Published in final edited form as:

Sex Transm Dis. 2012 January ; 39(1): 1–7. doi:10.1097/OLQ.0b013e31823b1922.

ONGOING SEXUALLY TRANSMITTED DISEASE ACQUISITION AND RISK TAKING BEHAVIOR AMONG U.S. HIV-INFECTED PATIENTS IN PRIMARY CARE: IMPLICATIONS FOR PREVENTION INTERVENTIONS

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SUMMARY

A study of HIV-infected persons in primary care in four U.S. found that 13% had a prevalent STD at enrollment and 7% an incident STD six months later.

Background—To better understand the factors associated with HIV and STD transmitting behavior among HIV-infected persons, we estimated STD prevalence and incidence and associated risk factors among a diverse sample of HIV-infected patients in primary care.

Methods—We analyzed data from 557 participants in the SUN study, a prospective observational cohort of HIV-infected persons in primary care in four U.S. cities. At enrollment and six months thereafter, participants completed an audio computer-assisted self interview about their sexual behavior, and were screened for genitourinary, rectal and pharyngeal *N. gonorrhoeae* and *C. trachomatis* infections by nucleic acid amplification testing, and for serologic evidence of syphilis. Women provided cervicovaginal samples and men provided urine to screen for *T. vaginalis* by polymerase chain reaction.

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No conflict of interest exists for any of the authors.

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Results—Thirteen percent of participants had a prevalent STD at enrollment and 7% an incident STD six months later. The most commonly diagnosed infections were rectal chlamydia, oropharyngeal gonorrhea, and chlamydial urethritis among the men, and trichomoniasis among the women. Other than trichomoniasis, 94% of incident STDs were identified in MSM. Polysubstance abuse other than marijuana, and having 4 sex partners in the six months prior to testing were associated with diagnosis of an incident STD.

Conclusions—STDs were commonly diagnosed among contemporary HIV-infected patients receiving routine outpatient care, particularly among sexually active MSM who used recreational drugs. These findings underscore the need for frequent STD screening, prevention counseling, and substance abuse treatment for HIV-infected persons in care.

Keywords

HIV infection; sexual risk; sexually transmitted infections

INTRODUCTION

The HIV epidemic continues unabated in the United States, with men who have sex with men (MSM) accounting for more than half of incident HIV infections, and African Americans being disproportionately affected compared with other racial or ethnic groups¹. Although about half of new HIV infections are transmitted by persons who do not know they are HIV infected², the rest are due to contact with individuals who are aware of their infection. HIV disease is now a chronic manageable illness requiring multiple regular contacts with medical care providers for optimal clinical outcomes³. Thus, HIV clinicians have a unique opportunity to routinely screen their patients for sexually transmitted diseases (STDs), and to assess their risk for HIV and STD transmission. Of particular concern are patients who are not on suppressive antiretroviral therapy, have an STD, or who are engaging in unprotected anal or vaginal intercourse, since each of these factors increases the likelihood of transmitting HIV^{4,5}. To better understand the factors associated with HIV and STD transmission behaviors among HIV-infected persons, we estimated STD prevalence and incidence, and associated risk factors, among HIV-infected persons enrolled in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (the 'SUN' Study), a prospective cohort study led by the Centers for Disease Control and Prevention (CDC).

METHODS

The SUN Study

The SUN Study is a prospective, observational cohort study that monitors the clinical course of HIV-infected individuals treated with highly active antiretroviral therapy (HAART) from seven HIV-specialty clinics in four US cities: St. Louis, Missouri (25% of the enrollees); Providence, Rhode Island (27%); Minneapolis, Minnesota (34%); and Denver, Colorado (13%)⁶. Of 1346 potential participants who met enrollment criteria, 700 HIV-infected patients were enrolled between March 1, 2004 and June 30, 2006. Reasons for non-enrollment generally focused on perceived study burden. The study's design, and its data collection and management methods have been described previously^{2,6}. Participants were generally healthy HIV-infected adults receiving routine outpatient care and were either treatment naïve, or had only been treated with HAART. Patient data, including sociodemographic characteristics, all diagnoses and treatments (including dosage and duration of all medications), and all clinical laboratory data were abstracted from medical charts and entered into an electronic database (Clinical Practice Analyst; Cerner Corporation, Vienna, VA) by trained staff. These data were reviewed for quality and

analyzed centrally. Additional data were collected through physical examination, non-invasive imaging, comprehensive testing for STDs, and an audio computer-assisted self interview (ACASI). The ACASI collected behavioral risk data and other health-related information including selected family history variables and use of tobacco, alcohol and non-prescribed (i.e., recreational) drugs. The study protocol was approved and reviewed annually by the CDC and each participating site's institutional review board.

