Impact of Hepatitis B Virus Infection on the Progression of AIDS and Mortality in HIV-Infected Individuals: A Cohort Study and Meta-Analysis

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(See the editorial commentary by Jain on pages 1772–4)

Background. The effect of hepatitis B virus (HBV) infection on the natural history of human immunodeficiency virus (HIV) disease remains uncertain. Therefore, a retrospective cohort study was conducted to examine the influence of HIV-HBV coinfection on AIDS development and overall mortality. Moreover, our results were added to those of previous studies in a literature-based meta-analysis.

Methods. Serum samples obtained from HIV-seropositive patients from 1984 through 2003 were retrospectively tested for hepatitis B surface antigen. Multivariable analyses were performed using Poisson and logistic regression models. For meta-analytic purposes, eligible articles were identified and relevant data were abstracted. Pooled estimates of effect were calculated applying fixed and random effects models.

Results. The prevalence of chronic HBV infection (documented hepatitis B surface antigen seropositivity for >6 months) among 1729 HIV-positive patients was ~6%. The multivariable analyses in our primary study revealed no significant impact of concomitant HIV-HBV infection on progression to AIDS and all-cause mortality. However, a meta-analysis performed on data from 12,382 patients enrolled in 11 studies revealed a significant effect of HIV-HBV coinfection on overall mortality (pooled effect estimate, 1.36; 95% confidence interval, 1.12–1.64). The increased rate of death among coinfected individuals was observed in the meta-analyses of studies conducted both before (pooled effect estimate, 1.60; 95% confidence interval, 1.07–2.39) and after (pooled effect estimate, 1.28; 95% confidence interval, 1.03–1.60) commencement of highly active antiretroviral therapy.

Conclusions. HIV-HBV coinfection seems to affect all-cause mortality, and strategies to reduce liver damage in patients coinfected with HIV and HBV are justified.

Coinfection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) is common because of their similar routes of transmission [1]. Chronic HBV infection has been diagnosed in 6%–14% of HIV-positive persons in industrialized countries [2]. The widespread use of highly active antiretroviral therapy (HAART) has increased the life expectancy of HIV-infected individuals, allowing the appearance of liver-associated complications due to HBV infection [3–5].

Concomitant HIV-HBV infection seems to increase the infectivity of HBV [3, 6, 7], the rate of HBV reactivation [8], and the risk of cirrhosis [6, 7]. However, the impact of HBV on the natural history of HIV infection remains debated. Epidemiological research has revealed an accelerated progression to AIDS [9] and a reduced rate of survival among coinfected subjects [10–12]. On the other hand, many studies have found no effect of HBV infection on the risk of acquiring an AIDS-defining condition [12–14] or on overall mortality [15, 16].

The aim of the present study was to estimate the prevalence of HBV infection among HIV-seropositive individuals in Greece and to evaluate the potential influence of concurrent HIV-HBV infection on progres-
Patients were divided into 4 categories: (1) HBsAg negative (negative results for both serum samples), (2) HBsAg positive (positive results for both serum samples), (3) HBsAg revertors (positive result for first sample and negative result for last sample), and (4) HBsAg converters (negative result for first sample and positive result for last sample). Characteristics were compared among the 4 groups with use of the χ² statistic and the Kruskal-Wallis test.

Patients contributed person-time to the denominator for the study starting on the date that the first sample was obtained and ending on 31 December 2003, the date lost to follow-up, or the date of a specific event (i.e., date of AIDS diagnosis or date of death), whichever came first. Poisson regression models were applied to estimate adjusted incidence rate ratios. Age, calendar period, time since entry into the study, CD4 cell counts, viral load levels, AIDS diagnosis (when death was the outcome of the analysis), initiation of HAART, and lamivudine and tenofovir use were modeled as time-dependent covariates. The incidence rate ratios were also adjusted for sex, mode of HIV transmission, nationality, and duration of HIV infection since diagnosis. The HBsAg-negative group was always the reference category. The analysis was repeated using 2 categories of exposure to HBV that allowed for converters and revertors to move from HBsAg-negative to HBsAg-positive status and vice versa, according to the results of the tests (treating HBsAg status as a time-dependent variable). Moreover, in an attempt to more accurately evaluate the effect of chronic HBV infection, the rates of AIDS development and death were compared among individuals with persistent HBs antigenemia (duration, >6 months) and HBsAg-negative patients.

