Use of Highly Active Antiretroviral Therapy Is Associated With Lower Prevalence of Anal Intraepithelial Neoplastic Lesions and Lower Prevalence of Human Papillomavirus in HIV-Infected Men Who Have Sex With Men

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Background: The incidence of anal intraepithelial neoplasia (AIN) and anal cancer is increased in HIV-positive men who have sex with men (MSM). Persistent high-risk human papillomavirus (HPV) infection is an important etiologic agent.

Methods: In this study, a group of 250 HIV-positive MSM was included to determine the prevalence of AIN and to investigate the role of highly active antiretroviral therapy (HAART), high-risk HPV, and other risk factors possibly associated with this prevalence.

Results: Among patients included, 108 (43.2%) had lesions suspicious for AIN. Histologic analyses showed AIN 1 in 24 patients (22.2%), AIN 2 in 6 patients (5.6%), and AIN 3 in 10 patients (9.3%). In multivariable analyses, the use of HAART was associated with the absence of AIN ($P = 0.045$). In MSM without HAART, HPV infection was detected significantly more often compared with those who used HAART ($P = 0.010$). AIN was associated with HPV types 16 and 6.

Conclusions: In this cross-sectional study in 250 HIV-positive MSM, the use of HAART was associated with lower prevalence of AIN and a significantly lower prevalence of HPV. This association between the prevalence of AIN and the absence of HAART may contribute to the current debate on when to start HAART in HIV-infected individuals.

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Anal cancer is an uncommon malignancy, with an estimated incidence in the general population between 0.8 and 1.4 cases per 100,000 person-years.[1] Numbers of patients with anal cancer and preneoplastic anal lesions (anal intraepithelial neoplasia [AIN]) in western European countries and the United States have increased in recent decades.[2–4] Recent studies conclude that the incidence of anal cancer ranges from 42 to 137 cases per 100,000 person-years of observation among HIV-positive men and women.[5] The relative risk of invasive anal cancer among men with AIDS compared with men without known HIV was up to 352 in the era of highly active antiretroviral therapy (HAART).[6]

Anal cancer may be preceded by AIN. Several investigators have reported a high and varying occurrence of AIN in men who have sex with men (MSM). Percentages up to 43% of high-grade AIN have been reported in both cross-sectional and longitudinal studies.[7–11] Reported percentages vary considerably partly depending on interpretation of the histology and the skills of the anoscopist in identifying clinical aspects suspicious for AIN and in taking representative biopsies of theses lesions.

Persistent high-risk human papillomavirus (HPV) infection is an important risk factor for AIN and anal cancer because of its ability to trigger carcinogenic development. HIV-infected MSM are at increased risk of persistent HPV infection.[12] There is evidence that the HPV types that are causally linked to cervical cancer are also linked to anal cancer.[13] HPV-associated malignancies have a latency of 5 years to several decades in immunocompetent individuals, immunosuppression probably accelerates the development of malignancies.[6] Low CD^4 cell counts have been reported to be associated with an increased risk of AIN 2 or 3 in both longitudinal and prospective, cross-sectional studies.[14–16]

Prevalences of HPV infection in MSM are high. A recent cohort study in Montreal detected HPV DNA in 97.9% of all 247 MSM tested. Median number of concomitant HPV types was 5. Most common types were HPV-16 and HPV-6. High prevalence of anal HPV has been reported not to decline with age.[17]

HAART suppresses HIV viral replication and partly restores cellular immunity. Whether HAART has any effect on the clinical course of an HPV infection, HPV persistence, or the incidence of AIN is still under debate.[6,18–23] HAART increases longevity, and thus the time at risk for the development of anal premalignancies and cancer.[6] HAART may also induce clearing of HPV infection, regression, and prevention of development of anal cancer. In women, HAART has been reported to

associate with increased cervical HPV clearance but not with decrease of cervical intraepithelial neoplasia (CIN) in longitudinal cohort studies.[24,25]

This cross-sectional study was performed to determine the prevalence of AIN in a group of 250 HIV-positive MSM in Rotterdam and to investigate the values of several predictors of AIN in the context of duration and response to HAART.

MATERIALS AND METHODS

Patients and Study Design

From February 2007 to March 2009, 250 individuals were included in a Rotterdam study on the screening of HPV-related anal premalignancies in HIV-positive MSM. All patients were recruited from the outpatient clinics of 4 hospitals. Participants gave written informed consent before start of the study. The institutional review board of our hospital approved the study.

