Prophylactic Effect of Lamivudine-Based Antiretroviral Therapy on Incident Hepatitis B Virus Infection Among HIV-Infected Patients

TO THE EDITOR—Patients with human immunodeficiency virus (HIV) infection are at high risk for hepatitis B virus (HBV) infection because of shared modes of transmission [1]. The presence of HBV coinfection complicates the management of HIV and increases the morbidity and mortality of HIV-infected patients [2]. A recent serological follow-up study conducted by Gatanaga and colleagues concluded that lamivudine- or tenofovir disoproxil fumarate (tenofovir)-containing antiretroviral therapy (ART) conferred protection against incident HBV infections among HIV-infected individuals in Japan [3], where the prevalence of chronic HBV infection in the general population and HIV-infected patients is 2%–7% and 6.4%, respectively [4, 5]. Although the finding that the risk of incident HBV infection could be reduced by nearly 90% for those who received lamivudine- or tenofovir-containing ART is encouraging, we are concerned about the complacency with the prophylactic effect of lamivudine or tenofovir among the HIV-treating physicians and the generalizability of the findings to areas of higher endemicity for chronic HBV infection. We believe that the risk of incident HBV infection will vary with the prevalence of HBV infection and the rate of vaccination against HBV among the HIV-infected patients and the general population.

In Taiwan, the prevalence of chronic HBV infection in the general population and HIV-infected patients is 15%–20% and 18%–20%, respectively [4, 6–8]. In our previous longitudinal follow-up study that was published in Clinical Infectious Diseases [7], we have identified 65 HIV-infected individuals who tested negative for any HBV serological markers (HBV surface antigen [HBsAg], anti-HBV core antibody [anti-HBc], and anti-HBsAg antibody [anti-HBs]) at baseline. Of the 65 patients, 61 eventually received lamivudine-containing ART for HIV. None of the patients received anti-HBV agents other than lamivudine (interferon, tenofovir, entecavir, adefovir, or telbivudine). During the follow-up, changes of HBV serological markers were detected in the sequentially stocked blood samples from 30 patients, including 4 patients with HBs antigenemia, 8 with positivity for anti-HBc and anti-HBs, 13 with isolated anti-HBc, and 5 with positivity for anti-HBs only (Table 1). Using the same definitions to estimate the incidence rate of HBV infections as those by Gatanaga and colleagues [3], 4 incident HBV infections occurred in the patients without lamivudine-containing ART and 21 in those with lamivudine-containing ART.

Table 1. Incident Infections of Hepatitis B, Hepatitis C, Hepatitis D, and Syphilis in HIV-Infected Patients With and Without Lamivudine During the Observation Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Lamivudine Treatment Period</th>
<th>Lamivudine Treatment Period</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total observation duration, person-years</td>
<td>22.98</td>
<td>145.03</td>
<td>. . .</td>
</tr>
<tr>
<td>Incidence rate, of hepatitis B virus infection, per 100 person-years (95% CI)</td>
<td>17.40 (4.75-44.59)</td>
<td>14.48 (8.97-22.15)</td>
<td>.73</td>
</tr>
<tr>
<td>Incident infections, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>4</td>
<td>21</td>
<td>. . .</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis D</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus rtM204V/I mutation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.
* Incident hepatitis B virus infections included 4 cases of hepatitis B surface (HBs) antigenemia, 8 hepatitis B core antibody (anti-HBc antibody) and anti-HBs, and 13 isolated anti-HBc antibody.
during the respective observation period (Table 1). The incidence rate of HBV infections was 17.40 per 100 person-years for the patients not on lamivudine-containing ART and 14.48 per 100 person-years for those on lamivudine-containing ART (incidence rate ratio, 1.20; 95% confidence interval, 0.41–3.50; \( P = .73 \)). The median interval from baseline to incident HBV infection was 1.87 years (range, 0.32–6.68 years). Proportional hazards model showed there was no significant difference in the incidence of HBV infection between the observation period when patients were not on lamivudine-containing ART and the period when patients were on lamivudine-containing ART (hazard ratio, 1.54; 95% CI, .50–4.76; \( P = .45 \); Figure 1).

Although the results of our analyses also support the findings of Gatanaga and colleagues [3] that HIV-infected patients receiving lamivudine-containing ART had a lower risk for incident HBV infections than those not receiving lamivudine-containing ART, the difference did not reach statistical significance because our case number was small. Compared with the incidence rates reported by Gatanaga and colleagues [3], the incidence rates in our patients were much higher, even in patients receiving lamivudine-containing ART (14.48 per 100 person-years vs 0.669 per 100 person-years). The discrepancy may be explained by the lack of tenofovir in our antiretroviral regimens during the study period and the different prevalences of chronic HBV infection among the HIV-infected patients and the general population between Japan and Taiwan. Of note in our follow-up study are occurrences of recent infections with hepatitis C virus, syphilis, and hepatitis D virus (HDV) that might occur simultaneously with incident HBV infection. Recent HDV infections should also raise concerns in the long-term successful management of chronic HBV infection because current potent anti-HBV agents may not provide any significant therapeutic or prophylactic effect [9]. Our study suggests that the findings of potent anti-HBV agents in preventing incident HBV infections should not preclude HIV-treating physicians from providing HBV vaccination to HIV-infected patients who are seronegative for HBV in the era of combination ART, when increased doses and frequency of HBV vaccination have significantly improved the efficacy of HBV vaccination among HIV-infected patients [10].

### Notes

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**References**

intramuscular double doses and 4 intradermal low doses vs standard hepatitis vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA 2011; 305:1432–40.

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