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MAJOR ARTICLE

Prevalence and Predictors of High-Grade Anal Dysplasia in People With HIV in One Southeastern Ryan White HIV/AIDS Program Clinic

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Background. Prevalence of anal cancer is increasing among people with HIV (PWH). Screening for anal cancer involves evaluating cytology and biopsy with high-resolution anoscopy (HRA) if indicated. In this study, we sought to identify the prevalence of abnormal anal cytology and biopsy-proven high-grade dysplasia, defined as anal intraepithelial neoplasia 2 and 3 (AIN2+).

Methods. Demographic and clinical data were collected from participants age ≥30 years with ≥1 anal Pap smear performed during the study period (12/18/2017–05/29/2021). A subgroup analysis was performed on those with ≥1 HRA. Logistic regression estimated adjusted odds ratios (aORs) for variables of interest such as age, race, gender, presence of HPV strains, and sexual practices.

Results. Of 317 participants, 48% (n = 152) had abnormal cytology (93% low-grade squamous intraepithelial lesion [SIL] or atypical cells of undetermined significance [ASCUS] and 7% high-grade SIL). Most with abnormal cytology proceeded to HRA (n = 136/152). Of those with HRA, 62% (n = 84/136) had AIN2+. History of anoreceptive intercourse (aOR 4.62; 95% CI 1.08–23.09; $P = .047$), HPV 16 (aOR 4.13; 95% CI 1.63–11.30; $P = .004$), and "other" high-risk HPV strains (aOR 5.66; 95% CI 2.31–14.78; $P < .001$) were significantly associated with AIN2+.

Conclusions. Nearly half of those screened had abnormal cytology, highlighting the high prevalence of anal dysplasia in PWH. Though only 7% had high-grade SIL on cytology, 62% of those biopsied had AIN2+, suggesting that cytology underestimates the severity of dysplasia on biopsy. HPV 16 and "other" high-risk strains were associated with AIN2 + and could be considered for risk-stratifying patients in the screening algorithm.

Keywords. HIV/AIDS; HPV; anal cancer screening; anal dysplasia; high-resolution anoscopy.

Prevalence of anal cancer in people with HIV (PWH) has been on the rise in the United States, reaching as high as 131 per 100 000 people per year in 2012 in men who have sex with men (MSM) [1, 2]. Among PWH, MSM carry the highest risk, but women and heterosexual men are also at increased risk compared with the general population [1]. Most anal cancer is caused by persistent infection with high-risk oncogenic strains of human papillomavirus (HPV) similar to cervical cancer [3, 4]. HPV 16 has been shown to be especially oncogenic in anal cancer [5]. Preventative strategies are available, including HPV vaccination and anal cancer screening. A quadrivalent HPV vaccine became available in 2006 to cover HPV 6, 11, 16, and 18 [6]. In 2015, a 9-valent vaccine became available to those age <26 years, and in October 2018, the Food and Drug Administration expanded this recommendation to all adults up to 45 years old [7, 8]. HPV vaccines are safe and have been shown to reduce incidence of HPV-associated cancers like cervical cancer [9, 10]. Screening for anal cancer involves cytological interpretation of anal Pap smears according to the Bethesda classification system, followed by high-resolution anoscopy (HRA) with biopsy to confirm pathology [11]. Hyfrecation (ie, thermoablation) is an evidence-based method used commonly in many centers to treat biopsy-confirmed high-grade dysplasia [12, 13, 14]. Many Ryan White HIV/AIDS Program (RWHAP) clinics around the country have adopted these screening methods with guidance from the International Anal Neoplasia Society; however, no comprehensive guidelines currently exist [13, 12]. In this study, we sought to define prevalence of abnormalities along the screening cascade and understand predictors of abnormal anal cytology and biopsy-proven high-grade dysplasia, defined as anal

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intraepithelial neoplasia 2 and 3 (AIN2+), in our clinic population to identify high-risk groups and better target screening awareness strategies.

