J Microbiol Immunol Infect.
2008;41:200-208

Original Article

Seroprevalence of viral hepatitis and infectious complications among human immunodeficiency virus-infected injection drug users at a referral hospital

Shiou-Haur Liang[1], Yi-Chun Lo[2], Hsi-Hsun Lin[1], Sui-Yuan Chang[3], Mao-Yuan Chen[2], Szu-Min Hsieh[2], Wang-Huei Sheng[2], Hsin-Yun Sun[2], Chien-Ching Hung[2], Shan-Chwen Chang[2]

[1]Section of Infectious Disease, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung County; [2]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; and [3]Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University College of Medicine, Taipei, Taiwan

Received: April 12, 2007 Revised: June 10, 2007 Accepted: July 31, 2007

Background and Purpose: The seroprevalence of viral hepatitis and spectrum of infectious complications among human immunodeficiency virus (HIV)-infected injection drug users (IDUs) remains unclear in Taiwan, although there has been a significant increase in the prevalence of HIV infection among IDUs in the last 2 to 3 years.

Methods: The medical records of HIV-infected IDUs who sought medical care at a referral hospital for HIV care from June 1994 to December 2006 were retrospectively reviewed. A standardized case record form was used to collect demographic, clinical, laboratory and microbiologic data.

Results: During the 12-year study period, a total of 102 HIV-infected IDUs with a median age of 39.5 years (range, 19 to 73 years) sought HIV care at the referral hospital. The male-to-female case ratio was 6 and males were significantly older than females (39.5 vs 28 years, $p<0.001$). The overall median CD4+ cell count and plasma HIV RNA load by reverse transcriptase-polymerase chain reaction at enrollment were 374 cells/μL and 4.45 $\log_{10}$ copies/mL, respectively. The CD4+ cell count of HIV-infected IDUs enrolled after year 2003 was significantly higher than those enrolled before 2003 (438 vs 23 cells/μL, $p<0.001$). The seroprevalence of hepatitis C virus (86.6% overall) increased over time, while that of hepatitis B virus decreased in the patients born after 1984, when nationwide hepatitis B vaccination was started in Taiwan. Gram-positive bacteria were causative for 69.7% of the 33 bacteremic episodes, and *Staphylococcus aureus* was the leading pathogen (16 episodes), with methicillin-sensitive *S. aureus* accounting for 11 bacteremic episodes (33.3%). The most common bacterial infection was infective endocarditis. Tuberculosis occurred more frequently in men, and extrapulmonary tuberculosis was more common than pulmonary tuberculosis and was associated with a lower CD4+ count.

Conclusions: Bacteremia, infective endocarditis and tuberculosis were the three most common patterns of infection among HIV-infected IDUs who sought medical care at a referral hospital; and methicillin-sensitive *S. aureus* was the most common etiology of bacteremia. The high seroprevalence of hepatitis B and C and subsequent hepatic complications may present a future challenge to the health care system.

Key words: Endocarditis; Hepatitis, viral, human; HIV infection; Substance abuse, intravenous; Tuberculosis

Introduction

Injection drug use and transmission of human immunodeficiency virus (HIV) via sharing needles or solvent present important challenges to public health programs worldwide [1]. Although injection drug use accounts for only an estimated 10% of cases of HIV infection globally [2], it is a more efficient way of spreading HIV than sexual intercourse. In the United States, approximately 25% of all HIV/acquired immunodeficiency syndrome (AIDS) cases are injection drug users (IDUs) [3], while in Taiwan, IDUs accounted for

Corresponding author: Dr. Chien-Ching Hung, Department of Internal Medicine, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: hcc0401@ntu.edu.tw

38.4% of 13,103 cases of HIV infection between 1984 and 2006 [4]. Over the past several years, an increasing proportion of HIV infection has been attributed to injection drug use in several Asian countries and countries of the former Soviet Union [1]. Similar trends are observed in Taiwan, where there has been a significant increase in the prevalence of HIV infection in IDUs in the last 2 to 3 years [4]; the proportion of IDUs among reported cases of HIV infection increased from 1.7% in 2002 to 68.6% in 2006 [4,5].

Injection drug use is associated with a wide range of medical complications. Infectious complications are the most common, being responsible for 60% to 80% of hospital admissions and for 20% to 30% of deaths [6,7]. It is apparent that the frequency and spectrum of infections among drug users is variable [8]; the risk of infection among IDUs are related to methods of injection and lifestyle practices, which may increase their exposure to microbial pathogens [9]. Use of nonsterile methods, equipment (needles, syringes, spoons and cups), or solutions may increase the risk of infectious complications. Both of these practices may allow microorganisms direct access to subcutaneous tissues, muscle and blood, resulting in either local or systemic infections [8], with the infecting organisms often present as colonizers of the skin or in the diluents used to dissolve drugs. In addition, the use of illicit drugs is associated with enhanced susceptibility to infectious diseases per se [9].

