



VPH y cáncer anal. Es hora de priorizar el cribado en poblaciones especiales

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AGENDA

- Clinical case
- HPV infection and cancer genesis
- “The post-ANCHOR era”
- Key population for anal cancer screening (without considering HPV infection)
- Priority risk groups within the key population for anal cancer screening
- Take home messages

Clinical case

- ❑ J.M is a **49 year-old MSM**, resident in Brasil, **current smoker**, cocaine and cannabis.
 - HIV infection, 1987
 - Nadir 52 cel/μL.**

- ❑ EVG/c + FTC/TAF + DRV.
 - HIV-VL: < 40 cop/mL y TCD4+: 445 cells/μL.

06

Basal Anal Cytology LSIL

- HPV genotype: **11, 16, 33, 52, 58, 59**

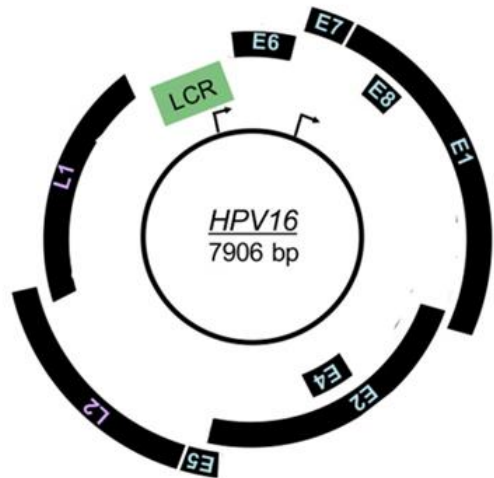


Table 1: Comparison of Cytological and Histological Classification of Anal Dysplasia	
Bethesda Classification System (2014) (describes cytology obtained at anal Pap)	
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells, high-grade squamous intraepithelial lesion (HSIL) cannot be excluded
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
Cancer	—
Anal Intraepithelial Lesion (or neoplasia [AIN]) (describes histology obtained at biopsy)	
Atypia	—
AIN I	Low-grade anal intraepithelial neoplasia
AIN II	Moderate-grade anal intraepithelial neoplasia; may be a low-grade or high-grade lesion
AIN III	High-grade anal intraepithelial neoplasia
CIS	Carcinoma in situ
Cancer	—

NY State Dep. Of Health AIDS Institute

<https://www.hivguidelines.org/hiv-care/anal-dysplasia-cancer/>

HPV genotypes, tropism and associated diseases



EARLY REGION: proteins necessary for viral replication

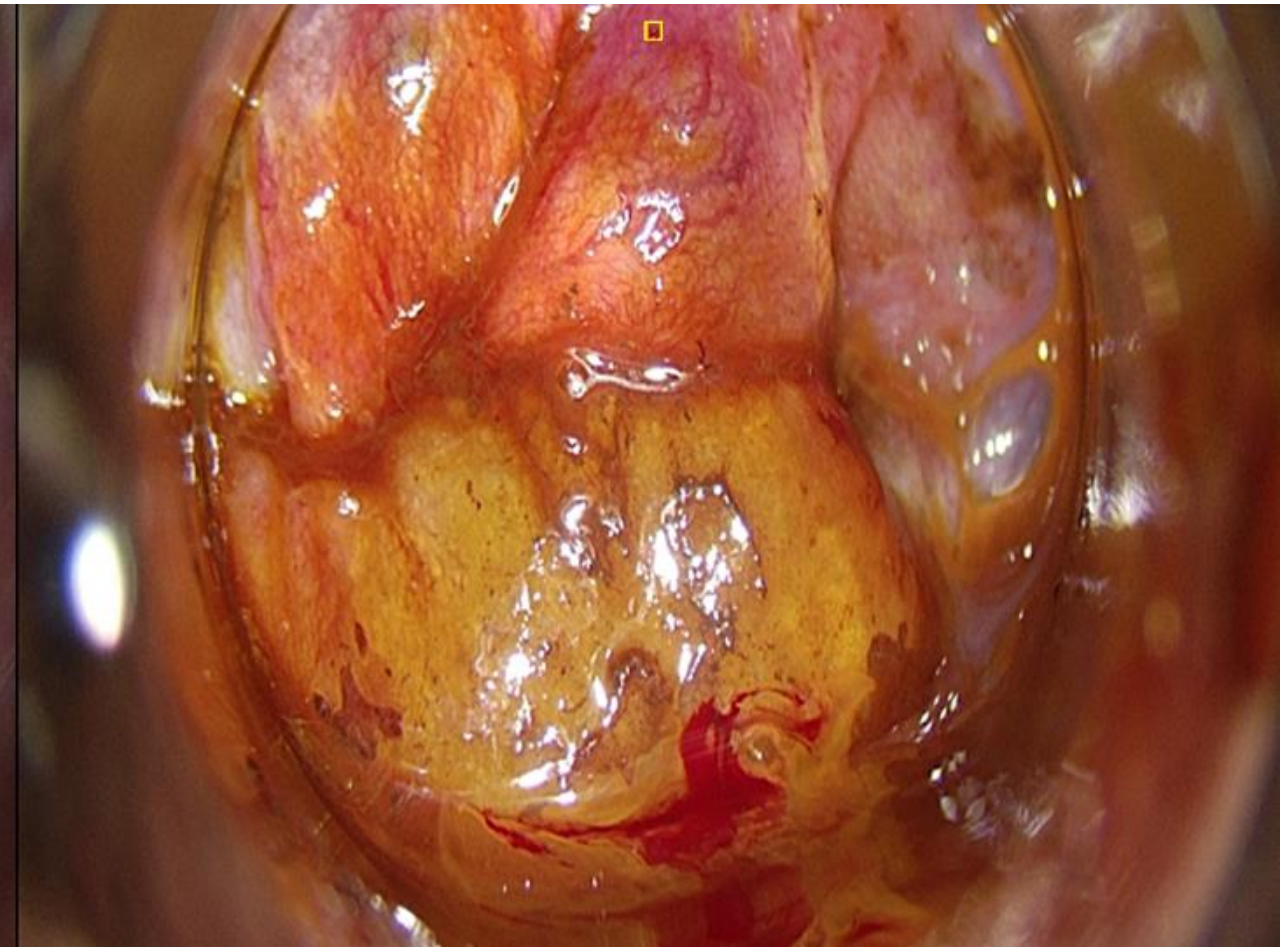
LATE REGION: viral capsid proteins

LONG CONTROL REGION: sequences controlling viral replication & transcription

ORF	HPV16 PROTEIN FUNCTION
E1	origin binding protein, ATPase-dependent helicase involved in genome replication
E2	regulator of viral gene transcription, association with E1 (origin binding), viral genome partitioning
E4	expressed abundantly as E1 ⁺ E4 fusion protein, cytokeratin network destabilization, virus release and transmission
E5	small transmembrane protein, interacts with EGF receptor activating mitogenic pathways
E6	drives cell cycle allowing genome amplification in upper epithelial layers, association with E6AP and degradation of p53, PDZ-protein binding, hTert activation
E7	drives cell cycle allowing genome amplification in upper epithelial layers, association with and degradation of pRB, mitotic mutator
E8	expressed as E8 ⁺ E2 fusion protein, acts as a repressor of transcription and replication during the viral life cycle
L1	major capsid protein, assembles into pentameric capsids forming the icosahedral virion (prophylactic vaccines)
L2	minor capsid protein, involved in viral DNA encapsidation, facilitates viral entry and trafficking

Genus	Species	Representative HPV types	Tropism	Associated Diseases
Alpha-PV	α1	32	mucosal	Heck's disease
	α2	3, 10, 28	cutaneous	flat warts
	α4	2, 27, 57	cutaneous	common warts
	α7	18, 39, 45, 59, 68	mucosal	intraepithelial neoplasia, invasive carcinoma
	α9	16, 31, 33, 35, 52, 58	mucosal	intraepithelial neoplasia, invasive carcinoma
			13	
Beta-PV	β1c	5, 8, 12, 14, 19, 20, 21, 24, 25, 36, 47	cutaneous	Epidermodysplasia verruciformis
	β2	9, 15, 17, 22, 23, 37, 38	cutaneous	Epidermodysplasia verruciformis
	β3	49	cutaneous	Epidermodysplasia verruciformis
Gamma-PV	γ1	4, 65	cutaneous	Warts
	γ4	60	cutaneous	Warts
Mu-PV	μ1	1	cutaneous	plantar warts
	μ2	63	cutaneous	Warts
Nu-PV	v	41	cutaneous	Warts

Clinical case



Clinical case

09

Anal Cytology HSIL

10

Anal Cytology HSIL

11

Anal Cytology LSIL

12

Anal Cytology HSIL

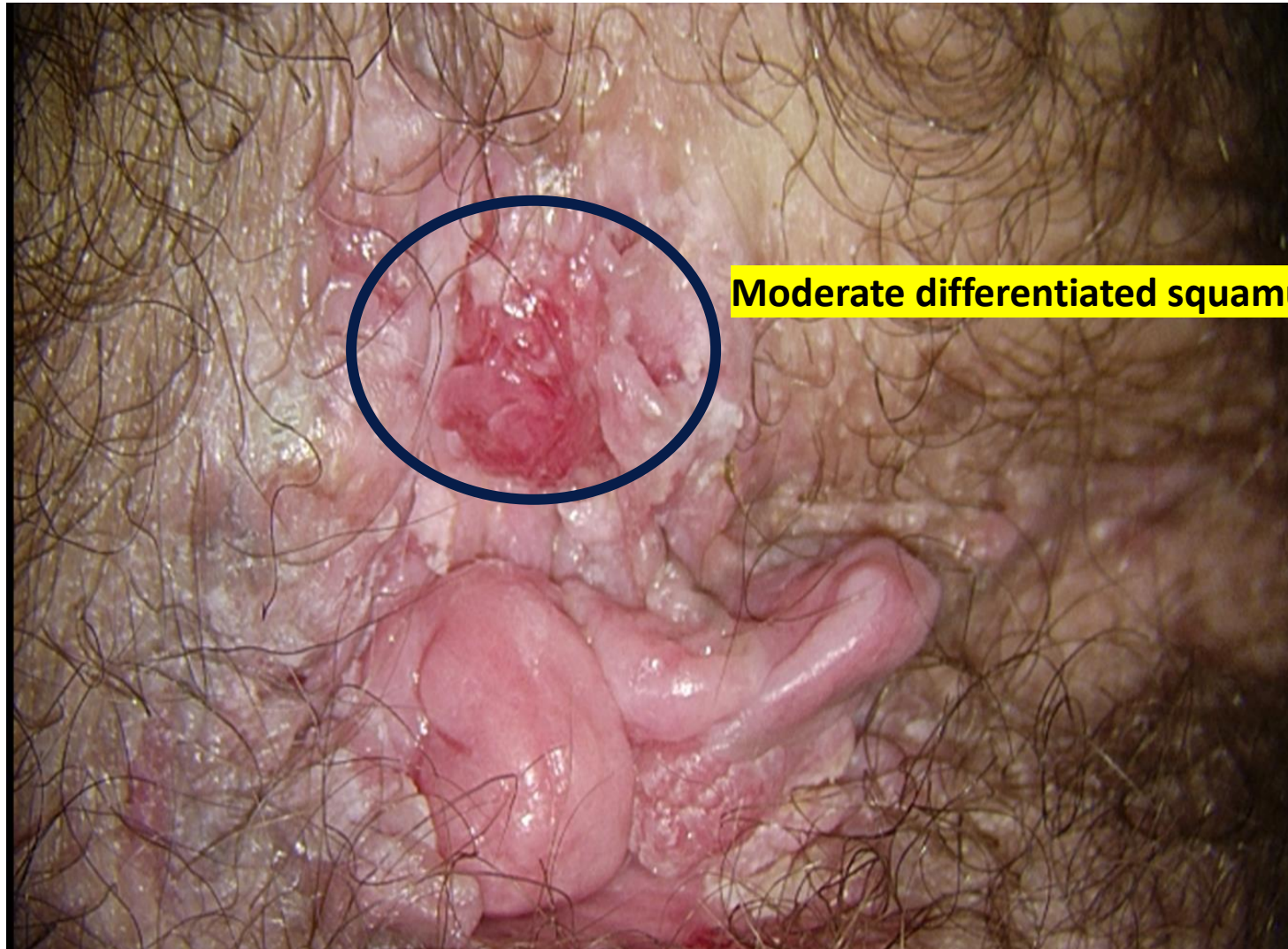
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Anal Cytology LSIL