METHODS

Establishing an Anal Cancer Screening Clinic

An anal cancer screening clinic was established on December 18, 2017, at the RWHAP clinic at the University of Virginia. This is a subspecialty clinic staffed by a nurse educator and 3 clinicians (a gynecology nurse practitioner, a colorectal surgeon, and an infectious disease physician) who perform anal cytology and HRA. Based on expert opinion and society recommendations, our clinic offers screening to all PWH over the age of 30 years, including annual anal cytology followed by HRA with up to 8 mucosal biopsies if abnormalities are noted on cytology [13, 12, 14].

Anal Cytology Collection and Interpretation

Anal Pap smears are collected using liquid-based cytology with cytobrush swabs. Patients are placed in the left lateral position with hips and knees flexed. To collect cells at the transition zone, clinicians insert a cytobrush at least 3 cm into the anal canal and rotate it in a circular motion while applying gentle pressure against the anal canal and slowly withdrawing over ~30 seconds. Cells are released into preservative by vigorously rotating the swab and/or using an applicator and then processed using liquid-based cytology (ThinPrep). Cytopathologists use the Bethesda System to interpret results [11]. The same specimen is used for HPV co-testing via real-time polymerase chain reaction (PCR) assay (Roche Cobas HPV), which has been internally validated at University of Virginia Medical Labs but is not Food and Drug Administration approved for use in anal samples. No specimens were self-collected in this study.

High-Resolution Anoscopy, Biopsy, and Ablation

If anal cytology returns abnormal, patients are asked to proceed to HRA for anal biopsy. Most HRAs are performed in the clinic setting. The anoscopist inserts an anoscope into the anal canal using lubricant. A colposcope is used to magnify the anal mucosa and sequentially evaluate the transformation zone of all 8 octants with 5% acetic acid and Lugol's solution. If abnormalities are noted, the patient returns for hyfrecation (ie, ablation) with electrocautery of high-grade intraepithelial lesions and repeat HRA for surveillance.

Study Population

The study population included all PWH who were at least 30 years old and classified as "enrolled" in RWHAP services at the University of Virginia from December 18, 2017 to May 29, 2021. "Enrolled" status required that a participant be reachable by case managers to assess RWHAP eligibility. Participants were excluded if they did not have an anal cytology during the study period.

Data, Definitions, and Outcomes

All participants had the following data available: age, self-reported gender, race/ethnicity, federal poverty level (FPL), HIV diagnosis date, last CD4 count, last HIV viral load, documentation of anoreceptive intercourse or having documentation of anal gonorrhea/chlamydia infection, age of first intercourse, tobacco use status, history of sexually transmitted infections (STIs), self-reported or clinician-documented history of anogenital warts, patient-reported anal symptoms at the time of anal cytology or HRA, and dates of HPV vaccination. Due to the small sample size in the subgroup analysis, race/ethnicity was grouped as White (indicating non-Hispanic White) and non-White (indicating non-Hispanic Black, Hispanic, Asian, Pacific Islander, Native American, Alaskan Native, multiple races or missing race). STIs were defined as self-reported or clinician-documented history of gonorrhea, chlamydia, trichomonas, syphilis, or genital herpes simplex virus. Anal symptoms were defined as rectal bleeding, pain/discomfort, itching, or notable anal and perianal lesions. Anal cytology, HPV, and anal biopsy results were also collected from the electronic medical record during the study period. For those missing data for FPL (n = 3) and age of first intercourse (n = 20), participants were assigned the mean value of the total cohort. HPV PCR results included strains 16, 18, and "other" high-risk (HR) strains. "Other" strains included at least 1 of the following: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68. If a participant had >1 HPV strain detected during the study period, the cumulative strains were documented. Data were extracted from the clinic-specific CAREWare database and collected through chart review via the electronic medical record [15].

Outcomes

The primary outcome was presence of abnormal cytology, which included low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), and high-grade squamous intraepithelial lesion (HSIL). If a participant had >1 abnormal cytology result during the study period, the highest-grade lesion was recorded. LSIL and ASCUS were considered low-grade, and HSIL and ASC-H were considered high-grade. Negative for intraepithelial lesion or malignancy (NILM) and insufficient numbers of epithelial cells for adequate cytologic interpretation were possible cytology results that were excluded as an outcome. A subgroup analysis was performed on those who had biopsies with AIN2+ as the secondary outcome.

