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行政院衛生署疾病管制局九十六年度科技研究發展計畫

愛滋病防治中心

The HIV/AIDS Control and Study Center

# 研 究 報 告

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＊ 本研究報告僅供參考，不代表衛生署疾病管制局意見＊

# 目　　錄

# 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：**本年度係愛滋病防治中心第二期五年計畫之第五年，今年延續第一期五年計畫的工作，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。

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。本中心 10 年來在衛生署疾病管制局大力資助下已達到初期的成果，不論是臨床醫療服務或是基礎研究皆可謂成果豐碩，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 AIDS 防治與醫療的重要責任，因為 AIDS 的流行涉及社會文化、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 AIDS 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，尤其注重衛生教育，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。初期希望以醫護學院學生及醫療院所工作人員為對象，再進一步擴大至特定群體，包括性工作者、男同性戀者、藥物毒癮者、船員、不穩定的流動人口，社會各機關團體及一般民眾等。為加強年輕人對預防 AIDS 的能力，使年輕人遠離感染 HIV 的風險，希望儘快架設 AIDS 防治與醫療網站，提供免費的諮詢服務與最新的訊息。

為響應政府之減害政策，本中心每週五由孫幸筠醫師、洪健清醫師及護理師等輪流至雲林第一監獄、雲林第二監獄、嘉義監獄：1.診視新診斷愛滋病毒感染或新入監的收容人。2.了解危險因子、目前身體健康狀況告知相關衛教知識，並回答病患問題 CD4/CD8、愛滋病毒病毒量、A、B、C 肝炎病毒、肝功能、及其他基本生化檢查長住監獄之收容人。3.追蹤 CD4/CD8、HIV 病毒量、肝功能變化，決定何時開始使用抗愛滋病毒藥物。4.雲林分院積極實施美沙酮替代療法。

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之角色，應有相當之資源規劃教育訓練及建置並執行 PP line 等項目，今年由盛望徽醫師主持以台大醫院愛滋病防治中心醫師、護理人員、檢驗師為主，並與台北市立聯合醫院疾病管制院區(昆明院區)合作，針對 HIV 體液暴露者建立完整且統一的 HIV 體液暴露事件處理流程。提供 24 小時 HIV 篩檢及專線諮詢與衛教服務，以降低 HIV 感染的機會及減輕諮詢者其不安及焦慮。另外，提供快速且單一 HIV 檢驗管道，以便於 24 小時內知道污染源是否已感染檢驗 HIV 病毒。若確定污染源已感染 HIV 病毒，則於 24-36 小時內提供免費預防藥物，並通報衛生機關，發揮有效之防疫功能。

第二期五年計畫(第五年)的實施重點有四大主題，如下列：

主題一、各科醫事人員愛滋感染者照護之相關在職訓練：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。

主題二、HIV 抗藥性監測與臨床處理之相關研究：監測 HIV 抗藥性及研究與抗藥性相關之臨床處理方法之成效。

主題三、HIV 臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

主題四、接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

**主要發現：**

一、配合政府之減害政策及因應日漸增加的毒癮愛滋病患；特別派洪健清醫師、孫幸筠醫師等至雲林監獄和雲林第二監獄、嘉義監獄，病患抽血及肝炎腹部超音波檢查，一直是監獄頭痛的問題，需有大量戒護人力帶收容人至醫院抽血及接受檢查。希望有機會找到人力入監抽血及檢查。並於雲林分院實施美沙酮替代療法。

二、HIV個案管理運作模式之加強；中心特別在台大醫院的醫療體系內建立一HIV個案管理運作模式，並訂立標準，未來可以顯示更多元化不同等級個案管理模式的效益。

三、為提昇本中心的衛教服務功能，及因應日趨嚴重的毒癮愛滋病患的增加問題；今年共舉辦了許多場全國性的大型研討會 5 場、2 場 HIV/AIDS Workshop、3 場 HIV 個案管理師訓練課程為配合臨床試驗之需求，為提昇國內臨床研究人員之參與力與能力，並期導入我國臨床試驗能力與國際接軌，特與財團法人台灣癌症基金會、台灣感染症醫學會於 96 年 10/6、7、20、21 日 (共四天)，舉辦「感染症專科醫師藥品臨床研究設計及執行研習班」。延續去年與財團法人護理人員愛滋病防治基金會繼續合辦「愛滋病個案管理師訓練」初階課程及進階課程，分別於 5/18~20 日(南區 110 人參加) 、6/1~3 日(北區 244 人參加)、6/29~30 日(進階 153 人參加)。

四、希望再充實本中心醫療設備；為了不使一般民眾發生排斥的心理，隔離病房將改善通風、紫外線等設備，內視鏡室亦需要再充實。

五、外籍勞工與新娘的防治問題；國內目前引進大批外籍勞工及〝東南亞新娘〞、〝大陸新娘〞等，他們當地的身體檢查報告有些不確實的地方，因此造成許多的家庭悲劇。

六、有關WHO對台灣防治愛滋病的認知；因WHO將台灣視為中國大陸的一部份，所以我們所有的努力均被忽略了，一些醫療及研究成果亦被稀釋，期望以後能透過有關單位向國際間爭取，以獲得國際衛生組織的認可，甚至可以提供我們的經驗去幫忙其他需要援助的開發中國家及地區。

七、抗藥性HIV的出現及繼續更新〝HIV/AIDS處置通則與治療導引〞；台灣自86年4月本中心發動全國性HAART療法，一時療效奇佳，住院病患顯著減少，死亡率激降，但好景不長，抗藥性HIV不久出現。國人對於抗HIV之特效藥，忍耐力低，服藥順從性亦低，因此抗藥性之出現較歐美人快速；如何解決此艱難工作，將是重要課題。

**結論與建議：**

一、 繼續提昇本中心的衛教服務功能，今年共舉辦了許多場全國性的大型研討會 5 場、2 場 HIV/AIDS Workshop、3 場 HIV 個案管理師訓練課程。每一場報名人數都非常踴躍，場場大爆滿，而且與會者迴響熱烈，可見愛滋病照護的相關問題目前受到重視的程度，往後應該繼續定期舉辦；並希望能擴大辦理讓其他科別的醫師也能來參與。

二、 整合國內 AIDS 防治醫療資源，建立資源與資訊交流支援網絡，以充份運用有限資源、有限病床，使每位病患獲得最適照護，進而達成最大的防治功效。

三、 加強調派醫師等至雲林監獄、雲林第二監獄、嘉義監獄診視新診斷愛滋病毒感染或新入監的收容人希望有機會找到人力入監抽血及檢查。並將於雲林分院開始實施美沙酮之維持療法。進行藥癮愛滋精神流行病學研究。

四、 男女性感染愛滋比例由 92 年的 20:1 拉近為 96 年的 10:1；另毒癮愛滋婦女佔女性感染族群 55.98%，並且 86.62%為 20~49 歲育齡婦女。以逐年比較男女性別比發現，我國女性感染愛滋的比例急劇增加，鑑此，婦女愛滋病毒感染者其相關之疾病的探究、治療的方式、以及母子垂直感染的議題，都是我們未來重要的課題。

五、 HIV 抗藥性監測與臨床處理之相關研究：監測 HIV 抗藥性及研究與抗藥性相關之臨床處理方法之成效。

六、 HIV 臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

七、 隨著抗病毒藥物的引進死亡率大幅降低，從高效能抗愛滋病毒藥物引進以前的 33.75 每 100 人/年降低至藥物引進的 6.51 每 100 人/年 (P<0.0001)；而且和藥物引進前比較，2000 年到 2004 年免疫球低於 200/μL 的感染者死亡的風險降低高達 62%之多，但是，發病後第一年的死亡仍然高達 8-9%。這些結果顯示感染者就醫有提早的現象，但是以轉診醫院的角度來看仍然有相當大的改善空間。愛滋病雞尾酒療法之長期研究仍然需要持續進行(如存活率等)。

八、 接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

**關鍵詞：**愛滋病毒、愛滋病、愛滋病防治中心、靜脈毒癮者、減害(Harm Reduction)、台灣地區愛滋病研究群、高效抗反轉錄病毒療法(HAART) 、伺機性感染、靜脈毒癮愛滋病毒感染

# Abstract

**Objectives:** Prevention and treatment of Acquired Immunodeficiency Syndrome, AIDS patient care, and AIDS related research studies.

**Research methodology:** The five-year Phase II program of the HIV/AIDS Control and Study Center enters its fourth year this year. This year, the center shall be continuing the work pursued in the five-year Phase I program, that is tracing the "Highly active antiretroviral therapy" (HAART) treatment conducted on AIDS patients at the NTU Hospital; including tracing opportunistic infections, clinical research, and new virus strains. This year, under a stable manpower environment, the study plans to continue the active usage of the software and hardware facilities of the center, and bring to fore the features of the center. The program shall mainly revolve around clinical medical services, and on the side, tackle fundamental research and behavioral science studies, enhance services provided to outpatients, and see to the improvement of composite therapy and medicine side effects.

Since the establishment of the NTU Hospital "The HIV/AIDS Control and Study Center" in June 1997, the entire staff of the Center had aggressively worked on AIDS prevention and clinical studies, and reached greater accomplishments through the years. Under the strong support of the Department of Health Centers for Disease Control, the HIV/AIDS Control and Study Center achieved the initial goals in the 10 years that past. Moreover, both in terms of clinical medical service and fundamental research studies, the Center achieved inconsiderable results. As personnel training and organization reached a level of stability, and the center laboratory operations reached a notable scale, the center entered a key stage in its operations, that of setting trends and examples for the future to follow. We wasted no time in upholding the important duty of preventing the spread of AIDS and providing treatment to victims. The growing popularity of AIDS involves changes in the social, cultural, and sex habits; hence the fight against AIDS is a social reform campaign and not just a simple health and hygiene problem. Therefore, in addition to AIDS treatment and medical care, the HIV/AIDS Control and Study Center shall coordinate the educational, cultural, and social sectors for a joint promotion of the AIDS prevention plan. Special attention is given to the subject matter of health education. Through the available resources of the HIV/AIDS Control and Study Center and the hospitals in northern Taiwan, the campaign plans to hold a series of health education orientations and seminars. It is believed that proper prevention education is made available to all is the best way to stem the vicious cycle of HIV infection. The initial goal of the campaign is to mobilize medical school students and hospital personnel to join the campaign, and thereafter, widen the scale of operations to include certain specific groups; such as prostitutes, homosexual males, drug dependents, ship crew, the unstable mobile population, civic and social organizations or groups, and the general public, thus, strengthening the AIDS prevention consciousness among young people. The campaign is aimed to reduce the risk of HIV infection among young people and, in the soonest possible time, set up AIDS prevention and treatment websites to provide the public with free consultation information and the latest updates on AIDS related developments.

In response to the Harm Reduction policy of the government, Dr. Sun Hsing-Yun, Dr. Hung Chien-Ching and a team of nurses of the HIV/AIDS Control and Study Center regularly conduct clinics at the Yunlin First Prison, Yunlin Second Prison, and Chiayi Prison on Fridays. The clinics provided the following services: 1. Checkup and diagnose conditions of AIDS sufferers or new inmates. 2. Understand the risk factors involved, and advice inmates of the related health education information relevant to their physical conditions. Provide answers to questions pertaining to CD4/CD8, AIDS virus count, Hepatitis A, B, and C virus counts, liver functions, and

other basic biochemical tests received from long-term prison inmates. 3. Trace CD4/CD8, HIV virus count, liver function changes, and determine the time to start patient on the anti-AIDS virus drugs. 4. Actively implement the methadone substitution treatment at the Yunlin branch hospital .

In amelioration and consolidation of the medical resource and AIDS patient related information of the nation's designated AIDS treatment hospitals, nationwide cross-hospital HIV clinical epidemiology related studies were conducted. The joint studies sought to understand the clinical symptoms of domestic AIDS sufferers, the treatment and prevention measures employed against opportunistic infection, patient inclination to seek medical attention, high risk behaviors, drug resistance and side effects of therapy treatments, and other related clinical epidemiology studies. The studies aimed to provide a reference for the future establishment or amendment of subsequent treatment and infection prevention related policies. Moreover, it is imperative that the the HIV/AIDS Control and Study Center should take a leading position in the domestic AIDS related prevention and treatment efforts, possess sufficient resource planning, education, training, and establishment capacity, and implement the PP line. This year, Dr. Sheng Wang-Hui headed a team of the HIV/AIDS Control and Study Center doctors, nurses, and medical technicians, and together with the Branch for Communicable Disease Control of Taipei City Hospital (Kun-Ming Branch Hospital), established a sound and standardized post-exposure prophylaxis procedure for the HIV infection. The center provides a 24-hour HIV screening test and a PP line information and health education service to reduce chances of HIV infection and ease the burden and anxiety of the inquirers. Furthermore, an express testing channel for the singular HIV test has been established to determine the presence of HIV virus in patients within a 24-hour period. Once a patient is tested to be HIV positive, free preventive treatment is immediately administered within a 24- to 36-hour window; information is thereafter forwarded to the health authorities to ensure the implementation of effective epidemic prevention measures.

The four major subject matters of the Two-Phase Five-Year Plan ($5^{th}$ year) implementation plan are as follow:

Subject matter 1, the AIDS patient care and treatment related in-job training courses for the medical staff of the respective hospital departments: The planning and implementation of AIDS patient care and treatment related in-job training for the medical staff of the respective hospital departments.

Subject matter 2, HIV drug resistance surveillance and clinical procedure related studies: The surveillance and study of HIV drug resistance conditions, and an evaluation of the results of the drug resistance related clinical procedures and methods.

Subject matter 3, HIV clinical epidemiology related studies: The consolidation of the medical resource and AIDS patient related information of the nation's designated AIDS treatment hospitals, and the collaboration of clinical studies conducted, aim to understand the clinical symptoms of domestic AIDS sufferers, the treatment and prevention measures employed against opportunistic infection, patient inclination to seek medical attention, high risk behaviors, and the drug resistance and side effects of therapy treatments.

Subject matter 4, the establishment of the AIDS contact Post Exposure Prophylaxis line/PP line: The planning, establishment, and execution of the AIDS contact Post Exposure Prophylaxis line/PP line.

**Significant Findings:**

1. In line with the Harm Reduction policy of the government and in response to the problem of a growing AIDS infected drug dependent population, Dr. Hung Chien-Ching and Dr. Sun Hsing-Yun were designated to the Yunlin First Prison, Yunlin Second Prison, and Chiayi Prison to conduct blood tests and the hepatitis abdominal ultrasound tests on prison inmates.

The regular clinics had become a huge headache for the prison authorities as they needed to mobilize a huge force of prison guards to take the inmates to the hospital for blood sampling and test procedures. It is hoped to find the needed manpower to conduct the blood and medical tests in the prison, and implement the methadone substitution treatment at the Yunlin Branch Hospital.

2. For the enhancement of the HIV case management operating model, the Center especially created the HIV case management operating model within the NTU Hospital medical system, as well as set the related standards. In the future, the system shall manifest more diversified, multilevel case management operating models.
3. Numerous forums and seminars were launched this year in an effort to upgrade the HIV/AIDS Control and Study Center health education service program and in response to the problem of a growing AIDS infected drug dependent population, such as the five large-scale AIDS forum, one "HIV/AIDS Workshop for Drug Resistance and Treatment Options", and three courses of the Training Program of HIV Case Administrators. The training courses were conducted in response to clinical test requirements, in enhancement of the participation and skills of domestic clinical study personnel, and in fostering the coordination of domestic clinical test standards with international standards. For this purpose, the center coordinated with the Formosa Cancer Foundation and the Infectious Diseases Society of Taiwan and jointly hosted the "Seminar on Design and Implementation of Clinical Studies on Drugs for Infectious Disease Physicians" held on October 6, 7, 20, and 21, 2007 (four days in all). The course is a sequel to "The Training Program of HIV Case Administrators" beginner and advance courses we hosted last year together with the Nurses AIDS Prevention Foundation. The seminars were held on May 18 to 20 (south region seminar attended by 110 trainees), June 1 to 3 (north region seminar attended by 244 trainees), and on June 29 to 30 (advance class attended by 153 trainees). Applications for the foregoing seminars, workshops, and lecture classes had been enthusiastic and had exceeded the room seating capacity; hence we needed to change location to a larger venue. Size of the classes grew exponentially and participants avidly interactive during the sessions.
4. The center hopes to beef up the medical equipment of the HIV/AIDS Control and Study Center to provide each member of the public a sense of receiving fair and equal treatment. The ventilation system and UV disinfecting system of isolation wards should be improved; moreover equipment in the endoscope room should be upgraded.
5. The problems of prevention work among foreign workers and brides: There is now a large population of foreign workers, "Southeast Asian brides", and "Mainland Chinese brides" in Taiwan. The medical reports prepared in their home countries are not all as factual as expected, a matter that had become the cause of many a home tragedy.
6. As for the matter of the WHO understanding of the AIDS prevention work in Taiwan, since the WHO sees Taiwan as an integral part of China, our efforts in this area had been ignored. Some medical and study findings had been diluted. It is hoped that the government authorities should present our case to the international community and gain their support for the WHO recognition of Taiwan. In fact, we could contribute information from our experiences to help developing nations and regions requiring assistance.
7. The emergence of the drug resistant HIV strain and the continued updating of the "HIV/AIDS Health Care Criteria and Therapy Guide": The nationwide launching of the HIV/AIDS Control and Study Center HAART therapy in April 1997 allowed Taiwan to witness the emergence of a highly efficient medical treatment. The death rate of AIDS patients in hospitals began to plunge; unfortunately, this happy scenario did not last long due to the emergence of the drug resistant HIV not long after. The tolerance of Taiwan patients to the HIV-resistant remedy had

been low; hence their inclination to undertake the treatment had been low as well. Thus, the spread of the drug resistant strain here had been faster than those in Europe and the United States. The solution of this complicated problem had remained an important issue to the medical sector.

**Conclusion and Recommendations:**

1. Numerous forums and seminars were launched this year to ensure the continued upgrading of the HIV/AIDS Control and Study Center health education service program, such as the five large-scale AIDS forum, one HIV/AIDS related workshop, and three HIV case administrator training courses. Applications for the courses had been enthusiastic and had exceeded the room seating capacity; moreover, the center received wonderful feedbacks on them. It was apparent that AIDS health care related problems are a matter of serious concern today. In the future, we shall continue to hold regular courses on the subject, as we hope to expand classes open to doctors from other fields of specialization.
2. The consolidation of the medical resources of the nation's AIDS treatment hospitals, the establishment of a resource and information sharing and support network for the optimization of limited hospital resources and beds had allowed patients to receive the proper treatment. In consequence, we saw the optimization of the nation's prevention performance.
3. The campaign of assigning doctors to the Yunlin First Prison, Yunlin Second Prison, Chiayi Prison to check up and diagnose conditions of AIDS sufferers or new inmates. It is hoped to find the needed manpower to conduct blood sampling and testing procedures in the prison. Moreover, the methadone sustenance therapy procedure and a psychological epidemiology on drug-dependent inmates were implemented at the Yunlin branch hospital.
4. The ratio between the male and female AIDS sufferers has narrowed from the 20:1 in 2004 to 10:1 in 2006. In the female sufferer population, 53.91% were drug dependents, and 90.31% of which belong to the 19 – 49 age bracket. A comparison with the gender population ratio of AIDS sufferers of the past years revealed that population of female AID sufferers is rising dramatically in the country. In light of which, studies delving into the HIV infection among women, AIDS treatment procedures, and the vertical infection problem between mother and child shall become the important issues of our future agenda.
5. HIV drug resistance surveillance and clinical procedure related studies: The surveillance and study of HIV drug resistance conditions, and an evaluation of the results of the drug resistance related clinical procedures and methods.
6. HIV clinical epidemiology related studies: The consolidation of the medical resource and AIDS patient related information of the nation's designated AIDS treatment hospitals, and the collaboration of the clinical studies conducted, aim to understand the clinical symptoms of domestic AIDS sufferers, the treatment and prevention measures employed against opportunistic infection, patient inclination to seek medical attention, high risk behaviors, and the drug resistance and side effects of therapy treatments.
7. The long-term study of the AIDS Cocktail Therapy (e.g., survival rate, etc.).
8. The establishment of the AIDS contact Post Exposure Prophylaxis line/PP line: The planning, establishment, and execution of the AIDS contact Post Exposure Prophylaxis line/PP line.

**Keyword:** 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，由台大醫院與性病防治所先行辦理「愛滋病防治中心」第一期五年計劃，進行相關防治與研究事宜；本計劃為第二期五年計劃之第五年關鍵性工作。

目前全球約有1,320萬的靜脈藥癮者，其中78%在發展中國家，亞洲地區即佔333萬人，多數地區的藥癮人口均在近20年間快速成長，據估計，台灣的靜脈藥癮者約有6萬人。根據衛生署疾病管制局截至96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至2006年10月底已達15,345人（本國籍為14,711人）近年來以毒癮者增加幅度最大，1988~2007年10月底通報本國籍毒癮感染者有5,699人(其中來自監所3,764人，約占66%)。在年齡層分布方面，感染愛滋的年齡層以20至29歲最多，佔38.04%，其次為30至39歲，佔35.44%，兩者共佔全體感染者的73.48％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。

聯合國愛滋病防治組織過去就曾發出警告，注射毒品是愛滋大流行的引爆點，一但愛滋病毒在毒品注射群體中流行時，毒癮愛滋族群會再透過不安全之性行為傳染給一般群體，如此將使愛滋疫情面臨爆炸性成長，故專家提出警告：如果我國再不採取積極態度去遏止愛滋病毒的蔓延，所賠上的慘痛代價，將不是用金錢可以比擬的。台灣毒癮愛滋病患增加的速度令人憂心，毒癮愛滋人數在五年內暴增，而且嚴重地影響國內公共衛生與醫療型態，將來流行必將日趨惡化，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

主題一、各科醫事人員愛滋感染者照護之相關在職訓練：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。

定期分區舉辦「臨床醫師愛滋病研習會」，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，擬規劃實施方法及進行步驟如下：(1)、初階教育課程，課程內容包括：台灣愛滋病政策與法令及流行病學介紹；HIV 之基因與分子流行病學；HIV 感染之檢驗、診斷及臨床表徵；抗愛滋病毒藥物治療指引；愛滋病毒之伺機性感染及治療；HIV 門診時之相關醫師衛教；母子垂直感染防治政策及成果；懷孕婦女之抗病毒治療與預防；台灣嬰幼兒愛滋病感染之現況與抗病毒治療；HIV 檢驗前後之諮商及家屬衛生教育指導；醫療環境防護措施及人員針扎事件之處理原則；HIV/AIDS 之護理照顧。(2)、進階教育課程，課程內容包括：HIV/AIDS 抗病毒藥物治療之副作用與交互作用；愛滋病毒之伺機性感染個論；HIV/AIDS 之慢性 B 型和 C 型肝炎處置；愛滋病毒感染者之糖尿病；愛滋病毒感染者之心血管疾病與高血脂症之處置；愛滋病毒感染者之糖尿病；愛滋病毒感染者之腸胃疾病；愛滋病毒感染者之腫瘤；愛滋病毒感染者之神經系統疾病；愛滋病毒感染者之性病；愛滋病毒感染者之骨科疾病；抗藥性病毒株之監測及處理；HAART 治療失敗之的病人的處理。(3)、靜脈毒癮 HIV 感染者相關之教育訓練課程，課程內容包括：台灣 HIV 感染及靜脈毒

癮 HIV 感染者之流行病學介紹；台灣 HIV 感染及靜脈毒癮 HIV 感染者之分子流行病學介紹；HIV/AIDS 毒癮者之治療經驗；HIV/AIDS 毒癮者之一般性感染與處置；HIV/AIDS 毒癮者之慢性 B 型和 C 型肝炎處置；HIV/AIDS 毒癮者之精神疾病與處置；HIV/AIDS 毒癮者之護理照護經驗；「減少傷害 Harm Reduction」之相關工作坊及訓練課程。(4)、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。(5)、將申請臺灣醫學會、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。(6)、全程參加者結業時將頒發授課證明。(7)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。

主題二、HIV抗藥性監測與臨床處理之相關研究：監測HIV抗藥性及研究與抗藥性相關之臨床處理方法之成效。

採用 QIAamp Viral RNA Mini Kit (QIAGEN)商用試劑組，抽取檢體中的人類免疫不全病毒 RNA。在分離出的週邊血液單核細胞（PBMCs）中加入 200 μl 的紅血球溶解緩衝液（0.32M 蔗糖溶液，10 mM Tris-HCl [pH 7.5]，5 mM 氯化鎂溶液及 1%Triton X-100）。當大多數紅血球溶解後，離心並去除上清液。再加入 200 μl 含有 Proteinase K 的紅血球溶解緩衝液（10 mM Tris-HCl [pH 8.3]，50 mM 氯化鉀溶液，2.5 mM 氯化鎂溶液，0.45% Nonidet P-40 及 0.45% Tween 20），在 55℃水浴槽中水浴一小時。之後用酚－氯仿溶液萃取出 DNA，再用酒精沈澱，最後溶於 100 μl 的二次水中，並在 260 nm 波長下測其吸光度以決定 DNA 濃度。萃取自人類免疫不全病毒的 RNA，須先經由反轉錄酶反應，做成 cDNA 後，再經由聚合酶連鎖反應（PCR）來放大 env 和 gag-RT 可轉錄區域。首先，取 10 μl 萃取自人類免疫不全病毒的 RNA，加入 1 μl oligo dT (0.5 μg/μl)，在 70℃作用 5 分鐘。再加入適當的反轉錄酶緩衝液、dNTP、 及反轉錄酶，在 40℃作用一小時。之後，在 70℃作用 15 分鐘，使反應停止後即可。所得之 cDNA 可接著做聚合酶連鎖反應，或者保存於-20℃。利用聚合酶連鎖反應（PCR）來放大 gag-RT 可轉錄區域（coding regions）。針對 gag-RT 基因，第一次 PCR 所用的引子對為 Gag1（5’ ATG CCA GAA ATA GCA GGG CCC 3’ ）和 Pol1A（5’ CTA GGT ACT ATG TCT GTT AGT GCT 3’ ）。在 50 μl 的 PCR 標準反應溶液中（10mM Tris-HCl [pH9.0]，50mM 氯化鉀溶液，1.5mM 氯化鎂溶液，0.1%(w/v) gelatin，1% Triton X-100，0.25mM dNTPs，每個 primer 10 pmol 及 1 單位的 Taq DNA 聚合酶），約加入 1 μl 的 cDNA。PCR 放大反應的溫度及條件為 95° C/3 分鐘，再跑 35 個循環：95° C /1 分鐘，62° C/1 分鐘，72° C/1 分鐘。接著將初次的 PCR 產物稀釋 50 倍，用 Gag2（5’ AGC AGA GCC AAC AGC CCC ACC A 3’ ）和 RT1（5’ CTA AAT CCC TGG ATA AAT CTG A 3’ ）這兩個引子來進行第二次 PCR 放大反應。溫度的設定和初次的 PCR 相同，也跑 35 個循環。最後預期的 PCR 產物大小約為 1200bp。所有的 PCR 反應產物，都將藉由電泳及 Ethidium bromide 染色確定其純度。為了之後進行核酸定序反應，聚合酶連鎖反應之產物需先經由電泳分離出單一產物，再經由玻璃纖維基質 (Gel-M™ Gel Extraction System, Viogene) 以去除反應鹽類及引子，進而純化之。首先，將 PCR 反應產物進行一次電泳。之後，將基因片段所在位置之洋菜膠以刀片切下來，切下之洋菜膠裝在 1.5ml 微量離心管中，稱重，加入洋菜膠重量 1000 倍體積的 GEX 緩衝液，

再將微量離心管置於 60℃水浴 10 分鐘。待洋菜膠完全溶於 GEX 緩衝液後，再把所有液體移到玻璃纖維基質微量離心管柱（Gel-M™ Column）中，在室溫下靜置 5 分鐘。再以 13,000 rpm 離心 30 秒，丟棄濾出液。如此反覆數次，直到所有檢體液都過濾完全。再加入 500 μl WF 清洗緩衝液，以轉速 13,000 rpm 離心 1 分鐘。除去濾液之後，加入 500 μl WS 清洗緩衝液，以轉速 13,000 rpm 離心 1 分鐘。去除過濾液之後，再以轉速 13,000 rpm 離心 3 分鐘，以完全去除 WS 清洗緩衝液中的酒精成分。再將玻璃纖維基質管柱移到新的 1.5 ml 微量離心管中，在玻璃纖維基質的中央加入 30-50 μl E 析出緩衝液，在室溫下靜置 5 分鐘，再以 13,000 rpm 離心 1 分鐘，收集含有 DNA 之濾出液。取 3 μl DNA 濾出液，以 1.0% 洋菜膠，經電泳確認其 DNA 純度及濃度。其餘 DNA 濾出液則保存於-20℃，待日後 DNA 定序所用。PCR 純化的產物將利用 Dye Terminator Cycle Sequencing Kit（Applied Biosystems, Foster City, CA, U.S.A.）來作定序。將利用引子 ENV2（5’ TCA GCA CAG TAC AAT GYA CAC ATG G3’）及 ENV3（5’ CCA ATT GTC CYT CAT ATY TCC TCC T 3’）來作 env 區域的定序。模擬兩可的序列可用另兩個上游引子 CL1101（5’ AAT GTC AGC ACA GTA CAA TGT ACA C 3’）和 MK 648(5’ CAG TAG AAA AAT TCC CCT CCA CAA TT 3’)作定序來解決。針對 gag-RT PCR 產物，Gag2（5’ AGC AGA GCC AAC AGC CCC ACC A 3’）和 RT1（5’ CTA AAT CCC TGG ATA AAT CTG A 3’）將被用作 gag-RT 區域的定序。模擬兩可的序列可用另兩個引子 Gag3 （5’ CCA GGA ATG GAT GGC CCA AAG 3’）和 RT2（5’ ATT GTT TAT ACT AGG TAT GGT ATA 3’）作定序來解決。每一個產物的核酸序列都由產物的五端及三端各定序一次，以確求基因序列的正確性。373A DNA 定序儀（Applied Biosystems）將被用來作核酸序列的定序，其操作方法完全依照操作手冊的敘述來作。所得到的 DNA 序列將利用 Sequencher 3.1 電腦軟體來作初步基因序列的整理。所有病毒株的核甘酸序列都會用來進行病毒株的亞型及抗藥性的基因型分析。我們將利用電腦程式 PHYLIP，version 3.573（Phylogeny Inference Package）來作基因系統樹分析(phylogenetic analysis)，所得到的種系樹狀圖將被用來決定病毒株之亞型。利用電腦網站 Stanford HIV RT and Protease Sequence Database- HIVdb（http://hivdb.stanford.edu/hiv/）的軟體來進行抗藥性的基因型分析。它利用專家及臨床醫師的觀察結果（The Stanford database）設定了內建式的規則（algorithm），可依病毒基因序列上的胺基酸變異形式，決定病毒對於目前常用的 19 種藥物的敏感程度。目前共可分為五級分別為具敏感性（sensitive）、可能有抗藥性（potential resistance）、低程度的抗藥性（low-level resistance）、中程度的抗藥性（medium-level resistance）、及高程度的抗藥性（high-level resistance）。而 19 種藥物則包括 NRTI 類的 zidovudine (AZT)、stavudine (d4T)、didanosine (ddI)、emtricitabine (FTC)、abacavir (ABC)、tenofovir (TDF)、及 lamivudine (3TC)；NNRTI 類的 nevirapine (NVP)、delavirdine (DLV)、efavirenz (EFV)、及 entecavir (ETV)；蛋白胺抑制藥物 saquinavir (SQV)、darunavir (DRV)、indinavir (IDV)、nelfinavir (NFV) 、fosamprenavir (FPV)、lopinavuir (LPV)、tipranavir (TPV) 、及 atazanavir(ATV)。

主題三、HIV臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

(A)、進行「台灣地區愛滋病毒感染研究群」研究：自從2004年開始，共有台大醫院、台北市立聯合醫院仁愛院區、疾病管制院區昆明院區、新竹馬偕紀念醫院、基督教門諾會醫院、署立桃園醫院、中國醫藥學院附設醫院、台中榮民總醫院、彰化基督教醫院、成功大學附設醫院、高雄醫學大學附設醫院等11家衛生署指定之愛滋病毒感染治療的專責醫療院所，持續進行收集感染者到院就醫的相關臨床資料。收集目的，是要了解台灣地區愛滋病患常見的臨床病徵、愛滋病毒治療成效、合併感染以及預後與存活。截至今年7月份止，合併台大醫院過去持續收集的世代研究資料，我們一共收集4,176位感染者的相關資料。

(B)、靜脈毒癮者為愛滋病毒與 HCV 雙重感染者其 HCV 病毒基因變異之長程分析：研究對象為台大醫院過去住院之愛滋病毒感染者，經檢測 C 型肝炎抗體後，約有 6-7% 有 HCV 感染，相當大部分之 CD4 小於 100。這些病患有定期收集 10 西西之血清冷凍於攝氏-70 度供將來研究之用。病患之血清若在用藥前與用藥一年以上均有找到血清者即納入本研究；進行 HCV 之 HVR-1 (hypervariable region-1) 研究核酸萃取及 DNA 片段增幅：以 RNA extraction kit 抽取 200ul 血清中之 RNA。利用反轉錄酶以 random primers 製備 cDNA.以 PCR purification kit 純化後，接下來做 nested PCR，反應條件為 94℃ 2 min, 94℃ 1 min 65℃ 2 min 72℃ 2 min 共 35 個循環, 72℃ 10 min，將 HCV 的 HVR-1 基因放大， PCR 產品直接於 agarose gel 電泳，經由 ethidium bromide 作用後於紫外線光下觀察並回收純化,然後直接做 PCR products 的 sequencing。核酸定序及病毒株種異分析( sequencing and analysis of quasi species)：每一 PCR 產品以 dye-terminator 做基因列序分析。經由螢光標的的 ddNTP，於雷射激發的不同波長轉成訊號，由電腦收集分析。

(C)、台灣地區 HIV 感染者合併 C 型肝炎病毒感染之臨床流行病學及其治療：實驗對象為目前在台大醫院追蹤治療的 HIV 合併 HCV 感染之病患，估計約有 80-100 人。流行病學部分：收集病患之臨床資料，包括年齡、性別、感染 HIV 及 HCV 之危險因子、肝功能、免疫缺損程度（CD4 淋巴球數及血清病毒量），發生 C 型肝炎之危險因子及預後，並持續定期追蹤病患是否發生肝功能異常；是否有做肝臟切片之病理報告、是否有發生肝臟功能代償失調、肝硬化或肝腫瘤。病患約每 4 個月抽血檢驗 HIV 病毒量和肝功能。病毒學部分：以未來一年所收存的血清，針對 C 型肝炎帶原者依序進行 HCV RNA 的定性與定量作分析，以得知 HCV 之病毒量及基因型。治療部份：患者有慢性活動性 C 型肝炎時(定義為肝功能 GOT 或 GPT 大於 100 U/L)，則安排肝臟穿刺檢查確認肝臟損傷的程度，若合乎健保給付者將給予長效型干擾素(pegylated interferon)每週一次，每次 180 萬單位持續 24 週加上 Ribavirin 800-1,200 毫克/天進行標準之治療，並於治療結束及六個月後監測肝功能、HIV 及 HCV 病毒量和肝切片。

(D)、愛滋病毒感染之毒癮患者之病毒性肝炎流行病學：在台大雲林分院就診、雲林監獄(第一監獄、第二監獄)、嘉義監獄入獄的愛滋病毒感染之毒癮患者，收集相關之臨床資料(使用靜脈注射毒品時間長短、急性肝炎發作、肝硬化、或肝癌)、檢測其血中 anti-HAV IgM/IgG、HBsAg、HBsAb、HBcAb、anti-HCV 之有無、每三至四個月追蹤血中之 CD4，肝功能相關指數(CBC、PT、Albumin、total/direct Bilirubin、GOT/GPT 等)，HBV、HCV、愛滋病毒之病毒量，並研究彼此之間的影響。1.實施方法：a.收集病患之臨床資料(急性肝炎發作、肝硬化、肝癌)。b.偵測病患血中 anti-HAV Ab IgM/IgG, HBsAg, anti-HBsAg, anti-HBcAg, anti-HCV, HBV DNA, HCV DNA, HCV genotype 的基礎值。c. 除基礎值外，每三至四個月偵測病患之 CD4/CD8, HIV RNA, GOT/GPT, Plt, PT, Albumin 等生化數據。d.對未曾感染 HAV[anti-HAV(-)]、或無 HBV[HBsAg(-)、anti-HBsAb(-)、anti-HBcAb(-)]或 HCV[anti-HCV(-)]帶原者，每三至四個月定期追蹤 anti-HAV IgM/IgG、HBsAg/anti-HBsAb/anti-HBcAb、anti-HCV。e.測定在有單獨存在抗核抗體病患其血液中之 HBV 的病毒量。f.測定 HCV 的基因型(genotype)及 HCV 病毒量高低。2.分析方法：a. A、B、C 型病毒感染在國內這群新感染

HIV 病毒毒癮者之盛行率及發生率。b.急性肝炎、肝硬化、肝癌在這群病患之盛行率。c.有單獨存在抗核抗體病患體內含有 HBV 的病毒的比例。

(E)、進行「第一與第二孕程愛滋病毒的母子垂直傳染」研究：實驗對象為HIV陽性的孕婦，懷孕中期或初期，徵得書面同意之下，盡量收集胎兒器官檢體，利用ISH檢測HIV-1的抗原。方法：(1)、檢體收集：要有書面的informed consent，用PBS清洗過後，小心取得胚胎之組織，用direct cover vitrification (DCV)方法，予以冷凍，將來一起做檢驗。(2)、DCV冷凍方法：我們實驗室改進的方法，將小組織用7.5% (v/v) ethylene glycol加上 7.5% (v/v) DMSO 跟20% FBS 作用10 min，接著移到15% EG跟15% DMSO與0.5 M sucrose 作用 2 min。然後液態氮直接到入塑膠cryovial中，這樣溫度下降非常快速，組織損壞最低，根據之前卵巢檢體的經驗看來，結果非常好，可以擁有跟新鮮組織一樣的活力，也生出很多正常的小鼠(Chen SU, 2006)。(3)、IHC (原位組織免疫染色)：我們選擇的是用paraffin切片，mouse anti HIV-I gp24 單株抗體 (RayBiotech Inc., IP-05-152) 與 rabbit anti HIV-1 gp41多株抗體(RayBiotech Inc., IP-05-160)兩種，稀釋濃度分別為500:1。Positive control選擇的是early HIV有病變的淋巴結。

(F)、進行「台灣愛滋病患延遲診斷之危險因子研究」：實驗對象：96 年 1 月至 96 年 11 月之台大醫院新診斷 HIV 感染者。研究方法：以問卷方式進行，輔以訪談以了解就醫行為之細節。所有符合收案的研究對象，在研究者的個案面談中，說明問卷與訪談的目的，若研究對象同意參與研究，則由研究助理指導填寫問卷，回答在診斷愛滋病感染者前一年內有就醫行為者，再安排個人訪談以了解就醫行為之細節。問卷的設計除參考國內外相關文獻外，就有關的議題，計畫先與部分患者進行訪談，以發展出本研究之問卷。問卷變項包括性別、年齡、傳染途徑、教育程度、職業有無、工作收入、婚姻狀況等社會人口變項，初始臨床表現、初始 CD4 量、診斷前一年是否有就醫行為等醫療變項。回答診斷愛滋病毒感染前一年內有就醫行為者，再進一步詢問其就醫時間與次數、各次就醫症狀與診斷、是否住院、該醫療單位層級、醫療照護者是否曾詢問愛滋病毒感染者的危險因子或建議實施愛滋病毒感染檢測。採用結構性問卷訪談，問卷項目擬定後，先針對十名患者進行試測，再與愛滋病臨床專家學者討論後，修改問卷內容細節，並擴大收案對象為所有新診斷愛滋病毒感染者，區分延遲診斷組(CD4<200)與非延遲診斷組(CD4≧200)以進行比較與分析。與患者訪談的同時，輔以諮商與衛教，希望加強患者對疾病的瞭解，提高安全行為與對醫囑的遵從性。統計分析方法使用 SPSS 軟體(version 12.0, 2003 SPSS Inc. Chicago, IL)，類別變項使用$\chi^2$ 或 Fisher's exact test。

(G)、愛滋病患醫療照顧及健康諮商個案管理制度效益評估(二年計畫)：本計畫主要目標為針對HIV個案進行個案管理服務後，針對個案、利用醫療情形、危險行為、服藥順從行為、社會穩定度等方面的效益評估。在計畫進行期間，由個管師進行深度會談後，進入長期追蹤個案的生理、行為及社會穩定度，以在適當時機提供個案必要的衛教指導、諮詢及社會資源聯結，以及適當轉介至減害服務。愛滋個管尚屬發展階段，如何將此制度建立、收案標準、收案評估內容、處置流程、衛教諮詢、主動追蹤流程，乃至於個管師的個案負荷量等，都需要建立標準，以進行評估與討論。

主題四、接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

實施方法：

（一）蒐集各種相關文獻，彙集各醫護中心及其他國家對於疑似愛滋病毒體液污染事件處理流程並透過專家學者研究及討論，規劃針扎事件統一處理流程。

（二）成立疑似愛滋病毒體液污染事件處理及諮詢中心，提供 24 小時專線電話諮詢服務，

服務所有可能暴露愛滋病毒體液污染人員（包括醫事人員、警消、矯治、社區藥局、一般民眾）。

（三）可立即諮詢中心醫師在第一時間內予以診斷及治療。

（四）提供快速及免費之檢驗，可在兩小時內知道汙染源是否已感染愛滋病。

（五）將諮詢及追蹤結果作成記錄，以留未來統計研究之用。

實施方式：

(一) 利用國內外資訊管道蒐集各種相關文獻，並彙集各醫護中心及其他國家對於疑似愛滋病毒體液污染事件處理流程等資料。成立 24 小時「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。制定疑似愛滋病毒體液污染事件處理流程及方法討論會，邀請國內專家學者，規劃統一處理流程。

(二) 加強愛滋病毒防治之宣傳。印製「愛滋病毒感染須知」供個案參考。內容包括服務時間、愛滋病疑問、如何預防及檢驗等。並與台北市立性病防治所合作實行宣導，提供快速且正確的檢驗、診斷及治療，降低感染的機會，並能及時給予心理支持，減少焦慮及不安的產生。及時的諮詢、診斷後，可避免感染情形的擴大。

(三) 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。電話先由護理人員予以回答，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第一時間內予診斷及治療。

(四) 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。提供快速及免費之愛滋病檢驗，可在兩小時內知道汙染源是否已感染愛滋病。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」。未確定之個案每三個月追蹤一次，一年後如仍為「未確定」則不再追蹤。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。

## (三)結果

主題一、各科醫事人員愛滋感染者照護之相關在職訓練：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。

為提昇本中心的衛教服務功能，及因應日趨嚴重的毒癮愛滋病患的增加問題，今年共舉辦了許多場全國性的大型研討會、工作坊及教育訓練，每一場的報名人數都非常踴躍，且得到與會者熱烈的迴響，可謂成果豐碩。鑑於愛滋病毒感染等相關的知識日新月異，新藥物與治療的研發，蓬勃發展，因此對於這些醫療知識的獲取，對於照護愛滋病患的醫事人員格外重要，故愛滋病防治中心將扮演領導國內治療與防治相關之角色，並且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。

(1)、4/14~15 日舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」，參加人員以衛生署指定醫療院所照護愛滋病毒感染者之專責臨床醫師為主，共有 43 位參加，特別邀請到西班牙 University of Barcelona Dr. Esteban Martinez 做專題演講 〝Metabolic Complications of Antiretroviral Therapy: Pathogenesis and Management.〞並全程參與國內臨床個案之討論。

(2)、6/2 日舉辦「Update management of HIV: Workshop for HIV co-infection disease」參加人員以衛生署指定醫療院所照護愛滋病毒感染者之專責臨床醫師為主，共有 41 位參加，特別邀請到腸胃科及泌尿科的醫師來做專題演講，不同科別的醫師齊聚一堂提供意見踴躍討論。

(3)、6/23日召開本年度之「醫療人員愛滋病治療專業能力初階教育訓練課程」之「愛滋病毒感染治療藥物新進展介紹」，介紹目前愛滋病毒感染治療藥物及未來進展，參加對象包括對於照護愛滋病患有興趣之醫療人員〈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〉，預定約有200位參與，本次研討會申請相關醫學會學分認證，全程參加者結業時頒發授課證明。特別邀請到法國Nantes University Hospital Professor François Raffi做專題演講 〝Initial Treatment with HAART and Switch Strategies.〞。

(4)、9/29 日舉辦本年度的 HIV/AIDS Workshop for Drug Resistance and Treatment Options，邀請來自加拿大 The Toronto General Hospital 的 Professor Sharon Walmsley 除了做專題演講外，並與台灣的 58 位資深專家學者共同討論交換意見及經驗分享。

(5)、為配合感染症醫師臨床試驗之需求，針對有興趣從事臨床研究之感染症醫師特舉辦此訓練課程，以期提昇國內臨床研究人員之參與力與能力，並期導入我國臨床試驗能力與國際接軌。此次研習會名稱為「感染症專科醫師藥品臨床研究設計及執行研習班」，希望藉此讓年輕醫師在資深專科主治醫師指導下，以指定的題目或有興趣的研究題目完成計畫書的撰寫，讓年輕醫師有交流及互相學習的機會。此次研習會於 2007 年 10 月 13、14、20、21 日，假大同大學尚志教育館一樓 106 會議室及 103 電腦教室舉行，共有 4 天課程，課程內容涵蓋 Introduction to Epidemiology、Observational epidemiology (1)Cohort study & (2)Case-control study 、 Introduction to basic biostatistics 、 Introduction to clinical trials 、 Experimental epidemiology、Statistical softwares for clinical trial data analysis: an introduction 、Human subject protection in research 、 Informed consent 、 Interpretation of data---Interaction and confounding---Interpretation of negative studies、Introduction of biostatistics software:data collection, entry and exploration、Good clinical practice、Hypothesis testing and sample size

determination 等。每一個主題均由國內、外知名大學具十多年教學及臨床經驗的教授及醫師講授，而後以提問方式進行，並於每天進行分組討論及論文研讀，由有研究經驗的助教帶領，著重參與課程之學員依個人研究興趣與指導教師和其他學員作有效性之小組討論。本次課程共 39 人報名，學員現職多數為臨床醫師，課程中與講師、助教有許多的提問及討論。本次研習會開辦期間因柯羅莎強烈颱風襲台，原訂在 10/6~7 日的課程臨時順延至 10/13~14 日舉辦，學員仍踴躍前來受訓，精神可嘉。

(6)、目前愛滋病毒感染者服用 HAART 藥物所造成新陳代謝的相關副作用問題非常複雜，故 2007 年 11/3 日假台北市徐州路 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」教育訓練課程。參加對象包括對於照護愛滋病患有興趣之醫療人員〈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〉，特別邀請來自澳洲的 Professor Andrew Carr 及香港的 Dr. Patrick Li 做專題演講，共有 180 位參與。

(7)、HIV 體液暴露後的處理，是十分重要的事。由於感染 HIV 之後，絕大部分的人會進展到 AIDS，使個人、家庭蒙受重大的損失，因此了解如何在 HIV 體液暴露的意外事件後正確地處理及追蹤檢查，是十分重要的一件事。使用抗 HIV 藥物來做為暴露後的預防醫療（post-exposure prophylaxis，PEP），已是一個為醫學界所接受的作法。但由於各種暴露 HIV 後的感染性不同，加以抗 HIV 藥物的副作用頗大，以及新抗 HIV 藥物的問世，所以最好是能尋求專家的意見，以兼顧效果與避免藥物毒性。特別於 96 年 12/15 日假台北市仁愛路一段 1 號台大醫學院 101 講堂，針對醫、護、警、消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，故舉辦此「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。

(8)、延續去年與財團法人護理人員愛滋病防治基金會繼續合辦「愛滋菴個案管理師訓練」初階課程及進階課程，分別於5/18~20日(南區110人參加)、6/1~3日(北區244人參加)、6/29~30日(進階153人參加)，完成課程者並頒發授課證明。

(9)、本中心延續以往每週一次的愛滋病研討會，固定于每週二早上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。1~12月份擬進行35場，其題目及演講者如表一。(詳細成果報告詳附件一)

主題二、HIV抗藥性監測與臨床處理之相關研究：監測HIV抗藥性及研究與抗藥性相關之臨床處理方法之成效。

我們一共分析 108 件病人檢體，其中 71 件是病人尚未接受任何治療前的檢體；37 件是治療失敗的病人檢體。治療失敗病人的抗藥性基因型分析結果：37 件治療失敗的病人檢體，病人平均年紀為 37.9 歲，以男性為主(96.4%)。病人換藥前的平均病毒量、CD4 細胞數、CD8 細胞數分別為 87,090 copies/mL、189 counts/mL、及 1,048 counts/mL。37 件治療失敗的病人檢體中，有 24 人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑具有抗藥性的基因突變(圖一)。其中 9 人對於蛋白酶抑制劑具有抗性，17 人對於類核苷酸類反轉錄酶抑制劑具有抗性，18 人對於非類核苷酸類反轉錄酶抑制劑具有抗性。此外， 3 人對於蛋白酶抑制劑及類核苷

酸類反轉錄酶抑制劑都具有抗性，9 人對於類核苷酸類反轉錄酶抑制劑及非類核苷酸類反轉錄酶抑制劑都具有抗性，而 4 人對於三種抑制劑都具有抗性。這 24 人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑藥物種類具有抗藥性。在這 37 件治療失敗的病人檢體中，只有 18 人在報告截止前有回來持續地追蹤。這些病人換藥前的平均病毒量、CD4 細胞數、CD8 細胞數分別為 98,089 copies/mL、126 counts/mL、及 887 counts/mL。換藥後的平均病毒量、CD4 細胞數、CD8 細胞數分別為 34,942 copies/mL、127 counts/mL、及 1,023 counts/mL。這 18 人中有 13 人(72.2%)的病毒量有明顯的改善，其中雖然有三人的病毒量原本就小於 1,000 copies/mL，減少的幅度不大，但是整體來說，抗藥性基因型分析對於臨床醫師選擇換藥時可提供參考的依據，且可改善病人的治療結果。對於台灣地區人類免疫不全病毒第一型(HIV-1)原生抗藥性的盛行率，我們一共分析 73 件病人檢體。這群病人的平均年紀為 35.2 歲，以男性為主(90.4%)，平均病毒量、CD4 細胞數、CD8 細胞數分別為 287,245 copies/mL、248 counts/mL、及 934 counts/mL。病毒亞型及危險因子分析結果如圖二。病毒亞型以 B 亞型為主(71%)，次為 CRF07_BC(14%)、CRF01_AE(12%)、及 C(3%)。危險因子主要以男同性戀(MSM, men having sex with men)為主(63%)，次為異性戀(22%)、及藥物毒癮者(IDU, intravenous drug user)(3%)。根據我們的實驗結果，原生抗藥性的盛行率為 9.6%(7/73)，遠高於 WHO 所建議的 5%。其中 2 人對於蛋白酶抑制劑具有抗性，3 人對於類核苷酸類反轉錄酶抑制劑具有抗性，2 人對於非類核苷酸類反轉錄酶抑制劑具有抗性。沒有人對於兩種以上的藥物具有抗性。而對於藥物具有抗性的 7 人中，有 6 人(85.7%)是藉由性接觸所傳染的。(詳細成果報告詳附件三)

主題三、HIV臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

(A)、進行「台灣地區愛滋病毒感染研究群」研究：自從 2004 年開始，共有台大醫院、台北市立聯合醫院仁愛院區、疾病管制院區昆明院區、新竹馬偕紀念醫院、基督教門諾會醫院、署立桃園醫院、中國醫藥學院附設醫院、台中榮民總醫院、彰化基督教醫院、成功大學附設醫院、高雄醫學大學附設醫院等 11 家衛生署指定之愛滋病毒感染治療的專責醫療院所，持續進行收集感染者到院就醫的相關臨床資料。收集目的，是要了解台灣地區愛滋病患常見的臨床病徵、愛滋病毒治療成效、合併感染以及預後與存活。截至今年 7 月份止，合併台大醫院過去持續收集的世代研究資料，我們一共收集 4,176 位感染者的相關資料。目前已經逐步進行資料分析。目前我們已經完成慢性 B 型肝炎的流行病學分析和論文寫作。我們希望了解在台灣地區，自從 1984 年展開的 B 型肝炎疫苗接種計畫，對於愛滋病毒感染者的影響為何？是否新生兒、幼兒或小學追加 B 型肝炎疫苗接種計畫對於後來感染愛滋病毒造成免疫系統下降時，是否接種後產生的抗體效價會下降？並且了解是否有追加接種疫苗的必要性？我們的研究顯示出生於 1984 年之前的感染者不論是否使用毒品男同性戀或異性戀慢性 B 型肝炎的帶原率相同；1984 年之後出生的愛滋病毒感染者的帶原率則已經下降到 5.6%和對照組並無差異。新生兒、幼兒或小學期間曾接種疫苗的感染者，他們的抗體效價，比較文獻中

所報告台灣地區一群在出生時接種疫苗的 15 歲青少年來得高；愛滋病毒感染者的抗體效價高低與 CD4 淋巴球數有正相關，意即：CD4 越高抗體效價越高。我們的研究顯示愛滋病毒感染者接種過 B 型肝炎疫苗後，可能在後來因為有機會多次接觸肝炎帶原者，形成自然 B 型肝炎疫苗的追加接種。相關伺機性感染與存活的分析目前仍持續進行中。(詳細成果報告詳附件二)

(B)、靜脈毒癮者為愛滋病毒與 HCV 雙重感染者其 HCV 病毒基因變異之長程分析：HCV 病毒之 genetic drift 雖然早為人所知，但在演化過程中何種變種病毒會脫穎而出，其決定之因素眾說紛紜，尚無定論，甚至有作者認為病毒僅是不斷的變化，其中並無環境選擇因素。但不少研究者認為取而代之的變種病毒或是病毒本身較有競爭力或是具有較佳逃避宿主免疫力等等方成為主流病毒。HIV/HCV 雙重感染者替免疫假說論提供了相當多之研究題材。HAART 之使用人為的使得免疫力發生改變，隨著免疫壓力，研究顯示 HCV 變異性高的區段 HVR 確實在 HAART 使用後產生基因變異，且其基因變異產生氨基酸列序變異之比率較高,顯示為有目地之變異。在我們的計劃裏,考慮的是愛滋病患之免疫力極度缺乏,在 HAART 使用後初期之免疫力仍有殘缺，因此病毒可能有較長之期限去累積逃避宿主免疫力之突變.的確，在 CD4 較低之病患裏有五位病患在氨基酸位置 328 至 503 間有七個以上的氨基酸列序變異，且較集中發生於 HVR 區域。而唯一 CD4 較高者僅有兩個位置改變。此外，一位幾乎不服用藥物者在八個月間並未發現其體內 HCV 基因出現 genetic drift，此亦反証免疫壓力之存在。至於 core 基因則看不出氨基酸列序變異數目與 CD4 細胞數目之相關性。有可能是此一位置並非免疫系統攻擊之對象,因此發生 genetic drift 之機轉不同。此項 HCV 在 HAART 使用後之變化尚待較多之 C 型肝炎病毒株的資料，尤其是從 CD4 細胞較高患者身上取得之病毒株,才能得到較強之支持証據。同時也需要 cloning 這些 PCR product 去分析 genetic drift。在未產生抗藥性突變的病患也觀察到 HAART 使用一段時間後 HBV 基因有些位置發生變異。比較從兩位 CD4>200 以及一位 CD4<100 之患者得來的三對 HBV 基因發現兩個重要的不同；一是基因變異之數目，從 CD4 少的病患取得之 HBV 遠大於 CD4 數目多者(22 vs. 7 and 6) 。二是 22 個基因變異位置有集中於 C 及 pre-S1 基因之現象，從 CD4 多的病患取得之 HBV 則無此情形。研究 HBV 經過 25 年在慢性肝炎患者體內之基因變異發現較多出現於 C 及 pre-S/S/Pol 重疊區域，且經 dS/dN ratio 分析推測應與逃避宿主免疫機轉有關。根據以上兩點之發現，我們因而推論經由 HAAT 治療之愛滋病患，可能因免疫力之急遽變化，導致 HBV 病毒產生 genetic drift。總之，在愛滋病患者(AIDS)以 HAART 治療後，若病患同時有其他病毒感染者，我們發現這些病毒會受到選擇壓力而產生 genetic drift。就 parvovirus B19 而言，genetic drift 從未被發現於其他非愛滋病患之持續 B19 感染者中，而 HBV/HCV 則是在免疫力缺乏的愛滋病患比免疫力尚可的 HIV 感染者有較大幅度的基因變異。因此，選擇壓力的來源最可能的是恢復中之免疫力。當然此方面之研究受限於檢體數目不多，有待將來更多資料來證實。國人 B 型肝炎病毒盛行率較高，理論上 HBV/HIV 雙重感染者之愛滋病患，也有可能於 HAART 之影響產生較多之 genetic drift。不同於 HCV，HBV 有重疊的 open reading frame，基因變異受到限制。此外，HAART 中含有 lamivudine，HBV 因此受到免疫系統與藥物之雙重壓力。藥物壓力導致抗藥性病毒基因突變，我們觀察到兩位 CD4<200 之愛滋病患，產生 lamivudine 抗藥性，表三列出他們抗藥性病毒基因突變以及其他位置於 HAART 治療後 HBV 基因的變化。可以看出這些變化與非 HIV 感染者體內之抗藥性 HBV 病毒相較，在數目上接近且位置上亦無特殊之處。(詳細成果報告詳附件四)

(C)、台灣地區 HIV 感染者合併 C 型肝炎病毒感染之臨床流行病學及其治療：本研究資料收集自 1997 年至 2007 年 6 月在本院追蹤之 HCV 感染個案，共 189 位患者（不包括台大雲林

分院個案)，其中基因型第 1 型有 21 位（40%)，包括基因型 1a：2 位，1b：18 位，1a+1b：1 位，基因型第 2 型有 18 位(34%)，包括基因型 2a：15 位，2b：3 位，其他型：14 位(26%)。男性患者有 168 人，女性 21 人，HBs 同時帶原者有 34 人（18%)，感染 HIV 之危險因子在同性戀者為 56 人，異性戀者 39 人，靜脈藥癮者為 88 人，輸血者 2 人，未知感染者 4 人。追蹤過程中發現 12 人有肝硬化，26 位患者死亡，其中 3 位與 HCV 相關之肝炎併發症有關，1 位為肝癌，3 位死於靜脈藥癮之心內膜炎感染或動脈瘤（金黃色葡萄球菌菌血症)，1 位患者死於 AIDS 相關之伺機性感染，3 位死於惡性腫瘤（淋巴瘤：2 位，口腔癌：1 位)，2 位死於毒癮藥物過量。在 53 位合併 HCV 感染病患，與 387 位 HIV 但未有 B 型肝炎病毒及 C 型肝炎病毒感染之病患作比較。兩組患者在基本資料的比較合併感染 C 型肝炎之患者年齡較非 C 型肝炎感染患者大(39 歲比 35 歲，P=0.01)，合併 C 型肝炎感染者其靜脈藥物毒癮比例(17%)比未有 C 型肝炎感染者(0.8%)高出許多(P<0.001)(表一)。兩組患者在平均 2.2 年(791 天)的追蹤觀察中發現合併 HIV 及 C 型肝炎病毒感染患者急性肝炎發作的頻率為每 100 人年 13.89 次(95%信賴區間為 13.31-14.49 次/人年)相較 HIV 患者但未有 B 型及 C 型肝炎者其急性肝炎發生率為每 100 人年 6.39 次(95%信賴區間為 6.24-6.55 次/人年)，顯示合併 C 型肝炎感染患者比其他患者多 2.769 倍危險(95%信賴區間為 1.652-4.640)，兩組有明顯之統計學上之意義(表二)。另外對三合一抗愛滋病毒療法的治療療效比較方面，有 C 型肝炎合併感染的患者，以 HAART 治療可上升 137/μL 的 CD4 T 淋巴球相較未有 C 型肝炎感染患者 CD4 T 淋巴球上升 157/μL 相似，未有統計學上之意義。在 HAART 治療過程中，有 C 型肝炎合併感染之患者並不會比沒有合併 C 型肝炎患者容易發生新的伺機性感染(相對危險為 1.826，95%信賴區間為 0.738-4.522，未達統計學上差異)。在預後(死亡)的比較方面，有 C 型肝炎感染之患者死亡率並不會比沒有 C 型肝炎感染者高(相對危險為 0.781，95%信賴區間 0.426-1.432，未達統計上意義)，由我們研究的結果發現，HIV 患者合併 C 型肝炎感染有較高的危險發生急性肝炎，但有無合併 C 型肝炎感染並不會影響 HAART 治療之病毒量控制，CD4 淋巴球上升及發生新的伺機性感染，也不會影響患者的預後。13 位 HCV 感染者接受標準之雷巴安素（ribavirin）及長效型干擾素（pegylated interferon）之治療。基因型第 1 型者為 5 位，第 2 型者為 8 位，平均之 HCV 起始病毒量為 78400 copies/mL（範圍為 144,000 至 54,100,000 copies/mL)，以 Ribavirin 800~1,200mg/天（依體重區分）以及干擾素（Peg-INF）180 μg/day 治療，至治療 1 個月時共有 7 位（53.8%）HCV 病毒量可達到測不到。至治療結束時（第 6 個月)，共有 10 位（76.9%）HCV RNA 可達到測不到，停藥後 6 個月，基因型第 1 型只有 1 位 HCV RNA 測不到(20%)，而基因型第 2 型有 4 位 HCV RNA 測不到(50%)。(詳細成果報告詳附件五)

(D)、愛滋病毒感染之毒癮患者之病毒性肝炎流行病學：自民國94年4月1日至民國96年10月31日，共709位HIV感染者曾至台大醫院雲林分院就醫，其中672(94.8%)位為經由靜脈注射海洛英感染到HIV；這672位患者中，45位(6.7%)為女性患者，627位(93.3%)為男性患者；其年齡之中位數為33歲(範圍19至60歲)，CD4之中位數為390 cells/mL (範圍10-1943 cells/mL)；病毒量之中位數為4.03 $\log_{10}$ copies/mL (範圍2.60-5.88 $\log_{10}$ copies/mL)。曾感染過A型肝炎者佔60.7%；而B型肝炎帶原者佔20.2%；149位曾接受HBV DNA檢查者，49位有偵測到HBV DNA，其中41人(83.7%) HBV genotype為B，3人(6.1%)為B+C，5人(10.2%)為genotype為C。

C型肝炎病毒感染高達99.3%；92曾接受HCV RNA檢查者中，71人有測到HCV RNA，其基因型為1a(16, 22.5%)、1b(12, 16.9%)、2a(41, 57.7%)、2b(2, 2.8%)。在就醫時曾接受過肝功能檢查的患者中，21.0%和10.9%的病患其GPT及GOT高於正常值兩倍以上；在曾接受至少兩次以上肝功能檢查的患者中，其GPT的最高值，有14.8%高於正常值三倍以上，GOT的最高值，有8.4%高於正常值三倍以上。(詳細成果報告詳附件六)

(E)、進行「第一與第二孕程愛滋病毒的母子垂直傳染」研究：婦女與新生兒 HIV 的感染，在過去幾年中已漸漸有定論，2005 年開始，政府機關也著手全面篩檢，這部分的工作已經穩定前進中，約有 70-85%的人有篩檢到。2005 年共有 47 例孕婦，這些人通常第一次產檢就會被檢查並告知，但是不是馬上需要 HAART 的治療，還是像 WHO 建議的，輕微案例只用 AZT？還有，什麼時候開始用？選哪一些藥物？用到什麼時候停？太早給藥，如第一孕程，得到的好處跟胎兒潛在的畸形危險，或媽媽胃口的降低，與這些壞處比起來，值不值得？有人說有傳染的情形，也有人說沒有。最近英國有一份大型調查顯示(Townsend CL, 2006)，第一孕程，使用藥物有先天異常機會是 3.7% (20/541)，沒有用藥物的人，先天異常機會是 3.1% (80/2,579)，他們認為是沒有明顯相關。可惜文獻上的早期懷孕作胎兒 HIV 檢驗的報告，人數都很少，結論無法真正說服人(見下面表一)。但多年臨床經驗看來，子宮收縮，或母血胎兒血少量互通，是有很多證據的。如果是這樣，那麼早期垂直感染是非常有可能的。我們採取兩個不同的抗原，anti-gp24 與 anti-gp41，其組織染色有其獨立性。從 positive control 的淋巴結切片顯示，這兩個抗體可以很明顯的顯示出細胞遭到 HIV 的感染。但在胚胎組織中，卻沒有檢測到，而在蛻膜組織(代表母體)，卻可以檢測到，所以綜合證據顯示，應該在早期 HIV-1 不容易傳染給胎兒。亦即，沒有急迫的需要，在此時期就給予抗 HIV-1 的藥物治療。原先我們以為，這些案例都經過一段時間的子宮收縮藥物刺激，說不定會有 false positive 出現可是仍然沒有發現。不過，因為本實驗的案例還是少，結論可能還不足以作代表。還有，本實驗用 IHC，特異性高，但敏感性可能稍嫌不足，例如文獻上許多人用 PCR 或 culture 來作證據，就有許多比例是陽性，但相同的道理，他們的敏感度高，相對地，特異性可能就不高，難以看出哪一種細胞(例如 $CD3^+$)陽性？比例有多少？會被其他細胞污染嗎？所以我們選擇 IHC，而且兩種不同抗原，若有結果，比較可靠。我們在 decidua 發覺有陽性，代表我們的敏感度還可以，至於胎盤或其他胎兒組織沒出現，可能真的早期垂直傳染病不存在。 (詳細成果報告詳附件七)

(F)、進行「台灣愛滋病患延遲診斷之危險因子研究」：針對自 96 年 1 月至 96 年 11 月之台大醫院新診斷 HIV 感染者收案共 113 位，其中男性 110 名，女性 3 名，延遲診斷者(CD4<200)計 72 名，佔 64%，與本院過去研究 CD4<200 病患所佔比例相符合。113 名患者的傳染途徑中，男同性戀(含雙性戀)為 79 名(70%)，異性戀為 27 名(24%)，靜脈毒癮者為 5 名(4.4%)。將 70 名患者分為延遲診斷者(CD4<200)與非延遲診斷者(CD4≧200)兩組比較，進行單變項分析，可以發現，在年齡、居住地、教育程度、職業有無等項目上，兩組並無統計上顯著差異。工作收入以延遲診斷者較高，月收入在 3 萬元以上者，在延遲診斷組達 75%，非延遲診斷組僅 49%(p=0.016)。感染愛滋病毒的危險因子方面，男同性戀在兩組比例相近，異性戀在延遲診斷組所佔比例較高(29% vs.15%)，達統計上顯著差異(p=0.018)。檢驗愛滋病毒感染的理由，延遲診斷組有 79%是因患者出現症狀經醫師或匿名篩檢而診斷，非延遲診斷組則 63%的患者都無症狀，而是經由篩檢(匿篩、孕篩、獄篩、役篩、捐血篩檢等)發現愛滋病毒感染，兩組有明顯差異(p<0.0001)。在合併感染症方面，B 型肝炎、C 型肝炎感染率與梅毒血清檢驗陽性率，兩組無顯著差異。在家庭關係方面，是否與家人同住、男同性戀是否已向家人出

櫃等項目上，兩組並無統計上差異。延遲診斷組的患者，父母均健在的比例較低(54% vs. 66%, p=0.049)，其家人知道患者感染愛滋病毒的比例較高(64% vs.38%)，有顯著差異(p=0.033)。第一次性行為年齡、曾有性伴侶的數目、目前性伴侶數目、是否有肛交、口交經驗等項目，兩組並無統計上差異。保險套使用狀況方面，與固定伴侶或非固定伴侶發生性行為時會總是使用保險套的比率，口交或肛交使用保險套的比率，兩組均無顯著差異。口交從不使用保險套的比例，兩組都極高(96% vs.97%)。雖然靜脈毒癮者僅有 5 名，曾使用違禁藥品的患者比例卻達 33%，在延遲診斷組較低(21% vs. 54%)，達統計上顯著差異(p<0.001)。其中搖頭丸佔所有違禁藥品使用的第一位(81%)，大麻佔第二位(35%)，值得注意。診斷愛滋病毒感染前一年，延遲診斷組與非延遲診斷組的患者的就醫次數，中位數分別為 5 次以上與 2-3 次，有顯著差異(p=0.03)，其中排名前三位的就診科別為耳鼻喉科、皮膚科、牙科。由病人口述其一年內就醫診斷，依臨床判斷可能提早於該次就醫時就懷疑愛滋病毒感染，兩組皆達 20%以上。其中在延遲診斷組有 4 例口腔念珠菌感染、4 例脂漏性皮膚炎、2 例肺結核，2 例帶狀疱疹，乾癬、不明原因貧血、傳染性濕疣、不明原因體重減輕各 1 例。(詳細成果報告詳附件八)

(G)、愛滋病患醫療照顧及健康諮商個案管理制度效益評估(二年計畫)：自民國95年1月至96年12月止，共收納243位在台大醫院就醫之HIV個案。經納管後個案在CD4數、HIV病毒量控制情形、HIV相關症狀及服藥順從性方面，都有顯著改善成效。在危險性行為方面，可以增加使用保險套頻率達顯著意義，個管師的確可見減少危險性行為及控制危險注射行為的成效。在社會、心理層面也有舒緩焦慮、沮喪情緒、增加告知診斷的正面成效。個管對個案的效益，可以從個案的生理穩定度及個案整體穩定度皆呈現大幅改善的顯著成效。在個案的服藥順從行為及社會穩定度方面，可增加社會支持、降低副作用嚴重度等。經由增加個案的社會穩定度，因而減少使用急性醫療的頻率及費用，是個管服務對個案及醫療資源的直接效益。在減少醫療費用方面的成效，比較經納管後HIV個案利用醫療的情形，可見顯著減少門診、急診次數及人數，減少住院天數，因而減少住院費用，達顯著差異水準。因此，個管制度的運用在兩年內即可以顯現有降低醫療費用的成效。個管的角色功能、服務內容方面，所有接受個案管理滿意度調查個案對個管服務都持正向、肯定的看法，對提供的服務也逐漸依賴此管道，與個管師更建立正向、信賴的護病關係。尤其有20位皆填需要提醒就醫(佔46.5%)，而主動將電話號碼留下。打破原先以為個案爲保護隱私不喜歡被電話打擾的思維，實是個管服務的一大突破。個管師提供電話專線諮詢服務，服務內容中以門診就醫175次(30.33%)為最主要服務項目，快速解決個案的醫療及健康問題發揮個管最大功能。主動追蹤服務，也是個管重要角色功能之一。個管師共主動追蹤38位未到診個案，而避免個案流失。此外，針對新換藥物為預防嚴重藥物不良反應，共及時處理7位發生藥物不良反應的個案，而避免更嚴重Steven-Johnson syndrome發生而需住院治療。(詳細成果報告詳附件十)

主題四、接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

自 96 年 1 月至 96 年 10 月，共有 271 通諮詢電話，其中民眾針扎及諮詢共有 113 通，醫護人員共 129 通，警員、義消及救護車隨行急救人員共 19 通，減害計畫針筒回收藥局人員共 10 通。因確定針扎及 HIV 體液暴露者於 1 月至 10 月共有 49 件，其中醫護檢驗人員有

37 位，警員義消 9 位，民眾及藥品針筒回收人員 3 位，經過 HIV 諮詢專家醫師篩檢 HIV 感染風險評估而接受 HIV 預防性用藥者有 15 位，以 8 月份 5 位最多（佔 30%），其中 3 位為新執業之護理人員（見表 2）。此 15 位確定 HIV 針扎或體液暴露者醫師有 2 位，服藥期間分別為 2 週及 4 週。護士有 5 位，其中一名護士經針扎來源血確定為陰性反應，因此立即停藥，共服藥 2 天。其餘 4 位護士均服藥 4 週。檢驗師有 1 位，服藥期間為 2 週，藥師有 1 位，服藥期間為 4 週，民眾（協助減害計畫針筒回收），服藥期間為 4 週，志工 1 位，服藥期間為 4 週，警員義消 4 位，服藥期間均為 4 週。研究進行前後已進行五次針扎計畫相關會議，包括 96.01.04（籌備針扎針畫會議）；96.01.24（進行針扎計畫討論）；96.02.13（針扎計畫期中監察）；96.03.27（針扎計畫期中監察）；96.10.16（針扎計畫期末監察及檢討）。針對醫護警消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，故計畫於 96.12.15 於台大醫學院 101 講堂進行「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」，以幫助醫療院所醫護人員進而了解 HIV 體液暴露流程之執行方法，期末監察會議並建議另外在中區、南區也舉辦相關研討會，以加強地區醫療院所的衛教，並考慮製作問卷，調查各 HIV 指定照顧醫院有關 HIV 體液暴露之流行病學及後續追蹤記錄。(詳細成果報告詳附件八)

其他、

(A)、有關與國外交流方面：

洪健清、孫幸筠、黃昱聰醫師代表本中心參加 2007 年 3/31~4/3 日在德國慕尼黑舉辦之 17th European Congress of Clinical Microbiology and Infectious Diseases 會議並發表論文。7/31 日為越南國家人口、家庭暨兒童委員會考察團一行 20 人做簡報及接待參觀本中心。

(B)、學術論文、專書著作：

2007 年度已有豐碩的成果展現，每篇內容均具原創性、代表性及本土性，計有英文 14 篇，明細如附表二所列 (3)，篇篇都是傑作，特附上已發表之論文影印本如附錄。

台大醫院「愛滋病防治中心」成立至今已屆十年，本中心同仁十年來合計發表了 120 篇的論文，涵蓋病毒學、免疫學、臨床診斷與治療、伺機性感染與惡性腫瘤，社會心理學等各層面。值此成立十週年之際，為了緬懷莊哲彥教授過去的開創與領導，暨感謝衛生署疾病管制局及台大醫院歷年來各級長官的支持與指導，將本中心同仁十年來愛滋病相關之優秀論文集結成此論文集，以供各界參考。此論文集依論文性質分成六大類如下—Section I：HIV Virology and Epidemiology and Host Responses ，Section II：Viruses and Host Responses，Section III：Opportunistic Infections and Malignancies，Section VI： Coinfections，Section V：Antiretroviral Therapy and its Complications，Section IV：Psycho-Social Problems。合計有 120 篇，每篇內容均具原創性、代表性及本土性，而且大多數是發表於世界著名期刊上，冀望能提供給社會各界及醫護人員繼續教育之參考，也為同仁們辛勤的工作成果做一個註腳。

(C)、經費使用：

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 |
|---|---|---|---|---|---|
| 96/1月至96/12月 | 8,100,000 元 | 5,282,284 元 | 2,617,716 元 | 200,000 元 | $0 |

## (四)討論

主題一、各科醫事人員愛滋感染者照護之相關在職訓練：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。

本計畫在今年結束後，已舉辦大型在職進階教育訓練課程 4 次，每次皆有 150~180 人次參與並接受在職訓練，對國內愛滋病防治之醫療教育貢獻良多。小型 Workshop 2 次，每次皆有 40~60 人次國內資深愛滋病臨床照護醫師參與並討論，對提昇國內醫療水準大有幫助。「感染症專科醫師藥品臨床研究設計及執行研習班」一梯次，對提昇國內臨床研究人員之參與力與能力，對於導入我國臨床試驗能力與國際接軌多有助益。每週一次的愛滋病防治中心研討會，本年度擬繼續聘請了各方面的專家來進行全方位的研討，內容將軍包括有臨床醫學、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；並將加強個案討論，以期大家能各憑專業集思廣益互相交流。根據我們的統計每次研討會的參加者仍以內科感染症醫師為主，其次為家庭醫學科，婦產科、兒科、精神科、外科、牙科等醫師非常少，希望明年能與這些科的相關醫學會多多聯繫，鼓勵其他科別的醫師能夠來參與愛滋病的醫療與防治。明年度希望加強定期舉辦各次專科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對於愛滋病毒感染的認知。

主題二、HIV抗藥性監測與臨床處理之相關研究：監測HIV抗藥性及研究與抗藥性相關之臨床處理方法之成效。

在我們所收集的 108 件來自台大醫院新近感染人類免疫不全病毒的病人檢體中，71 件是病人尚未接受任何治療前的檢體；37 件是治療失敗的病人檢體。在 37 件治療失敗的病人檢體中，有 24 人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑具有抗藥性的基因突變，而其中甚至有 16 人對於兩種以上的病毒抑制劑具有抗性。由於目前國內可使用的藥物有限，而一些藥物間的干擾作用或是 cross-resistant，這種對於兩種以上的病毒抑制劑具有抗性的病毒株將是臨床醫師未來在做藥物選擇上的一項挑戰，也會嚴重影響病人的治療效果。在這 37 件治療失敗的病人檢體中，很可惜只有 18 人在報告截止前有回來持續地追蹤。但是，整體來說，病人的病毒量有改善。因此對於治療失敗的病人，抗藥性基因型分析可提供臨床醫師選擇換藥時的參考依據。

主題三、HIV臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

(A)、進行「台灣地區愛滋病毒感染研究群」研究：我們的研究顯示出生於 1984 年之前的感

染者不論是否使用毒品男同性戀或異性戀慢性 B 型肝炎的帶原率相同；1984 年之後出生的愛滋病毒感染者的帶原率則已經下降到 5.6%和對照組並無差異。新生兒、幼兒或小學期間曾接種疫苗的感染者，他們的抗體效價，比較文獻中所報告台灣地區一群在出生時接種疫苗的 15 歲青少年來得高；愛滋病毒感染者的抗體效價高低與 CD4 淋巴球數有正相關，意即：CD4 越高抗體效價越高。我們的研究顯示愛滋病毒感染者接種過 B 型肝炎疫苗後，可能在後來因為有機會多次接觸肝炎帶原者，形成自然 B 型肝炎疫苗的追加接種。相關伺機性感染與存活的分析目前仍持續進行中。

(B)、靜脈毒癮者為愛滋病毒與HCV雙重感染者其HCV病毒基因變異之長程分析：近年來經由靜脈毒癮導致愛滋病毒感染者超過其它感染途徑。這些病患大部分均同時有HCV病毒感染。將來產生肝硬化或腫瘤的可能性極高。C型肝炎病毒容易突變，慢性感染的過程中原先佔多數的病毒株會被突變種取代。此種變異可能會影響治療C型肝炎病毒之療效。C型肝炎病毒的基因變遷影響因素複雜，包括病毒本身之適應度與宿主免疫力等均可能影響。愛滋病毒感染者其免疫力隨時間遞減，但開始治療後又會回升。本計劃比較未用HAART前與使用後C型肝炎病毒基因變遷。將HCV core及envelope基因以nested PCR幅增後分析其氨基酸序列之變動，多對HCV基因在服用HAART前後確有基因變異。Core基因中氨基酸列序更動之數目與病患之CD4數目並無相關性。反之，較諸一位CD4>300之病患，其HCV env基因出現二個氨基酸序列變異，多達五位CD4<200之患者有七處以上之氨基酸序列變異，且集中在hypervariable region。反觀一位CD4<100之愛滋病患，因幾乎不服用HAART藥物，HCV基因並未出現變異。由於HIV/HBV雙重感染者亦被觀察到其HBV基因於HAART治療後之變異也有類似現象，我們推論愛滋病患末期的病人在使用HARRT後，由極端免疫缺乏到恢復部份免疫力之過程，變動劇烈，可產生選擇壓力(selection pressure)迫使病毒突變。此方面之研究受限於檢體數目不多，有待將來更多資料來證實。

(C)、台灣地區HIV感染者合併C型肝炎病毒感染之臨床流行病學及其治療從本地與國外經驗看來，在尚稱短期的觀察研究中，HCV感染似乎沒有增加因肝病致死的機會，但HCV感染或HBV感染，確實會增加HIV患者發生急性肝炎的機會。HCV感染與否，並不影響他們接受高效能抗病毒藥物後病毒量下降的反應。至於HCV是否影響免疫功能的復原，和加速HIV病程，仍有待更多的研究證實。以Ribavirin加上長效型IFN治療對於基因型第1型在治療結束後6個月只有20%之治療反應率，而基因型非第1型者有50%治療反應率，因此對於HCV基因第1型的治療在HIV患者應考慮延長至48週治療。對於HIV合併HCV感染之追蹤和治療，建議所有HIV感染者，特別是靜脈毒癮者都應檢查anti-HCV。若有進展為慢性肝病或肝功能異常時應作HCV RNA檢測。疑為HCV之急性感染，而anti-HCV檢測為陰性，應考慮作HCV RNA之檢測。HIV合併HCV感染者皆需考慮C型肝炎之治療，但在CD4淋巴球小於200/㎕L的患者，需先治療HIV，而非先考慮治療HCV。CD4淋巴球介於201-350/㎕L的患者，可考慮先治療HIV，HIV治療穩定之後再考慮治療HCV。CD4淋巴球大於350/㎕L的患者，可考慮治療HCV。在治療HCV前，需檢測肝功能（AST、ALT）、HCV基因型和病毒量，以及是否合併其他肝病或系統性疾病。開始治療前需要作肝病理檢查（血友病患者例外）以了解患者HCV感染程度與預後以決定治療方式。開始治療HCV前，可能要考慮患者接受三合一抗HIV療法是否達到穩定階段（CD4是否持續增加，HIV病毒量控制）。在三合一抗HIV療法的處方需避免didanosine（ddI）及stavudine（d4T），因為與ribavirin之交互作用，可能造成乳酸中毒及肝代償失調。另外若有使用zidovudine（AZT）造成骨髓抑制現象也需考慮停止AZT替換其他藥物。HIV合併HCV感染者之治療，以長效性pegylated interferon及ribavirin合併治療為優先

選擇，建議劑量為：① HCV基因型第一型患者，依患者耐受程度，建議在體重≦75kg時，使用ribavirin 1000 mg/day治療，而體重＞75kg時，建議ribavirin 1,200 mg/day。HCV基因型第二型及第三型，ribavirin建議為800 mg/day。HCV RNA病毒量之測量，建議在IFN治療前、治療第12週、治療第24週及治療完成時（治療第48週），以及停藥後第6個月追蹤檢查。HIV RNA病毒量則依據CDC標準每3至6個月檢查。HIV合併HCV感染者，建議peg-IFN及ribavirin治療時間為48週，特別是HCV基因型第一型，而HCV基因型第二型及第三型可考慮治療至48週。治療前需檢測血液計數（CBC）（第2、4、6及每4週），血糖，肝腎功能（每4週），凝血時間，甲狀腺功能（每3至6個月），尿液懷孕檢測，治療期間需定期追蹤，而針對數值不正常可密切觀察追蹤，並需提醒患者注意避孕。對於臨床上明顯發生ribavirin或pegylated IFN相關副作用可考慮先減量使用，必要時需停止使用。Ribavirin不可與didanosine一起服用（藥物性急性胰臟炎（pancreatitis）及乳酸中毒（lactic acidosis）之藥物交互作用明顯增加。使用干擾素常會造成leukopenia（白血球低下）或ribavirin造成之貧血，因此應避免同時使用zidovudine。必要時可考慮使用growth factors（G-CSF及EPO）。

(D)、愛滋病毒感染之毒癮患者之病毒性肝炎流行病學：在本研究中可看到感染 HIV 的毒癮患者，同時有 C 型肝炎感染者高達 99.3%，B 型肝炎帶原者亦有 20.2%。雖然目前大部分的病患 CD4 仍高，不需接受雞尾酒治療，但隨著時間過去，因本研究觀察時間過短，無法看出這些病毒肝炎感染之相關罹病率、死亡率；但根據本研究結果，基礎值肝功能異常者(GPT 或 GOT 高於正常值兩倍以上)佔 10.9-21.0%，在有接受肝功能接受者中，有 14.8%的病患 GPT 高於正常值三倍以上，8.4%的病患 GOT 高於正常值三倍以上，可見有急慢性肝炎的患者在這族群中所佔的比例不小；將來在照顧這些病患時，HBV 或 HCV 感染的併發症，如急性肝炎發作、肝硬化、食道或胃靜脈瘤出血、或肝癌勢必在未來幾年為照顧這些 HIV 感染者之重要課題。因肝膽腸胃科醫生主導國內病毒性肝炎之併發症處理及肝炎治療，有必要給予相關教育訓練，以免屆時沒有醫生願意治療病患。再者，公衛護士入監教育病患時，除 HIV 相關之知識，也應告知病毒肝炎感染之相關知識；再者，因目前對 HBV 及 HCV 肝炎治療已有有效藥物治療，在可考慮制定出準則，讓成功戒毒或規則服用美沙酮之患者接受肝炎治療。另外 20 位未曾接觸過 B 型肝炎病毒且無抗體者，更應建議其接受 B 型肝炎疫苗注射，以避免感染 B 型肝炎病毒。隨著台灣公共衛生的進步，一般年輕民眾(一至二十歲者)A 型肝炎感染的盛行率下降至 1-4.8%，本研究中亦觀察到此現象，年齡層在 21-25 歲中患者，曾感染 HAV 的盛行率僅 4.8%，意味著有高達 90%的年輕族群可被 A 型肝炎感染；根據國外的研究，成年人的 A 型肝炎感染症狀較嚴重，亦可能變成猛暴性肝炎，且若同時為慢性 C 型肝炎病毒帶原者，死亡率更高。在本研究的年輕族群中，其慢性 C 型肝炎病毒帶原者高達 99.3%，為感染 A 型肝炎且有併發症之高危險族群。因目前 A 型肝炎疫苗對預防 A 型肝炎感染十分有效，在經費許可下，可考慮給予 A 型肝炎疫苗注射，以減少未來感染 A 型肝炎的機率，進而避免可能之猛暴性肝炎或肝衰竭。本研究因觀察時間過短，無法看出 A 型肝炎感染的發生率。本研究中有 16.2%的病患帶有 B 型肝炎之「單獨存在抗核抗體」，和一般的捐血者相較(2-5%)，此種血清學表現在本研究病患中之盛行率偏高(16.2%)，但和其他 HIV 感染者相較(42%-80.7%)卻是偏低；在本研究的這些病患中，有近 12.5%的病患可偵測到 B 型肝炎病毒；因目前僅做了一部分病患之 HBV DNA 測定，更詳細之分析，有待之後的結果。本研究中 B 型肝炎病毒的 genotype 以 B 為主(83.7%)，而 C 型肝炎病毒基因型以 type

1 為主(1a 16, 22.5%; 1b 12, 16.9%)，皆為國內常見之基因型。另外，國內其他研究者所報告在國內感染 HIV 和 HCV 之毒癮者所見之 HCV 基因型 6a，在本研究中卻沒有看到，可能是因目前僅做了一部分病患之 HCV RN 檢測。

(E)、進行「第一與第二孕程愛滋病毒的母子垂直傳染」研究：以目前的證據顯示，並無法證實早期懷孕 HIV-1 就會通過胎盤，到達胎兒。既然如此，目前給藥政策就無須改變，亦即，14 週以後才開始給 HAART 的藥物治療。但是，以後如果有新的證據，還可以再討論。

(F)、進行「台灣愛滋病患延遲診斷之危險因子研究」：本研究企圖找出延遲診斷者與非延遲診斷者的差異，結果發現年齡、性別、職業有無與保險套使用頻率，兩組並無差異。收入較高者、異性戀者、非因篩檢而診斷者，較易為延遲診斷者。異性戀者、非因篩檢而診斷者較易為延遲診斷者，國外已有多篇文獻報告過，作者多認為與未有高危險群之自我覺察有關。收入較高者易為延遲診斷者，與國外文獻報告相反，可能與我國實施全民健保，就醫方便，收入較高者可能因工作忙碌無暇就醫，或是自覺身體健康狀況良好有關。同性戀者、因篩檢而診斷者、父母親均健在者、曾使用違禁藥品者，較易為非延遲診斷者。同性戀者、因篩檢而診斷者較易為延遲診斷者，與國外文獻報告相同。父母親均健在，與非延遲診斷的關連性，尚未有其他文獻報告過，可能與華人文化裡家庭力量對就醫行為影響有關，值得進一步探究。曾使用違禁藥品者，可能因被警察逮捕而獲得 HIV 檢驗，因此與非延遲診斷有關，此外此一族群當中的男同性戀，是否可能因危險行為於事後更願意利用篩檢方式檢驗 HIV，導致較早期診斷，則需要進一步做次群體分析。由於違禁藥品的使用相當普遍，在本研究中高達 33%，而且以搖頭丸、大麻為主，非海洛因之違禁藥品與 HIV 傳播的關連性，是值得衛生主管單位與研究者關注的問題。本研究發現兩組感染者在診斷前已認知自己是 HIV 感染高危險群的比例均不到 50%，因此考慮篩檢與接受篩檢的比率均不盡理想。與非延遲診斷有關連的因子為擁有感染 HIV 的朋友、固定接受 HIV 篩檢，顯示願意公開自己為 HIV 感染者的人，可能增強周遭人對 HIV 的自我覺察，從而利用篩檢或妥善就醫。而固定接受 HIV 篩檢，雖然可能早期診斷 HIV 感染，但在 25 為固定篩檢者中，仍有 11 位(44%)診斷 HIV 感染時其 CD4 淋巴球數已經小於 200 cell/μL，因此仍應強調固定篩檢的頻率與持續性。針對危險族群進行的宣導、民間團體活動、匿名篩檢等，應繼續推廣與增進可近性。延遲診斷者與非延遲診斷者在診斷前一年就醫次數，中位數分別為 5 次以上與 2-3 次，就醫對象仍以社區的耳鼻喉科、皮膚科、牙科診所居多，因此社區照護體系應有警覺心，除了在一般醫療行為上做好標準防護措施，也應時刻將 HIV 感染列入診斷考慮中。診斷前一年就醫時有可懷疑 HIV 感染之相關診斷，兩組均達 20%以上，若能再配合患者曾罹患性病或帶狀疱疹的病史，則可提早發現約 50%患者之 HIV 感染。利用簡單的病史詢問，即可早期偵測出許多已感染 HIV 的患者，減少患者日後發生更嚴重的併發症，早期轉介患者至愛滋病照護系統。衛生主管機關與相關之醫學會，應針對社區照護體系內常被 HIV 感染者先接觸到的醫療專科，提供 HIV 相關繼續教育課程，以增進各科醫師對 HIV 感染的熟悉度，減少因醫師延誤診斷造成患者承受後續的嚴重後果。本研究顯示不論在患者自我覺察上，與醫師臨床診斷上，都有亟待加強的空間。研究成果提供後續防治相關政策制訂與醫療照護者教育訓練的參考，以加強第一線醫療照顧者對診斷愛滋病的警覺心，促進愛滋患者的早期診斷。

(G)、愛滋病患醫療照顧及健康諮商個案管理制度效益評估(二年計畫)：每位個管師對管理個案的個案負荷量(Case Load)，約在5~10位(10%)危機處理個管、15~20位(20%)加強個管及70~80位(70%)支持性個管為宜，合理個案負荷量約在100人/個管師。唯有，維持在合理的個案負荷量才能維持對個案狀況的深度掌握、避免個案流失。主管當局應持續舉辦愛滋個管師每年進階教育訓練，以增加個管師的文化敏感度。盡速建立愛滋個管師的工作標準及處置流

程，以及長期監測成效之機制，以培訓各院所愛滋個管師發揮最大功能，進而降低醫療費用、提高愛滋醫療團隊之服務品質。

主題四、接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

因為患有 HIV 感染的病人愈來愈多，醫事人員在工作上因暴露而感染 HIV 的危險性也愈來愈大。在美國的一項追蹤報告中指出，自 1984 年第一個案例出現後至 1999 年 6 月份止，已有 55 位醫事人員因工作上的暴露而感染了 HIV，其中由於針扎或 HIV 體液暴露呈現陽轉的因子包括帶血空心針頭，深部暴露患者為末期 AIDS 患者等有關。在台灣雖尚無類似的報告，卻值得我們深切注意。因之，了解暴露後的處理原則，是十分重要的事。根據國外許多醫療院所的研究報告調查發現：醫事人員在 3% ~ 50%的醫療行為中會接觸到病患的血液；在 0.1% ~ 15.4%的醫療行為中會發生銳器扎傷，其中尤以針扎最為常見。再教育的工作，以減少後續曝露的意外：對於發生暴露意外的醫事人員，應進行再教育的工作，以減少後續的暴露意外。Garner 等人曾提出下列幾項工作上的注意事項，以減少暴露的意外：

1. 設立專職單位，教導病人、醫事人員甚或訪客們，各種注意事項及責任。
2. 定期評估醫事人員對各注意事項的執行情形。
3. 接觸病人後應嚴格執行洗手的工作。
4. 戴手套以避免接觸病患的血液及體液。
5. 視醫療行為的必要而穿戴口罩、隔離衣、護目鏡及面罩。
6. 病患所使用過的醫療用器及設施，可重複使用的，應妥善消毒；不可重複使用的，應密封丟棄。
7. 針頭及銳器的處理：使用過的針頭，最好不要嘗試著去回套針蓋、弄彎或折斷針頭；使用過的針頭應丟棄在無法刺穿的容器中並緊緊密封。其它銳器的處理原則也是相同。
8. 病人應置於獨立病室中或集中管理（cohorting）。

在本研究收到之 271 通電話針扎及 HIV 體液暴露專線諮詢中，仍有不少（113 通）為民眾諮詢（41.6%），HIV 相關之病程、症狀、檢驗或為愛心感染 HIV 之問題，而並非針扎或 HIV 體液暴露相關，經由醫師評估過針扎及 HIV 體液暴露之危險，在 49 件執業人員之暴露傷害中，確認為需接受預防性用藥者約為 15 件（30.6%）。而以醫護人員佔絕大多數（75.5%），因此針扎及 HIV 體液暴露之再教育及流程知悉與否，相形重要，而接受預防性用藥，我們追蹤被暴露者之血液檢測的結果（範圍一個月至半年）均為 HIV 陰性。也顯示開始預防性藥物投與之時間及重要性。HIV/AIDS 是人人避之唯恐不及的的疾病，但醫事人員與警察義消急救人員無法不接觸到此類的病患。在盡心照顧病患的同時，也應留心自身的安全。而預防勝於治療，;熟悉體液接觸隔離原則，能減少許多暴露的機會。萬一不幸發生暴露的意外，應冷靜聽從專家的建議與指導，以盡量減低感染的機率，而此針扎及 HIV 體液暴露之處理流程則應利用教育訓練或研討會提供危險執業人員知悉。

## (五)結論與建議

一、 繼續提昇本中心的衛教服務功能，今年共舉辦了許多場全國性的大型研討會 5 場、2 場 HIV/AIDS Workshop、3 場 HIV 個案管理師訓練課程。每一場報名人數都非常踴躍，場場大爆滿，而且與會者迴響熱烈，可見愛滋病照護的相關問題目前受到重視的程度，往後應該繼續定期舉辦；並希望能擴大辦理讓其他科別的醫師也能來參與。

二、 整合國內 AIDS 防治醫療資源，建立資源與資訊交流支援網絡，以充份運用有限資源、有限病床，使每位病患獲得最適照護，進而達成最大的防治功效。

三、 加強調派醫師等至雲林監獄、雲林第二監獄、嘉義監獄診視新診斷愛滋病毒感染或新入監的收容人希望有機會找到人力入監抽血及檢查。並將於雲林分院開始實施美沙酮之維持療法。進行藥癮愛滋精神流行病學研究。

四、 男女性感染愛滋比例由 92 年的 20:1 拉近為 96 年的 10:1；另毒癮愛滋婦女佔女性感染族群 55.98%，並且 86.62%為 20~49 歲育齡婦女。以逐年比較男女性別比發現，我國女性感染愛滋的比例急劇增加，鑑此，婦女愛滋病毒感染者其相關之疾病的探究、治療的方式、以及母子垂直感染的議題，都是我們未來重要的課題。

五、 HIV 抗藥性監測與臨床處理之相關研究：監測 HIV 抗藥性及研究與抗藥性相關之臨床處理方法之成效。

六、 HIV 臨床流行病學相關研究：結合全國愛滋病指定醫院醫療資源及感染者相關資料，協力從事臨床研究，藉以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。

七、 隨著抗病毒藥物的引進死亡率大幅降低，從高效能抗愛滋病毒藥物引進以前的 33.75 每 100 人/年降低至藥物引進的 6.51 每 100 人/年 (P<0.0001)；而且和藥物引進前比較，2000 年到 2004 年免疫球低於 200/μL 的感染者死亡的風險降低高達 62%之多，但是，發病後第一年的死亡仍然高達 8-9%。這些結果顯示感染者就醫有提早的現象，但是以轉診醫院的角度來看仍然有相當大的改善空間。愛滋病雞尾酒療法之長期研究仍然需要持續進行(如存活率等)。

八、 繼續進行接觸愛滋病毒污染體液處理諮詢專線之建置：規劃、建立及執行接觸愛滋病毒污染體液處理諮詢專線（Post Exposure Prophylaxis line/PP line）。

## (六)參考文獻


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3. 96 年度台大同仁有關 HIV/AIDS 論文(詳附錄)。
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12. Hung CC, Chen MY, Hsieh SM, et al. Clinical spectrum, morbidity, and mortality of acquired immunodeficiency syndrome in Taiwan: a 5-year prospective study. J Acquir Immune Defic Syndr 2000;24:378-385.
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14. Sheng WH, Kao JH, Chen PJ, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. Clin Infect Dis 2007;45:1221-1229.
15. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBS response rate in HIVinfected patients. Effects on HIV-1 viral load. Vaccine 2000;18:1161–1165.

表一、愛滋病防治中心 96 年 1~11 月 HIV/AIDS 專題研討會

| 次數 | 日期 | 演講者 | 題目 | 任職單位 |
|---|---|---|---|---|
| 1 | 2-Jan | 黃昱璁 | Detection of Aspergillus antigen in HIV-infected patients with penicilliosis | 台大醫院內科住院醫師 |
| 2 | 9-Jan | 陳宜民 | 簡介愛滋病病毒的亞型及其重要性 | 陽明大學教授 |
| 3 | 16-Jan | 孫幸筠 | 雲林的愛滋病患 | 台大醫院主治醫師 |
| 4 | 23-Jan | 張麗玉 | 南區矯正機關愛滋諮商與衛教實務探討 | 美和技術學院社工系講師 |
| 5 | 30-Jan | 黃苔晏/林杰民 | Response to Antiretroviral Therapy after a Single, Peripartum Dose of Nevirapine; A prognostic index for AIDS-associated Kaposi's sarcoma in the era of Highly active antiretroviral therapy | 台大醫院 5E3 病房住院醫師 |
| 6 | 6-Feb | 羅一鈞 | 愛滋病患延遲診斷之危險因子分析 | 台大醫院內科住院醫師 |
| 7 | 6-Mar | 李欣純 | What we have learned from the HCV epidemic to HIV outbreak among injection drug users in Taiwan | 成大醫院主治醫師 |
| 8 | 13-Mar | 洪健清 | HIV Research Report: Amebiasis, HBV Seroepidemiology | 台大醫院主治醫師 |
| 9 | 20-Mar | 蔡靜華 | Valtrex: Easy and Convenient way to Manage Herpes | 荷商葛蘭素史克藥廠 |
| 10 | 27-Mar | 王永衛 | 靜脈毒癮者愛滋病感染–北部監所受刑人的流行病學分析 | 台北市立聯合醫院昆明院區醫務長 |
| 11 | 10-Apr | 杜昀真 | Viral hepatitis in HIV infection | 台大醫院 5E3 病房住院醫師 |
| 12 | 17-Apr | 王敏吉 | 邊緣的邊緣--灰色巨塔 | 臺灣高雄第二監獄精神科醫師 |
| 13 | 24-Apr | 吳明義 | HIV(+)孕婦之抗愛滋病毒治療 | 台大醫院婦產科主治醫師 |
| 14 | 1-May | 盛望徽 | B 型肝炎血清標記變化 | 台大醫院主治醫師 |
| 15 | 8-May | 李思賢 | 女性靜脈毒癮與愛滋病毒感染 | 師大公衛所副教授 |
| 16 | 15-May | 蔡季君 | 熱帶醫學介紹 | 高醫附設醫院感染科主治醫師 |
| 17 | 22-May | 施鐘卿 | 個案管理師介紹 | 台大醫院個案管理師 |
| 18 | 29-May | 謝慕揚 | 病例報告與烏菲氏青霉菌 | 台大醫院 5E3 病房住院醫師 |
| 19 | 5-Jun | 孫幸筠 | Tuberculosis and HIV infection | 台大醫院主治醫師 |
| 20 | 12-Jun | 楊秀菊 | Langerin is a natural barrier to HIV-1 transmission by Langerhans cells | 防治中心研究助理 |
| 21 | 26-Jun | 吳家麟 | Case Discussion | 台大醫院 5E3 病房住院醫師 |
| 22 | 4-Sep | 楊靖慧 | Implications and Implementation for Routine HIV Screening | 疾病管制局首席防疫醫師 |
| 23 | 2-Oct | 曾御慈 | HIV 感染者合併高脂血症之治療 | 台大醫院感染科總醫師 |

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|---|---|---|---|---|
| 24 | 9-Oct | 盛望徽 | HIV 患者之 HDV 感染 | 台大醫院主治醫師 |
| 25 | 16-Oct | 林宜慧 | 新版愛滋防治條例與人權權益問題 | 愛滋感染者權益促進會秘書長 |
| 26 | 23-Oct | 林育寬 | 愛滋病感染者旅遊相關問題 | 台大醫院感染科總醫師 |
| 27 | 30-Oct | 廖斌志 | Case Discussion | 台大醫院 5E3 病房住院醫師 |
| 28 | 6-Nov | Dr. Francis Morey | Epidemiology of HIV/AIDS in Belize | 貝里斯首都醫院內科醫師 |
| 29 | 13-Nov | 陳伯杰 | 男同志愛滋篩檢諮商經驗分享 | 社團法人台灣同志諮詢熱線協會主任 |
| 30 | 20-Nov | 陳茂源 | HIV/TB | 台大醫院主治醫師 |
| 31 | 27-Nov | 住院醫師 | Case Discussion | 台大醫院 5E3 病房住院醫師 |
| 32 | 4-Dec | 顏雅玲 | (邀請中) | 臺灣雲林第二監獄衛生科科長 |
| 33 | 11-Dec | 巫沛瑩 | 匿名篩檢工作經驗分享 | 防治中心研究助理 |
| 34 | 18-Dec | 張麗玉 | (邀請中) | 美和技術學院社工系講師 |
| 35 | 25-Dec | 住院醫師 | Case Discussion | 台大醫院 5E3 病房住院醫師 |

時間：每週二上午 7:00-9:00　*當天中午 12:00-14:00

地點：台大醫院西址綜合病房討論室〈舊五東病房三樓，由販賣部上樓〉

# 表二、九十六年度計畫論文及著作明細表

| 序號 | 計　畫　產　出　名　稱 | 產出形式 | SCI* |
|---|---|---|---|
| 1 | Fang CT, Chang YY, Hsu HM, et al. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy. *Q J Med* 2007;100:97-105. | 期刊 | ∨ |
| 2 | Fang CT, Chang YY, Hsu SM, et al. Cost-effectiveness of highly active antiretroviral therapy for HIV infection in Taiwan. *J Formos Med Assoc* 2007;106:631-40. | 期刊 | ∨ |
| 3 | Ho YC, Shih TF, Lin YH, et al. Osteonecrosis in patients with human immunodeficiency virus Type 1 infection in Taiwan. *Jap J Infect Dis* 2007;(in press). | 期刊 | ∨ |
| 4 | Hsieh SM, Chen MY, Pan SC, et al. Aberrant induction of regulatory activity of CD4+CD25+ T cells by dendritic cells in HIV-infected persons with amebic liver abscess. *J Acquir Immun Defic Syndr* 2007;44:6-13. | 期刊 | ∨ |
| 5 | Hung CC, et al. Prevalence of intestinal infection due to *Cryptosporidium* species among Taiwanese patients with human immunodeficiency virus infection in Taiwan. *J Formos Med Assoc* 2007;106:31-5. | 期刊 | ∨ |
| 6 | Hung CC, Hung MN, Hsueh PR, et al. Risk of nontyphoid *Salmonella* bacteremic in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. *Clin Infect Dis* 2007;45:e60-7. | 期刊 | ∨ |
| 7 | Hung CC. Amoebiasis: current in Australia. [Letter to the editor]. *Med J Austral* 2007;187:372-3. | 期刊 | ∨ |
| 8 | Huang YT, Hung CC, Hsueh PR. *Aspergillus* galactomannan antigenemia in penicilliosis marneffei. *AIDS* 2007;21:1990-1. | 期刊 | ∨ |
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| 11 | Sheng WH, Hung CC, Kao JH, et al. Impact of hepatitis D virus infection on the long-term outcomes of patients with hepatitis B virus and HIV coinfection in the era of highly active antiretroviral therapy: a matched cohort study. *Clin Infect Dis* 2007;44:988-95. | 期刊 | ∨ |
| 12 | Sheng WH, Hung CC, Wu RJ, et al. Clinical impact of GB virus C viremia on patients with HIV type 1 infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2007;44:584-90. | 期刊 | ∨ |
| 13 | Sheng WH, Kao JH, Chen PJ, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2007;45:1221-9. | 期刊 | ∨ |
| 14 | Sun HY, Hung CC, Lin PH, et al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *J Antimicrob Chemother* 2007;60:599-604. | 期刊 | ∨ |

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

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# Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy

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## Summary

**Background:** Limited data are available on the life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy (HAART).
**Aim:** To provide such an estimate using a semi-parametric projection.
**Design:** Statistical analysis.
**Methods:** Follow-up data for patients newly diagnosed with HIV infection in Taiwan (HIV/AIDS Cohort) from 1 May 1997 to 30 April 2003 ($n=3351$, only 1% are injecting drug users) were analysed using the Kaplan-Meier method. The survival function for an age- and gender-matched reference population was generated by the Monte Carlo method from the life-table of the general population. A constant excess hazard model was used to project long-term survival of HIV-infected patients, with linear extrapolation of a logit-transformed curve of survival ratio between HIV-infected patients and the reference population.
**Results:** The 5-year survival rate was 58% in patients who had already developed AIDS at diagnosis (AIDS group), and 89% in those who had not (non-AIDS group). Extrapolation yielded an expected mean survival time of 10.6 years after diagnosis for the AIDS group, and 21.5 years after diagnosis for the non-AIDS group.
**Discussion:** Our results support the expansion of HIV screening programs to minimize delay in diagnosis. With continuing advances in HAART, this estimate of survival in initially asymptomatic patients may be conservative. Their long life expectancy raises questions about what kind of preventive heath services should be offered. These should be addressed through further analysis of overall benefit and cost-effectiveness.

## Introduction

The introduction of highly active antiretroviral therapy (HAART) has dramatically improved the short-term survival of patients with human immunodeficiency virus (HIV) infection.[1–3] However, there has been a lack of empirical data on long-term survival. A valid estimation of life expectancy after diagnosis would be of great value, not only for public health policy-making but also for formulation of clinical guidelines.[4]

Most literature reports regarding the estimated survival time of HIV-infected patients in the HAART era are based on Markov models with Monte Carlo simulation.[5–12] However, survival time estimated by Markov modelling was highly dependent on

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assumptions about the efficacy of antiretroviral therapy.[7] For practical purposes, a more robust approach is needed.

Parametric survival modeling[13,14] is not a suitable alternative in this scenario, because of a high rate of right-censoring in HIV cohorts. As the follow-up time increases, the age factor and various comorbid diseases unrelated to HIV could influence the expected survival time.[12,15] It is therefore very difficult, if not impossible, to take into account mathematically all these factors, and produce a specific functional formula.[16] To consider both HIV-related excess hazard and non-HIV-related background hazard, we have developed a semi-parametric method to incorporate the life expectancy information of background general population into the estimation process.[17–21] If the HIV-related excess hazard remains constant in the chronic stage of a stable disease, HIV-infected patients' long-term survival can be projected from the available follow-up data using the lifetime survival function of an age- and gender-matched reference population as reference. The survival function of this reference population can be generated by Monte Carlo methods from the life table of the general population.[17]

In this study, we first evaluated the validity of this method using follow-up data from the Taiwan HIV/AIDS Cohort, which included all identified HIV-positive patients in Taiwan. We then applied this method to estimate the life expectancy of patients with newly-diagnosed HIV infection in the HAART era. The estimates were compared with the results obtained from standard parametric survival modelling.

