Annals of Internal Medicine ORIGINAL RESEARCH

Incident Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected Men Who Have Sex With Men From Pre-HAART to HAART Periods

A Cohort Study

Oluwaseun Falade-Nwulia, MD, MPH; Eric C. Seaberg, PhD; Anna E. Snider Charles R. Rinaldo, PhD; John Phair, MD; Mallory D. Witt, MD; Chloe L. Thio, MD

Background: Men who have sex with men (MSM) are at high risk for hepatitis B virus (HBV) infection. Data on the effect of highly active antiretroviral therapy (HAART) on incident HBV infection in HIV-infected and HIV-uninfected MSM are limited.

Objective: To determine predictors of incident HBV infection in MSM during pre-HAART and HAART periods.

Design: Observational cohort study.

Setting: Cohort of MSM who have, or are at risk for, HIV infection.

Patients: 2375 HBV-uninfected MSM in the Multicenter AIDS Cohort Study.

Measurements: Poisson regression was used to compare incidence rates of HBV infection in the pre-HAART and HAART eras and to identify factors associated with incidence of HBV infection.

Results: In 25 322 person-years of follow-up, 244 incident HBV infections occurred. The unadjusted incidence rate was higher in HIV-infected MSM than in HIV-uninfected MSM (incidence rate ratio [IRR], 1.9 [95% CI, 1.5 to 2.4]) and was significantly lower in the HAART era than in the pre-HAART era among HIV-infected (IRR, 0.2 [CI, 0.1 to 0.4]) and HIV-uninfected (IRR, 0.3 [CI, 0.2 to 0.4]) MSM. Age younger than 40 years (IRR, 2.3 [CI, 1.7 to 3.0]), more than 1 recent sexual partner (IRR, 3.1 [CI, 2.3 to 4.2]), and HIV infection (IRR, 2.4 [CI, 1.8 to 3.1]) were independently associated with higher incidence of HBV infection, whereas HBV vaccination was protective (IRR, 0.3 [CI, 0.2 to 0.4]). Highly active antiretroviral therapy with HIV RNA levels less than 400 copies/mL was associated with protection (IRR, 0.2 [CI, 0.1 to 0.5]), but HAART in those with HIV RNA levels of 400 copies/mL or greater was not.

Limitation: The observational nature limits inferences about causality.

Conclusion: Effective HAART is associated with lower incidence of HBV infection; however, even in the HAART era, incidence of HBV infection remains high among MSM.

Primary Funding Source: National Institute of Allergy and Infectious Diseases.

Ann Intern Med. doi:10.7326/M15-0547 **www.annals.org**

For author affiliations, see end of text.

This article was published online first at www.annals.org on 13 October 2015.

Worldwide, chronic hepatitis B virus (HBV) infection is the leading cause of end-stage liver disease and hepatocellular carcinoma (1). In the United States, sexual transmission among men who have sex with men (MSM) is a principal cause of incident infection. Approximately 15% to 25% of new HBV infections in the United States are among MSM, although this group accounts for only 2% of the U.S. population (2, 3).

Although the HBV vaccine has greater than 95% efficacy and was first recommended in 1982 by the Advisory Committee on Immunization Practices for MSM, vaccination rates remain low in MSM (4, 5). Little is known about prospective trends and risk factors for incident HBV infection in MSM, and this knowledge is needed to refocus efforts to prevent HBV infection in this population.

Incidence of HBV infection has declined in the general population (6), but data suggest an increasing incidence in HIV-infected persons (7). In a study of HIV-infected U.S. military personnel and their dependents, a decline in incidence of HBV infection from 1997 to 2000 was followed by an increase from 2000 to 2008, with men having an 8-fold increased risk for incident HBV infection compared with women (7). In HIV-infected persons, lamivudine- or tenofovir disoproxil fumarate (TDF)–containing antiretroviral therapy has been associated with reduced incidence of HBV infection (7–9). To our knowledge, no systematic studies of incident HBV infection in prospectively followed cohorts of MSM have included both HIV-infected and HIV-uninfected persons to determine the effect of highly active antiretroviral therapy (HAART) on the incidence of HBV infection.

The Multicenter AIDS Cohort Study (MACS), a prospectively followed cohort of MSM established in 1984, is ideal to investigate incident HBV infection among HIV-infected and HIV-uninfected MSM because the cohort has been followed systematically since the beginning of the HIV epidemic. To determine risk factors for and trends in incident HBV infection in MSM since the early HIV epidemic, we tested prospectively collected specimens from men in MACS without evidence of a previous HBV infection at study entry.

Methods

Study Participants

Men in MACS who have, or are at risk for, HIV infection from 4 metropolitan areas in the United States (Baltimore, Maryland/Washington, DC; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California) were studied. The details of MACS are de-

EDITORS' NOTES

Context

Men who have sex with men (MSM) are at increased risk for hepatitis B virus (HBV) infection.

Contribution

In a cohort study of MSM, the rate of incident HBV infection was higher in HIV-infected men than in HIV-uninfected men and in those with 2 or more sexual partners in the previous 6 months. Highly active antiretroviral therapy in HIV-infected men with HIV RNA levels less than 400 copies/mL was protective. The HBV vaccine was protective with 1 dose or more.

Caution

The study design limited inferences about causality.

Implication

For MSM, receipt of HBV vaccine, control of HIV infection, and education from their health care providers about risk for HBV infection should be encouraged.

scribed elsewhere (10–12). In brief, participants were initially recruited from 1984 to 1985 and subsequently in 1987 to 1991 and 2001 to 2003. They were assessed semiannually with interviews and laboratory testing, including HIV enzyme-linked immunosorbent assay and Western blot confirmatory testing in HIV-uninfected men. The institutional review boards at each MACS site approved the study, and all participants provided written informed consent.