To assess virological response to HAART, patients were further classified according to their HBsAg status on the date that they commenced HAART. Individuals were included in the analysis if they had initiated HAART during the period of observation and had viral load measurements recorded in the 6-month period before commencing HAART and during the 6–12 months after beginning HAART. Virological response was defined as the first suppression of viral load (<400 copies/mL) 6–12 months after the initiation of HAART. In multivariable logistic regression models, odds ratios were adjusted for sex, age at initiation of HAART, HIV risk group, nationality, duration of HIV infection since diagnosis, AIDS and antiretroviral treatment prior to HAART, CD4 cell counts and viral load levels at commencement of HAART, class of antiretroviral drugs received, and date of HAART initiation. The whole analysis was repeated using a cutoff point of 50 copies/mL.

Meta-analysis. A comprehensive search with PubMed, Scopus, and Google Scholar was conducted until December 2007 to retrieve studies that addressed the association between HIV-HBV coinfection and progression to AIDS or death. The following index terms or a combination of them were used: HIV, HBV, and coinfection. An appraisal of the references cited in publications and a manual search of abstracts from conference meetings were also performed.

Cohort or case-control studies involving HIV-positive patients with recorded HBV serologic test results were included in the analysis if (1) they examined the effect of HBV infection, as the primary exposure of interest, on the development of AIDS or all-cause mortality and (2) they provided sufficient data to calculate an estimate of effect size in the form of risk ratio, incidence rate ratio, odds ratio, or hazard ratio together with a 95% confidence interval (CI).

For each study, the following information was registered on a structured form: (1) author, journal, year of publication, geographical location, and study design; (2) cases and exposure definitions; (3) number of participants and length of follow-up; (4) characteristics of patients, such as sex, HIV transmission category, and age; (5) effect estimates and 95% CIs; and (6) control for confounding. The estimate with the largest number of variables in the multivariate model was selected for studies in which >1 effect measures were provided [17]. If measures of an estimate’s variability were not explicitly presented in the text, specific methods were applied to assign a CI to the estimate [18, 19].

The heterogeneity among studies was evaluated using the χ²-based Cochran’s Q statistic [17], which was considered to be significant if P<.10, and the inconsistency index I² [20]. Data were combined using both fixed and random effects models [17]. Meta-analysis was stratified by study design, year of publication, number of subjects enrolled, study location, HIV transmission group, and the use of adjustment. Unless stated differently, pooled measures of random effects are reported.