Surgical treatment of Internal Hemorrhoids (Private Hospital) Squamous cell carcinoma (IASCC)

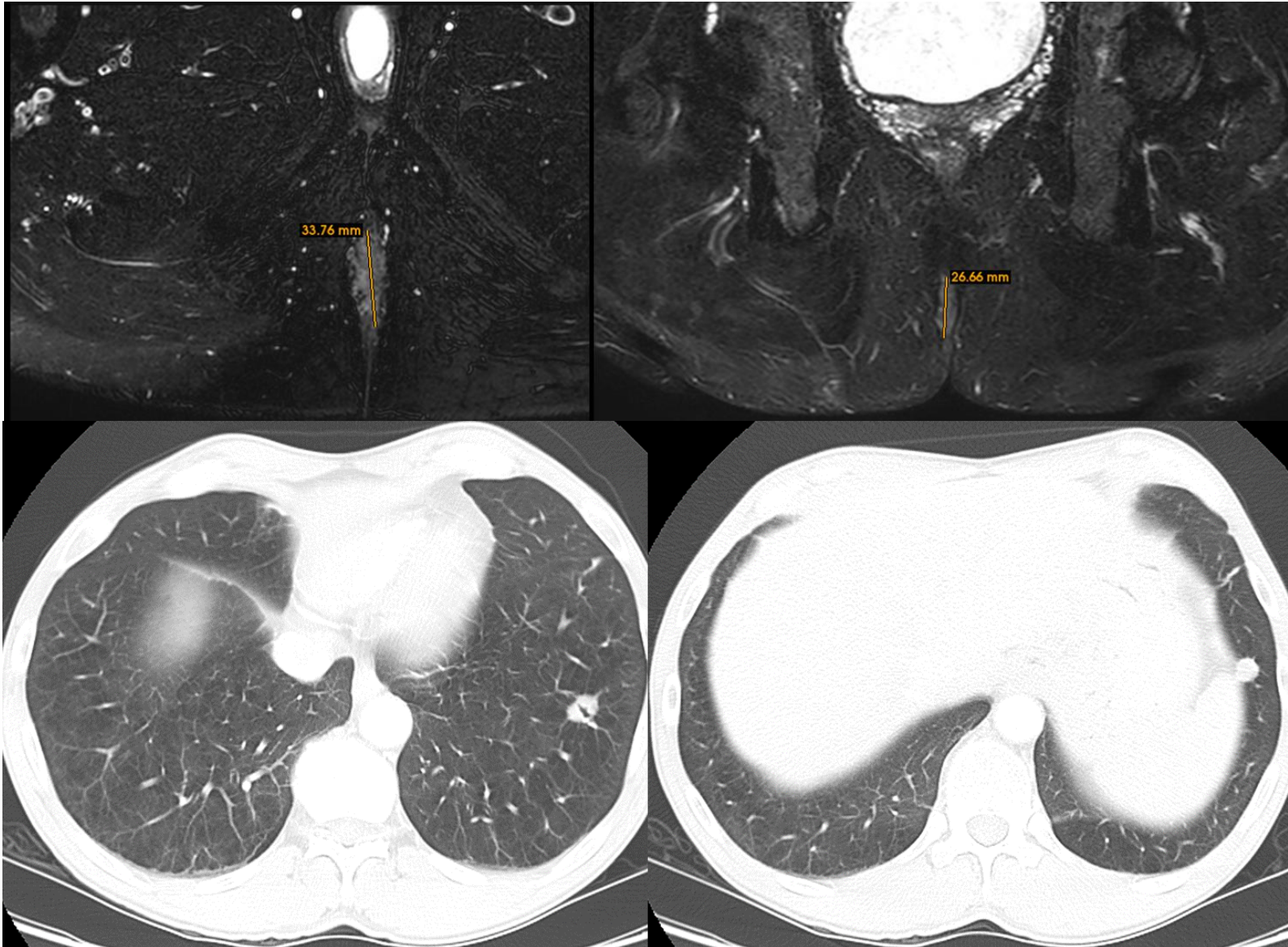
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Moderate differentiated squamous cell carcinoma

Clinical case

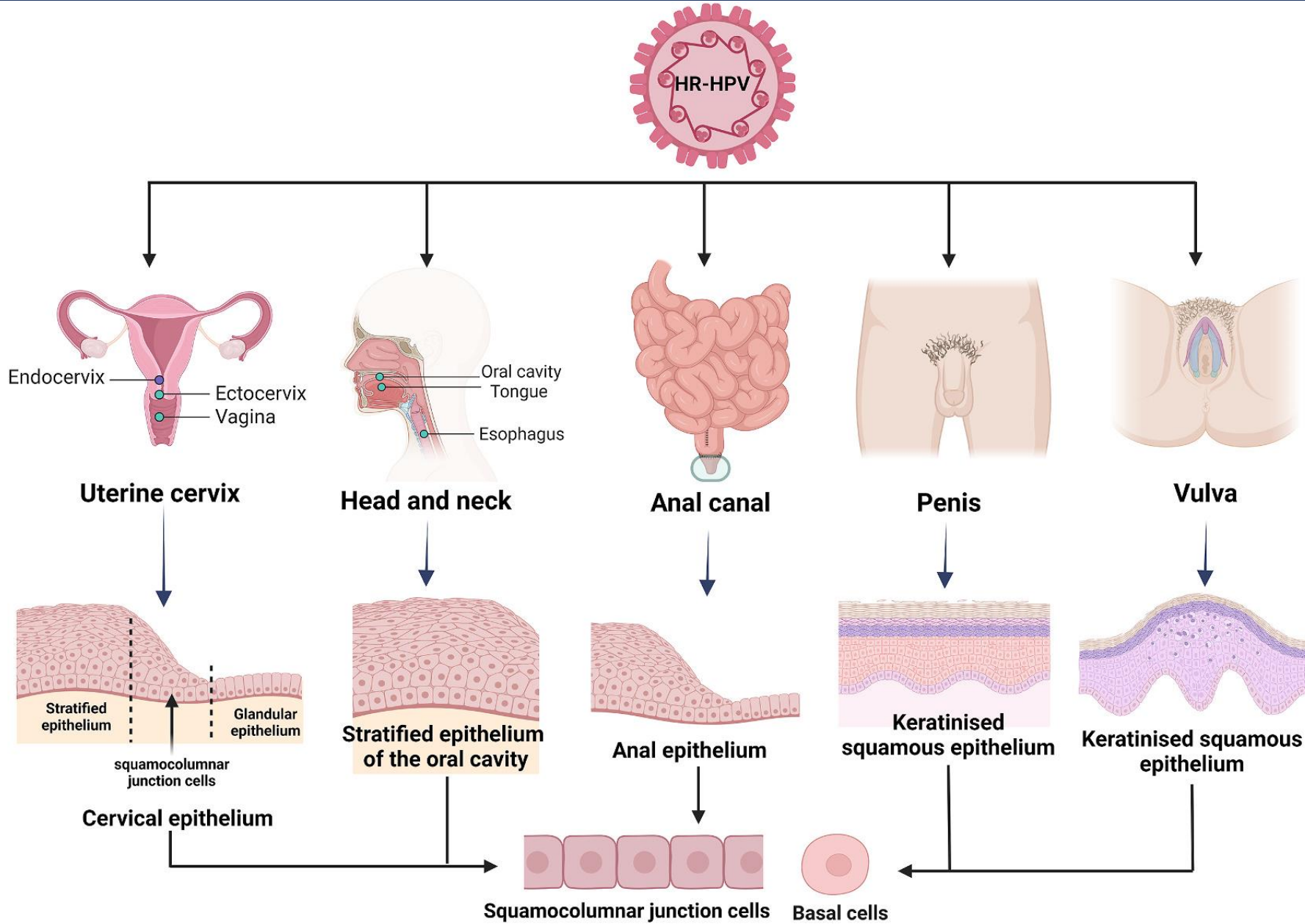
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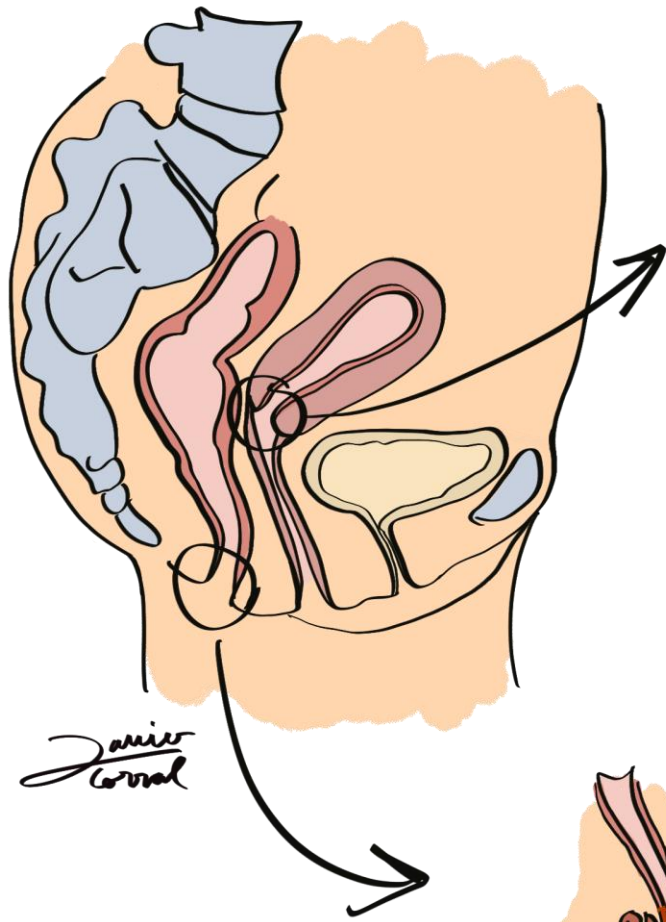


□ HIV infection
(Nadir 52 cel/ μ L)

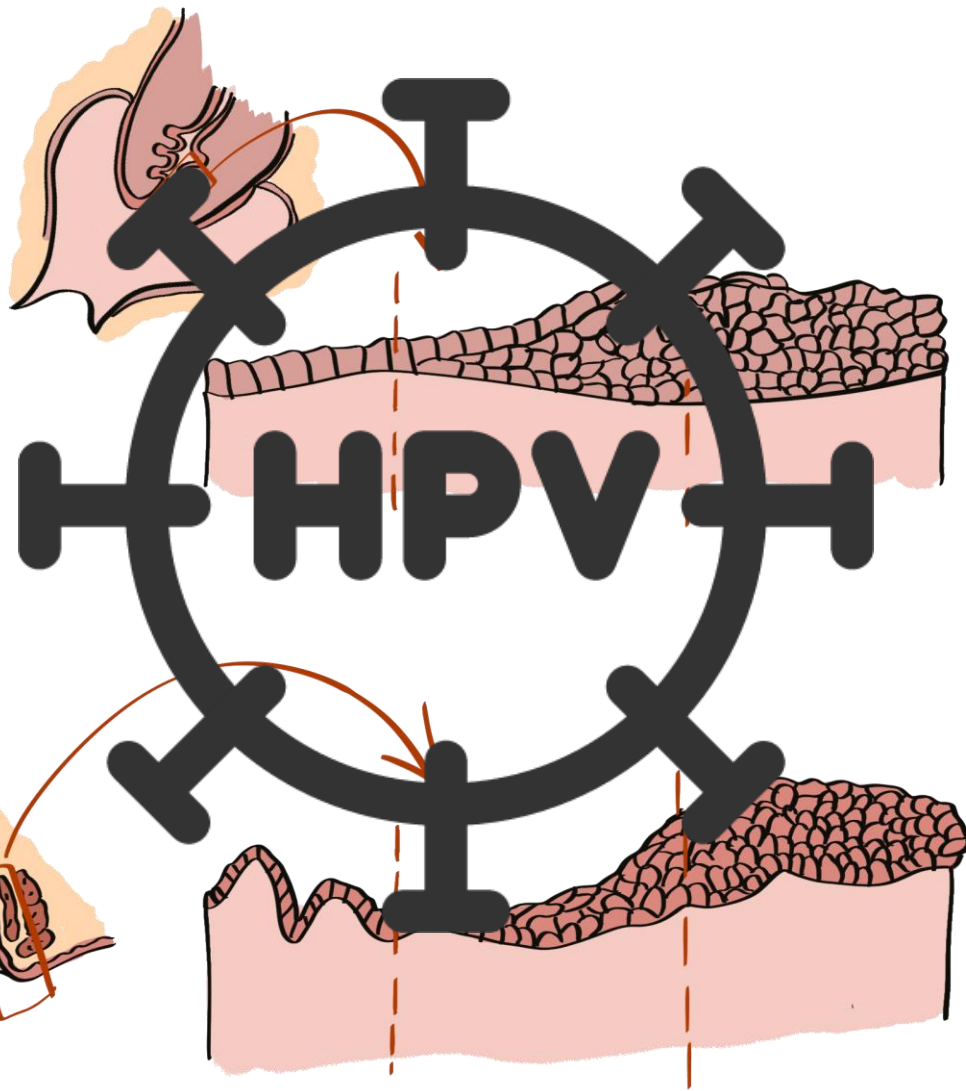
□ Anal cancer
T2N1AM1 (IV)

