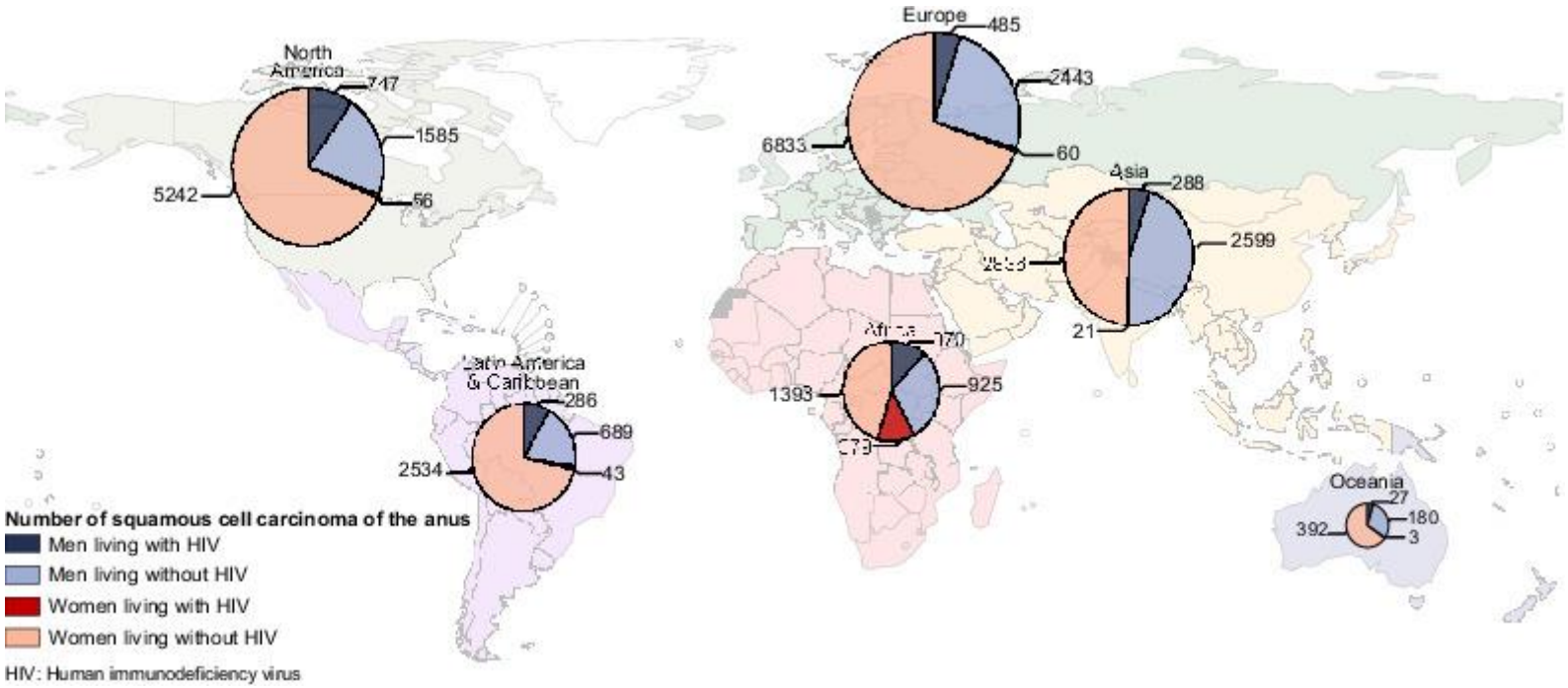
UCSF School of Medicine

HPV genotype distribution in PLWH for anal screening and early detection of anal cancers