At study entry, men were tested for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and antibody to HBsAg. The inclusion criteria were negative test results for anti-HBc and HBsAg at the first MACS visit on or after 1 January 1985 and 1 sample or more from a subsequent visit that was available for testing. To reduce the inherent variability that occurs when collecting and processing samples in the start-up phase of cohort studies (13), a study entry date on or after 1 January 1985 was chosen for the present study. Incident HBV infection was defined as seroconversion to a positive HBsAg or anti-HBc result as determined by one of the following testing protocols: 1) For men whose only HBsAg and anti-HBc tests were done at study entry or whose last documented anti-HBc and HBsAg results were both negative, the samples collected at the most recent MACS visit on or before 31 December 2013 were tested for anti-HBc. Men with negative results were classified as HBV-uninfected, and men with positive results were classified as having incident HBV infection. 2) Those who already had positive results on HBsAg or anti-HBc testing documented during follow-up were also classified as having incident HBV infection. Then, for all men identified as having incident HBV infection, the date of infection was narrowed by anti-HBc testing at a visit between the last known visit with a negative anti-HBc result and the first known visit with a positive result until no specimens remained within the seroconversion interval. The sample from the visit immediately before the first with a positive anti-HBc result was then tested for HBsAg because HBsAg can be positive before anti-HBc is positive. The date of incident HBV infection was defined as the midpoint between the last negative and first positive anti-HBc or HBsAg test result, whichever was positive first. Timing of incident HBV infection could be narrowed between 2 consecutive visits separated by less than 12 months in 88% of cases. Most of the incident HBV infections were defined by positive results on 2 serologic HBV tests. Patients whose first positive test result was at their last MACS visit were included as having incident HBV infection in the primary analysis but were then excluded during a sensitivity analysis because they lacked positive results on 2 tests.

Outcomes and Measurements

The men were followed until the date of incident HBV infection, the last follow-up visit, or 31 December 2013, whichever came first. The primary outcome was incident HBV infection. Data on age, race, number of sexual partners, injection drug use, alcohol use, HIV status, CD4 cell count, HAART use, anti-HBV agent (lamivudine, emtricitabine, or TDF) use, and report of at least 1 dose of HBV vaccine were abstracted for each participant at semiannual visits. Alcohol use was quantified in drinks per week based on participant self-report at each visit. Because of the low levels of alcohol use, heavy use was defined as greater than 13 drinks per week.

Before 1996, few persons in MACS received HAART, but by December 1996 and December 1997, 50% and 65% of HIV-infected persons, respectively, had initiated HAART (14). On the basis of these data, incident HBV infection before 1996 was considered to have occurred in the pre-HAART era and during or after 1996 in the HAART era.

Laboratory Testing

Anti-HBc and HBsAg testing were done on serum or plasma stored at −70 °C using a commercially available enzyme immunoassay (ETI-AB-COREK PLUS and ETI-MAK-2 PLUS, DiaSorin, respectively) according to manufacturer's instructions.

Statistical Analysis

Descriptive statistics were used to describe study participants. Chi-square tests were used to compare proportions, and *t* tests were used to compare continuous variables. Incidence rates were determined using a person-years (PYs) analysis. For participants who became HIV-positive during follow-up, the PYs of time accrued before or after HIV seroconversion were classified among the seronegative or seropositive group, respectively. We fit univariable and multivariable Poisson regression models to the entire study cohort and then stratified by HIV infection, HAART status, and calendar period to examine the association of incidence of HBV infection with these primary exposure measures plus HIV response and the use of HBV-active drugs. The

Table 1. Baseline Characteristics of HBV-Uninfected Men at Entry Into MACS, by HIV Status

Variable	All (*n* = 2375)	HIV-Uninfected (*n* = 1784)	HIV-Infected (*n* = 591)	*P* Value*
Median CD4 cell count (IQR), × 10^9 cells/L†	–	–	0.57 (0.39–0.76)	
Median age (IQR), *y*	32 (27–38)	32 (27–37)	32 (28–38)	0.66
Race, *n (%)*				<0.001
White	1738 (73)	1388 (78)	350 (59)	
Nonwhite	637 (27)	396 (22)	241 (41)	
Education level, *n (%)*‡				<0.001
Less than 12th grade	113 (5)	60 (3)	53 (9)	
12th grade	311 (13)	206 (12)	105 (18)	
Greater than 12th grade	1940 (82)	1508 (85)	432 (73)	
Consume >13 alcoholic drinks/wk, *n (%)*	264 (11)	201 (11)	63 (11)	0.76
IDU, *n (%)*	60 (3)	35 (2)	25 (5)	0.001
>2 sexual partners in preceding 6 mo, *n (%)*	1585 (67)	1203 (67)	382 (65)	0.21
Recent syphilis diagnosis, *n (%)*	18 (0.8)	3 (0.2)	15 (2.6)	<0.001
Received ≥1 dose of HBV vaccine at baseline, *n (%)*	723 (31)	491 (28)	232 (41)	<0.001

HBV = hepatitis B virus; IDU = injection drug use; IQR = interquartile range; MACS = Multicenter AIDS Cohort Study.
* Compares HIV-uninfected and HIV-infected men.
† Data provided only in study participants with HIV.
‡ Data from 2364 men, 1774 of whom were HIV-uninfected and 590 of whom were HIV-infected, who provided information on educational status at their baseline visits.

