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Incidence and Predictors of Abnormal Anal Cytology Findings Among HIV-Infected Adults Receiving Contemporary Antiretroviral Therapy

Lois J. Conley[1], **Timothy J. Bush**[1], **Teresa M. Darragh**[2,3], **Joel M. Palefsky**[2,3], **Elizabeth R. Unger**[2,3], **Pragna Patel**[1], **Martin Steinau**[2,3], **E. Milu Kojic**[4], **Harold Martin**[5,a], **E. Turner Overton**[6], **Susan Cu-Uvin**[4], **John Hammer**[7], **Keith Henry**[8], **Kathleen Wood**[9], **John T. Brooks**[1], and **SUN Study Group**

[1]Division of HIV/AIDS Prevention, National Center for HIV, Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]University of California–San Francisco; [4]Miriam Hospital, Providence, Rhode Island; [5]Park-Nicollet Clinic, Minneapolis, Minnesota; [6]University of Alabama School of Medicine, Birmingham; [7]Denver Infectious Disease Consultants, Colorado; [8]Hennepin County Medical Center, Minneapolis, Minnesota; [9]Cerner, Vienna, Virginia

Abstract

Background.—Anal cancer rates are higher for human immunodeficiency virus (HIV)–infected adults than for uninfected adults. Limited published data exist characterizing the incidence of precursor lesions detected by anal cytology.

Methods.—The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy was a prospective cohort of 700 HIV-infected participants in 4 US cities. At baseline and

Correspondence: Lois J. Conley, MT, MPH, Centers for Disease Control and Prevention, DHAP/NCHHSTP, 1600 Clifton Rd NE, Mailstop E-45, Atlanta, GA 30333 (ljc2@cdc.gov).
[a]Present affiliation: Gilead Sciences, Foster City, California.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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annually thereafter, each participant completed a behavioral questionnaire, and healthcare professionals collected anorectal swabs for cytologic examination and human papillomavirus (HPV) detection and genotyping.

Results.—Among 243 participants with negative baseline results of anal cytology, 37% developed abnormal cytology findings (incidence rate, 13.9 cases/100 person-years of follow-up; 95% confidence interval [CI], 11.3–16.9) over a median follow-up duration of 2.1 years. Rates among men having sex with men, among women, and among men having sex with women were 17.9 cases/person-years of follow-up (95% CI, 13.9–22.7), 9.4 cases/person-years of follow-up (95% CI, 5.6–14.9), and 8.9 cases/person-years of follow-up (95% CI, 4.8–15.6), respectively. In multivariable analysis, the number of persistent high-risk HPV types (adjusted hazard ratio [aHR], 1.17; 95% CI, 1.01–1.36), persistent high-risk HPV types except 16 or 18 (aHR, 2.46; 95% CI, 1.31–4.60), and persistent types 16 or 18 (aHR, 3.90; 95% CI, 1.78–8.54) remained associated with incident abnormalities.

Conclusions.—The incidence of abnormal anal cytology findings was high and more likely to develop among persons with persistent high-risk HPV.

Keywords

abnormal anal cytology; HPV; HIV; incidence; persistence

The incidence of anal cancer in the United States is increasing [1–3] and is greater for both human immunodeficiency virus (HIV)–infected men, especially gay, bisexual, and other men who have sex with men (MSM), and HIV-infected women, compared with the incidence among HIV-uninfected persons [4–11]. Additionally, rates of anal cancer and precursor lesions have remained elevated and may be increasing in HIV-infected MSM, men who have sex with women (MSW), and women despite the introduction and widespread use of combination antiretroviral therapy (ART) [1, 4, 5, 7, 8, 10–16], although conflicting findings have been published [9, 17]. Reported rates of precursor lesions, specifically histologically identified high-grade anal intraepithelial neoplasia (HGAIN) and cytologically identified high-grade squamous intraepithelial lesions (HSILs), have been 8.5%–29% per year among HIV-infected persons [12, 17, 18], compared with rates of 3.3%–8% per year among HIV-uninfected individuals [12, 18], although the majority of data are from MSM. In two studies of abnormal anal cytology findings (defined as low-grade squamous intraepithelial lesions [LSILs] or HSILs) among HIV-infected women, one found a prevalence of 14% with an incidence of 22 cases/100 person-years of follow-up [13], while the second found 17% and 13 cases/100 person-years of follow-up, respectively [14]. To our knowledge, no data regarding incident precursors in MSW have been reported.

Human papillomavirus (HPV) infection is a known risk factor for anal cancer [19–22], and its precursor lesions HSIL or HGAIN [18–24]. HPV types 16 and 18 have been associated with almost three quarters of invasive anal cancers [19], although other high-risk HPV types have also been detected [22, 25, 26]. Additionally, detection of multiple HPV types has been associated with anal cancer and development of abnormal anal cytology findings [26, 27, 28]. HPV types 16 and 18, particularly if persistent, have also been associated with incident HGAIN in HIV-infected MSM [12, 17, 29–31].

To better understand how the epidemiology of abnormal anal cytology findings might be changing in the contemporary era, we investigated the 5-year incidence of and risk factors for abnormal cytology findings among a diverse cohort of HIV-infected MSM, women, and MSW who were or were not naive to ART.

