MAJOR ARTICLE

Prevalence of Chronic Hepatitis B and Incidence of Acute Hepatitis B Infection in Human Immunodeficiency Virus–Infected Subjects

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We determined incidence and risk factors for acute and chronic hepatitis B virus (HBV) infection and HBV vaccination rates among human immunodeficiency virus (HIV)–infected subjects from the Adult/Adolescent Spectrum of HIV Disease Project, during 1998–2001. Among 16,248 HIV-infected patients receiving care, the incidence of acute HBV was 12.2 cases/1000 person-years (316 cases), was higher among black subjects (rate ratio [RR], 1.4; 95% confidence interval [CI], 1.0–2.0), subjects with alcoholism (RR, 1.7; 95% CI, 1.2–2.3), subjects who had recently injected drugs (RR, 1.6; 95% CI, 1.1–2.4), and subjects with a history of AIDS-defining conditions (RR, 1.5; 95% CI, 1.2–1.9) and was lower in those taking either antiretroviral therapy (ART) with lamivudine (RR, 0.5; 95% CI, 0.4–0.6), ART without lamivudine (RR, 0.5; 95% CI, 0.3–0.7), or ⩾1 dose of HBV vaccine (14% of subjects) (RR, 0.6; 95% CI, 0.4–0.9). Prevalence of chronic HBV was 7.6% among unvaccinated subjects. HBV rates in this population were much higher than those in the general population, and vaccination levels were low. HBV remains an important cause of comorbidity in HIV-infected persons, but ART and vaccination are associated with decreased disease.

Persons at risk for infection with human immunodeficiency virus (HIV), through high-risk sexual and drug-using behaviors, are at higher risk for acute and chronic hepatitis B virus (HBV) infection. Previous studies have shown high prevalence of acute and chronic HBV infection in subjects at risk for HIV [1–4]. In addition, persons with HIV infection are at higher risk for HBV-related cirrhosis than are HBV-infected persons without HIV infection, and coinfection with both viruses has been shown to decrease survival time [5].

Although estimates of HBV prevalence [6] (0.4%) and incidence [7] (0.033 cases /1000 person-years [PY]) in the general US population are available, similar data on rates of HIV and HBV coinfection in the era of highly active antiretroviral therapy (HAART) are limited [2, 8, 9]. Furthermore, since the approval, in 1998, of lamivudine for the treatment of chronic HBV infection, few studies have examined the beneficial effects that lamivudine taken as part of HAART regimens has on chronic HBV [10–12], and no published studies have examined the effect that HAART has on the incidence of acute HBV infection in HIV-infected subjects. Finally, vaccination of high-risk persons (e.g., men who have sex with men [MSM] and injection drug users [IDUs]) has been recommended since the early 1990s [13], and studies suggest that persons with HIV are inadequately vaccinated against a variety of different antigens, including HBV [14–18].

In this study, we estimated incidence of acute HBV and prevalence of chronic HBV, in HIV-infected subjects enrolled in the Adult/Adolescent Spectrum of HIV Disease Project (ASD), a longitudinal, medical-record–review study. In addition, we estimated HBV vaccination rates, determined risk factors for acute HBV infection, and examined the effect that antiretroviral therapy (ART) regimens have on incidence and prevalence of HBV.

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SUBJECTS AND METHODS

The ASD Project. The methods used by ASD have been reported elsewhere [19]. In brief, ASD is a national surveillance project of the Centers for Disease Control and Prevention (CDC), conducted in collaboration with researchers and state and local health departments, in 11 geographic areas. Data collection began at selected project sites in 1990 (Atlanta, Dallas, Houston, San Antonio, Denver, Detroit, Los Angeles, New Orleans, and Seattle), 1991 (New York City), and 1992 (Bayamon, Puerto Rico). More than 100 facilities—including hospitals, outpatient offices, and emergency rooms—participate in the ASD study. It has enrolled >55,000 HIV-infected subjects ⩾13 years old and has monitored them for >130,000 PY, as of January 2002.

On patient enrollment, a 12-month, retrospective chart abstraction was performed. In addition, information on whether the patient ever had acute or chronic HBV infection and whether they ever had been vaccinated against HBV was collected. Subsequently, data were abstracted for 6-month intervals until death or loss to follow-up. Before 1998, data on acute HBV–infection status were collected by use of *International Classification of Diseases, 9th Revision* codes, whereas data on chronic HBV–infection status have been collected since 1990. Our analysis of acute HBV infection used data abstracted during 1998–2001.

