HPV: screening, terapia e prevenzione

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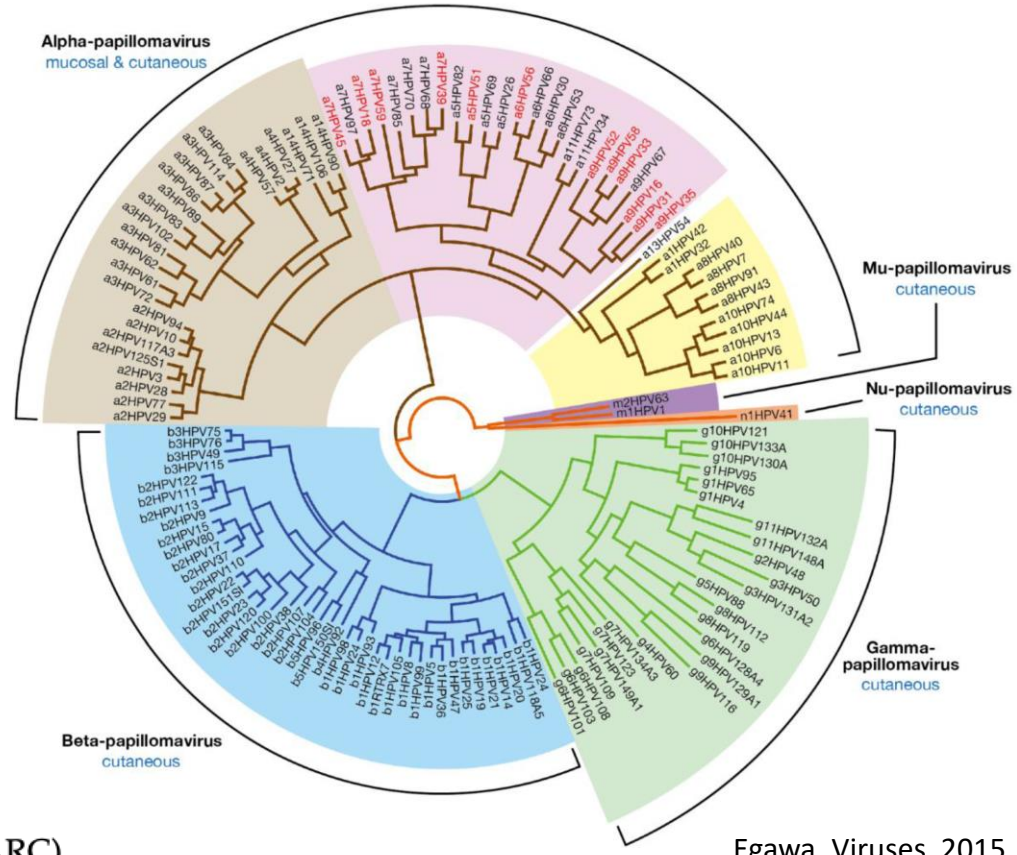
The Human Papillomarvirus (HPV)

- HPV: double-stranded DNA virus, containing 8 genes and over 160 HPV types
- 5 genera involved in human infection:
- αHPV genus comprises most of the clinically significant HPV strains
- βHPV and γHPV also isolated in PLWH
- μHPV and νHPV are related to cutaneous diseases
- HPV genotypes are also classified based on their oncogenic potential



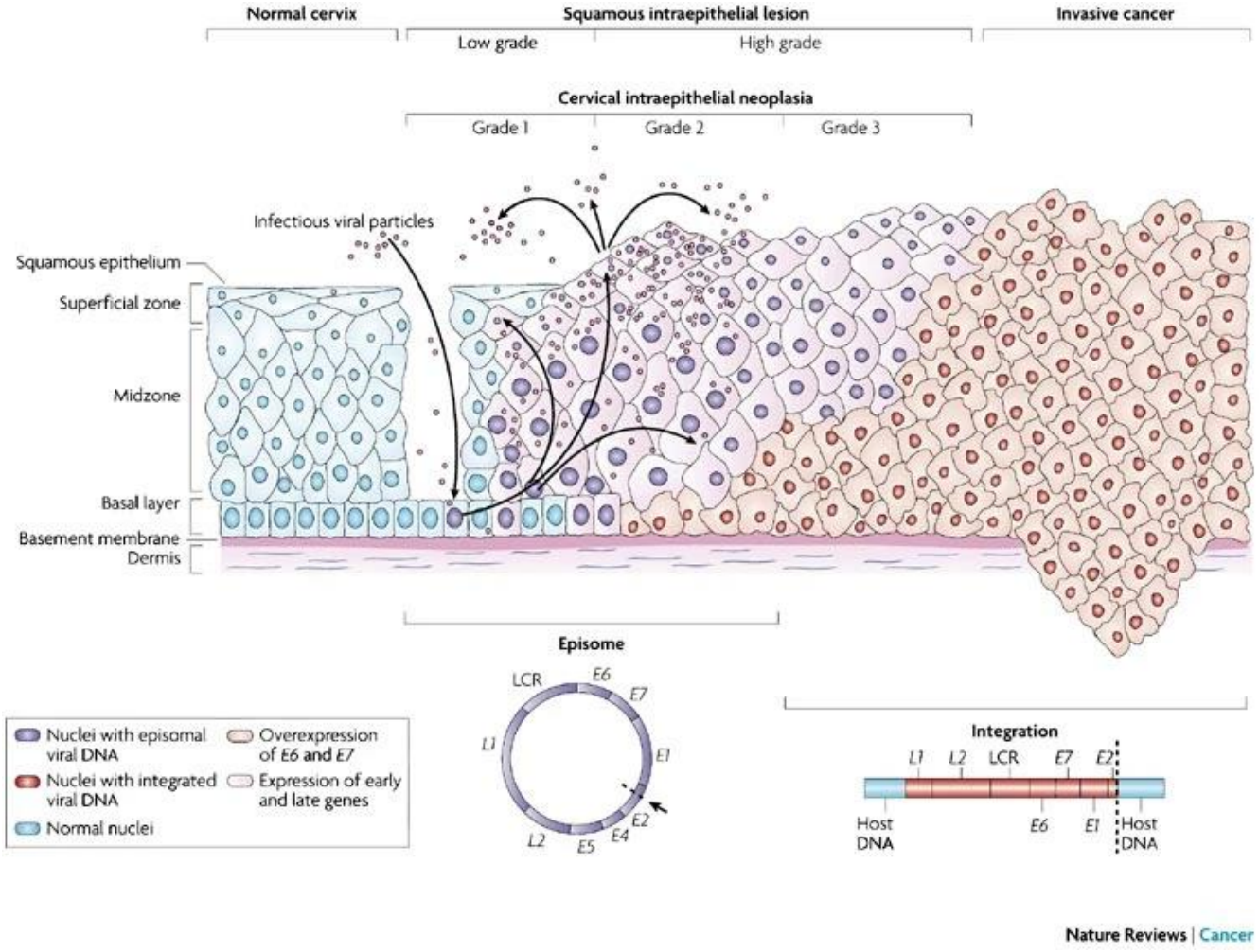
Egawa, Viruses, 2015

Pérez-González, Microrganisms, 2022

Table 1. HPV classification according to the oncogenic risk (IARC).

Classification	HPV Types
High risk (group 1)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably high risk (group 2A)	68
Possibly carcinogenic to humans (group 2B)	26, 53, 66, 67, 70, 73, 82 30, 34, 69, 85, 97
Unclassifiable as to carcinogenicity in humans (group 3)	6, 11

Natural History of HPV infection



- The interval between HPV infection and the eruption of squamous intraepithelial lesions (SILs) usually requires several years

- At the histological level, the progression of HPV infection correlates with different changes or stages

- The initial stages of the disease involve mild or moderate changes in the epithelium with these lesions being termed low-grade (L) SILs

- A considerable proportion of LSIL spontaneously regress; a small number of LSILs may progress further and become high-grade (H) SILs which
  - most of them naturally resolve or remain stable
  - might progress further and transform into squamous cell carcinoma (SCC)

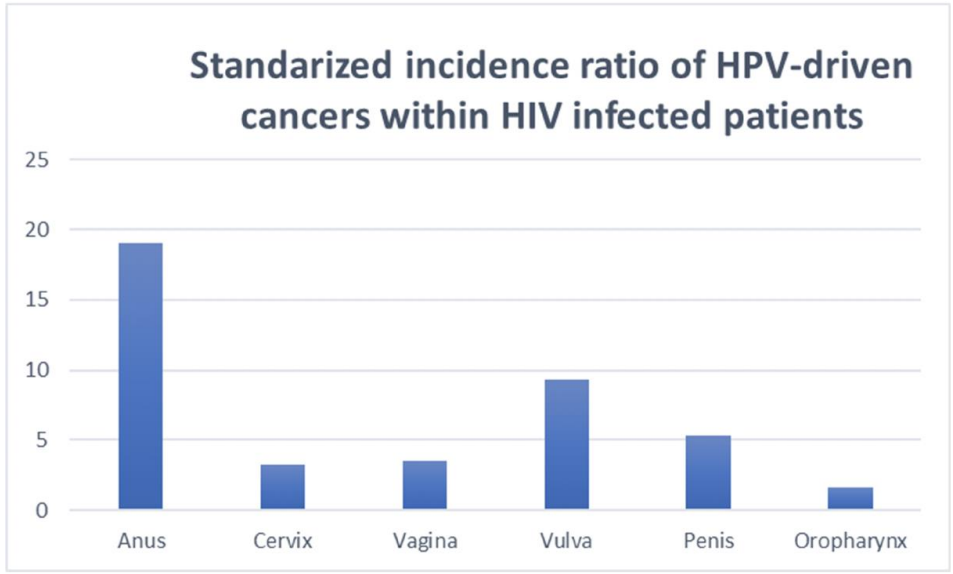
Woodman et al. Nat Rev Cancer, 2007

Pérez-González, Microrganisms, 2022

Anal Dysplasia and Squamous Cell Carcinoma in PLWH

- PLWH
- **MSM**: incidence of 85 (95% [CI] 82–89) per 100 000 person-years, ranging from 16.8 per 100 000 person-years for < 30 years up to 107.5 per 100 000 person-years for > 60 years
- **MSW**: 32 (95% CI 30–35) per 100 000 person-years
- **Women** have an incidence of aSCC of 22 (95% CI 19–24) per 100 000 person-years

- HIV risk in HIV negative individuals (less studied)
- cervical cancer survivors: 9 (95% CI 8–12); cervical dysplasia (CIN 2/3): 6 (95% CI 5–7) per 100 000 person-years
- vulvar cancer survivors: 48 (95% CI 38-61) per 100 000 person-years
- **MSM**: 19 (95% CI 10–36) per 100 000 person-years per 100 000 person-years
- **SOT** recipients (renal), > 10 years: women incidence of 50 (95% CI 35.4–67.5); men 25 (95% CI 16.3–35.4) per 100 000 person-years



