ELSEVIER

Assessment of Sexually Transmitted Diseases as Risk Factors for HIV Seroconversion in a New Orleans Sexually Transmitted Disease Clinic, 1990–1998

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PURPOSE: This investigation examined the role of ulcerative and non-ulcerative sexually transmitted diseases (STDs) in increasing susceptibility to HIV seroconversion in a large population of uninfected and predominantly heterosexual persons attending a New Orleans STD clinic.
METHODS: A retrospective cohort of clients with repeat HIV tests between January 1990 and April 1998 was constructed using three independent sources of information. Multivariate Cox regression was used to identify risk factors for HIV seroconversion while controlling for the effects of behavioral risk factors. A time-dependent covariate for STD allowed HIV seroconversion to be examined in relation to the timing of STD diagnosis.
RESULTS: Having a recent syphilis or GUD diagnosis was associated with significantly increased hazards of seroconversion (among men: hazard ratio [HR], 4.2 [2.4–7.2]; among women: 5.0 [1.9–13.0]). Among men with no history of GUD or syphilis, those with recent gonorrhea within 1 year prior to seroconversion were 2.8 (1.5–5.2) times as likely to seroconvert.
CONCLUSIONS: This study suggests that both ulcerative and non-ulcerative STD may be associated with increased risk of HIV transmission and therefore comprehensive STD control strategies may be particularly effective tools for HIV prevention.
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KEY WORDS: Gonorrhea, Heterosexuality, HIV Infections, HIV Seroprevalence, Longitudinal Studies, Proportional Hazards Models, Sexually Transmitted Diseases.

INTRODUCTION

The vast majority of HIV infections worldwide are acquired through sexual contact. Numerous studies conducted in many populations with varied definitions of sexually transmitted disease (STD) exposure and varying degrees of control for behavioral risks have found that other STDs are associated with a greater risk of HIV infection in uninfected persons. Observed relative risks for HIV infection associated with syphilis and other genital ulcer disease (GUD) range between 2 and 11, with the strongest evidence to date reported from studies conducted in Africa (1–13). In contrast, convincing studies demonstrating an association between non-ulcerative STDs and HIV transmission are far less common. Two well-designed longitudinal studies conducted among commercial sex workers in Africa found relative risks associated for gonorrhea and chlamydia of 2.3 and 2.7, respectively (4, 5), whereas a third study found no association (14).

While it has become widely accepted that STDs may facilitate HIV transmission to some degree (15), epidemiologic studies of longitudinal data are necessary to determine with any certainty whether an STD exposure of interest is likely to have preceded HIV infection. Relatively few such studies exist in the US, with even fewer in predominantly heterosexual populations. In addition, these studies have been limited by inherent difficulties in identifying HIV seroconverters, low power due to low prevalence of ulcerative STDs (10, 16), and the availability of reliable data on the assessment and timing of STD exposures (13, 17). Taken altogether, such methodological issues make epidemiologic findings on the STD–HIV relationship more difficult to interpret definitively.

The purpose of this study was to examine the role of ulcerative and non-ulcerative STDs in increasing susceptibility to HIV seroconversion in uninfected persons while controlling for demographic and behavioral risk factors. Important distinctions of this investigation include the longitudinal study design providing information on

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Selected Abbreviations and Acronyms

AIDS = acquired immune deficiency syndrome
CI = confidence interval (95%)
GUD = genital ulcer disease
HIV = human immunodeficiency virus
HR = hazard ratio
IDU = injection drug users
MSM = men who have sex with men
NGU = non-gonococcal urethritis
RR = relative risk

seroconversion, a large, US-based predominantly heterosexual and routinely screened population, the availability of limited behavioral measures, and the use of well-defined reference groups for exposures that considered the timing of STD diagnosis in relation to seroconversion.

MATERIALS AND METHODS

This investigation is a retrospective cohort study of STD clinic patients attending a public sexually transmitted disease clinic located in New Orleans from 1990 to 1998. The clinic serves a predominantly low-income, African-American population and provides free STD-related services, including routine STD screening and treatment, partner notification, STD/HIV prevention education, HIV counseling and testing, and referrals to other services. Patients are routinely screened for syphilis, gonorrhea, and chlamydia unless they are attending the clinic for a follow-up visit. HIV tests are offered on a voluntary basis to all clinic patients not HIV tested in the previous 90 days.