METHODS

Data Source

We used data from the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN), a prospective observational cohort of 700 HIV-infected persons enrolled from 7 clinics in 4 US cities: Denver, Colorado; Minneapolis, Minnesota; Providence, Rhode Island; and St. Louis, Missouri. Enrollment occurred between March 2004 and June 2006, with follow-up through May 2012 [32]. Informed consent was obtained from all study participants, and the study was approved and renewed annually by the institutional review boards of all participating institutions and the Centers for Disease Control and Prevention (CDC). The cohort and detailed study methods have been described elsewhere [32]. Briefly, at baseline and every 6 months thereafter, data were collected through physical examination, audio computer-assisted self-interviews (ACASIs), laboratory examination, and medical chart abstraction. Data on HPV vaccine receipt were not specifically collected, as the indication for its use was not applicable to this population. The ACASIs collected extensive behavioral information, including data on sexual behavior, alcohol use, tobacco use, and nonprescription-drug use. Study-specific laboratory examination consisted of testing for sexually transmitted infections, including oropharyngeal and rectal Neisseria gonorrhoeae and Chlamydia trachomatis infection, and annual collection of anal samples for cytology and HPV detection and typing.

Anal Cytology

Samples were collected for anal cytology by healthcare professionals at baseline and annually thereafter by inserting a polyethylene terephthalate–tipped swab moistened with tap water and inserted approximately 2.5–5.0 cm into the anal canal [33]. The swab was rotated 360° at least twice while applying external pressure against the anal canal and then placed into PreservCyt (Hologic, Marlborough, Massachusetts) for preparation of a ThinPrep slide. All samples were sent to a single cytopathologist (T. M. D.) for examination and interpretation. Anal cytology results were reported according to the Bethesda system terminology [34]. If the anal sample was satisfactory (ie, of sufficient cellularity), results were reported as negative; atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells, cannot exclude high-grade SIL (ASC-H); LSIL; HSIL; or carcinoma. On the basis of these results, participants were referred for appropriate follow-up per their institution’s standard of practice.

Anal HPV Testing

An anal sample was collected at baseline and annually thereafter for detection of HPV, using the same method as that used for the cytology specimen, except that the swab was placed into Digene Specimen Transport Medium (Qiagen, Valencia, California) and stored at 4°C until shipment at ambient temperature to the CDC. Within 7 days of receipt, a 150-μL

aliquot was extracted using the MagNA Pure LC DNA Isolation Kit III (Bacteria, Fungi) (Roche Diagnostics, Manheim, Germany) and the MagNA Pure LC system. The final eluate of 100 μL was stored at −20°C until testing. The Roche Linear Array (LA) HPV Genotyping Test (Roche Diagnostics, Indianapolis, Indiana) was used following the manufacturer's protocol modified to accommodate a 10-μL aliquot in a 100-μL reaction. The assay detects 37 HPV types (high-risk types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52 [XR], 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, and IS39; low-risk types 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, and 89) and, as an amplification control, β-globin. Owing to cross-reactivity between the XR probe and HPV 33, 35, and 68, the presence of HPV 52 was confirmed by an HPV 52–specific quantitative polymerase chain reaction (PCR) when XR and cross-reacting types were present [35]. Samples negative for both β-globin and HPV were considered inadequate for evaluation and were not included.

Statistical Analysis

In this analysis, we included participants with a negative result of baseline anal cytology and at least one satisfactory follow-up specimen for anal cytology and HPV detection. We defined an anal cytology finding as abnormal on the basis of cytopathological interpretation of the finding as ASC-US, ASC-H, LSIL, and HSIL. Participants contributed observation time until an abnormal finding was identified, they were lost to follow-up, or the study ended. HPV persistence was defined as detection of the same type at the baseline and 1-year visit; persons without a 1-year visit were excluded. We used a hierarchical order of persistent HPV 16 or 18, other persistent high-risk HPV types, low-risk HPV types; and no persistent HPV types.

To compare demographic and clinical characteristics across participant groups, we used the Pearson χ^2 test, the Fisher exact test, and the Wilcoxon rank sum test. We used Kaplan–Meier product-limit analysis to determine differences in times to abnormal anal cytology findings for selected variables [36] and the log-rank test to establish significance. Cox proportional hazards models were used for univariate and multivariable analysis to test for associations between incident abnormal cytology findings and potential risk factors [37]. Multivariable analyses using backward elimination were performed on data from persons with complete data. Data from the 1-year visit were used for analysis of all potential risk factors, for consistency with the HPV persistence definition. We performed analyses for all participants combined, as well as for MSM, women, and MSW separately. Variables potentially significant in univariate analysis ($P < .10$) were included in multivariable proportional hazards models, in which persistent HPV 16 or 18 and other persistent high-risk HPV types were compared to the reference category of no persistent high-risk HPV type. All final models were determined using backward selection with a cutoff P value of $< .05$. Data analyses were performed with SAS, version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Study Population

Of the 700 participants enrolled in the SUN study, 457 were excluded from this analysis: 297 had an abnormal anal cytology finding, and 59 had an unsatisfactory baseline specimen for anal cytology or HPV detection, and 101 had no follow-up specimen. None of the remaining participants had a known prior diagnosis of anal cancer.

