ANAL DYSPLASIA
Update on treatments

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Dermatología Hospital Clínic,
Universitat de Barcelona 2021

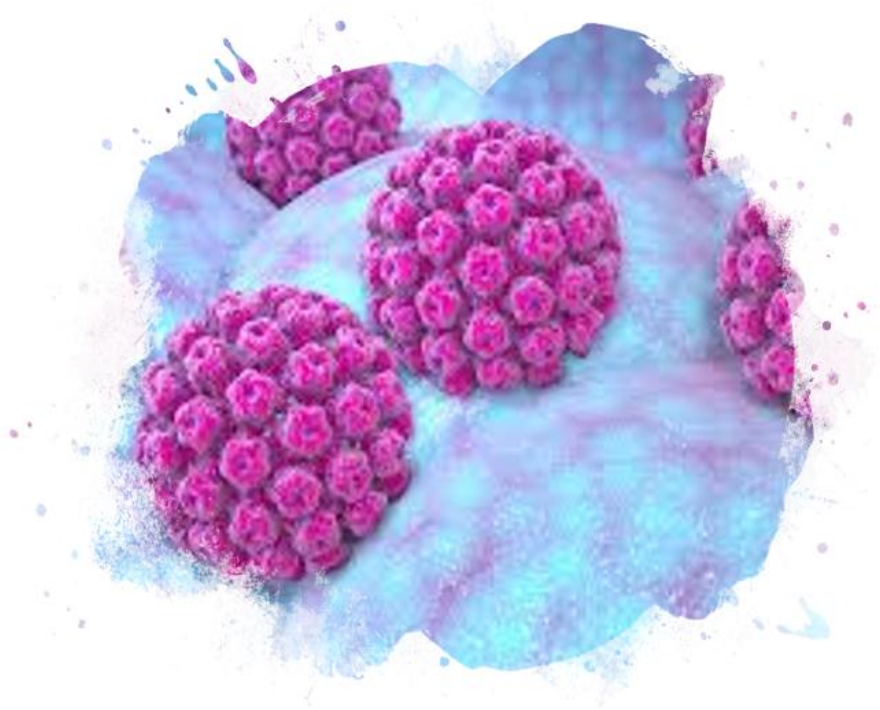
INDEX OF CONTENTS

Anal HSIL update on treatments

What are we dealing with?

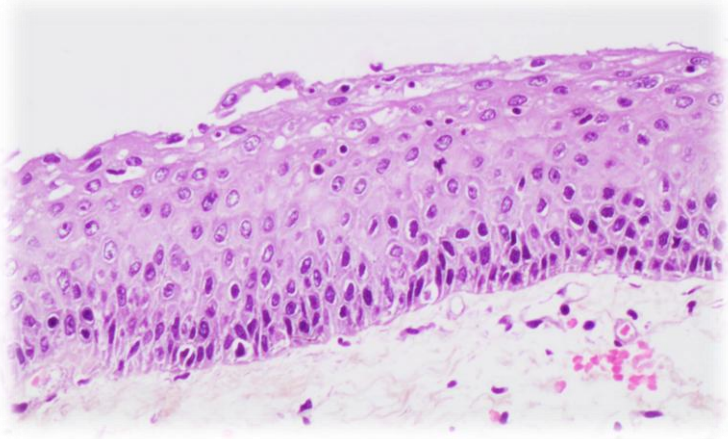
- High grade squamous intraepithelial lesion