Between January 1, 1990 and April 30, 1998, the clinic recorded 98,824 patient visits, corresponding to 54,855 individuals. Initially HIV-negative individuals presenting with a new STD-related condition who subsequently returned to the clinic and received at least one additional HIV test were eligible for inclusion into the study population. Patient demographics, HIV test results, STD diagnoses, STD history, and risk behavior information were gathered using three independent linkable sources: counseling and testing data from the Louisiana HIV/AIDS Program, the state registry of STD case reports from the Louisiana STD Control Program, and clinic patient and visit database residing at the clinic. Table 1 presents the diagnostic approaches used at the clinic. Because data were merged from three independent sources, there was great potential to detect and correct discrepancies within and between clinic visits. Discrepancies in the data were resolved by ongoing medical record review at the clinic. In addition, the visit dates and HIV test results of all suspected seroconversions were confirmed by medical record review.

Behavioral risk information was collected in the context of routinely-offered voluntary HIV counseling and testing. Risk behaviors since 1978 were assessed during confidential pre-test counseling sessions and subsequently classified according to the Centers for Disease Control and Prevention standard risk categories: men reporting sex with men (MSM), injection drug use (IDU), sex with HIV-infected partner, sex with an injection drug user, and sex with a bisexual male (for females). An additional risk category was added to assess association with commercial sex work: exchanging money or drugs for sex. Multiple risk behaviors per counseling episode were recorded. Study subjects were considered to have a risk behavior if that behavior was ever reported during the study period.

Univariate HIV incidence was calculated as incidence density, computed as the number of seroconverters divided by the total person-time of observation. Person-time of follow-up observation for each eligible subject was measured from the time of first HIV test to the last negative or first positive test recorded. Seroconverters could contribute HIV-negative follow-up time provided they had multiple negative tests before seroconversion. Confidence intervals for incidence density ratios were computed by Taylor's series expansion.

TABLE 1. Diagnostic approaches and tests for HIV and STD during study period

Condition*	Diagnostic approach and tests
HIV seroconversion	Enzyme-linked immunosorbant assay (ELISA) confirmed by western blot; first positive HIV test preceded by a negative test during the study period
Non-ulcerative STDs	
Gonorrhea	Culture of cervical or urethral specimens from 1990–1994 and by DNA probe tests beginning in 1994
Chlamydial infection	DNA probe tests of urethral or cervical specimens beginning in 1994
Non-gonococcal urethritis (NGU)	Urethral discharge on exam in men only with negative tests for gonorrhea and chlamydia
Ulcerative STDs	
Syphilis (recorded in four stages: primary, secondary, early latent, late latent)	Combination of VDRL and microhemaglutination for *Treponema pallidum* (MHA-TP) serologic tests, clinical examination, and history of past treatment for syphilis.
Genital ulcer disease (GUD)	Culture of ulcer exudates or by clinical presentation with no syphilis diagnosis

*Other STDs not in this table were not consistently diagnosed or recorded and were not considered in this investigation.

Multivariate analyses to identify predictors of seroconversion were performed using Cox's proportional hazards methods with time-dependent covariates (using SAS procedure PHREG). For seroconverters, time of seroconversion was estimated as the midpoint of the seroconversion interval. For all others, censoring occurred at the time of the last negative test recorded.

The selection of variables for inclusion in the multivariate models was guided by evidence from the univariate incidence calculations, with the exception of factors widely known to be associated with risk of HIV. Demographic and behavioral risk information were treated as fixed covariates. Covariates reflecting recent STD status were defined as time-dependent covariates, permitting the timing of STD diagnosis to be examined in relation to HIV seroconversion. Thus, the effects of STDs were assessed during a time interval known to precede estimated seroconversion. The values of time-dependent covariates were assessed at each event time for all individuals not yet censored or seroconverted, using an indicator variable for STD diagnosis in a preceding defined interval. For most analyses, that preceding interval was considered to be 2 years. Among analyses with adequate sample size, the interval was also reduced to the preceding year to explore the effects of STDs under a more restricted and more precise time period.

Due to the large number of time-dependent covariates that would be necessary to account precisely for the recent STD experience of each individual, the analysis was conducted in two steps in an effort to disentangle the effects of the various STDs. The first step involved constructing overall models to establish which broad groupings of recent STD types were associated with seroconversion. These broad groupings were: 1) recently diagnosed non-ulcerative STDs only, and 2) any recently diagnosed syphilis or GUD.

