Association Between Smoking and Size of Anal Warts in HIV-infected Women

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Abstract

While the association between smoking and HPV infection, cervical cancer, and anal cancer has been well studied, evidence on the association between cigarette smoking and anal warts is limited. The purpose of this study was to investigate if cigarette smoking status influences the size of anal warts over time in HIV-infected women in a sample of 976 HIV-infected women from the Women's Interagency HIV Study (WIHS). A linear mixed model was used to determine the effect of smoking on anal wart size. Even though women who were currently smokers had larger anal warts at baseline and slower growth rate of anal wart size after each visit than women who were not current smokers, there was no association between size of anal wart and current smoking status over time. Further studies on the role of smoking and interaction between smoking and other risk factors, however, should be explored.

Keywords

Anal warts; HIV infection; human papillomavirus; smoking

INTRODUCTION

The prevalence of genital warts among sexually active adults in the United States is estimated to be approximately 1%.[1] HIV-infected persons are more likely to have genital warts than HIV-uninfected persons; they also have a greater risk for recurrence of warts.[2,3] Specifically, anal warts pose a major problem for HIV-infected individuals and thus, should receive special attention for several reasons. They have not been studied separately from genital warts, and yet there are indications that anal warts might be more common than

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cervical warts in women.[4] Furthermore, once infected with one type of HPV, patients are more likely to be infected with other HPV types (both low- and high-risk). In fact, some studies have recently shown that 20–50% of genital warts are co-infected with HPV high-risk types[5,6]. There is also evidence for a strong association between the presence of anal warts and the development of anal intraepithelial neoplasia (AIN), a precancerous lesion for anal cancer.[7] Accordingly, Carter at et.[7] reported that men with anal warts were 4.70 times (95% CI: 1.81–12.20) more likely to develop AIN than men without anal warts. Recently, from a Danish study of approximately 50,000 patients with genital warts, Blomberg et al.[8] found that genital wart diagnosis is strongly associated with anal cancer (standardized incidence ratio: 12.5 and 7.8 for men and women, respectively). Finally, the serious economical[9,10] and psychological[11,12] burdens associated with having anal warts must also be considered. In 1997, the estimated cost of HPV burden was $3.8 billion (excluding HPV-related cervical cancer) or more than one third of the $10 billion spent annually on common STDs (excluding HIV) and related syndromes.[9] Also different studies have reported decreased self-esteem and increased psychological distress, embarrassment, anger, shame, negative self-perception, anxiety, and relationship difficulties among patients with anogenital warts.[11,12] It is therefore important to determine risk factors for the development, progression or regression of anal warts.

The role of smoking in cervical cancer was first reported by Naguib et al. in 1966.[13] The concentration of nicotine was 45 times higher in cervical tissue than in serum of smoking women.[14] Tobacco smoke is likely to contribute to carcinogenesis through its impact on immune function thereby altering the natural history of HPV infection and acting as a co-carcinogen in cervical tissue.[15] Also, the relationships between cigarette smoking and HPV infection,[16–18] as well as cervical and anal cancer[19–30] have been explored and are well-documented. Evidence on the association between cigarette smoking and anogenital warts, in general, and anal warts, in particular, is limited and has only recently received attention in the literature. Accordingly, Feldman et al.[31] reported that the incidence of genital warts was almost 3 times higher in smokers than non-smokers, both in HIV-infected women (13.3 vs. 5.0, respectively) and HIV-uninfected women (1.5 vs. 0.5, respectively). However, to date, there has been no study published on the association between cigarette smoking and anal warts.

Given the burden of disease and lack of understanding of risk factors for development of anal warts (i.e., smoking), we investigated whether cigarette smoking status is associated with the size of the largest anal wart in HIV-infected women over time using the public dataset obtained from the WIHS, an on-going cohort study of HIV-infected and HIV-uninfected women in the United States.