Age is a strong risk factor in the development of aSCC

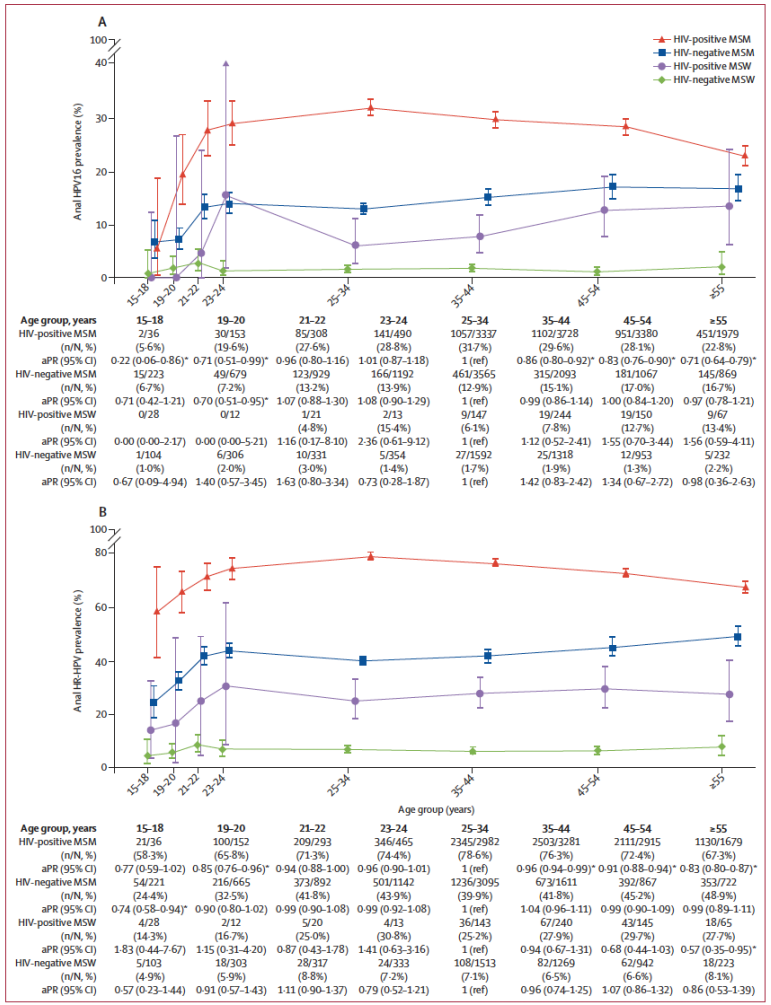
Multiple cohort studies and data from cancer registries show aSCC increasing as a function of age for all risk groups

The median age of anal cancer diagnosis is about **60** years old in the general population, decreasing to about **47** years in men living with HIV

Barroso II et al al, Clin Infect Dis, 2022;
Perez-Gonzalez, Microrganisms, 2022

What are the reasons underlying increased risk of HPV disease progression in PLWH?

High Prevalence of HR Genotypes in PLWH



Age group, years	15–18	19–20	21–22	23–24	25–34	35–44	45–54	≥55
HIV-positive MSM	2/36	30/153	85/308	141/490	1057/3337	1102/3728	951/3380	451/1979
(n/N, %)	(5·6%)	(19·6%)	(27·6%)	(28·8%)	(31·7%)	(29·6%)	(28·1%)	(22·8%)
aPR (95% CI)	0·22 (0·06–0·86)*	0·71 (0·51–0·99)*	0·96 (0·80–1·16)	1·01 (0·87–1·18)	1 (ref)	0·86 (0·80–0·92)*	0·83 (0·76–0·90)*	0·71 (0·64–0·79)*
HIV-negative MSM	15/223	49/679	123/929	166/1192	461/3565	315/2093	181/1067	145/869
(n/N, %)	(6·7%)	(7·2%)	(13·2%)	(13·9%)	(12·9%)	(15·1%)	(17·0%)	(16·7%)
aPR (95% CI)	0·71 (0·42–1·21)	0·70 (0·51–0·95)*	1·07 (0·88–1·30)	1·08 (0·90–1·29)	1 (ref)	0·99 (0·86–1·14)	1·00 (0·84–1·20)	0·97 (0·78–1·21)
HIV-positive MSW	0/28	0/12	1/21	2/13	9/147	19/244	19/150	9/67
(n/N, %)			(4·8%)	(15·4%)	(6·1%)	(7·8%)	(12·7%)	(13·4%)
aPR (95% CI)	0·00 (0·00–2·17)	0·00 (0·00–5·21)	1·16 (0·17–8·10)	2·36 (0·61–9·12)	1 (ref)	1·12 (0·52–2·41)	1·55 (0·70–3·44)	1·56 (0·59–4·11)
HIV-negative MSW	1/104	6/306	10/331	5/354	27/1592	25/1318	12/953	5/232
(n/N, %)	(1·0%)	(2·0%)	(3·0%)	(1·4%)	(1·7%)	(1·9%)	(1·3%)	(2·2%)
aPR (95% CI)	0·67 (0·09–4·94)	1·40 (0·57–3·45)	1·63 (0·80–3·34)	0·73 (0·28–1·87)	1 (ref)	1·42 (0·83–2·42)	1·34 (0·67–2·72)	0·98 (0·36–2·63)

Age group, years	15–18	19–20	21–22	23–24	25–34	35–44	45–54	≥55
HIV-positive MSM	21/36	100/152	209/293	346/465	2345/2982	2503/3281	2111/2915	1130/1679
(n/N, %)	(58·3%)	(65·8%)	(71·3%)	(74·4%)	(78·6%)	(76·3%)	(72·4%)	(67·3%)
aPR (95% CI)	0·77 (0·59–1·02)	0·85 (0·76–0·96)*	0·94 (0·88–1·00)	0·96 (0·90–1·01)	1 (ref)	0·96 (0·94–0·99)*	0·91 (0·88–0·94)*	0·83 (0·80–0·87)*
HIV-negative MSM	54/221	216/665	373/892	501/1142	1236/3095	673/1611	392/867	353/722
(n/N, %)	(24·4%)	(32·5%)	(41·8%)	(43·9%)	(39·9%)	(41·8%)	(45·2%)	(48·9%)
aPR (95% CI)	0·74 (0·58–0·94)*	0·90 (0·80–1·02)	0·99 (0·90–1·08)	0·99 (0·92–1·08)	1 (ref)	1·04 (0·96–1·11)	0·99 (0·90–1·09)	0·99 (0·89–1·11)
HIV-positive MSW	4/28	2/12	5/20	4/13	36/143	67/240	43/145	18/65
(n/N, %)	(14·3%)	(16·7%)	(25·0%)	(30·8%)	(25·2%)	(27·9%)	(29·7%)	(27·7%)
aPR (95% CI)	1·83 (0·44–7·67)	1·15 (0·31–4·20)	0·87 (0·43–1·78)	1·41 (0·63–3·16)	1 (ref)	0·94 (0·67–1·31)	0·68 (0·44–1·03)	0·57 (0·35–0·95)*
HIV-negative MSW	5/103	18/303	28/317	24/333	108/1513	82/1269	62/942	18/223
(n/N, %)	(4·9%)	(5·9%)	(8·8%)	(7·2%)	(7·1%)	(6·5%)	(6·6%)	(8·1%)
aPR (95% CI)	0·57 (0·23–1·44)	0·91 (0·57–1·43)	1·11 (0·90–1·37)	0·79 (0·52–1·21)	1 (ref)	0·96 (0·74–1·25)	1·07 (0·86–1·32)	0·86 (0·53–1·39)

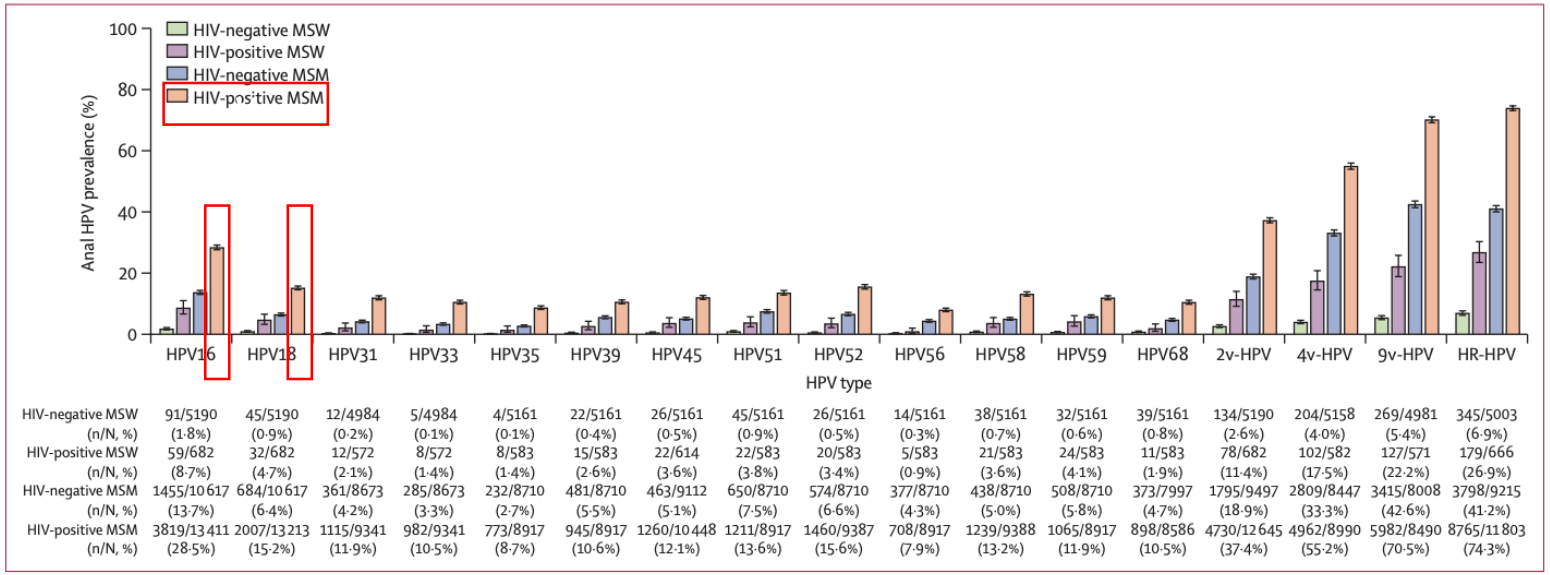
Figure 3: **Age-specific prevalence of HPV16 (A) and HR-HPV (B) infection in four male risk groups**
Error bars show 95% CIs. PRs were adjusted for study. HR-HPV includes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV=human papillomavirus. HR-HPV=high-risk HPV. MSM=men who have sex with men. MSW=men who have sex with women. aPR=adjusted prevalence ratio. *Significant aPRs relative to the reference group.

