CONCISE COMMUNICATION

Risk factors for anal high-grade squamous intraepithelial lesions in HIV-positive MSM: is targeted screening possible?

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Objective: HIV-positive MSM are at increased risk for developing anal squamous cell carcinoma. Detection of precursor lesions of anal cancer [anal high-grade squamous intraepithelial lesions (HSIL)] is cumbersome and expensive. Our objective was to identify potential risk factors for anal HSIL in HIV-positive MSM to develop more stringent screening criteria.

Design: We studied a cohort of MSM screened by high-resolution anoscopy at three HIV clinics in Amsterdam, the Netherlands.

Methods: For every first high-resolution anoscopy performed in a patient, we analyzed five demographic and seven HIV-related potential risk factors for four different outcome measures: histologically proven anal HSIL vs. no squamous intraepithelial lesions (SIL), HSIL-anal intraepithelial neoplasia 2 vs. no SIL, HSIL-anal intraepithelial neoplasia 3 vs. no SIL, and HSIL vs. no HSIL. We used univariable and multilevel, multivariable logistic regression.

Results: From 2008 through 2015, 497 out of 1678 (30%) screened HIV-positive MSM had anal HSIL. The mean age was 49 years (SD 9.6), 96% used combination antiretroviral therapy, and median duration of combination antiretroviral therapy use was 7.8 years (interquartile range 4.0–12.4). Increasing age [adjusted odds ratio (aOR) 0.82, 95% confidence interval (CI) 0.70–0.94, $P = 0.006$] and years living with suppressed viral load [1–5 years suppressed aOR 0.52 (95% CI 0.34–0.80), 5.01–10 years aOR 0.47 (95% CI 0.29–0.74), >10 years aOR 0.54 [0.34–0.87], all compared to less than 1 year suppressed, $P = 0.009$] were found to be protective for HSIL vs. no SIL.

Conclusion: Young HIV-positive MSM without viral suppression are statistically at highest risk for anal HSIL, but given the high prevalence among all virally suppressed men, we advise that all HIV-positive MSM should be screened for HSIL.

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Keywords: anal intraepithelial neoplasia, HIV, human papillomavirus, risk factor, squamous intraepithelial lesion

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Introduction

HIV-positive MSM are increasingly at risk for developing anal squamous cell carcinoma compared to the general population [1]. Clinics have been set up to detect precursor lesions of anal squamous cell carcinoma, called squamous intraepithelial lesions (SIL) [2–5]. High-resolution anoscopy (HRA)-guided biopsies are the gold standard for identifying anal SIL. SIL is histopathologically graded anal intraepithelial neoplasia (AIN) 1, 2, or 3 and categorized as low-grade SIL (LSIL; AIN1) or high-grade SIL (HSIL; AIN 2 and 3). The prevalence of histological HSIL (hHSIL) in HIV-positive MSM is around 40% [6] and, as HRA is a costly and cumbersome procedure, more stringent screening criteria for HIV-positive MSM receiving HRA are needed.

Anal cytology can be used for the detection of HSIL (cytological HSIL), but its use is limited by low sensitivity [7–11]. Several studies have identified risk factors for hHSIL in HIV-positive MSM, but results are not always consistent and studied populations were often relatively small [12–15], limiting their potential to identify the patients at highest risk for hHSIL.

We investigated potential demographic and HIV-related risk factors for the presence of histopathologically proven intra- and perianal HSIL in 1681 HIV-positive MSM screened by HRA in Amsterdam, the Netherlands.

Methods

Patients and setting

HIV-positive MSM visiting one of three outpatient HIV clinics in Amsterdam, the Netherlands, were offered AIN screening by their HIV-treating physician. The only exclusion criterion was a life expectancy of less than 12 months. HRA was performed by individually trained anoscopists, did not include anal cytology, sexually transmitted disease (STD), or human papillomavirus (HPV) testing and consisted of a digital rectal examination followed by intra- and perianal inspection with a colposcope (ZEISS opmi pico surgical microscope; Oberkochen, Baden-Württemberg, Germany) after repeatedly applying acetic acid (3–5% solution) and staining with Lugol's iodine when indicated. Lesions suspicious for SIL were biopsied and graded by pathologists specialized in SIL. In clinics A and C, pathologists used p16 staining for AIN2 graded biopsies, as described by the College of American Pathologists in The Lower Anogenital Squamous Terminology standardization project, whereas, in clinic B, p16 staining was not always used in accordance to the College of American Pathologists Lower Anogenital Squamous Terminology criteria [16]. The highest grade biopsy defined the overall diagnosis.