METHODS

Study population

Data used for the current analysis were obtained from the public dataset (release 09) of WIHS. WIHS is an on-going prospective study of HIV-infected and uninfected women from six locations in the US: Bronx/Manhattan, NY; Brooklyn, NY; Washington DC; Los Angeles/Southern California/Hawaii; San Francisco/Bay Area, CA; and Chicago, IL. Details

on the WIHS study were described previously.[32,33] Briefly, WIHS recruited study participants through two enrollment phases: 1994–1995 and 2001–2002. The first enrollment phase was between October 1994 and November 1995. Initially, 2,059 HIV-infected women and 569 HIV-uninfected women were recruited from both clinic-based and population-based sources. Inclusion criteria in the first enrollment phase were: 1) being at least 13 years of age; 2) giving informed consent; 3) being tested for HIV; 4) ability to complete the interview in either English or Spanish; 5) ability to travel to and from the clinic site to participate in a baseline visit; and 6) giving blood for laboratory testing. During the second enrollment phase between October 2001 and September 2002, 1,144 women were recruited. Besides the above criteria, participants who were recruited in the second enrollment also met the following criteria: 1) documented results of an HIV ELISA and confirmatory Western blot for HIV-infection or documented HIV-negative status (within 30 days before recruitment); 2) no history of clinical AIDS-related conditions (confirmed by medical record abstraction); 3) documented laboratory testing results of HIV RNA levels and CD4 counts surrounding the HAART period for those enrolled as HAART exposed; and 4) consent to give specimens (31). During the first enrollment phase, frequency matching (age, ethnicity, education level, injection drug use since 1978, and total number of sex partners since 1980) was employed to ensure the comparability between HIV-infected and HIV-uninfected groups.

The WIHS study protocols included a baseline visit and follow-up visits every 6 months, conducted by trained interviewers and examiners. Information obtained during interview included general medical history, obstetric and gynecologic history, HAART use, alcohol and cigarette use, and sexual behaviors. Medical examination, gynecologic examination, and medical record abstraction were conducted during baseline and follow-up visits. Medical examination included height/weight/vital signs, lymph nodes, and abdomen. Gynecologic examination included external genitalia, internal vagina and cervix, cervical-vaginal lavage, bimanual and rectal exam, and colposcopy, biopsy, and dysplasia treatment if necessary. Medical record abstraction included development of cancer, infectious diseases or opportunistic infections, and any biopsies, surgeries or hospitalization as well as medications received.[32,33]

Details on specimens and laboratory techniques were previously reported by Barkan et al.[32] and Bacon et al.[33] Key clinical information collected in follow-up visits was CD4 and CD8 cell count, HIV sero-status among HIV-uninfected women, and Pap smear outcomes.[34]

Variables of interest and measurement

Outcome variable—The outcome variable for the current analysis was size of the largest anal wart present at the given visit. For this purpose, only those who had at least one anal wart during the course of follow-up were included in the analysis. During the gynecologic examination, a trained examiner identified the presence of anal warts, and then measured the length and width (in millimeters) of the largest wart. The size (area) of the anal wart was calculated by multiplying the width and length of the reported largest anal wart. The wart was identified as an anal wart if it presented in one of the following locations: "anus upper left", "anus lower left", "anus upper right", "anus lower right", "perineum left", and

"perineum right". We assumed that the largest wart is an anal wart if there were multiple warts reported.

Independent variable—The independent variable for this analysis was current smoking status. This was obtained as "Yes"/"No" answer to the following question at baseline and each subsequent visit: "Do you currently smoke cigarettes?"

