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Incident Anal HPV and HPV-Related Sequelae in HIV-Infected vs. HIV-Uninfected Adolescents in the United States

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Abstract

Background—Little is known about the incidence of anal HPV infection and related sequelae, and factors associated with these outcomes, among adolescents who are HIV-infected vs. uninfected but at-risk.

Methods—We analyzed data from a multisite U.S. study, the Reaching for Excellence in Adolescent Care and Health Project. Adolescents aged 12–18 years who were behaviorally HIV-infected (n=319) or HIV-uninfected but at-risk (n=177) were recruited. Incidence rates for anal HPV, high-risk anal HPV, anogenital warts, and anal dysplasia were calculated using Poisson modeling. Factors associated with these outcomes were examined using Cox proportional hazards modeling.

Results—Mean age at entry was 16.8 years; mean follow-up time for detection of anal HPV was 22.4 months (SD 10.8). Most participants (76%) were female; 70% were black non-Hispanic. HIV-infected (vs. -uninfected) women had significantly higher incidence of anal HPV (30 vs. 14 per 100 person-years; p=0.002), high-risk anal HPV (12 vs. 5.3 per 100 person-years; p=0.04), and anogenital warts (6.7 vs. 1.6 per 100 person-years; p=0.002) but not anal dysplasia. Although incidence rates were higher for these outcomes among HIV-infected vs. -uninfected men, the differences were not statistically significant. Among women, factors associated with anal HPV and related sequelae differed by HIV status and included biological, behavioral, and HIV-related factors. No factors were associated with outcomes in men.

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Conflicts of Interest

Dr. Mullins and the co-authors have no relevant conflicts of interests to disclose.

Conclusions—HIV-infected vs. -uninfected adolescent women had higher rates of anal HPV and anogenital warts. Because HIV-infected youth are at increased risk of these outcomes, enhanced HPV prevention efforts, such as vaccination, are warranted for this group.

INTRODUCTION

Anogenital human papillomavirus (HPV) is a common sexually transmitted infection (STI) in the U.S. The prevalence of anal HPV infection is 27–51% in adult women^{1–4} and 24–42% in adult men.^{5,6} HPV viral types are classified as low-risk or high-risk based on their oncogenic potential. Infection with low-risk types 6 or 11 is associated with anogenital warts. Persistent anal infection with high-risk types, including types 16 and 18, is associated with the development of anal dysplasia and anal cancer. Among adults, incident anal HPV infection has been associated with greater number of sexual partners,^{1,2,5} baseline anal HPV infection,^{1,5} and anal intercourse.¹ However, little is known about the acquisition of anal HPV, or factors associated with acquisition, among adolescents because most studies of incident anal HPV infection have been conducted in adults, who may have more lifetime sexual partners and a longer duration of sexual experience when compared to adolescents.

Adults who are infected with human immunodeficiency virus (HIV) are disproportionately affected by HPV and its sequelae,^{3,7} and anal carcinoma incidence has increased over time among HIV-infected adults.⁸ However, the impact of HIV infection on acquisition of new HPV infection, or development of HPV-related sequelae, may differ for HIV-infected adolescents compared to HIV-infected adults because adolescents may not have developed the same degree of immunosuppression. A previous study (using the cohort of HIV-infected and uninfected youth examined in the present study) demonstrated that HIV-infected, compared to HIV-uninfected, adolescents had a higher prevalence of anal HPV infection, although this finding was significant only among women; HIV infection was independently associated with prevalent abnormal anal cytology in men.⁹ Higher prevalence of anal HPV and related sequelae among HIV-infected vs. uninfected adolescents may be related to increased rates of HPV acquisition or decreased rates of HPV clearance. To our knowledge, no prior studies have explored acquisition of new anal HPV infections as an explanatory factor for these differences in anal HPV prevalence among HIV-infected vs. HIV-uninfected adolescents.