Without well-defined reference groups in studies of STD clinic clients, non-ulcerative STDs may appear protective if the reference group includes those with syphilis or GUD diagnoses. To prevent this spurious finding, the second step consisted of separate analyses on two subsets of the study sample: those subjects with any history of syphilis or GUD diagnoses (the "ulcerative STD history" subset) and those with no evidence of syphilis or GUD in the entire study period (the "no ulcerative STD history" subset). Analysis of the latter subset permitted estimation of the increased seroconversion risk associated with non-ulcerative STDs. Analysis of the ulcerative STD history subset permitted estimation of the increased risk associated with specific stages of syphilis according to an assumed hierarchy of ulceration from lowest to highest: no ulcerative STD in interval, latent syphilis, and ulcerative STD. Early latent and late latent syphilis diagnoses were considered together, reflecting the uncertainty surrounding the timing of primary infection in these diagnoses.

RESULTS

Of the 54,855 clients visiting the clinic during the study period, 75% were voluntarily tested for HIV, a percentage that remained relatively stable over the study period. Among those, 10,879 initially HIV-negative clients accepted at least two voluntary HIV tests during the study period, of which the first test result was negative.

Among the 8161 men in the study population (Table 2), gonorrhea was diagnosed most frequently (63%), followed by non-gonococcal urethritis (NGU) (37%), chlamydia (21%), and any stage of syphilis (11%). Among men reporting sex with men, 70% were diagnosed with an STD.

TABLE 2. Correlates of HIV seroconversion rates among repeat HIV testers

Characteristic	N	Sero-converters	Rate/100 person-years	Rate ratio	95% CI
Total	10,879	135	0.49		
Gender					
Men	8,161	106	0.50	1.0	
Women	2,718	29	0.47	1.0	0.6, 1.4
Risk behaviors in men					
No risk	5,848	45	0.31	1.0	
IDU	418	9	0.78	2.5	1.2, 5.2
MSM	491	21	1.52	4.9	2.9, 8.3
Partner of IDU	290	6	0.68	2.2	0.9, 5.2
Partner HIV+	43	0			
Exch. sex for money/drugs	1,791	41	0.76	2.5	1.6, 3.8
Risk behaviors in women					
No risk	2,289	19	0.37	1.0	
IDU	88	2	0.79	2.1	0.5, 9.0
Partner of IDU	152	4	0.97	2.6	0.9, 7.6
Partner HIV+	22	2	3.77	10.1	2.3, 43.1
Exch. sex for money/drugs	220	5	0.82	2.2	0.8, 5.9
Partner of MSM	103	0			
STD history among men					
No STD diagnoses	2,008	10	0.21	1.0	
Gonorrhea	5,154	80	0.56	2.6	1.4, 5.4
NGU	3,058	32	0.35	1.6	0.8, 3.3
Chlamydia	1,704	10	0.19	0.9	0.4, 2.2
Genital ulcer disease	466	19	1.38	6.5	3.0, 13.9
Any syphilis diagnosis	900	35	1.39	6.5	3.2, 13.1
Primary syphilis	439	17	1.35	6.3	2.9, 13.8
Secondary syphilis	142	8	2.11	9.9	3.9, 25.0
Early latent syphilis	254	8	1.19	5.6	2.2, 14.2
Late latent syphilis	102	7	2.15	1.0	3.8, 26.3
STD history among women					
No STD diagnoses	1,029	7	0.31	1.0	
Gonorrhea	1,024	16	0.64	2.0	0.8, 4.9
Chlamydia	765	8	0.46	1.5	0.5, 4.1
Genital ulcer disease	43	1	0.89	2.9	0.4, 23.2
Any syphilis diagnosis	555	11	0.80	2.6	1.0, 6.6
Primary syphilis	44	2	1.95	6.2	1.3, 30.0
Secondary syphilis	224	4	0.70	2.3	0.7, 7.7
Early latent syphilis	243	3	0.50	1.6	0.4, 6.3
Late latent syphilis	74	2	1.04	3.3	0.7, 16.1

Among 2718 women in the study population, gonorrhea (38%), chlamydia (28%), and syphilis (20%) were most common.