Data were extracted from the clinical records by two of the investigators (MLSH and EM); behavioral data were patient self-reported to the clinician. HIV-related data were obtained from the Stichting HIV monitoring database [17]. Data collection were performed using the OpenClinica open source software, version 3.6 (OpenClinica LLC and collaborators, Waltham, Massachusetts, USA).

The study (ref. W15_047 # 15.0058) was approved by the Medical Ethics Review Committee of the Academic Medical Center, Amsterdam, the Netherlands.

Statistical analysis

Only data of the first HRA of each participant were included. Baseline characteristics of the study population were explored using descriptive statistics, comparing characteristics between participants with no dysplasia, LSIL and HSIL using χ^2 test for categorical data and one-way analysis of variance, and Kruskal–Wallis test for continuous data.

Assessed outcome variables were: HSIL vs. no SIL, HSIL-AIN2 vs. no SIL, HSIL-AIN3 vs. no SIL, and HSIL vs. no HSIL. Five demographic and seven HIV-related variables were included in univariable logistic regression analysis (Suppl. Table 1, http://links.lww.com/QAD/B156). For $CD4^+$ cell count and HIV viral load measurements, the measurements closest to the date of HRA were selected. Years living with viral suppression was defined as having a viral load of less than 200 copies/ml in tests from August 1999 onwards, and allowing for one blip in viral load below 400 copies/ml between measurements with viral load less than 200 copies/ml [18]. For samples tested prior to August 1999 the cut-off of detectability of the laboratory assay was the cut-off used to define viral suppression.

Multivariable logistic regression analysis was used to determine independent risk factors for HSIL among HIV-positive MSM. All variables that were significantly associated in univariable logistic regression analysis with HSIL diagnosis (at $P < 0.2$, Wald test) were included in the multivariable analysis, as well as the following a priori selected parameters (risk factors for HSIL in other studies [10,19–22]): age at time of HRA, a history of at least one AIDS defining illness, nadir $CD4^+$ cell count, current $CD4^+$ cell count, and years living with viral suppression. A backward selection method was used to create a parsimonious model in which a priori selected variables were forced. We conducted multilevel multivariable logistic regression analyses to correct for potential similarities of participants within each clinic. Multicollinearity was tested with the variance inflation factor and if present, the most objective measurable variable remained in the model, whereas the other variable was dropped. However, the effect of this exclusion was checked in a sensitivity analysis. To assess whether the

effect of risk factors differed by clinic, interaction was tested in the multivariable model. Also, risk factors for HSIL were assessed separately for intra-anal and perianal HSIL. Variables were considered significantly associated when *P* value was less than 0.05. Statistical analyses were performed using Stata (version 13.1; Stata Corp, College Station, Texas, USA).

Results

Characteristics of study population

Between 12 February 2008 and 24 November 2015, 1681 HIV-positive MSM underwent their first HRA. Potential risk factors for histological (H)SIL of 311 HIV-positive MSM have been previously described [15]. Three participants were excluded based on the diagnosis of SCC (two intra-anal and one perianal SCC). The mean age was 49 years (SD 9.6) and 96% of participants used combination antiretroviral therapy (cART). Median duration of cART use was 7.8 years [interquartile range (IQR) 4.0–12.4], median nadir $CD4^+$ cell count was 220 cells/μl (IQR 130–320), and median current $CD4^+$ cell count was 620 cells/μl (IQR 480–790). Only 354 (22%) participants had at least one AIDS-defining illness prior to HRA (Table 1). There were some statistically significant (but clinically not important) differences between patients from the three clinics (Suppl. Table 2, http://links.lww.com/QAD/B156).