Other variables—CD4+ cell count (<200, 200–500, and >500 cells/mm^3) and HIV viral load (<4,000, 4,000–20,000, 20,001–100,000, and >100,000 copies/mL) were analyzed descriptively, as they are important variables in the WIHS study. Potentially confounding variables included in the current analysis were: race/ethnicity (African-American, Caucasian, and others), number of sex partners in the past six months (0 and 1 sex partners), education level (less than high school education, high school education or GED, some college, and college graduate or graduate school), annual household income ($6,000, $6,001–$12,000, $12,001–$24,000, and 24,001), marital status (married or living with partner; widowed, separated or divorced; and never married), enrollment phase (enrollment phase 1 and enrollment phase 2), and HAART use ("Yes"/"No" if on HAART at that particular visit).

Blood was drawn at each visit for determination of HIV status, CD4+ cell count and HIV viral load. Laboratories certified by the AIDS Clinical Trial Groups measured CD4+ cell count level using an established flow cytometry technique.[32] Serum HIV viral load was measured using the nucleic acid sequence-based amplification assay (NASBA) by Organon Teknika (Oklahoma City, OK). HIV viral load tests were conducted at the National Institute of Allergy and Infectious Diseases, AIDS Program, Virology Assurance HIV RNA Proficiency Program.[32] A person was considered on HAART if she met one of the following criteria: 1) Two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitors (NNRTI); 2) One NRTI in combination with at least one PI and at least one NNRTIs; 3) Regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTI; 4) An abacavir or tenofovir containing regimen of 3 or more NRTIs in the absence of both PI and NNRTIs, except for the three-NRTI regimens consisting of: abacavir + tenofovir + lamivudine or didanosine + tenofovir + lamivudine. Combination of zodovudine (AZT) and stavudine (d4T) with either a PIT or NNRTI were not considered HAART. Monotherapy is considered as taking one NRTI, or only PI, or only NNRTI. This definition of HAART use followed the guidelines of the US Department of Health and Human Services,[35] the International AIDS-Society Panel Antiretroviral Guidelines[36] and is consistent with previous analyses from WIHS.[37,38]

Statistical analysis

The distributions of socio-demographic characteristics were examined. We calculated mean and standard deviation of continuous variables and counts and their respective frequencies of categorical variables. Initially, CD4+ cell count and HIV viral load were provided as continuous variables. We used 10 copies/mL for those whose HIV viral load were suppressed to undetectable levels as it was identified and validated by Norteman et al.[39]

CD4+ cell count was categorized into three groups (<200, 200–500, and >500 cells/mm$^{3)}$) and HIV viral load was categorized into four groups (<4,000, 4,000–20,000, 20,001–100,000, and >100,000 copies/mL) as in previous WIHS studies.[37,40–43]

A linear mixed model was employed to determine the relationship between size of the largest anal wart and current smoking status at each visit. We chose this model over other statistical methods because of the following advantages. First, it is able to deal with missing values which are common in longitudinal studies. Second, it adjusts for the highly correlated nature of repeated measurements within and between individuals in longitudinal studies. Third, it is able to deal with the problem of unbalanced measurements (i.e., number of visit in our study) of subjects and the time interval between measurements.[44] In WIHS study, the time interval between measurements was approximately equal (i.e., 6 months between visits).

An unadjusted model was first developed to determine the total variation of growth velocity.[44] Next, an adjusted model was built including the following covariates: number of sex partners in the past six months, education level, marital status, enrollment phase, HAART use, and annual household income. Current smoking status (i.e., independent variable), was treated as a time-dependent variable in both the unadjusted and adjusted models. In the adjusted models, number of sex partners in the past six months, education level, marital status, annual household income, and HAART use were also treated as time-dependent variables. In other words, they were entered into the adjusted model both as a main effect and as a product with time (represented by visit number). The time-independent variables included race/ethnicity and enrollment phase and were entered in to the adjusted model as a main effect only. We use those covariates because they have been identified as potential confounders and been used consistently throughout other analyses in WIHS study.[37,43,45–48] CD4+ cell count and HIV viral load were not included in the final model because we previously reported that there was no association between them and the size of anal warts.[49] The PROC MIXED command of SAS 9.2 statistical package (Cary, NC) was used in the modeling process.[50] All tests were two-sided and $P = 0.05$ was used as the cut-off for significance.

