients

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sulfamethoxazole

who achieved a decline of plasma HIV RNA load by ≥ 2 $\log_{10}$ after 4 weeks of cART (good short-term virological response) and those who failed to achieve the goal (poor short-term virological response). Clinical information was collected on the demographics, immunological and virological responses, prophylactic antibiotics used, episodes of recurrent NTS bacteremia, and mortality.

Results: During the study period, 49 patients with 52 episodes of NTS bacteremia were included: 29 patients in the good virological response group, in which 16 received secondary prophylaxis; and 20 patients in the poor response group, in which 15 received secondary prophylaxis. There were no recurrent episodes of NTS bacteremia in the good-response group, whereas the incidence rate of recurrent NTS bacteremia was 5.21 per 100 person-years and 56.42 per 100 person-years of follow-up in patients receiving and not receiving prophylaxis, respectively, in the poor-response group. No patients died in the good-response group, whereas five patients (25%) in the poor-response group died. The resistance rate of 52 NTS isolates tested to ciprofloxacin was 7.7%.

Conclusion: The risk of recurrent NTS bacteremia is low in HIV-infected patients who achieve short-term virological response to cART, regardless of secondary prophylaxis.

Introduction

Bacteremia has been an important cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients.[1–4] In developing countries, nontyphoid *Salmonella* (NTS) continues to be the leading cause of bacteremia that causes high mortality and recurrence rates.[4] According to the United States Centers for Disease Control and Prevention, recurrent NTS bacteremia is one of the AIDS-defining opportunistic infections.[5] After the introduction of combination antiretroviral therapy (cART), the incidence of bloodstream infections in HIV-infected patients has decreased with the improvement of immunologic status.[6] However, in patients with low CD4 lymphocyte counts, bacteremia, especially NTS bacteremia, remains a threat in developing countries.[1,2,4]

The guidelines of the United States Department of Health and Human Services in 2014 recommend that HIV-infected patients with recurrent gastroenteritis or NTS bacteremia, or those with CD4 counts < 200 cells/μL and severe diarrhea receive secondary prophylaxis against recurrent NTS bacteremia.[9] However, the optimal duration of secondary prophylaxis for this purpose has not been well established, in contrast to the recommendations for primary and secondary prophylaxis against *Pneumocystis jirovecii* pneumonia. It is suggested to stop secondary prophylaxis until the resolution of *Salmonella* infection and response to cART with sustained viral suppression and CD4 cell count > 200 cells/μL.[9] However, the prolonged exposure to antibiotics raises several concerns, such as drug toxicity and increasing antibiotic resistance. In our previous study, the incidence of NTS bacteremia has significantly decreased by 96% after the introduction of cART. Moreover, HIV-infected patients who received fluoroquinolones as secondary prophylaxis for ≤ 30 days did not experience a higher incidence of recurrent NTS bacteremia than those who received secondary prophylaxis for > 30 days. However, the effectiveness of secondary prophylaxis with fluoroquinolones may be compromised given the finding that the proportion of NTS isolates resistant to fluoroquinolones has significantly increased over the three study periods.[8]

In this retrospective study, we aimed to reassess the risk of recurrent NTS bacteremia in the cART era. Our hypothesis is that in HIV-infected patients who receive cART with good adherence and a good short-term virological suppression, prolonged secondary prophylaxis for NTS bacteremia may not be needed.

Methods

Study design and inclusion and exclusion criteria

From January 2006 to June 2014, all HIV-infected patients who were aged 18 years or older and received a diagnosis of NTS bacteremia at the National Taiwan University Hospital, Taipei, Taiwan and Far Eastern Memorial Hospital, New Taipei City, were included in this retrospective observational cohort study. A standardized case record form was used to collect clinical and microbiological data. We excluded the patients who had to receive prolonged (> 3 months) broad-spectrum antibiotics for other opportunistic infections, such as disseminated nontuberculous mycobacterial infections or recurrent pneumonia, because the prolonged use of antibiotics would interfere with the interpretation of the results of secondary prophylaxis against NTS bacteremia. We also excluded the patients who died during hospitalization when the first episode of NTS bacteremia developed, who were lost to follow-up within 2 months after the bacteremia, who had not received appropriate antibiotic treatment for NTS bacteremia, and who did not have sufficient laboratory data. The appropriate antibiotics for NTS bacteremia included a third- or

fourth-generation cephalosporin, or a fluoroquinolone that demonstrated *in vitro* activity against the NTS isolate tested.

The duration of secondary prophylaxis was defined as the duration of oral antibiotics after the patients had completed the 14-day course of effective parenteral antibiotic treatment. Recurrent NTS bacteremia was defined as blood cultures that yielded NTS > 1 month after the discontinuation of antibiotic treatment or when the patient continued to receive antibiotic prophylaxis.

Rapid reduction of viremia in response to treatment was one of the important predictors of achieving long-term viral suppression.[7] Therefore, the patients included in the study were divided into two groups according to their short-term virological suppression status: the good virological suppression group, which included patients who achieved a decline of plasma HIV RNA load (PVL) by ≥ 2 $\log_{10}$ after taking 4 weeks of cART; and the poor virological suppression group, which included those who failed to achieve a decline of PVL by 2 $\log_{10}$. The patients in each group were further divided into two groups: those who received secondary prophylaxis against recurrent NTS bacteremia and those who did not.

Laboratory investigations

Isolation of *Salmonella* species was performed according to the standard methods from the blood samples. *Salmonella* serogroups B and D were further identified by the serotypes (Kauffman and White scheme), by using somatic and flagellar antigens (Denka Seiken Agglutinating Sera Salmonella Antisera Sets (Denka Seiken Co. Ltd., Tokyo, Japan)), and by conventional methods and the Phoenix System (panel type, NMIC/ID4; Becton Dickson). Disk diffusion susceptibility tests were performed for the *Salmonella* isolates, and results were interpreted according to the guidelines provided by the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards).[10] Minimum inhibitory concentrations (MICs) of ampicillin, trimethoprim/sulfamethoxazole (TMP/SMX), ceftriaxone, and ciprofloxacin were determined using the agar dilution method or VITEK 2 microbial identification system (BioMérieux, Marcy-l'Etoile, France), according to the Clinical and Laboratory Standards Institute guidelines.[10] Both of the microbiology laboratories at the National Taiwan University Hospital and Far Eastern Memorial Hospital followed the same guidelines.

CD4 lymphocyte count was determined using flow cytometry (BD FACSCalibur, Becton Dickinson and Coulter Epics XL, Beckman Coulter, Brea, CA, USA). PVL was quantified using the Cobas AmpliPrep/Cobas TaqMan HIV-I test (version 2.0; Roche Molecular Systems, Inc.) with a lower detection limit of 20 copies/mL since June 2012.

Treatment and prophylaxis

During the study period, treatment of NTS bacteremia included parenteral administration of ceftriaxone or other third-generation cephalosporins, or a fluoroquinolone, that was administered for a 14-day course, followed by oral switch to ciprofloxacin administered at a dose of 500 mg twice daily or other newer fluoroquinolones as secondary prophylaxis. The duration of fluoroquinolone prophylaxis was at the discretion of treating physicians. All patients were recommended to start cART at the time when they received a diagnosis of HIV infection with AIDS according to the national HIV treatment guidelines of the Taiwan Centers for Disease Control.[11]

Data collection

A standardized case record form was used to collect the baseline information such as age, sex, white blood cell counts, CD4 cell count, and PVL in patients with NTS bacteremia. According to the national HIV treatment guidelines, second tests for CD4 cell count and PVL will be performed 4 weeks after the initiation of cART, which are performed every 3 months subsequently during the 1st year of cART. The duration of oral TMP/SMX for the prophylaxis of *P. jirovecii* infection was also recorded.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (version 20.0; SPSS Inc., Chicago, IL, USA). The variables were compared using the Mann–Whitney *U* test. The patients were followed until December 31, 2014, death, or loss to follow-up, whichever occurred first. The incidence of recurrent NTS bacteremia was calculated as the number of episodes per 100 person-years of follow-up (PYFU). Exact 95% confidence intervals (95% CI) for incidence rates were calculated on the basis of the Poisson distribution. The resistance rates of fluoroquinolone were compared using the Mid-P exact tests.

Results

Patient characteristics

During the 8-year study period, 60 patients with 68 episodes of NTS bacteremia were identified (Figure 1). In seven episodes of NTS bacteremia, the patients died during the hospitalization course; the patients was lost to follow-up soon after four episodes; in two episodes, the patients had to receive prolonged broad-spectrum antibiotics for other reasons; in one episode, NTS bacteremia was diagnosed at an outpatient clinic for which the patient did not receive appropriate antibiotic treatment; and there were no sufficient data for two episodes. After excluding these 16 episodes, 49 patients who had 52 episodes of NTS bacteremia were included for analysis.

Except for one woman, all patients were male, with a median age of 33 years and 69.4% of them being younger than 40 years (Table 1). The median CD4 cell counts at the onset of NTS bacteremia were 30 cells/μL (range, 1–140 cells/μL). For treating NTS bacteremia, one patient received a fourth-generation cephalosporin, four patients received fluoroquinolones, and others had a third-generation cephalosporin. Twenty-nine patients (59.2%) were defined as having good short-term virological response to cART, and 20 patients (40.8%) were defined as having

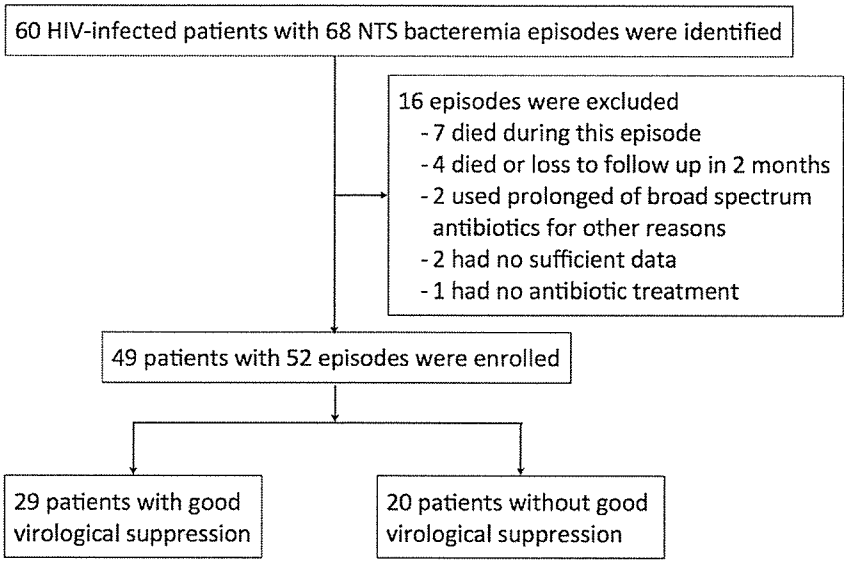

Figure 1. Disposition of patients with nontyphoid *Salmonella* (NTS) bacteremia.

poor short-term virological response. In the good virological response group, 16 patients received secondary prophylaxis and 13 did not receive prophylaxis, whereas in the poor virological response group, 15 patients received secondary prophylaxis and five did not receive prophylaxis. Twenty-four of the 49 patients (50.0%) also received TMP/SMX for the prevention of *P. jirovecii* pneumonia: 16 (16/29, 55.2%) in the good-response group (9 patients with secondary prophylaxis for NTS bacteremia and 7 without prophylaxis) and eight (8/20, 40.0%) in the poor-response group (6 patients with secondary prophylaxis for NTS bacteremia and 2 without prophylaxis). The median duration of TMP/SMX for primary or secondary prophylaxis for pneumocystosis was 28 days (range, 0–280 days) in the good-response group with prophylaxis and 0 day (range, 0–122 days) without prophylaxis; and 0 day (range, 0–154 days) in the poor-response group with prophylaxis and 0 day (range, 0–203 days) without prophylaxis (Table 1).

Immunological and virological responses

All but one patient received cART after the diagnosis of NTS bacteremia was made (Table 1). After 4 weeks of cART, the median CD4 cell count increased to 160 cells/μL (range, 12–772 cells/μL) in patients with good virological response, and 123 cells/μL (range, 3–615 cells/μL) in the poor-response group. The median follow-up duration was 1385 days (range, 330–3171 days) in the good-response group with prophylaxis and 584 days (range, 265–2968 days) without prophylaxis; and 506 days (range, 85–2826 days) in the poor-response group with prophylaxis and 526 days (range, 225–712 days) without prophylaxis (Table 2). At the end of follow-up, the median CD4 cell counts were 333 cells/μL (range, 21–731 cells/μL) in the good-response group and 61.5 cells/μL (range, 3–385 cells/μL) in the poor-response group (Table 1). In patients who had good virological response and received antibiotic prophylaxis, the CD4 cell counts at the end of follow-up were the highest among the four groups (median, 423 cells/μL; range, 80–691 cells/μL). Compared with patients with good virological response, the patients in the poor-response group, regardless of antibiotic prophylaxis for NTS bacteremia, had significantly lower median CD4 cell counts at the end of follow-up: with prophylaxis, 55 cells/μL (range, 3–385 cells/μL); without prophylaxis, 68 cells/μL (range, 3–139 cells/μL). The patients in the good-response group had a median increase of CD4 cell counts of 321 cells/μL (range, 5–678 cells/μL), whereas the CD4 count decreased by 4 cells/μL (range, −342–340 cells/μL) in the poor-response group.