multivariable analyses included statistical adjustment for factors previously shown to be associated with the risk of HBV acquisition plus the MACS site of enrollment. All covariates except race and MACS site were examined as time-varying covariates by partitioning follow-up into intervals defined according to when these covariates were assessed. To ensure validity of covariates, persons who were infected with HBV during a prolonged interval (that is, >5 years between their last visit with a negative HBV result and first visit with a positive HBV result) were censored as HBV-uninfected at their last visit with a negative HBV test result. Follow-up for all other prolonged intervals during which a participant did not have an HBV infection was censored at 2.5 years. A *P* value less than 0.05 was considered significant. All analyses were done with Stata, version 13.0 (StataCorp). The Poisson procedure was used to fit the Poisson regression models, and we examined the fit of the Poisson models by testing for overdispersion using the Stata nbreg procedure to fit corresponding negative binomial regression models. For each model reported, the overdispersion variable was not significantly different from 0, which indicates an acceptable fit of the Poisson regression models to the data.

Role of the Funding Source

This study was funded by the National Institute of Allergy and Infectious Diseases. The funding source had no involvement in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

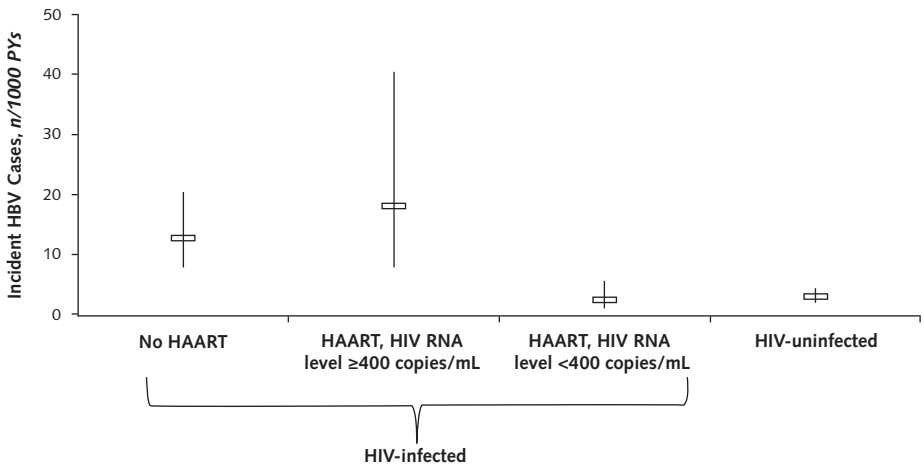
Of 6972 men enrolled in MACS through 2003, a total of 2375 had negative results for HBsAg and anti-HBc at the first study visit on or after 1 January 1985 and had at least 1 follow-up visit. Of these, 1784 (75%) were HIV-uninfected and 591 (25%) were HIV-infected, and 151 (8.5%) of the HIV-uninfected men had HIV seroconversion during the study period. Median follow-up was 9.5 years for the HIV-infected group, including persons who seroconverted during follow-up, and 9.7 years for the HIV-uninfected group.

Compared with HIV-uninfected men, men infected with HIV at baseline were significantly ($P < 0.05$) less likely to be white, had fewer years of education, and were more likely to have used injection drugs in the past 6 months (Table 1). Overall, only 31% reported receiving at least 1 dose of the HBV vaccine, with a higher proportion in HIV-infected men than in HIV-uninfected men at baseline (41% vs. 28%; $P < 0.001$). The proportion of men who received at least 1 dose of the HBV vaccine increased to 60% by the end of the study period (67% and 58% among HIV-infected and HIV-uninfected men, respectively).

The 2375 men accrued 25 322 PYs of follow-up, during which 244 incident HBV infections occurred, yielding an overall unadjusted HBV incidence rate of 9.6 per 1000 PYs (95% CI, 8.5 to 11.0). We saw 94 incident HBV infections in 6301 PYs among HIV-infected men (incidence rate, 14.9 per 1000 PYs [CI, 12.2 to 18.3]) and 150 incident HBV infections in 19 020 PYs among HIV-uninfected men (incidence rate, 7.8 per 1000 PYs [CI, 6.7 to 9.3]). The incidence rate was significantly higher in the HIV-infected group (incidence rate ratio [IRR], 1.9 [CI, 1.5 to 2.4]). The HBV incidence rates declined significantly from the pre-HAART to HAART era among both HIV-infected (IRR, 0.2 [CI, 0.1 to 0.4]) and HIV-uninfected (IRR, 0.3 [CI, 0.2 to 0.4]) men.

To further explore the effect of HIV infection and HAART on incident HBV infection, we then restricted the analysis to follow-up time accrued during the HAART era and stratified by HAART use and HIV RNA level. The incidence rate for men receiving HAART who had HIV RNA levels less than 400 copies/mL was 2.6 per 1000 PYs (CI, 1.2 to 5.8), which was similar to the incidence rate of 3.1 per 1000 PYs (CI, 2.1 to 4.6) in HIV-uninfected men during the HAART era ($P = 0.69$) and significantly lower than the incidence rate among men receiving HAART who had an HIV RNA level of 400

Figure. Incidence rate of HBV infection, stratified by HIV infection and HAART use status.



The incidence rate and 95% CI are represented for each HIV/HAART group. HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; PY = person-year.

copies/mL or greater (18.2 per 1000 PYs [CI, 8.2 to 40.5]); $P < 0.001$). Furthermore, the incidence rate among men receiving HAART who had HIV RNA levels of 400 copies/mL or greater was similar to that in HIV-infected men who were not receiving HAART (12.8 per 1000 PYs [CI, 8.0 to 20.6]) (**Figure**). The men in this study reported being at least 95% adherent to their HAART regimens for more than 90% of follow-up.