RESULTS

In the current study (between October 1994 and March 2006), the follow-up has 23 possible visits with 3,766 HIV-infected and -uninfected women. Exclusion criteria were HIV-uninfected women ($n = 958$), women who sero-converted during the study ($n = 16$) or those with unknown HIV sero-status ($n = 1$), women without anal warts during the entire follow-up period ($n = 1,777$), and women who underwent treatment for anal warts during the study ($n = 38$). Women who received treatment for anal warts were excluded because the various treatment modalities could greatly influence the size of anal warts in differing ways during follow-up, and there were not enough participants in this group to conduct a meaningful sub-group analysis. Finally, a sample of 976 women was available for this analysis (Figure 1).

Approximately 20% of participants had a CD4+ cell count less than 200 cells/mm^{3}, and 50% had a HIV viral load more than 100,000 copies/mL. More than 65% of participants

were current smokers at the baseline visit. Approximately 66% of study participants were African-American while the frequencies of Caucasian and the other race/ethnicity groups (i.e., Hispanic, Asian/Pacific Islanders, and Native America/Alaskan Native) were similar (19.42% and 19.94%, respectively) (Table 1).

In both unadjusted and adjusted models (Table 2), there was no significant association between size of anal wart at the baseline visit and current smoking status over time. In the unadjusted model, at the baseline visit, women who were current smokers had anal warts that were 21.79 mm^2 larger than women who were not current smokers. The growth rate of the largest anal wart after each visit in a woman who was also current smoker was 1.48 mm^2 less than that of a woman who was not a current smoker. However, those results were not statistically significant ($P = 0.41$ and $P = 0.56$, respectively).

DISCUSSION

In the current analysis, we did not find an association between smoking status and the size of the largest anal wart over time in HIV-infected women from an on-going prospective cohort study in the US. To our knowledge, this is the first study using a linear mixed model to investigate whether smoking status is a predictor for the size of anal warts over time among HIV-infected women. We, therefore, cannot compare our findings directly with any other study. There are, however, a few studies reporting the relationship between smoking status and presence of genital warts. In a previous analysis of a subset of WIHS participants, Feldman et al.[31] reported that current smokers were 5.2 times (95% CI 1.02–26.0) more likely to develop genital warts than non-smokers. The major difference between our study and their study [31] is the outcome variable examined. In our study we examined anal warts only, while Feldman et al.[30] also investigated genital warts. We looked into the changes of the size of anal wart over time (i.e., anal wart was already presented); whereas Feldman et al.[31] examined the presence or absence of genital warts.

One interesting issue is that the largest wart in current smokers was larger than that in non-current smokers at baseline, even though it was insignificant in the adjusted model. It is plausible that when a current smoker has large wart at baseline, the growth rate (or speed of development) will be slower in subsequent visits when compared to non-smokers.

Even though we did not find an association between the size of the largest anal wart and current smoking status among HIV-infected women in the current analysis, this relationship should be further explored for several reasons. The effects of cigarette smoke by-products on HPV infection, in general, and the risk of cancer, in particular, have been examined previously with the majority of support coming from the cervical cancer literature.. Accordingly, McArdle et al.[51] reported that in the occurrence of cervical neoplasia, there was a reduction of Langerhans cells in smokers that leads to mitigation of the effect of host immunity against HPV. Tobacco smoke likely exerts its actions via two classes of compounds: nitrosamines and polycyclic aromatic hydrocarbons (PAHs).[52] In particular, nitrosamine 4-(methylnitrosamino)-1-(3-pryridyl)-1-butanone (NNK), which is the most active carcinogen in animal models,[53] has been reported in high levels in the cervical mucus of women who smoke compared to non-smokers (mean±SD: 46.9±32.5ng/g vs.

