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Incidence of Sexually Transmitted Infections in HIV-Infected and HIV-Uninfected Adolescents in the United States

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Summary

Little is known about the incidence of bacterial sexually transmitted infections (STIs) among HIV-infected vs. HIV-uninfected adolescents. This secondary analysis of a national, multisite study included adolescents aged 12–18 years who were behaviorally HIV-infected (n=346) or HIV-uninfected but at-risk (n=182). Incidence rates of bacterial STIs (gonorrhea, chlamydia [CT], and trichomonas [TV; females]) were calculated using Poisson modeling. Factors associated with incident STIs were explored using Cox proportional hazards modeling. HIV-infected vs. HIV-uninfected women had higher TV incidence (1.3 vs. 0.6/100 person-months; p=0.002). HIV-uninfected vs. HIV-infected women had higher CT incidence (1.6 vs. 1.1/100 person-months; p=0.04). Among women, demographic, behavioral, and HIV-related factors were associated with incident STIs. Among men, there were no differences in incident STIs. In this first analysis comparing STI incidence between HIV-infected and HIV-uninfected adolescents, bacterial STI incidence among women significantly differed by HIV status, and factors associated with incident STIs varied by STI and HIV status.

Keywords

Adolescent; HIV; STI; Incidence

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Introduction

Human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) remain prominent public health issues for youth in the U.S. More than one-third of new HIV infections occur in persons aged 13–29 years,¹ and the highest rates of *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) occur in this age group.² STIs are associated both with increased risk of HIV transmission via increased HIV-1 RNA viral load (VL) in genital secretions³ and with increased risk of HIV acquisition.⁴ Further understanding of these related epidemics in adolescents will allow clinicians to target their prevention and screening efforts more effectively.

STI incidence has been described in HIV-infected adults, particularly women, but is less well understood in adolescents. Among adult women, HIV infection was not associated with *Trichomonas vaginalis* (TV) infection.^{5,6} Factors associated with incident STIs among HIV-infected adults included higher CD4+ T-cell (CD4) count,⁷ and current antiretroviral therapy (ART) and lower VL (among men).⁸ One previous study examined STI incidence among HIV-infected adolescent women over an 18-month period.⁹ However, because adolescents are at high risk for STIs, comparing incidence rates between HIV-infected and HIV-uninfected adolescents is necessary to determine differences in risk factors between these populations and whether STI incidence may be associated with HIV-infection related factors such as CD4 count, VL, disease stage, and/or ART.

The aims of this study were to determine rates of incident bacterial STIs (GC, CT, and TV) and factors associated with incident STIs among adolescents who are HIV-infected or HIV-uninfected but at risk. We used data from the Reaching for Excellence in Adolescent Care and Health (REACH) project, a multicenter longitudinal cohort study conducted through the Adolescent Medicine HIV/AIDS Research Network in the U.S. from 1996–2000.

Materials and Methods

The parent study, REACH, was an observational study designed to improve understanding of HIV infection and its comorbidities (including STIs) among adolescents.^{10,11} Adolescents with HIV were behaviorally infected, predominantly through sexual exposure.¹² HIV-uninfected adolescents were sexually experienced and matched for substance use, age, gender, race, ethnicity, and clinical site. Participants, aged 12–18 years at recruitment, underwent audio computer-assisted self-administered interview assessment of sexual behaviors and gynecologic/urogenital examination every 6 months. For HIV-infected adolescents, VL was obtained every 3 months, and CD4 counts were obtained every 6 months. STI testing was conducted using ligase chain reaction (LCR) of cervical and urinary samples every 6 months and anal samples every 12 months, independent of symptoms or exposure. Evaluation for TV in women included saline wet mount and trichomonal cultures every 6 months; trichomonads also were identified incidentally on Papanicolaou testing. STIs were treated per Centers for Disease Control and Prevention recommendations. Further description of STI-related methods has been published.¹³ For the current analysis, data were available for 548 participants. Inclusion was limited to those who had at least one follow-up visit (17 excluded). Three participants who became HIV-infected during the study were

excluded. Therefore, 528 adolescents were included. This secondary analysis was reviewed by the relevant Institutional Review Board and deemed nonhuman subjects research.