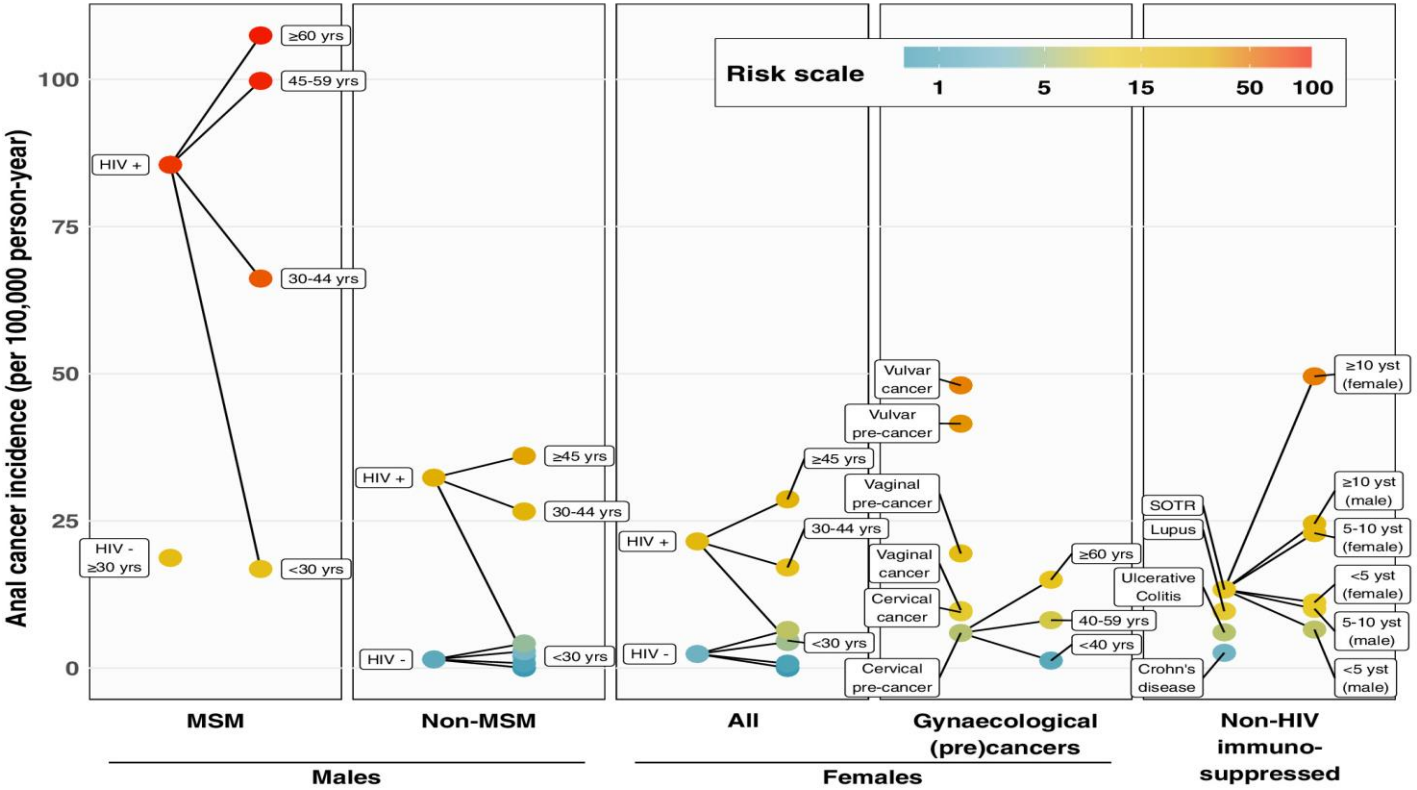
Sona Chowdhury, Ph.D.

