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Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs

Nicola M. Zetola¹, Kyle T. Bernstein², Ernest Wong², Brian Louie², and Jeffrey D. Klausner^{1,2}

¹*Division of Infectious Diseases, University of California, San Francisco, San Francisco, California*

²*San Francisco Department of Public Health, San Francisco, California*

Abstract

Background—It is hypothesized that sexually transmitted diseases (STDs) increase the risk of HIV acquisition. Yet, difficulties establishing an accurate temporal relation and controlling confounders have obscured this relationship. In an attempt to overcome prior methodologic shortcomings, we explored the use of different study designs to examine the relationship between STDs and HIV acquisition.

Methods—Acutely HIV-infected patients were included as cases and compared to 1) HIV-uninfected patients (matched case-control), 2) newly diagnosed, chronically HIV-infected patients (infected analysis), and 3) themselves at prior clinic visits when they tested HIV-negative (case-crossover). We used t-tests to compare the average number of STDs and logistic regression to determine independent correlates and the odds of acute HIV infection.

Results—Between October 2003 and March 2007, 13,662 male patients who had sex with men were tested for HIV infection at San Francisco's municipal STD clinic and 350 (2.56%) HIV infections were diagnosed. Among the HIV-infected patients, 36 (10.3%) cases were identified as acute. We found consistently higher odds of having had an STD within the 12 months (matched case-control, OR 5.2 [2.2-12.6]; infected analysis, OR 1.4 [1.0-2.0]; case-crossover, OR 1.3 [0.5-3.1]) and 3 months (matched case-control, OR 34.5 [4.1-291.3]; infected analysis, OR 2.3 [1.1-4.8]; case-crossover OR 1.8 [0.6-5.6]) prior to HIV testing among acutely HIV-infected patients. We found higher odds of acute HIV infection among patients with concurrent rectal gonorrhea (17.0 [2.6 - 111.4], $p < 0.01$) or syphilis (5.8 [1.1 - 32.3], $p = 0.04$) when compared to those HIV-uninfected.

Conclusions—Acute HIV infection was associated with a recent or concurrent STD, particularly rectal gonorrhea, among men at San Francisco's municipal STD clinic. Given the complex relationship between STDs and HIV infection, no single design will appropriately control for all the possible confounders; studies using complementary designs are required.

Background

The inability to conduct experimental human studies to clarify the role of bacterial sexually transmitted diseases (STDs) in HIV acquisition forces us to rely on observational data. Several studies suggest an association between bacterial STDs and HIV infection. However, the role

Corresponding Author: Jeffrey D. Klausner, MD, MPH, Director, STD Prevention and Control Services, San Francisco Department of Public Health, 1360 Mission Street, Suite #401, San Francisco, CA, 94103. Tel 415-355-2000; Fax 415-554-9636; Email: E-mail: Jeff.Klausner@sfdph.org.

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of these STDs in the causal pathway of HIV acquisition has been difficult to determine partly due to the limitations intrinsic to study designs used to explore this relationship¹⁻³.

To be a causal factor in HIV acquisition, bacterial STDs need to be present before HIV infection occurs. Many studies fail to establish this temporality of events. Despite advances in HIV testing, the most commonly used technologies can only detect HIV infection an average of four weeks after HIV acquisition and cannot reliably distinguish between recent and chronic infection. On the other hand, most bacterial STDs have short incubation periods and are either treated or resolve spontaneously within a few weeks after becoming symptomatic. It is even more difficult to determine the duration of the infection when it is asymptomatic. Therefore, in most cases it is impossible to determine if bacterial STDs were present before HIV acquisition, even when patients are diagnosed with a bacterial STD at the time of HIV diagnosis.

