Acute HIV Infection Is Beneficial for Controlling Chronic Hepatitis B

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Background. Coinfection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is common. Most studies have concentrated on the effects of chronic HIV infection on HBV infection; however, studies on the effects of acute HIV infection on HBV infection are especially important to elucidate the potential mechanisms leading to complications from HIV/HBV coinfection.

Methods. We evaluated the HBV DNA, hepatitis B surface antigen (HBsAg), and hepatitis B “e” antigen (HBeAg) in stored serum samples from 25 men with chronic hepatitis B who had acquired acute HIV infection.

Results. All of the 25 men had decreased HBV DNA levels during acute HIV infection. Three men converted from HBsAg positive before HIV infection to HBsAg negative during acute HIV infection, and 10 men converted from HBeAg positive before HIV infection to HBeAg negative during acute HIV infection.

Conclusions. These data suggest that the early effects of HIV infection improve the immune response against HBV.

Keywords. acute HIV infection; HBV; HBsAg; HBV DNA.

Human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) are both transmitted through sexual and percutaneous routes; thus, coinfection with both viruses is common. It is estimated that 10% of the 40 million HIV-infected individuals worldwide have chronic hepatitis [1–7]. Most studies on HIV/HBV-coinfected patients have shown a negative effect of HIV on the outcome of HBV-positive patients with decreased hepatitis B “e” antigen (HBeAg) clearance, high HBV DNA levels, and increased risk for cirrhosis and liver-related death [8, 9]. Most studies, however, concentrate on chronic HIV infection. Thio et al [10] reported that patients with acute HIV infection are not consistently associated with an increased blood HBV DNA level; in fact, the majority of patients have marked decreases in HBV DNA levels.

The vigor and breadth of the immune response to HBV infection determines clinical outcome, which is correlated with the blood level of HBV DNA [11]. At one end of the spectrum, there are individuals with a strong HBV-specific immune response who eliminate HBV proteins from the blood, have very low HBV DNA levels, and are at a very low risk for end-stage liver disease [12]. At the other extreme, HBV-infected individuals with a weak, narrowly focused immune response tend to have high HBV protein and DNA levels in the blood and are at increased risk of end-stage liver disease [13, 14].

The immune response varies greatly during different stages of HIV infection; for example, an intense, early cytokine storm has been reported in acute HIV-1 infection [15]. Although coinfection with HIV and HBV is common, there are limited data about the effect of acute HIV infection on HBV infection. Such a study is especially important, as it may elucidate potential mechanisms for the complications of HIV/HBV coinfection. In this study, we investigated the effect of acute HIV infection on chronic hepatitis B (CHB) based on a prospective cohort of HIV-infected men who have sex with men (MSM) in China [16–20] by determining their HBV DNA and hepatitis B surface antigens.

References

antigen (HBsAg) and HBeAg levels at several time points before and during acute HIV infection.

**PATIENTS AND METHODS**

**Study Participants**
This study used subjects from a clinical cohort study of acute HIV-1–infected individuals in Beijing [16–20]. Starting in October 2006, MSM were enrolled into a longitudinal prospective cohort study if they were at least 18 years old and HIV negative at baseline. After enrollment, the HIV-negative men were monitored every 2 months for plasma HIV antibodies, HIV RNA levels, and clinical signs of acute infection. By the end of December 2013, 410 individuals with acute HIV-1 infection were identified, 25 of whom were found to also have CHB. The 25 subjects were classified according to the acute HIV infection staging system proposed by Fiebig et al [15, 21] (Table 1):

- Stage I: HIV RNA positive; p24 antigen negative and antibody negative.
- Stage II: HIV RNA positive; p24 antigen positive and antibody negative.
- Stage III: HIV RNA positive, enzyme-linked immunosorbent assay (ELISA) positive, and Western blot negative.
- Stage IV: HIV RNA positive, ELISA positive, and Western blot indeterminate.
- Stage V: HIV RNA positive, ELISA positive, Western blot positive, and Western blot p31 negative.
- Stage VI: HIV RNA positive, ELISA positive, Western blot positive, and Western blot p31 positive.