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are two major etiologies of chronic liver disease in Taiwan. Among IDUs in Taiwan, the seroprevalence of HBV and HCV were estimated at 22.1% [10] and 81.0% [11], respectively, before intravenous drug use emerged as the leading transmission route for HIV infection. With the increased proportion of IDUs in the HIV-infected population in Taiwan, the seroprevalence of HBV or HCV infection may change in this population. In this study, we aimed to describe the seroprevalence of viral hepatitis and infectious complications among HIV-infected IDUs at a referral hospital for HIV care in Taiwan.

Methods

Patients and data collection

The National Taiwan University Hospital is a major referral hospital for HIV and AIDS care in Taiwan. Highly active antiretroviral therapy (HAART) is provided free of charge to all HIV-infected patients at designated hospitals and clinics around Taiwan according to updated recommendations and treatment guidelines, since April 1, 1997. The medical records of consecutive non-hemophiliac HIV-infected IDUs at the National Taiwan University Hospital from June 1994 to December 2006 were retrospectively reviewed. A standardized case record form was used to collect demographic, clinical, laboratory, and microbiologic data.

Laboratory tests

CD4+ counts were determined with FACSFlow™ (BD Biosciences, San Jose, CA, USA), and HIV RNA plasma virus load (PVL) was determined with reverse transcriptase-polymerase chain reaction (Roche Amplicor, version 1.5, Branchburg, NJ, USA), with a lower detection limit of 400 (2.60 $\log_{10}$) copies/mL, which was introduced into clinical practice in 1999.

HBV and HCV status were routinely tested because of sharing the same transmission route as HIV, and high seroprevalence in Taiwan [12]. Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc) were determined using enzyme immunoassay (EIA; Abbott Laboratories, Abbott Park, IL, USA), and anti-HCV antibody using commercialized microparticulate EIA (AxSym anti-HCV, version 3.0; Abbott Laboratories, Abbott Park, IL, USA).

To determine genotype of HCV, total RNA was extracted from plasma using the QIAamp Viral RNA Mini Kit (QIAGEN, Valencia, CA, USA) and reverse transcriptase-polymerase chain reaction was performed to amplify the HCV NS5B fragment, as described previously [13]. Population-based nucleotide sequence analysis of the polymerase chain reaction fragments was conducted using an automatic sequencer (ABI PRISM® 3100-Avant Genetic Analyzer; Applied Biosystems, Foster City, CA, USA). Sequences were aligned with the ClustalW (Molecular Evolutionary Genetics Analysis [MEGA], Version 3.0; Institute of Molecular Evolutionary Genetics, University Park, PA, USA) analytical package [14], with minor manual adjustments. The phylogenetic trees were constructed by the neighbor-joining method based on the Kimura 2-parameter distance matrix listed in the MEGA software.

Definitions

Based on the definitions of the Centers for Disease Control and Prevention [15], true bacteremia was defined as more than one blood culture yielding bacteria in the presence of fever (body temperature ≥38°C) that

was not attributable to other causes. Cases for which a single blood culture yielded coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., or *Propionibacterium acnes* were considered contamination.

Catheter-related infection was defined as isolation of the identical species of microorganism from a semi-quantitative culture of the vascular catheter tip (15 colony-forming units/mL or more using the Maki roll-plate technique [16]), with the same antibiotype as the microorganism isolated from peripheral blood specimens; or as the microorganism isolated from the skin exit site of the catheter with signs and symptoms of infection. Primary bacteremia was defined as a bloodstream infection without an infectious focus. Diagnosis of infective endocarditis (IE) was made according to the clinical, microbiological and echocardiographic criteria described by Durack et al (modified Duke's criteria) [17].

Tuberculosis (TB) was defined as definitive when *Mycobacterium tuberculosis* was isolated from any clinical specimen; probable TB was defined as demonstration of acid-fast bacilli or granulomatous inflammation or caseous necrosis in clinical specimens without positive cultures, plus a favorable response to antituberculous therapy; and possible TB was defined as consistent radiographic findings and clinical symptoms, plus a favorable response to antituberculous therapy. Multidrug-resistant TB (MDR-TB) was defined by isolation of a strain of *M. tuberculosis* resistant to isoniazid and rifampin.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Chicago, IL, USA) software package. Categorical variables were compared by using the chi-squared test or Fisher's exact test. Continuous variables were compared by use of *t* test or Mann-Whitney *U* test. All tests were two-tailed, and a p value <0.05 was considered significant.