Risk factors associated with HIV acquisition are, in most cases, also associated with bacterial STDs⁴⁻⁶. Thus, bacterial STDs are both a marker for high-risk behavior and a possible causal factor in HIV acquisition⁶. Difficulties identifying incident HIV infections further complicate the determination of risk factors and behaviors associated with HIV acquisition. Given that risk factors and behaviors may change at the individual and community level over time, it is possible that factors identified at the time of HIV diagnosis (including the presence of STDs) are different from the ones relevant at the time of infection. Time-dependent factors might change the individual risk of acquiring either STDs or HIV in a population (e.g. increased prevalence of STD, introduction of more infectious strains to the community, etc.). Lastly, the presence of unmeasured factors and biological factors predisposing an individual to STD acquisition could also increase the likelihood of HIV acquisition. This association between STDs and HIV acquisition through unmeasured biological factors could create the illusion of a causal relationship where none exists.

Acute HIV infection refers to the period, typically up to six weeks in HIV-infected patients, between exposure to HIV and the development of detectable HIV antibodies. Diagnosing acute HIV infection is the most reliable way to identify an incident HIV infection. Patients diagnosed within this period are the ideal population to study to understand the contribution of risk factors to HIV acquisition⁷⁻⁹. Given the shorter time between HIV infection and diagnosis during acute HIV infection, recall bias and time-dependent confounders are minimized, and the temporality of the event in relation to possible risk factors, such as STD, could be better established.

To maximize our ability to establish a temporal relationship between STDs and HIV acquisition, and to limit our analysis to truly incident HIV cases, we restricted our cases to acutely HIV-infected patients. Then, in order to determine the role of bacterial STDs in sexually transmitted HIV infection in men who have sex with men (MSM), we used three methodological designs comparing acutely HIV-infected cases with three different control populations: 1) To account for possible time-dependent factors in the community that could have affected secular trends in HIV or STD incidence (e.g. Gay Pride parades, street fairs, varying STD or HIV prevalence, etc.), we compared acutely HIV-infected patients with patients testing negative for HIV infection using a nested case-control design. Controls were matched by time of HIV testing. 2) To identify factors unique to the time when HIV infection occurred, we compared acutely HIV-infected patients with newly diagnosed, chronically HIV-infected patients. 3) Finally, to reduce confounding by subject characteristics that may remain stable over time (e.g., unmeasured biological factors and unknown or undisclosed behavioral factors) that could predispose an individual for HIV acquisition, we used a case-crossover design to compare acutely HIV-infected patients with themselves at prior clinic visits.

Methods

Study population

All patients with confirmed acute-HIV infection were included as cases. Given that all the acute-HIV infections occurred only among MSM, the comparison groups were also restricted to MSM seeking HIV testing. Three separate analyses were performed: 1) *Matched nested case-control analysis*: Acutely HIV-infected cases were compared to HIV-negative persons by using a matched nested case-control study design. For this analysis, each acutely HIV-infected patient was matched with four controls randomly selected from the population of MSM testing negative for HIV infection at the San Francisco municipal STD clinic. The controls were matched by date of testing (within the prior two weeks) and sexual orientation and were eligible to become cases at a later point in time. 2) *“Infected” analysis*: Acutely HIV-infected cases were also compared to all the newly diagnosed, chronically HIV-infected patients detected during the same period using a case-control study design. 3) *Case-crossover analysis*: Finally, we created a retrospective cohort of the subset of acutely HIV-infected cases who had previously tested HIV-negative at the clinic. We compared the risk factors reported at the time of HIV diagnosis with the ones reported at previous visits using a matched case-crossover analysis in which patients were compared to themselves at prior visits¹³. Because patients were at risk for HIV infection each time they tested negative, we allowed cases to have multiple “control” encounters. The risk hazard period was defined as 3 months prior to HIV testing. This risk period was decided due to biological and practical reasons. First, acute HIV infection typically lasts 3 to 6 weeks after infection. To facilitate HIV acquisition, bacterial STD must be present before this period. On the other hand, during the clinical encounter at the time of HIV testing, clinicians routinely ask about behaviors and practices during the prior 3 months.