HR-HPV genotypes and cancer





Jaime Corral



CERVICAL
100%

ANAL
90%

Infecciones

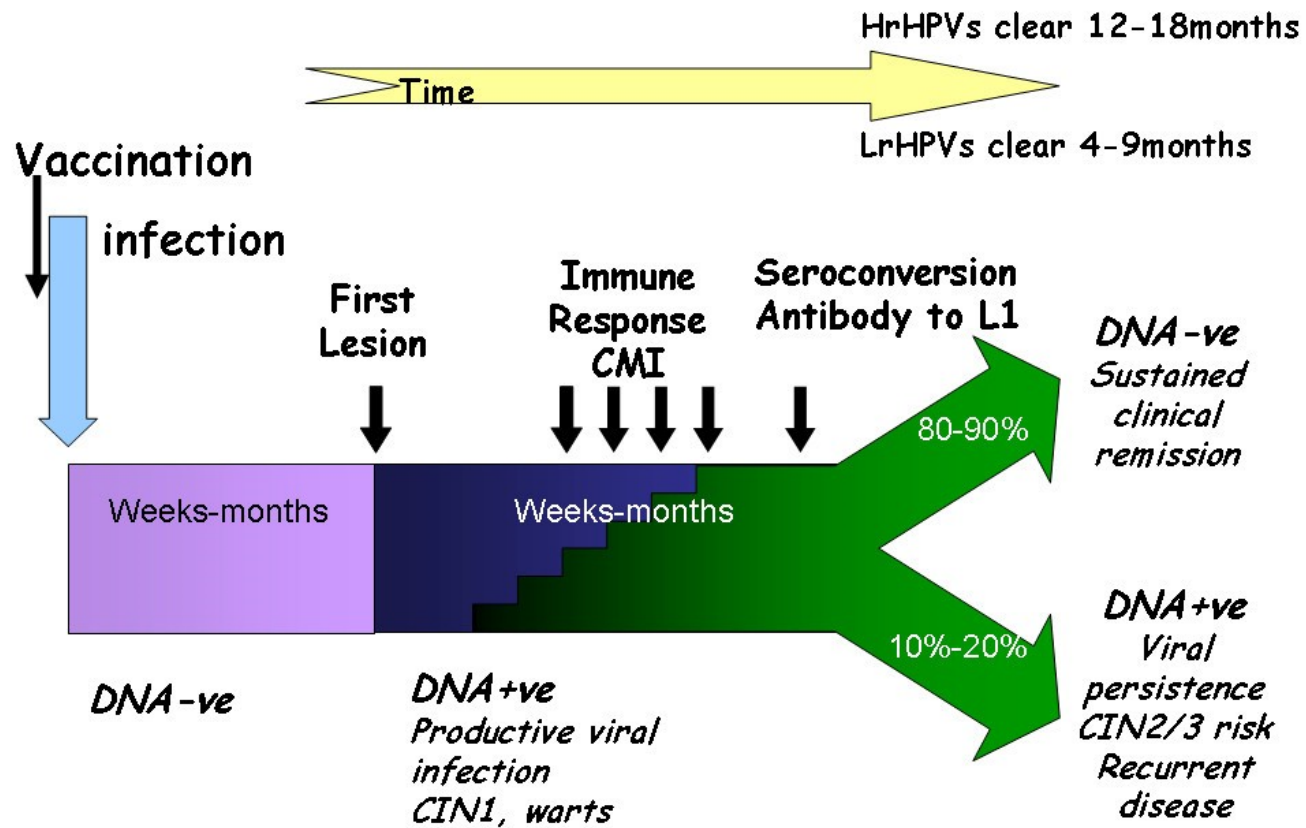


Cáncer

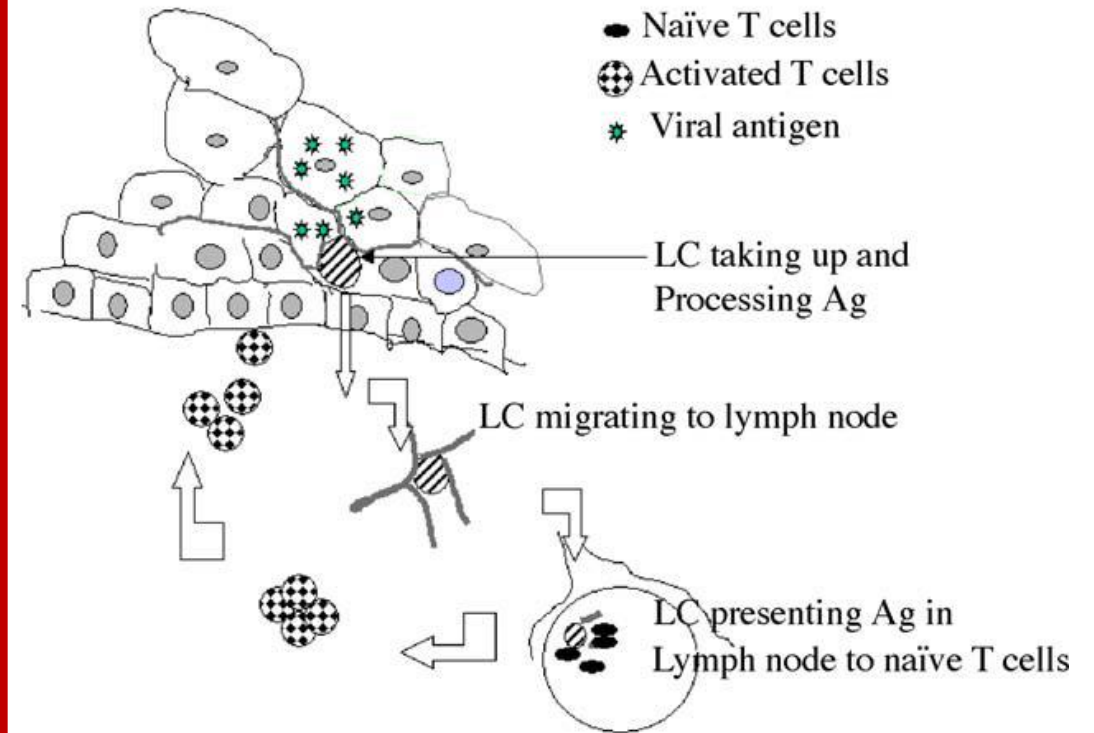
HPV Infection

*HPVs infections are very common and it is estimated that 50-80% of sexually active men and women will acquire a genital HPV (both high and low risk) in their lives