Of the 1678 HIV-positive MSM, 396 (24%) were diagnosed with AIN1, 289 (17%) with AIN2, and 208 with AIN3 (12%). The prevalence of HSIL was 30% (497/1678 participants). The prevalence of HSIL did not differ significantly between clinics (Suppl. Table 2, http://links.lww.com/QAD/B156). Compared to participants with no dysplasia, participants with LSIL and HSIL were younger ($P < 0.001$), had more sex partners in the preceding 6 months ($P = 0.016$), had a lower number of years on cART ($P < 0.001$), had a different distribution of nadir $CD4^+$ cell counts ($P = 0.005$), had more often a detectable HIV viral load ($P = 0.001$), and had less years living with viral suppression ($P < 0.001$; Table 1).

Univariable logistic regression analyses

Associated variables for HSIL vs. no SIL in univariable logistic regression analyses were age, duration of cART use, having had an STD in the preceding 6 months, HIV plasma viral load, and number of years living with viral suppression. Nadir and current $CD4^+$ cell count were not associated with HSIL. Univariable associations between risk factors and outcome were largely similar between the four outcome measures (Suppl. Table 1, http://links.lww.com/QAD/B156).

Multivariable logistic regression analyses

In multivariable logistic regression analysis, nested within clinic and comparing HSIL vs. no SIL, increasing age [adjusted odds ratio (aOR) 0.82, 95% confidence interval

Table 1. Characteristics of the study population of the anal intraepithelial neoplasia cohort study by histological high-grade squamous intraepithelial lesion status, Amsterdam 2008–2015 (*N* = 1678).

	Total (*N* = 1678)		No dysplasia (*N* = 785)		LSIL (*N* = 396)		HSIL (*N* = 497)		
	No.	%	No	%	No.	%	No.	%	*P* value
Demographic variables									
Age in years (mean/SD)[a]	49	(9.6)	50	(9.4)	48	(10.0)	48	(9.3)	<0.001
Continent of birth[b]									0.710
Europe	1279	82%	566	82%	305	81%	408	84%	
Americas	188	12%	83	12%	50	13%	55	11%	
Oceania	11	1%	5	1%	1	0%	5	1%	
Asia	46	3%	22	3%	14	4%	10	2%	
Africa	28	2%	13	2%	8	2%	7	1%	
Smoking status[c]									0.481
Never smoked	598	38%	275	38%	145	39%	178	39%	
Previously smoking	379	24%	191	26%	83	22%	105	23%	
Currently smoking	577	37%	256	35%	145	39%	176	38%	
Number of sex partners in the preceding 6 months (median/IQR)[d]	2	(1–6)	1	(1–5)	2	(1–6)	2	(1–7)	0.016
Number of sex partners in the preceding 6 months[d]									0.166
0–1	598	49%	295	52%	141	48%	162	44%	
2–5	304	25%	131	23%	77	26%	96	26%	
≥6	316	26%	136	24%	73	25%	107	29%	
Had an STD in the preceding 6 months									0.066
No	1586	95%	750	96%	376	95%	460	93%	
Yes	92	5%	35	4%	20	5%	37	7%	
HIV-related variables									
Currently using cART[e]									0.124
No	73	4%	26	3%	23	6%	24	5%	
Yes	1580	96%	743	97%	368	94%	469	95%	
Duration of cART use in years (median/IQR)[f]	7.8	(4.0–12.4)	8.9	(4.8–12.8)	6.6	(3.6–11.8)	7.5	(3.1–12.3)	<0.001

Table 1 (*continued*)