Testing for sexually transmitted diseases

At study enrolment (i.e., baseline) and every 6 months thereafter, study nurses screened participants for oropharyngeal and rectal *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) infections using swabs provided by the APTIMA COMBO 2® nucleic acid amplification test kits (Gen-Probe, Inc; San Diego, CA). The specimens were tested centrally at CDC. Genitourinary *Neisseria gonorrhoeae* and *Chlamydia trachomatis* testing was performed using the FDA-approved commercial method employed at each local clinic's laboratory. Women were screened for vaginal *Trichomonas vaginalis* (TV) infection using self-administered swabs and men were screened for TV using centrifuged urine pellets by polymerase chain reaction^{6,7}; this testing was conducted centrally at Emory University. Site staff were centrally trained to ensure diligence with regard to specimen handling and shipping to optimize the integrity of test results. Sera were tested for syphilis at each site using non-specific assays (e.g., VDRL, RPR) with reflex confirmation assays (e.g., MHA-TP, FTA-Abs) if positive. Medical record abstracted data were reviewed by Infectious Disease physicians, who categorized new infectious from previously treated ones using common clinical algorithms, based on USPHS guidelines. Symptom data for GC, CT and TV infections were collected at the time of specimen collection on specimen collection forms.

Statistical analysis

The outcome variables included prevalent and incident STD diagnoses at baseline and 6 months later, respectively. Assuming all prevalent STDs were treated at baseline, an incident STD was defined as a new STD diagnosis at 6 months. The Mantel Haenszel χ^2 or Fisher's exact test was used to compare categorical variables and Student's *t*-test or the Kruskal-Wallis test was used to compare continuous variables in univariate analysis. Multivariate logistic regression models were used to explore associations with the outcome variables. Variables with a *p*-value < 0.10 in univariate analysis were entered stepwise into a regression model to determine the best multivariate model. *P*-values were two-tailed and considered significant at *p* < 0.05. All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Participant Characteristics

The sample consisted of 557 participants for whom complete STD data were available at the baseline and 6-month visits. This sample did not differ demographically from the larger group of participants for only whom baseline data were available. At baseline, the mean age was 42 years (range, 21– 69 years), 79% were men, 61% were non-Hispanic white and 10% were Hispanic. Almost two-thirds of the cohort consisted of men who described themselves per ACASI as men who had sex with men (65%), 21% were women, and 13% were self-described men who had sex with women. The median CD4 cell count of the participants was 479 cells/mm³ and 78% were currently prescribed HAART, of whom 87% had plasma HIV RNA levels of less than 400 copies/mL. Additional characteristics are shown in Table 1.

STD prevalence and incidence

At baseline, 13% of the participants had at least one STD (Table 2); all were asymptomatic. At baseline, participants from Denver and St. Louis had significantly higher STD prevalence (22% and 21%, respectively) than those enrolled in Minneapolis (10%) or Providence (9%) ($p = 0.001$). However, the six month follow-up STD rates did not significantly differ by site (data not shown). Rectal CT infection was most common (5%), followed by oropharyngeal GC infection (3%), trichomonas (3%), and urethral CT infection (2%). Approximately 1% of the cohort had syphilis, oropharyngeal CT infection or rectal GC infection. Two participants (one MSW, one woman) had asymptomatic urethral GC infection. Among women, 14% had vaginal TV infection at baseline. No significant differences in STD prevalence were seen when data were stratified by age, race/ethnicity, or level of education (data not shown). All STDs were treated by the participants' primary care providers according to standard of care. Six months later, 7% of the cohort had developed at least one new STD. Rectal CT infection remained most common (3%), with about 1% of the participants developing each of the other infections. No men were diagnosed with either prevalent or incident urethral TV infections.

The majority of the STD diagnoses were in MSM, who accounted for 65% of the prevalent and 87% of all of the incident STDs, and 82% and 94% of all prevalent and incident STD diagnoses excluding trichomoniasis. At baseline, 13% of the MSM in the study had an STD compared to 9% at 6 months. The most common STD among MSM was rectal CT infection, which was present in 7% of the MSM at baseline and 5% at the 6-month visit, followed by rectal GC infection (2% at baseline and 2% at 6 months) and oropharyngeal GC infection (3% and 1% respectively).

