MAJOR ARTICLE

$CD4^+$ Cell Count and HIV Load as Predictors of Size of Anal Warts Over Time in HIV-Infected Women

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Background. Little is known about the associations between $CD4^+$ cell counts, human immunodeficiency virus (HIV) load, and human papillomavirus "low-risk" types in noncancerous clinical outcomes. This study examined whether $CD4^+$ count and HIV load predict the size of the largest anal warts in 976 HIV-infected women in an ongoing cohort.

Methods. A linear mixed model was used to determine the association between size of anal wart and $CD4^+$ count and HIV load.

Results. The incidence of anal warts was 4.15 cases per 100 person-years (95% confidence interval [CI], 3.83–4.77) and 1.30 cases per 100 person-years (95% CI, 1.00–1.58) in HIV-infected and HIV-uninfected women, respectively. There appeared to be an inverse association between size of the largest anal warts and $CD4^+$ count at baseline; however, this was not statistically significant. There was no association between size of the largest anal warts and $CD4^+$ count or HIV load over time.

Conclusions. There was no evidence for an association between size of the largest anal warts and $CD4^+$ count or HIV load over time. Further exploration on the role of immune response on the development of anal warts is warranted in a larger study.

Human papillomavirus (HPV) is a necessary cause of cervical cancer [1, 2] and has also been shown to be strongly associated with anal cancer [3]. Although the high-risk HPV types 16 and 18 account for the majority of cancers [1, 2], low-risk HPV genotypes (eg, 6 and 11) are responsible for the development of anogenital warts [4, 5]. Recent estimates predict that approximately 1% of sexually active adults in the United States have visible genital warts [6], and the prevalence may be much higher among individuals infected with human immunodeficiency virus (HIV). A previous study reported that HIV-infected women were 9.32 times (95% confidence interval [CI], 3.04–38.00) more likely to have genital warts than HIV-uninfected women [7]. Furthermore, immunocompromised patients were found to have more recurrence of anogenital warts than immunocompetent persons [8].

Among risk factors shown to be associated with HPV infections and their clinical outcomes, $CD4^+$ cell count and HPV load have been studied extensively, particularly in HIV-infected populations. Accordingly, several studies have reported that a person with a high $CD4^+$ cell count and a low HIV load is less likely to be infected with HPV than a person with a low $CD4^+$ cell count and a high HIV load [9–14]. Although there are numerous studies on how HPV high-risk types, $CD4^+$ cell counts, and HIV loads collectively impact certain clinical outcomes (eg, cervical cancer), little is known about the associations with HPV low-risk types and important noncancerous clinical outcomes (ie, anogenital warts). As a result, the factors that predict changes in size of anal warts have not been identified. In 2002, Conley et al [15] reported that compared with an HIV-infected woman with $CD4^+$ cell count >500 cells/mm^3, a person with a $CD4^+$ cell count <200/mm^3 is 1.66 times (95%

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CI, 1.03–2.69) more likely to have incident perianal warts. Although this study lends support to the hypothesis that $CD4^+$ cell count is associated with the risk of anal wart development, a longitudinal study with enough power to examine temporal patterns in the way $CD4^+$ cell count, HIV load, and other factors influence the development and progression of anal warts is warranted.

Anal warts pose a major problem for immunocompromised individuals, but they have not been studied separately from genital warts in previous research. This is tremendously problematic given the evidence that the prevalence of anal warts may be higher than that of intravaginal warts among women [16]. Additionally, a person infected with low-risk HPV types, which result in warts, is more likely to be infected with high-risk HPV types, and there is a strong indication that the presence of anal warts is associated with the development of anal intraepithelial neoplasia, which can lead to anal cancer [17, 18]. For these reasons, in addition to the economic and psychosocial burdens associated with this condition, it is important to determine which factors drive changes in size of anal warts.

The purpose of the current study was to determine, using data from the Women's Interagency HIV Study (WIHS), an ongoing longitudinal study of HIV-infected and HIV-uninfected women in the United States, whether $CD4^+$ cell count and HIV load predict the size of the largest anal warts in HIV-infected women.

