Rectal Gonorrhea and Chlamydia Reinfection Is Associated With Increased Risk of HIV Seroconversion

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Introduction: HIV infection continues to disproportionately affect men who have sex with men (MSM). Identification of modifiable risk factors for HIV infection among MSM is critical for effective prevention.

Methods: We examined the relationship between number of prior rectal *Neisseria gonorrhoeae* (GC) or *Chlamydia trachomatis* (CT) infections and HIV seroconversion in a retrospective cohort of HIV-uninfected MSM diagnosed with a rectal infection. Number of rectal CT or GC infections in the prior 2 years was the primary exposure. Univariate and multivariate Cox proportional hazards models were used to estimate the association between prior rectal infections and HIV seroconversion.

Results: A total of 541 MSM were observed for a total of 1197.96 person-years. Overall, 27 (4.99%) of the MSM became infected with HIV, for an estimated annual incidence of 2.25% [95% confidence interval (CI): 1.49 to 3.26]. In multivariate analysis, an early syphilis diagnosis in the past 2 years (hazard ratio = 4.04, 95% CI: 1.19 to 13.79) and 2 prior CT or GC rectal infections in the past 2 years (hazard ratio = 8.85, 95% CI: 2.57 to 30.40) were associated with incident HIV.

Conclusions: Among MSM infected with rectal GC or CT, a history of 2 additional prior rectal infections was associated with an 8-fold increased risk of HIV infection. HIV-uninfected MSM with multiple rectal infections represent a population in need of innovative HIV-prevention interventions.

Key Words: HIV, rectal gonorrhea, rectal chlamydia, men who have sex with men

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INTRODUCTION

Twenty-five years after the first report of HIV/AIDS, the Centers for Disease Control and Prevention estimates that over 56,000 new HIV infections occurred in the United States in 2006.[1] Men who have sex with men (MSM) still account for the majority of new infections, with 53% of new HIV infections in 2006 among MSM.[1] In San Francisco, considered the epicenter of the HIV epidemic in the United States, it is estimated that nearly 1000 new HIV diagnoses were made in 2006, and over 75% were MSM.[2] Although decades of research have been dedicated to the prevention of HIV infection, there remains a substantial amount of new HIV infections annually.

The modifying roles of bacterial sexually transmitted diseases (STDs) in the transmission and acquisition of HIV infection are just beginning to be fully understood.[3–7] Because many of the sexual behaviors that place someone at risk for an STD are the same risk factors for HIV infection, it is unclear whether associations between STDs and HIV infection are a result of overlapping causal pathways or if STDs independently increase risk for HIV infection. Our prior work has suggested that a recent or concurrent STD was associated with acute HIV infection.[7] Since the beginning of the HIV/AIDS epidemic, gonococcal infections have been identified as one of the strongest and most consistent risk factors associated with HIV seroprevalence and seroconversion.[8–11] It is hypothesized that chancres from syphilis or chancroid provide a more efficient entryway for HIV to enter the body[12] and the inflammatory response that results from gonococcal or chlamydial infections may also facilitate HIV acquisition.[13] For HIV-uninfected patients, an STD diagnosis is both a marker for possible high-risk activity and a potential cofactor for HIV acquisition.

With the realistic prospect of effective HIV vaccines many years off, efforts should remain focused on developing effective primary-prevention interventions for communities at risk for HIV infection. Identifying populations at particularly high risk can focus those prevention efforts. We examined a high-risk population, HIV-uninfected MSM diagnosed with a rectal chlamydia (CT) or gonorrhea (GC) infection at our municipal STD clinic, to determine whether the number of prior CT or GC rectal infections was associated with HIV seroconversion.

METHODS

The San Francisco City Clinic (City Clinic) is the only municipal STD clinic in San Francisco and has approximately 22,000 patient visits annually. Nearly 40% of these visits are

by MSM. All patients visiting City Clinic see a clinician and MSM are offered rectal testing for GC or CT if they report anal sex in the past 6 months. Rectal specimens are collected by the clinician and tested for CT and GC using transcription mediated amplification (Gen-Probe APTIMA Combo 2). Additionally, all patients are offered HIV testing. Sociodemographic and sexual risk behavior information is collected through clinician interview on standardized instruments and captured in our electronic medical record system.