The median baseline PVL was 5.38 $\log_{10}$ copies/mL (range, 4.3–6.97 $\log_{10}$ copies/mL) and 4.76 $\log_{10}$ copies/mL (range, 1.3–5.79 $\log_{10}$ copies/mL) in the good-response group and the poor-response group, respectively (Table 1). After 4 weeks of cART, the median decrease of PVL was 2.8 $\log_{10}$ copies/mL (range 2.09–3.7 $\log_{10}$ copies/mL) in patients with prophylaxis and 2.69 $\log_{10}$ copies/mL (2.15–4.04 $\log_{10}$ copies/mL) in those without prophylaxis in the good-response group, whereas it was 0.51 $\log_{10}$ copies/mL (range −3.49–1.98 $\log_{10}$ copies/mL) in patients with prophylaxis, and 0 $\log_{10}$ copies/mL (range −1.1–1.4 $\log_{10}$ copies/mL) in those without prophylaxis in the poor-response group.

Incidence and survival rate of recurrent NTS bacteremia

For the 16 patients who had good virological response and received secondary prophylaxis for NTS bacteremia, the median duration of prophylaxis was 19 days (range, 3–280 days), whereas for the 15 patients in the poor-response group who received prophylaxis, the median duration was 12 days (range, 2–52 days; Table 2). There were no recurrent episodes of NTS bacteremia in the good-response group, regardless of whether the patients received prophylaxis. In the poor virological response group, it was

Table 1 Characteristics of 49 human immunodeficiency virus (HIV)-infected patients with nontyphoid *Salmonella* bacteremia.

Variable	Good virological response		Poor virological response		All patients
	Prophylaxis	No prophylaxis	Prophylaxis	No prophylaxis	49
	16	13	15	5	
Age (y)	31.5 (22–53)	35 (29–50)	33 (23–64)	43 (26–52)	33 (22–64)
Male	16 (100)	13 (100)	14 (93.3)	5 (100)	48 (98)
WBC count at diagnosis (cells/μL)	5145 (2140–25,090)	4750 (2540–13,360)	4500 (2130–18,690)	5240 (3570–6470)	5130 (1540–25,090)
CD4, at diagnosis (cells/μL)	15.5 (4–71)	21 (9–410)	54 (1–386)	38 (7–138)	30 (1–410)
CD4, 4 wk after taking cART (cells/μL)	153.5 (23–276)	160 (12–772)	163 (3–615)	68 (17–139)	139 (3–772)
CD4, at the end of follow-up (cells/μL)	423 (80–691)	328 (21–731)	55 (3–385)	68 (3–139)	199 (3–731)
Increase of CD4 at the end of follow-up (cells/μL)	378 (20–678)	304 (5–647)	0 (−342–340)	−12 (−35–132)	167 (−342–678)
Log_{10} PVL, at diagnosis	5.34 (4.44–6.97)	5.38 (4.3–5.89)	3.68 (1.3–5.79)	5.02 (4.71–5.33)	5.24 (1.3–6.97)
Log_{10} PVL, 4 wk after taking cART	2.55 (1.3–4.02)	2.81 (1.3–3.46)	3.67 (1.3–5.58)	5.05 (3.83–5.91)	3.12 (1.3–5.91)
Decrease of log_{10} PVL	2.8 (2.09–3.7)	2.69 (2.15–4.04)	0.51 (−3.49–1.98)	0 (−1.1–1.41)	2.31 (−3.49–4.04)
Starting HAART after bacteremia,	16 (100)	13 (100)	15 (100)	4 (80)	48 (98)
Taking TMP/SMX	9 (56.3)	7 (53.8)	6 (40)	2 (40)	24 (50)
Duration of TMP/SMX (d)	28 (0 to 280)	0 (0–122)	0 (0–154)	0 (0–203)	0 (0–280)

Data are presented as *n* (%) or median (range).
cART = combination antiretroviral therapy; HAART = highly active antiretroviral therapy; PVL = plasma HIV RNA load; TMP/SMX = trimethoprim/sulfamethoxazole; WBC = white blood cells.

5.215 per 100 PYFU (95% CI, 0.8743–17.23) with prophylaxis, and 56.42 per 100 PYFU (95% CI, 17.93–136.1) without prophylaxis.

In the poor virological response group, two patients who received prophylaxis each developed one episode of recurrent NTS bacteremia (Table 2). In the no-prophylaxis group, a patient developed one episode and another patient developed three episodes of recurrent NTS bacteremia. There was no difference between the two subgroups (receiving or not receiving prophylactic antibiotics) in the good virological response group in the incidence of recurrent NTS bacteremia, nor was there any difference between the two groups of patients who received prophylactic antibiotics and achieved good response or those who failed to achieve good virological response ($p = 0.55$).

Serotypes of NTS isolates and the antimicrobial susceptibility

Of all 52 isolates, 44 were *Salmonella* O9 (serogroup D1) and five were *Salmonella* O4 (serogroup B; Table 2). In the good virological response group, three of the 29 isolates (10.3%) were resistant to ciprofloxacin, whereas in the poor-response group, one of the 23 isolates (4.3%) was resistant to ciprofloxacin. In patients receiving a fluoroquinolone for prophylaxis, either in good or poor virological response group, two out of 32 isolates (6.3%) were resistant to ciprofloxacin. In patients without fluoroquinolone prophylaxis, two out of 20 isolates (10.0%) were resistant to ciprofloxacin ($p = 0.653$). The overall resistance rate to ciprofloxacin for all 52 isolates was 7.7% (Table 2) and the resistance rate to ampicillin, ceftriaxone, and TMP/SMX was 44.2%, 1.9%, and 26.9%, respectively.

Characteristics of patients with recurrent NTS bacteremia

Four patients accounted for six episodes of NTS bacteremia. Their clinical characteristics are shown in Table 3. All four patients had baseline CD4 cell counts < 100 cells/μL and three had CD4 cell counts < 50 cells/μL. Patient 1 had three episodes of recurrent NTS bacteremia, and died during the third episode of recurrent NTS bacteremia. His CD4 cell count was 38 cells/μL, and he had a PVL of 51,000 copies/mL when the first episode occurred. He refused to start cART despite counseling. Other than NTS bacteremia, he had disseminated *Mycobacterium avium* complex infection and *P. jirovecii* pneumonia that led to death. Patient 2 had discontinued cART for 2 years prior to admission to the hospital for cryptococcal meningitis. The CD4 cell count was 41 cells/μL, and his PVL was 111,000 copies/mL. He did not receive secondary prophylaxis for NTS bacteremia. Recurrent NTS bacteremia developed when the CD4 count decreased to 18 cells/μL. He died of cerebral septic embolism, which occurred after he received chemotherapy for subsequent anaplastic large-cell lymphoma. Patient 3 discontinued cART despite the fact that his CD4 cell count had fallen to 1 cell/μL and his PVL was 62,300 copies/mL. Ciprofloxacin was prescribed for 28 days for secondary prophylaxis. However, recurrent NTS

Table 2 Outcome of recurrence of nontyphoid *Salmonella* bacteremia, survival, and antibiotics resistance.

Variable	Good virological response		Poor virological response	
	Prophylaxis (n = 16)	No prophylaxis (n = 13)	Prophylaxis (n = 15)	No prophylaxis (n = 5)
Duration of secondary prophylaxis (d)	19 (3–280)	0	12 (2–52)	0
Follow-up duration (d)	1385 (330–3171)	584 (265–2968)	506 (85–2826)	526 (225–712)
Having recurrent NTS bacteremia	0	0	2	2
Episodes of recurrent NTS bacteremia	0	0	2	4
Incidence, per 100 PYFU (95% CI)	0	0	5.215 (0.8743–17.23)	56.42 (17.93–136.1)
Survived	15 (39.8)	11 (84.6)	9 (60)	1 (20)
Died	0	0	2 (13.3)	3 (60)
Lost to follow-up	1 (6.3)	2 (15.4)	4 (26.7)	1 (20)
Isolates	16	13	16	7
Salmonella O9 (Group D1)	15 (93.8)	8 (61.5)	15 (93.8)	6 (85.7)
Salmonella O4 (Group B)	1 (6.3)	2 (15.4)	1 (6.3)	1 (14.3)
Antimicrobial susceptibility				
Resistant to ampicillin	6 (37.5)	8 (61.5)	8 (50)	1 (14.3)
Resistant to ciprofloxacin,	2 (12.5)	1 (7.7)	0	1 (14.3)
Resistant to ceftriaxone	0	1 (7.7)	0	0
Resistant to TMP/SMX	5 (31.3)	2 (15.4)	6 (37.5)	1 (14.3)

Data are presented as n, n (%), or median (range).
95% CI = 95% confidence interval; NTS = nontyphoid *Salmonella* bacteremia; PYFU = person-years of follow-up; TMP/SMX = trimethoprim/sulfamethoxazole.

bacteremia developed 2 months after his discharge from the hospital, and he subsequently died of *P. jirovecii* pneumonia. Patient 4 had poor adherence to cART and presented with *P. jirovecii* pneumonia, HIV nephropathy with nephrotic syndrome, and cytomegalovirus pneumonitis when NTS bacteremia occurred. NTS bacteremia recurred despite ciprofloxacin prophylaxis. He subsequently died of respiratory failure.

Discussion

In this study, we found that HIV-infected patients who had good short-term virological response to cART that was defined as a decline of PVL of ≥ 2 $\log_{10}$ after 4 weeks of cART were at a low risk of having recurrent NTS bacteremia. Regardless of the use of secondary prophylactic antibiotics, none of the 29 patients on cART with short-term virological response developed recurrent NTS bacteremia.

NTS is an important etiology of bacterial infection in immunocompromised hosts and infants in Taiwan,[12,13] and the leading cause of bacteremia in patients with advanced HIV infection.[14] The incidence of recurrent NTS bacteremia of patients without prophylaxis and poor virological suppression in the current study (56.42 per 100 PYFU) is lower than that in the pre-cART era in our previous report (70.56 per 100 PYFU).[8] The decrease may be related to the partial treatment effect of cART. For patients with good virological control, there was no recurrence of NTS bacteremia in this study (which was conducted between 2006 and 2014) compared with the incidence of 2.56 per 100 PYFU in our previous study (1997–2006).[8] Twenty-eight of the 49 patients (57.1%) were antiretroviral-naïve at the first episode of NTS bacteremia, and 42 patients (85.7%) either started cART or had changes made to the antiretroviral regimens after the episodes of NTS bacteremia. These findings highlight the importance of early diagnosis of HIV, early initiation of cART, and retention of the patients in the HIV care system for the prevention of recurrent NTS bacteremia. With good virological suppression, the role of secondary prophylaxis for NTS bacteremia may be minimized. Our findings suggest that, regardless of the baseline CD4 cell count, for patients who start cART with good adherence and virological response, prophylactic antibiotics for the prevention of recurrent NTS bacteremia may not be needed.

Patients with a low CD4 cell count are at high risk of NTS bacteremia.[15] In our previous study, we found that patients with NTS bacteremia had depleted CD4 cell counts [median, 8 cells/μL and 20 cells/μL in the pre-highly active antiretroviral therapy (HAART) and post-HAART era, respectively].[8] In this study, the patients with poor virological suppression continued to have lower CD4 cell counts at the end of follow-up (median CD4 cell count, 55 cells/μL and 68 cells/μL in patients with prophylaxis and those without prophylaxis, respectively). By contrast, patients with good virological suppression had significant increases of CD4 counts to 423 cells/μL and 328 cells/μL in patients with prophylaxis and those without prophylaxis, respectively. The CD4 cell counts at the end of follow-up of the four patients who had recurrent NTS bacteremia were all $<$ 50 cells/μL. This suggests that a poor immunological recovery and poor adherence to cART and secondary prophylaxis prescribed may have contributed to the higher incidence of recurrent NTS bacteremia observed.[8]

In the good virological response group, nine patients received a prophylactic dose of TMP/SMX for pneumocystosis in addition to a fluoroquinolone, and seven patients received TMP/SMX without other antibiotics. None of the patients in both groups developed recurrent NTS

Table 3 Clinical and laboratory characteristics of the four patients with recurrent nontyphoid *Salmonella* bacteremia.

Patient	1	2	3	4
Age (y)/Sex	43/M	30/M	23/M	37/M
Recurrent episodes	3	1	1	1
Salmonella serotype	O9, serogroup D1	O9, serogroup D1	O9, serogroup D1	O9, serogroup D1
Risk for HIV infection	Unknown	MSM	Unknown	MSM
Baseline CD4 count (cells/μL)	38	29.6	1	71
CD4 count at 4 wk of cART (cells/μL)	17	34.2	1	174
CD4 count at the end of follow-up (cells/μL)	3	17.5	3	40.5
Baseline PVL (copies/mL)	51,000	64,900	623,000	111,000
PVL at 4 wk of cART (copies/mL)	51,000	818,000	376,000	4630
Secondary antibiotic prophylaxis	None	None	Levofloxacin	Ciprofloxacin
Duration of prophylaxis (d)	0	0	20	12
Duration of TMP/SMX (d)	0	203	0	0
Other OIs	Disseminated MAC infection, PJP	Cryptococcal meningitis	PJP, pulmonary TB	PJP, oral candidiasis
Follow-up duration (d)	526	433	67	85

cART = combination antiretroviral therapy; MAC = *Mycobacterium avium* complex; MSM = men who have sex with men; OI = opportunistic infection; PJP = *Pneumocystis jiroveci* pneumonia; PVL = plasma HIV RNA load; TMP/SMX = trimethoprim/sulfamethoxazole; TB = tuberculosis.

bacteremia. In the poor-response group, six patients and two patients received TMP/SMX with and without a secondary prophylactic antibiotic, respectively. Only one of four patients with recurrences (Patient 3) received TMP/SMX, with poor adherence. In our study, the resistance rate to TMP/SMX among these 52 isolates was 27.0%. With such a high resistance rate, whether receiving TMP/SMX is effective or the dose administered for preventing recurrent NTS bacteremia is appropriate remains unknown. Furthermore, the multiple adverse effects related to TMP/SMX may limit its prolonged use in the HIV-infected population.[16]

In African adults and children, the estimated mortality rate associated with NTS bacteremia was 20–25%.[17] In our study, no patient died in the good virological response group, whereas five patients (25%) died in the poor virological response group: two received antibiotic prophylaxis and three did not. However, none of these five patients died of NTS bacteremia, but of other opportunistic infections or complications. This finding suggests that the recurrence of NTS bacteremia could be a marker of poor treatment response or adherence to cART, and the patients remain at a significantly higher risk for other coexistent life-threatening opportunistic illnesses.

