ANCHOR Update

Barcelona HPV Course
October 4, 2023

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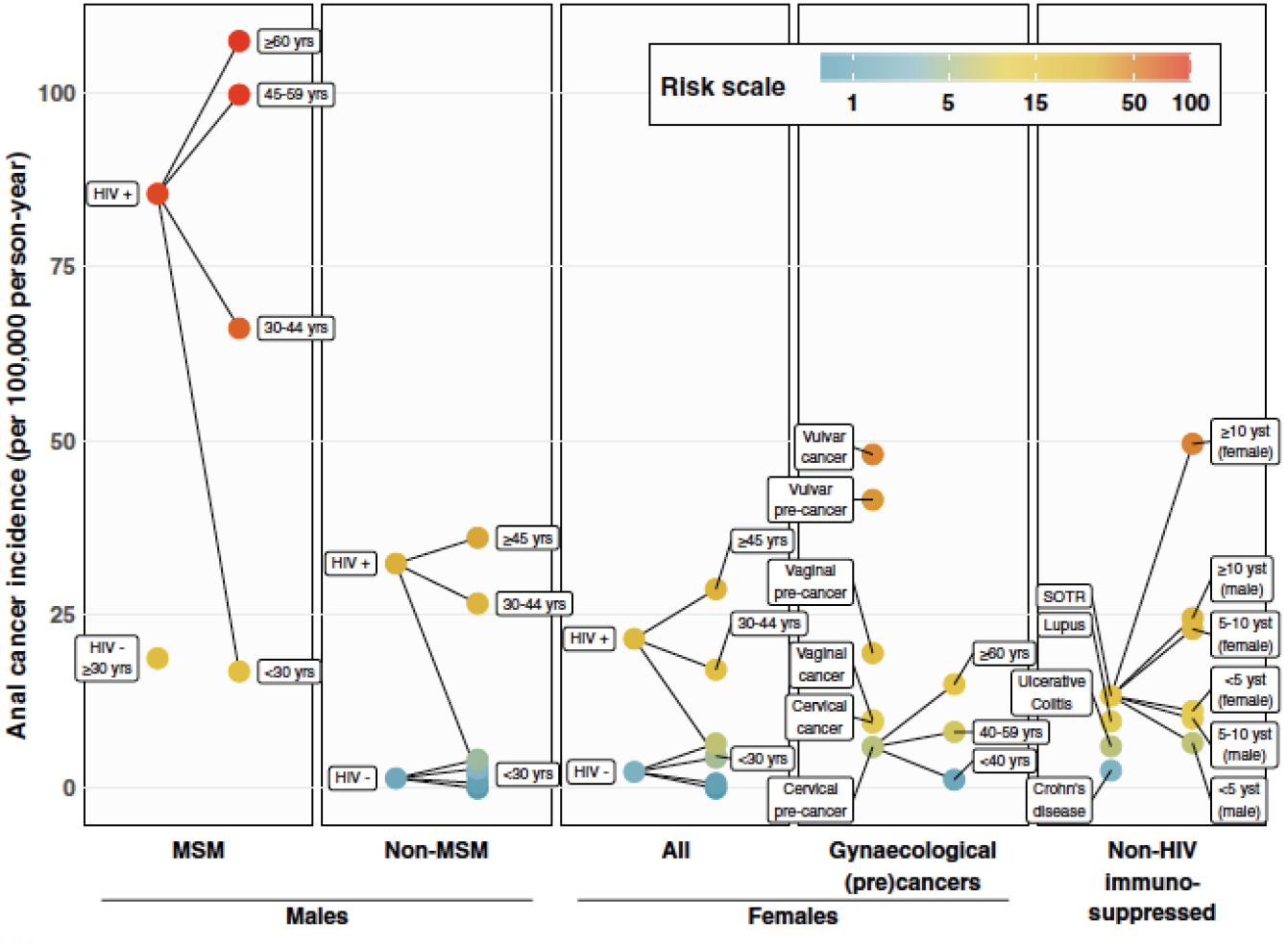
Disclosure

- Vir Biotechnology, Virion Therapeutics, Antiva Biosciences, Roche Diagnostics, Abbott, Spotlight Therapeutics -consultant
- Merck- advisory board member, speaker

Objectives

- Summarize the main findings of the ANCHOR Study
- Describe current status of the ANCHOR Study
- Describe implications of the ANCHOR Study for approaches to screening and treating people living with HIV for prevention of anal cancer

Anal cancer risk scale



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Clifford et al. Int. J. Cancer. 2020;1–11. https://doi.org/10.1002/ijc.33185

Why try to prevent anal cancer?