Because anal HPV infection can result in significant long term sequelae, including anogenital warts, anal dysplasia, and anal cancer, determining factors associated with acquisition of anal HPV is an important first step in designing interventions to decrease rates of infection. HIV infection may impact both incidence rates of HPV and related sequelae and the factors that are associated with incident anal HPV infection. Therefore, the objectives of this study were to determine rates of incident anal HPV infection (overall and high-risk anal HPV) and related sequelae (anogenital warts and anal dysplasia), and factors associated with these outcomes, among adolescents who are HIV-infected and HIV-uninfected but at risk, over the course of a 6 year study. Data for the present study originated from the Reaching for Excellence in Adolescent Care and Health (REACH) project, a multisite longitudinal cohort study conducted in the U.S. through the Adolescent Medicine HIV/AIDS Research Network (AMHARN) from 1996–2001.

MATERIALS AND METHODS

The parent study for this secondary analysis, REACH, has been described previously.¹⁰ The overall aims of REACH were to prospectively examine biomedical, behavioral, and psychosocial outcomes among HIV-infected adolescents aged 12–18 years at recruitment. Participants were recruited from 15 clinical sites across the U.S. HIV-infected adolescents were infected through sexual exposure or intravenous drug use (IVDU). Most youth were infected via sexual exposure; only 2 youth reported IVDU.¹¹ HIV-uninfected participants were matched for drug use behaviors and were all sexually experienced at the time of enrollment. In total, 578 participants enrolled in the study: 367 HIV-infected and 211 HIV-uninfected. Study visits occurred every 6 months and consisted of audio computer-assisted self-administered interview assessment of sexual behaviors and gynecologic/urogenital examination. For HIV-infected participants, HIV-1 RNA viral load (VL) testing and CD4+ T-cell (CD4) counts were measured as previously described.⁹ VL was performed every 3 months. CD4 counts and cervical HPV testing were performed every 6 months. Anal HPV testing and anal cytology were performed every 12 months. A Dacron swab was used by clinicians to obtain anal samples for HPV DNA testing and cytology. Samples were stored in PreservCyt solution (Cytoc Corp, Bosborough, Massachusetts, USA), and both HPV DNA testing and anal cytology analyses were performed from these samples in a centralized laboratory. HPV types were detected by a dot blot analysis for individual types as well as probe mixes (e.g. 31/33/35, 59/68/70). Anal cytology was classified according to the Bethesda rating system.¹² Details regarding anal HPV testing and cytology-related methods for the REACH study have been published previously.⁹

Data were available for 548/578 participants; 30 participants had no data collected after enrollment. Those who had no follow-up visits (N=17) and those who became HIV-infected during the study (N=3) were excluded. Analyses for each outcome were further restricted by excluding participants who had the outcome at baseline or insufficient follow-up data, leaving 496 participants eligible for inclusion in at least one of the analyses: 319 HIV-infected (238 women, 81 men) and 177 HIV-uninfected (139 women, 38 men). For analyses of any anal HPV infection and high risk anal HPV infection, 261 individuals were eligible for analyses: 31 participants had no HPV testing results, 164 were positive for anal HPV at baseline or had only one visit with a positive HPV test and no other HPV testing, and 72 had only one HPV test result (negative). We excluded those with positive baseline HPV testing in order to minimize the risk of attributing an incident infection to reactivation. For analyses examining anogenital warts as an outcome, we excluded 64 participants who had baseline anogenital warts or had only one result for anogenital warts; therefore, 464 participants were eligible for these analyses. For analyses examining anal dysplasia as an outcome, we excluded 258 participants who had anal dysplasia at baseline or who had only one result for anal dysplasia testing. This secondary analysis of a public use dataset with no participant identifiers was reviewed by the Cincinnati Children's Hospital Medical Center Institutional Review Board and deemed nonhuman subjects research.