HIV testing and routine acute-HIV screening

Since October 1, 2003, all HIV-antibody-negative plasma samples from patients tested for HIV infection at the San Francisco's municipal STD clinic were routinely screened for HIV ribonucleic acid.¹⁰ According to standard practices at this clinic, all patients testing for HIV are also offered STD testing and are interviewed to assess risk behaviors. Following informed consent and counseling, a 5-ml plasma precipitator tube (PPT) of peripheral blood was drawn by a trained and certified phlebotomist. Patient plasma samples were tested for HIV antibodies by an enzyme-linked immunosorbent assay (Genetic Systems™ HIV-1/HIV-2 plus O EIA, BioRad Laboratories, Redmond Washington). Reactive EIA samples were tested for confirmation by an immunofluorescence assay (Fluorognost HIV-1 IFA, Sanochemia Pharmazeutika, Vienna, Austria). Samples with discordant EIA and IFA results were further evaluated by testing for HIV-1 RNA using Transcription Mediated Amplification (TMA, Aptima HIV-1 RNA Qualitative Assay, Gen-Probe Inc., San Diego, CA). Patients with reactive EIA samples that tested IFA and TMA negative were considered not infected with HIV. Results of HIV-antibody testing were reported as HIV-EIA-positive, negative, or indeterminate. HIV-antibody-positive cases were considered to have chronic HIV infection. HIV-antibody negative or indeterminate specimens were pooled weekly for HIV-RNA testing in a single-step sequence^{11, 12}.

Main outcome and exposure

Our main outcome was incident HIV infection (acute-HIV infection), defined as a positive HIV-RNA test result in an HIV-antibody-negative specimen. Exposures were defined as documented bacterial STDs in three different time periods: within the 12 and 3 months prior to HIV testing and at the time of HIV testing. A documented bacterial STD was defined as a positive test result for *N. gonorrhoeae* or *C. trachomatis* on a clinical specimen or a documented serological or clinical diagnosis of syphilis in the presence of lesions consistent with syphilis.

To account for the possibility that the number of diagnosed STDs might depend on the number of STD tests performed on a patient, we included the total number of STD tests performed per patient in each of the analyses. For the case-crossover analysis, the risk (hazard) period was defined as 3 months prior to HIV testing.

Data source

All data were obtained from the electronic records of patients seeking medical care at the San Francisco's municipal STD clinic. The database contains selfreported patient demographics, prior STD diagnoses, drug use, sexual risk behavior and characteristics of recent sex partners. The database also contains all positive test results for gonorrhea, chlamydia or syphilis (reported morbidity) for San Francisco residents.

Statistical analyses

We used t-tests to compare the average number of STDs across groups. We used conditional logistic regression to assess factors associated with acute-HIV infection in each of the three analyses described above. Time-dependent factors that were included in all analyses were the number of male and female partners within the three months prior to HIV testing and reason for HIV testing. Models included terms for STD (gonorrhea, chlamydia and/or syphilis) testing and diagnosis during the 3 and 12 months prior to HIV testing, and for concurrent STD at the time of HIV testing. The total number of STD tests performed and the total number of STD diagnoses for each of those time periods were also included in those models. Comprehensive data on sexual behaviors, substance use, and sexual and social networks were not available. Two-sided $P < .05$ was considered statistically significant. We used STATA version 10.0 (StataCorp Inc, College Station, Texas) for analyses.

Human subjects

The University of California San Francisco Committee on Human Research approved this study and waived patient consent requirements.

Results

Between October 1, 2003 and March 31, 2007, 13,662 male patients who reported having sex with men were tested for HIV infection at the San Francisco municipal STD clinic, and 350 (2.56%) HIV infections were diagnosed. Among the HIV-infected patients, 36 (10.3%) cases were acutely infected and 314 (89.7%) were chronically infected. Among the remaining 13,312 patients testing negative for HIV infection, 144 controls matched by sexual orientation and date of testing were randomly selected for matched case-control analyses. The characteristics of those patients are shown in Table 1.