# Methods

## Taiwan HIV/AIDS Cohort

The Taiwan HIV/AIDS Cohort includes all identified HIV-positive citizens in Taiwan. Both HIV infection and acquired immunodeficiency syndrome (AIDS) are reportable diseases in Taiwan.[22] All identified HIV cases must be confirmed by Western blot and reported to the Center for Disease Control (Taipei, Taiwan). AIDS is defined according to the Centers for Disease Control and Prevention (Atlanta, USA) 1993 revised criteria,[23] but with three minor modifications: (i) Disseminated or extrapulmonary infection due to *Penicillium marneffei*,[24] an opportunistic pathogen endemic in southeast Asia, is considered an AIDS-defining condition. (ii) Because of a high incidence (50–75 cases per 100 000 population per year) of pulmonary tuberculosis in the non-HIV general population,[25] pulmonary tuberculosis is an AIDS-defining condition only if the patient's CD4 count is <200/$\mu$l. (iii) Patients who have a CD4 count <200/$\mu$l are considered to have AIDS only after they develop at least one AIDS-defining opportunistic infection. Center for Disease Control (Taipei, Taiwan) maintains a periodically-updated data profile, including the date of diagnosis, age, gender, date of development of AIDS, and date of death for each Western-blot-confirmed case.

## HAART

HAART was introduced in Taiwan in 1997, and was freely offered to all identified HIV-positive citizens through the National Health Insurance system.[26] The timing of initiating HAART, and the regimens, both followed the evolving guidelines recommended in the US.[27–29] Initially, early treatment was encouraged, except for those with blood HIV-RNA levels <5000 copies/ml and a CD4 cell count $\geqslant$500/$\mu$l. In 2002, the practice of initiating HAART in asymptomatic patients was gradually changed to the new criteria of a CD4 count <350/$\mu$l or a peripheral blood HIV-RNA level >55 000 copies/ml.[29,30] In 1997, only unboosted protease inhibitor (PI)-based regimens were available. Non-nucleoside reverse transcriptase inhibitor-based and boosted PI-based combinations became the first-line regimens in 2000 and 2001, respectively.

## Survival in patients with newly diagnosed HIV infection in the HAART era

We included all cases diagnosed in the period from 1 May 1997 to 30 April 2003. Being newly diagnosed in HAART era, these patients were all treatment-naive when HAART was started. The survival status of each patient was further verified by cross-checking with the national death certification database maintained by the Ministry of the Interior, Taiwan.[31] We used the Kaplan-Meier method to estimate survival function, stratified by whether they had already developed AIDS-defining conditions at diagnosis of HIV infection, using the follow-up data from 1 May 1997 to 30 April 2003.

## Survival in the reference population

Life tables for the general population were obtained from vital statistics published by Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan. Life expectancy at birth in Taiwan has gradually increased from 75.04 years in 1999 to 75.87 years in 2002. Because individual survival time of subjects in a hypothetical cohort cannot be

directly derived from the life table of the general population, we used a Monte Carlo method to generate the simulated remaining survival time of age- and gender-matched hypothetical subjects for each patient in the Taiwan HIV/AIDS Cohort. For example, the remaining survival time of a hypothetical subject corresponding to a male patient of age $x$ may be generated as follows.

From the life table of the general population, we first find $P_{x+k}^{x+k+1}$, which is the proportion of male persons alive at the beginning of age interval $(x+k,\ x+k+1)$ but dead during the interval for $k \geqslant 0$. The conditional survival function of the male general population who have survived to age $x$ is given by $S(t|x) = \prod_{k=0}^{t}(1 - P_{x+k}^{x+k+1})$, for $t>0$, and $S(0|x)=1$. Secondly, a uniform random number between 0 and 1 is generated. The time $t_x$ such that $S(t_x|x)=u$ equals the uniform random number is a survival time for the hypothetical subject. The total collection of hypothetical subjects was used as the reference population. The ratio between numbers of hypothetical subjects and each real patient was set to make the final size of the reference population up to 100 000. The survival curve of the reference population is then obtained by applying the Kaplan-Meier method to the simulated survival times.

## Logit survival ratio extrapolation

The survival ratio between the survival functions of two populations is defined by the formula: $W(t) = S(t|\text{patient population})/S(t|\text{reference population})$. Because the patient population has a worse survival than the reference population, the value of $W(t)$ initially equals 1 at time point $t=0$, then gradually decreases due to disease-associated excess mortality. Because the value of $W(t)$ is limited to the range from 0 to 1, linear regression for temporal trend is not applicable. We therefore used the logit transformation of $W(t)$, or $\log[W(t)/(1-W(t))]$.[17] A higher logit $W(t)$ value corresponds to a higher $W(t)$ value, but the range of values was transformed from $0 \sim 1$ to that of $-\infty \sim +\infty$. Furthermore, if the HIV-associated excess hazard remains constant over time, the curve of the logit of $W(t)$ will converge to a straight line, as shown below.

Let $H(t|\text{patient}) = H(t|\text{reference}) + \text{HIV-associated excess hazard } C_1$, where $C_1$ is a positive constant. Using the definition of hazard function $H(t) = -[dS(t)/dt]/S(t)$, this equation can be rewritten as $dS(t|\text{patient})/S(t|\text{patient}) = dS(t|\text{reference})/S(t|\text{reference}) - C_1 \times dt$. We integrate both sides of this equation to obtain $\ln[S(t|\text{patient})] = \ln[S(t|\text{reference})] + C_0 - C_1 \times t$. Therefore, we obtain the following equation:

$$\text{logit } W(t) = \ln\left[\frac{\exp(C_0 - C_1 \times t)}{1 - \exp(C_0 - C_1 \times t)}\right] = C_0 - C_1 \times t - \ln[1 - \exp(C_0 - C_1 \times t)].$$

Because $C_1 > 0$, the residual item $\ln[1 - \exp(C_0 - C_1 \times t)]$ will converge to 0 when $t \to \infty$. As a result, when $t \to \infty$, logit $W(t)$ will approximate to $C_0 - C_1 \times t$, a straight line with slope $-C_1$.

The extrapolation process consisted of three phases. First, a plot of logit $W(t)$ over time was created. The time point $T_s$ after which the logit $W(t)$ curve became a nearly straight line was then identified. Second, we fitted a simple linear regression for logit $W(t)$ from $T_s$ to the end of follow-up $T_f$, that is:

$$\log\left(\frac{W(t)}{1 - W(t)}\right) = \alpha + \beta t + N_t, \quad \text{for } T_s \leq t \leq T_f$$

where the noise term $N_t$ is independently and normally distributed with mean 0 and variance $\sigma^2$. Finally, given the least squares estimates of the two parameters, $\hat{\alpha}$ and $\hat{\beta}$, we project the long-term survival curve of patient population beyond the follow-up limits as:

$$\hat{S}(t|\text{index}) = \hat{S}(t|\text{ref})\frac{(\exp(\hat{\alpha} + \hat{\beta}t)}{1 + \exp(\hat{\alpha} + \hat{\beta}t)}$$

for $t > T_f$. The standard error of survival estimates was obtained through a bootstrap method by implementing the extrapolation process with data simulated by repeatedly sampling with replacement from the real data set 1000 times.

To facilitate the computation, we developed a software program MC-QAS, which was built in the R and S-PLUS 2000 (MathSoft) environment and can be freely downloaded from [http://www.stat.sinica.edu.tw/jshwang] (released in December 2004).

## Parametric survival modelling

For comparison, a standard parametric survival regression and extrapolation was also applied to the same follow-up data. Models based on the versatile three-parameter extended generalized gamma distribution were chosen, of which the popular two-parameter Weibull distribution is a special case. S-PLUS 2000 (MathSoft) and SAS Proc Lifereg (SAS Institute) (distribution = gamma or Weibull) were used for computation.

# Results

## Characteristics of patients

A total of 3351 HIV-positive patients, of whom 718 (21%) had already developed AIDS-defining conditions at diagnosis (the AIDS group) and 2633 had not (the non-AIDS group), were diagnosed between 1 May 1997 and 30 April 2003. The great majority of the 3351 were men (93%). The most common age at diagnosis was 20–29 years (37%), followed by 30–39 years (35%), and 40–49 years (13%). Sexual contacts (98%) were the predominant risk factor, followed by intravenous drug use (IVDU) (1%). The mean age at diagnosis in the AIDS group was significantly higher than that in the non-AIDS group (40.6 vs. 33.1 years, $p<0.001$).

## Observed 6-year survival curves

The Kaplan-Meier survival curves for the AIDS group ($n=718$) and the non-AIDS group ($n=2633$) are shown in Figures 1a and 1b, respectively. The longest follow-up period was 6 years. The 5-year survival rate in the non-AIDS group was 89%. For the AIDS group, the survival rate dropped rapidly to 66% at the end of the first year, and then gradually decreased to 58% at the end of the fifth year.

## Temporal trend of logit $W(t)$

The plots of logit $W(t)$ in the AIDS group and the non-AIDS group are shown in Figures 2a and 2b, respectively. In both groups, the logit $W(t)$ curve underwent an initial rapid decline, then levelled off after the first year, and eventually converged to a straight line with a negative slope of −0.008/month and −0.010/month, respectively. If stratified according to gender or age at diagnosis of HIV infection, the logit $W(t)$ curves still followed the same temporal trend, and eventually converged to a straight line with a negative slope of −0.007/month (women), −0.009/month (men), −0.007/month (age <40 years) and −0.010/month (age >40 years). This indicates that the observed survival data of HIV-positive patients met the assumption of a constant HIV-associated excess hazard.

## Validity of extrapolation

The first 3-year follow-up data (1 May 1997–30 April 2000) from the 1264 patients diagnosed in that period were analysed to extrapolate the survival curve to 3 years beyond 30 April 2000. The 1999 life-table of the general population was used as the reference. Predicted 6-year survival curves were then compared with those actually observed from 1 May 1997 to 30 April 2003. The validity of the parametric survival models was examined using the same data.

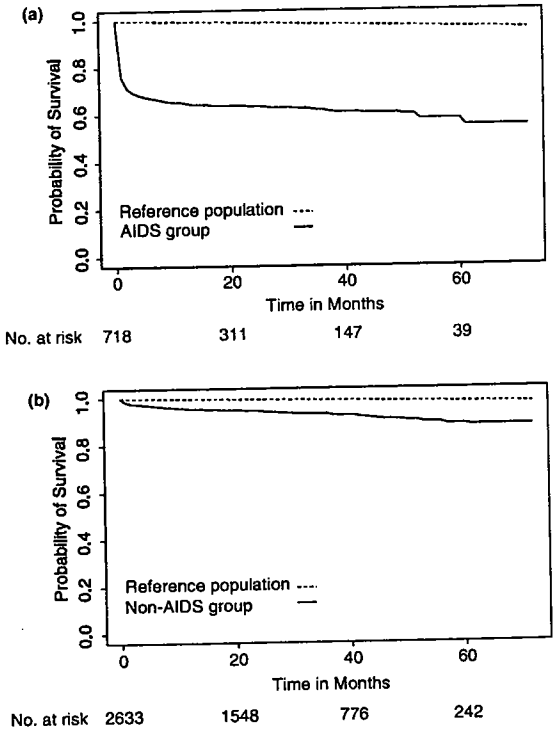


**Figure 1.** Survival curve for 3351 HIV-positive Taiwanese patients diagnosed and treated between 1 May 1997 and 30 April 2003. **a** Patients who had already developed AIDS at diagnosis (AIDS group) ($n=718$); **b** Patients who had not yet developed AIDS at diagnosis (non-AIDS group) ($n=2633$). The hypothetical survival curves for an age- and gender-matched reference population generated by the Monte Carlo method from the 2002 life-table for the general population are also shown.

The logit survival ratio extrapolation method predicted that the AIDS group ($n=326$) would have a mean survival time (±SE) of 43.3 ± 2.2 months at the end of the 6-year follow-up. There was no significant difference (95%CI −4.9 to 6.9 months) from the actual value (42.3 ± 2.0 months). The predicted survival curve matched quite well with the actual curve (Figure 3a). In comparison, the Weibull survival model and the extended generalized gamma model predicted mean survival times of 38.3 months and 41.6 months, respectively. The Weibull survival model failed to capture the feature of an abrupt decrease in hazard after initial months in AIDS group, and did not achieve a good match between the predicted and the actual survival curves, while the more versatile extended generalized gamma model yielded a better match (Figure 3a).

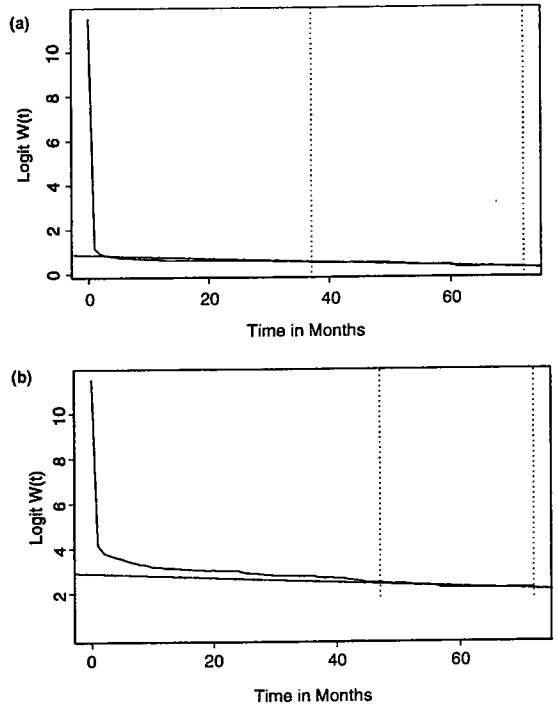


**Figure 2.** Logit transformation of the survival ratio $W(t)$ between the survival functions of HIV-positive patients and that of the age- and gender-matched reference population generated by the Monte Carlo method. The two dotted lines mark the time period when the logit survival ratio data were used for extrapolation. The solid line is the linear regression line. **a** AIDS group. **b** non-AIDS group.

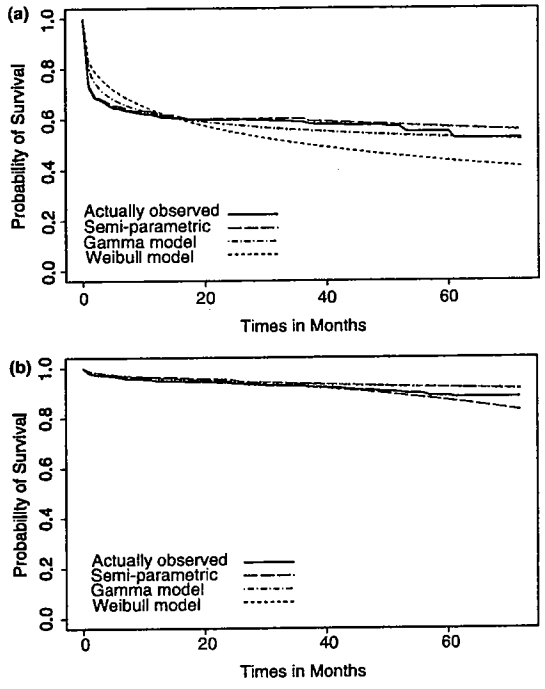


**Figure 3.** Comparison of the 6-year survival curves extrapolated from the data for 1 May 1997 to 30 April 2000 (by semi-parametric logit survival ratio extrapolation, Weibull model or extended generalized gamma model) and the actual 6-year survival curves observed from 1 May 1997 to 30 April 2003. **a** AIDS group ($n=326$). **b** Non-AIDS group ($n=938$). The dotted line (Weibull model) overlaps the dashed line (gamma model) in **b** because the two models yielded almost identical predictions.

Similarly, the logit survival ratio extrapolation method predicted that the non-AIDS group ($n=938$) would have a mean survival time (±SE) of 65.6±1.9 months at the end of the 6-year follow-up. There was no significant difference (95%CI −4.7 to 3.1 months) from the actual value (66.4±0.6 months). Both the Weibull and the extended generalized gamma survival models predicted a mean survival time of 67.7 months. The logit survival ratio extrapolation method, as well as the Weibull and the extended generalized gamma models, achieved a reasonable match between the predicted and the actual 6-year survival curves in the non-AIDS group (Figure 3b).

## Long-term survival after diagnosis

The 6-year follow-up data (follow-up from 1 May 1997 to 30 April 2003) of the 3351 patients diagnosed in that period were used to extrapolate the survival curve to the 50th year after diagnosis for estimation of the life expectancy. The 2002 life-table of the general population was used as the reference.

The 50-year survival curves predicted via the logit survival ratio extrapolation method for patients initially with or without AIDS are shown in Figures 4a and 4b, respectively. For the AIDS group ($n=718$), the predicted survival probability was 0.58 at the end of the fifth year, 0.43 at the end of the 10th year, 0.31 at the end of the 15th year, and 0.07 at the end of the 30th year (Figure 4a). The estimated mean±SE lifetime survival was 10.6±3.2 years after diagnosis. For the non-AIDS group ($n=2633$), the predicted survival probability was 0.89 at the end of the fifth year, 0.80 at the end of the 10th year, 0.69 at the end of the 15th year, and then 0.25 at the end of the 30th year (Figure 4b). The estimated mean±SE lifetime survival was 21.5±5.7 years after diagnosis.

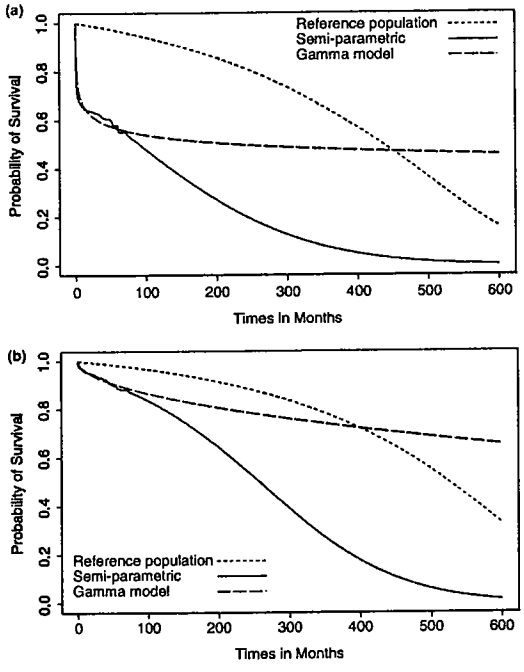


**Figure 4.** Predicted 50-year survival curve for 3351 HIV-positive Taiwanese patients. **a** AIDS group ($n=718$). **b** Non-AIDS group ($n=2633$) (semi-parametric logit survival ratio extrapolation and extended generalized gamma model). The hypothetical survival curves for an age- and gender-matched reference population generated by the Monte Carlo method from the 2002 life-table for the general population are also shown.

In comparison, the standard parametric survival model based on extended generalized gamma distribution yielded erroneous predictions of long-term survival curves (Figures 4a and 4b). HIV-positive patients are expected to have a worse long-term survival. However, the extended generalized gamma model predicted a better survival in the HIV-positive patients at 30–40 years after diagnosis than in the age- and gender-matched reference population. This indicates that standard parametric models may yield grossly deviated results in the prediction of long-term survival for HIV patients.

## Discussion

In our analysis, the semi-parametric logit survival ratio extrapolation method performed better than parametric survival models. Our results are however limited by uncertainty regarding the stability of excess hazard in the extrapolation period. For example, the efficacy of HAART may gradually decrease over time due to accumulation of resistance mutations. Although this may be balanced by the introduction of a more potent salvage therapy, the impaired immune functions and the adverse effects of some HAART regimens on metabolic profiles may also take their toll in the late course of the illness, and may interact synergistically rather than additively with underlying diabetes mellitus or coronary artery disease.[32] Since the HIV-related excess hazard is unlikely to be exactly constant throughout the extrapolation period, a certain degree of prediction error is unavoidable.[17] Despite this, our semi-parametric method avoids the gross deviations in long-term projections seen with the extended generalized gamma survival models, with the advantage of an input of information from the life table of the background general population.

Our results should be interpreted with another important limitation in mind. With the introduction of more potent new-generation first-line HAART regimens and advances in medical care for opportunistic infections and malignancies,[29,33,34] survival in HIV-positive patients is likely to see improvements in the future beyond those in our 1997–2003 data. This trend is supported by recent epidemiological evidence.[15] Despite the concern of widespread transmission of drug-resistant virus among the population,[35] a cohort study in the US showed a continuing decrease from 1997 to 2003 in the annual death rate of non-IVDU HIV-positive patients.[15] As a result, our prediction based on the 1997–2003 follow-up data is likely to be a conservative estimate.

Despite these limitations, our method yielded similar estimates to those reported in recent studies using calibrated Markov models.[8,10–12] Before 2001, when HAART was still in its infancy, researchers conducting Markov modelling used a conservative assumption of an initial round of HAART effective for a maximum of only 2 years followed by a single round of less effective salvage therapy.[7] This led to the conclusion that patients with newly-diagnosed HIV infection had a mean expected survival of only 2.84–9.13 years after diagnosis.[5,7] In recent years, observational cohort data with increasing follow-up length became available and allowed calibration of the probability parameters. Using these updated models, Braithwaite *et al.* estimated a median survival time of 20.4 years for newly diagnosed HIV-infected patients, and 12.2 years for those with a CD4 count of 200/$\mu$l and a viral load of 1 000 000 copies/ml.[12] Similarly, King *et al.* estimated a median survival time ranging from 15.4 to 26.6 years for HIV patients with an initial CD4 count >200/$\mu$l, and 8.5 years for those with a CD4 count $\leqslant$200/$\mu$l.[8] Paltiel *et al.* also estimated that newly-diagnosed HIV patients would have a mean

survival of 19.0–19.6 years.[10] These results, based on approaches entirely different from ours, support the robustness of our estimates.

Our results show that, even under a National Health Insurance system which provides HIV-positive patients free access to HAART and medical care, there was still a significant portion (21%) of patients who did not receive HIV testing until they developed AIDS-defining conditions. This delay was associated with a high risk of mortality within 1 year, and a much worse life expectancy. HIV screening programs, which have been shown to be cost-effective in two simulation studies,[10,11] should be expanded to minimize such a delay in diagnosis and unnecessary premature mortality. On the other hands, newly diagnosed asymptomatic patients have an expected mean survival time of at least 21.5 years, which will probably continue to improve in the coming years. One probabilistic model predicted that 36–72% of them would die from causes not directly attributable to HIV.[12] For clinicians providing medical care for HIV-positive persons, a compelling question is: what kind of preventive heath services should be offered to them? Should they be exactly the same as individuals without HIV? Should they be less? Should they depend upon prognostic markers? Formulation of clinical guidelines needs to consider the overall benefit and the cost-effectiveness, with remaining life expectancy as an important determinant.[4,12]

Several important features of our estimates should be recognized. First, derived from the national cohort data, our estimates account for effects such as unsatisfactory drug adherence among less motivated patients and even interruption of treatment for various reasons. Highly motivated individuals with stricter drug adherence, such as those seen in clinical trials, may have a much better long-term survival than our estimates. But patients with unfavourable risk profiles such as those with HBV or HCV coinfections[36] may have a life expectancy significantly worse than our estimates. Second, only 1% of patients in our cohort were IVDUs. Therefore, our results may not be generalizable to this population, which may have a worse long-term survival than other non-IVDU HIV-infected patients.[36] Third, our estimates were based on the scenario that HIV-positive patients have free access to HAART. Because access to HAART is an important determinant of long-term survival for people living with HIV/AIDS,[37–39] our estimates do not account for those without such access, for economic or other reasons. Fourth, in addition to the above clinical factors, there are other important determinants of life expectancy in newly diagnosed HIV patients. These include socioeconomic factors such as average income, as well as the performance of public health systems and the quality of medical care.[40] Our estimates are therefore not directly applicable to developing countries that have less favourable socioeconomic conditions and a much shorter life expectancy at birth. To calculate the corresponding estimate for a specific country, local data should be used regarding life-tables of the general population and the survival of patients with HIV/AIDS.

In conclusion, by incorporating information from the life-table of the general population, estimation using the logit survival ratio extrapolation method is a robust approach to calculating the life expectancy of HIV-positive patients. Patients who have already developed AIDS at presentation have a high risk of mortality within 1 year, and a much worse life expectancy. HIV screening programs should be expanded to minimize delay in diagnosis. Patients with newly diagnosed asymptomatic HIV infection in the HAART era are expected to survive for a mean of 21.5 years after diagnosis according to current projections. Because of continuing advances in HAART, our current estimate is likely to be conservative. This long life expectancy raises questions about what kind of preventive heath services should be offered, that need to be addressed through further analysis of overall benefit and cost-effectiveness.

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ORIGINAL ARTICLE

# Cost-effectiveness of Highly Active Antiretroviral Therapy for HIV Infection in Taiwan

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**Background/Purpose:** Since the late 1980s, the Taiwanese government has provided all HIV-infected citizens with free access to antiretroviral therapy. Recently, there is controversy as to whether or not free access to expensive highly active antiretroviral therapy (HAART) should be continued for HIV-infected patients. This study aimed to evaluate the cost-effectiveness of HAART therapy.

**Methods:** HAART-associated improvement in survival was obtained by analyzing the follow-up data of all HIV-positive patients identified during April 1984 to March 1997 (pre-HAART era) and May 1997 to April 2003 (HAART era) in Taiwan. Data on quality of life in HIV-positive patients was obtained from a cross-sectional survey of 224 patients using standard gamble method and World Health Organization Quality of Life-BREF instrument. Information regarding the cost of HAART was obtained from the National Health Insurance (NHI).

**Results:** In 2000, the average annual NHI expenditure on HAART per HIV-positive patient receiving HAART was NT$210,018 (US$6177, at an exchange rate of 34.0 NT$/US$). In the AIDS group, the cost was NT$176,441 (US$5189) per life year gained and NT$241,700 (US$7109) per quality-adjusted life year gained. For non-AIDS patients, the corresponding costs were NT$226,156 (US$6652) and NT$332,582 (US$9782), respectively. These estimates have not yet included the additional cost savings from HAART-associated reduction in hospitalization and use of antimicrobial agents for opportunistic infections, and the additional life years gained from the reduction in HIV transmission under the universal availability of HAART.

**Conclusion:** HAART for HIV infection is cost-effective, especially when the societal and epidemiologic factors are considered. We recommend that the policy of providing free HAART to all HIV-infected citizens be continued. [*J Formos Med Assoc* 2007;106(8):631–640]

**Key Words:** cost-effectiveness, HAART, health policy, highly active antiretroviral therapy, HIV infection

From the beginning of the human immunodeficiency virus (HIV) epidemic in Taiwan in 1986, the Taiwanese government decided to ensure that all HIV-infected citizens had free access to antiretroviral therapy.[1] The introduction of highly active antiretroviral therapy (HAART) in April 1997 dramatically improved the survival of patients with HIV infection.[1–3] These antiretroviral agents, however, are expensive and must be used in combination.[4–6] The wholesale prices in the United States ranged from approximately US$2500 per patient per year for the nucleoside analogs to



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US$8000 per patient per year for one of the protease inhibitors in 1998.[7,8] Furthermore, the combination therapy must be continued throughout the patient's life.[4-6]

In Taiwan, when the number of HIV-infected patients was small, the National Health Insurance (NHI) could cover the cost and provide all HIV-infected citizens with free access to such therapy.[1] Since 2003, however, a new wave of HIV epidemic of CRF07_BC subtype was introduced from southwest China via heroin-trafficking routes into Taiwan.[9] Up till the end of 2006, at least 5034 intravenous heroin abusers have already been infected.[10] With the anticipated huge financial burden on the NHI due to the explosive growth in the number of new HIV cases, controversy has emerged with regard to whether the policy of providing free HAART should be continued.

Several studies have suggested that HAART is cost-effective,[8,11-13] with the incremental cost per life year (LY) gained estimated at US$12,000–21,000 in the United States,[8] US$22,110 in Swizerland,[11] US$12,813–14,587 in Canada,[12] and US$675–1622 in South Africa.[13] These studies, nevertheless, were either based on hypothetical computer simulations[8,11] or on databases from only a few hospitals.[12,13] The present study aimed to evaluate the cost-effectiveness of HAART in HIV-infected patients through analyzing nationwide databases in Taiwan.

## Methods

### *Study design*

This was an intervention study comparing treatment effectiveness before versus after the introduction of HAART in Taiwan in April 1997. We calculated the incremental cost-effectiveness ratio[14] based on the average cost and the quality-adjusted life expectancy (estimated mean quality-adjusted lifetime survival) after the diagnosis of HIV infection. Comparisons were made between the pre-HAART era (April 1, 1984 to March 31, 1997) (as the baseline scenario) and the HAART era (May 1, 1997 to April 30, 2003).

### *Survival data of HIV-infected patients*

Both HIV infection and acquired immunodeficiency syndrome (AIDS) are reportable diseases in Taiwan.[15] All identified cases must be confirmed by Western blot and reported to the Centers for Disease Control (Taipei, Taiwan). For each case confirmed by Western blot, the Centers for Disease Control maintains a periodically updated data profile, including the date of diagnosis, age, gender, date of development of AIDS,[3] and date of death. The survival status of each patient is further verified by cross-checking with the national death certification database maintained by the Department of Health and Ministry of the Interior, Taiwan.[16]

### *Survival analysis and extrapolation*

The follow-up data were analyzed by the Kaplan–Meier method[17] to yield the estimated survival function of HIV-infected patients in the two eras. A constant excess hazard model was used to project long-term survival of HIV-infected patients, with linear extrapolation of a logit-transformed curve of survival ratio between HIV-infected patients and an age- and gender-matched reference population.[3] The survival function of this reference population was generated by a Monte Carlo method[18] from the life table of the general population of Taiwan. At the end of 2006, Taiwan had a population of 22,876,527, of whom 16,443,867 (71.2%) were aged 15–64 years, and a life expectancy at birth of 77.5 years. The statistics and life tables for the general population were obtained from vital statistics published by the Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan (available online at http://www.moi.gov.tw/W3/stat/). The methodologic details have been described elsewhere.[3,18-22] To facilitate the computation, we developed a software program MC-QAS, which was built in the R and S-PLUS 2000 (MathSoft Inc., Cambridge, MA, USA) environment; it can be freely downloaded from http://www.stat.sinica.edu.tw/jshwang (released in December 2004). The standard error of the survival estimate was obtained using a bootstrap method.[23] Life expectancy was estimated by

extrapolating the survival curves to 50 years after the diagnosis of HIV infection.[3]

### *Quality of life data*

Quality of life data from HIV-positive patients during the HAART era in Taiwan was obtained from a cross-sectional survey of 224 patients in 2000–2001. Health profiles were measured using the abbreviated version of the World Health Organization Quality of Life Instrument (WHO-QOL-BREF),[24,25] and health utility was assessed using standard gamble method.[26] Part of the results using WHOQOL-BREF have been reviewed and published.[25] The domain scores were expressed as a percentage of the highest possible scores. To analyze the temporal trend in the quality of life after the diagnosis of HIV infection, the scores were plotted against the interval between the diagnosis of HIV infection and the time of the survey. The kernel type smoother with a bandwidth of 0.1 was used to estimate the mean quality of life over time. As there were no data on the quality of life in HIV-infected patients in the pre-HAART era in Taiwan, we used a conservative best-case analysis and assumed it to be the same as that of the HAART era.

### *Quality-adjusted survival*

Quality-adjusted survival was defined by the integration of survival and quality of life using the following formula:[18,19]

$$E(QAS_{\lceil} x_i) = \int_0^{\infty} E(q(t_{\lceil} x_i)) S(t_{\lceil} x_i)\, dt$$

where $E(QAS_{\lceil} x_i)$ is the expected value of quality-adjusted survival of patient population $x_i$, $E(q(t_{\lceil} x_i))$ is the expected health utility of patient population $x_i$, $S(t_{\lceil} x_i)$ is the survival function of patient population $x_i$, and $x_i$ is the patient population either during the pre-HAART era or the HAART era.

The unit of $E(QAS_{\lceil} x_i)$ is the quality-adjusted life year (QALY). The quality-adjusted life expectancy (QALE) after the diagnosis of HIV infection was calculated by the integration of life expectancy and temporal trend of health utility.

### *Cost of antiretroviral therapy*

The medication cost of HAART per patient per year was calculated by dividing the total national expenditure on HAART with the number of HAART users in the year 2000. Because no data were available for the cost of antiretroviral therapy in the pre-HAART era in Taiwan, we assumed that the cost of single nucleotide reverse transcription inhibitor (NRTI) therapy commonly used in the pre-HAART era in Taiwan was 1/6 that of a HAART regimen using 2 NRTIs +1 protease inhibitor, according to the reported ratio of wholesale drug prices in the United States (US$2500 per patient per year for the nucleoside analogs; US$8000 per patient per year for one of the protease inhibitors).[7,8]

Because the above-stated HAART cost data from the NHI was cross-sectional, we reconstructed the longitudinal average cumulative cost by the following method. The average medication cost per patient in the $n^{th}$ year after the diagnosis was estimated by multiplying unit medication cost per patient per year with the average of probabilities of survival at the beginning and at the end of the $n^{th}$ year. Since 2002, the practice of initiating HAART in asymptomatic HIV-infected patients has changed to the new criteria of CD4 count < 350/μL or peripheral blood HIV-RNA level > 55,000 copies/mL.[4,5] We therefore assumed that, on average, no HAART was needed in the first 2 years after diagnosis for HIV-positive patients without initial presentation of AIDS-defining illnesses.[3] The cumulative cost was adjusted by a 3% annual discount rate.

### *Incremental cost-effectiveness ratio*

The incremental cost-effectiveness ratio of HAART was calculated by the following formula:

Incremental cost per LY or QALY gained= (Estimated lifetime cost of antiretroviral drugs per patient in the HAART era – Estimated lifetime cost of antiretroviral drugs per patient during the pre-HAART era)/(Estimated mean lifetime survival or mean quality-adjusted survival in the HAART era – Estimated mean lifetime survival or mean quality-adjusted survival during the pre-HAART era).

*Sensitivity analysis*

Due to uncertainties in the estimation of long-term survival time after diagnosis of HIV-infected patients in the HAART era, we conducted sensitivity analysis on survival estimates to see whether the length of survival time had a significant effect on the incremental cost-effectiveness ratio.

## Results

*HAART-associated survival improvements*

A dramatic improvement in patients' survival was observed during the HAART era compared with the pre-HAART era. The Kaplan–Meier survival curves of patients presenting with AIDS (AIDS group) during the pre-HAART era ($n=259$) and the HAART era ($n=718$) are shown in Figure 1A, and those of patients initially without AIDS-defining illness (non-AIDS group) during the pre-HAART era ($n=997$) and the HAART era ($n=2633$) are shown in Figure 1B. The estimated lifetime survival curves are shown in Figure 2. In the AIDS group, the life expectancy (mean survival time) after the diagnosis of HIV infection increased from $1.47\pm1.70$ years (mean ± standard error) during the pre-HAART era to $10.61\pm3.15$ years during the HAART era; in the non-AIDS group, the corresponding increase was from $10.45\pm2.16$ years to $21.53\pm5.72$ years during the HAART era (Table).

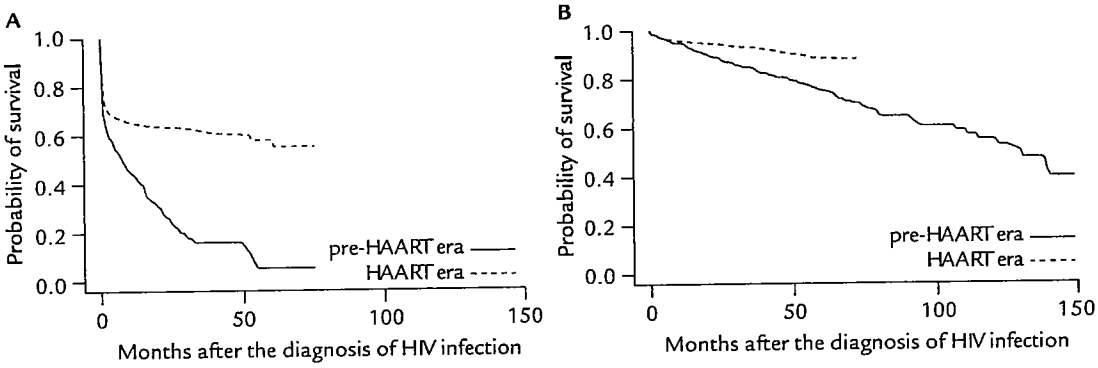


**Figure 1.** Observed survival curves for HIV-positive patients during the pre-HAART era (April 1, 1984 to March 31, 1997) and the HAART era (May 1, 1997 to April 30, 2003): (A) AIDS group ($n=259$ *vs.* 718); (B) non-AIDS group ($n=997$ *vs.* 2633).

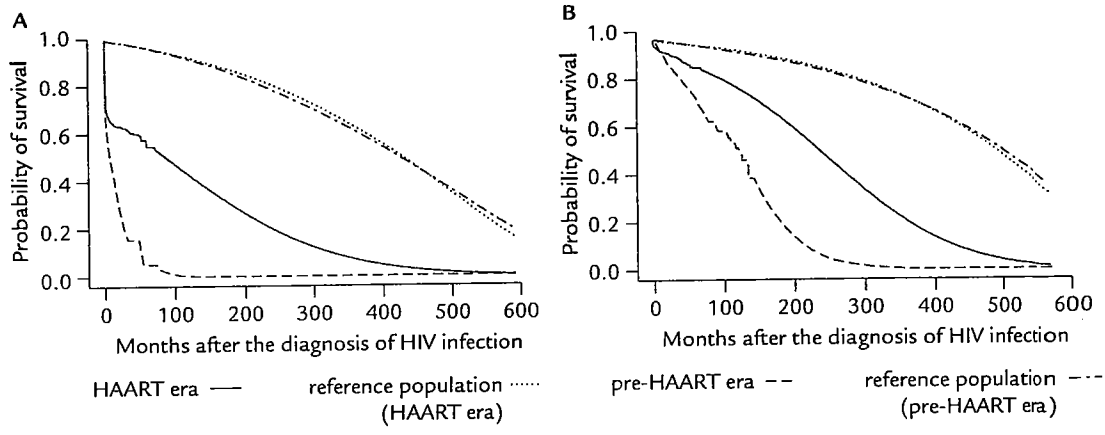


**Figure 2.** Projected lifetime survival curves for HIV-positive patients during the pre-HAART and HAART eras: (A) AIDS group; (B) non-AIDS group.

*Estimation of QALE gained after HAART*

Figure 3 shows the temporal trend in health profiles and health utility after the diagnosis of HIV infection, calculated from cross-sectional data from a total of 224 patients including 63 AIDS patients (22 diagnosed during the pre-HAART era) and 161 non-AIDS patients (58 diagnosed during the pre-HAART era). The longest follow-up

**Table.** Cost and cost-effectiveness of highly active antiretroviral therapy (HAART)

| | HAART era | | Pre-HAART era | |
|---|---|---|---|---|
| | AIDS group | Non-AIDS group | AIDS group | Non-AIDS group |
| Estimated mean ± SEM survival time, year | 10.61 ± 3.15 | 21.53 ± 5.72 | 1.47 ± 1.70 | 10.45 ± 2.16 |
| Estimated mean ± SEM QALE, QALY | 7.75 ± 2.30 | 14.64 ± 3.89 | 1.07 ± 1.24 | 7.11 ± 1.47 |
| Mean lifetime cost of ART per patient (NT$) | 1,658,913 | 2,744,176 | 46,246 | 238,370 |
| Incremental cost per LY gained (NT$) | 176,441 | 226,156 | – | – |
| Incremental cost per QALY gained (NT$) | 241,700 | 332,582 | – | – |

*SEM = standard error of the mean; QALE = quality-adjusted life expectancy; QALY = quality-adjusted life-year; ART = antiretroviral therapy; LY = life-year.*

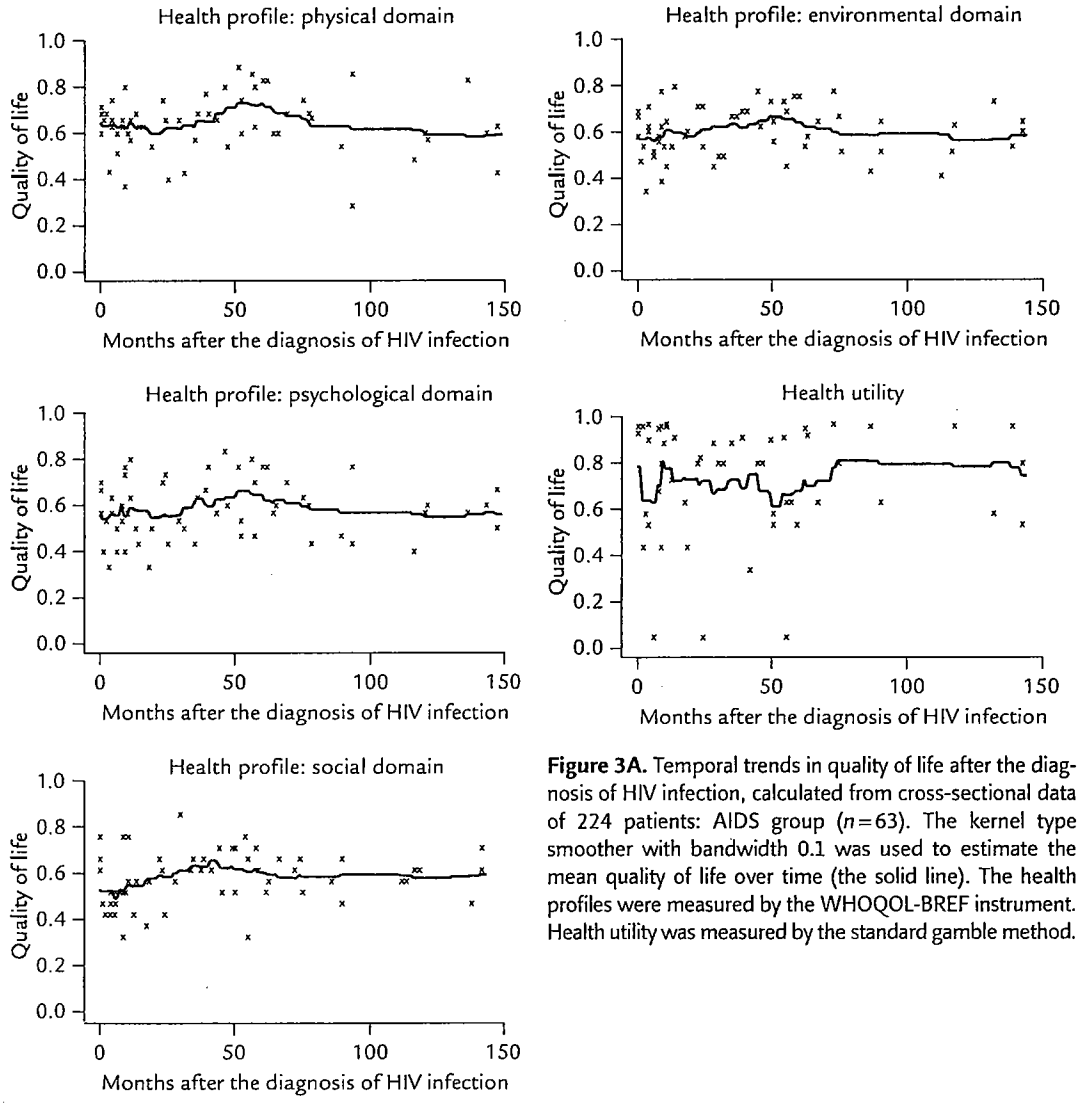


**Figure 3A.** Temporal trends in quality of life after the diagnosis of HIV infection, calculated from cross-sectional data of 224 patients: AIDS group ($n=63$). The kernel type smoother with bandwidth 0.1 was used to estimate the mean quality of life over time (the solid line). The health profiles were measured by the WHOQOL-BREF instrument. Health utility was measured by the standard gamble method.

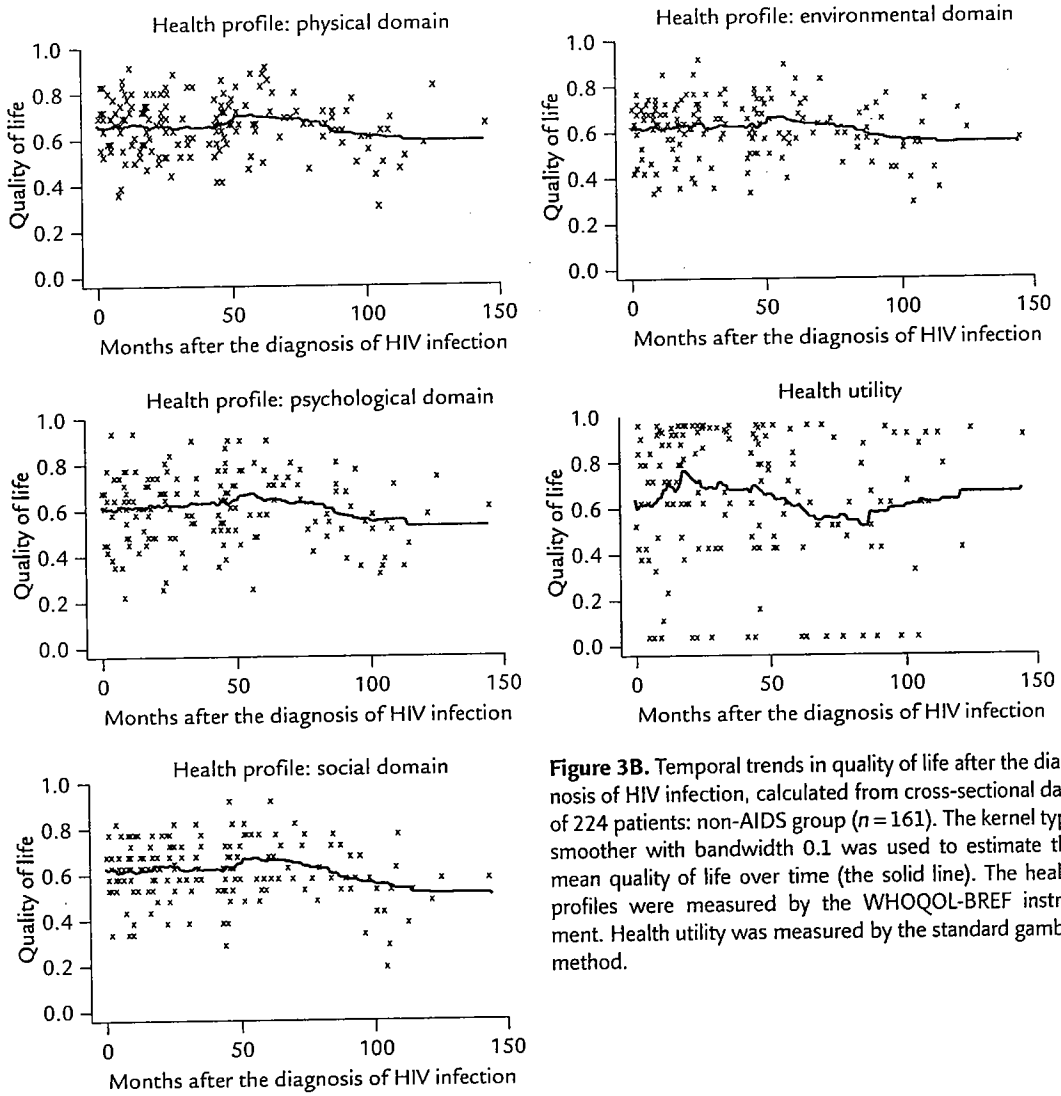


**Figure 3B.** Temporal trends in quality of life after the diagnosis of HIV infection, calculated from cross-sectional data of 224 patients: non-AIDS group ($n = 161$). The kernel type smoother with bandwidth 0.1 was used to estimate the mean quality of life over time (the solid line). The health profiles were measured by the WHOQOL-BREF instrument. Health utility was measured by the standard gamble method.

time after diagnosis among these 224 patients was 12.25 years. Both the AIDS and non-AIDS groups showed no temporal trend of decrease in either health utility or any health profile over the follow-up period (Figure 3). We therefore applied a constant value for health utility in the QALE estimation. The QALE of AIDS patients after diagnosis increased from 1.07±1.2 QALY to 7.75±2.30 QALY, while that of non-AIDS patients increased from 7.11±1.47 QALY to 14.6±3.89 QALY (Table).

### *Cost of antiretroviral therapy*

In 2000 in Taiwan, the average annual NHI expenditure on HAART per HIV-positive patient receiving HAART was NT$210,018 (US$6177 at an exchange rate of 34.0 NT$/US$). There was no change in the price of HAART from 2000 to 2004. Based on the assumptions of a stable price for HAART afterwards, and an annual discount rate of 3%, the cumulative cost of lifetime HAART was estimated to be NT$1,658,913 per patient in the AIDS group, and NT$2,744,176 per patient in the non-AIDS group. The annual cost of antiretroviral therapy during the pre-HAART era was estimated to be NT$35,003 per patient. The cumulative cost of lifetime antiretroviral therapy during the pre-HAART era was estimated to be NT$46,246 and NT$238,370 in the AIDS and non-AIDS groups, respectively.

*Incremental cost for each LY and QALY gained*

The incremental costs are shown in the Table. For the AIDS group, the cost was NT$176,441 (US$5189) per LY gained and NT$241,700 (US$7109) per QALY gained. For the non-AIDS group, the corresponding costs were NT$226,156 (US$6652) and NT$332,582 (US$9782), respectively.

*Sensitivity analysis*

Uncertainty in estimated survival time in the HAART era has a minimal effect on the incremental cost-effectiveness ratio. A variation within one standard error of the mean in estimated survival time in the HAART era resulted in a range of incremental cost-effectiveness ratio from NT$159,747 (US$4698) to NT$210,691 (US$6197) per LY gained for the AIDS group. Similarly, a variation within one standard error of the mean in estimated survival time in the HAART era resulted in a range of incremental cost-effectiveness ratio from NT$187,053 (US$5502) to NT$348,716 (US$10,256) per LY gained for the non-AIDS group.

## Discussion

Our analyses showed that the incremental cost-effectiveness ratio of HAART for HIV infection was NT$176,441–226,156 (US$5189–6652) per LY gained and NT$241,700–332,582 (US$7109–9782) per QALY gained, depending on the stage of HIV diseases. Although there has been no objective cut-off value in the interpretation of the results of cost-effectiveness, most authorities have agreed that the threshold for cost-effectiveness is somewhere between US$20,000/QALY and US$100,000/QALY, with thresholds of US$50,000–60,000/QALY frequently proposed in other developed countries.[27–31] An incremental cost-effectiveness ratio of NT$241,700–332,582 (US$7109–9782, at 34.0 NT$/US$) per QALY gained in Taiwan seems well below the lower cut-off value of US$20,000/QALY, or, is much better than those reported from the United States (US$13,000–23,000/QALY)[8] or Canada (US$12,913–14,587/LY).[12]

A major determinant of the cost-effectiveness ratio, of course, is the drug price. We found that the unit cost of HAART per patient per year (NT$210,018 or US$6177 in 2000) in Taiwan was significantly lower than those anticipated from the wholesale price in the United States (US$2500 per patient per year for the nucleoside analogs to US$8000 per patient per year for one of the protease inhibitors in 1998).[7,8] It appeared that Taiwan obtained a reasonable discount during price negotiations. In many parts of the world, however, concerns about access to HAART and market competition have resulted in mass production of less expensive generic drugs and reduction in the prices of many brand-name products.[32–34] Generic antiretroviral drugs may cost only one-tenth of the brand-name products.[33] As a result, South Africa can reach an incremental cost-effectiveness ratio of as low as US$675–1622 per LY gained.[13] In Taiwan, there was no change in the price of HAART from 2000 to 2004 because the efficacy of generic drugs remained uncertain during this period and brand-name products were therefore used to ensure the quality and effectiveness of antiretroviral agents. If the quality of generic drugs can be demonstrated, introduction of these less expensive products to replace brand-name ones may significantly reduce the financial burden of providing HAART. The cost reduction of antiretroviral agents would likely further improve the cost-effectiveness profile of HAART in the future.

There are several limitations and underestimations in the present assessment of the cost-effectiveness of HAART. First, since quality of life data were unavailable during the pre-HAART era, we used a conservative best-case analysis, assuming that the quality of life in HIV-infected patients was the same between the pre-HAART and HAART eras. Several studies, however, have shown that treatment with HAART actually improved the overall quality of life.[35,36] Therefore, the actual QALY gain during the HAART era might have been better than our estimates. Second, in

the present study, we did not consider the costs of medical care other than HAART, the intangible cost of fear and suffering, and the indirect cost to patients and their families. Because the medical costs other than HAART included at least the use of ventilator for pneumonia and various expensive antimicrobial agents for opportunistic infections, which depended on the standard of clinical care and have been rapidly evolving, it is difficult to objectively model a longitudinal trend in cost by analyzing available cross-sectional data. It is also difficult to quantify the intangible cost and indirect cost longitudinally. Since many studies consistently showed that HAART decreased the risks of opportunistic infections and associated hospitalization,[2,4–6,37] we would anticipate an adjustment in a favorable direction if we consider the cost of medical care other than HAART. In addition, HAART also provides renewed health, more employment[38] and hope for the future[39] for HIV-infected patients. Therefore, there will be a further favorable adjustment.

From an epidemiologic viewpoint, the universal availability of HAART also greatly benefit people who are not yet infected. HAART profoundly suppresses HIV-RNA levels in blood and other body fluids and therefore decreases the infectiousness of HIV-infected patients,[1,2] which probably slowed down the spread of the HIV epidemic in Taiwan during 1997–2002 and was demonstrated in our previous study.[1] Thus, a universal HAART policy will contribute additional LY gain through averting new HIV cases. Although HAART alone cannot eradicate the HIV epidemic and must be accompanied by effective HIV-related risk-reduction intervention,[40] the ethical acceptability and the willingness to participate in voluntary screening and counseling programs actually depend on the availability of HAART.[41,42] If these factors are also considered, the cost-effectiveness ratio of HAART would be even better than the current estimates.

In conclusion, our analyses show that HAART for HIV infection is cost-effective, with an incremental cost-effectiveness ratio of NT$176,441–226,156 (US$5189–6652) per LY gained and NT$241,700–332,582 (US$7109–9782) per QALY gained. If we consider the cost of medical care other than HAART, the intangible cost, the indirect cost to patients and their families, the reduction of HIV transmission, and the facilitation of HIV screening and risk reduction programs, the cost-effectiveness ratio would be even better. We therefore recommend that providing free access to HAART to all HIV-infected citizens should be continued.

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**Original Article**

# Osteonecrosis in Patients with Human Immunodeficiency Virus Type 1 Infection in Taiwan

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**SUMMARY**: Osteonecrosis, a disabling complication associated with antiretroviral therapy (ART) and human immunodeficiency virus (HIV) infection, has rarely been reported in an Asian population. After an observation of 3,250 person-years (PY), 11 of 967 (1.1%) HIV-infected patients at a median age of 34 years developed osteonecrosis involving the hip joints (incidence, 3.4 per 1,000 PY). Their median CD4+ lymphocyte count had increased from 35 cells/$\mu$L at the diagnosis of HIV infection to 297 cells/$\mu$L at the diagnosis of osteonecrosis. The crude rate of osteonecrosis increased from 0% in patients without exposure to ART to 2.6 and 1.7% in patients with exposure to nucleoside reverse transcriptase inhibitors (NRTIs) and who had undergone highly active antiretroviral therapy (HAART) for 5 years or longer, respectively ($P$ = 0.18 and 0.09, respectively). Among the patients receiving HAART, the estimated incidence of osteonecrosis was 4.2 per 1,000 PY. Patients with osteonecrosis had a longer duration of exposure to NRTIs (1,641 versus 1,264 days, $P$ = 0.26) and to HAART (1,603 versus 1,251 days, $P$ = 0.42), a higher serum triglyceride (median, 1,130 versus 351 mg/dl; $P$ = 0.09), and a higher proportion of lipodystrophy (81.8 versus 15.0%, $P$ < 0.0001). Our report suggests that osteonecrosis is a rare complication in HIV-infected patients with prolonged exposure to ART with resultant metabolic complications.

## INTRODUCTION

Osteonecrosis, also known as avascular necrosis, has been increasingly reported in association with human immunodeficiency virus (HIV) infection (1-3) since the first case report in 1990 (4). In a cross-sectional study, 4.4% of HIV-infected patients had asymptomatic osteonecrosis (5). Its morbidity threatens the quality of life and increases the cost of medical care when highly active antiretroviral therapy (HAART) remarkably prolongs life span of patients with HIV infection. Although osteonecrosis has been a well-known illness in the general population, its prevalence is indeed higher in HIV-infected patients (6).

The pathogenesis of osteonecrosis in HIV-infected patients remains unclear (7), although various hypotheses and predisposing factors such as use of corticosteroids, alcoholism, hyperlipidemia, hypercoagulability, and osteoporosis have been proposed with varying strength of evidence by analysis of case series and control studies (1,5,6,8-10). Almost all of those cases were described among HIV-infected patients in Western countries with earlier and better access to antiretroviral therapy (ART); however, the incidence of and factors associated with osteonecrosis are rarely reported in Asian populations. With the increasing expansion of HAART programs in most Asian countries, osteonecrosis is expected to be an emerging threat to long-term successful management of HIV infection when mortality and morbidity related to HIV infection decrease dramatically. In the present study, we aimed to review cases of osteonecrosis in patients receiving HIV care at a university hospital in Taiwan where free access to HAART was begun in 1997.

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## MATERIALS AND METHODS

**Study population**: Between June 1994 and December 2003, non-hemophiliac HIV-infected patients aged 15 years or greater were consecutively enrolled in an open cohort study to investigate complications related to HIV infection and ART at the National Taiwan University Hospital (NTUH), a major referral hospital for provision of HIV care in Taiwan (11). The medical records of all patients with HIV infection were periodically reviewed to identify patients who were diagnosed as having osteonecrosis. A standardized case record form was used to retrieve data regarding demographics, risk of HIV transmission, baseline and latest CD4+ lymphocyte count and plasma HIV RNA load (PVL), concomitant medical illness, types and duration of ART and HAART, and serum cholesterol and triglyceride levels. Patients with a diagnosis of osteonecrosis within 1 month of enrollment were excluded from analysis.

ART and HAART were introduced into Taiwan in 1988 and 1997, respectively, and all patients with HIV infection were offered free access to HIV care and HAART in designated hospitals around Taiwan. HAART was prescribed as clinically indicated by the following and updated US Department of Health and Human Services guidelines (12).

**Laboratory and radiographic investigations**: Blood biochemistry tests, including cholesterol and triglyceride, CD4+ count and PVL, were determined every 3 to 4 months. PVL

was quantified using the Cobas Amplicor HIV-1 Monitor test (Cobas Amplicor version 1.5; Roche Diagnostics Corp., Indianapolis, Ind., USA) with a lower detection limit of 400 (2.60 $\log_{10}$) copies/mL, and CD4+ count was determined using FACFlow (BD FACS Calibur; Becton Dickinson, San Jose, Calif., USA).

Patients with joint pain were subjected to radiographic examinations after evaluation by the treating physicians, including plain radiography and magnetic resonance imaging (MRI). Bone mineral density (BMD) as determined by dual energy X-ray absorptiometry (DEXA, Hologic QDR-4500A; Hologic, Waltham, Mass., USA) was performed on an as-needed basis. Osteonecrosis was diagnosed by the characteristic radiographic findings on plain joint radiography or MRI interpreted by radiologists blinded to the status of HIV-infected patients, and all of the radiographic examinations were reviewed by one of the co-authors (TTF Shih).

**Definitions**: HAART was defined as the combination of at least three antiretroviral agents containing nucleoside reverse transcriptase inhibitors (NRTIs) plus protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), or triple NRTIs. Lipodystrophy was defined by clinical presentations of peripheral fat wasting (face, arms, buttocks, or legs) or central fat accumulation (abdomen or dorsocervical pad) observed by the treating physicians (13). Weight change without peripheral fat wasting or central adiposity was not classified as lipodystrophy.

**Statistical analysis**: All statistical analyses were performed using SPSS software (version 12.0; SPSS, Inc., Chicago, Ill., USA). Categorical variables were compared using $\chi^2$ or Fisher's exact test whereas non-categorical variables were compared using Wilcoxon's rank-sum test. Point estimation for Poisson distribution was used for estimating the incidence and 95% confidence intervals (CI) of osteonecrosis. Univariate analysis was used to identify the factors associated with osteonecrosis, such as age, sex, risk behavior for HIV transmission, baseline CD4 count and PVL, initial presentation of AIDS-related diseases, and use and duration of ART and HAART. All tests were two-tailed and a $P$ value <0.05 was considered significant. The observation duration of affected patients was estimated from date of enrollment to diagnosis of osteonecrosis, while that of patients without osteonecrosis was estimated from date of enrollment to death, the last follow-up at this hospital and other designated hospitals in Taiwan, or the end of this observational study on 31 December, 2005.

## RESULTS

Over a 9-year study period, 968 patients sought HIV care at the NTUH and 12 patients received a diagnosis of osteonecrosis. One patient who presented to this hospital because of an established diagnosis of HIV infection and osteonecrosis at another hospital was excluded, and therefore 11 patients were enrolled in this study. Demographics, clinical, immunological, and virological characteristics of the 11 patients with osteonecrosis and 956 patients without osteonecrosis are shown in Table 1. Patients with and those without osteonecrosis did not differ in demographics and baseline clinical, immunologic, and virological characteristics. All of the patients with osteonecrosis were males and had depleted CD4+ counts (median, 35 cells/$\mu$l), while 72.7% had AIDS-defining opportunistic illnesses when HIV infection was diagnosed.

Osteonecrosis developed in patients with prolonged exposure to ART and HAART. The median interval between

Table 1. Characteristics of HIV-infected patients with and without osteonecrosis

| Variable | Patients with osteonecrosis | Patients without osteonecrosis | Total | $P$ |
|---|---|---|---|---|
| Patient, no. | 11 | 956 | 967 | |
| Age, median (range) (y) | 34 (30, 47) | 34 (15, 83) | 34 (15, 83) | 0.64 |
| Male, no. (%) | 11 (100) | 884 (92.5) | 895 (92.6) | 0.99 |
| Risk factor, no. (%) | | | | |
| Homosexual/bisexual | 4 (36.4) | 583 (61.0) | 587 (60.7) | 0.24 |
| Heterosexual | 6 (54.6) | 310 (32.4) | 316 (32.7) | |
| Others | 1 (9.1) | 63 (6.6) | 64 (6.6) | |
| AIDS at baseline, no. (%) | 9 (81.8) | 650 (68.9) | 659 (69.0) | 0.52 |
| AIDS-OI at baseline, no. (%) | 8 (72.7) | 535 (56.0) | 543 (56.2) | 0.36 |
| CD4+ lymphocyte count at baseline, median (range), cells/$\mu$l | 35 (3, 710) | 76.5 (0, 1,202) | 73 (0, 1,202) | 0.21 |
| PVL at baseline, median (range) ($\log_{10}$), copies/ml | 4.58 (2.60, 5.78) | 5.19 (2.60, 5.88) | 5.19 (2.60, 5.88) | 0.30 |
| Lipodystrophy, no. (%) | 9 (81.8) | 143 (15.0) | 152 (15.7) | <0.0001 |
| Lipemia > 2 times, no. (%) | 4 (50.0) | 174 (32.2) | 178 (32.5) | 0.28 |
| Peak triglyceride, (range) mg/dl | 1,130 (301, 2,190) | 351 (201, 3,200) | 351 (201, 3,200) | 0.09 |
| Peak cholesterol, (range) mg/dl | 287 (225, 401) | 256.5 (40, 618) | 257 (40, 618) | 0.40 |
| Duration of exposure to NRTI, (range) days | 1,641 (452, 4,631) | 1,264 (0, 5,854) | 1,281 (0, 5,854) | 0.26 |
| Duration of exposure to HAART, (range) days | 1,603 (452, 2,254) | 1,251 (0, 3,533) | 1,261 (0, 3,533) | 0.42 |
| Duration of exposure to PIs, (range) days | 1,056.5 (156, 1,977) | 820 (0, 3,447) | 822.5 (0, 3,447) | 0.55 |
| Total observation duration (person-years) | 46 | 3,204 | 3,250 | 0.12 |

AIDS-OI, AIDS defining opportunistic illness; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PIs, protease inhibitors; PVL, plasma HIV RNA load.

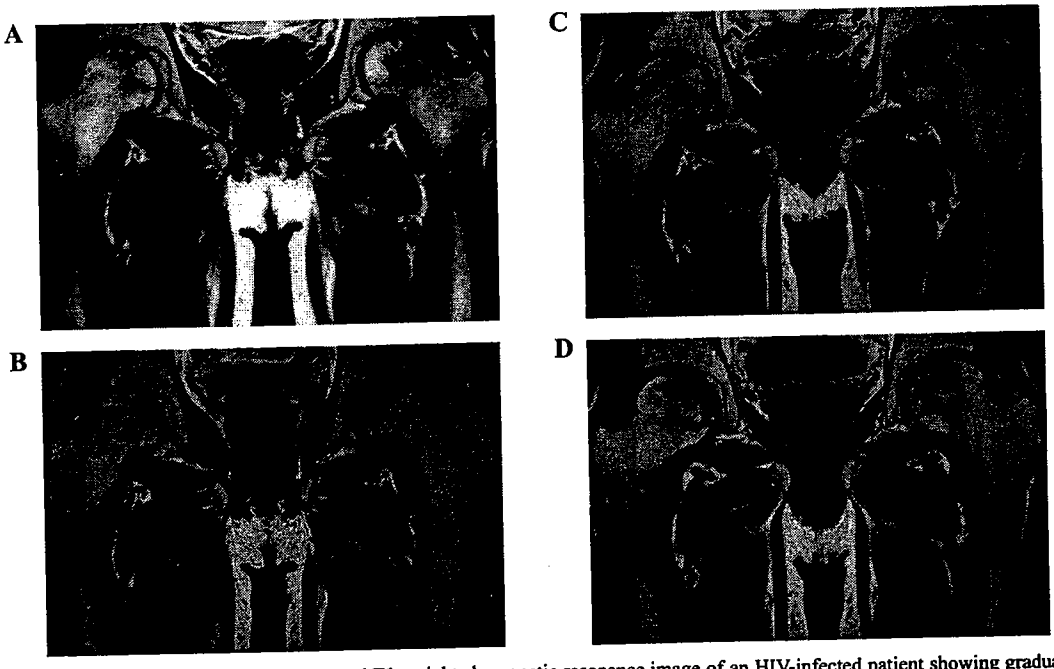


Fig. 1. Follow-up gadolinium-enhanced T1-weighted magnetic resonance image of an HIV-infected patient showing gradual progression of osteonecrosis. (A) Grade II osteonecrosis over the left femoral head and grade III osteonecrosis over the right side were present with geographic interserpinginous lesions bilaterally. (B) In the serial non-enhanced T1-weighted images, osteonecrosis of the left hip joint progressed to a grade III lesion at 20 months after diagnosis. A slow progression was observed at 27 months (C) and 36 months (D) after diagnosis.

initiation of NRTIs, PIs, and HAART and development of osteonecrosis was 1,641 days (range, 452 to 4,631 days), 1,056.5 days (range, 156 to 1,977 days), and 1,603 (range, 452 to 2,254 days), respectively. After HAART, patients with osteonecrosis had a good immunologic response with a median CD4+ count increase of 275 cells/$\mu$l (range, -15 to 925 cells/$\mu$l), from 35 cells/$\mu$l at baseline to 297 cells/$\mu$l (range, 25 to 927) ($P < 0.0001$), with 54.6% of the patients achieving un-detectable PVL at the diagnosis of osteonecrosis. Compared with patients without osteonecrosis, patients with osteonecrosis had higher peak triglyceride levels (1,130 versus 351 mg/dl, $P = 0.09$) and a higher proportion of lipodystrophy (81.8 versus 15.0%, $P < 0.0001$) when osteonecrosis was diagnosed.

The total observation duration of the cohort was 3,250 person-years (PY); therefore, the overall incidence rate of osteonecrosis of the cohort was 3.4 per 1,000 PY (95% CI, 3.2, 3.6 per 1,000 PY). The incidence rate of osteonecrosis in patients exposed to NRTIs and HAART was 4.2 per 1,000 PY (95% CI, 3.9, 4.4 per 1,000 PY) and 4.2 per 1,000 PY (95% CI, 4.0, 4.5 per 1,000 PY), respectively. Longer duration of exposure to NRTIs and HAART was associated with increased risk of osteonecrosis, which increased from 0% in those without ever exposure to NRTIs and HAART to 2.6 and 1.7% in those with exposure to NRTIs and HAART for 5 years or greater, respectively ($P = 0.18$ and $P = 0.09$, respectively).

Of the 11 patients diagnosed with osteonecrosis, 10 had involvement of 20 hip joints with severity grading of 3 to 4, and one had involvement of bilateral knee joints with a severity grading of 3. All of the patients underwent assessment of BMD and their median BMD was 0.9165 g/cm$^2$ (range, 0.6090 to 1.107 g/cm$^2$) and median T-score was −0.81 (range, −2.93 to 0.69); 3 were diagnosed with osteoporosis and 3 osteopenia. Bilateral hip joint replacement was performed in 4 patients and unilateral hip joint replacement in 1 patient because of progression of pain and limitation of ambulation. Eight patients received alendronate when it was found to be of benefit in delaying progression of osteonecrosis (14); however, 3 patients finally underwent bilateral hip joint replacement because of progression of symptoms, while three others experienced persistent symptoms but declined the suggestion of surgical intervention and 2 patients continued to receive alendronate with stable disease status clinically and radiographically by MRI (Fig. 1A-D).

## DISCUSSION

HIV-infected patients were reported to have a 100-fold greater risk of developing osteonecrosis than the general population (15), although the incidence of osteonecrosis is likely underestimated because only patients with disabling joint symptoms underwent MRI. In a cross-sectional survey of 339 asymptomatic patients, up to 4.4% of osteonecrosis was documented by MRI (5). The incidence of MRI-diagnosed osteonecrosis (0.65 cases per 100 PY) was found to be greater than the incidence of osteonecrosis that is symptomatic (0.26 cases per 100 PY) (15). The annual incidence of symptomatic osteonecrosis in HIV-infected patients was reported to be 0.080-1.33% (2,7,9). The differences of incidence rates among the published studies may vary with study population, co-morbidity, and duration of HIV infection and exposure to ART. For example, the estimated incidence rate of osteonecrosis in our population (4.0 per 1,000 PY) is higher than that of a French study (0.45 per 1,000 PY) (1), which may be related to the fact that our enrolled patients had a lower CD4+ count (73 versus 280 cells/$\mu$L), a lower proportion of them were intravenous drug abusers (6.6 versus 19.4%); a higher proportion had AIDS (69 versus 20.5%), and our patients had a longer duration of exposure to ART

(40 months versus 3.9 months).

Although no definite etiology of osteonecrosis is identified, various risk factors have been proposed, including alcohol consumption (10), steroids exposure (5,10), dyslipidemia (16), use of lipid-lowering agents (5), testosterone exposure (5), body-building (5), antiphospholipid antibody (5), HIV infection (1), and HAART (1,17). HIV infection itself, through increased antiphospholipid antibody production (16), may promote intraosseous platelet aggregation resulting in bone necrosis (17,18). The immunological response to treatment, which may be evaluated by an increase in CD4+ cell counts from nadir, was found to be associated with osteonecrosis (8).

Whether ART is a direct cause of osteonecrosis has been debated. The adjusted relative risk was reported to increase from 2.6 among patients who had been treated with ART for less than 12 months to 9.6 among those treated for more than 60 months (1). In our study, longer duration of exposure to NRTIs and HAART appeared to be associated with increased risk of osteonecrosis, which increased from 0% in those with no exposure to NRTI and HAART to 2.6 and 1.7% in those with exposure to NRTIs and HAART for 5 years or greater, respectively ($P = 0.18$ and $P = 0.09$, respectively). PIs have been suggested as a link to osteonecrosis (17,19,20), although some studies disagree with this suggestion (1,3,5,7,9,10,21). Although each antiretroviral agent has been examined for the correlation with osteonecrosis (10), it is difficult to attribute the effect to any single class of antiretroviral agents because combination therapy is the standard of care and a change in therapies is common.

HAART-related dyslipidemia may accelerate the atherosclerotic process and occlude the bone-feeding vessels, which may contribute to avascular necrosis (16,18,22). However, dyslipidemia may be either a cause of osteonecrosis, or simply a reflection of prolonged treatment and duration of HIV infection. In our study, patients with osteonecrosis had a significantly higher incidence of lipodystrophy (84.6 versus 14.8%, $P < 0.0001$). Lawson-Ayayi et al. also described an increased risk of osteonecrosis in patients with lipodystrophy (adjusted matched OR, 64.06, $P = 0.09$) (10). Lipodystrophy has been estimated to be 20-84% in HIV-infected patients (23-25), while 20-50% of patients were estimated to develop lipodystrophy within 2 years of HAART exposure (24,25). Therefore, increased risk of osteonecrosis in patients exposed to a longer duration of HAART implies not only the immunologic and metabolic effects of HAART on osteonecrosis, but also the duration of HIV infection. Although no effective treatment has been developed to date (26), lipodystrophy may potentially be a marker for clinicians to increase their vigilance of osteonecrosis.

The causal relationship of lipodystrophy and osteonecrosis remains unclear. In HIV-infected patients with lipodystrophy, Jan et al. (27) reported lower leptin mRNA levels, higher interleukin (IL)-6 levels, and higher tumor necrosis factor (TNF)-$\alpha$ mRNA levels. Leptin, an adipokine, was reported to be associated with diminished bone mineral density (28,29). Peripheral leptin administration in obese leptin-resistant mice was reported to have a stimulating effect on bone growth (29,30). Sighinolfi et al. (19) suggested that HIV itself, through increased production of IL-6 and TNF-$\alpha$, could be associated with osteonecrosis, which imply that HIV infection, with a resultant increase in the production of proinflammatory cytokines, may be associated with both lipodystrophy and osteonecrosis.

Adiponectin, another adipocytokine, was reported to be lower in serum and adipose tissue in lipodystrophic, HIV-infected patients receiving HAART than in those without lipodystrophy (31). Decreased production of adiponectin in lipoatrophic adipose tissue has been proposed to be a possible cause of insulin resistance and higher triglyceride levels (31). Whether adiponectin is associated with osteonecrosis remains unknown. However, since hypertriglyceridemia had been suggested to be a risk factor of osteonecrosis (1), adiponectin might play an indirect role in the development of osteonecrosis.

The clinical course of HIV-related osteonecrosis is highly variable. In one recent study, more than half of the patients remained clinically stable while one-third worsened (6). In comparison with asymptomatic patients, a more rapid progression to total hip replacement in symptomatic patients was observed (15). Half of the patients with hip involvement required joint replacement at 2 years after the first osteonecrosis episode (6). In a follow-up study of 339 patients, 59% of 22 symptomatic patients underwent total hip replacement at a median of 10 months after diagnosis (15), especially those involving more than 50% of the hip joint (15). The majority of patients that did not undergo operation had persistent pain requiring long-term analgesics, and functional limitation was reported in 78% of them. Neither resolution nor improvement was found on MRI (15).

Allison et al. proposed an algorithm for evaluation and management of osteonecrosis in HIV-infected patients (7). Currently, the treatment of osteonecrosis is based on symptom relief (26). Although beneficial effect has been demonstrated in HIV-uninfected patients with osteonecrosis receiving bisphposphonate therapy (14), its effectiveness in HIV-infected patients remains to be studied. Generally, the orthopedic procedure is found to be safe for these patients (6). In a 2.3-year follow-up of 40 HIV patients with osteonecrosis who underwent surgical intervention, all patients retained well-functioning arthroplastic hips except for one case of staphylococcal infection, which was related to the patient's persistent intravenous drug abuse (32).

There are several limitations in our study. The incidence rate of osteonecrosis was underestimated because osteonecrosis was diagnosed only in patients with joint symptoms for which MRI was performed. The small case number of patients with osteonecrosis precluded us from performing multivariate analysis to exclude possible confounders or identify interactions. Some risk factors, including antiphospholipid antibodies, were lacking in most cases in this retrospective analysis.

In conclusion, the incidence of osteonecrosis remains low in ethnic Chinese patients with HIV infection who have had prolonged exposure to HAART. The presence of lipodystrophy, a clinical clue of prolonged HAART exposure and HIV infection, may serve as a potential marker for early workup for osteonecrosis in symptomatic patients.

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# Aberrant Induction of Regulatory Activity of $CD4^+CD25^+$ T Cells by Dendritic Cells in HIV-Infected Persons With Amebic Liver Abscess

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**Summary:** To know why HIV-1–infected persons are particularly susceptible to amebic liver abscess (ALA), we investigated the role of $CD4^+CD25^+$ T cells in the susceptibility of HIV-1–infected persons to this disease. Herein we show, in early stage HIV-1–infected subjects, that $CD4^+$ T-cell responses to *Entamoeba histolytica* antigen (EhAg) were selectively impaired, especially in those with ALA. EhAg-specific $CD4^+$ T-cell responses were normalized by depletion of $CD4^+CD25^+$ cells or by addition of anti-cytotoxic T lymphocyte antigen 4 (CTLA4) antibody. Regulatory activity of $CD4^+CD25^+$ T cells to suppress the EhAg-specific $CD4^+$ T-cell response could be induced by EhAg-primed dendritic cells (DCs) in HIV-1–infected subjects, especially in those with ALA, but not in healthy controls. Exogenous Tat-incubated DCs derived from HIV-negative subjects also could upregulate CTLA4 expression on autologous $CD4^+CD25^+$ T cells and selectively suppress the EhAg-specific $CD4^+$ T-cell response. The results imply an interaction of the two pathogens: HIV-1, perhaps through the effect of Tat on DCs, may upregulate EhAg-specific regulatory T-cell activity to suppress T-cell response to *E. histolytica*, thus increasing the susceptibility to invasive amebiasis in even early-stage HIV-1–infected persons.

**Key Words:** amebic liver abscess, dendritic cell, cytotoxic T lymphocyte antigen 4 (CTLA4) regulatory T cells

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Amebic liver abscess (ALA) is the most common extra-intestinal manifestation of invasive infection by *Entamoeba histolytica*.[1] Despite being rarely reported in persons with HIV-1 infection in Western countries,[2] invasive amebiasis has been reported as an emerging parasitic infection with increasing importance in HIV-1–infected persons in Asia, although the incidence of invasive amebiasis in general population is decreasing due to improvement in environmental and public hygiene.[3–5] In the 5 years from 2000 to 2004, 88% of cases of ALA diagnosed in our hospital had been demonstrated to have co-existing HIV-1 infection (unpublished data). In contrast to other opportunistic infections that often occur during the later stages of HIV-1 infection, ALA commonly occurs at an earlier stage and may be the initial presentation of HIV-1 infection, and the disease severity of invasive amebiasis is not related to $CD4^+$ T-cell count.[3,5,6] Although the high prevalence of intestinal colonization with *E. histolytica* in HIV-1–infected persons, especially in homosexuals, has been documented,[6] why HIV-1–infected persons, even at early stage, are susceptible to invasive amebiasis, especially ALA, remains unclear. Because ALA is rarely reported in homosexuals without HIV-1 infection, and because the majority of ALA patients also have some kinds of immune impairment,[1,7] we hypothesized that the host defense against *E. histolytica* may be impaired even at the early stages of HIV-1 infection, before any marked depletion of $CD4^+$ T cells.

The immune response to pathogens is highly regulated to protect a host from invasion of pathogens and to avoid immune-mediated damage to a host. A minor population of $CD4^+$ T cells that constitutively express the IL-2 receptor (IL-2R) α chain (CD25) have been identified as natural regulatory T cells and have potent suppression properties (see reviews in references 8 and 9). Regulatory T cells may not only play a key role in the maintenance of immune tolerance, the control of autoreactive T cells, but may also downregulate pathogen-specific immune responses. Human studies have addressed the possible role of regulatory T cells in the immunopathogenesis of some chronic infections, such as hepatitis C virus (HCV),[10] *Mycobacterium tuberculosis*,[11] and *Helicobacter pylori*.[12] Recent studies also showed that HIV-1 infection or HIV-1–related proteins may induce suppressive activity of regulatory T cells to suppress antiviral immune response to HIV-1, cytomegalovirus (CMV), and vaccinia virus in vivo or in vitro.[13–15] Thus we hypothesize when the HIV-1–infected hosts encounter the invasion of *E. histolytica*, the suppressive activity of regulatory T cells may be induced to suppress *E. histolytica*-specific T-cell reactivity, then resulting in the increased susceptibility to invasive amebiasis in persons with early stage of HIV-1 infection.

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## PATIENTS AND METHODS

### Subjects

Three subject groups were enrolled: 16 HIV-1–negative healthy volunteers ($HIV^-$), 13 early-stage asymptomatic HIV-1–infected subjects ($HIV^+ALA^-$), and 8 early-stage HIV-1–infected subjects diagnosed with ALA and without other concomitant infections ($HIV^+ALA^+$). $HIV^+ALA^+$ subjects were enrolled in this study only after their ALA had recovered completely. Ages were similar in the three groups (Table 1). All subjects are males and positive for antiamebic antibody, which was defined as indirect hemagglutination (IHA) assay titer over 1:32 (Cellognostics, Boehringer Diagnostics GmbH, Marburg, Germany), indicating past exposure to *E. histolytica*. In our pilot study, if the subjects had not been exposed to *E. histolytica* before (that is, they were seronegative for antiamebic antibody), the EhAg-specific T-cell response was nearly undetectable. This study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects.

### Case Definition

ALA was defined if image studies demonstrated the presence of intrahepatic abscesses and if at least two of the following criteria were fulfilled: (1) histological evidence (erythrophagocytic trophozoites identified in aspirates or biopsy tissue); (2) serologic evidence (initial or following IHA titer over 1:128); or (3) clinical evidence (good response to metronidazole treatment and the bacterial cultures of blood and abscess aspirates showing negative results).

### Antigens/Proteins and Mitogens

*E. histolytica* antigen (EhAg) used in this study is a phosphate-buffered saline (PBS) extract of *E. histolytica* trophozoites (Antibody System, TX). Briefly, trophozoites of *E. histolytica* were grown in cell-free axenic culture to log phase, washed, harvested by centrifugation in sterile PBS, and sonicated on ice for 10-second bursts at 100 W. The sonicate was centrifuged at 10,000 rpm for 30 minutes at 5°C. The supernatant was retained as PBS extract of *E. histolytica* and stored at −85°C until used (at a concentration of 10 μL/mL). Cytomegalovirus (CMV) antigen was used for a recall antigen (1:8 diluted solution from a commercially prepared lysate of CMV-infected fibroblasts; BioWhittaker, Walkersville, MD) at a concentration of 10 μL/mL. Recombinant biologically active HIV-1 Tat protein was obtained from ImmunoDiagnostics (Woburn, MA). The full-length Tat (2 exons, 86 amino acid) was produced in an *Escherichia coli* expression system with >99% purity and <0.01 EU/mg endotoxin. HIV-1 p24 and gp120 were purchased from Research Diagnostics (Flanders, NJ). Mitogens used in this study include phorbol 12-myristate 13-acetate (PMA, 25 ng/mL, Sigma, Saint Louis, MO) and anti-CD3 monoclonal antibodies (mAb) (purified HIT3a, mouse IgG2a, 2 μg/mL, PharMingen, San Diego, CA).

### Preparation of Monocyte-Derived Dendritic Cells (DCs)

Peripheral blood mononuclear cells (PBMC) were prepared from heparinized blood and isolated by differential centrifugation over endotoxin-free Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden). Monocytes were negatively isolated from PBMC using Monocyte Negative Isolation™ kit (Dynal, Oslo, Norway). Negatively isolated monocytes were suspended in complete RPMI (Gibco, Grand Island, NY) supplemented with penicillin/streptomycin, 10% fetal calf serum (Gibco), recombinant human IL-4 (1000 U/mL, PharMingen), and GM-CSF (50 ng/mL, PharMingen) in 24-well plates (1 mL/well) with a cell concentration of $8 \times 10^5$/mL, in triplicate. These monocytes would show the phenotype of immature DCs after 6 days of culture demonstrated by positive staining with mAbs to CD11c (phycoerythrin (PE)-conjugated B-ly6, mouse IgG1, PharMingen), CD80 (B7.1, fluorescein isothiocyanate (FITC)-conjugated L307.4, mouse IgG1), and CD86 (B7.2, FITC-conjugated IT2.2, mouse IgG2b) by using a FACScan cytometer and CellQuest software (Becton Dickinson, San Jose, CA). The immature DCs would be primed with antigens (EhAg, CMV Ag) or soluble CD40 ligand (recombinant human soluble CD40L, 2 μg/mL; Research Diagnostics, Inc., Flanders, NJ) for another 24 hours to achieve maturation state (confirmed by staining with mAb to CD83 (FITC-conjugated HB15a, mouse IgG2b, Immunotech, Marseille, France). The optimal doses of EhAg, CMV Ag, and soluble CD40L had been titrated to achieve similar maturation state of DCs in terms of the mean fluorescein intensity of CD80 and CD86 and frequencies of CD83 expression (detail data not shown) to avoid the impact of maturation status of DCs on regulatory cell induction.

### Cell Isolation

$CD4^+$ T cells were positively isolated from PBMC and detached from beads by an immunomagnetic method (CD4 Positive Isolation Kit; Dynabeads® plus DETACHaBEAD®, Dynal) according to the instructions of the manufacturer. The resulting purity was >99%, and viability was >95%. In some

TABLE 1. Demographic Features of Enrolled Subjects*

| | $HIV^-$ (n = 16) | $HIV^+/ALA^-$ (n = 13) | $HIV^+/ALA^+$ (n = 8) | *P* Value† |
|---|---|---|---|---|
| Median age (range), in years | 32 (25–38) | 31 (20–37) | 30 (22–41) | 0.53 |
| Median $CD4^+$ cell count (range), per μL | NA | 610 (432–785) | 623 (356–763) | 0.48 |
| Median plasma HIV RNA (range), in copies/mL | NA | 85,000 (15,000–163,000) | 63,000 (18,000–213,000) | 0.76 |
| Opportunistic infection other than ALA | No | No | No | |

*$HIV^-$, HIV-1–negative healthy volunteers; $HIV^+/ALA^-$, asymptomatic early-stage HIV-1–infected subjects; $HIV^+/ALA^+$, early-stage HIV-1–infected subjects diagnosed with ALA and without other concomitant infections.

†*P* values for comparison between $HIV^+ALA^-$ and $HIV^+ALA^+$ subjects.

experiments, purified $CD4^+$ T cells were used for positive or negative selection of $CD4^+CD25^+$ T cells (CD25 Isolation Kit; Dynabeads®, Dynal). $CD4^+$ or $CD25^+$ cells were identified by staining with anti-CD4 (CyChrome-conjugated RPA-T4, mouse IgG1, PharMingen) or anti-CD25 (FITC-conjugated M-A251, mouse IgG1, PharMingen), respectively. In the ELISPOT experiments, $CD8^+$ T cells were depleted from PBMC, also by an immunomagnetic method (CD8 Isolation Kit; Dynabeads®, Dynal).

## Measurement of $CD4^+$ T-Cell Responses

Because DCs are essential for eliciting T-cell immunity in vivo,[16] we determined the $CD4^+$ T-cell responses by incubating with isolated $CD4^+$ T cells with autologous DCs in a final volume of 200 μL RPMI ($2 \times 10^5$ $CD4^+$ T cells with $2 \times 10^4$ $CD11c^+$ DCs per well of a 96-well plate in triplicate) for 3 days. The $CD4^+$ T cells were then harvested for T-cell proliferation assay, ELISPOT assay, or surface marker staining. The Ag-specific $CD4^+$ T-cell responses were defined as [$CD4^+$ T-cell responses elicited by Ag-primed DCs] minus [$CD4^+$ T-cell responses elicited by immature DCs]. To assess the role of CTLA4 expression on $CD4^+CD25^+$ T cells in the suppression of EhAg-specific $CD4^+$ T-cell responses, varying doses of blocking anti-CTLA4 (purified BNI3, mouse IgG2a, PharMingen), and isotype control (mouse IgG2a, purified) were added simultaneously when $CD4^+$ T cells were incubated with DCs. To determine the suppressive activity of $CD4^+CD25^+$ T cells, varying numbers and varying stimulation conditions of $CD4^+CD25^+$ T cells were added to $CD4^+CD25^-$ T cells, which had been incubated with EhAg-primed DCs, and then the proliferation activity of $CD4^+CD25^-$ T cells was assessed.

## Proliferation Assay

Proliferation activity of $CD4^+$ T cells was assessed by determining the frequencies of $CD4^+$ T cells with bromodeoxyuridine (BrdU) incorporation after incubating PBMC ($2 \times 10^5$ per well of a 96-well round-bottom plate) with mitogens or after incubating $CD4^+$ T cells with DCs, using BrdU Flow Kit (BD PharMingen) in a final volume of 200 μL RPMI per well in triplicate. BrdU (final concentration 10 μM) was added 24 hours before harvest. Cells with BrdU incorporation were detected by flow cytometry after being fixed with paraformaldehyde, permeabilized with saponin, and stained with anti-BrdU-FITC according to the BrdU Flow Kit protocol from the manufacturer.

## ELISPOT Assay

$CD4^+$ T cells were added to the IFN-γ and IL-4 ELISPOT plate (Becton Dickinson, San Jose, CA) at $2 \times 10^5$ cells/well and then incubated at 37°C and 5% $CO_2$ for 48 hours. This assay was performed at least in triplicate per individual, according to the instructions of the manufacturer. The IL-4– and IFN-γ–producing cells were enumerated by ImmunoSpot® Series 2 Analyzer with ImmunoSpot® software. Unstimulated $CD4^+$ T cells were used as negative controls, and background spots in the negative control should be detected at a frequency of $<10$ per $10^5$.

## Statistical Analysis

Statistical significance was determined using a nonparametric test (Mann-Whitney $U$ test) if two groups were compared; or one-way analysis of variance (ANOVA) if $\geq 3$ groups were compared. All tests are two-tailed, and $P < 0.05$ was considered statistically significant. All data are shown as mean + standard deviation (SD).

# RESULTS

## EhAg-Specific $CD4^+$ T-Cell Response Was Selectively Impaired in HIV-1–Infected Subjects

To compare the general $CD4^+$ T-cell reactivity in the three groups of subjects, we incubated their PBMCs with mitogens (PMA or anti-CD3 mAb) and then assessed the $CD4^+$ T-cell responses by proliferation assay and ELISPOT assay. No significant differences in the $CD4^+$ T-cell reactivity to mitogens were found between these subjects (data not shown). We next determined the $CD4^+$ T-cell responses elicited by primed DCs. Our data showed that the $CD4^+$ T-cell responses elicited by CMV Ag or CD40L-primed DCs were also similar in the three groups; however, the $CD4^+$ T-cell responses elicited by EhAg-primed DCs were decreased significantly in $HIV^+ALA^-$ subjects and were even more decreased in $HIV^+ALA^+$ subjects when compared to HIV subjects (Figs. 1A, B). Our data also showed that the $CD4^+$ T-cell responses elicited by EhAg-primed DCs were T-helper type 2 (Th2) responses with predominantly high IL-4 responses (Fig. 1B).

## Depletion of $CD4^+CD25^+$ Cells Normalized the EhAg-Specific $CD4^+$ T-Cell Responses in HIV-1–Infected Subjects With or Without ALA

To know whether the impaired EhAg-specific $CD4^+$ T-cell responses was attributed to suppressive activity of $CD4^+CD25^+$ T cells, we determined the EhAg-specific $CD4^+$ T-cell responses with and without depletion of $CD25^+$ cells from $CD4^+$ T cells before $CD4^+$ T cells were incubated with EhAg-primed DCs. We found that EhAg-specific $CD4^+CD25^-$ T-cell responses (ie, responses of $CD4^+$ T cells with depletion of $CD25^+$ cells, assessed by proliferation assay or enumerating the IL-4-producing cells by ELISPOT assay) in $HIV^+ALA^-$ and $HIV^+ALA^+$ subjects were comparable to those in HIV-negative subjects (Fig. 2).

## Suppressive Activity of $CD4^+CD25^+$ T Cells Is Inducible by EhAg-Primed DCs in HIV-1–Infected Subjects With or Without ALA

To clarify whether the $CD4^+CD25^+$ T cells could suppress the EhAg-specific $CD4^+$ T-cell responses, we assessed the EhAg-specific $CD4^+CD25^-$ T-cell responses after 48-hour incubation of varying numbers of $CD4^+CD25^+$ T cells (which had been incubated with EhAg-primed DCs for 3 days) to $CD4^+CD25^-$ T cells (which had also been incubated with EhAg-primed DCs for 3 days) with a suppressor: responder ratios of 0:1, 0.1:1, and 0.5:1 were observed in $HIV^-$, $HIV^+ALA^-$, and $HIV^+ALA^+$ subjects, respectively. The

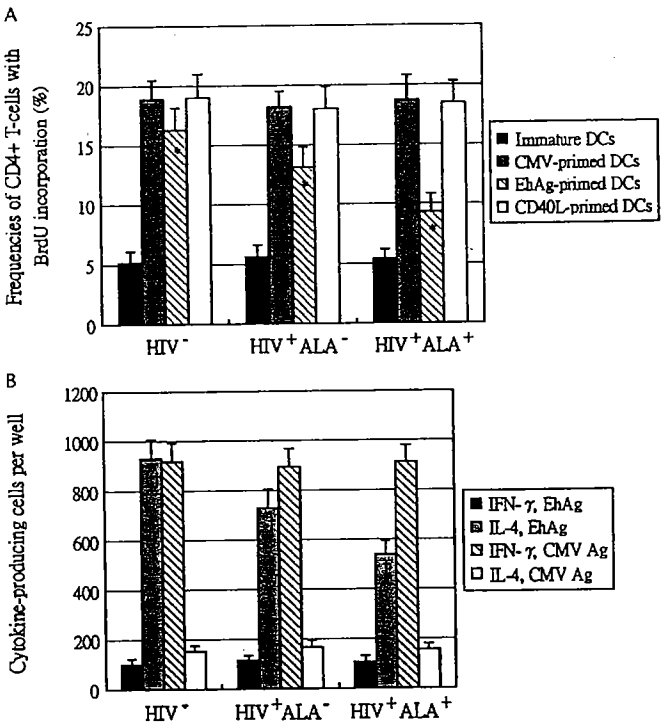


**FIGURE 1.** $CD4^+$ T-cell responses to *E. histolytica* antigen (EhAg) were impaired in the early-staged HIV-1–infected subjects with or without amebic liver abscess (ALA). $CD4^+$ T-cell responses, elicited by autologous monocyte-derived DCs that remained immature or were primed by EhAg, CMV Ag, or soluble CD40L, were assessed by (A) proliferation assay and (B) the IL-4 and IFN-γ–producing cells enumerated by ELISPOT assay, in healthy controls ($HIV^-$, n = 16), HIV-1–infected subjects without ALA ($HIV^+ALA^-$, n = 13), and HIV-1–infected subjects with ALA ($HIV^+ALA^+$, n = 8). Data are presented as mean + SD. $^*P < 0.001$; $\dagger P < 0.001$ (by one-way ANOVA).

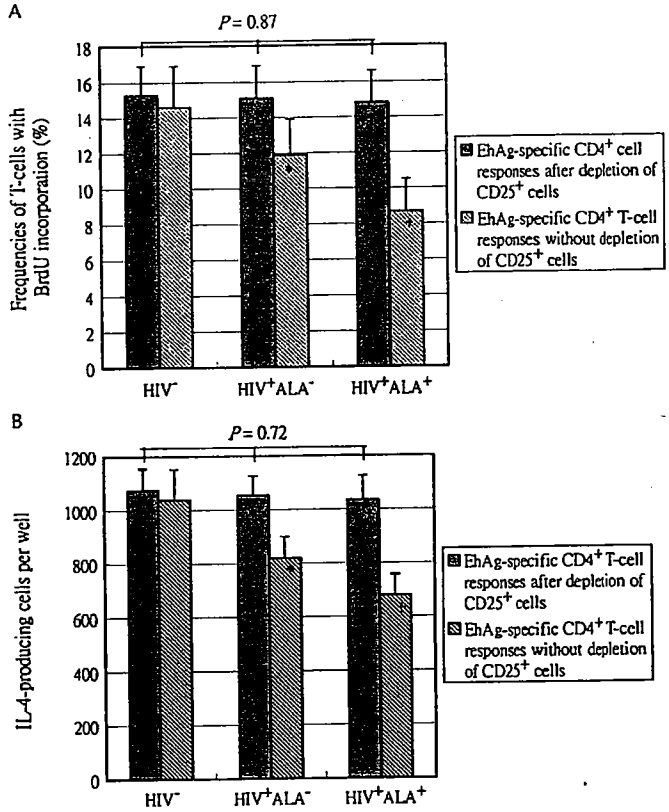


**FIGURE 2.** Depletion of $CD4^+CD25^+$ T cells normalized the EhAg-specific $CD4^+$ T-cell responses in HIV-1–infected subjects with or without ALA. EhAg-specific $CD4^+$ T-cell responses were compared in the three subject groups with or without depletion of $CD25^+$ T cells from their $CD4^+$ T cells isolated from PBMC. In the CD25-depletion experiments, $CD25^+$ cells were depleted before $CD4^+$ T cells stimulated with EhAg-primed autologous DCs. EhAg-specific $CD4^+$ T-cell responses were determined by (A) proliferation assay ($^*P = 0.001$, $\dagger P < 0.001$ by Mann-Whitney *U* test) and (B) ELISPOT assay ($^*P < 0.001$, $\dagger P < 0.001$ by Mann-Whitney *U* test), in healthy controls ($HIV^-$, n = 16), HIV-1–infected subjects without ALA ($HIV^+ALA^-$, n = 13), and HIV-1–infected subjects with ALA ($HIV^+ALA^+$, n = 8). After depletion of $CD25^+$ cells, the EhAg-specific $CD4^+$ T cells were comparable in the three subject groups. Data are presented as mean + SD.

results showed that the added $CD4^+CD25^+$ T cells could suppress the EhAg-specific $CD4^+CD25^-$ T-cell responses with a dose-related fashion in HIV-1–infected subjects with or without ALA but not in healthy controls (Fig. 3A). The doses of EhAg or the methods of priming DCs or the cell ratios of $CD25^+$:$CD25^-$ cells that we used in this study may not be enough to induce observable inhibitory responses in HIV-negative subjects, but they may have been enough to induce sufficient inhibitory responses to suppress EhAg-specific T-cell responses in $HIV^+$ subjects.

To know whether the suppressive activity of $CD4^+CD25^+$ T cells was induced by DCs, we assessed the EhAg-specific $CD4^+CD25^-$ T-cell responses after adding varying stimulation conditions of $CD4^+CD25^+$ T cells to $CD4^+CD25^-$ T cells in HIV-1–infected subjects with ALA. The $CD4^+CD25^+$ T cells were prepared as follows: no incubation with DCs; incubation with immature DCs for 3 days; or incubation with EhAg-primed DCs for 3 days, and were then added to the $CD4^+CD25^-$ T cells that had already been incubated with EhAg-primed DCs for 3 days. DCs were removed before coculture of $CD4^+CD25^-$ and $CD4^+CD25^+$ T cells. We found that the EhAg-specific $CD4^+CD25^-$ T-cell responses were significantly suppressed only when $CD4^+$ $CD25^+$ T cells had been incubated with EhAg-primed DCs but not by the $CD4^+CD25^+$ T cells that had been incubated with immature DCs or that had not been incubated with DCs (Fig. 3B). The results indicated the $CD4^+CD25^+$ T cells could exert immunosuppressive activity, which was inducible by EhAg-primed DCs, to reduce the EhAg-primed $CD4^+$ T-cell responses in HIV-1–infected subjects.

## Role of CTLA4 Expression on $CD4^+CD25^+$ T Cells in Suppression of EhAg-Specific $CD4^+$ T-Cell Responses in HIV-1–Infected Subjects

The frequencies of CD25 expression on isolated $CD4^+$ T cells in the three subject groups were compared. Results showed no significant difference in the frequencies of CD25

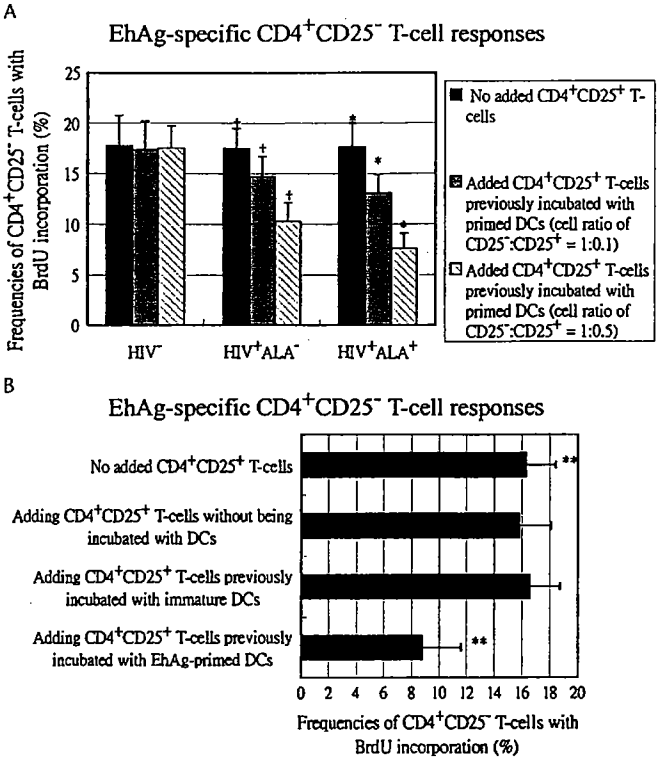


**FIGURE 3.** Suppressive activity of $CD4^+CD25^+$ T cells was induced by EhAg-primed DCs in HIV-1–infected subjects with or without ALA. A, EhAg-specific $CD4^+CD25^-$ T-cell responses were assessed after 48-hour incubation of varying numbers of $CD4^+CD25^+$ T cells (which had been incubated with EhAg-primed DCs for 3 days) to $CD4^+CD25^-$ T cells (which had also been incubated with EhAg-primed DCs for 3 days) with a suppressor: responder ratios of 0:1, 0.1:1, and 0.5:1 in $HIV^-$ (n = 16), $HIV^+ALA^-$ (n = 13), and $HIV^+ALA^+$ (n = 8) subjects. $^*P < 0.001$, $\dagger P = 0.001$ (by one-way ANOVA). B, EhAg-specific $CD4^+CD25^-$ T-cell responses after adding varying stimulation conditions of $CD4^+CD25^+$ T cells to $CD4^+CD25^-$ T cells with a ratio of 1:10 in $HIV^+ALA^+$ subjects (n = 8). $CD4^+CD25^+$ T cells could suppress the EhAg-specific proliferation of $CD4^+CD25^-$ T cells only when $CD4^+CD25^+$ T cells had been incubated with EhAg-primed DCs. $^{**}P < 0.001$ (by Mann-Whitney *U* test).

expression between the $HIV^-ALA^-$, $HIV^+ALA^-$, and $HIV^+ALA^+$ groups on the freshly prepared $CD4^+$ T cells (mean ± SD: 15.6% ± 2.9% vs. 16.2% ± 2.8% vs. 15.9% ± 2.6%, respectively; $P = 0.88$) or on the $CD4^+$ T cells after being incubated with EhAg-primed DCs (mean ± SD: 15.8% ± 2.8% vs. 16.1% ± 2.6% vs. 15.6% ± 2.5%, respectively; $P = 0.92$, respectively). Because there was evidence that the expression of cytotoxic T-lymphocyte antigen-4 (CTLA4) may be essential for the suppressive function of regulatory T cells in vivo,[17–20] we determined the frequencies of CTLA4 expression on $CD4^+CD25^+$ cells after 72-hour incubation of $CD4^+$ T cells (isolated from PBMC) with or without autologous DCs in the three subject groups (with a $CD4^+$ T cells/DCs ratio of 10:1). We found that CTLA4 expression on DCs-incubated $CD4^+CD25^+$ T cells was upregulated (when compared to that in $CD4^+CD25^+$ T cells not incubated with DCs), and the frequencies of CTLA4 expression on $CD4^+CD25^+$ T cells that were incubated with DCs primed by CMV Ag or CD40L or immature DCs were similar in the three subject groups (Fig. 4A). However, only the frequencies of CTLA4 expression on $CD4^+CD25^+$ T cells incubated with EhAg-primed DCs increased significantly in $HIV^+ALA^-$ subjects, and these increased even more in $HIV^+ALA^+$ subjects when compared to HIV subjects ($P < 0.001$, Fig. 4A).

To know the requirement CTLA4 in the suppression of the EhAg-specific $CD4^+$ T-cell responses, we assessed the impact of blocking anti-CTLA4 Ab on the EhAg-specific $CD4^+$ T-cell responses. The EhAg-specific $CD4^+$ T-cell responses were determined after addition of the blocking anti-CTLA4 Ab with varying doses or isotype control in the 72-hour incubation of $CD4^+$ T cells with autologous EhAg-primed DCs ($CD4^+$ T cells/DCs ratio of 10:1). We found adding the blocking anti-CTLA4 Ab increased the EhAg-specific $CD4^+$ T-cell responses in a dose-dependent fashion (Figs. 4B, C). At a dose of 20 μg/mL, the blocking anti-CTLA4 Ab increased the EhAg-specific $CD4^+$ T-cell responses in HIV-infected subjects with or without ALA to levels comparable to those of HIV-negative subjects (Figs. 4B, C). Furthermore, after depletion of $CD25^+$ cells from $CD4^+$ T-cell population, no more significant increase in the EhAg-specific $CD4^+$ T-cell responses (frequencies of $CD4^+$ T cells with BrdU incorporation and IL-4–producing cells per well) could be observed after adding any of the three doses of the anti-CTLA4 antibody (5, 10, and 20 μg/mL, detailed data not shown). These results may imply that $CD4^+CD25^+$ T cells may suppress EhAg-specific $CD4^+$ T-cell responses through CTLA4-related mechanisms in HIV-1–infected subjects.

