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CD4 Trajectory Models and Onset of Non–AIDS-Defining Anal Genital Warts, Precancer, and Cancer in People Living With HIV Infection-1

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Background: It is unclear how the characteristics of CD4 counts predict non–AIDS-defining human papillomavirus–related anogenital warts (AGWs) and anal high-grade squamous intraepithelial lesions/cancer ($HSIL^+$) in people living with HIV infection-1 (PLWH). We compared the associations between 3 CD4 counts measures and these disease outcomes in the study.

Methods: Retrospective sociobehavioral and clinical data from electronic health records of 4803 PLWH from 2006 to 2018 were included. Three different measurements of CD4 counts—(*a*) nadir, (*b*) median, and (*c*) trajectory—were estimated. Six CD4 trajectory groups were constructed using the group-based trajectory modeling from all patients older than 18 years with ≥3 clinical visits. Univariate and multivariable logistic regression models were used to assess the associations with AGW and $HSIL^+$, separately.

Results: A total of 408 AGW, 102 anal $HSIL^+$ (43 HSIL, 59 cancer), 4 penile cancer, and 15 vaginal cancer cases were observed. Median CD4 (<200 cell/μL) was associated with AGW (odds ratio [OR], 2.2 [95% confidence interval {CI}, 1.6–3.0]), and anal $HSIL^+$ (OR, 2.7 [95% CI, 1.5–5.0]; each, $P < 0.001$). Low nadir CD4 (<200 cell/μL) was associated with AGW (OR, 1.8 [95% CI, 1.3–2.6]) and anal $HSIL^+$ (OR, 2.4 [95% CI, 1.2–4.7]; each, $P \leq 0.001$). Different patterns (declining and sustained low CD4 counts) of CD4 trajectories showed the strongest associations with onset of both AGW (OR, 1.8–3.1) and $HSIL^+$ (OR, 2.7–6.7).

Conclusions: People living with HIV infection-1 with the same median CD4 could have very different CD4 trajectories, implying different dynamics of immune status. CD4 trajectory could be a better predictor of incident AGW and $HSIL^+$ among PLWH.

AIDS-related morbidity and mortality have dramatically declined since the emergence of combination antiretroviral therapy (cART). People living with HIV infection-1 (PLWH) can expect nearly normal life expectancy, if diagnosed early and adhere to ART.[1,2] Along with longer life expectancy, a growing number of non–AIDS-defining (NAD) conditions have been observed.[3,4] For example, incidence of anogenital clinical conditions resulting from human papillomavirus (HPV) infections are common and often regress less among PLWH than the general population.[5] Furthermore, there is no clear evidence that cART compliance helps clear HPV infection or prevent the occurrence and progression of precancer lesions.[6,7]

Human papillomavirus, a known etiologic factor in several cancers, is one of the most common sexually transmitted infections in the United States.[8] More than 79 million Americans are currently infected with HPV, with an estimate of 14 million new infections every year.[8] The prevalence of genital HPV infection is 1.5 to 2.5 times higher in women living with HIV,[9,10] and anal HPV infection is 1.5 to 2 times more prevalent among women living with HIV and men who have sex with men compared with their HIV-negative counterparts.[11–13] A meta-analysis estimated that the pooled incidence rates of anal intraepithelial neoplasia and cancer were 8.5% to 15.4% per year among men living with HIV and 45.9 cases per 100,000 men living with HIV.[14] These estimates were nearly 3 and 9 times higher than that among HIV-negative men, respectively.[14] Human papillomavirus infection may result in precancerous high-grade squamous intraepithelial lesions (HSILs) and eventually develop to squamous cell carcinomas in the infected anogenital tract. High rates of anogenital HSIL are observed in general among PLWH.[15] Likewise, anogenital warts (AGWs), a sexually transmitted disease caused by HPV, are significantly common among PLWH.[16]

Plasma CD4 T-cell count (CD4) is a key immune indicator in PLWH. It reflects the host's defensibility against pathogens, infections, and illnesses.[17] Recovery and maintenance of an adequate CD4 count facilitate the necessary immune responses to control coinfections and reduce the risk of comorbidities in the course of HIV-1 infection.[17,18] Although CD4 is an important indicator of immune function, its predictive ability of the onset of incident HPV-related clinical conditions, especially NAD conditions, among PLWH is not fully known. CD4 counts are often characterized as nadir and median CD4 counts (measured at a point during a defined period after HIV infection) in the existing literature.[19–21] A study reported that CD4 count 6 to 7 years before cancer diagnosis was a significant predictor;

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Ethics Statement: The study was approved by the UAB Institutional Review Board for Human Use and performed in accordance with the ethical guidelines of the Declaration of Helsinki. Animals were not used in the study.