1) Acutely HIV-infected cases compared to matched HIV-negative controls (matched case-control analysis)

No difference in age, race/ethnicity, reason for HIV testing or number of total, male or female partners during the three months prior to HIV testing was found between acutely HIV-infected cases and HIV-negative controls (Table 1). We found a significantly higher average number of gonococcal (0.11 [CI, 0.00 - 0.22] vs. 0.01 [CI, -0.01 - 0.02], $p < 0.001$), chlamydial (0.08 [CI, 0.01 - 0.18] vs. 0.01 [CI, -0.01 - 0.02], $p < 0.01$), and syphilis (0.03 [CI, -0.03 - 0.08] vs. 0.01 [CI, -0.01 - 0.02], $p = 0.05$) infections during the three months prior to testing among acutely HIV-infected cases when compared to HIV-negative controls. The odds of acute-HIV infection given composite STD diagnosis are shown in Table 2.

2) Acutely HIV-infected cases compared to newly diagnosed, chronically HIV-infected cases ("infected" analysis)

No difference in age, race/ethnicity, reason for HIV testing or number of total, male or female partners during the three months prior to HIV testing was found between acutely HIV-infected cases and newly diagnosed, chronically HIV-infected patients (Table 1). When acutely HIV-infected cases were compared to newly diagnosed, chronically HIV-infected cases, we found a significant difference in the average time since the last HIV test (286.4 [CI, 197.7 - 375.2] days vs. 655.5 [557.2 - 753.8] days, $p < 0.01$).

We found a higher average number of gonococcal (0.11 [CI, 0.00 - 0.22] vs. 0.04 [CI, 0.02 - 0.06], $p=0.04$) and chlamydial (0.08 [CI, 0.01 - 0.18] vs. 0.02 [CI, 0.00 - 0.03], $p=0.01$) but not syphilis (0.03 [CI, -0.03 - 0.08] vs. 0.03 [CI, 0.01 - 0.04], $p=0.93$) infections among acutely HIV-infected cases during the three months prior to HIV testing when compared to newly diagnosed, chronically HIV-infected patients. We did not find differences in the average number of individual STDs during the 12 months prior to HIV testing between acutely infected cases and chronically infected patients (gonorrhea (0.33 [CI, 0.12 - 0.55] vs. 0.17 [CI, 0.12 - 0.22], $p=0.06$), chlamydia (0.19 [CI, 0.04 - 0.35] vs. 0.12 [0.09 - 0.16], $p=0.27$), and syphilis (0.08 [CI, -0.01 - 0.18] vs. 0.05 [CI, 0.02 - 0.08], $p=0.44$) infections). The odds of acute-HIV infection given composite STD diagnosis are shown in Table 2.

3) Acutely HIV-infected cases compared to themselves at a prior time (case-crossover analysis)

Data on 54 prior clinic visits were available from 25 (70 of all acute-HIV cases) acutely HIV-infected patients. No differences were found between the characteristics of the 25 patients with information available from prior clinic visits when compared to the patients without such information. No differences in reason for HIV testing or number of total, male or female partners during the three months prior to HIV testing were found at the time of diagnosis of acute-HIV infection compared to HIV testing at a prior time. When the average number of STDs at the time of acute-HIV diagnosis was compared to that at prior visits, we found a higher number, though not statistically significant, of gonococcal (0.16 [CI, 0.01 - 0.31] vs. 0.07 [CI, 0.00 - 0.13], $p=0.19$) and chlamydial infections (0.12 [CI, -0.02 - 0.26] vs. 0.03 [CI, -0.01 - 0.08], $p=0.13$) during the three months prior to testing. The odds of acute-HIV infection given STD diagnosis are shown in Table 2.

Discussion

Our results show consistently higher rates of bacterial STDs among acute-HIV cases when compared with non-acute and two types of uninfected controls. The odds of a bacterial STD diagnosis among acute HIV cases were higher within the three months prior to HIV testing and at the time of HIV testing. Although the direction of the effect was consistent throughout the different analyses and designs, the association between bacterial STDs and acute-HIV infection was not statistically significant in all analyses, likely due to the lack of power. Higher odds of bacterial STD diagnosis among acute-HIV cases were also found within the twelve months prior to HIV testing. However, this difference was primarily driven by the STD tests performed within the three months prior to HIV testing and disappeared after those tests were excluded from the analysis (data not shown). Altogether, these results suggest a reliable association between HIV acquisition and bacterial STD. The higher magnitude of the odds of bacterial STD diagnosis found around the time when HIV acquisition was likely to occur (i.e. within 3 months prior to acute-HIV infection) suggest that in order to increase the risk for HIV infection, bacterial STDs need to precede or coexist with HIV exposure^{1, 5, 6}. In addition, the lack of an association between STD diagnoses within the prior 12 months before HIV testing after excluding any diagnosis occurring in the immediate prior 3 months to HIV testing supports