MATERIALS AND METHODS

Study Population

Data used for this study were obtained from the public dataset (release P09) provided by WIHS. WIHS is an ongoing prospective cohort study and has been described in detail elsewhere [19, 20]. In brief, WIHS included clinical consortia in 6 locations across the United States: Bronx/Manhattan, New York; Brooklyn, New York; Washington, District of Columbia; Los Angeles/Southern California/Hawaii; San Francisco/Bay Area, California; and Chicago, Illinois. WIHS has 2 enrollment phases: The first enrollment phase was between October 1994 and November 1995, during which 2059 HIV-infected and 569 HIV-uninfected women were recruited; the second enrollment phase was between October 2001 and September 2002, during which 1143 HIV-infected and 406 HIV-uninfected women were recruited.

The WIHS protocols include a baseline visit and follow-up every 6 months. During the baseline visit, a standardized in-person questionnaire was administered by trained interviewers. Self-reported information during the interview included general medical history, highly active antiretroviral therapy (HAART) use, obstetric and gynecologic history, alcohol and cigarette use, sexual behaviors, and history of physical and sexual abuse. Medical examination included height/weight/vital signs and examination of skin, abdomen, and breasts. Gynecologic examination included external genitalia, examination of internal vagina and cervix, cervical-vaginal lavage, bimanual and rectal examination, and colposcopy, biopsy, and dysplasia treatment if necessary. Follow-up visits [21] assessed key clinical characteristics such as $CD4^+$ and $CD8^+$ cell counts, HIV serostatus (HIV-uninfected women only), HIV load (HIV-infected women only), and Pap smear. For the current analyses, only those who had at least 1 anal wart over the study course were included.

Variables of Interest and Measurement

Outcome Variable

The outcome variable was the size of the largest anal wart at each visit. Presence of anal warts was recorded on the gynecologic exam form. The length and width (in millimeters) of the largest anal wart was measured and recorded. The physicians and physician assistants were instructed to complete the form and code the lesions and diagnoses. In current analysis, anal warts were defined as warts in one of the following locations: anus upper left, anus lower left, anus upper right, anus lower right, perineum left, and perineum right. The size of the anal wart was calculated by multiplying the width and length of the reported anal wart. In case of multiple warts, we assumed that the largest wart is an anal wart.

Independent Variables

Blood was drawn at each visit for determination of HIV serostatus, $CD4^+$ cell count, and HIV load. The level of $CD4^+$ cell count was quantified using flow cytometry at laboratories certified by the AIDS Clinical Trial Groups [19]. HIV load was measured in serum using a nucleic acid sequence-based amplification assay from Organon Teknika. HIV load tests were done at the National Institute of Allergy and Infectious Diseases AIDS Program, Virology Assurance HIV RNA Proficiency Program, National Institutes of Health [19].

Covariates

Covariates included in the current analysis were race/ethnicity (African American, white, and others); number of sex partners in the past 6 months (0 and $\geq$1); education level (less than high school education, high school education or general educational development test, some college, and college graduate or graduate school); annual household income ($\leq$\$6,000, \$6001-\$12 000, \$12 001–\$24 000, and $\geq$24 001); enrollment (enrollment 1 and enrollment 2); HAART use (yes/no); and marital status (married or living with partners, widowed, separated or divorced, and never married). The HAART use definition in the current analysis was based on the guidelines from the US Department of Health and Human Services, version 2002 [22] and the International AIDS Society Panel Antiretroviral Guidelines [23] and was consistent with previous WIHS analyses [24, 25]. A person was considered on HAART if she met 1 of the following criteria: (1) $\geq$2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least 1 protease inhibitor (PI) or

1 nonnucleoside reverse transcriptase inhibitor (NNRTI); (2) 1 NRTI in combination with at least 1 PI and at least 1 NNRTI; (3) regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTI; and (4) an abacavir- or tenofovir-containing regimen of ≥3 NRTIs in the absence of both PIs and NNRTIs, except for the 3 NRTI regimens consisting of abacavir + tenofovir + lamivudine or didanosine + tenofovir + lamivudine. Combination of zodovudine and stavudine with either a PI or NNRTI were not considered HAART. Monotherapy is considered as taking 1 NRTI, or only PI, or only NNRTI [22, 23].

Statistical Analysis

The distributions of sociodemographic characteristics were examined. For continuous variables, means and their standard deviations were calculated. Incident cases of anal warts were defined as persons who did not have an anal wart at the baseline visit but developed ≥1 anal warts during the follow-up period. Prevalence of anal warts for the entire WIHS cohort and in HIV-infected and HIV-uninfected women at baseline was calculated by taking respective number of persons with warts present at baseline divided by respective total samples. Incidence rates were calculated as the total number of incident cases divided by total follow-up time (ie, person-years) for HIV-infected, HIV-uninfected, and seroconverters separately. The 95% CIs for prevalence and incidence rates were based on a normal distribution if the number of cases was >30 and on the exact Poisson distribution if the number of cases was <30 [26].

