Prophylactic Effect of Antiretroviral Therapy on Hepatitis B Virus Infection

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Background. Hepatitis B virus (HBV) infection is common in individuals infected with human immunodeficiency virus, especially in men who have sex with men (MSM). Almost all currently used regimens of antiretroviral therapy (ART) contain lamivudine (LAM) or tenofovir disoproxil fumarate (TDF), both of which have significant anti-HBV activity. However, the prophylactic effect of ART on HBV infection has not been assessed previously.

Methods. Non-HBV-vaccinated HIV-infected MSM were serologically evaluated for HBV infection using stocked serum samples. Cases negative for HBV surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to HBV core antigen (anti-HBc) in first serum samples were serologically followed until last available stocked samples. HBV genotype and LAM-resistant mutation (rtM204V/I) were analyzed in cases that became HBsAg-positive.

Results. The first stocked samples were negative for all analyzed HBV serological markers in 354 of 1434 evaluated patients. The analysis of their last samples indicated HBV incident infection in 43 of them during the follow-up period. The rate of incident infections was lower during LAM- or TDF-containing ART (0.669 incident infections in 100 person-years) than during no ART period (6.726 incident infections in 100 person-years) and other ART (5.263 incident infections in 100 person-years) (P < .001). Genotype A was most prevalent (76.5%), and LAM-resistant HBV was more frequent in incident infections during LAM-containing ART (50.0%) than in those during no ART and other ART (7.1%) (P = .029).

Conclusions. LAM- and TDF-containing ART regimens seem to provide prophylaxis against HBV infection, although drug-resistant strains seem to evade these effects.

Keywords. lamivudine; tenofovir disoproxil fumarate; resistant; chronic infection.

Patients with human immunodeficiency virus (HIV) infection are at high risk for both hepatitis B virus (HBV) infection and development of chronic infection [1–4]. Based on information from Western countries, the rate of coinfection varies according to risk categories; the highest rate is in men who have sex with men (MSM), with a slightly lower rate among intravenous drug users, and much lower in individuals infected through heterosexual contacts [5–8]. In Japan, HIV/HBV coinfection is also significantly associated with MSM [9, 10]. The progression of chronic HBV infection to cirrhosis, end-stage liver diseases, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in those with chronic HBV infection alone [11, 12]. Vaccination of non-HBV-immunized HIV-infected individuals is recommended to prevent HBV infection [13]. However, all current recommended antiretroviral therapy (ART) regimens contain lamivudine (LAM) or tenofovir disoproxil fumarate (TDF), both of which have significant anti-HBV activity [14]. Do these ART regimens provide any prophylaxis against HBV infection? This is an important question, as a positive answer could influence the strategy applied to prevent HBV infection in HIV-infected individuals. To delineate the hepatitis B prophylactic effect of ART, we used stocked samples for serological evaluation of HBV infection in HIV-infected MSM. The present
study included those patients who had tested negative for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) using their first stocked blood samples, who were followed up serologically to identify new HBV incident infections among them. The other part of the study covered analysis of the relation between the frequency of incident infection and ART regimens.

METHODS

Patients
Since April 1997, we have collected serum samples taken at routine clinical practice from HIV type 1 (HIV-1)–infected patients who visited the Outpatient Clinic of the AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan, under signed informed consent for use in virologic research. Every patient had been interviewed at the first visit by clinical nurse specialists at the HIV outpatient clinic using a structured questionnaire that includes items on sexual history and history of HBV vaccination. Most of the patients regularly visited our clinic every 1–3 months, and we had collected and stored their sera at almost all visits. The ethics committee of the National Center for Global Health and Medicine approved the collection and analysis of the samples. First, we selected HIV-1-infected MSM who met the following inclusion criteria: (1) the first visit to our clinic was between April 1997 and December 2009, (2) they had not received HBV vaccination before the first visit, and (3) at least 2 serum samples were available and collected at least 6 months apart. The first sample was defined as the baseline serum sample, and baseline clinical data were defined as those recorded on the date of sampling of the first stocked serum. Patients’ baseline characteristics, including age, race, hepatitis C virus antibody, results of Treponema pallidum hemagglutination assay, and CD4+ cell count were collected from the medical records.