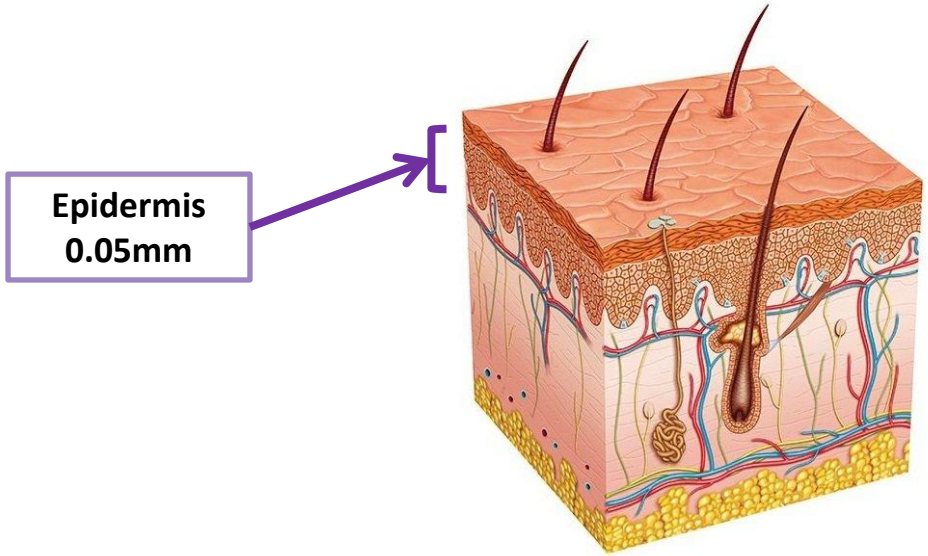
- HPV infection



Anal HSIL update on treatments

What are we dealing with?





Anal HSIL, update on treatments

Surgical excision

- Sedation + Anaesthesia required
- Complete excision (hard to achieve)
- High persistence or recurrence rate (18-30%)
- Associated morbidity **(stenosis, fibrosis, incontinence, fistulae..)**

Brown SR, Skinner P, Tidy J, Smith JH, Sharp F, Hosie KB. Outcome after surgical resection for high-grade anal intraepithelialneoplasia (Bowen's disease). Br J Surg. 1999 86(8):1063–1066

Scholefield JH, Ogunbiyi OA, Smith JH, Rogers K, Sharp F. Treatment of anal intraepithelial neoplasia. Br J Surg. 1994 Aug;81(8):1238-40.

Chang GJ, Berry JM, Jay N, *et al*. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. Dis Colon Rectum. 2002;45:453–458.

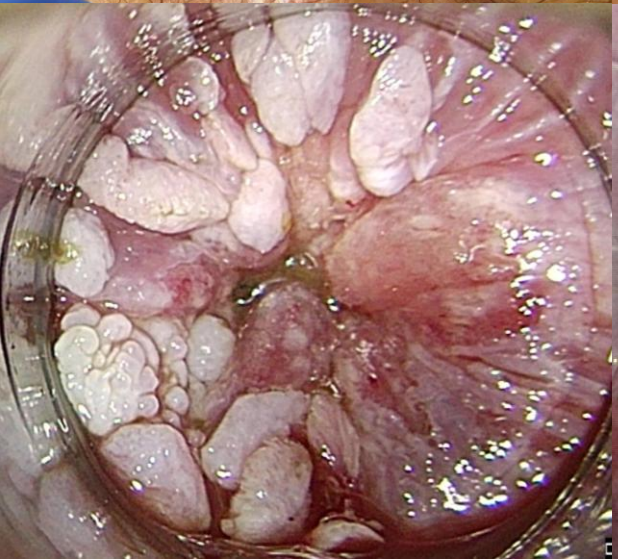
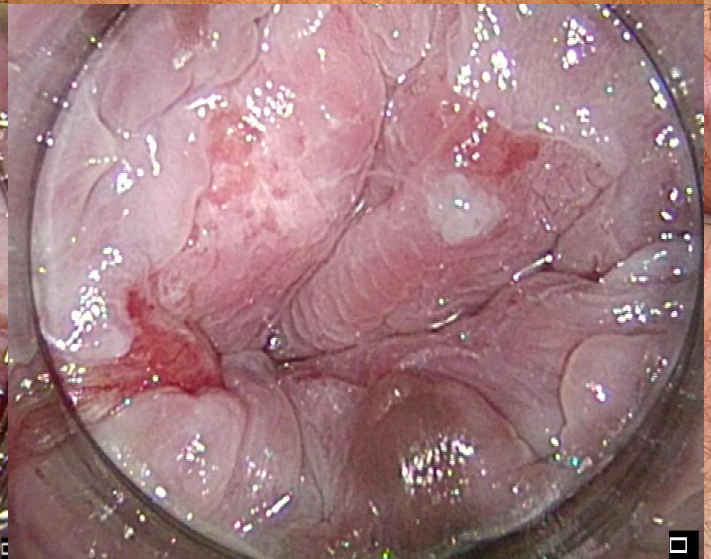
Anal HSIL, update on treatments