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however, it did not look for the trend of CD4 over time.[22] CD4 count trajectory, which requires longitudinal data, has not been widely adopted, and no studies have compared the different measures of CD4 counts as predictors of incident NAD HPV-related clinical conditions. We therefore examined and modeled NAD incident anogenital HPV-related clinical conditions including warts and anatomical site–specific HSIL/cancer ($HSIL^+$) as a function of median, nadir, and CD4 count trajectory over a 12-year follow-up among PLWH from an academic clinic in Alabama.

METHODS

Study Population and Source of Data

A retrospective study nested within an ongoing clinical cohort in the 1917 HIV Clinic at the University of Alabama at Birmingham was conducted using electronic health records (EHRs) between January 1, 2006, and March 30, 2018. Patients who started receiving care from the clinic before 2006 were followed up since January 1, 2006; patients who came to the clinic after January 1, 2006, would be followed up since their first clinical visit dates. The UAB HIV Clinic is the largest HIV clinic in the state of Alabama with extensive regional catchment and referral network, as previously described.[23] Since its inception in 1987, the prospective clinic cohort has collected more than 7000 patients' sociodemographic and psychosocial data, comorbidities, medications, vital signs, laboratory results, and corresponding dates since the database establishment in 1992. More than 3500 patients currently receive their routine HIV care from the clinic, representing 30% of all PLWH in the state.[23] Data were obtained by query of the cohort's electronic database using MS SQL Server 2008 before analyses.

This present study was approved by the UAB Institutional Review Board.

Eligibility Criteria

Patients who (1) were at least 18 years old at HIV diagnoses and (2) had 3 or more CD4 tests measured longitudinally were eligible for analyses. For those patients who started receiving care from the HIV clinic before January 1, 2006, medical records in the previous 2 years were reviewed. We only assessed non–AIDS-defining conditions so cervical HSIL/cancer was not included in the analyses. All individuals with prevalent AGW or NAD $HSIL^+$ (penile and anal for men and vaginal and anal for women) at baseline and/or during the 2 years prior (for those with medical records as described earlier) were excluded from the study. The study population was based on an actual clinical cohort, which means participants did not undergo special screening tests before the study. Also, neither AGW nor $HSIL^+$ is routinely screened in the clinic because they are NAD conditions and are not part of routine clinical care. All PLWH's health care–related data were directly extracted from EHR. Therefore, we excluded PLWH with AGW and/or $HSIL^+$ at baseline and/or 2 years prior and only included incident cases, as defined previously.

Statistical Analysis

CD4 and HPV-Related Clinical Outcome Measures

There were 3 different measures of CD4 analyzed. Nadir CD4 was defined as the lowest CD4 count, median CD4 was defined as the midvalue of CD4 distribution, and CD4 trajectory was grouped based on the patterns of CD4 count trends during the follow-up, as described hereinafter. For patients who developed AGW or anatomical site–specific HSIL/cancer during the study period, the follow-up began in the study enrollment and ended in the diagnoses dates of the conditions. For patients who stayed warts- and HSIL/cancer-free during the study period, the follow-up was counted since their study enrollment until the end of their last clinical visit dates or until March 30, 2018.

The primary outcomes of interest included incident clinical conditions related to HPV infections, AGW, and anatomical site–specific precancerous lesions and cancer diagnosed and recorded in the clinical chart dated within the study period. Most HSIL will not progress to cancer; thus, we have combined anatomical site–specific HSIL and cancer patients, denoted as $HSIL^+$ for the analysis. In addition, we have conducted the analyses separately for HSIL and anal cancer.

Univariate Analyses

Univariate analyses were conducted to compare sociodemographic (gender, race, and sexual behavior, mean age at HIV diagnosis, mean age at study entry) and clinical (nadir and median CD4 T cell counts, and $\log_{10}$ mean viral load) data between each defined HPV-related condition group and the condition-free group (noncases). Nadir and median CD4 counts were categorized as <200, 200–499, and >500 cells/μL. Continuous variables were compared by *t* tests, and categorical variables were compared by χ^2 tests, with $P < 0.05$ as the significance threshold.