## HIV-1 Tat-Upregulated CTLA4 Expression on $CD4^+CD25^+$ T Cells and Suppressed the EhAg-Specific $CD4^+$ T-Cell Responses in HIV-Negative Subjects

To explain why the EhAg-primed DCs could upregulate CTLA4 expression on $CD4^+CD25^+$ T cells to suppress the EhAg-specific T-cell responses in the HIV-1–infected persons, we hypothesized that the some biological activities of DCs when encountering EhAg may be modified by some HIV-related proteins. Tat, the trans-activation protein of HIV-1, can be very efficiently taken up by DCs and may reprogram the maturation and immunostimulatory functions of DCs.[21–24] We negatively isolated monocytes from PBMCs from five HIV-negative subjects among the 16 healthy volunteers, as described in the Subjects section under Patients and Methods. Recombinant Tat protein was added with varying doses in the monocyte culture from the first day (monocytes) to day 6 (immature DC) of incubation with IL-4 and GM-CSF. After Tat was washed, these Tat-incubated immature DCs were harvested for antigen priming, subsequently incubated with autologous $CD4^+$ T cells for 72 hours, and then assessed for CTLA4 expression and the $CD4^+$ T-cell responses (as described in "Measurement of $CD4^+$ T-Cell Responses" in Patients and Methods). After being primed with EhAg, the Tat-incubated DCs could induce the CTLA4 upregulation on the $CD4^+CD25^+$ cells (Fig. 5A). The $CD4^+$ T-cell responses to EhAg, assessed by lymphocyte proliferation assay (Fig. 5B)

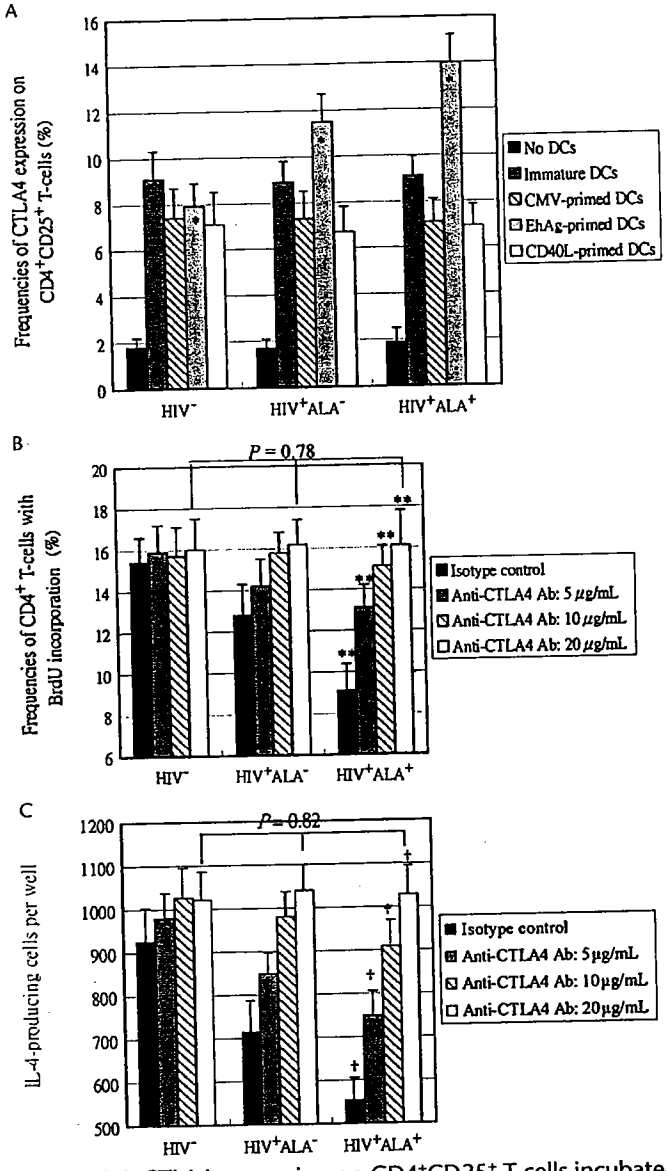


**FIGURE 4.** CTLA4 expression on CD4+CD25+ T cells incubated with EhAg-primed DCs in HIV-1–infected subjects. A, Determination of the frequencies of CTLA4 expression on CD4+CD25+ T cells after 72-hour incubation of CD4+ T cells (isolated from PBMC) with or without autologous DCs which remained immature or were primed with CMV Ag, EhAg, or soluble CD40L (ratio of CD4+ T cells/DCs = 10:1) in healthy controls (HIV−, n = 16), HIV-1–infected subjects without ALA (HIV+ALA−, n = 13), and HIV-1-infected subjects with ALA (HIV+ALA+, n = 8). EhAg-specific CD4+ T-cell responses were determined after adding the blocking anti-CTLA4 Ab with varying doses or isotype control (5 μg/mL) in the 72-hour incubation of CD4+ T cells with autologous EhAg-primed DCs (ratio of CD4+ T cells/DCs = 10:1). These responses were assessed by (B) proliferation assay and (C) IL-4 ELISPOT assay. Data are presented as mean ± SD. $*P < 0.001$; $**P < 0.001$; $\dagger P < 0.001$ (by one-way ANOVA).

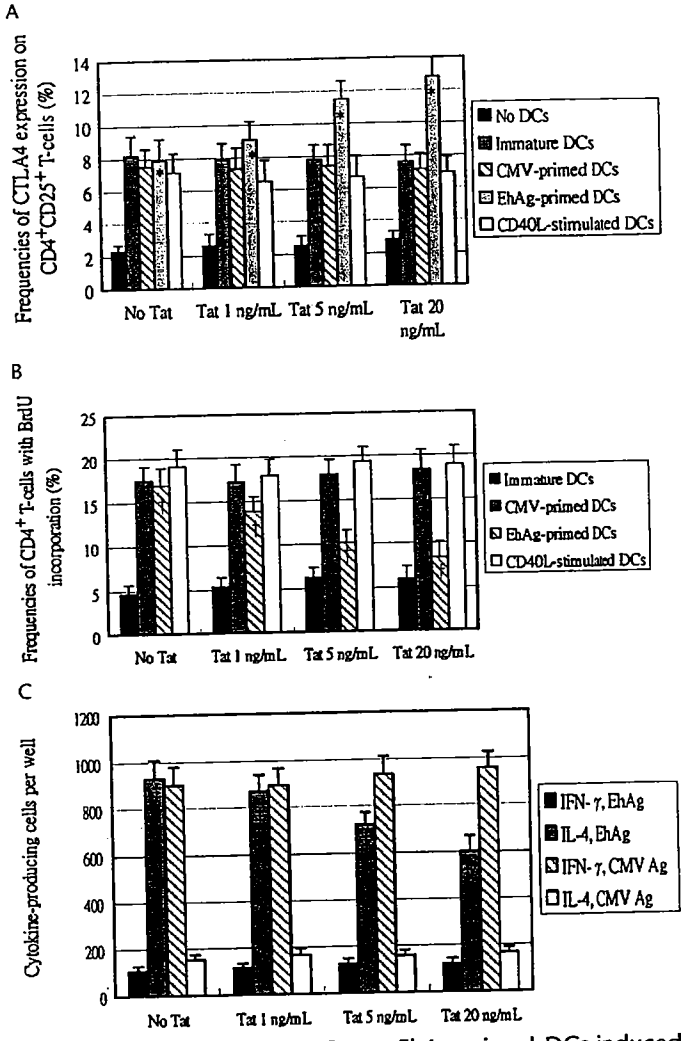


**FIGURE 5.** Impact of HIV-1 Tat on EhAg-primed DCs-induced CTLA4 expression on CD4+CD25+ T cells and CD4+ T-cell responses to EhAg in HIV-negative subjects. Monocytes were negatively isolated from PBMCs from five HIV-negative subjects. Recombinant Tat protein was added with varying doses in the monocyte culture from day 1 (monocytes) to day 6 (immature DC) of incubation with IL-4 and GM-CSF. The Tat-incubated immature DCs were harvested for antigen priming and were subsequently incubated with autologous CD4+ T cells for 72 hours (with a ratio of CD4+ T cells/DCs = 10:1). These CD4+ T cells were then analyzed for (A) the CTLA4 expression on the CD4+CD25+ cells by flow cytometry, and for the CD4+ T-cell responses by (B) lymphocyte proliferation assay and (C) ELISPOT assay. $*P < 0.001$, $\dagger P < 0.001$, $\ddagger P < 0.001$ (by one-way ANOVA).

and enumeration of IL-4-producing cells by ELISPOT assay (Fig. 5C) were suppressed in a Tat dose-related fashion. The Tat-incubated DCs, after being primed with CMV Ag or stimulated with CD40L, had no similar impact on CTLA4 expression or CD4+ T-cell responses to EhAg. Furthermore, recombinant HIV-1-p24 (Gag) or gp120 (Env) did not provide similar results of CTLA4 upregulation or suppression of CD4+ T-cell response to EhAg as Tat did, ie, the frequencies of

CTLA4 expression on $CD4^+CD25^+$ T cells and the $CD4^+$ T-cell responses to EhAg in autologous $CD4^+$ T cells that were incubated with EhAg-primed DCs that previously incubated with p24 or gp120 with varying doses (from 1 to 20 ng/mL), were similar to those in autologous $CD4^+$ T cells that were incubated without any antigen (detailed data not shown).

## DISCUSSION

In this study, we demonstrate the evidence that the EhAg-specific $CD4^+$ T-cell responses in HIV-1–infected persons have been selectively impaired even in early-stage HIV-1 infection. The early impaired $CD4^+$ T-cell responses to EhAg may be explained by the aberrant induction of suppressive activity of $CD4^+CD25^+$ T cells by EhAg-primed DCs derived from HIV-1–infected persons. The explanation is supported by the EhAg-specific $CD4^+$ T-cell responses were normalized if $CD4^+CD25^+$ T cells were depleted, and the EhAg-specific $CD4^+CD25^-$ T-cell responses were suppressed when the autologous $CD4^+CD25^+$ T cells were added. However, the EhAg-specific $CD4^+CD25^-$ T-cell responses were suppressed in HIV-1–infected persons only when their $CD4^+CD25^+$ T cells had been incubated with EhAg-primed DCs. In addition, DC-elicited activity of $CD4^+CD25^+$ T cells to suppress the EhAg-specific $CD4^+$ T-cell responses could only be observed in HIV-1–infected subjects, especially in those who had developed ALA, and not in healthy controls. Furthermore, recombinant Tat-incubated DCs derived from HIV-negative subjects could result in similar results of CTLA4 upregulation on $CD4^+CD25^+$ T cells and suppression of EhAg-specific $CD4^+$ T-cell responses to those observed in HIV-infected subjects, in a Tat dose-related fashion. According to these data, we propose a novel immunopathogenesis of HIV-1–related opportunistic infections: HIV-1 infection, perhaps through the biological activity of Tat protein, may modify the behavior of DCs when encountering invasion of *E. histolytica* to aberrantly upregulate suppressive activity of regulatory T cells to weaken the immunity against *E. histolytica*, thus leading to the increased host susceptibility to invasive amebiasis.

Although in vitro data have demonstrated a role for cell-mediated response in host defenses against *E. histolytica* in the activation of macrophages and neutrophils to kill *E. histolytica* trophozoites, mucosal immunity by anti-Gal/GalNAc lectin IgA may play a major role for host protection from invasive amebiasis.[25–27] Because Th2 cells can produce IL-4, IL-5, and TGF-β, and the latter cytokine can induce isotype switch of immunoglobulin to IgG2b and IgA,[28] we propose that if specific Th2 responses are suppressed by regulatory T cells, as in the condition of invasive amebiasis in HIV-1–infected persons, specific mucosal IgA production may be impaired to decrease the protective mucosal immunity against invasive amebiasis. That may also help to explain the relationship between suppression of EhAg-specific Th2 response and increased risk for development of invasive amebiasis, as suggested in our data.

There has been evidence that cell–cell contact through the engagement of CD80/CD86 by expressed CTLA4 molecules is essential for suppressive function of regulatory T cells.[17–20] Although a CTLA4 blockade could not reverse the anergic state of freshly isolated $CD4^+CD25^+$ T cells,[29,30] our study, consistent with studies by Read and others[17] and Takahashi and others,[18] showed that addition of blocking anti-CTLA4 Ab can abrogate the suppressive effects of regulatory T cells to increase antigen-specific T-cell reactivity. In mice, the enhanced T-cell immunity through CTLA4 blockade has also been documented in pathogen-specific response[31] and antitumor immunity.[32] In this study, we found that a CTLA4 blockade may markedly enhance EhAg-specific Th2 response in HIV-1–infected persons, especially in those with ALA. These results are supported by previous studies that showed CTLA4 to be a critical and potent inhibitor of Th2 differentiation,[33] and the treatment by blocking anti-CTLA4 Ab may enhance protective Th2 immunity to nematode infection in mice.[34] Thus CTLA4 expression may be essential to the activity of regulatory T cells to suppress the cellular immunity against *E. histolytica* in HIV-1–infected persons.

HIV-1 Tat, a regulatory protein of HIV-1, is essential for HIV-1 gene expression, replication and infectivity (reviewed in reference 35). Tat may target DCs and reprogram their maturation and immunostimulatory functions, perhaps through modifying the signal transduction pathways, with either expressed Tat or exogenous biological active Tat protein.[21–24] In our study, Tat-incubated DCs increased the suppressive activity of regulatory T cells to selectively decrease the EhAg-specific $CD4^+$ T-cell responses. We propose that the impact of Tat on the upregulation of CTLA4 expression on $CD4^+CD25^+$ T cells and selective suppression of $CD4^+$ T-cell reactivity to EhAg may be through Tat-related DC modulation. From this model, it would be possible to investigate how Tat modifies EhAg-primed DCs to upregulate CTLA4 expression and what signal transduction pathways in DCs are affected. Our preliminary data have showed that Tat may modify the cell signaling involving protein kinase C (PKC)–nuclear factor κB (NF-κB) pathway to affect the capacity of EhAg-primed DCs to aberrantly induce the EhAg-specific suppressive activity of regulatory T cells.

Some limitations and unanswered questions were noted in this study. Although we define the exposure to *E. histolytica* by the positive antiamebic serology, we do not know the duration of exposure and cannot assess the impact of duration on the modification of cellular immunity in these subjects. Although our data may explain why HIV-1-infected persons are more susceptible to ALA than are HIV-1–negative subjects, in this study we cannot explain why some of HIV-1–infected persons are more susceptible to ALA when encountering *E. histolytica* than other HIV-1–infected persons. It may be attributes to colonization state, genetic factors, or dose of invaded pathogens. From our data, we also cannot be sure whether the higher potential of DCs to induce suppressive activity of regulatory T cells renders increased host susceptibility to ALA or whether ALA itself may result in the potential of DCs to induce suppressive activity of regulatory T cells. A long-term prospective study for the HIV-1–infected persons with exposure to *E. histolytica* to evaluate the capacity of EhAg-primed DCs in inducing the suppressive activity of regulatory T cells and in correlating their subsequent occurrence of invasive amebiasis will be helpful in answering these questions.

In conclusion, our data suggest a possible interaction between two pathogens. This interaction could be exhibited as an increased host susceptibility to invasion of one pathogen (*E. histolytica*) resulting from modified DC capacity mediated by the other pathogen (HIV-1) through upregulating the suppressive function of regulatory T cells. Future studies should be conducted to evaluate the potentials of anti-CTLA4 treatment or other ways to inhibit the activity of regulatory T cells to decrease the host susceptibility or to enhance the host defense against pathogen invasion.

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ORIGINAL ARTICLE

# Prevalence of Intestinal Infection due to *Cryptosporidium* Species Among Taiwanese Patients with Human Immunodeficiency Virus Infection

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**Background/Purpose:** Cryptosporidiosis causes significant morbidity and mortality in human immunodeficiency virus (HIV)-infected patients who do not receive highly active antiretroviral therapy. Related data on cryptosporidiosis in Taiwanese HIV-infected patients are very limited. This study assessed the prevalence of intestinal infection due to *Cryptosporidium* spp. among Taiwanese patients with HIV infection.
**Methods:** This retrospective review included 1044 patients with HIV infection treated between June 1994 and June 2004. Intestinal colonization due to *Cryptosporidium* spp. was identified by polymerase chain reaction and restriction fragment length polymorphism of stool specimens collected from 332 of the HIV-infected patients without gastrointestinal symptoms, 90% of whom were receiving highly active antiretroviral therapy.
**Results:** Five out of 1044 (0.5%) HIV-infected patients had a diagnosis of intestinal cryptosporidiosis by endoscopic biopsy or examinations of stool specimens. Intestinal colonization due to *Cryptosporidium* spp. was found in four of 332 (1.2%) asymptomatic HIV-infected patients between 2001 and 2003; two were due to *C. hominis*, and one each were due to *C. felis* and *C. meleagridis*.
**Conclusion:** Our findings indicate that the prevalence of intestinal colonization due to *Cryptosporidium* is low among HIV-infected patients in Taiwan. [*J Formos Med Assoc* 2007;106(1):31–35]

Key Words: AIDS, colonization, cryptosporidiosis, *Cryptosporidium parvum*, HIV infection, Taiwan

Cryptosporidia are an important etiology of enteric infections in patients with human immunodeficiency virus (HIV) infection, and cryptosporidiosis, either intestinal or extraintestinal, is associated with a shorter survival.[1,2] The prevalence of cryptosporidiosis in HIV-infected patients with diarrhea has been reported to range from 3% to 16% in developed countries, depending on the population studied, degree of immunosuppression, and use of antiretroviral therapy.[3–5]

With the introduction of highly active antiretroviral therapy (HAART), the incidence of cryptosporidiosis has declined,[6,7] and chronic diarrhea and cryptosporidial infection often resolves with increases in CD4 lymphocyte count.[8–10] However, cryptosporidiosis still occurs in patients



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who continue to have low CD4 count despite HAART.[10]

In Taiwan, cryptosporidia were detected in most of the surface water specimens.[11] However, intestinal cryptosporidiosis has rarely been reported among HIV-infected[12] and HIV-uninfected patients. In this retrospective study, we investigated the prevalence of intestinal cryptosporidiosis by retrospective case review and of intestinal colonization due to *Cryptosporidium* species by means of the polymerase chain reaction (PCR) and PCR–restriction fragment length polymorphism (RFLP) analyses among patients with HIV infection in Taiwan, a country where HIV-infected patients have free universal access to antiretroviral therapy and HIV care.

## Materials and Methods

### *Retrospective case review of enteric cryptosporidiosis*

The medical records of 1044 consecutive non-hemophiliac HIV-infected adult patients aged ≥ 15 years seen at the National Taiwan University Hospital between 1994 and 2004 were reviewed. A standardized case record form was used to collect demographic information, clinical and immunologic status of HIV infection, laboratory data, and the presence of intestinal cryptosporidiosis. A standardized protocol was used to investigate the etiologic diagnosis of diarrhea among cases.[13] In brief, at least two stool specimens were obtained for bacterial cultures for patients with diarrhea. Concentrated wet mount preparations of stool specimens were examined by direct microscopy. Fecal smears were stained with modified acid-fast. Upper gastrointestinal endoscopy and colonoscopy and biopsy for histopathologic examination were performed when routine examinations of the stool specimens remained nondiagnostic in patients who had persistent diarrhea. A patient was diagnosed as having intestinal cryptosporidiosis when cryptosporidia were identified in stool or biopsy specimens from patients with diarrhea.

### *Intestinal cryptosporidial colonization in asymptomatic HIV-infected persons using PCR and PCR-RFLP*

Between 2001 and 2003, stool specimens were prospectively collected from 332 HIV-infected patients without diarrhea who were followed at this hospital after diagnosis of HIV infection for investigation of amebic infection.[14] The institutional review board of the hospital approved the study protocol.

Total DNA was isolated from fresh stool specimens by the diatom beads adsorption of nucleic acid in the presence of guanidine thiocyanate and Nonidet P-40 as described elsewhere.[14]

The presence of cryptosporidial nucleic acid in the stool samples was demonstrated by nested PCR developed by Xiao et al[15] with modifications using 18S rRNA gene as the template. Forward primer 5′-TTCTAGAGCTAATACATGCG-3′ and reverse primer 5′-CCCTAATCCTTCGAAACAGGA-3′ were used for the primary amplification. A total volume of 100 μL of reaction mixture containing 0.4 μM primers, 1X PCR buffer, 6 mM $MgCl_2$, 2 μL DNA sample, 0.2 mM dNTP (each) and 2.5 U of *Taq* polymerase (5 U/μL; Invitrogen™ Life Technologies, Brazil) was used. The reaction consisted of 35 cycles of denaturation at 94°C for 45 seconds, annealing at 59°C for 45 seconds, extension at 72°C for 60 seconds, with an initial denaturation at 94°C for 3 minutes and a final extension at 72°C for 7 minutes. In the secondary amplification, forward primer 5′-GGAAGGGTTGTATTTATTAGATAAAG-3′ and reverse primer 5′-AAGGAGTAAGGAACAACCTCCA-3′ were employed, and the reaction conditions were the same as for the primary reaction, except that 4 mM $MgCl_2$ was used.

For restriction fragment assays, 10 μL each of the secondary PCR products were digested in a 20 μL volume with 5 U of *Ssp* I (New England BioLabs, USA) and *Vsp* I (MBI Fermentas, USA) at 37°C for 1 and 4 hours, respectively. The digested products were fractionated on 3% gel (3:1 Nusieve agarose) and visualized by ethidium bromide staining.

## Results

The demographic and clinical characteristics of the two study populations are shown in the Table. Most of the 1044 patients in the retrospective case review were in the late stage of HIV infection at baseline, with a median CD4 count of 81 cells/μL; more than two-thirds of them were diagnosed as having AIDS because of CD4 counts < 200 cells/μL (66.2%) or presence of AIDS-opportunistic illnesses[16] (67.3%) when they first sought HIV care at this hospital. Between 1994 and 2004, only five (0.5%) HIV-infected patients, four males and one female, were diagnosed as having intestinal cryptosporidiosis. Three of them were heterosexuals and two men were homosexuals. All of the five patients had depleted CD4 lymphocyte counts when cryptosporidiosis was diagnosed, with a median CD4 count of 40 cells/μL (mean, 26 cells/μL; range, 1–49 cells/μL). Three cases were diagnosed by acid-fast stained smears of the stool specimens and the other two by endoscopic biopsy of the duodenum. One of the five patients was receiving two nucleoside reverse transcriptase inhibitors when cryptosporidiosis was diagnosed before the introduction of HAART in Taiwan in 1997. He died 4 months later without HAART and anti-cryptosporidial therapy. Of the other four patients who were antiretroviral-naïve, HAART was initiated without anti-cryptosporidial therapy, and all survived as of July 2005. The species of cryptosporidial isolates were not further identified.

The demographic and clinical characteristics of the 332 asymptomatic HIV-infected patients were described previously (Table).[14] In brief, there were 310 males and 22 females, with a median age of 37 years (range, 17–80 years); 62% were men having sex with men; 64.5% had had AIDS-related opportunistic illnesses within 1 month of stool collection. More then 90% of them were receiving HAART and the latest median CD4 lymphocyte count was 265 cells/μL (range, 1–1230 cells/μL); 40% of them had CD4 lymphocyte counts < 200 cells/μL. Of the 332 stool specimens, four (1.2%) were positive for cryptosporidia by PCR (Figure 1). Using nested PCR and RFLP analyses, we were

**Table.** Baseline characteristics of HIV-infected persons aged ≥ 15 years for retrospective case review and prospective investigation of intestinal infection due to *Cryptosporidium* species*

| | Retrospective case review | Prospective survey |
|---|---|---|
| Patients (*n*) | 1044 | 332 |
| Age (yr) | 34 (15–83) | 37 (17–80) |
| Male gender | 92.7 | 93.4 |
| Risk behavior | | |
| Homosexual/bisexual | 61.4 | 62.1 |
| Heterosexual | 31.7 | 35.2 |
| IDU | 2.3 | 0.9 |
| Others | 4.6 | 1.8 |
| Baseline CD4 count (cells/μL) | 81 (0–1202) | 265 (1–1230) |
| < 200 | 66.2 | 39.9 |
| 200–349 | 14.6 | 23.9 |
| ≥ 350 | 19.3 | 36.2 |
| Baseline PVL ($log_{10}$ copies/mL) | 5.17 (2.60–5.88) | 2.60 (2.60–5.88) |
| Naïve to antiretroviral therapy | 75.4 | 9.3 |
| AIDS-OI within 1 mo of enrollment | 67.3 | 64.5 |
| Persons initiating HAART | 80.1 | 90.7 |

**Data presented as median (range) or %. IDU = injection drug use; PVL = plasma HIV-RNA load by RT-PCR; AIDS-OI = AIDS-defining opportunistic illnesses of CDC[16] plus Penicilliosis marneffei; HAART = highly active antiretroviral therapy.*

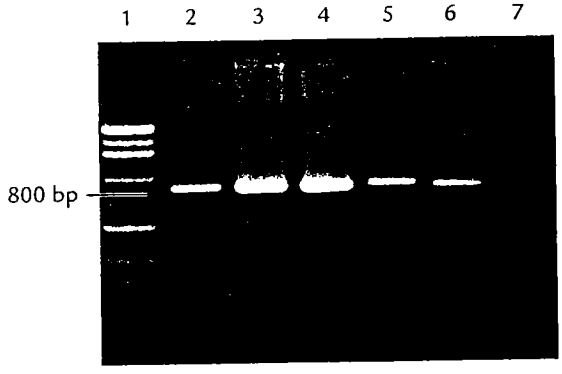


**Figure 1.** Nested PCR products (826–864 bp) for *Cryptosporidium* spp. SSUrRNA gene sequences in stool specimens from four HIV-infected persons (lanes 3–6). Lane 1 = 100 bp marker; lane 2 = positive control for *C. parvum* bovine genotype; lane 7 = negative control.

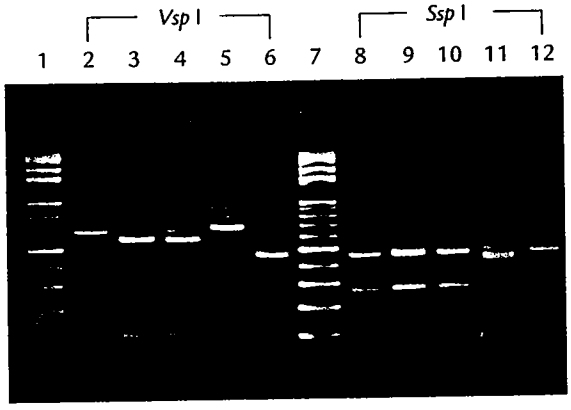


**Figure 2.** PCR-RFLP of cryptosporidia SSUrRNA gene sequences. Lanes 2–6 and lanes 8–12 show the restriction fragments using *Vsp* I and *Ssp* I, respectively. Lane 2 is the positive control for *C. parvum* bovine genotype with *Vsp* I restriction fragments with sizes of 102, 104 and 628 bp. Lanes 3–6 show the *Vsp* I restriction maps from HIV-infected persons: lanes 3 and 4 = *C. hominis* (70, 102, 104 and 561 bp); lane 5 = *C. felis* (102, 104 and 656 bp); lane 6 = *C. meleagridis* (102, 104, 171 and 456 bp). Lanes 8–12 are the *Ssp* I restriction maps: lane 8 = positive control (108, 254 and 449 bp); lanes 9 and 10 = *C. hominis* (108, 254 and 449 bp); lane 11 = *C. felis* (385 and 448 bp); lane 12 = *C. meleagridis* (108, 254 and 449 bp). Lanes 1 and 7 = 100 bp markers.

able to identify the four isolates as *C. hominis* (2), *C. felis* (1), and *C. meleagridis* (1) (Figure 2). All of the four patients were receiving HAART, and their mean CD4 count had increased to 230 cells/μL when they submitted stool specimens for investigation. None of them had ever been diagnosed as having cryptosporidiosis before.

## Discussion

*Cryptosporidium* spp. appeared to be infrequent etiologies in patients seeking medical care for diarrhea in Taiwan. In a survey investigation using modified acid-fast smears of stool specimens of 1485 patients with diarrhea that was conducted in five major hospitals in Taipei in 1990, only six (0.4%) tested positive for cryptosporidia.[17] In this study, we also found that the prevalence of enteric disease and colonization due to *Cryptosporidium* spp. was low through a 10-year retrospective case review and 3-year prospective survey of stool specimens among HIV-infected patients in Taiwan.

There are several explanations for the low prevalence of enteric disease and colonization due to *Cryptosporidium* spp. among HIV-infected patients in Taiwan. The lower prevalence of infection may be because of lower risk of exposure to contaminated water in Taiwan. Although a high frequency of cryptosporidia can be found in the untreated (77%) and treated (76%) water specimens collected from potable water treatment plants in Taiwan,[11] people in Taiwan are not used to drinking unboiled tap water. Risk of infection due to *Cryptosporidium* spp. can be eliminated by boiling of drinking water.[1]

Under-detection by microscopy might account for the low rate of cryptosporidiosis in HIV-infected patients in our study and for that in the HIV-uninfected patients with diarrhea in Taiwan mentioned previously.[16] However, our step-wise approaches to those immunosuppressed patients with chronic diarrhea through performance of endoscopy and biopsy should be able to provide appropriate diagnostic yields.[13] Though a small sample size, an investigation of stool specimens of 109 asymptomatic school children in mountainous schools in Taiwan using nested PCR did not identify any cryptosporidial infection [Tsaihong, unpublished data].

Risk of infection due to *Cryptosporidium* spp. and development of enteric or extraintestinal cryptosporidiosis in HIV-infected patients depend on the status of immunosuppression.[1,2] HAART restores immunity in the gastrointestinal mucosa

of HIV-infected patients, which may confer those persons protection from cryptosporidial infection and subsequent development of diseases.[7–10] After HIV infection is diagnosed, the majority of our patients initiate HAART with increases of CD4 count. Therefore, the risk for persistent colonization due to cryptosporidia and subsequent development of enteric disease will be significantly reduced.

There are several limitations in our study, and the results should be interpreted with caution. Although the hospital provided both inpatient and outpatient services to HIV-infected patients all around Taiwan, we did not specifically investigate whether the risk for cryptosporidiosis was related to their place of residence because the degree to what extent the surface water was contaminated might be different and their residence might change. This study of identification of cases of cryptosporidiosis in HIV-infected patients was retrospective in study design at a referral center for HIV care; cases of cryptosporidiosis in patients in the earlier stages of HIV infection may not be identified. In the detection of intestinal cryptosporidial colonization, a cross-sectional survey may not be able to detect patients who intermittently shed cryptosporidia and, therefore, the prevalence of cryptosporidial infection may be underestimated. Longitudinal follow-up of HIV-infected patients using PCR and RFLP that is more sensitive than microscopy may provide a more complete insight into the epidemiology of enteric cryptosporidial infection in HIV-infected patients in Taiwan.

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MAJOR ARTICLE

# Risk of Recurrent Nontyphoid *Salmonella* Bacteremia in HIV-Infected Patients in the Era of Highly Active Antiretroviral Therapy and an Increasing Trend of Fluoroquinolone Resistance

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***Background.*** Risk of recurrent nontyphoid *Salmonella* (NTS) bacteremia and trends of antimicrobial resistance of NTS remain unknown in human immunodeficiency virus (HIV)–infected patients receiving highly active antiretroviral therapy (HAART).

***Methods.*** Ninety-three patients who received a diagnosis of NTS bacteremia from June 1994 through June 2006 were prospectively followed up. Incidence of recurrent NTS bacteremia was compared between the pre-HAART era (June 1994–March 1997) and the HAART era (April 1997–June 2006). Prevalence of antimicrobial resistance was compared among the NTS isolates obtained in the pre-HAART era, the early HAART era (April 1997–June 2002), and the late HAART era (July 2002–June 2006).

***Results.*** Compared with patients enrolled in the pre-HAART era, patients who received HAART had an incidence of recurrent NTS bacteremia that was significantly reduced by 96%; the incidence of recurrent NTS bacteremia was 2.56 cases per 100 person-years in the HAART era, compared with 70.56 cases per 100 person-years in the pre-HAART era (rate ratio, 0.036; 95% confidence interval, 0.012–0.114; $P < .001$). In the HAART era, the incidence of recurrent NTS bacteremia did not increase among patients receiving fluoroquinolone prophylaxis for ≤30 days (1.69 cases per 100 person-years), compared with among patients receiving fluoroquinolones for >30 days (3.95 cases per 100 person-years), with a rate ratio of 0.43 (95% confidence interval, 0.07–2.58). Although resistance to ampicillin, cotrimoxazole, and chloramphenicol decreased, the proportion of NTS isolates resistant to fluoroquinolones increased from 0% in the pre-HAART era to 6.2% in the early HAART era and 34.2% in the late HAART era ($P = .002$).

***Conclusions.*** The risk of recurrent NTS bacteremia decreased significantly in the HAART era, although NTS isolates obtained from HIV-infected patients were increasingly resistant to fluoroquinolones.

Nontyphoid *Salmonella* (NTS) is the leading etiology of community- acquired bacteremia in patients with HIV infection in developed or developing countries [1–9]. The incidence of NTS bacteremia was found to be 20- to 100-fold higher among HIV-infected patients than among HIV-uninfected patients [10, 11]. In HIV-infected patients, NTS bacteremia tends to occur in patients with low CD4 lymphocyte counts and is associated with a high mortality rate in patients without access to appropriate antimicrobial therapy [1, 2, 6, 7, 12].

Before the introduction of HAART in 1996, recurrences of NTS bacteremia had been well described in HIV-infected patients despite appropriate antimicrobial therapy [12–16]. Indeed, recurrent NTS bacteremia is one of the several AIDS-defining opportunistic infectious diseases that are caused by bacteria [17]. In the pre-HAART era, as many as 43% of the patients with

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NTS bacteremia had a recurrent episode, and multiple recurrences were not uncommon [12]. The risk of recurrent NTS bacteremia may be related to the geographic prevalence of NTS infection, invasiveness of the infecting strains, the type and duration of antibiotic therapy prescribed for NTS bacteremia, the immune status of the patients, and receipt of antiretroviral therapy [12, 16, 18, 19].

After the introduction of HAART, the incidences of several major AIDS-related opportunistic infections and the mortality rate have decreased, and primary and secondary prophylaxis against several opportunistic infections can be safely discontinued in patients responding to HAART [20]. Similarly, the risk of bacteremia and associated mortality decrease with standard clinical management and the introduction of HAART [8, 9, 21, 22]. As for NTS bacteremia, clinical studies to assess the optimal duration of secondary prophylaxis for NTS bacteremia in HIV-infected patients are lacking, although long-term secondary prophylaxis with ciprofloxacin has been recommended by the Department of Health and Human Services guidelines [23]. However, the recommendation does not take into consideration the increasing trends of NTS isolates with reduced susceptibility or resistance to fluoroquinolones and other antibiotics worldwide [24–28]. With such increasing trends, prescription of orally bioavailable antibiotics as secondary prophylaxis will become problematic in this population at high risk for recurrent NTS bacteremia.

In this study, we aimed to compare the incidence of recurrent NTS bacteremia before and after the introduction of HAART and to assess the trends of fluoroquinolone resistance of NTS isolates in HIV-infected patients in Taiwan.

## METHODS

*Setting.* All HIV-infected patients with NTS bacteremia diagnosed at the National Taiwan University Hospital from June 1994 through June 2006 were identified from the database of our prospective observational cohort study [29]. A standardized case record form was used to collect clinical and microbiological data for the patients with NTS bacteremia. During the 12-year study period, 1397 HIV-infected patients were consecutively enrolled in the cohort study. Most of the patients were in the late stage of HIV infection, with a median CD4 cell count of 96 cells/mL (range, 0–1202 cells/mL); 62.4% of the patients had a baseline CD4 cell count <200 cells/mL.

During the study period, standard treatment of NTS bacteremia was therapy with ceftriaxone or other third-generation cephalosporins for 7–14 days, followed by ciprofloxacin administered at 500 mg twice daily or other newer fluoroquinolones as secondary prophylaxis. Although secondary prophylaxis with fluoroquinolones for NTS bacteremia was not discontinued in the pre-HAART era, the duration of fluoroquinolone prophylaxis in patients receiving HAART was at the discretion of treating physicians. HAART, introduced into Taiwan in April 1997, was defined as the combination of at least 3 antiretroviral agents containing protease inhibitors or nonnucleoside reverse-transcriptase inhibitors and nucleoside reverse-transcriptase inhibitors. Antimicrobial prophylaxis against AIDS-related opportunistic infections and initiation of HAART were prescribed by following the guidelines, with the exception of rifabutin for prophylaxis against *Mycobacterium avium* complex because of concerns over the emergence of rifamycin-resistant *Mycobacterium tuberculosis.*

***Laboratory investigations.*** Isolation of *Salmonella* species from blood samples was performed according to standard methods. Isolates of *Salmonella* serogroups B and C were further identified to the serotype level, according to the Kauffman and White scheme, by using somatic and flagellar antigens (Denka Seiken) and also by conventional methods and the Phoenix System (panel type, NMIC/ID4; Becton Dickson).

Disk diffusion susceptibility tests on the NTS isolates and interpretation of the results were performed by following the guidelines provided by the Clinical and Laboratory Standards Institute (formerly NCCLS) [30]. MICs of ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole (cotrimoxazole), ceftriaxone, and ciprofloxacin were determined using the agar dilution method according to the Clinical and Laboratory Standards Institute guidelines [31].

Genotyping of the isolates from the patients with recurrent NTS bacteremia was determined by the pulsotypes generated by PFGE. The DNA extraction and purification were also performed as described previously [32]. In brief, the DNA was digested by the restriction enzymes *Spe*I, *Xba*I, and *Bln*I, and the restriction fragments were separated in a CHEF DRIII unit (Bio-Rad). Interpretation of the PFGE profiles was in accordance with the description by Tenover et al. [33]. Isolates belonging to the similar pulsotypes (within 6-band differences) by each of the 3 restriction enzymes were defined as the same genotypes. Isolates with identical pulsosubtypes (no band differences) by the 3 restriction enzymes were defined as the same genosubtypes (i.e., clones).

Plasma HIV RNA load was quantified using the Cobas Amplicor HIV-1 Monitor test (Cobas Amplicor, version 1.5; Roche Diagnostics) with a lower detection limit of 400 copies/mL, and CD4 cell count was determined using FACFlow (BD FACS Calibur; Becton Dickinson). The CD4 cell counts and HIV RNA load were monitored every 3–4 months.

***Statistical analysis.*** All statistical analyses were performed using SAS statistical software, version 8.1 (SAS Institute). Categorical variables were compared using $\chi^2$ or Fisher's exact test, whereas noncategorical variables were compared using the Wilcoxon rank sum test. The $\chi^2$ test was used to test the trends of resistance to ampicillin, chloramphenicol, cotrimoxazole, ceftriaxone, and ciprofloxacin of NTS strains that were isolated

from June 1994 through March 1997 (the pre-HAART era), from April 1997 through June 2002 (the early HAART era), and from July 2002 through June 2006 (the late HAART era). In cases of recurrence, only the antibiotic-susceptibility results of the first isolates were analyzed. The incidence rate of recurrent NTS bacteremia was calculated as number of episodes per 100 person-years of observation. Exact 95% CIs for incidence rates were calculated on the basis of the Poisson distribution. The follow-up duration of the patients enrolled in the pre-HAART era was from the date when NTS bacteremia was first diagnosed to the date of last clinic contact, date of death, or 30 September 1997, whichever occurred first, whereas that of the patients enrolled in the HAART era was the date of last clinic contact, date of death, or 31 December 2006, whichever occurred first. The generalized estimating equations were used to assess the association between duration of fluoroquinolone therapy and NTS recurrences [34].

## RESULTS

***Prevalence of NTS bacteremia and incidence rate of recurrent NTS bacteremia.*** During the 12-year study period, 93 (6.7%) of 1397 HIV-infected patients developed 105 episodes of NTS bacteremia, including 16 (9.1%) of 175 patients in the pre-HAART era and 77 (6.3%) of 1222 patients in the HAART era ($P = .22$). The clinical and demographic characteristics of the 93 patients with NTS bacteremia are shown in table 1. In the pre-HAART era, 4 (25%) of 16 patients had recurrent NTS bacteremia, compared with 3 (3.9%) of 77 patients in the HAART era (OR, 8.222; 95% CI, 1.633–41.4; $P = .03$).

In the pre-HAART era, 16 patients whose median CD4 cell count at NTS bacteremia diagnosis was 8 cells/$\mu$L (range, 1–144 cells/$\mu$L) developed 23 episodes of NTS bacteremia: 2 patients with 3 episodes each, 3 patients with 2 episodes each, and 11 patients with 1 episode each. The median interval between 2 episodes of NTS bacteremia among the patients with recurrences was 45.5 days (range, 18–136 days). None of the patients with recurrent NTS bacteremia interrupted secondary prophylaxis with ciprofloxacin and/or cotrimoxazole. As of 30 September 1997, 12 deaths and 2 losses to follow-up had occurred. The total observation duration was 9.92 person-years in the pre-HAART era, and the incidence rate of recurrent NTS bacteremia was 70.56 cases per 100 person-years (95% CI, 28.27–145.4 cases per 100 person-years).

In the HAART era, 77 patients whose median CD4 cell count was 20 cells/$\mu$L (range, 0–431 cells/$\mu$L) developed 82 episodes of NTS bacteremia. One patient with primary CNS lymphoma who was receiving cytoreductive chemotherapy containing steroids developed 1 recurrent episode. Each of 2 other patients who did not adhere to HAART and antibiotic therapy developed 2 recurrent episodes. The median interval between 2 episodes of NTS bacteremia of each patient with recurrences was 59 days (range, 15–543 days). Genotyping results confirmed that all of the recurrent episodes in each case patient were caused by strains with PFGE patterns identical to those of the first isolate (figure 1). The total observation duration was 195.12 person-years, and therefore, the incidence rate of NTS relapse was 2.56 cases per 100 person-years (95% CI, 0.83–5.98 cases per 100 person-years). Compared with the incidence rate for patients enrolled in the pre-HAART era, patients enrolled in the HAART era had a statistically significant reduced risk of recurrent NTS bacteremia, with a rate ratio of 0.036 (95% CI, 0.011–0.114; $P < .001$).

***Serotypes and changes in the antimicrobial susceptibility of NTS isolates.*** Antimicrobial susceptibility by disk diffusion method of 13 available isolates obtained during the pre-HAART era and 70 isolates obtained during the HAART era are shown in table 2. There were no demographic or clinical differences between 83 patients with antimicrobial susceptibility test results and 10 patients without such results (data not shown). In the 3 study periods (i.e., the pre-HAART, early HAART, and late HAART eras), the number of NTS isolates that were resistant to ampicillin, cotrimoxazole, and chloramphenicol was decreasing, and all of the isolates remained susceptible to ceftriaxone in each of the 3 study periods (table 2 and figure 2). In contrast, the prevalence of NTS isolates that were ciprofloxacin-resistant increased from 0% in the pre-HAART era to 6.2% in the early HAART era and 34.2% in the late HAART era ($P = .002$) (table 2 and figure 2).

Of the 82 isolates (88.2%) that were serotyped, 23 were *Salmonella enterica* serotype Choleraesuis, 29 were *S. enterica* serotype Enteritidis, and 30 were *S. enterica* serotype Typhimurium. Fourteen isolates (63.9%) of *S.* Choleraesuis were ciprofloxacin resistant according to the disc diffusion method, compared with 1 isolate (3.4%) of *S.* Enteritidis and none of the *S.* Typhimurium isolates. Nine (60.0%) of the 15 ciprofloxacin-resistant isolates were also resistant to all other antibiotics tested, except ceftriaxone.

Seventy-two NTS isolates were available and had MICs determined. The $MIC_{90}$ values of ampicillin, chloramphenicol, cotrimoxazole, and ceftriaxone remained largely unchanged throughout the 3 study periods (table 2). In contrast, the $MIC_{90}$ of ciprofloxacin increased significantly, from 0.25 $\mu$g/mL in the pre-HAART era to 16 $\mu$g/mL in the late HAART era (table 2).

***Incidence rate of recurrent NTS bacteremia and duration of secondary fluoroquinolone prophylaxis in the HAART era.*** As of 31 December 2006, 70 patients (90.9%) enrolled during the HAART era started HAART, and 30 deaths (39.0% of patients) and 6 losses to follow-up (7.8% of patients) occurred. The median interval between the first episode of NTS bacteremia and death was 160 days (range, 2–1558 days). Six (20%) of the 30 deaths in the HAART era occurred within 30 days after diagnosis of NTS bacteremia (median duration, 10 days;

**Table 1. Characteristics of 93 nonhemophiliac HIV-infected patients aged ≥15 years with nontyphoid *Salmonella* (NTS) bacteremia in the pre-HAART (June 1994–March 1997) and HAART (April 1997–June 2006) eras.**

| Variables | Pre-HAART era ($n$ = 16) | HAART era ($n$ = 77) | $P$ |
|---|---|---|---|
| Age, median years (range) | 36.5 (26–51) | 34 (22–73) | .68 |
| Sex, male/female | 15/1 | 75/2 | .87 |
| Episodes of NTS bacteremia | 23 | 82 | |
| Recurrence | 4 (25) | 3 (3.9) | .02 |
| Recurrent NTS bacteremia, no. of episodes | 7 | 5 | |
| CD4 cell count at onset of NTS bacteremia | | | |
| Median cells/μL (range) | 8 (1–144) | 20 (0–431) | .08 |
| <50 cells/μL | 13/15 (86.7) | 57/75 (76.0) | .30 |
| Concurrent AIDS-defining opportunistic infection | 15 (93.8) | 67 (87.0) | .80 |
| Duration of antibiotic therapy for NTS bacteremia | | | |
| Median days (range) | 10 (5–30) | 10 (1–152) | .16 |
| ≤14 days | 12/16 (75.0) | 63/77 (81.8) | .75 |
| HAART initiated | 6 (37.5) | 70 (90.9) | <.001 |
| Receipt of cotrimoxazole after NTS bacteremia | 16 (100) | 60 (77.9) | .06 |
| Duration of cotrimoxazole prophylaxis after NTS bacteremia, median days (range) | 176 (5–651) | 30.5 (3–1408) | .056 |
| Receipt of ciprofloxacin after NTS bacteremia | 16 (100) | 56 (72.7) | .02 |
| Duration of ciprofloxacin prophylaxis after NTS bacteremia | | | |
| Median days (range) | 176 (5–651) | 22 (3–669) | .001 |
| ≤14 days | 2/16 (12.5) | 15/56 (26.8) | .60 |
| ≤30 days | 3/16 (18.8) | 35/56 (62.5) | .004 |
| ≤180 days | 8/16 (50.0) | 51/56 (91.1) | .002 |
| Observation duration, median days (range) | 176 (5–651) | 665 (2–2918) | .001 |
| Total observation duration, person-years | 9.92 | 195.12 | |
| Incidence (95% CI) of NTS bacteremic recurrence per 100 person-years[a] | 70.56 (28.27–145.4) | 2.56 (0.83–5.98) | <.001 |
| Outcome at the end of observation | | | |
| Survived | 2 (12.5) | 41 (53.2) | .01 |
| Death | 12 (75.0) | 30 (39.0) | |
| Lost to follow-up | 2 (12.5) | 6 (7.8) | |
| Time to death, median days (range) | 138 (5–541) | 160 (2–1588) | |
| Death within 30 days after bacteremia | 3/12 (25) | 6/30 (20) | .99 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.

[a] Rate ratio, 0.036 (95% CI, 0.012–0.114).

range, 2–26 days). Fifty-six patients received secondary prophylaxis with fluoroquinolones for a median duration of 22 days (range, 3–669 days): 35 (62.5%) for ≤30 days and only 5 (8.9%) for>180 days. At discontinuation of fluoroquinolone therapy, the median CD4 cell count was 41 cells/μL (range, 1–588 cells/μL), and the median plasma HIV RNA load was 1440 copies/mL (range, <400 to >750,000 copies/mL). Of the 53 patients who survived >30 days after diagnosis of NTS bacteremia, duration of fluoroquinolone therapy was a median of 26 days (range, 7–669 days); 81.1% of the patients received fluoroquinolones for <90 days. After HAART, the median CD4 cell count increased from 20 cells/μL at baseline to 216 cells/μL (range, 0–985 cells/μL) at the end of follow-up ($P$ < .001).

Of the 15 patients with NTS isolates that were resistant to ampicillin, chloramphenicol, cotrimoxazole, and ciprofloxacin, 1 died of primary CNS lymphoma 10 days after NTS bacteremia was diagnosed; 4 received fluoroquinolones for tuberculosis (1 patient) and disseminated *M. avium* complex infection (3 patients); and 10 other patients, including 8 patients with *S.* Choleraesuis isolates, did not receive ciprofloxacin prophylaxis, although they continued to receive cotrimoxazole prophylaxis for pneumocystosis (at a trimethoprim dosage of 160 mg daily). However, there were no recurrences during HAART for a median observation duration of 745 days (range, 160–2337 days). With HAART, the CD4 cell count of the patients increased from a median of 62 cells/μL (range, 7–431 cells/μL) at diag-

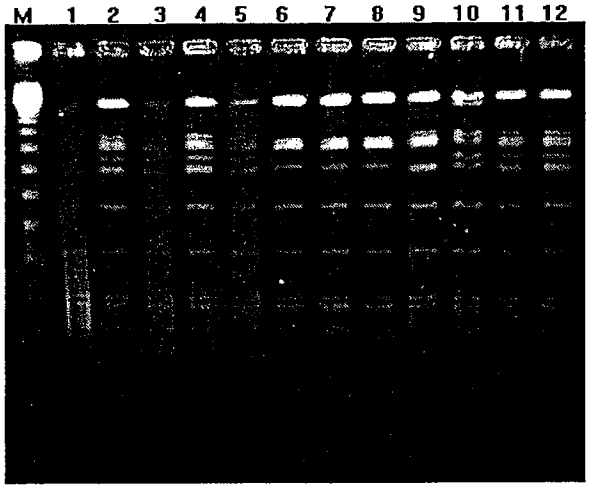


**Figure 1.** Genotyping of 12 isolates of nontyphoid *Salmonella* obtained from 7 patients in the HAART era, determined by the pulsotypes that are generated by PFGE. Identical PFGE patterns are shown for 3 patients with recurrent nontyphoid *Salmonella* bacteremia: patient 1, isolates 1 and 2; patient 2, isolates 3–5; and patient 3, isolates 6–8.

nosis of NTS bacteremia to 344 cells/$\mu$L (range, 140–814 cells/$\mu$L) at the end of follow-up.

The incidence of recurrent NTS bacteremia in patients receiving fluoroquinolone prophylaxis for ≤30 days, including those who did not receive fluoroquinolone prophylaxis, did not increase, compared with the incidence in patients receiving fluoroquinolones for >30 days. In the former group of patients, the incidence of recurrent NTS bacteremia was 1.69 cases per 100 person-years (95% CI, 0.19–6.09 cases per 100 person-years), while in the latter, the incidence was 3.95 cases per 100 person-years (95% CI, 0.79–11.45 cases per 100 person-years) (rate ratio, 0.43; 95% CI, 0.07–2.58; $P = .61$). By generalized estimating equations, we were not able to find an association between duration of ciprofloxacin use and the incidence of recurrent NTS bacteremia after adjustment for CD4 cell count and plasma HIV RNA load at discontinuation of fluoroquinolone prophylaxis ($P = .11$).

## DISCUSSION

In this study, we found that the incidence of recurrent NTS bacteremia was significantly reduced by 96% among patients who achieved favorable immunological and virological responses after receiving HAART, compared with the incidence among patients enrolled in the pre-HAART era (table 1). Despite an increasing trend of fluoroquinolone-resistant NTS, a shorter duration of secondary prophylaxis did not appear to increase the risk of recurrent NTS bacteremia in patients receiving HAART.

The type of antibiotic therapy prescribed for NTS bacteremia and secondary prophylaxis may have been related to the risk of recurrences before HAART was introduced. In an African study, chloramphenicol failed to eradicate NTS bacteremia in 47% of the episodes [12]. After treatment with ampicillin or extended-spectrum cephalosporins for 2–3 weeks, recurrent NTS bacteremia continued to occur [13, 14]. Ciprofloxacin prophylaxis administered for 1–8 months was found to effectively prevent recurrent NTS bacteremia in 4 HIV-infected patients [15]. In this study, we found that 25% of the patients enrolled in the pre-HAART era developed recurrences while they were receiving 175 days of ciprofloxacin prophylaxis, after receiving ceftriaxone or ciprofloxacin as initial therapy for NTS bacteremia. It was not until the introduction of HAART that the incidence of recurrent NTS bacteremia significantly decreased, from 70.56 cases per 100 person-years to 2.56 cases per 100 person-years (table 1).

Recurrent NTS bacteremia has been found to occur mainly in patients with low CD4 cell counts. In this study, patients presenting with NTS bacteremia had depleted CD4 cell counts (median CD4 cell count, 8 cells/$\mu$L and 20 cells/$\mu$L in the pre-HAART and HAART eras, respectively) (table 1). They would have been at high risk for recurrences if their CD4 cell counts had remained low without antiretroviral therapy. After HAART, the median CD4 cell count increased from 20 cells/$\mu$L to 216 cells/$\mu$L, and >60% of the patients had achieved undetectable HIV RNA loads. Therefore, our study suggests that favorable immunological and virological responses contributed to a decreased risk of recurrent NTS bacteremia.

In our study, we found a significant increase in ciprofloxacin-resistant NTS isolates obtained from HIV-infected patients. The increase may be related to the emergence of fluoroquinolone resistance in *S.* Choleraesuis in Taiwan [25, 32], immunosuppression, and prior use of antimicrobial agents [35]. In patients with and patients without HIV infection, antimicrobial-resistant NTS strains cause more cases of bacteremia and more hospitalizations than do strains that are pansusceptible [19, 35]. Despite drug resistance, recurrences did not develop in 10 of our patients who were infected with ciprofloxacin-resistant NTS and did not receive effective secondary prophylaxis. Similar to the studies of the discontinuation of primary or secondary prophylaxis for several opportunistic infections in the HAART era, we believe that significant increases in CD4 cell counts have conferred protection against recurrences in patients who did not receive fluoroquinolones as secondary prophylaxis.

The appropriate duration of fluoroquinolone prophylaxis for HIV-infected patients receiving HAART remains unknown, despite the recommendation for long-term secondary prophylaxis with ciprofloxacin by the Department of Health and Human Services guidelines [23]. Our preliminary analysis, performed in the absence of ciprofloxacin resistance, suggested that a 30-day course of ciprofloxacin prophylaxis appeared to be effective

**Table 2. Antimicrobial susceptibility of nontyphoid *Salmonella* isolates causing bacteremia determined using disc diffusion methods in the pre-HAART (June 1994–March 1997), early HAART (April 1997–June 2002), and late HAART (July 2002–June 2006) eras.**

| Variable | Pre-HAART era | Early HAART era | Late HAART era | Overall | *P* |
|---|---|---|---|---|---|
| No. (%) of patients | 16 | 36 | 41 | 93 | |
| No. (%) of patients with susceptible isolates, by drug | | | | | |
| Ampicillin | 4/13 (30.8) | 16/31 (51.6) | 20/38 (52.6) | 40/82 (48.8) | .37 |
| Chloramphenicol | 2/13 (15.4) | 14/29 (48.3) | 20/37 (54.1) | 36/79 (45.6) | .051 |
| Cotrimaxazole | 7/13 (53.8) | 24/31 (77.4) | 30/38 (78.9) | 61/82 (74.4) | .18 |
| Ceftriaxone | 13/13 (100) | 32/32 (100) | 38/38 (100) | 83/83 (100) | >.99 |
| Ciprofloxacin | 13/13 (100) | 30/32 (93.8) | 25/38 (65.8) | 68/83 (81.9) | .002 |
| No. of isolates | 14 | 27 | 31 | 72 | |
| $MIC_{90}$, μg/mL | | | | | |
| Ampicillin | >128 | >128 | >128 | >128 | |
| Chloramphenicol | >128 | >128 | >128 | >128 | |
| Cotrimaxazole | 16 | >128 | >128 | >128 | |
| Ceftriaxone | 0.12 | 0.12 | 0.06 | 0.12 | |
| Ciprofloxacin | 0.25 | 0.25 | 16 | 16 | |

in preventing recurrent NTS bacteremia in patients receiving HAART [37]. In this study, which involved a larger sample size and a longer observation duration, we further demonstrated that the incidence of recurrent NTS bacteremia in patients receiving fluoroquinolones for ≤30 days was similar to that in those receiving fluoroquinolones for >30 days in the era of HAART.

There are several limitations to our current study. First, this is not a randomized clinical trial, and the duration of ciprofloxacin prophylaxis was not predetermined before this observational study was started. In view of a low incidence of recurrent NTS bacteremia in the HAART era, a large study population is needed to determine the appropriate timing of discontinuation of ciprofloxacin prophylaxis after HAART. Second, a large proportion of patients in this study who survived NTS bacteremia received HAART with virological suppression. Our results may not be generalizable to patients who experience virological and immunological failure or to patients with limited access to HAART. Third, the number of NTS isolates that are resistant to fluoroquinolones remains small. More studies are needed to assess the impact of fluoroquinolone resistance on the selection of antimicrobial prophylaxis. Fourth, cotrimoxazole, with variable in vitro antimicrobial activities against NTS isolates, was prescribed for pneumocystosis prophylaxis in most (77.9%) of our patients who were enrolled in the HAART era when they discontinued ciprofloxacin prophylaxis. We were not able to completely exclude the possibility that cotrimaxazole, when administered at a prophylactic dose, may

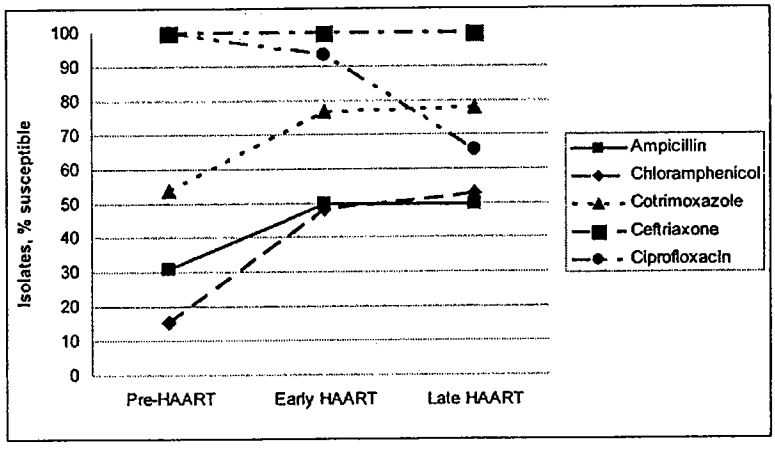


**Figure 2.** Trends of antimicrobial resistance of nontyphoid *Salmonella* isolates to ampicillin, chloramphenicol, cotrimoxazole, ceftriaxone, and ciprofloxacin for 3 study periods: the pre-HAART era (June 1994–March 1997), the early HAART era (April 1997–June 2002), and the late HAART era (July 2002–June 2006).

confer protection against recurrent NTS bacteremia. However, the effect of prevention, as shown in a previous study, may be negligible [18]. In our study, the $MIC_{90}$ of cotrimoxazole was high (>128 μg/mL), and 25% of the patients who received cotrimoxazole prophylaxis in the pre-HAART era developed recurrences. Finally, *S.* Choleraesuis, for which higher prevalences of resistance to fluoroquinolones and to third-generation cephalosporins have been reported in Taiwan than in other industrialized countries [25, 32], accounted for 28.0% of the NTS isolates in this study. Therefore, our findings may not be generalizable to other countries where *S.* Choleraesuis is not the predominant NTS serotype, such as the United States and several European countries [24, 26–28, 35, 36]. However, concerns have been raised regarding the increasing prevalence of other NTS serotypes isolated from humans and from imported meat that are resistant to nalixidic acid and that exhibit reduced susceptibility to ciprofloxacin ($MIC_{90}$, 0.125–2 mg/L) in several industrialized countries [27, 28]. Surveillance studies are needed to assess the trends of antibiotic resistance of NTS isolates in HIV-infected patients.

In conclusion, our findings suggest that the risk of recurrent NTS bacteremia decreased significantly in the HAART era, although the prevalence of fluoroquinolone resistance was increasing in Taiwan. If our findings are confirmed by other investigators, a shorter course of secondary ciprofloxacin prophylaxis can be recommended to prevent recurrences of NTS bacteremia in HIV-infected patients who continue to receive HAART with favorable responses.

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***Potential conflicts of interest.*** All authors: no conflicts.

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## Amoebiasis: current status in Australia

Chien-Ching Hung

**TO THE EDITOR:** I read with great interest the recent updated review of amoebiasis by van Hal and colleagues[1] and their previous letter[2] describing three cases of locally acquired amoebiasis due to *Entamoeba histolytica* in Australian men who have sex with men (MSM). These articles should alert clinicians to the emergence of invasive amoebiasis and the possibility of person-to-person transmission of *E. histolytica* through oral–anal or oral–genital sex among MSM in developed countries. The same phenomenon has been reported in Taiwan[3] and Japan.[4]

The prevalence or incidence of intestinal amoebiasis among people at risk may have been underestimated in the past, as microscopy of stool specimens has lower sensitivity and specificity than *E. histolytica* antigen

detection methods for diagnosing the disease.[1,5] Cases of amoebiasis may evade detection using the diagnostic algorithm proposed by van Hal and colleagues,[1] which suggests using microscopy of stool specimens to detect *E. histolytica* complex followed by confirmation with specific antigen detection methods or molecular methods. To increase diagnostic sensitivity and specificity, I suggest revising the diagnostic algorithm for intestinal amoebiasis in developed countries to include more accurate first-line detection methods. For example, specific antigen detection methods or polymerase chain reactions, as proposed by Tanyuksel and Petri,[5] could be incorporated.

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3 Hung CC, Deng HY, Hsiao WH, et al. Invasive amebiasis as an emerging parasitic disease in patients with human immunodeficiency virus type 1 infection in Taiwan. *Arch Intern Med* 2005; 165: 409-415.
4 Nozaki T, Kobayashi S, Takeuchi T, Haghighi A. Diversity of clinical isolates of *Entamoeba histolytica* in Japan. *Arch Med Res* 2006; 37: 277-279.
5 Tanyuksel M, Petri WA Jr. Laboratory diagnosis of amebiasis. *Clin Microbiol Rev* 2003; 16: 713-729. ❑

## *Aspergillus* galactomannan antigenemia in penicilliosis marneffei

*Penicillium marneffei* usually causes pneumonia and other systemic diseases in HIV-infected patients, especially those who live in or travel to endemic areas [1]. In recent years, this organism has emerged in Taiwan among immunocompromised patients, particularly in HIV-infected patients in whom aspergillosis was rarely encountered [2]. The detection of galactomannan by the Platelia enzyme-linked immunosorbent assay (ELISA; Bio-Rad, Hercules, California, USA) has been widely used in diagnosing invasive aspergillosis [3]. False positives have been identified in patients receiving certain batches of piperacillin–tazobactam, amoxicillin–clavulanic acid [4,5]. In-vitro

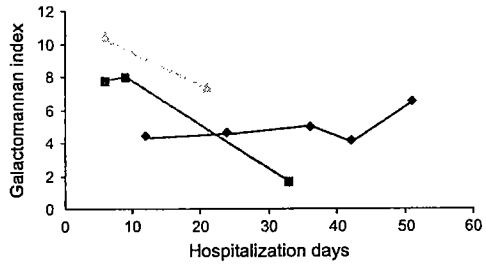


**Fig. 1. Serial optical density index of serum galactomannan for three patients with penicilliosis marneffei.** ◆ Patient A; ■ patient B; ▲ patient C.

cross-reactivity of the Platelia ELISA with *Penicillium* galactomannan and *Cryptococcus* galactoxylomannan have been reported, and this cross-reactivity has also been reported in a human case with penicilliosis marneffei [6–8].

Patient A, a 47-year-old male heroin abuser with HIV infection, was referred with cough and fever lasting for one month. The blood culture at admission revealed *Mycobacterium avium-intracellulare* complex. A chest computed tomography scan revealed a cavitation over the left lower lung field. The serum galactomannan sent for suspicious *Aspergillosis* was positive [optical density (OD) index 4.419] and bronchial washing culture on the next day revealed *P. marneffei*. His blood culture (Bactec 9240 Myco/F Lytic bottle; Becton Dickinson, Sparks, Maryland, USA) was negative for *P. marneffei* and the serum galactomannan OD index remained positive 33 days after treatment (OD index 6.527; Fig. 1).

Patient B was a 34-year-old man with HIV infection suffering from fever and dry cough for half a month. A chest radiograph revealed a patchy lesion over the right upper lung region. Blood culture at admission revealed *P. marneffei*. The serum galactomannan test before initiating amphotericin B treatment was positive (OD index 7.752) and remained positive 27 days after treatment when the blood culture was sterile (OD index 1.586).

Patient C was a 39-year-old man with HIV infection known for 2 years with poor drug compliance. He was admitted for fever and diarrhea lasting for one month. The chest radiograph showed a ground glass lesion over the left perihilar area. Blood culture at admission revealed *P. marneffei*. The serum galactomannan test before starting amphotericin B treatment was positive (OD index 10.48) and remained positive 15 days after treatment when the blood culture was sterile (OD index 7.356).

The initial CD4 cell counts of these three AIDS patients were 9, 30 and 4 cells/μl for patients A, B, and C, respectively. None of the three patients received piperacillin–tazobactam or amoxicillin–clavunalic acid during their hospital stay. All three patients were not neutropenic and survived the episodes of penicilliosis marneffei. No *Aspergillus* species was ever isolated from their sputum or any clinical specimens.

The results confirm the cross-reactivity of the Platelia ELISA kit with *P. marneffei* and with serum from patients with penicilliosis marneffei, which remained positive even after effective treatment. The length of galactomannan antigenemia might have been caused by the possibly lower clearance rate of *Penicillium* galactomannan compared with *Aspergillus* galactomannan or the presence of *Penicillium* in the lesion, with a continuous secretion of galactomannan, which enters the bloodstream. The cross-reactivity could be used as a rapid diagnosis for penicilliosis marneffei, although the test was not performed before positive cultures for *P. marneffei* were obtained. Effective treatment does not, however, decrease the titer but instead remains positive, indicating that this test may not be useful for monitoring treatment outcomes.

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# Detection of Circulating Galactomannan in Serum Samples for Diagnosis of *Penicillium marneffei* Infection and Cryptococcosis among Patients Infected with Human Immunodeficiency Virus[▽]

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**Galactomannan (GM) is a heteropolysaccharide in the cell walls of most *Aspergillus* and *Penicillium* species. Cross-reactivity of *Cryptococcus neoformans* galactoxylomannan in an *Aspergillus* GM test has also been reported. In this study, we used a Platelia *Aspergillus* enzyme immunoassay kit (Bio-Rad) to test serum samples obtained from 48 human immunodeficiency virus (HIV)-infected patients (15 with penicilliosis [7 with fungemia alone, 4 with cavitary lung lesions alone, 3 with both fungemia and cavitary lung lesions, and 1 with disseminated disease], 22 with cryptococcosis [11 with fungemia alone, 5 with cavitary lung lesions, 3 with both, and 3 with meningitis alone], and 11 without any invasive fungal infection [control]) for GM levels. None of the patients had aspergillosis or concurrent use of piperacillin-tazobactam or amoxicillin-clavulanate. The median time between diagnosis of fungal infection and collection of serum samples was 0 days for penicilliosis and 1.5 days for cryptococcosis. Of patients with penicilliosis, cryptococcosis, and controls, 73.3%, 13.6%, and 9%, respectively, had GM optical density (OD) indices of >0.5 ($P = 0.0001$). GM OD indices were higher for penicilliosis (median OD index, 4.419; range, 0.158 to >20) than for cryptococcosis (median, 0.247; range, 0.112 to 3.849) cases ($P < 0.001$). Patients with fungemic penicilliosis had higher OD indices (median, 10.628; range, 0.401 to >20) than patients with nonfungemic penicilliosis (median, 0.378; range, 0.158 to 4.419) and patients with cryptococcemia (median, 0.231; range, 0.112 to 1.168) ($P < 0.001$). Of the 15 patients with cavitary lung lesions, those with penicilliosis had higher antigen levels (median OD index, 1.641; range, 0.247 to >20) than those with cryptococcosis (median, 0.227; range, 0.112 to 3.849) ($P = 0.011$). This study showed that the GM OD index was significantly elevated for HIV patients with penicilliosis. The use of the GM antigen assay may facilitate earlier diagnosis of *Penicillium marneffei* infection for HIV-infected patients in areas of endemicity.**

Invasive fungal infections are common opportunistic infections associated with significant morbidity and mortality for patients with human immunodeficiency virus (HIV) infection, and the risk of invasive fungal infection varies with host immunity as well as environmental exposure (7, 14, 17, 18, 19). *Penicillium marneffei* and *Cryptococcus neoformans* are important endemic fungi in Southeast Asia that cause systemic infections in HIV-infected patients, especially those who have low CD4 counts (17, 21). The clinical presentations of *P. marneffei* infection and cryptococcosis for HIV-infected patients may mimic those of tuberculosis, histoplasmosis, and other infections. Early diagnosis and timely initiation of appropriate therapy are complicated by nonspecific signs and symptoms as well as by difficulties in obtaining tissues for histological recognition. Microbiologic isolation and species identification of the pathogens may be time-consuming (7, 19, 21). Rapid, noninvasive microbiological diagnostic modalities for invasive fungal infections other than determinations of cryptococcal and histoplasma antigens are not available in most parts of the world (2, 3, 9). Although antigen detection to identify *P. marneffei* infection by using monoclonal antibodies specific for *P. marneffei* has been reported (2, 3), these tests are not commercially available, which hampers their usefulness.

Galactomannan (GM) is a heteropolysaccharide composed of a nonimmunogenic mannan core and immunoreactive galactofuransyl side chains in the cell walls of most *Aspergillus* and *Penicillium* species (10, 11, 15). A double-sandwich enzyme-linked immunosorbent assay for determination of *Aspergillus* GM was recently approved by the U.S. Food and Drug Administration (FDA) to facilitate early diagnosis of invasive aspergillosis. Studies have shown that a monoclonal antibody against *Aspergillus* GM reacted with serum and tissue samples from a *P. marneffei*-infected guinea pig as well as with samples from an HIV-infected patient with penicilliosis (14, 20). In addition, extracts and purified galactoxylomannan of *C. neoformans* gave positive reactions by the *Aspergillus* GM test (4). While clinical experience with the *Aspergillus* GM test in invasive aspergillosis is accumulating (11, 13), data on penicilliosis and cryptococcosis remain limited. In this study, we aimed to compare the GM antigen levels detected by the *Aspergillus* test for *P. marneffei* infection versus cryptococcosis in HIV-infected patients.

## MATERIALS AND METHODS

**Patients and serum samples.** Cases and controls were selected from HIV-infected patients who were hospitalized between January 2000 and December

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TABLE 1. Baseline characteristics and clinical data of 48 patients enrolled for serum GM testing by the *Aspergillus* enzyme immunoassay

| Characteristic[a] | Group | | |
|---|---|---|---|
| | Penicilliosis ($n$ = 15) | Cryptococcosis ($n$ = 22) | Control ($n$ = 11)[b] |
| Age (median [range]) | 37.3 (20–81) | 38.1 (23–65) | 35.6 (23–58) |
| Gender (female/male) | 2/13 | 0/22 | 0/11 |
| Neutrophil count (cells/μl) | | | |
| Range | 1,530–12,665 | 959–10,943 | 840–7,323 |
| Median | 3,680 | 2,482 | 2,522 |
| CD4 cell count (cells/μl) | | | |
| Range | 1–53 | 1–94 | 22–431 |
| Median | 6 | 33 | 238 |
| Interval between diagnosis of fungal infection and blood sampling (days) | | | |
| Range | −7 to 6 | 0 to 6 | NA |
| Median | 0 | 1.5 | NA |
| No. (%) of patients with cavitary lung lesions | 7 (46.7) | 8 (36.4) | NA |
| No. of positive cultures/total no. of cultures (%) by specimen type | | | |
| Blood | 10/15 (66.7) | 14/22 (63.6) | NA |
| Bone marrow | 3/6 (50.0) | 1/3 (33.3) | NA |
| CSF | 0/4 (0.0) | 12/21 (57.1) | NA |
| Lung aspirate | 5/7 (71.4) | 1/4 (25.0) | NA |
| Lymph node biopsy | 2/3 (66.7) | 0/2 (0.0) | NA |
| Skin biopsy | 4/4 (100) | 0/4 (0.0) | NA |
| Sputum | 7/15 (46.7) | 2/22 (9.1) | NA |
| No. (%) of patients with concomitant opportunistic infections | | | |
| Oral candidiasis | 11 (73.3) | 20 (90.9) | 0 |
| Disseminated NTM | 4 (26.7) | 2 (9.1) | 0 |
| Tuberculosis | 2 (13.3) | 1 (4.6) | 0 |
| Salmonellosis | 0 (0.0) | 4 (18.2) | 0 |
| CMV retinitis | 2 (13.3) | 1 (4.6) | 0 |
| CMV pneumonitis | 1 (6.7) | 1 (4.6) | 0 |
| Toxoplasmosis | 0 (0.0) | 1 (4.6) | 0 |
| HSV esophagitis | 1 (6.7) | 0 (0) | 0 |
| PCP | 0 (0.0) | 3 (13.6) | 0 |

[a] CMV, cytomegalovirus; CSF, cerebrospinal fluid; HSV, herpes simplex virus; NTM, nontuberculous mycobacteria; PCP, *Pneumocystis carinii* (*jiroveci*) pneumonia.
[b] NA, not applicable.

2006 at the National Taiwan University Hospital, the largest referral hospital for HIV care in Taiwan. Medical records of HIV-infected patients diagnosed with penicilliosis or cryptococcosis in an ongoing prospective cohort study were reviewed using a standardized case record form (17, 18). Infection due to *P. marneffei* or *C. neoformans* was diagnosed by identifying the fungus by microscopy and cultures of clinical specimens, including blood, bone marrow aspirate, cerebrospinal fluid, lung aspirate, lymph node biopsy, skin biopsy, and sputum specimens. India ink smears and determinations of cryptococcal antigen levels in clinical specimens by the Latex-Crypto antigen detection system (Immuno Mycologics, Inc., Norman, OK) were also included for the diagnosis of cryptococcosis (17, 21).

Stored serum samples from patients with penicilliosis and cryptococcosis were retrieved for analysis. The serum samples, obtained once the diagnoses of HIV infection and opportunistic infection were made, were stored at −80°C before use. Serum samples from 11 randomly selected HIV-infected patients without active opportunistic infections were obtained as controls. Patients who were receiving piperacillin-tazobactam or amoxicillin-clavulanate within 3 days of serum collection were not included for serum GM detection because both antibiotics have been demonstrated to cause elevation of *Aspergillus* GM antigen levels (12, 16).

**GM antigen detection.** GM levels were determined using the Platelia *Aspergillus* enzyme immunoassay (Bio-Rad, Marnes-la-Coquette, France) by following the manufacturer's instructions. The test uses a rat anti-GM monoclonal antibody, EB-A2, to recognize the galactofuranoside side chain of the GM molecule (15). Because there was no cutoff value for GM antigen levels in the diagnosis of *P. marneffei* and *C. neoformans* infections in the literature, we analyzed the results using three different optical density (OD) cutoff indices: 0.5, 1.0, and 1.5. For the diagnosis of aspergillosis, a cutoff index of 0.5 is accepted by the FDA, while a cutoff index of 0.7 is commonly used in Europe. Besides, 1.5 was the cutoff value initially proposed.

**Statistical analysis.** All statistical analyses were performed using SPSS software (version 12.0, 2003; SPSS Inc., Chicago, IL). Categorical variables were compared using a $\chi^2$ test or Fisher's exact test, whereas noncategorical variables were compared using Wilcoxon's rank-sum test. Because both invasive fungal infections are often associated with fungemia and cavitary lung lesions in HIV-infected patients (18), subgroup analyses of patients with fungemia and patients with cavitary lung lesions were performed, and comparisons of the GM OD indices of serum samples from patients with penicilliosis and cryptococcosis were stratified by the presence or absence of fungemia and the presence or absence of cavitary lung lesions.

## RESULTS

We selected 48 serum samples obtained from 48 HIV-infected patients, including 15 patients with penicilliosis, 22 pa-

TABLE 2. Serum GM OD indices of patients with penicilliosis, cryptococcosis, and controls

| Patient group | GM OD index | | No. (%) with a GM OD index of: | | | |
|---|---|---|---|---|---|---|
| | Range | Median | >1.5 | >1.0 | >0.5 | <0.5 |
| Penicilliosis | | | | | | |
| With fungemia ($n$ = 10) | 0.401–>20 | 10.628[a] | 8 (80.0) | 8 (80.0) | 9 (90.0) | 1 (10.0) |
| Without fungemia ($n$ = 5) | 0.158–4.419 | 0.378[b] | 2 (40.0) | 2 (40.0) | 2 (40.0) | 3 (60.0) |
| All ($n$ = 15) | 0.158–>20 | 4.419[c] | 10 (66.7) | 10 (66.7) | 11 (73.3) | 4 (26.7) |
| Cryptococcosis | | | | | | |
| With fungemia ($n$ = 14) | 0.112–1.168 | 0.231[a] | 0 (0.0) | 1 (7.1) | 1 (7.1) | 13 (92.9) |
| Without fungemia ($n$ = 8) | 0.115–3.849 | 0.263[b] | 1 (12.5) | 1 (12.5) | 2 (25.0) | 6 (75.0) |
| All ($n$ = 22) | 0.112–3.849 | 0.247[c] | 1 (4.5) | 2 (9.1) | 3 (13.6) | 19 (86.4) |
| Control ($n$ = 11) | 0.15–1.024 | 0.234 | 0 (0) | 1 (9.1) | 1 (9.1) | 10 (90.9) |

[a] $P < 0.001$ for comparison of GM OD indices for *Penicillium* fungemia and cryptococcal fungemia.
[b] $P = 0.464$ for comparison of GM OD indices for nonfungemic penicilliosis and nonfungemic cryptococcosis.
[c] $P < 0.001$ for comparison of GM OD indices for all cases of *Penicillium marneffei* infection versus all cases of cryptococcosis.

tients with cryptococcosis, and 11 controls without invasive fungal infection. The clinical characteristics of these 48 patients are shown in Table 1. Among 15 patients with penicilliosis, 7 had fungemia alone, 4 had cavitary lung lesions alone, 3 had both, and 1 had *P. marneffei* isolated from lymph node aspirate, sputum, and skin biopsy specimens. All of the four cases of cavitary lung lesions alone due to penicilliosis were diagnosed by positive cultures of computed tomography- or sonography-guided lung aspirates. Among 22 patients with cryptococcosis, 11 had fungemia alone, 5 had cavitary lung lesions alone, 3 had both, and 3 had meningitis alone. Serum cryptococcal antigen titers ranged from 1:4 to 1:4,096 (median, 1:512). None of the 48 patients had *Aspergillus* spp. isolated from their clinical specimens during the 2-month follow-up.

The median time between diagnosis of invasive fungal infection and collection of serum samples was 0 days (range, −7 to 6 days) for penicilliosis and 1.5 days (range, 0 to 6 days) for cryptococcosis. Fourteen patients with penicilliosis had their serum samples collected before the initiation of antifungal therapy. Of 22 patients with cryptococcosis, 14 had sera collected prior to the initiation of antifungal therapy, 5 within 24 h of the initiation of antifungal therapy, and 3 within 2 days of therapy.

The median OD index was significantly higher for the 15 patients with penicilliosis (4.419) than for the 22 patients with cryptococcosis (0.247) ($P < 0.001$) and the 11 controls (0.234) ($P = 0.001$) (Table 2; Fig. 1 and 2). Among patients with fungemia, the 10 patients with penicilliosis also had a higher median OD index than the 14 patients with cryptococcosis (10.628 versus 0.231; $P < 0.001$) (Table 2; Fig. 2). Among nonfungemic patients, the median OD indices of the penicilliosis and cryptococcosis groups were not significantly different (0.378 versus 0.263; $P = 0.464$). Among the 15 patients with cavitary lung lesions, the median OD index was higher for the 7 penicilliosis patients (median, 1.641; range, 0.247 to >20) than for the 8 cryptococcosis patients (median, 0.227; range, 0.112 to 3.849) ($P = 0.011$).

Of patients with penicilliosis, cryptococcosis, and controls, 73.3%, 13.6%, and 9%, respectively, had GM OD indices higher than 0.5 ($P = 0.0001$) (Table 2). Of the four patients with penicilliosis who had OD indices below 0.5 (26.7%), one had his serum sample obtained 7 days before the collection of the first positive blood culture, two had nonfungemic penicilliosis with cavitary lung lesions, and one had *P. marneffei* isolated from lymph node aspirate, sputum, and skin biopsy samples. Of the three patients with cryptococcosis who had OD indices greater than 0.5 (13.6%), one with an OD index of 3.849 presented with a cavitary lung lesion without fungemia; however, tissue biopsy was not performed. The OD indices of the other two patients, who had no cavitary lung lesions, were 0.655 and 1.168, respectively. No microbiological evidence of aspergillosis or penicilliosis was documented during the follow-up period. One of the 11 control patients (9.0%) had an elevated OD index of 1.024. After follow-up for 6 months, he did not develop invasive fungal infections or lung lesions.

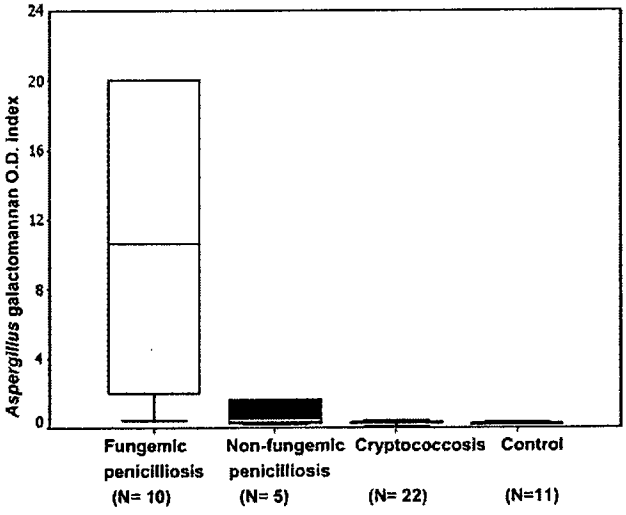


FIG. 1. GM antigen levels for HIV-infected patients with fungemic penicilliosis, nonfungemic penicilliosis, or cryptococcosis and for controls. The bar in each box represents the median value of the GM OD index for that patient group, while the error bars indicate the range. The upper and lower limits of each box represent the 75th and 25th percentiles, respectively, of the OD index for the group. For values greater than 20, the OD index of 20 is used as the upper limit in the box.

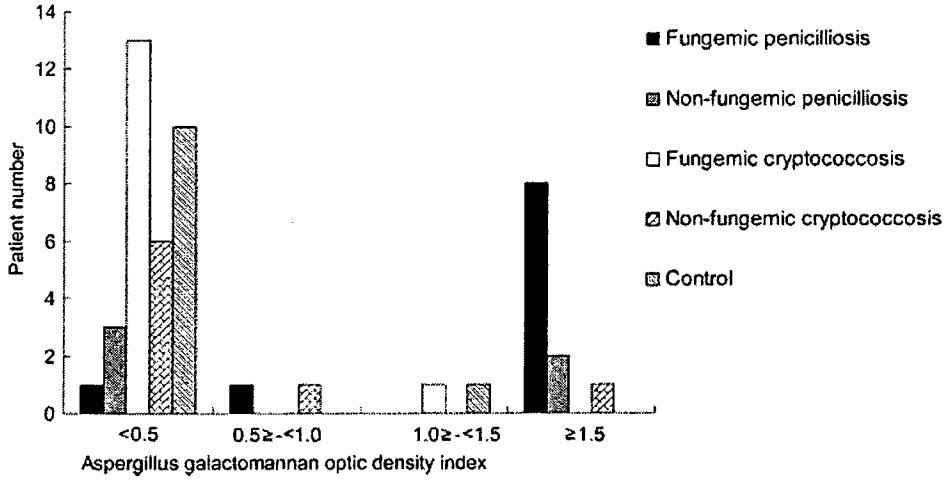


FIG. 2. Distribution of *Aspergillus* GM OD indices among HIV-infected patients with penicilliosis, HIV-infected patients with cryptococcosis, and controls.

## DISCUSSION

In this study, we found that patients with fungemia due to *P. marneffei* had the highest GM OD indices by the *Aspergillus* enzyme immunoassay and that these levels were significantly higher than those for patients with penicilliosis but without fungemia, patients with cryptococcosis, and control patients.

Since invasive aspergillosis was very rare in our HIV cohort (18), we did not compare GM levels between HIV-infected patients with aspergillosis and those with penicilliosis. Compared with GM OD indices for patients with invasive aspergillosis (1, 11), this study showed relatively high GM antigen levels for patients with fungemic penicilliosis (median, 10.628). This finding is in accordance with the fact that *P. marneffei* is more likely to be isolated from blood samples of HIV-infected patients than *Aspergillus* spp. (8, 17).

The median GM OD index was significantly lower for patients with cryptococcosis than for patients with penicilliosis. However, 3 of 22 patients (13.6%) with cryptococcosis had GM OD indices higher than 0.5. Concomitant penicilliosis cannot be excluded. Alternatively, this finding may be caused by *C. neoformans* galactoxylomannan, which cross-reacts with the *Aspergillus* GM antigen assay (4). However, the cross-reactivity was not confirmed in a recent comprehensive study (5). Since determination of serum cryptococcal antigen levels using a latex agglutination test is sensitive and specific for immunocompromised hosts, it will not hamper the usefulness of the GM antigen assay in the diagnosis of invasive fungal infections in HIV-infected patients.

Pulmonary aspergillosis has been reported to be a main cause of cavitary lung lesions for HIV-infected patients (6), and the incidence of aspergillosis among HIV-infected patients was 3.5 cases per 1,000 person-years in a surveillance study between 1990 and 1998 (8). However, of 1,182 HIV-infected patients monitored at this hospital, only 3 patients (0.3%) had invasive aspergillosis diagnosed before the introduction of highly active antiretroviral therapy (18). This and our previous studies showed that a higher proportion of HIV-infected patients with penicilliosis or cryptococcosis had cavitary lung lesions (17, 18). As a result, penicilliosis should be included in the differential diagnosis of cavitary lung lesions for HIV-infected patients, and possibly for other immunocompromised patients, who have GM antigenemia in areas of endemicity (22).

This study has several limitations. First, the sample size is small. More studies are needed to elucidate the role of this GM antigen assay in the diagnosis of penicilliosis in areas of endemicity. Second, diagnosis of nonfungemic penicilliosis may be limited by the relatively low levels of GM in serum. Therefore, bronchoscopy or aspiration/biopsy guided by computed tomography or sonography should be considered for such patients. Third, the GM index was determined by using stored serum samples, and the influence of freezing and thawing on the GM antigen assay is not clear. Fourth, only one serum sample from each patient was used for analysis. A previous report showed that the GM OD index for an HIV-infected patient with penicilliosis declined after treatment for 2 months (14). The temporal trend of GM antigen levels following initiation of antifungal therapies and the question of whether the antigen levels can be used to monitor the response to antifungal therapies remain to be investigated.

In conclusion, our data suggest that the OD index of the GM antigen detected by the *Aspergillus* enzyme immunoassay is significantly elevated for HIV patients with penicilliosis compared with HIV-infected patients with cryptococcosis or controls. Determination of the GM OD index by the *Aspergillus* assay may facilitate earlier diagnosis of *P. marneffei* infection for HIV-infected patients with compatible clinical presentations before the results of microbiologic cultures are available.

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# Impact of Hepatitis D Virus Infection on the Long-Term Outcomes of Patients with Hepatitis B Virus and HIV Coinfection in the Era of Highly Active Antiretroviral Therapy: A Matched Cohort Study

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***Background.*** Triple infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis D virus (HDV) is rare. The influence of HDV infection on the responses to highly active antiretroviral therapy and hepatic complications in patients with HBV-HIV coinfection remains uncertain.

***Methods.*** Twenty-six HDV-infected case patients and 78 HDV-uninfected matched control subjects were identified between 1 January 1995 and 30 June 2003. Clinical and immunologic outcomes were noted, and HBV and HIV loads and genotypic resistance of HBV to lamivudine were determined.

***Results.*** Case patients had a higher rate of injection drug use (7.7% vs. 1.3%; $P = .05$) and lower serum levels of HBV DNA (median level, 4.04 vs. 5.75 $\log_{10}$ copies/mL; $P = .07$) than control subjects. During a median observation period of 54.7 months, HDV infection did not have an adverse impact on clinical, virological, or immunologic responses to highly active antiretroviral therapy. However, case patients had higher rates of hepatitis flares (57.7% vs. 23.1%; $P = .002$), hyperbilirubinemia (34.6% vs. 14.1%; $P = .04$), liver cirrhosis (26.9% vs. 5.1%; $P = .009$), hepatic decompensation (23.1% vs. 5.1%; $P = .007$), and death (adjusted hazard ratio, 5.41; 95% confidence interval, 1.39–23.85; $P = .02$), although these patients had a lower risk of genotypic resistance to lamivudine (0% vs. 57.1%; $P = .003$).

***Conclusions.*** HDV infection did not affect clinical, virological, or immunologic responses to highly active antiretroviral therapy in patients with HBV-HIV coinfection. HDV infection increased risk of hepatitis flares, liver cirrhosis, hepatic decompensation, and death in patients with HBV-HIV coinfection.

It is estimated that 6%–10% of HIV-infected patients have hepatitis B virus (HBV) coinfection in Western countries [1, 2]. Coinfection with HBV has been shown to increase the risk of acute hepatitis, hepatic decompensation, liver-related mortality, and virological failure in HIV-infected patients receiving HAART [1–3].

Hepatitis D virus (HDV) is a defective satellite virus that requires a helper function provided by HBV [4]. It has been estimated that ~5% of HBV carriers are also coinfected with HDV, resulting in ~15 million persons infected with HDV worldwide [5]. Most studies suggest that the majority of HDV infections are acquired through parenteral and sexual routes [6–8], which are also important routes for HIV transmission. In HIV-uninfected patients with chronic HBV infection, HDV coinfection may suppress HBV replication with subsequent clearance of hepatitis B surface antigen (HBsAg) [9–11] by exerting an inhibitory effect on the host DNA-dependent RNA polymerase that is involved in HBV transcription [12, 13].

Clinical studies regarding the impact of HDV infection on patients with HBV-HIV coinfection were limited and yielded inconsistent results before the introduction of HAART [14–17]. Some suggested that HIV

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coinfection might worsen chronic liver damage caused by HDV [6, 14], and patients with long-term HDV infection were more likely to develop cirrhosis than were patients with HBV infection alone [18], whereas others showed that the course of long-term HDV infection was not influenced by concomitant HIV infection [15–17]. Regarding the interaction with HBV, HDV coinfection was shown to significantly suppress HBV replication, which might ameliorate the damage incurred as a result of HBV infection [18]. However, HDV coinfection may lead to exacerbation and rapid progression of chronic liver disease, hepatic failure, and death in patients with HBV infection [6, 8]. These discrepancies may be related to patient selection and the shorter survival of patients before the introduction of HAART. The long-term impact of HDV infection on clinical outcomes and on the emergence of lamivudine-resistant HBV in HIV-infected patients with chronic HBV infection receiving prolonged lamivudine therapy is unknown. The improved survival rates among HIV-infected patients since the introduction of HAART in 1996 may allow complications and liver-related deaths involving chronic hepatotrophic virus infection to emerge [19]. Taking advantage of a higher prevalence of chronic HBV infection (15%–20%) in the general population and a higher prevalence of patients with HIV infection in Taiwan (21.7%) [3], we conducted a matched cohort study to investigate the impact of HDV infection on the immunologic, virological, and clinical responses to HAART of patients who had HBV-HIV coinfection.

## PATIENTS AND METHODS

***Setting.*** HIV-infected patients with test results positive for HBsAg for at least 6 months (i.e., with chronic HBV infection) who were seen at the National Taiwan University Hospital from 1 January 1995 to 30 June 2003 were enrolled. Although HAART has been provided without charge to all patients with HIV infection since April 1997, newer therapeutic agents for treating HBV infection, such as adefovir, entecavir, and tenofovir, were not available in Taiwan during this study period.

***Case-control matching.*** For patients with chronic HBV infection, serum samples were tested for antibody to HDV (anti-HDV); those patients with positive results were considered to be HDV-infected patients (case patients), and those patients with negative test results were considered to be control subjects. Each case patient was matched with 3 control subjects with respect to age (±2 years), sex, baseline $CD4^+$ cell count, date of enrollment (±3 months), serum albumin level (±0.5 g/dL), and serum bilirubin level (±0.3 mg/dL). When several potential control subjects were found, the control subject with the date of enrollment nearest to that of the case patient was selected. Patients with chronic alcoholism, test results positive for antibody to HCV or HCV viremia, total bilirubin levels >2.0 mg/dL, decompensated liver disease, and cirrhosis of the liver documented by abdominal sonography at enrollment were excluded. Six patients who had negative anti-HDV test results at enrollment but who experienced seroconversion and had positive test results at the last visit were also excluded. The study was approved by institutional review board of the hospital (NTUH-9261700889).

***Laboratory tests and radiographic investigations.*** Liver function tests were performed and serum aminotransferase and bilirubin levels, $CD4^+$ cell count, and plasma viral load of HIV (HIV-PVL) were determined every 3–4 months. HIV-PVL was quantified using the Cobas Amplicor HIV-1 Monitor test, version 1.5 (Roche Diagnostics), with a lower limit of detection of 400 copies/mL (2.60 $\log_{10}$ copies/mL), and $CD4^+$ cell count was determined using FACFlow (BD FACS Calibur; Becton Dickinson).

Patients underwent testing with an EIA for HBsAg, antibody to HBsAg, hepatitis B e antigen, antibody to hepatitis B e antigen, and anti-HDV at enrollment and either in December 2004 or at the last hospital visit. Antibody to HCV was assayed using a third-generation EIA (Ax Sym HCV III; Abbott Laboratories). HCV RNA level was determined using the Cobas Amplicor HCV Monitor assay, version 2.0 (Roche Diagnostics), for patients with a baseline $CD4^+$ cell count of <200 cells/μL.

HDV RNA was extracted from preserved serum samples from patients with test results positive for anti-HDV at enrollment using the QIAamp Viral RNA Mini Kit (Qiagen), and the purified RNA was subjected to nested RT-PCR. The primer sets for HDV are shown in the Appendix. The amplification condition was 30 cycles at 94°C for 30s, 55°C for 1 min, 72°C for 2 min, and a final extension at 72°C for 7 min. A 1-μL aliquot of the first-round PCR product was used for the second-round PCR, which was performed under the same conditions as the first round. The expected size for the PCR product was 419 base pairs, and the PCR results were visualized by gel electrophoresis.

HBV DNA was extracted from 200 μL of serum using the High Pure Viral Nucleic Acid Kit (Roche Molecular Biochemicals); real-time PCR was performed using a LightCycler hybridization probe assay system, as described elsewhere [20]. The primer sets for HBV are shown in the Appendix. It was estimated that the sensitivity corresponded to ~$10^3$ copies/mL. HBV genotypes were determined using PCR restriction fragment–length polymorphism of the surface gene of HBV, as described elsewhere [9], and 6 genotypes (A–F) could be identified. To analyze genotypic resistance to lamivudine, we amplified the polymerase gene containing the tyrosine-methionine-aspartate-aspartate (YMDD) motif of patients with detectable HBV DNA at the last hospital visit using a PCR assay. The presence of the YMDD variant (rt pol gene mutations rtM204V plus rtM204I) and/or rtL180M was confirmed by

directly sequencing the PCR product with an automatic ABI-DNA sequencer, model 377 A (Applied Biosystems).

Abdominal sonography and quantification of α-fetoprotein by chemiluminescent microparticle immunoassay (Architect AFP; Abbot Laboratories) were performed for patients with chronic HBV infection twice per year. In patients with abnormal liver function test results or abdominal symptoms localized at the right upper quadrant or the epigastrium, abdominal sonography was performed on an as-needed basis. CT of the abdomen was performed when a space-occupying lesion was detected by abdominal sonography. During the study period, 13 patients (4 case patients and 9 control subjects) underwent liver biopsy when hepatitis was diagnosed. The biopsy specimens were submitted for immunohistochemical staining of HBsAg and HBV core antigen in addition to routine staining and microbiological culturing.

***Assessment of virological and immunologic responses to antiretroviral therapy and HIV progression and definitions.*** Virological response to HAART was assessed by the proportion of patients achieving an undetectable HIV-PVL within 6 months of the end of study or patient death, whichever occurred first. Virological failure was defined as failure to achieve an undetectable HIV-PVL after ≥4 months of HAART. Patients with missing HIV-PVL data for an interval of ≥6 months were also counted as having experienced treatment failure (on the basis of the intention-to-treat principle). Immunologic response was assessed by the change in $CD4^+$ cell count from baseline to within 6 months of the end of the study or patient death and by the proportion of patients achieving an increase in $CD4^+$ cell count of either ≥100 cells/μL or ≥200 cells/μL during the follow-up period. HIV progression was defined as a relapse or the development of an AIDS-defining opportunistic illness [21] within 1 month after study entry. To better define the mortality rate and survival duration, we searched mortality report data from the vital statistics office of the Department of Health, Taiwan, to identify deaths among patients who might have been followed up at other designated hospitals.

Hepatitis flare was defined as 5-fold elevation in serum aspartate and alanine aminotransferase levels (upper limits of normal for aspartate and alanine aminotransferase levels, 31 U/L and 41 U/L, respectively), and hyperbilirubinemia was defined as a total serum bilirubin level ≥2.0 mg/dL (upper limit of normal, 1.0 mg/dL) with >50% conjugated bilirubin without evidence of hemolysis. Hepatic decompensation was defined according to the Child-Pugh criteria [22] as presence of hepatic encephalopathy, coagulopathy, ascites, and prolonged hyperbilirubinemia for ≥3 months, which was not attributable to concurrent AIDS-defining opportunistic illness and other medical causes. HAART was defined as the combination of at least 3 antiretroviral agents containing protease inhibitors or non-nucleoside reverse-transcriptase inhibitors. Cirrhosis of the liver was documented if cirrhotic changes were noted on histological examination of the liver or the presence of coarse echogenecity and irregular liver surface accompanied by splenomegaly was detected by sonography or CT.

***Statistical analysis.*** All statistical analyses were performed using SPSS software, version 12.0 (SPSS). Categorical variables were compared using $\chi^2$ or Fisher's exact test, and noncategorical variables were compared using the Wilcoxon rank-sum test. Logistic regression was used to assess the impact of HDV coinfection on the risk for acute hepatitis, progression of HIV disease, immunologic and virologic responses to HAART with adjustment for baseline HIV-PVL, risk behavior for HIV transmission, baseline opportunistic illness, use and duration of lamivudine and HAART, HBV genotypes, baseline HBV load, and genotypic resistance to lamivudine of HBV. ORs and 95% CIs were calculated for logistic regression analyses. The survival probabilities were estimated using the Kaplan-Meier method. The Cox proportional-hazard model was used to compare the difference in mortality rate between the 2 groups, with the same adjustments as above. Hazard ratios and 95% CIs were calculated for survival analyses. The survival duration of patients was estimated from the date of enrollment to death, last follow-up visit at our hospital (National Taiwan University Hospital, Taipei, Taiwan) or at another designated hospital in Taiwan, or the end of this observational study on 30 June 2005.

## RESULTS

***Patients.*** Over the 8-year study period, 36 (22.2%) of 162 HIV-infected patients with chronic HBV coinfection had test results positive for anti-HDV antibody. Two of the 36 patients with anti-HDV antibody and 4 of the 126 patients without anti-HDV antibody were excluded because of decompensated liver disease and cirrhosis at baseline. Of the remaining 34 patients with anti-HDV antibody, 3 with antibody to HCV at baseline and 5 with new HDV infection during follow-up were also excluded. Therefore, 26 patients with HDV, HBV, and HIV triple infection (case patients) and 78 matched control subjects with HBV and HIV dual infection were enrolled.

The patients' baseline demographic data and clinical characteristics are summarized in table 1. Case patients had a higher proportion of injection drug use than did control subjects (7.7% vs. 1.3%; $P = .05$). Almost all patients received lamivudine-containing antiretroviral therapy (100% and 98.7% for case patients and control subjects, respectively) during the observation period. There was no significant difference regarding duration of exposure to HAART and lamivudine-containing antiretroviral therapy (median duration of HAART, 51.5 vs. 50.3 months; $P = .81$; median duration of lamivudine therapy, 36.2 vs. 40.4 months; $P = .62$).

***HBV genotype, viral loads, evolution of serologic markers, and lamivudine resistance.*** Data on HBV genotypes, baseline

**Table 1. Demographic and clinical characteristics and antiretroviral treatment of patients with HIV, hepatitis B virus (HBV), and hepatitis D virus (HDV) coinfection and patients with HIV-HBV coinfection.**

| Characteristic | HIV-HBV-HDV coinfected ($n$ = 26) | HIV-HBV coinfected ($n$ = 78) | $P$ |
|---|---|---|---|
| Age, median years (range) | 35 (25–61) | 34 (25–62) | .93 |
| Male sex | 25 (96.2) | 75 (96.2) | 1.0 |
| Risk factor for HIV infection | | | |
| MSM | 14 (53.8) | 52 (66.7) | .13 |
| Heterosexual sex | 9 (34.6) | 24 (30.8) | .47 |
| IDU | 3 (7.7) | 1 (1.3) | .05 |
| Hemophilia | 0 (0) | 2 (2.6) | .56 |
| CD4$^+$ cell count at baseline | | | |
| Median cells/$\mu$L (range) | 100 (2–723) | 101 (0–739) | .89 |
| <100 cells/$\mu$L | 11 (42.3) | 33 (42.3) | 1.0 |
| 100–199 cells/$\mu$L | 6 (23.1) | 18 (23.1) | 1.0 |
| 200–349 cells/$\mu$L, (%) | 5 (19.2) | 15 (19.2) | 1.0 |
| ⩾350 cells/$\mu$L | 4 (15.4) | 12 (15.4) | 1.0 |
| HIV-PVL at baseline[a] | | | |
| Median $\log_{10}$ copies/mL (range) | 4.99 (2.60–5.88) | 4.66 (2.60–5.88) | .83 |
| ⩾5 $\log_{10}$ copies/mL | 9 (42.8) | 33 (47.1) | .71 |
| OI at baseline | 12 (46.2) | 32 (41.4) | .65 |
| ART containing lamivudine | 26 (100) | 77 (98.7) | .55 |
| Duration of lamivudine use, median months (25th–75th percentile) | 36.2 (20.0–57.2) | 40.4 (26.5–62.6) | .62 |
| Duration of HAART, median months (25th–75th percentile) | 51.1 (25.5–69.2) | 50.3 (29.7–68.8) | .81 |
| AST level at baseline, median IU/L (range) | 36 (17–158) | 35 (14–153) | .63 |
| ALT level at baseline, median IU/L (range) | 30 (11–148) | 27 (8–168) | .41 |
| Albumin level at baseline, median g/dL (range) | 3.4 (2.7–4.4) | 3.6 (2.5–4.6) | .65 |
| Total bilirubin at baseline, median mg/dL (range) | 0.7 (0.1–2.0) | 0.5 (0.2–2.0) | .72 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; IDU, injection drug use; MSM, men who have sex with men; OI, AIDS-defining opportunistic illness; PVL, plasma viral load.

[a] Baseline HIV-PVL data were available for 21 of the HIV-HBV-HDV–coinfected patients and 70 of HIV-HBV–coinfected patients.

HBV loads, and changes of HBV serologic markers during follow-up are shown in table 2. Case patients tended to have lower HBV loads ($P$ = .07) and a higher rate of HBsAg clearance during follow-up ($P$ = .02). Control subjects had a higher rate of genotypic resistance to lamivudine than did case patients at the end of study (57.1% vs. 0%; $P$ = .003) (table 2). Three (75%) of 4 case patients and 5 (55.6%) of 9 control subjects had immunohistochemical staining of hepatocytes of the liver biopsy specimens with results positive for HBsAg and HBV core antigen, suggesting acute exacerbation of chronic hepatitis B.

***Hepatic outcomes and immunologic, virological, and clinical responses to HAART.*** During follow-up, case patients were more likely than control subjects to develop hepatitis flares, hyperbilirubinemia, liver cirrhosis, and hepatic decompensation (table 3 and figure 1). For example, 57.7% of case patients developed hepatitis flares, compared with 23.1% of control subjects, with an adjusted OR of 5.88 (95% CI, 1.96–17.54; $P$ = .002). HDV infection has no statistically significant impact on responses to HAART in patients with HBV and HIV coinfection (table 3). The median increase of CD4$^+$ cell count from baseline was 201 cells/$\mu$L for case patients, compared with 237 cells/$\mu$L for control subjects ($P$ = .69); 50% of case patients and 57.7% of control subjects had an increase in CD4$^+$ cell of ⩾200 cells/$\mu$L ($P$ = .45). At the end of the study, 65.4% of case patients and 88.5% of control subjects achieved an undetectable HIV-PVL ($P$ = .09), and 23.1% and 15.4%, respectively, developed virological failure ($P$ = .17). A similar proportion of the case patients (26.9%) and control subjects (12.8%) developed new AIDS-defining opportunistic illness during follow-up ($P$ = .38) (table 3).

***Mortality.*** Ten patients died during follow-up (table 3 and figure 2). Compared with control subjects, the adjusted hazard ratio for death in case patients was 5.41 (95% CI, 1.39–23.85; $P$ = .02). A total of 4 patients died of complications of AIDS-related opportunistic infections (2 patients), pseudomonal bacteremia (1 patient), and lymphoma (1 patient). Six patients died of end-stage liver disease, including 4 case patients and 2 control subjects. Compared with control subjects, the adjusted

**Table 2. Characteristics of hepatitis markers and hepatic outcomes of patients with HIV, hepatitis B virus (HBV), and hepatitis D virus (HDV) coinfection and patients with HIV-HBV coinfection.**

| Characteristic | HIV-HBV-HDV coinfected ($n$ = 26) | HIV-HBV coinfected ($n$ = 78) | $P$ |
|---|---|---|---|
| HBV genotype | | | |
| Genotype B[a] | 12 (92.3) | 50 (79.4) | .28 |
| Genotype C[a] | 1 (7.7) | 13 (20.6) | .28 |
| HBV load at baseline[b] | | | |
| Median $\log_{10}$ copies/mL (range) | 4.04 (2.76–9.80) | 5.75 (2.01–10.01) | .07 |
| ≥5 $\log_{10}$ copies/mL | 5 (38.5) | 31 (54.4) | .06 |
| Viral hepatitis markers | | | |
| HBeAg positive at baseline | 5 (19.2) | 25 (32.1) | .32 |
| Anti-HBe positive at end of study | 1 (3.8) | 5 (6.4) | .53 |
| HBsAg clearance at end of study | 7 (26.9) | 6 (7.7) | .02 |
| New HCV infection | 2 (7.7) | 3 (3.8) | .59 |
| Genotypic resistance to lamivudine[c] | | | |
| Any | 0 | 20 (57.1) | .003 |
| HBV load of 3–6 $\log_{10}$ copies/mL | 0 | 12 (34.3) | .04 |
| HBV load >6 $\log_{10}$ copies/mL | 0 | 8 (22.8) | .19 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. Anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

[a] HBV genotype data were available for 13 of the HIV-HBV-HDV–coinfected patients and 63 of the HIV-HBV–coinfected patients during the study period.

[b] Baseline HBV loads were available for 13 of the HIV-HBV-HDV–coinfected patients and 57 of the HIV-HBV–coinfected patients.

[c] HBV DNA had been detected in 5 of the HIV-HBV-HDV–coinfected patients and 35 of the HIV-HBV–coinfected patients at the end of the study. The mutations conferring genotypic resistance to lamivudine for 20 HBV DNA from HIV-HBV-HDV–coinfected patients were rtM204V plus rtL180M (18 patients) and rtM204I (2 patients).

hazard ratio for hepatic death in case patients was 6.49 (95% CI, 1.16–6.85; $P$ = .03). There was no significant difference in mortality between patients with anti-HDV who cleared HBsAg at the end of study, compared with those who did not (1 [14.3%] of 7 vs. 5 [26.3%] of 19; $P$ = .47).

***Impact of HDV viremia at enrollment.*** HDV RNA was detectable in preserved serum samples from 7 (36.8%) of 19 case patients at enrollment. There were no significant differences in demographic data, risk factors for HIV infection, baseline $CD4^+$ cell count, plasma HIV and HBV loads, and changes of hepatitis B markers between the 7 patients with HDV viremia and their 21 matched control subjects (data not shown). After adjustment, there were no significant differences in $CD4^+$ cell count increase (median $CD4^+$ cell count increase, 189 cells/$\mu$L vs. 232 cells/$\mu$L; $P$ = .47) or in the percentage of individuals with undetectable HIV-PVL after HAART (57.1% vs. 85.7%; $P$ = .32) between patients with HDV viremia and their matched control subjects. However, patients with HDV viremia had higher rates of hepatitis flares (71.4% vs. 14.3%; $P$ = .01), hepatic decompensation (42.9% vs. 9.5%; $P$ = .08), liver cirrhosis (42.9% vs. 9.5%; $P$ = .08), and death (42.9% vs. 4.8%; $P$ = .06), but they had fewer occurrences of genotypic resistance to lamivudine (0% vs. 47.6%; $P$ = .03).

## DISCUSSION

Our results demonstrate that HDV infection may increase risk for progression of chronic liver disease in patients with chronic HBV-HIV coinfection who may otherwise benefit from receipt of HAART that prolongs AIDS-free survival, although HDV coinfection does not have an adverse impact on clinical, virological, or immunologic responses to HAART. It is estimated that 1.9%–5% of HIV-infected patients are coinfected with both HBV and HDV; coinfection is especially common among patients who are injection drug users [23, 24]. In our cohort, which had a lower proportion of injection drug users, we showed a higher prevalence of HDV infection (22.2%) among patients with HBV-HIV coinfection than that in the general population of Taiwanese HBsAg carriers (2.7%–5%) [9, 10, 25]. The higher rate of HDV coinfection among our HIV-infected patients in Taiwan, where HBV infection is hyperendemic and sexual contact is the major risk factor for HIV transmission [26], may be related to multiple sexual exposures [7].