$CD4^+$ cell count and HIV load at each visit were provided as continuous variables in the WIHS public data set. During follow-up, some participants had HIV loads suppressed to undetectable levels. We used 10 copies/mL for undetectable level, as it was validated by Notermans et al [27]. In this analysis, $CD4^+$ cell counts were categorized into 3 groups (<200, 200–500, and >500 cells/mm^3), and HIV load was categorized into 4 groups (<4000, 4000–20 000, 20 001–100 000, and >100 000 copies/mL). These categories were chosen for consistency with previous WIHS analyses [24, 28–31]. Both $CD4^+$ cell count and HIV load were used in each visit in the longitudinal modeling process.

The linear mixed model was chosen for the current analysis because of its ability to deal with missing values that are common in a longitudinal studies, deal with the highly correlated nature of repeated measurements within individuals and between individuals in a longitudinal study, and account for unbalance measurements (ie, number of visits) of subjects and the time interval between measurements [32]. Unadjusted models were first constructed to determine the total variation in growth velocity [26]. In the adjusted models, time-dependent covariates included number of sex partners in the past 6 months, education level, marital status, annual household income, and HAART use. Each of these variables was entered into the model both as a main effect and as a product with time. The time-independent covariates in the adjusted models were race/ethnicity and enrollment. Those covariates had been identified and used in previous analyses of WIHS [13, 24, 31, 33–35] and were treated as potential confounders in the current analysis. All statistical analyses were performed using command PROC MIXED of the SAS 9.2 statistical package [36]. All tests were 2-sided, and $P = .05$ was used as the significance level.

RESULTS

WIHS consisted of 3766 HIV-infected and HIV-uninfected women. Participants were excluded from the current analysis if (1) they were HIV-negative (n = 958); (2) they were seroconverters (n = 16) or had unknown HIV status (n = 1); (3) they did not have any anal warts during follow-up (n = 1777); or (4) they had received treatment for anal warts during the study period (n = 38) (Figure 1). HIV-infected women who received treatment for their anal warts were excluded because these treatments could have greatly influenced the size of the anal wart, many different types of treatment were received, and there were too few participants in the treatment group to perform a meaningful subanalysis.

Of the 1141 women who had at least 1 anal wart during follow-up, 477 women (441 HIV-infected vs 34 HIV-uninfected women) were identified with anal warts at baseline. Therefore,

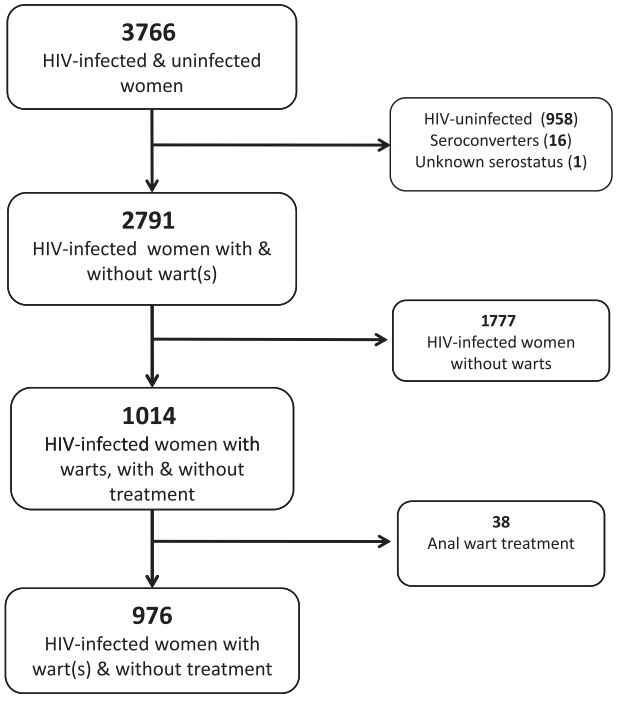

Figure 1. Flowchart of inclusion and exclusion of participants in current analysis. Abbreviation: HIV, human immunodeficiency virus.

