Differences in the Incidence of Hepatitis B and Human Immunodeficiency Virus Infections among Injecting Drug Users

Orin S. Levine,* David Vlahov, Ron Brookmeyer, Sylvia Cohn, and Kenrad E. Nelson

Both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) type 1 seroconversions have been considered as outcome measures to evaluate the effectiveness of needle exchange programs. To assess the relationship between incident HBV and HIV infections among injecting drug users (IDUs), seroconversions were prospectively studied among a cohort of 240 HBV- and HIV-seronegative IDUs. The incidence of HBV seroconversion declined from 24.41/100 person-years in 1988 to 0 seroconversions in 1992. In contrast, HIV seroconversion rates varied little from the overall rate of 3.29/100 person-years. HBV seroconversion predicted subsequent HIV seroconversion among male IDUs (relative incidence [RI] = 4.23) but not among female IDUs (RI = 0.86). Because of different transmission dynamics, HBV seroconversion probably has limited utility as a surrogate outcome measure for incident HIV. However, HBV seroconversion itself is an appropriate and important outcome measure for evaluation of prevention programs among IDUs.

Prospective studies of human immunodeficiency virus (HIV) seroconversion not only provide timely data on the current course of the HIV epidemic but also provide meaningful outcome measures to evaluate the effect of HIV infection prevention programs [1–3]. However, mounting HIV seroconversion studies is a daunting task because incidence rates in most areas of the United States are <2%, thereby requiring that seroconversion studies follow enormous populations to demonstrate effects over time and by intervention status [4]. Other, perhaps more economical, approaches warrant consideration.

Because, like HIV infection, hepatitis B virus (HBV) infection is blood-borne, transmissible through parenteral, sexual, and perinatal routes [5], it has been used as an analogy for HIV infection in some studies of injecting drug users (IDUs) in areas where the prevalence of HIV infection is low and that of HBV infection is high. In the Tacoma, Washington, needle exchange project, one report noted that existing data from the Centers for Disease Control and Prevention’s (CDC) Sentinel County Study of acute viral hepatitis showed an abrupt decline in the number of hepatitis B cases among injection drug users that occurred ~6 months after the introduction of the needle exchange program [6]. In a separate study from Tacoma, cases defined as new infection with HBV were compared with controls who were HBV-seronegative, and the controls were more likely to have used the needle exchange program [7].

The extent to which temporal trends of HBV accurately reflect trends of HIV infection at the population level and the extent to which HBV seroconversion is a marker or predictor of HIV seroconversion at the individual level remain unclear. While HBV and HIV share certain epidemiologic characteristics, important differences in the dynamic of transmission are known. Compared with HIV, HBV is more infectious and more resilient against environmental degradation [8], suggesting that prevention of HBV infections should be effective against HIV infections. However, unlike HIV infection, which is considered to result uniformly in chronic, life-long infection, HBV infections among adults typically resolve after the acute phase (90%–95%) and confer lasting immunity [9]. The effect of these differing dynamics of infection on the ability to draw inferences from the incidence of one to the other has not been well characterized.

Data on the incidence of HIV and HBV infections within a single sample of IDUs are sparse [10–13]. In particular, given the similarity and differences between HBV and HIV infections, studies are needed that clarify the extent to which HBV incidence can be used as a surrogate marker for HIV incidence at either the population or the individual level of analysis.

To explore these issues and evaluate the utility of incident HBV infection as a surrogate for incident HIV infection among IDUs, we conducted a prospective study of HBV and HIV infections among a population of IDUs in Baltimore. From a cohort of 2921 IDUs recruited through street outreach, we identified 240 participants who were susceptible to both HBV and HIV infections. The incidence of HBV and HIV seroconversions in this sample was monitored between February 1988 and December 1992. This report describes temporal trends in the incidence rates of HBV and HIV and compares relative incidence rates by demographic group in this population of IDUs.
Methods

Study population. The population of IDUs evaluated in this study was recruited for a longitudinal study of HIV infection (the AIDS Links to Intravenous Experience, or ALIVE Study) in 1988–1989 by use of extensive community outreach techniques as described elsewhere [14]. During 13 months, 2921 IDUs were enrolled in the study and underwent venipuncture and a face-to-face interview by a trained interviewer in a private room. The questionnaire included demographic characteristics and 10-year histories of illnesses, drug use, and sex practices. After extensive counseling, subjects were tested for serum HIV antibody and returned for their HIV test results in 3 weeks; at this visit, recommendations for clinical and immunologic follow-up visits and medical referrals were made, when appropriate.