Natural Course of Genital HPV Infection

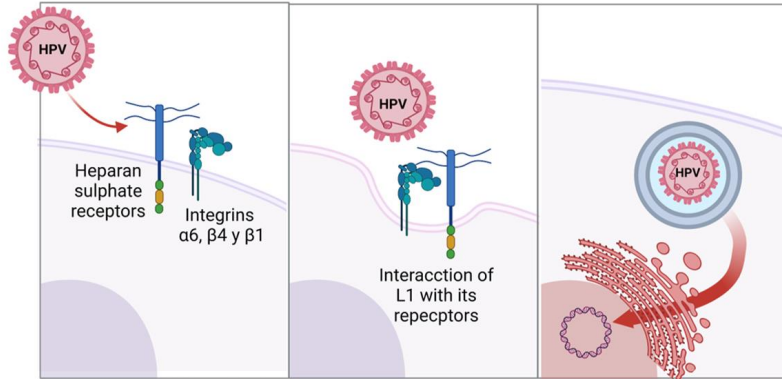


Antigen processing and presentation by Langerhans cells

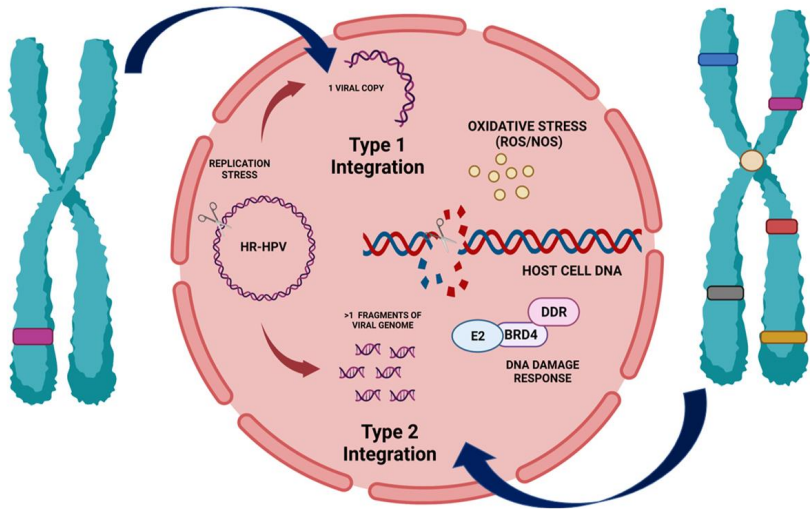


HR-HPV genotypes and cancer

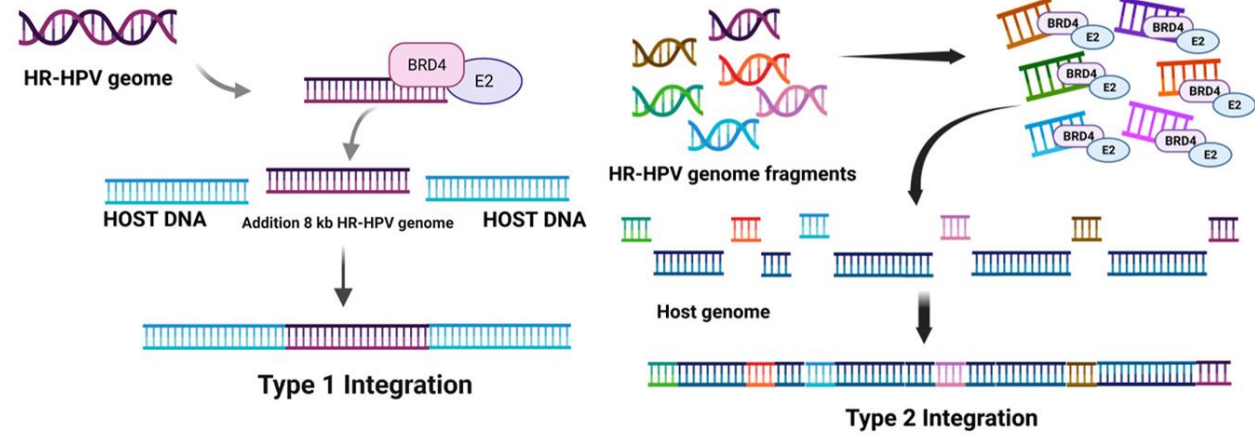
A) INTERNALIZATION OF HR-HPV



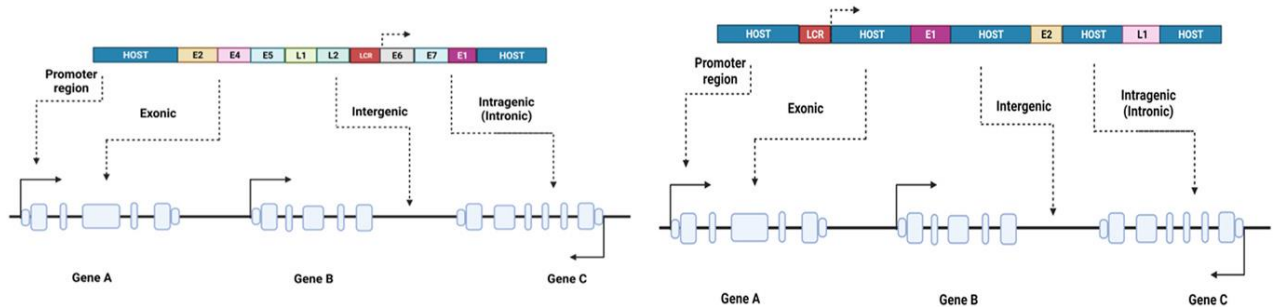
B) FACTORS PROMOTING INTEGRATION



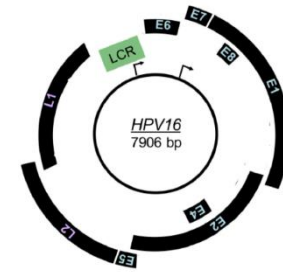
C) HR-HPV INTEGRATION TYPES



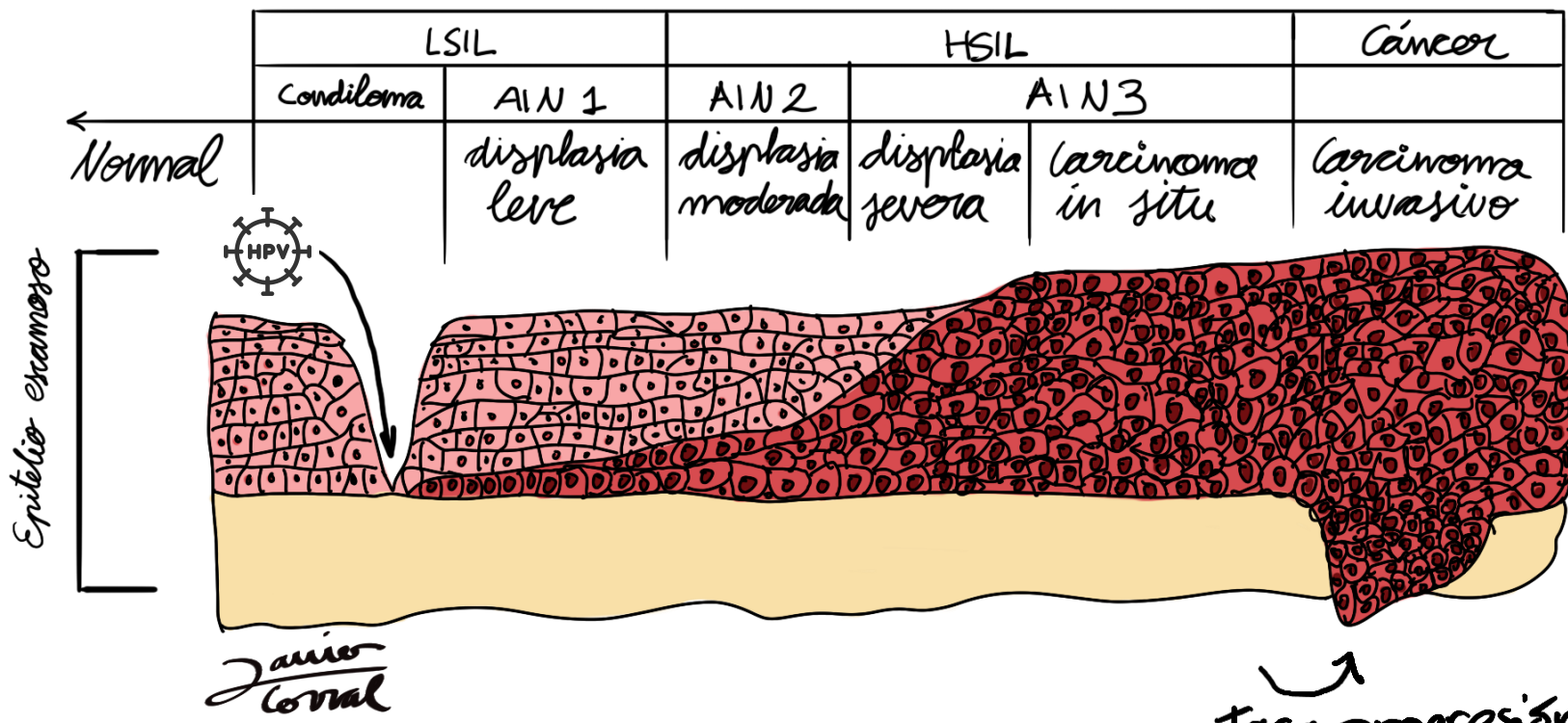
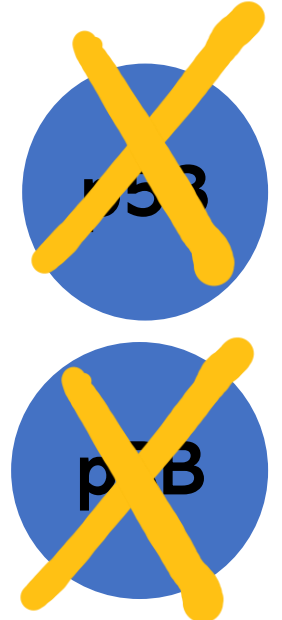
D) INTEGRATION SITES IN THE HOST GENOME



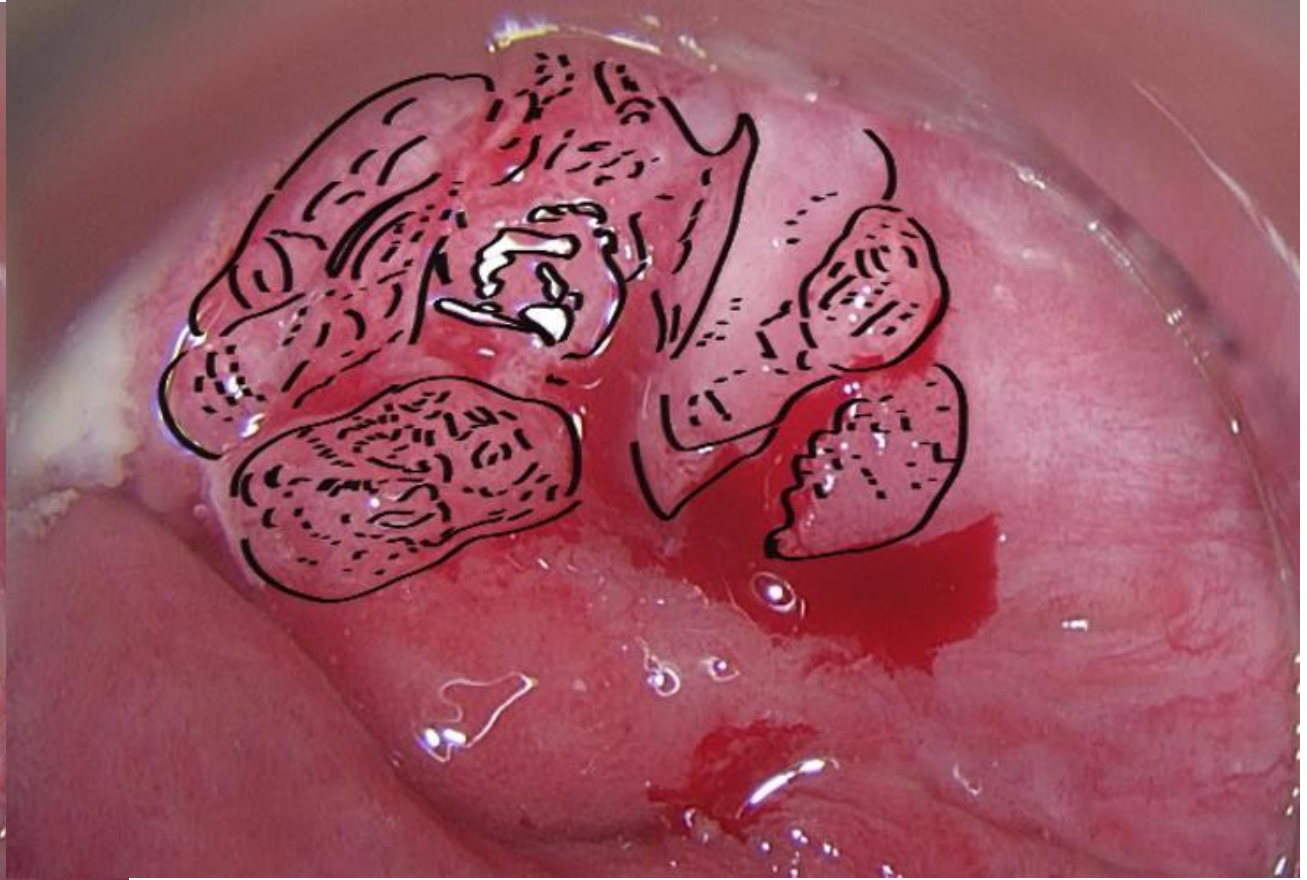
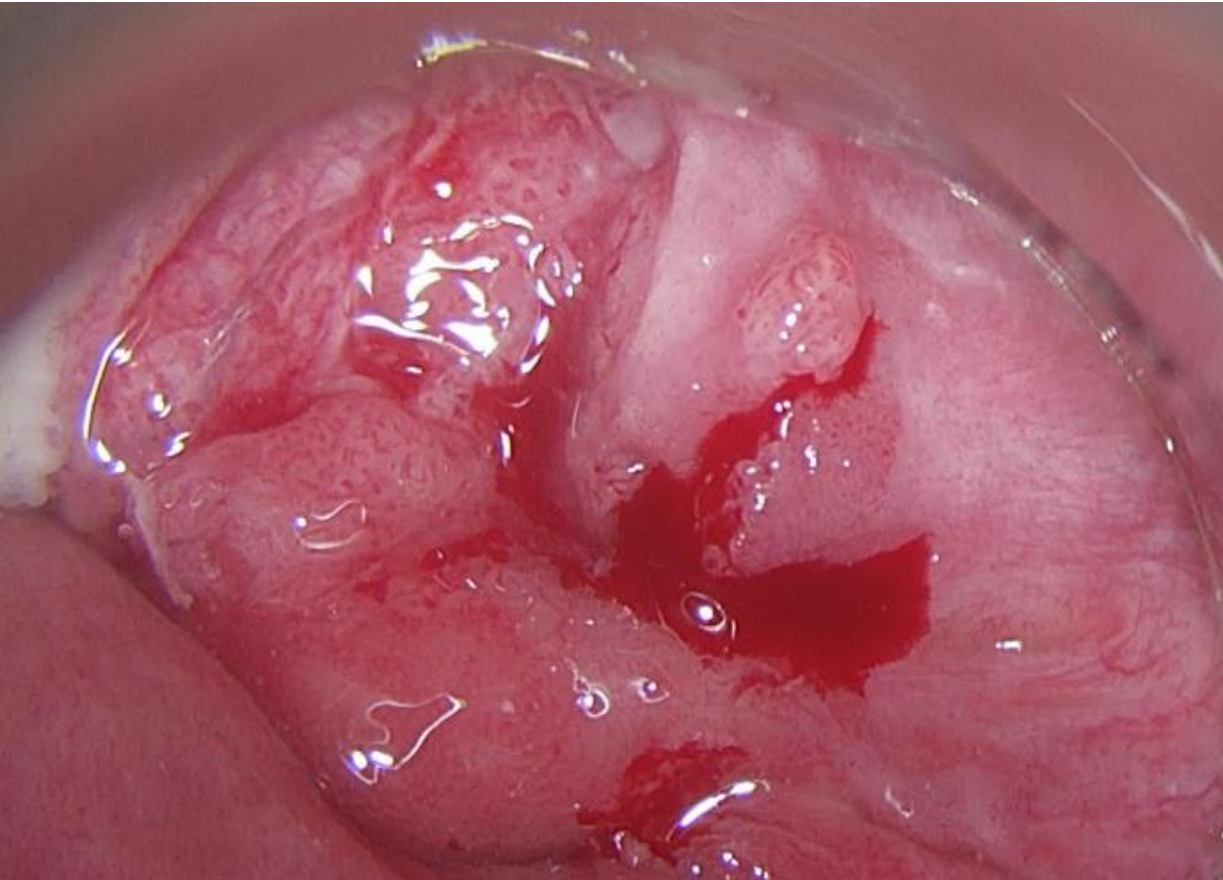
From anal dysplasia to cancer.