	Total (*N* = 1678)		No dysplasia (*N* = 785)		LSIL (*N* = 396)		HSIL (*N* = 497)		
	No.	%	No	%	No.	%	No.	%	*P* value
$CD4^+$ T-cell count cells/μl (median/IQR)[g]	620	(480–790)	620	(480–800)	605	(450–780)	630	(490–800)	0.236
$CD4^+$ T-cell count cells/μl [g]									0.423
<350	168	10%	75	10%	48	12%	45	9%	
350–500	323	20%	153	20%	81	21%	89	18%	
>500	1163	70%	541	70%	265	67%	357	73%	
Nadir $CD4^+$ T-cell count cells/μl (median/IQR)[h]	220	(130–320)	220	(130–310)	220	(120–320)	222	(130–351)	0.357
Nadir $CD4^+$ T-cell count cells/μl[h]									0.005
<100	315	19%	146	19%	79	20%	90	18%	
100–199	368	22%	168	22%	86	22%	114	23%	
200–349	624	38%	315	41%	153	39%	156	32%	
>350	344	21%	138	18%	76	19%	130	26%	
HIV plasma viral load copies/ml (median/IQR)[i]	20	(1–40)	20	(1–40)	20	(1–40)	20	(1–40)	0.211
HIV viral load copies/ml[i]									0.001
<50	1347	89%	620	92%	315	85%	412	88%	
≥50	161	11%	51	8%	56	15%	54	12%	
Years living with viral suppression (median/IQR)[j,k]	6.3	(2.6–11.1)	7.2	(3.7–11.8)	5.1	(2.0–10.1)	5.9	(1.9–11.0)	<0.001
Years living with viral suppression[j,k]									<0.001
<1 year[l]	203	14%	61	9%	57	16%	85	18%	
1–5 years	411	28%	172	26%	117	33%	122	26%	
5.01–10 years	393	27%	187	28%	94	26%	112	24%	
>10 years	476	32%	238	36%	92	26%	146	31%	
Having had an AIDS defining illness[m,n]									0.803
No	1280	78%	575	78%	313	79%	392	79%	
Yes	354	22%	166	22%	83	21%	105	21%	
Clinic									
Clinic where HRA was done									0.008
Clinic A	710	42%	334	43%	163	41%	213	43%	
Clinic B	674	40%	288	37%	176	44%	210	42%	
Clinic C	294	17%	163	21%	57	14%	74	15%	
AIN diagnosis									
No dysplasia	785	47%							
AIN1	396	24%							
AIN2	289	17%							
AIN3	208	12%							
Location HSIL									
Intra-anal HSIL	474	28%							
Perianal HSIL	46	3%							

AIN, anal intraepithelial neoplasia; cART, combination antiretroviral therapy; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; LSIL, low-grade squamous intraepithelial lesion; STD, sexually transmitted disease.

[a]Total – 1 missing; no dysplasia – 1 missing; LSIL – 0 missings; HSIL – 0 missings.

[b]Total – 126 missings; no dysplasia – 96 missings; LSIL – 18 missings; HSIL – 12 missings.

[c]Total – 124 missings; no dysplasia – 63 missings; LSIL – 23 missings; HSIL – 38 missings.

[d]Total – 460 missings; no dysplasia – 223 missings; LSIL – 105 missings; HSIL – 132 missings.

[e]Total – 25 missings; no dysplasia – 16 missings; LSIL – 5 missings; HSIL – 4 missings.

[f]Total – 93 missings; no dysplasia – 39 missings; LSIL – 27 missings; HSIL – 27 missings.

[g]Total – 24 missings; no dysplasia – 16 missings; LSIL – 2 missings; HSIL – 6 missings.

[h]Total – 27 misisngs; no dysplasia – 18 missings; LSIL – 2 missings; HSIL – 7 missings.

[i]Total – 170 missings; no dysplasia – 113 missings; LSIL – 26 missings; HSIL – 31 missings.

[j]Total – 196 missings; no dysplasia – 127 missings; LSIL – 36 missings; HSIL – 33 missings.

[k]Viral suppression was defined as having a viral load of less than 200 in tests from 1 August 1999 onwards allowing for a onetime blip in viral load between 200 and 400 copies/ml. For samples tested prior to 1 August 1999 the cut-off of detectability of the laboratory assay that was used for that sample is the cut-off for viral suppression.

[l]Participants who never had an undetectable viral load are included in the category less than 1-year undetectable viral load.

[m]Total – 45 missings; no dysplasia – 44 missings; LSIL – 0 missing; HSIL – 1 missing.