Statistical Analysis

Analyses were performed using RStudio, version 1.4.1717 (R Foundation for Statistical Computing). Descriptive statistics were used to report the frequency of each characteristic in the study population and in the subgroup analysis. Individuals who identified as transgender (n = 7) were excluded from analysis due to small sample size and inability to draw meaningful conclusions in this population. Univariate logistic regression was performed with all covariates to produce crude odds ratios (ORs). Covariates with a P value of ≤.10 were included in the multivariate logistic regression model to produce adjusted ORs (aORs). Chi-square and Fisher exact tests were used to compare the frequency of characteristics across cohorts.

Informed Consent Statement

The design of the work was reviewed and approved by the University of Virginia Institutional Review Board for Health Sciences Research. Participant consent was not required because the University of Virginia Institutional Review Board for Health Sciences Research deemed that the project met criteria for exemption, as all data were collected for the purposes of anal cancer screening clinic program evaluation [16].

RESULTS

The cohort included 317 participants, with 52% identifying as male and 46% as White race. Anoreceptive sex was reported by 169 (53%) participants, including 145 (86%) males and 24 (14%) females. Additional demographic and clinical characteristics are described in Table 1. Forty-one percent had incomes ≤100% of the FPL. Most participants had at least 1 high-risk HPV strain identified by PCR (64%, n = 202/317). The distribution of HPV strains identified is reported in Table 1 and stratified by cytology in Figure 1. "Other" HPV strains were more common in men (107/164, 65%) than in women (75/153, 49%).

With an average age of 51 years, our cohort was mostly unvaccinated, with only 106 people (34%, 46 females, 60 males) starting the 3-dose 9-valent HPV vaccine series and 93 people (29%, 44 females, 49 males) completing the series. Of those with abnormal cytology (n = 152), 51 (33%) started the series and 43 (28%) completed the series. Of those with AIN2+ on biopsy (n = 84), 28 (33%) started the series and 25 (30%) completed the series. Of those eligible for HPV vaccination, abnormal cytology was more common among those who were unvaccinated (n = 9/10, 90%) compared with those who had started and not completed (n = 7/12, 58%) and those who had completed the vaccine series (n = 39/84, 46%; P = .02). There was no statistical difference in rate of AIN2+ among the 3 groups (P = .70).

With regards to anal cytology, 157 (50%) had NILM, 8 (2%) had insufficient samples, and 152 (48%) were abnormal. Of those with abnormal cytology, 142 (93%) were LSIL or ASCUS and 10 (7%) were ASC-H or HSIL. Biopsy results were available for 136 of the 152 (90%) people with abnormal cytology, of whom 84 (62%) were found to have high-grade histopathologic lesions of AIN2+ (Table 1).

Multivariate logistic regression showed that HPV 16 and "other" high-risk strains were associated with abnormal cytology (aOR, 2.35; 95% CI, 1.19–4.73; P = .02; and aOR, 2.75; 95% CI, 1.61–4.74; P < .001; respectively) and AIN2+ on biopsy (aOR, 4.13; 95% CI, 1.63–11.30; P = .004; and aOR, 5.66; 95% CI, 2.31–14.78; P < .001). HPV 18 was not significantly associated with abnormal cytology or AIN2+ on biopsy. Having a history of STIs was associated with abnormal cytology (aOR, 1.86; 95% CI, 1.11–3.14; P = .02), as was a history of anogenital warts (aOR, 1.81; 95% CI, 1.05–3.15; P = .03), though neither was associated with AIN2+ on biopsy. A history of anoreceptive intercourse was associated with AIN2+ on biopsy (aOR, 4.62; 95% CI, 1.08–23.09; P = .047) (Figure 2).

Given the strong association of HPV 16 with anal cancer, the model was rerun using a hierarchical grouping comparing those who were HPV negative with those with HPV 16 and those with non-HPV-16 strains. The presence of both HPV 16 and non-HPV-16 strains was significantly associated with abnormal cytology and AIN2+ (Supplementary Tables 5 and 6).