ORF	HPV16 PROTEIN FUNCTION
E1	origin binding protein, ATPase-dependent helicase involved in genome replication
E2	regulator of viral gene transcription, association with E1 (origin binding), viral genome partitioning
E4	expressed abundantly as E1^E4 fusion protein, cytokeratin network destabilization, virus release and transmission
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L1	major capsid protein, assembles into pentameric capsids forming the icosahedral virion (prophylactic vaccines)
L2	minor capsid protein, involved in viral DNA encapsidation, facilitates viral entry and trafficking



tasa progresión $\approx 2\%$ anual*
9,5 a 5 años



Risk of Invasive Anal Cancer in HIV-infected subjects With High-Grade Anal Dysplasia

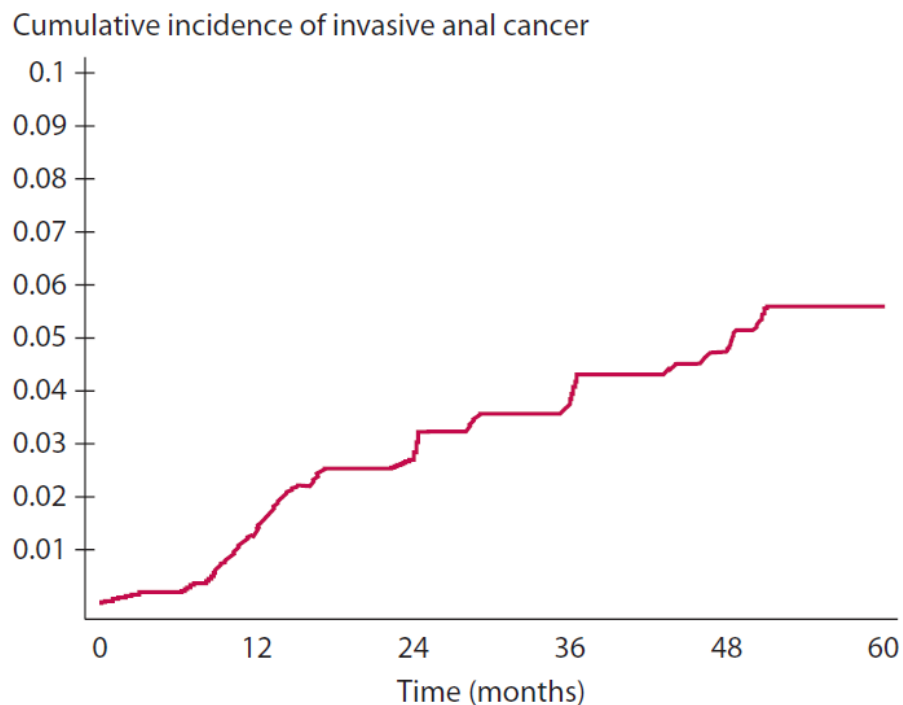


FIGURE 1. Cumulative incidence curve for invasive anal cancer among HIV-infected subjects with anal intraepithelial neoplasia grade III.

TABLE 2. Cumulative incidence of SCCA among those with baseline AIN III diagnosis, unadjusted

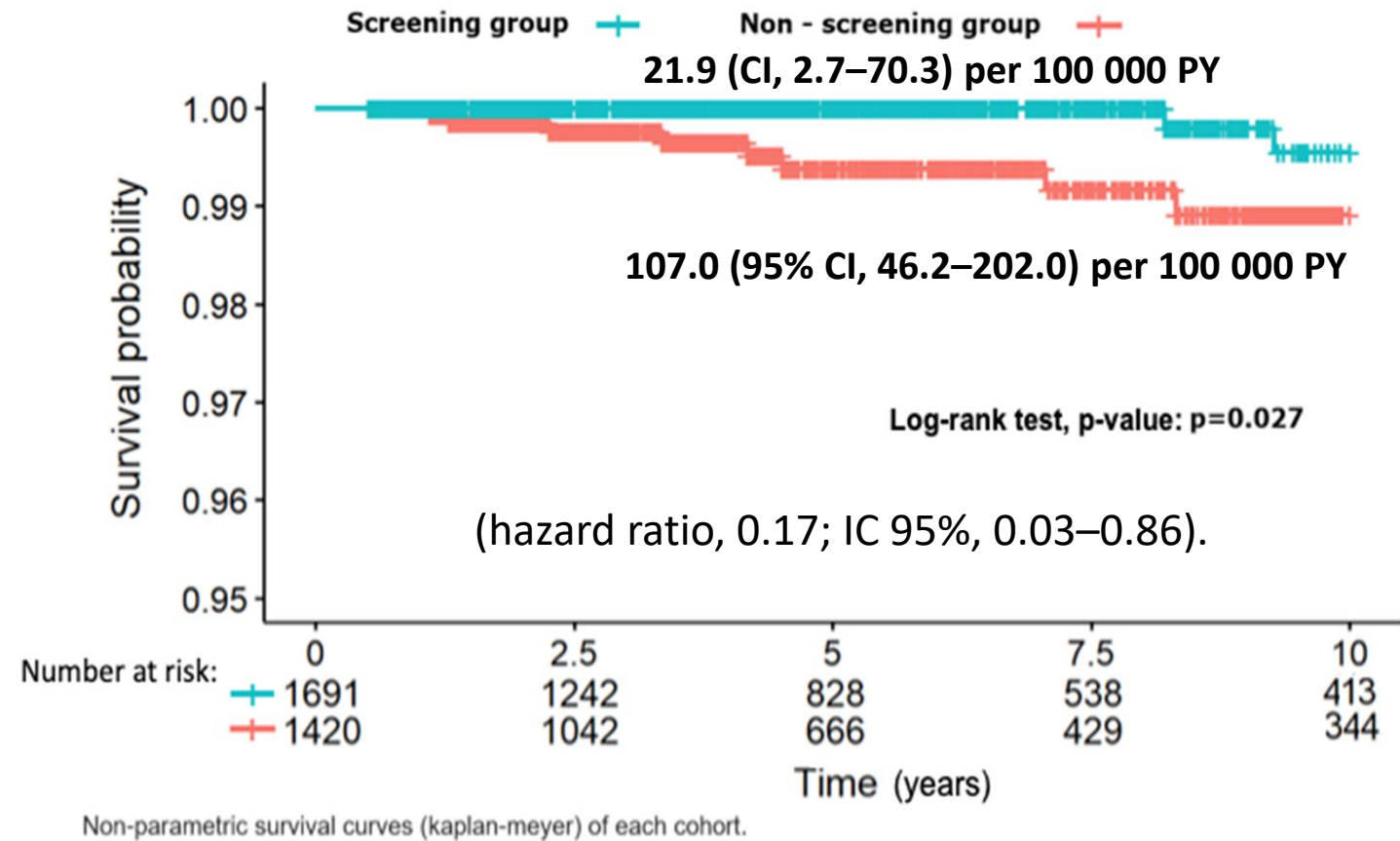
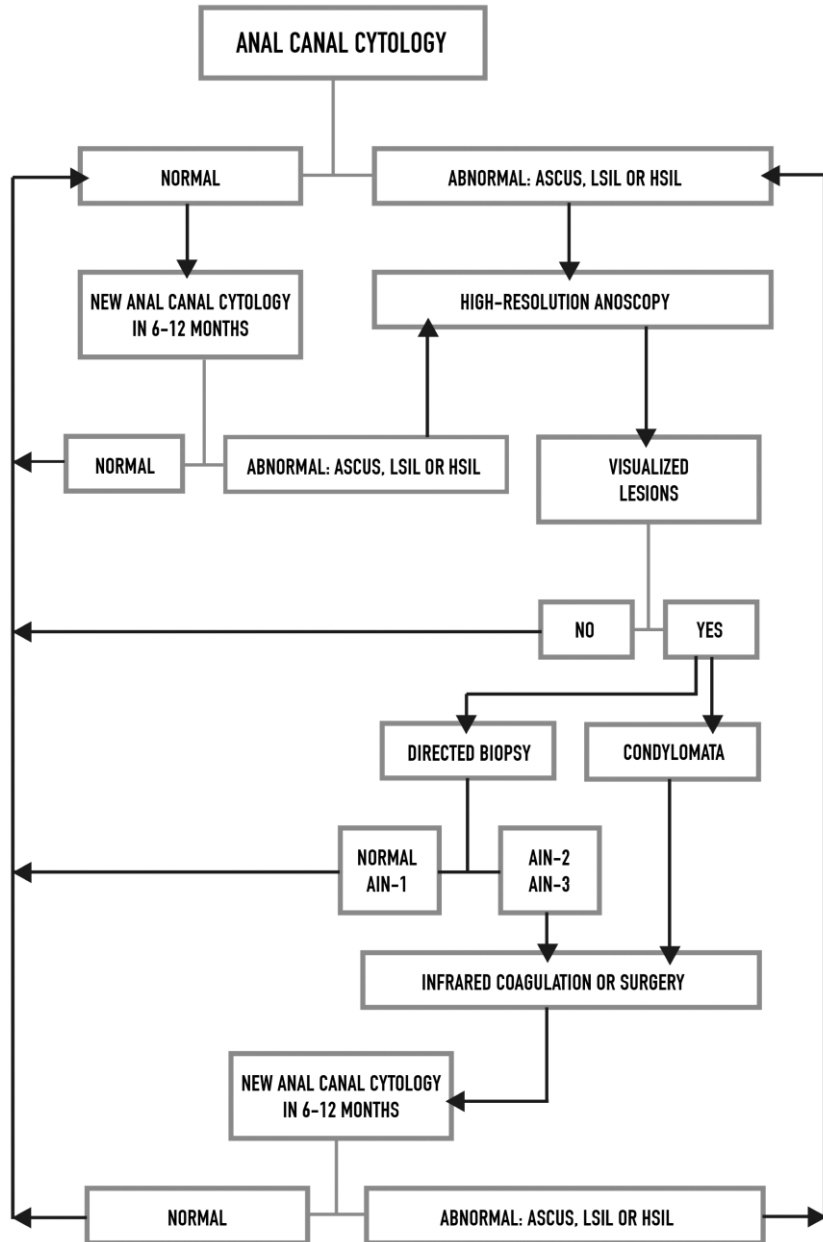
Time	Incidence, %	95% CI, %
12 months	1.2	0.7–2.5
24 months	2.6	1.6–4.3
36 months	3.7	2.4–5.6
60 months	5.7	4.0–8.1

AIN III = anal intraepithelial neoplasia, grade III; SCCA = squamous cell carcinoma of the anus.

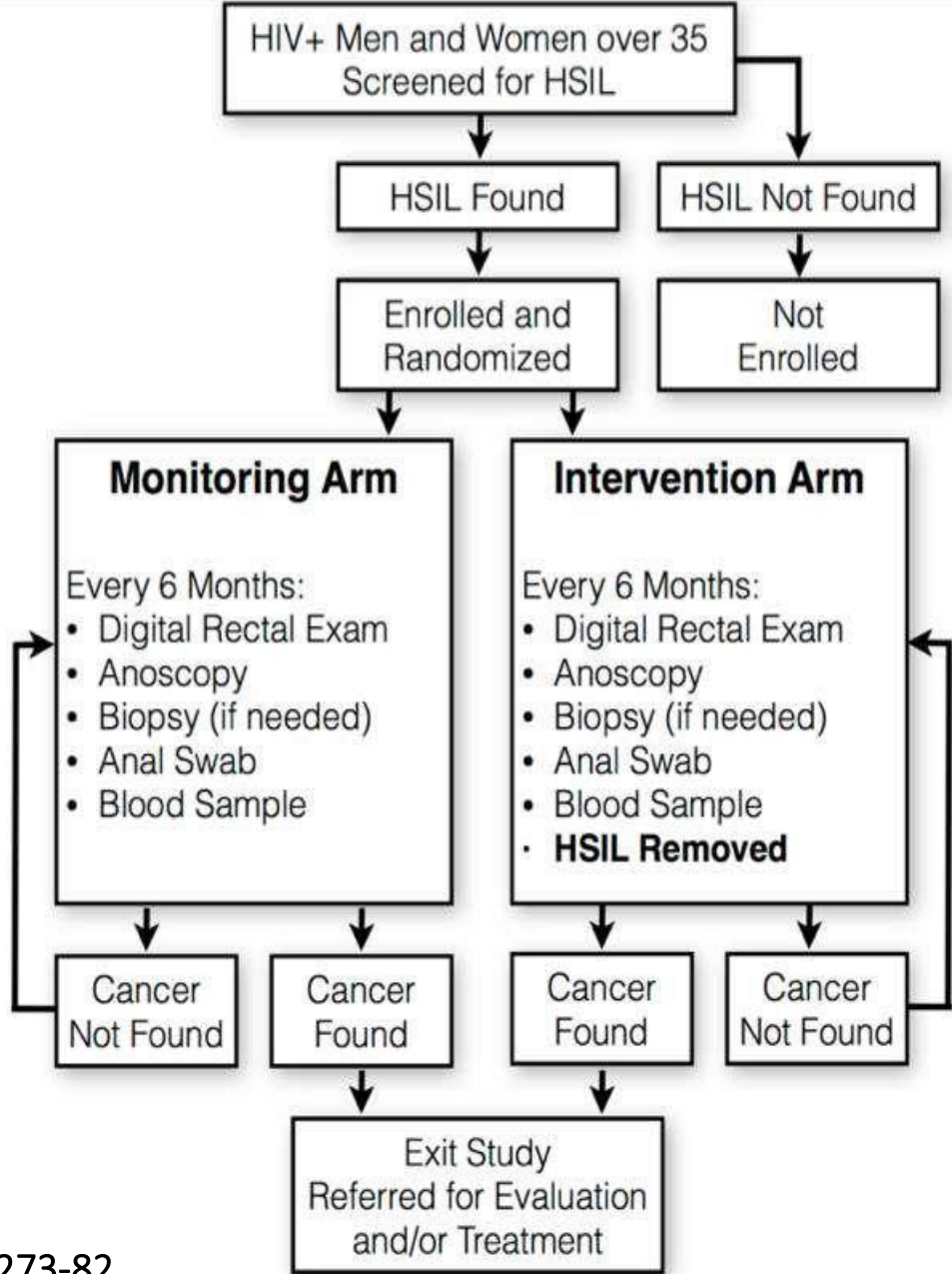
Anal dysplasia, treatment response...