ASD is, by design, a dynamic cohort: subjects may be enrolled on seeking care at a participating clinic, and, for as long as they are seen at that clinic will continue to contribute to follow-up time. If they drop out or transfer to a non-ASD clinic, their cases cease to contribute follow-up time to the denominator.

Inclusion criteria—incidence of acute HBV infection. To study risk for acute, symptomatic HBV infection, we restricted our analysis to HIV-infected subjects who had no known documented clinical or laboratory history of acute or chronic HBV infection and who had been clinically observed some time during July 1998–June 2001, regardless of when they were originally enrolled in ASD. Acute HBV infection was defined as medical-record documentation of the presence of IgM antibody to the hepatitis B surface antigen. The incidence density of acute HBV infection was computed in terms of 1000 PY of observation.

To determine the number of cases of acute HBV infection during the study period and to evaluate factors associated with acute HBV infection, we used a Poisson regression model. We examined demographic characteristics (age, race/ethnicity, sex, and study site), stage of HIV disease (history of AIDS-defining opportunistic infections and recent CD4 count during the 6 months before observation [<200, 200–500, and ⩾500 cells/μL [3]), social and behavioral factors (alcohol abuse [on the basis of subjective determination, by the attending physician, of excessive alcohol use], concurrent injection or noninjection drug use, during the 6 months before an observation of acute HBV infection, and mode of exposure to HIV), and clinical care (⩾1 dose of HBV vaccine and prescription of ART regimens with and without lamivudine, during the 6 months before observation of an acute HBV infection). Subjects were continuously evaluated for time-dependent covariates (e.g., age, vaccination status, history of AIDS-defining opportunistic infections, alcohol and drug abuse, CD4 count, and prescription of ART or HAART) each time that their charts were abstracted, so the number of observations per subject may be >1, and the total number of observations for these variables may exceed the number of subjects in our study. HAART was defined as 2 nucleoside reverse-transcriptase inhibitors in combination with either 1 protease inhibitor, 1 non-nucleoside reverse-transcriptase inhibitor, or abacavir, taken before a diagnosis of acute HBV infection. ART was defined as any other antiretroviral-therapy regimen. Interaction effects between significant risk factors and CD4 categories, antiretroviral categories, and AIDS diagnosis were tested.

Inclusion criteria—prevalence of chronic HBV infection. To determine the prevalence of chronic HBV infection in HIV-infected subjects, we performed a separate analysis on the entire pool of ASD participants. We defined chronic HBV infection as documentation of a positive hepatitis B surface antigen for >6 months. A diagnosis of chronic HBV infection was determined on the basis of a subject's complete available diagnostic history through the last observation interval during July 1998–June 2001. The 3-year prevalence of chronic HBV infection was expressed as a percentage of all subjects who had ⩾1 month of follow-up time during July 1998–June 2001. Subjects known to be previously vaccinated with ⩾1 dose of hepatitis B vaccine were excluded. Because there was no concomitant serosurvey to identify the prevalence of subclinical cases of chronic HBV infection and because some subjects with chronic HBV infection may have been diagnosed before they were enrolled in ASD, we were not able to estimate the incidence of chronic HBV infection. For the analysis of the prevalence of chronic HBV, we defined lamivudine use as having lamivudine prescribed before either diagnosis with HBV or the end of the study period. CIs for estimates of prevalence were determined by use of a normal approximation to the binomial distribution.

RESULTS

Incidence density of acute HBV infection. During July 1998–June 2001, 16,248 subjects with HIV were eligible for the analysis of acute HBV and were followed up for 25,978 PY, during which time 316 cases of acute HBV infection were documented, resulting in a crude incidence density of 12.2 cases/1000 PY.

Risk factors for acute HBV infection. Of the 16,248 subjects followed up during the study period, 2479 (14%) received

≥1 dose of the hepatitis B vaccine before or during the study period. Multivariate analysis showed higher rates of acute HBV infection among black subjects, subjects with a recent history (i.e., in the 6 months before an observation) of alcohol abuse and/or injection drug use (table 1). During the study period, ≥1 doses of hepatitis B vaccination and prescription of ART or HAART with and without lamivudine were associated with a decreased risk for acute HBV infection; however, the estimated rate ratios of the association between ART or HAART regimens with and without lamivudine and a lower incidence density of acute HBV infection were approximately equal to those of regimens without ART. Low CD4 counts were not significantly associated with acute HBV; however, a previous diagnosis of an AIDS opportunistic infection was associated with a higher incidence density of acute HBV infection.