Primary outcome variables were (1) incidence of any anal HPV infection, (2) incidence of high risk anal HPV, (3) incidence of anogenital warts, and (4) incidence of anal dysplasia. High risk anal HPV infection was defined as infection with types 16, 18, 31/33/35, 39, 45,

51, 52, 56, 58, or 59/68/70 (International Agency for Research on Cancer Groups 1 and 2A).¹³ Samples with negative beta globin testing were excluded. Anogenital warts were identified on physical examination. Anal cytology samples with abnormal squamous cells of unknown significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL) were classified as “anal dysplasia” for these analyses, consistent with a prior cross-sectional study of this cohort.⁹ Length of follow-up time for HPV infection was defined as the time between the first visit with negative HPV testing and either the first positive HPV test or the last visit with HPV testing for those remaining HPV negative. Follow-up time for high risk anal HPV, anogenital warts, and anal dysplasia were calculated in a similar manner. Incidence rates for the four outcomes were calculated as events per 100 person-months and events per 100 person-years to facilitate comparison with the published literature.

To determine factors associated with incident anal HPV and related sequelae, predictor variables were examined including demographics, behavioral variables, and HIV infection-related variables. Demographic variables included age at study entry (continuous variable), 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, history of receptive anal sexual intercourse, history of smoking (defined as smoking 100 or more cigarettes in lifetime), cervical HPV infection, and, for men, history of sexual contact with another man. Additional variables for HIV-infected participants included history of antiretroviral therapy (ART; baseline), current ART, VL, CD4 count, and CDC HIV disease classification stage (see footnote Table 1). For the model examining anal dysplasia, history of high risk anal HPV infection during the study was added as a predictor variable. VL was $\log_{10}$ transformed to facilitate comparison with the literature; CD4 count was $\log_{10}$ transformed due to highly skewed values.

Descriptive analyses were performed to examine participant characteristics and predictor variables. Incidence rates for the outcomes and confidence intervals were computed using Poisson modeling and stratified by gender and HIV status. Cox proportional hazards modeling was used to determine factors associated with incident anal HPV and related sequelae, also stratified by gender and HIV status because factors associated with outcomes were likely to differ by these characteristics. This modeling 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, history of receptive anal intercourse, history of smoking, cervical HPV infection, male sexual contact with another male, current ART, VL, CD4 count, and CDC classification stage. History of receptive anal sex among women was not included as a covariate due to few reports of this behavior. Proportional hazards assumptions were assessed using Schoenfeld’s residuals. Predictor variables with $p < 0.10$ were entered stepwise into the multivariable model; predictors that were significant at $p < 0.05$ in the multivariable model were considered to be significantly associated with the outcome variable.

RESULTS

Demographic and other baseline characteristics

Demographic data for the study population are presented in Table 1. Mean age at entry was 16.8 years (SD 1.2). The majority (76%) of participants were female; 70% were black non-Hispanic. Mean age at first sexual intercourse was 13.7 years. Mean follow-up time was 22.4 months for anal HPV infection, 29.0 months for anogenital warts, and 23.7 months for anal dysplasia. HIV-infected vs. HIV-uninfected participants had a longer follow-up time for anogenital warts only. HIV-infected participants had a greater number of lifetime partners, and more HIV-infected vs. HIV-uninfected males reported sexual contact with another male. Few women (23%) reported a history of receptive anal sex; significantly more HIV-infected vs. uninfected men reported this behavior (70% vs. 47%, $p=0.02$). At baseline, 75% of HIV-infected and 56% of HIV-uninfected women included in this analysis had cervical HPV infection ($p<0.001$). Overall, 55% of participants reported smoking 100 or more cigarettes in their lifetimes.

Incidence of anal HPV and related sequelae

HIV-infected women, compared to HIV-uninfected women, had higher incidence of any anal HPV infection (30 vs. 14 per 100 person-years; $p=0.002$), high risk anal HPV infection (12 vs. 5.3 per 100 person-years; $p=0.04$), and anogenital warts (6.7 vs. 1.6 per 100 person-years; $p=0.002$), as shown in Table 2. There was no significant difference in anal dysplasia between HIV-infected and uninfected women. HIV-infected men, compared to HIV-uninfected men, had consistently higher incidence rates of each of the four outcomes. None of these differences reached statistical significance, although differences in rates of anogenital warts and anal dysplasia approached significance (Table 2).