The univariable risk factors for incident HBV infection stratified by HIV status are shown in **Table 2**. Several multivariable models were constructed to determine factors independently associated with incident HBV infection. In a model including all men, incidence of HBV infection was significantly higher among men younger than 40 years (IRR, 2.3 [CI, 1.7 to 3.0]), those with at least 2 sexual partners in the preceding 6 months (IRR, 3.1 [CI, 2.3 to 4.2]), and HIV-infected men (IRR, 2.4 [CI, 1.8 to 3.1]) (**Table 3**). One dose or more of HBV vaccine was protective (IRR, 0.3 [CI, 0.2 to 0.4]). When stratified by HIV status, risk factors in HIV-uninfected persons were similar to the overall cohort (**Appendix Table 1**, available at www.annals.org).

The multivariable analysis restricted to HIV-infected men had associations similar to the overall cohort in terms of age, number of sexual partners, and receipt of HBV vaccine (**Table 3**). Men receiving HAART whose HIV RNA level was less than 400 copies/mL in the preceding 6 months had a significantly lower risk for incident HBV infection than men not receiving HAART (IRR, 0.2 [CI, 0.1 to 0.5]). However, this was not true for men receiving HAART whose HIV RNA level was 400 copies/mL or greater (IRR, 1.1 [CI, 0.5 to 2.5]). To determine if the HIV RNA association differed based on whether lamivudine or TDF was the primary anti-HBV drug, we stratified this analysis into pre-TDF (1996 to 2001) and TDF (2002 to 2013) periods and found that the IRRs for men receiving HAART whose HIV RNA levels were less than 400 copies/mL were the same in both periods (IRR, 0.3 [CI, 0.04 to 2.6] and 0.3 [CI, 0.1 to 0.8] for the pre-TDF and TDF periods, respectively). A sensitivity analysis excluding men whose first positive HBV serologic test result was at their last MACS visit did not change these associations.

To further characterize the association of HAART and HIV RNA with incident HBV infection, we fit a separate multivariable model for the pre-HAART and HAART periods and compared incidence of HBV infection among 4 groups: HIV-uninfected men, HIV-infected men not receiving HAART, HIV-infected men receiving HAART with HIV RNA levels less than 400 copies/mL, and HIV-infected men receiving HAART with HIV RNA levels greater than 400 copies/mL (**Appendix Table 2**, available at www.annals.org). In this adjusted model, HIV-infected men receiving HAART whose HIV RNA level was less than 400 copies/mL had a risk for incident HBV infection that was similar to that of HIV-uninfected men (IRR, 0.9 [CI, 0.4 to 2.3]). However, HIV-infected men not receiving HAART or those receiving HAART who had HIV RNA levels of 400 copies/mL or greater did not (IRR, 5.5 [CI, 2.2 to 13.6]). To assess for a potential differential effect of use of lamivudine, emtricitabine, or TDF on HBV incidence, we constructed a multivariable model similar to that reported for HIV-infected men in **Table 3**, with the exception that antiretroviral drug use was stratified as no HAART or no HBV-active drug as part of HAART, lamivudine- or emtricitabline-containing HAART, or TDF-containing HAART. In this analysis, we did not find a significant difference between the protective effect of a lamivudine- or emtricitabine-containing HAART regimen (IRR, 0.3 [CI, 0.1 to 0.7]) and a TDF-containing regimen (IRR, 0.2 [CI, 0.07 to 0.5]) compared with not receiving HAART or not having an HBV-active drug as part of the HAART regimen. Six of 262 men receiving HAART regimens that included an HBV-active drug (3 receiving TDF) who had an HIV RNA level less than 400

Table 2. Univariate Analysis for Risk Factors Associated With HBV Infection, by HIV Infection Status

Variable	HIV-Uninfected			HIV-Infected		
	IR/1000 PYs	IRR (95% CI)	*P* Value	IR/1000 PYs	IRR (95% CI)	*P* Value
Age						
<40 y	12.4	3.1 (2.2–4.5)	<0.001	22.8	3.1 (1.9–4.9)	<0.001
≥40 y	4.0	1		7.4	1	
Race						
Nonwhite	7.5	1		11.8	1	
White	8.0	1.1 (0.7–1.6)	0.81	16.5	1.4 (0.9–2.2)	0.150
Alcohol						
≤13 drinks/wk	8.1	1		14.0	1	
>13 drinks/wk	8.8	1.1 (0.6–1.9)	0.75	36.0	2.6 (1.4–4.8)	0.003
Ever IDU						
No	7.7	1		14.4	1	
Yes	14.0	1.8 (0.9–3.7)	0.100	21.2	1.5 (0.8–2.8)	0.25
Sexual exposure in previous 6 mo						
0–1 sexual partners	3.4	1		8.0	1	
≥2 sexual partners	12.2	3.5 (2.4–5.2)	<0.001	21.8	2.7 (1.7–4.3)	<0.001
≥1 dose of HBV vaccine						
No	13.8	1		33.8	1	
Yes	3.5	0.3 (0.2–0.4)	<0.001	8.0	0.2 (0.2–0.4)	<0.001
HIV-infected patients only						
HAART use						
No HAART	–	–		23.8	1	
HAART						
HIV RNA level ≥400 copies/mL	–	–		18.2	0.8 (0.3–1.8)	0.53
HIV RNA level <400 copies/mL	–	–		2.6	0.1 (0.05–0.3)	<0.001
CD4 cell count						
≥0.350 × 10^9 cells/L	–	–		13.2	1	
<0.350 × 10^9 cells/L	–	–		21.1	1.6 (1.0–2.5)	0.040

HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; IDU = injection drug use; IR = incidence rate; IRR = incidence rate ratio; PY = person-year.

copies/mL developed incident HBV infection (incidence rate, 2.6 [CI, 1.2 to 5.9]).

