Hepatitis B virus (HBV) coinfection is frequently seen in individuals infected with human immunodeficiency virus (HIV) at a prevalence of 6%–11% [1–3] and has increasingly become recognized as a pathogen that interacts uniquely with HIV. Although HBV is not a cytopathic virus, it has been associated with significant flares in the context of immune restoration [4–6]. Despite its prevalence and its unique association with increases in liver enzyme levels, HBV has an uncertain impact on overall mortality and progression to AIDS.

In this issue of Clinical Infectious Diseases, Nikolopoulos et al. [7] report on the findings of the first meta-analysis performed to examine the effect of HIV-HBV coinfection on all-cause mortality. In their primary study, the authors examined the overall risk of death in their HIV cohort but found the sample size too small to derive conclusive results. To overcome the limitation of sample size, the authors performed a meta-analysis [8] that included their primary data to estimate the excess risk of mortality attributable to HIV-HBV coinfection and the impact of coinfection on HIV disease progression. In the combined analysis of 12,382 patients, they found an excess risk of all-cause mortality attributable to the effect of HIV-HBV coinfection (pooled effect estimate, 1.36; 95% CI, 1.12–1.64). They did not, however, find an increased risk of AIDS progression or decreased efficacy of highly active antiretroviral therapy (HAART) among patients who had hepatitis B surface antigen detected.

The limitations of their analysis include the addition of publications from Asia, in which the mode of transmission (vertical or childhood) and type of HBV genotypes (genotype B and C) are very different from those in Western countries [9]. Differences in the duration of infection and HBV genotype may present a risk of death that varies from that in Western countries [10]. However, the authors did perform a sensitivity analysis to examine the impact of specific publications on overall risk. Another limitation of the meta-analysis is the lack of HBV load data, which makes it difficult to determine if individuals with high HBV loads were at increased risk of liver disease progression, compared with those with low HBV loads or inactive carriers who may not have been at risk at all. Additionally, it is unknown what proportion of the HIV-HBV–coinfected population also was infected with hepatitis C virus (HCV) or had diabetes or other co-morbidities that might have affected risk of death.

Regardless of the study’s limitations, these findings are important because they establish that HBV, which is a vaccine-preventable disease, is associated with an excess risk of all-cause mortality. In light of these findings, there needs to be a renewed focus on the prevention of HBV infection in adults. The incidence of acute HBV is highest among adults, who accounted for ~95% of the estimated 51,000 new infections in 2005 [11]. Because HBV vaccination is very effective and has no associated risks, all HIV-infected patients should be tested for hepatitis B surface antigen and, if results are negative, be offered HBV vaccination. However, the vaccine is less effective in individuals with CD4 cell counts <200 cells/μL [12] and is only partially effective in those with CD4 cell counts of 200–500 cells/μL [13]. Thus, if routine dosing or double doses of vaccine are given [14, 15], monitoring for hepatitis B surface antibody will be necessary to ensure that a protective level is achieved. In individuals for whom the vaccine will not be effective because of AIDS, ART is necessary and may improve response to HBV vaccination once undetectable plasma HIV RNA levels are reached [16]. In addition, the provider must educate the patient with regard to how HBV can be acquired and his or her
risks for acquiring the infection. Although most children are now vaccinated at birth and certainly by the time they enter school, many adults have not been vaccinated, and opportunities to educate and vaccinate should not be lost.

Furthermore, this study brings into sharp focus the impact of viral hepatitis, which can curtail the life-span of an HIV-infected individual. It shows that the increased risk of death is not attributable to HIV disease progression. In fact, the response to HAART in terms of HIV suppression was similar among those infected with HBV and those not infected with HBV. However, this study did not assess the impact of HIV-HBV coinfection on the increase in CD4 T cell count after initiation of HAART. If HIV-HBV–coinfected patients are responding to HAART and not progressing, what is the reason for the excess risk of mortality? Most likely, this excess risk is attributable to liver disease, but this is speculative, because the authors did not measure liver-related mortality. It is certainly possible that HIV-HBV coinfection is a marker for other types of high-risk behavior that may place this population at an increased risk for death attributable to non-AIDS-related causes. In a study by Hansen et al. [17] that examined mortality among siblings of HIV-HCV–coinfected patients, the authors found a higher mortality rate ratio among siblings of HIV-HCV–coinfected individuals than among siblings of individuals infected with HIV alone. Thus, HCV infection was a marker for familial factors that affected survival. So, too, could the detection of hepatitis B surface antigen be a marker for other behaviors that decrease survival in this population; this remains to be proven. Additional studies are needed to confirm whether excess all-cause mortality among HIV-HBV–coinfected individuals is truly attributable to liver-related deaths.

However, one piece of, albeit preliminary, information offers a glimmer of hope. Nikolopoulos et al. [7] examined mortality in the pre-HAART era (pooled effect estimate, 1.60; 95% CI, 1.07–2.39) and the post-HAART era (pooled effect estimate, 1.28; 95% CI, 1.03–1.60). Interestingly, they observed a decrease in the risk of death in post-HAART era. Although the excess risk of all-cause mortality in the pre-HAART era may be overestimated because of the small number of articles included, the decrease in the risk of all-cause mortality in the post-HAART era may be real even if it is modest. It offers us hope that perhaps HAART with treatment active against HBV may improve outcomes. Recent data released by the Data Collection on Adverse Events of Anti-HIV Drugs cohort showed that the relative risk of HBV- and liver-related mortality was lower than liver-related mortality attributable to HIV-HCV coinfection [18]. The authors postulated that this may be because of the use of HAART that includes treatment active against HBV.

In the past decade, our understanding and treatment of HBV has greatly improved. Population-based improvements with respect to outcomes of HBV infection require action on the individual level. Every HIV treatment provider must accurately diagnose HBV infection, document the level of viremia prior to starting ART, and monitor HBV DNA levels to ensure that suppression is achieved, to prevent progression to cirrhosis [19]. HIV treatment providers must monitor HBV response as carefully as they monitor HIV response to ART [20]. Because alcohol consumption has been found to significantly impact liver-related mortality [21], counseling patients regarding the elimination of alcohol consumption is also necessary. In addition to serologic tests to monitor response to treatment, it is important to obtain an ultrasound and α-fetoprotein measurement to screen for development of hepatocellular cancer, especially in those with cirrhosis.

When ART is used, 2 active HBV agents should be included, or 1 agent with acceptable potency, such as tenofovir, should be included [22]. Although lamivudine-
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