Seroprevalence of Viral Hepatitis and Sexually Transmitted Disease Among Adults with Recently Diagnosed HIV Infection in Southern Taiwan, 2000–2005: Upsurge in Hepatitis C Virus Infections Among Injection Drug Users

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Background/Purpose: The purpose of this study was to compare the seroprevalence of viral hepatitis and sexually transmitted disease (STD) co-infections among three populations at risk recently diagnosed with HIV infection.

Methods: A retrospective review of medical records was performed to determine the prevalence of several co-infections among adults recently diagnosed with HIV infection between 2000 and 2005 at National Cheng Kung University Hospital in Tainan, Taiwan.

Results: Among a total of 484 adults, 124 (25.6%) were men having sex with men (MSM), 105 (21.7%) were heterosexual adults, and 255 (52.7%) were injection drug users (IDUs). The case number of adults with recently diagnosed HIV infection increased annually, from 27 in 2000 to 142 in 2005 (p < 0.001). This trend appeared to be attributable to the upsurge in HIV infection among IDUs beginning in 2003. At the time of HIV diagnosis, mean CD4+ counts were significantly higher and plasma HIV-1 RNA loads were lower in the IDU group than the MSM or heterosexual groups. The hepatitis B virus (HBV) carrier rate was similar in all three groups, with an average rate of 16.5%. The prevalence of treponemal antibody and Entamoeba histolytica indirect hemagglutination antibody was higher in MSM (37.5% and 9.4%, respectively) than in heterosexuals (19.6% and 7.3%, respectively) or IDUs (3.2% and 2.1%). The seroprevalence of hepatitis A virus infection increased with age, with 94.2% (97/103) of patients who were older than 40 years. Hepatitis C virus (HCV) or HBV-HCV co-infections were noted more often in IDUs (97.9% and 16.9%, respectively) than in heterosexuals (10.9% and 2.2%, respectively) and MSM (5.3% and 3.6%, respectively).

Conclusion: There was a recent upsurge in HIV-HCV co-infected IDUs in southern Taiwan. A higher rate of co-infection with STDs among HIV-infected MSM highlights the need for integrated STD control efforts in current HIV prevention programs. [J Formos Med Assoc 2008;107(5):404–411]

Key Words: human immunodeficiency virus, sexually transmitted diseases, transmission routes, viral hepatitis

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The human immunodeficiency virus (HIV) epidemic in Taiwan continues to grow. The annual incidence of reported HIV infections among the general population was 1.6/100,000 in 1997 and increased to 3.7/100,000 in 2003. Such an explosive HIV epidemic has been related to the spread of HIV-1 CRF07_BC infections among injection drug users (IDUs) since 2003.

Due to shared transmission routes, co-infection with hepatitis B virus (HBV), hepatitis C virus (HCV), and sexually transmitted diseases (STDs) are not uncommon among HIV-infected persons. The prevalence of HIV/HCV co-infection varies markedly by country, with 35% in the United States and Europe, 16.1% in the CAESAR study, 13.1% in Australia, 8.2% in Nigeria, and 2.1% in India. The prevalence of HIV/HBV co-infection was 9% in the EuroSIDA cohort, 6.4% in India, and 6.3% in Australia. High prevalence of STDs was reported among HIV-infected patients, with 79.5% in northern Israel, 52% in Taiwan, 25% in New York, and 11.9–13.9% in Baltimore. Herpes simplex virus-2, syphilis, and genital warts were the three major STDs among people with HIV. Co-infections with HIV and viral hepatitis or other STDs are a major public health concern. Early diagnosis and implementation of preventive strategies are crucial for reducing further transmission.

In the literature, the prevalence of co-infections with HIV, viral hepatitis, and STDs varies notably with regard to the different risk populations. For example, IDUs had the highest prevalence rate of HIV/HCV co-infections, and men having sex with men (MSM) had a higher prevalence of HIV/HBV co-infections and STDs.