Participant Characteristics at the 1-Year Visit

Characteristics of the 243 participants at the 1-year visit included in this analysis were as follows: the median age was 43 years (interquartile range [IQR], 37–49 years), 74% were male, 58% were non-Hispanic white, 28% were non-Hispanic black, 10% were Hispanic, and 4% were of another or unknown race/ethnicity (Table 1). Among men, 73% were MSM, and 27% were MSW. During the preceding 6 months, 69% were sexually active, with a median of 1 partner (2 for MSM, 1 for women, and 1 for MSW). In the preceding 6 months, 46% of MSM and 7% of women reported engaging in receptive anal intercourse. Overall, 42% of participants were current cigarette smokers, 28% had used nonprescription drugs other than marijuana, and 2% used injection drugs. Eighty-three percent were prescribed ART. The HIV viral load was <400 copies/mL for 84%, and the median HIV viral load among the remaining 16% was 9081 copies/mL (IQR, 2151–20 780 copies/mL). The median 1-year and nadir $CD4^+$ T-cell counts were 537 and 200 cells/mm^3, respectively. Three rectal N. gonorrhoeae infections (1% of participants) and 14 rectal C. trachomatis infections (6% of participants) were detected during the previous year (2% and 10%, respectively, for MSM; 0% and 2%, respectively, for women; and 0% and 0%, respectively, for MSW). Participants were followed for a median of 2.1 years (IQR, 1.1–4.1 years).

Anal HPV Detection

At the 1-year visit, 82% of persons had anal HPV detected: 74% had any high-risk HPV type detected, and 63% had any low-risk HPV type detected (Table 1). With the exception of high-risk HPV, for which the frequency of detection was higher for women, the frequency of detection was higher among MSM (93% had any HPV, 82% had any high-risk HPV, 75% had any low-risk HPV, and 37% had types 16 or 18), compared with women (88%, 83%, 65%, and 15%, respectively; $P = .274$, .764, .138, and .002, respectively) and with MSW (42%, 38%, 22%, and 9%, respectively; $P < .001$ for all comparisons). The HPV prevalences among MSW were significantly lower than those among women, except for HPV types 16 or 18.

In persons with HPV detected, a median of 4 of any HPV type, 2 high-risk types, and 1 low-risk HPV type were detected. Other than any HPV type ($P = .038$), the median number of types did not differ significantly among MSM (4 of any type, 2 high-risk types, and 2 low-risk types) and women (3, 2, and 1, respectively). Similar results were found for women, compared with MSW (2 of any type [$P = .022$], 1 high-risk type, and 1 low-risk type). All comparisons were significantly different between MSM and MSW ($P < .01$ for all comparisons).

The overall frequency of persistent high-risk HPV was 59%. MSM and women had a higher frequency of persistent high-risk HPV than MSW (68% and 63%, respectively, vs 27%; $P < .001$ for both comparisons). However, MSM had greater frequency of HPV types 16 or 18 (28%), compared with women (8%; $P = .002$) and MSW (4%; $P < .001$).

Incident Abnormal Anal Cytology Findings

The incidence of an abnormal anal cytology finding per 100 person-years of follow-up was 13.9 cases (95% CI, 11.3–16.9; Figure 1) and was significantly higher for MSM, compared with women ($P = .019$) and MSW ($P = .026$). During follow-up, cytology findings for 151 persons (62%) remained negative (Table 2 and Supplementary Table 1). The remaining 92 individuals (38%) developed the following abnormalities: ASC-US, in 42 (17%); ASC-H, in 7 (3%); LSIL, in 40 (16%); and HSIL, in 3 (1%; Table 2). The development of abnormal cytology findings differed significantly among MSM, women, and MSW ($P = .024$). Rates were highest in MSM for all abnormal findings except HSIL, for which small numbers limited comparisons.

Survival Analyses for Incident Abnormal Anal Cytology Findings

In Kaplan–Meier analysis, an estimated 65% (95% CI, 54%–75%) of MSM, 38% (95% CI, 24%–56%) of women, and 42% (95% CI, 26%–63%) of MSW would have had an abnormal anal cytology finding after 5 years of follow-up ($P = .010$; Figure 2*A*). Among all persons, an estimated 69% with HPV types 16 or 18 detected at baseline, 63% with a high-risk HPV type other than 16 or 18 detected at baseline, 28% with a low-risk HPV type detected at baseline, and 32% with no HPV detected at baseline would have had an abnormal cytology finding if screened annually ($P < .001$; Figure 2*B*). We also estimated that 94% (95% CI, 76%–99%) of persons with persistent HPV types 16 or 18, 63% (95% CI, 51%–75%) with persistent high-risk HPV other than 16 or 18, and 36% (95% CI, 20%–59%) with no persistent high-risk HPV detected would have had an abnormal anal cytology finding after 5 years (Figure 2*C*).

Risk Factors for Incident Abnormal Anal Cytology Findings

In univariate analyses, factors at the 1-year visit that were associated with incident abnormal cytology findings included having engaged in any unprotected sex in the last 6 months, ever having receptive anal intercourse, having receptive anal intercourse in the last 6 months, having ≥4 sex partners in the last 6 months, and having rectal infection with *N. gonorrhoeae* during the previous year, as well as detecting a greater number of persistent high-risk HPV types and persistence of high-risk HPV types other than 16 and 18 or of HPV types 16 or 18 ($P < .10$ for all; Table 3). In multivariable analysis, independently associated factors included detecting a greater number of persistent high-risk HPV types (adjusted hazard ratio [aHR], 1.17 for each additional type; 95% CI, 1.01–1.36; $P = .040$), persistent high-risk HPV types other than 16 or 18 (aHR 2.46; 95% CI, 1.31–4.60; $P = .005$), and persistent HPV types 16 or 18 (aHR 3.90; 95% CI, 1.78–8.54; $P < .001$). These findings remained after controlling for being an MSM.