DISCUSSION

To our knowledge, this is the first study to examine rates of incident HBV infection in HIV-infected and HIV-uninfected MSM who were prospectively followed from the beginning of the HIV epidemic through the HAART era. Rates of incident HBV infection were substantially higher in HIV-infected men than in uninfected men, and rates in both groups were lower in the HAART era than in the pre-HAART era. Having HIV infection, having several sex partners, and being younger were associated with an increased risk for HBV infection, whereas receipt of at least 1 dose of the HBV vaccine was associated with a reduced risk. In HIV-infected men, HAART that achieved an undetectable HIV RNA level decreased the risk for HBV infection to a rate equal to that of HIV-uninfected men, regardless of whether HAART was given before or after the availability of TDF.

Our data are consistent with other studies in which the rate of incident HBV infection among MSM during the HAART era was higher than in the general population (0.009 per 1000 PYs in 2012) (6, 15). This rate is probably driven in part by high-risk sexual practices, which have been associated with high rates of other sexually transmitted diseases among MSM (16–19). It is especially concerning because an effective HBV vaccine has been recommended for MSM since 1982 (20, 21). In this study, only one third of the men reported at least 1 dose of the HBV vaccine at study entry, with rates of vaccination coverage increasing to 60% overall during follow-up, a proportion that remains low but is consistent with the reported HBV vaccination coverage rates of 42% in high-risk adults (4). This is supported by other studies in which as few as 9% of MSM received the HBV vaccine (4, 5, 22). Even among HIV-infected MSM who routinely access care, HBV immunization rates remain low at 25% (5). In our study, receiving at least 1 dose of the HBV vaccine decreased the risk for incident HBV infection by up to 70%. Thus, concerted efforts are needed to improve immunization rates in MSM.

Of note, even after adjustment for measured risk behaviors, HIV-infected men were twice as likely to acquire HBV infection as HIV-uninfected men. It is possible that, for the HIV-infected MSM, we could not adjust for certain behavioral risk factors that would increase the likelihood for exposure to HBV. It is also possible that reduced efficacy of the HBV vaccine in HIV-infected persons could contribute to the higher incidence rates in HIV-infected MSM (23). An impaired immune re-

Table 3. Multivariable Analysis for Incident HBV Infection Overall and in HIV-Infected Men*

Variable	All		HIV-Infected	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Age <40 vs. ≥40 y	2.3 (1.7–3.0)	<0.001	1.7 (1.1–2.8)	0.030
Race				
Nonwhite	1		1	
White	1.3 (0.9–1.8)	0.140	1.1 (0.7–1.8)	0.59
Multiple vs. 0–1 sexual partners in previous 6 mo	3.1 (2.3–4.2)	<0.001	2.5 (1.6–4.1)	<0.001
Ever IDU vs. never IDU	1.7 (1.0–2.7)	0.040	1.7 (0.9–3.3)	0.118
≥1 dose vs. no doses of HBV vaccine	0.3 (0.2–0.4)	<0.001	0.3 (0.2–0.5)	<0.001
HIV infected vs. uninfected	2.4 (1.8–3.1)	<0.001	NA	
CD4 cell count <0.350 vs. ≥0.350 × 10^9 cells/L	Not tested		1.3 (0.8–2.0)	0.31
Antiretroviral use				
No HAART	Not tested		1	
HAART				
HIV RNA level ≥400 copies/mL	–		1.1 (0.5–2.5)	0.88
HIV RNA level <400 copies/mL	–		0.2 (0.1–0.5)	<0.001

HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; IDU = injection drug use; IRR = incidence rate ratio; NA = not applicable.
* Model also adjusted for Multicenter AIDS Cohort Study site. All covariates except race and Multicenter AIDS Cohort Study site were used as time-varying covariates in the model. *P* values for all participants from negative binomial regression models to assess for overdispersion = 0.24; those for HIV-infected participants = 0.49.

sponse from HIV infection may increase the risk for incident HBV infection. Our data suggest that this impaired response can be restored, as demonstrated by our finding that men receiving effective HAART (HIV RNA level <400 copies/mL) had a similar risk for incident HBV infection as HIV-uninfected men, whereas men receiving HAART who had a detectable HIV RNA level did not experience this benefit. These data suggest that HIV-infected men receiving effective HAART have an immune response to HBV infection that substantially decreases the risk for a productive HBV infection that generates anti-HBc after exposure. Similar findings with apparent "resistance" to productive infection have been described for both HIV and hepatitis C virus where virus-specific T-cell immune responses are detected in persons whose test results are negative for antibodies to hepatitis C virus or HIV despite extensive exposure to these viruses (24, 25). This idea of "resistance" to a productive HBV infection is also supported by data showing an increased risk for incident HBV infection in HIV-infected persons with a history of AIDS-associated opportunistic infections compared with patients with non–AIDS-defined HIV infection (26). Further support also comes from a study demonstrating HBV-specific cytokine secretion and T-cell responses despite negative results for HBsAg and anti-HBc in sexual partners of persons with chronic HBV infection (27). Other data support the important effects of a HAART-related undetectable HIV RNA level on the immune response because it is associated with an increase in the absolute counts of memory CD4 T cells to values comparable to those measured in HIV-uninfected persons (28). This increase in memory CD4 T-cell counts was not seen in persons with similar CD4 counts who had detectable HIV RNA levels (28).