Publication bias was assessed by the Egger regression method.
Table 1. Characteristics of patients according to the results of hepatitis B virus surface antigen (HBsAg) detection testing.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HBsAg negative (n = 1528)</th>
<th>HBsAg positive (n = 107)</th>
<th>HBsAg revertors (n = 52)</th>
<th>HBsAg convertors (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, proportion (%) of all patients</td>
<td>1528/1729 (88.37)</td>
<td>107/1729 (6.19)</td>
<td>52/1729 (3.01)</td>
<td>42/1729 (2.43)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1238 (81.02)</td>
<td>102 (95.33)</td>
<td>47 (90.38)</td>
<td>34 (80.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, median years (IQR)</td>
<td>35.04 (29.23–43.70)</td>
<td>35.04 (27.55–41.31)</td>
<td>35.46 (27.16–43.38)</td>
<td>33.17 (27.39–38.72)</td>
<td>0.57</td>
</tr>
<tr>
<td>Estimated duration of HIV infection since diagnosis, median years (IQR)</td>
<td>1.41 (0.12–4.04)</td>
<td>1.03 (0.07–3.69)</td>
<td>1.23 (0.05–4.01)</td>
<td>2.04 (0.11–4.36)</td>
<td>0.41</td>
</tr>
<tr>
<td>Exposure group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>890 (58.25)</td>
<td>81 (75.70)</td>
<td>32 (61.54)</td>
<td>25 (59.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>IDU</td>
<td>51 (3.34)</td>
<td>7 (6.54)</td>
<td>3 (5.77)</td>
<td>2 (4.76)</td>
<td></td>
</tr>
<tr>
<td>Transfusion recipient or hemophiliac</td>
<td>131 (8.57)</td>
<td>4 (3.74)</td>
<td>6 (11.54)</td>
<td>5 (11.90)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>367 (24.02)</td>
<td>8 (7.48)</td>
<td>7 (13.46)</td>
<td>9 (21.43)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>89 (5.82)</td>
<td>7 (6.54)</td>
<td>4 (7.69)</td>
<td>1 (2.38)</td>
<td></td>
</tr>
<tr>
<td>Greek nationality</td>
<td>1305 (85.41)</td>
<td>91 (85.05)</td>
<td>46 (88.46)</td>
<td>39 (92.86)</td>
<td>0.53</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td>320 (20.94)</td>
<td>27 (25.23)</td>
<td>6 (11.54)</td>
<td>9 (21.43)</td>
<td>0.26</td>
</tr>
<tr>
<td>CD4+ T cell count at baseline, median cells/L × 10^9 (IQR)</td>
<td>305 (166–492)</td>
<td>322 (155–618)</td>
<td>338 (199–485)</td>
<td>329 (89–463)</td>
<td>0.87</td>
</tr>
<tr>
<td>Viral load at baseline, median log_{10} copies/mL (IQR)</td>
<td>3.96 (3.12–4.80)</td>
<td>3.82 (3.12–4.81)</td>
<td>4.46 (3.22–4.95)</td>
<td>4.45 (3.69–4.87)</td>
<td>0.25</td>
</tr>
<tr>
<td>Receipt of HAART before enrollment</td>
<td>478 (31.28)</td>
<td>36 (33.64)</td>
<td>3 (5.77)</td>
<td>11 (26.19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. For definitions of patient groups, see the Patients and Methods section. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men.

* CD4+ T cell counts at baseline were available for 546 patients, and viral load measurements at baseline were available for 1180 patients.
AIDS for individuals in the HBsAg-positive versus the HBsAg-negative groups created a combined response variable (i.e., AIDS or death) instead of analyzing an AIDS result individually [27–30]. Two studies that used antibody to HBV core antigen testing were considered to be ineligible [9, 25]. A total of 7 primary studies (including the present study) were included in the meta-analysis concerning AIDS, which involved 7021 subjects [7, 10–12, 14, 26]. Another 3 research groups created a combined response variable (i.e., AIDS or death) instead of analyzing an AIDS result individually [27–29]; 2 of these studies presented adjusted measures of effect, which were used in secondary analyses [27, 29]. Three studies were conducted during the pre-HAART era [7, 10, 14], and 2

### RESULTS

**Primary study.** A total of 1729 HIV-positive individuals were evaluated. According to the hepatic serologic tests, 1528 patients (88.37%) had negative results for HBsAg, 107 (6.19%) had positive results for HBsAg, 52 (3.01%) were HBsAg revertors, and 42 (2.43%) were HBsAg convertors. The median duration between collection of the tested samples was 3.91 years, without significant differences among the 4 groups (P = .13). Most HBsAg-positive individuals (101 [5.84%] of 1729) were probably chronically infected, because they had 2 positive samples obtained at least 6 months apart. The cohort characteristics are presented in detail in table 1.

Among 1367 persons without AIDS at baseline, 181 (13.24%) experienced their first AIDS-defining event during 6706.31 person-years of follow-up. With 4 categories of HBV exposure in the analysis, the adjusted incidence rate ratio of progressing to AIDS for individuals in the HBsAg-positive versus the HBsAg-negative group was 1.59 (95% CI, 0.95–2.65). The results remained insignificant in all alternative analyses. During 8969.73 person-years of follow-up, there were 190 deaths, resulting in an overall mortality rate of 2.12 deaths per 100 person-years (95% CI, 1.84–2.44 deaths per 100 person-years). The adjusted incidence rate ratio of death for individuals in the HBsAg-positive group versus the HBsAg-negative group was 1.72 (95% CI, 1.05–2.83), but the overall difference among the 4 HBV groups was insignificant (P = .19). HIV-HBV coinfection had no significant effects in all models assessed (table 2).