Highly Active Antiretroviral Therapy

Antiretroviral therapy was started in patients with CD^4 cell counts below 300×10^6 cells/L or in case of symptoms consistent with the diagnosis of AIDS. This has been standard treatment in The Netherlands for more than 5 years now.

HIV Viral Load Measurement

HIV RNA was in the majority of cases assessed quantitatively with the Cobas Ampliprep/Cobas Amplicor version 1.5 (lower limit of detection: 50 copies/mL; Roche Molecular Systems, Penzberg, Germany).

Data Collection

Behavioral data collected from all participants by means of a questionnaire included age, current smoking habits, sexual orientation, number of sex partners, including practice of anal sex and earlier diagnosis of anogenital warts. From the medical records, the following data were collected: length for known HIV positivity, use and duration of HAART, recent CD^4 cell count, nadir CD^4 cell count, HIV viral load, and the previous (lifetime) occurrence of an AIDS-defining event. All participants were asked to report complaints in the anal region, such as intermittent itch, pain, and bloody or purulent discharge.

High-Resolution Anoscopy

Anal examination was performed at the department of dermatology by the same experienced dermatologist in all patients. The examination consisted of visual inspection of the perianal and intra-anal area before and after acetic acid (5%) application. Acetic acid application increases visibility of HPV-related intraepithelial lesions. Inspection of the anal canal took place using high-resolution anoscopy. An HPV-related intraepithelial lesion was suspected in case of either local atypical aceto-whitening or (exophytic) elevated lesions easily distinguishable from the surrounding normal mucosa. Biopsies were taken from the centre of suspicious lesions detected during examination.

Histologic Examination

All biopsies were examined by the same pathologist using paraffin-embedded sections of formalin-fixed tissue stained with hematoxylin and eosin. AIN grade 1 or mild dysplasia was defined as lower third architectural disruption. In AIN grade 2 or moderate dysplasia, architectural disruption was seen in both lower and middle third of the squamous epithelium. AIN grade 3 or severe dysplasia was based on the finding of severe architectural disruption throughout the epithelium without disruption of the basal membrane.

HPV DNA Sample Collection

Specimens for assessment of HPV DNA were collected using a non-Dacron cotton swab moistened with sodium chloride 0.9% (Medical Wire & Equipment Co. (Bath) Ltd. Corsham, Wiltshire, United Kingdom), swabbing both the perianal and intra-anal area. The swabs were immediately placed into standard collecting tubes without transport medium and stored at −20°C before being sent to the Department of Virology for further processing. Total nucleic acids were isolated at the MagnaPureLC Isolation Station (Roche Applied Science).

Detection and Typing of HPV

Detection and typing of HPV DNA was performed using the INNO-LiPa HPV Genotyping *Extra* assay (Innogenetics, Ghent, Belgium). The INNO-LiPA HPV Genotyping Extra assay is a polymerase chain reaction-based line hybridization assay that utilizes several biotinylated consensus primers (SPF10) to amplify a region of the L1 gene of HPV types.[26] The assay covers all currently known high-risk HPV (HR-HPV) genotypes and probable HR-HPV genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82), as well as a number of low-risk HPV (LR-HPV) genotypes (6, 11, 40, 43, 44, 54, 70) and some additional types (69, 71, 74). Fully automated processing of the strips was executed by using Auto-LiPA, and automated interpretation of the strips was performed with LiRAS for LiPA HPV (Innogenetics).[26]

We used the epidemiologic classification according to Munoz et al[27] and Miyashita et al,[28] which groups HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 as high-risk and considered types 26, 53, 66, 70, 69 or 71, 74, and "unclassified" (X) as "unknown" with regard to risk.

Statistical Analyses

Data were compared in order to assess statistically significant differences in several characteristics (Tables 1 and 2), including the prevalence of HPV (Table 3) between the groups with and without dysplasia. Prevalence was calculated as the number of positive tests per 100 tested individuals. For testing differences between the groups, the exact χ^2 test was used, after all explanatory variables had been dichotomized. Age, number of lifetime sexual partners, length for known HIV positivity, and CD^4 cell count and viral load count were tested as continuous variables. Statistical significance was defined as a P value of less than 0.05.