this conclusion and argues against the role of STDs as a surrogate for time-stable risk factors not assessed in this study. For example, if the diagnosis of STDs were a surrogate for time-stable risk factors, one would expect an “X” number of STDs within the 3 months prior to HIV testing and a “4X” number of STDs within the 12 months prior to HIV testing.

The inability to use experimental designs to explore the relationship between bacterial STDs and HIV acquisition forces us to rely on observational data. Due to the complexity of this relationship, no single observational study can control for all potential confounders. However, different designs are complementary and account for different aspects of the relationship. Therefore, to understand the interaction between bacterial STDs and HIV acquisition, multiple studies must be interpreted together. By comparing acutely HIV-infected patients with chronically infected, newly diagnosed controls, we isolated factors unique to the time when HIV acquisition was likely to occur. The use of a case-crossover design allowed us to further reduce confounding by subject characteristics that remain stable over time (e.g., unmeasured biological factors and unknown or undisclosed behavioral factors) that could predispose an individual for HIV acquisition. In both of these analyses, STD infection was associated with acute-HIV infection, but was not statistically significant.

As expected, the magnitude of the association varied depending on the reference group and study design. Higher magnitudes of effects were found when acute-HIV cases were compared to patients testing HIV-negative. Although the nested matched case-control design accounted for the potential time trends in the exposure, and the analysis adjusted for the number of partners and reason for HIV testing, it is likely that cases and controls differed in unmeasured characteristics that led to a higher number of STD diagnoses and the eventual HIV infection. The case-crossover design accounted for these unmeasured confounders but failed to account for potential time trends in the exposure. Since case-crossover comparisons were made for each case between different points in time, the validity of the case-crossover analysis depended on assumptions regarding the overall risk for acquiring an STD in the population. If STD risk changes over time (e.g., increased STD prevalence, introduction of more infectious strains to the community, etc.) and case exposures are compared with referent exposures systematically selected from a different period in time, a bias may be introduced into estimates of the measure of association. Control for this bias depends on the ability to identify and measure the confounder. We believe that the results of the matched and case-crossover analyses are complementary.

The increased number of rectal gonococcal infections in acutely HIV-infected cases compared with chronically HIV-infected and non-infected patients suggests this infection may play a critical role in HIV acquisition. Interestingly, we found no cases of rectal chlamydial infection among acutely HIV-infected patients. Although this might reflect the small number of cases included in this study, it could also suggest a different risk for HIV acquisition associated with each of those infections. Prior data have shown a strong association between rectal gonorrhea and HIV incidence ¹⁴.

Acutely HIV-infected cases had a shorter mean time between HIV diagnosis and the last HIV-negative test compared to chronically HIV-infected patients. This finding may suggest more frequent HIV testing, and thus a higher likelihood of early diagnosis, during the acute period of HIV infection. It is also possible that the increased frequency of HIV testing among acute cases reflects patients' increased risk, whether perceived or real (i.e., due to high-risk behavior), that is not captured or recorded during the clinical encounter. However, given that our database only included HIV testing performed at the municipal STD clinic, it is possible that patients with chronic HIV infection were tested more frequently outside of the clinic.