In our study, 44 of the 52 (84.6%) NTS isolates were *Salmonella* O9 (Group D1) and five (9.6%) were *Salmonella* O4 (Group B). In another single-center study of NTS bacteremia in both HIV-infected and non-HIV patients in northern Taiwan, serogroup D was also the most prevalent serogroup, followed by serogroup B (23.4%), serogroup C2 (6.3%), and serogroup C1 (1.6%).[12] The resistance rate to ciprofloxacin of the 52 isolates tested was 7.7%. In our previous study,[8] it was 0% in the pre-HAART era (from June 1994 to March 1997), which increased from 6.2% in the early cART era (from April 1997 to June 2002) to 34.2% in the late cART era (from July 2002 to June 2006). The causes of the observed decrease in NTS with resistance to ciprofloxacin remain to be investigated, although shortened use of fluoroquinolones in the prevention of secondary NTS bacteremia may theoretically reduce the selection pressure for the emergence of antimicrobial resistance.

Our study had several limitations. First, the number of patients is small. In view of a low incidence of recurrent NTS bacteremia in the modern cART era, comparative clinical trials of a large sample size are necessary to assess the efficacy of a short course versus longer course of prophylaxis against recurrences. Second, this is a descriptive study. Owing to the small number of patients included, the study was underpowered to demonstrate statistically significant differences in several comparisons between groups. Third, unlike our previous study,[8] we did not perform molecular typing of the *Salmonella* isolates to differentiate relapse from reinfection with NTS. Last, the patients who had poor virological response might have been infected with HIV-1 with pretreatment resistance or emergence of drug resistance mutations to the antiretroviral regimens administered; however, we did not have the data on the baseline and follow-up resistance mutations of the HIV-1 strains.

In conclusion, HIV-infected patients who achieve good short-term virological response to cART are at a low risk of having recurrent NTS bacteremia, and a prolonged course of secondary prophylactic antibiotics may not be needed.

Conflicts of interest

All authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients

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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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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

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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

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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

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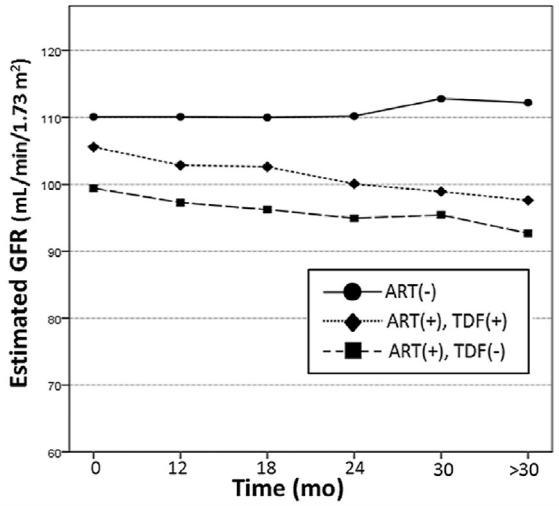

Months	0	12	18	24	30	>30
ART(-), *N*	140	77	66	53	21	12
ART(+),TDF(+), *N*	393	257	284	298	289	238
ART(+),TDF(-), *N*	242	220	217	95	12	4

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.

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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.

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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

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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.

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ORIGINAL ARTICLE

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☆

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Abstract *Background/Purpose:* Treatment response to switch regimens containing unboosted atazanavir and tenofovir disoproxil fumarate (TDF)/lamivudine guided by therapeutic drug monitoring in human immunodeficiency virus-infected patients is rarely investigated.
Methods: Consecutive patients with plasma human immunodeficiency virus RNA load < 200 copies/mL switching to unboosted atazanavir plus zidovudine–lamivudine (coformulated), abacavir–lamivudine (coformulated), or TDF/lamivudine > 3 months were included for determinations of treatment response, plasma atazanavir concentrations, and single-nucleotide polymorphisms of *MDR1*, *PXR*, and *UGT1A1* genes from 2010 to 2014. Treatment failure was defined as either discontinuation of atazanavir for any reason or plasma viral load ≥ 200 copies/mL within 96 weeks.
Results: During the study period, 128 patients switched to unboosted atazanavir with TDF/lamivudine (TDF group) and 186 patients switched to unboosted atazanavir with two other nucleoside reverse-transcriptase inhibitors (non-TDF group). There were no statistically significant differences in the distributions of single-nucleotide polymorphisms of *MDR1* (2677 and 3435), *PXR* genotypes (63396), and *UGT1A1*28* between the two groups. Recommended plasma atazanavir concentrations were achieved in 83.5% and 64.9% of the TDF group and non-TDF group, respectively ($p < 0.01$). After a median follow-up duration of 96.0 weeks, treatment failure occurred in 19 (14.9%) and 34 (18.3%) patients in the TDF group and non-TDF group, respectively ($p = 0.60$). Low-level viremia (40–200 copies/mL) before switch (adjusted hazard ratio, 2.12; 95% confidence interval, 1.12–4.01) and without therapeutic drug monitoring (adjusted hazard ratio, 2.08; 95% confidence interval, 1.16–3.73) were risk factors for treatment failure.
Conclusion: Switch to unboosted atazanavir with TDF/lamivudine achieves a similar treatment response to that with two other nucleoside reverse-transcriptase inhibitors in patients achieving virological suppression with the guidance of therapeutic drug monitoring.

Introduction

Protease inhibitors (PIs) boosted with ritonavir in combination with two nucleos(*t*)ide reverse-transcriptase inhibitors (NRTIs) are recommended antiretroviral regimens with good virological efficacy and a high genetic barrier to resistance.[1–3] Boosted atazanavir and darunavir are preferred for the initial treatment of human immunodeficiency virus (HIV) infection because each has demonstrated better lipid effects and tolerability than ritonavir-boosted lopinavir.[4–6] Despite being administered at a low dose (100 mg), ritonavir can lead to lipid disturbances, glucose intolerance, insulin resistance, liver enzyme elevations, gastrointestinal symptoms, and body fat abnormalities[7,8]; furthermore, the potential drug–drug interactions between ritonavir and nonantiretroviral medications may potentially lead to clinically significant adverse events.[9–11]

Randomized clinical trials have demonstrated similar virological efficacy between the switch regimens consisting of unboosted atazanavir and those consisting of boosted atazanavir in patients who had achieved suppression of HIV-1 replication after initial therapy with boosted atazanavir-containing regimens.[12–15] Regimens containing unboosted atazanavir may provide better efficacy in virological suppression and improvement of lipid parameters, compared with those containing other PIs such as boosted lopinavir, boosted or unboosted indinavir, boosted or unboosted saquinavir, and nelfinavir.[16] These issues were especially relevant to aging HIV-positive patients who are likely to have polypharmacy.[17]

Unlike other NRTIs, tenofovir disoproxil fumarate (TDF) is not recommended in combination with unboosted atazanavir because TDF may decrease atazanavir concentrations by 23–40%, although the mechanisms for this interaction remain unclear.[18–20] Lower plasma concentrations and higher interindividual variability due to the diverse distribution of genetic polymorphisms that are responsible for variations of atazanavir pharmacokinetics in different ethnic populations are the major concerns.[21] In the clinical setting, studies have revealed that coadministration with TDF was not associated with lower plasma exposure to unboosted atazanavir.[22,23] In terms of virological response, others studies have suggested that a combination of TDF with unboosted atazanavir may be safe in selected populations.[23–25]

In this study, we aimed to compare the treatment response to a switch regimen of unboosted atazanavir in combination with TDF and lamivudine versus regimens of unboosted atazanavir with two other NRTIs with the information provided with therapeutic drug monitoring (TDM) and pharmacogenetic investigations.

Methods

Study population

In this retrospective observational study, we included HIV-infected adults aged 20–65 years who switched to unboosted atazanavir plus two NRTIs after achieving

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plasma HIV RNA load (PVL) $<$ 200 copies/mL with combination antiretroviral therapy (cART) for .$>$ 3 months at the National Taiwan University Hospital in Taipei, Taiwan between 2010 and 2014. NRTIs were chosen with consideration of full treatment history, comorbidity, and available resources. Patients with a history of virological failure while receiving PI-based cART or with HIV-1 strains harboring resistance-associated mutations to PIs were excluded. Patients who were taking any H2 blockers or proton-pump inhibitors were also excluded. Patients were evaluated every 12 weeks after the treatment switch for $>$ 3 months to assess their tolerance and adherence and to undergo laboratory monitoring, including PVL, CD4 count, renal and liver function, fasting glucose, total cholesterol, and triglycerides. The study was approved by the Research Ethics Committee of National Taiwan University Hospital (registration no. 201103077RC) and the patients gave written informed consent for TDM of plasma atazanavir concentrations and pharmacogenetic investigations.

Measurement of plasma atazanavir concentration

TDM to measure plasma atazanavir concentrations was performed in patients switching to unboosted atazanavir-containing regimens after November 2011. After patients had taken atazanavir for 2 weeks or longer, measurements of plasma atazanavir concentrations, C12 (12 $\pm$ 1 hour after intake) or C24 (24 $\pm$ 1 hour after intake) based on feasibility, were performed during their routine clinic visits using high-performance liquid chromatography (HPLC) with a modified method reported by Müller et al.[26] Blood samples were collected into potassium and ethylenediaminetetraacetic acid-containing 10-mL tubes. Plasma was stored at -20°C prior to analysis. In brief, 400 μL of plasma was added to 400 μL of 2M sodium carbonate containing diazepam (internal standard). The resulting solution was extracted with 800 μL of ethyl acetate-n-hexane, 1:1 (vol/vol), and the organic layer was dried under nitrogen. The extract was then dissolved with 200 μL of methanol for HPLC analysis. The HPLC system consisted of a L-2130 HTA solvent delivery pump, a L-2200 autosampler, a L-2420 UV-Vis detector, and the HPLC D-2000 Elite on Windows (version 1.2, Hitachi High Technologies Corporation, Tokyo, Japan) chromatographic data system. Chromatography was performed on a Mightysil RP-18 GP column (250 $\times$ 4.6 mm, 5 μm; Kanto Corporation, Portland, OR, USA). The mobile phase was composed of 10mM phosphate buffer (pH 2.5) mixed with acetonitrile at a ratio of 58:42 (vol/vol), and the flow rate was 1 mL/min. The detection wavelength was at 245 nm. The injection volume was 20 μL. The retention time of atazanavir and internal standard was 11.95 minutes and 16.4 minutes, respectively. The calibration curve of atazanavir was linear over the range of 100–10000 ng/mL. The extraction recovery was 104%. The accuracy ranged from 94.0% to 104.0%. The peak area of the intra- and interassay coefficients of variation at 5000 ng/mL ranged from 1.22–3.5% and 0–1.19%, respectively.

Pharmacogenetic study

Single nucleotide polymorphisms [SNPs; multidrug resistance 1 (MDR1) 2677G->T/A, MDR1 3435C->T, and pregnane X receptor (PXR) 63396C->T] were reported to be associated with atazanavir concentrations, and differences in the frequencies of common alleles encoding these proteins among different ethnic groups can be related to the variability in drug response.[21,27,28] For example, the MDR1 G2677$\rightarrow$T/A polymorphism was more common in Asians (83–88%) than in Caucasians (67–69%).[21,29,30] In this study, DNA samples extracted from peripheral blood specimens were obtained from participants. MassARRAYiPLEX GoldSNP Genotyping was then performed to determine the SNPs of transcription factor binding sites of PXR regulatory regions and *MDR1* (*ABCB1*), while uridine diphosphate-glucuronosyltransferase 1A1 *(UGT1A1)* UGT1A1*28 were determined by methods described previously by Beutler et al.[31]

Assessment of treatment outcomes

Patients were divided into two groups according to NRTIs prescribed: TDF-based group in which patients received TDF, lamivudine, and unboosted atazanavir; and non-TDF-based group in which patients received coformulated zidovudine/lamivudine or abacavir/lamivudine and unboosted atazanavir. The primary outcome of interest was time-to-treatment failure, which was defined as virological failure (PVL $\geq$ 200 copies/mL) confirmed by a second test within 3 months; or regimen modification or discontinuation for any reason (intention-to-treat analysis), with the first date of PVL $\geq$ 200 copies/mL or the date of regimen modification as the failure date. The secondary primary outcome was treatment failure by 24 weeks and 48 weeks. Participants who did not experience the endpoint event were censored at the time of 96 weeks.

Absolute changes in lipid levels from baseline were summarized by treatment regimens through the last on-study visit or the visit when a lipid-lowering agent was added for the two groups of patients. Lipid data were excluded from analyses after the initiation of lipid-lowering agents.

Baseline characteristics and pharmacogenetic factors were assessed for the association with the occurrence of Grades 3–4 hyperbilirubinemia that was defined as a total bilirubin $>$ 2.5 times the upper limit of normal after a switch to unboosted atazanavir.