Table 1. Incidence Cases of Anal Warts, Follow-up Time, and Incidence Rate of the Entire Women's Interagency HIV Study by Serostatus Group

	Serostatus				
	HIV (+)	HIV (–)	Seroconverter[b]	Unknown[b]	Total
No. of incidence cases of anal warts	644	77	3	0	724
Person-years follow-up of anal warts incidence cases	1938	236	21		2195
Number of nonwart cases by serostatus group	1777	834	13	1	2625[a]
Person-years follow-up of never developed anal warts	13 578	5706	123	11	19 418
Total person-years follow-up (by groups)	15 516	5942	144	11	21 613
Incidence rate (person-years)	0.0415	0.0130	0.0208	0.0000	0.0335
	(95% CI, .0383–.0477)[b]	(95% CI, .0100–.0158)[b]	(95% CI, .007–.052)[c]		(95% CI, .0311–.0360)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a] This total already excludes 417 cases of anal warts at baseline visit.

[b] Calculation of 95% CI based on normal distribution.

[c] Calculation of 95% CI based on Poisson distribution.

the prevalence of anal warts at baseline was 12.67% (95% CI, 11.61%–13.73%). The respective prevalences of anal warts at baseline in HIV-infected and HIV-uninfected women were 15.80% (95% CI, 14.45%–17.15%) and 3.55% (95% CI, 2.38%–4.72%). These prevalences were significantly different ($P < .0001$). The incidence rates of anal warts by HIV serostatus for the entire WIHS study are presented in Table 1. Because 724 incident cases of anal warts were identified, the incidence rate was 3.35 cases per 100 person-years (95% CI, 3.11–3.60 cases per 100 person-years). A statistically significant difference ($P < .0001$) was observed in the incidence rate of anal warts in HIV-infected women (4.15 cases per 100 person-years; 95% CI, 3.83–4.77 cases per person-years) compared with HIV-uninfected women (1.30 cases per 100 person-years; 95% CI, 1.00–1.58 cases per 100 person-years).

Table 2 presents the baseline sociodemographic characteristics of study participants included in our analysis. Approximately 20% of participants had a $CD4^+$ cell count of <200 cells/mm^3, and 40% had a $CD4^+$ cell count of >500 cells/mm^3. Although 33% of participants had an HIV load of <4000 copies/mL, about 50% had an HIV load of $>20\,000$ copies/mL.

Table 3 presents results on the association between size of anal warts and $CD4^+$ cell count. There was no significant relationship between size of the largest anal warts and $CD4^+$ cell count over time in either the unadjusted or adjusted model. At baseline, women with moderate $CD4^+$ cell counts had, on average, an anal wart size of 1.61 mm^2 larger than that of women with the highest CD^+ cell count. Similarly, the size of the anal wart of women with the lowest $CD4^+$ cell count was 5.98 mm^2 larger than that of women with the highest $CD4^+$ cell count. However, those results were not statistically significant ($P = .93$ and $P = .76$, respectively). Interestingly, the growth rate of anal wart size after each visit in women with the lowest and moderate levels of $CD4^+$ cell count were 0.30 mm^2 and 0.64 mm^2, respectively, less than that of women with the highest $CD4^+$ cell level. However, these differences were not statistically significant.

Table 4 shows estimates on the association between size of anal wart and HIV RNA. Similar to $CD4^+$ cell count, there was no significant association between size of the largest anal wart and HIV load over follow-up time. There appeared to be a significantly larger growth rate of anal wart size among women with HIV load of 20 001–100 000 copies/mL than women in the reference group (HIV load of <4000 copies/mL) ($P = .003$). However, this difference was diminished in the adjusted model. In the adjusted model, women with an HIV load of $>100\,000$ copies/mL had a larger wart size at baseline (20 mm^2) but a slower growth rate of change than those of women with an HIV load of <4000 copies/mL. Again, these differences were not statistically significant in the adjusted model.

DISCUSSION

The current analysis examines the possible association between size of anal warts and $CD4^+$ cell count as well as HIV load over time among HIV-infected women using the public dataset from WIHS, an ongoing longitudinal study in the United States. Our study did not provide evidence of an association between the size of the largest anal warts and $CD4^+$ cell count or HIV load over time in HIV-infected women.