Prevalence of chronic HBV infection. Among 19,904 subjects eligible for analysis for the presence of chronic HBV infection who were followed up during the study period, we identified 1506 cases of chronic HBV infection, for a 3-year prevalence of 7.6% (table 2). The annual prevalences were 7.1%, 7.7%, and 8.0%, during July 1998–June 1999, July 1999–June 2000, and July 2000–June 2001, respectively. The median follow-up time was 42 months. The prevalence of chronic HBV infection was higher among men than among women and was lowest among Hispanics. The highest prevalence, by risk group, was among MSM who were IDUs. Among those ASD participants prescribed ART regimens with lamivudine, the prevalence of chronic HBV was 2.3%, compared with 7.8% among ASD participants who had previously been prescribed ART regimens without lamivudine and 22.1% among participants who had not been prescribed ART before the end of the study period.

DISCUSSION

ASD provides data on the largest longitudinal cohort of HIV-infected subjects yet studied. Because of its size and diversity, it provides unique opportunities to estimate the incidence and prevalence of opportunistic infections and comorbid conditions, such as HBV. In our population of HIV-infected subjects in care, the incidence of acute HBV infection was 12.2 cases/1000 PY, and the 3-year prevalence of chronic HBV infection among unvaccinated subjects was 7.6%. These estimates are considerably higher than the 1998 estimate of acute HBV–incidence (0.033 cases/1000 PY) [7] and the estimate of 1994 chronic HBV–prevalence (0.4%) [6] that were reported for the general US population.

We estimated the prevalence and incidence of HBV/HIV coinfection among HIV-infected persons in care in the United States. Specifically, we applied our estimates of acute and chronic HBV infections to the prevalence of HIV in the United States (850,000–950,000 persons, as of 2000), including persons who know their HIV status and those who do not [20], while excluding the ~14% who were vaccinated against HBV. We determined that, in the United States, 55,600–62,100 persons may be coinfected with chronic HBV/HIV coinfection. Similarly, the approximate range of incident cases of acute HBV infection in HIV-infected persons—excluding those with prevalent chronic HBV infection, those who have been vaccinated against HBV, and those with a previous, resolved acute HBV infection (~35%) [8]—may be as high as 5100–5700 cases/year. This finding highlights the enormous burden of acute and chronic HBV infection, in light of adverse sequelae from potentially hepatotoxic ART regimens, the lack of integration of HIV- and HBV-prevention efforts, the expanding market for treatment of HBV infection, and the inadequate vaccination of HIV-positive persons. Despite reported decreases in HBV seroincidence among high-risk groups—decreases associated with the adoption of safer sex practices and the availability of an effective HBV vaccine [21]—the results of this study confirm that HIV-infected persons remain at risk for HBV infection.

Although studies performed a decade ago have shown HBV/HIV coinfection rates to be >50% in some high-risk populations [22, 23], these estimates were derived from cohorts studied before the widespread use of HBV vaccine and potent HAART regimens. More-recent studies, of smaller cohorts, in the United States and Europe have reported prevalence estimates of chronic HBV that range from <7% [24] to 9% [9].

Higher incidence of acute HBV infection was associated with risk factors such as recent alcohol abuse or injection drug use. Although information about these variables depends on whether, during follow-up care, the provider asked subjects about them, these data are generally available in ASD because of their importance to the appropriate clinical management of both HIV infection and HBV infection. It is not surprising that higher rates of HBV infection might be found in IDUs, given that injection drug use is a highly efficient mode of HBV transmission. Subjects with a recent history of alcohol abuse might also be expected to have higher rates of diagnosed acute HBV infection, since they are more likely to have hepatitis serologies performed, as a result of higher levels of liver enzymes. Alternately, subjects with a history of alcohol abuse may be more likely to engage in high-risk behaviors. Finally, the higher rate of acute HBV infection among subjects with a history of an AIDS opportunistic infection may reflect more-intensive medical follow-up of the patient, increased severity of disease (resulting in a more-extensive clinical evaluation), or reactivation of a previously unknown case of HBV infection.