Primary outcome variables were (1) incidence of GC, (2) incidence of CT, (3) incidence of TV (women only), and (4) incidence of any bacterial STI (GC, CT, and, for women, TV). For GC and CT, incident infection was defined as any positive LCR testing of cervical, urinary, or anal samples at any visit after the baseline visit. Incident TV infection was defined as any positive laboratory testing for TV via saline wet mount, trichomonal culture, or Papanicolaou testing. Length of follow-up was defined as the time between the baseline visit and either the first positive STI test or the last visit with STI testing for those remaining STI negative.

To determine factors associated with incident STIs, predictor variables were examined, including demographic, behavioral, and HIV infection-related variables. Demographic variables included age at study entry, gender, and race (categorized as black non-Hispanic vs. other). Behavioral variables included age at first sexual intercourse (vaginal or anal), lifetime number of sexual partners (baseline), number of sexual partners in the prior 3 months, number of new sexual partners in the prior 3 months, and, for men, history of sexual contact with another man. For HIV-infected participants, additional variables included history of ART (baseline), current ART, VL, CD4 count, and CDC HIV disease classification stage.

Descriptive analyses were performed to examine participant characteristics and predictor variables. Incidence rates for STIs were computed using Poisson modeling and stratified by gender and HIV status. Cox proportional hazards modeling was used to determine factors associated with incident STI, stratified by gender and HIV status. This strategy allowed for inclusion of time-varying covariates, including number of partners in the prior 3 months, number of new partners in the prior 3 months, current ART, VL, CD4 count, CDC classification stage, and, for men, sexual contact with another man. Proportional hazards assumptions were assessed using Schoenfeld's residuals. VL and CD4 count were $\log_{10}$ transformed to maintain consistency with the published literature. Predictor variables were entered in a stepwise manner, and those with $p < 0.05$ were considered to be significantly associated with the outcome variable.

Results

Baseline characteristics

Demographic data are presented in Table 1. Mean age at study entry was 16.8 years; 76% of participants were female. The majority (69%) were black non-Hispanic. Mean age at first sexual intercourse was 13.6 years. Mean follow-up time was 31.8 months; HIV-infected participants had significantly longer follow-up periods. HIV-infected participants had a greater number of lifetime partners, and more HIV-infected (vs. HIV-uninfected) males reported sexual contact with another male

STI incidence

Incidence of CT was significantly greater in HIV-uninfected vs. HIV-infected women (1.6 vs. 1.1/100 person-months; $p=0.04$). Incidence of TV was significantly greater in HIV-infected vs. HIV-uninfected women (1.3 vs. 0.6/100 person-months; $p=0.002$). No significant difference was detected between HIV-infected and HIV-uninfected women in incidence of GC (0.6 vs. 0.4/100 person-months; $p=0.16$) or any bacterial STI (2.5 vs. 2.2/100 person-months; $p=0.41$). GC incidence was higher among HIV-infected vs. HIV-uninfected men (0.76 vs. 0.18/100 person-months), which approached significance ($p=0.05$). There was no significant difference between HIV-infected vs. HIV-uninfected men in incidence of CT (1.3 vs. 0.8/100 person-months; $p=0.22$) or any bacterial STI (1.7 vs. 0.9/100-person months; $p=0.10$).

Multivariable analyses

Among women, factors associated with incident STI differed by HIV status (Table 2). Among HIV-uninfected women, younger age and having one new partner in the prior 3 months were associated with CT infection, black non-Hispanic race was associated with TV infection, and having one new partner in the prior 3 months was associated with any bacterial STI.

For HIV-infected women, having three or more partners in the prior 3 months was associated with GC infection. Black non-Hispanic race, not currently taking ART, intermediate disease stage, and having more than three partners in the prior 3 months were associated with TV infection among HIV-infected women. Younger age, black non-Hispanic race, and having any partners in the prior 3 months were associated with any bacterial STI. In contrast to the analyses involving women, analyses of men demonstrated that no factors were significantly associated with incident STIs.