Among the 2569 ALIVE participants whose baseline serum specimens were screened for HBV serologic markers, 478 had nonreactive results for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) [15]. These participants were considered HBV-seronegative and, therefore, potentially still at risk for infection with HBV. Of the 478 subjects HBV-seronegative at baseline, 431 were also HIV-seronegative. Of these 431, 240 had at least one subsequent follow-up specimen and a sufficient quantity of serum to test for the presence of all three HBV serologic markers (anti-HBc, anti-HBs, HBsAg) after testing for HIV seroconversion. Thus, 240 HBV- and HIV-seronegative drug injectors were included in this study.

Serologic tests. All baseline serum specimens were stored at -70°C before testing, thawed, and tested under code for HBsAg, anti-HBs, and anti-HBc using EIA (AUSZYME, AUSAB, and CORZYME, respectively; Abbott, Abbott Park, IL). Specimens were screened for HIV by EIA (Genetic Systems, Seattle). Specimens that were repeatedly positive by EIA were confirmed by Western blot (Biotech HIV-I; DuPont, Wilmington, DE).

Statistical methods. HBV and HIV incidence rates were calculated as the ratio of the number of seroconvertors divided by the person-years at risk of seroconversion [16, 17]. In these analyses, the date of seroconversion was defined as the midpoint between the last visit when the person was seronegative and the first visit at which the person was seropositive. Incidence rates were calculated for each of 5 calendar years (1988–1992). Confidence intervals for the incidence rates and statistical significance tests to compare incidence rates were based on methods for Poisson data [17], and exact \( P \) values were computed.

Poisson regression methods were used to investigate multiple predictors of seroconversion. Separate regression models were developed for the incidence of HIV seroconversion and the incidence of HBV seroconversion. The analyses were based on person-time and numbers of seroconversions grouped into yearly intervals. Independent variables that were considered were calendar year, duration of injecting drug use, age, and gender. An additional analysis was also done to determine if incident HBV infection predicts subsequent HIV infection after accounting for other known risk factors. This analysis was based on a Poisson regression analysis of HIV seroconversion with an additional dichotomous independent variable defined as prior HBV infection (yes or no). This variable, prior HBV infection, was treated as a time-dependent variable in the sense that it may change during the course of follow-up [17] and subjects may contribute person-time to the prior HBV stratum only after the estimated time of HBV seroconversion.

Results

The participants included in this study of incident HBV and HIV infections were predominantly male, African-American, current IDUs who were \( \leq 30 \) years of age. While the median duration of injecting drug use before enrollment was 5 years, more than one-third were recent initiates, with \( < 3 \) years of experience injecting drugs. Table 1 compares the 240 HBV- and HIV-seronegative drug injectors in this study with the 191 HBV-seronegative drug injectors who were not included in the analysis. Participants in this analysis were similar to those not included in the analysis in terms of gender, income level, homelessness, employment, educational level, current injecting drug use, age, and duration of injecting drug use before baseline. Participants included in this analysis were more likely to be African-American than those not included in the analysis (86.2% vs. 64.9%, \( P < .001 \)).

A total of 75 HBV seroconversions and 22 HIV seroconversions were observed among the 240 HBV- and HIV-seronegative participants in this study between 1 February 1988 and 31 December 1992.

Figure 1 graphically depicts the temporal trends in incidence of HBV and HIV in this population between 1988 and 1992. While the overall incidence of HBV was 14.19/100 person-years between 1988 and 1992, HBV incidence rates declined over calendar time from 24.41/100 person-years in 1988 to 5.05/100 person-years in 1991, and in 1992 there were no HBV seroconversions, resulting in an incidence rate of 0. In contrast, the incidence of HIV varied little over time. An overall HIV incidence rate of 3.29/100 person-years was observed between
1988 and 1992. Annual HIV incidence rates ranged from 2.55/100 person-years in 1988 and 1990 to 4.31/100 person-years in 1991. The annual numbers of seroconversions and person-years of observation for each infection are shown in figure 1.

Table 2 presents the incidence of HBV and HIV by demographic group. The incidence of HBV infection did not vary significantly by gender ($P > .50$), duration of injecting drug use before baseline ($P = .32$), or ethnicity ($P > .50$). However, the HBV incidence rate was somewhat higher among younger injectors ($\leq 30$ years old; 17.02/100 person-years vs. 11.48/100 person-years; $P = .12$). The incidence of HIV infection, while not different by duration of injecting drug use before baseline ($P > .50$) or by ethnicity ($P > .50$), was significantly higher among female than male subjects (7.10/100 person-years vs. 2.27/100 person-years; $P = .02$) and somewhat higher among younger injectors ($\leq 30$ years old; 4.45/100 person-years vs. 2.11/100 person-years; $P = .15$).