Multivariable Analyses

Multivariable regression models were used to compare the association of different measures of CD4 count and onset of HPV-related conditions. All statistically significant factors from the univariate analyses were included in the multivariable models. Different CD4 measures were tested for multicollinearity. The variance inflation factors demonstrated that at least 2 of the 3 CD4 measures were highly correlated in each group of the condition (variance inflation factor ≥ 2.4). Both sets of models tested nadir, median, and CD4 count trajectory separately, adjusting for race, age at HIV diagnoses and study entry, and mean $\log_{10}$ viral load. Furthermore, self-reported sexual behavior was highly correlated with gender (Pearson $\rho = 0.93$). Therefore, we conducted 2 separate tests of multivariable models; in addition to other covariates that were significant in the univariate analyses, (1) model 1 (M1) only included gender and (2) model 2 (M2) only included sexual orientation. Survival analyses were first implemented using Cox proportional hazard regression models. However, the Cox proportional hazards assumption could not be justified because the 3 CD4 counts metrics were heavily time-dependent variables that did not produce constant hazard ratios over time. Thus, logistic regression was used as described previously.

Group-Based Trajectory Modeling

The group-based trajectory modeling (GBTM) approach identifies a finite number of groups of individuals exhibiting similar trajectories over a defined time of a single outcome.[24] The GBTM has 2 key components: identifying the polynomial order (shape) of the trajectory and determining a potential trajectory group for each patient in the data.[24] Briefly, the selection process started with a model consisting of one group with the highest polynomial order allowed in the method (quartic degree) and added one group at a time until the best-fitting model was found, as evidenced by the Bayesian information criterion. Subsequently, the polynomial order was reduced one at a time, whereas a *t* test was used to assess the fitness of each group to the polynomial order. Eventually, the lowest order with all significant groupings was determined and used as a new variable for multivariable regression.

The present study was derived from a clinical cohort, which had open enrollment instead of a unified study enrollment period. The number of CD4 tests among patients eligible for GBMT in our cohort varied between 3 and 50 in a maximum of 12-year follow-up (2006–early 2018). If all CD4 tests were used for trajectories, discrepancies among the counts of CD4 tests would bring measurement variance toward the later period of the follow-up, because not all participants had stayed in the study for a full 12-year period. Therefore, the median count of CD4 tests for all participants was used for any model using CD4 count trajectories. To reduce the impact of random fluctuations, laboratory imprecision, and incomplete model accuracy, CD4 series were square root transformed in all subsequent analyses.[25,26] Given the staggered entry due to different patients starting at different times, the starting point of each individual's follow-up was computed by subtracting each patient's enrollment date so each individual had a uniform start point in the analyses.

In addition to the statistical reasoning used in GBTM, clinical context was considered in grouping CD4 count trajectory in our analyses. For example, an immunocompetent person without HIV-infection typically has a CD4 range between 500 and 1000 cells/μL.[17] Likewise, PLWH with CD4 counts greater than 500 cells/μL are generally considered having a good immune recovery. Thus, consistent with prior literature,[27] in the current analysis, all trajectory CD4 counts at and greater than 500 cells/μL were grouped into one trajectory.

Based on the Bayesian information criterion, *P* values, and the consideration for clinical interpretation of the CD4 counts, described previously, the best-fitting model for GBTM consisted of 6 CD4 trajectory groups with a linear order for HSIL$^+$ (Fig. 1A) and AGW (Fig. 1B). Trajectory group membership was defined as the percent of the study population grouped to this CD4 trajectory pattern, and group of morbidity was defined as the percent of HSIL$^+$ or AGW among the trajectory group population. The model was tested for the AGW and anatomical site–specific anal HSIL$^+$, separately.