Among ten MSM who had at least one STD diagnosed at both the baseline and 6-month visits, seven had infections with either a new organism or infections with the same organism but at different anatomical sites. Of the other three men, two had rectal CT and one had oropharyngeal GC at both visits which were treated at baseline. By the time of the 6-month visit, 20% of the MSM had been diagnosed with one or more prevalent or incident STDs. Most of the GC and CT infections in MSM were detected at extra-genitourinary sites, with 86% and 88% infections at the baseline and 6-month visits, respectively, having been diagnosed at either the rectum or oropharynx.

Factors Associated with Prevalent and Incident STDs

Because the vast majority of the prevalent and incident STD's were diagnosed among MSM, additional analyses were performed to evaluate the factors associated with STD diagnoses in this population. MSM with prevalent and incident STDs were more likely to report unprotected anal sex, either insertive or receptive, and sex with four or more partners in the six months preceding testing ($p < 0.05$) (Table 3). Of note, 59% of the men with a prevalent STD and 37% of the men without a prevalent STD reported unprotected insertive or receptive anal sex, and 65% of the men with an incident STD and 34% of the men without an incident STD reported unprotected insertive or receptive anal sex. The percentage of MSM reporting unprotected anal sex did not decrease between the baseline and 6-month visits ($p = 0.257$). MSM with a prevalent STD were more likely to report insertive or receptive anal sex compared with MSM without an STD ($p = 0.006$ and $p < 0.001$, respectively); this difference remained significant for incident cases ($p = 0.002$ and $p = 0.007$, respectively). At least 60% of the men engaged in unprotected oral sex at either visit. Overall, 27% of the MSM in the SUN Study cohort had detectable plasma HIV RNA (Table 1), which included 29% of the 49 men with a prevalent STD and 24% of the 34 men with an incident STD.

Recreational drugs were commonly used by the MSM in the study (Table 3). About one-third of the men (35% at baseline and 32% at 6 months) reported using marijuana in the prior 6 months; 29% reported inhaling volatile nitrites at baseline and 28% at 6 months; 18% used erectile enhancement drugs at baseline and 20% at 6 months; 10% of the men reported cocaine use at baseline and 10% at 6 months. Although heroin use and any drug injection was rare in the cohort (two men reported using heroin at baseline and at 6 months; six men reported injecting drugs at baseline and five men at 6 months), alcohol abuse (at least 5 drinks at one time or bingeing at least once per week) was common, reported by 32% of the men at baseline and 31% at 6 months.

In univariate analyses, factors associated with having a prevalent STD included unprotected insertive or receptive anal, unprotected insertive oral sex, having four or more partners in the prior 6 months, and use of erectile dysfunction agents (Table 4). In the multivariate analysis, only having four or more partners in the prior 6 months remained significantly associated with diagnosis of a prevalent STD. In the univariate analysis, factors associated with having an incident STD included unprotected insertive or receptive anal, use of inhaled nitrites (i.e., poppers), polysubstance abuse (other than marijuana), use of club or party drugs, and use of erectile dysfunction agents (Table 4). In multivariate analysis, factors independently associated with diagnosis of an incident STD were having four or more partners and polysubstance abuse (other than marijuana) (Table 4). Variables that were not associated with increased risk for a prevalent or incident STD included age, race/ethnicity or educational status (data not shown).

Status of partners of MSM with an incident STD

Twenty-nine of the 34 (85%) MSM who had an incident STD reported unprotected anal or oral sex with at least one partner. Among these 29 MSM, 31% reported at least one episode of unprotected insertive anal sex, and 48% reported at least one episode of unprotected receptive anal sex with an HIV-uninfected partner or partner of unknown status (Table 5). The prevalence of unprotected oral sex with HIV-uninfected partners or partners of unknown status was 82% among MSM with an incident STD. Of these 29 men, six of 15 who reported unprotected insertive anal intercourse and four of the 18 who reported unprotected receptive anal intercourse only engaged in these practices with HIV-infected partners.

DISCUSSION

Despite the advent of HAART, which could conceivably slow the spread of HIV by decreasing the infectiousness of those who are treated⁸, the annual HIV incidence in the U.S. has remained unchanged during the past decade, with the number of new HIV diagnoses reported to CDC increasing among MSM, most notably among younger African-Americans¹. As reports from community-based samples have documented recent increases in sexual risk taking and STD diagnoses that could increase risk of HIV acquisition and transmission⁹⁻¹¹, our analysis demonstrates that a substantial subgroup of contemporary HIV-infected MSM in regular care have engaged in behaviors capable of transmitting HIV.