Results

Patients

During the 12-year study period, 1510 HIV-infected patients sought HIV care at this hospital and 102 (6.8%) were HIV-infected IDUs. The demographics and clinical characteristics of the HIV-infected IDUs are shown in Table 1. Their median age was 39.5 years (range, 19 to 73 years). Males were significantly older than females (p<0.001) with a male-to-female ratio of 6. The median CD4+ count and PVL at enrollment were 374 cells/μL and 4.45 $\log_{10}$ copies/mL, respectively. Female IDUs appeared to have a higher

Table 1. Characteristics of 102 human immunodeficiency virus-infected injection drug users

Variable	Male (n = 87) No. (%)	Female (n = 15) No. (%)	All patients (n = 102) No. (%)	p[a]
Age (years) [median (range)]	39.5 (19-73)	28 (20-45)	39.5 (19-73)	<0.001
Age distribution (years)				
≤20	3 (3.5)	1 (6.7)	4 (3.9)	<0.001
21-30	11 (12.6)	10 (66.7)	21 (20.6)	
31-40	27 (31.0)	3 (20.0)	30 (29.4)	
41-50	37 (42.5)	1 (6.7)	38 (37.3)	
>50	9 (10.3)	0 (0.0)	9 (8.8)	
Baseline CD4+ count (cells/μL)[b]				
Median (range)	349.5 (1-984)	528 (16-931)	374 (1-984)	0.09
>350	42 (50.0)	11 (78.6)	53 (54.1)	0.13
200-350	19 (26.6)	1 (7.1)	20 (20.4)	
<200	23 (27.4)	2 (14.3)	25 (25.5)	
Baseline PVL ($\log_{10}$ copies/mL)[a,b]				
Median (range)	4.47 (2.60-5.99)	4.22 (2.60-5.63)	4.45 (2.60-5.99)	0.26
≥5	24 (28.4)	4 (28.6)	28 (31.8)	0.12
Anti-HCV[c]	70 (85.4)	14 (93.3)	84 (86.6)	0.69
HBsAg[c]	16 (21.9)	1 (6.7)	17 (19.3)	0.29

Abbreviations: PVL = plasma virus load; anti-HCV = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen

[a]Fisher's exact test or Mann-Whitney *U* test.

[b]CD4+ cell count and PVL were available for 98 (84 males, 14 females) and 88 (74 males, 14 females) patients, respectively.

[c]Anti-HCV antibody and HBsAg were available for 97 (82 males, 15 females) and 88 (73 males, 15 females) patients, respectively.

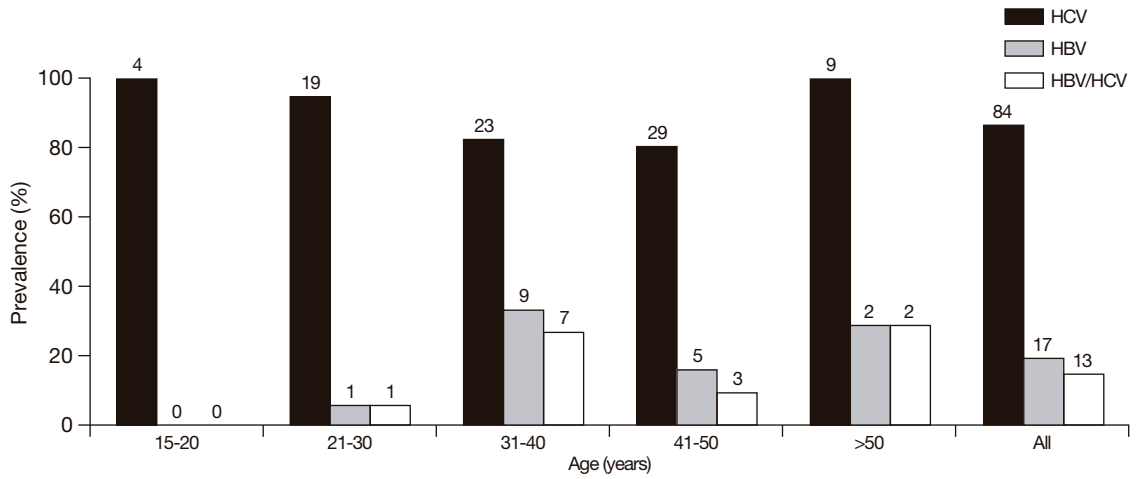

Fig. 1. Seroprevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) according to age group. Numbers at the top of bars denote case numbers.

CD4+ count than males, although the difference was not statistically significant (528 vs 349.5 cells/μL, p=0.09). The increased proportion of IDUs newly diagnosed as having HIV infection at this hospital (1.2% in 1998-2002 to 12.0% in 2003-2006) appeared to coincide with the rapid increase of prevalence of HIV infection among IDUs in Taiwan after 2003 [4]. Patients enrolled after 2003 had significantly higher CD4+ counts than those enrolled before 2003 (438 vs 23 cells/μL, p<0.001).