Response	Participants or Lesions, % [95% CI] (No./Total No.)		Risk Difference (95% CI), %	P Value ^b
	IRC Treatment	AM Arm		
Overall CILC rate (primary end point)	62 [48–74] (37/60)	30 [19–43] (18/60)	32 (13–48)	<.001
Overall CILC/PILC rate	82 [70–90] (49/60)	47 [33–60] (28/60)	35 (16–50)	<.001
Reason for failure				
HSIL at index biopsy	25 [15–38] (15/60)	65 [52–77] (39/60)	–40 (–56 to –22)	<.001
Withdrawal (without prior HSIL)	8 [3–18] (5/60)	5 [1–14] (3/60)	...	
Not evaluable at pathology or biopsy refused	5 [1–14] (3/60)	0 [0–6] (0/60)	...	
Free of HSIL (index or metachronous) at 12-mo visit ^c	71 [56–83] (36/51)	28 [17–42] (16/57)	43 (22–59)	<.001
Incident metachronous lesions ^d	47 [33–61] (25/53)	21 [11–34] (12/57)	26 (6–43)	.004
Index lesion–level clearance	63 [52–74] (51/81 lesions)	42 [30–54] (41/97 lesions)001

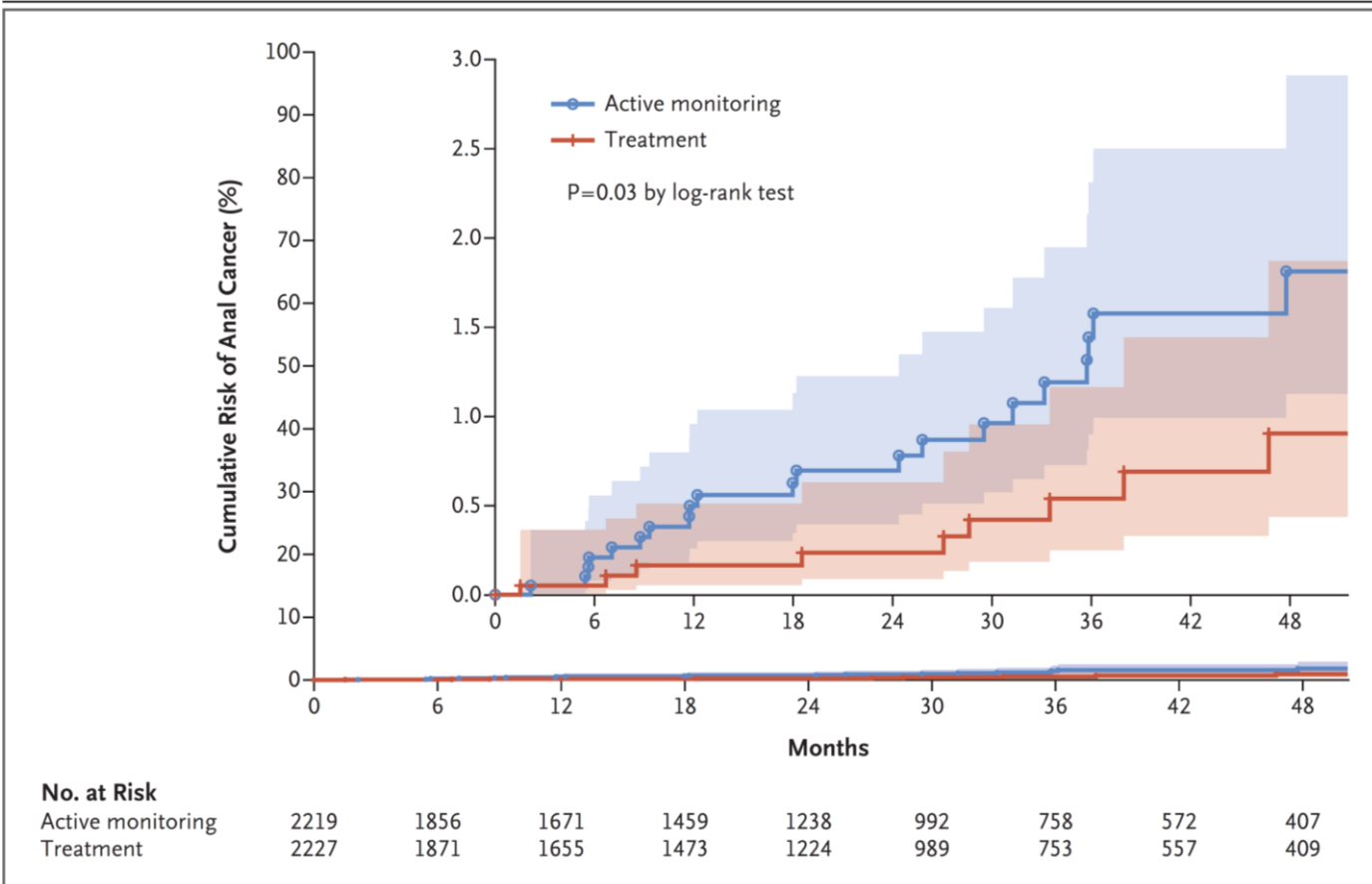
The Can Ruti Cohort



- Phase 3 trial at 25 U.S. sites.
- Treatment: office-based ablative procedures, ablation or excision under anesthesia, or the administration of topical fluorouracil or imiquimod.



The ANCHOR study – Outcomes



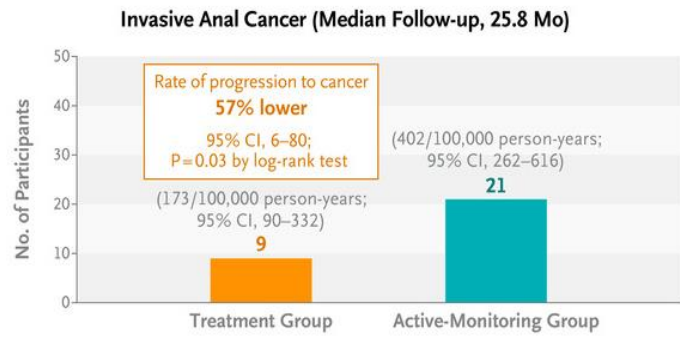
Rate of progression to cancer:

- 402 per 100,000 PY (95% CI, 262 to 616)
- 173 per 100,000 PY (95% CI, 90 to 332)

Cumulative incidence of progression to anal cancer at 48 months

- 1.8%
- 0.9%

- ❑ Electrocautery ablation 83.6%
- ❑ Infrared coagulation in 4.8%
- ❑ Ablation or excision under anesthesia 2.3%
- ❑ Topical fluorouracil /imiquimod 4.5% /0,5%



The ANCHOR – Supplementary Appendix

	Randomized population N=4,446	
	Treatment arm	Active monitoring arm
	N=2,227	N= 2,219
CD4 cells/uL at randomization (median, interquartile range) ⁸	602 (393-827)	607 (410-837)
Stratification factors at randomization N (%)		
Nadir CD4 cells/uL		
≤200 cells/uL	1130 (50.7)	1121 (50.5)
>200 cells/uL	1097 (49.3)	1098 (49.5)
HSIL size at screening		
>50% of anal canal/perianal region	285 (12.8)	282 (12.7)
≤50% of anal canal/perianal region	1942 (87.2)	1937(87.3)
HSIL size and nadir CD4 combination		
<i>HSIL size >50% of anal canal/perianal region</i>		
Nadir CD4 ≤200 cells/uL	165 (7.4)	163 (7.4)
Nadir CD4 >200 cells/uL	120 (5.4)	119 (5.4)
<i>HSIL size ≤50% of anal canal/perianal region</i>		
Nadir CD4 ≤200 cells/uL	965 (43.3)	958 (43.2)
Nadir CD4 >200 cells/uL	977 (43.9)	979 (44.1)

The proportional-hazards model showed that the time to progression to anal cancer was associated **with lesion size** (hazard ratio, 5.26; 95% CI, 2.54 to 10.87) **but not with nadir CD4 count** (hazard ratio, 1.93; 95% CI, 0.88 to 4.23).

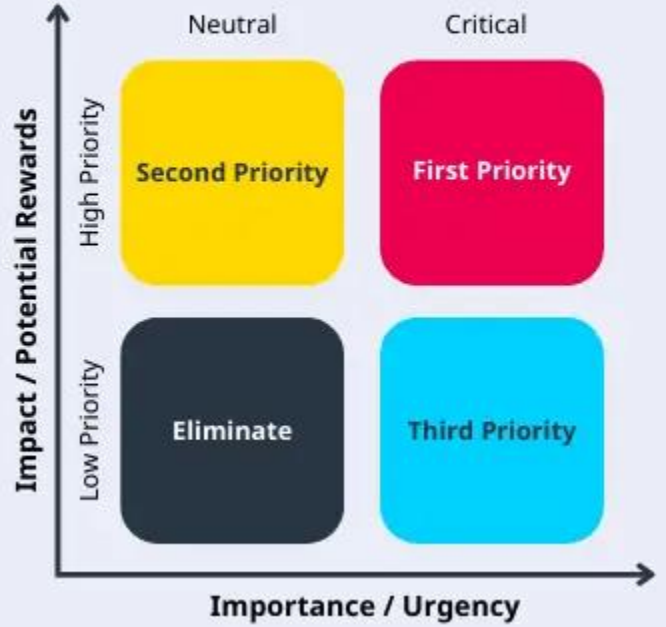
❑ **1047 per 100,000 person-years >50%**