Some studies have suggested that HBV-active drugs as part of HAART reduce the risk for incident HBV infection in HIV-infected persons by 50% to 90% (7–9), whereas others could not find an additional beneficial effect of HAART regimens that included an HBV-active drug compared with those that did not include HBV-active drugs in reducing incident HBV infection (26). Because this cohort received an HBV-active drug as part of the HAART regimen for 92% of follow-up time, we could not directly compare HAART regimens with or without HBV-active drugs. In addition, although TDF is known to have more potent anti-HBV activity, we did not find a significant difference between the effect of TDF-containing HAART regimens and lamivudine- or emtricitabine-containing regimens in preventing HBV infection. A potential explanation is that because the first step in HBV infection is transfer of the HBV genomic DNA to the hepatocyte nucleus to establish the reservoir of covalently closed circular DNA from which transcription occurs, it is reasonable that anti-HBV drugs do not prevent new infections because they do not interfere with this step. This hypothesis is supported by recent data from an in vitro study in primary human hepatocytes, suggesting that pretreatment with lamivudine or TDF does not prevent hepatocyte infection but can decrease cell-to-cell spread of HBV infection (29).

The first major strength of our study is that all men were systematically tested for incident HBV infection using protocols to determine HBV seroconversion between 2 consecutive MACS visits. Second, we used prospectively collected data on sexual and other risk behaviors, which permitted a more precise assessment of the effect of risk factors on incident HBV infection. Third, we included both HIV-infected and HIV-uninfected MSM in the same cohort followed during both pre-HAART and HAART periods, which gave us the unique ability to compare trends in incident HBV infection between these periods. Fourth, the inclusion of MSM from 4 sites across the United States allows our findings to be generalizable to MSM in large cities across the United States. However, we are limited in our ability to make inferences about causality by the observational nature of the cohort due to the potential for unmeasured confounders. Because men were recruited

into MACS during specific periods as opposed to on an ongoing basis, we could not estimate annual incidence of HBV infection in the general MSM population. However, we believe that our comparisons of incidence of HBV infection between HIV-infected and HIV-uninfected MSM in pre-HAART and HAART periods are meaningful and generalizable to MSM in the United States.

In conclusion, effective HAART is associated with reduced rates of incident HBV infection in HIV-infected men similar to those seen in HIV-uninfected men, which highlights an additional benefit of achieving an undetectable HIV RNA level among HIV-infected patients. However, even among HIV-uninfected MSM or MSM with well-controlled HIV, incident HBV infection rates remain unacceptably high. Thus, an urgent need remains for education of health care providers and MSM about HBV infection risk and the need for HBV vaccination. Intensified, targeted HBV prevention efforts in the MSM population at the highest risk, including those with several sexual partners and those infected with HIV, are also needed. These efforts should include HIV-infected persons receiving effective HBV-active HAART because these drugs were not 100% efficacious in preventing incident HBV infection. Without increased vigilance in HBV prevention in MSM, control of the epidemic in this population cannot be achieved.

From Johns Hopkins University, Baltimore, Maryland; University of Pittsburgh, Pittsburgh, Pennsylvania; Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles Medical Center, Torrance, California.

Grant Support: By the National Institute of Allergy and Infectious Diseases, with additional funding from the National Cancer Institute (UO1-AI-35042, UL1-RR025005, UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, UO1-AI-35041, UL1TR000124, and R03AI096918).

Disclosures: Dr. Seaberg reports grants from the National Institutes of Health during the conduct of the study. Dr. Phair reports grants from the National Institutes of Health during the conduct of the study and personal fees from Pfizer outside the submitted work. Dr. Thio reports grants from the National Institutes of Health during the conduct of the study and grants from Gilead Sciences outside the submitted work. Authors not listed here have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0547.

Reproducible Research Statement: *Study protocol:* Available at www.statepi.jhsph.edu/macs/macs.html. *Statistical code:* Available from Dr. Falade-Nwulia (e-mail, ofalade1@jhmi.edu). *Data set:* Available from Dr. Seaberg (e-mail, ecs@jhu.edu).

Requests for Single Reprints: Oluwaseun Falade-Nwulia, MD, MPH, Johns Hopkins University, 725 North Wolfe Street, Room 215, Baltimore, MD 21205; e-mail, ofalade1@jhmi.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Trépo C, Chan HL, Lok A.** Hepatitis B virus infection. Lancet. 2014;384:2053-63. [PMID: 24954675] doi:10.1016/S0140-6736(14)60220-8

2. **Purcell DW, Johnson CH, Lansky A, Prejean J, Stein R, Denning P, et al.** Estimating the population size of men who have sex with men in the United States to obtain HIV and syphilis rates. Open AIDS J. 2012;6:98-107. [PMID: 23049658] doi:10.2174/1874613601206010098

3. **Centers for Disease Control and Prevention.** Viral Hepatitis – CDC Recommendations for Specific Populations and Settings: Viral Hepatitis And Men Who Have Sex with Men. Accessed at www.cdc.gov/hepatitis/populations/msm.htm on 24 February 2015.