Global burden of HPV-attributable squamous cell carcinoma of the anus in 2020, according to sex and HIV status



Intl Journal of Cancer, First published: 28 August 2022, DOI: (10.1002/ijc.34269)

A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale

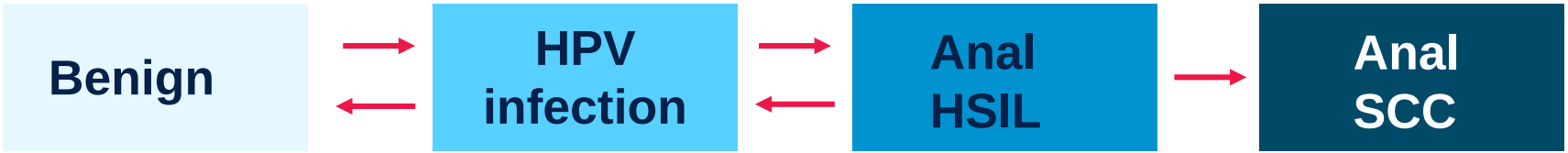


Intl Journal of Cancer, Volume: 148, Issue: 1, Pages: 38-47, First published: 04 July 2020, DOI: (10.1002/ijc.33185)

UCSF

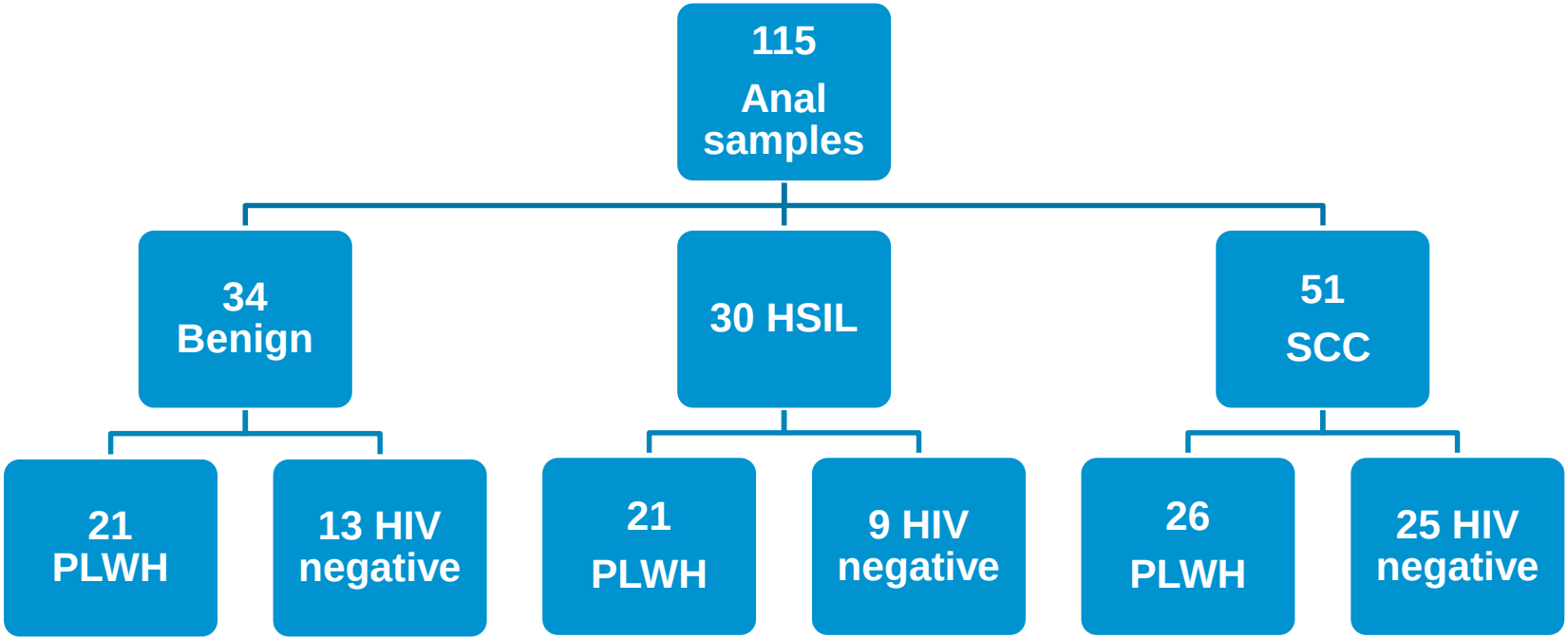
Objective

To study the type-specific prevalence of HPV in anal cancer and the anal cancer precursor, anal squamous intraepithelial lesion in PLWH and HIV-negative individuals and compare it to benign anal epithelium