Multivariable analyses

Among women, factors independently associated with incident anal HPV and related sequelae differed by HIV status (Table 3). Among HIV-uninfected women, concurrent cervical HPV infection was associated with anal HPV infection. No factors were independently associated with high risk anal HPV, anogenital warts, or anal dysplasia in HIV-uninfected women. Among HIV-infected women, smoking and late (vs. early) CDC disease progression stage were associated with high risk anal HPV infection; concurrent cervical HPV infection and higher VL were associated with anogenital warts; and late (vs. early) CDC disease progression stage and history of high risk anal HPV infection during the study period were associated with anal dysplasia. In contrast to these analyses in women, no factors were significantly associated with the outcomes in men.

DISCUSSION

We examined the incidence of anal HPV infection and related sequelae, and factors associated with these outcomes, in a longitudinal cohort of HIV-infected and HIV-uninfected adolescents. Despite the data originating from a study that ended in 2001, our findings remain highly relevant. Although the HPV vaccine is recommended for HIV-infected youth,^{14,15} the rate of vaccine uptake in this population is unknown. Studies have

demonstrated suboptimal HPV vaccination rates among HIV-uninfected youth,^{16,17} and given the competing health concerns of HIV-infected youth, rates of vaccination may be even lower in this group. The present study provides new information about anal HPV in HIV-infected youth, thus providing additional support for HPV vaccination in this group. This study is the first to compare incidence rates of anal HPV infection between HIV-infected and HIV-uninfected adolescents recruited from multiple sites across the U.S. and to examine factors associated with incident anal HPV infection and related sequelae among adolescents. Understanding factors associated with incident anal HPV and related sequelae, and how these factors may be different based on HIV status, will allow clinicians to tailor their HPV counseling and prevention efforts.

HIV-infected women had significantly higher incidence of any anal HPV infection, high risk anal HPV, and anogenital warts, as well as higher incidence of anal dysplasia (although this failed to reach significance). Thus, higher rates of acquisition of anal HPV infection among HIV-infected adolescent women may explain, at least in part, why these women have a higher prevalence of anal HPV when compared to HIV-uninfected adolescent women; alternatively, HIV-infected women may have delayed clearance of HPV. Similar to the current study, previous studies demonstrate higher prevalence of anal HPV⁹ and cervical HPV¹⁸ in HIV-infected vs. HIV-uninfected adolescent women, and higher incidence of genital warts in HIV-infected vs. HIV-uninfected adult women.¹⁹ Because HIV-infected adolescent women are at higher risk of acquiring anal HPV and developing HPV-related sequelae when compared to their HIV-uninfected peers, enhanced HPV prevention efforts targeting HIV-infected adolescent women are needed. Such prevention efforts should include developmentally appropriate education about HPV and administration of the HPV vaccine.

Among women, specific factors associated with anal HPV infection and related sequelae differed by HIV status. Among HIV-uninfected women, cervical HPV infection was associated with any anal HPV infection, consistent with prior literature.² The lack of association between cervical HPV and any anal HPV infection among the HIV-infected women in this cohort may be due in part to the significantly higher proportion of HIV-infected women who had cervical HPV at baseline (75% of HIV-infected vs. 56% of HIV-uninfected women); this lack of variability among HIV-infected women may limit our power to detect a relationship between cervical and anal HPV infection. Among HIV-infected women, smoking, which has been associated with prevalent HPV infection,²⁰ was associated with incident high risk anal HPV. A similar relationship between smoking and incident cervical HPV was described among adult HIV-infected women.²¹ Several HIV infection-related factors were associated with the outcomes. Late (vs. early) CDC disease stage was associated with high risk anal HPV and anal dysplasia, and higher VL was associated with anogenital warts. Thus, more advanced HIV disease was associated with HPV-related outcomes in this study. Although some studies of HIV-infected adults found no association between CD4 count or VL and prevalent anal HPV²² or prevalent abnormal anal cytology,^{22,23} other studies demonstrate that a low nadir CD4 count is associated with prevalent abnormal anal cytology²⁴ and progression to anal intraepithelial neoplasia.²⁵ While CD4 count was not associated with any outcome among the young women in our study, CDC disease stage – which includes nadir CD4 count as part of the staging system –