Wei, Lancet HIV, 2021

- Cervix: HPV-16 causes 55% of cancers
- Anus: HPV-16 causes 75-89% of cancers (HPV-18 and other HR: < 5%)

Barroso II et al al, Clin Infect Dis, 2022

Men, anal



	HPV16	HPV18	HPV31	HPV33	HPV35	HPV39	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV68	2v-HPV	4v-HPV	9v-HPV	HR-HPV
HIV-negative MSW	91/5190	45/5190	12/4984	5/4984	4/5161	22/5161	26/5161	45/5161	26/5161	14/5161	38/5161	32/5161	39/5161	134/5190	204/5158	269/4981	345/5003
(n/N, %)	(1·8%)	(0·9%)	(0·2%)	(0·1%)	(0·1%)	(0·4%)	(0·5%)	(0·9%)	(0·5%)	(0·3%)	(0·7%)	(0·6%)	(0·8%)	(2·6%)	(4·0%)	(5·4%)	(6·9%)
HIV-positive MSW	59/682	32/682	12/572	8/572	8/583	15/583	22/614	22/583	20/583	5/583	21/583	24/583	11/583	78/682	102/582	127/571	179/666
(n/N, %)	(8·7%)	(4·7%)	(2·1%)	(1·4%)	(1·4%)	(2·6%)	(3·6%)	(3·8%)	(3·4%)	(0·9%)	(3·6%)	(4·1%)	(1·9%)	(11·4%)	(17·5%)	(22·2%)	(26·9%)
HIV-negative MSM	1455/10617	684/10617	361/8673	285/8673	232/8710	481/8710	463/9112	650/8710	574/8710	377/8710	438/8710	508/8710	373/7997	1795/9497	2809/8447	3415/8008	3798/9215
(n/N, %)	(13·7%)	(6·4%)	(4·2%)	(3·3%)	(2·7%)	(5·5%)	(5·1%)	(7·5%)	(6·6%)	(4·3%)	(5·0%)	(5·8%)	(4·7%)	(18·9%)	(33·3%)	(42·6%)	(41·2%)
HIV-positive MSM	3819/13411	2007/13213	1115/9341	982/9341	773/8917	945/8917	1260/10448	1211/8917	1460/9387	708/8917	1239/9388	1065/8917	898/8586	4730/12645	4962/8990	5982/8490	8765/11803
(n/N, %)	(28·5%)	(15·2%)	(11·9%)	(10·5%)	(8·7%)	(10·6%)	(12·1%)	(13·6%)	(15·6%)	(7·9%)	(13·2%)	(11·9%)	(10·5%)	(37·4%)	(55·2%)	(70·5%)	(74·3%)

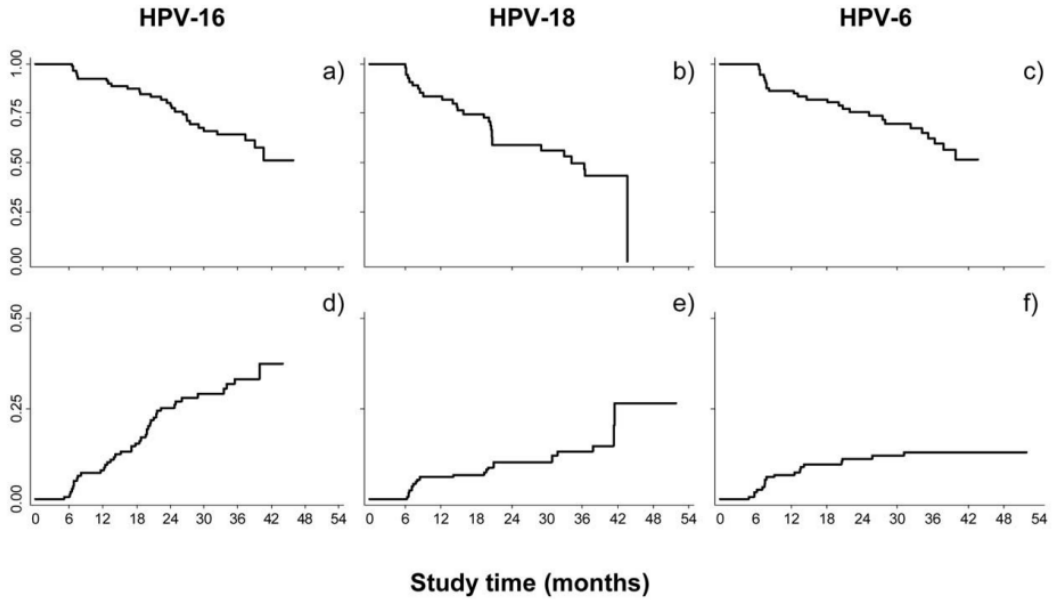
Wei, Lancet HIV, 2021

Impaired HPV Clearance in Men LWH

Table 2. Prevalence at enrollment and clearance of type-specific human papillomavirus (HPV) infection.

HPV type	Prevalence at enrollment, no. (%) of subjects	Clearance (for subjects positive at enrollment): Cleared episodes, no.	Person-months of follow-up, no.	Clearance rate, cleared episodes/1000 person-months (95% CI)	HPV infection retention time, months: Median (95% CI)	Mean (95% CI)
High risk						
16	92 (38.2)	28	2286.3	12.2 (8.5–17.7)	ND (37.4–ND)	35.8 (32.7–38.8)
18	59 (24.5)	28	1375.2	20.4 (14.1–29.5)	34.2 (20.6–ND)	29.8 (25.9–33.7)
31	42 (17.4)	25	801.4	31.2 (21.1–46.2)	22.8 (12.8–36.5)	23.7 (19.2–28.2)
33	40 (16.6)	20	690.1	29.0 (18.7–44.9)	23.4 (7.7–ND)	24.6 (18.9–30.4)
35	33 (13.7)	23	593.9	38.7 (25.7–58.3)	19.4 (12.5–25.1)	21.7 (17.0–26.4)
39	49 (20.3)	26	968.1	26.9 (18.3–39.4)	28.0 (14.8–36.9)	25.8 (21.1–30.4)
45	51 (21.2)	36	891.4	40.4 (29.1–56.0)	19.6 (12.9–25.6)	21.3 (17.2–25.3)
51	35 (14.5)	20	596.1	33.6 (21.6–52.0)	18.2 (9.4–31.8)	22.1 (16.7–27.6)
52	52 (21.6)	29	1096.6	26.4 (18.4–38.1)	25.1 (16.7–37.3)	26.4 (22.2–30.5)
56	42 (17.4)	26	728.0	35.7 (24.3–52.5)	14.4 (13.3–32.2)	21.4 (17.1–25.8)
58	48 (19.9)	25	892.8	28.0 (18.9–41.4)	21.9 (15.2–ND)	24.6 (20.3–28.9)
59	47 (19.5)	21	1075.1	19.5 (12.7–30.0)	32.8 (20.6–ND)	29.4 (25.0–33.9)
66	23 (9.5)	18	314.5	57.2 (36.1–90.8)	13.3 (6.9–22.3)	15.5 (11.1–19.9)
68	36 (14.9)	16	606.7	26.4 (16.2–43.0)	20.5 (12.5–ND)	24.7 (19.3–30.1)
82	14 (5.8)	10	254.8	39.3 (21.1–73.0)	13.5 (6.6–ND)	20.2 (12.5–27.9)
Low risk						
6	85 (35.3)	26	1931.4	13.5 (9.2–19.8)	ND (35.2–ND)	33.6 (30.3–36.8)
11	56 (23.2)	18	1276.0	14.1 (8.9–22.4)	44.2 (31.1–ND)	33.4 (29.1–37.7)
40	19 (7.9)	11	199.1	55.2 (30.6–99.7)	11.1 (6.8–13.5)	15.1 (8.4–21.8)
42	69 (28.6)	30	1499.1	20.0 (14.0–28.6)	36.3 (20.7–ND)	30.4 (26.4–34.4)
44	47 (19.5)	22	1031.2	21.3 (14.0–32.4)	33.1 (24.8–41.5)	29.2 (25.0–33.4)
54	26 (10.8)	21	447.6	46.9 (30.6–72.0)	14.6 (8.5–21.1)	18.9 (14.1–23.8)
61	48 (19.9)	20	795.2	25.1 (16.2–39.0)	25.3 (13.6–ND)	26.8 (21.5–32.0)
70	28 (11.6)	19	524.9	36.2 (23.1–56.7)	17.1 (7.8–27.9)	20.8 (15.9–25.8)
72	21 (8.7)	15	384.6	39.0 (23.5–64.7)	20.3 (9.1–28.0)	20.8 (15.5–26.2)
81	26 (10.8)	14	411.0	34.1 (20.2–57.5)	18.2 (7.6–ND)	21.6 (15.9–27.4)
89	40 (16.6)	25	660.0	37.9 (25.6–56.0)	15.5 (9.6–20.8)	22.5 (16.6–28.4)
Undetermined risk						
26	13 (5.4)	10	178.2	56.1 (30.2–104.3)	12.5 (6.9–25.6)	15.0 (9.5–20.6)
34	3 (1.2)	3	26.0	115.3 (37.2–357.5)	7.4 (5.1–ND)	8.7 (4.6–12.7)
53	44 (18.3)	26	858.5	30.3 (20.6–44.5)	25.6 (8.1–34.7)	23.3 (19.0–27.6)
62	21 (8.7)	12	440.2	27.3 (15.5–48.0)	20.2 (14.2–ND)	26.1 (19.3–32.9)
67	16 (6.6)	12	308.7	38.9 (22.1–68.4)	19.2 (13.0–27.5)	21.4 (15.5–27.3)
69	22 (9.1)	12	395.2	30.4 (17.2–53.5)	26.0 (6.4–39.6)	24.6 (17.7–31.5)
71	6 (2.5)	0	103.9	0 (ND)	ND	42.7 (42.7–42.7)
73	40 (16.6)	22	801.3	27.5 (18.1–41.7)	28.9 (12.8–40.5)	25.3 (20.7–30.0)
83	16 (6.6)	9	220.6	40.8 (21.2–78.4)	16.9 (7.4–ND)	18.2 (12.5–23.9)
84	51 (21.2)	33	769.3	42.9 (30.5–60.3)	14.1 (11.7–20.6)	20.6 (16.2–25.0)

NOTE. HPV types are classified by risk of anogenital cancer according to Munoz et al. [25]. CI, confidence interval; ND, not determined.



Kaplan-Meier estimates of the clearance times for human papillomavirus (HPV)–16 (a), HPV-18 (b), and HPV-6 (c) and of the cumulative incidence of infection with HPV-16 (d), HPV-18 (e), and HPV-6 (f).

de Pokomandy, JID, 2009

T-cell activation as an independent predictor of HPV-related dysplasia in PLWH

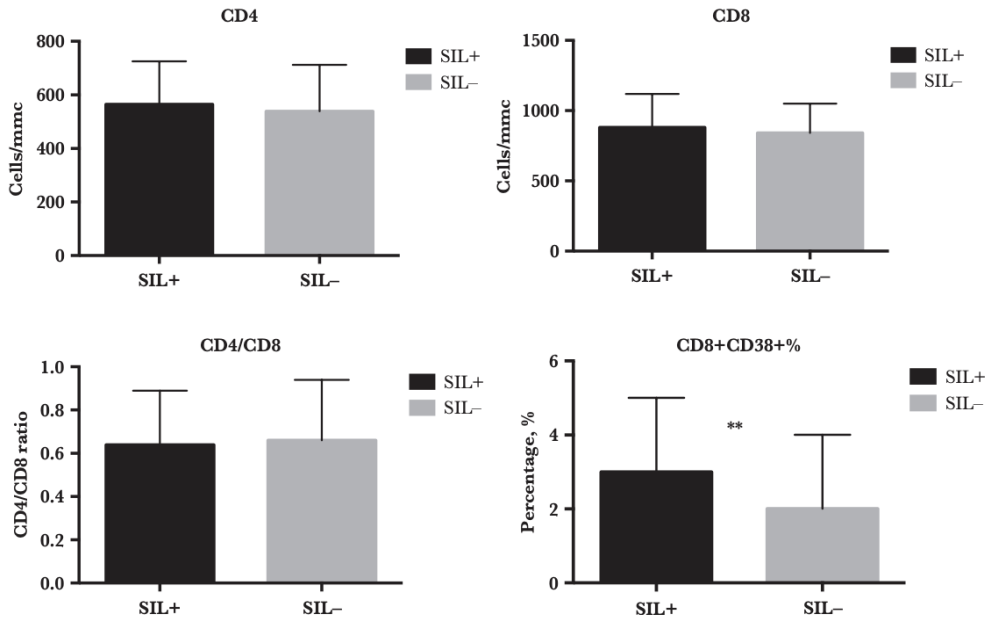


Table 2. Parameters Independently Associated With Cytologic HPV-Related Dysplasia by Fitting 2 Models of Multivariable Logistic Regression Analyses