Sensitivity Analysis

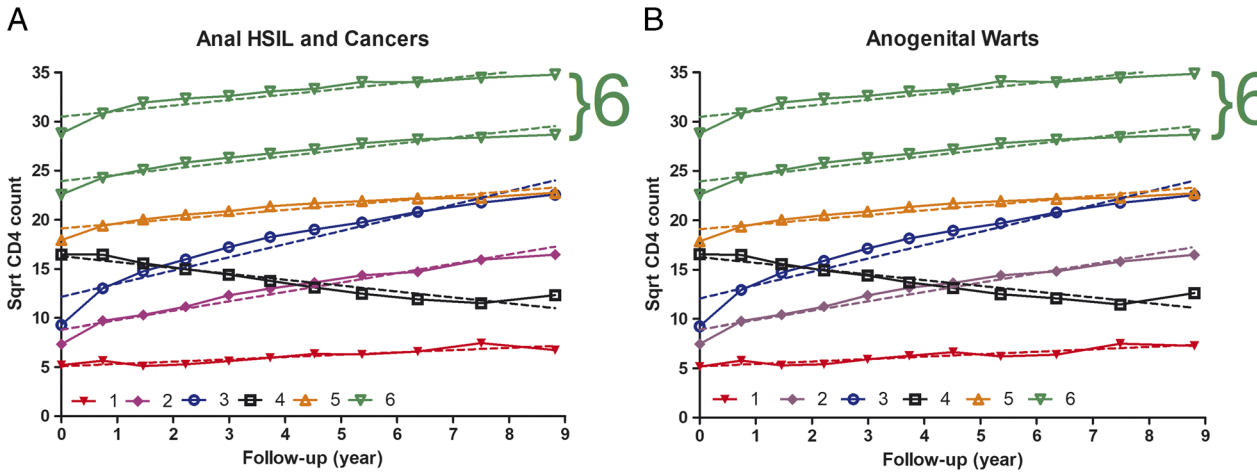
In order to confirm the trajectory grouping from using anal HSIL$^+$ as one outcome, sensitivity analysis was performed using anal HSIL and cancer as outcomes separately. Same GBTM methods were used.

RESULTS

A total of 4803 PLWH attended the 1917 Clinic between January 1, 2006, and March 30, 2018; 4020 and 4036 PLWH were eligible for eligible for AGW- and HSIL$^+$- related analysis, respectively (Table 1). During the follow-up, 408 incident cases of AGW and 102 incident cases of anal HSIL$^+$ (including 59 cases of HSIL and 43 cases of cancer), 4 incident cases of penile cancer (none with HSIL), and 15 incident cases of vaginal cancer (none with HSIL) were observed. Because of the small incident cases of penile and vaginal cancer patients (and no HSIL), we only conducted the analyses for anal HSIL$^+$. There were no overlapping patients who had anal HSIL$^+$ and penile or vaginal cancer.

Patients who developed incident AGW had lower median and nadir CD4 counts (<200 cells/μL) compared with those who did not (200–499 cells/μL and ≥500 cells/μL; $P < 0.0001$; Table 1). Similar findings were also observed in anal HSIL$^+$ ($0.0001 < P < 0.05$). Log_{10} viral loads were higher among individuals with any of the conditions than the comparable condition-free patients, with exception of anal HSIL$^+$ ($P = 0.71$). Men who have sex with men were at the highest risk for being diagnosed with AGW and HSIL$^+$.

All 3 CD4 measures were associated with incident anal HSIL$^+$ in both models M1, which only included gender, and M2, which only included sexual orientation (Table 2). In both models, patients with nadir and median CD4 counts <200 cells/



Group	Group membership	Group morbidity	Median CD4 counts
1	3.3	6.3	28
2	8.4	11.8	119
3	11.6	11.8	237
4	5.3	29.4	226
5	26.4	10.8	410
6	45.1	29.4	711

Group	Group membership	Group morbidity	Median CD4 counts
1	3.2	17.0	30
2	8.4	18.4	121
3	11.6	11.9	237
4	5.3	10.0	225
5	26.4	9.9	410
6	45.1	7.8	712

Figure 1. Trajectory CD4 counts for anal HSIL$^+$ (A) and AGWs (B). Percentages of trajectory group membership (the percent of the study population grouped to this CD4 trajectory pattern) and morbidity (the percent of HSIL$^+$ or AGW among the trajectory group population), and median CD4 count (in cells per microliters) of each trajectory group were given accordingly.

TABLE 1. Demographic and Clinical Characteristics of the Study Population (2006–2018)