The life span and quality of life of HIV-infected individuals have been greatly improved after the introduction of highly active antiretroviral therapy (HAART). However, patients co-infected with multiple hepatitis viruses will experience more complicated clinical problems than those without. Furthermore, there is an increased risk of progression to acquired immunodeficiency syndrome (AIDS) and AIDS-related death among people with HIV/HCV co-infections. Chronic HBV infection among people with HIV infection is the most important cause of liver cirrhosis and hepatocellular carcinoma, which certainly increases the likelihood of liver-related mortality. HBV infection is an endemic disease in Taiwan, with a chronic carrier rate of 15–20% in the general population prior to mass vaccination. The seroprevalence of HCV infection in Taiwan is estimated to be 2–5% of the general population and chronic HCV infection accounts for more than 30% of patients with hepatocellular carcinoma. Therefore, there is a substantial number of HIV-infected patients with multiple infections. However, there are limited data from Asian countries regarding the seroprevalence of co-infection among individuals with HIV infection.

The purpose of this study was to determine and compare the seroprevalence of viral hepatitis and STD co-infections among newly diagnosed HIV patients who acquired the disease via different modes of transmission. Such information will be helpful in implementing effective preventive programs to reduce the spread of not only HIV, but also HBV, HCV and STDs among specific populations at risk.

**Methods**

**Study design and population**

National Cheng Kung University Hospital was the site of the study and is one of the referral centers for HIV/AIDS care in southern Taiwan. There have been more than 700 cases of HIV infection since 1992. Serologic tests for co-infections of viral hepatitis, such as hepatitis A virus (HAV), HBV and HCV, and syphilis, were routinely performed for recently diagnosed HIV-infected patients. The medical records of patients between 2000 and 2005 were retrospectively reviewed. A standardized record form was used to collect data, which included the results of serologic tests, demographic data, risk routes of HIV transmission, receipt of antiretroviral therapy, initial plasma HIV RNA loads, and CD4+ and CD8+ T lymphocyte counts. Patients who were ≥15 years old at the time of HIV diagnosis and who had a recognized route of HIV...
infection were included in the analysis. In order to describe chronological changes in newly diagnosed patients who had different transmission modes, the national HIV epidemiologic data on Taiwan’s Centers for Disease Control website were retrieved to compare with the findings of the current study.19

**Laboratory procedures and definition**
The diagnosis of HIV infection was made when HIV-1 antibody was detected in serum samples by using a single-microparticle enzyme immunoassay (AxSYM HIV 1/2 gO; Abbott GmbH & Co. KG, Wiesbaden Delkenheim, Germany) and confirmed by Western blot (New Lav Blot 1; Biorad, Steenvoorde, France). CD4⁺ and CD8⁺ cell counts were determined using flow cytometry (EPICS-XL; Beckman Coulter, CA, USA). Quantification of HIV plasma viral load (pVL) was conducted by reverse transcription-polymerase chain reaction (RT-PCR) (Roche Amplicor, Version 1.5; Roche, Branchburg, NJ, USA) with a lower detection limit of 400 copies of RNA/mL. Nontreponenal antibodies to *Treponema pallidum* were measured by the rapid plasma regin test (RPR Card Test; Becton-Dickinson, Maryland, USA) and treponenal antibodies by *T. pallidum* hemagglutination (TPHA) assay (SERODIA-TPPA; Fujirebio, Taoyuan, Taiwan). Patients with TPHA titers ≥1:160 were considered to be seroreactive for *T. pallidum* infection. Serologic specimens were tested for IgG antibodies to HAV (HAV-IgG) (AxSYM HAVAB 2.0; Abbott GmbH Diagnostika, Wiesbaden-Delkenheim, Germany), hepatitis B surface antigen (HBsAg), antibodies to HBsAg (HBsAb) (AxSYM HBsAg V2 and AUSAB; Abbott GmbH & Co. KG), and antibodies to HCV (HCV Ab) (AxSYM HCV version 3.0; Abbott Laboratories, Abbot Park, IL, USA). Chronic HBV infection was defined by the presence of serum HBsAg, and HCV infection was defined by the presence of HCV Ab in serum. Serum antibodies to *Entamoeba histolytica* were determined by indirect hemagglutination (IHA) test (Cellognost-Amoebiasis; Dade Behring Marburg GmbH, Marburg, Germany).