A, Model 1 of logistic regression analysis: association between CD8+ CD38+ T-cell percentages and HPV-related anal/cervical dysplasia			
Parameter	aOR	95% CI	*P* Value
Log_{10} CD8+ CD38+ T cells, percentages, each additional unit	3.253	1.602–6.605	.001
B, Model 2 of logistic regression analysis: association between CD4/CD8 ratio and HPV-related anal/cervical dysplasia			
Parameter	aOR	95% CI	*P* Value
CD4/CD8 ratio, each unit more	0.998	0.242–4.109	.997

Mondatore, OFID, 2022

Impaired HPV-specific reponses in PLWH

SPANC

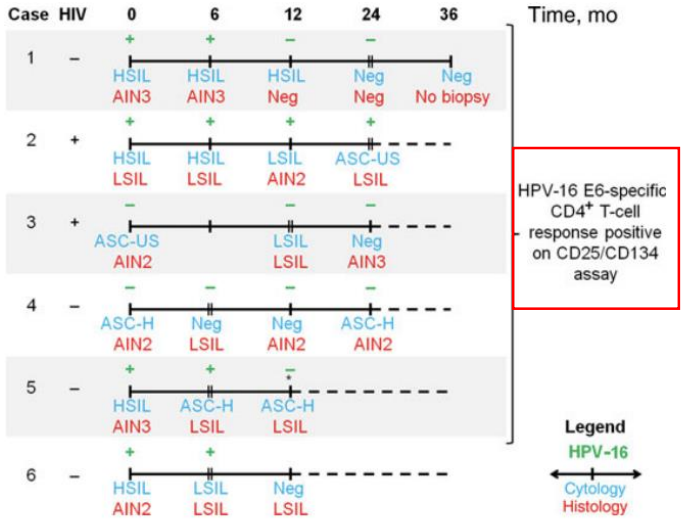
- HIV-, n=103
- HIV+, n= 31

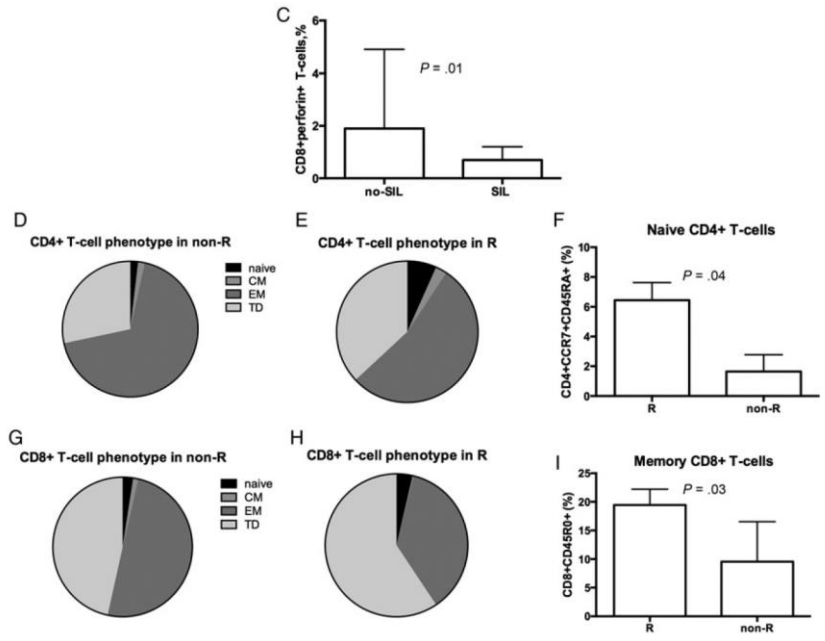
HSIL significantly associated with E7-specific CD8+ T-cell responses (odds ratio, 4.09 [95% confidence interval, 1.55–10.77], P = .004)

Table 2. Clinical Associations With Positive HPV-16 E6-Specific T-Cell Responses (Univariable Logistic Regression)

T-Cell Subset	CD4+						CD8+		
Assay	CD25/CD134			ICS			ICS		
	Prevalence, No. (%)	OR (95% CI)	P Value	Prevalence, No. (%)	OR (95% CI)	P Value	Prevalence, No. (%)	OR (95% CI)	P Value
Age, y			.06[a]			.13[a]			.21[a]
35–44	22 (68.8)	1		9 (28.1)	1		7 (21.9)	1	
45–55	26 (44.8)	0.37 (.15–.92)		9 (15.5)	0.47 (.16–1.34)		13 (22.4)	1.03 (.36–2.92)	
>55	20 (45.5)	0.38 (.15–.98)		6 (13.6)	0.40 (.13–1.28)		5 (11.4)	0.46 (.13–1.60)	
HIV status			.76			.81			.03[b]
Uninfected	53 (51.5)	1		18 (17.5)	1		15 (14.6)	1	
Infected	15 (48.4)	0.88 (.40–1.98)		6 (19.4)	1.13 (.41–3.16)		10 (32.3)	2.79 (1.10–7.09)	
$CD4^+/CD8^+$ T-cell ratio	. . .	0.80 (.55–1.16)	.24	. . .	1.19 (.75–1.87)	.46	. . .	0.90 (.55–1.46)	.66
Anal HPV status									
HPV-16			.82			.32			.52
Not detected	48 (52.2)	1		19 (20.7)	1		19 (20.7)	1	
Detected	19 (50.0)	0.92 (.43–1.95)		5 (13.2)	0.58 (.20–1.69)		6 (15.79)	0.72 (.26–1.97)	
Any high-risk HPV type			.06			.92			.59
Not detected	22 (41.5)	1		10 (18.9)	1		9 (17.0)	1	
Detected	45 (58.4)	1.98 (.97–4.03)		14 (18.2)	0.96 (.39–2.35)		16 (20.8)	1.28 (.52–3.17)	
No. of HPV types detected			.04[a,b]			.79[a]			.29[a]
0	8 (30.8)	1		5 (19.2)	1		3 (11.5)	1	
1–2	25 (55.6)	2.8 (1.01–7.80)		7 (15.6)	0.77 (.22–2.74)		9 (20.0)	1.92 (.47–7.83)	
≥3	34 (57.6)	3.1 (1.15–8.15)		12 (20.3)	1.07 (.34–3.43)		13 (22.0)	2.17 (.56–8.37)	
Anal SIL screening diagnosis									
Cytology			.09			.92			.43
≤ASC-H	50 (48.1)	1		18 (17.3)	1		22 (21.2)	1	
HSIL	15 (68.2)	2.31 (.87–6.14)		4 (18.2)	1.06 (.32–3.51)		3 (13.6)	0.59 (.16–2.17)	
Worst histology			.62			.69			.97
≤AIN2	50 (52.1)	1		18 (18.8)	1		18 (18.8)	1	
AIN3	18 (47.4)	0.83 (.39–1.76)		6 (15.8)	0.81 (.30–2.23)		7 (18.4)	0.98 (.37–2.57)	
High-grade disease[c]			.97			.95			.83
Not detected	42 (50.6)	1		15 (18.1)	1		15 (18.1)	1	
Detected	26 (51.0)	1.02 (.51–2.04)		9 (17.7)	0.97 (.39–2.42)		10 (19.6)	1.11 (.45–2.69)	

Tong, JID, 2015





Tincati, CID, 2016

How can we prevent morbidity and mortality of anal SCC?

Primary prevention through vaccination (prior to sexual debut)

GUIDELINES
Version 11.1
October 2022
English

Infection	Vaccination rationale	Comment
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	Vaccinate with 3 doses between ages 9 and 45 (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available. Persons treated for high grade dysplasia could benefit from a full course vaccination for secondary prevention

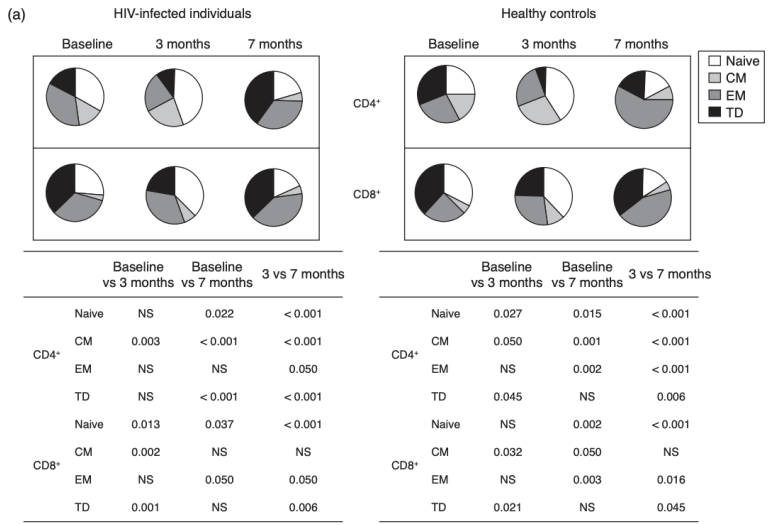
Immunizations for Preventable Diseases in Adults and Adolescents with HIV

Updated: April 13, 2023
Reviewed: April 13, 2023

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
		For exposed people who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).		
Human papillomavirus (HPV)	Adults and adolescents through age 26	Recombinant 9-valent human papillomavirus vaccine (Gardasil®9): 0.5 mL IM 3-dose series (0, 1–2, 6 months) **(AIII)**	If a significant delay occurs between doses, there is no need to restart the series. Routine vaccination is **not recommended** for people ages 27–45 years **(AI)**. Some PWH may benefit from vaccination in this age group, and shared clinical decision-making between the provider and patient is recommended in these situations.	No difference in recommendations
	Adults and adolescents who previously received bivalent or quadrivalent vaccine	For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, no recommendations exist for additional vaccinations; some experts would give an additional full series of recombinant 9-valent vaccine, but no data currently define who might benefit or how cost effective this approach might be **(CIII)**.	Vaccination is **not recommended** during pregnancy **(CIII)**. Delay until after pregnancy.	