- Survival rate is low for more advanced disease
- Among those who do survive, there is substantial morbidity associated with standard treatment, primarily due to radiation therapy

Why anal screening and treatment of HSIL might not work: the need for evidence for a RCT

- In many at-risk people lesions are large and multifocal
- Clinicians may miss lesions
- Clinicians may inadequately treat lesions
- New lesions often arise

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The ANCHOR Investigators Group
Protocol A01 of the AIDS Malignancy Consortium
UM1CA121947

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Aim 1: To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in PLWH

Aim 2: To determine the safety of treatment for anal HSIL

Aim 3: To develop and implement an instrument to measure the impact of ANCHOR procedures on QoL (ANCHOR Health-Related Symptom Index (A-HRSI)

Aim 4: Collect clinical specimens and data to create a bank of well-annotated specimens that will enable correlative science:
Identify host and viral factors in HSIL progression to cancer
Identify host and viral biomarkers of progression from HSIL to cancer

The NEW ENGLAND JOURNAL of MEDICINE

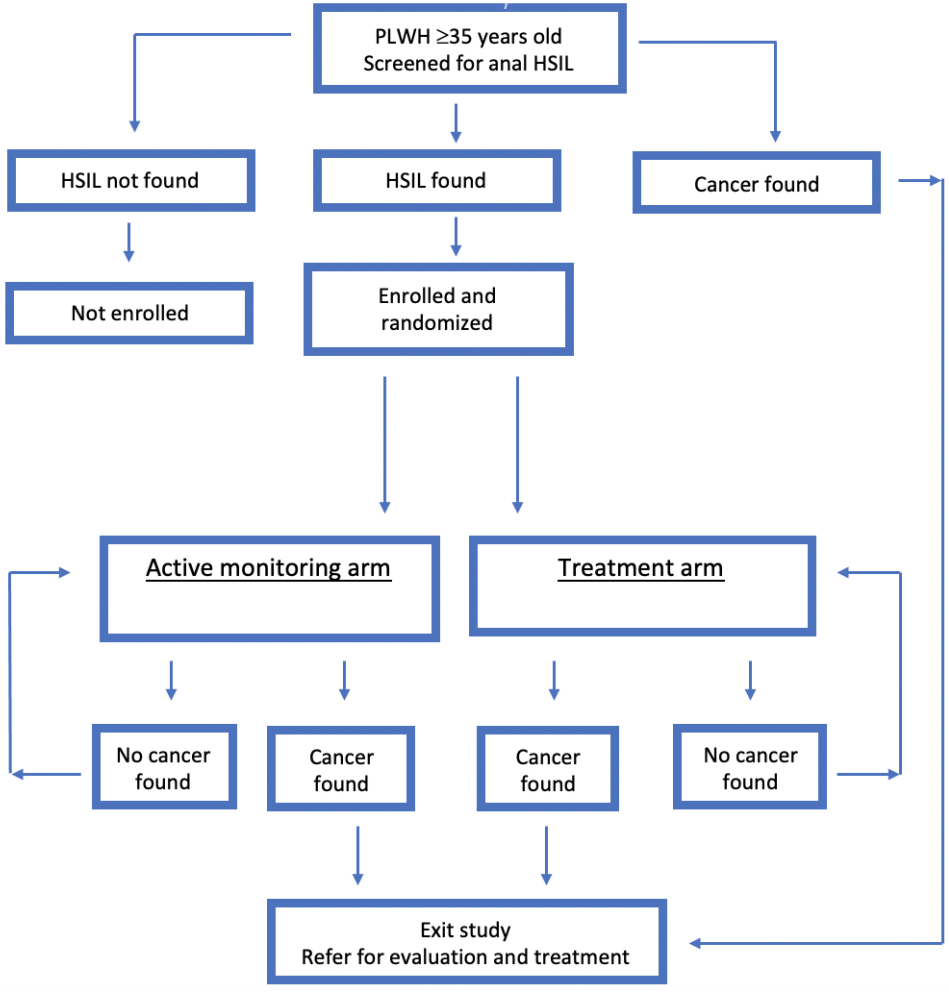
ORIGINAL ARTICLE

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

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

N ENGL J MED 386;24 NEJM.ORG JUNE 16, 2022

Study schema



Enroll 5,058