We repeated univariate and multivariable analyses of risk factors for incident abnormal anal cytology findings separately for MSM, women, and MSW (Table 3). Among MSM, factors

remaining associated in multivariable analyses were a greater number of persistent high-risk HPV types (aHR, 1.25; 95% CI, 1.06–1.48; $P = .008$) and persistent types 16 or 18 (aHR, 2.68; 95% CI, 1.07–6.71; $P = .036$). Among women and MSW, a 1-year-visit $CD4^+$ T-cell count of <500 cells/mm^3 and persistent high-risk HPV types other than 16 or 18 remained significantly associated (aHR, 2.91; [95% CI, 1.03–8.16; $P = .043$] and 4.92 [95% CI, 1.12–21.7; $P = .035$], respectively, for women; aHR, 5.99 [95% CI, 1.23–29.2; $P = .027$] and 6.13 [95% CI, 1.75–21.5; $P = .005$], respectively, for MSW).

We repeated both the Kaplan–Meier and Cox proportional hazards analyses for all persons and for MSM only, excluding ASC-US from the outcome to limit the potential weakening effect of less severe abnormalities, and found that our results were not altered substantively (data not shown). Owing to limited numbers, we were unable to repeat the same analyses for women and MSW.

DISCUSSION

In this large contemporary cohort of well-characterized, generally healthy, HIV-infected adults, the incidence of abnormal anal cytology findings was 13.9 cases/100 person-years of follow-up. The rate among MSM was almost twice that observed among women and MSW. For MSM, persistent infection with HPV 16 or 18 and a greater number of high-risk HPV types were associated with incident abnormal cytology findings. In both women and MSW, a 1-year-visit $CD4^+$ T-cell count of <500 cells/mm^3, and detection of persistent high-risk HPV types other than 16 or 18, were associated with incident abnormal anal cytology findings.

This study is one of the first that has allowed comparison of incidence rates of abnormal anal cytology findings among MSM, women, and MSW within one study population, although subanalyses for women and particularly for MSW were limited by small numbers. We previously reported that the prevalence of abnormal anal cytology findings in this population was significantly higher in MSM, compared with women and MSW, following the same pattern as incident abnormal findings [38].Previous studies have also found high incidence rates of abnormal cytology findings in MSM, especially those infected with HIV. In one of the first publications describing incidence, Palefsky et al found a 4-year incidence for HSIL of 49% in HIV-infected MSM and 17% in HIV-uninfected MSM [18]. Notably, both cytological and histological results were available.

Studies describing the incidence of ASC-US, LSIL, and HSIL in HIV-infected women have been more limited. Durante et al and Baranoski et al reported slightly higher incidence rates than those we found: 22 and 13.1 cases/100 person-years of follow-up, respectively [13, 14]. About 40% of the women (median, 1.4 years of follow-up) in the study by Durante et al and 79% (median, 1.9 years of follow-up) in the analysis by Baranoski et al were prescribed ART during the study. Our incidence rate of 9.4 cases/100 person-years of follow-up for women was similar to that observed by Baranoski et al, whose study population was comparable to ours in that the women were relatively healthy and that most were receiving ART. In contrast, the study by Durante et al was conducted earlier in the HIV epidemic (1995–1998), and a larger percentage of the women had baseline $CD4^+$ T-cell counts of

<500 cells/mm^3. Similar to our results, Baranoski et al found no association with nadir CD4$^+$ T-cell count.

Interestingly, the incidence of abnormal anal cytology findings that we observed for MSW, while similar to that for women, was much lower than that for MSM. We hypothesize that this finding may reflect the effects of the greater prevalence and persistence of HPV type 16 and 18 among MSM than among MSW or women. Previously published data have shown that HPV 16 is usually the most common type detected in HIV-infected MSM with incident AIN or SIL [16, 17] and that, when persistent, it is associated with progression to HGAIN [12, 17]. Although there are scant data regarding anal HPV types found in HIV-infected women with an incident abnormal anal cytology finding, some data exist for HIV-infected and uninfected women with prevalent abnormal findings. In contrast to MSM, studies of HIV-infected women [39], including a previous publication from the SUN Study [40], have generally found that although HPV 16 was often prevalent at the anus, HPV types other than 16 were more common. One study of anal disease among men noted that HPV type 16 was most frequently associated with HSIL in both MSM and MSW [25].

Although we found no association of incident abnormal anal cytology findings with nadir CD4$^+$ T-cell count, a CD4$^+$ T-cell count of <500 cells/mm^3 at the 1-year visit was significantly associated ($P = .043$) in the multivariable analysis of the women, as has been reported previously [13, 14].

Among MSM, current smoking, having any unprotected vaginal or anal sex, and having ≥4 sex partners in the last 6 months were associated with incident abnormal findings in univariate analysis, although these associations did not prove to be significant in multivariable analysis. This lack of association is similar to the finding by Palefsky et al [41]. Data regarding the association between the number of partners and incident abnormal cytology findings are sparse, although data regarding the association of sex partner number with AIN have been previously reported. De Pokomandy et al found an association of AIN with greater number of sex partners [17], whereas Phanuphak et al reported no association [12]. We hypothesize that the effect size of the risk associated with persistent HPV infection mitigated any additional risk from other potential risk factors with smaller effect sizes, including smoking and sexual behaviors.