Although prolonged use of lamivudine with resultant selection of lamivudine-resistant HBV and HIV has been a main concern [14, 27], the impact of HDV coinfection on the emergence of lamivudine-resistant HBV has not, to our knowledge,

been investigated before in patients with HBV-HIV coinfection. Among our patients, who received lamivudine 300 mg daily for both HIV and HBV infection for 3 years, 50% developed YMDD mutation, a rate similar to that in another cohort of HIV-uninfected patients receiving lamivudine 100 mg daily, in which YMDD variant HBV emerged in 57% of the patients [28]. In this study, we found that our patients with HDV infection, with or without viremia, tended to have lower HBV loads at baseline. This virological benefit is also supported by our findings that HBV genotypic resistance developed in none of the case patients after a median duration of 3 years of lamivudine-containing HAART.

Because the HBsAg carriers permit a continuous replication of HDV, HDV may play a role in the development of fulminant hepatitis and accelerate the progression of chronic liver damage in both HIV-uninfected [6, 25] and HIV-infected patients [17, 18, 23] with chronic HBV infection. Despite the fact that HDV coinfection conferred virological benefit by suppression of HBV replication at baseline and reduced the appearance of lamivudine-resistant HBV mutants, our study was not able to demonstrate its clinical benefit in HDV-HIV–coinfected patients. Instead, we found that patients with HDV coinfection remained at a higher risk for complications of chronic HBV infection. The findings imply that HDV coinfection has a much more important effect than HBV or YMDD variants on clinical hepatic events in patients who are receiving lamivudine-containing HAART.

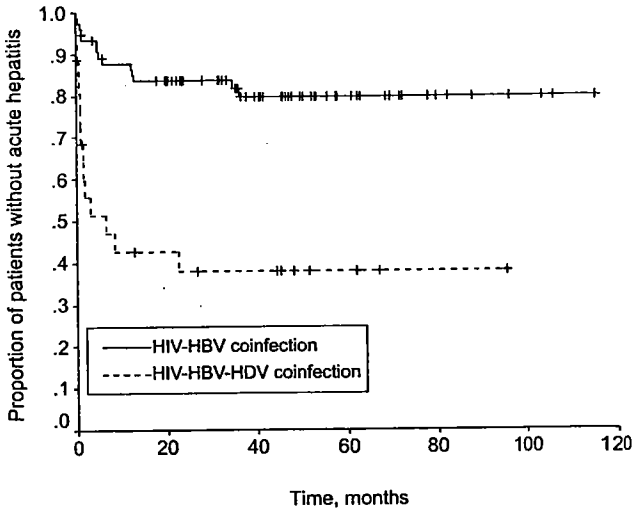


**Figure 1.** Kaplan-Meier estimates of hepatitis flares in patients with HIV, hepatitis B virus (HBV), and hepatitis D virus (HDV) coinfection and patients with HIV-HBV coinfection. $P = .001$, by log-rank test.

Anti-HDV antibody is not, in itself, diagnostic of persistent HDV infection, because it may also represent a serologic marker of previous HDV infection in HBV carriers. The rate of HDV

**Table 3. Hepatic, immunologic, virologic, and final outcomes for patients with HIV, hepatitis B virus (HBV), and hepatitis D virus (HDV) coinfection and patients with HIV-HBV coinfection.**

| Characteristic | HIV-HBV-HDV coinfected ($n$ = 26) | HIV-HBV coinfected ($n$ = 78) | Adjusted OR or HR[a] (95% CI) | $P$ |
|---|---|---|---|---|
| Hepatitis flares | 15 (57.7) | 18 (23.1) | 5.88 (1.96–17.54) | .002 |
| Hyperbilirubinemia | 9 (34.6) | 11 (14.1) | 3.40 (1.06–10.71) | .04 |
| Cirrhosis | 7 (26.9) | 4 (5.1) | 12.8 (1.78–72.89) | .009 |
| Hepatic decompensation | 6 (23.1) | 4 (5.1) | 9.68 (2.21–42.44) | .007 |
| Hepatocellular carcinoma | 1 (3.8) | 2 (2.6) | 1.57 (0.13–37.11) | .58 |
| Increase in CD4$^+$ cell count | | | | |
| Median cells/$\mu$L(range) | 201 (4–768) | 237 (2–835) | ... | .69 |
| $\geq$100 cells/$\mu$L | 20 (76.9) | 63 (80.8) | 0.69 (0.23–2.04) | .50 |
| $\geq$200 cells/$\mu$L | 13 (50) | 45 (57.7) | 0.70 (0.28–1.79) | .45 |
| New OI | 7 (26.9) | 10 (12.8) | 1.93 (0.45–8.19) | .38 |
| Undetectable HIV-PVL <400 copies/mL | 17 (65.4) | 69 (88.5) | 0.37 (0.12–1.18) | .09 |
| Virological failure[b] | 6 (23.1) | 12 (15.4) | 2.45 (0.67–8.89) | .17 |
| Death | | | | |
| Any cause | 6 (23.1) | 4 (5.1) | 5.41 (1.39–23.85) | .02 |
| Liver related | 4 (15.4) | 2 (2.6) | 6.49 (1.16–6.85) | .03 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. HR, hazard ratio; OI, AIDS-defining opportunistic illnesses; PVL, plasma viral load.

[a] Adjustment for risk behavior associated with HIV infection, baseline OI, baseline HIV-PVL $\geq 5$ $\log_{10}$ copies/mL, use and duration of lamivudine therapy and HAART, HBV genotypes, baseline HBV load $\geq 5$ $\log_{10}$ copies/mL, and HBV genotypic resistance to lamivudine.

[b] Antiretroviral-naive patients who initiated HAART at baseline and had at least 1 HIV-PVL $\geq$400 copies/mL during 6 months of follow-up; missing data equaled treatment failure.

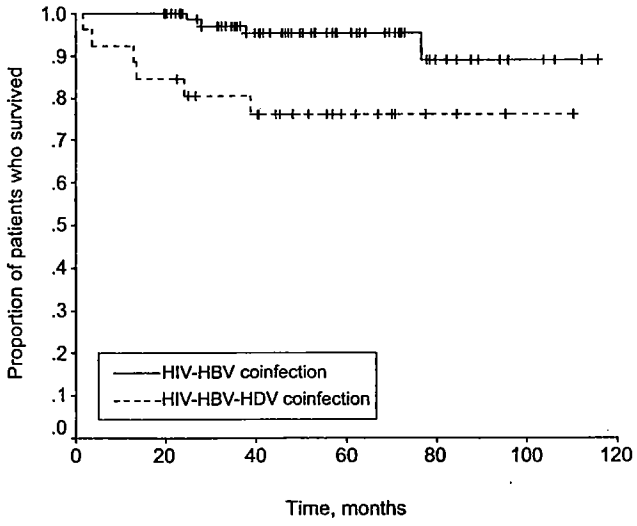


**Figure 2.** Kaplan-Meier survival estimates of mortality for patients with HIV, hepatitis B virus (HBV), and hepatitis D virus (HDV) coinfection and patients with HIV-HBV coinfection. $P = .02$, by log-rank test.

RNA detection among anti-HDV–positive patients in our study was 36.8%, which is compatible with the findings of the study by Lu et al. [29]. Despite the small number of cases included in the study, patients with detectable HDV RNA at enrollment had an increased risk of hepatitis flares and death, compared with control subjects. Because there is no concomitant HCV infection and HBV replication is suppressed in patients with HDV coinfection, the worse hepatic outcomes in patients with HDV viremia are likely to be attributable to ongoing HDV replication.

Our study is limited by the small number of cases included and the fact that HDV RNA testing and liver biopsy were not performed for each patient at baseline. Exclusion of patients with known cirrhosis or decompensated liver disease may underestimate the impact of HDV on the outcomes. The proportion of injection drug users was low, and we did not collect clinical information on the use of substances or over-the-counter medications associated with potential hepatotoxicity and drug-drug interactions with HAART. Furthermore, our patients received only lamivudine. Whether combination therapy with lamivudine and newer agents with more potent anti-HBV activities would have any impact on the interactions remains to be studied. Therefore, caution should be exercised in generalizing our study results.

In conclusion, our data suggest that HDV infection does not increase the risk of HIV progression among patients with HBV-HIV coinfection and may confer protection against the emergence of lamivudine-resistant HBV. However, HDV infection increases risk of hepatic complications and death in patients with HBV-HIV coinfection.

## Acknowledgments

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## APPENDIX

The primer pairs of hepatitis D virus (HDV) used in the PCR amplification were designed on the basis of the consensus sequences of HDV, and the locations of the primers were individually indicated in the parentheses. The first primer pair used was HDV F1: 5′-CGGATGCCCAGGTCGGACC'3' (850–868) and HDV R1: 5′-GGAGCWCCCCCGGCGAAGA-3′ (1379–1397). The second primer pair used was HDV F2: 5′-AGGTGG-AGATGCCATGCCGAC-3′ (875–895) and HDV R2: 5′-GGAYCACCGAAGAAGGAAGGCC'3′ (1275–1296).

The first primer pair of hepatitis B virus (HBV) used was HBV F1: 5′-CCGATCCATACTGCGGAAC-3′ (1261–1279) and HBV R1: 5′-GCAGAGGTGAAGCGAAGTGCA -3′ (1600–1580) with anchor probe: 5′-TCTGTGCCTTCTCATCTGCCGG-ACC-3′ (1552–1576) and sensor probe: 5′-TCTTTACGCGGA-CTCCCC-3′ (1533–1550). The second primer pair used was HBV F2: 5′-GCATGCGTGGAACCTTTGTG-3′ (1232–1251) and HBV R2: 5′-CAGAGGTGAAGCGAAGTGC-3′ (1599–1581) with anchor probe 5′-CGGCGCTGAATCCCGCGGAC-3′(1436–1455) and sensor probe 5′-ACGTCCTTTGTCTACGT-CCCG-3′ (1414–1434).

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# Clinical Impact of GB Virus C Viremia on Patients with HIV Type 1 Infection in the Era of Highly Active Antiretroviral Therapy

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***Background.*** The influence of GB virus C (GBV-C) viremia on clinical outcomes of patients with human immunodeficiency virus type 1 (HIV-1) infection remains controversial in the era of highly active antiretroviral therapy (HAART).

***Methods.*** A prospective observational study was conducted to describe the epidemiology of GBV-C viremia and assess its clinical impact on treatment responses to HAART in 385 HIV-1–infected patients during the period from January 1999 through June 2004.

***Results.*** A total of 59 patients (15.3%) had detectable GBV-C RNA viremia during a median observation of 3.6 years (range, 1.0–7.0 years); 47 patients (12.2%) had GBV-C viremia at enrollment, and 12 (3.1%) acquired GBV-C infection during follow-up. Thirty-two (68.1%) of the 47 patients with baseline GBV-C viremia had persistent GBV-C viremia. Compared with patients with clearance of GBV-C viremia ($n = 15$) and patients without detectable GBV-C viremia ($n = 326$), patients with persistent GBV-C viremia were more likely to be men who have sex with men (81.3% vs. 60.4%; $P = .02$), tended to have lower baseline plasma HIV RNA load (HIV RNA load $\geq 5$ $\log_{10}$ copies/mL, 31.3% vs. 49.4%; $P = .05$), and had a higher proportion of isolated anti–hepatitis B core antibody (37.5% vs. 17.2%; $P = .005$). There was no statistically significant difference in terms of virologic, immunologic, and clinical responses to HAART; occurrence of hepatic events; and mortality among the 3 groups.

***Conclusions.*** Persistent GBV-C viremia is significantly associated with male-male sex in HIV-infected patients with advanced immunodeficiency, and persistent GBV-C viremia does not confer short-term benefit in patients receiving HAART.

GB virus C (GBV-C) is an RNA virus that belongs to the Flaviviridae family and is closely related to hepatitis C virus (HCV) [1]. GBV-C infection may persist for decades without causing apparent clinical illness or death [2]. Like HIV, GBV-C can be transmitted through parenteral, sexual, or mother-to-child route; thus, exposure to GBV-C is common in HIV-infected patients [3–6]. Previous studies indicated that 14%–45% of HIV-infected patients have GBV-C coinfection [4–15].

GBV-C is a lymphotrophic virus that could replicate in CD4 cells [16]. Clearance of GBV-C viremia depends on host immunity; 60%–75% of immunocompetent persons clear GBV-C spontaneously, and the clearance usually coincides with the development of antibodies against the GBV-C surface envelope glycoprotein E2 [17]. In immunocompromised hosts, such as patients with HIV infection, GBV-C viremia may persist for several years [7]. In the special clinical context of coinfection with HIV and GBV-C, several reports have found that GBV-C may provide clinical benefit by delaying the progression of HIV infection [8–11]. Persistent GBV-C viremia has been shown to be associated with prolonged survival among HIV-infected patients, and the loss of GBV-C RNA might lead to poor prognoses [10, 13, 14]. Accordingly, GBV-C viremia is dynamic, and the presence of GBV-C at diagnosis does not necessarily represent long-term interaction between GBV-C and HIV [10, 13, 14].

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Although HAART has been in use for a decade, clinical data on interactions of GBV-C and HIV in patients receiving HAART are limited [12, 14, 18, 19]. To our knowledge, all of the published studies have not included follow-up examinations for GBV-C viremia while patients were receiving HAART. In this study, we aimed to describe epidemiology of GBV-C infection and to assess the impact of persistent GBV-C viremia on the immunologic, virologic, and clinical responses to HAART in HIV-infected patients receiving HAART during the period from 1999 through 2004.

## MATERIALS AND METHODS

***Patients.*** Patients who received a new diagnosis of HIV infection at the National Taiwan University Hospital (Taipei) from 1 January 1999 through 30 June 2004 were enrolled for GBV-C RNA testing after providing written informed consent. Demographic and clinical data were obtained from medical records using a standard case record form. To determine whether there was persistent GBV-C viremia after the initiation of HAART, 2 serum samples from the same patients were obtained (1 prior to initiation of HAART, and the other at the end of this study, at least 1 year separating the previous test, or at their last visits). Serum samples were stored at −70°C until use. To better assess the long-term impact of GBV-C on HIV-infected patients, subjects who were observed for <12 months were excluded from the study. HAART, defined as the combination of at least 3 antiretroviral agents containing protease inhibitors or nonnucleoside reverse-transcriptase inhibitors, has been provided without charge to all patients with HIV infection since April 1997. The end date of observation of this study was 31 December 2005. This study was approved by the Institutional Review Board at National Taiwan University Hospital.

Liver biochemical tests values, including serum aminotransferase and bilirubin levels, blood CD4 cell count, and plasma HIV RNA load (PVL), were determined every 3–4 months. PVL was quantified using a RT-PCR assay (Roche Amplicor, version 1.5; Roche Diagnostic Systems) with a detection limit of 400 copies/mL (2.60 $\log_{10}$ copies/mL), and the CD4 cell count was determined using FACFlow (Becton Dickinson). An ultrasensitive HIV PVL test with a lower detection limit of 50 copies/mL was performed if the previous HIV PVL was <400 copies/mL. Hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and anti–hepatitis B core antibody (anti-HBc) were checked at the time of enrollment by using EIAs (Abbott Laboratories). HBV DNA was extracted from 200 μL of serum samples of patients with isolated anti-HBc at enrollment by using the High Pure Viral Nucleic Acid Kit (Roche Molecular Biochemicals), and RT-PCR was performed using a LighterCycler instrument (Roche Molecular Biochemicals) in accordance with the manufacturer's instructions. It was estimated that the sensitivity corresponded to ~$10^3$ copies/mL. Antibodies to HCV were assayed using a third-generation EIA (AxSYM HCV III; Abbott Laboratories).

***Definitions.*** Hepatitis flare was defined as a serum aspartate aminotransferase (AST) or an alanine aminotransferase (ALT) level of ≥5 times the upper limit of normal (at National Taiwan University, these values are 31 and 41 U/L, respectively), and hyperbilirubinemia was defined as a total serum bilirubin level ≥2.0 mg/dL (upper limit of normal, 1.0 mg/dL), with >50% of conjugated bilirubin without evidence of hemolysis. Isolated anti-HBc pattern was defined as serum that tested positive for anti-HBc antibody but negative for both HBs antigen and anti-HBs antibody.

***Assessment of virologic and immunologic responses to antiretroviral therapy and HIV progression.*** Virologic response to HAART was assessed by the proportion of patients achieving an undetectable PVL at 6 months, 12 months, 24 months, and from the last available PVL data following initiation of HAART. Any virological failure was defined as failure to achieve an HIV PVL <400 copies/mL during the 6 months after initiation of HAART or as repeatedly detectable PVL, after initial suppression, to undetectable levels. Immunologic response was assessed by the increment of CD4 cell count at 6 months, 12 months, 24 months, and from the last available CD4 cell count data following initiation of HAART and by the proportion of patients achieving an increase of CD4 cell count by 100 and 200 cells/μL or greater during the follow-up period. HIV progression was assessed as relapse or new development of AIDS-defining illness [20] 1 month after initiation of HAART.

***GBV-C RNA detection and determination of nucleotide sequences.*** RNA was purified using 200 μL of serum or plasma from each sample using the QIAamp Viral RNA Mini Kit (Qiagen) in accordance with the manufacturer's instructions. RT-PCR products were amplified using nested PCR. The primers used in the nested RT-PCR were as follows: 5′-GGC CAA AAG GTG GTG GAT GG-3′ (outer-forward), 5′-ATT GAA GGG CGA CGT GGA CC-3′ (outer-reverse), 5′-GTG ATG ACA GGG TTG GTA GG-3′ (inner-forward), 5′-GTA CGT GGG CGT CGT TTG CC-3′ (inner-reverse). PCR products were sequencing on a 48-capillary 3730 DNA analyzer (GeneAmp PCR System 9700&2700; Applied Biosystems). The lower limit of detection for this GBV-C RNA assay used was ~100 copies/mL [21]. All PCR products were confirmed as a portion of the 5′-UTR of GBV-C sequences as assessed on http://www.ncbi.nlm.nih.gov/BLAST.

***Statistical analysis.*** All statistical analyses were performed using SPSS software; version 11.0 (SPSS). Categorical variables were compared using $\chi^2$ or Fisher's exact test, and a 2-sample *t* test was used for the comparison of continuous variables, with correction of unequal variances when appropriate. Noncategorical variables were compared using the Wilcoxon rank sum

test. The significance level was set at .05, and all $P$ values were 2-tailed. The survival probabilities were also estimated by the method of Kaplan-Meier. Equality of survival distributions was evaluated by the log-rank test. A multivariate Cox regression analysis, including categories of sex, age, risk factors for HIV infection, initial CD4 cell count, duration of HAART, initial HIV load, initial HBs antigenemia, and HCV infection and GBV-C status (persistent GBV-C viremia, clearance of GBV-C, or without GBV-C viremia), for mortality were performed. Patients who were lost to follow-up were included in the analyses, but the data were censored at the time of the last visit.

## RESULTS

There were 442 patients with newly diagnosed HIV-infection at the National Taiwan University Hospital during the study period. Fifty-seven patients (10.6%) observed for <12 months were excluded, and 385 were thus enrolled for analysis. No significant differences in terms of age, sex, risk factors for HIV infection, initial CD4 cell count, and HIV PVL were found between excluded patients and enrolled patients (data not shown). Forty-seven (12.2%) of 385 HIV-infected patients had detectable GBV-C viremia at baseline. After a median follow-up of 3.6 years (range, 1.0–7.0 years), 32 (68.1%) of the 47 patients had persistent GBV-C viremia, and 15 patients (31.9%) cleared GBV viremia, with a clearance rate of 8.48 per 100 person-years. In addition, 12 other patients acquired new or reemerging GBV-C infection, with an incidence of 0.92 cases per 100 person-years.

To study the impact of persistent GBV-C viremia on clinical, virologic, and immunologic response to HAART and hepatic outcomes in HIV-infected patients, 12 patients with newly acquired or reemerging GBV-C viremia were excluded for further analysis. Therefore, 32 patients with persistent GBV-C viremia (the persistent GBV-C viremia group), 15 patients with clearance of GBV-C (the GBV-C clearance group), and 326 patients without GBV-C viremia (the non–GBV-C group) were compared. The baseline demographic and clinical characteristics of the 3 groups of patients are summarized in table 1. There were no significant differences regarding age, sex, baseline CD4 cell count, AIDS-defining opportunistic illness at baseline, baseline serum alanine aminotransferase level and total bilirubin level among these groups. However, patients in the persistent GBV-C viremia group included a higher proportion of men who have sex with men (81.3% vs. 60.4%; $P = .02$) and tended to have a lower baseline HIV-RNA plasma viral load than did those without GBV-C viremia (proportion of patients with HIV PVL $\geq 5$ $\log_{10}$ copies/mL, 31.3% vs. 49.4%; $P = .05$). There were no statistically significant differences regarding baseline HBsAg positivity and HCV infection among the 3 groups (table 1). Detectable HBV DNA was found in 5 (7.2%) of 69 patients with isolated anti-HBc (occult HBV infection), and all of them were in the non–GBV-C group. Patients in the persistent GBV-C viremia group had a higher proportion of isolated anti-HBc antibodies than did those in the GBV-C clearance group and non–GBV-C group (37.5% vs. 6.7% [$P = .04$] and 37.5% vs. 17.2% [$P = .005$], respectively). GBV-C viremia was detectable in 11 (16.4%) of 67 patients with HBs antigenemia, compared with 48 (15.1%) of 318 patients without HBsAg ($P = .78$). However, GBV-C viremia was detectable in 10 (28.6%) of 35 patients with anti-HCV antibody, compared with 49 (14.0%) of 350 patients without anti-HCV ($P = .02$). There were no statistically significant differences regarding the duration of HAART, the initial HAART regimen, and patients switches to a PI during HAART (table 1).

The comparisons of hepatic, immunologic, virologic, and clinical outcomes among the 3 groups are shown in table 2. There were no differences in new episodes of hepatitis and hyperbilirubinemia, the extent to which CD4 counts increased, development of new opportunistic illnesses, and the proportion of patients achieving undetectable HIV PVL and ever-developing virological failure after initiation of HAART. A total of 21 patients (5.5%) died, including 2 (6.3%) of 32 in the persistent GBV-C viremia group, 2 (13.3%) of 15 in the GBV-C clearance group, 1 (8.3%) of 12 in the newly acquired GBV-C viremia group, and 16 (4.9%) of 326 in non–GBV-C group. Seventeen patients died of HIV-related opportunistic infections, 2 died of end-stage liver disease, and 2 died of malignancies. Kaplan-Meier survival estimates of the patients with or without GBV-C viremia are shown in figure 1; there was no significant difference among the groups ($P = .66$, by the log-rank test). Multivariate Cox regression analysis showed that only injection drug use (hazard ratio [HR], 6.17; 95% CI, 1.34–17.25; $P = .007$) and baseline CD4 cell count (HR, 0.996; 95% CI, 0.49–1.00; $P = .05$) were significantly associated with survival, and baseline HBs antigenemia was of borderline significance (HR, 2.42; 95% CI, 0.95–6.49; $P = .07$). Status of GBV-C viremia did not correlate with mortality ($P = .57$).

## DISCUSSION

In this prospective, observational study, we found that 12.2% of HIV-infected patients in Taiwan had concurrent GBV-C viremia, and we were unable to demonstrate the benefits of persistent GBV-C virema on clinical progression of HIV disease and short-term survival of patients receiving HAART. The prevalence of GBV-C viremia among HIV-infected patients ranges from 14% to 42% in Western countries, with higher rates occurring among men who have sex with men and injection drug users, probably because of increased risk for GBV-C exposure [4–7, 14]. In this study, GBV-C viremia was detected in 12.2% of HIV-infected patients, which is a much higher rate than in healthy blood donors (2.2%) and in the general population (3.4%–5.0%) in Taiwan [22–24]. Compared with Western stud-

**Table 1. Clinical characteristics of HIV-infected patients with persistent GB virus C (GBV-C) viremia (group 1), those with clearance of GBV-C (group 2), and those with non–GBV-C viremia (group 3).**

| Characteristic | Group 1 ($n$ = 32) | Group 2 ($n$ = 15) | Group 3 ($n$ = 326) | $P$ Group 1 vs. group 2 | $P$ Group 1 vs. group 3 |
|---|---|---|---|---|---|
| Age, median years (IQR) | 36 (23–63) | 39 (26–60) | 40 (29–64) | .81 | .78 |
| Male sex | 31 (96.9) | 13 (86.7) | 294 (90.2) | .24 | .34 |
| Risk for HIV transmission (%) | | | | | |
| Male-male sex | 26 (81.3) | 11 (73.3) | 197 (60.4) | .70 | .02 |
| Heterosexual sex | 5 (15.6) | 4 (26.7) | 111 (34.1) | .44 | .03 |
| IDU | 1 (3.1) | 0 (0) | 18 (5.5) | .99 | .99 |
| Baseline CD4 cell count | | | | | |
| Median cells/$\mu$L (range) | 153 (4–745) | 217 (23–802) | 174 (1–857) | .34 | .29 |
| ≤200 cells/$\mu$L | 19 (53.4) | 7 (46.6) | 184 (56.5) | .53 | .75 |
| 201–349 cells/$\mu$L | 5 (15.6) | 4 (26.7) | 65 (19.9) | .44 | .56 |
| ≥350 cells/$\mu$L | 8 (25.0) | 4 (26.7) | 77 (23.6) | .99 | .86 |
| Baseline HIV PVL | | | | | |
| Median $\log_{10}$ copies/mL (range) | 4.49 (3.36–5.88) | 4.85 (3.36–5.88) | 4.95 (3.89–5.88) | .39 | .17 |
| ≥5 $\log_{10}$ copies/mL | 10 (31.3) | 5 (33.3) | 161 (49.4) | .89 | .05 |
| Baseline OI | 9 (28.1) | 5 (33.3) | 102 (31.3) | .72 | .70 |
| Baseline viral hepatitis markers | | | | | |
| HBs antigenemia | 6 (18.8) | 3 (20.0) | 57 (17.5) | .99 | .86 |
| Isolated anti-HBc | 12 (37.5) | 1 (6.7) | 56 (17.2) | .04 | .005 |
| Positive anti-HCV | 5 (15.6) | 2 (13.3) | 27 (8.3) | .99 | .17 |
| Baseline ALT level, median IU/L (range) | 25 (12–107) | 21 (10–148) | 35 (14–153) | .87 | .43 |
| Baseline total bilirubin level, median mg/dL (range) | 0.5 (0.1–1.9) | 0.5 (0.2–2.2) | 0.7 (0.1–2.0) | .89 | .76 |
| Observation duration,[a] median days (range) | 1373 (464–2528) | 1397 (453–2349) | 1264 (336–2554) | .78 | .26 |
| HAART duration,[a] median days (range) | 1282 (373–2419) | 1266 (394–2277) | 1187 (323–2496) | .44 | .23 |
| Initial HAART regimen | | | | | |
| Use of protease inhibitors | 14 (43.8) | 7 (46.7) | 132 (40.5) | .85 | .72 |
| Ritonavir-boosted | 8 (57.1) | 4 (57.1) | 78 (59.1) | .99 | .89 |
| Nonboosted | 6 (42.9) | 3 (42.9) | 54 (40.9) | .99 | .75 |
| Use of NNRTI | 15 (46.9) | 6 (40.0) | 176 (54.0) | .66 | .44 |
| Use of triple-NRTIs | 3 (9.3) | 2 (13.3) | 18 (5.5) | .65 | .42 |
| Switch to PI from initial NNRTI or triple-NRTI regimen during HAART | 4 (22.2) | 3 (37.5) | 36 (18.6) | .63 | .75 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; anti-HBc, anti-hepatitis B core antibody; anti-HCV, anti-hepatitis C virus; HBs, hepatitis B surface antigen; IDU, injection drug use; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; OI, opportunistic illness; PI, protease inhibitor; PVL, plasma viral load.

[a] Five patients enrolled in non-GBV viremia group had their blood checked for GBV-C on the 336th, 340th, 345th, 351st, and 360th days, respectively. They all survived >365 days.

ies, the slightly lower prevalence of GBV-C viremia in Taiwanese HIV-infected subjects might be explained by the lower proportion of injection drug users (<5%). Consistent with other reports [25, 26], we also found that persistent GBV-C viremia occurred more commonly among men who have sex with men.

In this study, we found that patients with persistent GBV-C viremia had a lower baseline HIV PVL than those without GBV-C by 0.5 $\log_{10}$. Previous studies suggested that HIV-infected patients with GBV-C coinfection who received single or dual nucleoside reverse-transcriptase inhibitors had a more favorable outcome, with delayed progression to AIDS, compared to those with HIV infection alone [5, 7–11, 27]. Long-term persistence of GBV-C viremia is probably a key component of the beneficial outcome of GBV-C and HIV coinfection [10, 11] because of the interference with HIV replication within lymphocytes [28]. In addition, GBV-C could immunologically delay progression of HIV infection through induction of various cytokines and other soluble factors [29] or by maintaining an intact T-helper-1 cytokine profile [30].

In the HAART era, controversies exist regarding the beneficial effects of GBV-C viremia on HIV progression and responses to HAART [12, 14, 18, 19, 31]. The differences among

**Table 2. Hepatic, immunologic, virologic, and clinical outcomes of HIV-infected patients with persistent GBV-C viremia (group 1), those with clearance of GBV-C (group 2), and those with non–GBV-C viremia with or without GBV-C viremia (group 3).**

| Characteristics | Group 1 ($n$ = 32) | Group 2 ($n$ = 15) | Group 3 ($n$ = 326) | $P$ Group 1 vs. group 2 | $P$ Group 1 vs. group 3 |
|---|---|---|---|---|---|
| Acute hepatitis[a] | 4 (12.5) | 2 (13.3) | 40 (12.3) | .99 | .99 |
| Hyperbilirubinemia[a] | 3 (9.4) | 1 (6.7) | 20 (5.5) | .99 | 45 |
| At 6 months following HAART initiation | | | | | |
| Increment of CD4 cell count from baseline | | | | | |
| Median cells/μL (range) | 87 (−364 to 486) | 100 (−162 to 230) | 67 (−662 to 839) | .72 | .48 |
| Increase ≥100 cells/μL | 11 (34.4) | 6 (40.0) | 120 (36.8) | .71 | .79 |
| Increase ≥200 cells/μL | 6 (18.8) | 2 (13.3) | 44 (13.5) | .99 | .41 |
| Undetectable PVL <400 copies/mL | 25 (78.1) | 11 (73.3) | 238 (73.0) | .73 | .53 |
| At 12 months following HAART | | | | | |
| Increment of CD4 cell count from baseline | | | | | |
| Median cells/μL (range) | 127 (−362 to 550) | 162 (−339 to 532) | 140 (−668 to 996) | .68 | .87 |
| Increase ≥100 cells/μL | 20 (62.5) | 9 (60.0) | 210 (64.4) | .87 | .83 |
| Increase ≥200 cells/μL | 12 (37.5) | 7 (46.7) | 109 (33.4) | .55 | .64 |
| Undetectable PVL | | | | | |
| <400 copies/mL | 26 (81.3) | 13 (86.7) | 263 (80.7) | .99 | .94 |
| <50 copies/mL | 24 (75.0) | 12 (80.0) | 251 (76.9) | .99 | .80 |
| At 24 months following HAART[b] | | | | | |
| Increment of CD4 cell count from baseline | | | | | |
| Median cells/μL (range) | 203 (−336 to 995) | 150 (−200 to 509) | 165 (−631 to 823) | .47 | .64 |
| Increase ≥100 cells/μL (range) | 16 (64.0) | 8 (57.1) | 163 (66.3) | .67 | .82 |
| Increase ≥200 cells/μL (range) | 13 (52.0) | 6 (42.9) | 106 (43.1) | .58 | .39 |
| Undetectable PVL[b] | | | | | |
| <400 copies/mL | 19 (76.0) | 12 (85.7) | 195 (79.3) | .69 | .70 |
| <50 copies/mL | 18 (72.0) | 11 (78.6) | 187 (76.0) | .72 | .66 |
| At end of study | | | | | |
| Increment of CD4 cell count from baseline | | | | | |
| Median cells/μL (range) | 144 (−55 to 638) | 176 (−71 to 664) | 171 (−43 to 799) | .50 | .38 |
| Increase ≥100 | 18 (56.3) | 11 (73.3) | 228 (69.9) | .34 | .11 |
| Increase ≥200 | 10 (31.3) | 6 (40.0) | 139 (42.6) | .55 | .21 |
| Undetectable PVL | | | | | |
| <400 copies/mL | 25 (78.1) | 12 (80.0) | 253 (77.6) | .99 | .95 |
| <50 copies/mL | 21 (65.6) | 11 (73.3) | 205 (62.9) | .71 | .76 |
| Development of new OI | 4 (12.5) | 2 (13.3) | 33 (10.1) | .99 | .76 |
| Any virological failure | 11 (34.4) | 4 (26.7) | 121 (37.1) | .74 | .75 |
| Mortality | 2 (6.3) | 2 (13.3) | 16 (4.9) | .58 | .67 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. OI, opportunistic illness; PVL, plasma viral load.

[a] Hepatitis flare was defined as an increase in the serum aspartate and alanine aminotransferases levels to ≥5 times the upper limit of normal (normal upper limits at National Taiwan University Hospital, 31 and 41 U/L, respectively) and hyperbilirubinemia as a total serum bilirubin ≥2.0 mg/dL with >50% of conjugated bilirubin without evidence of hemolysis.

[b] Case number at 24th month following HAART was 25 patients in group 1, 14 in group 2, and 246 in group 3.

the findings of our study and the findings of the published studies may originate from differences in patients recruited, study design, definitions of virologic and immunologic responses to HAART, and persistence of GBV-C coinfection. In our study, we assessed the impact of persistent GBV-C viremia, whereas in the others [12, 18, 19], only baseline GBV-C viremia was assessed. The baseline immunologic or virologic status of HIV infection may affect the impact of GBV-C viremia after the initiation of HAART. In the studies by Rodriguez et al. [18], only 46.4% of the patients with GBV-C viremia who had depleted CD4 counts (60 cells/μL) achieved a virological response to HAART that was defined as <400 copies/mL at the final follow-up visit. In the study by Antonucci et al. [19], who enrolled a significantly higher proportion of injection drug users with higher CD4 counts (325 cells/μL), the time to achieve initial virological suppression or an increase of CD4 count by 200 cells/μL after HAART did not differ between patients with and those without baseline GBV-C viremia [19]. In our study, which assessed the responses to HAART at different time points, we did not find such additional beneficial effects of persistent GBV-C viremia. The reduction of PVL following HAART was as much as ≥2 $\log_{10}$ copies/mL after 12 months of HAART in

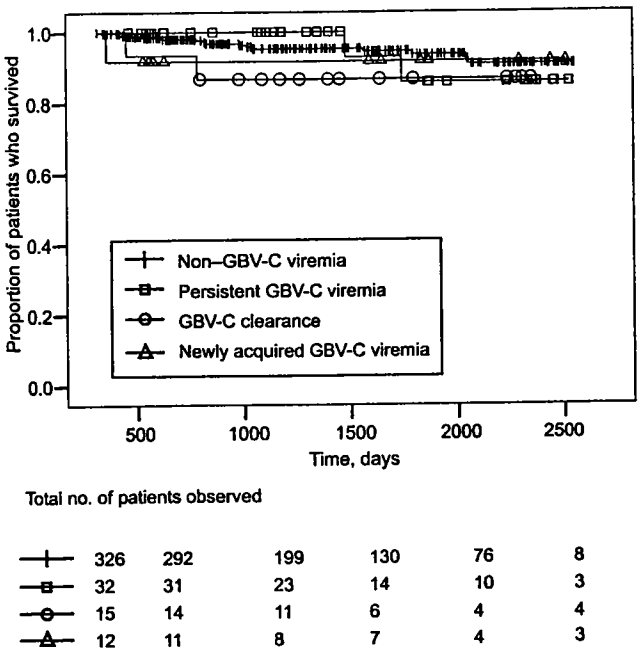


**Figure 1.** Kaplan-Meier survival estimates of the mortality among patients with or without GB virus C (GBV-C) viremia ($P = .66$, by the log-rank test).

our study (table 2); this is significantly higher than the 0.5–$\log_{10}$ copies/mL difference between patients with GBV-C viremia and patients without GBV-C viremia at baseline [27]. The benefit in terms of HIV progression and reduction of HIV PVL in our patients with GBV-C viremia may be masked by HAART.

In line with a previous report [32], our data suggested that GBV-C did not increase the risk of hepatitis flares or hyperbilirubinemia among HIV-infected patients, even in those with concurrent chronic HBV or HCV infection. However, isolated anti-HBc was more common among patients with persistent GBV-C viremia than those without persistent GBV-C viremia for which the reason remains unclear. Several possibilities may be speculated. First, GBV-C infection might result in the emergence of isolated anti-HBc by altering the immune response to HBV infection. Second, like HCV, GBV-C might suppress HBV replication, leading to the presentation of isolated anti-HBc and the lack of circulating HBsAg and anti-HBs [33]. Third, this association might reflect increased susceptibility to persistent GBV-C infection in patients with prior HBV infection.

There were several limitations of this study. First, patients with a short observation duration (<12 months) were not included in this analysis. Second, we did not test for anti-E2 antibody in these patients. It is likely that a large proportion of those without GBV-C RNA viremia may have had past infection (recovery from GBV-C viremia). Last, our sample size is small. Because HAART already significantly decreases morbidity and mortality in HIV-infected patients, whether persistent GBV-C viremia may confer marginal survival benefit in addition to HAART requires additional large studies with longer durations of follow-up.

In conclusion, persistence of GBV-C RNA in HIV-infected patients receiving HAART is common in Taiwan, and male-male sex may serve as an important transmission route. We were unable to demonstrate beneficial effects of persistent GBV-C infection on the virologic, immunologic, and clinical responses to HAART in HIV-infected patients.

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# Evolution of Hepatitis B Serological Markers in HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy

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***Background.*** Evolution of serological markers of hepatitis B virus (HBV) carriage or infection has rarely been investigated among human immunodeficiency virus (HIV)–infected patients receiving highly active antiretroviral therapy (HAART).

***Methods.*** During the period 1997–2002, a total of 633 HIV-infected patients were tested for HBV serological markers at baseline, including hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs ), antibody to hepatitis B core antigen (anti-HBc), hepatitis C virus (HCV) antibody (anti-HCV) antibody, HCV RNA level, and HBV DNA level, all of which were retested at least 1 year apart. Medical records were reviewed to identify clinical characteristics associated with evolution of these serological markers.

***Results.*** After a median duration of follow-up for 4.96 years, 161 patients (25.4%) had changes in HBV serological markers. Of 119 patients (18.8%) who tested positive for HBsAg at baseline, 6 (5.0%) developed anti-HBs, and 9 (7.6%) developed isolated anti-HBc. Of 270 patients (42.7%) who tested positive for anti-HBs, 18 (6.7%) lost anti-HBs. Of 179 patients (28.3%) in whom isolated anti-HBc had been detected, 73 (40.8%) developed anti-HBs, 18 (10.1%) lost all HBV markers, and 7 (3.9%) developed HBsAg. Of 65 patients (10.2%) who tested negative for all HBV markers, 13 (20%) developed anti-HBs, 13 (20%) developed isolated anti-HBc, and 4 (6.2%) developed HBsAg, indicating a high risk of HBV exposure. Patients in whom anti-HBc was detected at baseline were more likely to have acquired immunodeficiency syndrome ($P = .008$). Multivariate analysis revealed that an increase in the CD4 cell count after the commencement of HAART was significantly associated with persistence or subsequent development of anti-HBs in patients with anti-HBs or anti-HBc at baseline, respectively.

***Conclusions.*** Periodic measurements of HBV serological markers in HIV-infected patients are recommended, because new HBV infections and changes of HBV serological markers are not uncommon in patients with improved immunity after commencement of HAART.

Coinfection with hepatitis B virus (HBV) and HIV is common, because both viruses share similar transmission routes [1]. Chronic HBV infection has been shown to increase risk of virological failure of highly active antiretroviral therapy (HAART), development of acute hepatitis, hepatic decompensation, and liver-related mortality after initiation of HAART [2–4]. However, most studies have recognized HBV serological status as an invariant parameter (e.g., hepatitis B surface [HBs] antigenemia), without taking into account its evolution over time. In fact, HBV serological markers may change according to postinfection course, which is determined by host immunity and viral activities [5–10].

Among HIV-infected patients, several different HBV serological patterns may be encountered because of the patient's immunosuppression and increased risk of exposure to HBV. For example, presence of isolated

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antibody to hepatitis B core antigen (anti-HBc) and persistent chronic HBs antigenemia have been observed more often in HIV-infected patients because of impaired host immunity against HBV [5, 11–13]. However, factors associated with evolution of serological markers of HBV in HIV-infected patients receiving HAART remain unclear. With HAART, immune reconstitution may increase the frequency of HBV reactivation in hepatitis B surface antigen (HBsAg) carriers or the development of antibody to HBsAg (anti-HBs) [14, 15]. Previous studies that assessed the evolution of HBV serological patterns in HIV-infected patients were limited by the inclusion of only injection drug users [5] or patients who were not receiving HAART [6–10] or by a small number of patients in an area with a low prevalence of HBV infection [11]. In this longitudinal follow-up study, we aimed to assess the evolution of HBV serological markers in HIV-infected patients receiving HAART in Taiwan, where the prevalence of HBV coinfection in HIV-infected patients is much higher than that in Western countries (22% vs. 6%–10%) [2, 3].

## PATIENTS AND METHODS

*Patients.* During the period from 1 January 1997 through 31 December, 2002, HIV-infected patients who were antiretroviral naive and underwent serological testing for HBV infection before the initiation of HAART at the National Taiwan University Hospital (Taipei) were eligible for this longitudinal follow-up study. Patients who underwent repeated HBV serological testing in 2003 and 2004, with tests taken ≥1 year apart, were included in the analysis. To better understand the evolution of HBV serological markers, patients who had a known history of HBV vaccination were excluded—especially patients born after 1984, when universal HBV vaccination was launched in Taiwan [16].

***Determination of HBV and hepatitis C virus (HCV) serological markers and data collection.*** Demographic, clinical, serological, and virological data were recorded using a standardized data collection form. Patients without any HBV serological markers noted in consecutive tests were encouraged to undergo HBV vaccination. At the end of the study, 20 of 35 patients without any HBV serological markers subsequently received HBV vaccine and, therefore, were censored on the date of HBV vaccination. HBsAg, anti-HBs, and anti-HBc were determined using an EIA (Abbott Laboratories). All HBV serological tests were repeated. If discrepancies of results occurred between the 2 tests, a third test was performed. Antibodies to HCV (anti-HCV) were determined using a third-generation EIA (AxSYM HCV III; Abbott Laboratories).

***Quantification of HBV DNA level, HIV RNA level, and CD4 lymphocyte count.*** HBV DNA was extracted from 200 μL of serum obtained from all patients at enrollment and from patients who tested positive for HBs antigenemia or isolated anti-HBc in subsequent tests (High Pure Viral Nucleic Acid Kit; Roche Molecular Biochemicals). The HBV DNA level was quantified using a real-time PCR with the LighterCycler instrument (Roche Molecular Biochemicals), in accordance with the manufacturer's instructions. The detection limit of HBV DNA was estimated to be $10^3$ copies/mL.

The plasma HIV RNA level was determined using a commercial kit (Roche Amplicor, version 1.5), which has a detection limit of 400 copies/mL (2.60 $\log_{10}$ copies/mL). CD4 cell counts were determined using FACFlow (BD FACS Calibur; Becton Dickinson). Both the plasma HIV RNA level and the CD4 cell count were determined at enrollment, 1 month after initiation of HAART, and every 3–4 months thereafter.

***Definitions of isolated anti-HBc, virological and immunologic responses to antiretroviral therapy, and progression of HIV infection.*** Isolated anti-HBc was defined as an instance in which blood samples tested positive for anti-HBc but negative for both HBsAg and anti-HBs. Virological response to HAART was assessed by the proportion of patients who achieved an undetectable plasma HIV RNA level at 12 months, 24 months, and the last available assessment of the plasma HIV RNA level data. The analysis was performed on the basis of the on-treat principle. Virological failure was defined as failure to achieve an undetectable plasma HIV RNA level 6 months after the initiation of HAART or as a repeatedly detectable plasma HIV RNA level after initial suppression. Immunologic response was assessed by the increase in the CD4 cell count from baseline at 12 months, 24 months, and the last available assessment of CD4 cell count data and by the proportion of patients who achieved an increase in the CD4 cell count of 100 and 200 cells/μL or more during the follow-up period. Progression of HIV infection was defined as a relapse or new occurrence of an AIDS-defining opportunistic illness [17] 1 month after the initiation of HAART.

***Statistical analysis.*** All statistical analyses were performed using SPSS software, version 13.0 (SPSS). Categorical variables were compared using the $\chi^2$ test or Fisher's exact test, and noncategorical variables were compared using the Wilcoxon rank sum test. Point estimation for Poisson distribution was used for estimating the incidence and 95% CIs of changes of HBV serological markers. Multivariate analysis with the multiple logistic regression method and a stepwise forward and backward model was used to assess the impact of the variables (e.g., age, sex, risk behavior for HIV transmission, HCV coinfection, baseline CD4 cell count and plasma HIV RNA level, presence of AIDS-related diseases, use and duration of lamivudine and HAART, and CD4 cell count increase and undetectable plasma HIV RNA level after initiation of HAART) on the persistence or subsequent development of anti-HBs among patients with HBsAg, anti-HBs, and isolated anti-HBc detected at baseline. ORs and 95% CIs were calculated for logistic regression analyses. All tests were 2-tailed, and $P$ values $<.05$ were

considered to be statistically significant. Survival probabilities were estimated by the Kaplan-Meier method. The duration of observation for each patient was estimated from the date of the first HBV serological test to the date of the last HBV serological test. Equality of survival distributions was evaluated by the log-rank test. The duration of survival for patients was estimated from the date of enrollment to death, to last follow-up visit at this hospital and other designated hospitals in Taiwan, or to the end of this study (31 December 2005).

## RESULTS

***Characteristics of the population studied.*** During the period from January 1997 through December 2002, a total of 975 patients sought care for HIV infection at National Taiwan University Hospital; 342 patients were excluded from the study (figure 1), and 633 patients (583 male and 50 female patients) were enrolled. There were no significant differences in demographic characteristics and baseline clinical, virological, and immunologic data between patients who were enrolled and those who were excluded (data not shown). Sixty-three (18.4%) of the 342 excluded patients had tested positive for HBsAg.

Demographic, virological, and immunologic characteristics of the study patients are shown in table 1. At baseline, 568 patients (89.7%) tested positive for at least 1 serological marker of HBV infection: 119 patients (18.8%) had detectable HBsAg, 270 (42.7%) had detectable anti-HBs, and 179 (28.3%) had isolated anti-HBc; 65 patients (10.2%) did not have any serological marker of HBV infection detected. Hepatitis B envelope antigen was present in 26.9% of patients with HBsAg (table 1). At baseline, the HBV DNA level was detectable in 80 patients (67.2%) with HBsAg present, in 2 patients (0.7%) with anti-HBs present, in 13 patients (7.3%) with isolated anti-HBc present, and in 3 patients (4.6%) without any HBV markers.

Compared with patients who did not have any HBV markers, there were no significant baseline differences in terms of age, risk for HIV transmission, HCV seropositivity, and duration of HAART and lamivudine use in patients in the other 3 groups (table 1). However, there were more male patients who had any HBV serological markers ($P = .005–.08$), patients with isolated anti-HBc present had a greater level of immunosuppression, and patients with HBsAg present were more likely to have detectable HBV DNA ($P < .001$). The statistical results were unchanged after we excluded the 3 patients with detectable HBV DNA levels from the group of patients without any markers.

***HBV serological markers and patient outcomes.*** The patients were observed for a median duration of 4.96 years (range, 1.07–7.97 years). After initiation of HAART, patients with HBsAg present and those with isolated anti-HBc present had less robust increases in the CD4 cell count, compared with patients who did not have any HBV serological markers (at 24 months after initiation of HAART, the values were 140 and 117 cells/$\mu$L vs. 180 cells/$\mu$L, respectively; $P = .03$ and .04, respectively), and were less likely to achieve an undetectable plasma HIV RNA level (at 24 months after initiation of HAART, the proportions of patients were 69.8% and 75.6% vs. 89.1%, respectively; $P = .006$ and .03, respectively). Moreover, patients with HBsAg present were more likely to develop virological failure (42.9% vs. 27.7%; $P = .04$) and to die (22.7% vs. 7.7%; $P = .01$) than were patients without any HBV serological markers.

***Evolution of HBV serological markers.*** A total of 161 patients

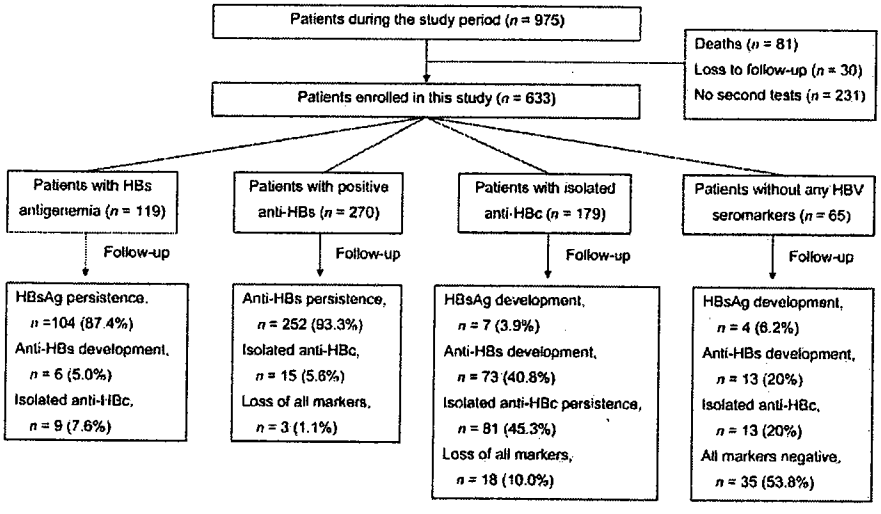


**Figure 1.** Evolution of serological markers of hepatitis B virus (HBV) among HIV-infected patients enrolled during 1997 and 2002. anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

**Table 1. Demographic, immunological, and virological characteristics of the HIV-infected patients who underwent hepatitis B virus (HBV) serological testing.**

| Characteristic | Group 1 ($n$ = 119) | Group 2 ($n$ = 270) | Group 3 ($n$ = 179) | Group 4 ($n$ = 65) | All patients ($n$ = 633) | $P$[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Group 1 | Group 2 | Group 3 |
| Age, years | 34 (20–62) | 33 (20–78) | 36 (19–81) | 33 (20–71) | 34 (19–81) | .60 | .61 | .11 |
| Male sex | 114 (95.8) | 252 (93.3) | 163 (91.6) | 54 (83.1) | 583 (92.1) | .005 | .008 | .08 |
| Risk group for HIV transmission | | | | | | | | |
| Men who have sex with men | 77 (64.7) | 177 (65.6) | 108 (60.3) | 39 (60.0) | 405 (64.0) | .53 | .40 | .96 |
| Heterosexual persons | 39 (32.8) | 84 (31.1) | 67 (37.5) | 22 (33.8) | 188 (29.7) | .88 | .66 | .61 |
| Injection drug users | 1 (0.8) | 6 (2.2) | 2 (1.1) | 2 (3.1) | 26 (4.1) | .29 | .69 | .29 |
| HCV coinfection | 9 (7.6) | 26 (9.6) | 15 (8.4) | 4 (6.2) | 54 (8.5) | .72 | .47 | .78 |
| Baseline CD4 cell count, cells/μL | 125 (2–1158) | 155 (1–1202) | 93 (0–977) | 147 (3–1280) | 132 (0–1280) | .57 | .82 | .04 |
| CD4 cell count <200 cells/μL | 68 (57.1) | 149 (55.2) | 121 (68.0) | 35 (53.9) | 373 (58.9) | .77 | .85 | .048 |
| Baseline plasma HIV RNA level,[b] $\log_{10}$ copies/mL | 4.99 (3.27–6.21) | 5.09 (3.55–6.61) | 5.08 (3.24–6.72) | 5.05 (3.36–6.57) | 5.07 (3.24–6.72) | .26 | .39 | .19 |
| Detectable HBV DNA level at baseline | 80 (67.2) | 2 (0.7) | 13 (7.3) | 3 (4.6) | 98 (15.5) | <.001 | .11 | .46 |
| Baseline HBeAg presence | 32 (26.9) | 0 (0) | 2 (1.1) | 1 (1.5) | 35 (5.5) | <.001 | | .61 |
| Receipt of HAART containing lamivudine | 113 (96.6) | 260 (97.3) | 161 (96.4) | 61 (96.8) | 585 (96.9) | .93 | .81 | .88 |
| Duration of lamivudine use, years | 4.59 (1.00–7.71) | 4.39 (1.01–7.69) | 4.53 (1.01–7.68) | 4.19 (1.09–7.62) | 4.45 (1.00–7.71) | .29 | .43 | .24 |
| Duration of HAART use, years | 4.80 (1.02–7.72) | 4.81 (1.01–7.74) | 4.75 (1.17–7.70) | 4.74 (1.09–7.67) | 4.77 (1.01–7.74) | .71 | .69 | .87 |
| Laboratory data 12 months after initiation of HAART | | | | | | | | |
| Increase in CD4 cell count, cells/μL | 75 (−428 to 418) | 87 (−647 to 1025) | 105 (−707 to 548) | 63 (−182 to 532) | 91 (−707 to 1025) | .52 | .27 | .15 |
| CD4 cell count increase of ≥100 cells/μL | 56 (47.1) | 121 (44.8) | 90 (50.3) | 29 (44.6) | 296 (46.8) | .75 | .97 | .43 |
| Undetectable plasma HIV RNA level | 74 (62.2) | 202 (74.8) | 128 (71.6) | 47 (72.3) | 451 (71.2) | .17 | .68 | .90 |
| Laboratory data 24 months after initiation of HAART[c] | | | | | | | | |
| Increase in CD4 cell count, cells/μL | 140 (−372 to 736) | 183 (−873 to 983) | 117 (−690 to 751) | 180 (−382 to 699) | 156 (−873 to 983) | .03 | .54 | .04 |
| CD4 cell count increase of ≥100 cells/μL | 68 (64.2) | 163 (66.5) | 88 (62.4) | 41 (74.5) | 360 (67.7) | .22 | .26 | .004 |
| CD4 cell count increase of ≥200 cells/μL | 37 (34.9) | 122 (49.8) | 62 (36.9) | 26 (47.3) | 247 (43.0) | .13 | .74 | .17 |
| Undetectable plasma HIV RNA level | 74 (69.8) | 180 (73.5) | 127 (75.6) | 49 (89.1) | 430 (74.9) | .006 | .01 | .03 |
| Laboratory data at the end of the study | | | | | | | | |
| Increase in CD4 cell count, cells/μL | 147 (−428 to 736) | 183 (−873 to 983) | 170 (−707 to 783) | 151 (−356 to 699) | 168 (−873 to 983) | .34 | .47 | .79 |
| CD4 cell count increase of ≥100 cells/μL | 76 (63.9) | 169 (62.6) | 91 (50.8) | 41 (63.1) | 377 (59.6) | .92 | .94 | .09 |
| CD4 cell count increase of ≥200 cells/μL | 40 (33.6) | 124 (45.9) | 63 (35.2) | 31 (47.7) | 258 (40.8) | .06 | .80 | .08 |
| Undetectable plasma HIV RNA level | 75 (63.0) | 194 (71.9) | 123 (68.7) | 49 (75.4) | 441 (69.7) | .09 | .57 | .31 |
| Duration of observation, years | 5.18 (1.12–7.78) | 4.85 (1.07–7.81) | 5.05 (1.21–7.94) | 4.76 (1.27–7.97) | 4.96 (1.07–7.97) | .13 | .43 | .22 |
| Any virological failure | 51 (42.9) | 88 (32.6) | 65 (36.3) | 18 (27.7) | 222 (35.1) | .04 | .45 | .21 |
| Death[d] | 27 (22.7) | 18 (6.7) | 25 (14.0) | 5 (7.7) | 75 (11.8) | .01 | .77 | .19 |

**NOTE.** Data are no. (%) of patients or median (range), unless otherwise indicated. Group 1 consisted of patients positive for hepatitis B surface antigen (HBsAg); group 2 consisted of patients positive for antibody to HBsAg ; group 3 consisted of patients positive for isolated antibody to hepatitis B core antigen; and group 4 consisted of patients who tested negative for HBV serological markers. HBeAg, hepatitis B envelope antigen; HCV, hepatitis C virus.

[a] For comparison with group 4.

[b] Plasma HIV RNA level was available for 98, 229, 148, and 51 patients in groups 1–4, respectively.

[c] CD4 cell counts and plasma HIV RNA level were available for 106, 245, 168, and 55 patients in groups 1–4, respectively, at 24 months after the initiation of HAART.

[d] There were 8, 1, 2, and 0 liver-related deaths among patients in groups 1–4, respectively. The causes of deaths of the 8 patients with HBsAg were cirrhosis of liver and hepatic failure ($n$ = 5), hepatocellular carcinoma ($n$ = 2), and fulminant hepatitis ($n$ = 1).

(25.4%) had changes of their HBV serological markers during follow-up (figure 1). Of the 119 patients with HBsAg present at baseline, 104 (87.4%) had persistent HBs antigenemia after follow-up for 5.18 years (range, 1.12–7.78 years); 6 patients (5.0%) became positive for anti-HBs, and 9 patients (7.6%) lost HBsAg and retained isolated anti-HBc. The incidence of HBsAg clearance and development of anti-HBs was 2.57 cases per 100 person-years (95% CI, 1.44–4.23 cases per 100 person-years) and 0.97 cases per 100 person-years (95% CI, 0.36–2.12 cases per 100 person-years), respectively. Of the 270 patients with anti-HBs present at baseline, 252 (93.3%) had persistent anti-HBs after follow-up for 4.85 years (range, 1.07–7.81 years); 18 patients (6.7%) lost anti-HBs, including 15 patients (5.6%) who developed isolated anti-HBc and 3 patients (1.1%) who lost all serological markers of HBV infection.

Of the 179 patients with isolated anti-HBc at baseline, 81 (45.3%) had persistence of isolated anti-HBc, 73 (40.8%) subsequently became positive for anti-HBs, 18 (10.0%) lost all HBV markers, and 7 (3.9%) developed HBsAg after follow-up for 5.05 years (range, 1.21–7.94 years). The incidence of development of HBsAg was 0.77 cases per 100 person-years (95% CI, 0.31–1.58 per 100 person-years). Of the 65 patients without any HBV markers at baseline, the median follow-up duration was 4.76 years (range, 1.27–7.97 years). Thirty patients (46.2%) without any HBV markers at baseline were later found to be ever exposed to HBV: 4 (6.2%) developed HBsAg, 13 (20%) anti-HBs, and 13 (20%) isolated anti-HBc. The incidence of new HBV infection in HIV-infected patients without any HBV markers at baseline was 9.69 per 100 person-years (95% CI, 6.28–13.30 per 100 person-years).

***Outcome analysis of patients with and without changes in serological markers.*** Among patients with HBsAg present at baseline, the characteristics of 104 patients with persistent HBs antigenemia and 6 patients with subsequent development of anti-HBs were compared. There were no significant differences with regard to age, sex, risk factor for HIV transmission, baseline CD4 cell count and plasma HIV RNA level, increase in the CD4 cell count during HAART, and virological response to HAART between these 2 groups (data not shown).

Among the patients with anti-HBs present at baseline, patients who subsequently lost anti-HBs during HAART had less robust increases in the CD4 cell count after the initiation of HAART, compared with patients who had persistent anti-HBs (40 vs. 93 cells/$\mu$L at 12 months [$P < .001$], 73 vs. 200 cells/$\mu$L at 24 months [$P < .001$], and 73 vs. 187 cells/$\mu$L at the end of study [$P < .001$]) (table 2); in addition, these patients were less likely to achieve an undetectable plasma HIV RNA level after the initiation of HAART (44.4% vs. 77.0% at 12 months [$P = .002$] and 44.4% vs. 73.8% at the end of the study [$P = .007$]) and had a higher mortality rate (27.8% vs. 5.2%; $P = .004$). Twenty-four months after the initiation of HAART, an increase in the CD4 cell count of $\geq$100 cells/$\mu$L was the only independent factor associated with persistence of anti-HBs (adjusted OR, 5.02; 95% CI, 1.31–19.24; $P = .02$); male sex (adjusted OR, 2.34; 95% CI, 0.92–10.41; $P = .06$) and initial plasma HIV RNA level $\geq 5$ $\log_{10}$ copies/mL (adjusted OR, 0.29; 95% CI, 0.08–1.12; $P = .07$) were of borderline significance.

Among the patients with isolated anti-HBc present at baseline, those who subsequently developed anti-HBs had a significantly greater increase in the median CD4 cell count, compared with patients who had persistence of isolated anti-HBc (223 vs. 83 cells/$\mu$L at 24 months after initiation of HAART [$P = .002$] and 216 vs. 92 cells/$\mu$L at the end of study [$P = .004$]); in addition, these patients had a higher likelihood of achieving an undetectable plasma HIV RNA level at the end of study (82.2% vs. 68.8%; $P = .04$) (table 3). Twenty-four months after the initiation of HAART, an increase in the CD4 cell count of $\geq$100 cells/$\mu$L was the only independent factor associated with the development of anti-HBs (adjusted OR, 4.65; 95% CI, 1.96–11.02; $P = .001$).

Survival estimates among the 4 groups of patients are shown in figure 2*A*. Patients with detected HBsAg had a shorter duration of survival than did patients in the other 3 groups. Patients with isolated anti-HBc detected at baseline had a shorter duration of survival than did patients with anti-HBs present ($P = .02$). Patients who had persistent HBsAg during follow-up had a worse duration of survival than did patients who had persistent anti-HBs ($P < .001$), those who had persistent isolated anti-HBc ($P = .07$), and those who subsequently developed anti-HBs ($P = .12$) (figure 2*B*).

## DISCUSSION

In this study, the prevalence of any exposure to HBV, which was defined as the presence of any serological marker of HBV infection (89.8%) and as chronic HBV infection (16.4%), in HIV-infected patients was similar to that of other Taiwanese adult populations, in which 90% of persons had exposure to HBV and 15%–20% were chronic carriers of HBV [18]. The higher HBV seroprevalence could be explained by the fact that, in Taiwan, most cases of HBV infection occur during the perinatal period or early childhood, before the implementation of the nationwide HBV vaccination program [18, 19].

The proportion of the patients in our study who had changes in HBV serological patterns (25.4%) was significantly higher than the proportions reported in other studies (12% and 16%, with median durations of follow-up of 2.2 years and 21 months, respectively) [5, 11]. Such changes of HBV serological markers after initiation of HAART mainly involved anti-HBs development in patients who had isolated anti-HBc and acquisition of HBV infection in those who had no HBV serological markers at baseline (45.3% and 18.6% of the 161 patients with changes of serological markers, respectively). The HBsAg clearance rate

**Table 2. Comparison of patients with persistent antibody to hepatitis B surface antigen (anti-HBs) and those who subsequently lost anti-HBs among patients who initially tested positive for anti-HBs.**

| Characteristics | Patients with persistent anti-HBs ($n$ = 252) | Patients who lost anti-HBs ($n$ = 18) | $P$ |
|---|---|---|---|
| HCV coinfection | 24 (9.5) | 2 (11.1) | .69 |
| Baseline CD4 cell count | | | |
| Median cells/μL (range) | 157 (1–1202) | 114 (3–868) | .27 |
| <200 cells/μL | 141 (56.0) | 8 (44.4) | .34 |
| Baseline plasma HIV RNA level,[a] median $\log_{10}$ copies/mL (range) | 5.09 (3.55–6.51) | 5.05 (3.75–6.19) | .49 |
| HAART duration, median years (range) | 4.81 (1.01–7.74) | 4.53 (1.04–7.68) | .52 |
| Receipt of lamivudine-containing HAART | 243 (96.4) | 17 (94.4) | .67 |
| Duration of lamivudine use, median years (range) | 4.43 (1.01–7.69) | 4.35 (1.04–7.68) | .69 |
| Laboratory data 12 months after initiation of HAART | | | |
| Increase in the CD4 cell count, median cells/μL (range) | 93 (−647 to 1025) | 40 (−441 to 469) | <.001 |
| Increase in the CD4 cell count ≥100 cells/μL | 119 (47.2) | 2 (11.1) | <.001 |
| Undetectable plasma HIV RNA level | 194 (77.0) | 8 (44.4) | .002 |
| Laboratory data 24 months after initiation of HAART[b] | | | |
| Increase in the CD4 cell count, median cells/μL (range) | 200 (−873 to 983) | 73 (−400 to 184) | <.001 |
| Increase in the CD4 cell count ≥100 cells/μL | 159 (68.5) | 4 (30.8) | .01 |
| Increase in the CD4 cell count ≥200 cells/μL | 120 (51.7) | 2 (15.4) | .02 |
| Undetectable plasma HIV RNA level | 172 (74.1) | 8 (61.5) | .34 |
| Laboratory data at the end of the study | | | |
| Increase in the CD4 cell count, median cells/μL (range) | 187 (−873 to 983) | 73 (−400 to 324) | <.001 |
| Increase in the CD4 cell count ≥100 cells/μL | 164 (65.1) | 5 (27.8) | .002 |
| Increase in the CD4 cell count ≥200 cells/μL | 122 (48.4) | 2 (11.1) | .002 |
| Undetectable plasma HIV RNA level | 186 (73.8) | 8 (44.4) | .007 |
| Duration of observation duration, median years (range) | 4.84 (1.07–7.81) | 4.94 (1.11–7.71) | .65 |
| Death | 13 (5.2) | 5 (27.8) | .004 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. HCV, hepatitis C virus.

[a] Plasma HIV RNA level was available for 213 and 16 patients with persistent anti-HBs and patients with subsequently undetectable anti-HBs antibodies, respectively.

[b] CD4 cell count and plasma HIV RNA level were available for 232 and 13 patients with persistent anti-HBs and patients with subsequently undetectable anti-HBs antibodies, respectively, at 24 months after the initiation of HAART.

among our patients (2.57 cases per 100 person-years) was low, even after immune reconstitution associated with HAART that contained lamivudine. The low HBsAg clearance rate is not surprising, because the overall incidence of HBsAg clearance has been low even in HIV-uninfected HBV-carrying adults [20]. Furthermore, the cumulative resistance rate of HBV to lamivudine is high in HIV-infected patients [21]. Despite recent advances in anti-HBV therapy, the seroconversion rate remains low, regardless of whether the agents are used in combination [22, 23].

Loss of hepatitis B immunity occurs in association with HIV infection [5, 10, 24]. Among HIV-infected patients who were not receiving HAART, loss of anti-HBs occurred in 13%–17% of patients with hemophilia [24] and 28% of men who have sex with men [25], compared with 0% of HIV-uninfected patients during observation periods of 2 and 3 years. Achieving an undetectable plasma HIV RNA level and greater gains in the CD4 cell count in association with HAART enables HIV-HBV–coinfected patients to achieve HBsAg clearance, anti-HBe seroconversion, and suppression of HBV replication [25]. In this study, >93% of such patients who received HAART continued to have detectable anti-HBs, despite severe immunosuppression; these patients tended to have better virological and immunologic responses to HAART than did patients who subsequently lost anti-HBs. These data suggest that preservation of anti-HBs requires better adherence to HAART to achieve better immune reconstitution.

Our results showed that determination of only HBsAg and anti-HBs data may miss patients who had isolated anti-HBc. In such patients in whom isolated anti-HBc is detected, determination of the HBV DNA level is important to clarify the status of their HBV infection [26, 27]. By determination of the HBV DNA level, we found that occult or window-period HBV infection occurred in 7.3% of the patients in our study who had isolated anti-HBc detected and in 4.6% of patients who did not have any HBV serological markers. The prevalence of

**Table 3. Comparison of patients with persistent isolated antibodies to hepatitis B core antigen (anti-HBc) and those who subsequently developed detectable anti-HBs among patients with initial isolated anti-HBc.**

| Characteristics | Patients who developed anti-HBs ($n$ = 73) | Patients with persistent isolated anti-HBc ($n$ = 81) | $P$ |
|---|---|---|---|
| HCV coinfection | 6 (8.2) | 7 (8.8) | .91 |
| Baseline CD4 cell count | | | |
| Median cells/$\mu$L (range) | 119 (2–877) | 88 (0–786) | .12 |
| <200 cells/$\mu$L | 49 (67.1) | 55 (67.9) | .91 |
| Baseline plasma HIV RNA level,[a] median $\log_{10}$ copies/mL (range) | 5.06 (3.24–6.68) | 5.11 (3.27–6.72) | .13 |
| HAART duration, median years (range) | 4.78 (1.17–7.64) | 4.55 (1.21–7.70) | .37 |
| Receipt of lamivudine-containing HAART | 68 (93.2) | 75 (92.6) | .89 |
| Duration of lamivudine use, median years (range) | 4.54 (1.01–7.68) | 4.49 (1.21–7.61) | .72 |
| Laboratory data 12 months after initiation of HAART | | | |
| Increase in the CD4 cell count, median cells/$\mu$L (range) | 117 (−707 to 479) | 9 (−354 to 548) | .23 |
| Increase in the CD4 cell count ≥100 cells/$\mu$L | 41 (56.2) | 7 (45.7) | .19 |
| Undetectable plasma HIV RNA level | 56 (76.7) | 58 (71.6) | .47 |
| Laboratory data 24 months after nictitation of HAART[b] | | | |
| Increase in the CD4 cell count, median cells/$\mu$L (range) | 223 (−590 to 567) | 83 (−551 to 751) | .002 |
| Increase in the CD4 cell count ≥100 cells/$\mu$L | 48 (72.7) | 2 (41.6) | <.001 |
| Increase in the CD4 cell count ≥200 cells/$\mu$L | 36 (54.5) | 19 (24.7) | <.001 |
| Undetectable plasma HIV RNA level | 52 (78.8) | 62 (80.5) | .80 |
| Laboratory data at the end of the study | | | |
| Increase in the CD4 cell count, median cells/$\mu$L (range) | 216 (−590 to 567) | 92 (−551 to 751) | .004 |
| Increase in the CD4 cell count ≥100 cells/$\mu$L | 52 (71.2) | 35 (43.2) | <.001 |
| Increase in the CD4 cell count ≥200 cells/$\mu$L | 39 (35.6) | 21 (20.0) | <.001 |
| Undetectable plasma HIV RNA level | 60 (82.2) | 55 (68.8) | .04 |
| Duration of observation duration, median years (range) | 4.98 (1.21–7.77) | 5.11 (1.22–7.94) | .48 |
| Death | 9 (12.3) | 16 (19.8) | .21 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. HCV, hepatitis C virus.

[a] Plasma HIV RNA level was available for 68 and 60 patients with subsequently detectable anti-HBs and patients with persistent isolated anti-HBc, respectively.

[b] CD4 cell counts and plasma HIV RNA level were available for 66 and 77 patients with subsequently detectable anti-HBs and patients with persistent isolated anti-HBc, respectively, at 24 months after the initiation of HAART.

occult or window-period HBV infection in our patients was much higher than that (0.6%) in another large cohort study [28]; this can possibly be attributed to a higher background prevalence of chronic HBV infection in Taiwan and lower baseline CD4 cell counts in our patients (132 vs. 414 cells/$\mu$L [28]).

The appropriate treatment for HIV-infected persons who have isolated anti-HBc remains unknown. HBV vaccination may be considered, because a recent study suggested that >60% of patients with isolated anti-HBc developed seroprotective anti-HBs titers [29]. However, determination of the HBV DNA level should be considered, to exclude the possibility of occult HBV infection in patients with isolated anti-HBc (as occurred in 7.3% in our patients) before HBV vaccine is to be administered. Of the patients in our study who did not receive HBV revaccination, 40.8% of those with isolated anti-HBc who achieved better virological and immunologic responses to HAART developed anti-HBs, suggesting that immune reconstitution may restore immunity against HBV.

Among patients without any HBV serological markers, we observed a higher rate of HBV infection (9.69 cases per 100 person-years) than has been observed in other reports (0.2–0.3 cases per 100 person-years) [3–5, 11] and in a study of HIV-uninfected persons in Taiwan [16]. The higher rates of HBV transmission may be associated with low CD4 cell counts and decreased cellular immunity against HBV infection by HIV infection after risky exposure. This finding highlights the importance of vaccination of all HIV-infected patients without HBV markers and of counseling against HBV infection.

There were limitations to our study. First, not all patients received sequential HBV serological tests, and patients with shorter observation periods (i.e., <1 year) were excluded from the study; thus, selection bias could not be avoided, although the characteristics of excluded patients were similar to those of enrolled patients. Second, our population is unique in that most patients with detected HBsAg were chronic HBV carriers since childhood, and the injection drug users and HIV-HCV–coin-

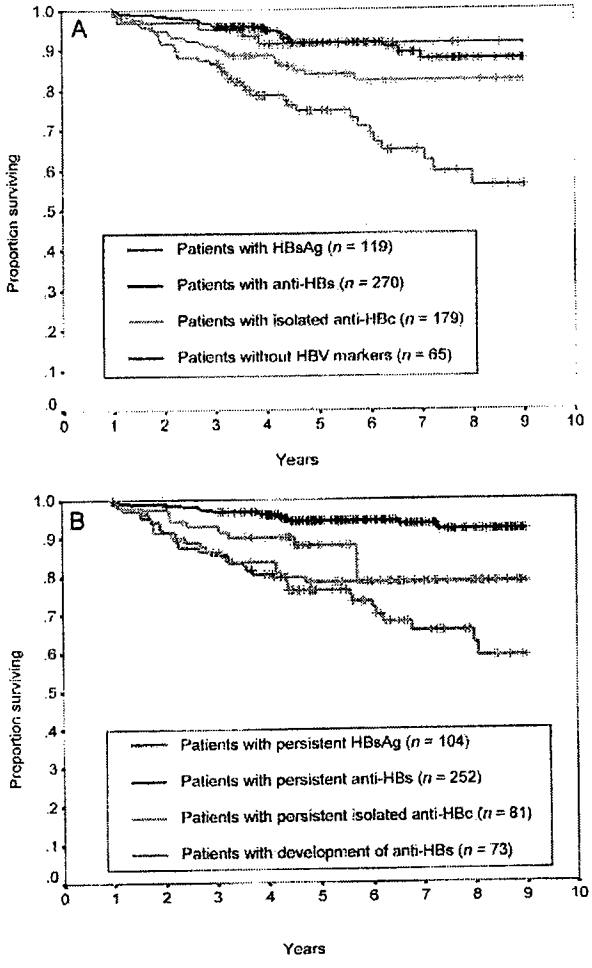


**Figure 2.** *A*, Kaplan-Meier survival estimates among patients with hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and isolated antibody to hepatitis B core antigen (anti-HBc) and without hepatitis B virus serological markers at baseline. Patients with HBsAg had shorter durations of survival than did those with anti-HBs, those with isolated anti-HBc, and those without HBV serological markers ($P < .001$ to .001). There were no statistically significant survival differences between patients with anti-HBs and those without any HBV serological markers ($P = .99$) or between patients with isolated anti-HBc and those without any HBV serological markers ($P = .16$). However, patients with isolated anti-HBc at baseline had shorter survival durations than did those with anti-HBs ($P = .02$). *B*, Kaplan-Meier survival estimates among patients with HBsAg persistence, patients with anti-HBs persistence, patients with isolated anti-HBc who subsequently developed anti-HBs, and patients who had persistent isolated anti-HBc noted in follow-up blood tests. Patients with HBsAg persistence had shorter durations of survival than did those with anti-HBs persistence ($P < .001$), those with isolated anti-HBc who subsequently developed anti-HBs ($P = .12$), and those with persistent isolated anti-HBc ($P = .07$). Patients with anti-HBs persistence had longer durations of survival than did those with persisted isolated anti-HBc ($P = .02$) and those who subsequently developed anti-HBs ($P < .001$).

fected patients accounted for only a small proportion of the study population. Thus, our findings might not be generalizable to other populations with different epidemiologic and demographic characteristics. Third, attempts to identify factors (e.g., baseline HBV DNA level) associated with changes in HBV serological markers after initiation of lamivudine-containing HAART may be limited by the small numbers of cases in certain groups (tables 2 and 3). Finally, we were not able to completely exclude the possibility that changes in HBV serological markers may have been caused by the variability of serological tests, although we repeated serological tests with each serum sample in our study.

In conclusion, changes in HBV serological markers are not uncommon in a region where HBV infection is endemic, and repeated measurement of HBV markers (including anti-HBc) in patients with HIV infection should be considered. Better virological and immunologic responses to HAART are associated with preservation and development of anti-HBs. HBV vaccination should be routinely advised to patients without any HBV markers.

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# Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan

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***Objectives*: To describe the incidence of hypersensitivity to abacavir and frequency of human leucocyte antigen (HLA)-B*5701 in HIV-infected Taiwanese persons.**

***Methods*: Medical records of 337 HIV-infected Taiwanese in whom abacavir-containing combination antiretroviral therapy (CART) was prescribed from 1 May 2001 to 31 December 2006 were reviewed, and HLA typing of the patients was performed in 320 patients (232 receiving abacavir and 88 not receiving abacavir) with available blood samples. HLA class I and II polymorphisms were determined by PCR with specific primers. HLA-B*5701 was further confirmed by sequence-based typing.**

***Results*: Of the 337 patients, median CD4 count was 166.5 cells/mm$^3$ (range, 1.0–1914.0) and 83 patients (24.6%) had AIDS-defining opportunistic infections. Thirty-eight patients (11.3%) discontinued abacavir within 6 weeks of starting abacavir-containing CART. Among them, 10 patients had successful abacavir re-challenge and another 11 patients had other specific reasons for abacavir discontinuation. Therefore, 14 patients (4.2%) were classified as cases in whom abacavir hypersensitivity could not be excluded, and 3 patients (0.9%) met the criteria of abacavir hypersensitivity. Of the 320 patients undergoing HLA typing, HLA-A02 was the most common allele and only one individual (0.3%) expressed HLA-B*5701. Along with some differences in allele distributions, there was a significant difference in the genetic frequency of HLA-B57 in our patients compared with those of previous studies in other Chinese populations.**

***Conclusions*: Abacavir hypersensitivity was less frequently encountered in HIV-infected Taiwanese initiating abacavir-containing CART than in Caucasians, which might be explained by the low frequency of the HLA-B*5701 allele.**

Keywords: pharmacogenetics, gene frequency, antiretroviral therapy

## Introduction

Approximately 5% to 8% of Caucasians with HIV infection who initiate combination antiretroviral therapy (CART) containing abacavir, a nucleoside analogue, have a hypersensitivity reaction,[1,2] and such reaction usually occurs within the first 6 weeks of treatment (median time to onset, 11 days) and is characterized by multisystem involvement with presentations of skin rash, fever, constitutional, gastrointestinal or respiratory symptoms.[1] Furthermore, re-challenge with abacavir after a hypersensitivity reaction might cause life-threatening hypotension and death.[1,3,4] Recently, strong associations between certain specific human leucocyte antigen (HLA) types and abacavir hypersensitivity have been demonstrated in populations mainly consisting of Caucasians.[5–7] In addition, prospective employment of routine screening for HLA-B*5701 with subsequent avoidance of abacavir prescription in HIV-infected patients carrying this allele has significantly reduced the incidence of abacavir hypersensitivity.[8–11]

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However, the frequency of HLA-B*5701 varies in different ethnic populations, such as <1% in sub-Saharan African, 1% to 2% in the Mediterranean, 5% to 20% in India, 0% in China and 4% to 10% in Thailand.[12,13] Furthermore, published data of the association between HLA-B*5701 and abacavir hypersensitivity in HIV-infected Asian patients are rarely reported.[14] In the present study, we aimed to describe the incidence of abacavir hypersensitivity and assess its relationship with HLA-B*5701 in HIV-infected Taiwanese patients who initiated abacavir-containing CART.

## Materials and methods

### *Patients*

From May 2001 to December 2006, 358 patients were prescribed abacavir as part of their CART from a cohort of ~1550 consecutively enrolled non-haemophiliac HIV-infected persons who received medical care at the National Taiwan University Hospital, the largest referral hospital for HIV inpatient and outpatient care in Taiwan. A standardized case report form was used to record patient demographics, route of HIV infection, history of food or drug allergies, CD4 and CD8 lymphocyte counts, plasma HIV RNA load, AIDS with or without opportunistic infections, concurrent medications within 6 weeks of abacavir use, outcome of abacavir prescription (still used at the end of observation, discontinuation within or after 6 weeks of abacavir use, reasons of abacavir discontinuation, re-challenge of abacavir) and the results of HLA typing. The end of observation was on 12 February 2007 (6 weeks after the last enrolment on 31 December 2006). Eighty-eight HIV-infected patients who did not receive abacavir were recruited as a control group to have their HLA typed for comparison. The study protocol was approved by the Institutional Review Board of the hospital and participants gave written informed consent.

### *Definitions*

Definite cases of abacavir hypersensitivity were defined as those who had onset of at least two of the following symptoms within 6 weeks of abacavir initiation:[5] fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea or abdominal pain), lethargy, malaise, arthralgia, myalgia or respiratory symptoms (dyspnoea, sore throat or cough); resolution of symptoms within 72 h of discontinuation of abacavir; and absence of an alternative likely explanation for the symptoms. Patients with abacavir tolerance were those in whom abacavir had been continued for at least 6 weeks. Patients with abacavir hypersensitivity not excluded were those for whom abacavir hypersensitivity could not be excluded because symptoms in the first 6 weeks of abacavir exposure did not meet diagnostic criteria.[5] Patients were categorized as the group of abacavir discontinuation with specific reasons if they had alternative explanations for their early discontinuation (within 6 weeks of initial abacavir use). Patients were excluded from the present study if there were not sufficient clinical data available to assess clinical reaction to abacavir-containing CART or follow-up duration was <6 weeks.

### *HLA typing*

High molecular weight genomic DNA was extracted from peripheral blood mononuclear cells using the Wizard® Genomic DNA Purification Kit (Promega). The concentrations of extracted DNA samples were determined by spectrophotometry and stored at −20°C before HLA typing. The HLA class I and II alleles with two-digit specificities were determined using RELI™ SSO typing kits (HLA-A, HLA-B, HLA-Cw, HLA-DRB1, HLA-DQB1 Typing kits; DYNAL BIOTECH) according to the manufacturer's instructions. The HLA-B57 subtypes with four-digit specificities were further determined by sequence-based typing. Because the Taiwanese population is not inbred, we used the assumption of Hardy–Weinberg equilibrium to estimate the gene frequency (GF) for each locus, $GF = 1 - \sqrt{1 - AF}$ (allele frequency).[15] The *Hsp70-Hom M493T* single nucleotide polymorphism (SNP) was determined using PCR and *Nco*I restriction fragment-length polymorphism described previously.[16]

### *Statistical analysis*

All statistical analyses were performed with SPSS version 12.0 (SPSS, Chicago, IL, USA). Categorical variables were compared by $\chi^2$ analysis or Fisher's exact test. Non-categorical variables were compared by the Wilcoxon rank sum test. All comparisons were two-tailed and a $P$ value <0.05 was considered significant.

## Results

Among 358 patients initiating abacavir-containing CART during the study period, 21 patients (5.9%) were excluded from further analysis and 337 patients were enrolled in the present study (Figure 1). The demographics of the 337 enrolled patients are shown in Table 1. One hundred and ninety-two patients (57.3%) met the criteria of AIDS, and concurrent AIDS-defining opportunistic infections occurred in 83 patients (24.6%) at abacavir prescription. Thirty-eight patients (11.3%) discontinued abacavir within 6 weeks, and 10 of them had successful re-challenge later (Figure 1). Another one patient stopped abacavir with unknown duration of abacavir use, but resumed it later successfully. Overall, 309 patients (91.7%) were categorized as abacavir tolerant.

Except for the 10 patients who resumed abacavir successfully, the remaining 28 patients who discontinued abacavir within 6 weeks were categorized into three groups: abacavir hypersensitivity (3 patients, 0.9%), abacavir hypersensitivity not excluded (14, 4.2%) and abacavir discontinuation with specific

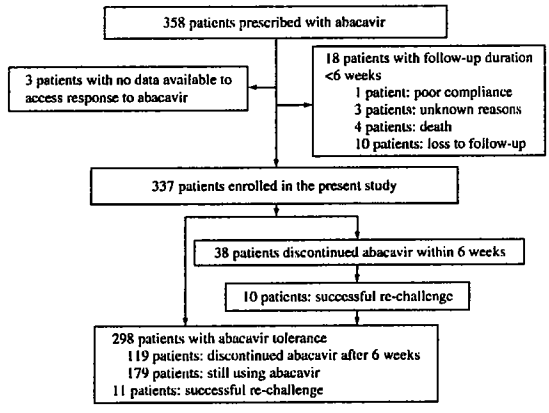


**Figure 1.** Flow chart of case enrolment and outcome.

JAC antiviral

**Table 1.** Demographics of 337 enrolled patients treated with highly active antiretroviral therapy containing abacavir

| Demographics | Data (patient number with data available) |
|---|---|
| Men (*n*, %) | 308, 91.4% (337) |
| Risk factor of HIV infection (*n*, %) | |
| homosexual/bisexual | 204, 60.5% (337) |
| heterosexual | 108, 32.0% (337) |
| others | 25, 7.5% (337) |
| Baseline data | |
| CD4 (median, range), cells/mm$^3$ | 69, 0–908 (321) |
| CD8 (median, range), cells/mm$^3$ | 513, 27–2957 (266) |
| plasma HIV RNA (median, range), $\log_{10}$ copies/mL | 5.3, 1.7–6.0 (264) |
| At abacavir prescription | |
| age (median, range), years | 37, 9–80 (337) |
| history of allergy (*n*, %) | 81, 24.2% (335) |
| AIDS (*n*, %) | 192, 57.3% (335) |
| concurrent OIs (*n*, %) | 83, 43.5% (191) |
| CD4 (median, range), cells/mm$^3$ | 166.5, 1–1914 (326) |
| CD8 (median, range), cells/ mm$^3$ | 743, 27–3658 (246) |
| plasma HIV RNA (median, range), $\log_{10}$ copies/mL | 4.1, 1.7–6.6 (328) |

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; OIs, opportunistic infections.

reasons (11, 3.3%). In the group of patients who discontinued abacavir with specific reasons, abacavir was discontinued (median interval from initiation to discontinuation, 26 days; range 1–36 days) because of patient's choice (3 patients), dizziness (2), regimen adjustment (1), structured treatment interruption (1), alopecia (1), eyelid swelling (1), abdominal pain caused by tuberculosis (1), and psychological and gastrointestinal upset (1). The symptoms of patients with abacavir hypersensitivity not excluded were rashes (6 patients), gastrointestinal symptoms with nausea (2) and vomiting (1), and both (1), fever (2), and generalized discomfort (2). All six patients with rashes had concomitant medications, such as efavirenz (2), clindamycin and primaquine (2), sulfamethoxazole/trimethoprim (co-trimoxazole) and nevirapine (1), and co-trimoxazole and carbamazepine (1). One of the two patients with fever also took co-trimoxazole at the same time.

Among the three patients (0.9%) with abacavir hypersensitivity, one (HLA-A02, -A33, -B39, -B58, -Cw07, -Cw10) developed fever, maculopapular rashes, dyspnoea and pneumonitis on day 28 of abacavir use, which resolved after abacavir discontinuation. The second patient (HLA-A*0203, -A33, -B46, -B58, -Cw01, -Cw10) had maculopapular rashes with itching sensation over the trunk, watery diarrhoea and vomiting on day 28 of abacavir use, and these symptoms disappeared after stopping abacavir. In the third case (HLA-A*0203, -A11, -B*1301, -B52, -Cw07, -Cw10), fever and rashes with itching sensation occurred after abacavir use for 10 days and concurrent co-trimoxazole for nocardiosis for more than 3 weeks, and symptoms improved after discontinuation of abacavir and co-trimoxazole. Although he had fever and rash again during the period of co-trimoxazole re-challenge, generalized skin rash and diarrhoea took place on day 15 after he resumed abacavir. No particular alleles were identified to be associated with abacavir hypersensitivity in these three patients.

Three hundred and twenty patients underwent HLA typing, 232 receiving abacavir- and 88 not receiving abacavir-containing CART. Seven HLA-I specificities were present in more than 10% of the study subjects: HLA-A02, HLA-A11 and HLA-A24

**Table 2.** Frequencies of HLA-A, HLA-B and HLA-C alleles in the study population and comparison with previous studies[17–19]

| | Gene frequency | | | | | |
|---|---|---|---|---|---|---|
| | this study | | | other studies | | |
| Allele | total study patients ($n = 320$) | enrolled group ($n = 232$) | control group ($n = 88$) | ref. 17 ($n = 673$) | ref. 18 ($n = 7137$) | ref. 19 ($n = 393$) |
| A01 | 0.001 | 0.002 | NA | 0.007 | 0.003 | 0.046* |
| A02 | 0.175 | 0.177 | 0.167 | 0.293* | 0.317* | 0.280* |
| A03 | 0.003 | 0.003 | 0.003 | 0.004 | 0.003 | 0.048* |
| A06 | 0.002 | 0.002 | NA | NA | NA | NA |
| A11 | 0.166 | 0.164 | 0.171 | 0.349* | 0.349* | 0.173 |
| A23 | 0.001 | 0.001 | NA | NA | NA | 0.011* |
| A24 | 0.104 | 0.103 | 0.105 | 0.158* | 0.166* | 0.127 |
| A26 | 0.014 | 0.014 | 0.014 | 0.023 | 0.013 | 0.038* |
| A30 | 0.005 | 0.004 | 0.006 | 0.016* | 0.012 | 0.076* |
| A31 | 0.009 | 0.008 | 0.011 | 0.025* | 0.012 | 0.047* |
| A32 | 0.001 | 0.001 | NA | 0.004 | 0.002 | 0.017* |
| A33 | 0.051 | 0.050 | 0.056 | 0.098* | 0.116* | 0.072 |
| A34 | 0.003 | 0.003 | NA | 0.001 | 0.001 | 0.001 |
| A68 | 0.001 | 0.001 | NA | NA | NA | 0.015* |
| A69 | 0.001 | NA | 0.003 | NA | NA | NA |

*Continued*

**Table 2.** *Continued*

| Allele | Gene frequency | | | | | |
|---|---|---|---|---|---|---|
| | this study | | | other studies | | |
| | total study patients ($n = 320$) | enrolled group ($n = 232$) | control group ($n = 88$) | ref. 17 ($n = 673$) | ref. 18 ($n = 7137$) | ref. 19 ($n = 393$) |
| B07 | 0.002 | 0.002 | 0.003 | 0.011* | 0.003 | 0.034* |
| B08 | 0.004 | 0.005 | NA | 0.002 | 0.001 | 0.023* |
| B13 | 0.036 | 0.037 | 0.032 | 0.085* | 0.083* | 0.112* |
| B18 | 0.001 | 0.001 | NA | NA | 0.002 | 0.017* |
| B27 | 0.012 | 0.013 | 0.009 | 0.032* | 0.027* | 0.023 |
| B35 | 0.017 | 0.017 | 0.017 | 0.029 | 0.015 | 0.068* |
| B38 | 0.019 | 0.020 | 0.017 | 0.033 | 0.037* | 0.041* |
| B39 | 0.014 | 0.013 | 0.017 | 0.002* | 0.026* | 0.020 |
| B40 | 0.001 | NA | 0.003 | NA | 0.001 | 0.108* |
| B44 | 0.007 | 0.006 | 0.009 | 0.008 | 0.005 | 0.036* |
| B45 | 0.001 | 0.001 | NA | 0.002 | 0.001 | 0.003 |
| B46 | 0.079 | 0.079 | 0.080 | 0.131* | 0.146* | 0.075 |
| B48 | 0.009 | 0.008 | 0.011 | 0.015 | 0.012 | 0.022* |
| B50 | 0.001 | 0.001 | NA | NA | 0.001 | 0.023* |
| B51 | 0.025 | 0.022 | 0.035 | 0.047* | 0.060* | 0.073* |
| B52 | 0.006 | 0.004 | 0.011 | 0.020* | 0.008 | 0.043* |
| B54 | 0.022 | 0.021 | 0.026 | 0.022 | 0.025 | 0.021 |
| B55 | 0.015 | 0.014 | 0.017 | 0.025 | 0.030* | 0.020 |
| B56 | 0.009 | 0.012 | 0.003 | 0.013 | 0.008 | 0.008 |
| B57 | 0.001 | 0.001 | NA | 0.006 | 0.008* | 0.009* |
| B58 | 0.046 | 0.047 | 0.044 | 0.097* | 0.107* | 0.051 |
| B60 | 0.104 | 0.103 | 0.105 | 0.219* | 0.209* | NA |
| B61 | 0.018 | 0.021 | 0.011 | 0.025 | 0.032* | NA |
| B62 | 0.023 | 0.025 | 0.020 | 0.053* | 0.087* | NA |
| B63 | 0.001 | 0.001 | NA | 0.001 | 0.001 | NA |
| B67 | 0.002 | 0.001 | 0.003 | 0.004 | NA | 0.003 |
| B71 | 0.005 | 0.004 | 0.006 | NA | NA | NA |
| B75 | 0.032 | 0.031 | 0.035 | 0.048 | 0.039 | NA |
| B76 | 0.001 | 0.001 | NA | NA | 0.001 | NA |
| Cw01 | 0.123 | 0.120 | 0.130 | 0.188* | NA | 0.127 |
| Cw02 | 0.001 | 0.001 | NA | NA | NA | 0.011* |
| Cw03 | 0.002 | 0.003 | NA | 0.071* | NA | 0.171* |
| Cw04 | 0.036 | 0.035 | 0.038 | 0.04 | NA | 0.074* |
| Cw05 | 0.004 | 0.003 | 0.006 | NA | NA | 0.006 |
| Cw06 | 0.007 | 0.008 | 0.006 | 0.034* | NA | 0.115* |
| Cw07 | 0.116 | 0.118 | 0.111 | 0.153* | NA | 0.161* |
| Cw08 | 0.049 | 0.050 | 0.047 | NA | NA | 0.088* |
| Cw09 | 0.030 | 0.028 | 0.035 | 0.055* | NA | NA |
| Cw10 | 0.104 | 0.108 | 0.092 | 0.107 | NA | NA |
| Cw12 | 0.020 | 0.018 | 0.023 | NA | NA | 0.076* |
| Cw14 | 0.018 | 0.018 | 0.017 | NA | NA | 0.041* |
| Cw15 | 0.013 | 0.011 | 0.017 | NA | NA | 0.055* |

NA, not available.
$\chi^2$ test was performed to compare the genetic frequencies of specific alleles between our enrolled and control groups or our overall study group with previous study results. An asterisk indicates a significant difference ($P \leq 0.05$) with our study group.

at the HLA-A locus; HLA-B60 at the HLA-B locus; and HLA-Cw01, HLA-Cw07, and HLA-Cw10 at the HLA-C locus. There was no significant difference in the allele frequency between the 232 patients initiating abacavir and the 88 not receiving abacavir; only one patient who received abacavir-containing CART had HLA-B*5701. This patient discontinued abacavir 19 days after initial prescription due to rash with concomitant efavirenz use and was grouped as abacavir

hypersensitivity not excluded. Because co-occurrence of HLA-B*5701, HLA-DR7 and HLA-DQ3 or HLA-B*5701 and a haplotypic *Hsp70-Hom M493T* were shown to be predictive of abacavir-induced hypersensitivity,[7] further analysis was conducted to analyse the polymorphisms of these regions in our HLA-B*5701 carriers. All the HLA-DR7, HLA-DQ3 and *Hsp70-Hom M493T* variant markers were present in this patient.

Since the Taiwanese population is not inbred, differences in HLA genetic frequencies have been observed in different ethnic groups of Taiwanese.[17,18] The genetic frequencies of the HLA-A, HLA-B and HLA-C of our patients were compared with those of published studies in Taiwanese and the Mainland Chinese populations (Table 2),[17–19] and some interesting findings were noted. First, there was no significant difference in the genetic frequencies of HLA class I between our enrolled patients and control patients. Second, the HLA-B57 frequency in our study patients was significantly lower than two of the published studies. Third, there were indeed some significant differences in genetic frequencies of specific alleles between our patients and those of published studies, such as HLA-A02, HLA-A11, HLA-A24, HLA-A30, HLA-A31 and HLA-A33 in the HLA-A locus; HLA-B07, HLA-B13, HLA-B27, HLA-B38, HLA-B39, HLA-B46, HLA-B51, HLA-B52, HLA-B57, HLA-B58, HLA-B60 and HLA-B62 in the HLA-B locus; and HLA-Cw03, HLA-Cw06 and HLA-Cw07 in the HLA-C locus.

## Discussion

Our present study showed the occurrence of abacavir hypersensitivity (0.9%) was lower in HIV-infected patients in Taiwan when compared with that (5% to 8%) in Western countries.[1,2] In addition, the incidence of abacavir hypersensitivity not excluded was also lower (4.2%) in our patient population than that (8.6-10.2%) in other countries without routine screening for HLA-B*5701.[8,11] Besides, the proportion of patients carrying HLA-B*5701 was only 0.4% in our patients initiating abacavir (0.3% in 320 HIV-infected patients with HLA typing), which was much lower than that (7.3% to 12.2%) in Caucasians.[8–11] Although one patient with abacavir hypersensitivity not excluded had HLA-B*5701 in the present study, none of the three patients who met the clinical criteria of abacavir hypersensitivity had this variant. Because only one patient had all the HLA-DR7, HLA-DQ3 and *Hsp70-Hom M493T* variant markers, it is difficult to reach a conclusion regarding the association between these HLA alleles and abacavir hypersensitivity from our observations. However, further studies might be needed to explore whether other specific genes are responsible for abacavir hypersensitivity in our population of ethnic Chinese, since abacavir hypersensitivity did occur in patients without these HLA alleles.

Studies of prospective screening for HLA-B*5701 prior to initiation of abacavir have illustrated significant reduction in the incidence of abacavir hypersensitivity, from 6.2–12.2% to 0–2.0%,[8–11] in Caucasians. Hughes *et al.*[20] also demonstrated that such practice appears to be cost-effective in terms of healthcare resources. However, application of routine HLA-B*5701 testing to other racial populations raises concerns because of lack of such an association of HLA-B*5701 and abacavir hypersensitivity in black Africans.[21,22] It is worth noting that few Asians were enrolled in these studies[8–11,23] although Mosteller *et al.*[14] has demonstrated comparable sensitivity (57% versus 50%) of HLA-B*5701 in Thai subjects (7 enrolled cases) and Caucasians (444 enrolled cases). Therefore, our study provided a missing piece of information with respect to incidence of abacavir hypersensitivity in 337 ethnic Chinese and prevalence of HLA-B*5701.

As compared with Caucasians in prior studies,[8–11] Chinese populations have a lower frequency of HLA-B*5701.[17–19] Different genetic frequency of specific alleles between our data and prior published reports existed (Table 2),[17–19] and such observations might result from our limited sample size or simply reflect the complex ethnic nature of Taiwanese. Nevertheless, our patients had significantly lower genetic frequency of HLA-B57 than other Chinese populations, which might explain the low incidence of abacavir hypersensitivity in the present study. Based on the above findings, we might conclude that HLA-B*5701 is not a common allele in Taiwanese, and utilization of routine testing for HLA-B*5701 might not be a sensitive or specific method to reduce the risk associated with abacavir hypersensitivity in Taiwan.

Because diagnosis of abacavir hypersensitivity depends mainly on clinical criteria, concurrent medications and opportunistic infections could potentially confound physicians' judgement given the possibly life-threatening result of abacavir continuation or re-challenge. Among 337 enrolled patients in our present study, 57.3% of them were in the stage of AIDS and one-fourth (24.6%) had concurrent opportunistic infections necessitating concurrent medications at abacavir prescription. When episodes of suspected abacavir hypersensitivity occurred, seven (50%) of the 14 patients with abacavir hypersensitivity not excluded had concomitant use of medications which might be responsible for the symptoms. Besides, abacavir hypersensitivity does occur in our patients and Caucasians with negative HLA-B*5701.[10] Such circumstances emphasize the importance of clinical vigilance in dealing with the reactions in HIV-infected patients who are treated with abacavir in the setting where the frequency of abacavir hypersensitivity is lower and no sensitive or specific biomarker is available to identify persons at risk.

Our study is limited by retrospective study design and a small sample size. However, we provide valuable experience of abacavir use and association of abacavir hypersensitivity and HLA-B*5701 in HIV-infected Taiwanese patients. In conclusion, our findings suggest that abacavir hypersensitivity is less frequently encountered in HIV-infected Taiwanese than in Caucasians, which might be explained by the low frequency of HLA-B*5701.

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## Transparency declarations

None to declare.