Statistical analysis

Categorical data were analyzed using Chi-square test or Fisher's exact tests as appropriate, and continuous variables, expressed as median and interquartile range, were compared using the Mann–Whitney *U* test. Paired *t*-test was used to analyze within-subject means over the two test conditions. The regression models were built using a forward stepwise procedure using demographic characteristics, clinical characteristics that included hepatitis B virus

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(HBV) or hepatitis C virus coinfection, and HIV status that included virological response to the prior cART, and CD4 counts. Logistic regression analysis was used to test predictive factors associated with Grades 3–4 hyperbilirubinemia. The confidence interval (CI) was set at 95%. All statistical tests were 2-tailed, and p values < 0.05 were considered to be statistically significant. The analysis was conducted using the statistical package SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

During the study period, 314 patients who switched to unboosted atazanavir in combination with two NRTIs were included: 128 (40.8%) switched to TDF, lamivudine plus unboosted atazanavir; and 186 (59.2%) to abacavir/lamivudine ($n = 161$) or zidovudine/lamivudine ($n = 25$) plus unboosted atazanavir. Baseline characteristics of both groups of patients are shown in Table 1. Compared with patients in the non-TDF group, patients in the TDF group were younger (38.7 years vs. 43.0 years, $p < 0.01$), had a higher proportion of chronic HBV infection (28.9% vs. 14.0%, $p < 0.01$), and lower fasting triglycerides (139.5 mg/dL vs. 222.0 mg/dL, $p < 0.01$) and total cholesterol levels (168.5 mg/dL vs. 213.5 mg/dL, $p < 0.01$) before the switch. The proportion of patients having achieved PVL < 40 copies/mL before the switch was 83.6% and 87.6% in the TDF group and non-TDF group, respectively ($p = 0.32$). Within-class substitution, from boosted PIs to unboosted atazanavir, was the most common switch strategy, especially in the TDF group. Deintensification from a ritonavir-boosted atazanavir-containing regimen to unboosted atazanavir-containing regimen was more common in the TDF group (67.2% vs. 20.4%, $p < 0.01$; Table 1).

Treatment response

After a median follow-up for 96 weeks (25th quartile, 74.0 weeks; 62.4% censored at Week 96), 53 (16.9%) experienced treatment failure. By Week 24, four patients (3.1%) in the TDF group and 12 (6.5%) in the non-TDF group experienced treatment failure (Chi-square test, $p = 0.19$); and by Week 48, 10 (7.8%) in the TDF group and 19 (10.2%) in the non-TDF group experienced treatment failure (Chi-square test, $p = 0.48$). There was no statistically significant difference between the two groups in time-to-treatment failure at Week 96 (14.9% vs. 18.3%, log-rank $p = 0.60$; Figure 1). Results of Cox proportional hazards model including all listed covariables are shown in Table 2. Independent risk factors for treatment failure included low-level viremia (40–200 copies/mL) before the switch

Table 1 Baseline characteristics of 314 patients who switched to unboosted atazanavir in combination with two nucleos(*t*)ide reverse-transcriptase inhibitors.[a]

Characteristics	Total ($n = 314$)	Tenofovir group ($n = 128$)	Nontenofovir group ($n = 186$)	p
Male sex	297 (94.6)	121 (94.5)	176 (94.6)	0.97
Age (y)	40.7 (33.9–46.9)	38.7 (32.1–43.5)	43.0 (34.9–48.9)	<0.01
Weight (kg)	65.0 (59.0–73.0)	65.1 (58.0–72.6)	64.0 (60.0–73.0)	0.44
BMI (kg/m^2)	22.4 (20.8–24.9)	22.5 (20.5–24.8)	22.3 (20.9–24.9)	0.56
Mode of transmission				0.18
MSM	234 (74.5)	102 (79.7)	132 (71.0)	
Heterosexual	57 (18.2)	16 (12.5)	41 (22.0)	
IDU	14 (4.5)	6 (4.7)	8 (4.3)	
Unknown	9 (2.8)	4 (3.1)	5 (2.7)	
HBsAg-positive	63 (20.1)	37 (28.9)	26 (14.0)	<0.01
Anti-HCV-positive	22 (7.0)	10 (7.8)	12 (6.5)	0.64
CD4 cell count at switch (cells/mm^3)	526 (370–682)	516 (355–665)	530 (393–696)	0.37
HIV-1 RNA < 40 copies/mL at switch	270 (86.0)	107 (83.6)	163 (87.6)	0.32
Triglycerides (mg/dL)	188.0 (109.0–329.0)	139.5 (96.0–221.0)	222.0 (128.5–393.5)	<0.01
Total cholesterol (mg/dL)	188.5 (157.0–232.0)	168.5 (145.0–202.0)	213.5 (167.5–250.0)	<0.01
Antiretroviral regimens before switching				<0.001
Boosted atazanavir + 2 NRTIs	124 (39.5)	86 (67.2)	38 (20.4)	
Boosted PI (nonatazanavir) + 2 NRTIs	79 (25.2)	17 (13.3)	62 (33.3)	
Raltegravir + 2 NRTIs	2 (0.64)	0 (0)	2 (1.1)	
NNRTI + 2 NRTIs	95 (30.3)	23 (18.0)	72 (38.7)	
3 NRTIs	14 (4.5)	2 (1.6)	12 (6.5)	

[a] Comparisons of continuous data are made using the Mann–Whitney *U* test and categorical variables using either Fisher's exact test or χ^2 test.
Data are presented as n (%) or median (interquartile range).
BMI = body-mass index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IDU = injecting drug user; MSM = men who have sex with men; NRTI = nucleos(*t*)ide reverse-transcriptase inhibitor; NNRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

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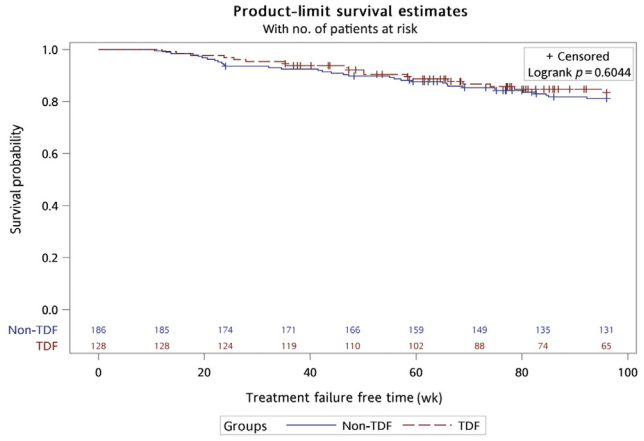

Figure 1. Time-to-virological failure in patients who switched to unboosted atazanavir plus two nucleos(*t*)ide reverse-transcriptase inhibitors (tenofovir-based vs. non-tenofovir-based regimens). TDF = tenofovir disoproxil fumarate.

[adjusted hazard ratio (AHR), 2.12; 95% CI, 1.12—4.01] and without TDM (AHR, 2.08; 95% CI, 1.16—3.73).

Reasons for treatment failure of the 53 patients are summarized in Table 3. Twenty patients, including five (3.9%) in the TDF group and 15 (8.1%) in the non-TDF group, experienced virological failure (PVL $\geq$ 200 copies/mL) during follow-up. Using Kaplan—Meier analysis, no statistically significant difference was found in time to virological failure between the two groups ($p = 0.18$). The adjusted Cox proportional hazards model revealed that low-level viremia before switch was a predictive factor of virological failure (AHR, 3.46; 95% CI, 1.34—8.92). No emergence of resistance-associated mutations to atazanavir or NRTIs was detected in the HIV-1 strains from the patients who experienced virological failure.

Table 3 Reasons for treatment failure in both groups of patients.

Reasons	Tenofovir-based ($n = 19$)	Nontenofovir-based ($n = 34$)
Plasma HIV RNA load > 200 copies/mL	5 (26)	15 (44)
Discontinuation of atazanavir	14 (74)	19 (56)
Loss to follow up	2 (11)	7 (21)
Irregular dosing interval	4 (21)	5 (15)
Jaundice	3 (16)	5 (15)
Alopecia	1 (5.2)	0
Elevated serum creatinine and proteinuria	2(10)	0
Unknown	2(10)	2 (6)

Data are presented as *n* (%).
HIV = human immunodeficiency virus.

Lipid profile and hyperbilirubinemia

After the switch to unboosted atazanavir plus two NRTIs, both groups showed similarly significant decrease of the total cholesterol levels from baseline: −16.6 mg/dL (95% CI, −11.8—−21.4) in the TDF group and −23.2 mg/dL (95% CI, −15.7—−30.7) in the non-TDF group ($p = 0.14$). A significant decrease in fasting triglycerides was also found after the switch in both groups: −58.1 mg/dL (95% CI, −25.9—−90.3) in the TDF group and −99.4 mg/dL (95% CI, −43.1—−155.6) in the non-TDF group ($p = 0.21$). During the study period, 23.2% of the patients experienced Grades 3—4 hyperbilirubinemia (32.8% and 16.7% for TDF and non-TDF group, respectively). In patients who switched from boosted atazanavir to unboosted atazanavir, the total bilirubin levels decreased from 2.48 mg/dL to 2.13 mg/dL [difference, −0.31 (95% CI, −0.43—0.17)] in the TDF group ($n = 86$) and from 2.17 mg/dL to 1.80 mg/dL [difference, −0.37 (95% CI, −0.74—−0.12)] in the non-TDF group ($n = 38$). In multivariate analysis, age (per 1-year increase, adjusted odds ratio 1.05; 95% CI, 1.01—1.09; $p < 0.01$) and HBV coinfection (adjusted odds ratio 2.73; 95%CI, 1.02—7.29; $p = 0.04$) were the two independent predictors of Grades 3—4 hyperbilirubinemia.

Plasma atazanavir concentrations

TDM of atazanavir concentrations (C12 and C24) were conducted in 197 patients (62.7%; TDF group vs. non-TDF

Table 2 Univariate and multivariate analysis for factors associated with virological failure in 314 patients.[a]

Variables	Reference	HR	95% CI	*p*	HR	95% CI	*p*
Tenofovir-based	Non-tenofovir-based	0.87	0.49—1.52	0.61			
Age (y)	Per 1-y increase	1.01	0.98—1.03	0.65			
HBsAg-positive	HBsAg-negative	1.10	0.58—2.10	0.76			
Anti-HCV-positive	Anti-HCV-negative	0.75	0.24—2.42	0.64			
CD4 count (cells/μL) before switch	Per 100-cell/μL increase	0.97	0.87—1.08	0.56			
Baseline plasma HIV RNA load (HIV RNA, 40—200 copies/mL)	HIV RNA < 40 copies/mL	2.08	1.11—3.90	0.02	2.12	1.12—4.01	0.02
Without therapeutic drug monitoring	With therapeutic drug monitoring	2.00	1.16—3.43	0.01	2.08	1.16—3.73	0.01

[a] HRs and 95% CIs were calculated using Cox regression analysis.
CI = 95% confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = hazard ratio.

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group, 80.5% vs. 50.5%, $p < 0.01$) and the results are shown in Figure 2. No statistically significant differences in the clinical characteristics were observed between the patients who had undergone TDM and those who had not (data not shown). In the TDF group, 16.5% (17/103) patients had plasma atazanavir concentrations below the recommended therapeutic values (230 ng/mL for C12 and 150 ng/mL for C24),[32] whereas in the non-TDF-based group, 35.1% (33/94) had atazanavir concentrations below the recommended therapeutic values ($p < 0.01$).

Pharmacogenetic study

The distributions of *UGT1A1* genotypes, *MDR1* genotype at positions 2677 and 3435, and the *PXR* genotype at position 63396 are shown in Table 2. There were no statistically significant differences in the clinical characteristics between the patients who had undergone genotyping for each gene and those who had not (data not shown). The distributions of SNPs of these three genes were similar between the two groups. For example, *UGT1A1* genotypes were characterized in 196 patients, for which TA6/TA6 was noted in 78.6%, TA6/TA7 in 21.4%, and TA7/TA7 in 0% (Table 4).

Subgroup analysis

When we limited the analyses to those with TDM ($n = 197$), we found that 12.2% of the patients experienced treatment failure (10 of 103 in TDF group and 14 of 94 in non-TDF group, Chi-square test, $p = 0.30$). In Cox regression, concentration above the recommended target (AHR, 0.61; 95% CI, 0.25–1.44), low-level viremia (AHR, 2.02; 95% CI, 0.74–5.53), and TDF-containing regimen (AHR, 0.79; 95%

Table 4 Genotyping results of the patients who switched to unboosted atazanavir in combination with tenofovir and lamivudine (tenofovir-based group) or two other non-tenofovir nucleoside reverse-transcriptase inhibitors (non-tenofovir-based group).

Genotype	Total	Tenofovir group	Nontenofovir group	*p*
*UGT1A1*28 ($n = 196$)				0.71
TA6/TA6	154 (78.6)	82 (79.6)	72 (77.4)	
TA6/TA7	42 (21.4)	21 (20.4)	21 (22.6)	
TA7/TA7	0	0	0	
MDR1 2677 ($n = 169$)				0.54
G/G	46 (27.2)	18 (26.1)	28 (28.0)	
G/T	62 (36.7)	25 (36.2)	37 (37.0)	
G/A	22 (13.0)	10 (14.5)	12 (12.0)	
T/A	21 (12.4)	6 (8.7)	15 (15.0)	
T/T	17 (10.1)	9 (13.0)	8 (8.0)	
A/A	1 (0.6)	1 (1.5)	0 (0)	
MDR1 3435 ($n = 122$)				0.47
C/C	12 (9.8)	3 (7.5)	9 (11.0)	
C/T	89 (73.0)	32 (80.0)	57 (69.5)	
T/T	21 (17.2)	5 (12.5)	16 (19.5)	
PXR 63396 ($n = 122$)				0.79
C/C	22 (18.0)	6 (15.0)	16 (19.5)	
C/T	55 (45.1)	18 (45.0)	37 (45.1)	
T/T	45 (36.9)	16 (40.0)	29 (35.4)	

Data are presented as *n* (%).