Hepatitis

The seroprevalence of HBV and HCV among different age groups is shown in Fig. 1. Among 88 HIV-infected IDUs who were tested for HBV serologies, 17 (19.3%) were positive for HBsAg; among 97 HIV-infected IDUs who were tested for HCV antibody, 84 (86.6%) were positive for anti-HCV; 13 patients (14.9%) were HBV/HCV co-infected. Most of the HCV belonged to genotype 1, which accounted for 56.1% (1a, 29.3%; 1b, 26.8%) of the 41 blood samples that could be amplified by polymerase chain reaction. Other less common genotypes were 6a (12.2%), 2a (9.8%), 3a (9.8%), 2b (4.9%), 6K (4.9%) and mixed (2.4%). The seroprevalence of HBV and HCV differed significantly between age groups and over time during the years of study; the seroprevalence of HCV was higher than 80.0% in all age groups (Fig. 1) and increased over time, from 58.8% during 1994-2002 to 92.5% during 2003-2006. In contrast, the seroprevalence of HBV was lower among the younger patient groups, especially among those aged 15 to 20 years or born after 1984 (Fig. 1 and Table 2), although the difference was not statistically significant due to the small sample size (p=0.58).

Bacterial infections

Of 56 episodes of bacterial infections, IE, pneumonia and cellulitis were the three most common patterns of infection, accounting for 15, 9 and 8 episodes,

Table 2. Seroprevalence of hepatitis B among human immunodeficiency virus-infected injection drug users, born before and after July 1, 1984

Test	Number of positive results/number tested (%)		Total	p^a
	Born before July 1, 1984	Born on and after July 1, 1984		
HBsAg	17/83 (20.5)	0/5 (0.0)	17/88 (19.3)	0.58
Anti-HBs	43/71 (60.6)	2/3 (66.7)	45/74 (60.8)	0.99
Anti-HBc	45/53 (84.9)	1/1 (100.0)	46/54 (85.2)	0.99
Isolated anti-HBc	8/11 (72.7)	0/0 (0.0)	8/11 (72.7)	NA[b]

Abbreviations: HBsAg = hepatitis B surface antigen; anti-HBs = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; NA = not applicable

[a]Fisher's exact test.

[b]There were no patients in this category.

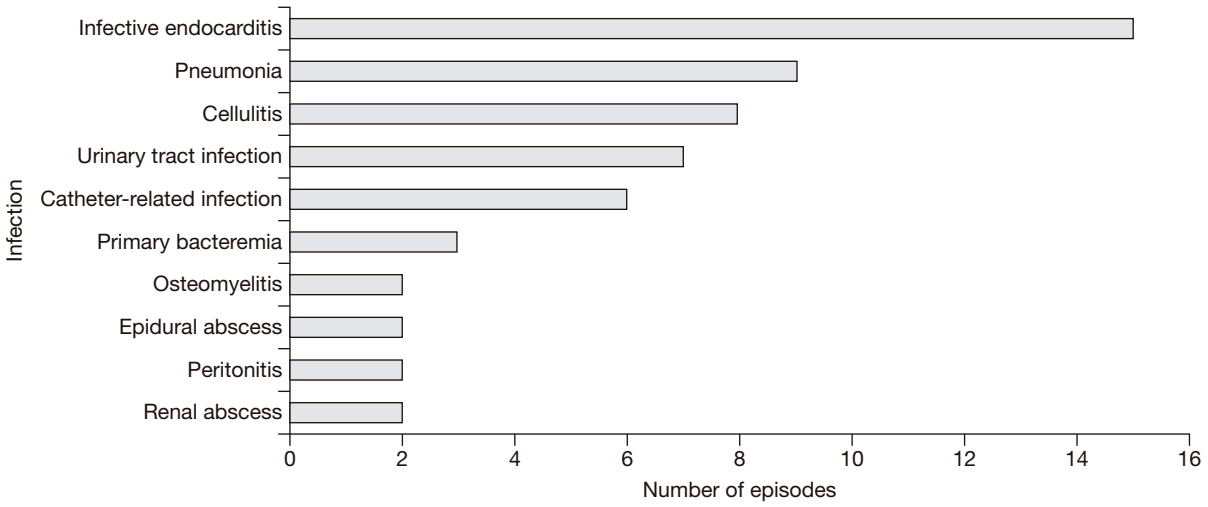

Fig. 2. Ten leading presentations of bacterial infection among human immunodeficiency virus-infected injection drug users.

respectively, as shown in Fig. 2. Other less common patterns of infection were urinary tract infection, vascular catheter-related infection, primary bacteremia, osteomyelitis, peritonitis, epidural abscess and renal abscess (Fig. 2).