HBV Analysis
In order to identify new HBV incident infection, we excluded patients with previously confirmed HBV infection. The baseline samples of the patients who met the inclusion criteria described above were serologically evaluated for HBsAg, anti-HBs, and anti-HBc using ARCHITECT HBsAg QT assay, anti-HBs assay, and anti-HBc assay, respectively (Abbott Laboratories, Chicago, Illinois) [15, 16]. Patients positive for any of HBsAg, anti-HBs, and anti-HBc at baseline were excluded from the serological follow-up. The remaining patients were considered to have never been infected with HBV before the baseline. Their last stocked sample taken before or in December 2010, or before HBV vaccination if performed during the follow-up period, was analyzed for HBsAg, anti-HBs, and anti-HBc. If the last sample was negative for all 3, the patient was considered to have never been infected with HBV up to the sampling date of the last stocked serum. If HBsAg, anti-HBs, or anti-HBc was positive in the last stocked serum, the patient was considered to have HBV incident infection during the follow-up period. In the latter case, the baseline samples were subjected to polymerase chain reaction (PCR) analysis for HBV DNA [17, 18], and all the stocked samples during the follow-up period were serologically analyzed to determine the date of HBV incident infection. The date of incident infection was defined as the sampling date of the first positive serum for any HBV serological marker. The time from the baseline to HBV incident infection was analyzed by the Kaplan-Meier method. The data were censored at the sampling date of the last stocked sample if it was negative for all analyzed HBV serological markers. Patients’ age and CD4+ cell count at the date of incident infection and alanine aminotransferase (ALT) values within 3 months of incident infection were collected. If an HBsAg-positive sample was available, HBV genotype and LAM-resistant mutation (rtM204V/I) were analyzed by PCR-invader assay [17–19]. The diagnosis of chronic HBV infection was considered when HBsAg was still positive in sera taken at 6 months or longer after the incidence infection.

Antiretroviral Therapy
To determine the type of ART under which HBV incident infection occurred, the regimen information of ART was collected from medical records over the period spanning from the baseline to the incidence infection or to the end of follow-up. The treatment status was divided into 4 categories: (1) No ART, no treatment with any antiretroviral agent; (2) Other-ART, ART with regimens that did not contain LAM, TDF, or emtricitabine (FTC); (3) LAM-ART, ART with LAM-containing regimens that did not contain TDF or FTC; and (4) TDF-ART, ART with TDF-containing regimens with or without LAM or FTC. Data were censored on the sampling date of the last stocked sample if it was negative for all analyzed HBV serological markers. When the treatment category was modified, the data were censored on the date of category change for the previous treatment category and a new follow-up as a different case was initiated for the replacement treatment category.

Statistical Analysis
The time from the baseline to HBV incident infection was analyzed by the Kaplan-Meier method. The Cox proportional hazards regression analysis was used to assess the risk of HBV incident infections. The impact of patients’ baseline characteristics, year of entry, the use of antiretroviral agents (any antiretroviral, and any of LAM, TDF, or FTC), and the frequency of changing ART regimen during the follow-up period was estimated with univariate analysis, and those with statistical significance were incorporated into multivariate analysis. The
frequency and risk of HBV incident infection during each treat-
mant category was also assessed by univariate Cox propor-
proportional hazards regression analysis. We used hazard ratios and 95% 

cidence intervals to estimate the impact of each variable on 

Patients’ age and CD4+ cell count on the 
date of incident infection, and peak value of ALT within 3 
months of incident infection were compared between transient 

The differences in rates of HBV genotype A and rtM204V/I 
mutation were compared with χ² test (ie, the Fisher exact test).