was associated with several outcomes. Although further studies are needed to investigate the impact of CD4 count on anal HPV infection and disease, improved antiretroviral therapy and adherence, leading to less HIV disease progression, may decrease rates of anal HPV and related sequelae. Further, because more advanced HIV disease was associated with high risk anal HPV and anal dysplasia, our data support early vaccination against HPV for HIV-infected young women.

HIV-infected men had higher incidence of anal HPV and related outcomes in this study when compared to HIV-uninfected men, but these differences failed to reach statistical significance. Among HIV-uninfected men, men who had sex with men had a higher incidence of anal HPV when compared to men who have sex with women.²⁶ Although the rate of incident anal HPV among HIV-uninfected men in our study is similar to that found among adult HIV-uninfected men who have sex with men, only 45% of our HIV-uninfected male participants reported sexual contact with another man. This finding suggests that the incidence of anal HPV among adolescent HIV-uninfected men may be higher than the rate among adult HIV-uninfected men. Alternatively, men may have underreported sexual contact with another man, or HPV infection may be due to autoinoculation.²⁷ We were unable to detect factors associated with the outcomes of interest in men, likely due to the small number of men (38 HIV-uninfected and 81 HIV-infected) and the low number of outcomes.

This study is subject to several limitations. First, some incident cases of HPV may represent reappearance of a prior infection and not new infection. However, we tried to minimize this possibility by removing participants who had anal HPV infection at baseline. Second, because HPV testing was done annually, some participants may have acquired and resolved detectable infection in the time between testing; rates of resolution of infection may have differed between HIV-infected and uninfected participants. Future studies using more frequent sampling may be useful in addressing this limitation. Third, because of the state of HPV typing at the time of the study, not all HPV types were identified using individual probes. Fourth, this study is a secondary data analysis, which limits the covariates and outcomes to those available in the dataset. However, the dataset was appropriate to address the study aims. Despite these limitations, this study provides novel information about incident anal HPV and HPV-related sequelae, and factors associated with these outcomes, among HIV-infected and HIV-uninfected adolescents.

In summary, we found that adolescent HIV-infected women had significantly higher incidence of anal HPV infection, high risk anal HPV infection, and anogenital warts when compared to HIV-uninfected but at-risk adolescent women. Because HIV-infected adolescents continued to acquire new anal HPV infections, these youth would benefit from targeted HPV prevention efforts, such as HPV vaccination, in order to prevent acquisition of anal HPV infection and subsequent development of HPV-related sequelae.

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Abbreviations

HPV	human papillomavirus
HIV	human immunodeficiency virus
STI	sexually transmitted infection
IVDU	intravenous drug use
VL	HIV-1 RNA viral load
CD4	CD4+ T-cell
ART	antiretroviral therapy
SD	standard deviation
REACH	Reaching for Excellence in Adolescent Care and Health
CDC	Centers for Disease Control and Prevention
AIDS	acquired immune deficiency syndrome

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Summary

New anal HPV infections occurred among HIV-infected adolescents. Incidence of anal HPV infection, high-risk anal HPV infection, and anogenital warts was significantly higher in HIV-infected vs. HIV-uninfected adolescent women.