**Statistical analysis**
Statistical analyses were conducted using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows. Descriptive statistics were calculated to describe the demographics, baseline immunologic and virologic statuses upon HIV diagnosis, and use of antiretroviral therapy across three risk groups. The difference in seroprevalence of viral hepatitis and STD co-infections was evaluated by Pearson’s χ² test. Continuous variables were analyzed by post hoc Scheffé’s tests. A value of *p* < 0.05 was considered statistically significant.

**Human participant protection**
Approval for this study was obtained from the institutional review board of National Cheng Kung University Hospital. Informed consent from the participants was not required due to the retrospective chart-review design of this study.

**Results**

**Epidemic trends**
Overall, 496 patients who were recently diagnosed with HIV infections visited the study hospital between 2000 and 2005. Excluding two children infected via mother-to-child transmission and 10 with uncertain transmission routes, a total of 484 adults were enrolled in this study. The annual case numbers of recently diagnosed HIV-infected persons among the three at-risk groups in the study hospital and Taiwan between 2000 and 2005 are shown in Figure 1. There was a significant increase in the number of recently diagnosed cases from 2000 to 2005 (*p* < 0.001). Such a trend could be attributed to the explosive HIV epidemic among IDUs beginning in 2003, since the case numbers of HIV-infected MSM and heterosexuals remained stable during the study period.

**Profile of adults with recently diagnosed HIV infection**
Of the 484 adults, 124 (25.6%) were MSM, 105 (21.7%) were exposed through heterosexual sex, and 255 (52.7%) were IDUs. Males (91.7%)
predominated in the study and the mean age was 35.6 years (range, 18–81 years). At the initial examination, 123 (26.2%) patients were diagnosed with AIDS as defined by CD4+ lymphocyte count < 200 cells/µL. Overall, 46.5% patients had already taken HAART at the end of 2005. The demographic and baseline clinical characteristics of study participants across the three at-risk groups are summarized in Table 1. At the time of HIV infection, the mean CD4+ and CD8+ counts were significantly higher and the plasma HIV-1 RNA load was significantly lower in IDUs than in MSM and heterosexuals.

**Seroprevalence of hepatitis viruses and STD co-infections**

Overall, among HIV-infected adults, the prevalence of TPHA seroreactivity was 15.5% (72/466), and

![Figure 1. Number of adults with recently diagnosed HIV infection at National Cheng Kung University Hospital (NCKUH) and Taiwan, 2000–2005.](image)

**Table 1.** Demographic and baseline clinical characteristics of adults recently diagnosed with HIV infections categorized by risk behaviors, 2000–2005*