RESULTS

Figure 1 shows the patient selection procedure. A total of 1434 

HIV-1–infected MSM met the inclusion criteria described in the Methods section. Of these, 146 patients (10.2%) were posi-
tive for HBsAg, 737 (51.4%) were positive for anti-HBs, and 

197 (13.7%) were solely positive for anti-HBc using baseline 
samples. The remaining 354 patients (24.7%; negative for 

HBsAg, anti-HBs, and anti-HBc at baseline), who were consid-
ered to have never been infected with HBV, were enrolled for 

serological follow-up. Table 1 lists their baseline characteristics. 

Sero
gical analysis of the last sample of each of these patients 

showed HBV incident infection during follow-up in 43 

(12.1%). Their baseline samples were found to be PCR-negative 

for HBV DNA, confirming that the incident infection in these 

patients occurred during the follow-up period. All stocked 
samples of the 43 patients were analyzed serologically to deter-

mine the date of HBV incident infection. HBV incident infec-
tions occurred every year between 1997 and 2010 except in 

1998. The median time period from the baseline to HBV inci-
dent infection was 1.6 years (interquartile range [IQR], 192 
– 1151 days; range, 28 – 4068 days). The total observation period 

was 1607 person-years (median, 3.7 years [IQR], 1.9 
– 6.5 years).

Figure 2 shows the Kaplan-Meier curve for the HBV incident 
infection for the whole cohort of enrolled patients.

In order to assess the risk of HBV incident infections, pa-
tients’ baseline characteristics, year of entry, the use of any anti-
retroviral agents, the use of any of LAM, TDF, or FTC, and the 
frequency of changing ART regimen during the follow-up


Table 1. Baseline Characteristics of the 354 Enrolled Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 354)</th>
<th>Year of Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>32.0 (27.0–38.0)</td>
<td>32.0 (27.8–37.3)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>340 (96.0)</td>
<td>59 (96.7)</td>
</tr>
<tr>
<td>Asian other than Japanese</td>
<td>4 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>10 (2.8)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>HCV antibody, positive</td>
<td>8 (2.3)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>TPHA positive</td>
<td>101 (28.5)</td>
<td>23 (37.7)</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³, median (IQR)</td>
<td>277 (151–404)</td>
<td>277 (169–417)</td>
</tr>
<tr>
<td>HIV RNA, log₁₀ copies/mL, median (IQR)</td>
<td>4.6 (3.8–5.2)</td>
<td>4.5 (3.6–5.2)</td>
</tr>
</tbody>
</table>

Data are No. (%) unless otherwise specified.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; TPHA, Treponema pallidum hemagglutination assay.
period were estimated using a proportional hazards model (Table 2). Younger age and higher CD4+ cell count correlated positively, and use of any antiretroviral, use of LAM, TDF, or FTC, and the frequency of changing ART regimen correlated negatively with HBV incident infection, with statistical significance in univariate analysis. However, in multivariate analysis, the use of LAM, TDF, or FTC continued to show significant relation. Then, we focused on the relation between treatment status and HBV incident infection. The observation period in each patient was divided into 4 categories by treatment status: No ART, no treatment with any antiretroviral agent; Other-ART, ART with regimens that did not contain LAM, TDF, or FTC; LAM-ART, ART with LAM-containing regimens that did not contain TDF or FTC; or TDF-ART, ART with TDF-containing regimens with or without LAM or FTC. No participant received FTC single tablet (Emtriva). All the participants who took FTC received the combination tablet of TDF/FTC (Truvada), and therefore, such treatment status was categorized as TDF-ART. The total categorized observation period of No ART, Other-ART, LAM-ART, and TDF-ART was 446, 114, 814, and 233 person-years, respectively. The number of the HBV incident infections was 30 during the No ART period, 6 during Other-ART period, 7 during LAM-ART period, and 0 during TDF-ART period. No incident infection occurred at the time of changing ART regimen. The proportional hazards model showed a significantly lower frequency of HBV incident infection during LAM- or TDF-ART (0.669 incident infections per 100 person-years) compared with that during No ART (6.726 incident infections per 100 person-years), although there was no significant difference between Other-ART (5.263 incident infections per 100 person-years) and No ART, suggesting that ART regimens with anti-HBV activity can reduce HBV incident infections by 90% (Table 3). During LAM-ART, the HIV-1 load around the period of incident infection remained below the detection limit in all the 7 infected patients, indicating excellent adherence to ART.