Table 1

Baseline Participant Demographics: Total, and by HIV status

Characteristic	Total (n=496)	HIV-uninfected (n=177)	HIV-infected (n=319)	p-value ^I
Age at study entry, mean (SD)	16.8 (1.2)	16.6 (1.2)	16.9 (1.1)	0.01
Follow-up time, mean (SD), months - anal HPV (n=261) ²	22.4 (10.8)	24.1 (11.8)	24.4 (11.4)	0.88
Follow-up time, mean (SD), months - anogenital warts (n=464) ²	29.0 (15.1)	28.5 (14.7)	33.1 (14.8)	0.001
Follow-up time, mean (SD), months - anal dysplasia (n=270) ²	23.7 (11.5)	24.6 (12.0)	25.2 (11.6)	0.70
Female, Number (%)	377 (76%)	139 (79%)	238 (75%)	0.33
Race, Number (%) ³				0.02
Black non-Hispanic	345 (70%)	112 (63%)	233 (73%)	
All Other	151 (30%)	65 (37%)	86 (27%)	
Age at first intercourse, mean (SD), years ⁴	13.7 (1.7)	14.0 (1.6)	13.5 (1.8)	0.01
Range	[9,18]	[9, 18]	[9, 18]	
Lifetime sexual partners (baseline); Number (%) ^{3,4}				0.001
< 4	161 (34%)	73 (43%)	88 (29%)	
5–9	169 (35%)	59 (35%)	110 (36%)	
10	147 (31%)	37 (22%)	110 (36%)	
Sexual partners in prior 3 months (baseline), Number (%) ^{4,5}				0.34
0	141 (28%)	44 (25%)	97 (30%)	
1–2	279 (56%)	107 (60%)	172 (54%)	
3	76 (15%)	26 (15%)	50 (16%)	
New sexual partners in prior 3 months (baseline), Number (%) ^{4,5}				0.58
0	250 (54%)	95 (56%)	155 (53%)	
1	129 (28%)	48 (28%)	81 (28%)	
2	85 (18%)	27 (16%)	58 (20%)	
Males reporting male sexual contact (baseline); Number (%) ^{4,5}	80 (68%)	17 (45%)	63 (79%)	<0.001
History of receptive anal sex – Females; Number (%)	85 (23%)	38 (28%)	47 (20%)	0.08
History of receptive anal sex – Males; Number (%)	74 (63%)	18 (47%)	56 (70%)	0.02
History of insertive anal sex - Males; Number (%)	71 (60%)	16 (42%)	55 (69%)	0.01
Cervical HPV infection, Number (%)	256 (68%)	77 (56%)	179 (75%)	<0.001
History of smoking (100 cigarettes in lifetime at baseline), Number (%)	271 (55%)	99 (56%)	172 (54%)	0.67
ART Ever, Number (%)			185 (58%)	
Currently on ART, Number (%)			135 (42%)	
HIV-1 RNA viral load: Mean (SD)			31,667 (107,430)	
Median [minimum, maximum]			4175 [40,1,400,000]	
CD4+ T-cell count: Mean (SD)			523 (261)	
Median [minimum, maximum]			488 [3, 1449]	
CDC progression stage (Number [%])				
Early stage			162 (51%)	
Intermediate stage			110 (34%)	

Characteristic	Total (n=496)	HIV-uninfected (n=177)	HIV-infected (n=319)	p-value ¹
Late stage			47 (15%)	

HIV: human immunodeficiency virus; SD: standard deviation; HPV: human papillomavirus; ART: antiretroviral therapy; CDC: Centers for Disease Control and Prevention; 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 Follow-up time was calculated separately for anal HPV, anogenital warts, and anal dysplasia because the number of participants included in each group varied.

³ For analysis, all other race/ethnicity categories were combined.

⁴ All values were from baseline visit, or, if missing at baseline visit, from first report following baseline visit.

⁵ Denominators may vary due to missing data.