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附件一

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 醫事人員愛滋病治療之相關在職訓練課程

研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：王素華、張乃慈、張上淳

執行期間：96 年 1 月 1 日至 96 年 12 月 31 日

＊＊本研究報告僅供參考，不代表本局意見＊＊

# 目　　錄



共　　（ 19 ）頁

# 摘要

台灣於 1986 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，過去幾年來每年新增比例都超過 15%，依此速度推估，到了西元 2010 年全台感染人數可能突破 2 萬人。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 2006 年 10 月底已達 15,345 人（本國籍為 14,711 人）近年來以毒癮者增加幅度最大，1988~2007 年 10 月底通報本國籍毒癮感染者有 4,950 人(其中來自監所 3,764 人，約占 76%)，約佔愛滋通報總人數的六成。聯合國和世界衛生組織已提出嚴重警告，當愛滋病毒散佈到注射毒品病患族群時，疫情將面臨爆炸性的成長。而美國疾病管制中心也根據各國毒品病患愛滋疫情現況，建議毒品注射群體愛滋病盛行率小於 5%之前，應多管齊下儘早推動防治計畫，才能有效預防毒癮病患愛滋疫情繼續擴散。在愛滋感染者年齡層方面，仍以 20-39 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。

另一方面為配合疾病管制局 042 公務預算給付專案，爾後照護 HIV/AIDS 之臨床醫師需每年參與愛滋病治療專業能力培訓，故將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，每年分北區、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，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，並將申請臺灣醫學會、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。



關鍵詞：愛滋病毒感染、抗病毒藥物、愛滋病治療專業能力、愛滋病治療之相關在職訓練課程

## (一)前言

台灣在 1984 年底，因一名患有 AIDS 之美籍同性戀者過境台北，一時造成國人之好奇與驚動；衛生署乃於 1985 年春，成立愛滋病防治小組。於 1986 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，近年來以毒癮者增加幅度最大。1988~2007 年 10 月底通報本國籍毒癮感染者有 4,950 人(其中來自監所 3,764 人，約占 76%)，約佔愛滋通報總人數的六成。新感染的個案數即不斷地增加，過去幾年來每年新增比例都超過 15%，依此速度推估，到了西元 2010 年全台感染人數可能突破 2 萬人。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 2007 年 10 月底已達 15,345 人（本國籍為 14,711 人）。在愛滋感染者年齡層方面，感染愛滋的年齡層以 20 至 29 歲最多，佔 38.04%，其次為 30 至 39 歲，佔 35.44%，顯示我國愛滋感染者幾乎集中在生產力旺盛的青壯族群。聯合國和世界衛生組織已提出嚴重警告，當愛滋病毒散佈到注射毒品病患族群時，疫情將面臨爆炸性的成長。而美國疾病管制中心也根據各國毒品病患愛滋疫情現況，建議毒品注射群體愛滋病盛行率小於 5%之前，應多管齊下儘早推動防治計畫，才能有效預防毒癮病患愛滋疫情繼續擴散。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。

另一方面為配合疾病管制局 042 公務預算給付專案，爾後照護 HIV/AIDS 之臨床醫師需每年參與愛滋病治療專業能力培訓，故將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，每年分北區、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，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，並將申請臺灣醫學會、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。

(二)材料與方法

定期分區舉辦「臨床醫師愛滋病研習會」，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，擬規劃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

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 治療失敗之的病人的處理

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、將申請臺灣醫學會、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、全程參加者結業時將頒發授課證明。

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

鑑於愛滋病毒感染等相關的知識日新月異，新藥物與治療的研發，蓬勃發展，因此對於這些醫療知識的獲取，對於照護愛滋病患的醫事人員格外重要，故愛滋病防治中心將扮演領導國內治療與防治相關之角色，並且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。

(1)、4/14~15日舉辦「醫療人員愛滋病治療專業能力進階教育訓練課程」，參加人員以衛生署指定醫療院所照護愛滋病毒感染者之專責臨床醫師為主，共有43位參加，特別邀請到西班牙University of Barcelona Dr. Esteban Martinez做專題演講 〝Metabolic Complications of Antiretroviral Therapy: Pathogenesis and Management.〞並全程參與國內臨床個案之討論。全體參與者踴躍提供意見成果豐碩。詳細課程如下：

***4 月 14 日(星期六): Advance HIV/AIDS Training***

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 13:30~14:20 | Register | | |
| 14:20~14:30 | Opening | | 張上淳 理事長 |
| 14:30~15:10 | Policy of HIV Prevention & Treatment in Taiwan | 楊靖慧 醫師 | 張上淳 理事長 |
| 15:10~15:50 | Management of Patients with HIV and HCV Co-infection | 盛望徽醫師 | 王立信 副院長 |
| 15:50~16:00 | Discussion | | 王立信 副院長 |
| 16:00~16:20 | Break | | |
| 16:20~17:00 | Epidemiology of HIV Resistance to ARV in Taiwan: Implications for Initial ARV | 張淑媛 助理教授 | 陳茂源 醫師 |
| 17:00~17:40 | Hyperlipidemia in HIV-infected Patients Receiving Antiretroviral Therapy: A Cross-Sectional Survey | 洪健清 醫師 | 陳茂源 醫師 |
| 17:40~18:30 | Metabolic Complications of Antiretroviral Therapy: Pathogenesis and Management | Dr. Esteban Martinez (University of Barcelona) | 李聰明 主任 |
| 18:30~18:50 | Discussion & Closing | | 李聰明 主任 |

***4 月 15 日(星期日): HIV/AIDS Workshop and Case Discussion***

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 08:30~08:50 | Virologic Failure in a Patient Receiving HAART | 何茂旺 醫師 | 王永衛 醫務長 |
| 08:50~09:10 | Diabetes Ketoacidosis: A Rare Complication of Anti-HCV Treatment | 羅一鈞 醫師 | 王永衛 醫務長 |
| 09:10~09:30 | TB and HIV Co-infection | 林育蕙 醫師 | 王永衛 醫務長 |
| 09:30~10:00 | Summary & Comment | Dr. Esteban Martinez | 王永衛 醫務長 |

(2)、6/2 日舉辦「Update management of HIV: Workshop for HIV co-infection disease」參加人員以衛生署指定醫療院所照護愛滋病毒感染者之專責臨床醫師為主，共有 41 位參加，特別邀請到腸胃科及泌尿科的醫師來做專題演講，不同科別的醫師齊聚一堂提供意見踴躍討論。詳細課程如下：

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 13:15~13:30 | Registration | | |
| 13:30~13:40 | Welcome address | | 張上淳 理事長 |
| 13:40~14:20 | Treatment update of chronic HBV infection | 陳健弘 醫師 | 張上淳 理事長 |
| 14:20~15:00 | Management of HBV and HIV co-infection | 盛望徽 醫師 | 洪健清 醫師 |
| 15:00~15:20 | Discussion | | 洪健清 醫師 |
| 15:20~15:40 | Tea Break | | |
| 15:40~16:20 | Simplification of HAART | 謝思民 醫師 | 林錫勳 主任 |
| 16:20~17:00 | Genital herpes simplex infection and HIV infection | 陳偉寶 醫師 | 王永衛 醫務長 |
| 17:00~18:00 | Discussion & Closing | | 王永衛 醫務長 |

(3)、6/23日召開本年度之「醫療人員愛滋病治療專業能力初階教育訓練課程」之「愛滋病毒感染治療藥物新進展介紹」，介紹目前愛滋病毒感染治療藥物及未來進展，參加對象包括對於照護愛滋病患有興趣之醫療人員〈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〉，預定約有200位參與，本次研討會申請相關醫學會學分認證，全程參加者結業時頒發授課證明。特別邀請到法國Nantes University Hospital Professor François Raffi做專題演講 "Initial Treatment with HAART and Switch Strategies."。課程內容如下：

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 08:30~09:00 | Registration | All | |
| 09:00~09:10 | Welcome address | | 張上淳 理事長 |
| 09:10~10:00 | 愛滋病毒感染之病毒學介紹 | 王甯祺 醫師 | 張上淳 理事長 |
| 10:00~10:20 | Coffee Break | All | |
| 10:20~11:10 | NRTI & NNRTI 藥物之介紹、進展及用藥建議 | 蔡季君 醫師 | 廖學聰 主任 |
| 11:10~12:00 | PI 藥物之介紹、進展及用藥建議 | 洪健清 醫師 | 廖學聰 主任 |
| 12:00~12:30 | Discussion | All | 廖學聰 主任 |
| 12:30~13:30 | Lunch | All | |
| 13:30~14:20 | Entry inhibitors 包括 Chemokine receptor antagonists, Fusion inhibitors 之介紹、進展及用藥建議 | 林錫勳 主任 | 黃立民 主任 |
| 14:20~14:40 | Coffee Break | All | |
| 14:40~15:30 | Integrase Inhibitors 之介紹、進展及用藥建議 | 羅一鈞 醫師 | 黃立民 主任 |
| 15:30~16:30 | Initial Treatment with HAART and Switch Strategies | Prof. François Raffi | 劉永慶 理事長 |
| 16:30~17:00 | Discussion & Closing | All | 劉永慶 理事長 |

(4)、9/29 日舉辦本年度的 HIV/AIDS Workshop for Drug Resistance and Treatment Options，邀請來自加拿大 The Toronto General Hospital 的 Professor Sharon Walmsley 除了做專題演講外，並與台灣的 58 位資深專家學者共同討論交換意見及經驗分享，內容如下：

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 12:30~13:30 | Lunch | ALL | ALL |
| 14:00-14:10 | Opening | 張上淳 理事長 | |
| 14:10~14:40 | Trends of Antiretroviral Drug Resistance in Treatment-Naive Patients with Human Immunodeficiency Virus Type 1 Infection in Taiwan | 張淑媛 助理教授 | 洪健清 醫師 |
| 14:40~15:40 | New treatment options for the antiretroviral-naïve and-experienced patients- balancing the known | Professor Sharon Walmsley, MD | 張上淳 理事長 |

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|---|---|---|---|
| | and unknown risks and benefits | | |
| 15:40~15:50 | Coffee break | ALL | ALL |
| 15:50~16:10 | Case discussion (I)* | 王永衛 醫師 | 陳茂源 醫師<br>Professor Sharon Walmsley, MD |
| 16:10~16:30 | Case discussion (II)* | 羅一鈞 醫師 | |
| 16:30~16:50 | Case discussion (III)* | 林育蕙 醫師 | |
| 16:50~17:10 | Q & A | ALL | ALL |
| 17:10~17:20 | Closing | 陳茂源 醫師 | |

(5)、為配合感染症醫師臨床試驗之需求，針對有興趣從事臨床研究之感染症醫師特舉辦此訓練課程，以期提昇國內臨床研究人員之參與力與能力，並期導入我國臨床試驗能力與國際接軌。此次研習會名稱為「感染症專科醫師藥品臨床研究設計及執行研習班」，希望藉此讓年輕醫師在資深專科主治醫師指導下，以指定的題目或有興趣的研究題目完成計畫書的撰寫，讓年輕醫師有交流及互相學習的機會。

此次研習會於 2007 年 10 月 13、14、20、21 日，假大同大學尚志教育館一樓 106 會議室及 103 電腦教室舉行，共有 4 天課程，課程內容涵蓋 Introduction to Epidemiology、Observational epidemiology (1)Cohort study & (2)Case-control study、Introduction to basic biostatistics、Introduction to clinical trials、Experimental epidemiology、Statistical softwares for clinical trial data analysis: an introduction 、Human subject protection in research、Informed consent、Interpretation of data---Interaction and confounding---Interpretation of negative studies、Introduction of biostatistics software:data collection, entry and exploration、Good clinical practice、Hypothesis testing and sample size determination 等。每一個主題均由國內、外知名大學具十多年教學及臨床經驗的教授及醫師講授，而後以提問方式進行，並於每天進行分組討論及論文研讀，由有研究經驗的助教帶領，著重參與課程之學員依個人研究興趣與指導教師和其他學員作有效性之小組討論。本次課程共 39 人報名，學員現職多數為臨床醫師，課程中與講師、助教有許多的提問及討論。本次研習會開辦期間因柯羅莎強烈颱風襲台，原訂在 10/6~7 日的課程臨時順延至 10/13~14 日舉辦，學員仍踴躍前來受訓，精神可嘉。此次研習班有進行學員課程評值，評值表之統計明細詳如附錄一，授課內容如下：

| 10/13 日(六) | Topic | Speakers |
|---|---|---|
| 08:30~09:00 | Registration | |
| 09:00~09:10 | Opening<br>Introduction to the program | 張上淳 理事長<br>劉滄梧 主任 |
| 09:10~10:00 | Introduction to Epidemiology | 簡國龍 副教授<br>台大公共衛生學院<br>預防醫學研究所 |
| 10:00~10:20 | Break | |
| 10:20~11:20 | Observational epidemiology (1)Cohort study | 簡國龍 副教授 |
| 11:20~12:20 | Observational epidemiology (2)Case-control study | 簡國龍 副教授 |
| 12:20~13:30 | Lunch | |
| 13:30~14:30 | Introduction to basic biostatistics (1) | 王玫 博士<br>醫藥品查驗中心 |
| 14:30~14:50 | Break | |
| 14:50~15:50 | Introduction to basic biostatistics (2) | 王玫 博士 |

| | | |
|---|---|---|
| 15:50~18:50 | Group work-reading of journal articles of each type of clinical research.<br>Group1：學員編號 01~10　助教：王振泰醫師<br>Group2：學員編號 11~20　助教：王玫博士<br>Group3：學員編號 21~30　助教：盛望徽醫師<br>Group4：學員編號 31~41　助教：洪健清醫師 | |

| 10/14 日(日) | Topic | Speakers |
|---|---|---|
| 09:00~10:00 | Introduction to clinical trials(1) | 張啟仁 教授<br>長庚大學臨床醫學研究所教授 |
| 10:00~10:20 | Break | |
| 10:20~11:20 | Introduction to clinical trials(2) | 張啟仁 教授 |
| 11:20~12:20 | Experimental epidemiology | 王豐裕 副教授<br>慈濟大學原健所 |
| 12:20~13:30 | Lunch | |
| 13:30~15:30 | Statistical softwares for clinical trial data analysis: an introduction　(場地：103 電腦教室) | 劉介宇 助理教授<br>台北護理學院護理學系 |
| 15:30~15:50 | Break | |
| 15:50~18:50 | Presentations & discussion of group work.<br>Group1：學員編號 01~10　助教：王振泰醫師<br>Group2：學員編號 11~20　助教：謝思民醫師<br>Group3：學員編號 21~30　助教：盛望徽醫師<br>Group4：學員編號 31~41　助教：洪健清醫師 | 全體學員、助教一起參加<br>場地：106 會議室 |

| 10/20 日(六) | Topic | Speakers |
|---|---|---|
| 08:30~09:00 | Registration | |
| 09:00~10:00 | Human subject protection in research | 郭英調 副教授<br>陽明大學臨床醫學研究所 |
| 10:00~10:20 | Break | |
| 10:20~11:20 | Informed consent | 郭英調 副教授 |
| 11:20~12:20 | Interpretation of data (1)<br>---Interaction and confounding<br>---Interpretation of negative studies | 于明暉 教授<br>台大公共衛生學院流行病學研究所 |
| 12:20~13:30 | Lunch | |
| 13:30~14:30 | Interpretation of data (2)<br>---Interaction and confounding<br>---Interpretation of negative studies | 于明暉 教授 |
| 14:30~14:50 | Break | |
| 14:50~16:50 | Introduction of biostatistics software (2): data collection, entry and exploration　(場地：103 電腦教室) | 林明薇 副教授<br>陽明大學公共衛生研究所 |
| 16:50~18:50 | Group work-reading of journal articles of experimental epidemiology.<br>Group1：學員編號 01~10　助教：丁德天研究生<br>Group2：學員編號 11~20　助教：施惟量研究生<br>Group3：學員編號 21~30　助教：連盈如研究生<br>Group4：學員編號 31~41　助教：廖雅堂研究生 | |

| 10/21 日(日) | Topic | Speakers |
|---|---|---|
| 09:00~10:00 | Good clinical practice | 林志六 醫師/律師<br>國衛院論壇生命暨醫療倫理委員會 |
| 10:00~10:20 | Break | |
| 10:20~11:20 | Hypothesis testing and sample size determination (1) | 吳雅琪 博士<br>醫藥品查驗中心 |
| 11:20~12:20 | Hypothesis testing and sample size determination (2) | 吳雅琪 博士<br>醫藥品查驗中心 |
| 12:20~13:30 | Lunch | |
| 13:30~14:30 | Presentations & discussion of group work (Group1)<br>Group1：學員編號 01~10 助教：丁德天研究生 | 全體學員、助教一起參加<br>指導老師：蕭金福 博士 |
| 14:30~15:30 | Presentations & discussion of group work (Group2)<br>Group2：學員編號 11~20 助教：施惟量研究生 | 全體學員、助教一起參加<br>指導老師：蕭金福 博士 |
| 15:30~15:50 | Break | |
| 15:50~16:50 | Presentations & discussion of group work (Group3)<br>Group3：學員編號 21~30 助教：連盈如研究生 | 全體學員、助教一起參加<br>指導老師：蕭金福 博士 |
| 16:50~17:50 | Presentations & discussion of group work (Group4)<br>Group4：學員編號 31~41 助教：廖雅堂研究生 | 全體學員、助教一起參加<br>指導老師：蕭金福 博士 |
| 17:50~18:00 | Closing remarks | 彭汪嘉康 院士<br>張上淳 理事長<br>劉滄梧 主任 |

(6)、目前愛滋病毒感染者服用 HAART 藥物所造成新陳代謝的相關副作用問題非常複雜，故 2007 年 11/3 日假台北市徐州路 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」教育訓練課程。參加對象包括對於照護愛滋病患有興趣之醫療人員〈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〉，特別邀請來自澳洲的 Professor Andrew Carr 及香港的 Dr. Patrick Li 做專題演講，共有 180 位參與，課程內容如下：

| Time | Topic | Speaker | Moderator |
|---|---|---|---|
| 08:40~09:10 | Registration | All | |
| 09:10~09:20 | Welcome address | All | 張上淳 理事長 |
| 09:20~10:00 | Hyperlipidemia among HIV/AIDS | 王甯祺 醫師 | 洪健清 醫師 |
| 10:00~10:40 | Metabolic Syndrome: Prevalence, Mechanism and Management | 楊偉勛 醫師 | 洪健清 醫師 |
| 10:40~11:00 | Coffee Break | All | |
| 11:00~11:40 | DM and HIV/AIDS | 羅一鈞 醫師 | 林錫勳 主任 |
| 11:40~12:20 | HIV-infection bone disease among patients receiving HAART | 何雅琦 醫師 | 林錫勳 主任 |
| 12:20~12:30 | Panel Discussion | All | 林錫勳 主任 |
| 12:30~14:00 | Lunch | All | |
| 14:00~14:50 | Metabolic Syndrome and Cardiovascular Disease under HAART | Prof. Andrew Carr | 陳茂源 醫師 |

| | | | |
|---|---|---|---|
| 14:50~15:40 | Neurological Complications of HIV Infection | Dr. Patrick Li | 陳茂源 醫師 |
| 15:40~16:00 | Discussion & Closing | All | 王永衛 醫務長 |

(7)、HIV 體液暴露後的處理，是十分重要的事。由於感染 HIV 之後，絕大部分的人會進展到 AIDS，使個人、家庭蒙受重大的損失，因此了解如何在 HIV 體液暴露的意外事件後正確地處理及追蹤檢查，是十分重要的一件事。使用抗 HIV 藥物來做為暴露後的預防醫療（post-exposure prophylaxis，PEP），已是一個為醫學界所接受的作法。但由於各種暴露 HIV 後的感染性不同，加以抗 HIV 藥物的副作用頗大，以及新抗 HIV 藥物的問世，所以最好是能尋求專家的意見，以兼顧效果與避免藥物毒性。特別於 96 年 12/15 日假台北市仁愛路一段 1 號台大醫學院 101 講堂，針對醫、護、警、消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，故舉辦此「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。課程內容如下：

| Time | Topic | Speaker |
|---|---|---|
| 13:00~13:20 | Registration | All |
| 13:20~13:30 | Welcome address | 張上淳 主任 |
| 13:30~14:10 | 醫療人員 HIV 體液暴露後之流行病學 | 楊靖慧 首席防疫醫師 |
| 14:10~14:50 | 醫療人員 HIV 體液暴露後之處理流程 | 王永衛 醫務長 |
| 14:50~15:00 | Panel Discussion | 全體講師 |
| 15:00~15:20 | Coffee Break | All |
| 15:20~16:00 | HIV 預防投藥之副作用及注意事項 | 洪健清 醫師 |
| 16:20~17:00 | HIV 體液暴露後之處理流程(實例說明) | 盛望徽 醫師 |
| 17:00~17:20 | Discussion & Closing | 全體講師 |

(8)、延續去年與財團法人護理人員愛滋病防治基金會繼續合辦「愛滋病個案管理師訓練」初階課程及進階課程，分別於 5/18~20 日(南區 110 人參加) 、6/1~3 日(北區 244 人參加)、6/29~30 日(進階 153 人參加)，完成課程，並頒發授課證明。

(9)、本中心延續以往每週一次的愛滋病研討會，固定于每週二早上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。1~12 月份擬進行 35 場，其題目及演講者如表一。

(四)結論與建議

本計畫已達成之目標、結論與建議如下：

一、本計畫在今年結束後，已舉辦大型在職進階教育訓練課程 4 次，每次皆有 150~180 人次參與並接受在職訓練，對國內愛滋病防治之醫療教育貢獻良多。

二、小型 Workshop 2 次，每次皆有 40~60 人次國內資深愛滋病臨床照護醫師參與並討論，對提昇國內醫療水準大有幫助。

三、「感染症專科醫師藥品臨床研究設計及執行研習班」一梯次，對提昇國內臨床研究人員之參與力與能力，對於導入我國臨床試驗能力與國際接軌多有助益。

四、每週一次的愛滋病防治中心研討會，本年度擬繼續聘請了各方面的專家來進行全方位的研討，內容將軍包括有臨床醫學、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；並將加強個案討論，以期大家能各憑專業集思廣益互相交流。

五、根據我們的統計每次研討會的參加者仍以內科感染症醫師為主，其次為家庭醫學科，婦產科、兒科、精神科、外科、牙科等醫師非常少，希望明年能與這些科的相關醫學會多多聯繫，鼓勵其他科別的醫師能夠來參與愛滋病的醫療與防治。

六、明年度希望加強定期舉辦各次專科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對於愛滋病毒感染的認知。

(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 8/16 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」。

表一、愛滋病防治中心96年1~12月HIV/AIDS專題研討會

| 次數 | 日期 | 演講者 | 題目 | 任職單位 |
|---|---|---|---|---|
| 1 | 2-Jan | 黃昱璁 | Detection of Aspergillus antigen in HIV-infected patients with penicilliosis | 台大醫院內科住院醫師 |
| 2 | 9-Jan | 陳宜民 | 簡介愛滋病病毒的亞型及其重要性 | 陽明大學教授 |
| 3 | 16-Jan | 孫幸筠 | 雲林的愛滋病患 | 台大醫院主治醫師 |
| 4 | 23-Jan | 張麗玉 | 南區矯正機關愛滋諮商與衛教實務探討 | 美和技術學院社工系講師 |
| 5 | 30-Jan | 黃苔晏/林杰民 | Response to Antiretroviral Therapy after a Single, Peripartum Dose of Nevirapine; A prognostic index for AIDS-associated Kaposi's sarcoma in the era of Highly active antiretroviral therapy | 台大醫院5E3病房住院醫師 |
| 6 | 6-Feb | 羅一鈞 | 愛滋病患延遲診斷之危險因子分析 | 台大醫院內科住院醫師 |
| 7 | 6-Mar | 李欣純 | What we have learned from the HCV epidemic to HIV outbreak among injection drug users in | 成大醫院主治醫師 |
| 8 | 13-Mar | 洪健清 | HIV Research Report: Amebiasis, HBV Seroepidemiology | 台大醫院主治醫師 |
| 9 | 20-Mar | 蔡靜華 | Valtrex: Easy and Convenient way to Manage Herpes | 荷商葛蘭素史克藥廠 |
| 10 | 27-Mar | 王永衛 | 靜脈毒癮者愛滋病感染--北部監所受刑人的流行病學分析 | 台北市立聯合醫院昆明院區醫務長 |
| 11 | 10-Apr | 杜昀真 | Viral hepatitis in HIV infection | 台大醫院5E3病房住院醫師 |
| 12 | 17-Apr | 王敏吉 | 邊緣的邊緣--灰色巨塔 | 臺灣高雄第二監獄精神科醫師 |
| 13 | 24-Apr | 吳明義 | HIV(+)孕婦之抗愛滋病毒治療 | 台大醫院婦產科主治醫師 |
| 14 | 1-May | 盛望徽 | B型肝炎血清標記變化 | 台大醫院主治醫師 |
| 15 | 8-May | 李思賢 | 女性靜脈毒癮與愛滋病毒感染 | 師大公衛所副教授 |
| 16 | 15-May | 蔡季君 | 熱帶醫學介紹 | 高雄醫學院附設中和紀念醫院感染科 |
| 17 | 22-May | 施鐘卿 | 個案管理師介紹 | 台大醫院個案管理師 |
| 18 | 29-May | 謝慕揚 | 病例報告與烏菲氏青霉菌 | 台大醫院5E3病房住院醫師 |
| 19 | 5-Jun | 孫幸筠 | Tuberculosis and HIV infection | 台大醫院主治醫師 |
| 20 | 12-Jun | 楊秀菊 | Langerin is a natural barrier to HIV-1 transmission by Langerhans cells | 防治中心研究助理 |
| 21 | 26-Jun | 吳家麟 | Case Discussion | 台大醫院5E3病房住院醫師 |
| 22 | 4-Sep | 楊靖慧 | Implications and Implementation for Routine HIV Screening | 疾病管制局首席防疫醫師 |
| 23 | 2-Oct | 曾御慈 | HIV感染者合併高脂血症之治療 | 台大醫院感染科總醫師 |
| 24 | 9-Oct | 盛望徽 | HIV患者之HDV感染 | 台大醫院主治醫師 |
| 25 | 16-Oct | 林宜慧 | 新版愛滋防治條例與人權權益問題 | 愛滋感染者權益促進會秘書長 |
| 26 | 23-Oct | 林育寬 | 愛滋病感染者旅遊相關問題 | 台大醫院感染科總醫師 |

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|---|---|---|---|---|
| 26 | 23-Oct | 林育寬 | 愛滋病感染者旅遊相關問題 | 台大醫院感染科總醫師 |
| 27 | 30-Oct | 廖斌志 | Case Discussion | 台大醫院5E3病房住院醫師 |
| 28 | 6-Nov | Dr. Francis Morey | Epidemiology of HIV/AIDS in Belize | 貝里斯首都醫院內科醫師 |
| 29 | 13-Nov | 陳伯杰 | 男同志愛滋篩檢諮商經驗分享 | 社團法人台灣同志諮詢熱線協會主任 |
| 30 | 20-Nov | 陳茂源 | HIV/TB | 台大醫院主治醫師 |
| 31 | 27-Nov | 住院醫師 | Case Discussion | 台大醫院5E3病房住院醫師 |
| 32 | 4-Dec | 顏雅玲 | (邀請中) | 臺灣雲林第二監獄衛生科科長 |
| 33 | 11-Dec | 巫沛瑩 | 匿名篩檢工作經驗分享 | 防治中心研究助理 |
| 34 | 18-Dec | 張麗玉 | (邀請中) | 美和技術學院社工系講師 |
| 35 | 25-Dec | 住院醫師 | Case Discussion | 台大醫院5E3病房住院醫師 |

時間：每週二上午7:00-9:00 *當天中午12:00-14:00

地點：台大醫院西址綜合病房討論室〈舊五東病房三樓，由販賣部上樓)

附錄一

## 九十六年度專科醫師臨床試驗教育訓練課程評值表
## 「感染症專科醫師藥品臨床研究設計及執行研習班」

有效數:25 份

1 您目前在醫院所屬單位: 1.醫院/臨床試驗中心(0 人) 2.醫院教(醫)研部 (1 人 4%)3.醫院（內科）感染症專科(22 人 88%) 4.醫院其他:兒科(2 人 8%)

2 您認為您的工作職稱是: 1.住院醫師(10 人 40%) 2.研究醫師(3 人 12%) 3.主治醫師(10 人 40%) 4.講師級以上主治醫師(2 人 8%)

3 您的教育程度: 1.大學(22 人 88%) 2.碩士(2 人 8%) 3.博士(1 人 4%)

4 您的年齡是: 1.20~25(0 人) 2. 26~30(8 人 32%) 3. 31~35(8 人 32%) 4. 36~40(5 人 20%) 5 .41~45(4 人 16%) 6.＞45 歲.

5 您加入醫療工作年資: 1.<1 年 2. 1~2 年(1 人 4%) 3. 3~5 年(11 人 44%) 4. 6~9 年(9 人 36%) 5. 10~15 年(2 人 8%) 6. >15 年(2 人 8%)

6 您對目前整體工作自我滿意狀況: 1.非常不滿意 2.不滿意(7 人 28%) 3.普通(7 人 28%) 4.滿意(11 人 44%) 5.非常滿意

7 您從何處得到本次上課訊息: 1.醫院公告(2 人 8%) 2.網路訊息(14 人 56%) 3.主管公告(1 人 4%) 4.同仁朋友(3 人 12%) 5.主辦單位通知(5 人 20%)

8 您覺得地點及教室安排: 1.非常不滿意 2.不滿意 3.普通(2 人 8%) 4.滿意(14 人 56%) 5.非常滿意(9 人 36%)

您的建議:1.希望有免費停車場

9 您覺得 4 天課程時間安排: 1.非常不滿意 2.不滿意 3.普通(3 人 12%) 4.滿意(17 人 68%) 5.非常滿意(5 人 20%)

您的建議:1.太密集；2.結束時間太晚；3.group discussion 時間可縮短，課程也三天半可完成

10 您覺得報名方式: 1.非常不滿意 2.不滿意 3.普通(1 人 4%) 4.滿意(16 人 68%) 5.非常滿意(7 人 29%)

您的建議: 無

11 您目前工作上遇到的最大困擾:1.時間不夠；2.缺研究經費、助理、微生物學專家；3.時間太少；4.統計方法；5.工作量及壓力大

12 您建議增加哪些臨床試驗課程: (可複選)

□法規(3.4%) □倫理(3.4%) □臨床試驗執行(18.2%) □新知(5.2%) □實例探討(31.0%) □臨床試驗設計專業發展(29.3%) □管理策略(6.9%) □病患教育(3.4%) □其他請詳述: survival analysis

13 您曾執行何種類型的臨床試驗: (可複選)

□ 單一院內研究計劃(44.4%) □多中心/多國合作組織計劃(11.1%) □藥廠進藥試驗計劃(44.4%) □無

(A)研究試驗分期 □ PhaseI(16.6%) □ PhaseII(16.6%) □ PhaseIII(25%) □ PhaseIV(41.6%)

(B) 如果有參加臨床試驗擔任角色為: □計劃主持人(25%) □計劃協同主持人(58.3%) □其他請詳述: (16.7%) case screening and follo up

14 您平均每週花在臨床試驗研究工作的時間: 1.＜1 天(8 人 50%) 2.1~2 天(7 人 44%) 3.2~4 天 4.＞4 天 5.其他: (1 人 6%)

15 可否簡述您的臨床試驗工作內容:

1.置放 foley 天數相對於院內泌尿道感染之臨床分析；2. vaccine efficacy trial；3. patient assessment

16 您的整體建議:

1. 內容相當完整，但上課時數太長，但特別是生物統計內容方面，可能時間要充足一點，以免有時未能充分了解老師所講，其他部分可能時間縮短或刪除，以縮短整體上課時間。
2. 希望能多多舉辦類似活動，並加入更多實例探討。
3. 課程的規劃極有幫助，對於區域或地區教學醫院的工作人員，提供再進修的機會及見習或參與研究的潛能增進。對於臨床試驗設計的課程，希望日後有機會再參與。
4. 可先不安排倫理方面之課程，讓其他統計課程可講久一點。
5. 很棒！

17 請以數字代碼表示於空格內：1.非常不滿意 2.不滿意 3.普通 4.滿意 5.非常滿意

| | 日期 | 評值項目 | 時間 | | 講師 | | | 內容 | | | 建議 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 課程主題 | 授課時段 | 課程時數 | 清晰有理 | 教材豐富 | 教學生動 | 有助臨床運用 | 提供新知觀念 | 符合學員需求 | |
| 1 | 10/13 | Introduction to Epidemiology | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 無 |
| 2 | 10/13 | Observational epidemiology (1)Cohort study | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 3 | 10/13 | Observational epidemiology (2)Case-control study | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 4 | 10/13 | Introduction to basic biostatistics (1) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 1. 前面簡單的講太多<br>2. 希望增加時間 |
| 5 | 10/13 | Introduction to basic biostatistics (2) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 希望增加時間 |
| 6 | 10/14 | Introduction to clinical trials(1) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 時數稍短 |
| 7 | 10/14 | Introduction to clinical trials(2) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 8 | 10/14 | Experimental epidemiology | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 9 | 10/14 | Statistical softwares for clinical trial data analysis: an introduction | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 10 | 10/14 | Presentations & discussion of group work (Group1 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 11 | 10/14 | Presentations & discussion of group work (Group2 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 12 | 10/14 | Presentations & discussion of group work (Group3 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 13 | 10/14 | Presentations & discussion of group work (Group4 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |

請以數字代碼表示於空格內：1.非常不滿意 2.不滿意 3.普通 4.滿意 5.非常滿意

| | 日期 | 評值項目 | 時間 | | 講師 | | | 內容 | | | 建議 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 課程主題 | 授課時段 | 課程時數 | 清晰有理 | 教具恰當 | 教學生動 | 有助臨床連接 | 提供新知觀念 | 需要繼續教授 | |
| 15 | 10/20 | Human subject protection in research | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 16 | 10/20 | Informed consent | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 時間關係，此 topic 幾乎沒有講到 |
| 17 | 10/20 | Interpretation of data (1) ---Interaction and confounding ---Interpretation of negative studies | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 18 | 10/20 | Interpretation of data (2) ---Interaction and confounding ---Interpretation of negative studies | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 19 | 10/20 | Introduction of biostatistics software (2): data collection, entry and exploration | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 希望增加時間 |
| 20 | 10/21 | Good clinical practice | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 21 | 10/21 | Hypothesis testing and sample size determination (1) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 22 | 10/21 | Hypothesis testing and sample size determination (2) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 23 | 10/21 | Presentations & discussion of group work (Group1 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 24 | 10/21 | Presentations & discussion of group work (Group2 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 25 | 10/21 | Presentations & discussion of group work (Group3 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 26 | 10/21 | Presentations & discussion of group work (Group4 ) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| 27 | | 整體課程 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |

您對此課程的其他建議：（敬請 您踴躍提供給我們寶貴的意見以便下次改進，謝謝！）

| |
|---|
| 1. 張啟仁教授講的很清楚，以後可以再邀請他，給他更久，更充足的時間。 |
| 2. 謝謝學會和工作同仁的辛勤勞動，時間與付出。 |
| 3. 廖雅堂老師很好。 |
| 4. 分組討論時間可縮減，指導老師略經驗不足。 |
| 5. 統計課程內容稍有重複。 |
| 6. 內容豐富，若許可也許可將學員進一步分類(例如有研究經驗或無研究經驗）分開授課更有效率。 |
| 7. 幫助很大，希望還有機會參加。 |
| 8. 可加強宣傳，好東西讓更多人分享。 |
| 9. 教學光碟級教材是否可取得及分享？ |
| 10. 謝謝愛滋病學會眾工作人員的用心，讓我們在食衣住行都能有最多的照顧。 |
| 11. 早上課程的 breal 也許可移到第二節下課。 |
| 12. 再次感謝主辦單位，老師們和辛苦的工作人員。 |
| 13. 請繼續舉辦這樣的活動。 |
| |
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| |
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| |

附件二

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

台灣地區愛滋病毒感染研究群
Taiwan HIV Study Group

# 研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：Taiwan HIV Study Group (成員：洪健清、柯文謙、李欣純、蔡季君、劉尊榮、王永衛、蘇世強、何茂旺、鄭舒倖、楊靖慧、林育蕙、繆偉傑)

執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共 33 頁

壹、中文摘要：

自從 2004 年開始，共有台大醫院、台北市立聯合醫院仁愛院區、疾病管制院區昆明院區、新竹馬偕紀念醫院、基督教門諾會醫院、署立桃園醫院、中國醫藥學院附設醫院、台中榮民總醫院、彰化基督教醫院、成功大學附設醫院、高雄醫學大學附設醫院等 11 家衛生署指定之愛滋病毒感染治療的專責醫療院所，持續進行收集感染者到院就醫的相關臨床資料。收集目的，是要了解台灣地區愛滋病患常見的臨床病徵、愛滋病毒治療成效、合併感染以及預後與存活。截至今年 7 月份止，合併台大醫院過去持續收集的世代研究資料，我們一共收集 4,176 位感染者的相關資料。目前已經逐步進行資料分析。目前我們已經完成慢性 B 型肝炎的流行病學分析和論文寫作。我們希望了解在台灣地區，自從 1984 年展開的 B 型肝炎疫苗接種計畫，對於愛滋病毒感染者的影響為何？是否新生兒、幼兒或小學追加 B 型肝炎疫苗接種計畫對於後來感染愛滋病毒造成免疫系統下降時，是否接種後產生的抗體效價會下降？並且了解是否有追加接種疫苗的必要性？我們的研究顯示出生於 1984 年之前的感染者不論是否使用毒品男同性戀或異性戀慢性 B 型肝炎的帶原率相同；1984 年之後出生的愛滋病毒感染者的帶原率則已經下降到 5.6%和對照組並無差異。新生兒、幼兒或小學期間曾接種疫苗的感染者，他們的抗體效價，比較文獻中所報告台灣地區一群在出生時接種疫苗的 15 歲青少年來得高；愛滋病毒感染者的抗體效價高低與 CD4 淋巴球數有正相關，意即：CD4 越高抗體效價越高。我們的研究顯示愛滋病毒感染者接種過 B 型肝炎疫苗後，可能在後來因為有機會多次接觸肝炎帶原者，形成自然 B 型肝炎疫苗的追加接種。

相關伺機性感染與存活的分析目前仍持續進行中。

關鍵詞：B 型肝炎病毒、B 型肝炎疫苗、愛滋病毒感染、靜脈毒癮者

貳、英文摘要

***Background & Aims*** The impact of nationwide hepatitis B virus (HBV) vaccination program on the prevalence of HBV infection remains unknown in persons infected with human immunodeficiency virus (HIV).

***Methods*** Prevalences of HBsAg, anti-HBs, anti-HBc and anti-HCV antibody were compared between 4176 HIV-infected and 2594 HIV-uninfected persons (control group) aged≧15 years and between the persons born before and after July 1984 when nationwide HBV vaccination program was implemented in Taiwan. Anti-HBs antibody titers were compared between 207 HIV-infected persons and 161 historical controls who had undergone HBV vaccination, and factors associated with existence of protective antibody titers (≧10 mIU/mL) were analyzed.

***Results*** Overall prevalence of HBsAg of HIV-infected persons was significantly higher than that of controls (20.1% vs. 13.2%) ($P$<0.001). However, no differences were observed in the prevalence of HBsAg (5.6% vs. 8.5%, $P$=0.530) or anti-HBc antibody (39.3% vs. 27.9%, $P$=0.187) between intravenous drug users (IDUs) and controls who were born after July1984, although prevalence of anti-HCV antibody was as high as 97.1% in HIV-infected IDUs. Among those persons who had ever undergone HBV vaccination, the proportion of maintaining protective anti-HBs antibody titers was higher in HIV-infected persons than in historical controls (67.1% vs. 45.3%, $P$<0.001), and factors associated with maintaining protective antibody titers were persons with CD4 counts≧350 cells/μL and those born after 1980.

***Conclusions*** Nationwide HBV vaccination in Taiwan was associated with significant reduction of HBsAg prevalence in HIV-infected persons. Higher levels of protective anti-HBs antibody titers persisted in the HIV-infected persons than historical controls

after HBV vaccination.

**Key words:** hepatitis B virus, human immunodeficiency virus, human immunodeficiency virus infection, hepatitis B vaccination, prevalence, intravenous drug user

## 參、本文

### （一）前言

Prevalence of chronic hepatitis B virus (HBV) infection has been found to be higher in human immunodeficiency virus (HIV)-infected population than in HIV-uninfected population since these two viruses share the same transmission routes.[1-3] However, the extent to which HBV prevalence of the two populations differ may vary with geographic regions where the predominant routes of HIV and HBV transmission are different. In regions with a low HBV endemicity, sexual exposure and intravenous drug use are the two major routes for HBV and HIV transmission, and both HIV and HBV infection may occur when persons engage themselves in high-risk behaviors. In regions of Africa and Asia where HBV endemicity is high, most HBV exposure occurs early in childhood or during perinatal period and people develop either chronic hepatitis B infection or immunity against HBV long before HIV infection occurs.[4] Therefore, studies have shown that exposure to HBV[5,6] and prevalence of chronic HBV infection[7-10] were similar between HIV-infected and HIV-uninfected persons in these regions.

Although highly active antiretroviral therapy (HAART) has successfully prolonged the survival of HIV-infected persons[11,12] and HAART containing lamivudine and/or tenofovir may provide additional virological benefits in terms of HBV replication, those persons co-infected with HBV remain at significantly higher risks for all-cause and liver-related mortality than those without.[1,2,13] Therefore, those persons at risk for or having a diagnosis of HIV infection who remain susceptible to HBV transmission are recommended to receive HBV vaccine.[14] However, prior studies have revealed that HIV-infected persons receiving HBV vaccination had lower response rates with lower levels and variable persistence of acquired antibody titers than HIV-uninfected

persons.[15-20] Furthermore, on a population level, benefits of nationwide or targeted HBV vaccination has seldom been evaluated in high-risk populations, such as HIV-infected persons or intravenous drug users (IDUs).[21]

In Taiwan, as many as 15% of adults are chronic HBV carriers[22] and vertical transmission had been the main route of HBV infection[23] before nationwide universal HBV vaccination program was implemented to vaccinate newborns of HBsAg-positive mothers in July 1984 which was subsequently extended to cover all newborns after July 1986.[24] The program was further extended to cover susceptible preschool children, school children, teenagers, and then adults from July 1987 to 1990. Since 1991, the vaccination records of school children aged 7 years were checked, and those children who were unvaccinated or incompletely vaccinated would be given catch-up HBV vaccination.[24,25] Seroepidemiologic surveillance studies from 1984 to 2004 have demonstrated long-term immunogenicity and efficacy of universal HBV vaccination among persons born after 1984 with significant reduction of the prevalence of hepatitis B surface antigen (HBsAg).[25-30] In this study, we aimed to compare the prevalence of HBV infection in HIV-infected persons of different transmission routes with that in general population before and after 1984; and we also compared the titers of anti-HB surface (anti-HBs) antibody between HIV-infected persons and historical controls who had ever undergone HBV vaccination.

（二）材料與方法

**Study populations**

**Study populations**

Four thousands one hundred and seventy-six HIV-infected persons aged ≧15

years seeking medical care at designated hospitals for HIV care in Taiwan were enrolled between 1994 and 2007; among them, 1393 (33.4%) identified themselves as men who have sex with men (MSM) and 598 (14.3%) as heterosexuals and 1483 (35.5%) as IDUs. Because multiple comparisons showed no differences of prevalence of HBV and HCV serological markers between MSM and heterosexuals (data not shown), they were analyzed together as sexual transmission group. Control group consisted of 2594 HIV-uninfected persons aged $\geqq 15$ years who sought health check-up at hospitals. A computerized standardized data collection form was used to extract their demographic and clinical data, which included birth date, sex, HIV transmission route, baseline CD4+ lymphocyte count and plasma HIV RNA load and test results of initial anti-HCV antibody, HBsAg, anti-HBs antibody, and anti-HB core (anti-HBc) antibody at baseline.

To compare the titers of anti-HBs antibody after HBV vaccination, HIV-infected persons were enrolled who were negative both for HBsAg and anti-HBc antibody and had measurements of anti-HBs antibody titers that were not available as a routine laboratory test until August 2006. In total, 207 HIV-infected persons met the enrollment criteria for comparison of anti-HBs antibody titers. One hundred and sixty-one persons who were aged 15 years and were negative for anti-HBc antibody after HBV vaccination in the study by Lu et al. were selected as historical controls.[31] The study was approved by the Institutional Review Board of the hospitals.

**Laboratory investigations**

HBsAg, anti-HBs antibody, and anti-HBc antibody were determined with the use of enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). Antibodies to HCV were determined with the use of a third-generation enzyme immunoassay (Ax SYM

HCV III, Abbott Laboratories, North Chicago, IL). Plasma HIV RNA load were quantified using RT-PCR (Roche Amplicor, version 1.5, NJ) with a lower detection limit of 400 (2.60 $\log_{10}$) copies/mL, and CD4 counts were determined using FACFlow (BD FACS Calibur, Becton Dickinson, CA). Determination of anti-HBs antibody titers was routinely performed with the use of radioimmunoassay (ARCHITECT i2000, Abbott Laboratories) among the blood samples submitted for testing for HBV serological markers after August 2006. Levels of anti-HBs antibody titers ≧10 mIU/mL were considered protective.[31,32]

**Statistical analysis**

All statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). Categorical variables were compared using $\chi^2$ or Fisher's exact test whereas non-categorical variables were compared using Mann-Whitney U test. A multivariate logistic regression model was built to identify independent variables associated with existence of a protective anti-HBs antibody titer. All tests were two-tailed and a *P* value <0.05 was considered significant.

（三）結果

The demographic and clinical characteristics of 4176 HIV-infected and 2594 HIV-uninfected persons enrolled are shown in Table 1. More HIV-infected persons than the control group were males (92.4% vs. 69.4%). A higher proportion of persons were aged less than 25 years in control group than in HIV-infected persons (37.7% vs. 7.3%), and most of the HIV-infected persons (71.0%) were aged between 26 to 45 years (Table 1). Compared with the persons of sexual transmission group, IDUs were significantly younger (median age, 34 vs. 38 years, *P*<0.001), had a significantly

higher CD4+ count (median, 407 vs. 165 cells/μL, $P<0.001$) and lower plasma HIV RNA load (median, 4.1 vs. 5.0 $\log_{10}$ copies/mL, $P<0.001$). Only 2.0% and 5.6% of IDUs had CD4 counts less than 100 and 200 cells/μL, respectively, but as high as 41.8% and 54.6% of persons in sexual transmission group, respectively, had CD4 less than 100 and 200 cells/μL ($P<0.001$).

Overall, HIV-infected persons had a significantly higher prevalence of HBsAg (19.8% vs. 13.2%, $P<0.001$) and anti-HBc antibody (77.6% vs. 57.5%, $P<0.001$) than persons of control group, while prevalence of anti-HBs antibody was lower in HIV-infected persons (56.4% vs. 61.9%, $P<0.001$) (Table 1 and Figure 1). However, prevalence of anti-HBs antibody differed among different risk groups for HIV transmission (Table 1 and Figure 2). For example, compared with control group, IDUs had a similar prevalence of anti-HBs antibody (61.7% vs. 61.9%, $P=0.918$) although they had a significantly higher prevalence of anti-HBc antibody (82.3% vs. 57.5%, $P<0.001$) and HBsAg (20.1% vs. 13.2%, $P<0.001$), suggesting a higher risk for HBV exposure and infection. On the contrary, sexual transmission group had a lower prevalence of anti-HBs antibody than control group (54.0% vs. 61.9%, $P<0.001$), but had a higher prevalence of HBsAg (20.1% vs. 13.2%, $P<0.001$) and anti-HBc antibody (75.8% vs. 57.5%, $P<0.001$).

Compared with persons of sexual transmission group, IDUs had a significantly higher prevalence of anti-HCV antibody (96.8% vs. 6.6%, $P<0.0001$), anti-HBc antibody (82.3% vs. 75.8%, $P<0.001$), and anti-HBs antibody (61.7% vs. 54.0%, $P<0.001$); however, prevalence of HBsAg was similar between IDUs and sexual transmission group (20.1% vs. 20.1%, $P=0.994$) (Table 1 and Figure 2), suggesting a higher risk for exposure to HCV and HBV and higher rate of seroconversion after HBV

exposure among IDUs. The difference between prevalence of anti-HBs antibody in the presence of similar prevalence of HBsAg appeared to be related to the status of immunosuppression. In sexual transmission group, the prevalence of anti-HBs antibody among persons with CD4 counts <350 cells/μL was statistically significantly lower (50.5% vs. 64.8%, $P<0.001$) and that of anti-HBc antibody (77.1% vs. 71.1%, $P=0.031$) was higher than that among persons with CD4 counts ≧350 cells/μL although both had similar HBsAg prevalence (20.8% vs. 17.0%, $P=0.095$) (Table 2). On the contrary, no significant difference in the prevalence of HBV serological markers was observed between IDUs with CD4 counts <350 cells/μL and IDUs with CD4 counts ≧350 cells/μL. Compared with persons of sexual transmission group who had CD4 <350 cells/μL, IDUs who had CD4 <350 cells/μL had significantly higher prevalence of anti-HBs (60.9% vs. 50.5%, $P=0.001$) and anti-HBc antibody (83.9% vs. 77.1%, $P=0.008$) but similar HBsAg prevalence (20.8% vs. 18.5%, $P=0.308$) (Table 2).

To evaluate the impact of universal HBV vaccination on the prevalence of HBsAg among persons at different risks for HIV transmission, comparisons were made between persons born before and after July 1, 1984 when nationwide HBV implemented was launched in Taiwan. For those persons born before July 1984, similar differences as described above were observed between HIV-infected persons and control group. In brief, compared with control group, HIV-infected persons had a higher prevalence of HBsAg (20.3% [615/3034] vs. 15.5% [269/1737], $P<0.001$) and anti-HBc antibody (78.8% [1927/2446] vs. 72.1% [1252/1737], $P<0.001$) and a lower prevalence of anti-HBs antibody (55.6% [1457/2621] vs. 59.6% [1035/1737], $P=0.009$) (Figure 3). Compared with control group, IDUs had a significantly higher prevalence of HBsAg (20.6% [221/1073] vs. 15.5% [269/1737], $P=0.001$) and anti-HBc antibody

(83.7% [719/859] vs. 72.1% [1252/1737], $P<0.001$); however, both groups had a similar prevalence of anti-HBs antibody (61.0% [529/867] vs. 59.6% [1035/1737], $P=0.483$). On the contrary, such differences between HIV-infected persons and controls were not observed among the persons born after July 1, 1984. The prevalence of HBsAg (3.3% [3/91] vs. 8.5% [73/857], $P=0.081$), anti-HBs antibody (71.2% [52/73] vs. 66.6% [571/857], $P=0.422$) and anti-HBc antibody (29.5% [18/61] vs. 27.9% [239/857], $P=0.785$) were similar between HIV-infected persons and controls who were born after July 1, 1984 (Figure 3). Although HIV-infected IDUs born after July 1984 had prevalence of anti-HCV antibody as high as 97.1%, there was no difference in the prevalence of hepatitis B markers when compared to control group: HBsAg, 5.6% (2/36) vs. 8.5% (73/857), $P=0.530$; anti-HBs antibody, 82.8% (24/29) vs. 66.6% (571/857), $P=0.069$; and anti-HBc antibody, 39.3% (11/28) vs. 27.9% (239/857), $P=0.187$.

To analyze the titers of anti-HBs antibody after HBV vaccination, 207 HIV-infected persons who had data of anti-HBs antibody titers and who were negative for both HBsAg and anti-HBc antibody were enrolled. Compared with other HIV-infected persons, these 207 persons were younger (median age, 30 vs. 37 year, $P<0.001$) and had a higher median CD4 count (335 vs. 294 cells/μL, $P=0.005$); in addition, a higher proportion of them were born after July 1984 (8.7% vs. 2.4%, $P<0.001$) and were IDUs (47.8% vs. 34.9%, $P<0.001$) (data not shown). When compared with the 161 historical controls,[31] HIV-infected persons were older and only 18 (8.7%) were born after July 1984 (Table 3). Among the HIV-infected persons, 47.8% were IDUs and 74.6% had CD4 counts $\geqq$200 cells/μL.

Of the 207 HIV-infected persons, 26 (12.6%) of them had undetectable titers

(recorded as 0 mIU/mL) and 11 (5.3%) had titers between 0 mIU/mL and 1 mIU/mL. As compared with 161 historical controls, more HIV-infected persons had protective anti-HBs antibody titers (67.1% vs. 45.3%, $P<0.001$) (Table 3). Besides, among 66 HIV-infected persons born after 1980, who might have undergone HBV vaccination in the catch-up program for HBV vaccination in their childhood, a higher proportion of them also had protective titers than historical controls who were born in 1988 (83.3% v. 45.3%, $P<0.001$). Furthermore, such findings were also observed in the comparison between 18 HIV-infected persons born after July 1984 and 161 historical controls (77.8% vs. 45.3%, $P=0.009$). As we categorized HIV-infected persons according to their CD4 counts (<200, 200-350, and >350 cells/μL), those with higher CD4 counts had higher anti-HBs antibody titers ($P=0.005$) (Figure 4).

To identify factors associated with maintaining protective anti-HBs antibody titers among HIV-infected persons, comparisons between persons with and persons without protective antibody titers were made (Table 4). Persons with protective antibody titers were younger than those without (29 vs. 32 years, $P=0.013$) (Table 4). Besides, more persons with protective antibody titers were born after 1980 (39.6% vs. 16.2%, $P=0.001$), acquired HIV infection through intravenous drug use (56.8% vs. 36.9%, $P=0.009$), and had HCV infection (60.3% vs. 38.5%, $P=0.004$), higher CD4 counts and lower plasma HIV RNA load than those without (Table 4). By multivariate logistic regression analysis, persons with CD4 counts $\geqq$350 cells/μL (odds ratio 3.240; 95% confidence interval, 1.575-6.664) and those born after 1980 (odds ratio 3.640; 95% confidence interval, 1.541-8.601) were independent factors associated with existence of protective anti-HBs antibody titers.

Table 1. Demographics of HIV-infected persons and subjects in control group

| | All HIV-infected persons | Sexual Transmission Group | IDUs | Control | [a] P value | [b] P value | [c] P value | [d] P value |
|---|---|---|---|---|---|---|---|---|
| Person number | 4176, 100% | 1991, 47.7% | 1483, 35.5% | 2594, 100% | -- | -- | -- | -- |
| Male, n (%) | 3858, 92.4% | 1853, 93.1% | 1362, 91.8% | 1800, 69.4% | <0.001 | <0.001 | <0.001 | 0.173 |
| Median age (range), y (person no. with data) | 37 (16-95) (4032) | 38, 16-95 (1856) | 34, 16-73 (1479) | 38, 16-94 (2594) | 0.022 | <0.001 | 0.034 | <0.001 |
| Age groups, n (%) | | | | | | | | |
| ≦25 years | 295 (7.3) | 123 (6.6) | 118 (8.0) | 977 (37.7) | <0.001 | <0.001 | <0.001 | <0.001 |
| 26-35 | 1524 (37.8) | 598 (32.2) | 691 (46.7) | 280 (10.8) | | | | |
| 36-45 | 1338 (33.2) | 649 (35.0) | 466 (31.5) | 276 (10.6) | | | | |
| 46-55 d | 542 (13.4) | 265 (14.3) | 178 (12.0) | 382 (14.7) | | | | |
| >55 | 333 (8.3) | 221 (11.9) | 26 (1.8) | 67 (26.2) | | | | |
| Born after July 1, 1984, n (%) | 108 (2.7) | 41 (2.2) | 43 (2.9) | 857, 33.0% | <0.001 | <0.001 | <0.001 | 0.201 |
| Median CD4 (range), cells/μL (person no. with data) | 299 (0-2760) (3578) | 165 (0-1202) (1885) | 407 (1-1943) (1171) | NA | -- | -- | -- | <0.001 |
| <100 cells/μL, n (%) | 943 (26.4) | 787 (41.8) | 24 (2.0) | NA | -- | -- | -- | <0.001 |
| <200 cells/μL | 1283 (35.9) | 1029 (54.6) | 66 (5.6) | NA | -- | -- | -- | <0.001 |
| Median PVL (range) $\log_{10}$ copies/mL (person no. with data) | 4.5 (1.7-7.2) (3326) | 5.0 (1.7-7.2) (1595) | 4.1 (1.7-6.0) (1186) | NA | -- | -- | -- | <0.001 |
| >5 $\log_{10}$ copies/mL, n (%) | 1058 (31.8) | 790 (49.5) | 118 (9.9) | NA | -- | -- | -- | <0.001 |
| All negative for HBV markers, n/N (%) | 208/2266 (9.2) | 152/1334 (11.4) | 34/750 (4.5) | 444/2594 (17.1) | <0.001 | <0.001 | <0.001 | <0.001 |
| HBsAg-positive | 628/3164 (19.8) | 337/1675 (20.1) | 223/1109 (20.1) | 342/2594 (13.2) | <0.001 | <0.001 | <0.001 | 0.994 |
| Anti-HCV-positive among those with HBs-positive | 247/577 (42.8) | 18/305 (5.9) | 205/214 (95.8) | NA | -- | -- | -- | <0.001 |
| Anti-HBs-positive | 1561/2768 (56.4) | 875/1619 (54.0) | 553/896 (61.7) | 1606/2594 (61.9) | <0.001 | <0.001 | 0.918 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Anti-HBc-positive | 1945, 77.6% (2507) | 1043, 75.8% (1376) | 730, 82.3% (887) | 1491/2594 (57.5) | <0.001 | <0.001 | <0.001 | <0.001 |
| Anti-HCV-positive | 1293/3061 (42.2) | 103/1571 (6.6) | 1060/1095 (96.8) | NA | -- | -- | -- | <0.001 |
| HBsAg-positive among those anit-HCV-positive | 247/1227 (20.1) | 18/97 (18.6) | 205/1035 (19.8) | NA | -- | -- | -- | 0.767 |

[a] Control vs. total HIV cases

[b] Control vs. sexual transmission group

[c] Control vs. IDU group

[d] Sexual vs. IDU group

Table 2. Comparisons of HBV serological markers between HIV-infected persons with CD4<350 cells/μL and those with CD4≧350 cells/μL in sexual transmission group and intravenous drug users (IDUs)

| | CD4 <350 cells/μL | CD4 ≧350 cells/μL | P [a] value |
|---|---|---|---|
| **Anti-HBc, n/N (%)** | | | |
| **Sexual transmission group** | 790/1025 (77.1) | 224/315 (71.1) | 0.031 |
| **IDUs** | 277/330 (83.9) | 431/528 (81.6) | 0.386 |
| **P [b] value** | 0.008 | <0.001 | |
| **HBsAg, n/N (%)** | | | |
| **Sexual transmission group** | 258/1238 (20.8) | 66/389 (17.0) | 0.095 |
| **IDUs** | 72/390 (18.5) | 142/660 (21.5) | 0.235 |
| **P [b] value** | 0.308 | 0.074 | |
| **Anti-HBs, n/N (%)** | | | |
| **Sexual transmission group** | 600/1188 (50.5) | 250/386 (64.8) | <0.001 |
| **IDUs** | 199/327 (60.9) | 321/520 (61.7) | 0.799 |
| **P [b] value** | 0.001 | 0.349 | |

[a] Persons with CD4 counts <350 cells/μL vs. persons with CD4 counts ≧350 cells/μL
[b] IDUs vs. persons in sexual transmission group

Table 3. Comparisons of anti-HBs titers between historical control group and HIV-infected persons who were negative for HBsAg and anti-HBc antibody and had detectable anti-HBs antibody

| Demographics | HIV-infected persons | Historical control | P value |
|---|---|---|---|
| Total person number | 207 | 161 | |
| Male, n (%) | 189 (91.3) | NA | |
| Median age (range), y | 30, (16-65) | 15 | |
| Born after July 1984, n (%) | 18 (8.7) | 161 (100) | <0.001 |
| Born after 1980 | 66 (31.9) | 161 (100) | <0.001 |
| Risk group, n (%) | | | |
| Sexual contact | 98 (47.3) | NA | |
| Intravenous drug use | 99 (47.8) | NA | |
| Others | 10 (4.8) | NA | |
| Median CD4 count (range), cells/μL) (persons with data) | 335 (2-2655) (181) | NA | |
| <200 cells/μL, n (%) | 46 (25.4) | NA | |
| 200-350 cells/μL | 48 (26.5) | NA | |
| >350 cells/μL | 87 (48.1) | NA | |
| Median plasma viral load (range), $log_{10}$ copies/mL (persons with data) | 4.4 (1.7-5.9) (191) | NA | |
| ≧5 $log_{10}$ copies/mL (n, %) | | NA | |
| Anti-HCV infection, n/N | 107/201 (53.2) | NA | |
| Anti-HBs titer | | | |
| All individuals (N=207) | | | |
| ≧10 mIU/mL (n, %) | 139 (67.1) | 73 (45.3) | <0.001 |
| ≧100 mIU/mL | 83 (40.1) | 20 (12.4) | <0.001 |
| <10 mIU/mL | 68 (32.9) | 88, (54.7) | <0.001 |
| 10-100 | 56 (27.1) | 53 (32.9) | |
| >100 | 83 (40.1) | 20 (12.4) | |
| Those born after 1980 (N=66) | | | |
| ≧10 mIU/mL n (%) | 55 (83.3) | 73 (45.3) | <0.001 |
| ≧100 mIU/mL | 34 (51.5) | 20 (12.4) | <0.001 |
| <10 mIU/mL | 11 (16.7) | 88 (54.7) | <0.001 |
| 10-100 | 21 (31.8) | 53 (32.9) | |
| >100 | 34 (51.5) | 20 (12.4) | |
| Those born after 1984 (N=18) | | | |
| ≧10 mIU/mL, n (%) | 14 (77.8) | 73 (45.3) | 0.009 |
| ≧100 mIU/mL | 9 (50.5) | 20 (12.4) | <0.001 |
| <10 mIU/mL | 4 (22.2) | 88 (54.7) | |
| 10-100 | 5 (27.8) | 53, (32.9) | |
| >100 | 9 (50.0) | 20 (12.4) | |

NA, not applicable

Table 4. Factors associated with maintaining protective anti-HBs antibody titer (≧10 mIU/mL) in 207 enrolled HIV-infected persons

| | <10 mIU/mL | ≧10 mIU/mL | P value |
|---|---|---|---|
| Person no. (%) | 68 (32.9) | 139 (67.1) | |
| Sex | 60 (88.2) | 129 (92.8) | 0.273 |
| Median age (range) | 32 (16-65) | 29 (21-63) | 0.013 |
| Birth date, n (%) | | | |
| Born after 1984 | 4 (5.9) | 14 (10.1) | 0.315 |
| Born after 1980 | 11 (16.2) | 55 (39.6) | 0.001 |
| HIV transmission risk, n (%) | | | |
| Sexual contact | 41 (63.1) | 57 (43.2) | 0.009 |
| Intravenous drug use | 24 (36.9) | 75 (56.8) | |
| HCV infection | 25 (38.5) | 82 (60.3) | 0.004 |
| Median CD4 count (range) cells (persons with data) | 271 (5-796) (57) | 383 (2-2655) (124) | 0.002 |
| <100 cells/μL, n (%) | 15 (26.3) | 16 (12.9) | 0.026 |
| <200 | 22 (38.6) | 24 (19.4) | 0.006 |
| >350 | 17 (29.8) | 70 (56.5) | 0.001 |
| <200 | 22 (38.6) | 24 (19.4) | 0.002 |
| 200-350 | 18 (31.6) | 30 (24.2) | |
| >350 | 17 (29.8) | 70 (56.5) | |
| Median PVL (range), $log_{10}$ copies/mL (persons with data) | 4.7 (2.6-5.9) (64) | 4.3 (1.7-5.9) (127) | 0.004 |
| PVL >5 $log_{10}$ copies/mL | 25 (39.1) | 29 (22.8) | 0.019 |

Figure 1. Comparisons of prevalences of HBsAg, anti-HBc Antibody, and anti-HBs antibody between HIV-infected persons and controls

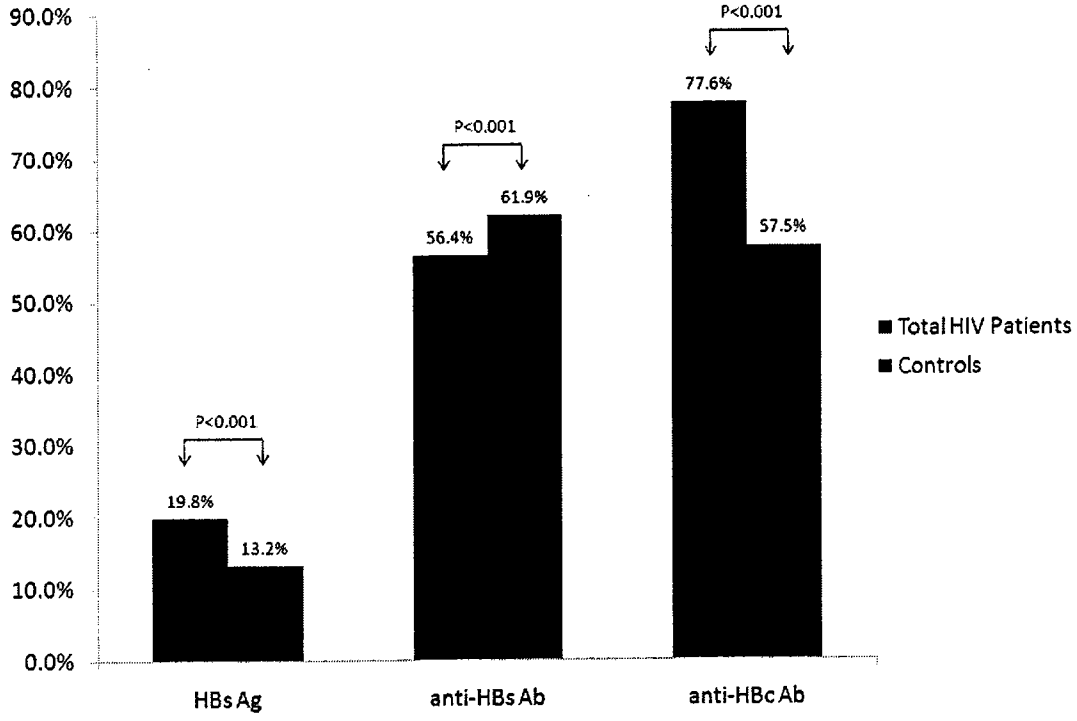


Figure 2. Comparisons of prevalences of HBsAg, anti-HBc antibody, and anti-HBs antibody between sexual and control groups, between intravenous drug users (IDUs) and controls, and between sexual group and IDUs.

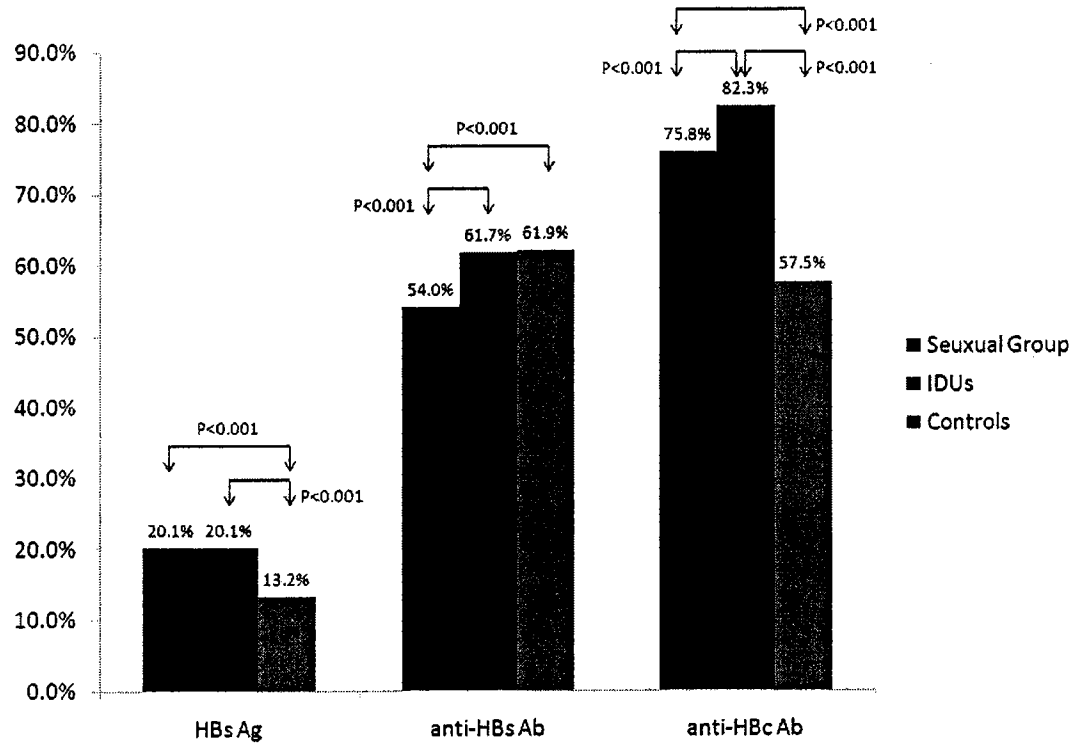


Figure 3. Comparisons of prevalences of HBsAg, anti-HBc antibody, and anti-HBs antibody between all HIV-infected persons and controls born before and after July 1984

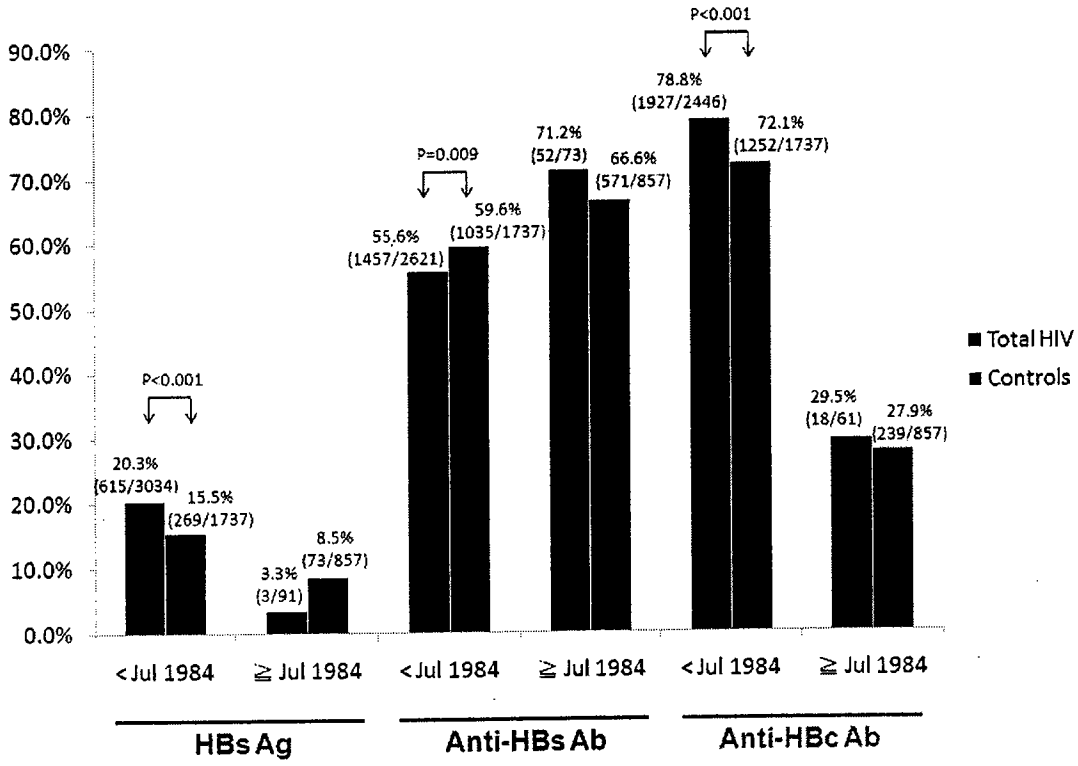
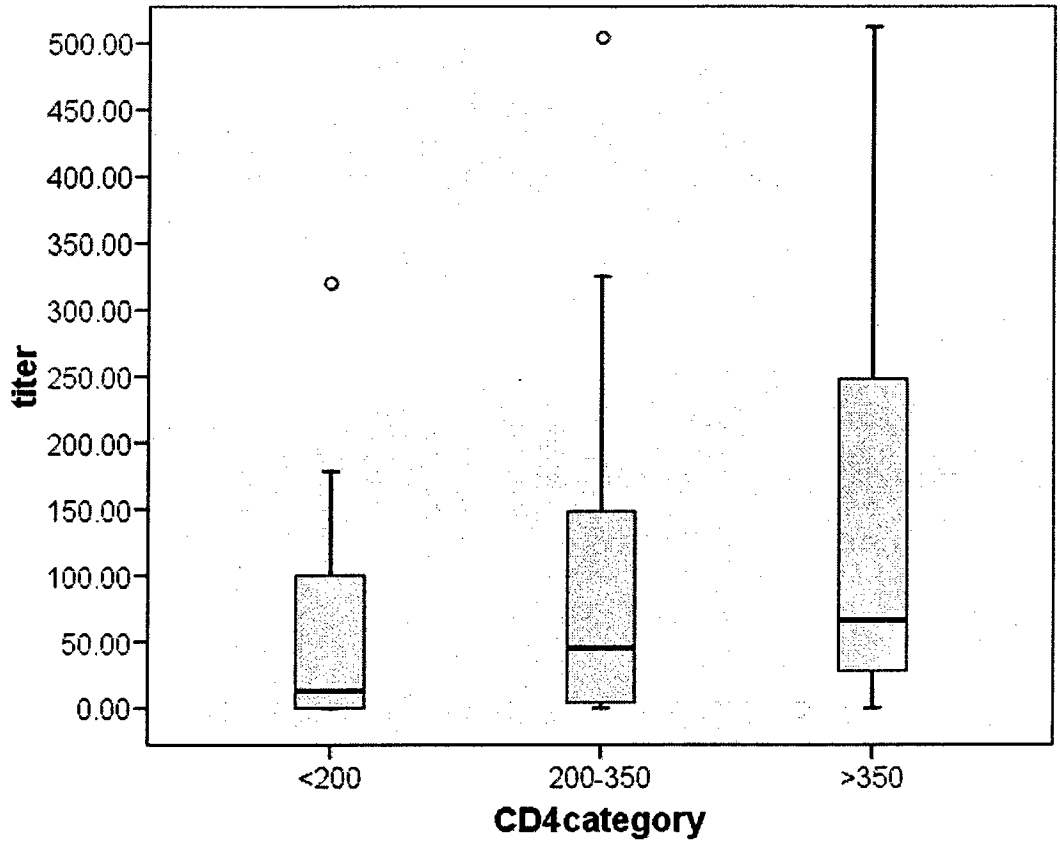


Figure 4. Anti-HBs antibody titer vs. CD4 categories (CD4 counts category vs. anti-HBs antibody titer, *P*=0.005).



（四）討論

In the present study conducted in an area with a high HBV endemicity in the general population and vertical transmission as the main route for HBV transmission,[22,23] we found that HIV-infected persons had a higher prevalence of HBsAg (19.8%) than HIV-uninfected persons who sought health check-up (13.2%) in this study and general population (17.3%) in a recent community survey in Taiwan[33] due to higher risk of exposure to HBV, as demonstrated by a higher prevalence of anti-HBc antibody (77.6% vs. 57.5%, $P<0.001$). The lower prevalence of anti-HBs antibody despite high risk of HBV exposure may be related to HIV-associated immunosuppression against HBV, as demonstrated by the finding that HIV-infected persons of sexual transmission group with lower CD4+ counts had a lower prevalence of anti-HBs antibody compared with IDUs.

In Taiwan, intravenous drug use has recently overtaken homosexual or bisexual contacts as the leading HIV transmission route after an outbreak of HIV transmission among IDUs occurred between 2003 and 2006.[34] Because mandatory HIV testing had been offered routinely to all inmates since1990, IDUs with HIV infection have a higher chance to be detected at early stage of HIV infection. [34] Therefore, compared with persons acquiring HIV through sexual contact, IDUs had a shorter duration of HIV infection and had relatively preserved immunity. Since IDUs are at higher exposure to both HIV and HBV, it is not unexpected that they had significantly higher prevalence of HBsAg (20.1% vs. 13.2%, $P<0.001$) and anti-HBc antibody (82.3% vs. 57.5%, $P<0.001$) than controls. However, prevalence of anti-HBs antibody was similar between IDUs and HIV-uninfected persons, which might be attributed to repeated natural booster by injection drug use and the relatively preserved HBV immunity

among IDUs with resultant seroconversion after HBV infection.

Interestingly, although HIV-infected persons in sexual transmission group had a lower risk than IDUs for HBV or HCV exposure as shown by a lower prevalence of anti-HBc antibody (75.8% vs. 82.3%, $P<0.001$) and anti-HCV antibody (6.6% vs. 96.8%, $P<0.0001$), both groups of HIV-infected persons had a similar HBsAg prevalence (20.1% vs. 20.1%, $P=0.994$). According to our previous studies, a substantial proportion of sexually-transmitted HIV-infected persons were diagnosed at late stage of HIV infection.[35,36] In this nationwide survey, we also showed that, as compared with IDUs, persons acquiring HIV through sexual routes had a lower median CD4+ count and a higher proportion of them had CD4 counts lower than 100 or 200 cells/μL. Furthermore, among persons in sexual transmission group, those with lower CD4 counts had lower prevalence of anti-HBs antibody. Therefore, the findings that the prevalence of anti-HBs antibody of sexual transmission group was lower than that of IDUs while HBsAg prevalence was similar between the two groups may be attributed to more immunsuppression in the former group because loss of anti-HBs antibodies with a serological pattern of isolated anti-HBc antibody is more common in immunosuppression.[37] IDUs in the present study had a comparable prevalence of anti-HBs antibody as HIV-uninfected controls did and there was no significant difference in the prevalence of anti-HBs antibody between IDUs with CD4 counts <350 cells/μL and those with CD4 counts $\geqq$350 cells/μL. The findings may be explained by natural booster during repeated needle sharing during intravenous drug use.

Similar to the findings that prevalence of HBV infection has declined dramatically in the general population after implementation of universal HBV vaccination program

in July 1984,[25-30] we also demonstrated that that receipt of HBV vaccination at birth or in the childhood also benefits the persons who may subsequently engage themselves in high-risk behaviors for HIV transmission in their adolescence or adulthood. Regardless of risk behaviors, the prevalence of HBsAg decreased from 20.3% in HIV-infected persons born before July 1984 to 3.3% in those born after July 1984, and that of anti-HBc antibody reduced from 78.8% to 29.5%; the two prevalence were similar to those observed in HIV-uninfected controls born after July 1984 (Figure 3). The findings demonstrate the impact of a nationwide HBV vaccination program on HBV prevalence in populations at low or high risk for HIV and HBV transmission.

Although HAART has significantly improved the immune status of HIV-infected persons, there are concerns that capability of mounting and maintaining appropriate immune response following HBV vaccination is impaired in HIV-infected persons compared with HIV-uninfected controls.[15-17,19,20,38] However, those studies of HBV vaccination were conducted in persons already known to be HIV-infected, and little is known regarding the antibody titers among the persons who receive HBV vaccine before they are infected with HIV. In the present study, we found that, compared with the 161 historical controls who were aged 15 years,[31] the proportion of persons maintaining protective level anti-HBs antibody titers ($\geqq$10 mIU/mL) was higher in our HIV-infected persons. Furthermore, in persons born after July 1984 or after 1980, similar observation was also noted, implying that although these persons received HBV vaccination at birth or in their childhood, protective anti-HBs antibody titer still existed after HIV infection. The persistence of higher anti-HBs antibody titers among the adults despite immunosuppression from HIV infection may be related to natural booster after they begin to engage themselves in high risk behaviors for HIV and HBV

transmission, and similar observation was also reported in an Italian study.[32]

In the present study, a positive association between CD4 counts and anti-HBs titers was observed (Figure 4). In addition, our study also demonstrated that persons with CD4 count $\geqq$350 cells/μL and those born after 1980 were the two independent factors associated with maintaining protective anti-HBs antibody titers. Owning to the catch-up programs of HBV vaccination in Taiwan, individuals born after 1980 who had vaccination-induced anti-HBs antibody, negative anti-HBc and positive anti-HBs antibody, were likely to receive HBV vaccination in their childhood. Therefore, our analysis suggested that relatively preserved immunity after HIV infection and childhood vaccination might play a role in the maintenance of protective antibody titers in HIV-infected persons. Further studies are needed to confirm our observation and whether this protective antibody titer can be maintained by timely initiation of HAART remains to be explored. Nevertheless, our findings suggests that in countries where HBV endemicity is high and HIV infection is transmitted by sexual route or intravenous drug use, the policy of nationwide universal HBV vaccination to newborns can effectively lower the prevalence of HBV infection not only in general population but also in individuals at high risk for HBV and HIV infection.

There are several limitations in the present study and interpretation of the results should be cautious. First, the number of HIV-infected persons who were born after 1984 is small because prevalence of HIV infection has been very low in the age groups of 15 to 25 years in Taiwan,[39] and continued surveys are needed when more persons born after 1984 are likely to be engaged in high-risk activities for HIV transmission. Second, the cross-sectional study design precludes us from determining whether the titers of anti-HBs antibody may wane over the ensuing years

among those HIV-infected persons who had undergone HBV vaccination. Third, because of the study design, we were not able to identify specifically HBV vaccination status and the date of vaccination of each person. However, given the high coverage rate of nationwide HBV vaccination program (86.9-98.0%)[25] and several catch-up programs of HBV vaccination to cover individuals born after 1977-1980 in their childhood,[24,25] it is quite likely that people having serological markers of HBV vaccination had received HBV vaccination in their childhood before HIV infection occurred.

In conclusions, we demonstrate that nationwide HBV vaccination in Taiwan is associated with significant reduction of HBsAg prevalence in HIV-infected persons who were born after 1984. Higher levels of protective anti-HBs antibody titers may persist in the HIV-infected persons who had ever received HBV vaccine before they acquired HIV infection.

## （五）結論與建議

In conclusions, we demonstrate that nationwide HBV vaccination in Taiwan is associated with significant reduction of HBsAg prevalence in HIV-infected persons who were born after 1984. Higher levels of protective anti-HBs antibody titers may persist in the HIV-infected persons who had ever received HBV vaccine before they acquired HIV infection.

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附件三

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 人類免疫不全病毒第一型(HIV-1)抗藥性監測與臨床處理之相關研究

# A Prospective Study on Antiretroviral Genotypic Analysis of Human Immunodeficiency Virus Type 1 (HIV-1) and Its Therapeutic Implications

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

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執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共　28　頁

壹、中文摘要：

目前，在台灣遭到人類免疫不全病毒感染的本國病患，皆可接受健保給付的三合一雞尾酒療法。雖然藥物治療已能有效地控制受感染者的病情，而且許多新型的藥物也不斷地推出，但是，治療失敗的例子也正在逐漸增加中。歸究其原因，除了藥物毒性所帶來的副作用外，抗藥性的產生已成為治療失敗的一個重要原因。而這些抗藥性病毒株的產生，不但造成所謂原生抗藥性病毒株的傳播，也使得一些藥物的治療效果大打折扣。由於考慮到抗藥性病毒株的傳播與感染所造成的影響，本計畫著重於（一）針對遭到人類免疫不全病毒感染的病患進行抗藥性基因型分析，並將其結果提供臨床醫師，作為治療這些病人時藥物選擇的參考。（二）對於治療失敗的病人，我們也會提供抗藥性基因型分析，希望能對於臨床醫師選擇換藥時會有所幫助。（三）調查並分析台灣地區人類免疫不全病毒第一型(HIV-1)原生抗藥性的盛行率。在本計畫中，我們一共分析108件病人檢體，其中71件是病人尚未接受任何治療前的檢體；37件是治療失敗的病人檢體。37件治療失敗的病人檢體中，只有18人在報告截止前有回來持續地追蹤。然而這18人中有13人(72.2%)的病毒量有明顯的改善，顯示抗藥性基因型分析對於臨床醫師選擇換藥時可提供參考的依據，且可改善病人的治療結果。對於台灣地區人類免疫不全病毒第一型(HIV-1)原生抗藥性的盛行率，根據我們的實驗結果，原生抗藥性的盛行率為9.6%，遠高於 WHO 所建議的5%。而其中85.7%(6/7)的人是藉由性接觸所傳染的。因此我們建議，台灣地區的病患，特別是藉由性接觸而感染到人類免疫不全病毒的病人，在接受治療前能作病毒抗藥性分析，以得到較好的醫療效果。

關鍵詞：愛滋病、抗藥性、原生抗藥性、基因型分析

貳、英文摘要

Since the availability of HAART (highly active antiretroviral therapy), the appearance of drug resistant viruses in treated individuals and the transmission of these drug resistant viruses have been reported by many groups. Antiviral drug resistance was observed in many primary infected individuals. As the transmission of primary drug resistant virus is increasing, the drug resistant test becomes important before patients receiving therapy. In our project, we aimed at (1) to provide the genotypic resistance report to patients who have not received antiretroviral therapy and hope that such information will help clinicians in choosing the optimal treatment regimen. (2) to provide the genotypic resistance report to patients who have failed antiretroviral therapy and hope that such information will help clinicians in choosing the optimal treatment regimen. (3) to determine the prevalence of primary drug resistance in Taiwan. We have analyzed a total of 108 specimens, in which 71 were from treatment naïve patients and 37 were from treatment failure patients. Among the 37 patients, only 18 have available laboratory data before the end of the study. Seventy-two percent of them have improved viral load, implicating enhanced efficacy of therapy. The prevalence of primary resistance is 9.6%, higher than the 5% threshold recommended by the WHO and further support the need of drug resistance test before the initiation of antiretroviral therapy. Among the 7 patients harboring resistant viruses, 6 (85.7%) were likely to be infected through sexual contacts. In conclusion, genotypic resistant test is recommended for HIV-1 patients, especially those infected through sexual contacts, before therapy.

Key words: AIDS、drug resistance、primary resistance、genotypic analysis

## 參、本文

### （一）前言

人類免疫不全病毒第一型(HIV-1)是造成人類後天性免疫不全症候群(愛滋病，AIDS)的主因,並已造成全球性的大流行[28]。至民國九十二年底為止，全球約有四千兩百萬人遭到感染，其中包括三千八百六十萬名成年人及三百二十萬名小於十五歲的孩童(http://www.unaids.org/hivaidsinfo/statistics)。而自民國七十五年，第一例人類免疫不全病毒感染病患在台灣被鑑定後，台灣人口的陽性病毒感染率，已逐年快速增加[29, 30]。根據衛生署疾病管制局的最新統計指出，在台灣已累積有六千二百五十五人遭到人類免疫不全病毒的感染(http://www.cdc.gov.tw)。在這些受感染的病患中，有二千一百三十六例(36.9%)可能是經由異性間的性接觸，二千零九例(34.7%)是經由同性間的性接觸，而六百三十八例(11.02%)是雙性戀者 (http://www.cdc.gov.tw)。這些加起來約佔人類免疫不全病毒感染人數的百分之八十。另一個與人類免疫不全病毒感染有關的危險因子---藥物注射，約佔台灣被感染人口的百分之三點四九，遠低於大陸的百分之六十八[31, 32](http://www.cdc.gov.tw)。因此，在台灣，性接觸可能是造成人類免疫不全病毒感染的主要途徑。而隨著社會風氣的開放，感染人類免疫不全病毒的平均年齡有逐漸下降的趨勢，並主要分布在二十至四十歲之間。值得注意的是，在這年齡層的人士是社會中最具有生產力的階層。此外，隨著治療藥物的進步，病人的平均壽命有逐年增加的趨勢。而目前台灣的健保政策是，全額補助受感染病患的藥物費用。因此，受感染的病患年齡層下降不僅會影響社會的生產力，也會增加社會的負擔。所以，如何能增進愛滋病感染者接受治療的品質及有效性是十分重要的。

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。第一類是擬似核甘酸衍生物的反轉錄酶抑制藥物(nucleoside reverse transcriptase inhibitors, NRTIs)。這類藥物的分子結構類似核苷酸衍生物，是以此特性來終止病毒 DNA 的生成，進而抑制病毒的複製。這類的藥物包括 zidovudine(AZT)、stavudine(d4T)、didanosine(ddI)、zalcitabine(ddC)、及 lamivudine(3TC)。第二類是非擬似核甘酸衍生物的反轉錄酶抑制藥物(non-nucleoside reverse transcriptase inhibitors, NNRTIs)。這類藥物的分子係藉由與病毒的反轉錄酶結合，達到抑制反轉錄酶活性及抑制病毒生長的效果。這類的藥物包括 nevirapine(NVP)、delavirdine(DLV)、及efavirenz(EFV)。第三類是蛋白酶抑制藥物 (Protease inhibitor, PI)，主要是抑制病毒蛋白酶的活性。這類的藥物包括 saquinavir(SQV)、ritonavir(RTV)、indinavir(IDV)、nelfinavir(NFV) 、amprenavir(APV)、lopinavuir(LPV)、及 atazanavir(ATV)。此外，一些抑制病毒進入宿主細胞的藥物也在積極開發中，其中 enfuvirtide(T-20)已應用在臨床治療上。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，儘管新的抗病毒藥物一直出現，治療失敗的例子卻時有耳聞。可能在服用藥物的過程中，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，使得病毒在患者體內衍生出抗藥性病毒株，造成治療失敗。而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[33, 34]。它不但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[35, 36]。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[37-42]。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[43]。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。

一般鑑定抗藥性病毒株的方法，可分為病毒基因型的分析（Genotypic assay）及病毒表現型的分析（Phenotypic assay）[2]。病毒基因型的分析，是直接分析與藥物抑制的機制相關的病毒基因變異。藉由分析經治療無效的病人檢體及細胞培養產生的抗藥性病毒株，在人類免疫不全病毒的 *pol* 基因上，已有許多與抗藥性相關的基因變異陸續被得知[44]。其中有些抗藥性病毒株的產生是經由逐漸累積的基因變異所導致，有些甚至是由單一基因變異所產生[1, 2](http://www.iasusa.org/)。而這些基因變異的分析，已成為決定病毒株抗藥性的重要工具之一[45]。目前市面上作病毒基因型的分析的方式分兩種：一種是直接將病人血漿檢體送交國外檢驗中心作分析。目前有三家廠商（產品名）可作此服務，分別為 Speciality Labs（GenotypR Plus™）、Virco（VircoGEN™）、及 ViroLogic（GeneSeq HIV™）。另一種是向廠商購買商業試劑組，自己做分析。目前有兩家廠商販賣這種試劑組，分別為 Visible Genetics/Bayer Diagnostics（Trugene™HIV-1 Genotyping kit Clip™）、及 Celera Diagnostics/Applied Viosystems/Abbott diagnostics（ViroSeq™ HIV-1 Genotyping System）。然而這些檢驗費用所費不貲，一個檢體約需兩百至四百美元不等。目前，由於有一些學校或公家機關所設立的電腦網站，例如 Stanford HIV RT and Protease Sequence Database- HIVdb（http://hivdb.stanford.edu/hiv/），可提供免費的電腦軟體以供病毒抗藥性基因變異的分析。因此許多實驗室開始自己作病毒基因序列的分析，大大降低操作的成本。本實驗室也於過去設立了病毒基因序列分析的方法，其特異性及敏感度都不比廠商的商業試劑組差。例如一些廠商建議病人檢體的病毒量，必須在 500-1000 copies/ml 以上才可偵測。然而根據本實驗室的方法，我們可在病毒量約 500 copies/ml 即可偵測到病毒基因。

另一種鑑定抗藥性病毒株的方法為表現型的分析。這種方法，主要是分析病毒本身在藥物不同濃度下的感受性(Drug susceptibility test)，定出可毒殺 50%病毒的藥物濃度（$IC_{50}$），來決定其抗藥程度。譬如說，經由藥物感受性實驗定出可毒殺 50%病毒的藥物濃度，臨床病毒株為實驗室野生病毒株（對藥物具有感受性）的十倍，我們即可說此臨床病毒株具有相當的抗藥性。一般來說，

這些臨床病毒株的取得可經由病人血液單核球（PBMC）的細胞培養方法來直接分離，或是經由基因重組方式在實驗室製造[46-48]。目前，由於利用傳統細胞培養法所得到的結果變異性較大，所以大多採用基因重組方式來製備重組臨床病毒株。而偵測病毒量的方法也從傳統的偵測 p24 的量或是反轉錄酶（reverse transcriptase， RT）的活性，轉變成較靈敏的具有冷光（luciferase）的指標性細胞（indicator cell）[48]。目前市面上作病毒表現型的分析方式是直接將病人血漿檢體送交國外檢驗中心作分析。目前有三家廠商（產品名）可作此服務，分別為 Virco（Antivirogram™）、ViroLogic（PhenoSense™）、及 VIRalliance（Phenoscript™）。一個檢體約需五百至六百美元不等。相較之下，病毒表現型的分析方法可較直接決定出病毒的抗藥性。但是它需要在第二級或第三級實驗室操作、實驗步驟較繁瑣、技術層面與費用較高、而且不同實驗室間的實驗結果變異性較大，所以比病毒基因型的分析法不普及。

最近一些研究指出，抗藥性基因變異的分析，比之前所用的病人服藥史、病人體內的病毒量及 CD4 細胞數，更能有效地預測短期藥物治療的效果[23, 49]。在一個回歸性的臨床研究中（retrospective cohort），抗藥性基因型分析能有效地預測曾接受過蛋白酶抑制藥物（PI）的病患再接受其它種蛋白酶抑制藥物（saquinavir/ritonavir）的治療效果[50]。另外一個大型的回歸性分析也顯示，對於曾接受過其它藥物治療的病人，抗藥性基因型分析也能幫助醫師選擇較適合的藥物組合，在短期內降低病人的病毒量[51]。除了回歸性分析之外，目前有四個大型的前瞻性臨床試驗（prospective cohort）在進行，分別為 Viradapt、Genotype-Associated Antiretroviral Resistance Testing (Gart) Study、Argenta、及 Havana。在這些研究中，學者們想證實抗藥性基因型分析是否能確實預測抗藥性的產生及幫助臨床醫師選擇適合的藥物組合以延遲抗藥性病毒株的產生。在 Viradapt 臨床研究中，學者選了 108 個曾經治療失敗的病人。他們想比較，根據抗藥性基因型的分析結果是否比只靠臨床症狀來給藥，更能增進治療效果。結果他們發現，抗藥性基因型的分析結果確實能在相同時間（六個月）內達到抑制更多病毒量的效果[52]。在 Gart 臨床研究中，研究族群為 153 個在接受雞尾酒療法達 16 週，病毒量卻一直無法下降的病人。

相同地，有接受抗藥性基因型分析的那一組在第 12 週時，病毒量小於 500 copies/ml 的病人百分比較控制組為高[53]。在 Argenta 臨床研究中，學者發現在第 12 週時，有接受抗藥性基因型分析的那一組有 27% 的病毒量低於 500 copies/ml 反較控制組只有 12% 達到相同標準。較不一樣的是，這種差異在第六個月時就不具統計學的意義[54]。至於在 Havana 臨床研究中，學者選了 247 個治療失敗的病人。他們發現抗藥性基因型分析及專家的解讀，確實對於病人的治療較有幫助[55]。總而言之，不論是回歸性或是前瞻性臨床試驗在在顯示抗藥性基因型分析對於曾經治療失敗的病人確實有幫助。至於抗藥性基因型分析對於未曾接受治療的病人是否有幫助，目前尚未有大型的研究成果發表，這也是我們想做的。

目前抗藥性相關的基因變異資料庫大多是依據 B 亞型病毒株的研究成果，對於其他非 B 亞型病毒株的研究並不多。非 B 亞型病毒株產生抗藥性的機制也許與 B 亞型病毒株不盡相同，進而引發不同的基因變異形式甚或造成交叉抗藥性（cross-resistance）[25-27]。在台灣，台大醫學院的李君男教授、陽明醫學院的陳宜民教授、長庚醫學院的張學賢教授及我們實驗室都曾做過人類免疫不全病毒亞型的分析[30, 56, 57]。包括人類免疫不全病毒 A、B、C、D、G、AG、CRF01_AE、及 CRF07_BC 亞型都曾被分離並報導過。其中以 B 亞型病毒株最為盛行，約佔台灣感染人數的百分之七十，並且在受感染的同性戀族群中占有相當高的比例（70-85%）。此外，CRF01_AE 亞型重組病毒株約佔台灣感染人數的百分之二十五，並主要分布在經由異性性接觸而被感染的病患中。其他曾在台灣地區分離之人類免疫不全病毒亞型，則包括 A、C 及 G 亞型。這些病毒株主要是經由異性性接觸而造成感染。值得注意的是，除了 CRF01_AE 亞型重組病毒株以外，兩株特殊的 A/G 亞型重組病毒株也曾在台灣地區感染的病人身上被分離出[57-59]。由此可知，在台灣地區，非 B 亞型病毒株也佔有相當比例。此外，近年來，CRF07_BC 亞型重組病毒株在台灣地區毒物注射的族群中造成大流行。其抗藥性相關的基因變異，是否將異於目前根據 B 亞型所知的基因變異，也將一併被列入分析。

由於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。研究追蹤台灣地區抗藥性病毒株的盛行率，對於未來人類免疫不全病毒的診斷與治療，有其不可抹滅的重要性。因此，希望本計劃的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

### 研究對象與檢體

人類免疫不全病毒（HIV）的血清型陽性檢體，將從國立台灣大學附設醫院取得。血液檢體將使用含 EDTA 抗凝劑的無菌管收集，離心所得之病人血漿將先行分裝，並保存於-80℃冰箱中，以為進一步分離病毒顆粒，並做萃取病毒 RNA 之用。血液檢體中所剩的血球部分，將利用 Ficoll-Hypaque gradient 的方法來分離週邊血液單核細胞（PBMC），儲存在-80℃冰箱中，已備日後當病人血漿中沒有足夠的病毒顆粒（<500 copies/mL）以萃取病毒 RNA 時，可用來萃取血球細胞中病毒 DNA，以為進一步的抗藥性基因序列分析所用。

### 病患資料收集

本研究所採的對象來自台大醫院感染 HIV 疾病的患者。這些患者的資料包括性別、年齡、傳染途徑危險因子、CD4 細胞數、血漿中病毒量和用藥處方。

### 萃取人類免疫不全病毒 RNA

我們採用 QIAamp Viral RNA Mini Kit (QIAGEN)商用試劑組，抽取檢體中的人類免疫不全病毒 RNA。首先，將收集到的血清檢體混勻後，取出 140 μl 血清，再加入 560 μl AVL 緩衝液，以震盪器充份混勻後，靜置於室溫下 10 分鐘。隨後加入 560 μl 100% 乙醇，再以震盪器充份混勻後，分次加入含矽膠膜之管柱(QIAamp spin column）中，以轉速 8,000 rpm 離心 1 分鐘，去除過濾液。如此反覆數次，直到所有檢體液都過濾完全。再加入 500 μl AW1 清洗緩衝液，以轉速 8,000 rpm 離心 1 分鐘。除去濾液之後，加入 500 μl AW2 清洗緩衝液，以轉速 14,000 rpm 離心 3 分鐘。去除過濾液之後，再以轉速 14,000 rpm 離心 3 分鐘，以完全去除殘留於矽膠膜管柱中的酒精。再將此矽膠膜管柱移至新的微量離心管中，最後加入 40 μl AVE 緩衝液，室溫靜置 1 分鐘，以轉速 8000 rpm 離心 1 分鐘，再收集含 RNA 之濾出液，保存於-20℃。

萃取人類 DNA

在分離出的週邊血液單核細胞（PBMCs）中加入 200μl 的紅血球溶解緩衝液（0.32M 蔗糖溶液，10 mM Tris-HCl [pH 7.5]，5 mM 氯化鎂溶液及 1%Triton X-100）。當大多數紅血球溶解後，離心並去除上清液。再加入 200μl 含有 Proteinase K 的紅血球溶解緩衝液（10 mM Tris-HCl [pH 8.3]，50 mM 氯化鉀溶液，2.5 mM 氯化鎂溶液，0.45% Nonidet P-40 及 0.45% Tween 20），在 55℃水浴槽中水浴一小時。之後用酚－氯仿溶液萃取出 DNA，再用酒精沈澱，最後溶於 100μl 的二次水中，並在 260 nm 波長下測其吸光度以決定 DNA 濃度。

反轉錄酶反應

萃取自人類免疫不全病毒的 RNA，須先經由反轉錄酶反應，做成 cDNA 後，再經由聚合酶連鎖反應（PCR）來放大 *env* 和 *gag-RT* 可轉錄區域。首先，取 10μl 萃取自人類免疫不全病毒的 RNA，加入 1μl oligo dT (0.5μg/μl)，在 70℃作用 5 分鐘。再加入適當的反轉錄酶緩衝液、dNTP、 及反轉錄酶，在 40℃作用一小時。之後，在 70℃作用 15 分鐘，使反應停止後即可。所得之 cDNA 可接著做聚合酶連鎖反應，或者保存於-20℃。

聚合酶連鎖反應（PCR）放大

我們利用聚合酶連鎖反應(PCR)來放大 *gag-RT* 可轉錄區域(coding regions)。針對 *gag-RT* 基因，第一次 PCR 所用的引子對為 Gag1（5' ATG CCA GAA ATA GCA GGG CCC 3' ）和 Pol1A（5' CTA GGT ACT ATG TCT GTT AGT GCT 3' ）。在 50 μl 的 PCR 標準反應溶液中（10mM Tris-HCl [pH9.0]，50mM 氯化鉀溶液，1.5mM 氯化鎂溶液，0.1%(w/v) gelatin，1% Triton X-100，0.25mM dNTPs，每個 primer 10 pmol 及 1 單位的 Taq DNA 聚合酶），約加入 1 μl 的 cDNA。PCR 放大反應的溫度及條件為 95° C/3 分鐘，再跑 35 個循環：95° C /1 分鐘，62° C/1 分鐘，72° C/1 分鐘。接著將初次的 PCR 產物稀釋 50 倍，用 Gag2（5' AGC AGA GCC AAC AGC CCC ACC A 3' ）和 RT1（5' CTA AAT CCC TGG ATA AAT CTG A 3' ）這兩個引子來進行第二次 PCR 放大反應。溫度的設定和初次的 PCR 相同，也跑 35 個循環。最後預期的 PCR 產物

大小約為 1200bp。所有的 PCR 反應產物，都將藉由電泳及 Ethidium bromide 染色確定其純度。

聚合酶連鎖反應產物純化

為了之後進行核酸定序反應，聚合酶連鎖反應之產物需先經由電泳分離出單一產物，再經由玻璃纖維基質 (Gel-M™ Gel Extraction System, Viogene) 以去除反應鹽類及引子，進而純化之。首先，將 PCR 反應產物進行一次電泳。之後，將基因片段所在位置之洋菜膠以刀片切下來，切下之洋菜膠裝在 1.5ml 微量離心管中，稱重，加入洋菜膠重量 1000 倍體積的 GEX 緩衝液，再將微量離心管置於 60℃水浴 10 分鐘。待洋菜膠完全溶於 GEX 緩衝液後，再把所有液體移到玻璃纖維基質微量離心管柱 (Gel-M™ Column) 中，在室溫下靜置 5 分鐘。再以 13,000 rpm 離心 30 秒，丟棄濾出液。如此反覆數次，直到所有檢體液都過濾完全。再加入 500μl WF 清洗緩衝液，以轉速 13,000 rpm 離心 1 分鐘。除去濾液之後，加入 500μl WS 清洗緩衝液，以轉速 13,000 rpm 離心 1 分鐘。去除過濾液之後，再以轉速 13,000 rpm 離心 3 分鐘，以完全去除 WS 清洗緩衝液中的酒精成分。再將玻璃纖維基質管柱移到新的 1.5 ml 微量離心管中，在玻璃纖維基質的中央加入 30-50μl E 析出緩衝液，在室溫下靜置 5 分鐘，再以 13,000 rpm 離心 1 分鐘，收集含有 DNA 之濾出液。取 3μl DNA 濾出液，以 1.0% 洋菜膠，經電泳確認其 DNA 純度及濃度。其餘 DNA 濾出液則保存於-20℃，待日後 DNA 定序所用。

DNA 定序

PCR 純化的產物將利用 Dye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, U.S.A.) 來作定序。將利用引子 ENV2 (5' TCA GCA CAG TAC AAT GYA CAC ATG G3' ) 及 ENV3 (5' CCA ATT GTC CYT CAT ATY TCC TCC T 3' ) 來作 *env* 區域的定序。模擬兩可的序列可用另兩個上游引子 CL1101 (5' AAT GTC AGC ACA GTA CAA TGT ACA C 3' ) 和 MK 648 (5' CAG TAG AAA AAT TCC CCT CCA CAA TT 3' ) 作定序來解決。針對 *gag-RT* PCR 產物，Gag2 (5' AGC AGA GCC AAC AGC CCC ACC A 3' ) 和 RT1 (5' CTA AAT CCC TGG ATA AAT CTG A 3' ) 將被用作 *gag-RT* 區域的定序。模擬兩可的序列可用另兩個引子 Gag3 (5' CCA GGA ATG GAT GGC CCA

AAG 3' ）和 RT2（5' ATT GTT TAT ACT AGG TAT GGT ATA 3' ）作定序來解決。每一個產物的核酸序列都由產物的五端及三端各定序一次，以確求基因序列的正確性。373A DNA 定序儀（Applied Biosystems）將被用來作核酸序列的定序，其操作方法完全依照操作手冊的敘述來作。所得到的 DNA 序列將利用 Sequencher 3.1 電腦軟體來作初步基因序列的整理。

資料分析

所有病毒株的核甘酸序列都會用來進行病毒株的亞型及抗藥性的基因型分析。

病毒株亞型之分析

我們將利用電腦程式 PHYLIP，version 3.573（Phylogeny Inference Package）來作基因系統樹分析(phylogenetic analysis)，所得到的種系樹狀圖將被用來決定病毒株之亞型[63-65]。各種亞型之參考序列將自美國 Los Alamos Laboratory 的人類免疫不全病毒基因序列資料庫取得(HIV sequence database, http://hiv-web.lanl.gov/content/hiv-db/SUBTYPE_REF/align.html)。至於無法直接由基因系統樹分析決定病毒株之亞型者，則使用電腦程式 BLAST 2.0 program(National Center For Biotechnology Information, USA)先行篩選，看是否與之前人類免疫不全病毒基因序列資料庫 (http://hiv-web.lanl.gov/content/hiv-db/SUBTYPE_REF/align.html)中已知的重組病毒株的序列有相關性。同時，電腦程式 Simplot 2.5 將會被用來決定是否有不同亞型病毒基因重組的現象，並決定其基因重組的接點(recombination breakpoints)[66]。

抗藥性的基因型分析

我們將利用電腦網站 Stanford HIV RT and Protease Sequence Database- HIVdb（http://hivdb.stanford.edu/hiv/）的軟體來進行抗藥性的基因型分析。它利用專家及臨床醫師的觀察結果（The Stanford database）設定了內建式的規則（algorithm），可依病毒基因序列上的胺基酸變異形式，決定病毒對於目前常用的 19 種藥物的敏感程度。目前共可分為五級分別為具敏感性（sensitive）、可能有抗藥性（potential resistance）、低程度的抗藥性（low-level resistance）、中程度的抗藥性（medium-level

resistance)、及高程度的抗藥性（high-level resistance）。而 19 種藥物則包括 NRTI 類的 zidovudine (AZT)、stavudine (d4T)、didanosine (ddI)、 emtricitabine (FTC)、abacavir (ABC)、tenofovir (TDF)、及 lamivudine (3TC)；NNRTI 類的 nevirapine (NVP)、delavirdine (DLV)、efavirenz (EFV)、及 entecavir (ETV)；蛋白胨抑制藥物 saquinavir (SQV)、darunavir (DRV)、indinavir (IDV)、nelfinavir (NFV) 、fosamprenavir (FPV)、lopinavuir (LPV)、tipranavir (TPV) 、及 atazanavir(ATV)。

## (三)結果

我們一共分析 108 件病人檢體，其中 71 件是病人尚未接受任何治療前的檢體；37 件是治療失敗的病人檢體。

### 一、 治療失敗病人的抗藥性基因型分析結果

37 件治療失敗的病人檢體，病人平均年紀為 37.9 歲，以男性為主(96.4%)。病人換藥前的平均病毒量、CD4 細胞數、CD8 細胞數分別為 87,090 copies/mL、189 counts/mL、及 1,048 counts/mL。

37 件治療失敗的病人檢體中，有 24 人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑具有抗藥性的基因突變(圖一)。其中 9 人對於蛋白酶抑制劑具有抗性，17 人對於類核苷酸類反轉錄酶抑制劑具有抗性，18 人對於非類核苷酸類反轉錄酶抑制劑具有抗性。此外， 3 人對於蛋白酶抑制劑及類核苷酸類反轉錄酶抑制劑都具有抗性，9 人對於類核苷酸類反轉錄酶抑制劑及非類核苷酸類反轉錄酶抑制劑都具有抗性，而 4 人對於三種抑制劑都具有抗性。這 24 人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑藥物種類具有抗藥性的清單詳列於表一。

在這 37 件治療失敗的病人檢體中，只有 18 人在報告截止前有回來持續地追蹤(表二)。這些病人換藥前的平均病毒量、CD4 細胞數、CD8 細胞數分別為 98,089 copies/mL、126 counts/mL、及 887 counts/mL。換藥後的平均病毒量、CD4 細胞數、CD8 細胞數分別為 34,942 copies/mL、127 counts/mL、及 1,023 counts/mL。這 18 人中有 13 人(72.2%)的病毒量有明顯的改善，其中雖然有三人的病毒量原本就小於 1,000 copies/mL，減少的幅度不大，但是整體來說，抗藥性基因型分析對於臨床醫師選擇換藥時可提供參考的依據，且可改善病人的治療結果。

### 二、 台灣地區人類免疫不全病毒第一型(HIV-1)原生抗藥性的盛行率

對於台灣地區人類免疫不全病毒第一型(HIV-1)原生抗藥性的盛行率，我們一共分析 73 件病人檢體。這群病人的平均年紀為 35.2 歲，以男性為主(90.4%)，平均病毒量、CD4 細胞數、CD8 細胞數分別為 287,245 copies/mL、248 counts/mL、及 934 counts/mL。病毒亞型及危險因子分析結果如圖二。病毒亞型以 B 亞型為主(71%)，次為 CRF07_BC(14%)、CRF01_AE(12%)、及 C(3%)。危險因子主要以男同性戀(MSM, men having sex with men)為主(63%)，次為異性戀(22%)、及藥物毒癮者(IDU, intravenous drug user)(3%)。

根據我們的實驗結果，原生抗藥性的盛行率為 9.6%(7/73)，遠高於 WHO 所建議的 5%。其中 2 人對於蛋白酶抑制劑具有抗性，3 人對於類核苷酸類反轉錄酶抑制劑具有抗性，2 人對於非類核苷酸類反轉錄酶抑制劑具有抗性。沒有人對於兩種以上的藥物具有抗性(表三)。而對於藥物具有抗性的 7 人中，有 6 人(85.7%)是藉由性接觸所傳染的。

(四)討論

在我們所收集的108件來自臺大醫院新近感染人類免疫不全病毒的病人檢體中，71件是病人尚未接受任何治療前的檢體；37件是治療失敗的病人檢體。在37件治療失敗的病人檢體中，有24人的檢體對於蛋白酶抑制劑或是反轉錄酶抑制劑具有抗藥性的基因突變，而其中甚至有16人對於兩種以上的病毒抑制劑具有抗性。由於目前國內可使用的藥物有限，而一些藥物間的干擾作用或是cross-resistant，這種對於兩種以上的病毒抑制劑具有抗性的病毒株將是臨床醫師未來在做藥物選擇上的一項挑戰，也會嚴重影響病人的治療效果。在這37件治療失敗的病人檢體中，很可惜只有18人在報告截止前有回來持續地追蹤。但是，整體來說，病人的病毒量有改善。因此對於治療失敗的病人，抗藥性基因型分析可提供臨床醫師選擇換藥時的參考依據。

根據國外的研究結果顯示，毒癮者及男同性戀族群為主要傳播抗藥性病毒株的族群(Bozzette, Berry et al. 1998)。根據本計劃研究結果顯示，台大醫院病人原生抗藥性的盛行率為9.6%(7/73)。在台灣，雖然因共用針頭而感染人類免疫不全病毒的病人在過去這幾年快速增加，但是根據本篇研究，在台灣，感染抗藥性病毒株的仍然以男同性戀族群為主(5/7, 71.4%)。在台大醫院的病人中，只有一位藥物毒癮者檢驗出抗藥性病毒株。但是我們無法排除本院所收因共用針頭而感染人類免疫不全病毒的病人數，相較於其他中南部院所來說偏低，所以可能低估其數值。考量感染人類免疫不全病毒的藥物毒癮者在過去這幾年快速增加，因此可能需要其他中南部院所或監獄執行類似的研究來決定，藥物毒癮族群中感染抗藥性病毒株的比例，以及早提供相關對策。

## （五）結論與建議

根據本計劃研究結果顯示，(1) 對於治療失敗的病人，抗藥性基因型分析可提供臨床醫師選擇換藥時的參考依據，(2)台大醫院病人原生抗藥性的盛行率為9.6%(7/73)，遠高於 WHO 所建議的 5%。因此，我們建議台灣地區的病患，特別是藉由性接觸而感染到人類免疫不全病毒的病人，在接受治療前能作病毒抗藥性分析，以得到較好的醫療效果。

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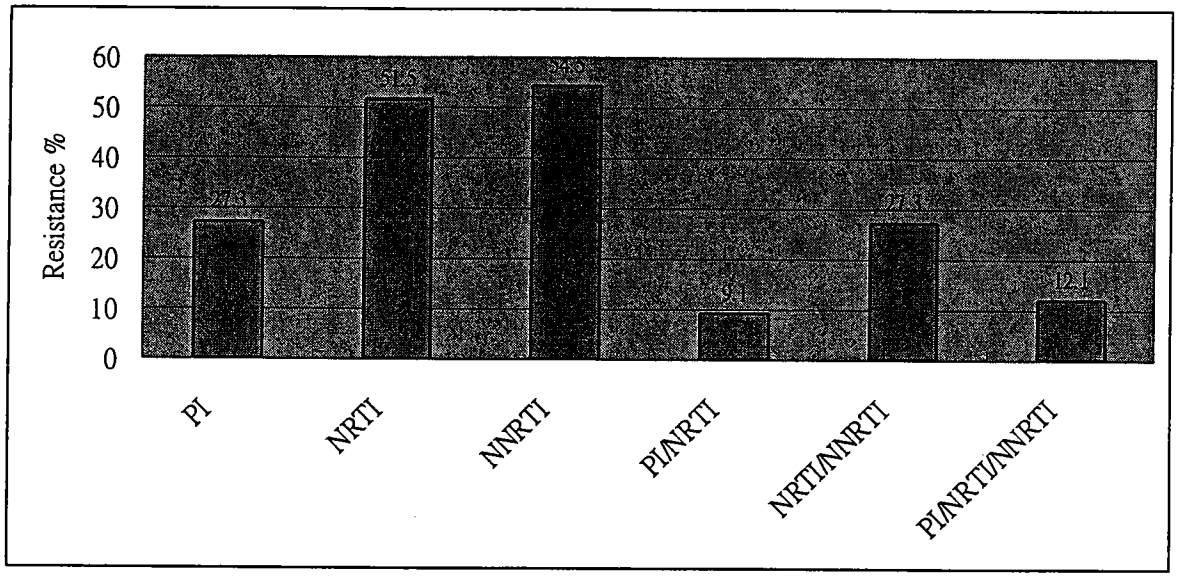
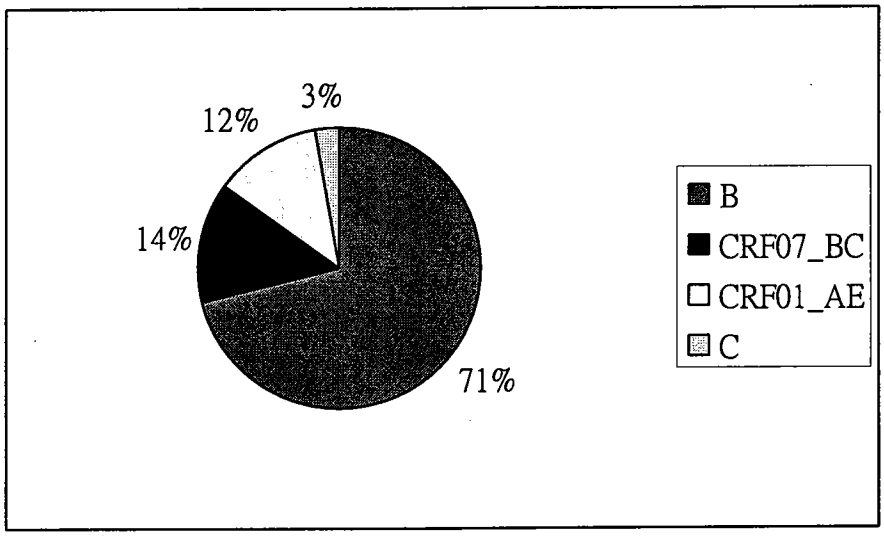
圖一　治療失敗病人的抗藥性基因型分析結果

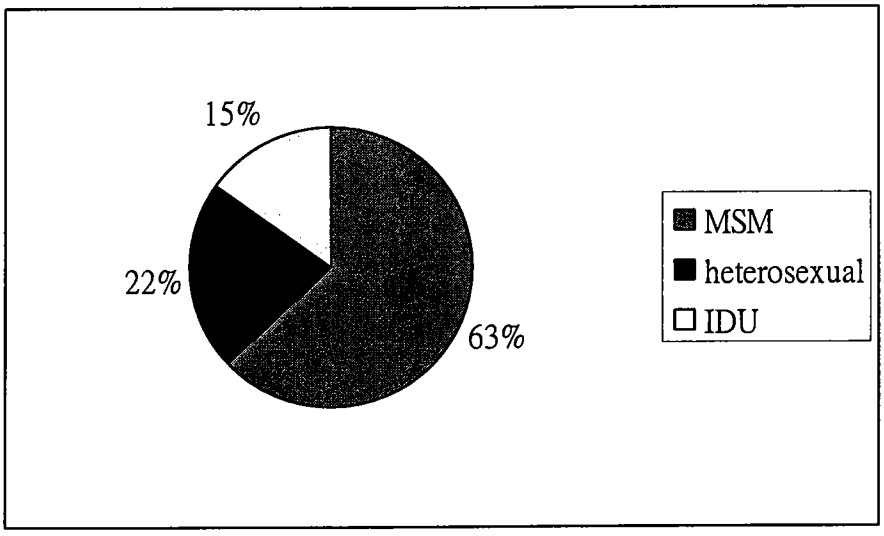


圖二　未接受治療病人的病毒亞型及危險因子分析

(A) 病毒亞型分析




(B) 危險因子分析



表一　治療失敗病人的抗藥性基因型分析結果(藥物種類分析)

| | PI | | | RTI | |
|---|---|---|---|---|---|
| | High level | medium level | low level | High level | medium level |
| Pt1 | | NFV | ATV, SQV | 3TC, ABC, DDI, FTC, DLV, NVP | EFV |
| Pt2 | | | TPV | | |
| Pt3 | | | | 3TC, FTC, DLV, EFV, NVP | |
| Pt4 | | NFV, SQV | ATV, IDV, LPV, fAPV | NVP | EFV |
| Pt5 | IDV, LPV, NFV, fAPV | ATV, SQV, TMC114, TPV | | 3TC, ABC, AZT, D4T, DDI, FTC, DLV, EFV, NVP | TDF |
| Pt6 | | | | DLV, EFV, NVP | |
| Pt7 | | | | NVP | EFV |
| Pt8 | | | | 3TC, FTC, DLV, EFV, NVP | ABC, AZT, D4T, DDI, TDF |
| Pt9 | | IDV, LPV, NFV | ATV, DRV, FPV, SQV, TPV | 3TC, FTC | ABC, DDI, TDF |
| Pt10 | | | | 3TC, FTC, DLV, EFV, NVP | ABC, AZT, D4T, ddI |
| Pt11 | | | | 3TC, FTC, DLV, EFV, NVP | ABC |
| Pt12 | | | | DLV,EFV,NVP | |
| Pt13 | IDV, NFV | ATV, DRV, FPV, and LPV | SQV and TPV | | ABC, DDI |
| Pt14 | | | | 3TC, FTC, DLV, EFV, NVP | |
| Pt15 | | | | | AZT, d4T |
| Pt16 | | | | 3TC, FTC, DLV, EFV, NVP | |
| Pt17 | | | | 3TC, FTC | |
| Pt18 | | | | DLV, EFV, NVP | |
| Pt19 | | | | | DLV, EFV, NVP |
| Pt20 | | ATV | | 3TC, FTC | ABC |
| Pt21 | | | | 3TC, FTC, DLV, EFV, NVP | ABC |
| Pt22 | NFV, SQV | ATV, FPV, IDV, TPV | DRV, LPV | ddI, DLV, EFV, NVP | ABC, AZT, d4T, ETV |
| Pt23 | NFV | ATV, FPV, IDV, LPV, SQV, TPV | DRV | | |
| Pt24 | | | | | |

表二　治療失敗病人的追蹤結果

| | before therapy | viral load(copies/mL) | CD4(counts/mL) | CD8(counts/mL) | after therapy | viral load(copies/mL) | CD4(counts/mL) | CD8(counts/mL) |
|---|---|---|---|---|---|---|---|---|
| Pt1 | 95/7/5 | 47800 | 3 | 30 | 95/10/30 | 1930 | 26 | 201 |
| Pt2 | 95/10/31 | 5900 | 73 | 300 | 96/2/13 | 5440 | 93 | 598 |
| Pt3 | 95/8/29 | 3510 | 70 | 1574 | 95/12/21 | 61200 | 94 | 2160 |
| Pt5 | 95/11/24 | 82300 | 19 | 417 | 96/2/9 | 5630 | 60 | 554 |
| Pt6 | 96/3/29 | 28100 | 394 | 1030 | 96/5/29 | 543 | NA | NA |
| Pt7 | 95/10/17 | 100000 | 106 | 907 | 96/7/24 | 100000 | 183 | 659 |
| Pt8 | 95/11/10 | 58400 | 251 | 1663 | 96/2/6 | 92800 | 195 | 1702 |
| Pt9 | 95/12/4 | 963 | 217 | 977 | 96/3/13 | 400 | 136 | 426 |
| Pt10 | 96/1/25 | 212000 | 80 | 786 | 96/4/30 | 400 | 302 | 2890 |
| Pt11 | 94/11/25 | 750000 | 123 | 445 | 94/12/30 | 100000 | NA | NA |
| Pt12 | 96/4/13 | 35400 | 68 | 1127 | 96/6/1 | 70800 | 34 | 1126 |
| Pt25 | 95/5/2 | 156000 | 28 | 639 | 95/8/7 | 6570 | 17 | 155 |
| Pt26 | 95/7/14 | 400 | 116 | 604 | 95/12/27 | 50 | 101 | 778 |
| Pt27 | 95/8/29 | 12350 | 325 | 1113 | 95/11/23 | 400 | 323 | 968 |
| Pt28 | 95/11/10 | 400 | 79 | 765 | 96/2/6 | 50 | NA | NA |
| Pt29 | 96/2/2 | 194000 | 122 | 1338 | 96/3/2 | 1360 | 128 | 942 |
| Pt30 | 96/2/1 | 74200 | 52 | 432 | 96/4/24 | 400 | 88 | 1002 |
| Pt31 | 96/1/29 | 3890 | 152 | 1826 | 96/3/29 | 181000 | 128 | 1197 |

表三　　原生性抗藥性基因型分析結果(藥物種類分析)

| | PI | | | RTI | | |
|---|---|---|---|---|---|---|
| | High level | medium level | low level | High level | medium level | low level |
| Pt201 | | | ATV, NFV | | | |
| Pt202 | | | | | | AZT |
| Pt203 | | | | | | AZT, d4T |
| Pt204 | | | | | | AZT, d4T |
| Pt205 | | | | NVP | | DLV, EFV |
| Pt206 | | | | NVP | | DLV, EFV |
| Pt207 | | | ATV, NFV | | | |

附件四

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 靜脈毒癮者為愛滋病毒與 HCV 雙重感染者其 HCV 病毒基因變異之長程分析
# Long term analysis of the genetic drift of HCV Virus in HIV-HCV coinfected patients.