Although trichomoniasis was commonly diagnosed among women in this study, the majority of STDs were diagnosed among MSM, who were 65% of the whole sample and had 87% of the incident STDs. The high co-prevalence of STD's in HIV-infected MSM has been noted in other studies.¹² The relative under representation of women (21%) and Black/African-Americans (26%) is a limitation of the study, compromising the ability to make comparisons about differences in STD burden in these populations, compared to Caucasian MSM. Because all study participants received state-of-the-art counseling, and all diagnosed STDs were promptly treated when diagnosed, the incidence of new STDs was attenuated,

and would therefore constitute a lower estimate of what might be seen in less controlled environments..

Similar to other studies^{13,14}, the anatomic site where asymptomatic gonorrhea and Chlamydia infections were most frequently detected was the rectum, which can serve as a reservoir potentiating transmission of these infections^{15,16}. The substantial prevalence and incidence of these rectal infections among MSM highlight the need for simpler screening methods of at-risk patients to optimize the likelihood that busy clinical providers will adopt routine rectal screening of sexually active patients. At present however, none of several highly sensitive nucleic acid amplification tests, including the one used in this study, have been granted FDA approval for diagnostic use at rectal or oropharyngeal sites.

Not only did MSM diagnosed with an STD in this study report increased numbers of sexual partners, 29 (8%) were at particularly high risk for transmitting HIV and other STDs insofar as they reported unprotected sex at the time of their STD. Of these men, 9 of 15 who reported unprotected insertive anal intercourse and 14 of 18 who reported receptive anal intercourse had HIV seronegative or status unknown partners, potentially leading to new HIV transmissions (Table 5). The other men reported unprotected anal intercourse exclusively with other HIV-infected partners, which could result in new STD transmission and acquisition, and potential superinfection. Such “serosorting” (the practice of selecting sexual partners who are also HIV-infected) may explain reports that have noted disproportionately increased rates of STD diagnoses among HIV-infected MSM compared with other MSM^{17,18,19}.

MSM with an incident STD were more likely to report polysubstance use than MSM without an STD. These findings support other recent observations that have shown an association between new HIV infections and STDs among substance-using MSM^{20,21,22}. Crystal methamphetamine use has been shown to be particularly highly correlated with increased sexual risk behaviors and correspondingly with the acquisition and transmission of STDs, and has been shown to decrease medication adherence, increasing the risk of virological failure, making users more infectious to their partners^{23,24,25}. In the current study, more than one fourth of the MSM in care had detectable plasma HIV RNA, including 29% of the 49 men with a prevalent STD and 24% of the 34 men with an incident STD, making them at risk for the efficient transmission of antiretroviral-resistant strains. Some have suggested that increased risk taking behaviors among MSM may reflect treatment optimism; e.g., the belief that the diagnosis of HIV infection is no longer as severe as previously construed^{26,27}.

These findings underscore the important role that primary HIV care providers should play in diagnosing and treating STDs and in providing counseling and referrals that can lead to decreased HIV transmission behaviors.²⁸ From the patient’s perspective, syphilis and possibly other STDs, if untreated, can accelerate the course of HIV disease^{29,30,31}. Thus, current CDC guidelines recommend that providers routinely ask their patients about their sexual behaviors and screen them for STDs annually, and more often (i.e., every three to six months) if they have a past history of any STD or have engaged recently in sexual behavior capable of transmitting HIV or STDs³². The most recent guidelines of the U.S. Department of Health and Human Services note that use of effective antiretroviral therapy regardless of CD4 count is likely to reduce transmission to the uninfected sexual partner.³³

In summary, we found a high prevalence of asymptomatic STDs among HIV-infected patients receiving routine outpatient care, particularly among MSM, corroborating a global trend.^{34,35} Six months later, following effective treatment, we observed that almost 10% were diagnosed with a new STD and that MSM with STDs and detectable HIV viral loads

had continued to engage in high-risk sexual behaviors that could transmit their HIV infection to others. The large majority of STDs among MSM were rectal or oropharyngeal; in the absence of FDA-approved simple methods for their diagnosis (e.g., NAAT) at these anatomic sites, many of these STDs might have gone undiagnosed. Our findings suggest that efforts are needed to ensure that HIV-infected patients in care not only adhere to treatment for their own benefit, but that they be screened and treated for STDs and modify their behavior to decrease their risk of transmitting HIV to others. Sexually active HIV-infected patients should also be offered culturally appropriate risk reduction interventions that address the underlying factors potentiating sexual risk-taking behaviors, including substance use. Further research is needed to develop new clinic-based prevention interventions that can be readily integrated into comprehensive HIV care, that build on existing evidence-based prevention interventions^{36,37}, in order to limit further HIV transmission by patients in care.