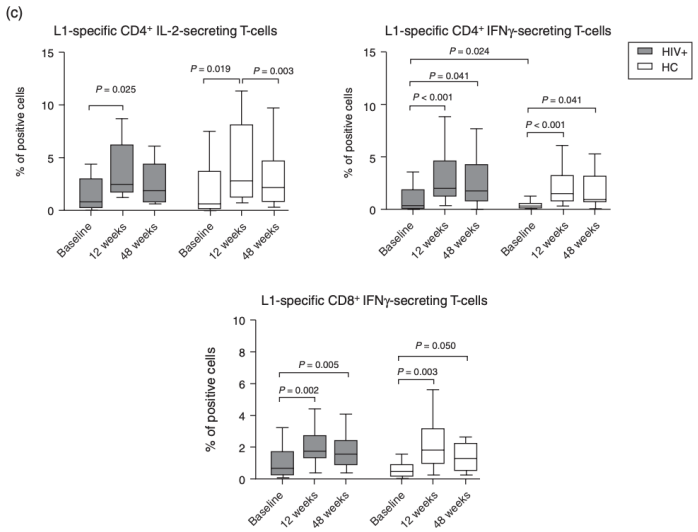
HPV vaccine in PLWH elicits immune responses

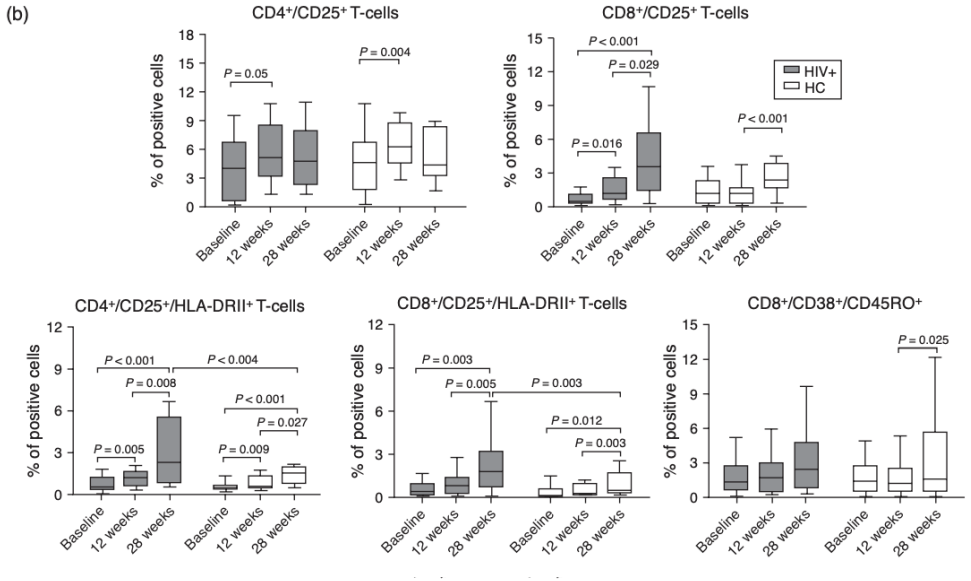
- three-dose QHPV vaccination
- N=46 adolescents and young adults

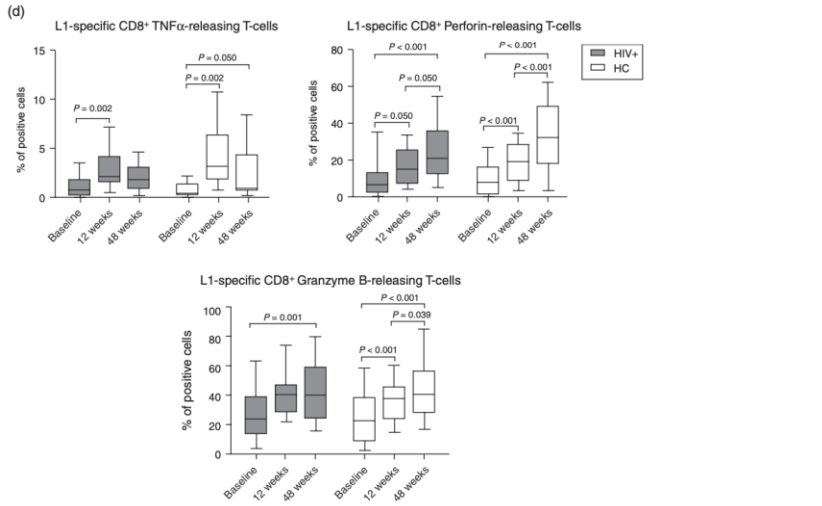


		Baseline vs 3 months	Baseline vs 7 months	3 vs 7 months
CD4+	Naive	NS	0.022	< 0.001
	CM	0.003	< 0.001	< 0.001
	EM	NS	NS	0.050
	TD	NS	< 0.001	< 0.001
CD8+	Naive	0.013	0.037	< 0.001
	CM	0.002	NS	NS
	EM	NS	0.050	0.050
	TD	0.001	NS	0.006

		Baseline vs 3 months	Baseline vs 7 months	3 vs 7 months
CD4+	Naive	0.027	0.015	< 0.001
	CM	0.050	0.001	< 0.001
	EM	NS	0.002	< 0.001
	TD	0.045	NS	0.006
CD8+	Naive	NS	0.002	< 0.001
	CM	0.032	0.050	NS
	EM	NS	0.003	0.016
	TD	0.021	NS	0.045



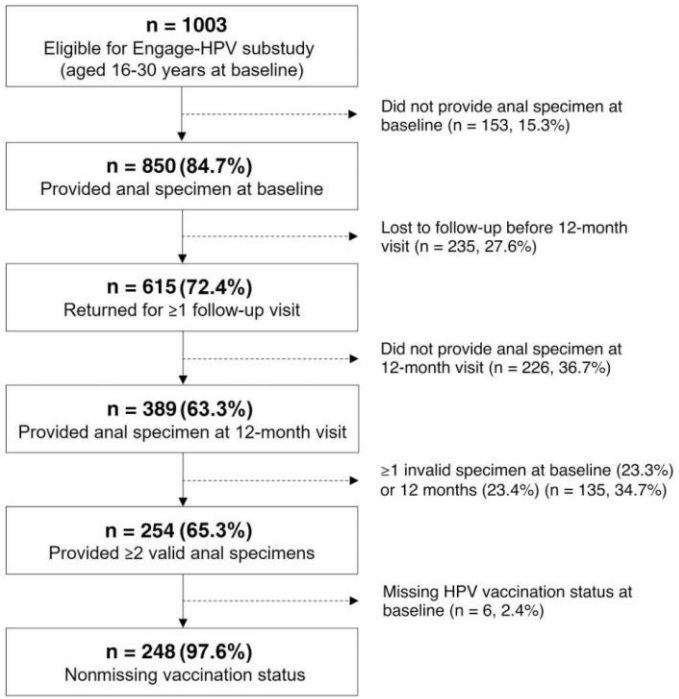




Rainone, AIDS, 2015

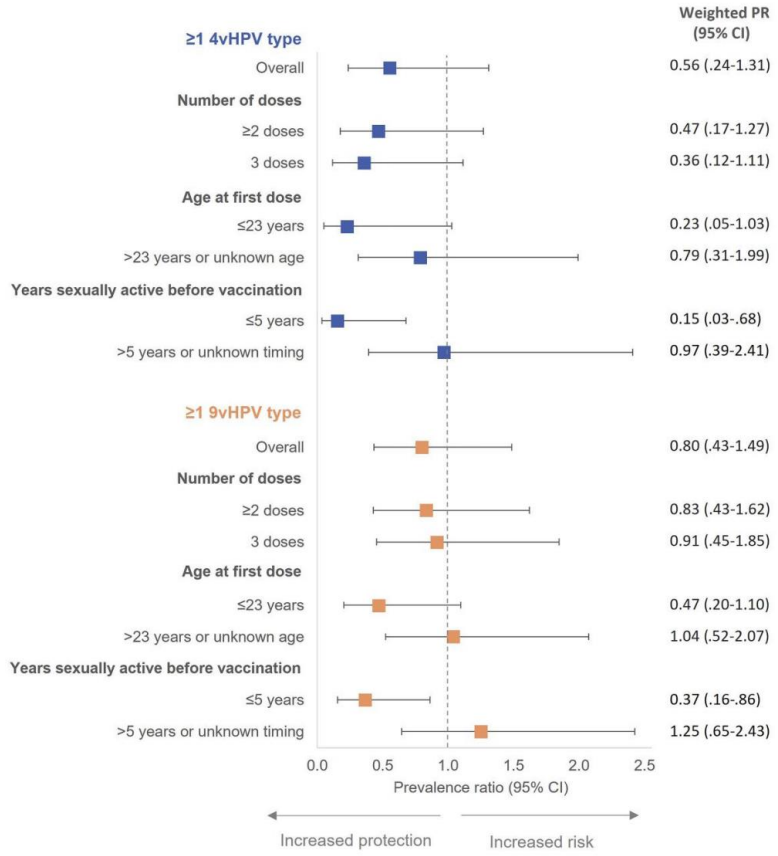
HPV vaccine effectiveness (anal HPV) in MSM

N=13 HIV+

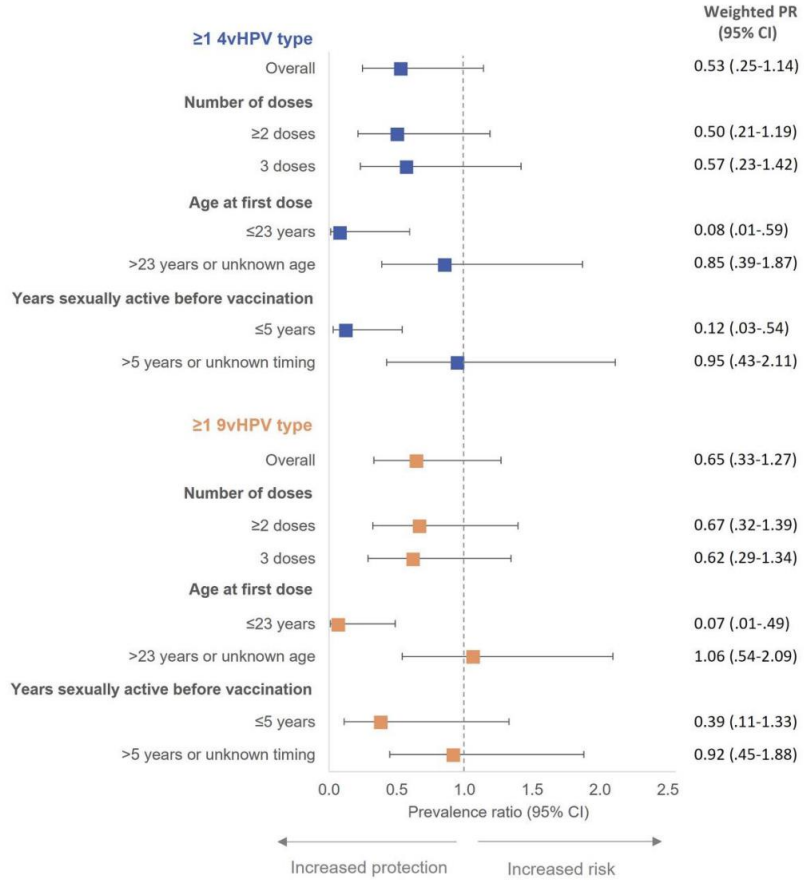


Age, 16-30

IPTW-weighted prevalence ratios for 12-month cumulative incidence of anal HPV infection



IPTW-weighted prevalence ratios for 12-month persistence of anal HPV infection



Chambers, JID, 2023

HPV vaccine effectiveness in Women LWH, yet Low Coverage Globally

Table 5. Comparison to Unvaccinated Historical Women Living With Human Immunodeficiency Virus

Endpoint	Unvaccinated Historical WLWH (Canadian Women's HIV Study) Rate per 100 Person-Years (95% CI)	Vaccinated WLWH (Present study) Rate per 100 Person-Years (95% CI)
Persistent qHPV	6.0 (4.6–7.7)	2.3 (1.1–4.1)
Genital warts	2.9 (2.1–3.9)	2.3 (1.2–4.1)
CIN2+	1.0 (0.5–1.9)	0 (0.0–0.9)

Abbreviations: CI, confidence interval; CIN2+, cervical intraepithelial lesion of grade 2 or higher; HIV, human immunodeficiency virus; qHPV, quadrivalent human papillomavirus (HPV6/11/16/18); WLWH, women living with HIV.