Table 3 presents the results of Poisson regression analysis of incident HBV and incident HIV infections. In this analysis, the relative incidence rates are calculated, adjusting for the effects of all other covariates in the model. Calendar year was the only significant covariate associated with incident HBV.

Table 2. Incidence of HBV and HIV seroconversions (per 100 person-years) in cohort of 240 injecting drug users, by demographic characteristics and history of injection.

<table>
<thead>
<tr>
<th>Characteristic (no.)</th>
<th>HBV</th>
<th></th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of seroconvertors</td>
<td>Incidence rate (95% CI)</td>
<td>No. of seroconvertors</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (189)</td>
<td>59</td>
<td>15 (11.34–18.89)</td>
<td>12</td>
</tr>
<tr>
<td>Female (51)</td>
<td>16</td>
<td>13 (7.82–20.82)</td>
<td>10</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 30$ (121)</td>
<td>44</td>
<td>17 (12.66–22.87)</td>
<td>15</td>
</tr>
<tr>
<td>$&gt;30$ (119)</td>
<td>31</td>
<td>11 (8.10–16.63)</td>
<td>7</td>
</tr>
<tr>
<td>Duration of injecting drug use before baseline, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 2$ (84)</td>
<td>30</td>
<td>17 (11.68–23.90)</td>
<td>8</td>
</tr>
<tr>
<td>$&gt;3$ (156)</td>
<td>45</td>
<td>13 (9.63–17.27)</td>
<td>14</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American (207)</td>
<td>67</td>
<td>14 (11.12–17.94)</td>
<td>20</td>
</tr>
<tr>
<td>All other (33)</td>
<td>8</td>
<td>15 (7.39–29.56)</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE. CI = confidence interval.
For incident HIV, female subjects were at a significantly increased risk of HIV infection (adjusted relative rate = 3.26; \( P < 0.01 \)), and although not statistically significant, the adjusted relative HIV incidence was 2.19 times higher among younger injectors (\( \leq 30 \) years) than older injectors (\( P = 0.09 \)).

Fourteen participants seroconverted to both HBV and HIV; in contrast, 61 participants seroconverted to HBV but not HIV and 8 seroconverted to HIV but not HBV. In general, HBV infection preceded HIV infection among participants who seroconverted to both viruses. Among the 14 participants who seroconverted to both HBV and HIV, HBV preceded HIV infection in 9, HIV preceded HBV in 3, and both HBV and HIV seroconversion were detected at the same visit in 2.

Table 4 presents the results of Poisson regression analysis of HBV infection as a predictor of subsequent HIV infection. Overall, participants who seroconverted to HBV were more likely to become infected subsequently with HIV (RI = 2.15; 95% confidence interval [CI] = 0.92–5.02). However, an interaction between being male and prior HBV infection was observed (RI = 4.23; 95% CI = 1.34–13.31). Among female IDUs, prior HBV infection did not predict subsequent HIV infection (RI = 0.86; 95% CI = 0.18–4.05).

### Discussion

The major findings of this study are that trends of incident HBV infection did not parallel trends of incident HIV infection in a population of IDUs followed over time but that at an individual level of analysis, incident HBV infection was a predictor of incident HIV infection among male but not female IDUs. The findings appear somewhat contradictory and require clarification.

At the population level, striking differences in the temporal trends of HBV and HIV incidence were observed. Differences in the dynamics of HBV and HIV transmission as a result of the differing prevalence of the two infections may have led to the observed differences in the temporal trends in incidence rates. While all of the drug injectors in this study sample were at risk for HBV infection, the overwhelming majority of IDUs in the ALIVE cohort had evidence of HBV infection before baseline and, therefore, were no longer susceptible [15]. Furthermore, only 8%–10% were HBsAg carriers capable of transmitting HBV [15]. The high incidence rates in the first 3 years (15–24 seroconversions/100 person-years) may have led to an exhaustion of the susceptible persons at highest risk of acquiring HBV. However, it should be noted that >90 participants were still susceptible to HBV in 1992. As our participants age and in light of the dynamics of cumulative exposure, within this study population it might be reasonable to consider that the likelihood of susceptible participants having continued contact with infectious persons (most of whom are transiently infectious) may have decreased over time.

The dynamics of HIV transmission are somewhat different. Only 24% of the IDUs in the ALIVE cohort were HIV-infected at baseline and, therefore, were no longer susceptible [18]. Unlike the case with HBV infection, virtually all HIV-seropositive persons are considered potentially infectious. These differences in transmission dynamics may contribute to the observed differences in trends of HBV and HIV incidence.