Acknowledgments

The authors thank Jean Richardson and Joel Milam, Keck School of Medicine, University of Southern California, Los Angeles, California; Paul Maruff, David Darby, and Angela Caveney, CogState Ltd., Melbourne, Victoria, Australia and Pinckney, Michigan; Suzette Bartley and Dollene Hemmerlein, Division of Scientific Resources, National Center for Infectious Diseases, CDC, Atlanta, Georgia; John Papp, Carol Farshy, and Christi Phillips, Division of AIDS, STDs and Tuberculosis Laboratory Research, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC, Atlanta, Georgia; Elizabeth Unger and David Swan, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC, Atlanta, Georgia; Angela Caliendo, Jessica Ingersoll, Tameka Bythwood, and Deborah Abdul-Ali, Emory University, Atlanta, Georgia; Teresa Darragh, Mt. Zion Medical Center, University of California, San Francisco, California; Roger Fielding, Andrea Desilets, and Sara Farnan-Colleary, Gerald J, and Dorothy R. Fiedman Body Composition Analysis Center, Tufts Medical Center, Boston, Massachusetts; John Gottdiener and Shuying Li, Echocardiography Lab, University of Maryland Hospital, Baltimore, Maryland; Howard Hodis and Yanjie Li, Blankenhorn Research Fund, University of Southern California, Los Angeles, California; and Matt Budoff and Angel Salano, Harbor UCLA Research and Education Institute, University of California, Los Angeles, Torrance, California.

Source of Support: Financial support was received from Centers for Disease Control and Prevention contracts 200-2002-00610, 200-2002-00611, 200-2002-00612, 200-2002-00613, 200-2007-23633, 200-2007-23634, 200-2007-23635, and 200-2007-23636. This work was supported in part by the Emory Center for AIDS research (P30 AI050409).

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Table 1

Baseline Characteristics of Participants, the SUN Study

Baseline Characteristics	All Participants (n=557)(%)	MSM (n=365)(%)	MSW (n=73)(%)	Women (n=119)(%)
Race/ethnicity				
White, non-Hispanic	342 (61)	279 (76)	23 (32)	40 (34)
Black, non-Hispanic	145 (26)	47 (13)	38 (52)	60 (50)
Hispanic	57 (10)	34 (9)	9 (12)	14 (12)
Other/Unknown	13 (2)	5 (1)	3 (4)	5 (4)
Median age at baseline	42	42	43	39
(IQR)	(36 – 47)	(36 – 48)	(38 – 47)	(30 – 45)
High school graduate	467 (88)	326 (94)	55 (85)	86 (73)
Currently employed	327 (60)	249 (70)	35 (50)	43 (38)
Median CD4 cell count	479	485	464	465
(IQR)	(334 – 691)	(342 – 696)	(294 – 555)	(336 – 704)
Viral load < 400	397 (71)	266 (73)	55 (75)	76 (64)
ARV naive	68 (12)	45 (12)	6 (8)	17 (14)
Current cART	436 (78)	288 (79)	62 (85)	86 (72)
Years since HIV diagnosis	4.9	5.1	4.0	4.9
(IQR)	(2.2 – 8.1)	(2.2 – 8.1)	(1.9 – 7.8)	(2.5 – 8.3)

IQR= interquartile range; cART=combination antiretroviral therapy; ARV=antiretroviral; MSM=men who have sex with men; MSW=men who have sex with women

Table 2

Prevalence and Incidence of Sexually Transmitted Diseases (STDs) in the SUN Study