A post hoc analysis was performed to assess the effect of gender on our findings. To do this, we reran the regression model stratified by gender. Anoreceptive sex was associated with abnormal cytology in men but not women. Gender-based differences were also seen in the association between HPV strain type and abnormal cytology as well as AIN2+ (Supplementary Tables 1–4). Of note, when stratified, the results were underpowered due to the decreased sample sizes of both groups.

DISCUSSION

In this study, we sought to understand the prevalence and predictors of abnormal anal cytology and biopsy-proven AIN2+ in our clinic population. Prior studies have shown rates of abnormal cytology ranging from 27% in women with HIV [17] to 94% in urban predominantly MSM with HIV [18]. Our study describes outcomes in a more rural Southern cohort with a mix of both men and women where prevalence of abnormal cytology is 48%. We found a high prevalence of dysplasia on cytology and biopsy that is similar to prior studies. About half our cohort had abnormal cytology, with two-thirds having anal HPV infections, which is similar to other published studies [17, 19, 20, 18]. Sixty-two percent of people biopsied had AIN2+. Additionally, though >90% of cytology results were low-grade, the majority of biopsies were high-grade, indicating that cytology underestimates the degree of dysplasia on biopsy, a finding that has been supported in the literature [17, 18, 21, 22]. This highlights a need for more precise diagnostic tools to risk-stratify patients along the screening cascade. The high

Table 1. Participant Characteristics

	Total Cohort (n = 317)	Abnormal Cytology (n = 152)	Received Biopsies (n = 136)	AIN2+ on Biopsy (n = 84)
Age, y				
Mean ± SD	51 ± 11	50 ± 11	52 ± 11	52 ± 11
Median	52	51	53	53
Gender, No. (%)[a]				
Male	164 (52)	103 (68)	92 (68)	63 (75)
Female	153 (48)	49 (32)	44 (32)	21 (25)
Race/ethnicity, No. (%)				
White	146 (46)	79 (52)	74 (54)	51 (61)
Non-White[b]	171 (54)	73 (48)	62 (46)	33 (39)
Federal poverty level, No. (%)				
≤ 100%	130 (41)	60 (40)	51 (37)	28 (33)
101%–138%	42 (13)	20 (13)	17 (13)	14 (17)
139%–250%	65 (21)	29 (19)	26 (19)	15 (18)
≥ 251%	80 (25)	43 (28)	42 (31)	27 (32)
HIV chronicity, y				
Mean ± SD	16 ± 9	16 ± 10	17 ± 10	17 ± 10
Median	16	15	16	15
History of anoreceptive sex, No. (%)				
No	62 (20)	26 (17)	26 (19)	9 (11)
Yes	169 (53)	109 (71)	95 (70)	67 (80)
Not documented	86 (27)	17 (11)	15 (11)	8 (9)
HPV 16 strain, No. (%)	82 (26)	61 (40)	56 (41)	47 (56)
HPV 18 strain, No. (%)	41 (13)	28 (18)	29 (21)	20 (24)
Other HPV strains, No. (%)	182 (57)	113 (74)	99 (73)	73 (87)
Age of first intercourse, y				
Mean ± SD	16 ± 4	16 ± 4	16 ± 4	16 ± 4
Median	16	16	16	16
History of STIs,[c] No. (%)	159 (50)	90 (59)	72 (53)	48 (57)
History of anogenital warts, No. (%)	122 (38)	73 (48)	69 (51)	42 (50)
Reported anal symptoms,[d] No. (%)	63 (20)	39 (26)	37 (27)	25 (30)
Tobacco use ever, No. (%)	191 (60)	89 (58)	82 (60)	51 (61)
Current CD4 count,[e] No. (%)				
≥ 200 cells/mm^3	307 (97)	144 (95)	133 (98)	82 (98)
<200 cells/mm^3	10 (3)	8 (5)	3 (2)	2 (2)
Current HIV-1 RNA viral load,[e] No. (%)				
Undetectable	298 (94)	141 (93)	128 (94)	81 (96)
Detectable	19 (6)	11 (7)	8 (6)	3 (4)
HPV vaccine, No. (%)				
Initiated	106 (34)	51 (33)	44 (32)	28 (33)
Completed	93 (29)	43 (28)	38 (28)	25 (30)
Cytology results, No. (%)				
LSIL/ASCUS	142 (45)	…	…	…
HSIL/ASC-H	10 (3)	…	…	…
NILM	157 (50)	…	…	…
Insufficient	8 (2)	…	…	…

Abbreviations: ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASCUS, atypical cells of undetermined significance; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; STI, sexually transmitted infection.