Characteristics	No AGW (n = 3612)	AGW (n = 408)	*P*	No Anal HSIL$^+$ (n = 3934)	Anal HSIL$^+$ (n = 102)	*P*
Gender						
Men	2669 (88.1)	359 (11.9)	<0.0001	2974 (96.8)	99 (3.2)	<0.0001
Women	897 (95.5)	42 (4.5)	937 (99.7)	3 (0.3)		
Transgenders*	16 (69.6)	7 (30.4)	23 (100)	0 (0.0)		
Race						
Black	2174 (97.2)	257 (2.8)	0.018	2397 (98.0)	50 (2.0)	0.0056
White	1294 (89.9)	146 (10.1)		1390 (96.5)	51 (3.5)	
Others	144 (96.6)	5 (3.4)		147 (99.3)	1 (0.7)	
HIV diagnosis age, y	35.1 (10.5)	30.4 (8.0)	<0.0001	34.7 (10.4)	32.4 (9.3)	0.031
Enrollment age, y	41.2 (11.2)	36.8 (9.7)	<0.0001	40.7 (11.2)	40.7 (10.8)	1.0
Median CD4, cells/μL						
<200	509 (84.7)	92 (15.3)	<0.0001	576 (96.2)	23 (3.8)	0.0062
200–499	1326 (88.9)	166 (11.1)		1458 (97.0)	45 (3.0)	
≥500	1777 (92.2)	150 (7.8)		1900 (98.2)	34 (1.8)	
Nadir CD4, cells/μL						
<200	1401 (87.4)	202 (12.6)	<0.0001	1554 (96.6)	54 (3.4)	0.022
200–499	1528 (90.9)	153 (9.1)		1657 (97.9)	35 (2.1)	
≥500	683 (92.8)	53 (7.2)		723 (98.2)	13 (1.8)	
Mean $\log_{10}$ viral load	3.3 (1.3)	3.6 (1.3)	0.0003	3.3 (1.3)	3.3 (1.4)	0.71
Sexual behavior	n = 3489	n = 396		n = 3802	n = 99	
Men having sex with men	1906 (86.6)	294 (13.4)	0.0001	2123 (96.0)	89 (4.0)	<0.0001
Heterosexual	1576 (94.0)	101 (6.0)		1671 (99.4)	10 (0.6)	
Others	7 (87.5)	1 (12.5)		8 (100)	0 (0.0)	

*Male-to-female.

μL had much higher odds of incident anal HSIL$^+$ than did the ones with corresponding CD4 counts >500 cells/μL. Similarly, the lowest-trajectory CD4 groups were more likely to present with anal HSIL/cancers (HSIL$^+$; Fig. 1A) and AGWs (Fig. 1B) than the ones in group 6 (Figs. 1A, B) with best CD4 recovery (Table 2).

There were 4020 and 3877 patients included in M1 and M2 for AGW-related analyses (Table 2). All 3 CD4 measures were associated with incident AGW in both models (Table 2). Patients with median CD4 count less than 200 cells/μL tended to be at higher risks of incident AGW. Trajectory group membership and group of morbidity for each condition are presented in lower panels in Figures 1A and B. Except for CD4 trajectory group 4, all the other trajectory groups seemed to have statistically higher odds of incident AGW than group 6 with the optimal CD4 trajectory (Figs. 1A, B; Table 2).

Sensitivity Analysis

Similar to anal HSIL$^+$, 6 trajectory CD4 groups were constructed when analyzing HSIL and cancer separately. The trajectory group memberships of HSIL (groups 1–6: 3.2%, 8.4, 11.5%, 26.3%, 5.1%, and 45.5%) and cancer (groups 1–6: 3.2%, 8.4%, 11.6%, 26.4%, 5.3%, and 45.1%) were all nearly identical to HSIL$^+$s (Fig. 1A). In addition to the group membership, the directions of 6 trajectories of HSIL and cancer were also the same as those of HSIL$^+$ (groups 1–6: starting and remaining low in CD4, starting low and increasing moderately in CD4, starting low and increasing substantially in CD4, starting moderate and decreasing substantially in CD4, starting moderate and increasing slightly in CD4, and starting high and remaining high in CD4, over the entire follow-up).

DISCUSSION

The present study examined 3 different CD4 count measures to evaluate associations with incident AGW and anal HSIL$^+$. Nadir, median, and CD4 count trajectory demonstrated statistically significant associations with HPV-related AGW and HSIL$^+$ in the study. Although most studies use nadir CD4 or median CD4 counts as key immune indicators for PLWH, our study shows that CD4 trajectory over time might be more meaningful than single CD4 measurement to assess overall immunity. Nadir CD4 count is important for disease prognosis in PLWH. Low nadir CD4 is usually linked with high risks of developing AIDS-defining conditions.[28] However, nadir CD4 was not consistently associated with incident AGW and HSIL$^+$ (Table 2). Median CD4 and trajectory CD4 counts indicated statistically significant associations with incident HPV-related AGW and HSIL$^+$. Patients with median CD4 counts <200 cells/μL were at higher odds of acquiring HPV-related conditions due to the heavily suppressed immune systems. CD4 trajectory, in addition, gave more precise odds of these clinical conditions in each trajectory group (Table 2). Although some existing literature suggests that virological suppression is as important as CD4 count in assessing overall HIV disease prognosis among PLWH, the definitions of virologically suppressed patients have been inconsistent.[29] For example, the length of the period that patients have retained an undetectable viral load is different among studies, and the threshold of the detectable viral load changes over time with advancing technologies.[29] Some early findings indicated that CD4 counts of virologically suppressed patients might be very different and presented different levels of risks for clinical outcomes.[30] Moreover, using longitudinal CD4 counts to plot trajectory is more clinically meaningful because the ranges of change are substantially less dramatic compared with viral load.