❑ **185 per 100,000 person-years <50%**

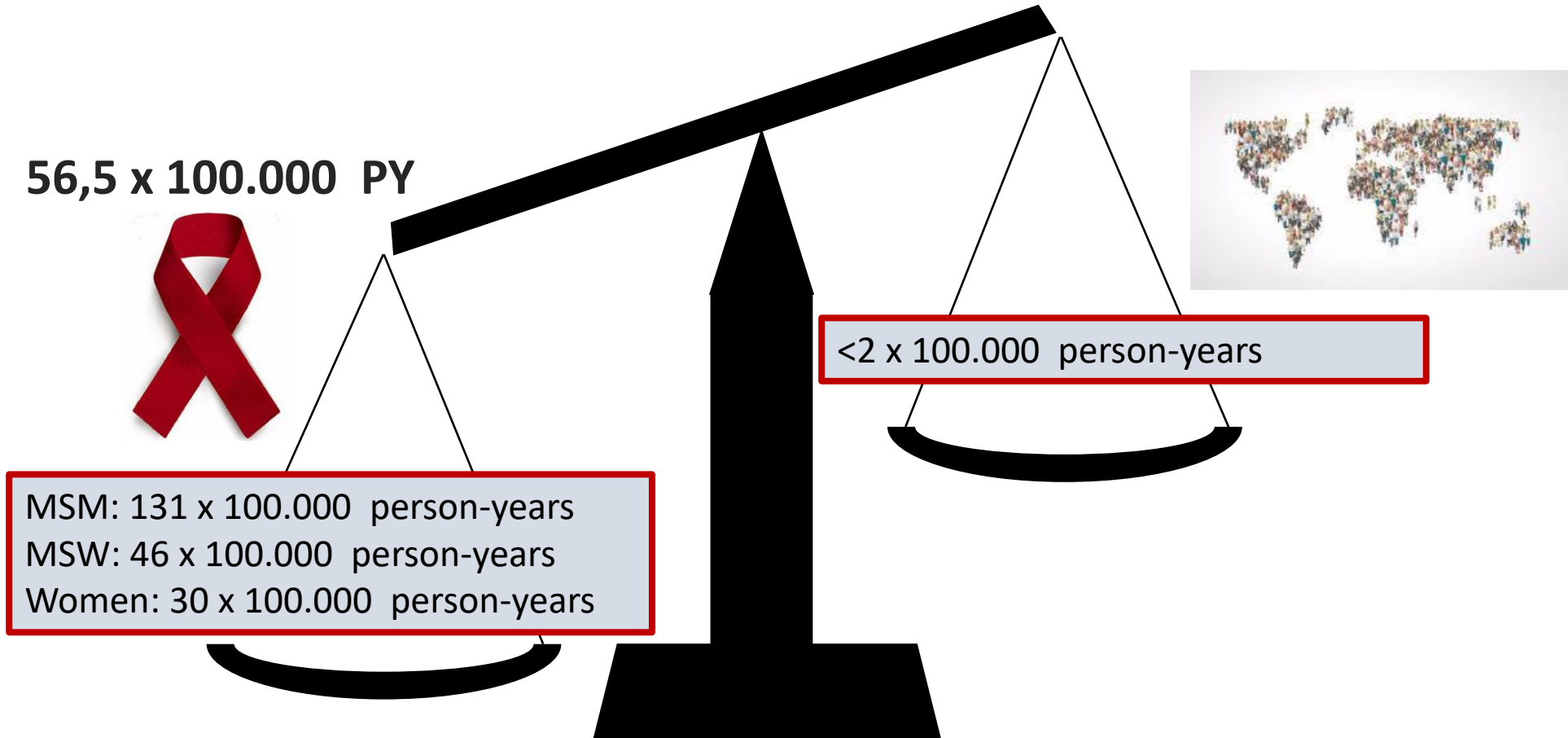
	Developed cancer N=30	Did not develop cancer N=4,416
≤200 cells/uL	21 (70.0)	2230 (50.5)
>200 cells/uL	9 (30.0)	2186 (49.5)
Lesion size at randomization N (%)		
>50% of anal canal/perianal region	13 (43.3)	554 (12.6)
≤50% of anal canal/perianal region	17 (56.7)	3862 (87.4)



Prioritization Matrix



Anal Cancer PLWH vs general population.

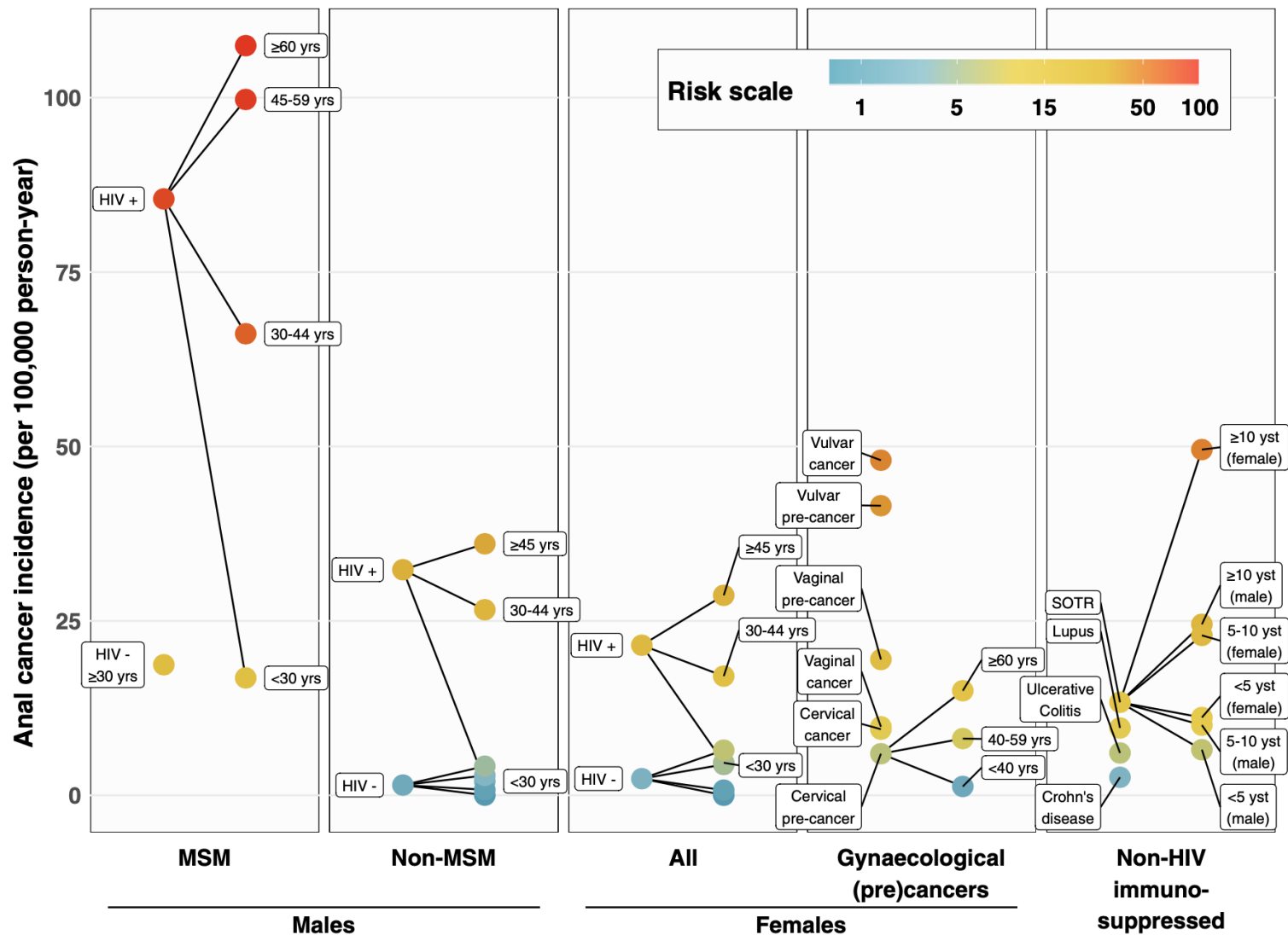


Koroukian et al, Cancer 2022;128(10):1987-1995

Mahale P, et al CID 2018; 67:50-57

Silvelberg MJ, et al. CID 2012; 7:1026-1034

Anal Cancer PLWH vs general population.



Progression risk to HGAIN in HIV+ MSM

Variables	Category or contrast	Cox proportional hazard ratios (57 events/4467 person-months)		Period prevalence logistic regression OR ^f (132 events/246 subjects)	
		No. of events/no. of person-months ^e	Age-adjusted OR (95% CI)	No. of events/no. of subjects ^e	Age-adjusted OR ^f (95% CI)
Age at baseline ^a	<40 Years	19/1485	1.0 (ref)	39/80	1.0 (ref)
	40–49 Years	28/1962	1.12 (.63–2.01)	66/113	2.17 (.94–5.03)
	≥50 Years	10/1020	0.79 (.37–1.70)	27/53	1.95 (.69–5.55)
Smoking status at baseline	Never	23/1477	1.0 (ref)	44/75	1.0 (ref)
	Former	18/1475	0.73 (.38–1.37)	41/77	0.93 (.34–2.57)
	Current	16/1516	0.64 (.33–1.23)	45/91	0.54 (.21–1.39)
Number of sexual partner in the previous year (reported at baseline)	<10	20/2147	1.0 (ref)	58/123	1.0 (ref)
	≥10	37/2320	1.85 (1.06–3.22)	73/121	2.18 (.98–4.85)
	Absolute CD4+ cell count, cells/mL ^b	>500	19/1768	1.0 (ref)	40/73
	200–500	30/2192	1.34 (.74–2.41)	59/116	0.75 (.31–1.80)
	<200	8/507	1.68 (.73–3.89)	31/56	1.60 (.54–4.70)
CD4+ cell count at beginning of current HAART, cells/mL	≥350	21/1657	1.0 (ref)	40/79	1.0 (ref)
	200–349	12/1169	0.82 (.40–1.68)	33/64	0.79 (.29–2.14)
	50–199	13/1200	0.89 (.44–1.80)	32/68	0.59 (.23–1.52)
	<50	5/148	3.44 (1.28–9.22)	14/16	6.31 (.69–57.53)
Duration of HAART (categorical)	Linear, per year	NA	0.97 (.84–1.12)	NA	0.88 (.72–1.07)
	<4 Years	31/2192	1.0 (ref)	114/205	1.0 (ref)
	≥4 Years	25/2244	0.78 (.45–1.33)	17/40	0.38 (.13–1.09)
Time since HIV diagnosis	Linear, per year	NA	0.99 (0.94–1.04)	NA	0.99 (0.92–1.06)
Baseline HIV load, copies/mL	<50	33/2384	1.0 (ref)	76/136	1.0 (ref)
	≥50	24/2083	0.79 (0.47–1.35)	53/107	1.03 (0.48–2.19)
HPV infection ^c					
HR HPV	Positive vs negative	55/3559	6.67 (1.62–27.42)	125/219	9.91 (3.09–31.78)
No. of HR HPV types	Linear	NA	1.39 (1.21–1.61)	NA	1.25 (1.06–1.48)
Multiple HR HPV	Positive vs negative	49/2595	4.59 (2.17–9.71)	118/198	8.09 (2.96–22.12)
HPV 16	Positive vs negative	26/1106	2.76 (1.63–4.69)	78/121	5.91 (2.39–14.60)
HPV 18	Positive vs negative	19/872	2.11 (1.20–3.73)	49/73	3.66 (1.45–9.20)
HR type other than HPV 16/18	Positive vs negative	15/1673	0.59 (0.33–1.07)	29/67	0.38 (0.16–.90)
	A10	29/2392	0.82 (0.48–1.40)	89/162	1.27 (0.57–2.82)
	A8	5/198	1.81 (0.71–4.61)	17/30	1.32 (.42–4.15)
	A1	18/1183	1.29 (0.73–2.28)	46/89	1.14 (0.52–2.50)
	A13	9/496	1.33 (0.64–2.78)	33/55	4.78 (1.56–14.61)
	A11	12/650	1.64 (0.85–3.16)	35/61	1.71 (0.69–4.28)
Alpha species ^d	A9	45/2470	3.19 (1.68–6.04)	117/196	10.52 (3.73–29.64)
	A7	42/2750	1.73 (0.96–3.14)	98/180	1.91 (0.82–4.43)
	A5	22/952	2.37 (1.37–4.09)	57/91	2.34 (1.03–5.31)
	A6	27/1897	1.19 (0.71–2.01)	64/128	1.75 (0.77–3.97)
	A15	0/71	ND	3/10	0.17 (0.03–.95)
	A3	30/2387	0.91 (0.54–1.53)	83/168	0.96 (0.43–2.18)

The Can Ruti Cohort

Table 3. Characteristics of Persons With Human Immunodeficiency Virus-1 Participating in the Study Diagnosed With Invasive Anal Squamous-cell Carcinoma

	Enrolled in the Screening Program (n = 2)				Not Enrolled in the Screening Program (n = 8)					
Age at IASCC, years	48	50	41	43	46	51	58	46	41	50
Symptoms at IASCC diagnosis	Hemorrhoids, anal pain	Anorectal mass	Anal Pain	No data	Anal pain	Anal pain, rectal bleeding	Rectal bleeding	Anal pain, rectal bleeding	No data	Anal pain
Length of follow-up in the cohort at cancer diagnosis, years	8.1	4.5	1.4	3.4	4.2	4.5	2.1	7.0	2.3	8.4
TNM stage	T1-2NxM0	T2N1M0	T2NxM0	T2NxM0	T2N2M0	T4N2M0	T2NxM0	T3N0M0	T2-3NxM0	T2N0M0
Sexual practice	MSM	MSM	Woman, HTSX	Woman, HTSX	MSW	MSW	MSM	MSM	MSM	MSM
Time with HIV, years	24	27	16	20	15	17	7	25	14	29
CD4 nadir, cells/ μ L	17	137	21	11	44	6	No data	115	41	109
CD4 at IASCC, cells/ μ L	317	806	107	No data	44	10	1418	366	349	555
HIV-RNA at IASCC, copies/mL	84	<40	<40	No data	1400	<40	<40	<40	140	<40
Basal anal cytology (year)	Normal	Normal	Not done	Not done	Not done	HSIL	Not done	Not done	Not done	Not done
Anal cytologies performed, ^a n	9	4	0	0	0	0	0	0	0	0
Worst cytological diagnosis and HRA result	LSIL, normal	ASCUS, normal	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
HPV genotypes at cytology sample	16, 33, 39	16, 59	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
At biopsy sample	Not done	Not done	39	Not done	Not done	Not done	16, 18, 56	Not done	Not done	Not done
Life status, final	Alive	Alive	Dead	Alive	Dead	Dead	Dead	Alive	Alive	Dead