McClymont, CID, 2019

Strong reduction in the risk of persistent cervical HPV infections has also been seen in HPV-vaccinated WLWH

Position Paper

No woman left behind: achieving cervical cancer elimination among women living with HIV

Kirthana Sharma*, Dorothy A Machalek*, Zheng Q Toh, Demisew Amenu, Mazvita Muchengeti, Andrew K Ndlovu, Alex Mremi, Bariki Mchome, Andrew J Vallely, Lynette Denny, Helen Rees, Suzanne M Garland

Lancet HIV 2023; 10: e412-20
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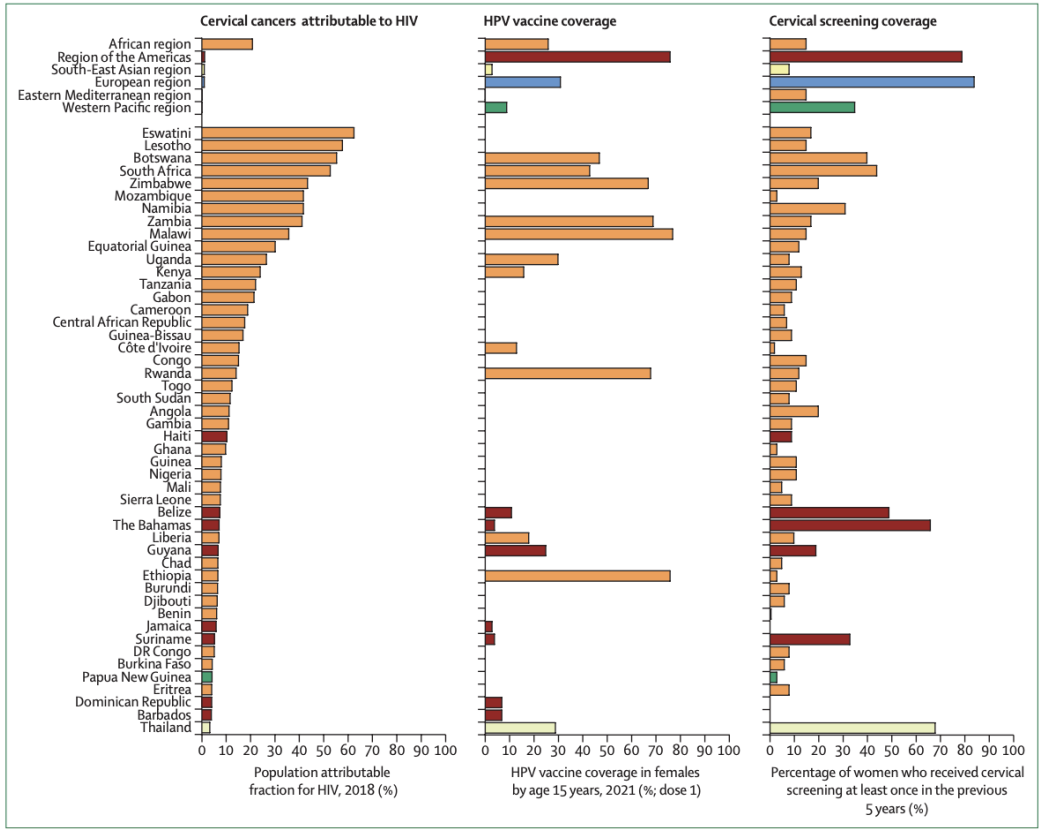
Cervical cancer is the fourth most common malignancy in women of reproductive age globally. The burden of this disease is highest in low-income and middle-income countries, especially among women living with HIV. In 2018, WHO launched a global strategy to accelerate cervical cancer elimination through rapid scale-up of prophylactic vaccination, cervical screening, and treatment of precancers and cancers. This initiative was key in raising a call for action to address the stark global disparities in cervical cancer burden. However, achieving elimination of cervical cancer among women with HIV requires consideration of biological and social issues affecting this population. This Position Paper shows specific challenges and uncertainties on the way to cervical cancer elimination for women living with HIV and highlights the scarcity of evidence for the effect of interventions in this population. We argue that reaching equity of outcomes for women with HIV will require substantial advances in approaches to HPV vaccination and improved understanding of the long-term effectiveness of HPV vaccines in settings with high HIV burden. Cervical cancer, just as HIV, is affected by social and structural factors such as poverty, stigma, and gender discrimination, that place the elimination strategy at risk. Global efforts must, therefore, be galvanised to ensure women living with HIV have optimised interventions, given their substantial risk of this preventable malignancy.

Key messages

- Ensuring the UNAIDS 95-95-95 targets for HIV testing, treatment, and viral suppression are met will be crucial for WHO's cervical cancer elimination strategy to succeed, given the higher risk of cervical cancer in women with HIV
- Current HPV vaccine coverage is inadequate in low-income and middle-income countries with high HIV burden, with monitoring needed to confirm whether two-dose or single-dose HPV vaccination schedules are protective for people with HIV
- There is an urgent need to determine optimal cervical screening and triage algorithms that are rapidly scalable for populations of women with HIV in low-income and middle-income countries, who have a high prevalence of oncogenic HPV
- Cervical cancer service integration with antiretroviral therapy services can offer crucial opportunities to expand accessible care for women with HIV
- The inclusion of HIV status as a required variable in population-based cancer registries in high HIV burden settings will be essential to monitor progress towards cervical cancer elimination for women with HIV
- Making gender equity a central tenet of cervical cancer interventions will be essential to meeting the ambitions of the WHO cervical cancer elimination strategy



HPV Vaccine (qHPV) effectiveness in Men LWH

Clinical Infectious Diseases

MAJOR ARTICLE

A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298

Timothy J. Wilkin,[1] Huichao Chen,[2] Michelle S. Cespedes,[3] Jorge T. Leon-Cruz,[2] Catherine Godfrey,[4] Elizabeth Y. Chiao,[5] Barbara Bastow,[6] Jennifer Webster-Cyriaque,[7] Qinghua Feng,[8] Joan Dragavon,[9] Robert W. Coombs,[9,10] Rachel M. Presti,[11] Alfred Saah,[12] and Ross D. Cranston[13]

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Clinical Infectious Diseases

MAJOR ARTICLE

High Prevalence of Anal High-Grade Squamous Intraepithelial Lesions, and Prevention Through Human Papillomavirus Vaccination, in Young Men Who Have Sex With Men Living With Human Immunodeficiency Virus

Joel M. Palefsky,[1,©] Shelly Y. Lensing,[2] Marvin Belzer,[3] Jeannette Lee,[2] Aditya H. Gaur,[4] Kenneth Mayer,[5] Donna Futterman,[6] Elizabeth A. Stier,[7] Mary E. Paul,[8] Elizabeth Y. Chiao,[9] Daniel Reirden,[10] Stephen E. Goldstone,[11] Maribel Tirado,[12] Edward R. Cachay,[13] Luis F. Barroso,[14] Maria Da Costa,[1] Teresa M. Darragh,[15] Bret J. Rudy,[16] Craig M. Wilson,[17] and Jessic A. Kahn[18]; for the AIDS Malignancy Consortium and Adolescent Medicine Trials Network for HIV/AIDS Interventions

See also metanalysis by Wei et al, JID, 2023:
"No significant VE against anal HPV infection or AIN was found in persons vaccinated at age >26 years (mainly people living with HIV)".

Table 2. Vaccine Efficacy for Persistent Anal Infection, Persistent Oral Infection, Anal High-Grade Squamous Intraepithelial Lesions on Anal Biopsy, and Abnormal Anal Cytology

Endpoint	Vaccine Group		Control Group		Efficacy (95.1% Confidence Interval)
Persistent anal infection	n	Endpoint	n	Endpoint	
mITT-including single detection at final visit	286	27	283	33	22% (–31% to 53%)
mITT-persistent infection only	286	14	283	17	21% (–61% to 61%)
Per protocol analysis	276	7	277	10	31% (–82% to 74%)
Full ITT	288	28	286	41	35% (–5% to 60%)
Persistent oral infection					
mITT-including single detection at final visit	288	7	286	10	32% (–80% to 74%)
mITT-persistent infection only	288	1	286	8	88% (2% to 98%)
Per-protocol analysis	278	1	280	3	66% (–70% to 96%)
Full ITT	288	6	286	14	58% (–9% to 84%)
Improvement of anal high-grade squamous intraepithelial lesions on anal biopsy outcomes[a]					
Full ITT	288	46	286	45	0% (–44% to 31%)
Abnormal anal cytology					
Week 52	231	123 (53%)	229	121 (53%)	0% (–19% to 16%)
Week 104	199	98 (49%)	198	108 (55%)	9% (–10% to 25%)
Week 156	130	58 (45%)	132	72 (55%)	17% (–6% to 35%)

Abbreviations: ITT, intention-to-treat analysis; mITT, modified ITT analysis.

[a]High-grade squamous intraepithelial lesions on anal biopsy specimens were not tested with human papillomavirus (HPV) DNA polymerase chain reaction to determine the causative HPV type.

Table 5. Low-Grade Squamous Intraepithelial Lesions or High-Grade Squamous Intraepithelial Lesions in the Merck 020 Per-Protocol Placebo Group Compared With the AMC-072 Per-Protocol Naive Vaccinated Group

Endpoint: Anal/Perianal LSIL/HSIL[a] Related to	Per-Protocol Merck 020 Placebo Group[b]				Per-Protocol AMC-072 Naive Vaccinated Group				
	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	*P*[c]
HPV6	144	10	298.5	3.4	15	0	25.0	0.0	.447
HPV11	144	6	298.2	2.0	35	0	55.2	0.0	.361
HPV16	170	6	341.9	1.8	39	0	65.4	0.0	.350
HPV18	193	4	387.4	1.0	47	0	75.6	0.0	.490
HPV6, 11, 16, or 18[d]	208	24	411.6	5.8	58	0	93.0	0.0	.008

Abbreviations: AMC, AIDS Malignancy Consortium; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; qHPV, quadrivalent human papillomavirus.

[a]Analyses required having both histology and anal biopsy HPV DNA determination at a given visit. AMC-072 participants with qHPV type–specific AIN1 or perianal condyloma at baseline were removed (HSIL was an exclusion criteria); "baseline" DNA HPV type based on visits 0 and 3. Case counting occurred after month 7 at visits 4, 5, and/or 6.

[b]The per-protocol Merck 020 placebo group were HIV-negative men who have sex with men, were naive for a given qHPV type, and did not have LSIL or HSIL at baseline.

[c]Merck placebo and AMC-072 naive group comparison of event rates based on exact Poisson calculation (1-sided test).

[d]Consistent with the reported Merck V503-020 combined endpoint, analysis of all participants who were eligible for ≥1 of the individual type-specific analyses. A participant would be counted more than once if multiple lesions of different HPV types developed.