STD	Prevalent Infections (Baseline)			Incident Infections (6-Month Visit)			
	MSM (N=365)	MSW (N=73)	Women (N=119)	Total (N=557)	MSM (N=365)	MSW (N=73)	Women (N=119)
Anorectum:							
- <i>C. trachomatis</i>	27 (7%)	0 (0%)	2 (2%)	29 (5%)	18 (5%)	0 (0%)	0 (0%)
- <i>N. gonorrhoeae</i>	7 (2%)	0 (0%)	1 (1%)	8 (1%)	6 (2%)	0 (0%)	0 (0%)
Oropharynx:							
- <i>C. trachomatis</i>	2 (1%)	1 (1%)	2 (2%)	5 (1%)	7 (2%)	0 (0%)	0 (0%)
- <i>N. gonorrhoeae</i>	12 (3%)	1 (1%)	2 (2%)	15 (3%)	5 (1%)	0 (0%)	2 (2%)
Genitourinary							
- <i>T. vaginalis</i>	0 (0%)	0 (0%)	17 (14%)	17 (3%)	0 (0%)	0 (0%)	3 (3%)
- <i>C. trachomatis</i>	8 (2%)	0 (0%)	3 (3%)	11 (2%)	3 (1%)	0 (0%)	0 (0%)
- <i>N. gonorrhoeae</i>	0 (0%)	1 (1%)	1 (1%)	2 (< 1%)	2 (1%)	0 (0%)	0 (0%)
Syphilis	5 (1%)	0 (0%)	0 (0%)	5 (1%)	2 (1%)	0 (0%)	0 (0%)
Any STD (1)	49 (13%)	3 (4%)	23 (19%)	75 (13%)	34 (9%)	0 (0%)	5 (4%)
- excluding <i>T. vaginalis</i>	49 (13%)	3 (4%)	8 (7%)	60 (11%)	34 (9%)	0 (0%)	2 (2%)
2 STDs	9 (2%)	0 (0%)	3 (3%)	12 (2%)	7 (2%)	0 (0%)	0 (0%)

Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women

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Table 4

Logistic Regression Analysis of Factors Associated with Prevalent and Incident STDs* among Men Who have Sex with Men, the SUN Study

Risk Factors	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p value [†]	OR (95% CI)	p value [†]
<i>For Prevalent STDs</i>				
Unprotected receptive anal sex	2.31 (1.25 – 4.26)	0.007		
Unprotected insertive anal sex	3.30 (1.76 – 6.16)	< 0.001		
Unprotected insertive oral sex	3.25 (1.55 – 7.68)	0.003		
4 partners	4.81 (2.59 – 9.13)	< 0.001	4.81 (2.59 – 9.13)	< 0.001
Use of inhaled nitrites	1.84 (0.98 – 3.41)	0.054		
Use of erectile dysfunction agents	2.00 (0.98 – 3.91)	0.048		
<i>For Incident STDs</i>				
Unprotected receptive anal sex	3.01 (1.47 – 6.22)	0.002		
Unprotected insertive anal sex	2.65 (1.27 – 5.45)	0.008		
Unprotected insertive oral sex	2.16 (0.99 – 5.23)	0.067		
4 partners	4.54 (2.18 – 9.64)	< 0.001	3.44 (1.82 – 7.56)	0.001
Use of inhaled nitrites	2.18 (1.05 – 4.47)	0.034		
Use of club or party drugs (including methamphetamine)	4.26 (1.55 – 10.7)	0.003		
Polysubstance abuse (other than marijuana)	7.58 (2.93 – 18.9)	< 0.001	5.00 (1.82 – 13.2)	0.002
Use of erectile dysfunction agents	3.18 (1.49 – 6.62)	0.002		

STD = sexually transmitted diseases; OR= odds ratio; CI=confidence interval

* STDs include syphilis, and oropharyngeal, rectal and urine *Neisseria gonorrhea* and *Chlamydia trachomatis*

[†] p-value calculated using Wald chi-square test

Table 5

HIV Status of Partners of Men Who Have Sex with Men with an Incident STD at the 6-Month Visit and Who Reported Unprotected Sexual Activity in the Preceding Last 6 Months (n=29), the SUN Study

Sex Behaviors	HIV Status of Partner			
	Positive	Negative	Unknown	Unknown or Negative
<i>Anal sex (n=22)</i>				
Insertive(n=15)(%)	10 (67)	1 (7)	8 (53)	9 (60)
Receptive (n=18)(%)	12 (67)	6 (33)	11 (61)	14 (78)
<i>Oral sex (n=28)</i>				
Insertive (n=26) (%)	16 (62)	13 (50)	15 (58)	23 (88)
Receptive (n=26) (%)	13 (50)	12 (46)	17 (65)	24 (92)