Seroconversion among Repeat Testers

During the study period, 135 (1.24%) seroconverted. Of the seroconverters, 78.5% were male and 98.5% were African-American, with a mean age at first clinic visit of 28.0 years (range, 15–62) for men and 23.9 years (range, 14–46) for women. The overall HIV incidence among repeat testers was 0.49 new infections per 100 person-years (Table 2). No differences in HIV incidence were observed between men and women. Several behavioral risk factors were strong predictors of HIV seroconversion in men, including men reporting sex with men (MSM) with a risk ratio (RR) of 4.9 (95% confidence interval [CI], 2.9, 8.3), injection drug use (IDU) (RR, 2.5; CI, 1.2, 5.2), and exchanging money or drugs for sex (RR, 2.5; CI, 1.6, 3.8). Among women, several risk behaviors were associated with elevated risk but only heterosexual contact with an HIV-infected partner was particularly strongly associated with seroconversion (RR, 10.1; CI, 2.3, 43.1). HIV incidence appeared to increase with age at first visit in men but not in women (data not shown). Because non-African-Americans represented only a small percentage of study subjects, race variables were not included in any subsequent analyses.

Men with gonorrhea were 2.6 times more likely to seroconvert than those with no STD diagnoses (CI, 1.4, 5.4). NGU and chlamydia were not significantly associated with seroconversion in men or women in the univariate analyses. Ulcerative STDs were strongly associated with seroconversion in men, with rate ratios for early syphilis or GUD above 6. Among women, incidence was elevated in all categories of syphilis, however only a history of primary syphilis was statistically significantly associated with an increase in risk of HIV seroconversion (RR, 6.2; CI, 1.3, 30.0).

Multivariate Analysis

Risk variables were dropped from the model if no seroconverters reported the risk. All fixed variables were checked for violations of the proportional hazards assumption by considering a time by covariate interaction term, all of which were not significant in the final models. Due to limitations in sample size for the females, only the 2-year interval for assessing recent STD exposure was considered.

In the overall models (Table 3), men reporting sex with men (hazard ratio [HR], 3.3 for 2-year interval; CI, 2.0, 5.3) and exchanging money or drugs for sex (HR, 1.5; CI, 1.0, 2.3) were significant covariates for increased hazard of seroconversion. Men with a recent syphilis or GUD diagnosis were significantly more likely to seroconvert than those with no STD diagnoses in the interval (HR, 4.2; CI, 2.4, 7.2). Men with only recent non-ulcerative STD diagnoses were not at increased risk of seroconversion. When reducing the interval from 2 years to 1 year, however, non-ulcerative STDs in the shorter interval had a slightly

TABLE 3. Cox's proportional hazards ratios for HIV seroconversion (with 95% confidence intervals) with time-dependent covariates for STD exposure: Overall models comparing STD diagnosis to no STD diagnosis during preceding intervals of 2 and 1 years

	With interval of previous 2 years		With interval of previous 1 year	
Characteristic	Hazard ratio	95% CI	Hazard ratio	95% CI
Men (n = 8044 repeat testers, 106 seroconverters)				
Age at first clinic visit	1.0	1.0, 1.0	1.0	1.0, 1.0
Male sex with male	3.3	2.0, 5.3	3.3	2.1, 5.4
Injecting drug use	0.9	0.4, 2.0	0.9	0.5, 2.0
Sex with IDU	0.7	0.3, 1.7	0.8	0.3, 2.0
Exch. money/drugs for sex	1.5	1.0, 2.3	1.6	1.0, 2.4
STD history within interval (compared to no STD exposure during interval)				
Non-ulcerative STD*	0.9	0.6, 1.3	1.4	0.9, 2.3
Any syphilis or GUD	4.2	2.4, 7.2	4.7	2.1, 10.2
Women (n = 2679 repeat testers, 29 seroconverters)				
Age at first clinic visit	1.0	1.0, 1.1		
Sex with HIV+ partner	9.5	2.1, 42.5		
Injecting drug use	0.7	0.1, 3.6		
Sex with IDU	2.0	0.6, 7.2		
Exch. money/drugs for sex	1.5	0.5, 4.6		
STD history within interval (compared to no STD exposure during interval)				
Non-ulcerative STD*	0.9	0.3, 3.1		
Any syphilis or GUD	5.0	1.9, 13.0		

*Non-ulcerative STD includes gonorrhea and chlamydia diagnoses for both men and women and NGU diagnosis for men only.

elevated hazard of seroconversion, although the association was not statistically significant (HR, 1.4; CI, 0.9, 2.3).