Figure 3 shows peak ALT levels for the 43 HBV incident infections. Among the 36 incident infections observed the No ART and Other-ART groups, 16 infections (44.4%) were asymptomatic and not associated with significant increases in ALT (peak ALT, <60 IU/L). We were able to serologically follow 33 of the 36 cases for 6 months after the date of incident infection (TDF-ART was introduced within 6 months of incident infection in the other 3 cases). Among the 33 patients, 13 (39.4%) developed chronic infection (HBsAg was still positive 6 months after the date of incident infection). The median CD4+ cell count was 200 cells/mm³ in the 13 patients who developed chronic infection.

Table 2. Cox Proportional Hazards Regression Analysis for the Risk of Hepatitis B Virus Incident Infection

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Year of entry, per 1 y increase</td>
<td>.942 (.860–1.033)</td>
<td>.207</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 1 y increase</td>
<td>.921 (.879–.965)</td>
<td>.001</td>
</tr>
<tr>
<td>Race (Japanese)</td>
<td>21.243 (.010–45657.613)</td>
<td>.435</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>.048 (&lt;.001–346.311)</td>
<td>.503</td>
</tr>
<tr>
<td>TPHA</td>
<td>1.475 (.792–2.747)</td>
<td>.220</td>
</tr>
<tr>
<td>CD4+ cell count, per 100 cells/mm³ increase</td>
<td>1.121 (1.008–1.246)</td>
<td>.035</td>
</tr>
<tr>
<td>HIV RNA, per 1 log_{10} copies/mL increase</td>
<td>1.387 (.999–1.924)</td>
<td>.051</td>
</tr>
<tr>
<td>Antiretroviral use during follow-up period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antiretroviral</td>
<td>.097 (0.562–1.848)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LAM, TDF, or FTC</td>
<td>.075 (0.039–1.146)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frequency of changing regimen</td>
<td>.245 (.145–.414)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LAM, lamivudine; TDF, tenofovir disoproxil fumarate; TPHA, Treponema pallidum hemagglutination assay.
other genotypes as previously reported [23], although the difference of chronic infection was higher in genotype A than in genotypes B, G, and H were also identified. However, their samples were available and only anti-HBc with (7 cases) or without (2 cases) anti-HBs were detected, although their samples were available and considered together, LAM seems to prevent acquisition of HBV infection, progression to symptomatic hepatitis, and development of chronic infection even after the development of infection, although these effects may be less pronounced in patients with LAM-resistant strains. However, it seems that LAM-resistant HBV incident infection. Furthermore, the results also suggested that LAM prevents progression to symptomatic hepatitis and development of chronic infection even after the development of HBV incident infection, provided such infection is caused by LAM-resistant HBV. Closed circles and squares: patients who developed chronic infection (HBsAg-positive 6 months after the date of incident infection). Checked circles and squares: patients who received TDF-containing ART within 6 months of incident infection. Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; LAM, lamivudine.

cell count was lower in the patients who developed chronic infection than in those with transient infection, although the difference was not significant (P = .068; Table 4), indicating that HIV-related immunodeficiency may play a role in the induction of chronic HBV infection. Among the 7 incident infections observed during LAM-ART, only 2 patients (28.6%) were symptomatic, had significant rise in ALT, and developed chronic HBV infection, and both of these infections were caused by LAM-resistant HBV (Table 5). The other 5 cases were asymptomatic and transient. Three of them were caused by LAM-sensitive strains and 1 was by LAM-resistant strain. HBsAg-positive serum sample was not available in the last case. LAM-resistant HBV was more frequently identified in analyzed incident infections during LAM-containing ART (50.0%) than in those during no ART and other ART (7.1%) (P = .029). Considered together, LAM seems to prevent acquisition of HBV infection, progression to symptomatic hepatitis, and development of chronic infection even after the development of infection, although these effects may be less pronounced in patients with LAM-resistant strains.