Segment A

Segment B

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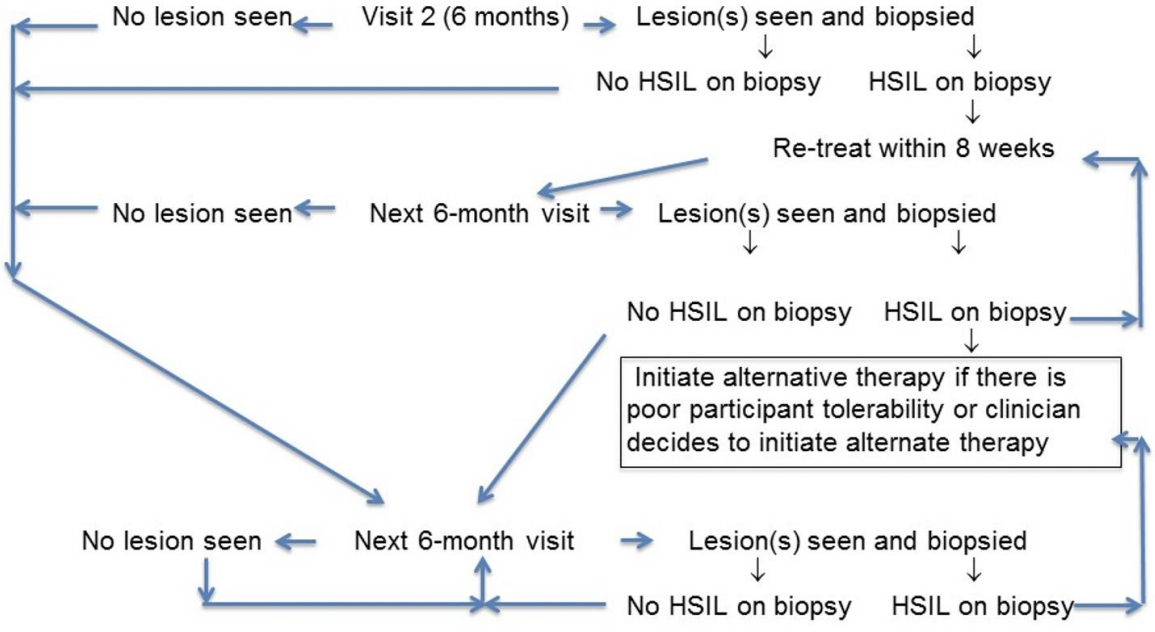
A study of the AIDS Malignancy Consortium
Funded by the National Cancer Institute

Treatment arm

- Treated immediately- hyfrecation, IRC, 5-FU, imiquimod

Figure 4-B: IRC, hyfrecation, or electrocautery performed at visit 1 (randomization visit)



If no lesions are seen, participant will return for HRA at the next 6 month visit. If HSIL is found, alternative treatment is initiated per guidelines

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Anal HSIL and cancer at screening

- 10,723 PLWH from 9/24/2014 to 8/5/2021
- 53.3% of men
- 47.2% of women
- 67.1% of transgender individuals
- 17 individuals (0.16%, 160/100,000) were diagnosed with anal cancer

Palefsky JM et al. New Engl J Med 2022; 386: 2273-82

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Demographics of randomized population

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Median age at randomization (years, IQR)	51.0 (44.0-57.0)	51.0 (44.0-57.0)	0.79
Median years at randomization since HIV diagnosis (years, IQR)	17.0 (10.0-24.0)	17.0 (10.0-25.0)	0.96
Months of follow-up (median, IQR)	25.3 (11.7 – 42.0)	27.2 (12.0 – 42.1)	0.77
Gender identity N (%)			0.30[2]
Male	1793 (80.5)	1782 (80.3)	
Female	346 (15.5)	365 (16.5)	
Transgender	85 (3.8)	68 (3.1)	
Neither male nor female	2 (0.1)	2 (0.1)	
Decline to answer	1 (0.0)	2(0.1)	