Next, the variables age, length for known HIV positivity, and use of HAART were compared between groups (Table 2). To adjust for confounding variables, logistic regression analysis was used. The primary selection of covariables for entering in the model, along with group, was based on univariable analysis in 2 by 2 tables; an exact P value below 0.05 was used. Analyses were done using SPSS 18.0.

RESULTS

A total of 250 males were included in this study, 210 without and 40 with AIN. Patients' characteristics are summarized in Table 1. The median age of all males included was 46.5 years (interquartile range [IQR]: 40.0–53.3). The median length of known HIV positivity was 8.0 years (IQR: 4.0–13.0).

TABLE 1. Characteristics of 250 HIV-Positive Man Who Have Sex With Men

	Total 250 (100.0)	No Dysplasia 210 (84.0)	AIN 1, 2, or 3 40 (16.0)	*P*
Median age (yr; IQR)	46.5 (40.0–53.3)	47.0 (40.0–54.3)	43.5 (36.3–49.0)	0.011
Circumcision before age of 10 yr	26 (10.4)	21 (10.0)	5 (12.8)	0.61
Age at sexual debut (median; IQR)	18.0 (15.0–21.0)	18.0 (15.0–21.0)	18.0 (16.0–21.0)	0.52
Bisexual orientation	3 (1.2)	3 (1.4)	0 (0)	0.31
No. lifetime sexual partners (median; IQR)	100.5 (50–500)	101 (45–500)	100 (50–400)	0.27
Receptive anal intercourse in previous 12 mo	174 (69.6)	144 (68.6)	30 (76.9)	0.29
Receptive anal intercourse ever	222 (88.8)	185 (88.5)	37 (94.9)	0.20
Current smoker	90 (36.0)	77 (36.7)	13 (33.3)	0.69
History of anal warts	111 (44.4)	92 (43.8)	19 (48.7)	0.57
Complaints in anal area (pain, itch, pus/blood)	86 (34.4)	68 (32.4)	18 (45.0)	0.13
Median length for known HIV positivity (yr; IQR)	8.0 (4.0–13.0)	8.0 (4.0–14.0)	6.0 (2.3–11.0)	0.040
Years of known HIV positivity				
≤5 yr	97 (38.8)	79 (37.6)	18 (45.0)	
6–10 yr	54 (21.6)	43 (20.5)	11 (27.5)	
11–15 yr	63 (25.2)	54 (25.7)	9 (22.5)	
>15 yr	36 (14.4)	34 (16.2)	2 (5.0)	0.075
Recent CD^4 cell count (median; IQR)	490 (358–640)	500 (350–680)	425 (370–540)	0.076
Nadir CD^4 cell count (median; IQR)	229 (120–310)	220 (120–310)	235 (138–358)	0.83
Recent HIV viral load (median; IQR)	50 (50–305)	50 (50–114)	50 (50–6100)	0.69
HIV viral load ≤50 log copies/mL	167 (66.8)	144 (68.6)	23 (59.0)	0.25
Previous occurrence of AIDS defining event	89 (35.6)	79 (46.2)	10 (30.3)	0.087
Use of HAART	201 (80.4)	176 (83.8)	25 (62.5)	0.004
Use of HAART for >8 yr	95 (38.0)	84 (47.7)	11 (44.0)	0.73

IQR indicates interquartile range; OR, odds ratio; CI, confidence interval; AIN, anal intraepithelial neoplasia; HAART, highly active antiretroviral therapy.

Of the cohort, 201 patients (80.4%) were on HAART. The median length of use of HAART was 7.0 years (IQR: 3.0–10.0). The median CD^4 cell count was 490.0×10^6 cells/L (IQR: 357.5–640.0), and the median nadir CD^4 cell count was 229.0×10^6 cells/L (IQR: 120.0–310.0). Of all patients, 67.1% had HIV RNA below the limit of 50 copies/mL. The median number of copies of those with detectable (>50 copies/mL) HIV RNA was 6285.0 (IQR: 322.5–38125.0).