[n]Included AIDS defining illnesses: candidiasis esophageal, Kaposi's sarcoma, recurrent pneumonia, chronic intestinal microsporidiosis, pneumocystis carinii pneumonia, *Mycobacterium kansasii*, pulmonary tuberculosis, chronic intestinal cryptosporidiosis, AIDS dementia complex/HIV encephalopathy, toxoplasmosis of the brain, other species/unidentified extrapulmonary mycobacterium, cytomegalovirus (CMV) retinitis, non-Hodgkin's lymphoma, CMV disease (other than lymph node, liver, spleen), herpes simplex virus, progressive multifocal leucoencephalopathy, extrapulmonary cryptococcosis, primary lymphoma of central nervous system, extrapulmonary tuberculosis, wasting syndrome because of HIV, disseminated or extrapulmonary histoplasmosis, visceral leishmaniasis, candidiasis of trachea/bronchi/lungs, disseminated or extrapulmonary coccidioidomycosis, extrapulmonary pneumocystis, other CDC C event.

Table 2. Risk factors of anal histologically proven high-grade squamous intraepithelial lesion.

	(1) Multivariable logistic regression HSIL vs. no SIL[a]			(2) Multivariable logistic regression AIN2 vs. no SIL[a]			(3) Multivariable logistic regression AIN3 vs. no SIL			(4) Multivariable logistic regression HSIL vs. no HSIL[a]		
	aOR	(95% CI)	*P*	aOR	(95% CI)	*P*	aOR	(95% CI)	*P*	aOR	(95% CI)	*P*
Demographic variables												
Age in years[b]	0.82	(0.70–0.94)	0.006	0.79	(0.66–0.93)	0.006	0.85	(0.70–1.04)	0.116	0.88	(0.77–1.00)	0.057
HIV-related variables												
$CD4^+$ T-cell count, cells/μl			0.427			0.757			0.290			0.397
<350	REF			REF			REF			REF		
350–500	1.08	(0.64–1.82)		1.05	(0.56–1.95)		1.13	(0.55–2.30)		1.15	(0.72–1.84)	
>500	1.29	(0.79–2.10)		1.18	(0.66–2.13)		1.50	(0.77–2.91)		1.31	(0.84–2.04)	
Nadir CD4 T-cell count, cells/μl[c]	0.97	(0.88–1.06)	0.494	1.02	(0.92–1.14)	0.671	0.89	(0.78–1.01)	0.076	1.00	(0.92–1.09)	0.924
Years living with viral suppression[d]			0.009			0.070			0.006			0.039
<1 year[e]	REF			REF			REF			REF		
1–5 years	0.52	(0.34–0.80)		0.53	(0.32–0.86)		0.49	(0.28–0.85)		0.61	(0.42–0.88)	
5.01–10 years	0.47	(0.29–0.74)		0.55	(0.32–0.94)		0.34	(0.19–0.64)		0.61	(0.41–0.92)	
>10 years	0.54	(0.34–0.87)		0.54	(0.31–0.93)		0.51	(0.28–0.94)		0.73	(0.48–1.11)	
Having had an AIDS defining illness			0.899			0.777			0.888			0.995
No	REF			REF			REF			REF		
Yes	0.98	(0.73–1.32)		0.95	(0.66–1.37)		1.03	(0.69–1.53)		1.00	(0.76–1.32)	

(1) High-grade squamous intraepithelial lesion vs. no squamous intraepithelial lesion; (2) Anal intraepithelial neoplasia 2 vs. no squamous intraepithelial lesion; (3) Anal intraepithelial neoplasia 3 vs. no squamous intraepithelial lesion; (4) High-grade squamous intraepithelial lesion vs. no high-grade squamous intraepithelial lesion (including anal intraepithelial neoplasia 1)[f]. CI, confidence interval; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; SIL, squamous intraepithelial lesion; STD, sexually transmitted disease.
[a]Multivariable model HSIL vs. no SIL includes 1120 participants; multivariable model AIN2 vs. no SIL includes 929 participants; multivariable model AIN3 vs. no SIL includes 847 participants; multivariable model HSIL vs. no HSIL includes 1480 participants.
[b]Per 10-year increase in age.
[c]Per 100 cells/μl increase.
[d]Viral suppression was defined as having a viral load of less than 200 in tests from 1 August 1999 onwards allowing for a onetime blip in viral load between 200 and 400 copies/ml. For samples tested prior to 1 August 1999 the cut-off of detectability of the laboratory assay that was used for that sample is the cut-off for viral suppression. This varies by time period (sensitivity of the assays increased over time) and hospital (based on the used assay).
[e]Participants who never had an undetectable viral load are included in the category less than 1-year undetectable viral load.
[f]Individuals were nested within clinic where HRA was done (multilevel analysis).

