Hepatitis B Virus and HIV Coinfection in Low-Income Countries: Unmet Needs

Massimo Puoti, Daniela Manno, Paola Nasta, and Giampiero Carosi
Department of Infectious Diseases, University of Brescia, Italy

(See the article by Rouet et al. on pages 361–6)

Approximately 350 million people (5%–7% of the world’s population) are chronically infected with the hepatitis B virus (HBV), and 600,000 (0.2%) die each year of HBV-related disease and hepatocellular carcinoma [1–3]. Sub-Saharan Africa and the Far East have high HBV endemicity (population prevalence, >8%); eastern and southern Europe, South America, and the rest of Africa and Asia have intermediate endemicity (population prevalence, 2%–8%); northern Europe, North America, and Australia have low endemicity (population prevalence, <2%) [2]. It is estimated that, worldwide, 40 million people live with HIV infection and that 3 million (7.5%) of them die of HIV-related tumors and opportunistic infections [4]. This striking difference in mortality between those with HIV infection and those with chronic HBV infection can explain why treatment of HIV infection has a priority over HBV treatment, to reduce mortality both in the general population and in the single coinfected patient.

In low-endemicity areas, most HBV infections occur in adolescents and young adults, and the majority of infections are acquired sexually or through percutaneous exposure. Thus, HBV and HIV share common transmission pathways in these areas, and the prevalence of hepatitis B surface antigen (HBsAg) reactivity in HIV-coinfected patients is 5%–10%, 2.5–10 times the population prevalence [5]. In high-endemicity areas of Africa and Asia, most HBV infections occur in the first 5 years of life. Perinatal transmission predominates in East and Southeast Asia; in Africa, most HBV transmission occurs before the age of 5 years, through close contact within households, medical procedures, traditional scarification, and, possibly, additional unidentified mechanisms [6, 7]. The vertical transmission rate may be lower in Africa than in Asia partly because of a lower prevalence of hepatitis B e antigen (HBeAg) in Africa, a major determinant of perinatal transmission [8]. Perinatal infection occurs in 70%–90% of women with HBeAg-positive chronic hepatitis B, compared with 0%–30% of those with HBeAg-negative chronic hepatitis B [9]. For these reasons, the prevalence of HBsAg reactivity in persons living with HIV infection from high HBV–endemicity areas reflects population prevalence. In fact, in these areas, HIV infections occur in young adults already exposed to HBV who have developed chronic HBV infection or immunity. However, the prevalence of HBsAg reactivity could be slightly higher in persons who are HIV positive than in the general population; in fact, 10% of HBV infections are acquired by adults, even in high-endemicity areas, because of transmission by sexual exposure and blood products; reactivation of HBV infection can occur in subjects with advanced HIV infection who have already cleared HBsAg. Finally, HIV-coinfected mothers in Africa show higher prevalence of HBeAg reactivity. Thus, worldwide prevalence of HBV coinfection could be estimated to be 5%–10% in persons living with HIV infection.

The article by Rouet et al. [10] published in this issue of Clinical Infectious Diseases reports the prevalence and evolution of hepatitis B in a cohort of children infected with HIV living in the Ivory Coast. The prevalence of HBsAg reactivity was high (12%), probably because of the higher rate of HBeAg reactivity and detectable HBV DNA in HIV-HBV–infected mothers. Eighty-two percent of coinfected children had, at baseline, high levels of serum HBV DNA and HBeAg reactivity, and 22% cleared HBeAg after 18 months of follow-up. Exposure to HAART did not influence the HBeAg seroconversion rate; however, available data on HBV DNA levels showed a trend toward a good suppression of HBV replication in adherent patients where lamivudine was a component of HAART.
In countries where HAART is now available, liver failure has emerged as a major cause of death in HIV-infected individuals. Data from the Data Collection on Adverse Events of Anti–HIV Drugs (D:A:D) study suggest that hepatitis B accounts for 2% of deaths among HIV-infected persons with access to HAART [11]. This relatively high liver-related mortality is due to the accelerated course of hepatitis B in HIV-seropositive patients. Persistent HBeAg reactivity and persistent high levels of HBV DNA have been associated with an increased progression of hepatitis B in HIV-coinfected persons [12]. Thus, lamivudine-induced inhibition of HBV replication, observed in this cohort, could be beneficial, at least for liver disease evolution.

HAART is a double-edged sword in patients with HIV-HBV coinfection: by restoring innate and adaptive immunity, it can induce anti–hepatitis B s and/or anti–hepatitis B e seroconversion with or without flares of necroinflammatory activity, but it can also cause flares without inducing change of serological status [12]. Three antiretrovirals—lamivudine, tenofovir, and emtricitabine—have “dual” activity and are able to suppress both HIV and HBV replication. Their use as components of HAART has been associated with prevention of new infections, histological improvement, and prevention of hepatitis B progression toward cirrhosis and hepatocellular carcinoma [12]. However, severe reactivations have been seen after withdrawal of medications with anti-HBV activity or after virologic breakthrough related to the occurrence of resistant HBV mutants selected by prolonged exposure to these drugs [12].