Although the association of median and trajectory CD4 was statistically significant, interpretations of these 2 measures could be very different. For example, 2 patients with opposing trajectories could have the same median CD4 count. Therefore, using a single (e.g., median) CD4 count may result in misclassification and bias. For example, in the anal HSIL$^+$ cohort (Fig. 1A), the median CD4 counts of subjects in trajectory groups 3 and 4 were 237 and 226 cells/μL, respectively. Therefore, both groups' median CD4 counts belonged to CD4 group 200–499 cells/μL. However, groups 3 and 4 had opposing trajectories: a steady increase in CD4

TABLE 2. Associations Between Nadir, Median, and Trajectory CD4 Counts With Anogenital Warts (AGW) and Anal Precancer/Cancer (HSIL$^+$) Among PLWH

	AGW		Anal HSIL$^+$	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Model 1	(n = 4020)		(n = 4036)	
Nadir CD4 group, cells/μL	—	0.0002	—	0.0037
<200	1.8 (1.3–2.6)	0.0009	2.4 (1.2–4.7)	0.012
200–499	1.2 (0.9–1.7)	0.28	1.3 (0.7–2.5)	0.44
≥ 500	Reference			
Median CD4 group, cells/μL	—	<0.0001	—	0.0035
<200	2.2 (1.6–3.0)	<0.0001	2.7 (1.5–5.0)	0.0014
200–499	1.5 (1.2–1.9)	0.0011	1.9 (1.2–3.0)	0.0098
≥500	Reference			
Trajectory CD4 group*	—	<0.0001	—	0.0023
Group 1	2.4 (1.4–4.0)	0.0016	5.0 (2.0–12.9)	0.0008
Group 2	2.9 (2.0–4.3)	<0.0001	2.8 (1.3–5.8)	0.0061
Group 3	1.8 (1.2–2.5)	0.0016	1.9 (0.9–3.8)	0.081
Group 4	1.3 (0.8–2.3)	0.33	4.9 (2.3–10.5)	<0.0001
Group 5	1.4 (1.0–1.8)	0.029	1.8 (1.0–3.0)	0.035
Group 6	Reference			
Model 2	(n = 3877)		(n = 3893)	
Nadir CD4 group	—	0.0002	—	0.0038
<200	1.8 (1.3–2.7)	0.0011	2.4 (1.2–4.7)	0.013
200–499	1.2 (0.8–1.7)	0.36	1.3 (0.7–2.5)	0.47
≥500	Reference			
Median CD4 group	—	<0.0001	—	0.0013
<200	2.2 (1.6–3.1)	<0.0001	2.6 (1.4–5.0)	0.0025
200–499	1.5 (1.1–1.9)	0.0027	1.8 (1.1–2.9)	0.016
≥500	Reference			
Trajectory CD4 group*	—	<0.0001	—	0.0002
Group 1	2.7 (1.5–4.6)	0.0004	6.7 (2.6–17.6)	0.0001
Group 2	3.1 (2.1–4.5)	<0.0001	2.7 (1.3–5.7)	0.011
Group 3	1.8 (1.2–2.5)	0.002	1.7 (0.8–3.6)	0.14
Group 4	1.4 (0.8–2.4)	0.3	5.1 (2.3–11.3)	0.033
Group 5	1.3 (1.0–1.7)	0.056	1.7 (1.0–2.9)	0.042
Group 6	Reference			

Ages at HIV diagnosis and study entry, mean $\log_{10}$ viral load, race, and gender (M1) or sexual orientation (M2) were adjusted for each model.

*n (%) for groups 1–6: 129 (3.2), 338 (8.4), 466 (11.6), 213 (5.3), 1061 (26.4), and 1813 (45.1), respectively, for AGW; 133 (3.2), 339 (8.4), 468 (11.6), 213 (5.3), 1064 (26.4), and 1819 (45.1), respectively, for anal HSIL.