Overall, 930 individuals had recorded HBsAg serologic results at the initiation of HAART. Nearly 58% of the HBsAg-negative individuals and 64% of the HBsAg-positive persons had suppressed viral loads (<400 copies/mL) 6–12 months after starting HAART (P = .50). Multivariable logistic regression analysis did not suggest an effect of HIV-HBV coinfection on the virological efficacy of HAART (odds ratio, 1.01; 95% CI, 0.35–2.90). With a cutoff value of 50 copies/mL, the response rate to HAART was comparable between the 2 groups (46% in the HBsAg-negative group vs. 50% in the HBsAg-positive group; P = .69).

**AIDS meta-analysis.** Two studies that used antibody to HBV core antigen testing were considered to be ineligible [9, 25]. A total of 7 primary studies (including the present study) were included in the meta-analysis concerning AIDS, which involved 7021 subjects [7, 10–12, 14, 26]. Another 3 research groups created a combined response variable (i.e., AIDS or death) instead of analyzing an AIDS result individually [27–29]; 2 of these studies presented adjusted measures of effect, which were used in secondary analyses [27, 29]. Three studies were conducted during the pre-HAART era [7, 10, 14], and 2

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**Table 2. Multivariable analyses of overall mortality with use of Poisson regression models.**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>HBsAg negative</th>
<th>HBsAg positive</th>
<th>HBsAg revertors</th>
<th>HBsAg convertors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>IRR (95% CI), not adjusted for CD4 count and viral load</td>
<td>1.00</td>
<td>1.72 (1.05–2.83)</td>
<td>1.00 (0.51–1.98)</td>
<td>1.16 (0.51–2.64)</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI), not adjusted for CD4 count</td>
<td>1.00</td>
<td>1.35 (0.82–2.23)</td>
<td>1.22 (0.47–3.16)</td>
<td>1.59 (0.56–4.53)</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>1.00</td>
<td>1.40 (0.79–2.47)</td>
<td>1.29 (0.42–3.98)</td>
<td>1.76 (0.58–5.38)</td>
</tr>
<tr>
<td>All-cause mortality, using 2 categories for HBsAg status</td>
<td>IRR (95% CI), not adjusted for CD4 count and viral load</td>
<td>1.00</td>
<td>1.35 (0.85–2.16)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI), not adjusted for CD4 count</td>
<td>1.00</td>
<td>1.31 (0.82–2.10)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>1.00</td>
<td>1.45 (0.85–2.48)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>All-cause mortality, chronically HBV-infected vs. HBsAg negative patients</td>
<td>IRR (95% CI), not adjusted for CD4 count and viral load</td>
<td>1.00</td>
<td>1.37 (0.80–2.34)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI), not adjusted for CD4 count</td>
<td>1.00</td>
<td>1.20 (0.73–1.99)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>1.00</td>
<td>1.32 (0.75–2.34)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** For definitions of patient groups, see the Patients and Methods section. Multivariable analyses were adjusted for age, highly active antiretroviral therapy, duration since entry into the study, AIDS, use of lamivudine and tenofovir, calendar period (time-dependent covariates), sex, human immunodeficiency virus (HIV) risk group, nationality, years elapsed since HIV diagnosis, most recent viral load measurements, and most recent CD4 cell counts, unless indicated otherwise. The total number of patients was 1729. Viral load levels were available for 1642 patients. CD4 cell counts and viral load levels were available concurrently for 903 patients. CI, confidence interval; IRR, incidence rate ratio.

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studies (including the present study) enrolled >500 participants [12]. Most studies were performed in Western countries, and only 1 took place in Asia [11]. All research teams used HBsAg as an HBV marker. One study was presented in an abstract form [26].

Fixed and random effects methods yielded identical nonsignificant results regarding the influence of coinfection on AIDS development. The combined effect estimate was 0.93 (95% CI, 0.75–1.15) (figure 1). There was no evidence of heterogeneity (P = .54), and the I^2 was 0%. The summary effect size was similar in all subanalyses (figure 2).