[a]Seven transgender individuals were removed from the total cohort due to small sample size and inability to make meaningful conclusions.

[b]Non-White race/ethnicity included those who self-identified as non-Hispanic Black, Hispanic, Asian, Pacific Islander, multiple races, Native American, Alaskan Native, or had missing data.

[c]STIs included prior history of syphilis, gonorrhea, chlamydia, genital herpes, and/or trichomoniasis.

[d]Anal symptoms at the time of anal Pap smear or HRA were defined as rectal bleeding, pain/discomfort, itching, or participant-reported lesion.

[e]CD4 count and viral load were measured at the end of the study period. Undetectable viral load was defined as <40 copies/mL.

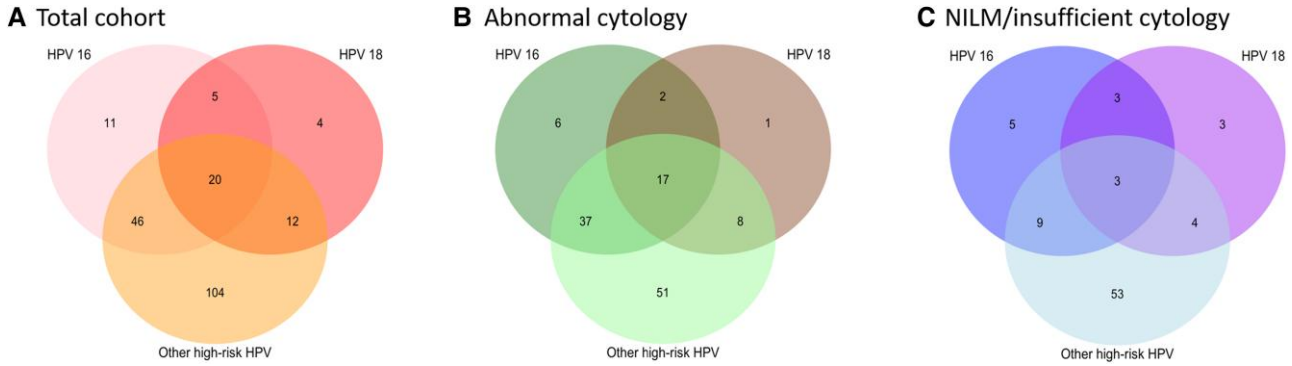

Figure 1. Prevalence and overlap of high-risk HPV strains: participants with each HPV strain from total cohort (*A*), those with abnormal cytology (*B*), and those with NILM/insufficient cytology (*C*). Abbreviations: HPV, hepatitis B virus; NILM, negative for intraepithelial lesion or malignancy; STI, sexually transmitted infection.

proportion of abnormalities on both anal cytology and HRA could also indicate underscreening in our clinic population. Qualitative studies have shown that anal cytology and HRA are feasible and acceptable to most PWH [23, 24]. However, barriers to screening still exist, such as stigma, lack of awareness about HPV, and psychological discomfort associated with anal cancer screening [25, 26]. These will be important factors to address moving forward to increase engagement and retention in screening.

Though factors associated with HIV, social determinants of health, and other cancer risk factors such as tobacco use and age were not associated with dysplasia in this cohort, we did find strong associations with the presence of certain high-risk HPV strains and abnormal cytology as well as AIN2+. Presence of HPV 16 is known to be associated with high-grade dysplasia and development of anal cancer, which is consistent with our findings [5, 27]. However, in this study cohort, "other" high-risk strains were equally associated with both abnormal cytology and AIN2+, whereas HPV 18 had no association. Given the strong and well-characterized association of HPV 16 with anal cancer, we investigated this association further and found that "other" high-risk HPV strains were slightly more common in males compared with females. We also reran our model using hierarchical grouping comparing outcomes of those with HPV 16 and non-HPV-16 strains with those that were HPV negative and still found that both HPV 16 and non-HPV-16 strains were significantly associated with abnormal cytology and AIN2+.