Lamuvudine has been shown to inhibit HBV replication in >80% of infected subjects with or without HIV coinfection [25–30]. Subjects prescribed ART regimens with or without lamivudine had lower rates of chronic HBV than did subjects with no history of being prescribed ART. With regard to lamiv-

Table 1. Incidence of acute hepatitis B virus (HBV) infection among human immunodeficiency virus (HIV)–infected subjects participating in the Adult/Adolescent Spectrum of HIV Disease Project, July 1998–June 2001.

Variable	Subjects	Incidence density, per 1000 PY	Adjusted rate ratio (95% CI)
Sex			
Male	11,497	11.1	Referent
Female	4751	14.8	1.2 (0.9–1.6)
Race			
White and other	4715	6.0	Referent
Black	7910	14.7	1.4 (1.0–2.0)
Hispanic	3330	16.1	0.7 (0.5–1.0)
HIV-transmission–risk category			
MSM	6237	7.1	Referent
IDU	2984	26.0	1.2 (0.9–1.8)
MSM/IDU	1151	8.5	1.0 (0.6–1.7)
Heterosexual	2526	13.3	0.8 (0.5–1.3)
Other/unknown	3350	11.2	0.8 (0.6–1.2)
Age, years[a]			
<25	884	8.1	0.9 (0.5–1.9)
⩾25	15,654	12.3	Referent
History of AIDS OI[a]			
Yes	5655	16.9	1.5 (1.2–1.9)
No	11,576	9.9	Referent
CD4 count[a]			
<200	6912	19.1	1.3 (0.9–1.8)
200–499	9592	11.2	1.0 (0.8–1.4)
⩾500	6115	10.2	Referent
Recent alcohol abuse[a]			
Yes	2628	22.8	1.7 (1.2–2.3)
No	15,227	11.1	Referent
Recent abuse of injection drugs[a]			
Yes	1172	35.2	1.6 (1.1–2.4)
No	15,805	11.3	Referent
Recent abuse of noninjection drugs[a]			
Yes	3133	18.7	1.0 (0.7–1.4)
No	15,220	11.4	Referent
Prescribed use of ART during previous 6 months[a]			
HAART with lamivudine	9102	10.3	0.5 (0.4–0.6)
HAART without lamivudine	3993	7.4	0.5 (0.3–0.7)
Other ART with lamivudine	2506	11.4	0.5 (0.4–0.9)
Other ART without lamivudine	2920	7.0	0.4 (0.2–0.6)
No ART	8598	20.2	Referent
One or more doses of HBV vaccine[a]			
Yes	2479	5.2	0.6 (0.4–0.9)
No	14,735	13.4	Referent

NOTE. ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antitretroviral therapy; HBV, hepatitis B virus; IDU, injection drug user; MSM, man who has sex with men; OI, opportunistic infection; PY, person-year.

[a] Time-dependent covariates, may not sum to total of subjects.

Table 2. Prevalence of chronic hepatitis B virus (HBV) among human immunodeficiency virus (HIV)–infected subjects participating in the Adult/Adolescent Spectrum of HIV Disease Project, July 1998–June 2001.

Variable	Subjects	Cases	Prevalence of chronic HBV, % (95% CI)
Sex			
Male	14,561	1263	8.7 (8.2–9.1)
Female	5343	243	4.6 (4.0–5.1)
Race			
White	5948	524	8.8 (8.1–9.5)
Black	9683	796	8.2 (7.7–8.8)
Hispanic	3945	163	4.1 (3.5–4.8)
Other/unknown	328	23	7.0 (4.2–9.8)
HIV-transmission–risk category			
MSM	7775	718	9.2 (8.6– 9.9)
IDU	3987	281	7.1 (6.3–7.8)
MSM/IDU	1580	184	11.7 (10.1–13.2)
Heterosexual	2701	106	3.9 (3.2–4.7)
Other	3858	217	5.6 (4.9,–6.3)
Age, years			
<25	1740	123	7.1 (5.9–8.3)
⩾25	18,164	1383	7.6 (7.2,–8.0)
Any history of ART			
Previous ART with lamivudine	12,940	298	2.3 (2.0–2.6)
Previous ART without lamivudine	2305	180	7.8 (6.7–8.9)
No previous ART	4659	1028	22.1 (20.9–23.3)

NOTE. ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; IDU, injection drug user; MSM, man who has sex with men.

udine treatment of HBV/HIV coinfected subjects, several researchers have addressed the issues of dosing, dual treatment of HIV infection and HBV infection, and emergence of lamivudine-resistant strains of HBV [11, 24, 28, 31–33], but studies specifically examining the effects of lamivudine and newer anti-HBV compounds are needed. It is possible that differences in duration of observation of subjects receiving and not receiving lamivudine could bias our findings, because longer follow-up was related to higher prevalence rates. However, when we controlled for length of observation, our results did not change (data not shown).