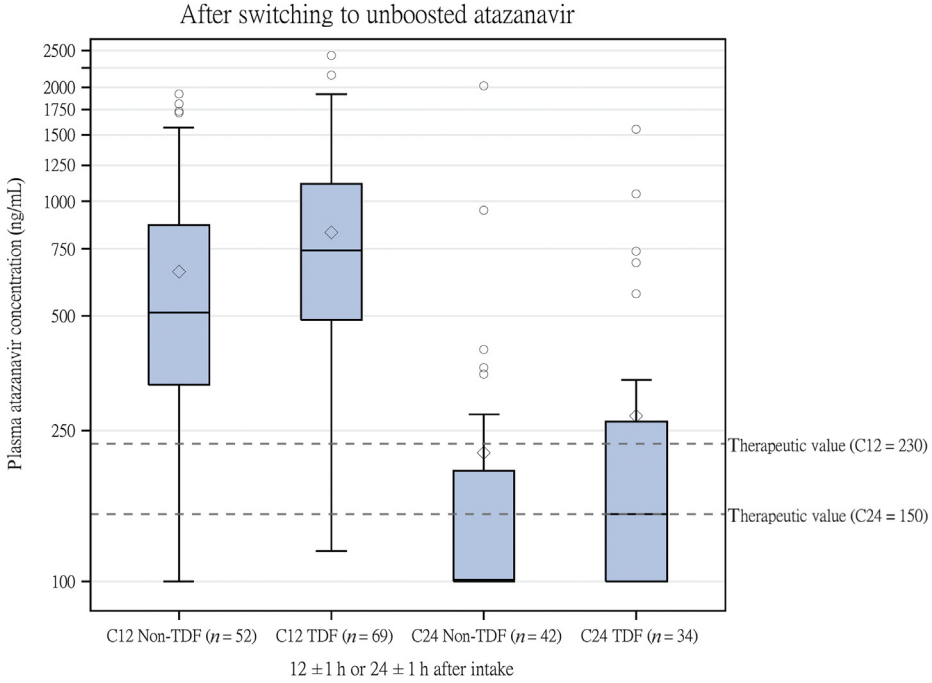

Figure 2. Plasma atazanavir concentrations, tenofovir/lamivudine + unboosted atazanavir, and abacavir-lamivudine (or zidovudine-lamivudine) + unboosted atazanavir.

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CI, 0.33—1.89) were not statistically significantly associated with treatment failure at Week 96.

To explore whether there was evidence that the difference in treatment response depended on genetic characteristics, a planned subgroup analysis was conducted and the results were plotted (Figure 3). It did not suggest a statistically significant advantage in terms of time to treatment failure for either group.

Discussion

In this study, we found that in HIV-positive patients on suppressive antiretroviral therapy without documented resistance-associated mutations to PIs, a switch to unboosted atazanavir in combination with TDF and lamivudine provided comparable antiviral effectiveness to unboosted atazanavir with two other non-TDF NRTIs. A switch to unboosted atazanavir-containing regimens resulted in lower total cholesterol and triglycerides without addition of lipid-lowering drugs.

In randomized controlled trials, regimens consisting of unboosted atazanavir plus two NRTIs caused less hyperbilirubinemia and improvement of lipid profiles,[12,14] which are also observed in our study. While TDF is not recommended to be combined with unboosted atazanavir, an ongoing open-label randomized control trial (NCT01351740) will examine the clinical effect of the potential drug—drug interactions between TDF and unboosted atazanavir in HIV-positive patients achieving viral suppression. In the retrospective analysis of 886 patients who switched to unboosted atazanavir-containing regimens in an European multicenter cohort collaboration, Pavie et al[25] found that TDF used in combination with unboosted atazanavir in 36.9% of the patients did not increase the risk of virological failure.

In our study, we found that the risk of virological failure could be reduced by 50% with the information of TDM, and atazanavir concentrations below recommended target were not correlated with virological failure in patients with TDM, which is in line with the finding of other studies.[24,33] There was a higher proportion of our patients (75%) who had atazanavir concentrations above the recommended target, which suggests that pharmacogenetics or environmental influences may influence plasma atazanavir concentration to a greater extent than the potential drug—drug interaction. Our subgroup analyses consistently demonstrated insignificant differences between TDF and non-TDF groups regarding time-to-virological failure in patients with virological suppression subdivided by genetic polymorphisms. Although the small sample size of the subgroups is a concern, the results may help minimize the bias and draw a robust conclusion.

Plasma atazanavir concentrations are associated with atazanavir-related hyperbilirubinemia.[24,34] Recent studies also suggested that boosted atazanavir-containing regimens are associated with an increased risk of clinically significant renal stones or cholelithiasis.[35—38] Therefore, TDM to optimize drug levels and to minimize adverse effects can be clinically relevant in the long-term successful management of cART for HIV-positive patients. Our study is the first study

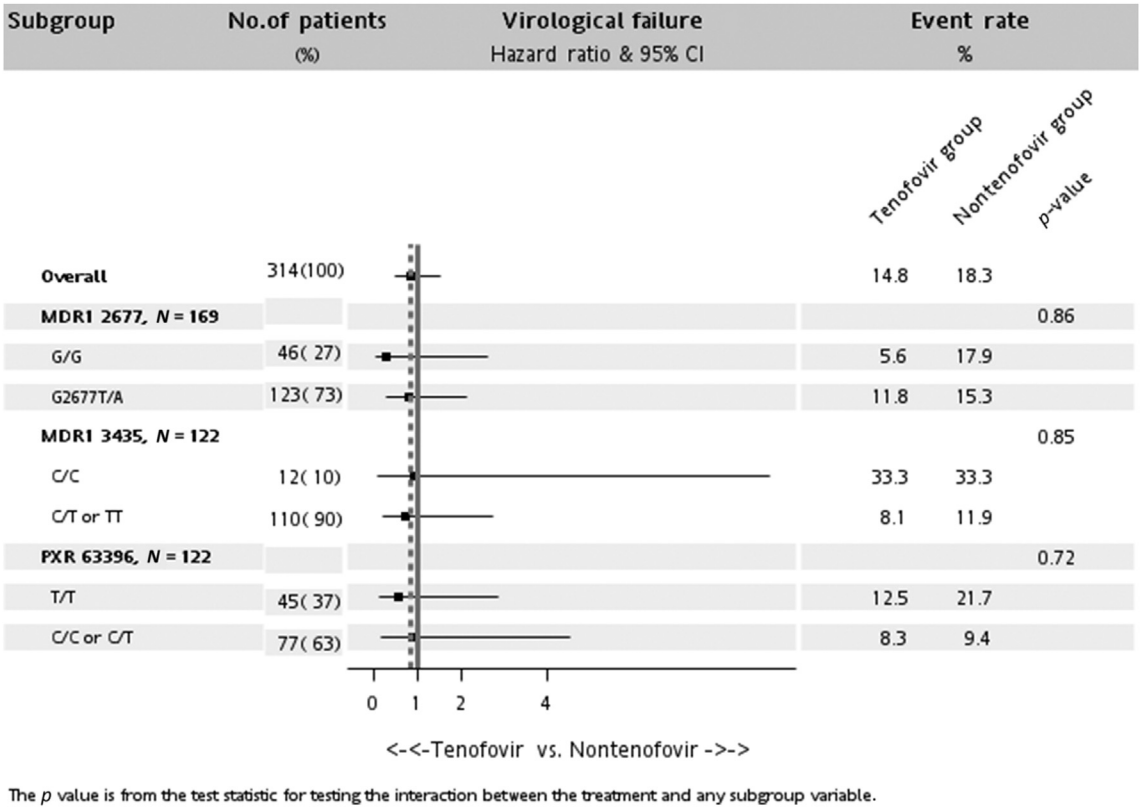

Figure 3. Forest plot showing the risk of virological failure according to subgroups. CI = confidence interval; MDR1 = multidrug resistance 1; PXR = pregnane X receptor.

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to use TDM in a clinical care setting to minimize the adverse impact of drug—drug interactions between atazanavir and TDF on virological response and the long-term metabolic effects of ritonavir. While more clinical and pharmacogenetic studies are warranted to confirm our findings, our finding that use of TDM reduced risk of treatment failure gives support to the use of TDM in management of patients on regimens containing boosted atazanavir.

There are several limitations to our study. This is not a randomized clinical trial, and selection bias is likely to have occurred. Patients who were deemed highly adherent to cART might be more likely to be switched to unboosted atazanavir combined with lamivudine and TDF than to unboosted atazanavir combined with two other non-TDF NRTIs, which may lead to an underestimation of the risk of virological failure in the TDF group. However, the two groups of patients had similar baseline characteristics and distributions of genetic factors on the whole, which may help minimize the bias. Secondly, limited by the sample size, our study was not powered to demonstrate the non-inferiority of one regimen to another. Thirdly, most of the patients were middle-aged men who have sex with men and, therefore, the results may not be generalizable to all HIV-positive patients. Fourthly, not all patients in this study underwent TDM and genotyping. While our study was the first study to address the clinical responses to unboosted atazanavir in combination with TDF and lamivudine with the information of drug concentrations and pharmacogenetics, the missing data on the plasma atazanavir concentrations preclude us from establishing a prediction model to identify atazanavir levels that might optimize trade-offs between virological responses and adverse effects. Fifthly, the distributions of the SNPs that are related to metabolism of atazanavir are likely to differ among different ethnicities, and therefore, our data may not be generalizable to ethnicities other than Taiwanese. Lastly, the observation duration was not long enough and a longer duration of follow-up is warranted to assess the durability of the regimen in virological suppression.

Unboosted ataznavir in combination with TDF and lamivudine is as effective as unboosted atazanavir in combination with two other NRTIs in patients who have achieved virological suppression. This regimen may represent a viable option in the treatment simplification strategies in populations with access to TDM.

Conflicts of interest

C.C.H. has received research support from Janssen (Beerse, Belgium) and speaker honoraria from Abbvie (North Chicago, Illinois United States) Bristol-Myers Squibb (New York City, United States), Gilead Sciences (Foster City, California United States) and ViiV (Brentford, Greater London United Kingdom), and served on advisory boards for Gilead Sciences and Abbvie.

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ORIGINAL ARTICLE

Incidence and risk factors of herpes zoster in human immunodeficiency virus-positive patients initiating combination antiretroviral therapy in Taiwan

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KEYWORDS
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varicella-zoster

Abstract *Background/Purpose:* To obtain current epidemiological data for better vaccination policies, this study aimed to assess the incidence and risk factors of herpes zoster in human immunodeficiency virus (HIV)-positive patients initiating combination antiretroviral therapy (cART) in Taiwan.
Methods: Between June, 2012 and May, 2015, we prospectively identified zoster cases in HIV-positive patients initiating cART. Clinical information was collected on demographics, prior zoster, plasma HIV-1 RNA load (PVL), and CD4 count at baseline and during follow up. A case–control study by 1:2 matched pairs was used to identify the risk factors for zoster development.
Results: During the 3-year study period, 826 patients with a mean age of 32.9 years were included, and 7.7% had prior zoster. The mean baseline CD4 count and PVL were 286 cells/μL and 4.90 $\log_{10}$ copies/mL, respectively. Fifty-four (6.5%) patients developed zoster after initiation of cART, with 43 episodes (79.6%) occurring within 1 year of cART initiation, which

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corresponded to an overall incidence rate of 3.61/100 person-years. The multivariate analysis revealed that prior zoster (adjusted odds ratio = 3.143; 95% confidence interval, 1.385–7.133) and baseline CD4 count < 200 cells/μL (adjusted odds ratio = 2.034; 95% confidence interval, 1.020–4.057) were independent risk factors for zoster in HIV-positive patients initiating cART. In case–control study, prior zoster and baseline PVL > 5 $\log_{10}$ copies/mL were risk factors for zoster development after cART initiation in multivariate analysis.

Conclusions: Herpes zoster occurred in 6.5% of HIV-positive Taiwanese patients after initiation of cART, which was associated with prior zoster and baseline CD4 count < 200 cells/μL or baseline PVL > 5 $\log_{10}$ copies/mL.

Introduction

Herpes zoster, also called shingles, is most often seen in the elderly population. It also commonly occurs in human immunodeficiency virus (HIV)-positive patients.[1–3] Prior to the introduction of combination antiretroviral therapy (cART), the incidence of herpes zoster was estimated to be 10–30 times greater in HIV-positive patients than in HIV-negative individuals.[1,4,5] Several studies reported incidence rates of 2.5–3.2 cases/100 person-years in different HIV-positive cohorts.[3,6] A low CD4 count was the risk factor for developement of herpes zoster.[4,7] After the introduction of cART, the incidence of herpes zoster declined significantly[7–10]; 1.2 cases/100 person-years was observed in Germany and 0.9 cases/100 person-years in the United States in the cART era.[9,10] This decrease was mainly attributable to the restoration of immunity with cART. However, the incidence remains higher in HIV-positive patients in the cART era than that in the general population of resource-rich countries, which ranges from 0.2/100 person-years to 0.5/100 person-years.[11,12] Complication rates are also higher in HIV-positive patients than in the age-matched general population (27–28% vs. 10–13%).[6,10,13,14] Therefore, use of herpes zoster vaccine may be considered in HIV-positive patients to prevent herpes zoster and its related complications.

Live attenuated herpes zoster vaccine (LAHZV) was recommended to HIV-positive adults with a CD4 count >200 cells/μL.[15,16] Recently, an adjuvanted herpes zoster subunit vaccine, called HZ/su vaccine, demonstrated significant risk reduction of herpes zoster in adults aged ≥ 50 years.[17] Given the concerns about the theoretical risk that the attenuated live vaccines may cause serious disease in immunocompromised hosts, this HZ/su vaccine has the potential to benefit HIV-positive patients.[18]

In Taiwan, Hung et al[7] reported that the incidence of herpes zoster in HIV-positive patients had declined from 17.21/100 person-years in the pre-cART era (prior to 1997) to 5.05/100 person-years in the post-cART era (between 1997 and 2003) ($p < 0.0001$), and baseline CD4 count was a significant risk factor associated with herpes zoster. To obtain current epidemiological data for better vaccination policies, this study aimed to assess the incidence and identify risk factors of herpes zoster in HIV-positive patients initiating cART in Taiwan.