The impact of non-16/18 HPV strains on the development of anal cancer and anal dysplasia is understudied. In a metanalysis by Wei et al. [19], prevalence of high-risk HPV strains was as high as 74.3% among MSM with HIV, with 28.5% of cases being HPV 16. Likewise, 64% of our cohort was positive for HR HPV, with 57% positive for non-16/18 strains and 26% positive for HPV 16. As the 9-valent HPV vaccine covers 5 of the 12 "other" high-risk HPV strains detected on our PCR assay, vaccination before sexual debut can offer an opportunity to reduce rates of infection with high-risk HPV strains and subsequent risk for anal dysplasia later in life.

Notably, our cohort was largely unvaccinated. A post hoc analysis was performed, showing that unvaccinated participants had higher rates of abnormal cytology compared with those who were vaccinated. There was no difference in rates of AIN2+ on biopsy among these groups, though due to attrition in the subgroup these results are underpowered. The PCR assay used was only able to provide individual genotype results for HPV 16 and HPV 18, while the remaining 12 high-risk HPV genotypes tested were reported as a pooled result of "other" high-risk HPV types. An important next step would be to determine if one strain is driving this association, and if it is not already included in the 9-valent HPV vaccine, modification of the current formulation to include this strain may be warranted.

A history of STIs and anogenital warts was also associated with abnormal cytology, though not with AIN2+. These could be markers of increased risk of exposure to HPV strains causing low-grade dysplasia, though they do not seem to play a role in AIN2+ when biopsied. Anoreceptive intercourse was associated with high-grade dysplasia, which is a known risk factor in the literature [28]. Those lacking documentation of anoreceptive intercourse had less abnormal cytology. This result is very likely due to measurement bias. Those who had abnormal cytology were more likely to have a second or third visit at the HRA clinic and therefore had greater chances of having a more complete documentation of their sexual activity.

An important strength of this study is the collection of extensive longitudinal data over 3 years. However, this study also has several limitations. First, as is the nature of retrospective studies, data collection with chart reviewing can be limited or inaccurate. For example, nadir CD4 counts would have been informative to include in the analysis, but we were unable to obtain reliable nadirs with our data collection. This was also a study performed in a 1-clinic setting, and our results may