Given the effect that lamivudine has in the prevention of reinfection after liver transplantation [10], we expected lamivudine-containing ART regimens to confer protection against acute HBV infection. However, rates of acute HBV infection were similar, regardless of whether the ART regimens contained lamivudine. This finding suggests that, in our study, in decreasing the acquisition of acute HBV infection, ART regimens with lamivudine were no more effective than those without lamivudine. This negative finding may be explained if it is found that health-care providers had systematically decided to use lamivudine-containing HAART regimens to treat those subjects perceived to be at highest risk for HBV infection (i.e., a situation of confounding by intention). If this were so, then the additional protective effect of lamivudine that is seen in the analysis of prevalence would not be seen in the analysis of incidence, because those at greatest risk would already be protected. Unfortunately, information with regard to why particular regimens have been prescribed is not routinely entered into the medical record and therefore is not available for data abstraction. To adequately identify the question of the effect that lamivudine has on acquisition of acute HBV infection, a randomized clinical trial would be the most appropriate study design.

In addition, in previous studies, the risk for progression from acute to chronic HBV infection in HIV-infected subjects varied from 21% to 40% [23, 34–36], compared with <5% in generally healthy adults [37]. In our cohort of HIV-infected subjects, acute HBV infection progressed to chronic HBV infection in ~7% of ASD participants (data not shown). However, in this relatively small number of subjects, we were unable to document that HAART regimens with and without lamivudine have a beneficial effect on progression from acute to chronic HBV infection, despite the biologic plausibility of this hypothesis. How lamivudine effects the process of conversion from acute

to chronic HBV infection remains a question for studies specifically designed to evaluate the rate of progression from acute to chronic HBV infection in HIV-infected subjects.

Because ASD participants are not systematically screened for markers of HBV infection, our data-collection methods may have underascertained cases of acute HBV infection, primarily those which were subclinical or mildly symptomatic (estimated to be ⩾30% in affected adults of unknown HIV status) [38]. In addition, cases of prevalent HBV may not have been identified if HBV infection occurred either before HIV diagnosis or before a patient had received care at an ASD facility. In addition, acute HBV was defined as IgM antibody to the surface antigen, not as anti–hepatitis B core IgM. As a result, some acute HBV infections may have been reactivations of chronic HBV disease.

Despite guidelines recommending vaccination of HIV-infected subjects, few subjects in our cohort were vaccinated against HBV [13]. In this population of HIV-infected subjects, vaccination against other diseases also has been shown to have been low [32]. This may be because some clinicians believe that, because of immunologic impairment with resultant decreased vaccine response, vaccination may be less effective in HIV-infected persons [36, 39–41]. This belief is supported by studies showing decreased HBV-vaccine efficacy among HIV-infected adolescents [42] and increased plasma HIV RNA after vaccination [43], although recent data suggest that, if they exist, plasma HIV-RNA increases after vaccination are transitory [44, 45].

Although we recognize that the rate of HBV vaccination may be underestimated, the data on our cohort suggest that most HIV-infected subjects were unvaccinated, despite receiving care for HIV. Other studies of vaccination rates in HIV-infected subjects [18, 46] report findings similar to ours. Although these findings highlight the need for health-care providers to be better educated with regard to recommendations for persons engaging in high-risk behaviors, they also suggest that a rethinking of prevention strategies, to better integrate preventive care for persons at high risk for HBV, regardless of their HIV serostatus, would be beneficial.

In developed countries, the introduction of potent new ART regimens has changed the course of the HIV epidemic. Because HBV and HIV are transmitted via the same routes, new cases of acute HBV infection, in persons known to have HIV infection, suggest that some HIV-infected persons do not adhere to traditional risk-reduction messages—that is, safe sex and/or safe injection practices. This finding suggests that prevention messages designed to decrease HIV transmission may not be effective or may be less effective, in the prevention of new comorbid infections such as HBV. Prevention programs specific for HIV-infected persons, such as the Serostatus Approach to Fighting the HIV Epidemic (SAFE) Initiative being developed by the CDC, will focus prevention efforts on HIV-infected persons, as well as on HIV-negative persons at high risk [47].

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