

# A Prospective Study of Syphilis and HIV Infection among Injection Drug Users Receiving Methadone in the Bronx, NY

## ABSTRACT

**Objectives.** The purpose of this study was to assess the relationship between syphilis and human immunodeficiency virus (HIV) infection in injection drug users.

**Methods.** A 6-year prospective study of 790 injection drug users receiving methadone maintenance treatment in the Bronx, NY, was conducted.

**Results.** Sixteen percent (4/25) of HIV-seroconverting patients, 4.8% (16/335) of prevalent HIV-seropositive patients, and 3.5% (15/430) of persistently HIV-seronegative patients were diagnosed with syphilis. Incidence rates for early syphilis (cases per 1000 person-years) were 15.9 for HIV-seroconverting patients, 8.9 for prevalent HIV-seropositive patients, and 2.9 for persistently HIV-seronegative patients. Early syphilis incidence was higher among women than men (8.4 vs 3.2 cases per 1000 person-years). Independent risks for early syphilis included multiple sex partners, HIV seroconversion, paid sex, and young age. All HIV seroconverters with syphilis were female.

**Conclusions.** Diagnosis of syphilis in drug-using women reflects high-risk sexual activity and is associated with acquiring HIV infection. Interventions to reduce the risk of sexually acquired infections are urgently needed among female drug users. (*Am J Public Health.* 1996;86:1112-1115)

Marc N. Gourevitch, MD, MPH, Diana Hartel, DrPH, Ellie E. Schoenbaum, MD, Peter A. Selwyn, MD, MPH, Katherine Davenny, MPH, Gerald H. Friedland, MD, and Robert S. Klein, MD

### Introduction

Heterosexual transmission of the human immunodeficiency virus (HIV) is an increasingly important problem among injection drug users and women.<sup>1-3</sup> Injection drug users and users of crack cocaine are also at substantial risk for syphilis.<sup>4-11</sup> The exchange of sex for money or drugs, common among drug users,<sup>3</sup> is an independent risk factor for syphilis infection.<sup>4</sup> To examine the potential relationship of sexual behavior to HIV transmission among drug users, we undertook a prospective study of the relationship between syphilis incidence, prevalent and incident HIV infection, and sexual activity in a cohort of current and former injection drug users.<sup>2,12</sup>

### Methods

Since 1985, we have been conducting a longitudinal study of HIV infection among injection drug users enrolled in a methadone maintenance program with on-site primary medical care in the Bronx, NY.<sup>2,12</sup> In this cohort study, syphilis infection and treatment history, along with drug use and sexual behavior, are assessed at baseline. Serum is analyzed for HIV antibody by enzyme immunoassay, with Western blot confirmation. Follow-up interview and laboratory data are collected semiannually. Data from patients during the time in which they were enrolled in the methadone program (for a minimum of 3 consecutive months) from July 1985 through April 1991 were analyzed.

Mandatory annual medical evaluations of methadone maintenance patients include determination of syphilis history and serology. Patients suspected clinically

of having syphilis while receiving on-site medical care also undergo serologic testing for syphilis. Specimens reactive to a nontreponemal test (automated reagin test or rapid plasma reagin) undergo a treponemal test (fluorescent treponemal antibody absorption test or microhemagglutination assay for antibodies to *Treponema pallidum*). Patients with reactive serologies are staged and treated if indicated. HIV and sexually transmitted disease prevention counseling is provided at research visits, annual physical examinations, and intermittently during the course of medical care.

We reviewed the research database and methadone program medical records of all patients who (1) reported a new history of syphilis since a previous interview, (2) demonstrated reactive serologic tests for syphilis, or (3) received on-site treatment for syphilis. Data were abstracted concerning history and prior treatment of syphilis, number of sexual partners per interview period, exchange

Marc N. Gourevitch, Diana Hartel, Ellie E. Schoenbaum, and Robert S. Klein are with the Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY. At the time of the study, Peter A. Selwyn, Katherine Davenny, and Gerald H. Friedland were with the Montefiore Medical Center, Albert Einstein College of Medicine. Peter A. Selwyn and Gerald H. Friedland are now with Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Conn. Katherine Davenny is now with the National Institute on Drug Abuse, National Institutes of Health, Rockville, Md.