Demographics of randomized population

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Current smoker N (%)	710 (31.9)	743 (33.5)	0.26
Plasma HIV-1 RNA copies/mL at randomization N (%)			0.27
<50	1852 (83.7)	1800 (81.8)	
51-199	155 (7.0)	160 (7.3)	
200-1000	83 (3.8)	93 (4.2)	
>1000	122 (5.5)	148 (6.7)	
CD4 cells/uL at randomization (median, IQR)	602 (393-827)	607 (410-837)	0.32

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Demographics of randomized population

	Randomized population N=4,446		P value[1]
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Stratification factors at randomization N (%)			
Nadir CD4 cells/uL			0.88
≤200 cells/uL	1130 (50.7)	1121 (50.5)	
>200 cells/uL	1097 (49.3)	1098 (49.5)	
HSIL size at screening			0.93[8]
>50% of anal canal/perianal region	285 (12.8)	282 (12.7)	
≤50% of anal canal/perianal region	1942 (87.2)	1937(87.3)	

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Results

- 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)
- Cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm

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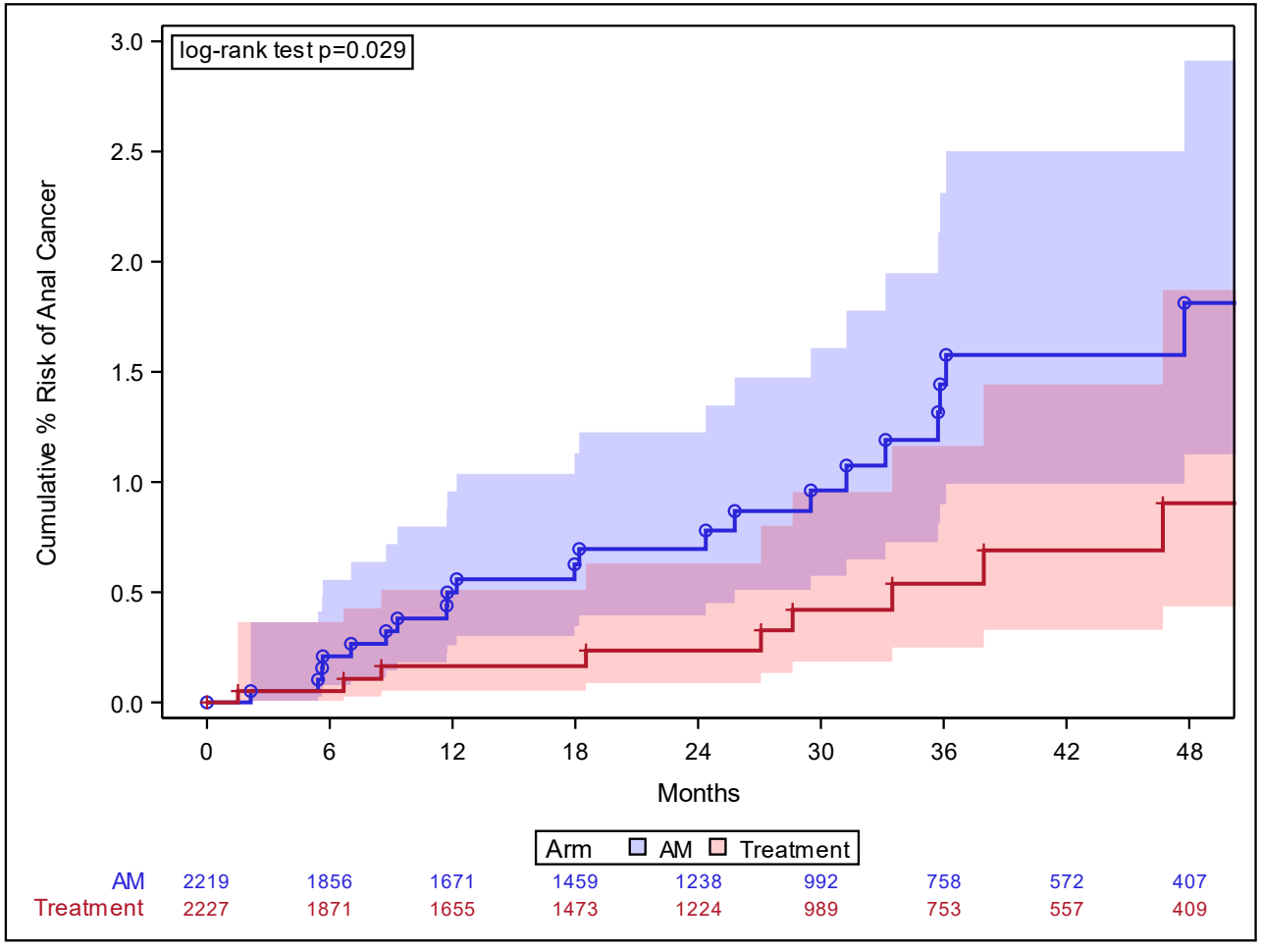
Kaplan-Meier curve of time-to-confirmed cancer cases