Materials and methods

Patients and setting

Between June 1, 2012 and May 31, 2015, we conducted a prospective cohort study to identify cases of herpes zoster in cART-naïve HIV-positive adult patients who initiated cART at the National Taiwan University Hospital, Taipei, Taiwan. Patients were followed from the initiation of cART until the date of first episode of herpes zoster, loss to follow up, death, or end of observation (December 31, 2015). Herpes zoster was diagnosed based on the characteristic skin findings, whereas previous herpes zoster was defined as having an episode of herpes zoster prior to the initiation of cART.

In Taiwan, cART has been provided free of charge since its introduction in April 1997, and HIV-positive Taiwanese patients receive HIV care according to the national treatment guidelines at designated hospitals around Taiwan. Plasma HIV-1 RNA load (PVL) and CD4 count were determined at baseline, 4 weeks after initiation of cART, and every 12 weeks thereafter within the 1st year of cART and every 24 weeks subsequently in patients who are on stable cART with good viral suppression. All of the patients were enrolled in the case management program implemented by the Taiwan Centers for Disease Control to provide support, counseling, and linkage to and retention in HIV care fort the HIV-positive patients.

During the study period, cART was defined as combinations of two nucleos(*t*)ide reverse-transcriptase inhibitors with one non-nucleoside reverse-transcriptase inhibitor, boosted protease inhibitor or unboosted atazanavir, or integrase inhibitor. PVL and CD4 count quantified with the use of the Cobas Amplicor HIV-1 Monitor Test, version 1.5, (Roche Diagnostics Corporation, Indianapolis, IN, USA) and FACSFlow (Becton Dickinson, CA), respectively.

Study design and data collection

We used a standardized case record form to collect information on the demographic and clinical characteristics of the patients, including age, sex, risk behaviors of HIV-1 transmission, prior episode of herpes zoster, duration from

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cART initiation to the development of herpes zoster, as well as PVL and CD4 count at baseline and during follow up. To better delineate the risk factor for development of herpes zoster, a case−control study was conducted with two control patients without herpes zoster who were matched for one case patient with herpes zoster with regard to age (±3 years), sex, risk behaviors, and date of cART initiation (±2 weeks). Only the first episode of herpes zoster was included for analysis. The patients were censored when herpes zoster occurred after initiation of cART, when the patients were lost to follow up, or when the observation ended (December 31, 2015), whichever occurred first.

The study was approved by the Research Ethics Committee of the hospital (Registration Number, 201003112R), and the requirement for written informed consent from participants prior to participation in the study was waived.

Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD), and compared using Student *t* test. Categorical variables were expressed as percentage of the total number of patients analyzed, and compared using chi-square test. To identify the factors associated with development of herpes zoster, the variables with p values < 0.05 in univariate analysis were entered into the multivariate logistic regression analysis. The Kaplan−Meier method was used to assess time to cumulative probabilities of herpes zoster free condition by different categories of baseline CD4 count (<200 cells/μL, 200−349 cells/μL, 350−499 cells/μL, and ≥500 cells/μL, respectively), which were compared using log-rank test. A p value < 0.05 was considered statistically significant.

Table 1 Clinical characteristics of HIV-positive patients with and without herpes zoster after initiation of combination antiretrovial therapy between June 1, 2012 and May 30, 2015.

Variable	All patients	Patients with zoster	Patients without zoster	*p*
Patient no.	826 (100)	54 (6.5)	772 (93.5)	
Age (y)	32.9 ± 9.3	36.3 ± 10.1	32.7 ± 9.2	0.005
Male sex	801 (97)	53 (98.1)	748 (96.9)	0.912
Risk of HIV infection				
Homosexuals	769 (93.1)	52 (96.3)	717 (92.9)	0.326
Heterosexuals	41 (5.0)	2 (3.7)	39 (5.1)	
IDU	15 (1.8)	0 (0)	15 (1.9)	
Others	1 (0.1)	0 (0)	1 (0.1)	
Prior herpes zoster	56 (7.7)	9 (18.8)	47 (6.9)	0.007
AZT use	358 (43.3)	25 (46.3)	333 (43.1)	0.650
Switch from AZT to other agents	248 (30.0)	18 (33.3)	230 (29.8)	0.583
Duration from ART initiation to the development of zoster (d)	227 ± 265	227 ± 265	NA	NA
<1 mo of ART use	NA	8 (14.8)	NA	NA
1−3 mo of ART use	NA	13 (24.1)	NA	NA
3−6 mo of ART use	NA	11 (20.4)	NA	NA
6−12 mo of ART use	NA	11 (20.4)	NA	NA
>12 mo of ART use	NA	11 (20.4)	NA	NA
Baseline CD4 (cells/μL)	286 ± 187	208 ± 156	292 ± 187	0.001
≥500 cells/μL	86 (10.5)	3 (5.6)	83 (10.8)	0.013
350−499 cells/μL	199 (24.2)	8 (14.8)	191 (24.9)	
200−349 cells/μL	271 (33.0)	15 (27.8)	256 (33.3)	
<200 cells/μL	266 (32.4)	28 (51.9)	238 (31.0)	0.002
CD4 1 mo post-ART (cells/μL)	401 ± 212	344 ± 179	405 ± 214	0.043
<200 cells/μL	139 (17.9)	13 (24.5)	126 (17.4)	0.193
CD4 4 mo post-ART (cells/μL)	453 ± 224	403 ± 213	457 ± 225	0.091
<200 cells/μL	101 (14.0)	11 (20.8)	90 (13.5)	0.142
Baseline PVL ($\log_{10}$ copies/μL)	4.90 ± 0.73	5.22 ± 0.72	4.87 ± 0.72	0.001
>5 $\log_{10}$ copies/μL	340 (41.3)	33 (61.1)	307 (39.9)	0.002
PVL 1 mo post-ART $\log_{10}$ copies/μL ($\log_{10}$ copies/μL)	2.60 ± 0.82	2.93 ± 0.84	2.58 ± 0.81	0.002
>2 $\log_{10}$ copies/mL	617 (78.5)	45 (84.9)	572 (78.0)	0.240
<200 copies/mL	288 (36.6)	11 (20.8)	277 (37.8)	0.013
PVL 4 mo post-ART ($\log_{10}$ copies/μL)	2.60 ± 0.82	2.16 ± 1.09	1.74 ± 0.79	0.008
>2 $\log_{10}$ copies/μL	165 (22.9)	21 (40.4)	144 (21.5)	0.002
<200 copies/mL	616 (85.4)	39 (73.6)	577 (86.4)	0.011

Data are presented as mean ± SD or *n* (%).
ART = antiretroviral therapy; AZT = zidovudine; HIV = human immunodeficiency virus; IDU = injected drug user; NA = not available; PVL = plasma HIV-1 RNA load; SD = standard deviation.

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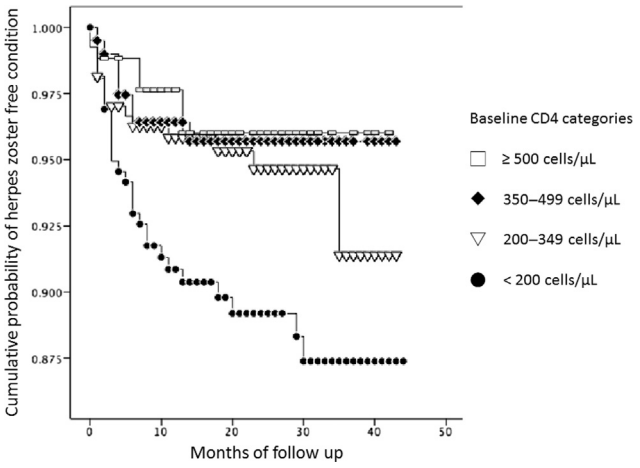

Figure 1. Kaplan–Meier plots showing the cumulative probability of herpes zoster-free condition in human immunodeficiency virus (HIV)-positive patients initiating combination antiretroviral therapy with different categories of baseline CD4 counts.

Results

During the 3-year study period, a total of 826 patients initiated cART at National Taiwan University Hospital. The patients had a mean age of 32.9 years; 97.0% were men; 93.1% were men who have sex with men; and 7.7% had prior herpes zoster. The mean baseline CD4 count and PVL were 286 cells/μL and 4.90 $\log_{10}$ copies/mL, respectively. Almost one-third of the patients (32.4%) had a baseline CD4 count < 200 cells/μL (Table 1). cART containing zidovudine/lamivudine was initiated in 43.3% (358/826) of the patients; however, 69.3% of those 358 patients initiating zidovudine-containing regimens had to switch from zidovudine/lamivudine to other nucleoside reverse transcriptase inhibitors.

After a mean observation duration of 634 days (SD, 348), herpes zoster developed in 54 patients (6.5%) after cART initiation, and nine (18.8%) of them had had herpes zoster prior to cART initiation. This corresponded to an overall incidence rate of 3.61/100 person-years. The mean interval from cART initiation to onset of herpes zoster was 227 days (SD, 265). Most of the episodes (79.6%) occurred within 1 year of cART initiation.

Demographic data and clinical characteristics between patients with and without development of herpes zoster after initiation of cART are shown in Table 1. Compared with patients without herpes zoster after cART, those with herpes zoster were older (mean age, 36.3 years vs. 32.7 years, $p = 0.005$) and more likely to have had prior herpes zoster (18.8% vs. 6.9%, $p = 0.007$), and had a lower mean baseline CD4 count (208 cells/μL vs. 292 cells/μL, $p = 0.001$) and a higher mean baseline PVL (5.22 $\log_{10}$ copies/mL vs. 4.87 $\log_{10}$ copies/mL, $p = 0.001$).

One month after initiation of cART, patients with herpes zoster continued to have a lower mean CD4 count (344 cells/μL vs. 405 cells/μL, $p = 0.043$) and a higher mean PVL (2.93 $\log_{10}$ copies/mL vs. 2.58 $\log_{10}$ copies/mL, $p = 0.002$). Four months after initiation of cART, patients with herpes zoster tended to have a lower mean CD4 count (403 cells/μL vs. 457 cells/μL, $p = 0.091$) but had a higher mean PVL (2.15 $\log_{10}$ copies/mL vs. 1.74 $\log_{10}$ copies/mL, $p = 0.010$).

Kaplan–Meier plots for cumulative probability of herpes zoster in patients with different categories of baseline CD4 counts during observation are shown in Figure 1. Patients with lower baseline CD4 counts were more likely to develop zoster (log-rank test $p = 0.012$; Figure 1). In multivariate analysis, prior herpes zoster [adjusted odds ratio (AOR) = 3.143; 95% confidence interval (CI), 1.385–7.133; $p = 0.006$] and baseline CD4 count < 200 cells/μL (AOR 2.034, 95% CI 1.020–4.057, $p = 0.044$) were independent risk factors for herpes zoster in HIV-positive patients initiating cART (Table 2).

In the case–control study, the clinical characteristics of the matched pairs (1:2) of patients with and without development of herpes zoster after initiation of cART are shown in Table 3. Six case patients did not have suitable controls, and only one matched control was identified for each of 10 patients. Compared with control patients, case patients were more likely to have prior herpes zoster (18.8% vs. 3.8%, $p = 0.012$), and had a lower mean baseline CD4 count (208 cells/μL vs. 284 cells/μL, $p = 0.015$) and a higher mean baseline PVL (5.22 $\log_{10}$ copies/mL vs. 4.80 $\log_{10}$ copies/mL, $p < 0.001$). One month and 4 months after initiation of cART, case patients had a higher mean PVL [2.93 $\log_{10}$ copies/mL vs. 2.51 $\log_{10}$ copies/mL ($p = 0.004$) and 2.15 $\log_{10}$ copies/mL vs. 1.71 $\log_{10}$ copies/mL ($p = 0.014$), respectively]. Associated factors with development of herpes zoster in multivariate analysis included prior herpes zoster (AOR = 4.735; 95% CI, 1.122–19.990; $p = 0.034$) and baseline PVL > 5 $\log_{10}$ copies/mL (AOR = 2.963; 95% CI, 1.001–8.774; $p = 0.050$) (Table 4).

Discussion

In this cohort of ART-naive HIV-positive patients, 6.5% experienced herpes zoster after cART initiation. Other studies of similar populations (homosexual males aged

Table 2 Multivariate analysis for risk factors associated with the development of zoster in HIV-positive patients after initiation of combination antiretroviral therapy.

Variable	Reference	OR	95% CI	*p*
Prior zoster	No prior zoster	3.143	1.385–7.133	0.006
Age	Continuous variables	1.016	0.985–1.047	0.317
Baseline CD4 count <200 cells/μL	Baseline CD4 < 200 cells/μL	2.034	1.020–4.057	0.044
Baseline PVL > 5 $\log_{10}$ copies/mL	Baseline PVL < 5 log copies/mL	1.542	0.789–3.013	0.205

CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PVL = plasma HIV-1 RNA load.

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Table 3 Clinical characteristics in matched pairs (1:2) of HIV-positive patients with and without herpes zoster after initiation of combination antiretroviral therapy.