4. **MacKellar DA, Valleroy LA, Secura GM, McFarland W, Shehan D, Ford W, et al; Young Men's Survey Study Group.** Two decades after vaccine license: hepatitis B immunization and infection among young men who have sex with men. Am J Public Health. 2001;91:965-71. [PMID: 11392942]

5. **Hoover KW, Butler M, Workowski KA, Follansbee S, Gratzer B, Hare CB, et al; Evaluation Group for Adherence to STD and Hepatitis Screening.** Low rates of hepatitis screening and vaccination of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2012;39:349-53. [PMID: 22504597] doi:10.1097/OLQ.0b013e318244a923

6. **Centers for Disease Control and Prevention.** Viral Hepatitis – Statistics & Surveillance: Surveillance for Viral Hepatitis – United States, 2012. 2015. Accessed at www.cdc.gov/hepatitis/Statistics/2012Surveillance/Commentary.htm#hepB on 24 December 2014.

7. **Chun HM, Fieberg AM, Hullsiek KH, Lifson AR, Crum-Cianflone NF, Weintrob AC, et al; Infectious Disease Clinical Research Program HIV Working Group.** Epidemiology of hepatitis B virus infection in a U.S. cohort of HIV-infected individuals during the past 20 years. Clin Infect Dis. 2010;50:426-36. [PMID: 20047484] doi:10.1086/649885

8. **Gatanaga H, Hayashida T, Tanuma J, Oka S.** Prophylactic effect of antiretroviral therapy on hepatitis B virus infection. Clin Infect Dis. 2013;56:1812-9. [PMID: 23487374] doi:10.1093/cid/cit145

9. **Heuft MM, Houba SM, van den Berk GE, Smissaert van de Haere T, van Dam AP, Dijksman LM, et al.** Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. AIDS. 2014;28:999-1005. [PMID: 24685742] doi:10.1097/QAD.0000000000000180

10. **Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr.** The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987;126:310-8. [PMID: 3300281]

11. **Detels R, Jacobson L, Margolick J, Martinez-Maza O, Muñoz A, Phair J, et al.** The Multicenter AIDS Cohort Study, 1983 to . . . . Public Health. 2012;126:196-8. [PMID: 22206985] doi:10.1016/j.puhe.2011.11.013

12. **Chmiel JS, Detels R, Kaslow RA, Van Raden M, Kingsley LA, Brookmeyer R.** Factors associated with prevalent human immunodeficiency virus (HIV) infection in the Multicenter AIDS Cohort Study. Am J Epidemiol. 1987;126:568-77. [PMID: 3651095]

13. **Mellors JW, Muñoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al.** Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997;126:946-54. [PMID: 9182471]

14. **Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Muñoz A; Multicenter AIDS Cohort Study.** Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS. 2001;15:347-55. [PMID: 11273215]

15. **Centers for Disease Control and Prevention (CDC).** Incidence of acute hepatitis B–United States, 1990–2002. MMWR Morb Mortal Wkly Rep. 2004;52:1252-4. [PMID: 14704650]

16. **Chen SY, Gibson S, Katz MH, Klausner JD, Dilley JW, Schwarcz SK, et al.** Continuing increases in sexual risk behavior and sexually transmitted diseases among men who have sex with men: San Francisco, Calif, 1999–2001, USA [Letter]. Am J Public Health. 2002;92:1387-8. [PMID: 12197957]
17. **Heffelfinger JD, Swint EB, Berman SM, Weinstock HS.** Trends in primary and secondary syphilis among men who have sex with men in the United States. Am J Public Health. 2007;97:1076-83. [PMID: 17463387]
18. **Leichliter JS, Haderxhanaj LT, Chesson HW, Aral SO.** Temporal trends in sexual behavior among men who have sex with men in the United States, 2002 to 2006–2010. J Acquir Immune Defic Syndr. 2013;63:254-8. [PMID: 23466645] doi:10.1097/QAI.0b013e31828e0cfc
19. **Menza TW, Kerani RP, Handsfield HH, Golden MR.** Stable sexual risk behavior in a rapidly changing risk environment: findings from population-based surveys of men who have sex with men in Seattle, Washington, 2003-2006. AIDS Behav. 2011;15:319-29. [PMID: 19830542] doi:10.1007/s10461-009-9626-y
20. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep. 1991;40:1-25. [PMID: 1835756]
21. **Centers for Disease Control and Prevention (CDC).** Recommendation of the Immunization Practices Advisory Committee (ACIP). Inactivated hepatitis B virus vaccine. MMWR Morb Mortal Wkly Rep. 1982;31:317-22, 327-8. [PMID: 6811846]
22. **Weinbaum CM, Lyerla R, Mackellar DA, Valleroy LA, Secura GM, Behel SK, et al; Young Men's Survey Study Group.** The Young Men's Survey phase II: hepatitis B immunization and infection among young men who have sex with men. Am J Public Health. 2008;98:839-45. [PMID: 18382012] doi:10.2105/AJPH.2006.101915
23. **Landrum ML, Hullsiek KH, Ganesan A, Weintrob AC, Crum-Cianflone NF, Barthel RV, et al; Infectious Disease Clinical Research Program HIV Working Group.** Hepatitis B vaccination and risk of hepatitis B infection in HIV-infected individuals. AIDS. 2010;24:545-55. [PMID: 19487908] doi:10.1097/QAD.0b013e32832cd99e
24. **Mizukoshi E, Eisenbach C, Edlin BR, Newton KP, Raghuraman S, Weiler-Normann C, et al.** Hepatitis C virus (HCV)-specific immune responses of long-term injection drug users frequently exposed to HCV. J Infect Dis. 2008;198:203-12. [PMID: 18505381] doi:10.1086/589510
25. **Miyazawa M, Lopalco L, Mazzotta F, Lo Caputo S, Veas F, Clerici M; ESN Study Group.** The 'immunologic advantage' of HIV-exposed seronegative individuals [Editorial]. AIDS. 2009;23:161-75. [PMID: 19098485] doi:10.1097/QAD.0b013e3283196a80
26. **Kellerman SE, Hanson DL, McNaghten AD, Fleming PL.** Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. J Infect Dis. 2003;188:571-7. [PMID: 12898445]
27. **Wiegand J, Meya S, Schlaphoff V, Manns MP, Mössner J, Wedemeyer H, et al.** HBV-specific T-cell responses in healthy seronegative sexual partners of patients with chronic HBV infection. J Viral Hepat. 2010;17:631-9. [PMID: 19889141] doi:10.1111/j.1365-2893.2009.01220.x
28. **Resino S, Galán I, Bellón JM, Navarro ML, León JA, Muñoz-Fernandez MA.** Characterizing the immune system after long-term undetectable viral load in HIV-1-infected children. J Clin Immunol. 2003;23:279-89. [PMID: 12959220]
29. **Watanabe T, Hamada-Tsutsumi S, Yokomaku Y, Imamura J, Sugiura W, Tanaka Y.** Postexposure Prophylactic Effect of Hepatitis B Virus (HBV)-Active Antiretroviral Therapy against HBV Infection. Antimicrob Agents Ch. 2015;59:1292-8.