<table>
<thead>
<tr>
<th></th>
<th>MSM (n = 124)</th>
<th>Heterosexual (n = 105)</th>
<th>IDU (n = 255)</th>
<th>Total (n = 484)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>124 (100)</td>
<td>79 (75.2)</td>
<td>241 (94.5)</td>
<td>444 (91.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Married</td>
<td>10 (8.1)</td>
<td>56 (53.8)</td>
<td>52 (22.7)</td>
<td>118 (25.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.9 ± 9.5</td>
<td>43.1 ± 14.8</td>
<td>34.7 ± 7.8</td>
<td>35.6 ± 11.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>2.8 ± 1.5</td>
<td>3.7 ± 1.6</td>
<td>1.8 ± 0.7</td>
<td>2.5 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline plasma HIV-1 viral load (log of RNA copies/mL)</td>
<td>4.8 ± 1.0</td>
<td>4.7 ± 0.8</td>
<td>4.2 ± 0.6</td>
<td>4.4 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline CD8+ counts (cells/µL)</td>
<td>938 ± 528</td>
<td>744 ± 505</td>
<td>1110 ± 498</td>
<td>988 ± 527</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline CD4+ counts (cells/µL)</td>
<td>253 ± 217</td>
<td>220 ± 338</td>
<td>462 ± 216</td>
<td>359 ± 272</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>37 (31.4)</td>
<td>19 (18.8)</td>
<td>170 (67.7)</td>
<td>226 (48.2)</td>
<td></td>
</tr>
<tr>
<td>200–350</td>
<td>28 (23.7)</td>
<td>20 (19.8)</td>
<td>73 (29.1)</td>
<td>121 (25.7)</td>
<td></td>
</tr>
<tr>
<td>100–199</td>
<td>11 (9.3)</td>
<td>14 (14.0)</td>
<td>4 (1.6)</td>
<td>29 (6.2)</td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>42 (35.6)</td>
<td>48 (48.0)</td>
<td>4 (1.6)</td>
<td>94 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Receipt of antiretroviral therapy</td>
<td>93 (78.8)</td>
<td>78 (72.1)</td>
<td>33 (14.1)</td>
<td>204 (45.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Data presented as n (%) or mean ± standard deviation; †number of people does not always add up to the subgroup case number because of missing data. MSM = men having sex with men; IDU = injection drug user.
54.2% (39/72) of those with TPHA seroreactivity had RPR titers ≥ 1:4. Serum titers of *E. histolytica* IHA antibody ≥ 1:128 were noted in 4.7% of 319 patients. Moreover, 65.8% (219/333) had been infected with HAV, as indicated by the presence of serum HAV IgG (Table 2). The prevalence of HAV-IgG increased with age and 94.1% of patients older than 40 years had detectable HAV-IgG in their sera (Figure 2). HBV carrier (i.e. presence of HBsAg in serum) rate was similar across the three groups, with an average of 16.5% (Table 2). The prevalence of HCV and HBV/HCV co-infections among HIV-infected adults was 56.7% and 10.5%, respectively.

The prevalence of *T. pallidum*, *E. histolytica*, HAV, HCV, and HBV/HCV co-infections were significantly different across the three HIV risk groups (Table 2). Seroreactivity of TPHA and *E. histolytica* IHA was more often found in MSM (37.5% and 9.4%, respectively) than in heterosexuals (19.6% and 7.3%, respectively) or IDUs (3.2% and 2.1%, respectively). HAV-IgG was more frequently found...
in heterosexuals (85.2%) than in IDUs (70.1%) or MSM (40.0%). Likewise, chronic HCV or HBV/HCV co-infections were more often present in IDUs (97.9% and 16.9%, respectively) than in heterosexuals (10.9% and 2.2%, respectively) or MSM (5.3% and 3.6%, respectively).

**Discussion**

After several HIV control policies were launched by the government, including free access to HAART since April 1997,\(^1\) there was a significant reduction in morbidity and mortality due to AIDS in Taiwan.\(^{20,21}\) It was speculated that IDUs in Taiwan do not usually share needles because of the easy availability of cheap, disposable needles from drug stores.\(^{22}\) However, the unexpected upsurge of an HIV epidemic in Taiwan and the high prevalence of HCV co-infections (97.9%) among IDUs, as observed in the present study, suggested that there was an efficient mode of HIV and HCV transmission contributing to the current epidemic. Two recent studies in Taiwan demonstrated that the majority (>90%) of HIV-1 isolates from IDUs identified between 2004 and 2005 harbored CRF07_BC sequences, resembling the dominant strains circulating among IDUs in China,\(^2,3\) and travel history to southwest China and sharing of needles or apparatuses could be traced in certain affected individuals.\(^3\) Accordingly, this evidence indicated that parenteral transmission contributes to the HIV epidemic among IDUs in Taiwan. Dramatic decrease in the numbers of newly diagnosed HIV-infected IDUs following the countrywide implementation of harm reduction programs (including methadone maintenance therapy and needle/syringe exchange in convenience stores) beginning in September 2005 was further evidence that sharing needles or apparatuses is common in this population and injection behaviors are still the key targets of intervention.\(^{23}\)

Early studies conducted between the 1980s and 1990s had revealed that parenteral transmission of blood-borne pathogens among IDUs was a problem and the prevalence of HCV infections was as high as 53–82.2%,\(^{24-27}\) which was higher than in non-injection drug users\(^{24,25}\) and the general population.\(^{18}\) Although national policies had been implemented to interrupt the spread of HCV infection in Taiwan,\(^{28,29}\) few efforts have been put into the prevention of HCV transmission in IDUs. As it shares the same route of transmission with HIV, the epidemiologic trend of HCV infection among IDUs would be expected to change following the HIV prevention intervention.