In the model among women, the behavioral covariate of "sex with an HIV-infected partner" was the only covariate associated with an increased hazard of seroconversion (HR, 9.5; CI, 2.1, 42.5). Those women with only a non-ulcerative STD diagnosis in the preceding 2 years were not at increased hazard of seroconversion (HR, 0.9; CI, 0.3, 3.1). Those with a syphilis or GUD diagnosis in the preceding 2 years were significantly more likely to seroconvert than those with no STD diagnoses in the interval (HR, 5.0; CI, 1.9, 13.0).

No Ulcerative STD History Subgroup. The "no ulcerative STD history" subset restricted analysis to clients with no history of GUD or syphilis in the entire study period (Table 4). Overall, non-ulcerative STD history in the preceding 2 years was not associated with increased hazard of seroconversion in this group (HR, 1.1; CI, 0.6, 1.9). When reducing the interval to preceding 1 year, however, men with any recent non-ulcerative STD diagnosis had a significantly higher hazard of seroconversion than those without a diagnosis in that period (HR, 2.8; CI, 1.5, 5.2). The point estimate of the hazard of seroconversion for women with a non-ulcerative STD in the preceding 2 years was substantially protective although not significant (HR, 0.3; CI, 0.0, 2.6).

Evidence from the literature suggests that among the non-ulcerative conditions documented in this study, gonorrhea warrants the most careful attention as a potential risk factor for seroconversion. Therefore, models were rerun comparing those with a gonorrhea diagnosis in the preceding interval to those without gonorrhea in that time period.

Among men, gonorrhea in the preceding 2 years was not significantly associated with increased hazard of seroconversion (HR, 1.4; CI, 0.8, 2.5). Under the more restrictive 1-year interval, men with a gonorrhea diagnosis had an increased hazard of seroconversion than those with no gonorrhea (HR, 2.8; CI, 1.5, 5.2). Among women, gonorrhea was not significantly associated with increased hazard of seroconversion (HR, 0.6; CI, 0.1, 4.9) in the preceding 2-year interval.

The "Ulcerative STD History" Subgroup. The "ulcerative STD history" subgroup was restricted to those with a history of syphilis (any stage) or GUD at any time during the study period (Table 5). Models in this subset compared three groupings of possible STD history in the preceding 2 years: those with any ulcerative STD diagnoses (primary or secondary syphilis or GUD), and those with early latent or late latent syphilis, compared with the remaining individuals with no syphilis or GUD diagnoses in the time interval.

Men with an ulcerative STD diagnosis in the preceding 2 years had a significantly increased hazard of seroconversion compared with those with no syphilis or GUD diagnosed in the time interval (HR, 2.1; CI, 1.1, 4.0). The early latent or late latent syphilis diagnosis category was not significantly associated with seroconversion, but did show some evidence a possible positive association (HR, 2.1; CI, 0.7, 5.8). When the time interval for assessing STD exposure was restricted to the preceding 1 year (data not shown), the hazard ratios were comparable in magnitude but not significant.

Women with an ulcerative STD in the preceding 2 years had a significantly increased hazard of seroconversion compared with those with no syphilis or GUD diagnosed in the time interval (HR, 6.7; CI, 1.6, 27.8). Those with early latent or late latent syphilis diagnosis in the preceding 2 years were also at increased hazard of seroconversion (HR, 7.4; CI, 1.7, 31.1).

DISCUSSION

This investigation demonstrated a substantial increased risk of HIV seroconversion in persons with ulcerative STDs and suggestive evidence of smaller increases in the risk of seroconversion in persons with non-ulcerative STDs after controlling for demographic and behavioral risk factors. The overall HIV incidence estimate of 0.49 seroconversions per 100 person-years was comparable in magnitude to other studies conducted among repeat testers in STD clinic settings (10, 11, 13).

When broad groupings of STDs were considered, a recent syphilis or GUD diagnosis in the preceding 2 years was strongly associated with HIV seroconversion in both men and women, with hazard ratios of 4.2 and 5.0, respectively. When the period of assessment of STD exposure in men was reduced to 1 year, recent syphilis or GUD remained a strong predictor. Considering the STD exposure experience of the entire population at risk, the overall models were comparable to methods used and results obtained in other longitudinal studies (10, 12). Although using a 2- and 1-year time interval before seroconversion substantially increases the interpretability of STDs on HIV susceptibility, the study is limited by the inability to observe whether the STD was present when HIV was acquired or whether the partner transmitted HIV and STD simultaneously. In this study, increased infectivity of the unobserved partner with both an STD and HIV would appear as increased susceptibility (biased away from the null) for HIV seroconverters diagnosed with an STD but biased toward the null for those without an STD.