Progression of anal disease

Anal FFPE samples



HPV type classification –IARC classification

High-risk types
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82

Probable high-risk types
26, 53, 66

Low-risk types
6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 84, 86, 87,62 and 34

Material & Methods

HPV genotyping

- DNA extracted from FFPE blocks
- Amplified by polymerase chain reaction (PCR)
- Primer set MY09/MY11 (MY-PCR).
- HPV genotyping was performed by dot-blot hybridization
- Biotin-labelled probe for 39 different HPV genotypes and a probe for beta-globin.

Nomenclature

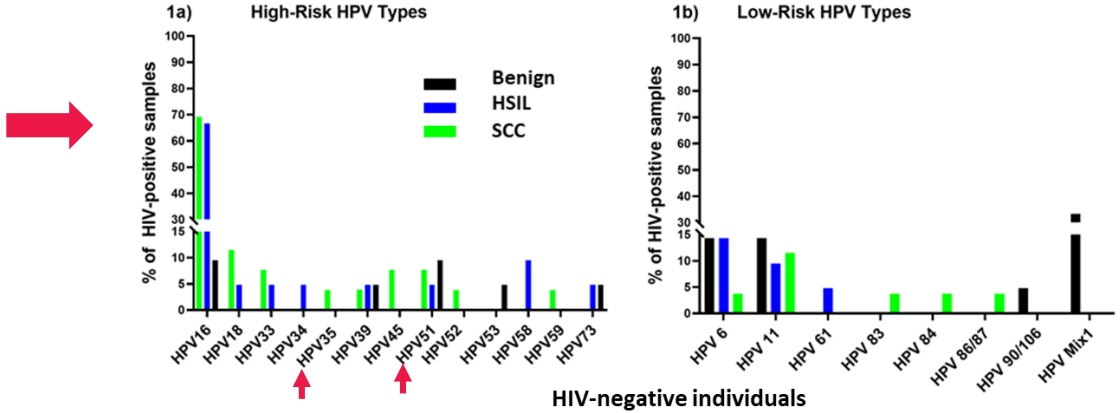
- Single infection : Infection with one HR or LR type only
- Multiple infection : more one HR
  : more than one LR
  : combination of HR + LR
- Type unknown : HPV genotype could not be detected
- Non-16 oncHPV : HR HPV type other than HPV 16

Medical characteristics of people living with HIV (PLWH) diagnosed with benign anal lesions anal HSIL and anal SCC