We created a retrospective cohort of HIV-uninfected MSM diagnosed with a rectal GC or CT infection to examine time to HIV seroconversion. All MSM who were diagnosed at City Clinic with a rectal GC or CT infection between March 1, 2003 and December 31, 2005, and tested HIV negative at the diagnosing visit, were included in this analysis. For men with multiple rectal infections during that period, their last rectal infection was the entry point to the study (entry rectal infection). The outcome of interest was time to HIV diagnosis, defined as the first visit at which the patient tested HIV positive at City Clinic or self-reported being HIV positive. Follow-up was through December 31, 2006, to allow at least 1 year for HIV seroconversion after the entry rectal infection. If HIV seroconversion did not occur, MSM were administratively censored on that date. MSM were excluded if an HIV diagnosis occurred within 30 days of the entry rectal infection to reduce the likelihood that the infections were acquired simultaneously.

Number of prior rectal CT or GC infections was the primary exposure. This was ascertained by assessing each patient's City Clinic medical history for diagnoses of rectal CT or GC infections and matching all patients to the San Francisco Department of Public Health's STD surveillance system to identify rectal infections diagnosed by other providers in San Francisco. Rectal CT or GC infection history was limited to those occurring 2 years before the date of the entry rectal CT or GC infection. Covariates were assessed at the time of the entry rectal CT or GC infection, including race/ethnicity, age, self-described sexual identity, treatment for the rectal infection (presumptive, the patient returned for treatment, or none documented), whether the rectal CT or GC infection was symptomatic, early syphilis diagnosis in the previous 2 years, and number of male and female sexual partners in the previous 2 months.

We used survival analysis to account for varying times to HIV infection. For MSM who became HIV infected, HIV-free time at risk was the period between the entry rectal CT or GC infection and the date of first HIV-positive test or first self-report of HIV-positive status. For MSM who remained HIV uninfected throughout the analytic period, HIV-free time at risk was the period from the diagnosis of entry rectal CT or GC infection to the administrative censoring date of December 31, 2006. Kaplan–Meier survival estimates of time to HIV diagnosis were examined. Cox proportional hazard models were used to explore univariate and multivariate factors associated with HIV infection. The final multivariate model included covariates that changed the coefficient of the primary exposure covariate (number of prior rectal CT or GC infections) by at least 10%.[14,15] All analyses were conducted using SAS 9.1 (SAS Institutes, Cary, NC) and Intercooled Stata 10 (Stata Corp, College Station, TX). As these were deidentified public health records undergoing retrospective analyses, this study was considered exempt from human subjects considerations in accordance with the Code of Federal Regulations, Title 45.

RESULTS

A total of 541 MSM were diagnosed with a rectal GC or CT infection between March 1, 2003 and December 31, 2005, and tested HIV negative on both standard antibody and pooled RNA tests on the date of diagnosis. These men contributed a total of 1197.96 person-years of follow-up, and 27 (4.99%) became HIV-infected during the analytic period for an estimated annual HIV incidence of 2.25% [95% confidence interval (CI): 1.49 to 3.26]. The median time from entry rectal CT or GC infection diagnosis to HIV diagnosis was 359 days (range 37–951 days). Among the 96 (17.7%) MSM with at least one additional rectal GC or CT infection after the entry infection, 83 (86.5%) had 1 prior rectal infection and 13 (13.5%) had 2 prior rectal infections.

Annual HIV-incidence rates and univariate hazard ratios (HRs) are shown in Tables 1 and 2, respectively. In this population of MSM, HIV incidence did not vary by age, sexual identity, race/ethnicity, treatment for rectal CT or GC infection, or numbers of male or female sexual partners. A diagnosis of early syphilis in the 2 years before the entry rectal infection was associated with a nearly 4-fold increased risk of HIV seroconversion (annual HIV seroincidence 8.33%, HR = 3.94, 95% CI: 1.18 to 13.10). Although a history of prior rectal CT or GC infections was associated with a higher HIV seroincidence, this finding did not reach statistical significance (Table 1). However, having 2 additional prior CT or GC rectal infections was associated with an increased risk of HIV infection (Fig. 1 and Tables 1, 2). MSM diagnosed with rectal GC or CT who had 2 additional rectal CT or GC infections in the past 2 years were over 8 times more likely to seroconvert compared with MSM with no prior rectal CT or GC infections (Table 2).