Diagnosis and screening of anal HSIL

Secondary prevention: identification and destruction of precursor lesions (aHSIL) to prevent progression to invasive cancer

1) screening test
2) further evaluation of screen positives with a high-resolution anoscopy (HRA) to detect anal HSIL
3) treatment of HSIL to prevent progression to anal cancer

Barroso II et al al, Clin Infect Dis, 2022

Diagnosis and screening of anal HSIL

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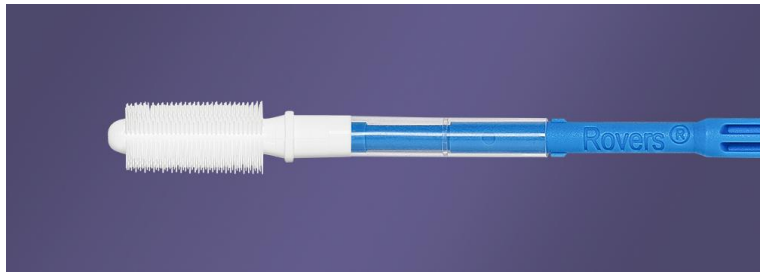
Barroso II et al al, Clin Infect Dis, 2022

Anal Cancer Screening Tests

Anal Pap smear

Liquid-based cytological brushing (ThinPrep®) with Anex® brush

(+ HPV genotype testing)



- Anal cytology is collected though insertion of a moistened polyester swab 4–6 cm into the anal canal
- The swab is then withdrawn while applying gentle rotating circumferential pressure and eluted into a liquid transport medium
- Results are reported per the Bethesda nomenclature

The specificity of the current screening test, anal cytology, is poor (46% - 65%), but its negative predictive value is high (~95%)

Barroso II et al al, Clin Infect Dis, 2022; Clarke et al, Cancer Cytopathol , 2018; Serrano-Villar et al, Plos One 2017

No well-defined evidence-based algorithm for interpretation and triage of abnormal results of anal cancer screening

Local practices based on local expert opinion and available resources

- anal cytology ± HPV testing, with HRA triage of abnormal result
- HRA for all MSM living with HIV over a certain age cut-off
- proceeding directly to HRA in all persons living with HIV over age 35
- repeating anal cytology every 6 months, yearly, or every 2 years

Barroso II et al al, Clin Infect Dis, 2022

Diagnosis and screening of anal HSIL

Secondary prevention: identification and destruction of precursor lesions (aHSIL) to prevent progression to invasive cancer

1) screening test
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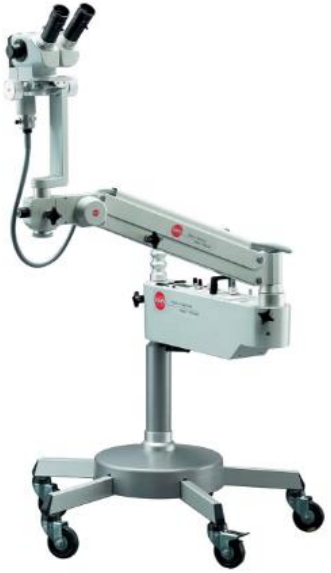
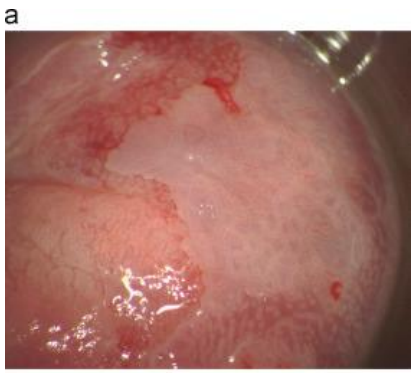
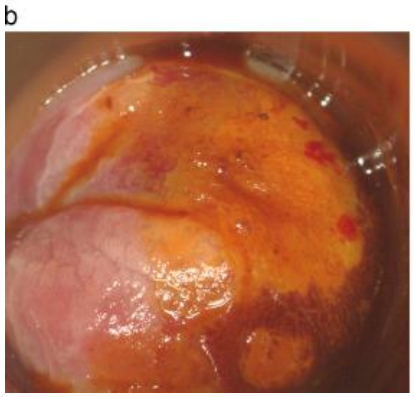
Barroso II et al al, Clin Infect Dis, 2022

The High Resolution Anoscopy (HRA) Exam







- The HRA exam begins with a well-performed DARE to assess for any palpable abnormalities.
- The anal canal is then visualized with a colposcope with a standard 10–15 mm anoscope
- The anal mucosal surface is stained with 5% acetic acid and an iodine (Lugol's) solution, to highlight specific abnormalities that can be **biopsied** under direct visualization for subsequent histologic diagnosis

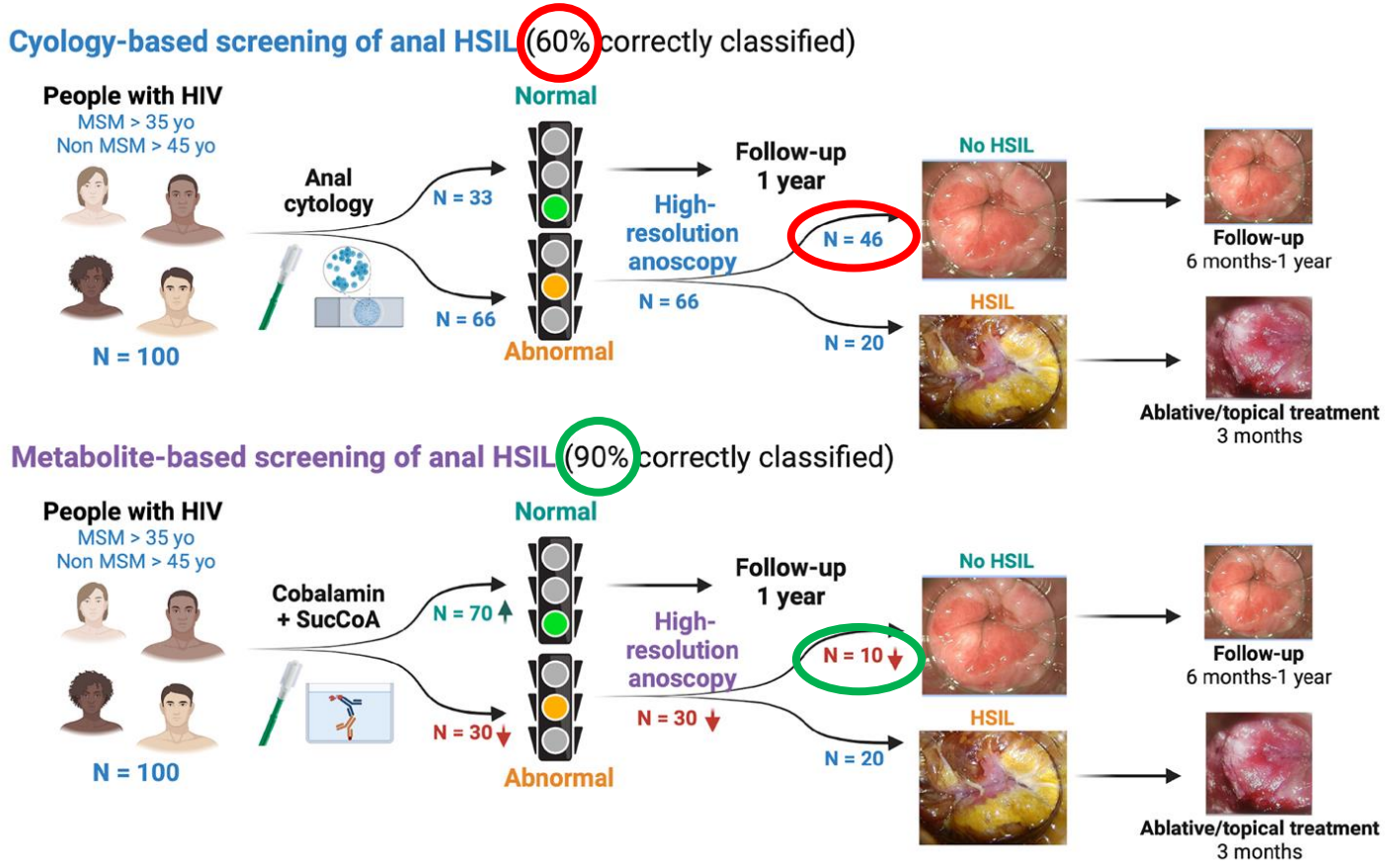
Jay, Papillomavirus Research, 2015

Barroso II et al al, Clin Infect Dis, 2022

Microbiome-based SCReening of Anal Cancer in PWH

SCRATCH study

Succinyl CoA and cobalamin reclassified to true negatives >80% of cytologic false positive results



Serrano-Villar et al. *Microbiome-Derived* Cobalamin and Succinyl-CoA as Biomarkers for Improved Screening of Anal Cancer. Nature Medicine 2023.

Diagnosis and screening of anal HSIL

Secondary prevention: identification and destruction of precursor lesions (aHSIL) to prevent progression to invasive cancer

1) screening test
2) further evaluation of screen positives with a high-resolution anoscopy (HRA) to detect anal HSIL
3) treatment of HSIL to prevent progression to anal cancer

Debate regarding the efficacy of anal cancer prevention through aHSIL diagnosis and treatment was directly addressed by the ANal Cancer/HSIL Outcomes Research (ANCHOR) trial

Barroso II et al al, Clin Infect Dis, 2022

Does Every aHSIL Lesion Require Treatment?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

N Engl J Med 2022;386:2273-82.
DOI: 10.1056/NEJMoa2201048

- HIV+ > 35 yrs
- biopsy-proven anal HSIL
- randomly assigned, in a 1:1 ratio, to receive either HSIL treatment* or active monitoring without treatment

* ablative procedures (infrared coagulation, electrocautery, and laser), ablation or excision under anesthesia, and topical treatments (imiquimod and fluorouracil)

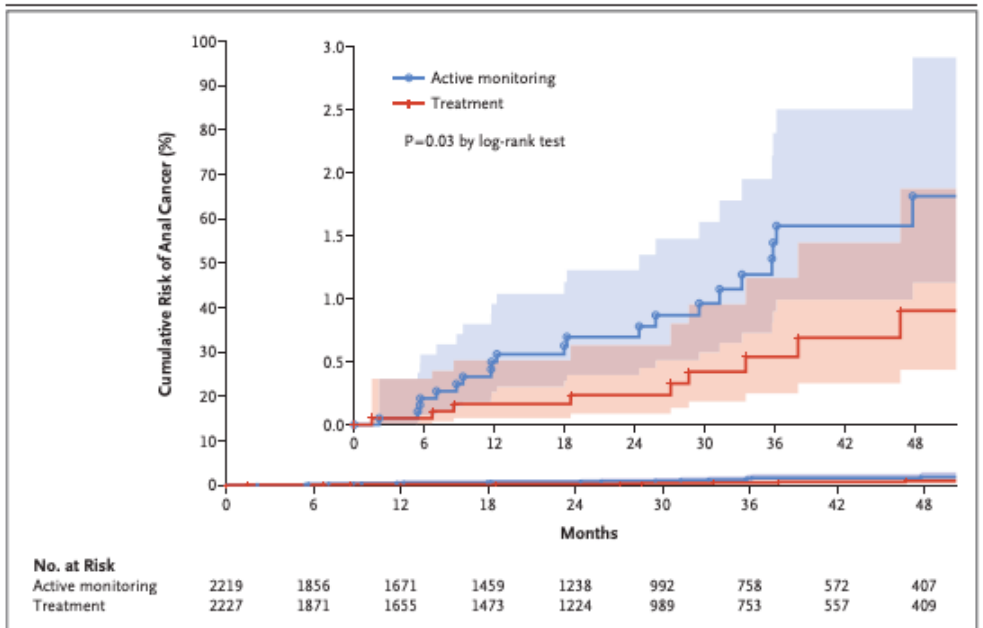


Figure 2. Kaplan–Meier Curve of the Time to Progression to Anal Cancer.
The inset shows the data on an expanded y axis. The shaded areas represent 95% confidence intervals.

