

Non-surgical management of anal/perianal disease

Barcelona HPV Course

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Joel Palefsky, M.D.
University of California, San Francisco

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Disclosures

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

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Objectives

- Understand the indications for treating anal HSIL
- Understand the rationale for selection of specific treatment modalities
- Understand the advantages and disadvantages of specific treatment modalities

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The NEW ENGLAND JOURNAL of MEDICINE

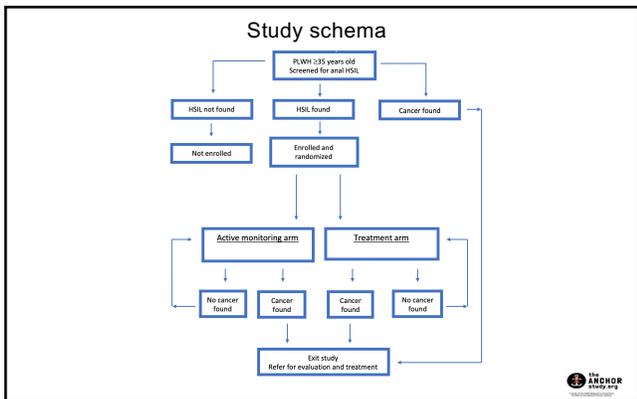
ORIGINAL ARTICLE

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

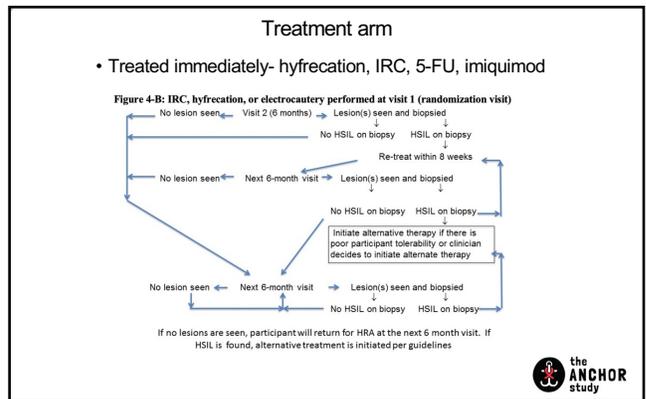
J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulaifa, J.T. Schouten, J. de la Ossa, 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

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Treatment arm

- Followed according to treatment algorithm
- Biopsied if suspicion for HSIL, re-treated as needed
- Examined every 6 months once treatment complete
- Seen every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer

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



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Results

For the participants in the treatment arm, initial treatment:

- Office-based electrocautery ablation (86.2%)
- Infrared coagulation (4.8%)
- TUA (2.3%)
- Topical 5-fluorouracil cream (4.5%)
- Topical imiquimod (0.5%)

Over the course of the study, one treatment modality only (86%)

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



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Footer Text

Results

- Median follow-up of 25.8 months, 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)



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Why treat anal HPV-related disease?

- To prevent invasive cancer
- To reduce symptoms such as itching, irritation, pain and bleeding, psychosocial distress

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Types of treatment

- No specific treatment for HPV
- Patient-applied including imiquimod, podofilox gel, sinecatechin, and 5% fluorouracil cream
- Clinician-applied topical
- 85% trichloroacetic acid, cryotherapy
- Clinician-applied ablative
- infrared coagulation, hyfrecation, laser ablation

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Setting expectations

- We are probably not removing all of the HPV
- High risk of recurrent disease after treatment
- Even higher risk of metachronous disease
- Multiple visits
- Long-term follow-up

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Choice of treatment

- Location internal or external
- Size of the lesion or volume of disease
- Type of lesion: Anal LSIL or HSIL
- Patient's overall health and immune function
- Patient preference and tolerance