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

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執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共 16 頁

# 摘要

近年來經由靜脈毒癮導致愛滋病毒感染者超過其它感染途徑. 這些病患大部分均同時有HCV病毒感染. 將來產生肝硬化或腫瘤的可能性極高. C型肝炎病毒容易突變, 慢性感染的過程中原先佔多數的病毒株會被突變種取代. 此種變異可能會影響治療C型肝炎病毒之療效. C型肝炎病毒的基因變遷影響因素複雜, 包括病毒本身之適應度與宿主免疫力等均可能影響. 愛滋病毒感染者其免疫力隨時間遞減, 但開始治療後又會回升. 本計劃比較未用HAART前與使用後C型肝炎病毒基因變遷. 將HCV core及envelope基因以nested PCR幅增後分析其氨基酸序列之變動, 多對HCV基因在服用HAART前後確有基因變異. Core基因中氨基酸列序更動之數目與病患之CD4數目並無相關性. 反之, 較諸一位CD4>300之病患, 其HCV *env*基因出現二個氨基酸序列變異, 多達五位CD4<200之患者有七處以上之氨基酸序列變異, 且集中在hypervariable region. 反觀一位CD4<100之愛滋病患, 因幾乎不服用HAART藥物, HCV基因並未出現變異. 由於HIV/HBV雙重感染者亦被觀察到其HBV基因於HAART治療後之變異也有類似現象, 我們推論愛滋病患末期的病人在使用HARRT後, 由極端免疫缺乏到恢復部份免疫力之過程, 變動劇烈, 可產生選擇壓力(selection pressure)迫使病毒突變. 此方面之研究受限於檢體數目不多, 有待將來更多資料來證實.

關鍵詞：愛滋病 、C型肝炎、 genetic drift

# 前言

愛滋病患 — 即發生伺機性感染或是腫瘤或是 CD4 細胞數目小於 200 者 — 於雞尾酒療法(HAART)後其免疫力會逐漸回昇，部份病患於治療數週後發生高燒及類似新感染症狀，但經多項檢查後發現是原來體內已有之感染如肺結核菌，巨細胞病毒或 *Mycobacterium avium* complex(MAC)之惡化，此種因免疫力恢復反導致感染發炎反應加劇之現象稱之為 immune reconstitution inflammatory syndrome (IRIS) [9-11]. 此時之免疫力雖然在恢復中但顯然還是不正常，因為我們經驗過一位愛滋病患，感染 parvovirus B19 病毒而導致長期貧血需定期輸血，在使用雞尾酒療法後雖然終於將病毒以自身恢復之免疫力清除，但已經過六個月[6]. 較之正常人絕大多數在一個月內就無法在血清中找到 B19 DNA，顯然有免疫不全. 因此愛滋病患於 HAART 治療後會有一短期對病原菌有免疫反應，但卻不足以控制住感染. 愛滋病患是後天免疫不全病毒感染之末期，免疫力幾乎完全喪失，常有潛伏性感染(latent infection)之復活(reactivation)，例如肺結核，toxoplasmosis, CMV retinitis, herpes zoster 等等. 伺機性感染治癒後往往需要預防性治療(prophylactic treatment)直到 CD4 大於 100. 故 HAART 治療後仍有一定程度之免疫不全持續數月.

慢性持續性之病毒感染在宿主體內隨著時間可觀察到主流病毒(dominant strain)基因之遷異(genetic drift)，例如 HIV, HBV, HCV 等. 引導 genetic drift 之因素極為複雜，一般相信宿主之免疫壓力，變種病毒之適應度(fitness)與宿主環境的變遷均有關. 較會產生 genetic drift 之病毒是複製過程含有反轉錄脢之步驟，因錯誤率高產生多種突變病毒株，因此病毒族群裏存在許多基因互有差別之病毒株稱之為 quasi-species. 產生 quasi-species 之條件包括一定數目以上之病毒長期複製，固定有之轉錄錯誤率使得突變種累積. 若某個突變種具有較佳之適應力即可成為數目最多之病毒株. 以 HBV 為例, quasi-species 之存在早已被證實, HBV 病毒株在 25 年之間的 genetic drift 亦曾被研究過[12-14]. 在前面提過之愛滋病患有 B19 病毒感染的情形裏，病患體內之 B19 病毒可達 $10^{11}$/mL 以上[7]，複製次數極多，雖然 B19 是 DNA 病毒，必需利用宿主細胞之 DNA polymerase, 出錯率低，然而在長期大量的複製次數下，仍然累積了不少 B19 quasi-species [15]. 然而過去研究顯示, B19 之基因非常穩定，它的 capsid protein VP1 基因的氨基酸列序有高度不變性 [16]，顯現 B19 已達演化上的最適應度. 因此一般相信在 B19 長期感染的病患體內不會看到 B19 的 genetic drift. 誠然，我們分析在診斷 B19 感染後一年後，去分析 B19 病毒是否產生基因變異，在未使用抗愛滋病毒藥物之下，即使有許多 quasi-species, 但無一個病毒變種隨著時間成為主要之病毒株(major circulating strain). 相反於沒使用 HAART

之病患，兩位被 B19 長期感染且已發生其他伺機性感染之病患，在使用抗愛滋病毒藥物治療後，B19 基因累積了不少突變，且大半突變均伴隨氨基酸序列之改變(non-conserved)，顯示為 positive selection [15]. 此一 genetic drift 產生之原因可能有多種因素，例如隨著 HAART 使用後，因免疫力逐漸恢復而使 B19 病毒量降低[6]，病毒族群之大小是會影響突變病毒株是否有機會取代成為主流病毒[17]. 其他的可能性當然包括逐漸恢復之免疫力，免疫力會選擇較不受抑制的病毒，影響之結果所產生之主流病毒應較有能力逃避宿主免疫力.

本國人士得到愛滋病感染之人數已於今年(2007)六月已突破一萬三千人. 過去三年內新增加者大半是靜脈毒癮者. 而其他危險因素而感染之新發現愛滋帶原病患增加之幅度仍約為每年百分之十五以上 [1]. 台灣之流行病毒是以 B 及 A/E 亞型為主[2]，但從 2004 年起新個案感染途徑分析，經由注射毒品者突然大增，短短幾年即累積了數千人，因而可能影響 B 及 A/E 亞型之消長. 而靜脈毒癮者其亞型與大陸類似，最多的亞型是 CRF BC 亞型[3]. 因此台灣愛滋病毒亞型之監測是必須進行之流行病學工作.

臺灣過去是 B 型肝炎的盛行區，因此臺灣之愛滋病毒感染者約有 1/4 是 B 型肝炎帶原者[4,5]. 由於 HAART 中幾乎均包括 lamivudine，大部分病患在 HBV 病毒量上可看到明顯降低. 然而 lamivudine 使用一段時期後，部分 HBV 產生抗藥性基因病毒突變，因此新變種病毒變成主流病毒. 此外慢性 B 型肝炎之感染者，在自然之感染過程中就可觀察到 genetic drift[14]，根據突變位置之 $d_S/d_N$ ratio，認定此種 genetic drift 與逃避宿主免疫力可能極為相關[14]. 因此在 HIV/HBV 同時感染之愛滋病患，以 HAART 治療時產生有趣的問題. 例如，若有 HBV 抗藥性基因突變，這些突變病毒是否會比非 HIV 感染者之 HBV 突變病毒具有較多位置之基因變化(即藥物突變壓力與免疫力壓力同時存在)? 同樣的，沒發生 HBV 抗藥性基因病毒突變者，是否會像 B19 病毒一樣，HAART 治療後被發現有基因多處之 genetic drift(可藉由比較 CD4 細胞數目高者與愛滋病患者之用藥後基因變異得知)?

靜脈毒癮得到愛滋病毒感染者有一新的問題產生，那就是同時有 C 型肝炎病毒感染. 臨床上 HIV-HCV 同時感染者其預後較差. 以干擾素及病毒藥物治療 HCV 之成效亦較不理想. HCV 已知有 quasi-species 存在，其原因一般相信是 RNA polymerase 較易產生突變有關. 因有 quasi-species 之故，HCV 病毒株會隨著時間而有主流族群的差異，亦即所謂 genetic drift[18]. 偵測 genetic drift 是由取得若干數目病毒株，計算某一有基因變異位置之病毒族群所佔有之比率，而一段時間後是再進行一次分析，比較是否不同. 由於 HIV-HCV 同時感染者其免疫力較差，因而有研究者認為會影響 quasi-species 中基因變異複雜度(complexity of genetic variation),

預期因免疫壓力減少, quasu-species之複雜度隨之減少[19]. 相反的, 使用HAART後免疫力回升, 則因選擇性壓力增加, 部分基因也會顯現明顯之genetic drift [20].

因此最近感染HIV的靜脈毒癮者病人, 其體內之HCV病毒隨時間進行之genetic drift, 可能不同於沒有 HIV 病毒感染者, 因此長期追蹤這些病患用藥前後的 C 型肝炎病毒之 genetic drift 應對免疫力與genetic drift 間的複雜相關性有釐清作用. 然而臺灣大部分靜脈毒癮患者因HIV病毒感染期尚短, 還未達到使用 HAART 之標準(CD4<300), 而我們較有興趣的愛滋病患中很少有毒癮者. 因此本報告仍然是以經性行為得到 HIV 病毒感染者為對象. 我們用來研究的是C型肝炎病毒的hypervariable region (HVR) –1 [20]. 已發病者(即AIDS病患)且有HCV感染者之免疫力在使用HAART後因免疫力處於青黃不接期, 預期HCV之基因可能會有較大的變動, 而與CD4在300附近用藥者會有不同.

# 材料與方法

## 研究對象

臺大醫院過去住院之愛滋病毒感染者，經檢測 C 型肝炎抗體後，約有 6-7% 有 HCV 感染，相當大部分之 CD4 小於 100. 這些病患有定期收集 10 西西之血清冷凍於攝氏-70 度供將來研究之用. 病患之血清若在用藥前與用藥一年以上均有找到血清者即納入本研究

## HCV 之 HVR-1 (hypervariable region-1) 研究

### 核酸萃取及 DNA 片段增幅

以 RNA extraction kit 抽取 200ul 血清中之 RNA. 利用反轉錄酶以 random primers 製備 cDNA.以 PCR purification kit 純化後，接下來做 nested PCR. 使用之 primers 如下:

First round PCR, outer primers

Sense nt 802-841

5`-GCG TCC GGG TTC TGG AAG ACG GCG TGA ACT ATG CAA CAG G-3`

Anti-sense nt 1639-1600

5'-AGG CTT TCA TTG CAG TTC AAG GCC TTG CTA TTG ATG TGC C-3`

反應條件為 94℃ 2 min, 94℃ 1 min 65℃ 2 min 72℃ 2 min 共 35 個循環, 72℃ 10 min.

Second round PCR, inner primers

Sense nt 1295-1327

5`-GGC ATG GGA TAT GAT GAT GAA CTG GTC CCC TAC-3`

Anti-sense nt 1626-1587

5`-AGT TCA AGG CCG TGC TAT TGA TGT GCC AAC TGC CGT TGG T-3`

反應條件為 94℃ 2 min, 94℃ 1 min 65℃ 2 min 72℃ 2 min 共 35 個循環, 72℃ 10 min.

將 HCV 的 HVR-1 基因放大, PCR 產品直接於 agarose gel 電泳，經由 ethidium bromide 作用後於紫外線光下觀察並回收純化,然後直接做 PCR products 的 sequencing.

### 核酸定序及病毒株種異分析( sequencing and analysis of quasi species)

每一 PCR 產品以 dye-terminator 做基因列序分析.經由螢光標的的 ddNTP, 於雷射激發的不同波長轉成訊號，由電腦收集分析.

## 結果

### HCV 於 HAART 治療前後之基因變異

收集到的檢體共有 21 對，分別在變異性高的地方以及 core 基因設計 2 對引子將之增幅.但由於每個病人HCV 基因變異頗大，致使PCR 成功率只有 62 % ( 15/24 )，且並非每一對血清中之 HCV 其從氨基酸位置一至 500 均被完整 amplified，因此只比對做出來之部分. 其餘 9 對都只有其中一段基因被增幅出,因此無法做有效的比對，相當可惜.

Core 基因部分:

比對 10 位病患用藥前後此段基因之變化 (表一)，發現基因變異之數目與免疫力(即用藥前 CD4 數目)並無相關性. 有趣的是突變位置重覆出現於不同病患，例如第 233 個氨基酸位置在 C,G 與 E 病患體內均出現變動，且均是變成 G; 此一巧合令人不禁聯想到此一基因變異是否源於逃避宿主之免疫攻擊. 可惜這三位病患之 HLA typing 並不清楚.

表一. HAART 用藥前後 core 基因中之突變

| 病患 | 基因突變位置(前後氨基酸變異以縮寫代表) | 用藥前 CD4 數目 |
|---|---|---|
| A | A217E, D218G | 114 |
| B | I200V | 87 |
| C | T49A, L189V, V192I, E233G, A260T | |
| D | K29Q, R70Q, T75A, M91L, S116L, V200I, V203I, V253I | 470 |
| E | M242I | 333 |
| F | V242I | 6 |
| G | S198T, K217Q, E233G, I292M, V299E | 52 |
| H | D233G, K235T, S236T, T301I | 41 |
| I | L293F | 154 |
| J | nil | 6 |

### HVR-1/ HVR-2 基因部分

根據文獻報告，HCV 變異性高的區段共有兩段，分別位於 HVR-1: 384~410 及 HVR-2: 474~480. 比較十對 HCV 基因變化時 (表二)，只有一位病患未發現 HCV 基因改變，此位病患可能常不服用 HAART，因期病毒量從未下降. 此外，病患 L 之病毒量雖在開始用藥後下降至測不到，但之後又數度回昇至數十萬/mL，因此也是服藥不規則. 病患中有一位病毒量較高，他的 HCV 基因也是變動最少者. 雖然我們的病患如果使用 HAART 前 CD4 數目小於 200 者，普遍有較多之變異，且多集中於 HVR-1，此一現象很可能是受愛滋病患在使用 HAART 後免疫力逐漸恢復，因選擇壓力迫使病毒產生突變以逃避宿主免疫力. 但此一假設需要有更多

CD4 細包數目較高者的用藥後資料來支持.

表二. HCV 氨基酸位置 328 至 503 間於 HAART 治療後發生之突變

| 病患 | 基因突變位置(前後氨基酸變異以縮寫代表) | 用藥前 CD4 數目 |
|---|---|---|
| E | V348I, N401R | 333 |
| F | S401R, F402L, P405S, G/D476D, G/D483D | 6 |
| G | I344V, G350E, W386Q, G389A, H394R, H397Y, F399V | 52 |
| I | I344V, I359M, H384N, T386Y, R391H, A392V, D395T, A398R, F399L, A400I,G401K, F402I, S403D, P404F, A406P, N409D, N414Y, T415S, F442L, R446K | 154 |
| J | V/I340V, N384H/Y, A393G/A, T/A395A, I399L, S400T, N401S, F403L, H445H/Y, K446R | 135 |
| K | V/R386R, T/A400A, N/S401N, P/S405P, A/S408A, Q/K434Q, I/L438L, L/M456L, S/R460S, Y/H474Y, A/D475A, E/L476E, N/H/Q478N, P/S480P | 6 |
| L | T388A, R/Q397R, G/S398G, L/F400L | 54 |
| M | M388T/M, A466A/T | |
| N | nil | 21 |
| O | I373I/V, N384E, R394H, S398G, T401S, H408N, R/K446K | 174 |

## 討論

HCV 病毒之 genetic drift 雖然早為人所知，但在演化過程中何種變種病毒會脫穎而出，其決定之因素衆說紛紜，尚無定論. 甚至有作者認為病毒僅是不斷的變化，其中並無環境選擇因素(Are they adapting or merely changing?) [21]. 但不少研究者認為取而代之的變種病毒或是病毒本身較有競爭力(fitness)或是具有較佳逃避宿主免疫力等等方成為主流病毒. HIV/HCV 雙重感染者替免疫假說論提供了相當多之研究題材[19,20]. HAART 之使用人為的使得免疫力發生改變，隨著免疫壓力，研究顯示HCV變異性高的區段HVR確實在HAART使用後產生基因變異，且其基因變異產生氨基酸列序變異之比率較高，顯示為有目地之變異(positive selection) [20]. 在我們的計劃裏，考慮的是愛滋病患之免疫力極度缺乏，在HAART使用後初期之免疫力仍有殘缺，因此病毒可能有較長之期限去累積逃避宿主免疫力之突變. 的確，在 CD4 較低之病患裏有五位病患在氨基酸位置 328 至 503 間有七個以上的氨基酸列序變異，且較集中發生於 HVR 區域. 而唯一 CD4 較高者僅有兩個位置改變. 此外，一位幾乎不服用藥物者在八個月間並未發現其體內 HCV 基因出現 genetic drift, 此亦反証免疫壓力之存在. 至於 core 基因則看不出氨基酸列序變異數目與 CD4 細胞數目之相關性. 有可能是此一位置並非免疫系統攻擊之對象，因此發生 genetic drift 之機轉不同. 此項 HCV 在 HAART 使用後之變化尚待較多之 C 型肝炎病毒株的資料，尤其是從 CD4 細胞較高患者身上取得之病毒株，才能得到較強之支持証據. 同時也需要 cloning 這些 PCR product 去分析 genetic drift.

國人 B 型肝炎病毒盛行率較高，理論上 HBV/HIV 雙重感染者之愛滋病患，也有可能於 HAART 之影響產生較多之 genetic drift. 不同於 HCV, HBV 有重疊的 open reading frame, 基因變異受到限制. 此外，HAART 中含有 lamivudine, HBV 因此受到免疫系統與藥物之雙重壓力. 藥物壓力導致抗藥性病毒基因突變，我們觀察到兩位 CD4<200 之愛滋病患，產生 lamivudine 抗藥性，表三列出他們抗藥性病毒基因突變以及其他位置於HAART治療後HBV基因的變化. 可以看出這些變化與非HIV感染者體內之抗藥性HBV病毒相較，在數目上接近且位置上亦無特殊之處.

**Table 3.** The position of nucleotide substitutions found in lamivudine-resistant HBV strains from two patients after HAART

| Patient A | | | Patient B | | |
|---|---|---|---|---|---|
| Position | amino acid change | region | Position | amino acid change | region |
| 667 T→A | L→M | P | 1 C→A | L→I | P |
| 739 A→G | M→V | P | 330 G→A | S→N | S |

| | | | | | |
|---|---|---|---|---|---|
| | | I→M | S | | No | P |
| 793 | G→G/A | A→A/T | P | 667 T→A | L→M | P |
| 814 | T→G | L→V | P | 739 A→G | M→V | P |
| | | No | S | | I→M | S |
| 1032 | G→A | no | P | 855 A→G | no | P |
| 1230 | A/G→G | no | P | 930 A→C | Q→H | P |
| 1613 | A/G→A | K/R→K | P | 2242 T→T/G | no | C |
| 1633 | G→A | G→E | X | 2724 G→A | V→I | P |

在未產生抗藥性突變的病患也觀察到 HAART 使用一段時間後 HBV 基因有些位置發生變異. 比較從兩位 CD4>200 以及一位 CD4<100 之患者得來的三對 HBV 基因(表 4,5), 發現兩個重要的不同; 一是基因變異之數目, 從 CD4 少的病患取得之 HBV 遠大於 CD4 數目多者(22 *vs.* 7 and 6). 二是 22 個基因變異位置有集中於 C 及 pre-S1 基因之現象, 從 CD4 多的病患取得之 HBV 則無此情形. 研究 HBV 經過 25 年在慢性肝炎患者體內之基因變異發現較多出現於 C 及 pre-S/S/Pol 重疊區域, 且經 d*S*/d*N* ratio 分析推測應與逃避宿主免疫機轉有關[22]. 根據以上兩點之發現, 我們因而推論經由 HAAT 治療之愛滋病患, 可能因免疫力之急遽變化, 導致 HBV 病毒產生 genetic drift.

**Table4.** Genetic changes of HBV in two HIV-infected patients whose CD4 cell counts are greater than 200/mm$^3$

| **Patient C** | | | **Patient D** | | |
|---|---|---|---|---|---|
| Position | amino acid change | region | Position | amino acid change | region |
| 286 A>G→G | no | S | 793 A/G→G | I/M→M | S |
| | N>D→D | P | | T/A→A | P |
| 987 A/G→A | no | P | 1106 C→C>T | T→T>I | P |
| 1090 T→T/A | F→F/I | P | 1123 A→A>C | S→S>R | P |
| 1128 C>A→A | D>E→E | P | 1128 A→A>C | K→K>N | P |
| 1730 G>A→G | no | X | 1134 T→T>C | no | P |
| 1961 T>C→T | S>P→S | C | 1139 A→A>C | N→N>T | P |
| 2047 A>T→A | no | C | | | |
| | | | | | |

**Table 5.** The genetic changes of HBV found in one AIDS patient after treatment with HAART for 8 months

| Patient E | | | Patient E | | |
|---|---|---|---|---|---|
| Position | amino acid change | region | Position | amino acid change | region |
| 216 T→T/C | L→L/S | S | 2323 A>G→G>A | no | C |
| | No | P | | Q>R→R>Q | P |
| 354 A/C→C | H/P→P | S | 2531 A/T→A | K/N→K | P |
| | No | P | | | |
| 639 T→T/A | L→L/Q | S | 2555 C/T→T | no | P |
| | No | P | | | |
| 705 T/C→C | V/A→A | S | 2666 A/T→A | K/N→K | P |
| | No | P | | | |
| 1909 T/C→T>C | no | C | 3002 A/G→G | N/S→D | pre-S1 |
| | | | 3003 A/G→A | E→G | P |
| 2038 A/T→T | E/D→D | C | 3010 C>A→C | P/Q/K→Q | pre-S1 |
| | | | 3011 C>A→A | A/D/E→A | P |
| 2045 A/T→T | T/S→S | C | 3017 C/T→T | A/V→V | pre-S1 |
| | | | | No | P |
| 2131 A/C→C | E/D→D | C | 3073 A>C→C | M>L→L | pre-S1 |
| | | | | N>T→T | P |
| 2160 C>G→G>C | T>S→S>T | C | 3081 G/A→G | no | pre-S1 |
| | | | | V/M→V | P |
| 2198 C/A→A | L/I→I | C | | | |
| 2241 C/T→C | T/I→T | C | | | |

## 結論與建議

總之，在愛滋病患者(AIDS)以 HAART 治療後，若病患同時有其他病毒感染者，我們發現這些病毒會受到選擇壓力而產生 genetic drift. 就 parvovirus B19 而言, genetic drift 從未被發現於其他非愛滋病患之持續 B19 感染者中，而 HBV/HCV 則是在免疫力缺乏的愛滋病患比免疫力尚可的 HIV 感染者有較大幅度的基因變異. 因此，選擇壓力的來源最可能的是恢復中之免疫力. 當然此方面之研究受限於檢體數目不多，有待將來更多資料來證實.

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附件五

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 台灣地區 HIV 感染者合併 C 型肝炎病毒感染之臨床流行病學及其治療

# Clinical manifestations, genotypic epidemiology and treatment of chronic hepatitis C among patients with HIV-1 co-infection in Taiwan

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

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執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共 22 頁

壹、中文摘要：

由於愛滋病毒及 C 型肝炎病毒皆經由接觸患者體液等相同途徑而感染(如輸血、針扎、性行為、毒癮等等)，因此愛滋病感染者較非愛滋病毒感染者容易發生 C 型肝炎感染。過去因愛滋病毒感染者存活時間較短，慢性 C 型肝炎相關的併發症，往往不易察覺，因為大多數患者都死於愛滋病毒感染相關的伺機性染或腫瘤。目前在高效能的抗愛滋病毒藥物(HAART)廣泛的使用下，病患得以長期存活，因此相關 C 型肝炎感染的併發症的發生機率逐漸增加，而且已成為西方國家的病患死亡的重要原因及處置愛滋病感染者之重點，特別是經由共用針頭的靜脈藥癮患者和注射污染的血液製品的血友病患為高危險族群，根據流行病學統計靜脈藥癮 HIV 患者和血友病 HIV 患者之 C 型肝炎盛行率接近 90%至 100%，而同性戀或異性戀 HIV 患者 HCV 感染是 HIV 感染患者最重要的病毒感染之一，特別是在以靜脈藥癮為主要傳染途徑的地區或國家。慢性 HCV 感染會造成肝硬化和肝癌等慢性肝炎併發症。HIV 感染者 HCV 感染後到發生慢性肝臟併發症，可能只需 6 年；在大規模使用高效能抗病毒藥物（highly active antiretroviral therapy; HAART）後，HIV 感染患者的伺機性併發症大為減少，存活大為延長後，HCV 感染所造成的慢性肝炎併發症出現的機會，將大為增加。

目前全球大約有 1.7 億人口感染 C 型肝炎，尤其以 HIV 患者與靜脈毒癮者最常見。據估計,台灣地區約有百分之二至四的人口感染 C 型肝炎，急性 C 型肝炎感染者約有一半以上會變成慢性 C 型肝炎(有人估計可高達百分之八十),而慢性 C 型肝炎約有百分之二十會變成肝硬化肝衰竭及肝癌，國外的研究顯示愛滋病患感染 C 型肝炎時會加速 C 型肝炎相關之慢性肝病如肝硬化及肝癌進行，另外合併感染 HIV 及 HCV 的患者對於抗 HIV 藥物之反應亦比較差，因此容易進展成 AIDS。感染 C 型肝炎所引起慢性活動性肝炎的原因包括 HCV 病毒量多寡、亞型（Genotype）、宿主的年齡、性別、是否有 HIV 或 HBV 合併感染，以及酗酒等。HCV 分為 6 種基因型 (Genotypes1 - 6)，第 1 型含 HCV-RNA 濃度最高，其所引起的肝炎程度最嚴重，且其干擾素治療之效果最差。懷疑慢性 C 型肝炎時，肝臟穿刺檢查可以確認肝臟損傷的程度，以評估預後。對於已經感染 C 型肝炎病毒且活動性高度(肝功能異常)的患者，使用干擾素與抗病毒口服藥 Ribavirin 合併使用是目前公認的標準治療。干擾素與 Ribavirin 合併使用的作用是在清除複製中的 C 型肝炎病毒，以降低傳染性，使肝功能指數正常化，並改善肝臟組織的損傷，避免肝硬化或肝癌的發生。根據國外研究顯示對 HIV 感染者使用長效型干擾素與 Ribavirin 合併治療一年的反應率（HCV 病毒量在停止治療 6 個月時測不到）約為 40%，非 HIV 感染者之長效型干擾素與 Ribavirin 合併治療反應率約為 60-80%，而國內仍尚未有此研究報告。

本研究共收集 53 位 HIV 合併 HCV 感染病患與 387 位 HIV 但未有 B 型肝炎病毒及 C 型

肝炎病毒感染之病患作比較。兩組患者在基本資料的比較C型肝炎病毒合併感染之患者年齡較非C型肝炎病毒感染患者大(39歲比35歲，P=0.01)，合併C型肝炎病毒感染者其靜脈藥物毒癮比例(17%)比未有 C 型肝炎病毒感染者(0.8%)高出許多(P<0.001)。兩組患者在平均2.2年(791 天)的追蹤觀察中發現合併 C 型肝炎病毒感染患者急性肝炎發作的頻率為每 100人年13.89次(95%信賴區間為13.31-14.49次/人年)相較HIV患者但未有C型肝炎者其急性肝炎發生率為每100人年6.39次(95%信賴區間為6.24-6.55次/人年)，顯示合併C型肝炎感染患者比其他未有C型肝炎患者多2.769倍危險(95%信賴區間為1.652-4.640)，兩組有明顯之統計學上之意義。另外對三合一抗愛滋病毒療法(HAART)的治療療效比較方面，有C型肝炎合併感染的患者，以HAART治療可上升137/μL的CD4 T淋巴球相較未有C型肝炎病毒感染患者CD4 T淋巴球上升157/μL相似，未有統計學上之意義。在HAART治療過程中，有C型肝炎合併感染之患者並不會比沒有合併C型肝炎患者容易發生新的伺機性感染(相對危險為1.826，95%信賴區間為0.738-4.522，未達統計學上差異)。在預後(死亡)的比較方面，有C型肝炎感染之患者死亡率並不會比沒有C型肝炎感染者高(相對危險為0.781，95%信賴區間0.426-1.432，未達統計上意義)，由我們研究的結果發現，合併C型肝炎感染有較高的危險發生急性肝炎，但有無合併C型肝炎感染並不會影響HAART治療之病毒量控制，CD4淋巴球上升及發生新的伺機性感染，也不會影響患者的預後。

本研究資料收集自1997年至2007年6月在本院追蹤之HCV感染個案，共189位患者（不包括台大雲林分院個案），其中基因型第1型有21位（40%），包括基因型1a：2位，1b：18位，1a+1b：1位，基因型第2型有18位（34%），包括基因型2a：15位，2b：3位，其他型：14位(26%)。男性患者有168人，女性21人，HBs同時帶原者有34人(18%)，感染HIV之危險因子在同性戀者為56人，異性戀者39人，靜脈藥癮者為88人，輸血者2人，未知感染者4人。追蹤過程中發現12人有肝硬化，26位患者死亡，其中3位與HCV相關之肝炎併發症有關，1位為肝癌，3位死於靜脈藥癮之心內膜炎感染或動脈瘤（金黃色葡萄球菌菌血症），1位患者死於AIDS相關之伺機性感染，3位死於惡性腫瘤（淋巴瘤：2位，口腔癌：1位），2位死於毒癮藥物過量。

其中有13位HCV感染者接受標準之雷巴安素（ribavirin）及長效型干擾素（pegylated interferon）之治療。基因型第1型者為5位，第2型者為8位，平均之HCV起始病毒量為78400 copies/mL（範圍為144000至54100000 copies/mL），以Ribavirin 800~1200mg/天（依體重區分）以及干擾素（Peg-INF）180 μg/day治療，至治療1個月時共有7位(53.8%)HCV病毒量可達到測不到。至治療結束時（第6個月），共有10位（76.9%）HCV RNA可達到測不到，停藥後6個月，基因型第1型只有1位HCV RNA測不到（20%），而基因型

第 2 型有 4 位 HCV RNA 測不到（50%），因此對於 HCV 基因第 1 型的治療在 HIV 患者應考慮延長至 48 週治療。

關鍵詞：C 型肝炎病毒、基因型、肝炎、愛滋病毒感染

## 貳、本文

### （一） 前言

依據衛生署九十年統計，惡性腫瘤在台灣地區主要死亡原因中佔首位，而肝癌佔癌症死亡原因第二位，在男性佔第一位，女性佔第二位。C 型肝炎病毒感染在全世界是引起慢性肝炎之主要原因，大約有 85%感染 C 型肝炎病毒的患者，其 C 型肝炎病毒會持續存在體內，有 20-50% 會演變成肝硬化。而這些與 C 型肝炎有關的肝硬化病人中，有 5%可能發展成肝癌。所以對於 C 型肝炎的認識與防治是相當重要的。由於愛滋病毒及 C 型肝炎病毒皆經由接觸患者體液等相同途徑而感染(如輸血、針扎、性行為、毒癮等等)，因此愛滋病感染者較非愛滋病毒感染者容易發生 C 型肝炎感染[1-3]。HIV 患者同時感染 C 型肝炎的比例在國外報告約為 30%，在某些靜脈毒癮患者甚至可高達 90%[1-3]，過去因愛滋病毒感染者存活時間較短，慢性 C 型肝炎相關的併發症，往往不易察覺，因為大多數患者都死於愛滋病毒感染相關的伺機性染或腫瘤[4]。HIV 病患同時感染 C 型肝炎往往較無合併 HCV 感染者有嚴重之併發症，如肝衰竭及肝硬化[5-9]這些慢性之併發症往往會導致 HIV 病患住院日數增加及死亡[10-15]，此外 HCV 相關之其他病症包括腎絲球腎炎(Glomerulonephritis)、胰島素不耐受症(Insulin resistance)、冷凝蛋白血症(Cryoglobulinemia)等等容易加速腎臟及心血管疾病之發生[4]，目前在高效能的抗愛滋病毒藥物(HAART)廣泛的使用下，病患得以長期存活[16]，因此相關 C 型肝炎感染的併發症的發生機率逐漸增加，而且已成為西方國家的病患死亡的重要原因。

C 型肝炎亦容易加速 HIV 感染病程之惡化導致愛滋病而增加死亡率[15,17,18]，目前高效能三合一抗愛滋病毒藥物(HAART)之使用大大地減少愛滋病患的罹病率及死亡率，但是 HAART 對於同時感染 HCV 的 HIV 病患之預後影響如何仍有爭議。急性 C 型肝炎感染者約有一半以上會變成慢性 C 型肝炎(有人估計可高達百分之八十),而慢性 C 型肝炎約有百分之二十會變成肝硬化肝衰竭及肝癌[5-9]，國外的研究顯示愛滋病患感染 C 型肝炎時會加速 C 型肝炎相關之慢性肝病如肝硬化及肝癌進行[8,9]，另外合併感染 HIV 及 HCV 的患者對於抗 HIV 藥物之反應亦比較差，因此容易進展成 AIDS。與未染有 C 型肝炎之病患相比較，患有 C 型肝炎患者之 HIV 病毒的進展與死亡率，皆是前者的三倍多[10-15]。原因是因為 C 型肝炎病毒會延遲免疫系統之重建與能對抗 HIV 病毒之 CD4 細胞的復原時間[16]。

感染 C 型肝炎所引起慢性肝炎的原因包括：HCV 病毒量、亞型（Genotype）、宿主的年齡、性別、共同感染的問題 (HIV、HBV)，以及酗酒等有關。C 型肝炎病毒被分為 6 種基因型 (Genotypes1 - 6)，C 型肝炎病毒基因型分布也有區域性之差異，基因型 1、2、3 及其亞型分布在世界各地，第四型分布於整個非洲，第五型分布於南非，第六型分布於亞洲。台灣地區最常見的 HCV 基因型為 Ib 型，約佔慢性 C 型肝炎患者的 66-71 % 及肝癌患者的 83

%，其次為 2a 型（20 %）和 2b 型（10 %）。C 型肝炎病毒基因型與慢性肝炎嚴重度有相當程度的關聯性， 在這六種基因型中分析血中 C 型肝炎病毒含量，以 type1 含 HCV-RNA 濃度最高，其所引起的肝炎程度最為嚴重，而且其干擾素治療之效果最差。如果是 HCV type 2 (主要在日本)，其含 HCV - RNA 濃度較低，其干擾素治療治療之效果通常反應也較佳。即表示病毒基因型是決定病毒濃度的重要因素。此外，病毒濃度驟增，不同基因型病毒混合感染和宿主免疫反應可能和慢性 C 型肝炎之急性發作有關。

懷疑慢性 C 型肝炎時，肝臟穿刺檢查可以確認肝臟損傷的程度，以評估預後之情形。對於已經感染 C 型肝炎病毒且活動性高度(肝功能異常)的患者，使用干擾素與抗病毒口服藥 Ribavirin 合併使用是目前公認的標準治療[17]。干擾素與 Ribavirin 合併使用的作用是在清除複製中的 C 型肝炎病毒，以降低傳染性，使肝功能指數正常化，並改善肝臟組織的損傷，避免肝硬化或肝癌的發生。根據國外研究顯示對 HIV 感染者使用長效型干擾素與 Ribavirin 合併治療一年的反應率（HCV 病毒量在停止治療 6 個月時測不到）約為 40% [18]，非 HIV 感染者之長效型干擾素與 Ribavirin 合併治療反應率約為 60-80%，而國內仍尚未有此研究報告。

本研究以臺大醫院現有追蹤之 HIV 病患合併 HCV 感染者收集其臨床病史，包括年齡、性別、HIV 感染危險因子、CD4 淋巴球數、血漿 HIV 病毒量、肝功能及預後，並將病患之血清，檢驗 HCV-RNA 及其基因型，並且對照臨床病程中發生急性肝炎的時機，針對 HIV 病患合併 HCV 感染而有慢性活動性之患者進行進行肝切片，以及進行標準之雷巴安素(ribavirin)及長效型干擾素(pegylated interferon)之治療。藉由本研究能了解 HIV 合併 HCV 感染病患之臨床流行病學調查及治療之本土資料，以提供臨床醫師做治療上之參考。

（二）材料與方法

實驗地點：臺大醫院愛滋病研究中心

實驗對象：目前在臺大醫院追蹤治療的 HIV 合併 HCV 感染之病患，估計約有 80-100 人

實驗期間：本計劃將進行一年，從 2007 年 1 月 1 日迄 2007 年 12 月 31 日。

研究方法：

流行病學部分

收集病患之臨床資料，包括年齡、性別、感染 HIV 及 HCV 之危險因子、肝功能、免疫缺損程度（CD4 淋巴球數及血清病毒量），發生 C 型肝炎之危險因子及預後，並持續定期追蹤病患是否發生肝功能異常；是否有做肝臟切片之病理報告、是否有發生肝臟功能代償失調、

肝硬化或肝腫瘤。病患約每 4 個月抽血檢驗 HIV 病毒量和肝功能。

病毒學部分

以未來一年所收存的血清，針對 C 型肝炎帶原者依序進行 HCV RNA 的定性與定量作分析，以得知 HCV 之病毒量及基因型，其研究方法如下：Anti-HCV antibody test (ELISA; Abbott HCV EIA, version 2.0), detectable quantitative HCV RNA level determined by PCR (Roche Amplicor HCV, version 2.0).實驗步驟如下:

**Extraction of small quantity of RNA in serum**

1.Into a 2.0mL sterile screw-capped microcentrifuge tube(Fisher 05-664-66), add:

450μL D-BPB solution.

100μL serum, mixing by pipeting up and down.

50μL 2 *M* NaAc, pH4.0 buffer, mix by swirling the tube.

500μL saturated phenol, pH4.3.

100μL chloroform/isoamyl alcohol 24:1.

2.Screw caps on tightly and shake the tubes on high speed for 30 min.

3.Chill the tubes on ice for 15 min.

4.Centrifuge for 15 min, 13,000g in a refrigerated microcentrifuge at 4℃.

5.Remove 400μL aqueous layer to a 2.0mL sterile screw-capped microcentrifuge tube containing 40μL glycogen-acetate mixture and 1mL absolute ethanol.

6.Mix well and place the tubes in -20℃ freezer overnight or -80℃ freezer for ~1h. This is a good point to stop and continue on the next day. Samples can be frozed at -80℃.

7.Centrifuge for 45 min, 13,000g in a refrigerated microcentrifuge at 4℃.

8.Pour off supernatant , and blot each tube lightly on Kimwipes Ex-L paper. Take care not to cross-contaminate specimens.

9.Add 1 mL 75℃ ethanol without disturbing the pellet. Do not shake the tube. Extraction can be stored at -80℃ at this point.

10.Centrifuge for 10 min, 13,000g in a refrigerated microcentrifuge at 4℃.

11.Pour off supernatant.

12.Swab the sides of the tube using a sterile cotton applicator. Do not touch the pellet.

13.Resuspend in 18μL blue TKTRID buffer, and flick the tube to dissolve pellet.

14.Place the tube in an incubator at 37℃ for 15 min and spin briefly. The RNA sample can be used immediately for PCR, or stored at -20℃ until sample is taken for PCR. Before each use, place the tube in an incubator at 37℃ for 15 min and spin briefly. RT-PCR will

be carried out within 7 d.

**Primers used for PCR, sequencing, and genotyping for HCV**

Primer for PCR Sequence Nucleotide position

Genotype 1a GGATAGGCTGACGTCTACCT 196–177

Genotype 1b CCTGCCCTCGGGTTGGCTA(AG) 222–203

Genotype 2a CACGTGGCTGGGATCGCTCC 178–159

Genotype 2b GGCCCCAATTAGGACGAGAC 325–306

Genotype 3a GCCCAGGACCGGCCTTCGCT 220–211

Genotype 3b CGCTCGGAAGTCTTACGTAC 164–145

Genotype 4 CCCGGGAACTTAACGTCCAT 87–58

Genotype 5a GAACCTCGGGGGGAGAGCAA 308–289

Genotype 6a GGTCATTGGGGCCCCAATGT 334–315

治療部份

患者有慢性活動性 C 型肝炎時(定義為肝功能 GOT 或 GPT 大於 100 U/L)，則安排肝臟穿刺檢查確認肝臟損傷的程度，若合乎健保給付者將給予長效型干擾素(pegylated interferon)每週一次，每次 180 萬單位持續 24 週加上 Ribavirin 800-1200 毫克/天進行標準之治療，並於治療結束及六個月後監測肝功能、HIV 及 HCV 病毒量和肝切片。

統計分析

Data will be analyzed by Fisher's exact test, the Chi-square test with Yates' correction and Student's *t*-test where appropriate. Variables that achieved statistical significance in univariate analysis will be subjected to multivariate analysis to determine the significantly independent factors. A *p*-value of less than 0.05 will be considered significant

（三）結果

本研究資料收集自 1997 年至 2007 年 6 月在本院追蹤之 HCV 感染個案，共 189 位患者（不包括台大雲林分院個案），其中基因型第 1 型有 21 位（40%），包括基因型 1a：2 位，1b：18 位，1a+1b：1 位，基因型第 2 型有 18 位（34%），包括基因型 2a：15 位，2b：3 位，其他型：14 位（26%）。男性患者有 168 人，女性 21 人，HBs 同時帶原者有 34 人（18%），感染 HIV 之危險因子在同性戀者為 56 人，異性戀者 39 人，靜脈藥癮者為 88 人，輸血者 2 人，未知感染者 4 人。追蹤過程中發現 12 人有肝硬化，26 位患者死亡，其中 3 位與 HCV 相關之肝炎併發症有關，1 位為肝癌，3 位死於靜脈藥癮之心內膜炎感染或動脈瘤（金黃色葡萄球菌菌血症），1 位患者死於 AIDS 相關之伺機性感染，3 位死於惡性腫瘤（淋巴瘤：2 位，口腔癌：1 位），2 位死於毒癮藥物過量。

在 53 位合併 HCV 感染病患，與 387 位 HIV 但未有 B 型肝炎病毒及 C 型肝炎病毒感染之病患作比較。兩組患者在基本資料的比較合併感染 C 型肝炎之患者年齡較非 C 型肝炎感染患者大(39 歲比 35 歲，P=0.01)，合併 C 型肝炎感染者其靜脈藥物毒癮比例(17%)比未有 C 型肝炎感染者(0.8%)高出許多(P<0.001)(表一)。兩組患者在平均 2.2 年(791 天)的追蹤觀察中發現合併 HIV 及 C 型肝炎病毒感染患者急性肝炎發作的頻率為每 100 人年 13.89 次(95%信賴區間為 13.31-14.49 次/人年)相較 HIV 患者但未有 B 型及 C 型肝炎者其急性肝炎發生率為每 100 人年 6.39 次(95%信賴區間為 6.24-6.55 次/人年)，顯示合併 C 型肝炎感染患者比其他患者多 2.769 倍危險(95%信賴區間為 1.652-4.640)，兩組有明顯之統計學上之意義(表二)。另外對三合一抗愛滋病毒療法的治療療效比較方面，有 C 型肝炎合併感染的患者，以 HAART 治療可上升 137/$\mu$L 的 CD4 T 淋巴球相較未有 C 型肝炎感染患者 CD4 T 淋巴球上升 157/$\mu$L 相似，未有統計學上之意義。在 HAART 治療過程中，有 C 型肝炎合併感染之患者並不會比沒有合併 C 型肝炎患者容易發生新的伺機性感染(相對危險為 1.826，95%信賴區間為 0.738-4.522，未達統計學上差異)。在預後(死亡)的比較方面，有 C 型肝炎感染之患者死亡率並不會比沒有 C 型肝炎感染者高(相對危險為 0.781，95%信賴區間 0.426-1.432，未達統計上意義)，由我們研究的結果發現，HIV 患者合併 C 型肝炎感染有較高的危險發生急性肝炎，但有無合併 C 型肝炎感染並不會影響 HAART 治療之病毒量控制，CD4 淋巴球上升及發生新的伺機性感染，也不會影響患者的預後(表二)。

13 位 HCV 感染者接受標準之雷巴安素（ribavirin）及長效型干擾素（pegylated interferon）之治療。基因型第 1 型者為 5 位，第 2 型者為 8 位，平均之 HCV 起始病毒量為 78400 copies/mL（範圍為 144000 至 54100000 copies/mL），以 Ribavirin 800~1200mg/天（依體重區分）以及干擾素（Peg-INF）180 μg/day 治療，至治療 1 個月時共有 7 位（53.8%）HCV 病毒量可達到測不到。至治療結束時（第 6 個月），共有 10 位（76.9%）HCV RNA 可達到測不到，停藥後 6 個月，基因型第 1 型只有 1 位 HCV RNA 測不到（20%），而基因型第 2 型有 4 位 HCV RNA 測不到（50%）。

（四）討論

由於愛滋病毒及 C 型肝炎病毒皆經由接觸患者體液等相同途徑而感染(如輸血、針扎、性行為、毒癮等等)，因此愛滋病感染者較非愛滋病毒感染者容易發生 C 型肝炎感染[1-3]。HIV 患者同時感染 C 型肝炎的比例在國外報告約為 30%，在某些靜脈毒癮患者甚至可高達 90%[1-4]，HIV 病患同時感染 C 型肝炎往往較無合併 HCV 感染者有嚴重之併發症，如肝衰竭及肝硬化[5-9]這些慢性之併發症往往會導致 HIV 病患住院日數增加及死亡[10-15]，此外 HCV 相關之其他病症包括腎絲球腎炎、葡萄糖不耐受症、冷凝蛋白血症等等容易加速糖尿病、腎臟及心血管疾病之發生[4]，目前在高效能的抗愛滋病毒藥物(HAART)廣泛的使用下，病患得以長期存活[16]，因此相關 C 型肝炎感染的併發症的發生機率逐漸增加，而且已成為西方國家的病患死亡的重要原因。C 型肝炎亦容易加速 HIV 感染病程之惡化導致愛滋病而增加死亡率[15,17,18]。

急性 C 型肝炎感染者約有一半以上會變成慢性 C 型肝炎(有人估計可高達百分之八十),而慢性 C 型肝炎約有百分之二十會變成肝硬化、肝衰竭及肝癌[5-9]，國外的研究顯示愛滋病患感染 C 型肝炎時會加速 C 型肝炎相關之慢性肝病如肝硬化及肝癌進行[8,9]，另外合併感染 HIV 及 HCV 的患者對於抗 HIV 藥物之反應亦比較差，因此容易進展成 AIDS。與未染有 C 型肝炎之病患相比較，患有 C 型肝炎患者之 HIV 病毒的進展與死亡率，皆是前者的三倍多[10-15]。原因是因為 C 型肝炎病毒會延遲免疫系統之重建與能對抗 HIV 病毒之 CD4 細胞的復原時間[19]。在過去 1994 年至 2002 年的流行病學追蹤中，我們報告臺灣愛滋病毒感染者約有 12%有慢性 C 型肝炎感染，這個盛行率雖然遠比台灣地區的一般非愛滋病毒感染者罹患慢性 C 型肝炎的比例(2%-4%)高很多，但與國外愛滋病患罹患 C 型肝炎的比例略低(約為 16-40%)，這是因為台灣地區在過去的愛滋病毒感染者鮮少有靜脈毒癮(2%)，仍以輸血或性行為感染為主。但是近年來靜脈毒癮患者的急速上升，台灣地區愛滋病患感染 C 型肝炎病毒的比例快速增加，因此臺灣地區 HIV 感染者合併 C 型肝炎病毒感染之臨床流行病學及其治療也越來越重要。

HCV 和 HIV 這兩種病毒感染間的交互作用，可以從 HIV 對於 HCV 感染的影響角度來看，也可以從 HCV 對 HIV 感染病程的影響角度來看。HIV 對於 HCV 感染的影響

角度來看，在研究中以施行肝臟切片，觀察發炎程度的文獻看來，大多得到一致的結果，即 HIV 感染者若同時有 HCV 感染時，他們的肝臟壞死發炎程度，會較沒有 HIV 感染的 HCV 感染患者，來得嚴重，而且 HCV 的病毒量也較高；如此，HCV 與 HIV 合併感染者，可能較沒有 HIV 感染的 HCV 感染患者容易發生慢性肝炎併發症。

慢性 HCV 感染對於 HIV 感染病程的影響，在過去的研究較少，而在高效能抗病毒藥物廣泛使用後，最近幾年中陸續出現了數篇大規模的觀察研究。這些研究都出自歐美國家，歐美國家的研究對象，主要是共用針頭的靜脈藥癮者，研究對象中高達 87%是靜脈藥癮者，同時並有 HIV 和 HCV 感染，包含法國、義大利和瑞士研究群所得的結果一致，顯示合併 HCV 感染的 HIV 患者，較易發生新的伺機性感染或腫瘤，較高的死亡機會；而合併 HCV 感染的 HIV 患者免疫功能的復原較慢或破壞較快。但是對於 HIV 病毒複製的控制，似乎不受有無合併 HCV 感染的影響。但是，Johns Hopkins 大學的研究人員以美國東北部巴爾地摩地區將近 2000 位 HIV 感染者為研究對象的研究中發現，研究對象約 45%是 HCV 慢性感染者，而且 HCV 感染者中，85%是靜脈藥癮者；這個研究追蹤期的中間值約為 2.19 年。研究開始時，僅有 13%接受高效能抗病毒藥物，在研究過程中，約有一半的人接受了高效能抗病毒藥物治療。在研究結束時，研究人員發現，不論是否有無 HCV 慢性感染，並不影響 HIV 病程進展到後天免疫不全症候群(acquired immunodeficiency syndrome; AIDS）和存活的機會。而免疫系統功能(CD4+免疫球)下降到少於 200/毫升的機會，也不受 HCV 慢性感染影響。這個研究發現，提供了初步令人振奮的訊息。因為，在過去長期以來 HCV 感染者，大多是靜脈藥癮者，他們被認為對於藥物和醫療照護的遵囑性較差，預期抗病毒藥物的療效較差；因此，醫生也較不願意給予靜脈藥癮者抗病毒藥物。但是，由此研究看來，只要接受了高效能抗病毒藥物，他們的治療成效似乎並不差，預後也和非 HCV 感染者並沒有統計學上顯著差異。這四個研究得到不一致的結果，大抵肇因於研究方法、對象、評估方式的差異。但是，從這四個研究結果看來，最終因末期慢性肝臟併發症而死亡的案例並不多。由此，我們尚不能忽視慢性 HCV 感染的影響，因為，這四個研究觀察時間最長為 33 個月，HCV 的影響恐怕得觀察 10 年到 20 年才能看得出來，但是，從非 HIV 感染者的觀察研究看來，HCV 確實增加慢性肝硬化與肝癌的機會。因此，針對併有 HIV 和 HCV 感染者，國外的研究人員紛紛進行大規模的治療試驗，以干擾素(interferon)和 ribaverin 合併治療 HCV 感染。由許多研究看來，是否有 HIV 感染並不影響他們接受抗 HCV 病毒治療的療效。

雖然學理上看來，併用 ribaverin 可能拮抗 zidovudine 或 stavudine 的抗 HIV 療效，似乎在臨床上實際影響並不存在，可能原因是，併用其他的蛋白胺抑制劑或非核酸反轉錄抑制劑時，抗病毒的功效已經很好，是否有 zidovudine 和 ribaverin 的拮抗作用，並不影響。至於接受抗 HCV 病毒治療的長期療效，能否降低慢性肝臟的併發症，一樣有待 10-20 年後的觀察，才能判斷。

抑制 HCV 病毒複製為治療 C 型肝炎的首要目的。每週注射三次傳統型干擾素 IFN，對於 HIV 感染者的病毒反應率（sustained virological response, SVR）約為 0~29%[20]。目前以長效型干擾素（pegylated-IFN）加上 ribavirin（雷巴威林） 48 週治療之 SVR 約為 28-44%，其中 HCV 基因型第一型之 SVR 約為 15-28%、第二型及第三型之 SVR 約為 60-70% [21, 22]。多變項統計分析顯示預測治療 SVR 之獨立因子為低 HCV 病毒量(HCVRNA＜400,000IU/mL)、非 HCV 基因型第一型、女性以及血液 CD4 淋巴球＞500cells/μL [21-23]。近年來有四個大型臨床研究比較 pegylated-IFN 150-180 g/週加上 ribavirin 800-1200 mg/天與傳統型 IFN 3 MU 每週三次加上 ribavirin 之療效分析[24-27]，這些研究皆收納血液 CD4 淋巴球較高(477-570cells/ L)的 HIV 患者，且超過 80%的患者接受三合一抗 HIV 病毒療法(82-94%)。接受 pegylated-IFN 組 48 週之 SVR 為 27-44%，其中 HCV 基因型第一型接受 pegylated-IFN 組之 SVR 為 14-38%，而非 HCV 基因型第一型接受 pegylated-IFN 組之 SVR 為 44-73%，而接受傳統型 IFN 組 48 週之 SVR 為 12-21%。另一個開放性研究(ACTG-A5071)以 24 週 pegylated-IFN 治療 HIV 患者之 SVR 為 27%（其中 HCV 基因型第一型為 14%，HCV 非第一型者為 73%）[28]，以 pegylated-IFN 治療 HCV 基因型第一型治療 24 週時 HCVRNA 測不到的患者，半年後有 52% HCVRNA 復發，而治療 HCV 基因型第二型或第三型 24 週時 HCVRNA 測不到的患者，半年後有 30-35% HCVRNA 復發[29, 30]。部份研究也發現在治療早期（≤12 週）若 HCVRNA 能降低 ≥2 $\log_{10}$ 以上時，才會有好的 SVR，因此對於以 pegylated-IFN 治療至 12 週時反應不好的患者（HCVRNA 仍測得到或 HCVRNA 下降未達 2 $\log_{10}$），可以考慮停止抗病毒治療[24, 25, 28]。使用較低劑量 RBV 800 mg/day 治療，有 25-35%HCV 基因型第一型者在停藥後 HCVRNA 復發[24, 26]。另一個研究 98 位以 pegylated-IFN 加上較高劑量 RBV（體重<65kg 者使用 800mg/day，

65-67kg 者用 1000mg/day，>75kg 者用 1200mg/day）來治療 HCV[31]，發現 HCV 基因型第一型及第四型的 SVR 之有無與血液的 RBV 血中濃度高低有關(RBV 濃度高者較容易達到 SVR)，而基因型第二型及第三型的 SVR 則無法以血液中 RBV 濃度預測[31]，HCV 患者若已進展為肝硬化並合併有肝代償失調症狀(如食道靜脈曲張出血、肝昏迷、腹水等)並不適合用 pegylated-IFN 治療[32, 33]。治療 HCV 的時機建議應於 CD4 淋巴球＞200 cell/ L [32-34]。CD4≦200 cell/ L 的 HIV 感染者應先治療 HIV 而非 HCV[24-27]。Ribavirin（雷巴威林）不可與 didanosine 一起服用（藥物性急性胰臟炎（pancreatitis）及乳酸中毒（lactic acidosis）之藥物交互作用明顯增加。使用干擾素常會造成 leukopenia（白血球低下）或 ribavirin 造成之貧血，因此應避免同時使用 zidovudine，必要時可考慮使用 growth factors（G-CSF 及 EPO）。由本研究看來以 Ribavirin 加上長效型 IFN 治療對於基因型第 1 型在治療結束後 6 個月只有 20%之治療反應率，而基因型非第 1 型者有 50%治療反應率，因此對於 HCV 基因第 1 型的治療在 HIV 患者應考慮延長至 48 週治療。

（五）結論與建議

從本地與國外經驗看來，在尚稱短期的觀察研究中，HCV 感染似乎沒有增加因肝病致死的機會，但 HCV 感染或 HBV 感染，確實會增加 HIV 患者發生急性肝炎的機會。HCV 感染與否，並不影響他們接受高效能抗病毒藥物後病毒量下降的反應。至於 HCV 是否影響免疫功能的復原，和加速 HIV 病程，仍有待更多的研究證實。以 Ribavirin 加上長效型 IFN 治療對於基因型第 1 型在治療結束後 6 個月只有 20%之治療反應率，而基因型非第 1 型者有 50%治療反應率，因此對於 HCV 基因第 1 型的治療在 HIV 患者應考慮延長至 48 週治療。

對於 HIV 合併 HCV 感染之追蹤和治療，建議所有 HIV 感染者，特別是靜脈毒癮者都應檢查 anti-HCV。若有進展為慢性肝病或肝功能異常時應作 HCV RNA 檢測。疑為 HCV 之急性感染，而 anti-HCV 檢測為陰性，應考慮作 HCV RNA 之檢測。HIV 合併 HCV 感染者皆需考慮 C 型肝炎之治療，但在 CD4 淋巴球小於 200/ L 的患者，需先治療 HIV，而非先考慮治療 HCV。CD4 淋巴球介於 201-350/ L 的患者，可考慮先治療 HIV，HIV 治療穩定之後再考慮治療 HCV。CD4 淋巴球大於 350/ L 的患者，可考慮治療 HCV。在治療 HCV 前，需檢測肝功能（AST、ALT）、HCV 基因型和病毒量，以及是否合併其他肝病或系統性疾病。開始治療前需要作肝病理檢查（血友病患者例外）以了解患者 HCV 感染程度與預後以決定治療方式。開始治療 HCV 前，可能要考慮患者接受三合一抗 HIV 療法是否達到穩定階段（CD4 是否持續增加，HIV 病毒量控制）。在三合一抗 HIV 療法的處方需避免 didanosine( ddI )及 stavudine( d4T )，因為與 ribavirin 之交互作用，可能造成乳酸中毒及肝代償失調。另外若有使用 zidovudine（AZT）造成骨髓抑制現象也需考慮停止 AZT 替換其他藥物。HIV 合併 HCV 感染者之治療，以長效性 pegylated interferon 及 ribavirin 合併治療為優先選擇，建議劑量為：① HCV 基因型第一型患者，依患者耐受程度，建議在體重≦75kg 時，使用 ribavirin 1000 mg/day 治療，而體重＞75kg 時，建議 ribavirin 1200 mg/day。HCV 基因型第二型及第三型，ribavirin 建議為 800 mg/day。HCV RNA 病毒量之測量，建議在 IFN 治療前、治療第 12 週、治療第 24 週及治療完成時（治療第 48 週），以及停藥後第 6 個月追蹤檢查。HIV RNA 病毒量則依據 CDC 標準每 3 至 6 個月檢查。HIV 合併 HCV 感染者，建議 peg-IFN 及 ribavirin

治療時間為48週，特別是HCV基因型第一型，而HCV基因型第二型及第三型可考慮治療至48週。治療前需檢測血液計數（CBC）（第2、4、6及每4週），血糖，肝腎功能（每4週），凝血時間，甲狀腺功能（每3至6個月），尿液懷孕檢測，治療期間需定期追蹤，而針對數值不正常可密切觀察追蹤，並需提醒患者注意避孕。對於臨床上明顯發生 ribavirin 或 pegylated IFN 相關副作用可考慮先減量使用，必要時需停止使用。Ribavirin 不可與 didanosine 一起服用（藥物性急性胰臟炎（pancreatitis）及乳酸中毒（lactic acidosis）之藥物交互作用明顯增加。使用干擾素常會造成 leukopenia（白血球低下）或 ribavirin 造成之貧血，因此應避免同時使用 zidovudine。必要時可考慮使用 growth factors（G-CSF 及 EPO）。

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## 參、圖表

表一、HIV 合併 HCV 感染患者與未有 HCV 感染之 HIV 患者臨床特質之比較

| 臨床特質 | HCV-感染者 (N=53) | HCV-未感染者 (N=387) | 統計 p 值 |
|---|---|---|---|
| 年齡(y)/年 | 39 (24-68) | 35 (15-75) | 0.01 |
| 性別 (男/女) | 51/2 | 354/33 | 0.23 |
| HIV 感染之危險因子 | | | |
| transmission (n=) (%) | | | <0.0001 |
| 雙性戀/同性戀 | 23 (43.4) | 215 (55.6) | |
| 異性戀 | 19 (35.8) | 157 (40.6) | |
| 靜脈毒癮 | 9 (17.0) | 3 (0.8) | |
| 輸血 | 1 (1.9) | 1 (0.2) | |
| 未知 | 1(1.9) | 11 (2.8) | |
| 資料收集年代 | | | |
| Pre-HAART (n=) (%) | 11 (20.8) | 84 (21.7) | 0.87 |
| Post-HAART (n=) (%) | 42 (79.2) | 303 (78.3) | |
| 以前未接受愛滋病毒治療(%) | 79.3 | 76.2 | 0.632 |
| 基礎 CD4+ (range) | | | |
| (x $10^6$/L) | 59 (1-794) | 46 (0-1,202) | 0.29 |
| CD4+<200 x $10^6$/L (%) | 74.5 | 75.1 | 0.521 |
| 200≤CD4+<350 x $10^6$/L (%) | 9.8 | 13.8 | |
| ≥350 x $10^6$/L (%) | 15.7 | 11.1 | |
| 基礎 HIV 病毒量 PVL (range) | | | |
| ($log_{10}$ copies/ml) | 5.32(2.60-5.88) | 5.32 (2.60-5.88) | 0.96 |
| ≥5 $log_{10}$ (%) | 75.0 | 64.2 | 0.27 |
| 發生伺機性感染比率(%) | 56.6 | 55.6 | 0.89 |
| 基礎 GOT (range) | | | |
| (U/ml) | 42 (18-170) | 33 (1-164) | 0.006 |
| 基礎 GPT (range) | | | |
| (U/ml) | 33 (9-170) | 24 (8-170) | 0.08 |
| 接受 HAART 比例 (%) | 88.7 | 84.0 | 0.37 |

表二、HIV 患者合併感染 HCV 與未合併感染 HCV 患者之預後分析

| 預後 | HCV 感染者 (N=53) | HCV 未感染者 (N=387) | Odds Ratio or Hazard Ratio Adjusted (95% CI) | Statistics 統計 P 值 |
|---|---|---|---|---|
| 急性肝炎 (%) | 39.6 | 16.3 | | |
| Overall incidence (per 100 PY) | 13.89 | 6.39 | 2.769 (1.652-4.640) | 0.0001 |
| Before HAART | 6.78 | 10.41 | 1.083 (0.124-9.467) | 0.94 |
| After HAART | 17.87 | 7.22 | 3.338 (1.929-5.774) | <0.0001 |
| 患者達到病毒測不到(≤400copies/ml)之比例 (%) | 76.7 | 74.9 | 1.105(0.521-2.343) | 0.80 |
| CD4 值上升≥100 x $10^6$/L(%) | 57.1 | 58.0 | 1.000(0.509-1.965) | 1.00 |
| CD4 淋巴球數上升(%) | 38.1 | 39.7 | 0.957(0.487-1.881) | 0.90 |
| 抗 HIV 病毒療法失敗之比例(%) | 39.5 | 35.2 | 1.084(0.563-2.087) | 0.81 |
| 新伺機性感染之發生率(%) | 39.6 | 20.9 | | |
| Overall incidence(per 100 PY) | 21.16 | 13.29 | 1.826 (0.738-4.522) | 0.01 |
| 粗死亡率 (per 100 PY) | 7.94 | 9.74 | 0.781 (0.426-1.432) | 0.42 |
| HAART 之前 | 13.56 | 35.15 | 0.465 (0.108-2.004) | 0.30 |
| HAART 之後 | 4.70 | 7.97 | 0.500 (0.199-1.255) | 0.14 |

表三、13 位合併 HIV 與 HCV 感染之患者接受 Rivavirin 及 Peg-INF 治療之追蹤

| 患者 | HCV 基因型 | 病毒量<br>第 0 週 | 開始治療<br>第 4 週 | 開始治療<br>第 12 週 | 結束治療<br>第 24 週 | 結束治療後<br>第 24 週 | SVR |
|---|---|---|---|---|---|---|---|
| 1 | 2a | 212000 | 8280 | <86 | <86 | 82100 | - |
| 2 | 2b | 104000 | 2670 | <86 | <86 | <86 | + |
| 3 | 1b | 784000 | 134000 | <86 | 3660000 | 29100000 | - |
| 4 | 1a | 4030000 | 2670 | <86 | 1370000 | 14400000 | - |
| 5 | 1a+1b | 25300000 | 237000 | 76200 | 10500 | 28100000 | - |
| 6 | 2a | 1740000 | <86 | <86 | <86 | <86 | + |
| 7 | 1b | 32900000 | 173000 | <86 | <86 | 8280 | - |
| 8 | 1b | 246000 | <86 | <86 | <86 | <86 | + |
| 9 | 2a | 144000 | <86 | <86 | <86 | <86 | + |
| 10 | 2a | 27900000 | <86 | <86 | <86 | <86 | + |
| 11 | 2a | 54100000 | <86 | <86 | <86 | 1180000 | - |
| 12 | 2a | 3400000 | 31400 | <86 | <86 | 246000 | - |
| 13 | 2a | 611000 | 123000 | <86 | <86 | 61400 | - |

SVR : Sustained virologic response (HCV)

附件六

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 愛滋病毒感染之毒癮患者之病毒性肝炎流行病學
# Epidemiology of Hepatitis markers in HIV-infected intravenous drug users

研 究 報 告

執行機構：台大醫院愛滋病防治中心

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執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共 22 頁

壹、中文摘要：

自民國 94 年 4 月 1 日至民國 96 年 10 月 31 日，共 709 位 HIV 感染者曾至台大醫院雲林分院就醫，其中 672(94.8%)位為經由靜脈注射海洛英感染到 HIV；這 672 位患者中，45 位(6.7%)為女性患者，627 位(93.3%)為男性患者；其年齡之中位數為 33 歲(範圍 19 至 60 歲)，CD4 之中位數為 390 cells/mL (範圍 10-1943 cells/mL)；病毒量之中位數為 4.03 $\log_{10}$ copies/mL (範圍 2.60-5.88 $\log_{10}$ copies/mL)。曾感染過 A 型肝炎者佔 60.7%；而 B 型肝炎帶原者佔 20.2%；149 位曾接受 HBV DNA 檢查者，49 位有偵測到 HBV DNA，其中 41 人(83.7%) HBV genotype 為 B，3 人(6.1%)為 B+C，5 人(10.2%)為 genotype 為 C。C 型肝炎病毒感染高達 99.3%；92 曾接受 HCV RNA 檢查者中，71 人有測到 HCV RNA，其基因型為 1a(16, 22.5%)、1b(12, 16.9%)、2a(41, 57.7%)、2b(2, 2.8%)。在就醫時曾接受過肝功能檢查的患者中，21.0%和 10.9%的病患其 GPT 及 GOT 高於正常值兩倍以上；在曾接受至少兩次以上肝功能檢查的患者中，其 GPT 的最高值，有 14.8%高於正常值三倍以上，GOT 的最高值，有 8.4%高於正常值三倍以上。

關鍵詞：A 型肝炎病毒、B 型肝炎病毒、C 型肝炎病毒、愛滋病毒感染、靜脈注射藥物使用者

## 貳、英文摘要

Among 709 HIV-infected patients seeking medical care at National Taiwan University Hospital, Yun-Lin Branch, 672 (94.8%) were intravenous drug users (IDUs) with median age of 33 years (range 19-60 years). There were 46 woman (6.7%) and 627 man (93.3%), and their median CD4 and plasma HIV RNA load were 390 cells/mL (range, 10-1943 cells/mL) and 4.03 $\log_{10}$ copies/mL (range, 2.60-5.88 $\log_{10}$ copies/mL). The prevalence of hepatitis A infection, hepatitis B carrier, and hepatitis C carrier was 60.7%, 20.2%, and 99.3%, respectively. Their HBV genotype were B (41, 83.7%), B/C (3, 6.1%), and C (5, 10.2%) among 41 patients with detectable HBV DNA. The HCV type of 71 patients with detectable HCV RNA were 1a (16, 22.5%), 1b (12, 16.9%), 2a (41, 57.7%), and 2b (2, 2.8%). Among patients with available baseline liver function tests, 21.0% and 10.9% of them had GPT and GOP level 2 times higher than the upper limit of normal. Among patients with followed liver function tests, 14.8% and 8.4% of them had GPT and GOT level 3 times higher than the upper limit of normal.

Keywords: Hepatitis A virus, hepatitis B virus, hepatitis C virus, HIV, intravenous drug user

## 參、本文

### （一） 前言

國內近年來，HIV 病毒藉由毒癮者施打毒品時，共用注射針具或共用稀釋液的危險行為，在毒癮者間快速傳播，使得國內每年感染 HIV 病毒個案增加的速度，從以往大概每年20%的成長(民國 83 年至 92 年之十年間；民國 92 年感染 HIV 病毒人數 861 人)，在民國 93 年增為 77%(民國 93 年感染 HIV 病毒人數 1520 人)，在民國 94 年更呈 123%成長(民國 93 年感染 HIV 病毒人數 3400 人)。民國 93 年起，毒癮 HIV 個案佔當年度通報數之 39%，首度超越男同性間性行為感染之百分比(含雙性戀合佔當年通報數之 32.5%)；民國 94 年毒癮 HIV 個案呈壓倒性多數（佔當年度通報數之 67%，即三個感染個案中有兩個來自毒癮者)，超越男同性間和異性間的總合(合佔通報數之 21%) [1、2]。另外，經由共用注射針或共用稀釋液，毒癮者除感染 HIV 病毒外，傳播途徑相同之 B 型或 C 型肝炎病，亦會在毒品使用者間傳播；而毒癮患者本身又是罹患 A 嫌肝炎的高危險群 [3]。根據以往國外相關的報告，這些肝炎病毒在國內這群病人的盛行率，及彼此對病患所造成之影響，有待研究。

近年來年毒癮戒治所和監獄的資料，使用靜脈毒品注射者，其 anti-HCV antibody 的盛行率可高達 66.4%至 89.8% [4-6]，而一般台灣民眾 anti-HCV antibody 的盛行率僅有 2-5% [7]。另外，台灣在 1984 年施行全國新生兒免費 B 肝炎疫苗注射前，一般民眾 HBsAg 的盛行率約為 15%-20%左右 [8、9]，而在台北及高雄毒癮戒治所，於 1986 及 1988 年於毒癮患者間所做的調查，可知其 HBsAg 的盛行率亦約在 15.8%(毒癮者)至 22.1%(靜脈毒癮者)左右 [10、11]。再者，於臺大醫院就醫的 HIV 感染者中，同時感染 HBV 者高達 21.7%，，同時感染 HCV 者有 12.0% [12、13]。

近年來台灣因為公共衛生之進步，根據 1999 年對台北市民所曾感染過 A 型肝炎有抗

體者，在年紀一至二十歲者僅佔 1-4.8% [14]，意味國內在年輕的一輩，有很多人可感染 A 型肝炎。A 型肝炎主要傳播途徑為糞口傳染，在毒癮患者間屢有疫情爆發的報導 [15-23]；美國 CDC 將使用毒品者(不論是使用靜脈注射或其他方式吸毒)，列為感染 A 型肝炎病毒的高危險群，建議需施打 A 型肝炎 [3]。雖然 A 型肝炎病毒致命危險低，也不像 B 肝或 C 肝會造成慢性帶原，不會引發肝硬化或肝癌，但仍有很少數人會變成猛暴性肝炎，導致死亡；尤其以年紀大之病患 (死亡率在小於 14 歲者為 0.14%，但在大於 40 歲者為 1.52%) [24、25]，或同時為慢性 C 型肝炎病毒帶原者，死亡率更高 [26]。

單獨存在抗核抗體 (Isolated anti-HBc antibody，antiHBcAb)的表現在同時有 HBV 和 HIV 感染的患者，和僅感染 HBV 的患者不同；其所代表的意義可能有以下三種情況：1)假陽性；2)病人曾感染 HBV，但已痊癒，不過血中 anti-HBsAb 的量低到測不到 3)病人為 B 型肝炎帶原者，但血中 HBsAg 的量低到測不到 [26]；在一般的捐血者，血中帶有單獨存在抗核抗體的比例僅 2-5% [27-30]，但在感染 HBV 之 HIV 患者，此比例可高達 42%-80.7% [31、32]。有些研究偵測這些病人的血液是否有 HBV DNA 存在，測到的比例有低至 0% [33]，亦有高達 89.5% [34]。當 HIV 感染病患有單獨存在之抗核抗體，是否該接收疫苗注射，目前仍無定論。

HIV 和 HBV 合併感染，可能會增加肝硬化的機會及引起和肝臟相關之疾病 [35-37]。在美國追蹤 5293 位男同志的研究中，觀察到同時感染 HIV 及 B 型肝炎病毒的患者，其和肝臟相關之死亡率，遠高於僅感染 B 型肝炎病毒者(14.2/1000 人年 vs. 0.8/1000 人年)。在使用 HAART 後，和肝臟相關之死亡率更增加兩倍(使用 HAART 前：12.3/1000 人年；使用 HAART 後：24.7/1000 人年) [36]。感染 HBV 之 HIV 感染患者在接受 HAART 後，較無感染 HBV 之 HIV 感染患，易產生和 HAART 相關之肝毒性 [12、38]。

在長期追蹤性的研究中，慢性 C 型肝炎病患約有 2-20%在 20 年內進展至肝硬化 [39]。若病患有酒精的使用、年紀大、或 HIV 感染，則 C 型肝炎進展成肝硬化的速度會加快 [39-41]。同時感染 HCV 和 HIV 的病患，較僅感染 HCV 的病患，進展至肝硬化之機會高 3 倍 [40]。不少研究顯示，同時感染 HIV 及 HCV 者，較有機會罹患和末期肝病相關之疾病或因此而死亡 [42-45]。在綜合 8 個研究之 meta-analysis 報告中，同時感染 HIV 及 HCV 者進展成肝硬化的速度較僅感染 HCV 者為快，且肝功能喪失(de-compensated liver disease)的機會較僅感染 HCV 者有 6 倍之高 [40]。在另一個研究中，肝癌在同時感染 HIV 及 HCV 患者較僅感染 HCV 者容易在較年輕的年紀產生，且存活期較短 [46、47]。有慢性 C 型肝炎之 HIV 感染患者在使用 HAART 時，易產生和藥物相關之肝毒性 [48]。另外在治療方面，同時感染 HIV 和 HCV 且 HCV genotype 為 1 之病患，治療前 HCV 病毒量大於 800,000 IU/ml 者較 HCV 病毒量小於 800,000 IU/ml 者，治療後 72 週之持續病毒抑制效果低(18% vs. 61%)；但 genotype 2 和 3 並無相類似的觀察 [49]。

有鑑於上述關於 HIV 對各種病毒性肝炎病毒病程及預後之影響，在最近這群新感染到 HIV 之靜脈毒癮者，其各種病毒性肝炎病毒之盛行率及發生率，及相關之罹病率、死亡率有必要了解。

（二）材料與方法

在台大雲林分院就診[包括雲林監獄(第一監獄、第二監獄)、嘉義監獄入獄者]的愛滋病毒(HIV)感染之毒癮患者，收集相關之臨床資料(使用靜脈注射毒品時間長短、急性肝炎發作、肝硬化、或肝癌)、檢測其血中 anti-HAV IgG、HBsAg、HBsAb、HBcAb、anti-HCV 之有無、每三至四個月追蹤血中之 CD4，肝功能相關指數(CBC、GOT/GPT 等)，HBV、HCV、愛滋病毒之病毒量。

## （三）結果

自民國 94 年 4 月 1 日至民國 96 年 10 月 31 日，共有 709 位 HIV 感染者至本院雲林分院就醫，其中 672(94.8%)位為經由靜脈注射海洛英感染到 HIV。這 672 位患者中，45 位(6.7%)為女性患者，627 位(93.3%)為男性患者；其年齡之中位數為 33 歲(範圍 19 至 60 歲)，CD4 之中位數為 390 cells/mL (範圍 10-1943 cells/mL)；病毒量之中位數為 4.03 $\log_{10}$ copies/mL (範圍 2.60-5.88 $\log_{10}$ copies/mL)。

至 10 月底為止，共 242 人接受 anti-HAV IgG 的檢查，其中 147 (60.7%)人為陽性；若照年紀將病患分組，可看到年紀 21-25 歲之患者，僅 4.8%的人曾感染過 A 型肝炎，但年紀 26-30 歲之患者，A 型肝炎病毒感染之盛行率升至 25.0%，年紀 31-35 歲之患者至 69.4%，年紀 36-40 歲之患者至 84.4%，年紀 40 歲以上，高達 96.7 至 100%(如圖一)。

571 人曾接受 anti-HCV 檢查，有高達 99.3%(567 人)的患者感染到 C 型肝炎病毒(HCV)；且不論年齡層如何，HCV 感染比例皆接近 99-100%(如圖一)；這些 HCV 感染者中，92 位曾接受 HCV 病毒量及基因型檢查。71 人有測到 HCV RNA，其病毒量之中位數為 659,000 copies/mL(範圍 1,250-7,940,000)。其基因型為 1a(16, 22.5%)、1b(12, 16.9%)、2a(41, 57.7%)、2b(2, 2.8%)。

579 位病患曾接受 HBsAg 血清學檢查，其中 20.2%(117 人)的病患為 B 型肝炎帶原者。在 507 位(75.4%)同時有接受 HBsAg、anti-HBs、anti-HBc 檢查的病患中，75 位(14.8%) anti-HBsAb 的產生是因接受 B 型肝炎疫苗注射[HBsAg(-)，anti-HBs(+)，

anti-HBc(-)]；233 位(46.0%)是因感染 B 型肝炎病毒後，自身產生 anti-HBsAb [HBsAg(-)，anti-HBs(+)，anti-HBc(+)]；82 位(16.2%)帶有「單獨存在抗核抗體」[HBsAg(-)，anti-HBs(-)，anti-HBc(+)]；20 位(3.9%)未曾接觸過 B 型肝炎病毒[anti-HBs[HBsAg(-)，anti-HBs(-)，anti-HBc(-)]。在不同的年齡層中，B 型肝炎血清學變化詳見圖二。143 位病患曾接受 HBV DNA 的檢測，其中 49 人測到 HBV DNA，其病毒量的中位數為 11280 copies/mL(範圍 438.7-619,200,000 copies/mL)，其中 41 人(83.7%) genotype 為 B，3 人(6.1%)genotype 為 B+C，5 人(10.2%)為 genotype 為 C。在 82 位帶有「單獨存在抗核抗體」的病患中，有 64 人曾檢測 HBV DNA，其中 8 人(12.5%)有測到 HBV DNA。

518(77.1%)及 530 人(78.9%)在剛開始就醫時曾接受過 GPT(中位數 42 IU/mL, 7-704 IU/mL)及 GOT(中位數 32 IU/mL, 12-334 IU/mL)檢查，其中各有 109 人(21.0%)和 53 人(10.9%)的 GPT 及 GOT 高於正常值兩倍以上；264 人及 262 人至少有兩次以上的肝功能檢查；其 GPT 的最高值，有 39 人(14.8%)高於正常值三倍以上，有 19 人(7.2%)高於正常值五倍以上，有 3 人(1.1%)高於正常值十倍以上；其 GOT 的最高值，有 22 人(8.4%)高於正常值三倍以上，有 11 人(4.2%)高於正常值五倍以上，有 2 人(0.8%)高於正常值十倍以上。

（四）討論

在本研究中可看到感染 HIV 的毒癮患者，同時有 C 型肝炎感染者高達 99.3%，B 型肝炎帶原者亦有 20.2%。雖然目前大部分的病患 CD4 仍高，不需接受雞尾酒治療，但隨著時間過去，因本研究觀察時間過短，無法看出這些病毒肝炎感染之相關罹病率、死亡率；但根據本研究結果，基礎值肝功能異常者(GPT 或 GOT 高於正常值兩倍以上)佔 10.9-21.0%，在有接受肝功能接受者中，有 14.8%的病患 GPT 高於正常值三倍以上，8.4%的病患 GOT 高於正常值三倍以上，可見有急慢性肝炎的患者在這族群中所佔的比例不小；將來在照顧這些病患時，HBV 或 HCV 感染的併發症，如急性肝炎發作、肝硬化、食道或胃靜脈瘤出血、或肝癌勢必在未來幾年為照顧這些 HIV 感染者之重要課題。因肝膽腸胃科醫生主導國內病毒性肝炎之併發症處理及肝炎治療，有必要給予相關教育訓練，以免屆時沒有醫生願意治療病患。再者，公衛護士入監教育病患時，除 HIV 相關之知識，也應告知病毒肝炎感染之相關知識；再者，因目前對 HBV 及 HCV 肝炎治療已有有效藥物治療，在可考慮制定出準則，讓成功戒毒或規則服用美沙酮之患者接受肝炎治療。另外 20 位未曾接觸過 B 型肝炎病毒且無抗體者，更應建議其接受 B 型肝炎疫苗注射，以避免感染 B 型肝炎病毒。

隨著台灣公共衛生的進步，一般年輕民眾(一至二十歲者)A 型肝炎感染的盛行率下降至 1-4.8% [14]，本研究中亦觀察到此現象，年齡層在 21-25 歲中患者，曾感染 HAV 的盛行率僅 4.8%，意味著有高達 90%的年輕族群可被 A 型肝炎感染；根據國外的研究，成年人的 A 型肝炎感染症狀較嚴重，亦可能變成猛暴性肝炎，且若同時為慢性 C 型肝炎病毒帶原者，死亡率更高[26]。在本研究的年輕族群中，其慢性 C 型肝炎病毒帶原者高達 99.3%，為感染 A 型肝炎且有併發症之高危險族群。因目前 A 型肝炎疫苗對預防 A

型肝炎感染十分有效，在經費許可下，可考慮給予 A 型肝炎疫苗注射，以減少未來感染 A 型肝炎的機率，進而避免可能之猛暴性肝炎或肝衰竭。本研究因觀察時間過短，無法看出 A 型肝炎感染的發生率。

本研究中有 16.2%的病患帶有 B 型肝炎之「單獨存在抗核抗體」，和一般的捐血者相較(2-5%)[27-30]，此種血清學表現在本研究病患中之盛行率偏高(16.2%)，但和其他 HIV 感染者相較(42%-80.7%)卻是偏低[31、32]；在本研究的這些病患中，有近 12.5%的病患可偵測到 B 型肝炎病毒；因目前僅做了一部分病患之 HBV DNA 測定，更詳細之分析，有待之後的結果。本研究中 B 型肝炎病毒的 genotype 以 B 為主(83.7%)，而 C 型肝炎病毒基因型以 type 1 為主(1a 16, 22.5%; 1b 12, 16.9%)，皆為國內常見之基因型。另外，國內其他研究者所報告在國內感染 HIV 和 HCV 之毒癮者所見之 HCV 基因型 6a，在本研究中卻沒有看到，可能是因目前僅做了一部分病患之 HCV RN 檢測。

## （五）結論與建議

1. HBV 或 HCV 感染的併發症勢必在未來幾年為照顧感染 HIV 的毒癮患者之重要課題；因目前對 HBV 及 HCV 肝炎治療已有有效藥物治療，可考慮制定出準則，讓成功戒毒或規則服用美沙酮之患者接受肝炎治療。

2. 年輕族群中感染 HAV 的比例偏低，若經費許可，可考慮給予 A 型肝炎疫苗注射，以減少未來感染 A 型肝炎的機率，進而避免可能之急性肝炎或肝衰竭發作。

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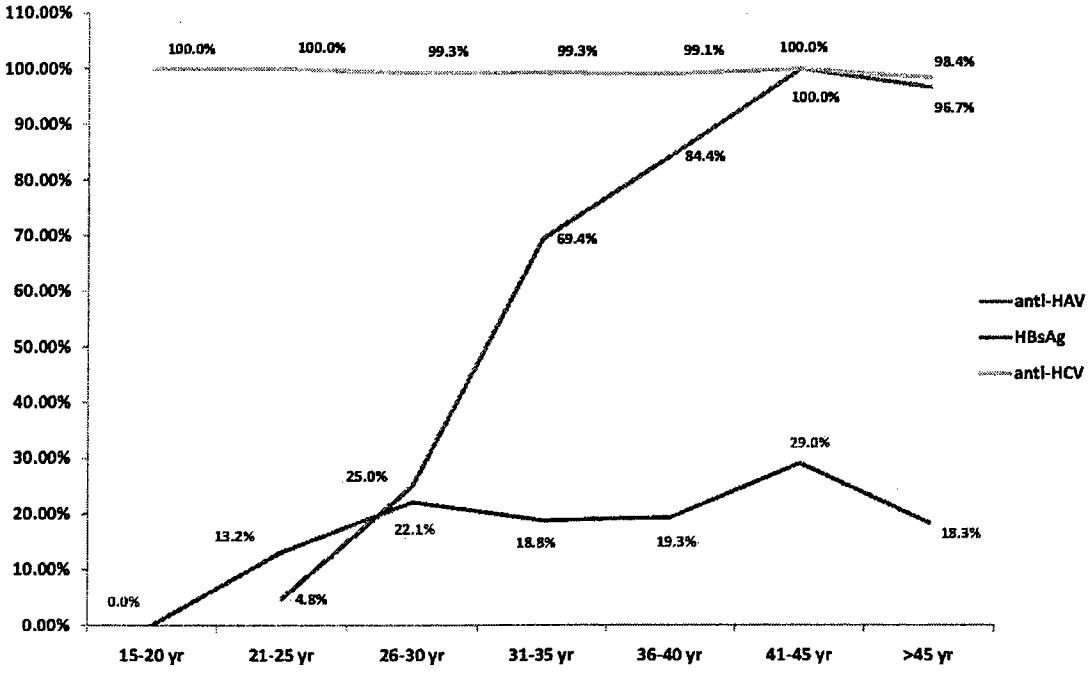
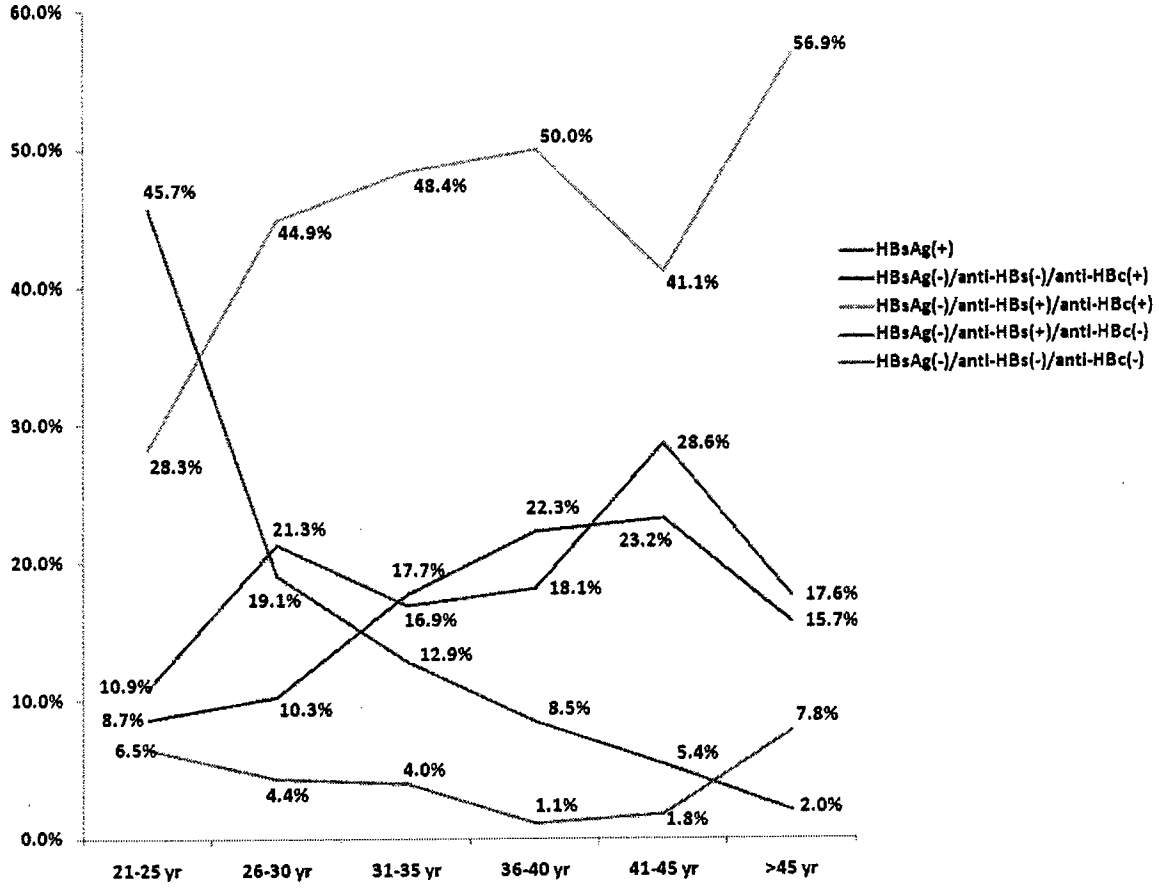
表一、感染 HIV 之靜脈注射藥物使用者之基本資料。

| | Data |
|---|---|
| Patient number | 672 |
| Men, n (%) | 627 (93.3) |
| Median age, range, yr | 33, 19-60 |
| 15-20 yr, n (%) | 4 (0.6) |
| 21-25 yr | 62 (9.2) |
| 26-30 yr | 178 (26.5) |
| 31-35 yr | 160 (23.8) |
| 36-40 yr | 123 (18.3) |
| 41-45 yr | 73 (10.9) |
| >45 yr | 72 (10.7) |
| Median CD4 cells/μL, range (patients no. with data) | 390, 10-1943 (573) |
| <200 cells/μL, n/N (%) | 31/573 (5.4) |
| 200-350 cells/μL | 201/573 (35.1) |
| >350 cells/μL | 341/573 (59.5) |
| PVL $\log_{10}$ copies/mL | 4.03, 3.60-5.88 (570) |
| >5 $\log_{10}$ copies/mL, n/N (%) | 30/570 (5.3) |
| Positive anti-HAV antibody, n/N (%) | 147/242 (60.7) |
| Positive anti-HCV antibody, n/N (%) | 567/571 (99.3) |
| Positive HBs Ag, n/N (%) | 117/579 (20.2) |
| Patients with 3 HBV markers measured, n (%) | 507 (75.4) |
| HBsAg (+), n/N (%) | 97/507 (19.1) |
| HBsAg (-), n/N (%) | 410/507 (80.9) |
| Anti-HBs(-)/anti-HBc(+), n/N (%) | 82/507 (16.2) |
| Anti-HBs(+)/anti-HBc(+) | 233/507 (46.0) |
| Anti-HBs(+)/anti-HBc(-) | 75/507 (14.8) |
| Anti-HBs(-)/anti-HBc(-) | 20/507 (3.9) |

圖一、在不同年齡層中，感染 HIV 之靜脈注射藥物使用者之 A (anti-HAV)、B (HBsAg)、C (anti-HCV)型肝炎感染之盛行率。



圖二、在不同年齡層中，感染 HIV 之靜脈注射藥物使用者之不同 B 型肝炎血清學之盛行率。



附件七

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 第一與第二孕程愛滋病毒的母子垂直傳染

研 究 報 告

執行機構：台大醫學院附設醫院婦產部

計畫主持人：吳明義

執行期間：96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共9頁

## 中文摘要

婦女與新生兒 HIV 的感染，在過去幾年中已漸漸有定論，政府機關也著手全面篩檢，這部分的工作已經穩定前進中，約有 70-85%的人有篩檢到。但是不是馬上需要 HAART 的治療？還有，什麼時候開始用？選哪一些藥物？用到什麼時候停？太早給藥，如第一孕程，得到的好處跟胎兒潛在的畸形危險，或媽媽胃口的降低，與這些壞處比起來，值不值得？可惜文獻上的早期懷孕作胎兒 HIV 檢驗的報告，人數都很少，結論無法真正說服人。但多年臨床經驗看來，子宮收縮，或母血胎兒血少量互通，是有很多證據的。本實驗用兩種 HIV-1 特異性的抗原，作組織免疫染色，結果在蛻膜組織看得到抗原陽性，但那是代表母親，非胎兒部分。反而在胎盤，或胎兒器官，如肝臟、肺臟、脾臟或腦部，都是陰性反應。所以沒有證據證明，早期胚胎會受到垂直感染。既然如此，目前政府給藥政策就無須改變，亦即，14 週以後才開始給 HAART 的藥物治療。但是，以後如果有新的證據，還可以再討論。



中文關鍵詞(至少三個)：人類免疫缺乏病毒 (HIV)，免疫染色，早期懷孕

英文摘要

At present, the vertical transmission rate of HIV-1 could be reduced to 2% or so. We may consider about the risk of mother-to-child transmission of HIV-1 at early stage of pregnancies. However, antiretroviral therapy (ART) in early pregnancy substantially may reduce the risk of vertical transmission, but concerns exist about the potential for teratogenic effects. Previous literature showed some cases with HIV-1 existence in the fetal tissue of early pregnancies; however, the cases number was so small. This study was undertaken to check the immunohistochemistry (IHC) evidence of HIV-1 in early pregnancies. In the decidual tissue, we proved the HIV-1 positive, but negative in the placenta, fetal brain, spleen, liver and lung. So according to this study, it is not necessary to change our present policy that we gave the HAART from the gestational age of 14 weeks. These findings are reassuring, but continued monitoring is essential in view of the increasing case number in the future.