Twenty HIV-infected IDUs developed 33 episodes of bacteremia. Overall, Gram-positive bacteria accounted for 23 episodes (69.7%), and Gram-negative bacteria for 10 episodes (30.3%). No statistically significant difference between Gram-positive and Gram-negative pathogens in terms of CD4+ counts (p=0.60) was observed. Of these 33 episodes of bacteremia, the leading 3 etiologies were *Staphylococcus aureus* (16 episodes), coagulase-negative staphylococci (3 episodes), and non-typhoid *Salmonella* (3 episodes). Of 16 episodes caused by *S. aureus*, 11 episodes (68.8%) were caused by methicillin-sensitive *S. aureus* (MSSA) and 5 episodes (31.2%) were caused by methicillin-resistant *S. aureus* (MRSA). Over the 12-year study period, none of the *S. aureus* isolates was glycopeptide-resistant. The median CD4+ count was higher in patients with MSSA bacteremia (473 cells/μL) than in those with MRSA bacteremia (273 cells/μL), although the difference was not statistically significant (p=0.36).

There were 15 episodes of IE in 13 patients (10 males, 3 females), with multiple complications during the study period; 3 episodes were noted in 1 patient. The mortality rate was 6.7% (1/15). *S. aureus* was the most common etiology of IE, especially MSSA, which caused 11 episodes of IE (73.3%); all IE cases involved the tricuspid valve. Metastatic complications were as follows: fourteen (14/15, 93.3%) with bilateral pneumonias or septic metastasis of the lung, with or without cavitations; three (20.0%) with empyema, three (20.0%) with septic shock, one (6.7%) with osteomyelitis, one (6.7%) with epidural abscess, one (6.7%) with paraspinal abscess, and one (6.7%) with pyomyositis. Organ failure associated with IE comprised respiratory failure in 3 patients (20.0%), renal failure in 1 (6.7%) and right heart failure in 1 (6.7%).

AIDS-related infectious complications

AIDS-related infectious complications and CD4+ count at diagnosis are shown in Fig. 3. The three most common infectious complications were tuberculosis, candidiasis and *Pneumocystis carinii* (*jirovecii*) pneumonia. For example, 17 HIV-infected IDUs (16.7%) developed TB, of which 7 had pulmonary TB (43.8%) and 10 extrapulmonary TB (56.2%). Of the 10 patients with extrapulmonary TB, 6 also had lung involvement. The median CD4+ count was 27 cells/μL. The most common site of infection was lung (13 episodes), followed by lymph node (7), bone marrow (2), retroperitoneum (2), pleura (2), skin (1), colon (1) and brain (1). Two patients (11.8%) had MDR-TB and both had extrapulmonary TB. Their CD4+ counts were 6 and 23 cells/μL, respectively. The median CD4+ count was significantly higher in patients with pulmonary TB (126 cells/μL) than in those with extrapulmonary TB (8, p=0.03) [Fig. 3].

Discussion

In this study, we found that the case number and proportion of HIV-infected IDUs were increased over time, from 1.2% in 1998-2002 to 12.0% in 2003-2006,