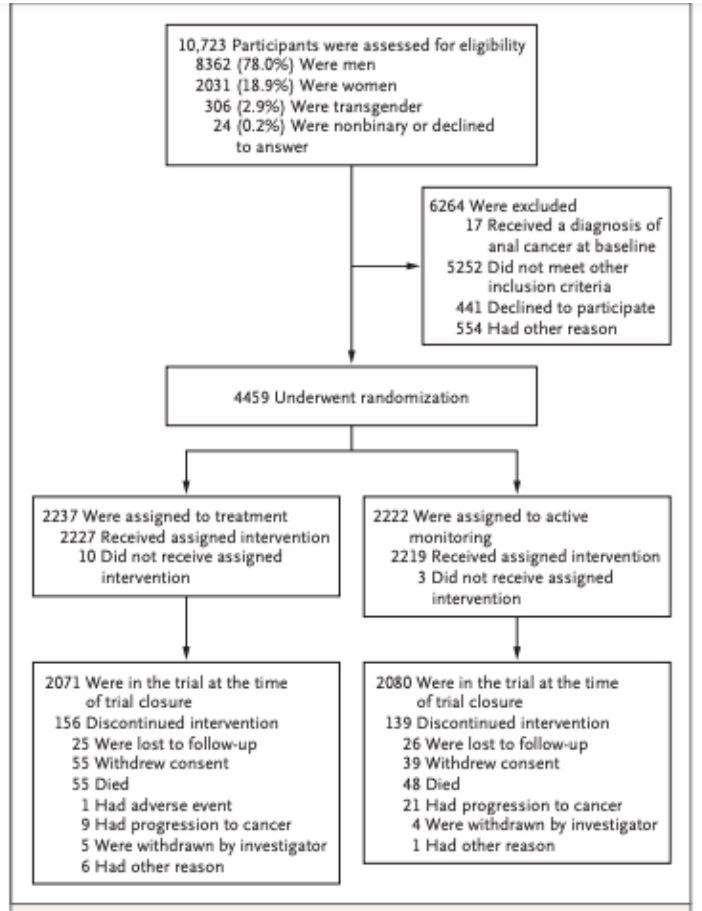


Figure 1. Screening, Randomization, and Follow-Up.
Of the six participants in the treatment group who discontinued the intervention for "other reason," two received a diagnosis of anal cancer but were ineligible for analysis and were discontinued from the trial because they were determined to have had anal cancer before randomization, three relocated to a nontrial site, and one received immunomodulatory agents after a kidney transplantation. Of the two participants in the active-monitoring group who discontinued the intervention for "other reason," both relocated to a nontrial site. A total of 25 of 2219 participants (1.1%) in the active-monitoring group were considered to be nonadherent because they had received treatment for anal high-grade squamous intraepithelial lesions at some time after randomization.

How to treat biopsy-confirmed aHSIL

- Treatment of anal HSIL is not standardized and is guided by available local resources and expertise
- No robust direct comparisons between different treatment options
- treatments achieve similar results
- recurrence remains problematic in high-risk populations
- Removal of the entire anal transformation zone would be a prohibitively morbid procedure
- Ablative methods
- infrared coagulation (IRC), electrocautery treatment (EC), or CO2 laser therapy
- Topical methods
- Imiquimod
- 5-fluorouracil (5-FU)

Barroso II et al al, Clin Infect Dis, 2022

Effectiveness of adjuvant HPV vaccination in AIN in Men LWH?

Age, Mean + SD : 49.3 ± 9.5

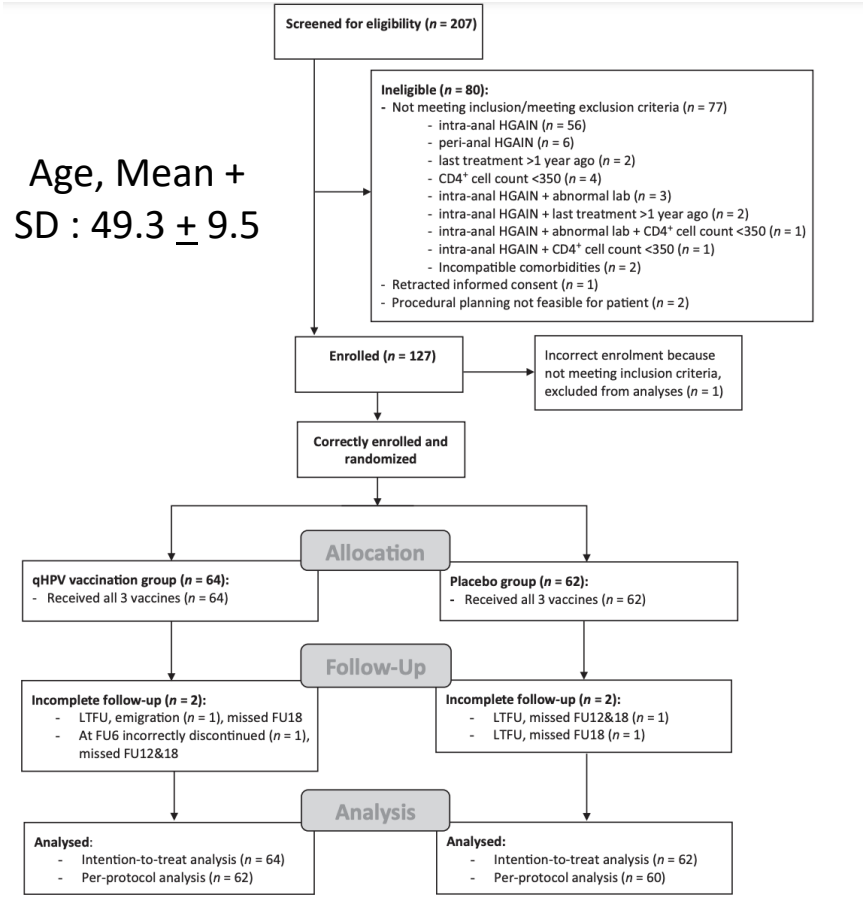
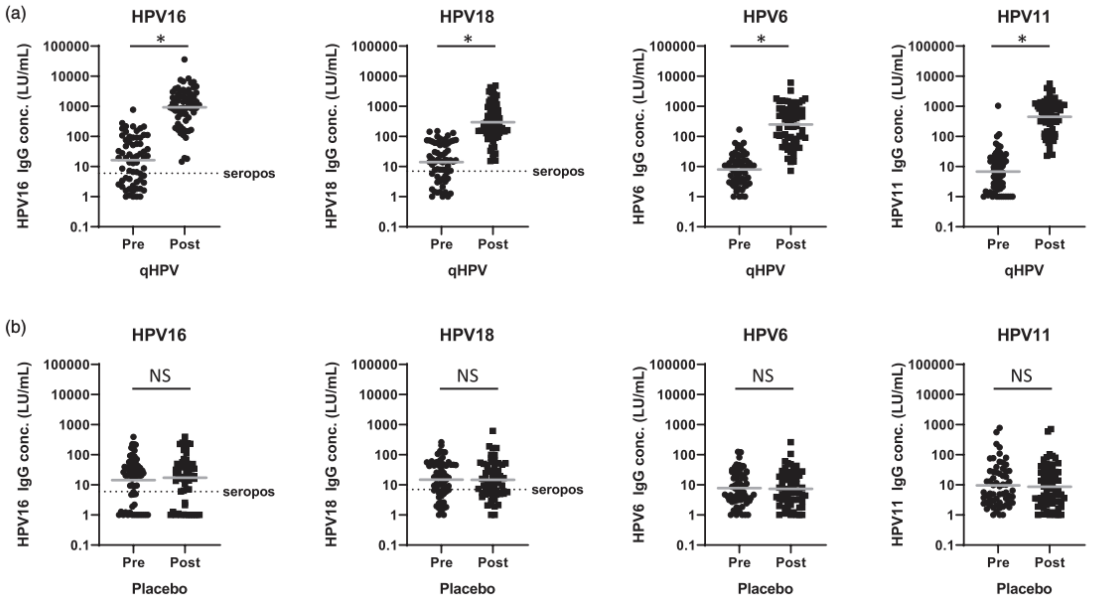
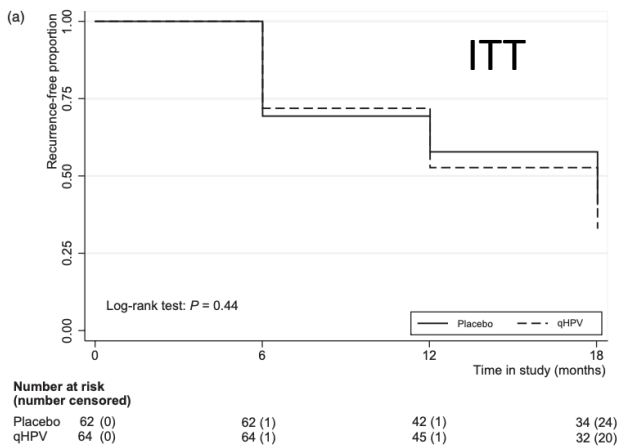
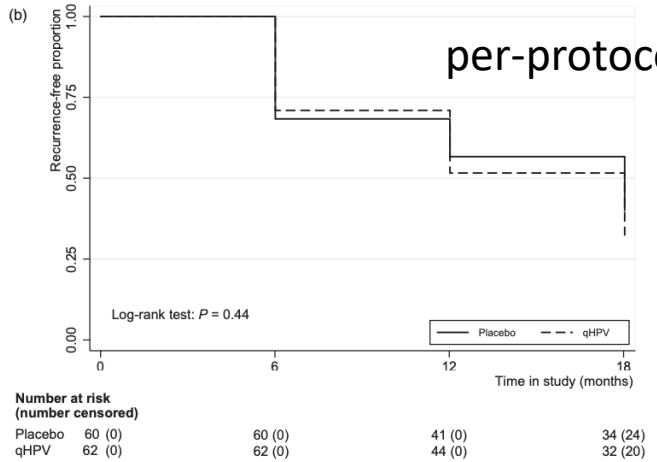


Fig. 1. Trial profile. FU, follow-up; HGAIN, high-grade anal intraepithelial neoplasia; LTFU, lost to follow-up; qHPV, quadrivalent human papillomavirus vaccine.



Proportion of participants free of recurrent high-grade anal intraepithelial neoplasia





Gosens, AIDS, 2021

Tertiary prevention: DARE (Digital And Rectal Examination)

DARE: low cost and readily available exam

- should be offered to all patients undergoing anal cancer screening
- can be offered as tertiary prevention when HRA is unavailable
- is an integral part of every HRA exam as it supplements the information gained from cytology and biopsy

Barroso II et al al, Clin Infect Dis, 2022

Conclusions

- HPV-related aSCC disproportionately affects MSM LWH

- multifactorial: role of behaviour, reduced HPV clearance, immunity

- likely to increase in the near future (aging population)

- Primary prevention through vaccination is most effective in younger age (prior to sexual debut)

- Secondary prevention lacks standardized approaches (screening and treatment)

- HIV-uninfected MSM also represent a risk group for aSCC (albeit lower incidence): possible future surge in cases?

- condomless sex (PrEP)

- vaccination after sexual debut

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