Discussion

We examined the incidence of bacterial STIs and factors associated with incident STIs in a longitudinal cohort of HIV-infected and HIV-uninfected adolescents. Although data were collected several years ago, the findings remain relevant: it is unlikely that significant changes in risk behavior have occurred because adolescents remain at highest risk for STIs. Our study is unique because it compares incidence rates between HIV-infected and HIV-uninfected adolescents recruited nationally from multiple sites, examines the impact of multiple HIV infection-related factors on incident STIs, and assesses STIs among adolescents over a longer follow-up period than reported previously. Understanding factors associated with incident STIs and how these factors may differ between HIV-infected and HIV-uninfected adolescents will allow clinicians to tailor their STI screening efforts to target those at highest risk.

HIV-infected adolescents acquired new STIs, indicating that these youth continue to practice risky sexual behaviors despite receiving standardized prevention counseling as part of the REACH study.¹⁰ Adults¹⁴ and adolescents¹⁵ often continue risky sexual behavior following their HIV diagnosis. Although brief office-based interventions targeting risky sexual

behavior among HIV-infected adults have been associated with lower rates of unprotected sex,¹⁶ similar effective interventions targeting behaviorally infected adolescents are needed.

Among women, incidence of CT and TV infection differed by HIV status. HIV-uninfected women had a higher incidence of CT than HIV-infected women, consistent with findings among adults.¹⁷ We found that HIV-infected women, compared to HIV-uninfected women, had a higher incidence of TV, which is consistent with one study of adult women¹⁸ although other studies did not find this association.^{5,6,17} In a prior study of HIV-infected adolescents, the combined incidence of CT, GC, TV, and syphilis was 1.4 per 100 person-months,⁹ which is somewhat lower than the rate in the current study for the combined incidence of CT, GC, and TV. Overall the rates of STIs in our study are higher than those previously published,¹⁹ which may reflect differences in the populations from which participants were recruited. Most HIV-infected REACH participants acquired HIV through sexual exposure, and the HIV-uninfected participants were recruited from the same clinical sites, were all sexually active, and were matched for drug-taking behaviors. Thus, the REACH cohort includes adolescents at particularly high risk for STIs.

Among women, factors associated with bacterial STIs differed based on HIV status. The difference in type of sexual partner associated with incident STI (new partners for HIV-uninfected women and any partners for HIV-uninfected women) may be related to the risk behaviors of those partners. For HIV-uninfected women, new partners may bring STIs into relationships. In contrast, for HIV-infected women who acquired HIV via sexual transmission, ongoing partners may be at particularly high risk for STIs. Race was associated with STIs, particularly TV, but such racial differences may reflect other less easily measured constructs, such as poverty or residence in communities with a high prevalence of STIs.²⁰ Prior studies have shown that personal sexual behavior does not account for such racial differences in rates of STIs,^{21,22} suggesting that sexual mixing patterns also may play an important role in explaining this difference.²² Younger age was associated with STIs in both HIV-infected and HIV-uninfected women, which may reflect poor condom use among this age group owing to the perception of invulnerability to STIs²³ or poor self-efficacy for condom use.²⁴ Younger women may also have less power in relationships, which may negatively impact their ability to negotiate condom use.²⁵ Programs targeting younger adolescents are needed to provide prevention messages to this vulnerable age group.

Among women, HIV infection-related variables were associated only with incident TV, with women not currently taking ART at increased risk of acquiring TV. Among adult women, ART use and higher CD4 count were associated with lower rates of TV infection in one study,⁶ but other studies found no association between TV infection and ART use²⁶ or CD4 count.⁵ Adolescent women not taking ART may practice riskier sexual behaviors, such as inconsistent condom use.¹⁴ Intermediate, but not late, CDC disease stage was also associated with increased risk of incident TV infection. Participants with more advanced HIV disease may be less likely to engage in sexual activity²⁷ and thus less likely to acquire STIs.

The incidence of GC, CT, and any bacterial STI was higher in HIV-infected vs. HIV-uninfected men, but this difference failed to reach statistical significance. The lack of significant findings among men in this study is most likely related to the small number of male participants and the small number of STI events among men. Some differences between HIV-infected and uninfected men may also be related to differences in male-to-male sexual exposure. Future studies recruiting larger numbers of adolescent men are needed to further explore the potential role of HIV infection-related factors in STIs.