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The evidence

- Therapies tested for resolution of HSIL, not cancer prevention

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RCT for treatment of HSIL

	Imiquimod				Fluorouracil				Electrocautery			
	nITT (n=54)	PP (n=63)	PP high-grade AIN(n=24)	PP low-grade AIN(n=21)	nITT (n=47)	PP (n=43)	PP high-grade AIN(n=28)	PP low-grade AIN(n=15)	nITT (n=45)	PP (n=36)	PP high-grade AIN(n=15)	PP low-grade AIN(n=17)
Complete response												
Number of participants	13	13	5	8	8	8	6	2	18	18	10	8
% (95% CI)	24% (15-37)*	20% (14-43)	24% (9-41)	38% (21-55)	17% (8-30)*	19% (9-33)	24% (10-49)	13% (7-39)	39% (26-54)*	50% (34-66)	52% (32-73)	47% (26-69)
Partial response												
Number of participants	0	0	0	NA	0	0	0	NA	3	3	3	NA
% (95% CI)	0%	0%	0%	NA	0%	0%	0%	NA	7% (2-18)	8% (2-23)	16% (5-38)	NA
No response												
Number of participants	26	26	13	13	20	20	16	13	15	15	6	9
% (95% CI)	48% (35-61)	58% (43-71)	54% (35-72)	62% (41-79)	60% (46-73)	67% (53-80)	57% (39-74)	87% (63-98)	33% (21-47)	42% (27-58)	32% (15-54)	53% (31-74)
Excluded												
Number of participants	9	NA	NA	NA	5	NA	NA	NA	10	NA	NA	NA
% (95% CI)	17% (9-29)	NA	NA	NA	10% (4-23)	NA	NA	NA	22% (12-36)	NA	NA	NA

nITT=modified intention to treat; PP=per protocol; AIN=anal intraepithelial neoplasia; NA=not applicable (in case of low-grade AIN partial response is not an option). *Difference between the three groups in complete response rate was significant in the nITT analysis (p<0.02); †Difference between the three groups in complete response rate was significant in the PP analysis (p<0.005).

Table 2. Response rates 4 weeks after the end of treatment



Richel O et al. Lancet Oncol 2013; 14:346-53

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5% imiquimod cream

- Often useful for treatment of external warts, particularly in immunocompetent patients
- Acts as an immune response modifier by stimulating local production of interferon
- Patients who fail on imiquimod may do well on podophyllotoxin or vice versa

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5% imiquimod cream

- Use for perianal HSIL has not been rigorously evaluated and if used, patients should be monitored and re-biopsied to determine efficacy
- May not work well in people living with HIV with CD4 lymphocyte counts below 200 but there are few data
- Some success reported in European studies

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5% fluorouracil cream

- To treat anal HSIL
- To debulk disease

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5% fluorouracil cream summary

- Optimal dosing unclear
- Delivery method needs to be standardized
- Must be able to insert cream correctly
- HSIL seems to respond better than condyloma
- High recurrence rates in some studies
- Probably effective, safe and good option for high volume
- Remains off-label

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0.5% podofilox gel

- Useful for treatment of external warts but can cause significant irritation around the anus

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15% sinecatechins

- FDA approved since 2006 for treatment of external genital warts
- Botanical topical ointment - purified aqueous extract of green tea leaves (*camellia sinensis*)
- Sinecatechin is active ingredient
- Applied by patient 3x daily until warts clear, up to 16 weeks

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85% trichloroacetic acid (TCA)

- Useful for small internal warts and small areas of anal LSIL or HSIL
- Small amount is put into cup
- Wooden end of cotton-tipped swab wicks up TCA
- is shaken off
- Directly applied to lesion until it turns white, avoid dripping and treatment of normal tissue
- Usually at 2-3 week intervals for up to 4 treatments

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Cryotherapy

- Useful for small external warts and small areas of perianal LSIL or HSIL
- Small amount of liquid nitrogen put into cup (or cryoprobe or spray gun)
- Cotton end of cotton tipped swab (or wooden end for very small lesions) placed in LN2
- Directly applied to lesion until it freezes and turns white (around 20 seconds)
- Usually 3 freeze-thaw cycles
- TCA can be applied after freezing

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Office-based ablation

- Different ablation methods are equivalent in efficacy and recurrence/metachronous disease rates
- Use the method with which you are most comfortable

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Retrospective analysis of electrocautery