The multivariate Cox proportional hazards models are shown in Table 2. Only number of prior CT or GC rectal infections in the prior 2 years and a diagnosis of early syphilis in the prior 2 years remained in the model (model 1). We also examined a model that included number of male sex partners, as this is an important confounding factor in the relationship between rectal CT or GC and HIV (model 2). Inclusion of number of male sex partners had a minimal effect on the association between number of prior rectal infections and HIV incidence. From model 1, history of early syphilis was associated with a 4-fold increase in risk of HIV infection after adjusting for history of rectal CT or GC infections (HR = 4.04, 95% CI: 1.19 to 13.79). Number of prior rectal CT or GC infections was also associated with HIV infection in the adjusted Cox models; MSM who had 2 rectal CT or GC infections in the past 2 years had more than 8 times the risk of HIV infection compared with MSM with no history of prior rectal CT or GC infections (HR = 8.85, 95% CI: 2.57 to 30.40).

TABLE 1. Annual HIV Incidence Among 541 HIV-Negative MSM Diagnosed With a Rectal Chlamydial or Gonococcal Infection at the San Francisco City Clinic Between March 2003 and December 2005

Characteristic	Number of Patients	Person-Years at Risk	Number of HIV Seroconversions	Annual HIV Incidence (%)	95% CI
Overall	541	1197.96	27	2.25	1.49–3.26
Age (yrs)					
<29	246	542.32	12	2.21	1.14–3.84
30–39	201	452.99	10	2.21	1.06–4.02
40–49	74	156.11	3	1.92	0.40–5.52
50+	18	40.31	2	5.00	0.61–16.92
Sexual orientation					
Straight	4	8.65	0	0	
Gay	461	1019.32	22	2.16	1.36–3.25
Bisexual	76	169.99	5	2.94	0.96–6.73
Race/ethnicity					
White	307	696.64	14	2.00	1.10–3.35
Black	31	69.68	2	2.86	0.35–9.94
Hispanic	103	212.63	6	2.82	1.04–6.03
Asian/Pacific Islander	95	208.45	4	1.92	0.53–4.85
Other/unknown	5	10.57	1	9.09	0.22–41.28
Treatment					
Presumptive	265	571.62	14	2.45	1.34–4.07
Returned	260	591.95	13	2.20	1.17–3.73
None documented	14	30.19	0	0	
Number of male sex partners (2 mo)					
0–1	106	242.24	2	0.83	0.10–2.95
2–3	178	396.18	9	2.27	1.04–4.27
4+	208	455.69	13	2.85	1.53–4.83
Missing	49	103.84	3	2.89	0.60–8.20
Any female sex partners					
Yes	21	44.91	0	0	
No	471	1049.20	24	2.29	1.47–3.39
Missing	49	103.84	3	2.88	0.60–8.20
Early syphilis diagnosis in prior 2 yrs					
Yes	19	35.58	3	8.33	1.75–22.47
No	522	1165.57	24	2.06	1.32–3.05
Rectal symptoms					
Yes	32	73.36	1	1.40	0.03–7.40
No	509	1124.60	26	2.31	1.52–3.37
Any prior rectal infections					
Yes	96	195.63	9	4.59	2.12–8.54
No	445	1002.33	18	1.80	1.06–2.82
Number of rectal infections in prior 2 yrs					
0	445	1002.33	18	1.80	1.07–2.82
1	83	175.84	6	3.41	1.26–7.27
2	13	19.79	3	15.00	3.21–37.89

DISCUSSION

Several studies have reported that bacterial STDs may increase the risk of both transmission and acquisition of HIV.[3–7,16–18] In our analysis of MSM with rectal GC or CT seen at San Francisco City Clinic, annual HIV incidence was 2.25%; for MSM with 2 or more rectal GC or CT infections in the prior 2 years, HIV incidence was 15.00%.

Although there is a dearth of research on rectal immunology and the biologic correlates of susceptibility to HIV infection among MSM, given the physiologic similarities between the cervix and the rectum, it is possible that mechanisms that place women with STDs at risk for HIV infection may be analogous for men who engaged in receptive anal sex. Levine and colleagues demonstrated that endocervical CD4 T cell counts were higher in women with nonulcerative STDs like CT and GC.[19] A similar increase in rectal CD4 T cells may occur among MSM with rectal CT or GC. Additionally, several studies have demonstrated increases

TABLE 2. Univariate and Multivariate HRs for HIV Infection Among 541 HIV-Negative MSM Diagnosed With a Rectal Chlamydial or Gonococcal Infection at the San Francisco City Clinic Between March 2003 and December 2005