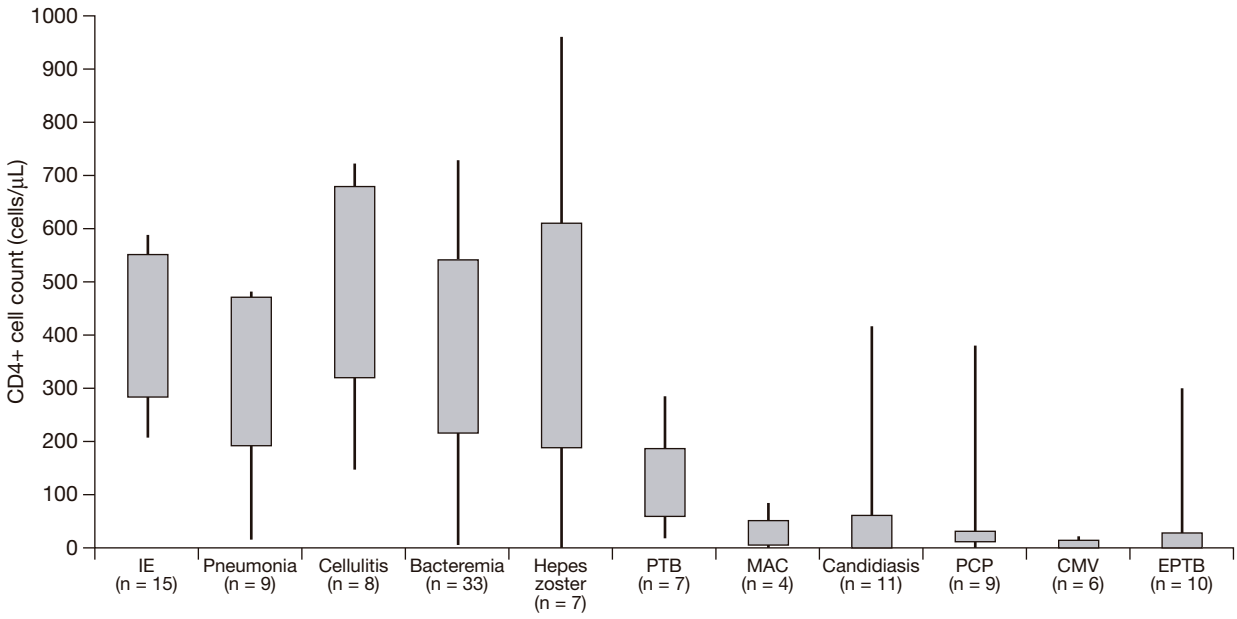

Fig. 3. Bacterial infections and acquired immunodeficiency syndrome-related infectious complications and their respective CD4+ counts. The bars denote interquartile range of CD4+ counts. IE = infective endocarditis; PTB = pulmonary tuberculosis; MAC = *Mycobacterium avium* complex infection; PCP = *Pneumocystis carinii* (*jirovecii*) pneumonia; CMV = cytomegalovirus disease; EPTB = extrapulmonary tuberculosis.

and a similar trend was observed for HCV seroprevalence (58.8% in 1994-2002 to 92.5% in 2003-2006). *Staphylococcus* spp., mostly MSSA (11 episodes, 33.3%), were the major bacterial pathogens causing bloodstream bacterial infections in HIV-infected IDUs. IE, pneumonia and cellulitis were the three most common bacterial infections. Extrapulmonary TB was more common than pulmonary TB and was associated with a lower CD4+ count (8 vs 126 cells/μL, p=0.03).

HIV-infected IDUs enrolled after 2003 in this study had higher initial CD4+ counts (438 vs 23 cells/μL, p<0.001). The proportions of persons with CD4+ count <200 cells/μL (25.5%) and PVL ≥5 $\log_{10}$ copies/mL (31.8%) were significantly lower than that of our previous study [18]. This may be related to early detection of HIV infection among IDUs; in Taiwan, all inmates (including IDUs) have been routinely tested for HIV in detention centers since 1990 [5].

Our previous cohort study of HIV-infected patients [19], in which just 3.5% were IDUs, suggested that the overall seroprevalence of HCV (9.6%) was higher than that of the general population aged ≥18 years in Taiwan (4.4%) [12], but significantly lower than levels reported in studies from western countries (16-45%) [20]. However, the seroprevalence of HCV among HIV-infected IDUs in Taiwan has been rapidly increasing, from 58.8% in 1995-2002 to 92.5% in 2003-2006 in the present study. The further increase of HCV seroprevalence may be related to the recent HIV outbreak among IDUs in Taiwan [5]. In HIV-infected patients, chronic HCV infection is associated with higher HCV RNA levels [21] and a more rapid progression of HCV-related chronic liver disease [22]. With improved survival in the post-HAART era, chronic HCV infection may predispose these patients to the development of hepatic complications, such as liver cirrhosis and hepatocellular carcinoma, and such chronic liver disease has become an increasingly important cause of hospitalization and death [23]. In addition, the HCV genotype 1 was the most common genotype in our HIV-infected IDUs (56.1%). HCV genotype 1 appears more difficult to treat with current therapeutic agents (ribavirin and interferon) [24]. The rapid increase in cases of IDUs co-infected with HCV in Taiwan will present a challenge to the health care system in the near future.

The seroprevalence of HBV (19.3%) in this study consisting solely of HIV-infected IDUs appears to be similar to that of our previous study [25], which suggests intravenous drug use is not associated with an increased prevalence of HBV co-infection among IDUs in Taiwan. The similar seroprevalence of HBV between the current study and our previous study may be related to the high endemicity of HBV infection

in the general population aged ≥18 years (17.3%) [12], in which vertical transmission has been the most common route of HBV transmission [26]. In this study (17.3%), we found a lower HBV seroprevalence among younger patients (<20 years old or born after 1984) [17.3%]. The nationwide HBV vaccination program initiated in 1984 in Taiwan has dramatically reduced HBV seroprevalence among persons born after 1984 [26]. Further studies, assessing the impact of the HBV vaccination program on HBV seroprevalence in HIV-infected patients would be useful.

Similar to the findings of other reports [27,28], we found that *Staphylococcus* spp. were the major bacterial pathogens (19 episodes, 57.6%) causing bloodstream bacterial infections in HIV-infected IDUs, with *S. aureus* responsible for 16 episodes (48.5%). *S. aureus* is not only responsible for considerable morbidity and mortality in HIV-infected patients, but is the most common etiology of bacteremia in these patients [29]. A higher rate of carriage of *S. aureus* among HIV-infected patients might be the cause [30,31]. Of the 16 episodes of *S. aureus* bacteremia, 5 (31.2%) were MRSA, which was similar to rates in western countries (31-32%) [29,32]. As in a previous study [29], low CD4+ count and intravenous drug use were the risk factors for developing MRSA bacteremia, although in the present study these associations were not statistically significant, probably because of a small sample size.