**Meta-analysis of overall mortality.** Eleven studies (including the present study) were eligible for inclusion in the meta-analysis of all-cause mortality [10–12, 14–16, 26, 30–32]. P value was the only information reported in 1 study and was used to construct a 95% CI [15]. Four studies were performed before the widespread use of HAART [10, 14, 30, 31], and 7 research groups recruited a relatively small number of patients (i.e., ≤500 patients) [10, 11, 14, 26, 30–32]. Two studies were conducted in an Asian region [11, 16]. The largest proportion of eligible studies (including the current study) concentrated on men who have sex with men [10–12, 15, 26, 30]. Three studies focused mostly on heterosexual participants [16, 32] or injection drug users [14], and 1 study examined the effect of HBV infection on the mortality of children aged <3 years [31].

The synthesis of the data from 12,382 patients demonstrated a significantly increased rate of mortality among HIV-HBV–coinfected subjects; the random effects estimate was 1.36 (95% CI, 1.12–1.64) (figure 1). The null hypothesis of no heterogeneity could not be rejected (P = .16), and the I^2 was 29.70%. Similar results were consistently found in most subsidiary analyses (figure 2). The significance of the increased rate of mortality among coinfected subjects was sustained when we analyzed studies conducted either before (pooled effect estimate, 1.60; 95% CI, 1.07–2.39) or after (pooled effect estimate, 1.28; 95% CI, 1.03–1.60) HAART commencement.

The results remained practically unchanged after omitting 1 study at a time or using alternative estimates of relative risk [10, 12, 14, 15, 32]. The synthesis of the 10 studies conducted before ours yielded a summary effect of 1.34 (95% CI, 1.09–1.65) that lies within the relatively narrow range of insignificant estimates (1.20–1.45) (table 2) derived from models that we applied in our primary research. The effect of HBV infection on overall mortality of HIV-infected patients became significant
Figure 2. Plots of subanalyses for the effect of hepatitis B virus infection on overall mortality and AIDS in human immunodeficiency virus–positive patients. For each subanalysis, the number of studies is shown in parentheses, followed by the $P$ value of the $Q$ test for heterogeneity. The estimates have been obtained from random effects models. CI, confidence interval; ES, Effect size; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; MSM, men who have sex with men.

The pooled effect remained constantly significant after the addition of the eighth estimate (chronologically) [12], but the effect was reduced and became stable at $\sim 1.36$. Statistical approaches did not suggest the existence of publication bias and met specific stringent criteria for proper use.

**DISCUSSION**

The current primary study contained data on 1729 HIV-infected individuals, including $>25\%$ of all reported persons with HIV infection in Greece through the end of 2003 [33]. A meta-analysis that included the insignificant results of our primary study and the results of former studies in the field revealed an increased overall rate of mortality among HIV-HBV–coinfected subjects.

The estimates of HBsAg prevalence (8%–9%) and of chronic HBV infection (5.84%) in our primary study are in accordance with the results of other cohort studies performed in Western countries [12, 34]. A previous study conducted in Greece presented a higher prevalence of HBsAg detection (12%); however, this study was conducted with a smaller sample size [35]. The observed proportion of HBV infection among HIV-seropositive individuals is almost 3 times greater than the prevalence reported in the general Greek population [36, 37]. Shared routes of transmission for the 2 viruses and the decreased ability of HIV-infected patients to clear HBsAg may explain this association [12].

The present study did not suggest a significantly increased risk for progression to AIDS in HIV-HBV–coinfected patients, a finding consistent with recent, methodologically sound research [11, 12]. The meta-analysis improved the precision of the estimate and confirmed the absence of any effect by HBV infection on AIDS development.

Many previous studies did not ascertain an effect of coinfection on all-cause mortality [15, 16, 26, 30–32], whereas other researchers reported an increased death rate among HIV-HBV–coinfected patients [10–12]. This variability motivated us to conduct a data synthesis, which, without statistically detectable heterogeneity or publication bias, demonstrated a relationship between coinfection and all-cause mortality. Meta-analysis overcomes limits of sample size [17]. The statistical analyses in our primary study produced nonsignificant estimates of the effect of HBV infection (insignificant effect estimate range, 1.20–1.45), whereas meta-analysis involving a large number of individuals provided a similar (pooled effect estimate, 1.36) but significant measure. The number of studies conducted that included injection drug user, Asian, or heterosexual populations was small, and additional research is needed to reach credible conclusions.