None of the 25 patients had undergone anti-HBV or anti-HIV therapy. The demographic and clinical characteristics of the 25 men with CHB and acute HIV infection are reported in Table 1. We recruited the 25 patients and tested their preinfection and acute HIV infection samples. We tested 2 time points from before HIV infection, which were available for most of the 25 patients, and the first HIV positive time point for all of the patients. The other 385 acute-HIV-infected patients were HBsAg negative prior to and after HIV infection, and 297 of the 385 acute-HIV-infected patients maintained hepatitis B surface (HBs) antibody positivity.

The study was approved by the Beijing You’an Hospital Research Ethics Committee, and written informed consent was obtained from each participant.

**HIV-1 RNA Load**
HIV-1 RNA (copies per milliliter of plasma) was quantified by nucleic acid sequence-based amplification (bioMérieux BV, Boxtel, the Netherlands). The assay selectively and directly amplified HIV-1 RNA in an isothermal, 1-step sandwich hybridization procedure using 2 oligonucleotide primers, 3 enzymes, nucleoside triphosphates, and the appropriate buffers, as previously described [22]. The sensitivity of viral RNA detection by this assay is 50 copies/mL of plasma.

**CD4+ T-Cell Counts**
CD4+ lymphocyte counts were determined by 3-color flow cytometry using human CD3+, CD4+, and CD8+ cell markers (BD Bioscience, San Diego, California) in whole peripheral blood samples from each patient using FACS Lysing solution (Becton Dickinson, San Diego, California) according to the manufacturer’s instructions. The numbers of CD4+ T cells per microliter of whole blood were determined.

**Detection of HBV Infections**
HBV-specific antigens in patient plasma were detected in the clinical laboratory at You’an Hospital using the Elecsys HBsAg Immunomessay (Roche Diagnostics GmbH, Mannheim, Germany) and the immunomessay analyzer Cobase411 (Roche Diagnostics GmbH) according to the manufacturer’s instructions.

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**Table 1. Demographic and Clinical Characteristics of 25 Men With Chronic Hepatitis B and Acute HIV Infection**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Fiebig Stage</th>
<th>CD4 Counts, Cells/µL</th>
<th>HIV Load, Copies/mL</th>
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<td>1</td>
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Abbreviation: HIV, human immunodeficiency virus.

* During the period of this investigation.
Plasma HBV DNA Monitoring
HBV DNA testing was conducted with real-time polymerase chain reaction (PCR) using the RealART HBV LC PCR kit (Artus GmbH, Hamburg, Germany) or Abbott RealTime HBV DNA (Abbott Molecular, Des Plains, Illinois).

Liver Function Tests
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined in the patient plasma using ultraviolet-lactate dehydrogenase method test kits (Fortress Diagnostics Limited, United Kingdom).

RESULTS
Conversion From HBsAg Positive to HBsAg Negative
Three of the 25 patients converted from HBsAg positive before HIV infection to HBsAg negative during acute HIV infection; 2 of the 3 patients were HBeAg negative, and 1 was HBeAg positive before HIV infection (Figure 1). The average HBV DNA levels of the 3 patients were 4.03 log_{10} copies/mL before HIV infection, and the HBV DNA levels were undetectable in the 3 patients after HIV infection (Figure 1). The average CD4 level and viral load of the 3 patients (patients 1, 2, and 3) during acute HIV infection were 539 cells/µL and 57,700 copies/mL, respectively (Table 1).

Conversion From HBeAg Positive to HBeAg Negative
Ten of the 25 patients converted from HBeAg positive before HIV infection to HBeAg negative during acute HIV infection (Figure 2) and, on average, the HBV DNA of the 10 patients decreased from 6.4 log_{10} copies/mL before HIV infection to 1.9 log_{10} copies/mL during acute HIV infection (Figure 2). The average CD4 level and viral load of the 10 patients (patients 4–13) during acute HIV infection was 518 cells/µL and 41,859 copies/mL, respectively (Table 1).