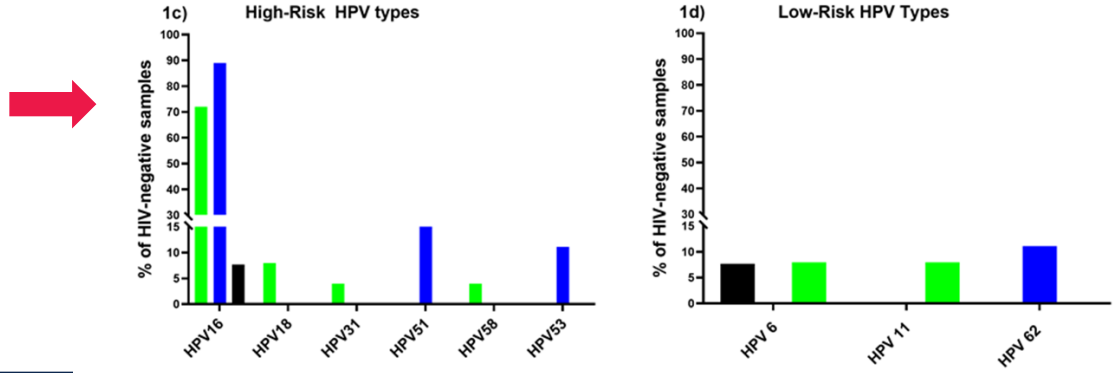
	Benign* (N=21, N%)	HSIL (N=21, N%)	SCC (N=26, N%)
Age, years			
<25	0	0	0
25-39	3 (14.3%)	6 (28.6%)	2 (7.7%)
40-49	7 (33.3%)	4 (19.1%)	6 (23.1%)
50-59	8 (38.1%)	7 (33.3%)	12 (46.2%)
60-69	3 (14.3%)	3 (14.3%)	5 (19.2%)
70 and above	0	1 (4.8%)	1 (3.9%)
Sex			
Male	19 (90.5%)	18 (85.7 %)	24 (92.3%)
Female	2 (9.5 %)	3 (14.3%)	2 (7.7%)
HIV viral load**			
>20 and <1000 /ml	9 (42.9%)	3 (14.3%)	4 (15.4%)
1000 - <4000/ml	1 (4.8%)	0	2 (7.7)
4000-99,999/ml	1 (4.8%)	1 (4.8%)	0
>100,000/ml	0	0	1 (3.9%)
Not detectable	10 (47.6%)	13 (61.9%)	17 (65.4 %)
No data	0	4 (19.1%)	2 (7.7%)
Immune status, $CD4^+$ counts ***			
CD4 >500/mm^3	10 (47.6%)	5 (23.8%)	9 (34.6%)
CD4, 200-500/mm^3	5 (23.8%)	8 (38.1%)	11 (42.3%)
CD4<200/mm^3	6 (23.6%)	5(23.8%)	4 (15.4%)
No data	0	3 (14.3%)	2 (7.7%)
Antiretroviral therapy (ART) use			
Yes	18 (85.7%)	16 (76.2%)	24 (92.3%)
No	3 (14.3%)	1 (4.8%)	1 (3.9%)
No data	0	4 (19.1%)	1 (3.9%)

Distribution of HPV types in benign, HSIL, SCC samples

People living with HIV (PLWH)



HIV-negative individuals



Single and multiple HPV infections (HPV16, Non-16 oncHPV, LR) found in benign, PLWH and HIV-negative individuals

2a) Benign	PLWH (N=21)	HIV-negative (N=13)
HPV 16 only	0	1 (7.7%)
HPV 16 + Non-16 oncHPV*	0	0
HPV 16 + LR**	1 (4.8%)	0
HPV 16 + Non-16 oncHPV + LR	1 (4.8%)	0
Non-16 oncHPV only	2 (9.5%)	0
More than one Non-16 oncHPV	0	0
Non-16 oncHPV + LR	1 (4.8%)	0
LR only	0	1 (7.7%)
More than one LR	5 (23.8%)	0
Type unknown	3 (14.3%)	2 (15.4%)
No HPV	8 (38%)	9 (69.2%)

Single and multiple HPV infections (HPV16, Non-16 oncHPV, LR) found in HSIL lesions in PLWH and HIV-negative individuals

2b) HSIL	PLWH (N=21)	HIV-negative (N=9)
HPV 16 only	9/21 (42.8%)	6/9 (66.7%)
HPV 16 + Non-16 oncHPV	3/21 (14.3%)	2/9 (22.2 %)
HPV 16 + LR	2/21 (9.5%)	0
HPV 16 + Non-16 oncHPV + LR	0	0
Non-16 oncHPV only	2/21 (9.5%)	0
More than one Non-16 oncHPV	0	0
Non-16 oncHPV + LR	3/21(14.3%)	1/9 (11.11%)
LR only	0	0
More than one LR	0	0
Type unknown	1/21 (4.7%)	0
No HPV	1/21 (4.7%)	0

Single and multiple HPV infections (HPV 16, Non-16 oncHPV, LR) found in SCC lesions in PLWH and HIV-negative individuals