Of all males, 247 (98.8%) had had sex with men only, in the preceding 6 months. Other patients were bisexual. A ma-

TABLE 2. Statistical Analysis for All 250 HIV-Positive Man Who Have Sex With Man

	All Males 250	Univariable OR (95% CI)	*P**	Multivariable OR (95% CI)	*P*
Median age (yr; IQR)	46.5 (40.0–53.3)	1.05 (1.01–1.09)	0.011	1.03 (0.99–1.07)	0.17
Circumcision before age of 10 yr	26 (10.4)	0.76 (0.27–2.14)	NS		
Age at sexual debut (median; IQR)	18.0 (15.0–21.0)	0.98 (0.92–1.04)	NS		
Bisexual orientation	3 (1.2)	—	NS		
NO. lifetime sexual partners (median; IQR)	100.5 (50–500)	1.00 (1.00–1.00)	NS		
Receptive anal intercourse in previous 12 mo	174 (69.6)	0.66 (0.29–1.46)	NS		
Receptive anal intercourse ever	222 (88.8)	0.42 (0.09–1.84)	NS		
Current smoker	90 (36.0)	1.16 (0.56–2.39)	NS		
History of anal warts	111 (44.4)	0.82 (0.41–1.63)	NS		
Complaints in anal area (pain, itch, pus/blood)	86 (34.4)	0.59 (0.30–1.16)	NS		
Median length for known HIV positivity (yr; IQR)	8.0 (4.0–13.0)	1.06 (1.00–1.13)	0.040	0.97 (0.91–1.04)	0.38
Years of known HIV positivity					
≤5 yr	97 (38.8)				
6–10 yr	54 (21.6)				
11–15 y	63 (25.2)				
>15 yr	36 (14.4)	1.34 (0.96–1.87)	NS		
Recent CD^4 cell count (median; IQR)	490 (358–640)	1.00 (1.00–1.00)	NS		
Nadir CD^4 cell count (median; IQR)	229 (120–310)	1.00 (1.00–1.00)	NS		
Recent HIV viral load (median; IQR)	50 (50–305)	1.00 (1.00–1.00)	NS		
HIV viral load ≤50 log copies/mL	167 (66.8)	0.66 (0.33–1.33)	NS		
Previous occurrence of AIDS defining event	89 (35.6)	1.98 (0.89–4.40)	NS		
Use of HAART	201 (80.4)	3.11 (1.49–6.50)	0.004	2.28 (1.02–5.09)	0.045
Use of HAART for >8 yr	95 (38.0)	1.16 (0.50–2.70)	NS		

*Only *P* values <0.10 are fully given.
OR indicates odds ratio; CI, confidence interval; NS, not significant.

TABLE 3. Results HPV-PCR in Intra-Anal Swabs of 247 HIV-positive Man Who Have Sex With Men

	No Dysplasia N = 208 (84.2)	AIN 1, 2, or 3 N = 39 (15.8)	*P**
HPV-6	27 (13.0)	12 (30.8)	0.009
HPV-11	23 (11.1)	9 (23.1)	0.064
HPV-16	27 (13.0)	12 (30.8)	0.009
HPV-18	18 (8.7)	6 (15.4)	NS
No HPV	21 (10.1)	2 (5.1)	NS
Single infection	49 (23.6)	8 (20.5)	NS
Multiple infections	138 (66.3)	29 (74.4)	NS
Only high-risk HPV	64 (30.8)	10 (25.0)	NS
No. types (median; IQR)	2 (1–4)	3 (1–5)	NS
	No HAART N = 47 (19.0)	**HAART N = 200 (81.0)**	***P****
HPV-6	7 (14.9)	32 (16.0)	NS
HPV-11	6 (12.8)	26 (13.0)	NS
HPV-16	7 (14.9)	32 (16.0)	NS
HPV-18	7 (14.9)	17 (8.5)	NS
No HPV	0 (0)	23 (11.5)	0.010
Single infection	9 (19.1)	48 (24.0)	NS
Multiple infections	38 (80.9)	129 (64.5)	0.037
Only high-risk HPV	17 (36.2)	56 (28.0)	NS
No. types (median; IQR)	3 (2–5)	2 (1–4)	NS

In 3 of 250 HPV specimens, analysis could not be performed.
*Only $P < 0.10$ are fully given.
IQR indicates interquartile range; NS, not significant.

jority of 69.6% reported to have had receptive anal sex in the preceding 12 months. In all, 111 patients (44.4%) reported a previous history of anogenital warts. Ninety patients (36.0%) were current smokers.

Males using HAART did not significantly differ from the ones without HAART with regard to circumcision before age of 10 years, age at sexual debut, sexual orientation, number of lifetime sexual partners, (recent) practice of receptive anal intercourse, complaints in the anal area, or smoking habit. Those who used HAART were significantly older (median, 48 vs. 39 years; $P < 0.0005$) and were longer known as being HIV-positive (median, 10 vs. 4 years; $P < 0.0005$).