In the cumulative meta-analysis of HBV infection and mortality, the combined estimate of effect became significant after the addition of the estimate from the fourth study (chrono-
logically) [10], and the significance, with some fluctuations, persisted thereafter, even though the magnitude of the estimate was slightly reduced. Moreover, meta-analysis stratified by publication time produced similar results. Previous studies repeatedly reported considerable rates of death due to liver-related causes in coinfected patients [1, 12, 38]. Chronic HBV infection is a strong determinant of liver-associated deaths, which constitute a remarkable proportion of non–AIDS-related fatalities [38]. Therefore, although our analysis was not designed to evaluate liver-related mortality, we speculate that severe hepatic complications could explain the reduced survival of HIV-HBV–coinfected individuals both before and after the introduction of HAART. The depletion of CD4 lymphocytes due to HIV infection in conjunction with HBV infection could result in serious hepatic injury through the induction of fibrogenic mechanisms or by enhancing the negative effect of opportunistic infections, alcohol abuse, or drugs used for prophylaxis or treatment [1]. HAART significantly improved the life expectancy of HIV-HBV–coinfected patients but, on the other hand, permitted the appearance of long-term consequences of HBV infection. HBV infection is associated with an increased risk of drug-related hepatotoxicity among coinfected persons receiving HAART, and the rigorous immune reconstitution induced by HAART can aggravate HBV infection leading to liver deterioration [1]. Apart from fatal hepatic events, HBV infection has been associated with death due to non–liver-related causes [39], and additional research is needed to explore the mechanisms of mortality in HIV-HBV–coinfected individuals.

With the assumption that overall mortality among coinfected patients is determined mainly by liver-related deaths, the reduction observed in the summary estimate of studies performed after 1997 implies a lower risk of death due to liver-related causes in the HAART era. However, the subanalysis of research performed before 1997 contains 4 relatively small studies [10, 14, 30, 31] with less rigorous multivariable analyses, which might have inflated the overall measure of association. One previous study of 472 HIV-positive patients [32] produced results that are in accordance with our finding; whereas, the large multicenter study of Konopnicki et al. [12] found no increase in liver-related mortality per calendar year. On the other hand, Thio et al. [1] examined 5293 men who have sex with men and observed a trend toward increased risk of liver-associated death after the introduction of HAART, but their finding lacked statistical significance. If liver-related mortality has indeed diminished in the age of potent combinations of antiretrovirals, this could be attributed to the increased use of agents with dual activity against HIV and HBV, in particular, tenofovir [40]. However, this hypothesis cannot be examined by our meta-analysis. A future pooling of studies with adequate data at an individual level might shed light on this issue.

Finally, HBV serostatus did not affect the virological efficacy of HAART. In spite of the heterogeneity in the definition of virological response in the literature, in most studies, coinfec-
tion was not associated with the likelihood of achieving undetectable viral load levels after starting HAART [12, 27–29].

Several limitations of the primary research should be discussed. Data about HBV-DNA levels were not available to determine if the disease was active. However, previous studies were also based on HBsAg testing, and contrary to previous research, we obtained serial HBV serologic data, and the prevalence of chronic HBV infection among HIV patients might have been more accurately estimated. Another drawback was the limited information about the cause of death and the hepatitis C virus infection status of the participants.

The statistical pooling of independent studies also has some disadvantages. First, meta-analysis cannot correct the limitations of primary research. Second, summarizing published literature is less accurate and complete than the quantitative synthesis of individual patient data, although the former is a practical and credible alternative [19]. Third, crude risk ratios or test-based estimates were used in some cases, but in these studies, the results were robust in sensitivity analyses and compatible with the conclusions drawn by the authors [17]. Finally, despite the lack of statistical evidence for heterogeneity and publication bias, because of the poor power of these statistical tests, there is still a possibility that heterogeneity and bias have affected our results.

HBV coinfection increases overall mortality among HIV-positive patients, as shown by our meta-analysis of existing publications. Our finding reiterates the significance of a comprehensive management of HIV-positive individuals that includes prevention, regular screening for HBV infection, and administration of potent anti-HBV therapy to coinfected patients according to current guidelines. Moreover, the long-term efficacy and safety of combination treatment with agents that exert activity against both viruses warrants further investigation.

Acknowledgments


Potential conflicts of interest. All authors: no conflicts.

References