A previous report suggested that HIV-related immunodeficiency may independently increase the risk of IE among IDUs [33], IE being one of the most severe complications of bacteremia among IDUs [34]. HIV-positive IDUs have a higher risk of right-sided IE [6] (100% in our study) than HIV-negative IDUs. Furthermore, IDUs often have recurrent IE [34]. Despite the high risk of IE, IDUs develop infections with pathogens similar to non-IDUs. *S. aureus* is the most commonly identified organism (60% to 70%; in our study, 73.3%) and is usually sensitive to methicillin. Accordingly, empirical antibiotic therapy in IDUs who develop IE should target *Staphylococcus* spp.

IDUs are at an increased risk of *M. tuberculosis* infection and are more likely to be non-compliant with TB screening and therapy [35]. Progression to active TB in people with latent or recently acquired *M. tuberculosis* infection will be accelerated by progressive immunosuppression from HIV infection [36,37]. TB in HIV-infected IDUs has contributed significantly to the recent increases of TB prevalence in several developed countries [38]. Although patients with HIV infection have a bacteriologic response to anti-TB treatment similar to non-HIV-infected individuals, the high prevalence (17/102, 16.7%) of TB among HIV-infected IDUs in this study should raise concerns, because HIV infection is the most potent risk factor in promoting the reactivation of TB infection or exogenous reinfection. Furthermore, incarceration may promote TB transmission [39].

There are several limitations of this study. First, it was a retrospective observational study, and the sample size is small. Second, our hospital, located in a metropolitan area, is a referral hospital for HIV care. HIV-infected IDUs who have less severe infectious complications might seek medical attention at other hospitals that are not designated for HIV care, and therefore, we were not able to describe the entire spectrum of infectious complications which may occur more commonly in IDUs, such as skin and soft tissue infection [8,40]. Third, we were not able to assess the incidence of infectious complications because IDUs typically had a low level of compliance with medical follow-up.

In conclusion, bacteremia, IE and TB were the three most common patterns of infection among HIV-infected IDU who sought medical care at this referral hospital for HIV care, and MSSA was the most common etiology of bacteremia. The high seroprevalence of HBV and HCV and subsequent hepatic complications may present a future challenge to the health care system.

References

1. AIDS epidemic update: December 2006. UNAIDS/WHO; 2006:1-86.
2. Aceijas C, Stimson GV, Hickman M, Rhodes T; United Nations Reference Group on HIV/AIDS Prevention and Care among IDU in Developing and Transitional Countries. Global overview of injecting drug use and HIV infection among injecting drug users. AIDS. 2004;18:2295-303.
3. Centers for Disease Control and Prevention. Cases of HIV infection and AIDS in the United States and dependent areas, 2005. HIV/AIDS Surveillance Report. 2007;17: 1-54. Available from: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/
4. Centers for Disease Control, Taiwan. HIV/AIDS data, 2006. Available from: http://www.cdc.gov.tw/website_en/health%20topics/Communicable%20Diseases%20&%20Prevention/Issues%20of%20HIV-AIDS/Statistics%20of%20HIVAIDS/Download%20HIV-AIDS%20Data.