Our designs were well suited to the study of a transient effect of an intermittent exposure (i.e., bacterial STDs) on the subsequent risk of a rare, acute-onset disease (HIV infection) hypothesized to occur a short time after exposure. The designs assumed that the exposure was brief, the time between exposure and event onset was short, and there was little or no carryover effect on the exposure. Most rectal bacterial STDs have short incubation periods and resolve completely after therapy. When rectal STDs are asymptomatic, some may resolve spontaneously over time, even without treatment. There is no known long-term effect of rectal bacterial STDs once they have been treated or resolved spontaneously. STD-screening tests have high sensitivity and specificity and are routinely performed on patients seeking medical attention or HIV testing at the San Francisco municipal STD clinic. Given that bacterial STDs fulfill these assumptions, we feel that our designs are appropriate for the study of their role on HIV acquisition.

We also assumed that if STDs increase the risk for HIV acquisition, they should occur more frequently during the period immediately prior to acute-HIV infection. However, the referent time period used for comparison should be representative of the expected distribution of exposure for follow-up time that does not result in a case. Although we did not have clear data to support this assumption, there was no reason to think otherwise.

Several limitations and potential biases must be acknowledged. In our sample, all the acutely HIV-infected cases were MSM. Given that we matched our cases to controls by age and sexual orientation, our sample was restricted to MSM. The distribution of age, race/ethnicity, number of sex partners and other risk factors in the sample was similar to that of all MSM seeking HIV testing at the SF municipal STD clinic (data not shown); thus, our results may be generalizable to this population. Furthermore, nearly all new HIV infections in San Francisco are among MSM, making these results relevant to the local epidemic. However, given the particular characteristics and risk factors of the highly selected patients included in our sample, our findings may not be generalizable to other populations of MSM or populations of non-MSM.

These data were collected in the setting of routine HIV testing and clinical care at the San Francisco municipal STD clinic and were not part of a prospective study specifically designed to determine the causal association between risk behaviors, STDs and HIV acquisition. Therefore, information, selection, referral and recall bias may have occurred. However, clinical protocols exist at the clinic that should have minimized these biases. Due to lack of specific and detailed questions regarding substance use, we could not account for that cofactor in our analyses.

Although our analyses were designed to clarify the role of STDs on HIV acquisition, the inability to accurately establish the temporality of events makes causal inference impossible. This problem was partly minimized by only using acute-HIV cases, the best marker for incident cases. Also, laboratories are required by law to report STDs to the health department. Their reports include the date when the test was performed, allowing us to determine, as accurately as possible, if an STD was diagnosed at the time when HIV infection likely occurred. In addition, all patients testing for HIV are routinely offered STD testing at the clinic, allowing us to determine if a STD was present at the time of HIV diagnosis. However, given the observational nature of our study, it is impossible to determine the number of acutely HIV-infected patients that acquired an STD at the same time that they also acquired HIV.

Finally, our definition of the risk (hazard) period could have resulted in non-differential exposure misclassification. If the duration of the risk period were overestimated, some “false exposures” would have become “exposures”. If the duration were underestimated, some of the “true exposures” would have been excluded.

Conclusion

Studies of acutely HIV-infected patients can provide important information regarding risk factors associated with HIV acquisition. Given the complex relationship between STDs and HIV infection, no single design will appropriately control for all the possible confounders; studies using complementary designs are required. We found that acute-HIV infection was associated with a recent or concurrent STDs, particularly rectal gonorrhea. While these results contribute to the literature supporting the role of frequent STD screening and treatment as a primary preventive strategy for HIV acquisition, further studies are needed to confirm the causal relationship between STDs and HIV acquisition, particularly in MSM. Given the increasing incidence of HIV infection in MSM, intervention studies to control STDs in MSM as a means of HIV prevention are urgently needed.

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Table 1

Characteristics of acutely HIV infected cases, newly diagnosed chronic HIV-infected controls and non-HIV-infected controls San Francisco Department of Public Health Municipal sexually transmitted diseases clinic, October 2003 to March 2007