Current Author Addresses: Dr. Falade-Nwulia: Johns Hopkins University, 725 North Wolfe Street, Room 215, Baltimore, MD 21205.
Dr. Seaberg: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room E-7634, Baltimore, MD 21205.
Ms. Snider and Dr. Thio: Johns Hopkins University, 855 North Wolfe Street, Room 533, Baltimore, MD 21231.
Dr. Rinaldo: University of Pittsburgh Graduate School of Public Health, A419 Crabtree Hall, 130 DeSoto Street, Pittsburgh, PA 15261.
Dr. Phair: Department of Medicine, Feinberg School of Medicine, 645 North Michigan Avenue, Suite 900, Chicago, IL 60611.
Dr. Witt: Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles Medical Center, 1124 West Carson Street, Building CDCRC, Torrance, CA 90502.

Author Contributions: Conception and design: O. Falade-Nwulia, E.C. Seaberg, C.R. Rinaldo, C.L. Thio.
Analysis and interpretation of the data: O. Falade-Nwulia, E.C. Seaberg, C.L. Thio.
Drafting of the article: O. Falade-Nwulia, E.C. Seaberg, C.L. Thio.
Critical revision of the article for important intellectual content: O. Falade-Nwulia, E.C. Seaberg, C.R. Rinaldo, M.D. Witt, C.L. Thio.
Final approval of the article: O. Falade-Nwulia, E.C. Seaberg, A.E. Snider, C.R. Rinaldo, J. Phair, M.D. Witt, C.L. Thio.
Provision of study materials or patients: M.D. Witt.
Statistical expertise: O. Falade-Nwulia, E.C. Seaberg.
Obtaining of funding: C.L. Thio.
Administrative, technical, or logistic support: E.C. Seaberg, J. Phair.
Collection and assembly of data: A.E. Snider, M.D. Witt, C.L. Thio.

Appendix Table 1. Multivariable Analysis for Incident HBV Infection in HIV-Uninfected Men*

Variable	IRR (95% CI)	*P* Value
Age <40 vs. ≥40 y	2.2 (1.5–3.2)	<0.001
Race		
Nonwhite	1	
White	1.2 (0.8–1.9)	0.41
Multiple vs. 0–1 sexual partners in prior 6 mo	3.5 (2.3–5.1)	<0.001
Ever IDU vs. never IDU	1.5 (0.7–3.2)	0.23
≥1 dose vs. no doses of HBV vaccine	0.3 (0.2–0.4)	<0.001

HBV = hepatitis B virus; IDU = injection drug use; IRR = incidence rate ratio.
* Model also adjusted for Multicenter AIDS Cohort Study site. All covariates except race and Multicenter AIDS Cohort Study site were used as time-varying covariates in the model. *P* value from negative binomial regression model to assess for overdispersion = 0.090.

Appendix Table 2. Multivariable Analysis for Incident HBV Infection, by HAART Period*

Variable	Pre-HAART Period, 1985–1995		HAART Period, 1996–2013	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Age <40 vs. ≥40 y	1.5 (1.1–2.2)	0.020	1.8 (1.0–3.2)	0.040
White vs. nonwhite	1.0 (0.7–1.6)	0.91	0.8 (0.4–1.5)	0.48
Multiple vs. 0–1 sexual partners in prior 6 mo	2.9 (2.1–4.1)	<0.001	3.8 (2.0–7.1)	<0.001
Ever IDU vs. never IDU	1.6 (0.9–3.1)	0.140	2.5 (1.2–5.3)	0.020
≥1 dose vs. no doses of HBV vaccine	0.3 (0.2–0.4)	<0.001	0.4 (0.2–0.7)	0.003
HIV/antiretroviral status				
HIV uninfected	1		1	
HIV infected not on HAART	2.7 (2.0–3.6)	<0.001	3.7 (2.0–6.9)	<0.001
HIV infected on HAART; HIV RNA level ≥400 copies/mL	–		5.5 (2.2–13.6)	<0.001
HIV infected on HAART; HIV RNA level <400 copies/mL	–		0.9 (0.4–2.3)	0.89

HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; IDU = injection drug use; IRR = incidence rate ratio.
* Model also adjusted for Multicenter AIDS Cohort Study site. All covariates except race and Multicenter AIDS Cohort Study site were used as time-varying covariates in the model. *P* values from negative binomial regression models to assess for overdispersion: pre-HAART period = 0.25; HAART period = 0.36.