Requests for reprints should be sent to Marc N. Gourevitch, MD, MPH, Department of Epidemiology and Social Medicine, Montefiore Medical Center, 111 E 210th St, Bronx, NY 10467.

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of sex for money, serologic studies, and initial date of confirmed HIV infection.

Patients with both reactive nontreponemal and treponemal tests on at least one serum specimen were considered syphilis case patients. Case patients were considered "incident" if they developed clinical and serologic evidence of primary or secondary syphilis (according to standard criteria<sup>13</sup>) or had reactive nontreponemal and treponemal tests within 1 year of prior negative syphilis serologic tests in the absence of clinical findings (early latent cases<sup>13</sup>). Case patients were considered "prevalent" if their syphilis serologic tests were reactive at baseline and they denied prior treatment (late latent cases).

Subjects were classified as HIV seronegative if a negative HIV test was documented 6 months or more following their date of syphilis diagnosis and HIV seropositive if they had a documented positive HIV test result prior to or within 6 months after their diagnosis of syphilis. Date of HIV seroconversion was defined as midway between the last negative and first positive HIV test.

Two-tailed chi-square or Fisher's exact tests were used in comparisons of proportions. Standard methods were used in calculating odds ratios, rate ratios, and associated confidence intervals (CIs).<sup>14</sup> All *P* values (given for two-tailed tests) were considered significant at the .05 level.

Logistic regression analyses were conducted to identify factors independently associated with syphilis.<sup>15</sup> Interactions between variables were tested, and models were assessed for goodness of fit. Adjusted odds ratios and their 95% confidence intervals were generated on the basis of regression coefficients and their variances.

Standard methods<sup>14</sup> (citywide rates of early syphilis by age and sex for 1990 [S. Rubin, New York City Dept of Health, written communication, December 1994]) were used in calculating the standardized morbidity ratio for early (primary, secondary, and early latent) syphilis in the cohort vs New York City overall.

## Results

Characteristics of longitudinal study participants and their demographic similarity to nonparticipants have been described previously.<sup>2,12,16</sup> Of 790 subjects with HIV serology results, 430 (54%) were HIV seronegative and 360 (46%) were HIV seropositive (including 25 HIV seroconverters). The average follow-up

**TABLE 1—Syphilis Occurrence over 6 Years among 790 Injection Drug Users in the Bronx, NY, by HIV Status, Sociodemographic Characteristics, and Sexual Risk Behaviors**

	Syphilis Cases		Odds Ratio	95% CI	<i>P</i>
	No.	%			
<b>HIV antibody status</b>					
Seroconverter	4/25	16.0	5.3	1.6, 17.3	.03
Prevalent positive	16/335	4.8	1.4	0.7, 2.9	
Persistent negative	15/430	3.5	1.0	Reference	
<b>Age at first interview<sup>a</sup></b>					
18–25 y	6/49	12.2	4.3	1.4, 12.6	.01
26–35 y	20/457	4.4	1.4	0.6, 3.1	
36 or older	9/284	3.2	1.0	Reference	
<b>Gender</b>					
Female	21/366	5.7	1.8	0.9, 3.7	.10
Male	14/424	3.5			
<b>Multiple sex partners</b>					
Yes	27/448	6.0	2.7	1.2, 6.0	.02
No	8/342	2.3			
<b>Paid sex</b>					
Yes	16/153	10.4	3.8	1.9, 7.6	<.001
No	19/637	3.0			

Note. Prevalent and incident syphilis cases are considered together in this table. Additional variables examined but not reaching statistical significance included education, income, homelessness, race/ethnicity, and marital status. HIV = human immunodeficiency virus; CI = confidence interval.

<sup>a</sup>OR = 3.43 (95% CI = 1.10, 8.99) for risk of syphilis among subjects ≤25 years of age compared with those >25.

times for HIV-seronegative and HIV-seropositive subjects were 4.1 and 3.6 years, respectively. Fifty-two percent of the subjects described themselves as Hispanic (mainly Puerto Rican), 25% described themselves as White, and 23% described themselves as African American. Most participants (68%) were on public assistance or had an income of less than \$10 000 annually.