However, we did find a higher prevalence of anal warts at baseline among HIV-infected women in the WIHS study than

Table 2. Sociodemographic Characteristics of the Women's Interagency HIV Study HIV-Infected Participants in Current Study

Characteristics	WIHS (n = 976), No. (%)
$CD4^+$ cell 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 load (copies/mL)	
Mean viral load ± SD	181 175 ± 1 039 797
<4000	331 (34.77)
4000–20 000	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 cigarettes 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)
Race/Ethnicity	
White	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)
Household annual income	
≤$6000	125 (25.61)
$6001–$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)
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

Table 2 continued.

Abbreviations: GED, general educational development test; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; SD, standard deviation.

[a] Among those with anal warts at baseline (n = 344 and n = 73 in enrollment 1 and 2, respectively).

reported elsewhere [6, 32, 37]. For example, the prevalence of anal warts at baseline found in our analysis is >3 times higher than that in the 1996 survey of the Australian Longitudinal Study on Women's Health, in which 3.1% of 14 762 women aged 18–23 years reported ever having been diagnosed with anal warts. Caution is warranted when comparing our finding with the prevalence of anal warts in Australia because warts were self-reported in that study and their population is younger than that of the WIHS. The incidence rate of anal warts among HIV-infected and HIV-uninfected women found in our analysis is similar to those in other studies [38–41]. For example, in a study also from the WIHS cohort in 2004, Massad et al [41] reported that the incidence of genital warts among HIV-uninfected and HIV-infected women in the WIHS study were 1.30 per 100 person-years, which is comparable to ours, and 5.41 per 100 person-years, which is somewhat higher than ours, respectively. One possible explanation for the higher incidence in their study is that the follow-up in our analysis is longer than the study by Massad et al [41], and as of October 2010, approximately 80% of WIHS participants had received HAART [21]. HAART was proven to be effective in reducing the incidence of anal warts [41], thus possibly explaining the reduced anal wart incidence in HIV-infected women reported herein.

To our knowledge, this is the first study to use the linear mixed model to address whether there is an association between the size of the largest anal warts over time and either $CD4^+$ cell count or HIV load. Therefore, we cannot compare our findings directly with any other study. However, there are a few studies reporting the relationship between presence and incidence of genital warts with $CD4^+$ cell count [39, 42]. In a previous analysis of the WIHS, Greenblatt et al [42] reported a significant inverse association between $CD4^+$ cell count and genital warts. Accordingly, HIV-infected women with a $CD4^+$ cell count of <200 cells/mm^3 were 6.78 times more likely to have genital warts than HIV-uninfected women. The difference between our study and the study by Greenblatt et al [42] is that we examined the size of anal warts, whereas they looked at the presence

Table 3. Linear Mixed Model of Size of Anal Warts and $CD4^+$ Cell Count of the Women's Interagency HIV Study HIV-Infected Participants in Current Study

	Unadjusted Model		Adjusted Model[e]	
	Estimates ± SD	*P* Value	Estimates ± SD	*P* Value
Intercept	59.37 ± 66.69	.47	2.29 ± 46.20	.96
Visit	−1.35 ± 5.31	.80	−1.96 ± 8.22	.81
$CD4^+$ <200 cells/mm^3	−57.87 ± 78.06	.46	5.98 ± 19.28	.76
$CD4^+$ 200–500 cells/mm^3	−42.45 ± 77.75	.59	1.61 ± 18.07	.93
$CD4^+$ >500 cells/mm^3	0[a]	…	0[c]	…
Visit ($CD4^+$ <200 cells/mm^3)	6.41 ± 6.44	.32	−0.64 ± 3.65	.86
Visit ($CD4^+$ 200–500 cells/mm^3)	9.56 ± 6.35	.13	−0.30 ± 3.48	.93
Visit ($CD4^+$ >500 cells/mm^3)	0[b]	…	0[d]	…

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

[a] Type 3, $P = .76$.

[b] Type 3, $P = .32$.

[c] Type 3, $P = .91$.

[d] Type 3, $P = .98$.

[e] Model adjusted for no. of sex partners in the last 6 months, race, highly active antiretroviral therapy use, enrollment, marital status, annual household income, and education level.

of genital warts. Another difference is that in our study, we investigated the development (ie, progression or regression) of anal warts based on the size of the wart longitudinally, whereas the study by Greenblatt et al [42] was a cross-sectional analysis of baseline visit only.

