

# Preventing Deaths in Persons With HIV/Hepatitis B Virus Coinfection: A Call to Accelerate Prevention and Treatment Efforts

Philip J. Peters<sup>1</sup> and Barbara J. Marston<sup>2</sup>

<sup>1</sup>Division of HIV/AIDS Prevention, and <sup>2</sup>Division of Global Disease Detection and Emergency Response, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia

(See the article by Chun et al, on pages 185–93.)

The prognosis associated with a new diagnosis of human immunodeficiency virus (HIV) infection has improved dramatically since the virus was first recognized [1]. However, the remarkable increases in survival have been attenuated in some groups because of the presence of comorbid infectious diseases and other illnesses. Globally, an estimated 5%–10% of the 33.3 million people living with HIV are coinfecting with the hepatitis B virus (HBV). This double-whammy of HIV/HBV coinfection has translated into poorer outcomes. For instance, in settings where expanded access to antiretroviral therapy (ART) has reduced deaths from HIV, liver-related death (from any of a variety of etiologies) has emerged as an important cause for the remaining mortality [2]. Infection with HIV increases the rate of replication of HBV, thereby accelerating progression to cirrhosis, hepatocellular carcinoma, and other liver-related morbidity [3]. There is not clear evidence that HBV impacts

the progression of HIV disease, but it has been speculated that HBV infection increases susceptibility to liver toxicity from ART and impairs the immunological response (eg, CD4 cell-count recovery) to HIV treatment. Evaluating whether HIV progression is an important element of the increased mortality seen in coinfecting patients has been challenging because of the heterogeneity of available HIV and HBV data in studies reported to date.

The report by Chun et al [4] in this issue of *The Journal* presents data from the U.S. Military HIV Natural History Study, which evaluates the impact of HBV coinfection on the composite endpoint of AIDS-defining illness or death. To minimize the influence of duration of HIV infection, the analysis was limited to the 2352 cohort participants whose date of HIV seroconversion could be estimated within 3 years, and whose HBV status was known or determined within 2 years of HIV seroconversion (although the timing of their HBV infection was not known). Each patient's HBV status was classified as either chronic (hepatitis B surface antigen [HBsAg] reactivity), resolved (hepatitis B core antibody [HBcAb] and surface antibody [HBsAb] reactivity with a negative HBsAg), isolated HBcAb (HBcAb

reactivity with negative HBsAb and HBsAg), or no evidence of past or current infection (negative HBcAb and HBsAg). Patients classified as having chronic HBV were observed to have a higher risk (approximately double the risk in adjusted analysis) for developing the composite outcome of AIDS-defining illness or death, compared with that of patients who were HBV negative. Hepatitis C virus (HCV) infection was uncommon in this cohort (1.7% of patients had a reactive HCV antibody test), but was also associated with an increased risk of developing an AIDS-defining illness or death.

Some strengths of this analysis were the focus on individuals with known dates of HIV seroconversion to minimize survivorship bias, and the classification of HBV status around the HIV seroconversion date to minimize misclassification bias. Although the findings suggest that HBV infection may impact HIV outcomes, as with any cohort study there are methodological limitations that restrict our ability to determine causality. A limitation is that HBV infection directly causes mortality, and these deaths would be counted toward the composite outcome. In both HIV-infected and -uninfected populations, HBV infection is associated with a higher risk of mortality

Received 26 September 2011; accepted 26 September 2011; electronically published 5 December 2011.

Correspondence: Barbara Marston, Centers for Disease Control and Prevention, 1600 Clifton Rd, Mailstop A-05, Atlanta, GA 30329 (bxm5@cdc.gov).