- 91 men
- The overall response rate at 18 months was 70% per lesion
- No serious AEs
- Lack of resolution after first treatment was a predictor of poor response at 18 months

Fuertes I et al. Response factors associated with electrocautery treatment of intra-anal high-grade squamous intraepithelial lesions in a population of HIV-positive men who have sex with men. International Journal of STD & AIDS 2021;Vol. 32(11) 1052-1059

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IRC and electrocautery ablation in HIV+ MSM

	Infra-red coagulation	Electrocautery*
Number of patients	68	132
Number of lesions treated	165	375
% lesions gone after 1 treatment	72%	75%
% with metachronous lesions	59%	49%

***No statistically significant differences**
Marks DK et al. J Acquir Immune Defic Syndr 2012; 59: 259-65

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AMC 076: RCT of IRC

- 121 participants
- CR for IRC and control arms was 63% and 27%, respectively, for a risk difference of 37% (95% CI: 18-53%, p<0.001)
- Any response (CR or PR) was 75% and 43%, respectively for a risk difference of 32% (95% CI: 13-49%, p<0.001)

Goldstone SE et al. Clin Infect Dis. 2019 Mar 19;68(7):1204-1212

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IRC vs hyfrecation

IRC	Hyfrecation
<ul style="list-style-type: none"> • More limited lesions • On top of hemorrhoids • Anal canal • Suitable anatomy of anal canal • No smoke evacuator 	<ul style="list-style-type: none"> • Larger lesions • Perianal lesions • Good for "nooks and crannies" • Less fragile, cheaper, more versatile • New smoke evacuator systems

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Carbon dioxide laser treatment

- Fifty-two patients with 72 HSILs were analyzed
- Complete was seen in 50% (n = 24)
- Partial response was seen in 20.8% (n = 10)
- No response 20.8% was seen in 29.1% (n = 14)
- No adverse events reported
- Being older than 40 years and having a CD4 T-cell count lower than 200 cells/ μ L were significantly associated with a poor response to treatment

Fuertes I et al. Short-term effectiveness and tolerability of carbon dioxide laser for anal high-grade squamous intraepithelial lesions in individuals living with HIV. International Journal of STD & AIDS 2022, Vol. 33(7) 709-717

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Lesion location HSIL (none approved)

	Anal canal	Perianal
Topical		
5-fluorouracil	✓	✓
Imiquimod	±	±
Sinecatechin	x	±
Podofilox gel	x	±
Cryotherapy	±	✓
TCA	✓	✓
Cidofovir	x	±
Office ablation	✓	✓
Surgical ablation/excision	✓	✓

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Lesion location
Condylomata

	Anal canal	Perianal
Topical		
5-fluorouracil	±	±
Imiquimod	±	✓
Sinecatechin	x	✓
Podofilox gel	x	✓
Cryotherapy	±	✓
TCA	±	±
Cidofovir	±	±
Office ablation	✓	✓
Surgical ablation/excision	✓	✓

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Lesion size

	Large/multifocal	Small
Topical		
5-fluorouracil	✓	±
Imiquimod	±	✓
Sinecatechin	±	✓
Podofilox gel	±	✓
Cryotherapy	±	✓
TCA	x	✓
Cidofovir	±	✓
Office ablation	✓	±
Surgical ablation/excision	✓	±

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New stuff

- Therapeutic vaccines (again)
- Radiofrequency ablation
- New topical therapies

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Conclusions

- The ANCHOR study has shown the effectiveness of treating anal HSIL to prevent invasive anal cancer
- Multiple treatment methods are often needed, sometimes simultaneous
- Careful follow-up is critical as patients tend to recur despite of the method of treatment
- Treatment for HSIL is improving but even better treatments are needed

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What kind of evidence do we need at this point to pick a treatment for anal cancer prevention?

- Now have evidence that HSIL treatment can prevent anal cancer
- Will evidence that a given treatment leads to resolution of HSIL suffice?
- Do we need placebo-controlled studies?
- Can we do placebo-controlled studies?
- Can we simply compare one treatment to another?

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Muchas gracias!

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