2c) SCC	PLWH (N=26)	HIV-negative (N=25)
HPV 16 only	11/26 (42.3%)	17/25 (68%)
HPV 16 + Non-16 oncHPV	3/26 (11.5%)	1/25 (4%)
HPV 16 + LR	4/26 (15.4 %)	0
HPV 16 + Non-16 oncHPV + LR	0	0
Non-16 oncHPV only	4/26 (15.4 %)	0
More than one Non-16 oncHPV	2/26 (7.7 %)	1/25 (4%)
Non-16 oncHPV + LR	1/26 (3.8 %)	1/25 (4%)
LR only	0	0
More than one LR	0	1/25 (4%)
Type unknown	1/26 (3.8 %)	3/25 (12%)
No HPV	0	1/25 (4%)

Associations of HPV16 with anal disease, overall and stratified by presence of HIV or Non-16 oncHPVs

Model	Stratum	N	Proportion of samples with HSIL/cancer (95% CI);	RR [of (HSIL/Cancer) v. (Benign)] (95% CI); p-value
	Overall	115	70.4 (62.6, 79.3)	
1	**HPV 16-**	54 #	42.6 (30.2, 56.0)	2.23 (1.63 to 3.06); p<0.0001
	HPV 16+	61	95.1 (85.8, 98.4)	
2	**HPV 16-, HIV-**	20	40.0 (23.4, 68.4)	
	HPV 16+, HIV-	27	96.3 (89.4, 100)	2.41 (1.40 to 4.14); p= 0.0015
	HPV 16-, HIV+	34	44.1 (30.2, 64.4)	1.10 (0.57 to 2.13); p=0.77
	HPV 16+, HIV+	34	94.1 (86.5, 100)	2.35 (1.37 to 4.05); p=0.002
3	**HPV 16-, Non-16 oncHPV -**	36 ^	22.2 (12.1, 40.9)	
	HPV 16+, Non-16 oncHPV -	51	96.1 (90.9, 100)	4.32 (2.34 to 7.99);p <0.0001
	HPV 16-, Non-16 oncHPV +	18	83.3 (67.8, 100)	3.75 (1.97 to 7.15); p< 0.0001
	HPV 16+, Non-16 oncHPV +	10	90.0 (73.2, 100)	4.05 (2.12 to 7.72);p <0.0001

Discussion-I

- HPV 16 is the main etiological agent for both anal HSIL and SCC irrespective of HIV serostatus
- Although the proportion of single infection with HPV 16 was more in HIV-negative individuals compared to PLWH
- Benign tissues from PLWH had a high proportion both HR and LR HPV types. Therefore, HIV serostatus influences HPV infection and prevents HPV clearance and increases the likelihood of development of anal disease

Discussion-II

- Non-16 oncHPV plays a role in development of anal disease
- HIV mediated immunosuppression was associated with a disproportionate increase in non-16 oncHPV types other than HPV 16 in PLWH
- Multiple HPV infection was a hallmark feature for all tissues from PLWH -indicating that PLWH are at a greater risk of infection with multiple HPV types which may be a marker of persistent disease