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Adverse events

	Treatment arm	Active monitoring arm
Adverse events (N)	683	635
Deaths	55	48
Serious adverse events (N)	586	568
Study-related adverse events (N)	43	4
Study-related serious adverse events (N)	7	1
Skin ulceration due to 5-fluorouracil	1	0
Anal abscess due to electrocautery	1	0
Pain due to electrocautery	1	0
Pain due to treatment under anesthesia	1	0
Pain due to infrared coagulation	1	0
Infection or abscess due to anal biopsy	2	1

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Progression to cancer

- Cumulative progression to cancer at 48 months was 0.9% in the treatment arm and 1.8% in the monitoring arm
- The cancer risk was 185/100,000 PY (95% CI: 115-298) and 1047/100,000 PY (95% CI: 608-1803) for those with lesions ≤50% and >50% of the anal/perianal canal, respectively (hazard ratio 5.26, 95% CI: 2.54-10.87)

HSIL persistence and regression, by arm

		HSIL status	1-year Visit		2-year Visit		3-year Visit		4-year Visit		5-year Visit	
Arm	N		N	%	N	%	N	%	N	%	N	%
Active Monitoring	2263	Present	1159/1611	71.9	792/1256	63.0	481/815	59	265/464	57.1	115/225	51.1
		Absent	452/1611	28.1	465/1256	37.0	334/815	41	199/464	42.9	110/225	48.9
Treatment	2272	Present	593/1568	37.8	338/1217	27.8	166/813	20.4	97/455	21.3	29/232	12.5
		Absent	975/1568	62.2	879/1217	72.2	647/813	79.6	358/455	78.7	203/232	87.5

Segment C

- DSMB recommended stopping the study for efficacy
- Recommendation made to treat all individuals in the monitoring arm
- Interim period, then Segment C

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Interim period

- Started September, 2021
- 816 participants, 1006 ablations
- Concluded July, 2022

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Segment C

- Segment C- all participants invited back
- Monitoring arm- offered therapy
- Treatment arm- offered HRA, therapy as needed
- More than 70% of participants retained
- All participants seen every 6 months or more often as needed
- Three anal swabs, biopsies of suspected HSIL or cancer
- Biopsies may be performed more frequently than every 6 months as clinically indicated.
- Clinicians may forego biopsy at the 6 month visit if in their judgment the lesions have not changed since the prior visit and there is no suspicion for cancer.
- Biopsies of all visible HSIL must be done at least annually
- Annual serology

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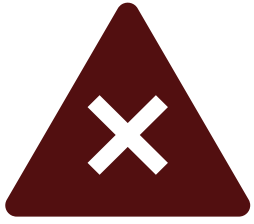
Additional anal cancers reported

Cases reported among participants formerly enrolled to both study arms since analysis

7 during interim period

At least 6 from segment C

Noncompliance with visit schedule and/or incomplete treatment common in most cases



Re-analysis of primary outcome will not be performed using additional cases

Case summaries will still be collected for future analyses

Implications of the study findings

- Rate of progression from anal HSIL to cancer is high
- Treatment of anal HSIL is effective in reducing the incidence of anal cancer
- There is room for improvement in treatment of anal HSIL
- There is a need for biomarkers for HSIL progression or regression