This study is subject to several limitations. First, because this study is a secondary analysis, covariates and outcomes were limited to those available in the dataset; however, the dataset was appropriate to address the study aims. Second, no pharyngeal STI testing was performed; therefore, the presented incidence of STIs may be underestimated. Third, participants may have received STI diagnoses and treatment from providers who were not affiliated with the study site, leading to underestimation of STI incidence. Last, generalizability of these findings may be impacted by two factors. First, the antiretroviral regimens used during REACH differed from those in use currently. Although current ART was protective for acquisition of TV in our study, newer ART regimens may affect STI acquisition differently. If the impact of current ART on TV is due to immune system recovery, we expect any ART regimen to have a similar impact. Second, LCR testing, which is no longer commercially available, was used to detect STIs in this study. However, currently available nucleic acid amplification tests have similar performance characteristics when compared to LCR. Although LCR was withdrawn in 2003 due to concerns about test sensitivity, the last LCR testing for REACH occurred in January 2001, prior to any issues related to test performance.

In this first analysis comparing rates of incident STIs between HIV-infected and HIV-uninfected adolescents, rates of bacterial STIs significantly differed among women, and factors associated with incident STIs among women varied by STI and HIV status. Because younger women were at higher risk of incident STIs, developmentally appropriate prevention messages targeting younger adolescents need to be designed in order to impact the overall rate of STIs. HIV-infected adolescents contracted new STIs, indicating continued sexual risk behaviors despite receipt of standard prevention counseling. This suggests that new effective interventions tailored to the unique needs of HIV-infected adolescents are needed in order to decrease their risk of STI acquisition and HIV transmission to uninfected sexual partners.

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Abbreviations

HIV human immunodeficiency virus

STI	sexually transmitted infection
GC	<i>Neisseria gonorrhoeae</i>
CT	<i>Chlamydia trachomatis</i>
VL	HIV-1 RNA viral load
TV	<i>Trichomonas vaginalis</i>
CD4	CD4+ T-cell
ART	antiretroviral therapy
SD	standard deviation
REACH	Reaching for Excellence in Adolescent Care and Health
LCR	ligase chain reaction
CDC	Centers for Disease Control and Prevention
AIDS	acquired immune deficiency syndrome

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Table 1

Baseline Participant Demographics: Total, and by HIV status

Characteristic	Total (n=528)	HIV-Uninfected (n=182)	HIV-Infected (n=346)	p-value ^I
Age at study entry, mean (SD), years	16.8 (1.1)	16.6 (1.2)	16.9 (1.1)	0.01
Follow-up time, mean (SD), months	31.8 (14.7)	28.4 (14.6)	33.7 (14.5)	<0.001
Female, Number (%)	399 (76)	142 (78)	257 (74)	0.34
Race, Number (%) ²				0.01
Black non-Hispanic	364 (69)	113 (62)	251 (73)	
Other	163 (31)	69 (38)	94 (27)	
Age at first intercourse, mean (SD), years ³	13.6 (1.7)	13.9 (1.6)	13.5 (1.7)	0.01
Range	(9, 18)	(9, 18)	(9, 18)	
Lifetime sexual partners (baseline), Number (%) ^{3,4}				<0.001
4		75 (43)	93 (28)	
5–10		60 (34)	118 (36)	
>10		39 (22)	120 (36)	
Sexual partners in prior 3 months (baseline), Number (%) ^{3,4}				0.15
0		45 (25)	110 (32)	
1–2		111 (61)	181 (52)	
3		26 (14)	55 (16)	
New sexual partners in prior 3 months (baseline), Number (%) ^{3,4}				0.47
0		98 (56)	166 (52)	
1		50 (29)	90 (28)	
2		27 (15)	63 (20)	
Males reporting male sexual contact (baseline), Number (%) ^{3,4}		19 (50)	72 (81)	<0.001
Ever received ART, Number (%)				
Currently receiving ART, Number (%) ⁵				
Viral load				
Mean (SD)			35,777 (118,864)	
Median (minimum, maximum)			4300 (40, 1,400,000)	
CD4 count				
Mean (SD)			513 (261)	