Among all 250 patients, 108 (43.2%) had lesions suspicious for HPV-related intraepithelial lesion. A total of 122 biopsies were taken. Of all these biopsies, 60 (49.2%) were taken from the perianal area and 62 (50.8%) from the intra-anal area. In 14 patients, both perianal and intra-anal biopsies were taken. Histologic analyses showed AIN 1 in 24 patients (22.2%), AIN 2 in 6 patients (5.6%), and AIN 3 in 10 patients (9.3%). AIN 3 was observed equally often at the perianal and intra-anal area. Of 10 males with AIN 3, 4 had clinically bowenoid AIN 3. Bowenoid lesions are characterized by pigmented papules, which are histologically similar to Bowen disease (i.e., severe dysplasia) and may have a less aggressive nature than other AIN 3 in HIV-positive MSM. These males were significantly younger than the patients with non-bowenoid clinical expression of their AIN 3 (median age, 27.0 vs. 50.0 years; $P = 0.019$). The results of all biopsies taken are summarized in Table 4.

In univariable analysis, age ($P = 0.011$), length for known HIV positivity ($P = 0.040$), and use of HAART ($P = 0.004$) were significantly associated with AIN. Neither CD^4 cell count, nadir CD^4 cell count nor HIV viral load were associated with the prevalence of AIN. All other characteristics in Table 1 were not related with AIN.

TABLE 4. Results of Biopsies Taken in Patients With Lesions Suspicious for HPV-Related Intraepithelial Lesion (N = 108)

Histopathology	N	%
AIN 3	10	9.3
AIN 2	6	5.6
AIN 1	24	22.2
ASCUS	1	0.9
Anogenital warts	32	29.6
Perianal (postinflammatory) hyperpigmentation	6	5.6
Perianal lichenoid dermatitis	1	0.9
(Thrombosed) hemorrhoid or anal fissure	2	1.9
Chronic inflammation of unknown origin	3	2.8
Granulomatous tissue of unknown origin	2	1.9
Normal histopathology	21	19.4

AIN indicates anal intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

In multivariable analyses, the use of HAART was associated with the absence of AIN (Table 2). This was the case when age, length for known HIV positivity, and use of HAART were used in the analyses.

Intermittent anal itch was reported by 59 (23.6%) patients and pain in the anal region on a regular basis by 34 (13.6%) patients. Sporadic bloody or purulent discharge was reported by 51 (20.4%) patients. None of these complaints were significantly more frequent in those diagnosed with AIN.

HPV types were identified in 224 of 247 samples (90.7%). Data are summarized in Table 3. In only 3 specimens (1.2%), no detection could be performed. A median number of 3 HPV types were detected in positive specimens (IQR: 1–4; maximum number: 13). Of those males with HPV, 171 of 224 (76.3%) had one or more HR-HPV type (). LR-HPV was detected in only 27 of 224 (12.1%) positive specimens. HPV types most often detected were HPV-52 (43.8%; HR-HPV), HPV-39 (24.1%; HR-HPV), HPV-74 (21.9%; unknown risk), HPV-54 (21.0%; LR-HPV), and HPV-51 (18.3%; HR-HPV). Well-known HR-HPV types 16 and 18 were detected in 17.4% and 10.7% of positive specimens, respectively. The LR-HPV types 6 and 11 were detected in 17.4% and 14.3% of positive specimens, respectively.

In MSM with AIN, the HPV types 6 and 16 were detected significantly more often compared with those with no dysplasia ($P = 0.009$ and 0.009)*P* in the sentence "In MSM with AIN, the HPV…" are OK as given.--. No differences were found regarding high-risk types, number of types, or multiple infections.

In MSM with HAART, the absence of any HPV infection was found significantly more often compared with those who did not use HAART (11.5% vs. 0%; $P = 0.010$). Multiple infections were detected more often in those who did not use HAART (80.9% vs. 64.5%; $P = 0.037$).

DISCUSSION

In this large cross-sectional study in a group of 250 HIV-positive MSM, the prevalence of AIN was 16.0%, which is in line with data from German and French studies.[7–9] Our study supports the data of the longitudinal cohort study by De Pokomandy et al[29] that usage of HAART may lower the risk on AIN.