We also found an inverse association between the size of anal warts and $CD4^+$ cell count at baseline visit with decreasing $CD4^+$ cell count category. One possible explanation is that because a person with a $CD4^+$ cell count of <500 cells/mm^3 probably has a larger anal wart than a person with a higher $CD4^+$ cell count, the growth rate would be slower when comparing the measurement of the size of anal warts between 2 visits. Even though we did not find an association between size of anal wart and $CD4^+$ cell count over time, the role of

Table 4. Linear Mixed Model of Size of Anal Warts and HIV Load of the Women's Interagency HIV Study HIV-Infected Participants in Current Study

	Unadjusted Model		Adjusted Model[e]	
	Estimates ± SD	*P* Value	Estimates ± SD	*P* Value
Intercept	38.73 ± 18.73	.03[f]	17.92 ± 34.36	.60
Visit	0.47 ± 1.58	.77	−2.68 ± 7.37	.71
Viral load <4000 copies/mL	0[a]		0[c]	
Viral load 4000–20 000 copies/mL	−17.35 ± 33.23	.60	−1.22 ± 17.53	.94
Viral load 20 001–100 000 copies/mL	−58.97 ± 30.15	.05	2.32 ± 15.68	.88
Viral load >100 000 copies/mL	−41.40 ± 29.05	.15	19.97 ± 15.39	.20
Visit (Viral load <4000 copies/mL)	0[b]		0[d]	
Visit (Viral load 4000–20 000 copies/mL copies/mL)	1.40 ± 3.06	.65	−0.61 ± 3.79	.87
Visit (Viral load 20 001–100 000 copies/mL)	8.97 ± 2.99	.003[f]	0.53 ± 3.24	.87
Visit (Viral load >100 000 copies/mL)	3.67 ± 3.00	.22	−3.25 ± 3.51	.36

Abbreviation: SD, standard deviation.

[a] Type 3, $P = .21$.

[b] Type 3, $P = .02$.

[c] Type 3, $P = .52$.

[d] Type 3, $P = .76$.

[e] Model adjusted for no. of sex partners in the last 6 months, race, highly active antiretroviral therapy use, enrollment, marital status, annual household income, and education level.

[f] Statistically significant at *P* value < .05.

immunity cannot be ruled out because $CD4^+$ cells play an important role in cell-mediated immunity against HPV infection. This is reflected by the increased incidence and progression of HPV infection among immunosuppressed persons. In a cohort of adolescent girls, Moscicki et al [43] observed that the risk for incident Cervical intraepithelial neoplasia (CIN) among HIV-infected adolescents was due to the persistence of Low grade squamous intraepithelial lesions (LSILs). HIV-infected persons are more likely to have multiple recurrences of cervical CIN, chronic condylomatous changes [44], and increased incidence of both cutaneous and genital warts [45]. Additionally, de Jong et al [46] observed a strong proliferative response against 1 or more peptide epitopes derived from HPV 16 E-2 T-cell antigen in peripheral blood mononuclear cell cultures of approximately half of healthy donors. They also found that most of these responses represented reactivity by memory $CD4^+$ T-helper 1–type cells, which are able to secrete interferon-γ on antigenic stimulation.

We were unable to find other studies directly comparing size of anal wart by HIV load, but Dolev et al [47] reported that HIV load was independently associated with the incidence of anogenital warts in the WIHS cohort. It is, however, noted again that the outcome used in our study is different from theirs because we used the size of anal warts and they used the presence of anogenital warts. Although HIV load has been identified as a risk factor for HPV infection [13, 14, 48, 49] and precancerous lesions of the cervix [14] caused by high-risk HPV, it has not been proven to play an important role in the development of anal warts caused by low-risk HPV types.

There are 2 strengths of our study. First, we used the linear mixed model to deal with the aforementioned difficulties inherent to longitudinal data. Second, the use of the linear mixed model allowed us to model the size of anal wart as a continuous outcome variable appropriately. One limitation of this analysis is that by using the size of the largest anal wart present at each visit, we might not be able to follow the same wart over time because the largest wart measured in the first visit might not be the same one that is measured in subsequent visits, especially if there are multiple warts. It is, however, acknowledged that measurement of the same wart over time, especially in a situation of multiple warts, is a not a clinically feasible task. For this reason, a separate study focused on this specific question is warranted.

In summary, we did not find evidence for the association between size of the largest anal warts and $CD4^+$ cell count or HIV load over time. We did, however, find an inverse correlation between the size of anal wart and $CD4^+$ cell count at baseline visit, although this association was not statistically significant. Further exploration on the role of immune function on the development (either progression or regression) of anal warts is warranted because the association between presence of anal wart and immune response has been established.

Notes

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