Characteristic	Univariate HR	95% CI	Multivariate Model 1 HR	95% CI	Multivariate Model 2 HR	95% CI
Age (yrs)						
<29	1					
30–39	1.01	0.44 to 2.34				
40–49	0.86	0.24 to 3.06				
50+	2.26	0.51 to 10.11				
Sexual identity						
Straight/bisexual	1					
Gay	0.78	0.29 to 2.05				
Race/ethnicity						
White	1					
Black	1.40	0.32 to 6.14				
Hispanic	1.39	0.53 to 3.61				
Asian/Pacific Islander	0.97	0.32 to 2.93				
Other/unknown	4.65	0.61 to 35.46				
Treatment						
Presumptive	1					
Returned	0.97	0.46 to 2.07				
None documented	Undefined					
Number of male sex partners (2 mo)						
0–1	1				1	
2–3	2.75	0.59 to 12.74			3.10	0.67–14.41
4+	3.43	0.77 to 15.22			3.12	0.70–13.89
Missing	3.40	0.57 to 20.36			2.88	0.47–17.59
Any female sex partners						
Yes	Undefined					
No	1					
Missing	1.23	0.37 to 4.08				
Early syphilis diagnosis in prior 2 yrs						
Yes	3.94	1.18 to 13.10	4.04	1.19 to 13.79	4.17	1.22–14.27
No	1		1		1	
Rectal symptoms						
Yes	0.60	0.08 to 4.45				
No	1					
Number of rectal infections in prior 2 yrs						
0	1		1		1	
1	1.87	0.74 to 4.71	1.69	0.66 to 4.31	1.60	0.61–4.16
2	8.16	2.39 to 27.88	8.85	2.57 to 30.40	8.81	2.48–31.29

in local cytokines, including tumor necrosis factor-α and interleukins associated with gonococcal infections, although none of the studies examined rectal GC infections.[20–26] Rectal STDs may also cause epithelial erosions that can increase susceptibility to HIV infections. Repeated rectal infections may not only increase the duration of the erosions and the local presence of immune target cells, but may also increase infectivity by altering host immune defenses.

Alternatively, it is possible that rectal GC and CT are not causally associated with HIV, but instead are confounders in the relationship between behavioral risks (eg, methamphetamine use, larger numbers of sex partners, unprotected receptive anal sex) and HIV acquisition. Because these behaviors are associated with the risk of both rectal infections and HIV infections, it is challenging to unravel this epidemiologic relationship with observational data. However, even if rectal STDs are not causally implicated in HIV transmission, they may represent an objective marker for identifying persons at extremely high risk for HIV infection.

We found that a recent early syphilis diagnosis was associated with HIV infection, consistent with others' findings.[11,27,28] Even after controlling for additional prior CT or GC rectal infections, MSM with a rectal CT or GC infection in our analysis who had been diagnosed with early syphilis in the prior 2 years had 4 times the risk of HIV infection compared with MSM with rectal CT or GC infections and no recent syphilis history. It is likely that in this analysis, history of an early syphilis infection acts as a marker for HIV exposure.

Interestingly, numbers of male sex partners in the 2 months before entry rectal CT or GC infection was not associated with HIV seroconversion. Larger numbers of recent sex partners is one of the most consistently identified risk factors