Lamivudine was introduced as an anti-HIV agent in the second half of the 1990s and is the most used antiretroviral agent worldwide, especially in areas with high HBV endemicity. The impact of exposure to lamivudine on liver-related death has been explored in 3 studies, summarized in table 1 [5, 13, 14]. Although 2 studies failed to identify an association between exposure to lamivudine and a reduced risk of liver-related death [5, 14], the study with the larger study population and with the higher number of outcomes demonstrated a 23% decreased risk of liver-related death for each year of exposure to lamivudine and a reduced risk of liver-related death in those who stopped treatment with lamivudine [13]. However, median follow-up of this study was 4 years. It has been demonstrated that lamivudine resistance occurs in >90% of HIV-HBV–coinfected patients exposed to lamivudine for >4 years [15]. In HIV-uninfected patients, lamivudine resistance is associated with loss of clinical benefit and, in cirrhotic patients, with a reduced survival rate [12]. There are no data on the clinical impact of resistance to lamivudine in large cohorts of HIV-HBV–coinfected persons; however, there are anecdotal descriptions of the occurrence of severe hepatitis B reactivation leading to death after appearance of lamivudine-resistant mutants [12]. In addition, in HIV-coinfected patients exposed to a failing lamivudine treatment for >3 years, multirad drug-resistant HBV strains and potential vaccine-escape mutants have been reported [15].

Transmission of lamivudine-resistant mutant HBV strains from HIV-infected persons has already been reported. Therefore, occurrence of lamivudine resistance could potentially give rise to the spread of mutant virus strains with primary resistance to lamivudine and/or ability to infect vaccinated subjects. Thus, occurrence of resistance to lamivudine could have important consequences, both for the single patient (it reduces or reverses the clinical benefit of anti-HBV treatment and reduces future therapeutic options) and in terms of public health. Tenofovir-disoproxil-fumarate is a potent anti-HBV drug that is effective in suppressing replication of lamivudine-resistant HBV mutants; several studies have clearly established its activity in the face of lamivudine-resistant HBV, with an average reduction of 4 logs in serum HBV DNA [16]. Thus, most of the current guidelines suggest that the combination of tenofovir with either lamivudine or emtricitabine is the preferred choice for HIV-HBV–coinfected patients with the need to treat HIV infection, irrespective of prior exposure to lamivudine; in fact, these 2 combinations have resulted in HBV DNA suppression and normalization of the alanine transaminase level, even in patients with lamivudine-resistant mutants [17]. Tenofovir use has been associated with rapid and persistent suppression of HBV replication and with

### Table 1. Lamivudine exposure and liver-related mortality in cohort studies.

<table>
<thead>
<tr>
<th>Author(s) (publication year)</th>
<th>No. of subjects</th>
<th>Median duration of follow-up (months)</th>
<th>No. of liver-related deaths</th>
<th>Liver-related mortality per 10^5 PYFU (95% CI)</th>
<th>LAM exposure (%)</th>
<th>Impact of LAM exposure</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puoti et al. (2006) [13]</td>
<td>2041</td>
<td>48</td>
<td>57</td>
<td>7.5 (5.6–9.7)</td>
<td>75</td>
<td>AR, 0.73 (95% CI, 0.59–0.91)</td>
<td>Age, CD4 count, DLD, and HCV infection</td>
</tr>
<tr>
<td>Konopnicki et al. (2005) [5]</td>
<td>498</td>
<td>54</td>
<td>18</td>
<td>7 (4–11)</td>
<td>67</td>
<td>RR, 0.65 (95% CI, 0.24–1.75)</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Thio et al. (2002) [14]</td>
<td>213</td>
<td>103</td>
<td>26</td>
<td>14.2</td>
<td>…a</td>
<td>No association</td>
<td>No association</td>
</tr>
</tbody>
</table>

**NOTE.** ARR, adjusted relative risk; DLD, decompensated liver disease; HCV, hepatitis C virus; LAM, lamivudine; PYFU, person-years of follow-up.

a Data on 67 of 213.
A reversion of cirrhosis, and it has still not been associated with the occurrence of virological breakthrough because of resistant mutants or to appearance of vaccine-escape HBV mutants [17]. Children with HIV-HBV co-infection usually live in resource-poor countries; if tenofovir is a preferred component of HAART, adequate pharmacokinetic and safety documentation on the use of tenofovir in pediatric patients is urgently needed from areas where this drug is currently used to treat children.

Antiretroviral therapy remains largely unaffordable to the resource-limited world, and there is a great demand for international collaboration to provide therapy. The major challenge for this collaboration is translating and disseminating therapeutic advances in the developed world to the developing countries, where the demand is greatest. However, collaboration does not consist merely of the implementation of experiences from the well-resourced settings. There are many epidemiological, social, cultural, economic, political, and technological differences that affect HIV and AIDS pharmacotherapy implementation in the resource-limited setting. Priorities include prevention of HIV transmission, treatment of pediatric patients, and availability of affordable medicines. It could be estimated that ≥3 million people from sub-Saharan Africa are coinfected with HIV and HBV; many of them are immunotolerant children with high levels of HBV replication, as reported by Rouet et al. [10]. There are many open issues in the management of HIV-HBV coinfection for regions where chronic hepatitis B is highly endemic; however, the incidence and spread of lamivudine-resistant and vaccine-escape HBV mutants is a major issue, in terms of public health [18]. Thus, optimization of HBV treatment in HIV-infected patients could become a priority and a new challenge for international collaboration. Availability of screening for HBsAg in HIV-infected persons, monitoring of liver enzyme levels in HIV-HBV–coinfected persons, availability of tenofovir for the treatment of those with elevated liver enzymes, and lamivudine-sparing strategies for the anti-HIV treatment of inactive carriers have been indicated as key issues for the management of HBV–HIV–coinfected patients in resource-limited countries [18]. However, the potential for effective international collaboration in this field will be enhanced when expertise and resources from the developed world are combined with an understanding of the unique priorities and epidemiologic setting of resource-limited countries. Therefore, we need many data on epidemiology, natural history, and response to therapy of HBV-HIV coinfection in resource-limited settings—mainly, from sub-Saharan Africa and the Far East. The article from Rouet and coworkers [10] is a brick in our wall of knowledge, but others are urgently needed.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References