13.0±9.3ng/g)[54]. Melikian et al.[55] identified benzo[*a*]pyrene metabolites in cervical mucus and DNA adducts in cervical tissues and suggested that PAHs from tobacco smoke and other environmental sources can be transported to the cervix where they are then metabolized in the cervical epithelium. Recently, Alam et al.[56] found that exposure of cervical cells to benzo[*a*]pyrene also induced high levels of HPV synthesis, thus facilitating the HPV-associated disease process. Since most of the literature on smoking and HPV disease has focused on cervical neoplasia, we have little to draw from for anal HPV disease. However, we feel confident that the interaction between HPV and smoking could be similar for the development of anal warts.

Another reason is that the relationship between smoking and HPV infection,[15–18] cervical cancer,[19–28] and anal cancer[29,30] have been well studied in numerous epidemiologic studies. Accordingly, current smokers are 1.6–4.6 times more likely to have pre-cancerous and invasive cervical cancer than non-smokers and that the risk increases with the intensity or duration of smoking (Odds ratio [OR] 5.9, 95% CI 1.0–35.6) for those who smoke more than 10 cigarettes per day. Furthermore, cigarette smoking influences not only the incidence or prevalence but also the natural history and pathogenesis of HPV infection. Giuliano et al.[57] found that "ever" smokers maintained an HPV infection significantly longer than women who never smoked (mean duration: 10.7 months vs. 8.5 months). Smokers were also found to have a lower probability of clearing oncogenic infections than women who never smoked (Hazard ratio [HR] 0.44, 95% CI 0.20–0.96, 8 cigarette/day). Recently, Matsumoto et al.[58] reported that smokers has significantly lower regression probability of low-grade cervical abnormalities than non-smokers (55.0% vs. 68.8%, $P = 0.004$).

Smoking has been shown to be both an independent risk factor and a co-factor that interacts with other risk factors, such as CD4+ cell count or prior history of external genital warts to enhance the development of genital warts. In a study of 5,622 asymptotic men, Wiley et al.[59] found that the risk of external genital wart development in a smoker who had a history of external genital warts and who had CD4+ cell count <200 cells/mm^3 was 6.9 (95% CI 4.7–10.1), compared to those who did not have a history of external genital warts and who had CD4+ cell count less than 200 cells/mm^3. They, however, did not report the difference in the incidence of genitals warts between smokers and non-smokers. Our study focuses on clinical outcomes, and the dataset obtained from the WIHS study did not allow us to investigate the molecular mechanisms of smoking on the size of anal warts. For this reason, further studies of this association at the molecular level are warranted.

Our study has two major strengths. First, using linear mixed modeling allows us to clearly address the association between the size of anal wart and current smoking status over time while other statistical methods cannot. The ability of the model to deal with the problems of high correlation of repeated measurements within and between individuals, missing values, nonlinear covariates, and unbalanced measurements greatly enhances our ability to utilize rich dataset to examine these important health outcomes among HIV-infected individuals. Furthermore, the use of linear mixed modeling also allows us to appropriately model the size of anal warts as a continuous outcome variable. Had we categorized the size of anal warts and used different approaches (i.e., logistic regression or Cox-proportional hazard regression), we would not have been able to detect subtle changes in the size of the wart

during follow-up. One limitation to the current study is the use of the size of the largest anal wart at each visit as the outcome variable. This does not allow us to follow the same wart over time because the largest wart measured at one visit might not be the same in subsequent visits, especially when there are multiple warts. Even though studying the progression or regression of the same wart over time is not feasible with our data, we felt that studying overall disease burden (as measured by the largest wart) was the best proxy measure available. While we were unable to validate the largest anal wart size as a proxy measure for overall disease burden, no other studies to our knowledge have examined this relationship.

In summary, we did not find evidence for the association between the size of anal warts and current smoking status over time in HIV-infected women. However, our results suggest that, at baseline, women who smoke had much larger warts than those who did not smoke. Further exploration of the role of smoking, the interaction between smoking status with other risk factors (e.g., CD4+ cell count or HIV viral load), and the molecular study of the mechanism of smoking on anal warts over time are warranted.