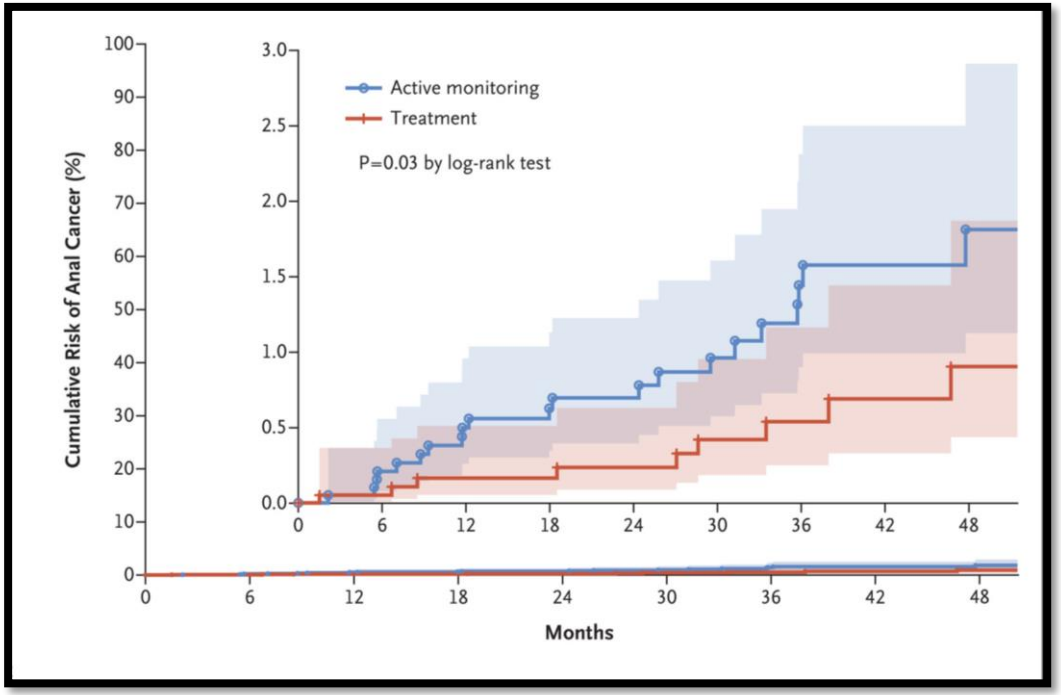
Anal Cancer/HSIL Outcomes Research Study (ANCHOR)

Whether treatment of anal HSIL reduces the progression to cancer and is a safe and effective strategy

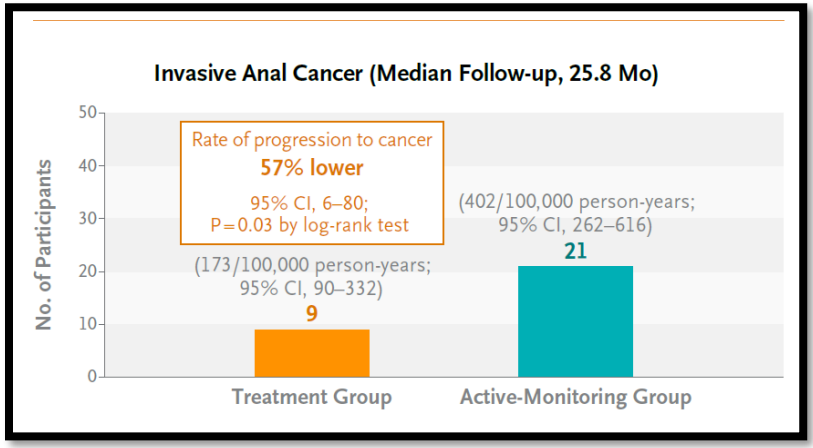
- Randomized controlled trial
- 4446 participants living with HIV-no prior anal cancer
- Treatment group/Monitoring group
- Primary outcome progression to anal cancer in a time-to-event analysis

Rate of progression to cancer was 57% lower in treatment group vs active monitoring group

A



B



Kaplan–Meier Curve of the Time to Progression to Anal Cancer

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

UCSF

Conclusion

- ANCHOR trial-supports the inclusion of routine screening with detection & treatment of anal HSIL –anal cancer prevention for PLWH
- Optimal screening algorithms based on HPV DNA testing are needed to identify individuals at highest-risk
- HPV 16 based screening programs may miss a subset of individuals
- Screening tests based on a broader range of oncogenic type are needed specifically for PLWH
- Low-risk types are not needed to be included in screening tests
- Prospective studies-we need to confirm these updated screening approaches

Acknowledgements

- Teresa M. Darragh
- J.M. Berry-Lawhorn
- Maria G. Isaguliants
- Maxim Vonsky
- Joan F. Hilton
- Ann A. Lazar
- Joel M. Palefsky
- Patients provided the samples
- National Institute of Health (NIH), National Cancer Institute (NCI), R01 CA217715/CA/NCI NIH HHS/ United States & extramural RFBR 17-54-30002 M.I, was supported by Latvian Science Fund LZP 2021/1-0484.

UCSF

END