Thirty-five of the 790 subjects met the case definition for prevalent (*n* = 18) or incident (*n* = 17) syphilis. The occurrence of syphilis (both prevalent and incident) by selected characteristics is shown in Table 1. Among subjects who were HIV seronegative at study entry, those undergoing HIV seroconversion were significantly more likely to be diagnosed with syphilis than those remaining HIV seronegative. All of the 4 seroconverters with syphilis, as compared with 9 of the 21 without syphilis, were women. Subjects with syphilis who underwent HIV seroconversion did so prior to or in the interview period immediately following diagnosis with syphilis. Age at first interview was the only sociodemographic variable significantly associated with syphilis.

As a means of studying incident syphilis more precisely, the 18 newly identified cases of latent syphilis of unknown duration were excluded. Seventeen cases of early (primary, secondary, or early latent) syphilis were diagnosed during 2981 person-years of follow-up, yielding an unadjusted rate of 5.7 cases per 1000 person-years. The age- and sex-adjusted standardized morbidity ratio of early syphilis in the study population vs New York City as a whole was 2.3 (95% CI = 1.32, 3.56).

Stratified by HIV status, syphilis incidence rates (in cases per 1000 person-years) were 15.9 for HIV-seroconverting subjects, 8.9 for prevalent HIV-seropositive subjects, and 2.9 for persistently HIV-seronegative subjects (Table 2). Women were at greater risk for incident syphilis than men (8.4 vs 3.2 per 1000 person-years; *P* = .06). Age at interview, being paid or paying for sex, and multiple sex partners (more than one partner during the interview periods preceding syphilis diagnosis) were also strongly associated with syphilis incidence (Table 2).

In a logistic regression analysis, paid sex and multiple sex partners were inde-

**TABLE 2—Syphilis Incidence over 6 Years among 772 Injection Drug Users in the Bronx, NY, by HIV Status, Sociodemographic Characteristics, and Sexual Risk Behaviors**

	No. Syphilis Cases	Cases/1000 Person-Years	Rate Ratio	95% CI	P
<b>HIV antibody status</b>					
Seroconverter	2/23	15.9	5.5	1.1, 28.2	.03
Prevalent positive	10/329	8.9	3.1	1.1, 9.0	
Persistent negative	5/420	2.9	1.0	Reference	
<b>Age at first interview</b>					
18–25 y	3/46	18.8	4.7	1.1, 21.0	.04
26–35 y	10/447	5.5	1.4	0.4, 4.4	
36 y or older	4/279	4.0	1.0	Reference	
<b>Gender</b>					
Female	12/357	8.4	2.6	0.9, 7.5	.056
Male	5/415	3.2			
<b>Multiple sex partners</b>					
Yes	16/437	8.6	9.6	1.3, 72.1	.002
No	1/335	0.9			
<b>Paid sex</b>					
Yes	9/146	16.2	4.9	1.9, 12.7	.002
No	8/626	3.3			

Note. HIV = human immunodeficiency virus; CI = confidence interval.

**TABLE 3—Variables Independently Associated<sup>a</sup> with Incident Syphilis among 772 Injection Drug Users in the Bronx, NY**

	Adjusted Odds Ratio	95% CI	P
HIV seroconverter <sup>b</sup>	6.39	1.1, 37.9	.04
Multiple sex partners	9.70	1.3, 74.7	.03
Paid sex	3.51	1.3, 9.5	.01
Age ( $\leq 25$ y vs $> 25$ y)	3.61	0.9, 14.2	.06

Note. HIV = human immunodeficiency virus; CI = confidence interval.

<sup>a</sup>Logistic regression model, overall chi square for goodness of fit,  $P < .001$ .

<sup>b</sup>Adjusted for initial HIV status (included in model but not statistically significant: OR = 2.62, 95% CI 0.86–7.96).

pendent predictors of incident syphilis (Table 3). Age was of borderline significance, and gender was not independently associated in this model. Tests of the interaction between gender and HIV risk behavior were undertaken but did not appreciably change the model. HIV seroconversion remained an independent predictor of incident syphilis after adjustment for initial HIV serologic status.