**Key words:** human immunodeficiency virus、immunohistochemistry (IHC)、early pregnancy

## I. 前言

台灣目前感染人類免疫缺乏病毒 (HIV)者，依據衛生署疾病管制局 96 年 9 月底的資料(*衛生署，2007 年 9 月*)，累計共 15,183 人。其中本國籍為 14,550 人，女性感染者累計 1,323 人(9.09%)，其中經由『異性戀途徑』傳染者 546 人，約佔女性感染者的 41.27%。以 2005 年而言，共有 45 個愛滋孕婦，47 例生產，其中只有 23 位採取剖腹產，不到一半的比率(48.9%)。預防性投藥情形為，28 週前投藥者有 13 位(27.7%)，之後投藥者有 10 位(21.3%)。產下嬰兒共 43 個，已知有 5 個小孩受感染，其他仍在追蹤當中。垂直傳染的部分，在近幾年國內外的醫療同仁的共識下，已經有列出幾個原則：第一，做孕婦的 HIV 篩檢，目前在台灣地區已經從 94 年 1 月開始，全面由衛生署提供免費的篩檢，共有 235,791 人接受篩檢，檢出 28 人，陽性率為 0.011%。第二，HIV 陽性者孕婦，必須接受適當藥物治療。第三，生產方式，要採取排程剖腹產，減少垂直感染機會。第四，不可哺餵母奶，必須以配方奶來餵食嬰兒。目前為止，已經發現到 12 位有垂直感染的案例，都是沒有遵照前面步驟的不幸結果。在垂直傳染的預防上，政策法令的規定或醫療處置的原則都已經很明確，比較沒有爭論。

我們目前 HIV 篩檢都在懷孕第一次產檢就執行，也就是在 10 週之前就可知道，或有些還沒懷孕就知道有 HIV (註：2005 年有 40%的愛滋孕婦不是經由篩檢得知)，或有些人目前有愛滋帶原，但對懷孕的垂直傳染安全性有疑慮。其中的問題是大家知道要預防性給藥，但是大家都在第二孕程才給，怕的是藥物的致畸胎作用，儘管有些藥都是 FDA 分類上屬於 category B 的藥*(Watts H, 2006)*。但問題是第一孕程感染的機會有多少？如果有，是不是要鼓勵早一點給藥？甚至懷孕前已知有病毒帶原者，即使 CD4 細胞或血漿病毒量沒有達到所謂的治療起始點，若想要懷孕者，是否也要開始給藥治療？

1990 年代初期，由於沒有完善的抗 HIV 治療，所以母子之間傳染性蠻高的，歐美地區達 14-33%，開發中國家更高達 43%。這些感染可以發生在子宮內(約 25-30%)，也可以發生在生產時或產後授乳時期(約 70-75%) *(Landesman SH, 1996)*。懷孕期間子宮內的傳染，抗 HIV 藥物的使用，在這幾年起了一些重要的變革。雖然藥物使用有一些危險，但是對於預防母子之間的傳染，還有母親本身健康的改善，都有益處。所以從 1994 到 1999 的各個時間段落比較中發現*(Minkoff H, 2001)*，懷孕期間使用抗 HIV 藥物的人，尤其是高效能藥物的比例逐年升高(從 0 %上升 到 42.1%)，CD4 細胞數也明顯增加了。一項研究顯示*(Sperling RS, 1996)* ，如果在懷孕 14 週就開始使用 ZDV，直到出生後 6 週，垂直感染機會可以降低三分之二（從 placebo 的 22.6%降到 ZDV 的 7.6%）。Lindergren 等人*(Lindergren ML, 1999)*的報告甚至可降低八成的感染。如果不想使用那麼久，短時間使用抗 HIV 藥物有沒有效呢？如果到 36 週才開使用，像非洲國家，成本可以比較便宜，約可降低 50%左右的垂直感染*(Shaffer N, 1999)*。

泰國一份報告顯示，早在第二孕程，就有 4.9%的胎兒受到 HIV 的感染*(Phuapradit W, 1999)*，這是可以理解的，因為在第二孕程中，偶爾還是會有子宮收縮的情形，病毒傳染是可能的。尤其，此報告中的流產胎兒，都是採用陰道生產，子宮內壓力更大，病毒

通過胎盤機會更多。但之前稍早的報告，不管是用 PCR 或病毒培養的方法，都顯示很多胎兒器官，在早期就已經有 HIV 的侵犯。但最近有南非一項報告指出*(Mohlala BK, 2005)*，如果在沒有子宮收縮情況之下，抽取羊水與臍帶血，儘管孕婦 HIV 的 RNA copies 平均已高達 33,700，結果羊水與臍帶血內都沒有 HIV 的存在，這一點推翻了產前 transmission 的說法。關於第一孕程，到底有沒有病毒穿過胎盤呢？理論上會有，因為在超音波檢查時，偶爾會看到 myometrial thickening，就是一種子宮收縮，子宮腔裡有血塊也很常見，懷孕初期在母血裡偶爾可以找到胎兒的血球細胞*(Krabchi K, 2006)*，所以 HIV 病毒的穿過也是很可能。在 8 週懷孕的案例中，就有報告胎兒的血球的前身細胞與巨噬細胞，發現有 HIV 的存在*(Lewis SH, 1990)*。因此最近的研究都建議，可以在第一孕程就使用藥物，而先天異常的機會並不會因此而升高*(Bucceri AM, 2002. Townsend CL, 2006)*。

WHO 目前對於 HIV 孕婦，若未達到治療標準者，建議 28 週開始用 AZT，固然有其世界觀，因為很多國家很貧窮。台灣目前則建議 14 週開始使用 HAART，因為台灣比較有錢。歐洲的英國義大利甚至建議全孕程使用 HAART，實際上經濟與醫療照護是相關的。目前的治療方式，如果只有 C/S，有 HAART 與沒有 HAART 之間的差異，前者是 2%，後者卻有 10.4%的垂直傳染機會*(The International Perinatal HIV group, 1999)*。這 2%可能是之前就已經感染的案例，透過本計畫，可以提供更準確的證據，來決定是否要擴充治療於第一孕程。

## II. 材料與方法

**實驗地點：**

臺大醫院婦產部

**實驗對象：**

HIV 陽性的孕婦，懷孕中期或初期，徵得書面同意之下，盡量收集胎兒器官檢體，利用 ISH 檢測 HIV-1 的抗原。

**實驗期間：**

從 2006 年 1 月 1 日迄 2006 年 10 月 31 日。

**實驗方法：**

(1)<u>檢體收集</u>：要有書面的 informed consent，用 PBS 清洗過後，小心取得胚胎之組織，用 direct cover vitrification (DCV)方法，予以冷凍，將來一起做檢驗。

(2)**<u>DCV 冷凍方法</u>**：我們實驗室改進的方法，將小組織用 7.5% (v/v) ethylene glycol 加上 7.5% (v/v) DMSO 跟 20% FBS 作用 10 min，接著移到 15% EG 跟 15% DMSO 與 0.5 M sucrose 作用 2 min。然後液態氮直接倒入塑膠 cryovial 中，這樣溫度下降非常快速，組織損壞最低，根據之前卵巢檢體的經驗看來，結果非常好，可以擁有跟新鮮組織一樣的活力，也生出很多正常的小鼠*(Chen SU, 2006)*。

(3) **IHC (原位組織免疫染色)**：我們選擇的是用 paraffin 切片，mouse anti HIV-I gp24 單株抗體 (RayBiotech Inc., IP-05-152) 與 rabbit anti HIV-1 gp41 多株抗體(RayBiotech Inc., IP-05-160)兩種，稀釋濃度分別為 500:1。Positive control 選擇的是 early HIV 有病變的淋巴結。

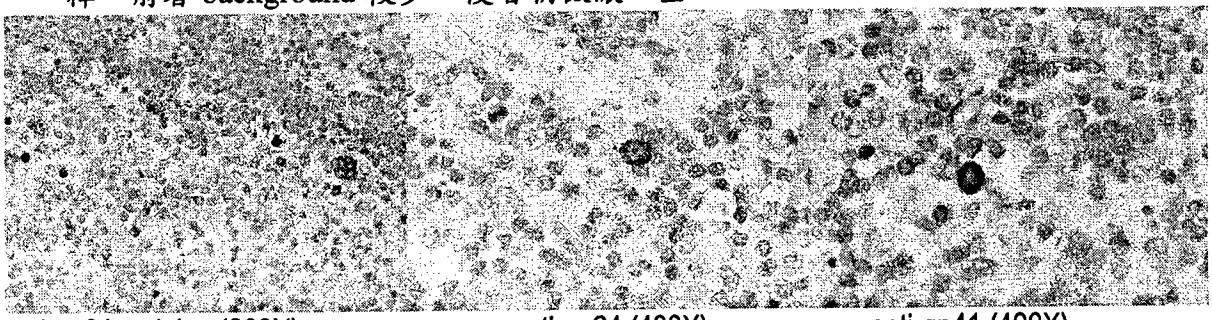
## Ⅲ、結果

(1) **檢體收集**：只收集到 5 例，其臨床資料如下表。

| | 懷孕(週) | 感染原因 | 催生方法 | 明顯宮縮時間 | 胎兒出生狀況 |
|---|---|---|---|---|---|
| Wang T | 17 | 異性戀 | cytotec + nalador | 26.5 hr | 130 gm, 0→0 |
| Chen KY | $18^+$ | IDU | cytotec + nalador | 7.5 hr | 400 gm, 0→0 |
| Chen LP | $13^+$ | IDU | cytotec + nalador | 2.5 hr | 20 gm, 0→0 |
| Oung CF | $13^+$ | IDU | cytotec + nalador | 6 hr | 40 gm, 0→0 |
| Pan CT | $15^+$ | IDU | cytotec + nalador | 5 hr | 130 gm, 0→0 |

IDU: 藥癮患者

(2) **positive control**：我們收集到近兩年的 HIV 患者，作淋巴結切片者有 4 位，但是有書面同意書，提供檢體作研究者，只有一位。因此 positive control 都來自同一位，檢體為 paraffin block，切片厚度為 4-5 μm，anti-human gp24 與 gp41 都是 500 倍稀釋，前者 background 較少，後者稍微濃一些。

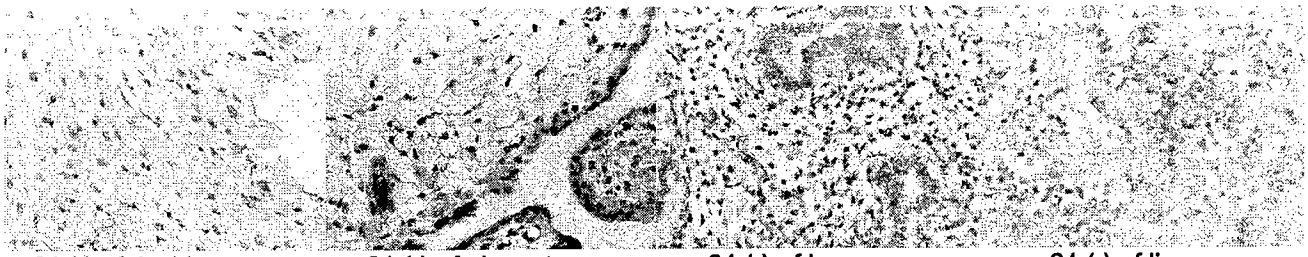


anti-gp24 staining (200X) anti-gp24 (400X) anti-gp41 (400X)

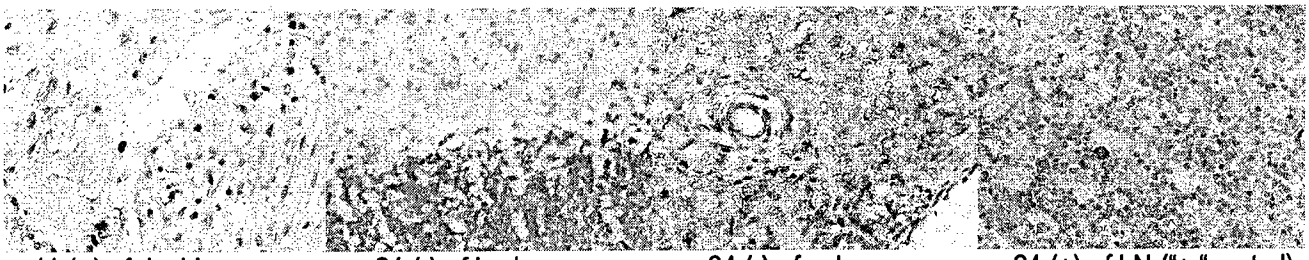
(3) **病理染色**：在我們有限的檢體當中，除了一個 decidua 有輕微陽性反應之外其餘都是陰性。

| | 懷孕(週) | decidua | placenta | brain | lung | liver | spleen |
|---|---|---|---|---|---|---|---|
| Wang T | 17 | NA | NA | NA | Both (-) | Both (-) | Both (-) |
| Chen KY | $18^+$ | NA | NA | NA | Both (-) | Both (-) | Both (-) |
| Chen LP | $13^+$ | NA | NA | NA | Both (-) | Both (-) | Both (-) |
| Oung CF | $13^+$ | gp41 (+) gp24 (±) | Both (-) | Both (-) | Both (-) | Both (-) | Both (-) |
| Pan CT | $15^+$ | NA | Both (-) | Both (-) | Both (-) | Both (-) | NA |

NA: not available



gp24 (-) of decidua　gp24 (-) of placenta　gp24 (-) of lung　gp24 (-) of liver



gp41 (±) of decidua　gp24 (-) of brain　gp24 (-) of spleen　gp24 (+) of LN ("+ "control)

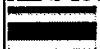
## Ⅳ、討論

婦女與新生兒 HIV 的感染，在過去幾年中已漸漸有定論，2005 年開始，政府機關也著手全面篩檢，這部分的工作已經穩定前進中，約有 70-85%的人有篩檢到。2005 年共有 47 例孕婦，這些人通常第一次產檢就會被檢查並告知，但是不是馬上需要 HAART 的治療，還是像 WHO 建議的，輕微案例只用 AZT？還有，什麼時候開始用？選哪一些藥物？用到什麼時候停？太早給藥，如第一孕程，得到的好處跟胎兒潛在的畸形危險，或媽媽胃口的降低，與這些壞處比起來，值不值得？有人說有傳染的情形，也有人說沒有。最近英國有一份大型調查顯示*(Townsend CL, 2006)*，第一孕程，使用藥物有先天異常機會是 3.7% (20/541)，沒有用藥物的人，先天異常機會是 3.1% (80/2,579)，他們認為是沒有明顯相關。可惜文獻上的早期懷孕作胎兒 HIV 檢驗的報告，人數都很少，結論無法真正說服人(見下面表一)。但多年臨床經驗看來，子宮收縮，或母血胎兒血少量互通，是有很多證據的。如果是這樣，那麼早期垂直感染是非常有可能的。

我們採取兩個不同的抗原，anti-gp24 與 anti-gp41，其組織染色有其獨立性。從 positive control 的淋巴結切片顯示，這兩個抗體可以很明顯的顯示出細胞遭到 HIV 的感染。但在胚胎組織中，卻沒有檢測到，而在蛻膜組織(代表母體)，卻可以檢測到，所以綜合證據顯示，應該在早期 HIV-1 不容易傳染給胎兒。亦即，沒有急迫的需要，在此時期就給予抗 HIV-1 的藥物治療。原先我們以為，這些案例都經過一段時間的子宮收縮藥物刺激，說不定會有 false positive 出現可是仍然沒有發現。不過，因為本實驗的案例還是少，結論可能還不足以作代表。

還有，本實驗用 IHC，特異性高，但敏感性可能稍嫌不足，例如文獻上許多人用 PCR 或 culture 來作證據，就有許多比例是陽性，但相同的道理，他們的敏感度高，相對地，特異性可能就不高，難以看出哪一種細胞(例如 $CD3^+$)陽性？比例有多少？會被其他細胞污染嗎？所以我們選擇 IHC，而且兩種不同抗原，若有結果，比較可靠。我們在 decidua 發覺有陽性，代表我們的敏感度還可以，至於胎盤或其他胎兒組織沒出現，可能真的早期垂直傳染並不存在。

表一 文獻上早期懷孕，HIV-1 垂直感染的證據

| 作者 / 年代<br>參考資料來源 | Material & Method<br>〔實驗方法、步驟、國家、人數〕 | Results<br>〔初步結果、推論、主要價值〕 |
|---|---|---|
| Lewis SH, 1990<br>Lancet 335:565-8<br>  , Columbia U<br>⊖ | HIV sero (+) pregnancy 8 weeks x 3 cases ⇨ D&C<br>做ISH，IHC of ❶ decidual leukocytes, ❷ trophoblast, ❸ villous mesenchyme, ❹ embryonic blood precursors | ❶ ❷ ❸ ❹<br>case 1 + ++ + +<br>case 2 + ++ + ±<br>case 3 ++ ± -<br>control - - - -<br>∴ HIV-1 gp41 antigen and was present in the fetal tissue |
| Lyman WD, 1990<br>AIDS 4:917-20<br>  <br>⊖ | ❶ 8 abortus from 7 HIV(+) mothers (one twins), ❷ 8 control abortus from 8 HIV(-) mothers | ❶ by PCR, 3/8 (+) in CNS, but only 2 (+) by ISH confirmation of HIV-1 DNA<br>❷ negative by PCR |
| Courgnaud V, 1991<br>AIDS Res Hum Retroviruses 7:337-41<br>  <br>⊖ | 33 fetal samples (thymus, spleen, PBMC) from 9 mid-trimester (16-24 weeks) ⇨PCR | PCR of HIV-1 DNA: 6/8 (+) of thymus, 8/9 (+) of spleen, 5/9 (+) of PBMC<br>The earliest one: 16 weeks<br>Viral culture of 33 samples: 0% (+) |
| Mano H, 1991<br>AIDS Res Hum Retroviruses 7:83-8<br>  <br>⊖ | 7 HIV(+) asymptomatic mothers, 10-23 weeks, HIV-1 PCR and virus isolation from brain, thymus, lung, liver, spleen, and placenta tissues | culture (+): 2/7 of spleen, 1/7 of thymus, 1/7 of liver, if $CD4^+$ cells of spleen or thymus, 40-60% HIV(+)<br>DNA(+): 4/7 of spleen, 3/7 of thymus, 1/7 of brain, 1/7 of lung, 2/7 of liver, 2/6 of placenta<br>可能是$CD4^+$細胞帶有病毒 |
| Brossard Y, 1995<br>AIDS 9:359-66<br>  <br>⊖ | 100 fetal thymus (15-26 weeks), IUFD = 4, SA = 4, mid-trimester termination = 92 ⇨DNA from thymus extract with 6 different primers | 2/100 with HIV-1 DNA (+) in thymus and other organs, one is IUFD from a case of advanced AIDS, the other is a case of repeated APH |
| Phuapradit W, 1999<br>AIDS 13:1927-31<br>  <br>⊖ | 41 pregnant HIV women (17-24 wk, no ZDV treatment)<br>⇨ 新鮮的abortus從heart取血 | ⇨ 2/41 (4.9%) fetal plasma HIV RNA (+), ❶ 18 weeks, maternal 126,454 ⇨ fetus=350 copies, ❷ 20 weeks, maternal 8,216 ⇨ fetus =50<br>無法排除短暫催生的藥劑，所產生的子宮收縮是造成胎兒血中RNA存在的原因 |
| Mohlala BKF, 2005<br>JID 192:488-91<br>  , U Cape Town<br>⊗ | 23 HIV(+) singleton pregnant women, 30-36 weeks recruited, ⇨ 38-40 wks, elective C/S, take ZDV from 34 wk or nevirapine 200 mg 4 h before C/S⇨ check amniotic fluid & cord blood HIV by PCR | ⇨ 0/23 (0%) of HIV in AF or cord blood<br>mean maternal RNA copies: 33,700/mL |

⊙實成存在，⊖模稜兩可，⊗反對存在。

## V、結論與建議

以目前的證據顯示，並無法證實早期懷孕 HIV-1 就會通過胎盤，到達胎兒。既然如此，目前給藥政策就無須改變，亦即，14 週以後才開始給 HAART 的藥物治療。但是，以後如果有新的證據，還可以再討論。

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附件八

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 台灣愛滋病患延遲診斷之危險因子研究

# Factors associated with delayed HIV diagnosis in Taiwan

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：洪健清、羅一鈞、林育寬、吳政信

執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共　17　頁

## 壹、中文摘要：

愛滋病與愛滋病毒感染的早期診斷，在臨床上與公共衛生上，都具有重要的意義。早期診斷，並適時開始投予抗病毒雞尾酒療法與伺機性感染預防用藥，可以減少患者的罹病率與死亡率，在公共衛生上，也可透過治療降低患者體內的病毒量，減少患者將愛滋病毒傳染給其他人的機會；再者，透過衛教諮商，感染者學習採取保護措施或者參與降低傷害的計畫以期降低愛滋病毒傳播的機會。儘管如此，仍有相當多的愛滋病毒感染者，在初次診斷愛滋病毒感染時，病程已經進展到了愛滋病的階段。根據台大醫院的統計，在 1994 到 2003 年之間就診的愛滋病毒感染者，初始 CD4 量小於 200/μL 的比例高達 68.2%，顯示國內的愛滋病毒感染者延遲就醫的現象仍然很普遍。延遲因為愛滋病毒感染就醫的原因，綜括而言可以包括：感染者就醫的行為(health seeking behavior)和醫療照護提供者對於愛滋病毒感染的認知程度。

本研究針對自 96 年 1 月至 96 年 11 月之台大醫院新診斷 HIV 感染者共 113 位進行一對一訪談，瞭解其安全性行為與診斷 HIV 前就醫行為，將訪談對象區分為延遲診斷組(CD4 淋巴球數<200 cell/μL)與非延遲診斷組(CD4 淋巴球數≧200 cell/μL)，進行統計分析，以找出延遲診斷的危險因子。其中延遲診斷組共 72 名，非延遲診斷組共 41 名。比較其基本人口學資料、傳染途徑、社經狀況、安全性行為、就醫行為、本身對 HIV 感染認知與篩檢行為等變項，發現月收入較高者、異性戀者較易為延遲診斷者，同性戀者、因篩檢而診斷者、父母親均健在者、曾使用違禁藥品者，較易為非延遲診斷者。本研究發現兩組感染者在診斷前已認知自己是 HIV 感染高危險群的比例均不到 50%。延遲診斷者與非延遲診斷者在診斷前一年就醫次數，中位數分別為 5 次以上與 2-3 次，就醫次數差異有明顯差異(p=0.03)。診斷前一年就醫時有可懷疑 HIV 感染之相關診斷，兩組均達 20%以上，若能再配合患者曾罹患性病或帶狀疱疹的病史，則可提早發現約 50%患者之 HIV 感染。本研究顯示不論在患者自我覺察上，與醫師臨床診斷上，都有亟待加強的空間。研究成果提供後續防治相關政策制訂與醫療照護者教育訓練的參考，以加強第一線醫療照顧者對診斷愛滋病的警覺心，促進愛滋患者的早期診斷。

關鍵詞：愛滋病、愛滋病毒感染、延遲診斷、危險因子

## 貳、英文摘要

Early diagnosis of HIV infection and AIDS is of great importance clinically and in the public health aspect. Early diagnosis, prompt initiation of highly active antiretroviral therapy (HAART) and prophylaxis of opportunistic infections can reduce the morbidity and mortality of HIV infected individuals. In the aspect of public health, suppression of viral load by HAART lower the risk of spreading HIV from patients to other individuals. Moreover, education and counseling may facilitate HIV infected individuals to take protective measures or participate in harm reduction program, resulting in the decrease of HIV transmission. However, many patients were already in the stage of AIDS when they were diagnosed to have HIV infection. Among HIV patients seeking medical care in the National Taiwan University Hospital between 1994 and 2003, the percentage of patients with initial CD4 count lower than 200/μL was as high as 68.2%. It shows that delayed presentation is still very common for HIV infected individuals in Taiwan. In general, the reason of delayed presentation for HIV patients comprises health seeking behavior and the knowledge of healthcare providers about HIV infection.

In this study, a total of 113 newly diagnosed HIV patients seeking medical care at the National Taiwan University Hospital between January and November 2007 were invited for a structured private interview to understand their safe sex practice and health seeking behavior before the diagnosis of HIV infection. The patients were categorized by their initial CD4 count into two groups: the delayed-diagnosis group (initial CD4 count <200/μL), and the non-delayed-diagnosis group (CD4 count≧200 cell/μL). Statistical analyses were performed to identify the risk factors of delayed diagnosis. There were 72 cases in the delayed-diagnosis group and 41 cases in the non-delayed-diagnosis group. The demographics, mode of transmission, socioeconomic status, safe sex practice and health seeking behavior between the two groups were analyzed. Higher income and heterosexuality were significantly associated with delayed HIV diagnosis. Factors that were associated with non-delayed HIV diagnosis included men who had sex with men (MSM), diagnosis via screening, both parents alive and history of illicit drug use. We discovered that less than 50% of the patients in both groups recognized themselves to be high risk for HIV infection. In average, patients in delayed-diagnosis group had more health seeking

behaviors than patients in the non-delayed-diagnosis group within one year before HIV diagnosis (median: >5 times vs. 2-3 times, p=0.03), and more than 20% of the given diagnoses in both groups could have legitimated clinical suspicions of HIV infection. Offering of HIV tests could be prompted to about 50% of the patients earlier if a history of sexual transmitted diseases or herpes zoster was obtained and further added on to the given diagnoses. This study showed not only a great number of newly diagnosed HIV individuals were not aware of self risk of acquiring HIV infection, but the healthcare providers also had deficiency in clinical suspicion of HIV infection. The results of this study provide a good reference for further designs of related policy and clinical educational training, so that first-line healthcare givers know when to offer HIV tests, and can achieve earlier diagnosis of HIV infection.

Keyword: HIV infection, AIDS, delayed diagnosis, risk factors

## 參、本文

### （一） 前言

愛滋病與愛滋病毒感染的早期診斷，在臨床上與公共衛生上，都具有重要的意義。早期診斷，並適時開始投予抗病毒雞尾酒療法與伺機性感染預防用藥，可以減少患者的罹病率與死亡率，在公共衛生上，也可透過治療降低患者體內的病毒量，減少患者將愛滋病毒感染傳染給其他人的機會；再者，透過衛教諮商，感染者學習採取保護措施或者參與降低傷害的計畫以期降低愛滋病毒傳播的機會。

儘管如此，仍有相當多的愛滋病毒感染者，在初次診斷愛滋病毒感染時，病程已經進展到了愛滋病的階段。許多國外的文獻顯示，愛滋病的延遲診斷相當普遍，有 20%到 40%的感染者得知自己感染愛滋病毒時，同時也已達到愛滋病的診斷標準[1-2]。根據台大醫院的統計，在 1994 到 2003 年之間就診的愛滋病毒感染者，初始 CD4 量小於 200/μL 的比例高達 68.2%，CD4 量的中位數僅有 71/μL[3]，顯示國內的愛滋病毒感染者延遲就醫的現象仍然很普遍。延遲因為愛滋病毒感染就醫的原因，綜括而言可以包括：感染者就醫的行為(health seeking behavior)和醫療照護提供者對於愛滋病毒感染的認知程度。愛滋病毒感染的高危險群並不認為自己處於高風險、發生感染後擔心歧視、隱私被侵犯和工作權被剝奪、經濟能力和工作時間造成就醫不便、無法自行決定是否就醫、不信任醫療人員、擔心藥物的費用與副作用等等，皆是造成延遲就醫的可能影響因素。我們必須瞭解國內感染者常見延遲就醫的原因，方能針對問題提供解決的辦法。

愛滋病毒感染者在病程已進入愛滋病時，可能因各器官系統的症狀前往就醫，而有機會先被各科第一線的醫療照顧者診斷出愛滋病。國外的研究顯示，愛滋病毒感染者在診斷感染前的五年內，有 61%因為口腔感染、肺炎、發燒、脂漏性皮膚炎、帶狀疱疹、體重減輕、淋巴結腫大、夜間盜汗等原因就醫[4]。雖然 86%的愛滋病毒感染者有男同性戀或靜脈毒癮等感染愛滋病毒的危險因子，卻只有 59%的患者在診斷愛滋病毒感染前五年內的就診病歷中，被記錄到這些危險因子，其中約四成是在診斷前一年內才記錄到危險因子[4]。國內尚無這方面的研究資料，但臨床上不乏反覆就醫仍未診斷出愛滋病毒感染的患者。根據台大公共衛生學院的研究指出，國內醫師及牙醫師對愛滋病所具有的專業知識不足，對愛滋病患的接受度低[5]。這些第一線醫療照顧者時在接觸未診斷的愛滋病毒感染者時，可能欠缺警覺心而未考慮愛滋病毒感染的可能性，也未詢問愛滋病毒

感染的危險因子，錯失早期診斷的良機，使患者在病程進展到更加後期時才被診斷，不僅有礙患者的健康，也影響愛滋病防治的效果。

在兩篇於日本感染症醫學雜誌發表的台大醫院愛滋病防治中心研究中[6,7]，我們發現：在高效能抗愛滋病毒藥物上市進入台灣之前，在台大就醫的愛滋病毒感染者的 CD4 淋巴球數僅有 28/μL；高效能抗愛滋病毒藥物引進台灣後，儘管藥物治療是免部分負擔感染者就醫時的 CD4 淋巴球數仍然僅有 117/μL。雖然，整體而言隨著抗病毒藥物的引進，死亡率大幅降低，從高效能抗愛滋病毒藥物引進以前的 33.75 每 100 人-年降低至藥物引進的 6.51 每 100 人-年 ($P$<0.0001)；而且和藥物引進前比較，2000 年到 2004 年免疫球低於 200/μL 的感染者死亡的風險降低高達 62%之多，但是，發病後第一年的死亡仍然高達 8-9%。這些結果顯示感染者就醫有提早的現象，但是以轉診醫院的角度，來看仍然有相當大的改善空間。

本研究計畫希望了解國內愛滋病患在初次診斷愛滋病前的就醫行為，分析延遲診斷的危險因子，提供後續防治相關政策制訂與醫療照護者教育訓練的參考，以加強第一線醫療照顧者對診斷愛滋病的警覺心，促進愛滋患者的早期診斷。

（二）材料與方法

實驗地點：臺大醫院愛滋病研究中心

實驗對象：96 年 1 月至 96 年 11 月之台大醫院新診斷 HIV 感染者

實驗期間：本計劃進行兩年，從 96 年 1 月 1 日迄 96 年 12 月 31 日。

研究方法：

本研究以問卷方式進行，輔以訪談以了解就醫行為之細節。所有符合收案的研究對象，在研究者的個案面談中，說明問卷與訪談的目的，若研究對象同意參與研究，則由研究助理指導填寫問卷，回答在診斷愛滋病感染者前一年內有就醫行為者，再安排個人訪談以了解就醫行為之細節。

問卷的設計除參考國內外相關文獻外，就有關的議題，計畫先與部分患者進行訪談，以發展出本研究之問卷。問卷變項包括性別、年齡、傳染途徑、教育程度、職業有無、工作收入、婚姻狀況等社會人口變項，初始臨床表現、初始 CD4 量、診斷前一年是否有就醫行為等醫療變項。回答診斷愛滋病毒感染前一年內有就醫行為者，再進一步詢問其就醫時間與次數、各次就醫症狀與診斷、是否住院、該醫療單位層級、醫療照護者是否曾詢問愛滋病毒感染者的危險因子或建議實施愛滋病毒感染檢測。

本研究採用結構性問卷訪談，問卷項目擬定後，先針對十名患者進行試測，再與愛滋病臨床專家學者討論後，修改問卷內容細節，並擴大收案對象為所有新診斷愛滋病毒感染者，區分延遲診斷組(CD4<200)與非延遲診斷組(CD4≧200)以進行比較與分析。與患者訪談的同時，輔以諮商與衛教，希望加強患者對疾病的瞭解，提高安全行為與對醫囑的遵從性。統計分析方法使用 SPSS 軟體(version 12.0, 2003 SPSS Inc. Chicago, IL)，類別變項使用$\chi^2$ 或 Fisher's exact test。

（三）結果

本研究針對自 96 年 1 月至 96 年 11 月之台大醫院新診斷 HIV 感染者收案共 113 位，其中男性 110 名，女性 3 名，延遲診斷者(CD4<200)計 72 名，佔 64%，與本院過去研究 CD4<200 病患所佔比例相符合。113 名患者的傳染途徑中，男同性戀(含雙性戀)為 79 名(70%)，異性戀為 27 名(24%)，靜脈毒癮者為 5 名(4.4%)。

將 70 名患者分為延遲診斷者(CD4<200)與非延遲診斷者(CD4≧200)兩組比較，進行單變項分析，可以發現，在年齡、居住地、教育程度、職業有無等項目上，兩組並無統計上顯著差異。工作收入以延遲診斷者較高，月收入在 3 萬元以上者，在延遲診斷組達 75%，非延遲診斷組僅 49%(p=0.016)。感染愛滋病毒的危險因子方面，男同性戀在兩組比例相近，異性戀在延遲診斷組所佔比例較高(29% vs.15%)，達統計上顯著差異(p=0.018)。(如表一)

檢驗愛滋病毒感染的理由，延遲診斷組有 79%是因患者出現症狀經醫師或匿名篩檢而診斷，非延遲診斷組則 63%的患者都無症狀，而是經由篩檢(匿篩、孕篩、獄篩、役篩、捐血篩檢等)發現愛滋病毒感染，兩組有明顯差異(p<0.0001)。在合併感染症方面，B 型肝炎、C 型肝炎感染率與梅毒血清檢驗陽性率，兩組無顯著差異。(如表一)

在家庭關係方面，是否與家人同住、男同性戀是否已向家人出櫃等項目上，兩組並無統計上差異。延遲診斷組的患者，父母均健在的比例較低(54% vs. 66%, p=0.049)，其家人知道患者感染愛滋病毒的比例較高(64% vs.38%)，有顯著差異(p=0.033)。(如表二)

第一次性行為年齡、曾有性伴侶的數目、目前性伴侶數目、是否有肛交、口交經驗等項目，兩組並無統計上差異。保險套使用狀況方面，與固定伴侶或非固定伴侶發生性行為時會總是使用保險套的比率，口交或肛交使用保險套的比率，兩組均無顯著差異。口交從不使用保險套的比例，兩組都極高(96% vs.97%)。(如表二)

雖然靜脈毒癮者僅有 5 名，曾使用違禁藥品的患者比例卻達 33%，在延遲診斷組較低(21% vs. 54%)，達統計上顯著差異(p<0.001)。其中搖頭丸佔所有違禁藥品使用的第一位(81%)，大麻佔第二位(35%)，值得注意。(如表三)

診斷愛滋病毒感染前一年，延遲診斷組與非延遲診斷組的患者的就醫次數，中位數分別為 5 次以上與 2-3 次，有顯著差異(p=0.03)，其中排名前三位的就診科別為耳鼻喉

科、皮膚科、牙科。由病人口述其一年內就醫診斷，依臨床判斷可能提早於該次就醫時就懷疑愛滋病毒感染，兩組皆達20%以上。其中在延遲診斷組有4例口腔念珠菌感染、4例脂漏性皮膚炎、2例肺結核，2例帶狀疱疹，乾癬、不明原因貧血、傳染性濕疣、不明原因體重減輕各1例。在非延遲診斷組有4例帶狀疱疹，菜花、乾癬、食道念珠菌感染、慢性腹瀉、單核球增多症、不明原因淋巴結腫各1例。患者過去曾罹患性病的比例，延遲診斷組與非延遲診斷組分別為32%與37%。若各科醫師能在上述可懷疑愛滋病毒感染的相關診斷時進行檢驗，或針對曾罹患性病者及曾罹患帶狀疱疹者進行愛滋病毒篩檢，有約一半(49.5%)的愛滋感染者可以被提早發現，顯示各科醫師對於愛滋病毒感染的提早診斷，雖有很大的進步空間，但有其極限，無法提早發現所有患者。(如表三)

在患者的自我認知方面，只有40%的感染者覺得自己是感染愛滋病毒的高危險群，兩組無顯著差異。非延遲診斷組較延遲診斷組，有較多人擁有已感染HIV的朋友(44% vs. 25%, p=0.038)。所有患者中，只有47%過去曾接受過愛滋病毒檢驗，以非延遲診斷組明顯較高(59% vs. 42%)，但未達統計上顯著差異(p=0.08)。固定接受愛滋病毒檢驗的患者，亦以非延遲診斷組較高(34% vs.15%)，達統計上顯著差異(p=0.02)。 (如表四)

（四）討論

本研究企圖找出延遲診斷者與非延遲診斷者的差異，結果發現年齡、性別、職業有無與保險套使用頻率，兩組並無差異。收入較高者、異性戀者、非因篩檢而診斷者，較易為延遲診斷者。異性戀者、非因篩檢而診斷者較易為延遲診斷者，國外已有多篇文獻報告過，作者多認為與未有高危險群之自我覺察有關。收入較高者易為延遲診斷者，與國外文獻報告相反，可能與我國實施全民健保，就醫方便，收入較高者可能因工作忙碌無暇就醫，或是自覺身體健康狀況良好有關。

同性戀者、因篩檢而診斷者、父母親均健在者、曾使用違禁藥品者，較易為非延遲診斷者。同性戀者、因篩檢而診斷者較易為延遲診斷者，與國外文獻報告相同。父母親均健在，與非延遲診斷的關連性，尚未有其他文獻報告過，可能與華人文化裡家庭力量對就醫行為影響有關，值得進一步探究。曾使用違禁藥品者，可能因被警察逮捕而獲得HIV檢驗，因此與非延遲診斷有關，此外此一族群當中的男同性戀，是否可能因危險行為於事後更願意利用篩檢方式檢驗 HIV，導致較早期診斷，則需要進一步做次群體分析。由於違禁藥品的使用相當普遍，在本研究中高達33%，而且以搖頭丸、大麻為主，非海洛因之違禁藥品與HIV傳播的關連性，是值得衛生主管單位與研究者關注的問題。

本研究發現兩組感染者在診斷前已認知自己是 HIV 感染高危險群的比例均不到50%，因此考慮篩檢與接受篩檢的比率均不盡理想。與非延遲診斷有關連的因子為擁有感染 HIV 的朋友、固定接受 HIV 篩檢，顯示願意公開自己為 HIV 感染者的人，可能增強周遭人對 HIV 的自我覺察，從而利用篩檢或妥善就醫。而固定接受 HIV 篩檢，雖然可能早期診斷 HIV 感染，但在 25 為固定篩檢者中，仍有 11 位(44%)診斷 HIV 感染時其 CD4 淋巴球數已經小於 200 cell/μL，因此仍應強調固定篩檢的頻率與持續性。針對危險族群進行的宣導、民間團體活動、匿名篩檢等，應繼續推廣與增進可近性。

延遲診斷者與非延遲診斷者在診斷前一年就醫次數，中位數分別為 5 次以上與 2-3 次，就醫對象仍以社區的耳鼻喉科、皮膚科、牙科診所居多，因此社區照護體系應有警覺心，除了在一般醫療行為上做好標準防護措施，也應時刻將 HIV 感染列入診斷考慮中。診斷前一年就醫時有可懷疑 HIV 感染之相關診斷，兩組均達 20%以上，若能再配合患者曾罹患性病或帶狀疱疹的病史，則可提早發現約 50%患者之 HIV 感染。利用簡單的病史詢問，即可早期偵測出許多已感染 HIV 的患者，減少患者日後發生更嚴重的併

發症，早期轉介患者至愛滋病照護系統。衛生主管機關與相關之醫學會，應針對社區照護體系內常被 HIV 感染者先接觸到的醫療專科，提供 HIV 相關繼續教育課程，以增進各科醫師對 HIV 感染的熟悉度，減少因醫師延誤診斷造成患者承受後續的嚴重後果。

本研究顯示不論在患者自我覺察上，與醫師臨床診斷上，都有亟待加強的空間。研究成果提供後續防治相關政策制訂與醫療照護者教育訓練的參考，以加強第一線醫療照顧者對診斷愛滋病的警覺心，促進愛滋患者的早期診斷。

## （五）結論與建議

1. 收入較高者、異性戀者、非因篩檢而診斷者，較易為延遲診斷者。同性戀者、因篩檢而診斷者、父母親均健在者、曾使用違禁藥品者、擁有感染 HIV 的朋友、固定接受 HIV 篩檢者，較易為非延遲診斷者。

2. 在 HIV 感染者被診斷前，曾經使用違禁藥品的情形相當普遍，在本研究中高達 33%，而且以搖頭丸、大麻為主，非海洛因之違禁藥品與 HIV 傳播的關連性，是值得衛生主管單位與研究者關注的問題。

3. 固定接受 HIV 篩檢，雖然可能早期診斷 HIV 感染，但在 25 為固定篩檢者中，仍有 11 位(44%)診斷 HIV 感染時其 CD4 淋巴球數已經小於 200 cell/μL，因此仍應強調固定篩檢的頻率與持續性。

4. 利用簡單的病史詢問，即可早期偵測出許多已感染 HIV 的患者，減少患者日後發生更嚴重的併發症，早期轉介患者至愛滋病照護系統。衛生主管機關與相關之醫學會，應針對社區照護體系內常被 HIV 感染者先接觸到的醫療專科，提供 HIV 相關繼續教育課程，以增進各科醫師對 HIV 感染的熟悉度，減少因醫師延誤診斷造成患者承受後續的嚴重後果。

5. 兩組感染者在診斷前已認知自己是 HIV 感染高危險群的比例均不到 50%，因此考慮篩檢與接受篩檢的比率均不盡理想。針對危險族群進行的宣導、民間團體活動、匿名篩檢等，應繼續推廣與增進可近性。

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表一：延遲診斷組與非延遲診斷組基本資料比較表

總樣本數為 113 名 (男性 110 位; 女性 3 位)

| | CD4<200 (N=72) | CD4>200 (N=41) | *p* value |
|---|---|---|---|
| 年齡 | | | 0.28 |
| 15-19 | 0 (0%) | 1 (2%) | |
| 20-29 | 24 (33%) | 20 (49%) | |
| 30-39 | 28 (39%) | 11 (27%) | |
| 40-49 | 14 (19%) | 7 (17%) | |
| 50-59 | 6 (8%) | 2 (5%) | |
| 居住地 | | | 0.70 |
| 城市 | 68 (94%) | 38 (93%) | |
| 鄉鎮 | 4 (6%) | 3 (7%) | |
| 教育程度 | | | 0.68 |
| 大專以上 | 44 (61%) | 26 (63%) | |
| 高中/高職/五專 | 19 (26%) | 12 (29%) | |
| 國中以下 | 9 (13%) | 3 (7%) | |
| 職業 | | | 0.50 |
| 有 | 63 (88%) | 34 (83%) | |
| 無 | 9 (12%) | 7 (17%) | |
| 收入 | | | 0.016 |
| 15,000 元以下 | 11 (15%) | 11 (27%) | |
| 15,000~30,000 | 7 (10%) | 10 (24%) | |
| 30,000 以上 | 54 (75%) | 20 (49%) | |
| 感染 HIV 的危險因子 | | | 0.018 |
| MSM | 50 (69%) | 29 (70%) | |
| Heterosexual | 21 (29%) | 6 (15%) | |
| IDU | 1 (1%) | 4 (10%) | |
| 其他 | 0 (0%) | 2 (5%) | |
| 因篩檢而診斷 | 15 (21%) | 26 (63%) | <0.0001 |
| HBsAg(+) | 16/70 (23%) | 5/37 (14%) | 0.24 |
| Anti-HCV(+) | 5/69 (7%) | 5/36 (14%) | 0.30 |
| VDRL(+) | 18/70 (26%) | 4/38 (11%) | 0.06 |

表二：延遲診斷組與非延遲診斷組家庭關係與性行為比較表

| | CD4<200 (N=72) | CD4>200 (N=41) | *p* value |
|---|---|---|---|
| 與家人同住 | 41/61 (67%) | 22/41 (54%) | 0.10 |
| 父母 | | | 0.049 |
| 均健在 | 32/59 (54%) | 27/41 (66%) | |
| 單親家庭 | 16/59 (27%) | 13/41 (32%) | |
| 均往生 | 11/59 (19%) | 1/41 (2%) | |
| (同志)已對家人出櫃 | 20/39 (51%) | 17/29 (59%) | 0.54 |
| 家人知道自己有 HIV | 36/62 (58%) | 15/41 (37%) | 0.033 |
| 第一次性行為的年齡 | | | 0.06 |
| 15-19 歲 | 25/59 (42%) | 24/39 (62%) | |
| 20-30 歲 | 34/59 (58%) | 15/39 (38%) | |
| 至今曾有性伴侶的數目 | | | 0.22 |
| <10 | 23/60 (38%) | 9/41 (22%) | |
| 10-50 | 25/60 (42%) | 22/41 (54%) | |
| >50 | 12/60 (20%) | 10/41 (24%) | |
| 曾有肛交經驗 | 41/60 (68%) | 30/41 (73%) | 0.60 |
| 曾有口交經驗 | 51/60 (85%) | 36/41 (88%) | 0.69 |
| 保險套使用狀況 | | | |
| 與固定伴侶使用保險套 | | | 0.57 |
| 從不 | 17/52 (33%) | 11/38 (29%) | |
| 偶爾 | 13/52 (25%) | 11/38 (29%) | |
| 經常 | 18/52 (35%) | 10/38 (26%) | |
| 總是 | 4/52 (8%) | 6/38 (16%) | |
| 與非固定伴侶使用保險套 | | | 0.14 |
| 從不 | 10/53 (19%) | 3/37 (8%) | |
| 偶爾 | 9/53 (17%) | 8/37 (22%) | |
| 經常 | 27/53 (51%) | 15/37 (41%) | |
| 總是 | 7/53 (13%) | 11/37 (30%) | |
| 口交時使用保險套 | | | 0.68 |
| 從不 | 49/51 (96%) | 35/36 (97%) | |
| 偶爾 | 1/51 (2%) | 1/36 (3%) | |
| 經常 | 1/51 (2%) | 0/36 (0%) | |
| 肛交時使用保險套 | | | 0.09 |
| 從不 | 7/41 (17%) | 1/30 (3%) | |
| 偶爾 | 11/41 (27%) | 9/30 (30%) | |
| 經常 | 21/41 (51%) | 14/30 (47%) | |
| 總是 | 2/41 (5%) | 6/30 (20%) | |

表三：延遲診斷組與非延遲診斷組既往史與就醫行為比較表

| | CD4<200 (N=72) | CD4>200 (N=41) | *p* value |
|---|---|---|---|
| 曾使用違禁藥品 | 15/72 (21%) | 22/41 (54%) | <0.001 |
| 搖頭丸 | 13/15 (87%) | 17/22 (77%) | |
| 大麻 | 5/15 (33%) | 8/22 (36%) | |
| 海洛因 | 1/15 (7%) | 4/22 (18%) | |
| 安非他命 | 2/15 (13%) | 4/22 (18%) | |
| 古柯鹼 | 1/15 (7%) | 0/22 (0%) | |
| K 他命 | 3/15 (20%) | 8/22 (36%) | |
| 曾經罹患性病 | 23/72 (32%) | 15/41 (37%) | 0.62 |
| 診斷前一年內就醫次數 | | | 0.03 |
| 0-1 | 10/72 (14%) | 5/41 (12%) | |
| 2-3 | 12/72 (17%) | 17/41 (41%) | |
| 4-5 | 9/72 (13%) | 3/41 (7%) | |
| >5 | 41/72 (57%) | 16/41 (39%) | |
| 有可懷疑 HIV 的相關診斷 | 16/72 (22%) | 10/41 (24%) | 0.79 |
| 有可懷疑 HIV 的相關診斷或曾罹患性病 | 32/72 (44%) | 22/41 (54%) | 0.34 |
| 有可懷疑 HIV 的相關診斷或曾罹患性病或曾罹患帶狀皰疹 | 34/72 (47%) | 22/41 (54%) | 0.51 |

- CD4<200: 肺結核(x2), 乾癬(x1), 脂漏性皮膚炎(x4), 口腔念珠菌感染(x4), 不明原因貧血, 帶狀皰疹(x2), molluscum contagiosum, 不明原因體重減輕
- CD4>200: 菜花, 帶狀皰疹(x4), 乾癬, 食道念珠菌感染, 慢性腹瀉, 單核球增多症, 不明原因淋巴結腫

表四：延遲診斷組與非延遲診斷組自我覺察與篩檢態度比較表

| | CD4<200 (N=72) | CD4>200 (N=41) | *p* value |
|---|---|---|---|
| 認知自己為高危險群 | 25/72 (35%) | 20/41 (49%) | 0.14 |
| 擁有 HIV(+)的朋友 | 18/72 (25%) | 18/41 (44%) | 0.038 |
| 曾考慮接受 HIV 檢查 | 27/72 (38%) | 21/41 (51%) | 0.16 |
| 曾接受過 HIV 檢查 | 30/72 (42%) | 24/41 (59%) | 0.08 |
| 固定接受 HIV 檢查 | 11/72 (15%) | 14/41 (34%) | 0.020 |

附件九

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 建立愛滋病毒體液暴露者之諮詢、檢驗、預防性投藥與追蹤專線

# Set-up line for counciling, test, post- exposure prophylaxis and followed-up of persons with HIV-contained body fluid exposure

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：黃香樺、張曉慧、盛望徽、王永衛

執行期間： 96 年 1 月 1 日至 96 年 12 月 31 日

# 目　　錄



共 21 頁

壹、中文摘要：

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，已逾一萬名以上，是衛生署傳染病防治工作的重要課題。愛滋病是由人類免疫缺乏病毒（Human Immunodeficiency Virus, HIV）透過血液或體液接觸而所傳染，全球各地主要之流行途徑多是經由性行為，因此亦為性病之一，防治之法無他，即倡導安全性行為之重要性，以及教導高危險群定期檢驗追蹤；已被感染者若能及早發現，一方面需要追蹤治療，另一方面藉由 100%之安全性行為，防堵已感染者將愛滋病毒進一步傳播。因此呼籲經常無保護措施性行為者、且性伴侶眾多者接受篩檢與專業心理諮詢，是非常重要的。

愛滋病患在現在的社會中，仍被認為是不名譽及不道德的疾病，反觀國內，依衛生署的統計資料顯示，94 年 1 月累積至 12 月，感染者數已經突破 3 千人，平均每 2~3 個小時發現 1 名新感染者；平均每一天半就有 1 名感染者發病；平均每 4.5 天就有 1 名感染者死亡。毒癮者佔 41.38%，顯示除性行為外，毒癮已成為另一重要危險因素；但嫖妓或色情氾濫的一夜情也隨網路發展而迅速增加，有危險性行為的民眾，均難以啟齒承認，尤其是同志更不願曝光，卻又擔心感染愛滋病，一方面憂慮檢驗結果出現陽性不敢面對；另一方面，檢驗結果若為陰性又懷疑其可靠性，產生重複檢測，形成種種的心身症，而心力交瘁，造成個人與家庭、工作、社會失調。在此情形下，為避免遲疑蹉跎，造成已被感染者不知自身之現況，繼續散播病毒，甚至拖延至發病才警覺，為時已晚矣，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。為確保 HIV 體液暴露者篩檢效果，及接受檢驗民眾能確實接受檢驗前及檢驗後的諮詢，由醫護人員負責使受檢人確實了解愛滋病的傳染途徑、高危險行為、空窗期觀念等。

本研究以臺大醫院愛滋病防治中心醫師、護理人員、檢驗師並與台北市立聯合醫院疾病管制院區(昆明院區)合作，針對 HIV 體液暴露者建立完整且統一的 HIV 體液暴露事件處理流程。提供 24 小時 HIV 篩檢及專線諮詢與衛教服務，並於 24 小時內以顆粒凝集試驗快速執行 HIV 檢驗，並於 24-36 小時內提供免費 HIV 預防藥物，自 96 年 1 月至 96 年 10 月，共有電話諮商者 271 通，進入針扎流程者共有 49 位，共有 37 位為

醫護人員和 9 位警員義消受到 HIV 體液暴露，總共有 15 位服用預防性 HAART 投藥，服藥期間由 2 天至 4 週不等，每位追蹤至 96 年 11 月（至少追蹤 6 個月），所幸並未有因執業時受到 HIV 體液暴露而導致 HIV 感染。因此，針對醫護警消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，以及提供醫療人員 HIV 體液暴露後之諮詢、檢驗、診斷及治療相關教育研討會以協助醫療警消人員了解 HIV 體液暴露之危險評估與正確處理流程，是十分重要而且有效的工作。

關鍵詞：愛滋病毒感染、體液暴露、愛滋病毒檢驗、抗愛滋病毒藥物

## 貳、本文

### （一） 前言

後天免疫缺乏症候群（愛滋病，Acquired Immunodeficiency Syndrome, AIDS），自從 1981 年在美國發現以來，已成為全世界二十一世紀最重要的公共衛生問題，國內自 1984 年首例迄今，已逾一萬名以上，是衛生署傳染病防治工作的重要課題。愛滋病是由人類免疫缺乏病毒（Human Immunodeficiency Virus, HIV）透過血液或體液接觸而所傳染，全球各地主要之流行途徑多是經由性行為，因此亦為性病之一，防治之法無他，即倡導安全性行為之重要性，以及教導高危險群定期檢驗追蹤；已被感染者若能及早發現，一方面需要追蹤治療，另一方面藉由 100%之安全性行為，防堵已感染者將愛滋病毒進一步傳播。因此呼籲經常無保護措施性行為者、且性伴侶眾多者接受篩檢與專業心理諮詢，是非常重要的。

根據國內醫界及衛生署的統計，自 1984 年第一個台灣的本土感染人類免疫不全病毒（HIV）的病例被報告後，感染 HIV 的病患逐年增加，截至 2006 年 2 月 28 日止，共有 10603 名本土病例；其中的 2480 人，並已進展到後天免疫不全症候群（acquired immunodeficiency syndrome），簡稱愛滋病（AIDS）；而在一般群眾中，血清抗 HIV 抗體成陽性的盛行率約為十萬分之 12.3 [1]。正因為患有 HIV 感染的病人愈來愈多，因 HIV 體液暴露而感染 HIV 的危險性也愈來愈大[2]。，HIV 體液暴露後的處理，是十分重要的事。由於感染 HIV 之後，絕大部分的人會進展到 AIDS，使個人、家庭蒙受重大的損失，因此了解如何在 HIV 體液暴露的意外事件後正確地處理及追蹤檢查，是十分重要的一件事。使用抗 HIV 藥物（antiretrovirals）來做為暴露後的預防醫療（post-exposure prophylaxis，PEP），已是一個為醫學界所接受的作法。但由於各種暴露 HIV 後的感染性不同，加以抗 HIV 藥物的副作用頗大，以及新抗 HIV 藥物的問世，所以最好是能尋求專家的意見，以兼顧效果與避免藥物毒性。

所謂暴露，指可能導致感染 HIV 者而言；包含因 1.經皮刺傷（如針扎、銳器切割傷等）；2.經黏膜接觸；3.經破損的皮膚接觸 HIV 感染病患的血液、組織、及其它具傳染性的體液[3]。所謂其它具傳染性的體液是指含血的體液、精液、陰道分泌物、腦脊髓液（cerebrospinal fluid）、滑囊液（synovial fluid）、胸水（pleural fluid）、腹水（peritoneal fluid）、以及羊水（amniotic fluid）等。而糞便、鼻腔分泌物、唾液、痰液、汗水、眼

淚、尿液、以及嘔吐物等，除非帶有血液，否則應視為不具傳染性 [4]。任何與含有 HIV 病毒的直接接觸，都應該加以評估是否有傳染的的危險性。被感染 HIV 的病人咬傷，也有少數的報告指出具有傳染性[5]。暴露後感染 HIV 的危險性，隨暴露的種類而有不同。一般而言，因經皮刺傷而暴露到感染 HIV 的血液，傳染的危險性大約為 0.3%；因黏膜接觸到感染 HIV 的血液，其傳染的危險性則約為 0.09% [6]。暴露的血量愈大，危險性愈高 [7]。至於暴露來源病患（source patient）血液中的病毒量和危險性高低的關係，目前尚未確切建立。其他種暴露後，感染 HIV 的危險性則尚無確切的統計資料可詢[8,9]。愛滋病抗體篩檢方法簡易，初步檢驗即酵素免疫反應法（Enzyme-Link Immunoassay, EIA）；顆粒凝集法(Particle Agglutination, PA)；快速檢驗法(Ora Quick)等，初步檢驗兩次陽性者再以西方墨點法（Westerm Blot,WB）證實[10]。應評估來源病人是否有 HIV 之感染。對於先前 HIV 感染與否未明的暴露來源，應於廿四小時內抽血得知其 HIV 抗體呈現陽性或陰性。若確定其為 HIV 抗體呈陽性，應進一步評估其 HIV 感染狀態。HIV 的感染狀態，可區分為第一級與第二級；所謂第一級是指沒有臨床症狀的 HIV 感染，或者是病患血中的病毒濃度少於 1500 RNA copies/mL；第二級則是指有臨床症狀的 HIV 感染，或已進展到愛滋病，或是病患為急性 HIV 感染，或是病患血中的病毒濃度很高。這關係到暴露後預防性用藥（postexposure prophylaxis, PEP）的選擇。

PEP 的投予：隨著抗 HIV 藥物的發展及高效性抗 HIV 治療方法（highly active antiretroviral therapy，HAART）的問世，感染 HIV 的病患已能借之而獲得病情的控制。需多專家很早即開始將此"治療"的效果，嘗試著是否可用於預防意外暴露 HIV 後，因之感染 HIV 的危險性。基於此種想法，乃有所謂的 PEP 出現。由許多前人的辛苦實驗及觀察，PEP 的角色已獲得認可[10-14]。但由於各種抗 HIV 藥物之毒性均不小，故投予何種 PEP，尚須評估其暴露導致感染的危險性。其投予的方式，我們將參考表一及表二；而各種藥物的用法、劑量，我們將參考表三。開始投予的時間，最好在暴露後 24 至 36 小時之內，若超過一個星期，就可能失去投予的意義。而使用 PEP 的時間，應為期四週。由於 PEP 的毒性並不小，藥物的選用必須考量暴露者的耐受性及順從性，並斟酌暴露來源患者所感染的 HIV 是否已具有抗藥性，故其使用仍應請教專家，聽從其建議與處方。Nevirapine，delavirdine，abacavir，及 zalcitabine 等藥物不適合用於醫事人員的 PEP。另外，懷孕中的婦女不宜使用 efavirenz，stavudine，及 didanosine；

若使用 indinavir，zidovudine 也應小心謹慎[15]。

本研究以臺大醫院愛滋病防治中心醫師、護理人員、檢驗師並與台北市立聯合醫院疾病管制院區(昆明院區)合作，針對 HIV 體液暴露者建立完整且統一的 HIV 體液暴露事件處理流程。提供 24 小時 HIV 篩檢及專線諮詢與衛教服務，以降低 HIV 感染的機會及減輕諮詢者其不安及焦慮。另外，提供快速且單一 HIV 檢驗管道，以便於 24 小時內知道污染源是否已感染檢驗 HIV 病毒。若確定污染源已感染 HIV 病毒，則於 24-36 小時內提供免費預防藥物，並通報衛生機關，發揮有效之防疫功能。

（二）材料與方法

實施方法

（一）蒐集各種相關文獻，彙集各醫護中心及其他國家對於疑似愛滋病毒體液污染事件處理流程並透過專家學者研究及討論，規劃針扎事件統一處理流程。

（二）成立疑似愛滋病毒體液污染事件處理及諮詢中心，提供 24 小時專線電話諮詢服務，服務所有可能暴露愛滋病毒體液污染人員（包括醫事人員、警消、矯治、社區藥局、一般民眾）。

（三）可立即諮詢中心醫師在第一時間內予以診斷及治療。

（四）提供快速及免費之檢驗，可在兩小時內知道汙染源是否已感染愛滋病。

（五）將諮詢及追蹤結果作成記錄，以留未來統計研究之用。

進行步驟

實施期間：96 年 1 月 1 日至 96 年 12 月 31 日止。

實施方式：

(一) 利用國內外資訊管道蒐集各種相關文獻，並彙集各醫護中心及其他國家對於疑似愛滋病毒體液污染事件處理流程等資料。成立 24 小時「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。制定疑似愛滋病毒體液污染事件處理流程及方法討論會，邀請國內專家學者，規劃統一處理流程。

(二) 加強愛滋病毒防治之宣傳。印製「愛滋病毒感染須知」供個案參考。內容包括服務時間、愛滋病疑問、如何預防及檢驗等。並與台北市立性病防治所合作實行宣導，提供快速且正確的檢驗、診斷及治療，降低感染的機會，並能及時給予心理支持，減少焦慮及不安的產生。及時的諮詢、診斷後，可避免感染情形的擴大。

(三) 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。電話先由護理人員予以回答，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第一時間內予診斷及治療。

(四) 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。提供快速及免費之愛滋病檢驗，可在兩小時內知道汙染源是否已感染愛滋病。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」。未確定之個案每三個月追蹤一次，一年後如仍為「未確定」則不再追蹤。

(五) 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。

（三）結果

自 96 年 1 月至 96 年 10 月，共有 271 通諮詢電話，其中民眾針扎及諮詢共有 113 通，醫護人員共 129 通，警員、義消及救護車隨行急救人員共 19 通，減害計畫針筒回收藥局人員共 10 通，其月份之分布列於表一。因確定針扎及 HIV 體液暴露者於 1 月至 10 月共有 49 件，其中醫護檢驗人員有 37 位，警員義消 9 位，民眾及藥品針筒回收人員 3 位，經過 HIV 諮詢專家醫師篩檢 HIV 感染風險評估而接受 HIV 預防性用藥者有 15 位，以 8 月份 5 位最多（佔 30%），其中 3 位為新執業之護理人員（見表 2）。此 15 位確定 HIV 針扎或體液暴露者醫師有 2 位，服藥期間分別為 2 週及 4 週。護士有 5 位，其中一名護士經針扎來源血確定為陰性反應，因此立即停藥，共服藥 2 天。其餘 4 位護士均服藥 4 週。檢驗師有 1 位，服藥期間為 2 週，藥師有 1 位，服藥期間為 4 週，民眾（協助減害計畫針筒回收），服藥期間為 4 週，志工 1 位，服藥期間為 4 週，警員義消 4 位，服藥期間均為 4 週（見表三及表四）。

研究進行前後已進行五次針扎計畫相關會議，包括 96.01.04（籌備針扎計畫會議）；96.01.24（進行針扎計畫討論）；96.02.13（針扎計畫期中監察）；96.03.27（針扎計畫期中監察）；96.10.16（針扎計畫期末監察及檢討）。針對醫護警消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，故計畫於 96.12.15 於台大醫學院 101 講堂進行「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」（課程內容詳見附件 1），以幫助醫療院所醫護人員進而了解 HIV 體液暴露流程之執行方法，期末監察會議並建議另外在中區、南區也舉辦相關研討會，以加強地區醫療院所的衛教，並考慮製作問卷，調查各 HIV 指定照顧醫院有關 HIV 體液暴露之流行病學及後續追蹤記錄。研究進行中，與 HIV 治療專家討論並根據 WHO 之 HIV 預防準則制定 HIV 體液暴露之危險判定標準，預防性用藥準則及追蹤流程，此 PEP 預防用藥及 HIV 體液暴露流程表詳見附件 2、3、4。

（四）討論

根據國內醫界及衛生署的統計，自 1984 年第一個台灣的本土感染人類免疫不全病毒（HIV）的病例被報告後，感染 HIV 的病患逐年增加，截至 2007 年 10 月 31 日止，共有 14711 名本土病例；其中的 4113 人並已進展到後天免疫不全症候群（acquired immunodeficiency syndrome），簡稱愛滋病（AIDS）；而在一般群眾中，血清抗 HIV 抗體成陽性的盛行率約為十萬分之 12.3[16]。正因為患有 HIV 感染的病人愈來愈多，醫事人員在工作上因暴露而感染 HIV 的危險性也愈來愈大。在美國的一項追蹤報告中指出，自 1984 年第一個案例出現後至 1999 年 6 月份止，已有 55 位醫事人員因工作上的暴露而感染了 HIV[17]，其中由於針扎或 HIV 體液暴露呈現陽轉的因子包括帶血空心針頭，深部暴露患者為末期 AIDS 患者等有關。在台灣雖尚無類似的報告，卻值得我們深切注意。因之，了解暴露後的處理原則，是十分重要的事。根據國外許多醫療院所的研究報告調查發現：醫事人員在 3%～50%的醫療行為中會接觸到病患的血液；在 0.1%～15.4%的醫療行為中會發生銳器扎傷，其中尤以針扎最為常見[18]。

再教育的工作，以減少後續曝露的意外：對於發生暴露意外的醫事人員，應進行再教育的工作，以減少後續的暴露意外。Garner 等人曾提出下列幾項工作上的注意事項，以減少暴露的意外[18]：

1. 設立專職單位，教導病人、醫事人員甚或訪客們，各種注意事項及責任。
2. 定期評估醫事人員對各注意事項的執行情形。
3. 接觸病人後應嚴格執行洗手的工作。
4. 戴手套以避免接觸病患的血液及體液。
5. 視醫療行為的必要而穿戴口罩、隔離衣、護目鏡及面罩。
6. 病患所使用過的醫療用器及設施，可重複使用的，應妥善消毒；不可重複使用的，應密封丟棄。
7. 針頭及銳器的處理：使用過的針頭，最好不要嘗試著去回套針蓋、弄彎或折斷針頭；使用過的針頭應丟棄在無法刺穿的容器中並緊緊密封。其它銳器的處理原則也是相同。
8. 病人應置於獨立病室中或集中管理（cohorting）。

在本研究收到之 271 通電話針扎及 HIV 體液暴露專線諮詢中，仍有不少（113 通）

為民眾諮詢（41.6%），HIV 相關之病程、症狀、檢驗或為愛心感染 HIV 之問題，而並非針扎或 HIV 體液暴露相關，經由醫師評估過針扎及 HIV 體液暴露之危險，在 49 件執業人員之暴露傷害中，確認為需接受預防性用藥者約為 15 件（30.6%）。而以醫護人員佔絕大多數（75.5%），因此針扎及 HIV 體液暴露之再教育及流程知悉與否，相形重要，而接受預防性用藥，我們追蹤被暴露者之血液檢測的結果（範圍一個月至半年）均為 HIV 陰性。也顯示開始預防性藥物投與之時間及重要性。

HIV/AIDS 是人人避之唯恐不及的的疾病，但醫事人員與警察義消急救人員無法不接觸到此類的病患。在盡心照顧病患的同時，也應留心自身的安全。而預防勝於治療，；熟悉體液接觸隔離原則，能減少許多暴露的機會。萬一不幸發生暴露的意外，應冷靜聽從專家的建議與指導，以盡量減低感染的機率，而此針扎及 HIV 體液暴露之處理流程則應利用教育訓練或研討會提供危險執業人員知悉。

（五）結論與建議

提供 24 小時 HIV 篩檢及專線諮詢與衛教服務，的確可以降低 HIV 感染的機會及減輕諮詢者其不安及焦慮。而對於執業中 HIV 體液暴露高危險工作者提供快速且單一 HIV 檢驗管道，以便於 24 小時內知道污染源是否已感染檢驗 HIV 病毒，並對於確定污染源已感染 HIV 病毒者於 24-36 小時內提供免費預防藥物，不但可以減少 HIV 感染之機會，亦可對於衛生機關發揮有效之防疫功能。由於 HIV 針扎處理需為及時性，48~72 小時內方能得到較有效之預防效益，由電話諮詢中發現不少個案已 HIV 體液暴露超過 72 小時，因此需對醫護人員再作持續性教育。對於服用 HAART 預防性投藥之 HIV 體液暴露人員，有必要請 HIV 個案管理師及醫師進行衛教及藥物順從性副作用之說明以加強服用 HAART 之預防效益。

進入體液暴露流程事件中，多位為警消人員，但現今台北市立聯合醫院昆明院區針扎計畫服務限於台北市警消人員，因本計畫人力資源不足，難擴充至全省警消單位。諮詢電話中，多通和體液暴露較無相關性，建議明年可宣傳 1922 防疫專線，由 1922 專線人員篩選，確定進入針扎流程再提供連絡方式，可節省成本及人力資源。尚有許多地區醫院、診所不清楚體液暴露後之專線及處理流程，決定今年 12 月 15 日在北區由台灣愛滋病學會主辦「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」，並建議另外在中區、南區也舉辦相關研討會，加強地區醫療院所的衛教。

對於 HIV 體液暴露目前在台灣仍未有一完整之追蹤報告，可考慮由防疫單位（疾病管制局或衛生局）設計問卷文件協助各 HIV 指定醫院蒐集 HIV 體液暴露人員之基本流行病學、服藥情形與追蹤結果，以了解台灣之本土資料。

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## 參、圖表

表一、「愛滋病毒體液暴露者之諮詢、檢驗、預防性投藥與追蹤專線」護理人員電話諮詢月報

| 月份 | 諮詢通數 | 民眾 | 醫護人員 | 警員義消 | 減害計畫針筒回收人員及其他 |
|---|---|---|---|---|---|
| 1 | 22 | 9 | 7 | 5 | 1 |
| 2 | 31 | 19 | 9 | 3 | 0 |
| 3 | 17 | 14 | 3 | 0 | 0 |
| 4 | 21 | 7 | 13 | 0 | 1 |
| 5 | 26 | 13 | 10 | 2 | 1 |
| 6 | 21 | 5 | 14 | 2 | 0 |
| 7 | 30 | 17 | 12 | 0 | 1 |
| 8 | 30 | 7 | 22 | 1 | 0 |
| 9 | 39 | 15 | 16 | 4 | 4 |
| 10 | 34 | 7 | 23 | 2 | 2 |
| 總計 | 271 | 113 | 129 | 19 | 10 |

表二、「愛滋病毒體液暴露者之諮詢、檢驗、預防性投藥與追蹤專線」針扎事件月報

| 月份 | 事件數 | 醫護檢人員 | 警員義消 | 其他 | 接受 PEP 藥物治療 |
|---|---|---|---|---|---|
| 1 | 3 | 1 | 2 | 0 | 2 |
| 2 | 6 | 3 | 3 | 0 | 1 |
| 3 | 4 | 4 | 0 | 0 | 2 |
| 4 | 7 | 7 | 0 | 0 | 2 |
| 5 | 4 | 2 | 2 | 0 | 1 |
| 6 | 4 | 3 | 1 | 0 | 1 |
| 7 | 5 | 5 | 0 | 0 | 0 |
| 8 | 7 | 5 | 0 | 2 | 5 |
| 9 | 5 | 5 | 0 | 0 | 0 |
| 10 | 4 | 2 | 1 | 1 | 1 |
| 總計 | 49 | 37 | 9 | 3 | 15 |

表三、「愛滋病毒體液暴露者之諮詢、檢驗、預防性投藥與追蹤專線」接受 PEP 藥物治療的職業別月報

| 月份 | 醫師 | 護士 | 檢驗師 | 藥師 | 看護 | 民眾 | 志工 | 警員義消 |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | 0 | 3 | 0 | 1 | 0 | 0 | 1 | 0 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 總計 | 2 | 5 | 1 | 1 | 0 | 1 | 1 | 4 |

表四、「愛滋病毒體液暴露者之諮詢、檢驗、預防性投藥與追蹤專線」接受 PEP 藥物治療個案月報

| 日期 | 醫院名稱 | 性別 | 職業 | 感染源 PA test | 個案 HIV test | 服藥情形 | 追蹤情形 |
|---|---|---|---|---|---|---|---|
| 96.01.02/14:00 | 台北市消防員 | 男 | 消防員 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.01.02/14:00 | 台北市消防員 | 男 | 消防員 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.01.11/09:00 | 中興醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.02.01/09:00 | 陽明醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.02.05/12:10 | 三張梨派出所 | 男 | 警員(替代役) | 陰性 | 陰性 | 否 | |
| 96.02.06/17:30 | 三重分局 | 男 | 警員 | 陰性 | 陰性 | 否 | |
| 96.02.05/09:15 | 和平院區 | 女 | 檢驗師 | 陰性 | 陰性 | 否 | |
| 96.02.15/11:25 | 台北看守所 | 女 | 檢驗師 | 陽性 | 陰性 | 是 | 服 2 週藥 |
| 96.02.16/10:00 | 松山分局 | 男 | 警員 | 陰性 | 陰性 | 否 | |
| 96.03.06/15:30 | 恩主公醫院 | 男 | 醫師 | 陽性 | 陰性 | | 服 2 週藥 |
| 96.03.15/16:30 | 和平院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.03.20/13:00 | 和平院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.03.28/16:50 | 臺安醫院 | 男 | 醫師 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.04.14/02:30 | 和信醫院 | 女 | 護士 | 陰性 | 陰性 | 是 | 服藥 2 天 |
| 96.04.15/19:30 | 中興醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.04.04/17:25 | 陽明醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 96.04.24/14:30 | 基隆監獄 | 女 | 護士 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.04.30/13:15 | 陽明醫院 | 女 | 看護 | 陰性 | 陰性 | 否 | |
| 96.04.28/12:00 | 中興醫院 | 男 | 醫師 | 陰性 | 陰性 | 否 | |
| 96.04.28/18:05 | 中興醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.05.03/10:00 | 金山分局 | 男 | 員警 | 陰性 | 陰性 | 否 | |
| 96.05.18/8:30 | 陽明醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.05.24/11:00 | 和平醫院 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.05.29/15:00 | 亞東醫院 | 男 | 警衛 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.06.22/10:00 | 台北縣派出所 | 男 | 警員 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.06.22/10:30 | 陽明醫院 | 男 | 實習醫師 | 陰性 | 陰性 | 否 | |
| 96.06.25/15:30 | 松德院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.06.29/11:00 | 忠孝院區 | 男 | 醫師 | 陰性 | 陰性 | 否 | |
| 96.07.05/10:40 | 陽明院區 | 女 | 實習護士 | 陰性 | 陰性 | 否 | |
| 96.07.12/14:50 | 松德院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.07.19/16:45 | 陽明院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.07.26/17:30 | 中興院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.07.31/17:05 | 中興院區 | 女 | 檢驗師 | 陰性 | 陰性 | 否 | |
| 960803/14:45 | 陽明院區 | 女 | 病房看護 | 陰性 | 陰性 | 否 | |
| 96.08.09/15:50 | 和平院區 | 女 | 檢驗師 | 陰性 | 陰性 | 否 | |
| 96.08.12/12:38 | 和平院區 | 女 | 護士 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.08.12/18:00 | 和平院區 | 女 | 護士 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.08.14/14:00 | 台大醫院 | 女 | 護士 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.08.16/13:00 | 昆明院區 | 男 | 志工 | 未確認 | 陰性 | 是 | 服藥一個月 |
| 96.08.20/12:30 | 南雅藥局 | 女 | 藥師 | 未確認 | 陰性 | 是 | 服藥一個月 |
| 960903/16:30 | 中興院區 | 女 | 看護 | 陰性 | 陰性 | 否 | |
| 96.09.10/09:45 | 中興院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.09.12/9:30 | 中興院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 96.09.19/10:45 | 中興院區 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 960924/15:30 | 宏日診所 | 女 | 護士 | 陰性 | 陰性 | 否 | |
| 961001/17:00 | | 男 | 民眾 | 陽性 | 陰性 | 是 | 服藥一個月 |
| 96.10.06/17:20 | 松德院區 | 男 | 警衛 | 陰性 | 陰性 | 否 | |
| 961009/10:30 | 和平院區 | 女 | 護士 | 陽性 | 陰性 | 否 | |
| 961017/08:50 | 陽明院區 | 女 | 病防助理 | 陰性 | 陰性 | 否 | |

附件一

## 「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」
## The Conference of HIV Post-Exposure Prophylaxis

宗　　旨：針對醫護警消等高危險 HIV 體液暴露職業者建立完整且統一的 HIV 體液暴露事件處理流程，以降低 HIV 感染的機會，故舉辦此教育訓練課程。

參加對象：對於照護愛滋病患有興趣之醫療人員〈包含感染科、婦產科、兒科、家庭醫學科、急診科、內科、外科等醫護人員及社工人員〉

學分認證：本次研討會將申請相關醫學會學分認證，全程參加者結業時頒發授課證明。

指導單位：衛生署疾病管制局

主辦單位：台大醫院愛滋病防治中心、台灣愛滋病學會

協辦單位：謝維銓教授感染醫學文教基金會

舉辦日期：96 年 12 月 15 日(星期六)

地　　點：台北市仁愛路一段 1 號台大醫學院 101 講堂

報名需知：請於 96 年 11 月 30 日前上網 www.aids-care.org.tw 報名，額滿即截止報名。

內　　容：

| Time | Topic | Speaker (邀請中) |
|---|---|---|
| 13:00~13:20 | Registration | All |
| 13:20~13:30 | Welcome address | 張上淳 主任 |
| 13:30~14:10 | 醫療人員 HIV 體液暴露後之流行病學 | 楊靖慧 首席防疫醫師 |
| 14:10~14:50 | 醫療人員 HIV 體液暴露後之處理流程 | 王永衛 醫務長 |
| 14:50~15:00 | Panel Discussion | 全體講師 |
| 15:00~15:20 | Coffee Break | All |
| 15:20~16:00 | HIV 預防投藥之副作用及注意事項 | 洪健清 醫師 |
| 16:20~17:00 | HIV 體液暴露後之處理流程(實例說明) | 盛望徽 醫師 |
| 17:00~17:20 | Discussion & Closing | 全體講師 |

附件二

參考資料一：因經皮刺傷導致暴露後，建議使用的預防性用藥(PEP)

| 暴露的種類 | 暴露來源病患的 HIV 感染狀態 | | | | |
|---|---|---|---|---|---|
| | 第一級感染狀態 | 第二級感染狀態 | 病患的感染狀態不詳 | 不知來源病患 | 未感染 HIV |
| 較不嚴重者* | 建議使用基本的 PEP§ | 建議使用強效的 PEP | 通常並不須要使用 PEP；但若來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 通常並不須要使用 PEP；但若推測可能的來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 不須使用 PEP |
| 比較嚴重者¶ | 建議使用強效的 PEP† | 建議使用強效的 PEP | 通常並不須要使用 PEP；但若來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 通常並不須要使用 PEP；但若推測可能的來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 不須使用 PEP |

*指如實心針頭（手術縫合針）或表淺的刺傷等。

¶指如大而中空的針頭、深入的刺傷、導致刺傷的器械上可見血液殘留、或被先前留置於病患血管中的針頭所刺傷。

§指下列組合中的任何一種：1. Zidovudine (RETROVIR™; ZDV; AZT) + Lamivudine (EPIVIR™; 3TC); 2. Zidovudine + Emtricitabine (Emtriva™; FTC); 3. Tenofovir DF (Viread™; TDF) + Lamivudine; 4. Tenofovir DF + Emtricitabine; 5. Lamivudine + Stavudine (ZERIT™; d4T); 6. Emtricitabine + Stavudine; 7. Lamivudine + Didanosine (Videx™; ddI); 8. Emtricitabine + Didanosine。以前四種組合為優先考量。

†指基本的 PEP 再加上下列任何一種藥物：1. Lopinavir/ritonavir (Kaletra™; LPV/RTV); 2. Atazanavir (Reyataz™; ATV) ± Ritonavir (Norvir™; RTV); 3. Fosamprenavir (Lexiva™; FOSAPV); 4. Indinavir (Crixivan™; IDV) ± Ritonavir; 5. Saquinavir (Invirase™; SQV) + Ritonavir; 6. Nelfinavir (Viracept™; NFV); 7. Efavirenz (Sustiva™; EFV)。以第一種藥物為優先考量。

參考資料二、因經黏膜或破裂的皮膚接觸所導致的暴露後，建議使用的預防性用藥(PEP)

| 暴露的種類 | 暴露來源病患的 HIV 感染狀態 | | | | |
|---|---|---|---|---|---|
| | 第一級感染狀態 | 第二級感染狀態 | 病患的感染狀態不詳 | 不知來源病患 | 未感染 HIV |
| 少量的暴露* | 建議使用基本的 PEP§ | 建議使用基本的 PEP | 通常並不須要使用 PEP；但若來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 通常並不須要使用 PEP；但若推測可能的來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 不須使用 PEP |
| 大量的暴露¶ | 建議使用基本的 PEP | 建議使用強效的 PEP† | 通常並不須要使用 PEP；但若來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 通常並不須要使用 PEP；但若推測可能的來源病患有感染 HIV 的危險性時，可考慮使用基本的 PEP | 不須使用 PEP |

*指如幾滴的血液或具傳染性的體液。。

¶指如大量的血液潑灑到。

§指下列組合中的任何一種：1. Zidovudine (RETROVIR™; ZDV; AZT) + Lamivudine (EPIVIR™; 3TC); 2. Zidovudine + Emtricitabine (Emtriva™; FTC); 3. Tenofovir DF (Viread™; TDF) + Lamivudine; 4. Tenofovir DF + Emtricitabine; 5. Lamivudine + Stavudine (ZERIT™; d4T); 6. Emtricitabine + Stavudine; 7. Lamivudine + Didanosine (Videx™; ddI); 8. Emtricitabine + Didanosine。以前四種組合為優先考量。

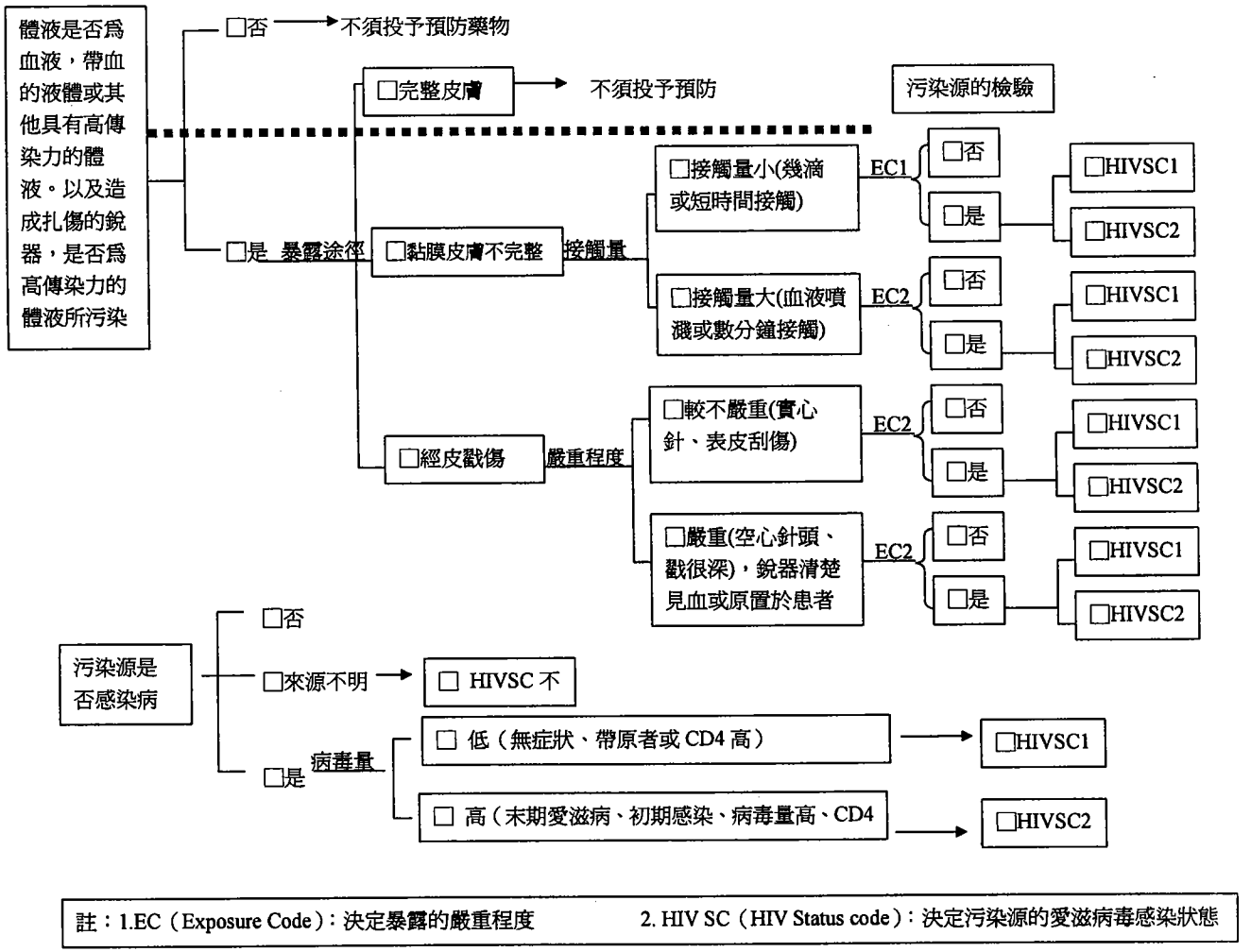
†指基本的 PEP 再加上下列任何一種藥物：1. Lopinavir/ritonavir (Kaletra™; LPV/RTV); 2. Atazanavir (Reyataz™; ATV) ± Ritonavir (Norvir™; RTV); 3. Fosamprenavir (Lexiva™; FOSAPV); 4. Indinavir (Crixivan™; IDV) ± Ritonavir; 5. Saquinavir (Invirase™; SQV) + Ritonavir; 6. Nelfinavir (Viracept™; NFV); 7. Efavirenz (Sustiva™; EFV)。以第一種藥物為優先考量。

參考資料三、各種用於預防性用藥(PEP)的抗 HIV 藥物的使用劑量

| 藥物名稱 | 使用劑量與方法 |
|---|---|
| Zidovudine + lamivudine | 300 mg / 150 mg，一天兩次 |
| Zidovudine + emtricitabine | 300 mg 一天兩次 / 200 mg 一天一次 |
| Tenofovir DF + lamivudine | 300 mg / 300 mg，一天一次 |
| Tenofovir DF + emtricitabine | 300 mg / 200 mg，一天一次 |
| Lamivudine + stavudine | 小於 60 公斤，150 mg / 30 mg 一天兩次<br>大於 60 公斤，150 mg / 40 mg 一天兩次 |
| Emtricitabine + stavudine | 小於 60 公斤，150 mg 一天一次 / 30 mg 一天兩次<br>大於 60 公斤，150 mg 一天一次 / 40 mg 一天兩次 |
| Lamivudine + didanosine | 300 mg / 400 mg 一天一次；或<br>150 mg / 200 mg 一天兩次 |
| Emtricitabine + didanosine | 200 mg / 400 mg 一天一次 |
| Lopinavir/ritonavir | 400 mg / 100 mg 一天一次 |
| Atazanavir | 400 mg 一天一次；若和 tenofovir DF 併用，建議是 300 mg 一天一次，並加上 ritonavir 100 mg 一天一次 |
| Fosamprenavir | 1400 mg 一天兩次；可以和 ritonavir 併用，併用時劑量為 1400 mg / 200 mg 一天一次或 700 mg / 100 mg 一天兩次 |
| Indinavir | 800 mg 每 8 小時一次；但建議和 ritonavir 併用，併用時劑量為 800 mg / 100 mg 一天兩次 |
| Saquinavir/ritonavir | 1000 mg / 100 mg 一天兩次 |
| Nelviravir | 1250 mg 一天兩次（和食物一起服用） |
| Efavirenz | 600 mg 一天一次，最好睡前服用 |

（附件三）

HIV（評估表）：接電話之護理人員諮詢至紅虛線以上，紅虛線以下轉給醫師處理




註：1.EC（Exposure Code）：決定暴露的嚴重程度　　2. HIV SC（HIV Status code）：決定污染源的愛滋病毒感染狀態

附件十

計畫編號：DOH96-DC-1009

行政院衛生署疾病管制局九十六年度科技研究發展計畫

# 愛滋病患醫療照顧及健康諮詢個案管理制度效益評估(二年計畫)

## 研 究 報 告

執行機構：台大醫院愛滋病防治中心

研究人員：謝思民、施鐘卿、田秀禾

執行期間： 96年 1月 1日至 96年 12月 31日

# 目　　錄

壹、中文摘要：

關鍵詞：愛滋病、個案管理

本計畫主要目標為針對 HIV 個案進行個案管理服務後，針對個案、利用醫療情形、危險行為、服藥順從行為、社會穩定度等方面的效益評估。在本計畫進行期間，由個管師進行深度會談後，進入長期追蹤個案的生理、行為及社會穩定度，以在適當時機提供個案必要的衛教指導、諮詢及社會資源聯結，以及適當轉介至減害服務。愛滋個管尚屬發展階段，如何將此制度建立、收案標準、收案評估內容、處置流程、衛教諮詢、主動追蹤流程，乃至於個管師的個案負荷量等，都需要建立標準，以進行評估與討論。

計畫進行期間自民國 95 年 1 月至 96 年 12 月止，共收納 243 位在台大醫院就醫之 HIV 個案。經納管後個案在 CD4 數、HIV 病毒量控制情形、HIV 相關症狀及服藥順從性方面，都有顯著改善成效。在危險性行為方面，可以增加使用保險套頻率達顯著意義，個管師的確可見減少危險性行為及控制危險注射行為的成效。在社會、心理層面也有舒緩焦慮、沮喪情緒、增加告知診斷的正面成效。個管對個案的效益，可以從個案的生理穩定度及個案整體穩定度皆呈現大幅改善的顯著成效。在個案的服藥順從行為及社會穩定度方面，可增加社會支持、降低副作用嚴重度等。經由增加個案的社會穩定度，因而減少使用急性醫療的頻率及費用，是個管服務對個案及醫療資源的直接效益。在減少醫療費用方面的成效，比較經納管後 HIV 個案利用醫療的情形，可見顯著減少門診、急診次數及人數，減少住院天數，因而減少住院費用，達顯著差異水準。因此，個管制度的運用在兩年內即可以顯現有降低醫療費用的成效。

個管的角色功能、服務內容方面，所有接受個案管理滿意度調查個案對個管服務都持正向、肯定的看法，對提供的服務也逐漸依賴此管道，與個管師更建立正向、信賴的護病關係。尤其有 20 位皆填需要提醒就醫(佔 46.5%)，而主動將電話號碼留下。打破原先以為個案爲保護隱私不喜歡被電話打擾的思維，實是個管服務的一大突破。個管師提供電話專線諮詢服務，服務內容中以門診就醫 175 次(30.33%)為最主要服務項目，快速解決個案的醫療及健康問題發揮個管最大功能。主動追蹤服務，也是個管重要角色功能之一。個管師共主動追蹤 38 位未到診個案，而避免個案流失。此外，針對新換藥物為預防嚴重藥物不良反應，共及時處理 7 位發生藥物不良反應的個案，而避免更嚴重 Steven-Johnson syndrome 發生而需住院治療。

本計畫建議，每位個管師對管理個案的個案負荷量(Case Load)，約在 5~10 位(10%)危機處理個管、15~20 位(20%)加強個管及 70~80 位(70%)支持性個管為宜，合理個案負荷量約在 100 人/個管師。唯有，維持在合理的個案負荷量才能維持對個案狀況的深度掌握、避免個案流失。主管當局應持續舉辦愛滋個管師每年進階教育訓練，以增加個管師的文化敏感度。盡速建立愛滋個管師的工作標準及處置流程，以及長期監測成效之機制，以培訓各院所愛滋個管師發揮最大功能，進而降低醫療費用、提高愛滋醫療團隊之服務品質。

## 貳、本文

### （一） 前言

根據疾病管制局台灣地區的統計資料，以每年愛滋新通報個案和增加率來看，民國93年較前一年的HIV年增率76%、94年為100%、95年9月止，較去年同期人數稍減。但隨新增個案增加，台灣的愛滋個案存活人數也逐年增加，到95年9月止，已經有10,916人，近三年皆呈現倍增現象。愛滋毒癮者的快速增加，共用針具感染HIV為主要原因。從91年毒癮愛滋個案僅佔該年總愛滋感染者的1.7%，竄升至93年的30.4%，94年新增毒癮個案達2414人，更佔總愛滋個案的62%，增加率高達2倍。靜脈藥癮已經超越同/雙性戀族群（33.6%），成為目前台灣愛滋病毒感染最主要的傳播途徑。台灣的愛滋存活人數不斷翻新!主要原因為，新感染者快速增加(尤以毒癮個案最快速)、感染個案年輕化趨勢，接受抗HIV藥物治療之個案服用抗HIV藥物後，其存活時間已大為延長、死亡率下降、伺機性感染減少且可維持更健康的身體狀況。愛滋個案服用抗HIV藥物後，仍可維持活躍性行為，如果其仍繼續不安全的性行為，將新增更多HIV感染者！

台灣目前的愛滋醫療現況，94年單年愛滋醫療支出已達到85.5億台幣。在95年1~4月疾病管制局對全國各區HIV感染者的問卷調查中(N=611)，顯示在就醫情形方面：HIV個案平均每年就醫次數約6.8次，平均11.8週會就醫一次。不同感染途徑族群之就醫情形，到指定醫院就醫情形，異性戀有73.5%、同性戀有83.1%、毒癮者有38.6%會就醫。每年平均就醫次數，異性戀6.5次、同性戀7.1次、毒癮者3.4次。平均多久就醫，異性戀15.8週、同性戀14.3週、毒癮者22.6週。HIV個案接受HAART藥物治療情形，粗估約有81%個案目前接受HAART的藥物治療中，其中有76%的個案服藥順從性很好，有20%時常會服用藥物，有約1%個案僅有時服用HAART藥物。在HAART的藥物治療中，僅有19%個案沒有出現藥物副作用，有3%個案會自行調整藥物，尤其女性及在南部地區的HIV個案較會自行調整藥物。結果也顯示，HIV個案最困擾的問題，有18%個案表示維護隱私是最在意的議題，其次是健康狀況佔13%，再其次是工作問題佔11%，同事的態度佔10%。有64%個案表示，最希望獲得醫療工作者的協助，其中有60%希望醫師協助，有25%希望得到社工的協助，尤其在40歲以下的個案，有18%希望有諮詢熱線的協助。最後在性行為方面結果，有54%個案表示仍持續有性行為，尤其18~40歲之個案仍有將進60%繼續有性行為。粗估約有77%個案當有性行為時會全程使用保險套。綜合以上結果，顯見當前台灣愛滋醫療服務的問題有：如何提高毒癮個案接受必要醫療

照顧服務?針對 24%服藥順從性較差的個案，如何提高其規律服藥，以降低 HIV 抗藥性產生且不浪費藥物費用達到治療效果?在醫療服務機構，如何兼顧維護個案隱私下，解決其健康問題及需求，並提供諮詢專線窗口，又可發現個案有社會資源需求下，提供適當的轉介? 專職 HIV 個案管理師，成為台灣愛滋醫療最急迫需建立的醫療服務制度。

歐美各國早出現與我國相同的挑戰，HIV 感染人數龐大，且多為較弱勢的族群，因此 HIV 感染者除須醫療治療服務以外，經濟、精神疾患、藥物濫用、同性戀社群、婦女、貧窮者等，有眾多複雜議題同時出現在 HIV 感染者身上。尤其，如何減少不安全行為(性行為及注射行為)成為公共衛生醫療最關注的議題，但如不改變 HIV 個案所處的社會環境，HIV 個案很難改變其原來的危險行為。提引 HIV 個案想改變危險行為的動機，成為預防 HIV 傳播的最重要策略!美國 CDC 因此，致力於專為 HIV 個案提供其所需的社會服務網路(如：居住、經濟、送餐、教育、戒毒、減害-Harm Reduction 等)。HIV/AIDS 個案管理制度(HIV/AIDS Case Management)在全美各地因應而生!!

HIV/AIDS 個案管理制度(HIV/AIDS Case Management)是一連續階段的過程，為 HIV 個案協調醫療及社會心理服務，有時還需包含 HIV 個案的家人及支持網路。HIV 個管是指經由接受個案、評估個案需求、擬定服務計畫、執行計畫、協調服務、監測追蹤、再評估、個案討論、危機處理及結案的一連串過程。HIV/AIDS 個案管理的活動是多樣化的，除了幫助個案得到及維持個別的服務外，還包含：磋商及代言個案所需的服務、照會、社會心理支持、支持性諮商及一般性的個案衛生教育。

HIV/AIDS 個案管理制度其主要目標是，增進並支持 HIV 個案獨立及其自我效能。因此，個案管理師必須主動參與 HIV 個案的問題決策過程，同時支持個案的隱私權、自我決定、自尊、不受歧視、同感-不受批判的照護，且必須具文化敏感性的高品質個案管理服務。

HIV 個案管理的目的(The Joint AIDS Case Management Protocols, Calif ,March, 2006)1.提供已出現症狀之 HIV 個案適當的治療服務 2.協助個案疾病處理(Disease management)、預防疾病傳染、穩定健康狀況、改善生活品質，及避免昂貴的機構式照護。3.當個案的醫療及社會心理狀況改善，就必須將個案轉介到更適當的服務計畫中。4.促進資源發展 5.加強提供服務者間的協調 6.避免服務重複 7.儘早讓未受到服務的族群，進入服務計畫中 8.爲需機構服務的失能者，提供居家式或社區式服務。藉由執行 HIV/AIDS 個案管理制度，可以促使 HIV 個案得到以下的結果(outcomes)—

1. 提早並持續利用廣泛的健康照護及社會服務
2. 經由整合不同機構的服務，可提供個案更完整的服務

3. 強化的持續性照護，不是片段式健康照護服務
4. 經教育減少疾病繼續傳播—利用緩害(Harm Reduction)技巧，並延緩 HIV 的病程進展
5. 增加其對 HIV 疾病的認識
6. 促進個案使用健康及社會服務資源
7. 加強正向的健康行為(positive health bahavior)，降低危險行為(Risk Reduction)
8. 賦權(Empowermwnt)
9. 改善生活品質

在醫療資源有限下，醫療個案管理(Medical/Nurse Case Management)運用於醫療照護模式在國外已行之有年。1970 年代，個案管理師(Case Manager)一詞最早出現在健康照護系統中，其主要目的是，在社區中(community-based service)持續爲個案協調並連結其可利用的健康照護及社會服務，提供給個案。隨著醫療模式的多樣化，各種醫療服務不斷出現，醫療保險給付複雜化給付更加困難，醫療費用逐漸有限。直到 1980 年代，將此模式引進到急性醫療院所(hospital-based service)，希望在控制醫療成本、有效運用床位下，同時也提供高品質的醫療服務給病患。護理個案管理師(Nurse Case Manager)位居醫院、付費者及病患三者之間的中央角色，經協調、聯結服務資源，爲三方共同創造出最大的利益。

護理個案管理(Nurse Case Management)是經由協調高品質的健康照護服務提供給病患，以符合經濟效益的原則下，滿足病患個別的需求，達到病患正向的健康結果(positive outcome)的一連串過程。護理個管師的角色功能，主要為評估、計畫、促進及代言。她(他)必須具備數種基本技巧，包括：建立正向關係，有效的語言及文件溝通能力，磋商技巧，契約及風險協調的知識，有能力影響改變，持續評值及批判思考分析能力，計畫、有效組織並促進病患及家屬的自主性。護理個案管理(Nurse Case Management)是主護護理的延伸，護理個管師與病患接觸於住院中，協調所有治療及出院計畫等業務，爲病患的治療過程把關、代言病患的需求，並持續服務於出院之後 1。護理個案管理師(Nurse Case Manager)必須與社工個案管理師(Social Worker Case Manager)共同合作，稱為個管核心團隊(Core Case Management Team)，此外還包含各種專業共同合作的團隊工作，如：醫師、精神科醫師、復健師等。經由護理個管師與社工個管師的合作協調，以達到啟動持續的個案評估、發展計畫、執行及評值服務計畫。

實行護理個管之前，需先訂立每科臨床領域中之高危險群的篩選標準。個案管理模

式的目的，在於有效運用醫療資源，進而提供病患完整而持續性的醫療照護，可以達到保證照護之經濟效益、提供機構化照護之選擇機會，最後可促進病患身心功能的提昇。護理個案管理模式的成功，可以有效縮短病患住院天數、提昇個案及家屬之滿意度、使病患的急診利用率下降、有效控制醫療成本並增加醫院床位之運轉率。因此，評估個案管理模式成效的指標，包含病床利用率、病床週轉率、平均住院日、再入院率、再返急診率、後續照護感染率、及病患滿意度。

國內的愛滋個案快速增加，由於提供免費抗 HIV 藥物治療，政府負擔龐大醫療費用，如何在有限的醫療資源下，照護更多的HIV感染者，成為醫療政策的最大挑戰！因此，在急性醫療中實行護理個案管理模式，控制愛滋個案的住院醫療費用、降低住院天數、減少利用急診醫療、減少發生伺機性感染、減少發生院內感染等，同時經護理個管師協調、聯結健康照護服務(跨科部照會、長期照護健康服務網路等)，對無法自我照顧的生活依賴個案，需協調計畫出院後的後續健康照護，以提供高品質的醫療照護。在急性醫療中，實行護理個案管理，成為在提供高品質醫療照護服務時，同時可有效控制愛滋醫療成本的成功契機。

國內大多數愛滋個案仍在社區中，近兩年來新診斷HIV個案的CD4仍高，目前這些愛滋個案健康狀況佳。據國外研究發現，愛滋感染者約有七成仍會繼續其危險行為。針對這些 HIV 感染者，應教育其正確的愛滋疾病及藥物治療觀念，減少危險行為的教育(Risk Reduction)，避免出現伺機性感染的自我照顧行為等，以延緩HIV疾病進展。針對毒癮愛滋個案，還需提供緩害(Harm Reduction)策略(包含針頭交換或維持療法資訊)、協助減少使用毒品、減少出現精神疾患(Mental Illness)、減少出現合併症(如C肝、心內膜炎、蜂窩組織炎、骨髓炎)等議題。針對這群 HIV 個案實行愛滋個案管理模式，經由減少危險行為，還可以避免HIV繼續傳播，威脅大眾健康。

本研究擬建立愛滋個案管理模式，聯合國外的護理個案管理及社工個案管理模式，以愛滋個案管理師在台大醫院內，與專業人員(個案管理師、護理師、社工師、精神科醫師、安寧療護等)及醫師聯合參與，強調多元化專業人力的組合，加上 HIV 感染者本身也負起自我照護的責任，藉由提供感染者愛滋病疾病護理諮商服務、提供衛教訊息、教導減少風險技巧、情緒支持、健康服務轉介及連結服務等，共同執行照護服務計畫及治療，增強疾病防治資訊連結互通共享，增強感染者改變其危險行為模式，避免再次傳染，提高服藥順從性以降低愛滋醫療成本。

（二） 方法

進行地點：臺大醫院愛滋病防治中心

收案對象：目前在臺大醫院追蹤治療的 HIV 病患，符合個案管理條件的個案，皆納入 HIV 個案管理及諮商模式的服務計畫中；自 95 年 1 月至 96 年 10 月底止，共有 243 位 HIV 個案受到 HIV 個案管理的服務。

收案期間：從 95 年 1 月至 96 年 10 月，計畫共進行二年。

本計畫已達成之工作目標：

**A. 建立本土之 HIV 個案管理及諮商模式**

已於計畫期間建立本土化之 HIV 個案管理及諮商模式並順利運作，進行情形如下--

**一、 成立愛滋個案管理諮商討論會：**

(1)依個案目前狀況召集醫師、護理師、個案管理諮商師、社工師等人，以個案討論會方式組成醫療團隊，整合各方意見，擬定最適當之照護目標及計畫。必要時，則聯結跨科部之醫療人員提供醫療服務，由個案管理師進行後續照護及醫療追蹤。

(2)必要時邀請愛滋病 NGO 團體或相關服務組織(如愛滋戒毒村，長期照護收容所)，共同參與愛滋個案資源聯結討論會，就特殊個案之行為、醫療照護和生活輔導等進行資源整合性討論。

**二、 建立並執行愛滋個案管理諮商服務模式：**

(1)專責愛滋個案管理諮商，主動追蹤個案並提供必要的醫療服務及諮商，以達連續性、整體性照護之目標。

(2)全面性評估 HIV 個案後，依其需 HIV 個案管理師主動諮商管理及追蹤之頻率與問題之嚴重性，將個案分別導入危機處理個案管理(Crisis Intervention Management)、加強性個案管理模式(Comprehensive Case Management Model)及支持性個案管理模式(Supportive Case Management Model)。

a. *危機處理個案管理(Crisis Intervention Management)*

指個案出現需緊急處理的危機狀態，此階段個管師需密集與個案會談或電訪、大量的溝通協調相關機構或資源，以先解決緊急問題為個管優先目標。常見危機處理議題包含：突同時診斷腫瘤、想自殺、經濟出現極大變動需緊急安置、情緒困擾、遊民、藥物過敏反應、剛換藥、剛開始藥物治療、需緊急外科開刀、出血等意外狀況的緊急處理、嚴重伺機性感染需緊急住院或瀕死危機處理等狀況。

*b. 加強性個案管理模式(Comprehensive Case Management Model；CCM)—*

指個案出現以上需 HIV 個案管理師收案之任一種情形，即由 HIV 個案管理師收

案，對個案進行全面性評估(包含:疾病進展、症狀治療、情緒評估、社會支持及經濟狀況評估、危險行為評估、自我照顧能力評估等等)，並進入加強性個案管理之服務模式。將視其狀況之嚴重程度，由HIV個案管理師主動追蹤頻率，從每週至每月一次不等（見附件一）。

c. *支持性個案管理模式(Supportive Case Management Model；SCM)*—

指HIV個案並未出現上述需HIV個案管理師收案管理之情形，無論治療、情緒、就醫、危險行為(包含用藥及性行為)等皆無變化，則由HIV個案管理師每3~6個月一次，規則評估個案之疾病、治療、情緒、就醫及危險行為即可。當發現個案出現上述收案標準的任一情形，則立即將個案轉入加強性個案管理模式。

(3) 提供HIV個案管理之主要服務內容：

服務時間從個案確診後開始，包含追蹤檢驗值、持續服藥等，過程中相關診療諮詢、檢驗、服藥指引、症狀處理、心理諮詢、自我照顧衛生教育（包含安全行為衛教）及追蹤輔導等。(圖一)

a. 初次全面性評估個案後，擬定問題及需求、訂立處置目標、進行處置措施及計畫、並主動追蹤評值結果。
b. 主動追蹤高危個案，如毒癮、孕婦、愛滋寶寶、新診斷、未按時就診、斷續服藥及新感染性病等愛滋個案
c. 探詢個案可能繼續傳播HIV的可能危險行為，加以適當的衛教、行為諮商處置，必要時引導進入緩害計畫中（清潔針具計畫或替代療法計畫中）。
d. 早期發現併發症或藥物副作用等症狀，並做適當服藥指引及症狀處置
e. 主動全面評估個案之醫療服務需求（包含資源轉介），提供適切的服務
f. 快速及適切的轉介給相關專科及相關專業組織（如愛滋權促會、戒毒機構等）
g. 提供必要的自我照顧衛教（包含安全行為衛教）

(4)執行愛滋個案管理之**加強性個案管理模式**，服務對象之收案標準—

a. ***新診斷：***

指最近一個月內，經Western Blot或PCR確定診斷為HIV+者，初次至本院就醫者。

b. ***服藥順從性差：***

①指最近6個月內，曾因各種因素未按醫師指示服下80%以上藥物

②或經HAART治療下，因服藥順從性差以致HIV病毒量仍無法達到undetectable之HIV個案。

c. ***半年以上未規則就醫：***

指個案上一次檢驗 CD4<200 個/ml，且近半年內皆未就醫追蹤或治療之個案。

*d. 需長期照護服務：*

①指個案之巴氏量表低於 80 分(生活無法自理)、有鼻胃管、尿管、或氣切等任一種管路留置之依賴個案。

②需長期復健(物理治療、職能治療等任一種)之 HIV 個案

③癌末愛滋個案，需安寧緩和照護之 HIV 個案。

*e. 毒癮愛滋：*

指曾有使用非法藥物史的 HIV 個案，近半年仍有繼續口服、吸食或注射藥物者

*f. 女性個案：*

指女性 HIV+之個案

*g. HIV+孕婦（垂直傳染）：*

指已經懷孕之 HIV+孕婦

*h. 疑似或確定 HIV 感染之寶寶：*

指 HIV+孕婦不論產前有無經 HAART 治療、或剖復產，產下之寶寶，尚未排除 HIV 感染的追蹤期；或已經確立被感染之 HIV 寶寶。

*i. 住院之 HIV 個案:*

指因伺機性感染、HAART 藥物副作用或其他 HIV 相關之併發症(如腫瘤)而住院之 HIV 個案。

三、 建立個案管理諮商之標準流程

(1)建立個案管理之收案標準(如附件二)

(2)建立 HIV 個案管理服務之收案處置程序（如附件三）

(3)建立 HIV 個案管理服務之工作目標（如附件四）

(4)建立 HIV 個案管理服務之追蹤標準（如附件五）

(5)建立 HIV 個案管理之基本資料庫，包含個案基本資料、服藥治療概況、社會心理經濟狀況，危險行為、個案管理處置目標及轉介社會資源情形(包含美沙冬門診及針具交換服務)（如附件六）。

**B. 評估 HIV 個案管理諮商制度之執行效益評估**

本計畫之另一重點為，對 HIV 個案管理諮商制度之執行效益評估。茲就評估效益依 HIV 個案、醫療及社會服務、公共衛生以及國家利益等層面加以評估。以在臺大醫院追蹤治療的 HIV 病患，符合個案管理條件的個案，皆納入 HIV 個案管理及諮商模式的服務計畫中；自 95 年 1 月至 96 年 10 月底止，共有 243 位受到 HIV 個案管理服務者，加以分析其尋求醫療、花費醫療資源及經個案管理模式處理後的效益評估，詳如下節所述。

## （三） 結果

### 一、 個案管理模式進行概況

本計畫在台大醫院進行，在 95 年 1 月至 96 年 10 月期間，針對 HIV 個案就醫時(包含門診、急診、住院等期間)，提供個案管理服務，共納管 243 位 HIV 個案。個管模式建立及運作，請見附件一；個管服務主要在感染科、免疫風濕科、婦產科門診時與個案做深度會談，當發生伺機性感染症狀或嚴重個案住院時，則以照會方式由個管師提供一連串相關服務，詳細收案標準請見附件二，處理個案流程請見附件三、附件四。收案納管後，對個案的追蹤標準請見附件五，不做贅述。

### 二、 納管 HIV 個案之基本資料概況

在計畫期間，總共收案納管 243 位 HIV 個案，所有個案之基本資料如表一所示。所有 243 位納管個案中，男性佔 90.53% 、大部分未婚 180 位佔 74.07% 、教育程度以大學居多 105 人佔 43.21% ，但也有 35 人 14.4% 是中學以下。從表一可見，教育程度為中學以下的個案中，以藥癮者 12 人佔 75% 為多數。年齡分布情形以 31~40 歲佔多數有 101 人佔 41.56% ，其次為 41~50 歲有 57 人佔 23.46% 。其中，不可忽略的是 30 歲以下的年輕人有 54 人佔 22.22% ，顯見感染 HIV 的年齡層在 30 歲以下仍為感染個案的主流。感染因子中，以同性戀(MSM)156 人佔 64.2% 為多數，其次為異性戀共 58 人佔 23.87% ，再其次為靜脈藥癮者 21 人佔 8.64% ，另有 1 人為經輸血而感染個案。在罹病史方面，有 19 人佔 7.82% 為最近 6 個月內診斷之新個案，罹病 13~24 個月內有 53 人佔 21.81% ，以罹病 25~60 個月內有 69 人佔 28.4% 為最多，五年以上個案共有 65 人佔 26.7% 。

在感染疾病的病程方面 CD4 數及 HIV 病毒量情形，有一半以上個案(127 人佔 52.26% )在初診斷 HIV 感染時 CD4<200 個/ml 已在發病階段；而有 14 人 5.76% 其 CD4 數仍高於 500 個/ml，健康狀況良好。初始 HIV 病毒量有 36 人佔 14.81% 已高於 750000 個/ml，屬高病毒量者(200000~750000)有 69 人佔 28.4% ，顯見有大約 43.2% 個案在診斷時，即在疾病快速惡化階段。當收案納管時，有 77 人佔 32.08% 的 CD4 數<200 個/ml，而 CD4 數>500 個/ml 有 50 人佔 20.83% ，與診斷時比較顯見個案的免疫狀況整體已有改善。而在收案納管後個案最後一次的 CD4 及 HIV 病毒量情形，如表一所示，CD4 數<200 個/ml 的人數僅有 48 人佔 20.0% ，而 CD4 數>500 個/ml 有 53 人佔 22.08% 。在 HIV 病毒量的情形，僅有 2 人佔 0.83% 的病毒量在 750000 個/ml 以上，有 143 人佔 59.6% 的 HIV 病毒量在 400 個/ml 以下，控制良好。在納管後有 173 人佔 71.78% 個案已經接受 ART 治療。

## 三、 個管納管後，對個案利用醫療服務方面之成效

所有 243 位收案納管的 HIV 個案，在計畫期間使用醫療的情形如表二所示。整體來看，所有納管個案使用醫療情形皆呈現減少的趨勢。從表二可見平均使用門診及急診次數接減少，(門診從 4.96→4.41，急診從 1.4 次→1.29 次)且使用急診的人數也從 25 人減少到 14 人。以門診來看，納管前後的門診次數減少達到呈現顯著差異(OR: 0.22~1.60，p<0.001)。再以就診間隔來看，納管個案是否皆規律就醫，平均就診間隔從 61.56 天減少到 60.6 天，且就醫人數從原先的 166 人上升到 230 人(少數剛收案個案尚未回診)，納管後就醫間隔的變化已達到顯著差異(OR:-10.22~-0.84) P<0.01，顯示個案管理師納管後，的確可以改變個案使用門、急診醫療頻率，持續規律就醫並減少利用急診醫療。

在使用住院醫療方面，個案在納管前後分別有 61、54 人次住院，總住院天數從納管前平均 27.74 天減少到納管後的 16.44 天。再以每次平均住院天數來看，從納管前平均住院天數 21.77 天/次減少到 12.34 天/次。雖在住院醫療方面，納管前後尚未達到顯著差異，可能是個案數不足(僅 21 人在納管前後皆有住院經驗)，故未顯現其差異。但就個案實際住院狀況比較，已呈現減少住院之趨勢。

再就納管前後醫療費用分析來看，門診平均費用從 20323.5 元/次上升到 31152.9 元/次呈現上升趨勢，乃因個案納管後大部分個案進入規律就醫及治療計畫，因增加 ART 藥費而大幅增加，達顯著差異(OR:-24914.66~-19724.19，P<0.001)。但在住院費用方面，納管後住院平均費用從 50480 元/次減少到 35569.5 元/次(OR:9858.96~39925，P<0.001)，平均每次住院可減少約 15000 元。