Demographic/characteristic	Acute HIV infected cases (N = 36)	HIV negative controls (N = 144)	Newly diagnosed chronic HIV infected controls (N = 314)
Sex			
Male	36 (100%)	144 (100%)	314 (100%)
Sexual orientation			
Gay	30 (83.3%)	117 (81.3%)	262 (83.4%)
Bisexual	6 (16.7%)	27 (18.8%)	52 (16.6%)
Race/ethnicity			
White	17 (47.2%)	75 (52.8%)	161 (51.3%)
Black	5 (13.9%)	6 (4.2%)	37 (11.8%)
Hispanic	11 (30.6%)	40 (27.8%)	81 (25.8%)
Asian	3 (8.3%)	22 (15.3%)	31 (9.9%)
Mean age, years (95% CI)	33.4 (23.9 - 42.9)	33.4 (31.8 - 35.0)	34.0 (33.1 - 35.0)
Mean number of sex partners within the past 3 months			
Total	3.8 (1.9 - 5.7)	5.2 (4.2 - 6.1)	5.4 (4.3 - 6.6)
Male	3.7 (1.8 - 5.7)	5.1 (4.1 - 6.0)	5.3 (4.2 - 6.4)
Female	0.1 (0.0 - 0.2)	1.9 (0.9 - 2.8)	0.2 (0.1 - 0.2)
Reason for visit*			
New symptom	18 (50.0%)	61 (42.4%)	143 (45.4%)
Partner diagnosed with and STD	4 (11.1%)	11 (7.6%)	39 (12.4%)
Contacted by the SFDPH	4 (11.1%)	5 (3.5%)	39 (12.4%)
Post-Exposure Prophylaxis	4 (11.1%)	12 (8.3%)	15 (4.8%)
Check up	23 (63.9%)	114 (79.2%)	228 (72.6%)
Time from last HIV test, days (95% CI)	286.4 (197.7 - 375.2)	489.3 (375.0 - 603.5)	655.5 (557.2 - 753.8)

95% CI = 95% confidence interval

* Given the possibility of more than one reason for visit, the percentages may not add up to 100%

Adjusted odds ratio for acute HIV infection. San Francisco Department of Public Health municipal sexually transmitted disease clinic, October 2003 to March 2007

Table 2

	Acutely HIV infected cases compared to HIV negative cases (Nested Matched Case-Control)		Acutely HIV infected compared to newly diagnosed chronically HIV infected cases (Infected Analysis)		Acutely HIV infected compared to themselves at a prior time (Case-Crossover)	
	Adjusted* odds ratio (95% CI)	P value	Adjusted* odds ratio (95% CI)	P value	Adjusted* odds ratio (95% CI)	P value
Diagnosis of an STD within the 12 months prior to HIV testing	5.2 (2.2 - 12.6)	0.000	1.4 (1.0 - 2.0)	0.060	1.3 (0.5 - 3.1)	0.560
Diagnosis of an STD within the 3 months prior to HIV testing	34.5 (4.1 - 291.3)	0.001	2.3 (1.1 - 4.8)	0.028	1.8 (0.6 - 5.6)	0.316
Concurrent STD at the time of HIV testing						
Rectal gonorrhea	17.0 (2.6 - 111.4)	0.003	2.7 (0.8 - 8.8)	0.111	1.8 (0.5 - 6.0)	0.359
Rectal chlamydia	NA		NA		NA	
Pharyngeal gonorrhea	0.6 (0.0 - 3.9)	0.599	0.6 (0.1 - 3.1)	0.542	1.3 (0.3 - 5.9)	0.779
Pharyngeal chlamydia	5.3 (0.4 - 78.3)	0.222	7.1 (0.7 - 70.3)	0.093	3.4 (0.3 - 39.0)	0.324
Urethral gonorrhea	0.6 (0.1 - 3.9)	0.704	NA	0.182	0.5 (0.1 - 2.7)	0.439
Urethral chlamydia	0.9 (0.1 - 9.6)	0.901	0.2 (0.0 - 2.0)		0.5 (0.1 - 5.3)	0.593
Syphilis	5.8 (1.1 - 32.3)	0.044	0.4 (0.1 - 2.4)	0.331	1.3 (0.3 - 5.9)	0.779

CI=confidence interval, STD=sexually transmitted diseases, NA=not applicable/predicted outcome completely

* Adjusted for number of partners within the 3 months prior to HIV testing and reason for HIV testing.