Among the 43 infection cases observed during total serological follow-up, HBsAg-positive samples were available in 34 cases and their HBV genotype was determined. Genotype A was the most frequent, as reported previously [10, 20–22], and genotypes B, G, and H were also identified. The rate of development of chronic infection was higher in genotype A than in other genotypes as previously reported [23], although the difference was not significant in our study. In the remaining 9 cases, only anti-HBc with (7 cases) or without (2 cases) anti-HBs were detected, although their samples were available and serologically analyzed at least every 3 months around the incident infection.

**DISCUSSION**

The results of this serological follow-up study indicated that LAM- and TDF-containing ART regimens protect against HBV incident infection. Furthermore, the results also suggested that LAM prevents progression to symptomatic hepatitis and development of chronic infection even after the development of HBV incident infection, provided such infection is caused by LAM-sensitive strains. However, it seems that LAM-resistant strains may evade this protective effect. One previous study that estimated the incidence of acute HBV infection among HIV-infected patients reported similar frequencies in patients receiving ART with and without LAM [5]. However, the authors defined immunoglobulin M anti-HBs positivity as a marker of HBV incident infection and did not exclude anti-HBc-positive patients at study entry. This probably made it difficult to distinguish incident infection from reactivation of chronic infection, as discussed in the report. In this study, we identified a

**Table 3. Frequency and Hazard Ratio of Hepatitis B Virus Incident Infection in Each Treatment Status Category**

<table>
<thead>
<tr>
<th>ART</th>
<th>Observation Period (Person-Years)</th>
<th>Incident Infection</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART</td>
<td>446</td>
<td>30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other-ART</td>
<td>114</td>
<td>6</td>
<td>.924 (.381–2.239)</td>
<td>.861</td>
</tr>
<tr>
<td>ART containing at least 1 of LAM, TDF, and FTC*</td>
<td>1047</td>
<td>7</td>
<td>.113 (.049–2.611)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LAM-ART</td>
<td>814</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-ART</td>
<td>233</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; FTC, emtricitabine; LAM, lamivudine; TDF, tenofovir disoproxil fumarate; LAM-ART, ART with LAM-containing regimens that did not contain TDF or FTC; Other-ART, ART with regimens that did not contain LAM, TDF, or FTC; TDF-ART, ART with TDF-containing regimens with or without LAM or FTC.

* No participant received FTC single tablet (Emtriva) during the observation period. All the participants who took FTC received the combination tablet of TDF/FTC (Truvada), and therefore, such treatment status was categorized into TDF-ART.

Figure 3. Peak alanine aminotransferase (ALT) values in hepatitis B virus (HBV) incident infections according to treatment regimen. Thirty, 6, and 7 HBV incident infections were observed during No antiretroviral therapy (ART), Other-ART, and lamivudine (LAM)–ART, respectively. No incident infection was identified during tenofovir disoproxil fumarate (TDF)–ART. No participant received emtricitabine (FTC) single tablet (Emtriva) during the observation period. All the participants who took FTC received the combination tablet of TDF/FTC (Truvada), and therefore, such treatment status was categorized into TDF-ART. Data are peak ALT values measured within 3 months of the date of incident infections. LAM-resistant mutation (rtM204V/I) was analyzed in 34 cases using the available hepatitis B surface antigen (HBsAg)–positive samples. Open squares: patients infected with LAM-resistant HBV. Closed circles and squares: patients who developed chronic infection (HBsAg-positive 6 months after the date of incident infection). Checked circles and squares: patients who received TDF-containing ART within 6 months of incident infection. Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; LAM, lamivudine.
significant number of isolated anti-HBc–positive patients, a finding in agreement with previous reports [24–27], and

excluded them from the serological follow-up to avoid improper inclusion of isolated anti-HBc–positive ones as HBV-naive [28, 29].