Characteristic	Total (n=528)	HIV-Uninfected (n=182)	HIV-Infected (n=346)	p-value ¹
Median (minimum, maximum)			480 (0, 1449)	
CDC progression stage, Number (%) ²				
Early			168 (49)	
Intermediate			118 (34)	
Late			60 (17)	

HIV: human immunodeficiency virus; SD: standard deviation; ART: antiretroviral therapy; CDC: Centers for Disease Control and Prevention; CD4: CD4+ T-cell; PI: protease inhibitor; AIDS: acquired immune deficiency syndrome

¹ p-value from two-sample *t*-test for continuous variables and from chi-square test for categorical variables.

² For analysis, all other race/ethnicity categories were combined.

³ All values were from baseline visit or, if missing at baseline visit, from first report following baseline visit.

⁴ Denominators may vary due to missing data.

⁵ Breakdown of current ART regimens, Number (%):

Monotherapy, no PI	23 (15.1%)
PI only	2 (1.3%)
Combo without PI	71 (46.7%)
Combo with PI	56 (36.8%)

⁶ CDC disease stage determination:

Early: CD4 count 200 AND no AIDS indicative illness or symptoms; OR AIDS symptoms with CD4 count 500

Intermediate: CD4 count < 200 AND no AIDS indicative illness or symptoms; OR AIDS symptoms with CD4 count 200–499; OR AIDS indicative illness with CD4 count 500.

Late: CD4 count <200 with AIDS symptoms; OR AIDS indicative illness with CD4 count < 500

Table 2

Factors independently associated with incident STI among women, by HIV status

STI	Predictor Variable	HIV-Uninfected (n=142) [/] Hazard Ratio (95% CI)	HIV-Infected (n=257) ² Hazard Ratio (95% CI)
Gonorrhea	Sexual partners in prior 3 months, No.	None	1.53 (0.75, 3.10)
	1-2 vs. 0		2.88 (1.06, 7.80)
Chlamydia	3 vs. 0		None
	Younger age (continuous)	1.39 (1.08, 1.79)	
	New sexual partners in prior 3 months, No.		
	1 vs. 0	2.14 (1.10, 4.17)	
Trichomonas	2 vs. 0	1.66 (0.62, 4.48)	
	Black non-Hispanic	2.99 (1.02, 8.79)	2.08 (1.11, 3.88)
	Not currently receiving ART		1.89 (1.20, 2.99)
	CDC disease stage		
	Intermediate vs. early		1.81 (1.12, 2.91)
	Late vs. early		0.97 (0.49, 1.91)
Any bacterial STI	Sexual partners in prior 3 months, No.		
	1-2 vs. 0		1.56 (0.93, 2.63)
	3 vs. 0		2.47 (1.17, 5.23)
	Younger age (continuous)		1.16 (1.01, 1.34)
	Black non-Hispanic race		1.59 (1.03, 2.47)
	Sexual partners in prior 3 months, No.		
	1-2 vs. 0		1.62 (1.08, 2.44)
	3 vs. 0		3.12 (1.80, 5.40)
	New sexual partners in prior 3 months, No.		
	1 vs. 0	2.11 (1.18, 3.76)	
	2 vs. 0	1.21 (0.46, 3.18)	

STI: sexually transmitted infection; HIV: human immunodeficiency virus; No.: number; CI: confidence interval; ART: antiretroviral therapy

[/] Covariates included age at study entry, race, number of lifetime partners at baseline (categorical), age at first intercourse, number of sexual partners in the prior 3 months (time-varying covariate), and number of new sexual partners in the prior 3 months (time-varying covariate). Due to significant correlation between number of sexual partners in the prior 3 months and number of new sexual partners in the prior 3 months, analyses were conducted stepwise with each of these variables in turn.

² Covariates included the variables in 1 above, as well as additional HIV-related variables including ever received ART, current ART (time-varying), viral load (log10 transformed, time-varying), CD4 count (log10 transformed, time-varying), and CDC disease progression stage (time-varying).