## Discussion

Syphilis was significantly associated with HIV seroconversion, both when prevalent and incident syphilis cases were considered together and when incident cases were analyzed separately. We believe that our data are the first to relate incident HIV infection and incident syphi-

lis in a population-based sample of drug users.

It is unlikely that syphilitic genital ulcer disease facilitated HIV infection<sup>17,18</sup> in these patients. HIV seroconversion preceded syphilis diagnosis in three of four seroconverters with syphilis. The patient diagnosed with syphilis during the period in which she seroconverted to HIV had late latent syphilis, suggesting that syphilis was acquired prior to HIV infection.

The association between HIV seroconversion and syphilis diagnosis in this study population is best explained behaviorally. The exchange of sex for money or drugs, especially in the context of crack cocaine use, places women in particular at high risk for sexually acquired infections.<sup>10,11,19–22</sup> Women were at greater risk

for incident syphilis than men, and all four seroconverters with syphilis were women. Among HIV-seronegative women, acquisition of syphilis may therefore be viewed as a marker of high risk for incident HIV infection. Our findings highlight drug-using women's high risk of acquiring HIV as a sexually transmitted disease, and underscore the importance of developing effective means by which these women may protect themselves from sexually transmitted diseases, including HIV.<sup>23–25</sup>

Despite the clear association in our data between incident HIV infection and syphilis, we did not find the same level of association between prevalent HIV infection and syphilis infection. We attribute the weakness of this association largely to the absence of a single common risk behavior for both infections in the study population. Most subjects had a history of injection drug use, a more powerful risk for HIV infection than sexual behavior in this population,<sup>2</sup> while only a subgroup of HIV-infected and HIV-uninfected subjects engaged in risk-conferring sexual behavior. In comparison, studies reporting an association between prevalent HIV infection and syphilis have been based on populations of homosexual men or sexually transmitted disease clinic patients, among whom HIV and syphilis share a single common route of transmission.<sup>19,26–28</sup> Indeed, one study of injection drug users found syphilis and HIV infection to be significantly associated only among homosexual and bisexual men.<sup>29</sup> Another, based in a sexually transmitted disease clinic in the Bronx, found that syphilis and HIV infection were associated among women without other identifiable risk behaviors (e.g., among women who were not injection drug users).<sup>7</sup> Needle sharing probably does not play a significant role in syphilis transmission, but this issue remains unresolved.<sup>30</sup>

Our use of prospectively identified cases of early syphilis reflects an improvement in the study of the epidemiology of syphilis among drug users. We compared the results of our logistic regression analysis restricted to incident (early) cases (Table 2) with a similar analysis (data not shown) that included incident as well as prevalent (late latent) syphilis (as is done in most studies). The incident case model differed from the mixed-case model in two important ways: all point estimates were greater in the incident model, and an important risk factor (multiple sex partners) showed an independent effect not found when prevalent cases were included, despite the larger number of

cases. To date, studies of syphilis epidemiology among drug users have not distinguished incident from prevalent cases and may therefore have underestimated or not detected risks associated with acquisition and transmission of syphilis.<sup>3,9,29</sup>

Our data have several limitations. The number of syphilis cases is modest. Information on the cumulative number of different sex partners per subject and the exchange of sex for drugs was not available. However, qualitative data obtained (not shown) suggest that exchange of sex for drugs was highly correlated with sex-for-money exchange, which we have reported here. Four subjects with syphilis were first tested for HIV within 6 months following syphilis diagnosis and found to be HIV seropositive. It is most likely that none had seroconverted to HIV within these 6 months. If any had, however, this would only have caused us to underestimate the HIV seroconversion rate among patients with syphilis. Finally, our syphilis patients were all receiving methadone treatment. The syphilis incidence rates we report may therefore be lower than those for out-of-treatment drug users, among whom risk-conferring behaviors may be more common.<sup>31</sup> However, we do not believe that these limitations biased our analyses or conclusions.

In summary, we identified a group of injection drug users at high risk for acquisition of syphilis and HIV infection. These findings underscore the need for targeting preventative services at drug users, particularly women, at high risk for acquiring sexually transmitted diseases, including HIV. Our data may also prove useful in identifying those HIV-seronegative patients at high risk for seroconversion who might be most likely to benefit from current and future interventions. □

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