The additional restriction of the analyses to distinctively different subsets, one of persons with a history of syphilis or GUD and one of persons without, facilitates isolating the effect of timing and type of STD diagnosis on risk of HIV seroconversion. With the acknowledged limitations of risk behavior information, this restriction minimized the effect of unmeasured risk factors common to these STDs, reducing

TABLE 4. Cox's proportional hazards ratios for HIV seroconversion with time-dependent covariates for STD exposure among clients with a history of only non-ulcerative STD: models comparing STD diagnosis (all non-ulcerative STD; gonorrhea only) to no STD diagnosis during preceding intervals of 2 and 1 years

	All non-ulcerative STD model				Gonorrhea only model			
	2-year interval		1-year interval		2-year interval		1-year interval	
Characteristic	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Men (n = 6470 repeat testers, 50 seroconverters)								
Age at first clinic visit	1.0	1.0, 1.0	1.0	1.0, 1.0	1.0	1.0, 1.0	1.0	1.0, 1.0
Male sex with male	3.0	1.5, 6.3	3.1	1.5, 6.5	3.1	1.5, 6.4	3.1	1.5, 6.6
Injecting drug use	1.4	0.5, 4.3	1.4	0.5, 4.3	1.4	0.5, 4.3	1.4	0.4, 4.2
Sex with IDU	0.7	0.2, 3.3	0.7	0.2, 3.3	0.7	0.2, 3.4	0.7	0.2, 3.3
Exch. money/drugs for sex	1.6	0.9, 3.0	1.6	0.8, 2.9	1.6	0.8, 3.0	1.6	0.8, 3.0
STD history within interval (compared to no STD exposure during interval)								
Non-ulcerative STD*	1.1	0.6, 1.9	2.2	1.2, 3.9				
Gonorrhea diagnosis					1.4	0.8, 2.5	2.8	1.5, 5.2
Women (n = 1813 repeat testers, 16 seroconverters)								
Age at first clinic visit	1.0	0.9, 1.1			1.0	0.9, 1.1		
Sex with HIV+ partner	10.9	1.2, 95.6			11.6	1.3, 101.7		
Sex with IDU	1.0	0.1, 9.6			1.0	0.1, 9.0		
Exch. money/drugs for sex	0.7	0.1, 6.1			0.8	0.1, 6.4		
STD history within interval (compared to no STD exposure during interval)								
Non-ulcerative STD*	0.3	0.0, 2.6						
Gonorrhea diagnosis					0.6	0.1, 4.9		

*Non-ulcerative STD includes gonorrhea and chlamydia diagnoses for both men and women and NGU diagnosis for men only.

residual confounding and enhancing validity (18, 19). The finding that ulcerative STD diagnoses within a previous recent time interval were associated with a two- to sevenfold increased risk of seroconversion is strong evidence of a true relationship, particularly given the homogeneity of the ulcerative STD history subset. The role of ulcerative STDs in men was still evident using a later, more conservative estimate of time of seroconversion.

The role of non-ulcerative STDs in HIV acquisition was less clear. The increased risk of 2.8 (CI, 1.5, 5.2) among men with a gonorrhea diagnosis was similar to the hazard ratio of 2.3 obtained in Laga's 1994 study in Kinshasa, in which precise timing of STD exposure and use of time-dependent STD covariates were applied as well (4). Even though the magnitude of the association between gonorrhea and HIV infection was far smaller than that for ulcerative STDs, the high prevalence of gonorrhea in many populations suggests that gonorrhea may potentially be responsible for more HIV transmission than less common ulcerative conditions.

An important finding was that MSM consistently remained a strong risk factor for incident HIV infection in the multivariate models among men. In general, risk behaviors are an important consideration in any study of STD and HIV infection because these infections share similar modes of transmission and behavioral risk factors and can serve as markers of unprotected sex. Although residual confounding from underreported and other unmeasured risk behaviors (e.g., the number of partners, frequency of partner change, condom use) limits the potential for controlling for confounding, it is reasonable to expect that the available data on risk may be reliable given the context of repeated counseling and risk assessment. Coupled with the controlling for individual behavioral characteristics, the grouping of the study population into ulcerative and no ulcerative STD histories provided further control for unobserved direct effects by making subgroups more homogeneous with respect to high risk behaviors and to some extent social networks.