Although for MSM, rectal *N. gonorrhoeae* was included in the multivariable analysis, it was not significantly associated with an incident abnormal finding. Among women, although a causal relationship between cervical *C. trachomatis* infections and cervical dysplasia has been hypothesized [42], epidemiological studies have produced ambiguous, sometimes conflicting results regarding both of these conditions [43–48]. To our knowledge, our analysis is the only one to have addressed this hypothesis for rectal infections among MSM, but our study was not adequately powered to conclusively detect an effect.

Our analysis is subject to several limitations. Although we did not have a large number of persons in all our participant categories, we had up to 5 years of follow-up and provided data on MSW, for whom scant data on the incidence of abnormal anal cytology findings have been published. Additionally, we were unable to investigate risk factors associated with

HSIL because we had few of these diagnoses. While we did not quantify the amount of HPV present, its persistence was highly associated with the development of abnormal cytology findings: we estimated that almost three-quarters of our population infected with a persistent high-risk HPV type (94% with 16 or 18, and 63% with other high-risk HPV types) would be expected to develop an abnormal cytology finding within 4 years. Although there has been a change in terminology recently to include both anal histology findings based on high-resolution anoscopy (HRA) and cytology findings in the definition of HSIL, we did not perform routine parallel HRA and directed tissue biopsies or histologic examination. Therefore, we could not confirm the presence of abnormal histology findings, and given the relatively low sensitivity of anal cytology, we may have underestimated the actual incidence of disease [49,50]. Finally, we did not collect comprehensive information regarding follow-up of abnormal cytology findings, which could have included invasive evaluation (eg, biopsies) and treatment. Therefore, we could not address regression of lesions or progression of the natural disease process, which would be critical to the development of targeted screening methods to identify persons at greatest risk of developing anal cancer.

In conclusion, our analysis of longitudinal data from this large prospective cohort study of HIV-infected MSM, women, and MSW has demonstrated a high incidence of abnormal anal cytology findings, particularly among MSM. As found in our prevalence analysis, anal cancer screening, not just among MSM but among all HIV-infected persons, should be taken into consideration when developing guidelines for the care of HIV-infected individuals, particularly for persons persistently infected with high-risk HPV types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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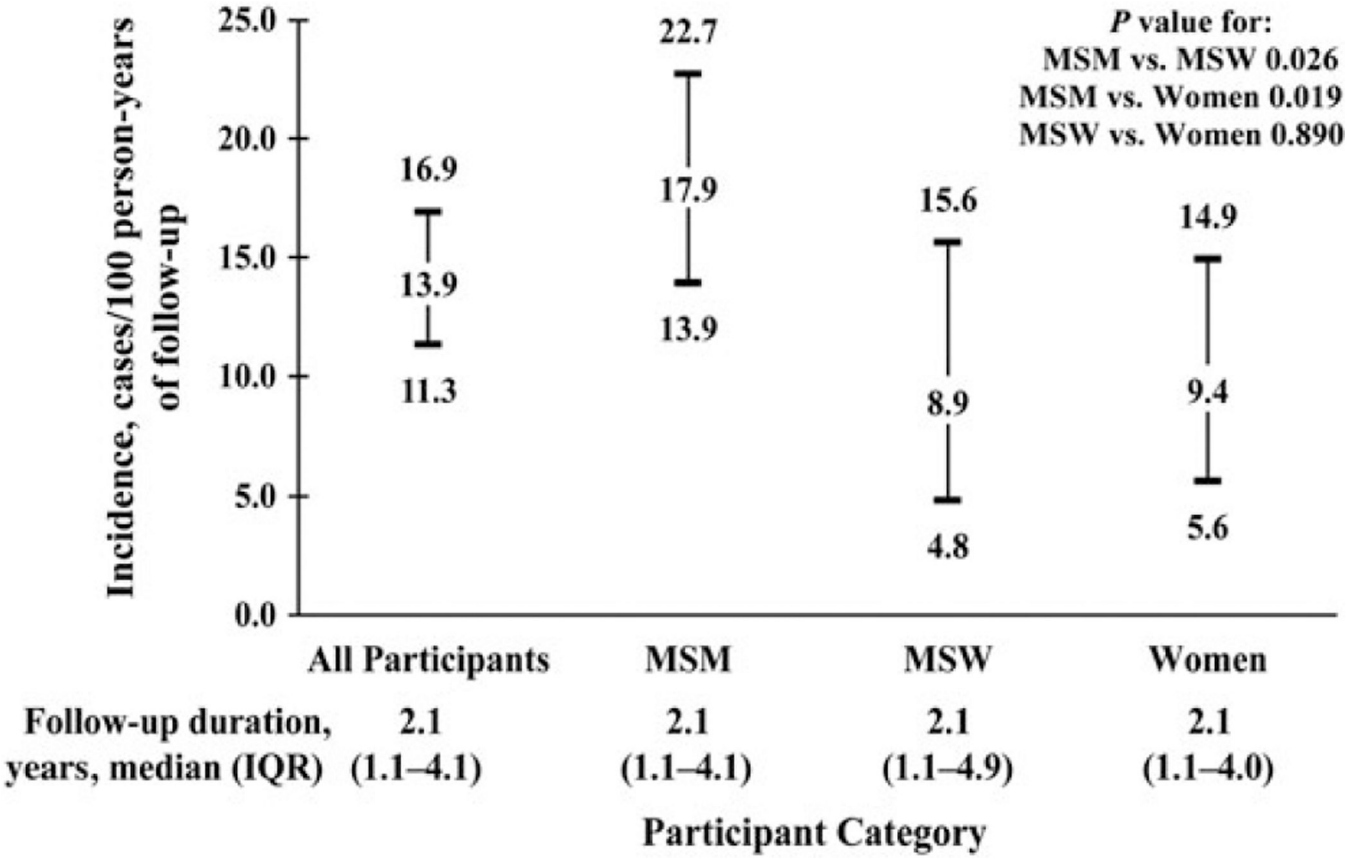