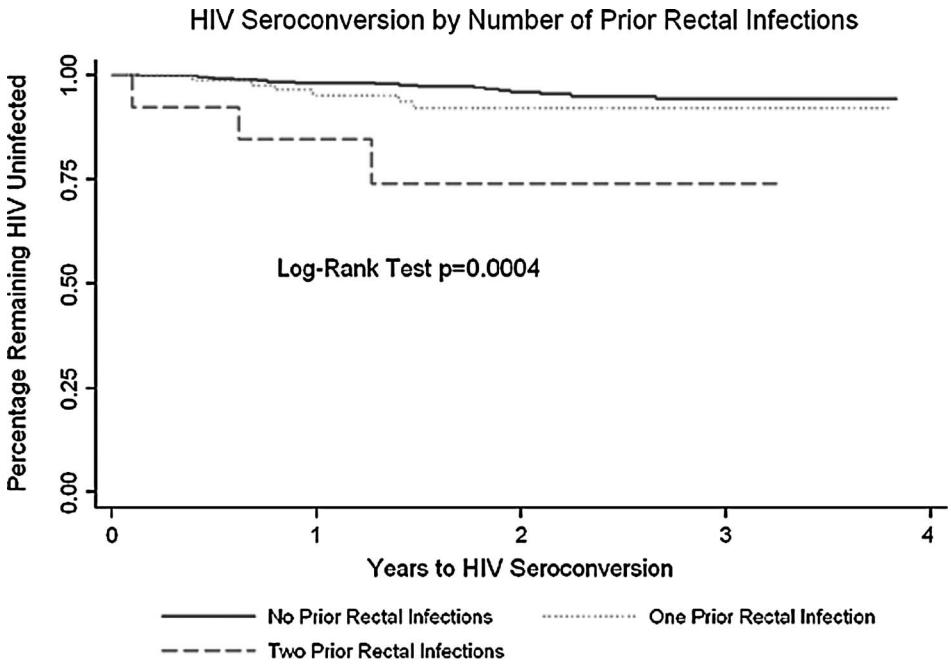

FIGURE 1. Kaplan–Meier survival function estimates of time to HIV infection among 541 HIV-negative men who have sex with men diagnosed with a rectal chlamydia or gonorrhea infection at the San Francisco City Clinic between March 2003 and December 2005, by number of prior rectal chlamydia or gonorrhea infections.

for HIV infection.[11,29–32] Our study population was MSM diagnosed with a rectal CT or GC infection, an outcome also associated with increased numbers of male sex partners.[33–35] The confounding effect of number of male sex partners on the relationship between prior rectal infections and HIV seroconversion was likely attenuated by restricting the cohort to MSM with at least one diagnosed rectal infection. The cohort analyzed here may represent a higher-risk population that is more homogenous with respect to traditional HIV and STD-risk factors than the general population of MSM in San Francisco or elsewhere.

Our findings underscore the need for more access to nucleic acid testing to detect CT and GC in nongenital sites, specifically rectal testing. Before the advent of nucleic acid testing, tools to aid in the diagnosis of rectal infections were limited and subject to poor validity. Although many nucleic acid–based tests have been Food and Drug Administration cleared for specimens collected from male and female genital sites, none are cleared for nongenital specimens. Our data further support the expansion and wider availability of rectal GC and CT diagnostic testing. Given that many rectal infections are asymptomatic,[36] routine screening is likely the most effective means for reducing the local burden of rectal infections and, in turn, HIV infections.

In this population of MSM, risk of HIV infection was high. More importantly, the risk of HIV infection increased 8-fold for MSM with 2 prior rectal CT or GC infections; for MSM with an average of one rectal infection per year, the annual incidence of HIV was 15 per 100 person-years. Among all diagnoses of HIV infection made at San Francisco City Clinic from March 2003 through December 2005, 35% had a rectal CT or GC diagnosis before their diagnosis of HIV infection. In HIV-uninfected populations, bacterial STD reinfection is both an endpoint in itself and a marker for high-risk behavior in relation to HIV. Nearly 80% of the MSM included in this analysis reported 2 or more male sex partners in the prior 2 months. It is likely that a history of rectal CT or GC infections is analogous to unprotected receptive anal sex with multiple male partners.

The results of this analysis must be considered in light of its limitations. Follow-up for HIV infection was limited to 33 months. Furthermore, HIV seroconversions were limited to those diagnosed in our STD clinic or reported by the patient; men who were diagnosed with HIV infection by another provider and did not subsequently visit the clinic would have been missed. This implies that the HIV-incidence estimates reported may be conservative. Additionally, the primary objective of this analysis was to examine history of prior rectal infections in relation to HIV infection, so we did not examine the time between prior rectal infections. Because this analysis was limited to MSM who were diagnosed at San Francisco City Clinic and relied on STD morbidity reported in San Francisco, rectal infections diagnosed outside of San Francisco or not reported were missed in this analysis. Finally, San Francisco is a unique urban environment and the results of this analysis may not be generalizable to other areas. However, although the estimates of HIV incidence may vary in other cities, we have no reason to believe that our primary finding of repeated rectal CT or GC infections being associated with increased risk of HIV infection would differ in other locales.

HIV among MSM in San Francisco has become hyperendemic,[37] highlighting the need for the development of innovative primary-prevention interventions for HIV and STDs. Disentangling the independent effect of multiple rectal infections from sexual behaviors that also increase risk of HIV is difficult. Regardless, a history of rectal CT or GC infections is a marker for a subpopulation in critical need of innovative prevention activities. As opposed to sexual

behaviors, condom use, and drug use, which may be subject to underreporting,[38–44] documented history of rectal CT or GC infections is an objective marker of increased risk for HIV. At the clinic level, repeated rectal infections can be used to identify patients who may benefit from more intensive risk-reduction counseling or other interventions designed to reduce the risk of HIV. Further research on rectal biology and the pathogenesis of rectal infections is needed to better understand the relationship between rectal CT and GC and HIV acquisition, and a randomized trial of screening and treatment for rectal CT and GC as an HIV prevention intervention may be warranted.

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