While we believe that this study contributes to the evidence of the biological effect of STDs on HIV susceptibility while controlling for various behavioral factors, the residual confounding from behavioral factors not directly observed in this study precludes a definitive distinction between the biological and the behavioral relationship of STDs on HIV susceptibility. To clearly distinguish between the biological and the behavioral relationship, one would need to observe comprehensively and precisely behavioral factors in a large population of discordant couples and contacts (for example, HIV-positive sex workers and their initially-negative clients) with routine and substantial follow- up for STD assessment, changes in risk behaviors, and HIV status preferably using viral detection tests for immediate identification of transmission. In addition, because the biological impact that STDs may have on HIV transmission in a population may decrease as HIV prevalence increases and the epidemic matures (20), exploring the distinctive social networks with variations in the incidence, prevalence, and initial introduction of HIV

TABLE 5. Cox's proportional hazards ratios for HIV seroconversion with time-dependent covariates for STD exposure (with confidence intervals) among clients with a history of any stage of syphilis and GUD diagnoses: models comparing ulcerative STD diagnosis to no STD diagnosis during preceding interval of 2 years

	With interval of previous 2 years	
Characteristic	Hazard ratio	95% CI
Men (n = 1574 repeat testers, 56 seroconverters)		
Age at first clinic visit	1.0	1.0, 1.1
Male sex with male	3.6	1.9, 7.0
Injecting drug use	0.6	0.2, 1.7
Sex with IDU	0.7	0.2, 2.1
Exch. money/drugs for sex	1.4	0.8, 2.4
STD history within interval (versus no STD during interval)		
Early latent or late latent syphilis	2.1	0.7, 5.8
Ulcerative STD*	2.1	1.1, 4.0
Women (n = 866 repeat testers, 13 seroconverters)		
Age at first clinic visit	1.0	0.9, 1.1
Sex with HIV+ partner	10.8	1.3, 92.8
Injecting drug use	0.9	0.1, 6.3
Sex with IDU	2.6	0.5, 14.3
Exch. money/drugs for sex	2.0	0.5, 8.8
STD history within interval (versus no STD during interval)		
Early latent or late latent syphilis	7.4	1.7, 31.1
Ulcerative STD*	6.7	1.6, 27.8

*Ulcerative STD in these models includes GUD, primary and secondary syphilis diagnosis.

infection may provide an opportunity to examine the effect of the maturity of the HIV epidemic on the contribution of STDs to HIV transmission.

The methodology necessitated the exclusion of clients who were not repeatedly HIV tested. Although clients who were not HIV tested did not differ substantially from those who were tested, all categories of risk and all types of STD diagnoses were higher among repeat testers compared with those tested only once, likely reflecting increased opportunities for HIV testing and risk behavior data collection during new STD visits. In addition, because no active follow-up was conducted and STDs were assessed only at visits to this public clinic, the true frequency of STD are likely to be underestimated, particularly with asymptomatic STDs. Additionally, early latent and late latent syphilis diagnosed after seroconversion may well have been primary syphilis infection at or before seroconversion, yet these diagnoses were not considered as possible exposures, biasing the measures of effect of ulcerative STDs toward the null.

An important methodological consideration distinguishing this investigation from other HIV/STD studies was the use of time-dependent covariates and the designation of a well-defined reference group for STD exposure. Examining exposures within exclusive levels of STD-related risks (ulcerative STD history and no ulcerative STD history) and defining exposure groups and exposure-free reference groups with respect to STD temporality are both important considerations for a study population in which many subjects have had an STD diagnosis at one point in time in their history.

Although the only two randomized community-based trials, both in Africa, show somewhat conflicting results as to whether STD treatment is effective in lowering HIV transmission (21–24), this study contributes to a growing body of evidence that confirm the role of ulcerative and non-ulcerative STD in increasing susceptibility to HIV infection and that treatment and prevention of these curable STDs should be an integral part of comprehensive HIV prevention efforts (25). Lastly, given the current outbreaks of gonorrhea and syphilis, particularly in populations of MSM (26, 27), the public health implications of reducing HIV spread through screening and presumptive treatment of easily-curable STDs in specifically-targeted populations such as MSM should be receive greater consideration in HIV prevention programs.

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