**The Journal of Infectious Diseases** 2012;205:166–8  
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.  
DOI: 10.1093/infdis/jir728

(because of liver-related deaths) [5]. Because data summarizing the causes of the AIDS-defining illnesses and deaths were not presented, it is not possible to determine the contribution of liver-related deaths to the composite outcome. Previous studies, however, suggest the contribution (especially in the ART era) of liver-related deaths may be high [2, 6]. In addition, important determinants of the likelihood of HBV disease progression, including the timing of HBV infection (recent as an adult vs remote during childhood, as occurs in many resource-limited settings internationally) and the severity of HBV infection, as determined with HBV DNA viral load testing or clinical staging, were not reported. If a majority of HBV infections were acquired at or shortly after the time of HIV seroconversion, individuals with more aggressive HIV infections may have been more likely to develop chronic HBV infection.

An additional confounder in this cohort study is that most HIV/HBV-coinfected patients were enrolled prior to the ART era, when the rates of AIDS-defining illness and death were higher. The authors have appropriately identified this confounder and have created multiple adjusted models to try to control for its effect, but we are not presented with data on the proportion of HIV/HBV-coinfected patients who received an antiretroviral regimen containing 2 agents with anti-HBV activity. Finally, although it has been speculated that HBV infection is associated with an accelerated immune deficiency in HIV/HBV-coinfected patients [7], Chun and colleagues showed no association between HBV coinfection and either a higher HIV load set-point or a lower CD4 cell count (only baseline CD4 values were presented, not rates of CD4 cell-count decline). As the authors point out, the findings of the study are most relevant to groups similar to the cohort studied, and may not be as applicable to coinfecting persons outside the United States, who are women, or who belong to groups with high rates of intravenous drug use.

The analysis of Chun et al moves us further toward an understanding of the increased mortality among persons with HIV/HBV coinfection. Although we remain with questions about whether HIV disease is indeed progressing more rapidly in these patients, there is no need to wait for answers before we amplify our response. This study adds to the weight of evidence that coinfection is deleterious by demonstrating that in this well-characterized cohort, it doubles the risk of AIDS-defining illness and death.

This finding reinforces the imperative to intervene where possible. Existing tools to prevent HIV and HBV infection have remarkable potential to reduce the burden of coinfection; now we need to improve implementation. The array of interventions to reduce the risk of HIV transmission—condoms, behavioral interventions, circumcision, preexposure prophylaxis, treatment of infected partners—is expanding quickly. Highly effective approaches to prevent HBV infection (ie, vaccination) have been available for many years, and the potential impact of expanded HBV vaccination is clear. For example, universal infant vaccination combined with aggressive screening and vaccination of at-risk adults has led to the virtual elimination of hepatocellular carcinoma and acute HBV in Native American populations in Alaska [8]. Global rates of infant vaccination with 3 doses of hepatitis B vaccine have skyrocketed to 70%, thanks to efforts such as those of the Global Alliance for Vaccines and Immunization, the World Health Organization, and the United Nations Children's Fund. In the United States, we are beginning to see the impact of routine childhood vaccination on coverage in adults, although even among at-risk populations, rates of vaccination are only about 50% [9]. Screening of blood products for both HBV and HIV is routine in the United States but must be expanded worldwide [10].

Prevention of HBV in persons who already have HIV is more complex, but

still, our tool kit is well stocked. The immunogenicity of HBV vaccine is reduced in HIV-infected persons, and a novel HBV vaccine or dosing schedule that achieves a seroconversion rate greater than 90% would have a significant impact. But even with the current vaccine, significant levels of seroconversion may be achieved if the vaccine were universally implemented. To maximize vaccine effectiveness, vaccination should be provided early (before the CD4 cell count declines to  $<350$  cells/ $\mu$ L); however, for persons with advanced immunosuppression, vaccination should also not be delayed while awaiting an increase in the CD4 cell count on ART [11]. The achievement of high rates of vaccination in some settings suggests the feasibility of this approach—among 21 564 HIV patients receiving care through Veteran's Administration hospitals, the proportion with documentation of immunity or a minimum of 1 dose of vaccine was 81%, and 1 facility achieved a rate of 98% [12]. However, rates of vaccination vary by setting, and in some settings remain unacceptably low [13].