Acknowledgments

ABBREVIATIONS

AZT	Zodovudine
CI	Confidence interval
d4T	Stavudine
GED	General education development
HAART	Highly active antiretroviral therapy
HPV	Human papillomavirus
PI	Protease inhibitor
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors

OR	Odds ratio
SD	Standard deviation
WIHS	Women's Interagency HIV Study

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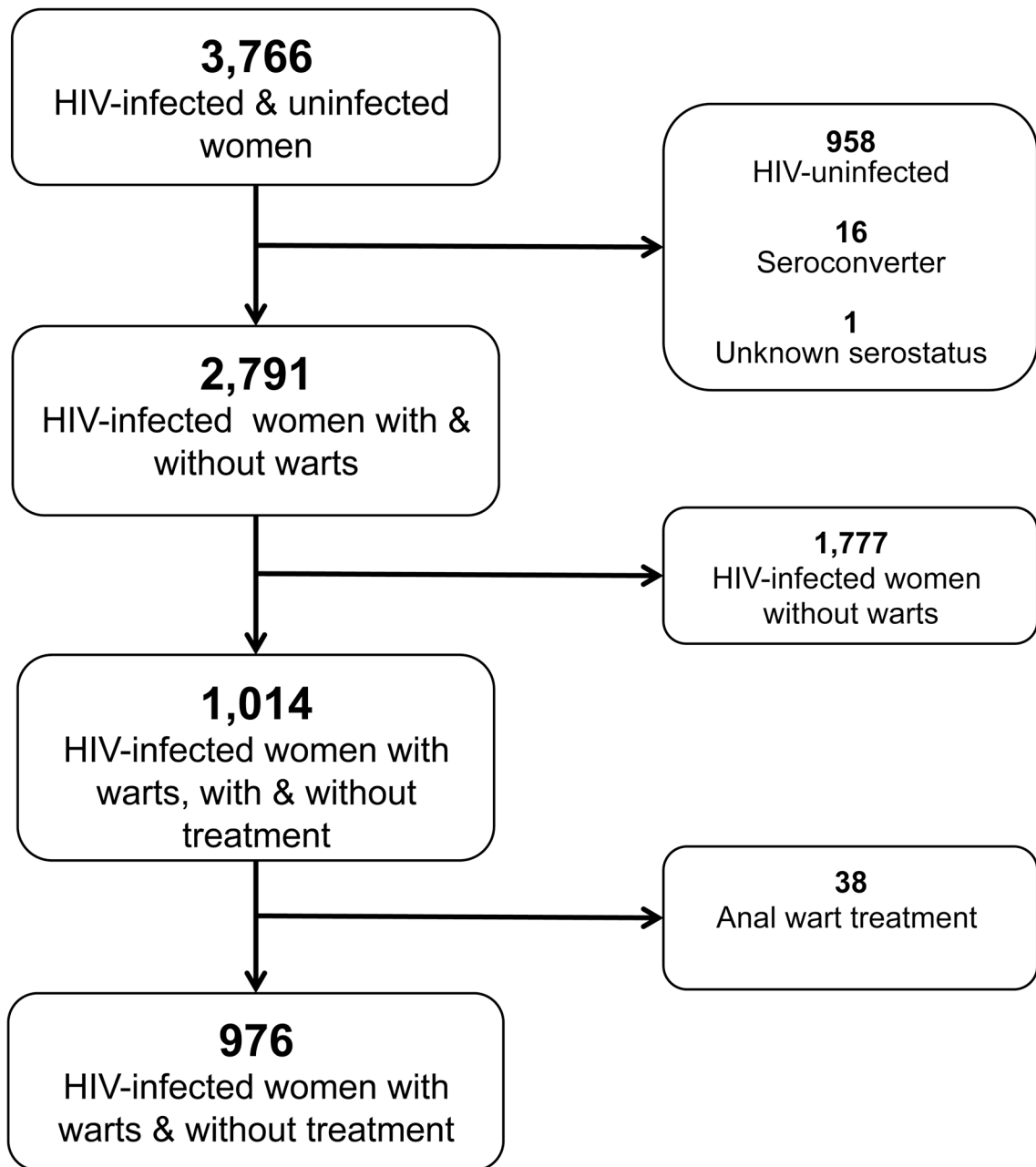
Figure 1.
Flowchart of inclusion and exclusion of participants in current analysis.