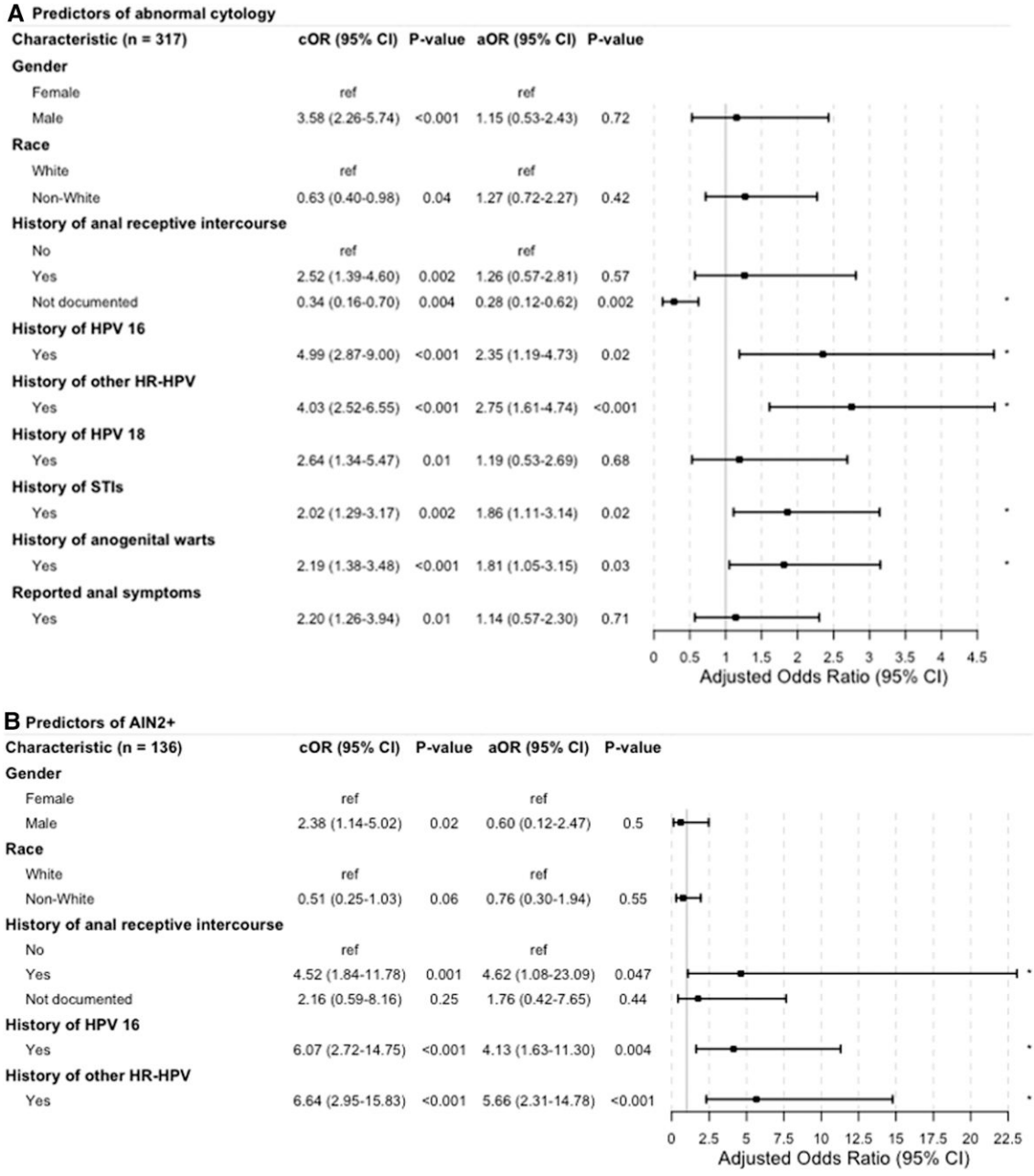

Figure 2. Predictors of abnormal cytology and AIN2+. List of crude and adjusted odds ratios with accompanying confidence intervals and *P* values for each characteristic included in the multivariate model for both the primary (abnormal cytology) and secondary (AIN2+) outcomes. Significant results noted by asterisks. Abbreviations: HPV, hepatitis B virus; NILM, negative for intraepithelial lesion or malignancy.

not be generalizable to all PWH. We had to remove transgender individuals from the cohort due to small sample size. This population deserves dedicated study to better understand predictors of dysplasia specific to this group. Lastly, due to small sample size, races/ethnicities were grouped into White and non-White categories. This method gives a crude understanding of trends between these 2 groups, but it lacks sufficient granularity to make firm conclusions about health disparities along racial/ethnic lines.

With growing evidence about the efficacy of anal cancer screening for PWH, these findings are relevant, timely, and practice-changing. This study shows that there is a high prevalence of abnormal cytology and biopsy-proven AIN2+ in PWH, and therefore highlights a need to expand screening efforts in PWH. We also found that the presence of HPV 16 and "other" high-risk HPV strains was prevalent and highly predictive of AIN2+ on biopsy. These results can serve as important markers of dysplasia in PWH and may have a role in risk-stratifying

people in the screening algorithm, for instance, expediting follow-up for those who test positive for 16 and "other" high-risk HPV strains. Finally, in our study cohort, cytology significantly underestimated the degree of dysplasia on biopsy, which also points to a need for more specific screening tools such as the addition of new staining techniques on cytology to more accurately predict clinically significant AIN2+ on biopsy.

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Data availability. Data are not publicly available except upon request.

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