To reduce the morbidity and mortality associated with HIV/HBV coinfection, we need to treat coinfecting persons and limit liver damage from other causes (ie, drugs, alcohol, or HCV). Providing HBV antiviral therapy to HIV/HBV-coinfected adults remains a significant challenge. Globally, an immense number of HIV-infected persons eligible for ART remain untreated; meeting this demand will significantly improve outcomes for both HIV-monoinfected and HIV/HBV-coinfected persons, and it should be a top priority. As yet, no reliable treatment to cure HBV infection in HIV-infected persons exists, a development that would have significant public health impact. However, several commonly used antiretroviral agents, including lamivudine, emtricitabine, and tenofovir, are active against both HIV and HBV, and earlier initiation of ART is associated with a reduction in liver disease in coinfecting persons [6]. Recent data suggest that inclusion of lamivudine as the sole

HBV active drug in an antiretroviral regimen is not enough to reliably suppress HBV viral replication or to prevent HBV-related complications; therefore, therapies including 2 drugs active against HBV (tenofovir plus either lamivudine or emtricitabine) are recommended [14].

There are undeniable barriers to achieving high rates of HBV vaccination and optimal treatment of HIV/HBV coinfection, both in the United States and internationally. However, effective interventions exist and can be integrated into public health practice and clinical care. Because chronic HBV infection is often asymptomatic, routine screening for HBV infection among HIV-infected persons initiating ART is necessary to identify which patients will benefit from ART that is optimally active against HBV. To improve vaccination rates in both HIV-infected and -uninfected populations, public and private insurance coverage should be expanded to routinely cover HBV vaccination in adults at high risk for HBV infection. Vaccination campaigns for adults at-risk for HIV and HBV infection, clinical quality improvement approaches (eg, provision of electronic reminders regarding HBV vaccination and optimal HIV/HBV treatment), campaigns to diagnose HIV at earlier stages of infection and link to treatment, and continued advocacy could all contribute to the needed expansion of both HBV vaccination and optimal HIV/HBV treatment. With compelling data confirming the risk for persons with coinfection, it is imperative that we commit

to implement these additional steps to combat hepatitis B now.

## Notes

**Potential conflicts of interest.** All authors: No reported 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.

**Disclaimer.** The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

## References

1. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* **2008**; 300:51–9.
2. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* **2006**; 166: 1632–41.
3. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. *Lancet Infect Dis* **2007**; 8:402–9.
4. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus co-infection negatively impacts HIV outcomes in HIV seroconverters. *J Infect Dis* **2011**; 205:185–93.
5. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and the risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* **2002**; 360: 1921–6.
6. Hoffman CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfecting HAART recipients. *AIDS* **2009**; 23:1881–9.
7. Dore GJ, Soriano V, Rockstroh J, et al. SMART INSIGHT Study Group. Frequent hepatitis B virus rebound among HIV–Hepatitis B virus–coinfecting patients fol-

- lowing antiretroviral therapy interruption. *AIDS* **2010**; 24:857–65.
8. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology* **2011**; 54:801–7.
9. Lu PJ, Byrd KK, Murphy T, Winbaum C. Hepatitis B vaccination coverage among high-risk adults 18–49 years, U.S., 2009. *Vaccine* **2011**; 29:7049–57.
10. World Health Organization. Blood safety and availability: Facts and figures from the 2007 blood safety survey. 2009. <http://www.who.int/mediacentre/factsheets/fs279/en/index.html>. Accessed 3 August 2011.
11. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Associations of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* **2009**; 58:1–207.
12. Backus LI, Boothroyd DB, Phillips BR, et al. National quality forum performance measures for HIV/AIDS care: The department of veterans affairs' experience. *Arch Intern Med* **2010**; 170:1239–46.
13. Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT. HIV Outpatient Study (HOPS) Investigators. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996–2007. *J Viral Hepat* **2010**; 17:879–86.
14. Matthews GV, Manzini P, Hu Z, et al. Impact of lamivudine on HIV and hepatitis B virus-related related outcomes in HIV/hepatitis B virus individuals in a randomized clinical trial of antiretroviral therapy in South Africa. *AIDS* **2011**; 25:1727–35.