Figure 1.

Incidence rates and 95% confidence intervals for abnormal anal cytology findings through 5 years of follow-up among participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, 2004–2011. Abbreviations: IQR, interquartile range; MSM, men who have sex with men; MSW, men who have sex with women.

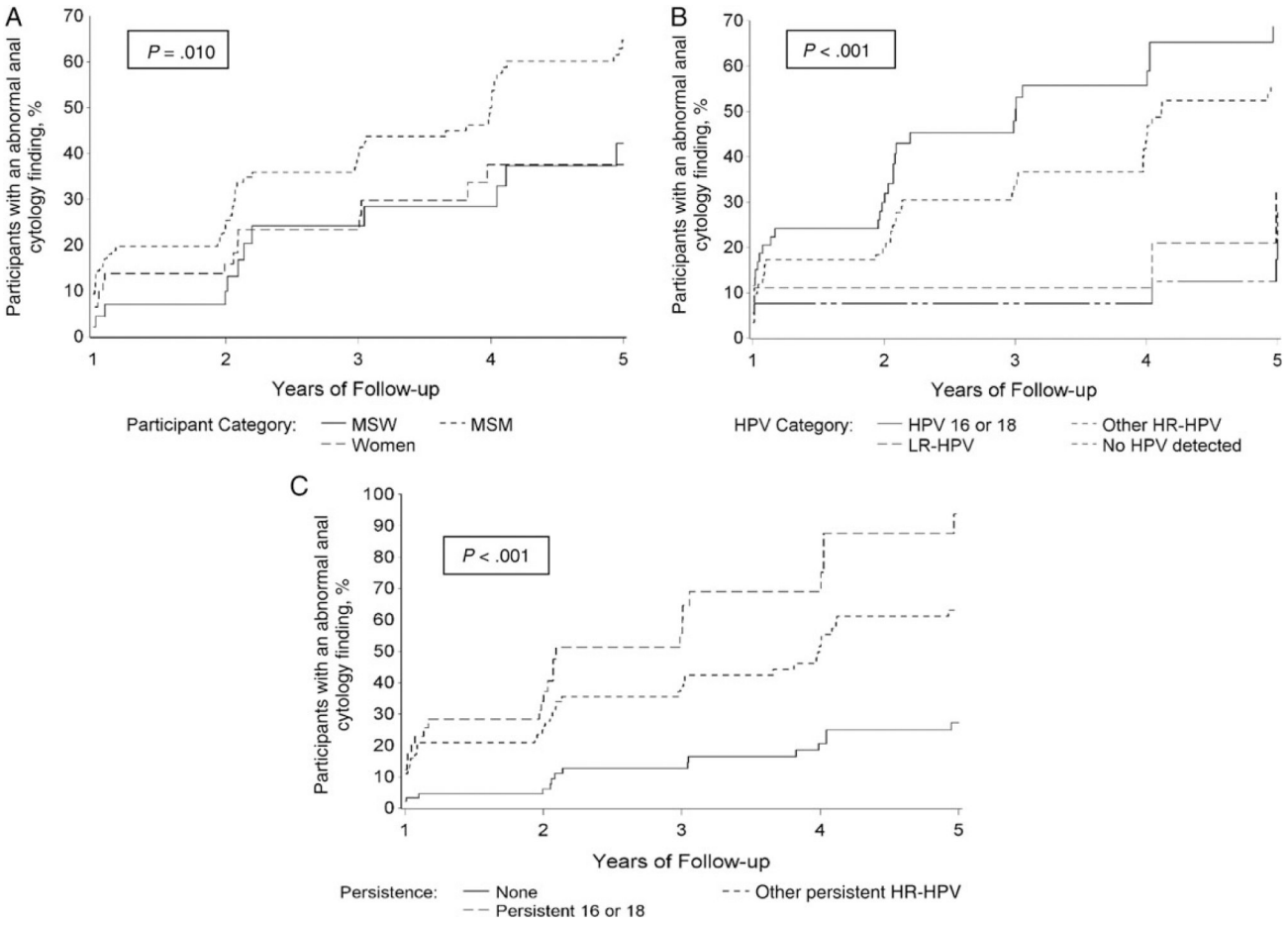

Figure 2.

Survival analyses for detection of incident abnormal anal cytology findings, by participant category (n = 243; *A*), human papillomavirus (HPV) type (n = 237; *B*), and persistence of HPV by year of follow-up (n = 230; *C*), among participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, 2004–2011. Data begin with the 1-year follow-up visit because all analyses were restricted to participants with at least 1 follow-up visit. Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women.