Data on the impact of HAART on the prevalence of AIN are scarce. Earlier studies did not report this association. This maybe due to small numbers of patients[18,22] or due to recent introduction of HAART.[21] In a more recent longitudinal study in a cohort of 357 HIV seropositive gay men in San Francisco, Palefsky et al did not assess the effect of antiretroviral therapy possibly because some of the patients in his study were still not using a full HAART regimen.[23] A single longitudinal cohort study on the effect of HAART on CIN showed that women on HAART were 40% more likely to demonstrate regression and less likely to demonstrate progression.[19] Another group confirmed a higher regression rate of CIN in HAART-treated women in a prospective longitudinal study.[30] In contrast, in a recent longitudinal cohort study in women with HIV and at-risk women without HIV by Paramsothy et al, HAART was associated with enhanced cervical HPV clearance, but not with Pap test regression.[24] In this study, only 20% of the women on HAART had HIV RNA <500 copies/mL due to low adherence, which may have underestimated the effects associated with HAART.

Data of the longitudinal cohort study by De Pokomandy et al[29] suggest that receiving HAART for more than 4 years may contribute to some benefit against AIN 2 or 3.

The prevalence of AIN in this study was not associated with duration of known HIV infection, (nadir) CD^4 counts, HIV viral load, or the previous occurrence of AIDS-defining events. This may be explained by the high percentage of patients successfully using HAART, with normal median recent CD^4 cell counts in both groups.

HPV infection, the etiologic agent of AIN, was detected significantly more often in treatment-naïve patients compared with those who used HAART (100% vs. 88.5%; $P < 0.010$). Differences regarding prevalence of HPV infections in both groups are in agreement with data from several previous studies.[1,20,31,32] Although this difference in our study is significant, a percentage of 88.5%, it is still a high rate of (probably persistent) HPV infections.

Despite potent anti-HIV therapy, with suppression of HIV replication and an increase of CD^4 cell counts, this may not be sufficient to reduce HPV persistence but it may be helpful to induce regression of newly acquired acute HPV infection. Our cross-sectional study cannot answer that question. Longitudinal studies on the effect of HAART on HPV persistence in women indeed do report significantly enhanced clearance of HPV after starting HAART.[24,33] One may hypothesize that longer duration of successful HAART could eventually diminish the risk of AIN.

In this study, the prevalence of AIN was significantly related with the prevalence of both HPV types 16 and 6. HPV type 16 has been linked to different types of anogenital cancers. There was no association between prevalence of AIN and other HR-HPV types or the number of high-risk types. This can be explained by the high prevalence (90.7%) of HPV in this group of patients, of which 76.3% had at least one high-risk type. The prevalence of at least one high-risk type was detected equally often in those with and without AIN.

In contrast to other studies, we did not find an association with nadir CD^4 cell count. The nadir CD^4 counts in our study were relatively high. This may explain the lower prevalence of AIN 2 or 3 in this study. In contrast to the study by De Pokomandy et al,[29] duration of HAART regimen was not related with the prevalence of AIN.

The strength of this study is the combination of the assessment of AIN and HPV in a group of patients with a high rate of successful HAART, with detailed clinical and laboratory parameters, such as the previous occurrence of AIDS-defining events, recent and nadir CD^4 counts, and HIV viral load. Furthermore, the same physician evaluated all patients.

This study was limited by the cross-sectional design. No anal cytology has been used as screening method for the detection of AIN. This limitation might explain the lower percentage of AIN found in this group of HIV-positive MSM compared with other groups where both histology and cytology were used. Due to these small numbers of AIN, it was not possible to separately examine data of AIN 1 versus AIN 2/3. Finally, HPV samples in this study were done on exfoliated anal cells and not from the biopsies taken. Although these superficial specimens are extremely sensitive, this might have influenced the outcomes of HPV infections.

In conclusion, in this cross-sectional study in 250 HIV-positive MSM, the use of HAART was associated with a significantly reduced prevalence of AIN (OR = 2.28; $P = 0.045$) and a significantly lower prevalence of HPV ($P = 0.010$). AIN was associated with HPV types 6 and 16. This association between the prevalence of AIN and the absence of HAART may contribute to the current debate on when to start HAART in HIV-infected individuals. Current European guidelines advice initiation of HAART in case of CD^4 cell counts between 350 and 500×10^6 cells/L. In patients coinfected with hepatitis B or C, HAART should be initiated even when CD^4 cell counts are 500×10^6 cells/L or above. Because HPV infection can be considered coinfection, earlier introduction in these patients may be useful, as it may influence its clinical course and related burden.

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