Vertical transmission was the major route of HBV infections in Taiwan, where more than 90% of the general population under the age of 40 years was infected with HBV, and 15–20% of them had chronic HBV infection before the implementation of HBV vaccination.\(^{17}\) All the participants in our study were born before 1984 when national HBV vaccination programs for neonates began.\(^{17}\) Therefore, no one had ever received active immunization before enrolment. A similar trend in HBV infections across all three at-risk groups, 14.2–17.4% having HBsAg, was present, as observed in the general population of Taiwan. Similarly, Chen et al reported that serum HBsAg could be noted among 20.3% of IDUs and 18.4% of non-injectors.\(^{30}\) Those facts support the speculation that most participants were exposed to HBV during the perinatal period and, therefore, sexual and/or parenteral transmission (such as needle sharing in IDUs) later in adulthood would not further increase HBV prevalence. Furthermore, from a public health viewpoint, mass HBV vaccination will reduce HBV-related liver morbidity among HIV-infected individuals born after 1984, as observed in the general population.\(^{17}\)

HAV and *E. histolytica* are uncommon enteric pathogens, but humans can contract these pathogens via ororectal sex. It can therefore be regarded as an STD. With improvements in socioeconomic status and environmental sanitation, shifting seroepidemiology of HAV infection from childhood to adulthood has been observed in many Asian countries.\(^{31,32}\) However, few seroconversions occurred in patients younger than 30 years in the study. Overall, one third of our HIV-infected adults remained susceptible to HAV.

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Co-infections among adults with recently diagnosed HIV infections
infections. These data indicate the urgent need for HAV vaccination for the susceptible population, in whom HBV or HCV co-infection was not uncommon, to decrease the risk of hepatitis A outbreak and to avoid severe hepatic injury among HBV or HCV co-infected individuals.

Recently, invasive amebiasis has been recognized as an emerging parasitic disease in patients with HIV-1 infections in Taiwan; HIV-infected patients with a high IHA titer (≥ 128) had a higher incidence of invasive amebiasis than those with a lower titer.33 We found that MSM often had significant IHA titer, which is consistent with Hung et al’s report.33 In addition, TPHA seroreactivity was more frequently present in MSM than in the other two risk groups at the time of HIV diagnosis. Such a finding echoed those of two surveillance studies in Taiwan; one studied gay bathhouses and another studied male homosexuals at drug/sex parties. Both studies showed a high prevalence of syphilis, with 16–25% of infected patients.34,35 These findings highlight the need for more effective measures to reduce the spread of syphilis in the MSM population in Taiwan.

Several limitations in this study should be addressed. First, the full scope of STD co-infections among HIV-infected individuals was not available due to the retrospective design. Therefore, we tried to use serologic markers for syphilis and two pathogens (amoeba and HAV), which are also transmissible via intimate contact, to imply the frequency of STDs by different HIV transmission modes. Second, information regarding risk behaviors was retrieved from medical charts, which relied on self-reported data. It is possible that there was some under-reporting of either illicit drug use or sexual engagement with men due to legal and identity considerations. Third, some of our patients may have exhibited dual or triple HIV risk behaviors. However, we assumed that concealed sexual identity or dual/triple risk behaviors would be uncommon in our study participants. Fourth, the sample size of each risk group for E. histolytica IHA was too small and therefore, the result of significant difference in seroprevalence of amebiasis among the three groups might have a type II error. Multicenter, large-scale serosurveillance is needed to further confirm this finding.

In conclusion, many lessons were learned from the surge in the HIV epidemic in Taiwan. The targets of public health policies to control HIV transmission should not only include medical care for HIV-infected persons, but also multidisciplinary preventive measures for different risk groups. A higher rate of co-infection with STDs among HIV-infected MSM highlights the need for integrated STD control efforts in current HIV prevention programs.

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