Despite the dissimilar temporal trends in incidence rates, on an individual level, incident HBV predicted subsequent HIV infection among male IDUs but not among female IDUs. This interaction between HBV and gender may reflect differences in the predominant mode of transmission of HBV and HIV by gender. For example, men may be more likely to become infected with both HBV and HIV by the parenteral route, whereas sexual transmission of HIV in women may be relatively more important than sexual transmission of HBV. This explanation is consistent with a growing body of evidence suggesting that sexual transmission of HIV plays a significant role among female IDUs, independent of parenteral transmission [19, 20].

Before drawing firm conclusions from these data, some limitations of the study should be considered. The population included in this analysis of incident HBV and HIV infection comprises a subset of IDUs who were seronegative for HBV.

### Table 3.


<table>
<thead>
<tr>
<th>Covariate</th>
<th>Incidence of HBV</th>
<th>Incidence of HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted relative rate</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Calendar year*</td>
<td>0.58</td>
<td>0.47–0.72</td>
</tr>
<tr>
<td>Duration of injecting drug use ( \leq 2 ) years†</td>
<td>0.78</td>
<td>0.49–1.25</td>
</tr>
<tr>
<td>Age ( \leq 30 ) years‡</td>
<td>1.39</td>
<td>0.88–2.22</td>
</tr>
<tr>
<td>Female</td>
<td>0.94</td>
<td>0.54–1.66</td>
</tr>
</tbody>
</table>

* Reference category: year 1988; subsequent years categorized as ordinal variable (e.g., year 1989 = 1, year 1990 = 2).
† Years of injecting drug use at baseline; reference category: >2 years.
‡ Age at baseline; reference category: >30 years.

### Table 4.


<table>
<thead>
<tr>
<th>Relative HIV incidence associated with previous HBV infection*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>4.23</td>
</tr>
<tr>
<td>Females</td>
<td>0.86</td>
</tr>
<tr>
<td>Overall</td>
<td>2.15</td>
</tr>
</tbody>
</table>

* Relative to no previous HBV infection. Analyses based on separate regressions for males, females, and overall. Analyses adjusted for calendar year.
and HIV infection at baseline. While in general the drug injectors in this analysis had less experience injecting drugs than the overall ALIVE population, they are not strictly “new” injectors and, as such, may not be representative of all recent initiates to injecting drug use. Therefore, the potential effect of some unmeasured survivor bias remains. However, it is reassuring that the risk factors for HBV and HIV in this subsample of the ALIVE population are consistent with the results of separate studies of the risk of HBV [15] and HIV [21] in the overall ALIVE population. Furthermore, since transmission dynamics may be affected by the prevalence of these infections in the community, caution should be used in applying the risks for these infections to other populations of IDUs in which the baseline prevalence of these infections may differ [10]. Further investigations of the relationship between incident HBV and HIV in populations in which IDUs can be stratified by sexual risk are warranted.

It is interesting to note that we observed a dramatic decline in HBV incidence in the absence of a needle exchange program. This could be due to a variety of factors, including saturation of the impact of undergoing interviews, which involve intensive personal inventories of high-risk behaviors, or other factors. It may also be that some IDUs escaped HBV infection because their social network for sharing injection equipment did not include anyone capable of transmitting HBV. Although it is not possible to disentangle the potential effects in this analysis, this observation highlights the need for appropriate nonintervention comparison groups when using incidence data as an outcome measure for evaluating interventions [1].

In summary, while on an individual level HBV seroconversion predicted subsequent HIV infection among male IDUs, the temporal trends in the incidence rates and the risk groups for HBV and HIV were different. Hence, while HBV infection may predict a proportion of drug injectors at risk for HIV, differences in transmission dynamics, the observation of substantial HIV transmission in the absence of prior HBV infection, and the lack of correlation between HBV and HIV incidence rates over time indicate that HBV infection is likely to be of limited utility as a surrogate for HIV infection among IDUs. However, the high incidence of HBV infection in this sample of IDUs at risk for HBV highlights the importance of prevention of HBV infections among IDUs. Risk factor data from an earlier cross-sectional study of HBV infection [15] suggest that transmission of HBV in this population of drug injectors occurs primarily by the parenteral route. Thus, HBV infection itself is an appropriate outcome measure for evaluation of needle-exchange programs.

Acknowledgments

We thank Ellen Taylor for providing laboratory support and Kate, Nicole, and Karen Robbins-Browne for assistance with data management.

References