Variable	Patients with zoster	Patients without zoster	*p*
No. of patients	54 (38.6)	86 (61.4)	
Age (y)	36.3 ± 10.1	34.3 ± 7.8	0.191
Male	53 (98.1)	86 (100)	0.386
Risk of HIV infection			
Homosexuals	52 (96.3)	85 (98.8)	0.681
Heterosexuals	2 (3.7)	1 (1.2)	
IDU	0 (0)	0 (0)	
Others	0 (0)	0 (0)	
Prior zoster	9 (18.8)	3 (3.8)	0.012
Baseline CD4 (cells/μL)	208 ± 156	284 ± 192	0.015
≥500 cells/μL	3 (5.6)	19 (13.8)	0.022
350–500 cells/μL	8 (14.8)	30 (21.7)	
200–349 cells/μL	15 (27.8)	49 (35.5)	
<200 cells/μL	28 (51.9)	28 (32.6)	0.023
AZT use	25 (46.3)	29 (33.7)	0.137
Switch from AZT to other agents	18 (33.3)	25 (29.1)	0.595
CD4 1 mo post-ART (cells/μL)	344 ± 179	374 ± 201	0.368
<200 cells/μL	13 (24.5)	15 (18.5)	0.403
CD4 4 mo post-ART (cells/uL)	403 ± 213	417 ± 210	0.705
<200 cells/μL	11 (20.8)	15 (18.5)	0.749
Baseline PVL (log_{10} copies/mL)	5.22 ± 0.72	4.80 ± 0.59	<0.001
>5 log_{10} copies/mL	33 (61.1)	28 (32.6)	0.001
PVL 1 mo post-ART (log_{10} copies/mL)	2.93 ± 0.84	2.51 ± 0.81	0.004
>2 log_{10} copies/mL	45 (84.9)	64 (78.0)	0.324
<200 copies/mL	11 (20.8)	36 (43.9)	0.006
PVL 4 mo post-ART (log_{10} copies/mL)	2.15 ± 1.08	1.71 ± 0.82	0.014
>2 log_{10} copies/mL	21 (39.6)	13 (16.3)	0.002
<200 copies/mL	39 (73.6)	72 (90.0)	0.013

Data are presented as mean ± SD or *n* (%).
ART = antiretroviral therapy; AZT = zidovudine; HIV = human immunodeficiency virus; IDU = injection drug user; PVL = plasma HIV-1 RNA load; SD = standard deviation.

approx.30–40 years) in the cART era reported a relatively higher prevalence of herpes zoster, ranging from 7.9% to 14.1%.[8,9,19] The discrepancy may be attributable to the different ethnicities and baseline CD4 counts of the patient populations.[8] Compared with a previous observational study in Taiwan,[7] this study showed lower incidence (6.5% vs. 10.7%, $p = 0.006$) with a significantly lower incidence rate than that in the pre-cART era (3.61/100 person-years vs. 17.2/100 person-years, $p = 0.004$) but a similar incidence rate when compared with that in the post-cART era (3.61/100 person-years vs. 5.05/100 person-years, $p = 0.754$). The decline in the incidence of herpes zoster was also demonstrated in other recent studies,[8,10,19] which could reflect the benefit of restoration of immunodeficiency and viral suppression by cART.

Our study found that baseline CD4 count < 200 cells/μL and prior herpes zoster were independent risk factors for the development of herpes zoster in patients initiating cART. Several recent studies also demonstrated a clear association between the CD4 counts and the risk of herpes zoster.[9,10,19,20] In the French study using insurance databases, Grabar et al[19] found an inverse dose–response relationship between the CD4/CD8 ratio < 0.9 and the risk of herpes zoster, independent of the CD4 count and PVL, in multivariate analysis. An association between CD8 count and the risk of herpes zoster has also been described by other studies.[21,22]

In the case–control study, we found that prior herpes zoster and baseline PLV > 5 log_{10} copies/mL were risk factors associated with development of herpes zoster, which was different from those (prior herpes zoster and baseline CD4 count < 200 cells/μL) identified in the overall study population. Blank et al[10] found that starting cART within 90 days of the zoster episode, having a PVL > 400 copies/mL, and a CD4 < 350 cells/μL were associated with increased risk of herpes zoster. These findings suggested that markers of poor immune function, such as high PVL and low CD4 count, were predisposing factors to the development of herpes zoster, and early initiation of appropriate regimens of cART may reduce the burden of herpes zoster in HIV-positive patients.

Because of higher incidence and complications of herpes zoster in HIV-positive patients, vaccination could provide potential benefits. LAHZV is recommended to HIV-positive adults with a CD4 count >200 cells/μL.[15,16] Despite concerns of causing disease in immunocompromised hosts, including HIV-positive populations, by LAHZV,[23,24] a recent study by Shafran[15] recommended the administration of LAHZV to HIV-positive adults with a CD4 count >200 cells/μL, which was safe and immunogenic with no cases of vaccine strain infection. However, the lower CD4 counts, the higher the probability of herpes zoster in HIV-positive patients. For HIV-positive patients with CD4 counts < 200 cells/μL, a recombinant subunit vaccine might be an appropriate choice to prevent herpes zoster.[25] A recent phase 1/2a clinical trial by Berkowitz et al[18] noted that an adjuvanted herpes zoster subunit candidate vaccine was immunogenic in both humoral and cellular immunity and had a clinically acceptible safety profile in HIV-positive adults, including patients with cART and CD4 count < 200 cells/μL.

This study should be viewed with necessary caution in light of several limitations. First, self-reported prior herpes zoster was not documented by a health professional, but high validity to self-reports of herpes zoster suggested that herpes zoster misclassification was likely to be very low.[26] Second, as patients might present with herpes zoster in a local primary care facility, the incidence of herpes zoster experienced by patients in this cohort was likely to be underestimated. Third, information on complications of herpes zoster were unavailable, such as postherpetic neuralgia, disseminated herpes zoster, bacterial superinfection, ocular involvement, and meningoencephalitis. This precludes us from evaluating the impact of herpes zoster on HIV-positive patients. Fourth, our results were derived from patients followed at a single, urban institution with a high proportion of men who have sex with men, and the results may not be generalized to other clinical settings.

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Table 4 Multivariate analysis for risk factors associated with the development of zoster in matched pairs of HIV-positive patients after initiation of combination antiretroviral therapy.

Variable	Reference	OR	95% CI	*p*
Age	Continuous variables	1.403	0.931–2.114	0.106
Prior zoster	No prior zoster	4.735	1.122–19.990	0.034
Baseline PVL >5 $\log_{10}$ copies/mL	Baseline PVL <5 $\log_{10}$ copies/mL	2.963	1.001–8.774	0.050
Baseline CD4 <200 cells/μL	Baseline CD4 >200 cells/μL	1.191	0.389–3.645	0.760

CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PVL = plasma HIV-1 RNA load.

In conclusion, 6.5% of HIV-positive Taiwanese patients developed herpes zoster after initiation of cART, with an overall incidence rate of 3.61/100 patient-years. The associated factors of zoster development included prior herpes zoster and baseline CD4 count < 200 cells/μL or baseline PVL > 5 $\log_{10}$ copies/mL.

Conflicts of interest

C.-C.H. has received research support from Janssen, Abbvie, and ViiV; and speaker honoraria from Bristol-Myers Squibb, ViiV, Abbvie, and Gilead Sciences; and served on advisory boards for Gilead Sciences and Abbvie. All other authors declare no conflicts of interest.

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Willingness of human immunodeficiency virus-positive patients to donate their organs for transplantation in Taiwan: a cross-sectional questionnaire survey

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ABSTRACT

Background: With the introduction of combination antiretroviral therapy (cART) that has significantly improved survival, human immunodeficiency virus (HIV)-positive patients may be potential organ donors to HIV-positive recipients in a few countries. Organ shortage remains a challenge for organ transplantation in Taiwan, where organ donation by HIV-positive patients remains prohibited by law.

Methods: We assessed the willingness of organ donation (should they be pronounced brain death, and the ban on HIV-positive organ donation be lifted) among HIV-positive patients who received regular HIV care at a university hospital in a cross-sectional survey between May and August 2015 with the use of an anonymous, self-administered questionnaire interview.

Results: Of the 1010 participants, 93.7% were receiving cART with the latest mean CD4 count and plasma HIV RNA load of 587 cells/mm^3 and 2.73 $\log_{10}$ copies/mL, respectively. Overall, 71.9% were willing to donate organs. In multivariate analysis, factors associated with willingness to donate organs included college or graduate school diploma (odds ratio [OR] 1.571, 95% confidence interval [CI] 1.166–2.191), registered willingness in the National Health Insurance system (OR 9.430, 95% CI 1.269–70.051), and knowledge of the information on HIV-positive deceased donors (HIVDD) (OR 1.673, 95% CI 1.073–2.608).

Conclusions: We concluded that a significant proportion (71.9%) of HIV-positive Taiwanese patients were willing to donate their organs. The willingness was associated with a higher education level, prior registered willingness to donate organs, and awareness of HIVDD.

KEYWORDS:

Organ transplantation, HIV, deceased donor

1 INTRODUCTION

Human immunodeficiency virus (HIV) infection was traditionally considered a contraindication for transplantation because of concerns about progression to acquired immunodeficiency syndrome (AIDS) with increased mortality and futile consumption of organs.[1] However, after combination antiretroviral therapy (cART) was introduced in 1996, the prognosis of patients with HIV infection has improved dramatically.[2] AIDS-defining illnesses have decreased steadily as a cause of death and life expectancy of treated HIV-positive patients is projected to be approaching that of the HIV-negative general population[3]; however, mortality from non-AIDS-related infections and malignancies and end-stage organ disease is increasing.[4] Improvement in the long-term prognosis of patients with HIV infection has initiated discussions of policies and studies regarding transplantation in HIV-positive patients. In carefully selected HIV-positive patients, the outcomes of kidney transplantation have significantly improved, with 1-year and 3-year patient survival rates of 94.6% and 88.2%, respectively, which were similar to those of HIV-negative populations, with no increase in HIV-associated complications.[5] The long-term outcomes of HIV-positive recipients after liver transplantation have improved over time with a 5-year and 10-year patient survival rate of 55.8% and 41.0%, respectively, with a 1.68-fold increase for death when compared with matched HIV-negative controls. [6]

With improved survival of HIV-positive patients, the prevalence of end-stage renal disease and end-stage liver disease has increased in these patients.[7,8] However, the limited supply of organs remains a challenge, and HIV-positive patients continue to have a higher waitlist mortality than their HIV-negative counterparts.[9,10] Recently, the use of organs from HIV-positive deceased donors (HIVDD) has been demonstrated to be safe and feasible in South Africa.[11,12] In 1988, the National Organ Transplant Act in the United States banned the use of organs procured from donors "infected with the etiologic agent for AIDS." The practice of HIV-positive transplantation to HIV-positive recipients, a reversal of the federal ban, was proposed by the HIV Organ Policy Equity (HOPE) Act in 2013[13], which mandates that the Secretary of the Department of Health and Human Services develop and publish criteria and conduct clinical research for organ transplantation from HIVDD.

According to Taiwan Organ Registry and Sharing Center, 7965 patients were on the waitlist for organ transplantation, while only 366 patients received organ transplantation in 2015.[14] Similar to what has been observed in Western countries, the mortality of HIV-positive patients has been significantly reduced in the era of cART in Taiwan, while death caused by liver disease and aging-related comorbidities has impacted the long-term management of HIV infection.[15,16] Regulations of the Taiwan Centers of Disease Control (CDC) have recently been revised to allow HIV-positive patients to be on the waitlist of organ transplantation after meeting certain selection criteria in 2015. To solve the shortage of organ supply, the ban on organ donation from HIV-positive individuals is under consideration to be lifted in Taiwan.

Regarding the opportunity to expand the organ pool from HIVDD, a nationwide investigation in the US reported an annual average of 494 (range, 441–533) potential HIVDD from HIV Research Network.[17] Deceased HIV-positive patients represented a potential of 500–600 donors per year for HIV-positive transplant candidates.[17] However, older donor age, comorbidities, and higher prevalence of positive hepatitis C virus (HCV) antibody have raised concerns about the quality of HIV-positive organs.[18] Other than the numbers of donated organs, the less explored issue is whether HIV-positive patients have intention or willingness to donate their organs before death. In anticipation of a possible revision of the law prohibiting organ donation by HIV-positive patients in the foreseeable future, we aimed to explore the attitude and factors associated with willingness to donate organs posthumously among HIV-positive patients in Taiwan.

2 MATERIALS AND METHODS

Patients and setting

This study was a cross-sectional survey conducted between May and August 2015. Over the 4-month study period, all HIV-positive patients regularly attending HIV outpatient clinic at the National Taiwan University Hospital (NTUH), Taipei, Taiwan, were invited to participate in this study. The NTUH has been the largest hospital providing inpatient and outpatient HIV care since the first case of HIV infection was diagnosed in Taiwan in 1984. The first living-related kidney, deceased-donor

kidney, and cardiac transplantations were performed successfully in Taiwan in 1968, 1969, and 1987, respectively, at this hospital.[19,20] The transplant team at NTUH is capable of performing heart, lung, liver, kidney, and pancreas transplantations. [21]

All participants completed an anonymous, self-administered questionnaire interview; the questionnaire was prepared in Chinese (the English-translated version is available as supplementary material Data S1). The content of this questionnaire comprised 3 parts: first, the general and basic data of age, gender, level of education, residency, occupation, religion, comorbidity (hepatitis B virus [HBV] or HCV infection), current HIV infection status (use of cART, CD4 count, and plasma HIV RNA load within 3 months of survey), and registered willingness of organ donation in the system of National Health Insurance (NHI) before HIV diagnosis; second, the knowledge of the information on the current status and policies of organ transplantation in HIV-positive patients in Western countries and Taiwan; and third, a hypothetical question of the willingness of organ donation, should the interviewees be pronounced brain death and the ban on HIV-positive donation be lifted. The questionnaire was piloted among the first 12 patients to identify the suitability and comprehensibility of the questionnaire, and no changes were made to the questionnaire thereafter. The Research Ethics Committee of the hospital approved the study (registration numbers, 201503054RINB) and waived the need for written informed consent from the patients.