Palefsky JM et al. New Engl J Med 2022; 386: 2273-82

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Implications of the study findings

- There is a need for optimization of screening algorithms for HSIL
- There is a need for a large scale-up of HRA training programs
- Extrapolation of our results to other groups at high risk of anal cancer

Palefsky JM et al. New Engl J Med 2022; 386: 2273-82

Screening recommendations

- CDC recommendations under final review for clearance
- IANS working on guidelines
- USPHS Taskforce- suspended further work for now

Screening recommendations

- DARE on all PLWH annually
- Screen MSMLWH and transgender people over 35 years and all other PLWH over 45 years IF you do HRA and treatment or you can refer to someone trained in HRA and treatment

What does screening look like?

- Combination of anal cytology and HPV co-testing when available

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Anal cytology testing only

- If screening with anal cytology only, PWH in whom screening has been initiated should have an anal cytology testing every 12 months
- If the results of three consecutive anal cytology tests are normal, follow-up anal cytology tests should be every 3 years.
- Persons with any abnormal cytology (≥ASC-US) should be referred for HRA

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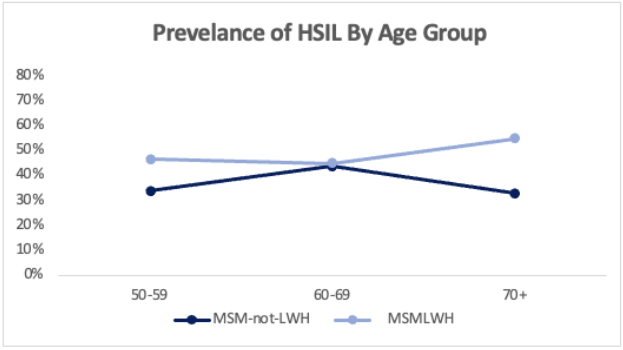
Normal anal cytology and HPV co-testing

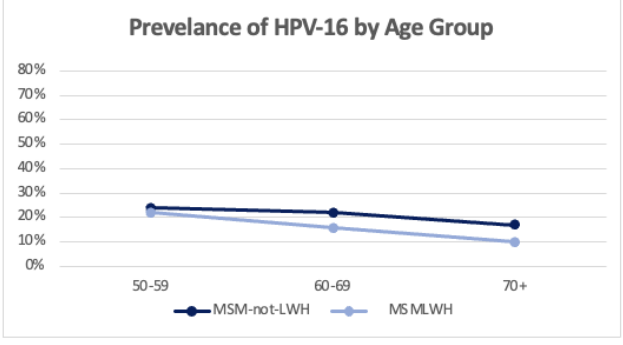
- Persons who co-test negative (i.e., a normal anal cytology and negative HPV test) can have their next anal cancer screening in 3 years
- If the initial anal HPV high-risk testing results identify HPV16 or HPV16/18, referral to HRA is recommended (regardless of cytology result)
- If high-risk HPV testing is positive, but the genotype-specific testing for HPV16/18 is negative, then repeat co-testing in one year is recommended. If either of the co-tests at one year is abnormal (i.e., abnormal anal cytology or positive high-risk HPV), referral to HRA is recommended

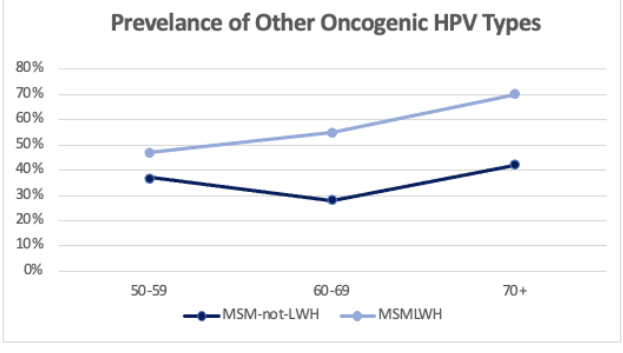
Abnormal anal cytology and HPV co-testing

- If ASC-US on cytology and high-risk HPV testing is positive, then referral for HRA is recommended.
- If ASC-US on anal cytology, and high-risk HPV testing is negative, then repeat co-testing (cytology and high-risk HPV testing) in 1 year. If either of the co-tests at one year is abnormal referral to HRA is recommended**.**
- For LSIL, ASC-H or HSIL on anal cytology, referral to HRA is recommended (regardless of high-risk HPV test result)

Hernandez A et al,
submitted for publication







*Other Oncogenic HPV (excluding HPV-16) = One or more of the following HPV types: 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68

Table 3: Association of anal HPV infections and biopsy-confirmed HSIL, adjusted for age, income, education, and for HIV status and current CD4+ level combined.