Table 1.

Select Characteristics at the 1-Year Visit Among Participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, 2004–2006

Characteristic	Overall (n = 243)	MSM (n = 132)	Women (n = 63)	MSW (n = 48)
Race/ethnicity				
Non-Hispanic white	140(58)	110 (83)	16 (25)	14(29)
Non-Hispanic black	69 (28)	9(7)	37 (59)	23 (48)
Hispanic	25(10)	10(8)	6(10)	9(19)
Other/unknown	9(4)	3(2)	4(6)	2(4)
Age, y	43 (37–49)	44 (38–50)	40 (32–48)	44 (39–49)
Drugs used in last 6 mo				
Marijuana	58 (24)	41 (31)	7(11)	10(21)
Any drug other than marijuana	68 (28)	51 (39)	9(15)	8(17)
Injection drugs	5(2)	2(2)	1 (2)	2(4)
No. of sex partners in last 6 mo				
0	74(31)	29 (22)	29 (48)	16(33)
1	95 (39)	39 (30)	30 (49)	26 (54)
2–3	36(15)	28 (21)	2(3)	6(13)
>3	36(15)	36 (27)	0(0)	0(0)
Receptive anal intercourse				
Ever[a] (n = 229)[b]	139(61)	114(93)	21 (36)	4(8)
In last 6 mo (n = 224)[c]	61 (27)	56 (46)	4(7)	1 (2)
ED agents[d] used in last 6 mo (men only)	25(14)	22 (17)	0(0)	3(6)
Current cigarette smoker	101 (42)	56 (43)	27 (45)	18(38)
$CD4^+$ T-cell count, cells/mm^3				
Nadir	201 (100–305)	217 (135–326)	212 (105–293)	118(34–264)
Current	537 (384–692)	553 (396–729)	545 (377–707)	482 (353–608)
Nadir during follow-up	374 (275–546)	408 (294–582)	374 (269–534)	361 (255–454)
HIV load <400 copies/mL	205 (84)	112 (85)	50 (79)	43 (90)
cART history				
Naive	15(6)	8(6)	6(10)	1 (2)
Current use	198 (83)	111 (85)	45 (74)	42 (89)
Duration, y	4.8 (3.0–7.5)	5.2 (3.2–8.0)	4.2 (2.5–6.3)	4.5 (2.9–6.7)
Rectal *N. gonorrhoeae* infection	3(1)	3(2)	0(0)	0(0)
Rectal *C. trachomatis* infection	14(6)	13 (10)	1 (2)	0(0)
Any HPV infection[e]	193 (82)	121 (93)	53 (88)	19(42)
High-risk HPV infection[e]	173 (74)	106 (82)	50 (83)	17 (38)
Low-risk HPV infection[e]	147(63)	98 (75)	39 (65)	10(22)
HPV type 16 or 18 infection[e]	61 (26)	48 (37)	9(15)	4(9)
For those with HPV detected[f]				

Characteristic	Overall (n = 243)	MSM (n = 132)	Women (n = 63)	MSW (n = 48)
Any HPV type				
No.	4 (2–5)	4 (2–6)	3 (2–5)	2 (1–3)
1–3	95 (49)	49 (41)	30 (57)	16(84)
>3	98(51)	72 (59)	23 (43)	3(16)
High-risk HPV types				
No.	2 (1–3)	2(1–4)	2(1–3)	1 (1 −2)
0	20(10)	15(12)	3(6)	2(11)
1–3	131 (68)	73 (60)	41 (77)	17 (89)
>3	42 (22)	33 (27)	9(17)	0(0)
Low-risk HPV types				
No.	1 (1–2)	2(1–3)	1 (0–2)	1 (0–1)
0	46 (24)	23 (19)	14(26)	9(47)
1–3	130(67)	84 (69)	38 (72)	8(42)
>3	17(9)	14(12)	1 (2)	2(11)
Persistent high-risk HPV types, no.[f]	1 (0–2)	1 (0–3)	1 (0–2)	0(0–1)
HPV persistence8’9				
No persistent HPV[e,g]	69 (30)	22(17)	16(27)	31 (69)
Persistent low-risk HPV	26(11)	18(14)	6(10)	2(4)
Persistent high-risk HPV types other than types 16 or 18	93 (40)	51 (40)	32 (54)	10(22)
Persistent HPV types 16 or 18	42 (18)	35 (28)	5(8)	2(4)

Data are no. (%) of participants or median value (interquartile range).

Abbreviations: cART, combination antiretroviral therapy; C. trachomatis, Chlamydia trachomatis; ED, erectile dysfunction; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; MSW, men who have sex with women; *N. gonorrhoeae, Neisseria gonorrhoeae*.

[a] Data are from baseline because this is the only time this question is asked for any anal sex.

[b] Data are for 123 MSM and 58 women.

[c] Data are for 122 MSM, 60 women, and 42 MSW.

[d] Sildenafil citrate, tadalafil, or vardenafil.

[e] Data are for 130 MSM, 60 women, and 45 MSW tested for HPV.

[f] Data are for 121 MSM, 53 women, and 19 MSW.

[g] Categories of persistence are mutually exclusive.

Table 2.