(CI) 0.70–0.94; $P = 0.006$], and years living with suppressed viral load were significantly protective for HSIL [1–5 years viral suppression aOR 0.52 (95% CI 0.34–0.80), 5.01–10 years viral suppression aOR 0.47 (95% CI 0.29–0.74), >10 years viral suppression aOR 0.54 (0.34–0.87), all compared to less than 1 year viral suppression, $P = 0.009$]. Outcome measures HSIL-AIN2 vs. no SIL, HSIL-AIN3 vs. no SIL, and HSIL vs. no HSIL yielded similar results (Table 2).

Based on multicollinearity, we excluded a priori cART use, HIV viral load and duration of cART use because this is largely represented in number of years living with viral suppression. We reran the model including duration of cART use instead of years living with viral suppression, yielding similar results. None of the interaction terms were significant, suggesting that the effect of the included risk factors did not vary by clinic (data not shown).

Additionally, we assessed risk factors for intra- and perianal HSIL vs. no SIL separately. Intra-anal HSIL showed results comparable to the overall model. Only being a current smoker was found to be a significant risk factor of perianal HSIL in multilevel multivariable logistic regression analyses [previously smoked aOR 2.41 (95% CI 0.77–7.57), current smoker aOR 4.90 (95% CI 1.80–13.35), compared to participants who never smoked, $P = 0.006$; Supplementary Table 3, http://links.lww.com/QAD/B156].

Discussion

We analyzed potential risk factors for anal HSIL (AIN2–3) in 1678 HIV-positive MSM. Of five demographic and seven HIV-related potential risk factors, only increasing age and years living with suppressed viral load were significantly protective for HSIL vs. no SIL. Sensitivity analyses, including duration of cART use instead of duration of viral suppression, showed a similar relation.

In contrast to our results, several smaller studies, with less than 400 patients each, reported various demographic and HIV-related risk factors that significantly increased the risk for anal hHSIL: the number of specific HPV types and current use of cART [13], increasing age and $CD4^+$ cell counts less than 50/μl before starting cART [12], and smoking [23,24]. We found smoking to be a risk factor, but for perianal HSIL only. We also confirmed that duration of cART use showed a reduced risk for hHSIL [12,25]. Living more than 1 year with viral suppression might reduce the risk for hHSIL as it could be a proxy for immune restoration over time. We have no good explanation how older age could be protective for anal HSIL.

The strength of this study is that it reports nearly 1700 patients from three HIV clinics, using hHSIL as an endpoint. This allowed for an extensive multivariable analysis without constraints in the number of covariates.

A limitation of our study is that no data were collected on anal HPV infections, but given that 95% of all HIV-positive MSM have anal HPV present, the value of this risk factor is debatable [13,26]. More specifically, HPV16 testing might be considered to have more discriminatory power, but given that HPV16 was the causative HPV type in only 60% of anal carcinomas in HIV-positive MSM in another study by our group [27], 40% of potential anal carcinomas would be missed. Also, patient populations differed significantly between clinics, which may be explained by differences in calendar year of starting with HRA screening and by the large study populations, easily leading to statistically significant but not clinically important differences. Furthermore, multiple anoscopists performed the HRAs, and given the long learning curve for HRA, some HSIL lesions may have been missed [28,29]. Also, in clinic B p16 staining was not always used to confirm AIN2 graded biopsies. Finally, social desirability bias might have occurred for self-reported STDs and sexual behavior.

Young HIV-positive MSM without viral suppression are statistically at highest risk for HSIL, but given the high prevalence of HSIL among all virally suppressed men, we advise that all HIV-positive MSM should be screened for the presence of anal HSIL.

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Conflicts of interest

There are no conflicts of interest.

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