HBV vaccination is recommended for individuals seeking evaluation or treatment for sexually transmitted diseases, HIV-infected patients, sexually active persons with >1 partner, and MSM [13]. However, the response and durability of adequate titers of anti-HBs are often reduced in HIV-infected patients [30–34]. Modified regimens of vaccination have been reported to improve anti-HBs response in HIV-infected patients, although the response rate was still low in those with low CD4+ cell counts [35–37]. Our study demonstrated the HBV prophylactic effects of LAM- and TDF-containing ART regimens, suggesting that ART should be initiated before HBV vaccination, especially in those with low CD4+ cell counts. Early introduction of ART was recommended recently not only for HIV-infected individuals, but also for prevention of transmission to others [38, 39]. Early introduction of treatment may also be recommended to prevent HBV infection to the patients themselves if they are HBV-naive. One randomized clinical trial reported the prophylactic effect of TDF combined with FTC in HIV prevention in seronegative MSM [40]. However, in that trial, HBV vaccination was offered to all susceptible participants, which made it impossible to estimate the prophylactic effect of the treatment on HBV prevention.

Our study carries certain limitations related to its retrospective nature. Patients on ART might have more opportunities to improve their behavior to prevent transmission of HIV to others, which could reduce HBV infection in themselves but

Table 5. Patient Characteristics and Clinical Features of Hepatitis B Virus Incident Infections During LAM-ART Treatment

<table>
<thead>
<tr>
<th>Factors</th>
<th>Transient (n = 5)</th>
<th>Chronica (n = 2)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>33.0 (30.3–36.5)</td>
<td>38.0 (33.0–43.0)c</td>
<td>.329</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³, median (IQR)</td>
<td>430 (267–648)</td>
<td>362 (360–364)c</td>
<td>.699</td>
</tr>
<tr>
<td>Peak ALT levelc, U/L, median (IQR)</td>
<td>22 (14–51)</td>
<td>1133 (941–1325)c</td>
<td>.051</td>
</tr>
<tr>
<td>HBV genotype, No. (%)</td>
<td>Genotype A</td>
<td>3 (60.0)</td>
<td>&gt;.999</td>
</tr>
<tr>
<td></td>
<td>Other genotypes</td>
<td>1 (20.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genotype unknown</td>
<td>1 (20.0)</td>
<td></td>
</tr>
<tr>
<td>HBV rtM204V/I mutation, No. (%)</td>
<td>Positive</td>
<td>1 (20.0)</td>
<td>.400</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3 (60.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; IQR, interquartile range. 

a Hepatitis B surface antigen–positive 6 months after the date of incident infection.

b P values calculated with Wilcoxon rank-sum tests for continuous variables and χ² tests for proportions.

c Minimum and maximum values.

d Peak ALT level within 3 months of incident infection.
introduce bias in our analysis. However, the results suggest prophylaxis against potential HBV infection by oral medications, which could be useful for nonimmunized medical care providers.

Notes

Acknowledgments. We thank Y. Takahashi and F. Negishi for the helpful assistance in sample processing, and A. Nakano for the excellent project coordination. We also thank all physicians and nurses at the AIDS Clinical Center, National Center for Global Health and Medicine, for the dedicated clinical practice and patient care.

Financial support. This work was supported in part by Grants-in-Aid for AIDS research from the Ministry of Health, Labor, and Welfare (H23-AIDS-001), and the Global COE Program (Global Education and Research Center Aiming at the Control of AIDS), MEXT, Japan.

Potential conflicts of interest. H. G. has received honoraria from MSD K.K., Abbott Japan, Janssen Pharmaceutical K.K., Torii Pharmaceutical, and ViIV Healthcare. S. O. has received honoraria and research funding from MSD K.K., Abbott Japan, Janssen Pharmaceutical K.K., Pfizer, Roche Diagnostics K.K., and ViIV Healthcare, and has received honoraria from Astellas Pharmaceutical K.K., Bristol-Myers K.K., Daisichisanyo, Dai nippon Sumitomo Pharma, GlaxoSmithKline, K.K., Taisho Toyama Pharmaceutical, and Torii Pharmaceutical. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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