總之，納管後 HIV 個案利用醫療的情形，可顯著減少門診、急診次數及人數，減少住院天數，因而減少住院費用，達顯著差異水準。因此，個管制度的運用在兩年內即可以顯現有降低醫療費用的成效。

## 四、 個管納管後對個案的 HIV 疾病、治療、相關症狀、風險及社會心理的成效

在 243 位納管個案中，比較個案在經過個管納管後在疾病、治療、症狀、危險行為、及社會心理、經濟狀態等方面的變化情形。由表三可見，在納管前後個案的疾病階段、症狀及治療等，皆顯現在納管前、後有顯著差異出現。經納管後，整體個案的 CD4 數及 HIV 病毒量控制情形，皆出現改善的變化 P<0.001。由於 ART 治療效果的顯現，個案的 HIV 相關活動功能情形(**The Karnofsky Performance Scale**)呈現上升，達顯著 P<0.001。在 HIV 相關症狀、服藥順從性方面，經過納管後個案也都有相同的改善，達顯著差異 P<0.001。顯見，個案的疾病及生理功能經過治療後，以及個管師的納管後都有顯著改善的成效。

在社會、經濟、心理層面(見表三)，經納管後個案在揭露人數及情緒、睡眠、進食狀態等方面，皆達到明顯改善效果，且統計上呈現顯著差異(P<0.01)。由以上結果可知，個案管理模式的處理後，的確可以幫助個案對較多人揭露此診斷(告知他人此診斷)，及在情緒狀態的紓解達到改善成效。

總之，經個案管理納管後，對個案的生理疾病層面有幫助改善；在危險行為方面有增加安全性行為的成效；在社會、心理層面也有舒緩焦慮、沮喪情緒、增加告知診斷的正面成效。

顯然，個案如果能規律就醫、接受個管服務必須有一定的穩定度。如進一步分別針對個案的生理、社會及個案的穩定度來看，生理穩定度指個案在疾病進展及身體狀況的穩定程度，在此以個案的 CD4 及 HIV 病毒量兩大指標相加為生理穩定度；個案目前的社會、經濟、情緒等總合為社會穩定度；而生理穩定度＊社會穩定度為個案的總體穩定度。如表四所示，經個管納管後，個案的生理穩定度及個案整體穩定度皆呈現大幅改善的顯著差異($P<0.001$)。顯示，個管的確可以大幅改善個案的生理及整體穩定度。

## 五、 個案管理對減少危險行為(性及注射行為)的成效

在危險性行為方面(請見表三)，收案納管個案中有 65 人，原與固定性伴侶平均有 71.38%會使用保險套，經納管後有固定性伴侶人數增加為 71 人，且與固定性伴侶平均有 82.39%會使用保險套，固定性伴侶人數及使用保險套頻率都增加，達統計上顯著差異($P<0.05$)。在不固定性伴侶方面，原有 14 人有不固定性伴侶，平均使用保險套為 52.86%；納管後僅 12 人仍有不固定性伴侶，而使用保險套達 39.25%。經統計檢驗後，固定性伴侶使用保險套頻率增加，達顯著意義($P<0.05$)。因此，在危險性行為方面，經個管納管處理後，可以改變使用保險套頻率達顯著意義，顯見個管在降低危險性行為方面頗具成效。

針對藥癮者使用藥物的危險注射行為頻率方面(請見表五)，18 位有用藥癮個案(包含注射及吸食或拉 k 等)的藥物濫用情形。有 13 人在納管期間已經停止使用注射藥物，持續使用毒品個案由 5 人減少為 4 人。使用海洛因情形，納管後藥癮者使用海洛因的情形及大部分個案都停止使用藥物 9 人(50%)，有 5 人(27.7%)個案僅在假日或偶而使用，或僅每月平均使用 1~3 次，處於可控制藥物的階段。仍有 3 人必須每週或每天固定注射藥物，處於成癮階段。大體來說，藥癮個案使用藥物的危險行為呈現減少的趨勢，因個案數較少因此尚未顯現其顯著成效。但所有藥癮者都知道美沙冬門診及針具交換站，且其中有 6 位同時固定每天到美沙冬門診服用美沙冬替代治療。

在藥癮個案使用藥物種類方面(請見表五)，除海洛因外，搖頭丸及 K 他命等個案在夜店用藥方面，因個案數很少（3 位），無法顯現其改變之成效。綜合以上結果，個管師針對減少個案危險行為方面，的確可見減少危險性行為及控制危險注射行為的成效。

## 六、 納管個案對個案管理服務的滿意度情形

為了解所有納管個案對提供個案管理服務的滿意度情形，乃抽樣 43 位個案進行服務滿意度調查，結果如表六所示。調查中以問卷方式，請個案就個案管理師提供的服務內容給予分數，以 Liker Scale 5 分量表，5-非常同意、4-同意、3 普通、2-不同意、1-非常不同意等勾選，其中對於尚不需服務或無此需要的服務項目則以沒有接觸 0 分計算。表六可見調查結果，個案對提供個案管理服務的整體滿意度達到 96.75 分(以滿分

100 分計算)。其中對於個管師的態度最為滿意(平均 4.91 分)、其次為尊重個案隱私(平均 4.81 分)、再其次為需要臨時加掛號時，會主動協助以提高服務的可近性(平均 4.76 分)。其中以提供社工服務及轉介的滿意度較低，乃因為需要此服務的個案數較少。有關提供法律方面訊息的服務，也因為個案大多無此方面的需求，而顯現較低滿意分數。尤其在調查中，特別針對為預防忘記到診，詢問個案是否須提供提醒就醫的電話提醒服務? 所有 43 位接受調查者中，有 20 位皆填需要(佔 46.5%)，且將電話號碼留下。打破原先以為個案爲保護隱私不喜歡被電話打擾的思維，實是個管服務的一大突破。

綜而言之，個案對個管服務都持正向、肯定的看法，對提供的服務也逐漸依賴此管道，與個管師更建立正向、信賴的護病關係。

## 七、 個案管理師經電話諮詢專線協助之成效

個管師提供單一諮詢電話專線，可以增加個案利用個管師的即時性及有效性。因此，個管師除被動提供各式諮詢服務外，還需針對未返診、換新治療藥物等個案，進行主動電話追蹤，以及時協助個案、及時處理不良藥物過敏反應，以避免健康惡化。因此，計畫期間共提供 577 次電話專線諮詢服務，如圖一及圖二所示，服務內容中以門診就醫 175 次(30.33%)為最主要服務項目，其次是症狀處理 136 次(23.57%)、再其次是用藥諮詢 67 次(11.61%)，可快速解決個案的醫療及健康問題。

此外，針對個案可能面臨的問題主動追蹤服務，也是個管重要角色功能之一。其中以個案未到診時的主動電話追蹤，最能預防個案流失，個管師共主動追蹤 38 位未到診個案，並安排後續追蹤門診以避免個案流失。此外，針對新換藥物為預防嚴重藥物不良反應，共約追蹤 40 位換新藥物個案，其中有 7 位個案發生藥物不良反應後，因個管師追蹤而立即適當處理，避免更嚴重 Steven-Johnson syndrome 發生。另，對因出現身體症狀而來電尋求支援之個案，個管師也與安排快速門診或急診治療，而縮短個案等待醫療的時間。

## 八、 經個管師轉介社會服務資源之成效

經收案納管之 HIV 個案中，個管師經深度會談後發現個案需危機處理、轉介其他社會服務資源者，立即進行聯絡相關社會服務資源及轉介事宜。在 243 位個案中，有 45 位需危機處理，其問題包含：突同時診斷腫瘤、想自殺、經濟出現極大變動需緊急安置、情緒困擾、遊民、早上剛自監獄出來、藥物過敏反應、剛換藥、剛開始藥物治療、需緊急外科開刀、出血等意外狀況的緊急處理、嚴重伺機性感染需緊急住院、瀕死危機處理等狀況。計畫中共有 22 位經個管師聯繫後，順利轉介安置或聯結社會服務資源，提供個案急難救助、緊急醫療補助、短期生活費支援等等。

因此，個管師在轉介社會資源方面發揮極大功能，將個案引導到穩定社會狀況，增加其社會穩定度，也發揮避免個案流失、花費更高醫療資源等結果。

## 九、 測服藥順從性之因子

此計畫中，針對個案的服藥順從行為及影響因子調查後，針對服藥順從性的預測因子進行回歸分析後，如表七所示。以多因子迴歸分析後，發現會顯著影響服藥順從性的因子有：藥物副作用的嚴重度、個案目前的 CD4 數、社會支持程度、罹病史、感染風險分數以及初診斷時之 CD4 數等因子，可預測個案的服藥順從行為，解釋力達 27%。經迴歸分析後，可知以下迴歸方程式: 服藥順從性=9.46 +0.294 副作用嚴重度－ 0.242 收案時 CD4 數+0.208 社會支持+0.227 罹病史+0.136 感染風險分數－0.122 初始 CD4 數。

從以上結果可知，欲增加個案的服藥順從行為可從增加社會支持、降低副作用嚴重度等方面加以著手。

## 十、 預測社會穩定度之因子

由相關性檢驗中發現，個案的社會穩定度與使用急診的次數相關係數達－0.662 (P:0.01)。因此社會穩定度是影響利用醫療的重要因子，為探討影響個案社會穩定度的影響因子，經迴歸分析後發現，教育程度、服藥順從分數、KPS (**Karnofsky Performance Scale**)、收案時 CD4 數、是否藥癮者及納管時間等變項為重要影響因子，可預測個案的社會穩定度，解釋力達 26.7%(P<0.001)。經迴歸分析後，可得以下迴歸方程式：社會穩定度=16.812+1.27 教育程度+0.16 服藥順從性分數+0.11KPS 分數－0.001 收案時 CD4 數－藥癮者+0.285 納管時間。

由以上結果可知，個管師納管個案有助於增加其社會穩定度，是個管服務對個案及醫療費用的直接效益。

## 十一、 個案討論會

本計畫中收案之 HIV 個案，因醫療需求複雜當需舉辦跨科部醫療會議時，則由個案管理者或醫師、社工主動召集，進行 HIV 個案討論會。自 95 年 1 月至 96 年 10 月底，因個案的不同醫療或服務需求而召開 74 次個案討論會，共有 96 位護理人員、35 位醫師及 59 人次社工參加。

參與個案討論會的主要成員：個案的 HIV 主治醫師、各科部醫師(小兒科、安寧療護、婦科、腫瘤科等)、HIV 個案管理師、社工師、義工等等。必要時也舉辦家屬討論會，主要在處理出院安置議題、複雜個案的社會資源聯結、轉介減害計畫等等，也讓愛滋醫療團隊成員間密切合作、且處理目標一致。尤其，個管師可藉由團隊討論後能練續性追蹤個案的重要問題，並達到長期監測預防個案的健康或社會狀況再度出現惡化狀況。

## 十二、 個管師之個案負荷量(Case Load)及成效

經由個管師運作個管服務 22 個月後，在處理個案醫療、社會、危險行為、轉介等

過程中，平均一位個案約需花費 20 分鐘深度會談。會談內容包含身體評估、治療評估、服藥行為評估及討論、性行為、用藥行為、社會及心理狀況等。每次深度會談所需時間，依個管分級來看，支持性個管約需 10 分鐘、加強性個管約需 20 分鐘、危機處理的個管則約需 40~60 分鐘。需危機處理的個案，後續須追蹤或會談的頻率應至少每週電話追蹤或會談，各級個管會談內容及追蹤頻率如附件五所示。本計畫中收案納管 243 位個案，危機處理個案有 45 人（18.5% ）、加強個管有 57 人（23.5% ）以及支持個管 141 人（58 % ），由兩位個管師每日超時處理個案問題。因此，每位個管師對處理個案的管理個案負荷量(Case Load)，約在 5~10 位(10%)危機處理個管、15~20 位(20%)加強個管及 70~80 位(70%)支持性個管為宜。維持在合理的個案負荷量才能維持對個案狀況的深度掌握、避免個案流失。

個管師對 HIV 個案除在維護高度隱私的原則下深度會談外，還需持續同時處理個案的行為問題、聯絡轉介、諮商衛教等，故平均處理個案所需時間及人力約為會談的 2~3 倍。以平均值計算，個管師每星期最多約可會談並處理 10~15 人(非初診個案)。本計畫中有 2 位個案管理師進行此計畫，目前約維持個案持續就診率為 98%，仍出現幾位個案流失之狀況。因此，合理個案負荷量約在 100 人/個管師。

## （四） 結論與建議

本計畫主要目標為針對 HIV 個案進行個案管理服務後，針對個案、利用醫療情形、危險行為、服藥順從行為、社會穩定度等方面的效益評估。在本計畫進行期間，由個管師進行深度會談後，進入長期追蹤個案的生理、行為及社會穩定度，以在適當時機提供個案必要的衛教指導、諮詢及社會資源聯結，以及適當轉介至減害服務。愛滋個管尚屬發展階段，如何將此制度建立、收案標準、收案評估內容、處置流程、衛教諮詢、主動追蹤流程，乃至於個管師的個案負荷量等，都需要建立標準，以進行評估與討論。

經納管個案的 CD4 數及 HIV 病毒量控制情形，皆出現改善的變化 P<0.001。由於 ART 治療效果的顯現，個案的 HIV 相關活動功能情形(The Karnofsky Performance Scale)也呈現上升，達顯著意義(P<0.001)。在 HIV 相關症狀及服藥順從性方面，經過納管後個案也都有相同的改善，達顯著差異 P<0.001。顯見，個案的疾病及生理功能經過治療後，以及個管師的納管後都有顯著改善的成效。在危險性行為方面，經個管納管處理後，可以增加使用保險套頻率達顯著意義，顯見個管在降低危險性行為方面頗具成效。個管師針對減少個案危險行為方面，的確可見減少危險性行為及控制危險注射行為的成效。因此，經個案管理對個案的生理疾病層面可幫助改善；在危險行為方面有增加安全性行為的成效；在社會、心理層面也有舒緩焦慮、沮喪情緒、增加告知診斷的正面成效。個管對個案的效益，可以從個案的生理穩定度及個案整體穩定度皆呈現大幅改善的顯著差異(P<0.001)，得知個管的確可以大幅改善個案的生理及整體穩定度。針對個案的服藥順從行為及社會穩定度方面，從上節結果可知，增加社會支持、降低副作用嚴重度等可增加個案的服藥順從行為。而個管師納管個案有助於增加其社會穩定度，因而減少使用急性醫療的頻率及費用，是個管服務對個案及醫療資源的直接效益。

個管的角色功能、服務內容方面，所有接受個案管理滿意度調查個案對個管服務都

持正向、肯定的看法，對提供的服務也逐漸依賴此管道，與個管師更建立正向、信賴的護病關係。尤其有 20 位皆填需要提醒就醫(佔 46.5%)，而主動將電話號碼留下。打破原先以為個案爲保護隱私不喜歡被電話打擾的思維，實是個管服務的一大突破。個管師提供電話專線諮詢服務，服務內容中以門診就醫 175 次(30.33%)為最主要服務項目，其次是症狀處理 136 次(23.57%)，快速解決個案的醫療及健康問題發揮個管最大功能。主動追蹤服務，也是個管重要角色功能之一。個管師共主動追蹤 38 位未到診個案，而避免個案流失。此外，針對新換藥物為預防嚴重藥物不良反應，共約追蹤 40 位換新藥物個案，並及時處理 7 位發生藥物不良反應的個案，而避免更嚴重 Steven-Johnson syndrome 發生而需住院治療。另，安排快速門診或急診治療對因出現身體症狀而來電尋求支援之個案而言，更縮短個案等待醫療的時間。

至於個案管理在減少醫療費用方面的成效，比較經納管後 HIV 個案利用醫療的情形，可見顯著減少門診、急診次數及人數，減少住院天數，因而減少住院費用，達顯著差異水準。因此，個管制度的運用在兩年內即可以顯現有降低醫療費用的成效。最後，每位個管師對管理個案的個案負荷量(Case Load)，約在 5~10 位(10%)危機處理個管、15~20 位(20%)加強個管及 70~80 位(70%)支持性個管為宜，合理個案負荷量約在 100 人/個管師。唯有，維持在合理的個案負荷量才能維持對個案狀況的深度掌握、避免個案流失。

進行本計畫後，針對國內愛滋個案管理的運作模式有以下幾點建議：

1、 爲讓個案管理師能充分發揮功能並顧及管理品質，建議愛滋個管師的個案負荷量約在 100 人/個管師。並將個案依其問題所需、劃分等級，以利後續追蹤及管理頻率。

2、 由於個案管理師需針對危險行為(性及注射行為)作深入會談評估，故應每年針對相關議題進行深入議題探討，以維持對這些危險行為次文化的敏感度，及運用減害的技巧。

3、 由於，愛滋個案管理尚屬建立雛型階段，建議主管當局應盡速建立工作標準、制訂相關工作手冊，以讓各醫療院所的個管師有一致的工作目標及標準流程可依循。

4、 由於個管師可明顯降低愛滋個案利用急診、住院醫療等資源及費用，建議擴大進行愛滋個管於所有愛滋指定醫療院所，以更有效紓解政府衛生當局的愛滋醫療費用的龐大成本支出。

5、 個案管理制度的運作，有利於各院所之愛滋醫療服務品質，建議可納入評鑑醫療照護團隊的功能及服務品質監測項目之一。

6、 爲長期監測個案管理的實務進行及實際效益，應建立中、長期評估機制，以深入評估此制度之中、長程效益。

7、 各院所愛滋個案急速增加，爲服務更多的個案，更有效追蹤個案之狀況，建議各機構內需建立資料庫軟體，供各院所管理師針對個案的問題建立個案資料庫，可節省個案管理師之時間及人力。

## （五） 參考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（六） 圖、表

## 表一、納管個案基本資料(N=243)

| | | Total | | 一般個案 | | 服藥順從性差 | | 藥癮 | | 暫停治療 | | 新診斷 | | 未治療 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 89 | 36.63 | 57 | 23.46 | 16 | 6.58 | 3 | 1.23 | 34 | 13.99 | 19 | 7.82 |
| 性別 | 女 | 23 | 9.47 | 16 | 17.98 | 1 | 1.75 | 1 | 6.25 | 1 | 33.33 | 2 | 5.88 | 1 | 5.26 |
| | 男 | 220 | 90.53 | 73 | 82.02 | 56 | 98.25 | 15 | 93.75 | 2 | 66.67 | 32 | 94.12 | 18 | 94.74 |
| 年齡 | 21~30 歲 | 54 | 22.22 | 10 | 11.24 | 11 | 19.30 | 2 | 12.50 | | | 16 | 47.06 | 8 | 42.11 |
| | 31~40 歲 | 101 | 41.56 | 35 | 39.33 | 30 | 52.63 | 9 | 56.25 | 2 | 66.67 | 9 | 26.47 | 9 | 47.37 |
| | 41~50 歲 | 57 | 23.46 | 27 | 30.34 | 12 | 21.05 | 4 | 25.00 | 1 | 33.33 | 5 | 14.71 | | |
| | 51~60 歲 | 22 | 9.05 | 12 | 13.48 | 2 | 3.51 | 1 | 6.25 | | | 3 | 8.82 | 2 | 10.53 |
| | >60 歲 | 9 | 3.70 | 5 | 5.62 | 2 | 3.51 | | | | | 1 | 2.94 | | |
| 婚姻 | 未婚 | 180 | 74.07 | 55 | 61.80 | 49 | 85.96 | 12 | 75.00 | 3 | 100.00 | 27 | 79.41 | 16 | 84.21 |
| | 已婚 | 34 | 13.99 | 17 | 19.10 | 6 | 10.53 | 2 | 12.50 | | | 3 | 8.82 | 2 | 10.53 |
| | 同居 | 4 | 1.65 | 3 | 3.37 | | | | | | | 1 | 2.94 | | |
| | 矜寡 | 11 | 4.53 | 10 | 11.24 | | | | | | | 1 | 2.94 | | |
| | 已婚但分居 | 1 | 0.41 | 1 | 1.12 | | | | | | | | | | |
| | 離婚、假結婚 | 13 | 5.35 | 3 | 3.37 | 2 | 3.51 | 2 | 12.50 | | | 2 | 5.88 | 1 | 5.26 |
| 教育程度 | 中學（含）以下 | 35 | 14.40 | 15 | 16.85 | 3 | 5.26 | 12 | 75.00 | | | 2 | 5.88 | 1 | 5.26 |
| | 高中、職 | 69 | 28.40 | 26 | 29.21 | 21 | 36.84 | 4 | 25.00 | | | 4 | 11.76 | 4 | 21.05 |
| | 二專、三專、五專 | 28 | 11.52 | 9 | 10.11 | 8 | 14.04 | | | 2 | 66.67 | 3 | 8.82 | 4 | 21.05 |
| | 大學、四技、二專 | 105 | 43.21 | 35 | 39.33 | 25 | 43.86 | | | 1 | 33.33 | 25 | 73.53 | 10 | 52.63 |
| | 碩、博士 | 6 | 2.47 | 4 | 4.49 | | | | | | | | | | |
| 感染因子 | MSM | 156 | 64.20 | 54 | 60.67 | 43 | 75.44 | | | 2 | 66.67 | 24 | 70.59 | 17 | 89.47 |
| | heter | 58 | 23.87 | 31 | 34.83 | 9 | 15.79 | 1 | 6.25 | 1 | 33.33 | 9 | 26.47 | 2 | 10.53 |
| | IDU | 21 | 8.64 | 4 | 4.49 | 1 | 1.75 | 15 | 93.75 | | | | | | |
| | Bisexal | 6 | 2.47 | | | 4 | 7.02 | | | | | 1 | 2.94 | | |
| | BT | 1 | 0.41 | | | | | | | | | | | | |
| 罹病史分級 | 0~6m | 19 | 7.82 | 1 | 1.12 | | | | | | | 17 | 50.00 | 1 | 5.26 |
| | 7~12ms | 37 | 15.23 | 14 | 15.73 | 1 | 1.75 | 2 | 12.50 | | | 16 | 47.06 | 3 | 15.79 |
| | 13~24ms | 53 | 21.81 | 19 | 21.35 | 11 | 19.30 | 7 | 43.75 | | | 1 | 2.94 | 4 | 21.05 |
| | 25~60MS | 69 | 28.40 | 26 | 29.21 | 22 | 38.60 | 6 | 37.50 | 1 | 33.33 | | | 9 | 47.37 |
| | 61~120MS | 36 | 14.81 | 16 | 17.98 | 13 | 22.81 | | | 1 | 33.33 | | | 2 | 10.53 |
| | 121~180MS | 23 | 9.47 | 11 | 12.36 | 8 | 14.04 | 1 | 6.25 | | | | | | |
| | >180MS | 6 | 2.47 | 2 | 2.25 | 2 | 3.51 | | | 1 | 33.33 | | | | |

## 表一、納管個案基本資料(N=243)(續)

| | | Total | | 藥物副作用 | | 感染性病 | | 治療失敗 | | 長照 | | 精神疾病 | | 其他* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 3 | 1.23 | 6 | 2.47 | 4 | 1.65 | 7 | 2.88 | 2 | 0.82 | 3 | 1.23 |
| 性別 | 女 | | | | | | | | | | | | | | |
| | 男 | 23 | 9.47 | 1 | 33.33 | | | | | | | | | | |
| 年齡 | 21~30 歲 | 220 | 90.53 | 2 | 66.67 | 6 | 100.00 | 4 | 100.00 | 7 | 100.00 | 2 | 100.00 | 3 | 100.00 |
| | 31~40 歲 | 54 | 22.22 | | | 4 | 66.67 | 1 | 25.00 | 1 | 14.29 | 1 | 50.00 | | |
| | 41~50 歲 | 101 | 41.56 | 1 | 33.33 | 2 | 33.33 | 1 | 25.00 | 2 | 28.57 | | | 1 | 33.33 |
| | 51~60 歲 | 57 | 23.46 | 2 | 66.67 | | | 2 | 50.00 | 2 | 28.57 | 1 | 50.00 | 1 | 33.33 |
| | >60 歲 | 22 | 9.05 | | | | | | | 1 | 14.29 | | | 1 | 33.33 |
| 婚姻 | 未婚 | 9 | 3.70 | | | | | | | 1 | 14.29 | | | | |
| | 已婚 | 180 | 74.07 | 2 | 66.67 | 6 | 100.00 | 3 | 75.00 | 5 | 71.43 | 2 | 100.00 | | |
| | 同居 | 34 | 13.99 | 1 | 33.33 | | | | | 1 | 14.29 | | | 2 | 66.67 |
| | 矜寡 | 4 | 1.65 | | | | | | | | | | | | |
| | 已婚但分居 | 11 | 4.53 | | | | | | | | | | | | |
| | 離婚、假結婚 | 1 | 0.41 | | | | | | | | | | | | |
| 教育程度 | 中學（含）以下 | 13 | 5.35 | | | | | 1 | 25.00 | 1 | 14.29 | | | 1 | 33.33 |
| | 高中、職 | 35 | 14.40 | | | | | 1 | 25.00 | 1 | 14.29 | | | | |
| | 二專、三專、五專 | 69 | 28.40 | 3 | 100.00 | 1 | 16.67 | 1 | 25.00 | 2 | 28.57 | | | 3 | 100.00 |
| | 大學、四技、二專 | 28 | 11.52 | | | | | | | 1 | 14.29 | 1 | 50.00 | | |
| | 碩、博士 | 105 | 43.21 | | | 5 | 83.33 | 2 | 50.00 | 2 | 28.57 | | | | |
| 感染因子 | MSM | 6 | 2.47 | | | | | | | 1 | 14.29 | 1 | 50.00 | | |
| | heter | 156 | 64.20 | 1 | 33.33 | 5 | 83.33 | 3 | 75.00 | 6 | 85.71 | 1 | 50.00 | | |
| | IDU | 58 | 23.87 | 2 | 66.67 | | | | | 1 | 14.29 | | | 2 | 66.67 |
| | Bisexal | 21 | 8.64 | | | | | 1 | 25.00 | | | | | | |
| | BT | 6 | 2.47 | | | 1 | 16.67 | | | | | | | | |
| 罹病史分級 | 0~6m | 1 | 0.41 | | | | | | | | | | | 1 | 33.33 |
| | 7~12ms | 19 | 7.82 | | | | | | | | | | | | |
| | 13~24ms | 37 | 15.23 | | | | | | | | | | | 1 | 33.33 |
| | 25~60MS | 53 | 21.81 | 1 | 33.33 | 4 | 66.67 | 1 | 25.00 | 2 | 28.57 | 2 | 100.00 | 1 | 33.33 |
| | 61~120MS | 69 | 28.40 | | | 1 | 16.67 | 1 | 25.00 | 3 | 42.86 | | | | |
| | 121~180MS | 36 | 14.81 | 1 | 33.33 | | | 1 | 25.00 | 2 | 28.57 | | | | |
| | >180MS | 23 | 9.47 | 1 | 33.33 | 1 | 16.67 | | | | | | | 1 | 33.33 |

＊ 外籍、輸血感染、癌症各1人

## 表一、納管個案基本資料(N=243)(續)

| | | Total | | 一般個案 | | 服藥順從性差 | | 藥癮 | | 暫停治療 | | 新診斷 | | 未治療 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 89 | 36.63 | 57 | 23.46 | 16 | 6.58 | 3 | 1.23 | 34 | 13.99 | 19 | 7.82 |
| 初始CD4（分級） | <200 | 127 | 52.26 | 52 | 58.43 | 39 | 68.42 | 3 | 18.75 | | | 18 | 52.94 | | |
| | 201~350 | 35 | 14.40 | 10 | 11.24 | 9 | 15.79 | 5 | 31.25 | 1 | 33.33 | 4 | 11.76 | 5 | 26.32 |
| | 351~500 | 27 | 11.11 | 9 | 10.11 | 3 | 5.26 | 2 | 12.50 | | | 3 | 8.82 | 10 | 52.63 |
| | >500 | 14 | 5.76 | 2 | 2.25 | 1 | 1.75 | 2 | 12.50 | 1 | 33.33 | 4 | 11.76 | 2 | 10.53 |
| | 無資料 | 40 | 16.46 | 16 | 17.98 | 5 | 8.77 | 4 | 25.00 | 1 | 33.33 | 5 | 14.71 | 2 | 10.53 |
| 初始PVL（分級） | 51~400 | 15 | 6.17 | 7 | 7.87 | 5 | 8.77 | 1 | 6.25 | 1 | 33.33 | | | | |
| | 401~50000 | 45 | 18.52 | 11 | 12.36 | 8 | 14.04 | 8 | 50.00 | 1 | 33.33 | 5 | 14.71 | 7 | 36.84 |
| | 50001~100000 | 20 | 8.23 | 7 | 7.87 | 2 | 3.51 | 2 | 12.50 | | | 3 | 8.82 | 4 | 21.05 |
| | 100001~200000 | 29 | 11.93 | 8 | 8.99 | 10 | 17.54 | 2 | 12.50 | | | 4 | 11.76 | 3 | 15.79 |
| | 200000~750000 | 69 | 28.40 | 29 | 32.58 | 16 | 28.07 | 1 | 6.25 | 1 | 33.33 | 14 | 41.18 | 2 | 10.53 |
| | >750000 | 36 | 14.81 | 14 | 15.73 | 10 | 17.54 | | | | | 7 | 20.59 | 2 | 10.53 |
| | 無資料 | 29 | 11.93 | 13 | 14.61 | 6 | 10.53 | 2 | 12.50 | | | 1 | 2.94 | 1 | 5.26 |
| 收案時CD4（分級） | <200 | 77 | 32.08 | 22 | 24.72 | 29 | 50.88 | 1 | 6.25 | | | 18 | 54.55 | | |
| | 201~350 | 49 | 20.42 | 19 | 21.35 | 11 | 19.30 | 4 | 25.00 | | | 8 | 24.24 | 4 | 21.05 |
| | 351~500 | 51 | 21.25 | 22 | 24.72 | 8 | 14.04 | 3 | 18.75 | 1 | 33.33 | 4 | 12.12 | 9 | 47.37 |
| | >500 | 50 | 20.83 | 24 | 26.97 | 5 | 8.77 | 5 | 31.25 | 2 | 66.67 | 2 | 6.06 | 6 | 31.58 |
| | 無資料 | 13 | 5.42 | 2 | 2.25 | 4 | 7.02 | 3 | 18.75 | | | 1 | 3.03 | | |
| 收案時PVL（分級） | <50 | 40 | 16.67 | 26 | 29.21 | 9 | 15.79 | | | | | | | | |
| | 51~400 | 82 | 34.17 | 48 | 53.93 | 18 | 31.58 | 3 | 18.75 | | | 3 | 9.09 | 1 | 5.26 |
| | 401~50000 | 47 | 19.58 | 6 | 6.74 | 12 | 21.05 | 9 | 56.25 | 2 | 66.67 | 8 | 24.24 | 8 | 42.11 |
| | 50001~100000 | 16 | 6.67 | 3 | 3.37 | 4 | 7.02 | 1 | 6.25 | 1 | 33.33 | 2 | 6.06 | 5 | 26.32 |
| | 100001~200000 | 12 | 5.00 | 1 | 1.12 | 3 | 5.26 | | | | | 4 | 12.12 | 3 | 15.79 |
| | 200000~750000 | 21 | 8.75 | 3 | 3.37 | 4 | 7.02 | | | | | 8 | 24.24 | 2 | 10.53 |
| | >750000 | 11 | 4.58 | 1 | 1.12 | 3 | 5.26 | | | | | 7 | 21.21 | | |
| | 無資料 | 11 | 4.58 | 1 | 1.12 | 4 | 7.02 | 3 | 18.75 | | | 1 | 3.03 | | |
| 收案時治療情形 | 無 | 66 | 27.27 | 6 | 6.74 | 10 | 17.54 | 12 | 75.00 | 3 | 100.00 | 14 | 41.18 | 17 | 89.47 |
| | 有 | 176 | 72.73 | 83 | 93.26 | 47 | 82.46 | 4 | 25.00 | | | 20 | 58.82 | 2 | 10.53 |
| | 無資料 | | | | | | | | | | | | | | |

## 表一、納管個案基本資料(N=243)(續)

| | | Total | | 藥物副作用 | | 感染性病 | | 治療失敗 | | 長照 | | 精神疾病 | | 其他* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 3 | 1.23 | 6 | 2.47 | 4 | 1.65 | 7 | 2.88 | 2 | 0.82 | 3 | 1.23 |
| 初始CD4（分級） | <200 | 127 | 52.26 | 2 | 66.67 | 2 | 33.33 | 4 | 100.00 | 5 | 71.43 | 1 | 50.00 | | |
| | 201~350 | 35 | 14.40 | | | 1 | 16.67 | | | | | | | | |
| | 351~500 | 27 | 11.11 | | | | | | | | | | | | |
| | >500 | 14 | 5.76 | | | 1 | 16.67 | | | | | | | 1 | 50.00 |
| | 無資料 | 40 | 16.46 | 1 | 33.33 | 2 | 33.33 | | | 2 | 28.57 | 1 | 50.00 | 1 | 50.00 |
| 初始PVL（分級） | 51~400 | 15 | 6.17 | | | | | | | 1 | 14.29 | | | | |
| | 401~50000 | 45 | 18.52 | | | 2 | 33.33 | | | 1 | 14.29 | | | 2 | 66.67 |
| | 50001~100000 | 20 | 8.23 | | | | | | | 1 | 14.29 | | | 1 | 33.30 |
| | 100001~200000 | 29 | 11.93 | | | | | | | 2 | 28.57 | | | | |
| | 200000~750000 | 69 | 28.40 | 2 | 66.67 | 1 | 16.67 | 1 | 25.00 | 1 | 14.29 | 1 | 50.00 | | |
| | >750000 | 36 | 14.81 | | | 1 | 16.67 | 2 | 50.00 | | | | | | |
| | 無資料 | 29 | 11.93 | 1 | 33.33 | 2 | 33.33 | 1 | 25.00 | 1 | 14.29 | 1 | 50.00 | | |
| 收案時CD4（分級） | <200 | 77 | 32.08 | | | | | 3 | 75.00 | 3 | 42.86 | 1 | 50.00 | | |
| | 201~350 | 49 | 20.42 | | | 2 | 40.00 | | | | | 1 | 50.00 | | |
| | 351~500 | 51 | 21.25 | 1 | 33.33 | | | 1 | 25.00 | 2 | 28.57 | | | | |
| | >500 | 50 | 20.83 | 1 | 33.33 | 3 | 60.00 | | | 1 | 14.29 | | | 1 | 50.00 |
| | 無資料 | 13 | 5.42 | 1 | 33.33 | | | | | 1 | 14.29 | | | 1 | 50.00 |
| 收案時PVL（分級） | <50 | 40 | 16.67 | 1 | 33.33 | 2 | 40.00 | | | 2 | 28.57 | | | | |
| | 51~400 | 82 | 34.17 | 1 | 33.33 | 1 | 20.00 | | | 3 | 42.86 | 2 | 100.00 | 2 | 100.00 |
| | 401~50000 | 47 | 19.58 | | | 1 | 20.00 | 1 | 25.00 | | | | | | |
| | 50001~100000 | 16 | 6.67 | | | | | | | | | | | | |
| | 100001~200000 | 12 | 5.00 | | | | | 1 | 25.00 | | | | | | |
| | 200000~750000 | 21 | 8.75 | | | 1 | 20.00 | 2 | 50.00 | 1 | 14.29 | | | | |
| | >750000 | 11 | 4.58 | | | | | | | | | | | | |
| | 無資料 | 11 | 4.58 | 1 | 33.33 | | | | | 1 | 14.29 | | | | |
| 收案時治療情形 | 無 | 66 | 27.27 | | | 2 | 40.00 | | | 1 | 14.29 | 1 | 50.00 | | |
| | 有 | 176 | 72.73 | 3 | 100.00 | 3 | 60.00 | 4 | 100.00 | 6 | 85.71 | 1 | 50.00 | 3 | 100.00 |
| | 無資料 | | | | | | | | | | | | | | |

＊ 外籍、輸血感染、癌症各1人

## 表一、納管個案基本資料(N=243)(續)

| | | Total | | 一般個案 | | 服藥順從性差 | | 藥癮 | | 暫停治療 | | 新診斷 | | 未治療 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 89 | 36.63 | 57 | 23.46 | 16 | 6.58 | 3 | 1.23 | 34 | 13.99 | 19 | 7.82 |
| 最近CD4(分級) | <200 | 48 | 20.00 | 11 | 12.36 | 20 | 35.71 | 1 | 6.25 | | | 11 | 32.35 | | |
| | 201~350 | 65 | 27.08 | 25 | 28.09 | 11 | 19.64 | 3 | 18.75 | | | 11 | 32.35 | 10 | 52.63 |
| | 351~500 | 44 | 18.33 | 19 | 21.35 | 7 | 12.50 | 3 | 18.75 | 2 | 66.67 | 8 | 23.53 | 4 | 21.05 |
| | >500 | 53 | 22.08 | 27 | 30.34 | 6 | 10.71 | 4 | 25.00 | 1 | 33.33 | 4 | 11.76 | 5 | 26.32 |
| | 無資料 | 30 | 12.50 | 7 | 7.87 | 12 | 21.43 | 5 | 31.25 | | | | | | |
| 最近PVL(分級) | <50 | 32 | 13.33 | 14 | 15.73 | 7 | 12.50 | 2 | 12.50 | | | 6 | 17.65 | | |
| | 51~400 | 111 | 46.25 | 64 | 71.91 | 19 | 33.93 | 5 | 31.25 | | | 12 | 35.29 | 3 | 15.79 |
| | 401~50000 | 37 | 15.42 | 2 | 2.25 | 11 | 19.64 | 3 | 18.75 | 3 | 100.00 | 9 | 26.47 | 7 | 36.84 |
| | 50001~100000 | 11 | 4.58 | 1 | 1.12 | 3 | 5.36 | 1 | 6.25 | | | | | 6 | 31.58 |
| | 100001~200000 | 4 | 1.67 | 1 | 1.12 | | | | | | | 2 | 5.88 | 1 | 5.26 |
| | 200000~750000 | 13 | 5.42 | | | 5 | 8.93 | | | | | 2 | 5.88 | 2 | 10.53 |
| | >750000 | 2 | 0.83 | | | | | | | | | 2 | 5.88 | | |
| | 無資料 | 30 | 12.50 | 7 | 7.87 | 11 | 19.64 | 5 | 31.25 | | | 1 | 2.94 | | |
| 最近治療情形 | 無 | 50 | 20.75 | 4 | 4.49 | 5 | 8.93 | 9 | 56.25 | 3 | 100.00 | 11 | 32.35 | 15 | 78.95 |
| | 有 | 173 | 71.78 | 83 | 93.26 | 41 | 73.21 | 5 | 31.25 | | | 23 | 67.65 | 2 | 10.53 |
| | 無資料 | 18 | 7.47 | 2 | 2.25 | 10 | 17.86 | 2 | 12.50 | | | | | 2 | 10.53 |

## 表一、納管個案基本資料(N=243)(續)

| | | Total | | 藥物副作用 | | 感染性病 | | 治療失敗 | | 長照 | | 精神疾病 | | 其他* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | 個案數 | 243 | 100.00 | 3 | 1.23 | 6 | 2.47 | 4 | 1.65 | 7 | 2.88 | 2 | 0.82 | 3 | 1.23 |
| 最近CD4(分級) | <200 | 48 | 20.00 | | | | | 3 | 75.00 | 2 | 28.57 | | | | |
| | 201~350 | 65 | 27.08 | | | 1 | 20.00 | | | 2 | 28.57 | 1 | 50.00 | 1 | 50.00 |
| | 351~500 | 44 | 18.33 | | | 1 | 20.00 | | | | | | | | |
| | >500 | 53 | 22.08 | 2 | 66.67 | 2 | 40.00 | | | 1 | 14.29 | | | | |
| | 無資料 | 30 | 12.50 | 1 | 33.33 | 1 | 20.00 | 1 | 25.00 | 2 | 28.57 | 1 | 50.00 | 1 | 50.00 |
| 最近PVL(分級) | <50 | 32 | 13.33 | 1 | 33.33 | | | | | 2 | 28.57 | | | | |
| | 51~400 | 111 | 46.25 | 1 | 33.33 | 2 | 40.00 | | | 2 | 28.57 | 1 | 50.00 | 2 | 100.00 |
| | 401~50000 | 37 | 15.42 | | | 2 | 40.00 | | | | | | | | |
| | 50001~100000 | 11 | 4.58 | | | | | | | | | | | | |
| | 100001~200000 | 4 | 1.67 | | | | | | | | | | | | |
| | 200000~750000 | 13 | 5.42 | | | | | 3 | 75.00 | 1 | 14.29 | | | | |
| | >750000 | 2 | 0.83 | | | | | | | | | | | | |
| | 無資料 | 30 | 12.50 | 1 | 33.33 | 1 | 20.00 | 1 | 25.00 | 2 | 28.57 | 1 | 50.00 | | |
| 最近治療情形 | 無 | 50 | 20.75 | | | 2 | 40.00 | | | 1 | 14.29 | | | | |
| | 有 | 173 | 71.78 | 3 | 100.00 | 3 | 60.00 | 3 | 75.00 | 5 | 71.43 | 2 | 100.00 | 3 | 100.00 |
| | 無資料 | 18 | 7.47 | | | | | 1 | 25.00 | 1 | 14.29 | | | | |

＊ 外籍、輸血感染、癌症各1人

表二、個案納管前後利用醫療之變化(N=243)

| 項目 | 收案時間 | 個數 | 平均數 | 標準差 | 範圍 | 最小值 | 最大值 | 95%信賴區間 | P |
|---|---|---|---|---|---|---|---|---|---|
| 門診次數 | 前 | 204 | 4.96 | 3.44 | 31.00 | 1 | 32 | 〔0.22~1.60〕 | ※※※ |
| | 後 | 239 | 4.41 | 3.41 | 19.00 | 1 | 20 | | |
| 急診次數 | 前 | 25 | 1.40 | 1.41 | 7.00 | 1 | 8 | 〔-6.61~10.61〕 | |
| | 後 | 14 | 1.29 | 0.61 | 2.00 | 1 | 3 | | |
| 就診間隔 | 前 | 166 | 61.56 | 31.36 | 177.50 | 4.5 | 182 | 〔-10.22~-0.84〕 | ※※ |
| | 後 | 230 | 60.60 | 29.01 | 211.50 | 5.5 | 217 | | |
| 住院次數 | 前 | 61 | 1.34 | 1.39 | 10.00 | 1 | 11 | 〔-0.69~10.61〕 | |
| | 後 | 54 | 1.35 | 0.62 | 2.00 | 1 | 3 | | |
| 總住院天數 | 前 | 61 | 27.74 | 30.52 | 153.00 | 2 | 155 | 〔-12.07~8.65〕 | |
| | 後 | 54 | 16.44 | 14.06 | 60.00 | 2 | 62 | | |
| 住院平均天數 | 前 | 61 | 21.77 | 20.95 | 105.00 | 2 | 107 | 〔-7.70~4.59〕 | |
| | 後 | 54 | 12.34 | 10.08 | 54.00 | 2 | 56 | | |
| 門診平均費用 | 前 | 142 | 20323.5 | 5414.9 | 42540.0 | 2729 | 45269 | 〔-24914.66~-19724.19〕 | ※※※ |
| | 後 | 239 | 31152.9 | 21761.4 | 104415.0 | 0 | 104415 | | |
| 住院平均費用 | 前 | 38 | 50480.0 | 54525.3 | 262481.0 | 84 | 262565 | 〔9858.96~39925.90〕 | ※※※ |
| | 後 | 54 | 10559.3 | 35569.5 | 227562.0 | 0 | 227562 | | |

※※ P<0.01；※※※ P<0.001

## 表三、HIV 個案納管前後之相關症狀、治療、風險及社會心理變化情形(N=243)

| 項目 | 項次 | 收案時間 | 個數 | 平均數 | 標準差 | 最小值 | 最大值 | P |
|---|---|---|---|---|---|---|---|---|
| 疾病階段 | CD4 分級# | 前 | 229 | 2.33 | 1.16 | 1 | 4 | ※※※ |
| | | 後 | 213 | 2.49 | 1.11 | 1 | 4 | |
| | PVL 分級## | 前 | 231 | 5.06 | 1.72 | 1 | 7 | ※※※ |
| | | 後 | 214 | 5.51 | 1.33 | 1 | 7 | |
| 症狀及治療 | 卡巴斯基功能程度量表分數### | 前 | 243 | 91.03 | 15.65 | 10 | 100 | ※※※ |
| | | 後 | 243 | 94.81 | 14.27 | 30 | 100 | |
| | 有無愛滋病相關症狀 | 前 | 243 | 0.17 | 0.38 | 0 | 1 | |
| | | 後 | 243 | 0.06 | 0.23 | 0 | 1 | |
| | 愛滋病症狀數 | 前 | 243 | 0.39 | 0.98 | 0 | 5 | ※※※ |
| | | 後 | 243 | 0.10 | 0.45 | 0 | 4 | |
| | 服藥順從性差分數 | 前 | 243 | 9.96 | 7.40 | 0 | 18 | ※※※ |
| | | 後 | 243 | 12.02 | 6.66 | 0 | 18 | |
| | 服藥順從性差程度 | 前 | 169 | 4.22 | 1.34 | 1 | 5 | ※※※ |
| | | 後 | 193 | 4.61 | 0.96 | 1 | 5 | |
| | 副作用症狀數 | 前 | 243 | 0.86 | 1.55 | 0 | 8 | |
| | | 後 | 243 | 0.92 | 1.53 | 0 | 9 | |
| | 副作用嚴重度 | 前 | 243 | 0.51 | 0.76 | 0 | 2 | |
| | | 後 | 243 | 0.56 | 0.75 | 0 | 2 | |
| | 感染風險分數 | 前 | 243 | 0 | 4 | 0.70 | 0.49 | |
| | | 後 | 243 | 0 | 4 | 0.68 | 0.47 | |
| | 固定伴侶使用保險套 | 前 | 65 | 71.38 | 39.68 | 0 | 100 | ※ |
| | | 後 | 71 | 82.39 | 34.29 | 0 | 100 | |
| | 不固定伴侶使用保險套 | 前 | 14 | 52.86 | 42.68 | 0 | 100 | |
| | | 後 | 12 | 39.25 | 44.12 | 0 | 100 | |

※※ P<0.01；※※※ P<0.001

【註】1. # CD4 分級：1=<200；2=201~350；3=351~500；4=>500

2. ## PVL 分級：1=>750000；2=401~750000；3=51~400；4=<50

3. ### 卡巴斯基功能程度量表分數 The Karnofsky Performance Scale

表三、HIV個案納管前後之相關症狀、治療、風險及社會心理變化情形(N=243)(續)

| 項目 | 項次 | 收案時間 | 個數 | 平均數 | 標準差 | 最小值 | 最大值 | P |
|---|---|---|---|---|---|---|---|---|
| 社會心理變化 | 揭露人數 | 前 | 243 | 1.61 | 1.32 | 0 | 7 | ※※※ |
| | | 後 | 243 | 1.73 | 1.29 | 0 | 7 | |
| | 揭露分數 | 前 | 243 | 2.91 | 4.31 | -12 | 18 | |
| | | 後 | 243 | 3.11 | 4.59 | -15 | 18 | |
| | 情緒狀態 | 前 | 241 | 7.59 | 2.39 | 0 | 10 | ※※※ |
| | | 後 | 241 | 6.91 | 3.01 | 1 | 10 | |
| | 社會支持分數 | 前 | 243 | 3.08 | 2.54 | 0 | 6 | |
| | | 後 | 243 | 3.12 | 2.48 | 0 | 6 | |
| | 居住情形 | 前 | 242 | 8.36 | 2.29 | 0 | 10 | |
| | | 後 | 243 | 8.47 | 2.21 | 0 | 10 | |
| | 工作情形 | 前 | 243 | 2.94 | 2.34 | 0 | 5 | |
| | | 後 | 243 | 3.00 | 2.30 | 0 | 5 | |
| | 經濟情形 | 前 | 243 | 4.00 | 1.22 | 0 | 5 | |
| | | 後 | 243 | 4.01 | 1.23 | 0 | 5 | |
| | 情緒狀況 | 前 | 241 | 6.91 | 3.01 | 10 | 2 | |
| | | 後 | 241 | 7.59 | 2.39 | 10 | 2 | |
| | 睡眠情形 | 前 | 243 | 3.08 | 1.37 | 0 | 4 | ※※ |
| | | 後 | 243 | 3.25 | 1.31 | 0 | 4 | |
| | 進食情形 | 前 | 239 | 2.77 | 0.53 | 0 | 3 | ※※ |
| | | 後 | 239 | 2.86 | 0.43 | 0 | 3 | |

※※ P<0.01；※※※ P<0.001

表四、個案穩定度變化情形(N=243)

| 項目 | 收案時間 | 平均數 | 標準差 | 最小值 | 最大值 | 差異的 95% 信賴區間 | | P |
|---|---|---|---|---|---|---|---|---|
| 生理穩定度 | 前 | 7.38 | 2.38 | 2 | 11 | -0.97 | -0.417 | ※※※ |
| | 後 | 7.96 | 1.92 | 1 | 11 | | | |
| 社會穩定度 | 前 | 31.09 | 7.60 | 4 | 43 | -5.12 | 10.627 | |
| | 後 | 32.34 | 6.91 | 3 | 44 | | | |
| 個案穩定度 | 前 | 217.91 | 94.80 | 0 | 387 | -41.61 | -19.327 | ※※※ |
| | 後 | 255.64 | 89.70 | 0 | 430 | | | |

※※※ P<0.001

表五、藥癮者用藥及危險行為概況(n=18)

| 收案時間 | | | 前 | | 後 | |
|---|---|---|---|---|---|---|
| 項目 | | VALUE | 次數 | 百分比 | 次數 | 百分比 |
| 靜脈藥物濫用 | 使用毒品 | 無 | 13 | 72.20 | 14 | 77.78 |
| | | 有 | 5 | 27.80 | 4 | 22.22 |
| | 不共用針具 | 無 | 13 | 72.22 | 14 | 77.78 |
| | | 有 | 5 | 27.78 | 4 | 22.22 |
| | 丟棄針具 | 無 | 15 | 83.33 | 14 | 77.78 |
| | | 有 | 3 | 16.67 | 4 | 22.22 |
| | 消毒部位 | 無 | 18 | 100.00 | 17 | 94.44 |
| | | 有 | | | 1 | 5.56 |
| | 安全注射分數 | 0 分 | 13 | 72.22 | 14 | 77.78 |
| | | 1 分 | 2 | 11.11 | 3 | 16.67 |
| | | 2 分 | 3 | 16.67 | 1 | 5.56 |
| 性行為 | 性行為 | 無 | 13 | 72.22 | 12 | 66.67 |
| | | 有 | 5 | 27.78 | 6 | 33.33 |
| | 口交 | 無 | 17 | 94.44 | 17 | 94.44 |
| | | 有 | 1 | 5.56 | 1 | 5.56 |
| | 肛交 | 無 | 16 | 88.89 | 16 | 88.89 |
| | | 有 | 2 | 11.11 | 2 | 11.11 |
| | 陰道交 | 無 | 15 | 83.33 | 14 | 77.78 |
| | | 有 | 3 | 16.67 | 4 | 22.22 |
| | 固定伴侶 | 無 | 14 | 77.78 | 13 | 72.22 |
| | | 有 | 4 | 22.22 | 5 | 27.78 |
| | 固定伴侶用套 | 50% | 1 | 5.56 | 1 | 5.56 |
| | | 70% | 1 | 5.56 | 4 | 22.22 |
| | | 100% | 2 | 11.11 | | |
| | 不固定伴侶 | 無 | 14 | 77.78 | 14 | 77.78 |
| | | 有 | 4 | 22.22 | 4 | 22.22 |
| | 不固定伴侶用套 | 50% | 1 | 5.56 | 1 | 5.56 |
| | | 100% | 3 | 16.67 | 3 | 16.67 |

表五、藥癮者用藥及危險行為概況(n=18)（續）

| 收案時間 | | | 前 | | 後 | |
|---|---|---|---|---|---|---|
| 項目 | | VALUE | 次數 | 百分比 | 次數 | 百分比 |
| 其他用藥 | 海洛因使用頻率 | 無 | 10 | 55.56 | 9 | 50.00 |
| | | 偶而 | 3 | 16.67 | 4 | 22.22 |
| | | 假日 | 1 | 5.56 | 1 | 5.56 |
| | | <1/月→1~3/月 | 1 | 5.56 | 1 | 5.56 |
| | | >3 次/週 | 2 | 11.11 | 2 | 11.11 |
| | | >3 次/天 | 1 | 5.56 | 1 | 5.56 |
| | 靜脈注射藥物 | 無 | 14 | 77.78 | 14 | 77.78 |
| | | 有 | 4 | 22.22 | 4 | 22.22 |
| | 海洛因 | 無 | 14 | 77.78 | 13 | 72.22 |
| | | 有 | 4 | 22.22 | 5 | 27.78 |
| | 吸食藥物 | 無 | 17 | 94.44 | 17 | 94.44 |
| | | 有 | 1 | 5.56 | 1 | 5.56 |
| | 安仔 | 無 | 16 | 88.89 | 16 | 88.89 |
| | | 有 | 2 | 11.11 | 2 | 11.11 |
| | 搖頭丸 | 無 | 17 | 94.44 | 17 | 94.44 |
| | | 有 | 1 | 5.56 | 1 | 5.56 |
| | 拉K | 無 | 15 | 83.33 | 15 | 83.33 |
| | | 有 | 3 | 16.67 | 3 | 16.67 |
| | 一粒眠 | 無 | 18 | 100.00 | 18 | 100.00 |

## 表六、納管個案對個案管理服務滿意度狀況(n=43)

| 題次 | 項目 | 平均數 | 標準差 | 變異數 | 個數 | 最小值~最大值 |
|---|---|---|---|---|---|---|
| 12 | 態度親切和善 | 4.91 | 0.29 | 0.09 | 43 | 4~5 |
| 11 | 尊重個案隱私 | 4.81 | 0.40 | 0.16 | 42 | 4~5 |
| 3 | 協助加掛號 | 4.76 | 0.44 | 0.19 | 33 | 4~5 |
| 4 | 保持聯絡管道 | 4.71 | 0.46 | 0.21 | 35 | 4~5 |
| 5 | 立即協助就醫、掛號(於出現症狀時) | 4.70 | 0.47 | 0.22 | 33 | 4~5 |
| 7 | 防止再次感染性病之衛教 | 4.70 | 0.46 | 0.22 | 40 | 4~5 |
| 1 | 針對個案健康狀況提供詳細健康指導及諮詢服務 | 4.69 | 0.52 | 0.27 | 42 | 3~5 |
| 6 | 立即協助症狀處理、教導處理症狀的方法或技巧 | 4.68 | 0.47 | 0.23 | 34 | 4~5 |
| 13 | 提供戒癮或美沙冬治療轉介、相關的服務資源 | 4.67 | 0.49 | 0.24 | 12 | 4~5 |
| 2 | 提供個案詳細的藥物治療指導 | 4.65 | 0.54 | 0.29 | 37 | 3~5 |
| 8 | 提供別科就醫訊息、協助掛號 | 4.61 | 0.50 | 0.25 | 31 | 4~5 |
| 9 | 提供相關法律訊息 | 4.56 | 0.65 | 0.42 | 25 | 3~5 |
| 10 | 提供社工服務及轉介 | 4.30 | 1.02 | 1.04 | 23 | 1~5 |
| 14 | 服務整體滿意度分數(1~100 分) | 96.75 | 5.04 | 25.42 | 40 | 80~100 |

【註】5=非常同意；4=同意；3=普通；2=不同意；1=非常不同意；0=沒有接觸；999=未填

## 表七、服藥順從行為預測因子

| 進入變項順序 | 多元相關係數 | 決定係數 R | 增加量 △R2 | 淨 F 值 (△F) | B | Beta (β) |
|---|---|---|---|---|---|---|
| 截距 | | | | | 9.463 | |
| 副作用嚴重度 | 0.3518 | 0.1238 | 0.1238 | 31.781 | 2.634 | 0.294 |
| CD4 數 | 0.4187 | 0.1753 | 0.0515 | 13.992 | -0.007 | -0.242 |
| 社會支持分數 | 0.4572 | 0.2091 | 0.0338 | 9.528 | 0.563 | 0.208 |
| 罹病史 | 0.4882 | 0.2384 | 0.0293 | 8.536 | 0.031 | 0.227 |
| 感染風險分數 | 0.5057 | 0.2557 | 0.0174 | 5.156 | 1.299 | 0.136 |
| 初使 cd4 | 0.5199 | 0.2702 | 0.0145 | 4.378 | 0.000 | -0.122 |

【註】1. 非標準化迴歸方程式

2. 服藥順從性=9.46+0.294 副作用嚴重度-0.242 收案時 CD4 數+0.208 社會支持+0.227 罹病史+0.136 感染風險分數-0.122 初始 CD4 數

## 表八、個案社會穩定度預測因子

| 進入變項順序 | 多元相關係數 | 決定係數 R | 增加量△R2 | B | Beta(β) |
|---|---|---|---|---|---|
| (常數) | | | | 16.812 | |
| 教育程度 | 0.304 | 0.093 | 0.089 | 1.269 | 0.216 |
| 服藥遵從分數 | 0.386 | 0.149 | 0.142 | 0.158 | 0.170 |
| K.P.S 分數# | 0.440 | 0.194 | 0.183 | 0.110 | 0.238 |
| CD4 分級 | 0.479 | 0.229 | 0.216 | -0.001 | -0.208 |
| 藥癮者 | 0.503 | 0.253 | 0.237 | -4.421 | -0.169 |
| 納管時間 | 0.517 | 0.267 | 0.248 | 0.285 | 0.122 |

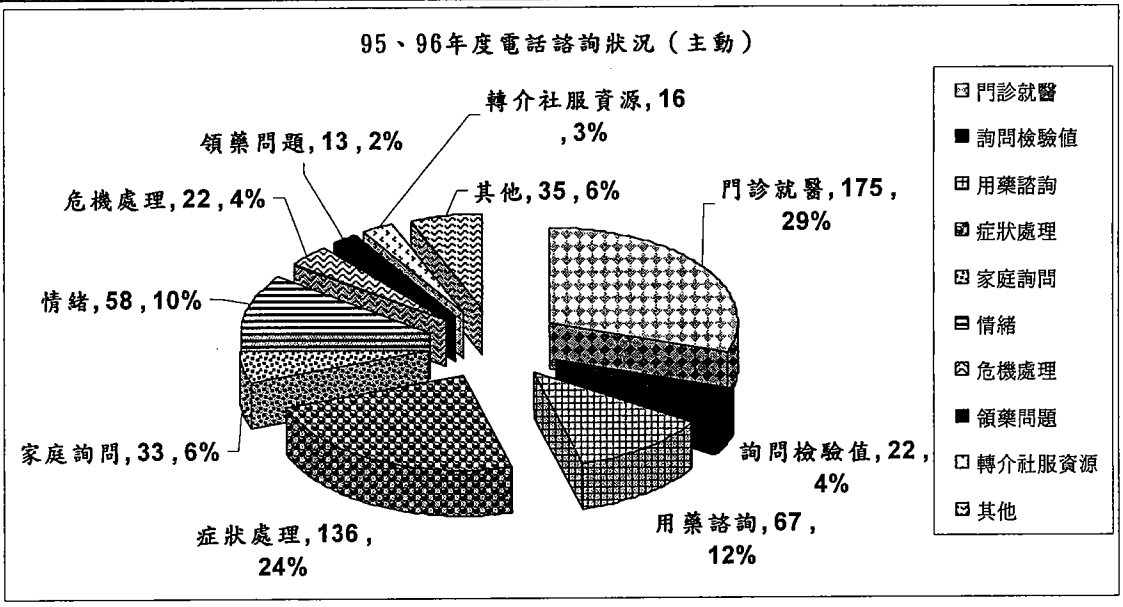
【註】1. 社會穩定度=16.812+1.27 教育程度+0.16 順從性分數+0.11KPS 分數-0.001 收案時 CD4-藥癮者+0.285 納管時間

2. # 卡巴斯基功能程度量表分數 The Karnofsky Performance Scale

## 圖一、電話諮詢狀況

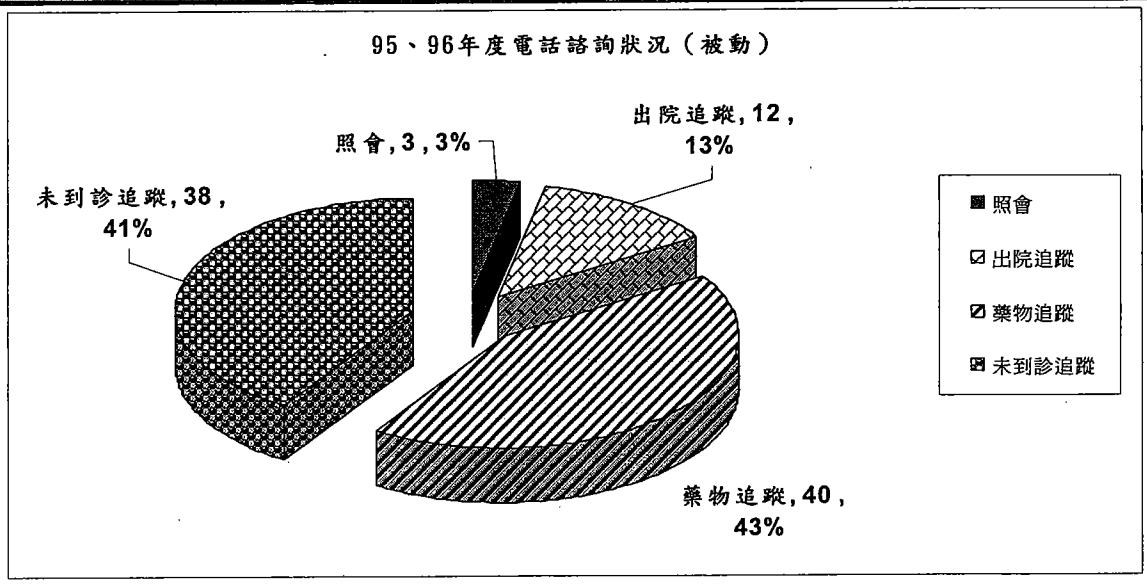
1. 主動電話諮詢狀況

| 年度 | 來電次數 | 門診就醫 | 詢問檢驗值 | 用藥諮詢 | 症狀處理 | 家庭詢問 | 情緒 | 危機處理 | 領藥問題 | 轉介社服資源 | 其他 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 95、96 年度 | 577 | 175 | 22 | 67 | 136 | 33 | 58 | 22 | 13 | 16 | 35 |
| 比率 | 100% | 30.33% | 3.81% | 11.61% | 23.57% | 5.72% | 10.05% | 3.81% | 2.25% | 2.77% | 6.07% |




2. 被動電話諮詢狀況

| 年度 | 去電次數 | 照會 | 出院追蹤 | 藥物追蹤 | 未到診追蹤 |
|---|---|---|---|---|---|
| 95、96 年度 | 73 | 3 | 12 | 40 | 38 |
| 比率 | 43.98% | 1.81% | 7.23% | 24.10% | 22.89% |



（七） 附錄

## 附錄一、HIV 個案管理之模式及定義

「個案管理」是經由多重階段的過程，為 HIV+個案協調其需要的醫療及社會心理服務，甚至還需包含個案的家屬或親密的支持系統。「個案管理」的過程包含：收案、評估需求、擬定服務計畫、執行服務計畫、協調所需的服務、監測及追蹤、再評估、個案討論、危機處理等。

「個案管理」的活動是多樣的。除了幫助個案得到及維持特定的服務以外，個案管理的活動，有時需爲個案與提供服務者磋商或代言、提供服務者的照會、給與個案社會心理支持、支持性諮商及一般的個案衛教。

臺大醫院的 HIV 個案管理制度主要針對已經診斷為 HIV+之個案，提供醫療、護理、衛生教育、諮詢、社會心理及情緒支持、社會資源聯結轉介、危險行為改變處置、主動關懷追蹤之全面性照護服務模式。

HIV 個案管理師將全面性評估個案的疾病健康狀態、社會心理狀況、危險行為現況、社會支持(包含經濟、居住狀態)等，依其現況及需求將個案導入「加強性個案管理」(Comprehensive Case Management)、「支持性個案管理」(Supportive Case Management)、「危機處理故案管理」(Crisis Intervention Case Management) 等三等級，提供個案全面性醫療、危險行為及社會服務的照護。

### 一、「加強性個案管理」(Comprehensive Case Management)

是一主動式的個案管理模式，目的是爲了照護有較複雜的健康、心理社會及健康需求的 HIV 個案、家屬或個案的支持系統。此模式是爲了需較長時間、密集處置、跨科部或多重專業協調合作加強處置的個案管理服務。全面性個管的內容是一計畫性服務，是執行對無論是個案或其家屬(親密)支持系統的健康或心理社會需求的全面性評估、再評估等服務的連結。此模式是由一個專責個管師，處理個案具體的服務需求，例如健康照護、情緒、安置等；當然還包括與個案建立必要的關係，以協助個案處理其他問題，如：藥物濫用、外籍人士、家庭暴力等議題。

### 二、「支持性個案管理」(Supportive Case Management)

支持性個案管理主要在處理 HIV 個案短時間(3 個月內)或單一的需求。此模式適用在個案的需求是個別的，而且可以在短時間內解決。當然也用在已經解決大部分問題的全面性個管個案，但短時間內還需個管師的支持時。支持性個管的主旨是藉由個管的追蹤，以確保個案無出現其他健康狀況或社會資源的需求。如果個案一再重複出現相同的危機或問題，此時則應將個案導入加強性個管的服務模式。

支持性個管的目標是，滿足個案立即的健康及社會心理需求，以重建個案穩定性。藉此建立關係後，日後個案一旦需加強個管時，可以很快受到協助及服務。

### 三、「危機處理個案管理」(Crisis Intervention Case Management)

危機處理個管的目標是，針對個案出現的危機狀況做立即、適當的處理，擬定適當目

標及處理計畫。快速穩定個案的危機狀況，再做中長程個管計畫及服務。個管主要目的在促進個案的社會、健康等逐漸邁向穩定的階段。此階段個管師需密集與個案會談或電訪、大量的溝通協調相關機構或資源，以先解決緊急問題為個管優先目標。

常見危機處理議題包含：突同時診斷腫瘤、想自殺、經濟出現極大變動需緊急安置、情緒困擾、遊民、藥物過敏反應、剛換藥、剛開始藥物治療、需緊急外科開刀、出血等意外狀況的緊急處理、嚴重伺機性感染需緊急住院或瀕死危機處理等狀況。

## HIV 個案管理之收案初步評估(Initial Assessment)

HIV 個案收案進入個案管理模式前，需經過一全面式評估，根據個案管理師的評估結果，將 HIV 個案導入適當之追蹤管理模式，支持性、加強性或危機處理個管模式。初次收案評估項目內容分述如下：

a.醫療評估－就醫經過、HIV 診療(包含 HIV 疾病之免疫力、疾病階段)評估、生理評估、疾病感染之篩檢評估、性病史、旅遊史等。

b.護理評估－身體檢查與評估、意識狀態、健康狀況、飲食型態、照護者、HIV 疾病傳染、危險行為（性行為及注射行為）、服藥順從性、用藥史（含非法藥物）、營養狀態、過敏史、情緒狀態等。

c.身體功能評估－身體活動程度、日常生活自理能力、巴氏量表分數、個案所需照護的層級。

d.心理社會狀態評估－情緒狀態、家人支持程度、家庭是否出現危機狀態、是否告知家人或性伴侶此診斷、其他親友（含性伴侶）的支持程度、受社會歧視或家人排斥程度。

e.經濟評估－工作情形、收入、家庭整體經濟狀況。

f.居住環境評估－同住者、居住地就醫的可近性、是否有活動障礙。

g.危險行為改變動機－評估危險行為的改變動機意向（含性行為及注射行為）

h.危機評估－是否有勒戒或戒治問題、法律問題(緩刑或即將受刑)外籍人士、家暴、虐待、安全威脅、暴力行為、遊民等。

i.接觸者追蹤情形 (性伴侶及共用注射器者)－目前的主要性伴侶、非固定性伴侶、伴侶的 HIV 狀態、性伴侶曾接受 HIV 檢驗否。

j.生育情形－近幾年內生育小孩的 HIV 檢驗追蹤、是否有生育計畫、採取預防垂直傳染之措施。

k.基本權益受損情形－病情曝光、就醫權、就學權、工作權、人權、保險權益等問題。

## 附錄二、HIV個案管理之收案標準

針對HIV個案，個案管理師將評估個案的全面性狀況後，依其現況及需求將個案導入「加強性個案管理模式」(Comprehensive Case Management Model)或「支持性個案管理模式」(Supportive Case Management Model)，以提供HIV個案長期全面性醫療及社會服務的照護。

各種模式不同收案標準，分述如下:

一、「加強性個案管理」(Comprehensive Case Management)收案管理對象之標準—

*a. 新診斷：*

指最近一個月內，經Western Blot或PCR確定診斷為HIV+者。

*b. 服藥順從性差：*

①指最近6個月內，曾因各種因素未按醫師指示服下80%以上藥物

②或經HAART治療下，因服藥順從性差以致HIV病毒量仍無法達到undetectable之HIV個案。

*c. 半年以上未規則就醫：*

指個案上一次檢驗CD4<350個/ml，且近半年內皆未就醫追蹤或治療之個案。

*d. 需長期照護服務：*

①指個案之巴氏量表低於80分(生活無法自理)、有鼻胃管、尿管、或氣切等任一種管路留置之依賴個案。

②需長期復健(物理治療、職能治療等任一種)之HIV個案

③癌末愛滋個案，需安寧緩和照護之HIV個案。

*e. 毒癮愛滋：*

指曾有使用非法藥物史的HIV個案，近半年仍有繼續口服、吸食或注射藥物者

*f. 女性個案：*

指女性HIV+之個案

*g. HIV+孕婦（垂直傳染）：*

指已經懷孕之HIV+孕婦

*h. 疑似或確定HIV感染之寶寶：*

指HIV+孕婦不論產前有無經HAART治療、或剖復產，產下之寶寶，尚未排除HIV感染的追蹤期；或已經確立被感染之HIV寶寶。

*I. 住院之HIV個案:*

指因伺機性感染、HAART藥物副作用或其他HIV相關之併發症(如腫瘤)而住院之HIV個案。

*J. ART治療失敗個案：*

指因長期ART治療下，仍出現高病毒量情形，醫師診斷為Virological Failure，或經抗藥性分析後確定出現抗藥性HIV之個案。

二、「支持性個案管理」(Supportive Case Management) 收案管理對象之標準—

HIV個案無出現任一「加強性個案管理模式」收案標準之情形者，皆屬「支持性個案管理模式」服務之個案。

## 三、危機處理個案管理

HIV 個案出現需危機處理之議題包含：突同時診斷腫瘤、想自殺、經濟出現極大變動需緊急安置、情緒困擾、遊民、藥物過敏反應、剛換藥、剛開始藥物治療、需緊急外科開刀、出血等意外狀況的緊急處理、嚴重伺機性感染需緊急住院或瀕死危機處理等狀況時。

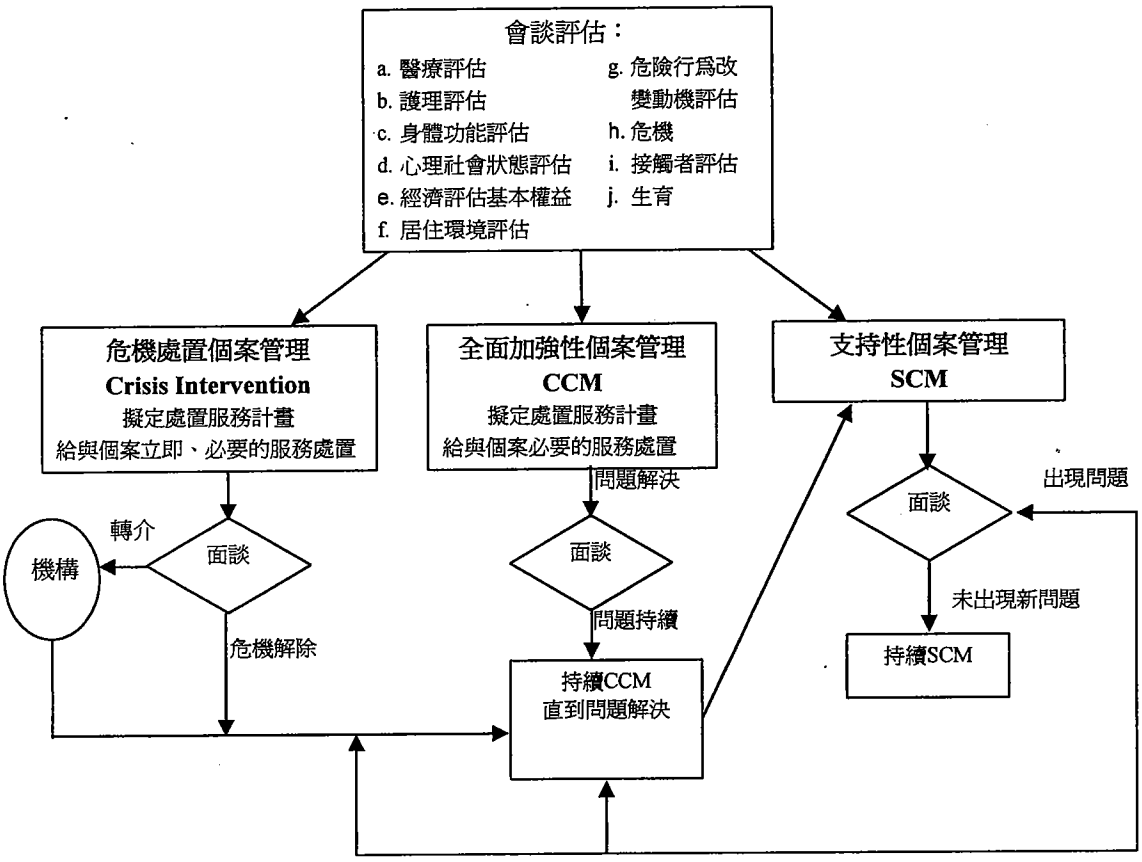
## 附錄三、HIV 個案管理之收案處置流程

一、 HIV 個案管理之個案來源—

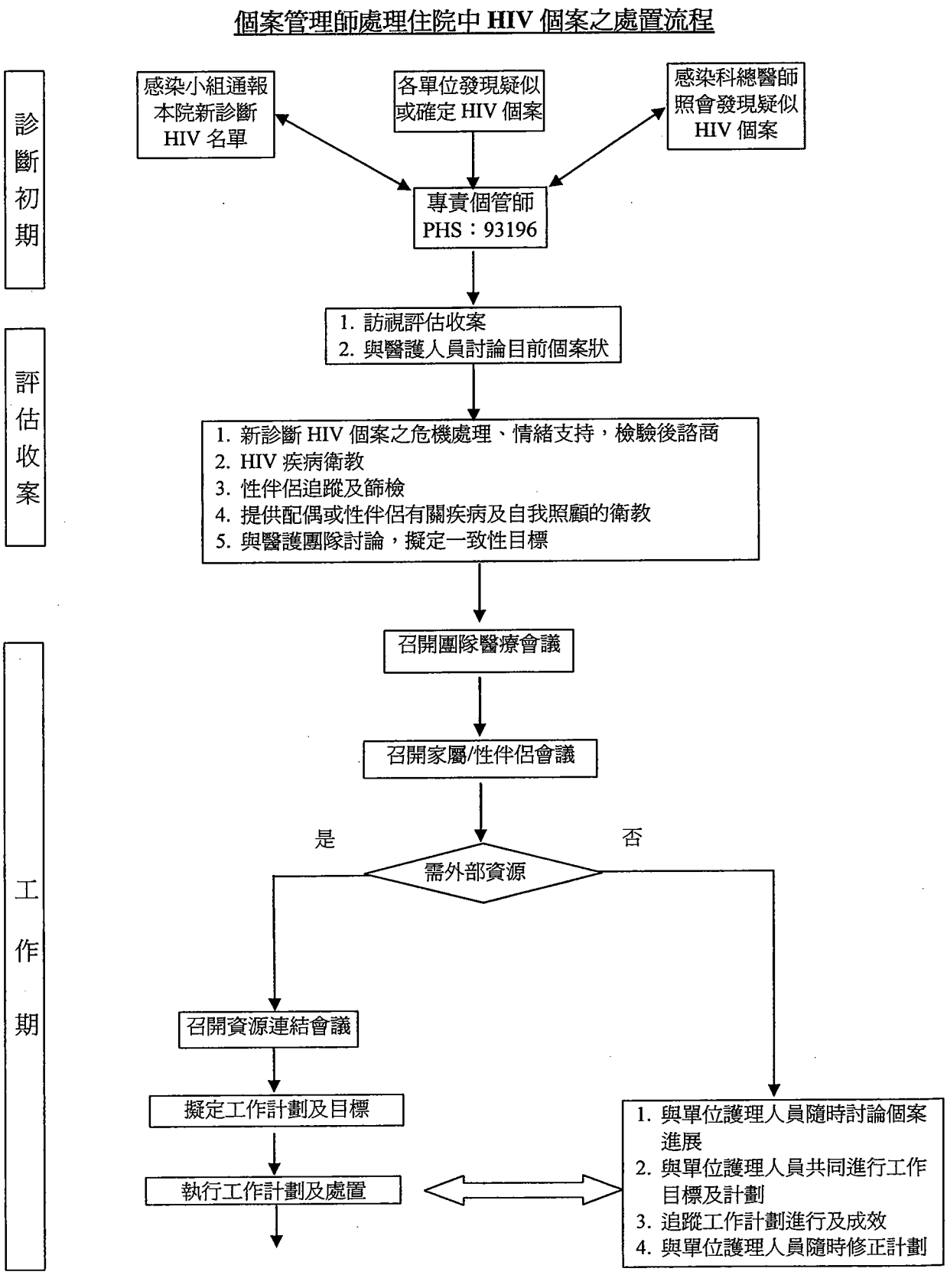
1. 在台大醫院住院之 HIV+個案，包含總院、公館分院、北護分院等，跨科部包含：婦科、產科、小兒科、外科、腫瘤科、牙科、骨科、安寧療護、加護病房、精神科等。
2. 在臺大醫院就診之 HIV+個案，包含門診、急診等。

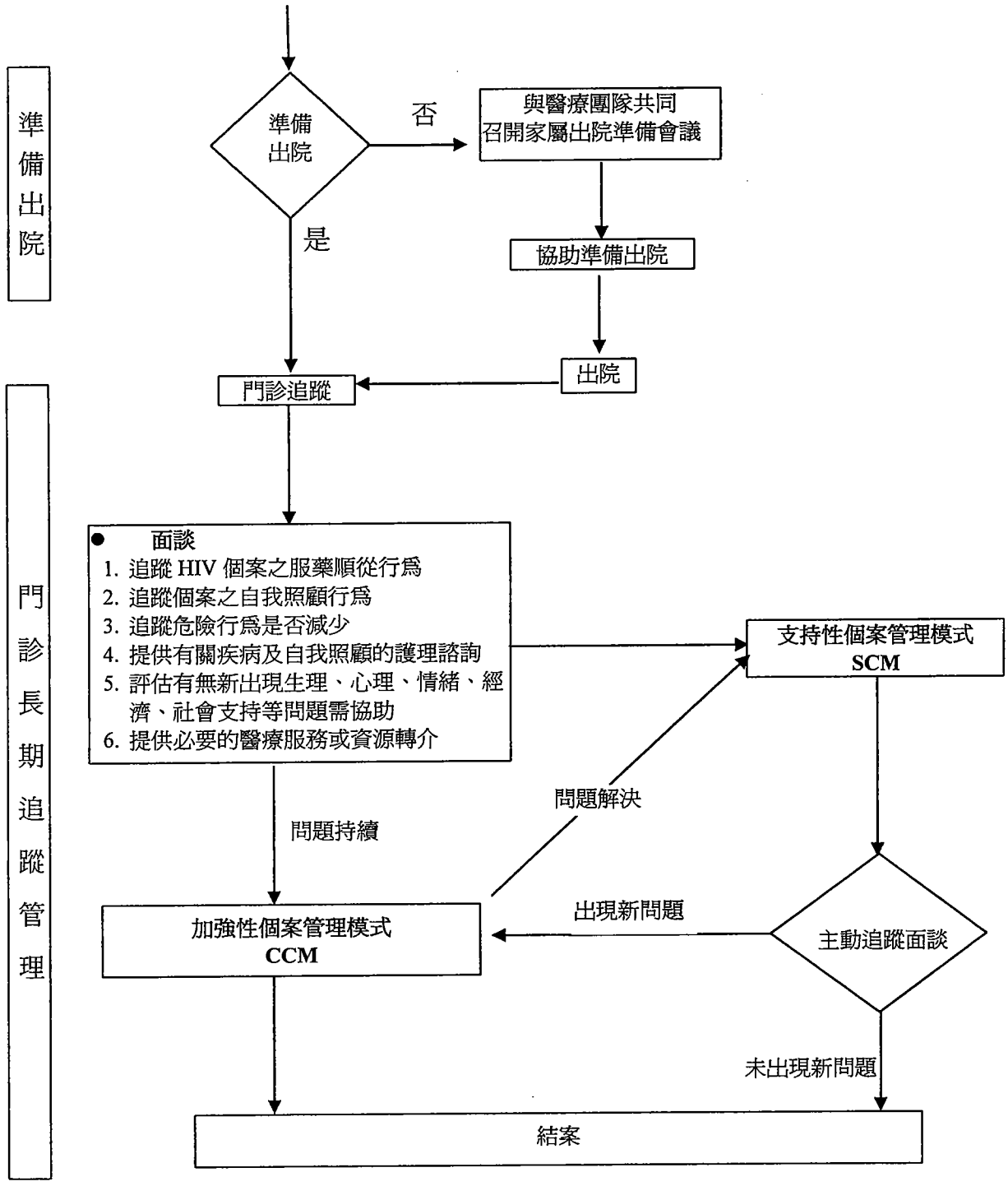
二、 HIV 個案管理師收案處理流程如下

1. 門診 HIV 個案



2. 住院之 HIV 個案處置流程




準備出院
準備出院
否
與醫療團隊共同召開家屬出院準備會議
協助準備出院
是
出院
門診追蹤
門診長期追蹤管理
● 面談
1. 追蹤 HIV 個案之服藥順從行為
2. 追蹤個案之自我照顧行為
3. 追蹤危險行為是否減少
4. 提供有關疾病及自我照顧的護理諮詢
5. 評估有無新出現生理、心理、情緒、經濟、社會支持等問題需協助
6. 提供必要的醫療服務或資源轉介
支持性個案管理模式 SCM
問題持續
問題解決
加強性個案管理模式 CCM
出現新問題
主動追蹤面談
未出現新問題
結案

## 附錄四、HIV 個案管理之工作目標及處置過程

### 一、 HIV 個案管理之工作目標

1. 針對住院中 HIV 個案的工作目標—

（1） 協助新診斷個案的告知及危機處理。
（2） 提供降低 HIV 個案危險行為(包含性行為及注射行為)的衛教處置。
（3） 增進 HIV 個案的服藥順從行為。
（4） 協助處理超長住院個案的安置問題。
（5） 需跨科部處理醫療問題時，協助與醫療照護團隊溝通合作。
（6） 提供 HIV 個案的家屬及性伴侶，有關疾病及自我照護的衛生教育。
（7） 擬定 HIV 複雜個案的醫療照護計劃。
（8） HIV 檢驗後諮商、危機處理及情緒支持。
（9） 主動追蹤接觸者(配偶、性伴侶或小孩)做 HIV 篩檢，直到排除或確定感染。
（10） 協助聯結個案必須的社會服務資源，如:安置機構、減害計畫、權促會、露德之家、社工部等，以共同解決個案之問題。

2. 針對出院後（門診）HIV 個案的工作目標—

（1） 持續定期監測 HIV 個案出院後的檢驗、危險行為、服藥順從行為、藥物副作用及自我照顧行為，及早發現症狀後，給與服藥指引及症狀處理。
（2） 處理 HIV 個案新發生之生理、心理、精神或行為問題，提供適當之護理處置及諮詢。
（3） 提供個案必要的跨科部或跨院之醫療協助，或社會資源轉介服務，如安置機構、減害計畫、權促會、露德之家、社工部等。
（4） 持續解決個案住院期間尚未解決之醫療或照護問題，並追蹤評值結果，直到問題被解決。
（5） 適當處理個案的情緒問題(尤其是憂鬱、沮喪)，給與必要的情緒支持，或轉介精神科、心理諮商服務之專業服務。

### 二、 HIV 個案管理之處置過程

HIV 個案管理的處置過程是一系列連續性、多階段的過程，包含評估、訂立處置目標、擬定處置計畫、執行計畫、追蹤及結果評值。

（1） 全面性評估個案的生理、心理社會、行為等層面之現況
（2） 與個案共同訂立目前的處置目標
（3） 擬定處置服務計畫(service plan)
（4） 執行計畫
（5） 追蹤計畫進行狀況並評值結果

## 附錄五、HIV 個案管理之主動追蹤

所有接受個案管理模式服務的個案，無論個案目前是否須服藥治療 HIV，都需由個案管理師進行主動追蹤。主動追蹤的方式，可在個案前來台大醫院就醫(門診、接受治療或檢查)或領藥(持慢性處方簽)時，與個案做面對面會談（約至少 15~20 分鐘），或主動與個案經電話直接會談。

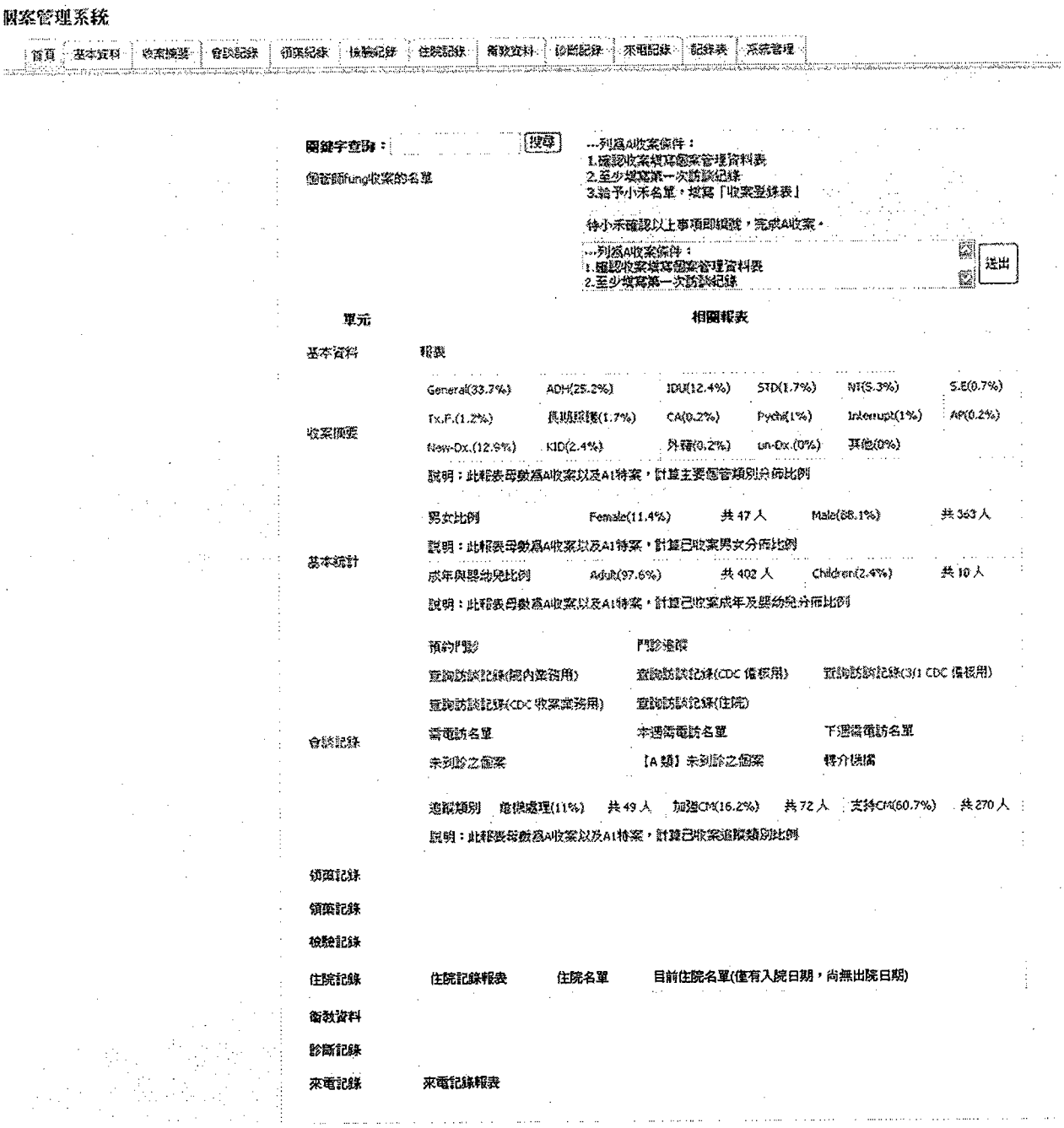
一、 HIV 個案管理師主動追蹤的目的：

（1） 確保個案仍繼續在醫療服務系統內接受照護服務沒有失聯
（2） 持續動態評估個案的一般健康及社會狀態，以了解是否出現須密集醫療、社會專業服務的需求
（3） 可即時協助個案解決困難，恢復穩定狀況。
（4） 即時降低個案危機事件的傷害程度。
（5） 避免重複利用服務資源

二、 主動追蹤 HIV 個案的內容及頻率標準如下:

| | 追蹤內容 | 追蹤頻率 |
|---|---|---|
| 危機處理個案管理 | 1. 針對危機狀況做立即、適當的處理目標及計畫。<br>2. 常見議題包含：突同時診斷腫瘤、想自殺、經濟出現極大變動需緊急安置、情緒困擾、遊民、早上剛自監獄出來、藥物過敏反應、剛換藥、剛開始藥物治療、需緊急外科開刀、出血等意外狀況的緊急處理、嚴重伺機性感染需緊急住院、瀕死危機處理等狀況。 | 1. 至少每週一次電訪或會談<br>2. 必須追蹤轉介社會服務資源聯結情形<br>3. 必須做個案討論會 |
| 「加強性個案管理」(CCM) | 1. 針對上次面談後，需繼續處置或追蹤的所有議題進行評估、處理並進度追蹤。<br>2. 持續全面性評估個案的所有現況，如疾病、健康、自我照顧、社會心理、情緒、工作、告知診斷、危險行為、生育、家庭支持、接觸者追蹤、法律議題等等。 | 1. 各種進入 CCM 之個案，至少每 2~4 周必須主動追蹤面談或電訪一次。最多可以密集的每週會談或面談並在個案的管理紀錄中做紀錄。 |
| 「支持性個案管理」(SCM) | 1. 快速簡單的全面性評估個案的所有現況，如疾病、健康、自我照顧、社會心理、情緒、工作、告知診斷、危險行為、生育、家庭支持、接觸者追蹤、法律議題等等。 | 1. 各種進入 SCM 之個案，至少每 3~6 個月必須主動追蹤會談一次。並在個案的管理紀錄中做紀錄。 |

# 附錄六、HIV 個案管理資料庫系統



# 附錄七、HIV 個案管理資料庫系統之會談評估與紀錄表

- A 部份範例：

姓名 *王小明 病歷號碼 5987654 日期 2007/10/31 就診醫師

BH: cm BW: kg BMI :

最近: 2007/3/6 下午 05:12:00 CD4: 3
最近: HIV Viral Load:

*活動狀況評估（The Karnofsky Performance Scale） :

A. 症狀 ☐ 無症狀

A-1. HIV-related symptoms ○ 有 ○ 無

A-1. 其他症狀 ○ 有 ○ 無

| 問題 | 處置或建議 |
| --- | --- |
| | |

A-2. 伺機性感染症狀

☐ 口腔念珠菌 ☐ 帶狀皰疹 ☐ 夜間盜汗 ☐ 發燒 ☐ 乾咳 ☐ 腹瀉 ☐ 呼吸喘 ☐ 喉嚨痛 ☐ 頭痛 ☐ 疲倦
☐ 紅疹 ☐ 體重減輕

# 附錄七、HIV個案管理資料庫系統之會談評估與紀錄表（續）

- B部份範例：

**B. HAART /** ☐ NT

**B-1 Assessment of adherence**

○ poor ○ poor→moderate ○ moderate ○ moderate→good ○ good

Number of missed doses:

忘記或漏吃時

○ 下次多吃 ○ 想到時馬上補 ○ 問醫師 ○ 算了 ○ 其他

0 1. 服用醫師指定的所有藥物
0 2. 遵照指定時間
0 3. 遵照劑量
0 4. 遵照注意事項
0 5. 會服用另外食物
0 6. 按時回門診
0 7. 自行減少次數或劑量

0從未；1很少；2時常；3總是

**B-2 Side Effects**

0→2

| | | | |
|---|---|---|---|
| 0 1 倦怠 | 0 2 肌肉痠痛 | 0 3 沮喪 | 0 4 注意力差 |
| 0 5 頭痛 | 0 6 頭暈 | 0 7 肢體末梢麻 | 0 8 畏光 |
| 0 9 失眠 | 0 10 口乾 | 0 11 味覺 | 0 12 噁心 |
| 0 13 嘔吐 | 0 14 腹瀉 | 0 15 腹痛 | 0 16 口腔潰爛 |
| 0 17 胃酸倒流 | 0 18 脹氣 | 0 19 消化不良 | 0 20 心律不整 |
| 0 21 心悸 | 0 22 氣喘 | 0 23 呼吸困悶 | 0 24 腰痛 |
| 0 25 下肢edma | 0 26 頻尿 | 0 27 尿混濁 | 0 28 黃疸 |
| 0 29 皮膚疹 | 0 30 痲疹 | 0 31 蕁麻疹 | 0 32 lipodystrophy |
| 0 33 Hyper-lipidemia | 0 34 Hyper-glycemia | | |

**Discussion of problem / barriers to adherence**

# 附錄七、HIV 個案管理資料庫系統之會談評估與紀錄表（續）

- C、D 部份範例：

**C. ARV Treatment Education**

**Treatment Education topics:**

- ☐ Importance of adherence
- ☐ ARV Therapy
- ☐ Motivation, and ability to obtain medicines
- ☐ Medications and their side effects
- ☐ Expected outcomes & goals
- ☐ Resistance to medications
- ☐ Dosing information

**ARV Treatment Intervention**

- ☐ Discussion of strategies to improve adherence
- ☐ Re-set the medication schedule
- ☐ Discussion of how to manage side effect

**D. Infection & STI assessment (recently 3 mons)** ☐ 無會談此部份

***D-1 Infection Risk***

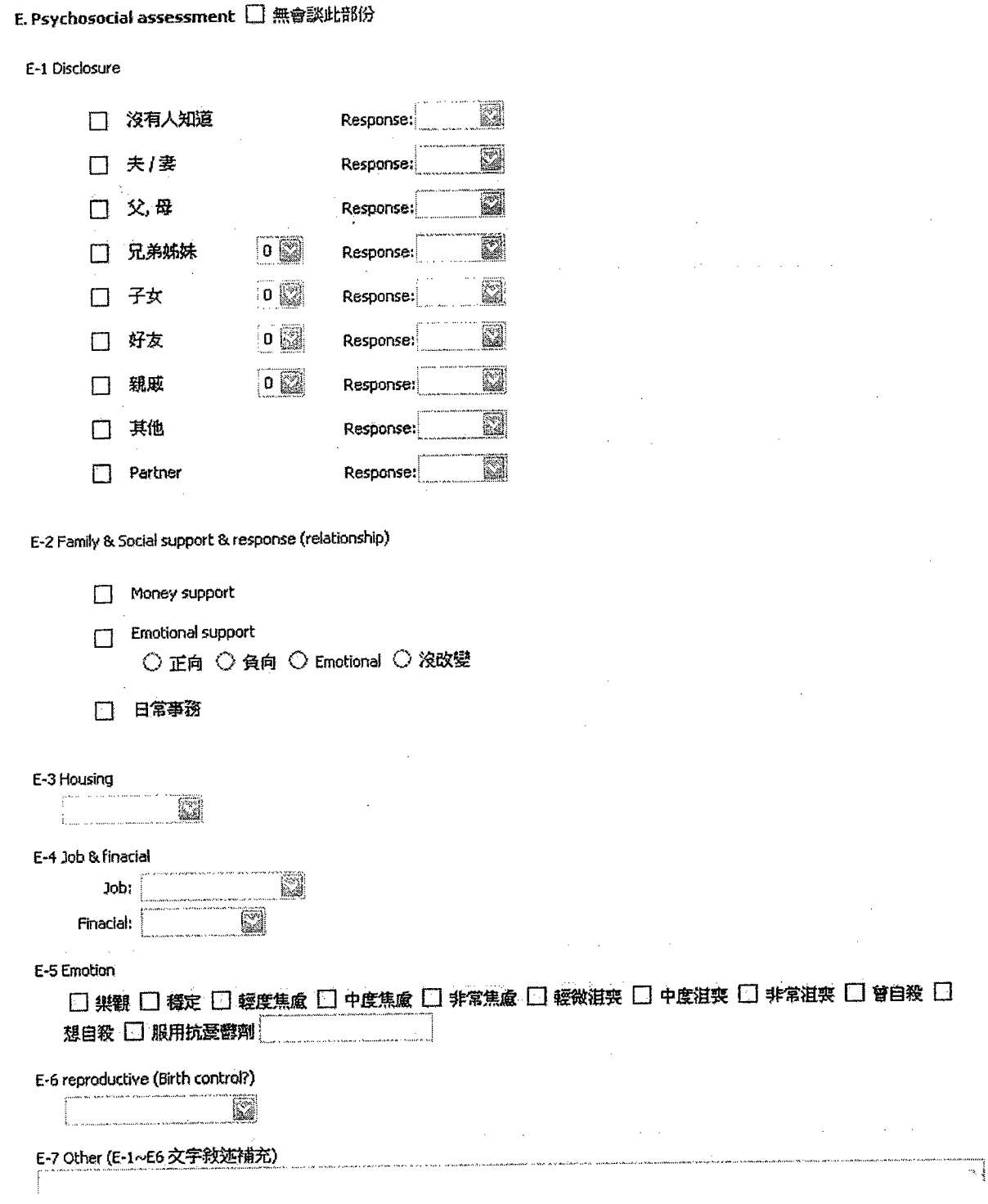
- ☐ 1. Start HARRT less than 6 months.
- ☐ 2. Have been herpes before. when? _____ where? _____
- 0 3. Avoid going into people or wear Mask
- ☐ 4. Has been TB before.
- ☐ 5. Has been STI. what kind? _____
- ☐ 6. Drug user.
- ☐ 7. IDU using
  - ☐ not sharing.
  - ☐ ster-site.
  - ☐ disposable needle.

***D-2 STI Risk***

1. 5 behavior ☐ or ☐ an ☐ V
- ☐ 2. Fix partners. relations? _____
3. Fix partner use condom (____%)
- ☐ 4. Causual partners. resource? _____
5. Causual partner use condom (____%)
6. Safer sexual. _____

# 附錄七、HIV 個案管理資料庫系統之會談評估與紀錄表（續）

- E 部份範例：



# 附錄七、HIV個案管理資料庫系統之會談評估與紀錄表（續）

- F、G部份範例：

**F. Mental Health or Hx** ☐ 無會談此部份

F-1 Sleeping / Appetlite

Sleeping: 1.

Appetlite:

F-2 Mental illness or Hx

☐ 沒問題 ☐ 服精神科藥物 ☐ 焦慮

☐ 躁鬱症 ☐ 憂鬱症 ☐ 精神分裂

☐ 恐慌 ☐ 幻聽 ☐ Psychosis

F-3 Other

**G. Drug** ☐ 無會談此部份

Smoking: ○ 無 ○ 一天一包 ○ 0~1/2包 ○ 1/2~1包/天 ○ 1包以上/天

Drink: ○ 無 ○ 社交 ○ 1小杯/天 ○ 0~1瓶/天 ○ 1~2瓶/天 ○ >2瓶/天

Drugs: ○ >3次/天 ○ 1~3次/天 ○ 1~2次/週 ○ >3次/週 ○ <1/月→1~3/月 ○ 假日 ○ 偶而

☐ Heroin ☐ Amphetamin ☐ 搖頭丸 ☐ K他命 ☐ 一粒眠

☐ injection ☐ inhalation ☐ smoke ☐ IM ☐ shorting ☐ rectume

Other

# 附錄七、HIV 個案管理資料庫系統之會談評估與紀錄表（續）

- SUMMARY-1 部份範例：

**Summary - Basic Patient Education**

**Topics of HIV education**

- ☐ Assessment of patient understanding of HIV information
- ☐ Transmission risks/factors
- ☐ Information about the virus/pathenesis[HIV 101]
- ☐ Importance of CD4 count/viral load monitoring
- ☐ Importance of regular care
- ☐ Effects on the immune system
- ☐ HIV stage & prognosis

**Prevention/Wellness Education**

- ☐ HIV self-care
- ☐ Nutrition education
- ☐ Making healthy life choices("living with HIV)
- ☐ Set CD4 goal
- ☐ HBV/HCV diet
- ☐ Hyperlipidemia-diet
- ☐ Hyperlipidemia-exercise
- ☐ DM-diet
- ☐ DM-exercise
- ☐ H/T

**Risk Reduction**

- ☐ Safer sexual relations-condom
- ☐ Safer sexual relations-sex type
- ☐ Harm reduction-Prevent OD
- ☐ Harm reduction-Safe injection
- ☐ Harm reduction-Dosing
- ☐ Harm reduction-Needle exchange program
- ☐ Harm reduction-Methadone program

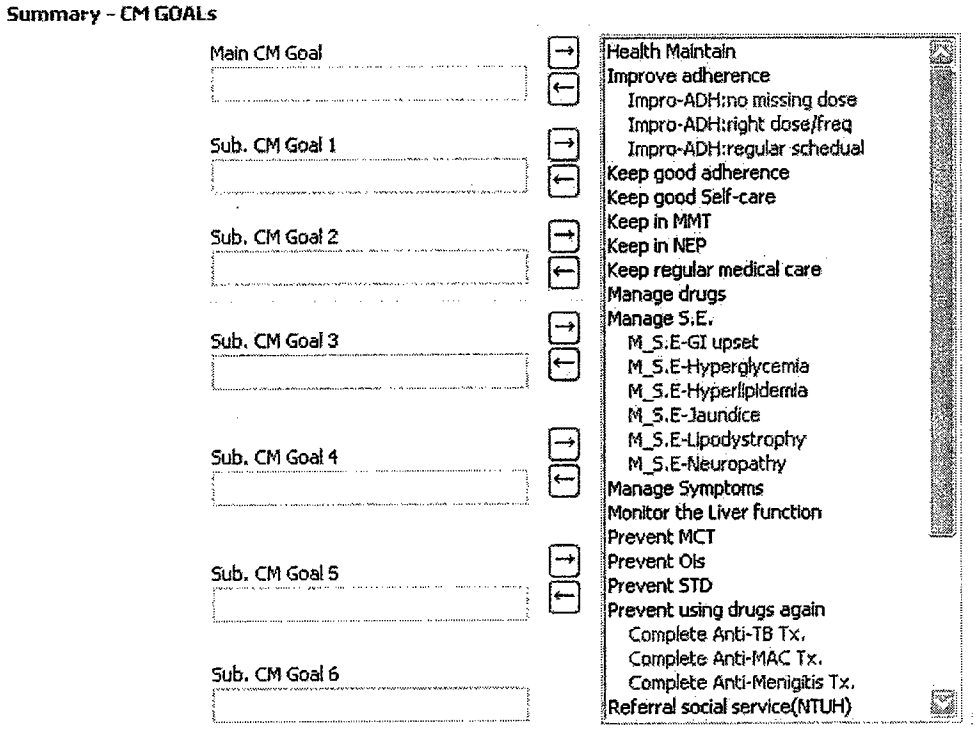
- ☐ **Symptom management**
- ☐ **Disclosure**
- ☐ **Trance exposure**

☐ **Referral** ☐ 台大社工 ☐ 愛慈 ☐ 美沙關 ☐ 露德 ☐ 關愛 ☐ 針具交換 ☐ 本院他科 ☐ 其他醫院 ☐ 其他

本院他科： 其他醫院： 其他：

# 附錄七、HIV 個案管理資料庫系統之會談評估與紀錄表（續）

- SUMMARY-2 部份範例：




○ 危機處理　☐ 電訪追蹤：○ 每週；○ 每2週；○ 每4週
☐ 轉介追蹤：○ 每2週；○ 每4週

○ 加強CM　☐ 電訪追蹤：○ 每週；○ 每2週；○ 每4週
☐ 轉介追蹤：○ 每2週；○ 每4週

○ 支持CM　下次OPD F/U

☐ 需電訪名單

電訪內容：☐ 症狀追蹤 ☐ 用藥追蹤 ☐ 轉介 F/u ☐ 提醒就醫 ☐ 家屬協談 ☐ 召集會議/聯絡 ☐ 追蹤危險行為
☐ 換藥 ☐ 新診斷 ☐ 抽血追蹤 ☐ 回報檢驗值 ☐ 情緒追蹤 ☐ 其他

預定電訪追蹤期間：　至

下次需追蹤事項(請條列)

電訪追蹤記錄(請條列)

## 附錄八、HIV個案管理師滿意度調查問卷

親愛的先生女士：您好！

為提高醫療服務品質，懇請您利用幾分鐘時間填寫這份問卷，以提供我們改進的方向，以下的問題，請您就本次就醫經驗作答選擇您認為合適答案，本問卷將由專人辦理，並對回答內容予以保密，照顧您的醫護人員或其他工作人員並不會看到您的作答，敬請安心，完成問卷後請將本資料丟入意見箱，謝謝您的合作與支持。敬祝早日康復。

臺大醫院 內科門診服務　　敬上

### 壹、 基本資料

一、 請問您是初次在本院門診看病? □是 □否

二、 請問您最近一次的看診日期是: ____年___月 ____日 □上午 □下午

三、 請問您本次看診科別為？□內科部 □外科部 □婦產科 □小兒科

四、 請問您的身分是：□病患本人 □家屬 □朋友 □男、女朋友

五、 您的性別：□男 □女

六、 您出生的年次: _____年次

七、 您的學歷：

□小學 □國中 □高中/職 □大專/技術學院 □大學 □碩士 □博士

八、 請問您去年曾經有接受過專責護理師(或個案管理師)的專業服務嗎?

□有 □無

九、 您的專責護理師(或個案管理師)是_____

十、 如果您忘記來門診時，需要專責護理師提醒您嗎?

□要；我的聯絡電話是_____ □不需要

## 附錄八、HIV個案管理師滿意度調查問卷（續）

貳、 以下請您對本院提供專責護理師(個案管理師)服務的同意度，給予評量。請依您的經驗，選適當的選項，若該項目未曾經歷過，請選「沒有接觸」

1. 專責護理師有針對您的健康狀況提供詳細的健康指導及諮詢服務?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
2. 專責護理師有提供詳細的藥物治療指導?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
3. 當您需要更改就醫日期時，專責護理師有協助加掛號?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
4. 當您身體出現症狀時，可立即聯絡上專責護理師?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
5. 當您出現症狀需協助時，專責護理師有立即協助就醫(掛號)?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
6. 當您出現症狀需協助時，專責護理師有立即教導處理症狀的方法或技巧?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
7. 專責護理師有和我討論性行為時，如何保護自己不再感染性病的方法?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
8. 您需要別科就醫時，專責護理師有提供訊息或協助掛號?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
9. 專責護理師有提供相關法律訊息?
   □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
10. 當您需要社工服務時，專責護理師有幫助您轉介到社工的服務資源?
    □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
11. 專責護理師有尊重您的隱私?
    □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
12. 專責護理師的態度親切和善?
    □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸
13. 當我需要戒癮或美沙冬治療時，專責護理師有幫助我轉介到相關的服務資源?
    □非常同意 □同意 □普通 □不同意 □非常不同意 □沒有接觸

參、請您為本次專責護理師的服務整體同意度打一個分數(1~100分) _____分

肆、如果您或您的親友需要門診醫療服務,您會選擇再來或介紹親友來本院就醫嗎？

□會 □不會 □不一定