CI indicates confidence interval; OR, odds ratio.

count in group 3 and a decline in group 4. Although the 2 group median CD4 counts were in the middle group, 200 to 499 cells/μL, only trajectory CD4 counts were capable of differentiating the odds of the condition. Similarly, discrepancies were also detected in AGW as well (Fig. 1B). CD4 counts may be acutely influenced by inactivity, lack of sleep, stress, smoking, or other medical treatments, so using a single CD4 test to quantify the risk of the onset of HPV-related conditions is insufficient. Rather than using an individual time-point CD4, it is biologically meaningful to monitor any trends in CD4 cell count over time.[18]

In our study, it did not seem that CD4 trajectory was more precise in linking immune recovery with incident AGW compared with median CD4 (Table 2). For instance, trajectory group 4 (the declining group) failed to indicate higher odds of developing AGW compared with the immune recovery group (group 6). Trajectory CD4 groups could not fully interpret the risk of AGW with respect to immune status in the current study. In a previous study in Women's Interagency HIV Study cohort, no evidence of association was observed between genital warts and CD4 counts over time.[30] This could suggest that longitudinal CD4 counts might not be strongly associated with the onset of AGW, potentially because of underlying biological mechanisms, yet not known.

We are aware that cART plays a critical role in viral suppression, and hence, it influences host immunity. Overall, CD4 counts serves as a proxy for effectiveness of cART and immune status among PLWH. It is difficult to assess the adherence of cART treatment and also there were heterogeneity in treatment over time, and some of the medications are no longer used in clinical practice. It is unlikely that cART interacts directly with HPV or disease development but rather through the immune response, which is measured by CD4 counts. Thus, in the present study, we focused on the dynamics of changes of CD4 counts overtime regardless of the cART regimens.

As with all clinical cohort studies, there are several limitations to this study. For example, using clinical data from the EHR could result in underestimating the number of HPV-related cases, specifically AGW, because seeking medical attention is solely based on patient willingness. In addition, entry of a diagnosis into the EHR by a provider is required and quality of medical record keeping may vary between providers and conditions (i.e., a provider may be more likely to enter a condition for which they have to take action such as a referral for anoscopy or medical prescription). In addition, they may be more likely to enter more serious conditions (e.g., cancer) on a diagnosis list as opposed to less serious conditions (e.g., wart). However, the current findings also reflect the actual HPV-related health care burden that PLWH in the southeastern US face. The southeastern US is the epicenter of the domestic HIV epidemic.[1] Thus, a better understanding of CD4

count measures in this population is valuable for the development of HPV-related screening programs for NAD conditions other than cervical cancer. Another limitation stems from the open nature of the clinical cohort: not all patients had the same length of follow-up and times of routine HIV care, such as CD4 and viral load measurements. In addition, some patients received more frequent CD4 tests because they were participating in trials or were suspected to have ART resistance. Furthermore, the numbers of NAD $HSIL^+$ conditions other than anal cancer (penile and vaginal $HSIL^+$) were very small and did not have sufficient power to conduct any meaningful statistical analyses in the current study.

With the effective treatment, NAD malignancies and clinical conditions represent a large number of comorbidities among PLWH who are living longer. Human papillomavirus infection is common among PLWH, and new diagnoses of anal cancer are on the rise. However, unless PLWH report uncomfortableness, anogenital areas are not screened for AGW or $HSIL^+$. As shown in our study, measurements of CD4 counts could identify target subpopulations requiring more medical attention for HPV-related anogenital conditions. Clinical settings where longitudinal data of CD4 count are well documented may consider using them to develop risk assessment models for HPV-related anogenital conditions. In the era of rising NAD conditions among PLWH, such clinically relevant guiding tools could be very helpful but warrant thorough investigations.