Table 1

Baseline Socio-demographic Characteristics of the WIHS HIV-infected Participants in the Current Study

Characteristics	WIHS study (976) (n, %)
CD4+ cells count (cells/mm^3)	
Mean CD4+ cell count±SD	324.59±293.04
<200	148 (19.79)
200–500	328 (43.85)
>500	272 (36.36)
HIV RNA viral load (copies/mL)	
Mean viral load±SD	181,175±1,039,797
<4,000	331 (34.77)
4,000–20,000	164 (17.23)
20,001–100,000	215 (22.58)
>100,000	242 (25.42)
Cigarette smoking status	
Current smokers	565 (65.39)
Not current smokers	299 (34.61)
Number of cigarette smoked per day among current smokers	
<10 cigarettes/day	288 (64.16)
10–20 cigarettes/day	44 (11.43)
20 cigarettes/day	94 (24.42)
Age (Median±SD)	36.56±7.85
25	66 (6.77)
26–35	383 (39.28)
36–45	407 (41.74)
>45	119 (12.21)
Ethnicity	
Caucasian American	189 (19.42)
African American	590 (60.64)
Others	194 (19.94)
Education	
<High school education	317 (36.35)
High school education or GED	295 (33.83)
Some college	207 (23.74)
College graduate or graduate school	53 (6.08)
Annual household income	
$6,000	125 (25.61)
$6,001–$12,000	171 (35.04)
$12,001–$24,000	118 (24.18)
24,001	74 (15.16)
Marital status	
Married or living with partner	245 (35.00)

Characteristics	WIHS study (976) (n, %)
Widowed	55 (7.86)
Separated or divorced	146 (20.86)
Never married	254 (36.29)
Number of male sex partners in the past 6 months	
0	259 (27.52)
1	682 (72.48)
HAART use at baseline	
No	285 (97.60)
Yes	7 (2.40)
Mean size of anal warts (mm^2) ±SD[a]	13.65±127.71

Abbreviations: GED, General education development; SD, Standard deviation.

[a] Among those with anal warts at baseline (*n*=417)

Table 2

Linear Mixed Model of Size of Anal Warts and Current Smoking Status in the WIHS HIV-infected participants of the Current Study in Unadjusted and Adjusted Models

	Unadjusted model		Adjusted model[†]	
	Coeff ±SE	p-value	Coeff ±SE	p-value
Intercept	5.20±21.25	0.81	59.26±33.38	0.07
Visit	4.07±2.02	0.04[*]	−6.76±6.79	0.32
Not current smokers	Ref.[a]	.	Ref.[c]	.
Current smokers	21.79±26.48	0.41	−10.39±13.08	0.44
Visit × (not current smokers)	Ref.[b]	.	Ref.[d]	.
Visit × (current smokers)	−1.48±2.51	0.55	0.87±2.71	0.75

Abbreviations: HAART, Highly active antiretroviral therapy; SE, Standard error.

[a]Type 3 p=0.41;

[b]Type 3 p=0.56;

[c]Type 3 p=0.44;

[d]Type 3 p=0.75;

[†]Model adjusted for number of sex partner in the last 6 month, race/ethnicity, HAART use, enrollment, marital status, annual household income and education level.

[*]Statistically significant at P value<0.05