Figure 1. Serial hepatitis B virus (HBV) DNA level, hepatitis B surface antigen (HBsAg), and hepatitis B “e” antigen (HBeAg) in patients 1, 2, and 3 at different time points of infection. The first 2 time points in each graph are before HIV infection, and the HBsAg and HBeAg statuses at each time point are shown above each graph. The patient numbers correspond to those in Table 1. Abbreviations: +, positive; −, negative; AH1, acute human immunodeficiency virus infection; HIV, human immunodeficiency virus.
HBV Antigen Seroconversion in the Remaining Patients

In the remaining 12 patients (14–25), HBV DNA levels decreased, but no HBV antigen seroconversion occurred. The average HBV DNA level of 5 patients (patients 14–18) decreased from 7 log_{10} copies/mL from before HIV infection to 3.7 log_{10} copies/mL during acute HIV infection (Figure 3).
The average HBV DNA level of 7 patients (patients 19–25) decreased from 7.7 log_{10} copies/mL from before HIV infection to 7.3 log_{10} copies/mL during acute HIV infection (Figure 3). The average CD4 level and viral load of the 12 patients (patients 14–25) were 444 cells/µL and 304,060 copies/mL, respectively, during acute HIV infection (Table 1).

**Figure 3.** Serial hepatitis B virus (HBV) DNA level, hepatitis B surface antigen (HBsAg), and hepatitis B “e” antigen (HBeAg) in patients 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 at different time points of infection. The first 2 time points in each graph are before HIV infection, and the HBsAg and HBeAg statuses at each time point are shown above each graph. The patient numbers correspond to those in Table 1. Abbreviations: +, positive; −, negative; AHI, acute human immunodeficiency virus infection.

The HIV RNA load and the immune status of the body may affect the body’s immune responses to HBV. Therefore, we compared the HIV RNA load and CD4 counts in different outcome of HBV antigen seroconversion groups. We found that, compared with the HBs or HBe antigen seroconversion groups,
no antigen seroconversion patients showed higher HIV RNA load and lower CD4 counts. Due to the limited number of cases, we did not perform statistical analyses (Figure 4).

**ALT and AST Levels**

To further describe the status of the 25 patients, we tested the ALT and AST levels from prior to and during acute HIV infection (Supplementary Table 1). We found that the ALT and AST levels were normal before HIV infection and were slightly elevated during acute HIV infection (Supplementary Table 1).

**DISCUSSION**

In this study, we found 3 patients who converted from HBsAg positive before HIV infection to HBsAg negative during acute HIV infection. Ten patients showed marked decreases in HBV DNA levels, along with the loss of HBeAg, which were consistent with a previous report [10]. These data suggest that the early effects of HIV infection are advantageous in controlling HBV infection. This effect may occur through activation of noncytopathic cytokine-dependent pathways, as it was reported that acute HIV-1 infection triggers an intense early cytokine storm that includes interferon-α [23]. In addition, during early HIV infection, immune activation increases without obvious immune anergy, which may increase the specific immune response against HBV such that there is increased clearance of HBV. Therefore, it is important to analyze the HBV-specific immune response during acute HIV infection.

In addition, we found that HBV DNA levels before HIV infection were lower in patients with HBsAg seroconversion than in patients with HBeAg seroconversion without HBs-specific antigen seroconversion. The HBV DNA levels before HIV infection were highest in patients who had not undergone HBV-specific antigen seroconversion. It may be that patients with low HBV DNA levels before HIV infection are prone to HBV antigen conversion during acute HIV infection, as it has been reported that HBeAg seroconversion is associated with low pretreatment HBV DNA levels [24].

In summary, we found that acute HIV infection improves the immune response against HBV. However, further studies are needed to understand how acute HIV infection inhibits the course of HBV infection.

Figure 4. Comparison of the CD4 counts (A) and HIV RNA loads (B) in different outcome of the hepatitis B virus (HBV) antigen seroconversion groups. Comparison of CD4 counts (C) and HIV RNA loads (D) in different outcome of HBV antigen seroconversion groups in Fiebig stage III and IV. Bars indicate the means with standard errors of the mean. Abbreviations: HBeAg, hepatitis B “e” antigen; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus.
Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential 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.

References