REFERENCES

1. CDC. Diagnoses of HIV infection in the United States and dependent areas, 2017. HIV Surveill Rep 2018; 2018:29.
2. van Sighem AI, Gras LA, Reiss P, et al, ATHENA national observational cohort study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS 2010; 24:1527–1535.
3. Deeken JF, Tjen-A-Looi A, Rudek MA, et al. The rising challenge of non–AIDS-defining cancers in HIV-infected patients. Clin Infect Dis 2012; 55:1228–1235.
4. Farahani M, Mulinder H, Farahani A, et al. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: A systematic review and meta-analysis. Int J STD AIDS 2017; 28:636–650.
5. Adler DH. The impact of HAART on HPV-related cervical disease. Curr HIV Res 2010; 8:493–497.
6. Stier EA, Baranoski AS. Human papillomavirus–related diseases in HIV-infected individuals. Curr Opin Oncol 2008; 20:541–546.
7. Shrestha S, Sudenga SL, Smith JS, et al. The impact of highly active antiretroviral therapy on prevalence and incidence of cervical human papillomavirus infections in HIV-positive adolescents. BMC Infect Dis 2010; 10:295.
8. de Sanjosé S, Brotons M, Pavón MA. The natural history of human papillomavirus infection. Best Pract Res Clin Obstet Gynaecol 2018; 47:2–13.
9. Bruni L, Diaz M, Castellsagué X, et al. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010; 202:1789–1799.
10. Clifford GM, Tully S, Franceschi S. Carcinogenicity of human papillomavirus (HPV) types in HIV-positive women: A meta-analysis from HPV infection to cervical cancer. Clin Infect Dis 2017; 64:1228–1235.
11. Palefsky JM, Holly EA, Ralston ML, et al. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. AIDS 1998; 12:495–503.
12. Palefsky JM, Holly EA, Hogeboom CJ, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 17:314–319.
13. Holly EA, Ralston ML, Darragh TM, et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. J Natl Cancer Inst 2001; 93:843–849.
14. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. Lancet Oncol 2012; 13: 487–500.
15. Gaisa M, Ita-Nagy F, Sigel K, et al. High rates of anal high-grade squamous intraepithelial lesions in HIV-infected women who do not meet screening guidelines. Clin Infect Dis 2017; 64:289–294.
16. Dhumale SB, Sharma S, Gulbake A. Ano-genital warts and HIV status—a clinical study. J Clin Diagn Res 2017; 11:WC01–WC04.
17. Moir S, Chun TW, Fauci AS. Pathogenic mechanisms of HIV disease. Annu Rev Pathol 2010; 6:223–248.
18. Bordoni V, Brando B, Piselli P, et al. Naïve/effector CD4 T cell ratio as a useful predictive marker of immune reconstitution in late presenter HIV patients: A multicenter study. PLoS One 2019; 14:e0225415.
19. International Study Group on CD4-monitored Treatment Interruptions. CD4 cell-monitored treatment interruption in patients with a CD4 cell count >500 − 106 cells/l. *AIDS* 2005; 19:287–294.
20. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4 T-cell count and numbers of CD28 CD4 T-cells predict functional responses to immunizations in chronic HIV-1 infection. AIDS 2003; 17:2015–2023.
21. Psomas CK, Barber TJ, Rutsaert S, et al. Highlights from the 9th IAS Conference on HIV Science, 23–26 July 2017, Paris, France. J Virus Erad 2017; 3:242–249.
22. Bertisch B, Franceschi S, Lise M, et al. Risk factors for anal cancer in persons infected with HIV: A nested case-control study in the Swiss HIV cohort study. Am J Epidemiol 2013; 178:877–884.
23. Willig JH, Aban I, Nevin CR, et al. Darunavir outcomes study: Comparative effectiveness of virologic suppression, regimen durability, and discontinuation reasons for three-class experienced patients at 48 weeks. AIDS Res Hum Retroviruses 2010; 26:1279–1285.
24. Nagin DS, Jones BL, Passos VL, et al. Group-based multi-trajectory modeling. Stat Methods Med Res 2018; 27:2015–2023.
25. Lange N, Carlin BP, Gelfand AE. Hierarchical Bayes models for the progression of HIV infection using longitudinal CD4 T-cell numbers: Rejoinder. J Am Stat Assoc 1992; 87:631.
26. McNeil AJ, Gore SM. Statistical analysis of zidovudine (AZT) effect on CD4 cell counts in HIV disease. Stat Med 1996; 15:75–92.
27. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. AIDS 2010; 24:1867–1876.
28. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: Results from the EuroSIDA study. Ann Intern Med 1999; 130: 570–577.
29. Ford N, Stinson K, Gale H, et al. CD4 changes among virologically suppressed patients on antiretroviral therapy: A systematic review and meta-analysis. J Int AIDS Soc 2015; 18:20061.
30. Luu HN, Amirian ES, Chan W, et al. CD4+ cell count and HIV load as predictors of size of anal warts over time in HIV-infected women. J Infect Dis 2012; 205:578–585.