2.2 Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were reported as mean ± standard deviation, and compared with Student's *t*-test. Categorical variables were expressed as percentage of the total number of patients analyzed, and compared with chi-square test. To identify factors associated with willingness of organ donation, the variables with a *P*-value < 0.05 in univariate analysis were entered into the multivariate logistic regression analysis. A *P*-value of < 0.05 was considered statistically significant. Missing data were excluded for analysis.

3 RESULTS

During the 4-month study period, 2530 HIV-positive patients sought HIV care at our hospital, and a total of 1010 (39.9%) HIV-positive patients participated in the study and completed the questionnaire. The demographic and clinical characteristics of the participants are shown in Table 1. The participants had a mean age of 37.3 ± 9.5 years, 98.1% were of male gender, 93.7% were receiving cART when the survey was conducted, 13.3% had chronic HBV infection, and 4.4% tested positive for HCV antibody. Their mean CD4 lymphocyte count and plasma HIV RNA load was 587 ± 243 cells/mm^3 and 2.73 ± 0.21 $\log_{10}$ copies/mL, respectively.

Overall, 726 (71.9%) participants expressed their willingness of organ donation for transplantation to HIV-positive patients, once the current ban on organ procurement from HIV-positive donors was lifted in Taiwan; 73 (7.2%) refused, and 211 (20.9%) were undecided regarding organ donation. Comparisons of the demographic and clinical characteristics between the patients willing and those unwilling or undecided to donate organs are shown in Table 1. Compared with the patients unwilling or undecided to donate organs, patients with willingness for organ donation were younger (mean age, 36.7 vs. 38.7 years, P = 0.004), had higher educational achievement with diploma of college and graduate school (78.3% vs. 65.7%, P < 0001), and were less likely to have received the diagnosis of HIV infection >10 years ago (14.6% vs. 20.0%, P = 0.038). No statistically significant difference was found in terms of having religious belief between the 2 groups (56.2% vs. 59.8%, P = 0.303). The proportion of patients receiving cART (93.9% vs. 93.0%, P = 0.565), mean CD4 lymphocyte count (592 vs. 572 cells/mm^3, P = 0.241), and mean plasma HIV RNA load (2.73 vs. 2.71 $\log_{10}$ copies/mL, P = 0.256) within 3 months of survey were also similar between the 2 groups. Patients willing to donate organs were more likely to have registered the willingness for organ donation before their HIV diagnosis on their personal NHI identification card than those without such intentions (3.8% vs. 0.4%, P = 0.004).

Regarding the knowledge of current status and policies for organ transplantation and donation in HIV-positive patients in Western countries, patients with willingness of organ donation were better informed than those without (22.7% vs. 16.2%, P = 0.022; 17.2% vs. 10.2%, P = 0.005,

respectively). As for the knowledge on the upcoming plans to lift the ban on organ transplantation and donation in HIV-positive population by the Taiwan CDC, no statistically significant differences were seen between the 2 groups (17.7% vs. 14.1%, P = 0.178; 14.1% vs. 10.6%, P = 0.142, respectively).

The results of multivariate analysis to identify factors associated with willingness of organ donation in HIV-positive patients are shown in Table 2. HIV-positive patients with college or graduate school diploma (odds ratio [OR], 1.571, 95% confidence interval [CI], 1.126–2.191, P = 0.008), those who previously had registration of willingness of organ donation in the system of NHI (OR 9.430, 95% CI 1.269–70.051, P = 0.028), and those who were aware of the current status of organ transplantation in HIV-positive patients (OR 1.673; 95% CI 1.073–2.608, P = 0.023) were more willing to donate their organs, should they be pronounced brain death and the ban be lifted.

DISCUSSION

This is the first study, to our knowledge, to describe the willingness of organ donation and its associated factors among HIV-positive patients who sought HIV care regularly in the Asia-Pacific region. We found that a significant proportion of HIV-positive patients (71.9%) were willing to donate their organs for transplantation if the legal restrictions on organ procurement from HIV-positive donors for HIV-positive recipients were removed. Patients with college and graduate

school diploma, who previous registered willingness of organ donation, or with knowledge of policies regarding HIVDD were more willing to donate their organs, should they be pronounced brain dead.

Attitudes toward organ donation may differ among the populations studied from different countries. In a survey evaluating the attitude of organ donation among the general population in Taiwan conducted in 1994, 499 individuals were interviewed or completed the questionnaire. While the idea of organ donation after brain death was accepted by 82.9% of the participants, only 17.1% agreed to donate their organs should they develop brain death.[22] This survey also revealed that participants with a college diploma, unmarried status, having no children, and acceptance of brain death being equal to death were more willing to donate their organs. The differences in the study population and the study year may explain the difference in the willingness of organ donation between this survey and our current study.

Several other factors have been identified to be associated with attitudes toward organ donation, such as higher level of education, favorable opinion of one's partner, carrying out pro-social activities, favorable knowledge of one's religion, and information regarding donation.[23–27] On the other hand, fear and lack of information were commonly cited as barriers to organ donation.[23–27] Furthermore, a study showed an educational program could alter attitudes, behavior, and knowledge among medical nurses about organ donation.[28] In this study, we also found the more knowledge regarding HIVDD and the higher education level our study participants had, the more

they were willing to donate their organs. Therefore, our findings suggest that raising awareness by campaigns through mass or social media or organizations may be an effective method to facilitate the registration and willingness of organ donation.

In the study by Taha et al.[29] assessing the attitudes of HIV-positive patients toward organ transplantation between HIV-positive patients in Coventry, United Kingdom, 62% of the participants would consider donating either any organ or a specific organ(s) to another HIV-positive patient, and 55% of them would consider receiving an organ from an HIV-positive patient.[29] They found that ethnicity had a significant effect on the attitude towards donating organs to HIV-positive patients, while the durations of being diagnosed as having HIV infection and being on cART affected attitude towards receiving an organ from HIV-positive patients. However, several differences exist between their study and ours. Their study participants were older with a mean age of 42 ± 5.66 years, 70% were black Africans, 54% were women, and 50% had comorbidities, while ours were younger with a mean age of 37.3 ± 9.5 years, 100% were of Asian ethnicity, 98.1% were men, and 13% had HBV infection. They assessed both attitudes toward donating organs to and receiving an organ from HIV-positive patients in their study, and we only explored attitude toward donating organs. Furthermore, they did not assess the education levels and knowledge of current status and policies for organ transplantation and donation in HIV-positive patients among the study participants, and this might explain their finding that black African participants were more likely than Caucasian participants to indicate they were not sure about organ donation.

The HOPE Act was passed in 2013, reversing the federal ban on the use of organs from HIV-positive donors for HIV-positive recipients in the US. In translating this policy into practice, the biological risks of using HIV-positive donors need to be carefully evaluated, such as aspects of HIV superinfection, viral tropism, antiretroviral therapy options, transmitted or acquired drug resistance, opportunistic infections, and HIV-related organ dysfunction.[30] The issue of greatest concern was HIV superinfection in the organ recipients, which could have adverse impact on clinical outcomes and pose a concern for subsequent options of antiretroviral treatment. [31] Therefore, selection criteria for HIVDD should be carefully established.[30]

Several limitations in our study deserve attention. First, we did not have a control group, such as HIV-negative individuals, for comparison. Second, the study was conducted using anonymous questionnaire interview and the correctness of responses could not be verified. Third, the size of HIV-positive organ supply could not be estimated, and the willingness to accept HIV-positive organs among HIV-positive patients on the waitlist could not be assessed by the current study design. Fourth, this is a single-center study and all the study participants are of Asian ethnicity. Thus, our findings may not be generalized to patients of other ethnicities and countries. Fifth, we did not investigate the types of religious beliefs of the participants that may drive positive or negative attitudes towards organ donation, and, therefore, further social science research is needed to explore the relationship between religious beliefs and the willingness of organ donation among HIV-positive patients in Taiwan. Similarly, our study did not assess the opinion of one's

partner/family, an important factor that may affect attitudes toward organ donation.[23] Last, while we believe that altruism is present in the Taiwanese society, the interviewees might have provided socially desired responses to the hypothetical questions in this survey.

5 CONCLUSIONS

A significant proportion (71.9%) of HIV-positive Taiwanese patients receiving regular HIV care at a university hospital were willing to donate their organs, which was associated with a higher education level, their prior registered willingness to donate organs in the system of NHI, and awareness of current policies regarding organ transplantation in the context of HIV infection.

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Author contributions: Y.-C.L. drafted the article. C.-C.H. designed the study and revised the article. A.C. reviewed the English questionnaire. W.-C.L. performed the experiments. P.-Y.W., S.-P.Y., J.-Y. Z., Y.-Z.L., and H.-Y.C. performed the questionnaire interview. H.-Y.S. designed the study, analyzed the data, and revised the article. S.-C.C. gave conceptual advice.

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SUPPORTING INFORMATION

Supporting information is available online at the supporting information tab with this article:

DATA S1 Survey questionnaire about organ transplantation in HIV-positive patients.

TABLE 1 Univariate analysis of factors associated with the willingness to donate organs in human immunodeficiency virus (HIV)-positive patients

Variables	Patients willing to donate	Patients unwilling or undecided	Statistics *P*-value
Patient number, n (%)	726 (71.9)	284 (28.1) (refused 73; undecided 211)	
Age, mean ± SD, years	36.7 ± 9.1	38.7 ± 10.4	0.004
Male, n (%)	716 (98.6)	275 (96.8)	0.060
Diploma, % (n/N)			<0.001
College or graduate school	78.3 (568/725)	65.7 (186/283)	
Others	21.7 (157/725)	34.3 (97/283)	
Residency, % (n/N)			0.169
Taipei City	40.2 (291/724)	35.2 (100/284)	
New Taipei City	47.2 (342/724)	50.7 (144/284)	
Other cities	12.0 (87/724)	13.4 (38/284)	
Abroad	0.6 (4/724)	0.7 (2/284)	
Any religious belief, % (n/N)	56.2 (388/691)	59.8 (165/276)	0.303

Occupation, % (n/N)			0.008
Military service	0.4 (3/716)	0.4 (1/273)	
Public service	2.9 (21/716)	5.5 (15/273)	
Education service	4.2 (30/716)	5.9 (16/273)	
Business service	26.7 (191/716)	32.6 (89/273)	
Computer science	8.7 (62/716)	7.3 (20/273)	
Others	49.9 (357/716)	40.7 (111/273)	
Students	3.6 (26/716)	4.0 (11/273)	
Unemployed or retired	3.6 (26/716)	3.7 (10/273)	
Years since HIV diagnosis, % (n/N)			0.010
Less than 5 years	50.5 (363/719)	54.2 (149/275)	
5 to 10 years	34.9 (251/719)	25.8 (71/275)	
More than 10 years	14.6 (105/719)	20.0 (55/275)	
Receiving cART, % (n)	93.9 (68.2)	93.0 (264)	0.565
Latest CD4 lymphocyte count, mean ± SD, cells/mm^3	592.3 ± 243.9	572.4 ± 239.6	0.241
Latest PVL, mean ± SD, log_{10} copies/ml	2.73 ± 0.21	2.71 ± 0.22	0.256
HBV infection, % (n/N)	12.2 (45/369)	14.7 (24/163)	0.424
HCV infection, % (n/N)	3.9 (14/363)	5.6 (9/161)	0.372
Registered willingness in the system of NHI, % (n/N)	3.8 (27/705)	0.4 (1/272)	0.004
Knowing policies regarding			

organ transplantation in HIV-positive patients			
Knew of transplantation of HIV-positive patients in western countries (question 1[a]), % (n/N)	22.7 (165/726)	16.2 (46/284)	0.022
Knew of revising policies to allow HIV-positive patients to be a transplantation recipient in Taiwan (question 2[b]), % (n/N)	17.7 (128/725)	14.1 (40/283)	0.178
Knew of HIV-deceased donor in United States (question 3[c]), % (n/N)	17.2 (125/726)	10.2 (29/284)	0.005
Knew of revising policies of HIV-deceased donor in Taiwan (question 4[d]), % (n/N)	14.1 (102/725)	10.6 (30/283)	0.142

[a]Question 1. Before participating in this study, did you know that HIV-positive patients can undergo organ transplantation (mainly liver and kidney transplantation) in Western countries (such as United States, Spain, and France)? □ Yes, □ No.

[b]Question 2. Before participating in this study, did you know that Taiwan's Center for Disease Control and Prevention (CDC) is revising the policies to allow HIV-positive patients to be transplant recipients? □ Yes, □ No.

[c]Question 3. Before participating in this study, did you know that HIV-positive patients in the United States can donate their organs to other HIV-positive patients? □ Yes, □ No.

[d]Question 4. Before participating in this study, did you know that Taiwan's CDC is revising the policies to allow HIV-positive patients to donate their organs to other HIV-positive patients in need? □ Yes, □ No.

SD, standard deviation; cART, combination antiretroviral therapy; PVL, plasma HIV RNA load; HBV, hepatitis B virus; HCV, hepatitis C virus; NHI, National Health Insurance; CDC, Centers of Disease Control.

TABLE 2 Multivariate analysis for factors associated with the willingness to donate organs in human immunodeficiency virus (HIV)-positive patients

Variables	References	OR (95% CI)	*P*-value
Age	Continuous variable	0.990 (0.974 - 1.007)	0.251
Men	Women	1.032 (0.363 - 2.932)	0.953
College/Graduate school diploma	Other diploma	1.571 (1.126 - 2.191)	0.008
Awareness of HIV infection for > 10 years	Awareness of HIV infection for less than 10 years	0.871 (0.576 - 1.317)	0.513
Registered willingness of organ donation in the system of NHI	No registration	9.430 (1.269 - 70.051)	0.028
Knowing current status of organ donation in HIV-positive patients*	Not knowing	1.673 (1.073 - 2.608)	0.023

*Question: Before participating in this study, did you know that HIV-positive patients in the United States can donate their organs to other HIV-positive patients?

OR, odds ratio; CI, confidence interval; NHI, National Health Insurance.