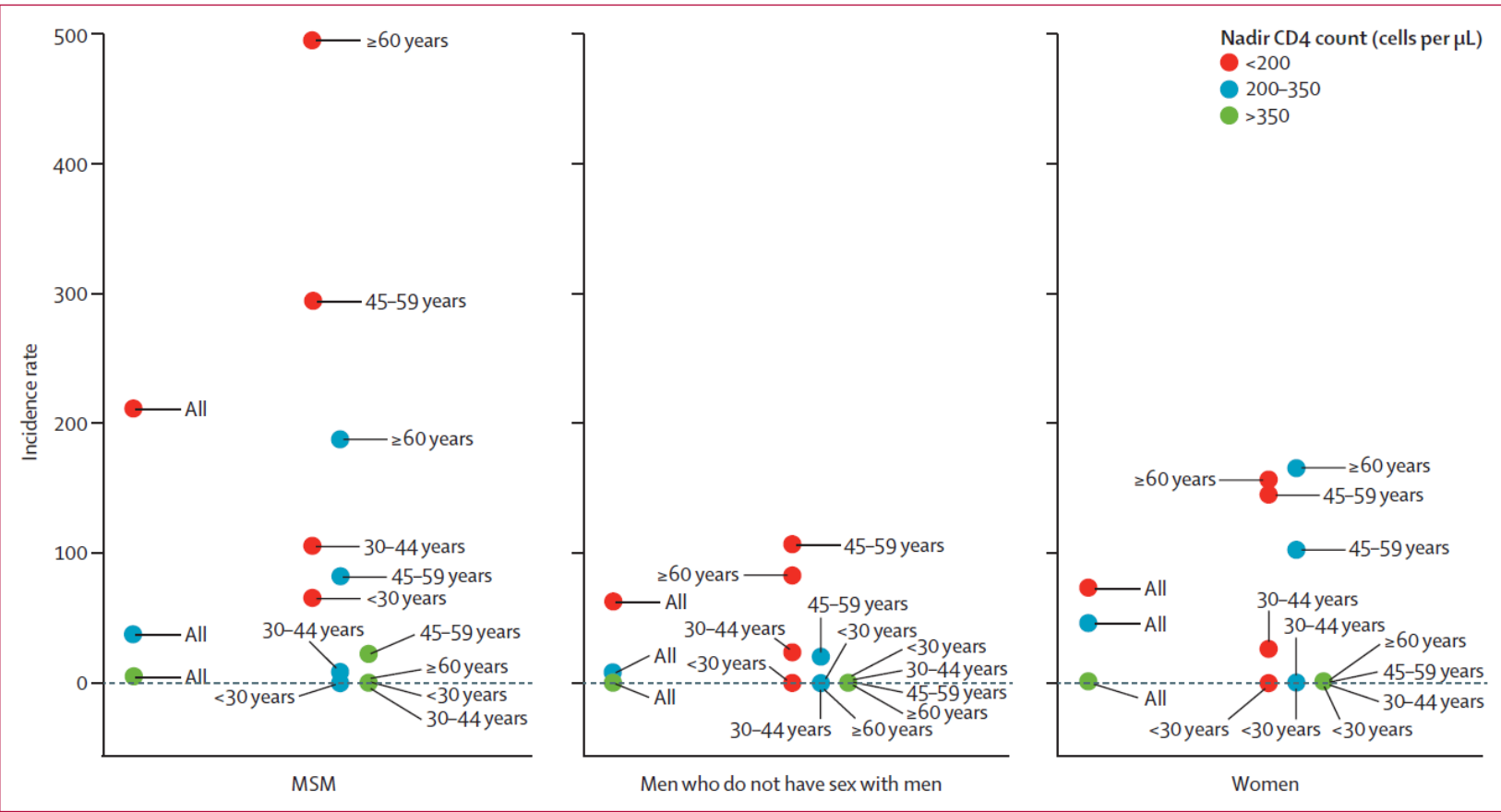
Anal Cancer and Related Risk Factors in PLWH

Variables	Anal carcinoma (n = 26)	Non-anal carcinoma (n = 16,248)	Total (n = 16,274)	P-value
Age at HIV diagnosis, years	38 (28-45)	34 (28-42)	34 (28-42)	0.12
Age at cohort entry	39 (32-46)	35 (29-43)	35 (29-43)	0.12
Age at diagnosis of anal carcinoma, years*	43 (35-51)	41 (34-50)	41 (34-50)	0.64
Sex				
Male	26 (100%)	13833 (85.1%)	13859 (85.2%)	0.033
Female	0 (0%)	2415 (14.9%)	2415 (14.8%)	
Mode of transmission				
MSM	23 (88.5%)	10017 (61.6%)	10040 (61.7%)	
Non MSM	2 (7.7%)	4480 (27.6%)	4482 (27.5%)	
IDU	1 (3.8%)	1130 (7.0%)	1131 (6.9)	0.044
Other/unknown	0 (0%)	621 (3.8%)	621 (3.8%)	
Origin				
Spain	16 (61.5%)	9527 (58.6%)	9543 (58.6%)	
Western Europe	3 (11.5%)	1791 (11%)	1794 (11%)	
Eastern Europe	0 (0%)	337 (2.1%)	337 (2.1%)	
Sub-Saharan Africa	0 (0%)	737 (4.5%)	737 (4.5%)	
Northern Africa	0 (0%)	199 (1.2%)	199 (1.2%)	
Latin America	6 (23%)	3512 (21.6%)	3518 (21.6%)	
Other	0 (0%)	81 (0.5%)	81 (0.5%)	0.19
Unknown	1 (2.8%)	64 (0.4%)	65 (0.4%)	
Education level				
No studies	0 (0%)	478 (2.9%)	478 (2.9%)	
Primary (6-12 years old)	3 (11.5%)	1538 (9.5%)	1541 (9.5%)	
Secondary (12-16 years old)	4 (15.4%)	2652 (16.3%)	2656 (16.3%)	
High school (16-18 years old)	14 (53.9%)	4586 (28.2%)	4600 (28.3%)	
University	4 (15.4%)	4118 (25.3%)	4122 (25.3%)	
Other	0 (0%)	264 (1.6%)	264 (1.6%)	0.095
Unknown	1 (3.9%)	2612 (16.1%)	2613 (16.1%)	
Prior diagnosis of an AIDS-defining illness **				
No	17 (65.4%)	13819 (85%)	13836 (85%)	0.005
Yes	9 (34.6%)	2429 (15%)	2438 (15%)	
Smoking or having ever smoked				
No	7 (26.9%)	4773 (29.4%)	4780 (29.4%)	
Yes	9 (34.6%)	6264 (38.6%)	6273 (38.5%)	0.78
Unknown	10 (38.5%)	5211 (32.1%)	5221 (32.1%)	
Alcohol consumption or have ever drink				
No	5 (19.2%)	4548 (28%)	4553 (28%)	
Yes	5 (19.2%)	3429 (21.1%)	3434 (21.1%)	0.51
Unknown	16 (50.9%)	8271 (51%)	8287 (51%)	
Currently on ART				
No	1 (2.8%)	1748 (10.8%)	1749 (10.8%)	0.25
Yes	25 (96.8%)	14500 (89.2%)	14525 (89.2%)	
Nadir CD4 count, cells/ μ L	115 (38-285)	303 (170-444)	303 (169-443)	0.0004
Acme HIV-1 viral load, Log copies/mL	5.2 (4.0-5.5)	4.9 (4.4-5.4)	4.9 (4.4-5.4)	0.15
Median time on follow-up, years	3.3 (0.9-6.9)	5.3 (2.2-9.5)	5.3 (2.2-9.5)	0.02

Age group (years)	Number of cases of anal cancer	Incidence/100.000 persons/year	95% CI
< 30	5	19.94	8.3 – 47.9
30 – 44	12	22.94	13.03 – 40.39
45 – 59	4	21.63	8.12 – 57.64
\geq 60	1	35.38	4.98 – 251.18

Identifying risk factors for anal cancer in people with HIV in Spain: a multicentre retrospective cohort study nested in the PISCIS cohort

Josep M Llibre, Boris Revollo, Jordi Aceiton, Yesika Díaz, Pere Domingo, Joaquim Burgos, Patricia Sorni, Maria Saumoy, Hernando Knobel, Marta Navarro, Elena Leon, Amat Orti, Laia Arbonés, Arantxa Mera, Elisabet Deig, Guillem Sirera, Josep M Miró, Jordi Casabona, Raquel Martin-Iguacel, on behalf of the PISCIS Cohort Study Group*

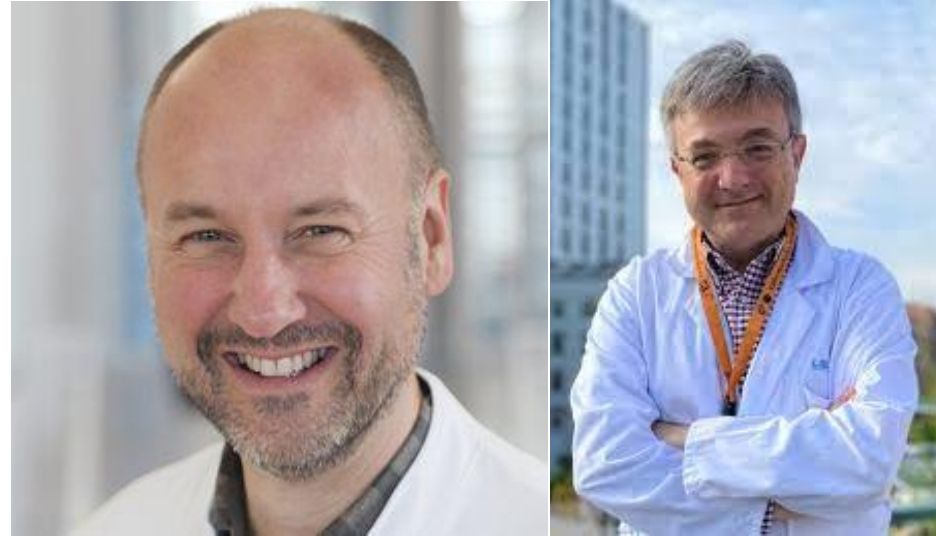


Take home....

- ❑ Treatment of anal HSIL, significantly reduced the risk of progression to anal cancer among persons living with HIV.
- ❑ HSIL: prioritize non-invasive treatments.
- ❑ Nadir CD4 counts of less than 200 cells per μL were associated with the highest risk of developing anal cancer, especially among MSM.
- ❑ MSM and patients with severe immunosuppression (current /past) should be prioritized for anal cancer screening.

Agradecimientos

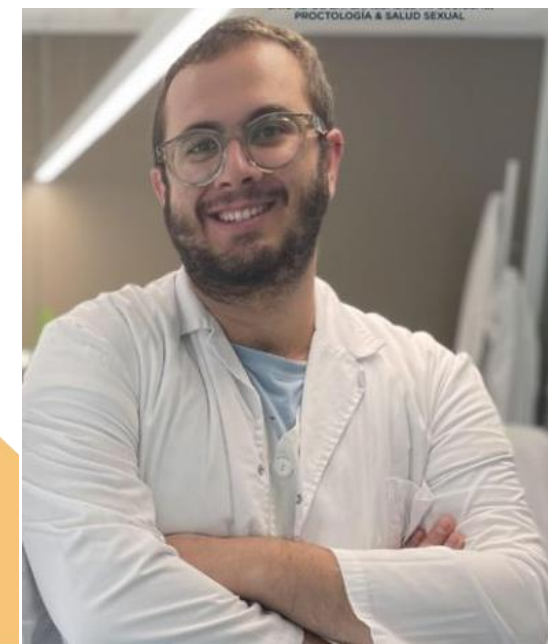
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