files/2006.files/9512Monthly%20Report.pdf
5. Chen YM, Kuo SH. HIV-1 in Taiwan. Lancet. 2007;369: 623-5.
6. Miró JM, del Río A, Mestres CA. Infective endocarditis and cardiac surgery in intravenous drug abusers and HIV-1 infected patients. Cardiol Clin. 2003;21:167-84.
7. White AG. Medical disorders in drug addicts. 200 consecutive admissions. JAMA. 1973;223:1469-71.
8. Brettle RP. Infection and injection drug use. J Infect. 1992; 25:121-31.
9. Friedman H, Newton C, Klein TW. Microbial infections, immunomodulation, and drugs of abuse. Clin Microbiol Rev. 2003;16:209-19.
10. Chung DC, Ko YC, Chen CJ, Chen ER, Wu CC, Wu PS. Seroepidemiology of hepatitis B virus, hepatitis D virus, and human immunodeficiency virus infections among parenteral drug abusers in southern Taiwan. J Med Virol. 1989;28:215-8.
11. Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, Chen PJ, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis. 1990;162:817-22.
12. Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J Formos Med Assoc. 2007;106:148-55.
13. Morice Y, Roulot D, Grando V, Stirnemann J, Gault E, Jeantils V, et al. Phylogenetic analyses confirm the high prevalence of hepatitis C virus (HCV) type 4 in the Seine-Saint-Denis district (France) and indicate seven different HCV-4 subtypes linked to two different epidemiological patterns. J Gen Virol. 2001;82:1001-12.
14. Kumar S, Tamura K, Jakobsen IB, Nei M. MEGA2: molecular evolutionary genetics analysis software. Bioinformatics. 2001;17:1244-5.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128-40.
16. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med. 1977;296:1305-9.
17. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96:200-9.
18. Sun HY, Chen MY, Hsieh SM, Sheng WH, Chang SY, Hsiao CF, et al. Changes in the clinical spectrum of opportunistic illnesses in persons with HIV infection in Taiwan in the era of highly active antiretroviral therapy. Jpn J Infect Dis. 2006;59:311-6.
19. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Impact of chronic hepatitis C infection on outcomes of patients with an advanced stage of HIV-1 infection in an area of low prevalence of co-infection. Int J STD AIDS. 2005;16:42-8.
20. Tedaldi EM, Baker RK, Moorman AC, Alzola CF, Furhrer J, McCabe RE, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Clin Infect Dis. 2003;36:363-7.
21. Thomas DL, Shih JW, Alter HJ, Vlahov D, Cohn S, Hoover DR, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis. 1996;174:690-5.
22. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33:562-9.
23. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994-1998. J Infect Dis. 2002;186:1023-7.
24. Yoo TW, Donfield S, Lail A, Lynn HS, Daar ES; Hemophilia Growth and Development Study. Effect of hepatitis C virus (HCV) genotype on HCV and HIV-1 disease. J Infect Dis. 2005;191:4-10.
25. Sheng WH, Chen MY, Hsieh SM, Hsiao CF, Wang JT, Hung CC, et al. Impact of chronic hepatitis B virus (HBV) infection on outcomes of patients infected with HIV in an area where HBV infection is hyperendemic. Clin Infect Dis. 2004;38:1471-7.
26. Ni YH, Chang MH, Huang LM, Chen HL, Hsu HY, Chiu TY, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. Ann Intern Med. 2001;135:796-800.
27. Petrosillo N, Viale P, Nicastri E, Arici C, Bombana E, Casella A, et al. Nosocomial bloodstream infections among human immunodeficiency virus-infected patients: incidence and risk factors. Clin Infect Dis. 2002;34:677-85.
28. Wang JT, Sheng WH, Chen MY, Fang CT, Hsieh SM, Hsueh PR, et al. Nosocomial bloodstream infection in human immunodeficiency virus-infected patients in Taiwan: descriptive epidemiology and risk factors for mortality. J Formos Med Assoc. 2004;103:743-8.
29. Tumbarello M, de Gaetano Donati K, Tacconelli E, Citton R, Spanu T, Leone F, et al. Risk factors and predictors of mortality of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in HIV-infected patients. J Antimicrob Chemother. 2002;50:375-82.

30. McDonald LC, Lauderdale TL, Lo HJ, Tsai JJ, Hung CC. Colonization of HIV-infected outpatients in Taiwan with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. Int J STD AIDS. 2003;14:473-7.
31. Nguyen MH, Kauffman CA, Goodman RP, Squier C, Arbeit RD, Singh N, et al. Nasal carriage of and infection with *Staphylococcus aureus* in HIV-infected patients. Ann Intern Med. 1999;130:221-5.
32. Chang FY, MacDonald BB, Peacock JE Jr, Musher DM, Triplett P, Mylotte JM, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore). 2003;82: 322-32.
33. Manoff SB, Vlahov D, Herskowitz A, Solomon L, Muñoz A, Cohn S, et al. Human immunodeficiency virus infection and infective endocarditis among injecting drug users. Epidemiology. 1996;7:566-70.
34. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. Ann Intern Med. 1993;119:1017-28.
35. Perlman DC, Salomon N, Perkins MP, Yancovitz S, Paone D, Des Jarlais DC. Tuberculosis in drug users. Clin Infect Dis. 1995;21:1253-64.
36. Guidelines for implementing collaborative TB and HIV programme activities. World Health Organization; 2003: 1-78.
37. Castilla J, Gutiérrez A, Guerra L, Pérez de la Paz J, Noguer I, Ruiz C, et al. Pulmonary and extrapulmonary tuberculosis at AIDS diagnosis in Spain: epidemiological differences and implications for control. AIDS. 1997;11:1583-8.
38. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in western Europe. Bull World Health Organ. 1993;71:297-306.
39. Chaves F, Dronda F, Cave MD, Alonso-Sanz M, Gonzalez-Lopez A, Eisenach KD, et al. A longitudinal study of transmission of tuberculosis in a large prison population. Am J Respir Crit Care Med. 1997;155:719-25.
40. Shepherd SM, Druckenbrod GG, Haywood YC. Other infectious complications in intravenous drug users. The compromised host. Emerg Med Clin North Am. 1990;8: 683-92.