	All Participants (N=235, 100 events)		
Characteristic*	**aOR****	**(95% CI**)**	**P-value*****
HIV Status and CD4+ Level			
No HIV	Ref		0.2356
HIV and CD4:500+	1.12	(0.55-2.29)	
HIV and CD4: 200-499	2.46	(0.95-6.33)	
HIV and CD4: <200	2.49	(0.39-15.8)	
Age	1.00	(0.96-1.15)	0.8152
Income	0.94	(0.85-1.03	0.1890
Education	1.28	(0.98-1.67)	0.0618
Anal HPV Infection			
None	Ref		<0.0001
Other Oncogenic HPV (not HPV-16)	5.71	(2.72-12.0)	
HPV-16	32.7	(12.2-88.0)	

**Adjusted odds ratio (aOR) and exact 95% confidence interval (CI); ***p-value from model likelihood ratio statistic; Ref, reference

Characteristic	N	(%)	Incident HSIL N	Incident HSIL (%)	No incident HSIL N	No incident HSIL (%)	Chi square P value
Total N	97	(100)	19	(19.6)	78	(80.4)	
HIV status	.		.		.		
.....No, HIV-	47	(49)	8	(17.0)	39	(83.0)	0.5069
.....Yes, HIV+	49	(51)	11	(22.4)	38	(77.6)	
Median age	59.9	(±7)	55.1	(±5)	61	(±7)	<.0001
Aged <60, 60-70, 70+	.		.		.		
.....50 to 59	55	(57.3)	16	(29.1)	39	(70.9)	0.0263
.....60 to 70	33	(34.4)	3	(9.1)	30	(90.1)	
.....70+	8	(8.3)	0	(0)	8	(100)	
Race 5 categories	.		.		.		
.....1.Asian, American Indian or Alaskan Native, N	9	(9.5)	4	(22.2)	5	(6.5)	0.1466
.....2.Black or African American	7	(7.4)	0	(0)	7	(9.1)	
.....3.Non-Hispanic White	57	(60)	9	(50)	48	(62.3)	
.....4.Hispanic White	8	(8.4)	1	(5.6)	7	(9.1)	
.....5.Other/Mixed	14	(14.7)	4	(22.2)	10	(13)	
Employment Status	.		.		.		
.....1:Full Time Emp	20	(20.8)	4	(21.1)	16	(20.8)	0.1226
.....2:Part Time Emp	11	(11.5)	3	(15.8)	8	(10.4)	
.....3:Retired	31	(32.3)	2	(10.5)	29	(37.7)	

Hernandez A et al, manuscript in preparation

People with HIV >50 years of age

- If have prevalent HSIL, may have been there a while, risk of progressing to cancer increases with age
- 50-59- risk of incident HSIL is highest
- Follow-up intensity based on HPV status
- 16> other HR-HPV types>negative

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How to treat

- Office-based ablation (e.g., hyfrecation) for amenable lesions
- Referral to surgery for disease too bulky to treat in office
- Treat with 5-fluoro-uracil cream to de-bulk

Correlative Science Plans

Screening (A) and Randomization (B) Segments

	Screening	Randomized to Active Monitoring	Randomized to Treatment
Optimizing screening for prevalent HSIL/cancer	✓		
Molecular marker/pathogenesis/risk factor for prevalent HSIL/cancer	✓	✓	
Molecular marker/pathogenesis/risk factor for progression from HSIL to cancer		✓	
Molecular marker/pathogenesis/risk factor for from regression from HSIL to normal		✓	
Molecular marker/pathogenesis/risk factor for incident metachronous HSIL			✓
Molecular marker/pathogenesis/risk factor for failure of treatment to prevent progression from HSIL to cancer			✓
Molecular marker/pathogenesis/risk factor for failure of treatment to resolve HSIL			✓

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Muchas gracias!

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