Anal Cytology Results at the Last Follow-up Visit Among Participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, 2005–2011

Result	Overall, No. (%)(n = 243)	MSM, No. (%) (n = 132)	Women, No. (%) (n = 63)	MSW, No. (%) (n = 48)
Negative	151 (62)	68 (52)	47 (75)	36 (75)
ASC-US	42 (17)	29 (22)	7(11)	6(13)
ASC-H	7(3)	5(4)	1 (2)	1 (2)
LSIL	40 (16)	29 (22)	7(11)	4(8)
HSIL	3(1)	1 (1)	1 (2)	1 (2)

All cytology results are based on the Bethesda system terminology.

Abbreviations: ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; MSM, men who have sex with men; MSW, men who have sex with women.

Table 3.

Cox Proportional Hazards Analysis of the Association Between Characteristics at the 1-Year Visit and Incident Abnormal Anal Cytology Findings Among 243 Participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, 2005–2011

	All Participants				MSM				Women				MSW			
	Univariate (n = 243)		Multivariable (n = 230)		Univariate (n = 132)		Multivariable (n = 126)		Univariate (n = 63)		Multivariable (n = 59)		Univariate Analysis (n = 48)		Multivariable (n = 45)	
Characteristic	**RR (95% CD**	***P* Value**	**aRR (95% CD**	***P* Value**	**RR (95% CD**	***P* Value**	**aRR (95% CD**	***P* Value**	**RR (95% CD**	***P* Value**	**aRR (95% CD**	***P* Value**	**RR (95% CD**	***P* Value**	**aRR (95% CD**	***P* Value**
Age	1.001.98–1.02)	.992	…		0.99 1.96–1.02)	.700	…		1.02 1.97–1.07)	.534	…		0.97 1.91–1.04)	.431	…	
$CD4^+$ T-cell count																
Nadir <200 cells/mm^3	1.27 (.84–1.92)	.250	…		1.48 1.90–2.41)	.120	…		1.72(.64–4.63)	.281	…		0.64 1.19–2.16)	.475	…	
Current <500 cells/mm^3	1.12 (.74–1.70)	.582	…		0.73 (.43–1.24)	.246	…		2.70 (.98–7.39)	.054	2.91 (1.03–8.16)	.043	3.07 (.83–11.4)	.094	5.99(1.23–29.2)	.027
HIV viral load <400 copies/mL	0.67 (.39–1.13)	.130	…		0.76 1.41–1.43)	.395	…		0.68 (.22–2.12)	.546	…		0.18 1.02–1.84)	.149	…	
ART naive	0.86 (.35–2.13)	.752	…		0.85 (.31–2.33)	.746	…		0.67 (.09–5.07)	.696	…		Undefined	Undefined	…	
Current cigarette smoker	1.26 1.84–1.91)	.265	…		1.76(1.06–2.91)	.028	…		1.10 1.41–2.94)	.848	…		0.54 1.15–2.02)	.363	…	
Any unprotected anal or vagina sex in last 6 mo	1.75 (1.14–2.68)	.010	…		1.64 (1.00–2.70)	.051	…		0.98 (.28–3.46)	.975	…		1.72 (.37–7.99)	.488	…	
Receptive anal intercourse ever (n = 225)	1.74(1.07–2.83)	.026	…		0.95 (.30–3.06)	.936	…		0.71 (.22–2.31)	.571	…		2.94 1.64–13.5)	.166	…	
Receptive anal intercourse in last 6 mo (n = 224)	1.46 (.93–2.26)	.097	…		1.02 (.61–1.69)	.942	…		2.72(.61–12.1)	.189	…		Undefined	Undefined	…	
≥4 sex partners in last 6 mo	2.15(1.34–3.45)	.001	…		1.70 (1.02–2.84)	.042	…		Undefined	Undefined	…		Undefined	Undefined	…	
Rectal *N. gonorrhoeae*	4.56(1.43–14.6)	.010	…		3.60(1.11–11.7)	.033	…		Undefined	Undefined	…		Undefined	Undefined	…	
Rectal *C. trachomatis*	1.90 1.87–4.12)	.106			1.96 (.87–4.39)	.104	…		Undefined	Undefined	…		Undefined	Undefined	…	
No. of persistent high-risk HPV genotypes	1.38 (1.24–1.53)	<.001	1.17 (1.01–1.36)	.040	1.38(1.22–1.57)	<.001	1.25(1.06–1.48)	.008	1.23 1.95–1.59)	.109	…		2.29(1.30–4.06)	.004	…	
Persistence																
No persistent high-risk HPV	Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference	
Persistent high-risk H PV other than 16 and 18	3.24(1.85–5.69)	<.001	2.46(1.31–4.60)	.005	2.82 (1.36–5.86)	.005			4.72(1.05–21.1)	.042	4.92 (1.12–21.7)	.035	3.41 (.90–12.8)	.07	6.13(1.75–21.5)	.005
Persistent HPV 16 or 18	6.15(3.29–11.5)	<.001	3.9 (1.78–8.54)	<.001	4.92(2.28–10.6)	<.001	2.68(1.07–6.71)	.036	5.25 (.73–37.9)	.100	…		18.7(3.01–116)	.002	…	

Abbreviations: aRR, adjusted relative risk; ART, antiretroviral therapy; CI, confidence interval; C. trachomatis, Chlamydia trachomatis; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; MSW, men who have sex with women; *N. gonorrhoeae, Neisseria gonorrhoeae*; RR, relative risk.