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

Incidence of HPV and HPV-related events among females and males, by HIV status

Outcome	Females			Males		
	HIV-uninfected (n=139)	HIV-infected (n=238)	p-value	HIV-uninfected (n=38)	HIV-infected (n=81)	p-value
Any anal HPV						
Events, n (sample n)	21 (76)	79 (137)		6 (14)	22 (34)	
Per 100 person-mos (95% CI)	1.2 (0.8, 1.8)	2.5 (2.0, 3.2)	0.002	2.0 (0.9, 4.4)	3.4 (2.2, 5.1)	0.24
Per 100 person-yrs (95% CI)	14 (9.3, 22)	30 (24, 38)		24 (11, 52)	40 (27, 61)	
High risk anal HPV						
Events, n (sample n)	8 (76)	35 (137)		3 (14)	17 (34)	
Per 100 person-mos (95% CI)	0.4 (0.2, 0.9)	1.0 (0.7, 1.4)	0.04	0.9 (0.3, 2.7)	2.3 (1.4, 3.6)	0.13
Per 100 person-yrs (95% CI)	5.3 (2.6, 11)	12 (8.4, 16)		11 (3.4, 33)	27 (17, 44)	
Anogenital warts						
Events, n (sample n)	5 (136)	36 (214)		1 (37)	16 (77)	
Per 100 person-mos (95% CI)	0.1 (0.05, 0.3)	0.6 (0.4, 0.8)	0.002	0.1 (0.01, 0.7)	0.7 (0.5, 1.2)	0.06
Per 100 person-yrs (95% CI)	1.6 (0.7, 3.8)	6.7 (4.8, 9.3)		1.2 (0.2, 8.6)	8.8 (5.4, 14)	
Anal Dysplasia						
Events, n (sample n)	9 (80)	35 (142)		4 (16)	19 (32)	
Per 100 person-mos (95% CI)	0.47 (0.3, 0.9)	1.0 (0.7, 1.4)	0.05	1.1 (0.4, 2.9)	3.1 (2.0, 4.9)	0.06
Per 100 person-yrs (95% CI)	5.7 (2.9, 11)	12 (8.6, 17)		13 (5.0, 35)	37 (24, 58)	

HPV: human papillomavirus; HIV: human immunodeficiency virus; mos: months; yrs: years; CI: confidence interval

Table 3Factors independently associated with incident HPV and HPV-related events among females, by HIV status¹

Event	Predictor variable	HIV-uninfected ² Hazard ratio (95% CI)	HIV-infected ³ Hazard ratio (95% CI)
Any anal HPV	Cervical HPV infection	2.45 (1.01, 5.92)	None
High risk anal HPV	Smoking	None	3.46 (1.21, 9.89)
	CDC disease progression stage		
	Intermediate vs. Early		1.73 (0.79, 3.75)
	Late vs. Early		2.80 (1.18, 6.67)
Anogenital warts	Cervical HPV infection	None	4.28 (1.29, 14.19)
	Viral load (log)		1.55 (1.12, 2.17)
Anal dysplasia ⁴	CDC disease progression stage	None	
	Intermediate vs. Early		1.51 (0.51, 4.49)
	Late vs. Early		7.02 (2.18, 22.59)
	Ever had high risk anal HPV		3.72 (1.52, 9.12)

HPV: human papillomavirus; HIV: human immunodeficiency virus; CI: confidence interval; ART: antiretroviral therapy

¹ Only covariates that remained significant in the multivariable models are shown.² Covariates included age at study entry, race (Black non-Hispanic vs. other), number of lifetime partners at baseline (categorical), age at first intercourse, history of smoking (> 100 cigarettes in lifetime; time-varying covariate), cervical HPV infection (time-varying covariate), 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. History of receptive anal sex was not included as a covariate due to few female respondents reporting this behavior.³ Covariates included variables in Footnote 2 above, as well as additional HIV-related variables including ART ever, current ART (time-varying), viral load (log-10 transformed; time-varying), CD4 count (log-10 transformed; time-varying), and CDC disease progression stage (time-varying).⁴ Covariates included the variables in Footnotes 2 and 3 above, as well as an additional variable reflecting whether the participant had ever had high risk anal HPV.