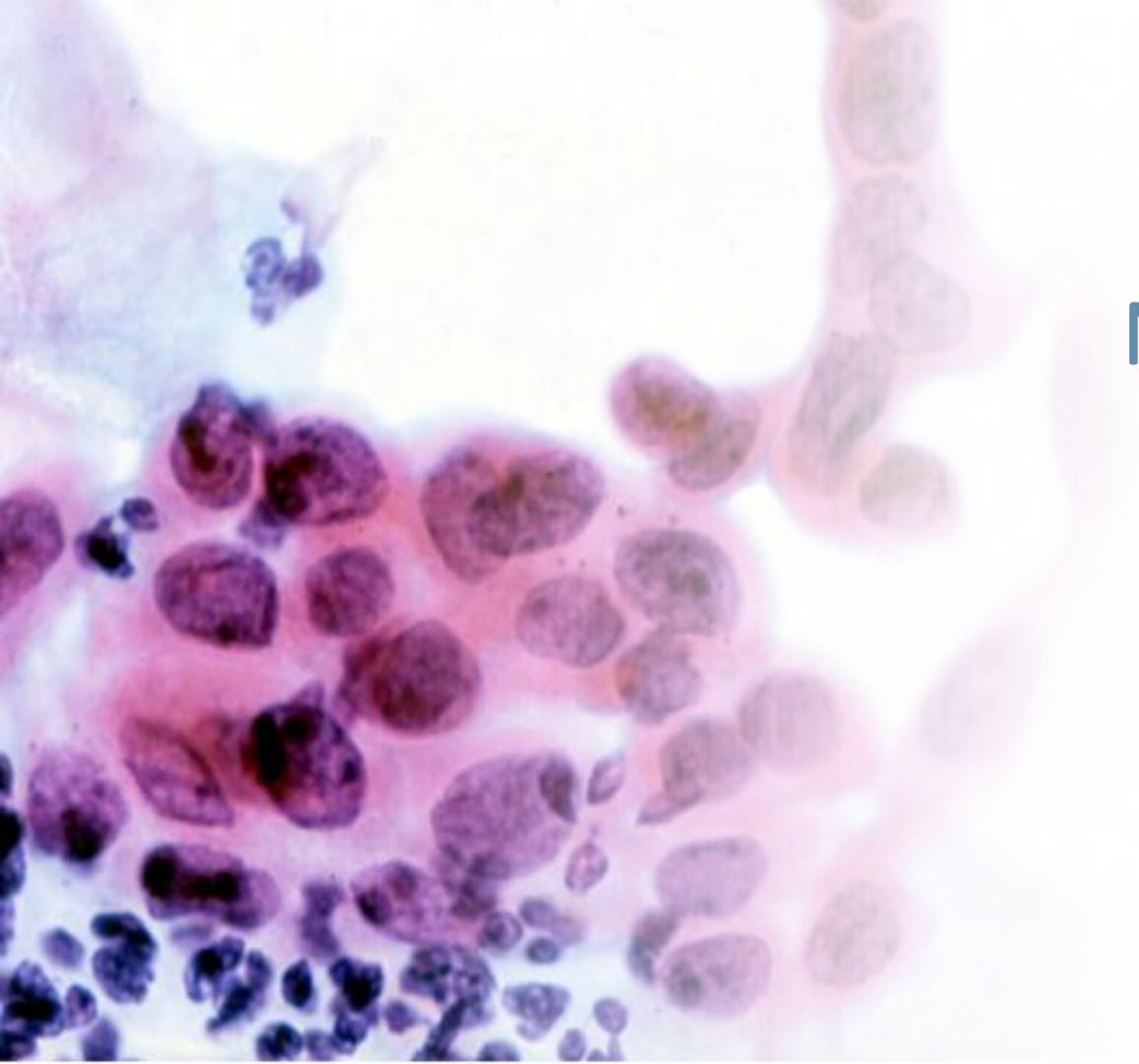
- **Surgical excision**:

> *"you still need a surgeon in your team"*
> *(in case you're not a surgeon)*

  - Condylomatosis
  - Non-neoplastic surgical pathology
  - Persistent / Equivocal lesions
  - SISCA (invasion ≤ 3mm / extension ≤ 7 mm)
    - Superficially invasive anal squamous cell carcinoma



Minimally invasive treatments

Anal HSIL, update on treatments

ABLATIVE TREATMENTS

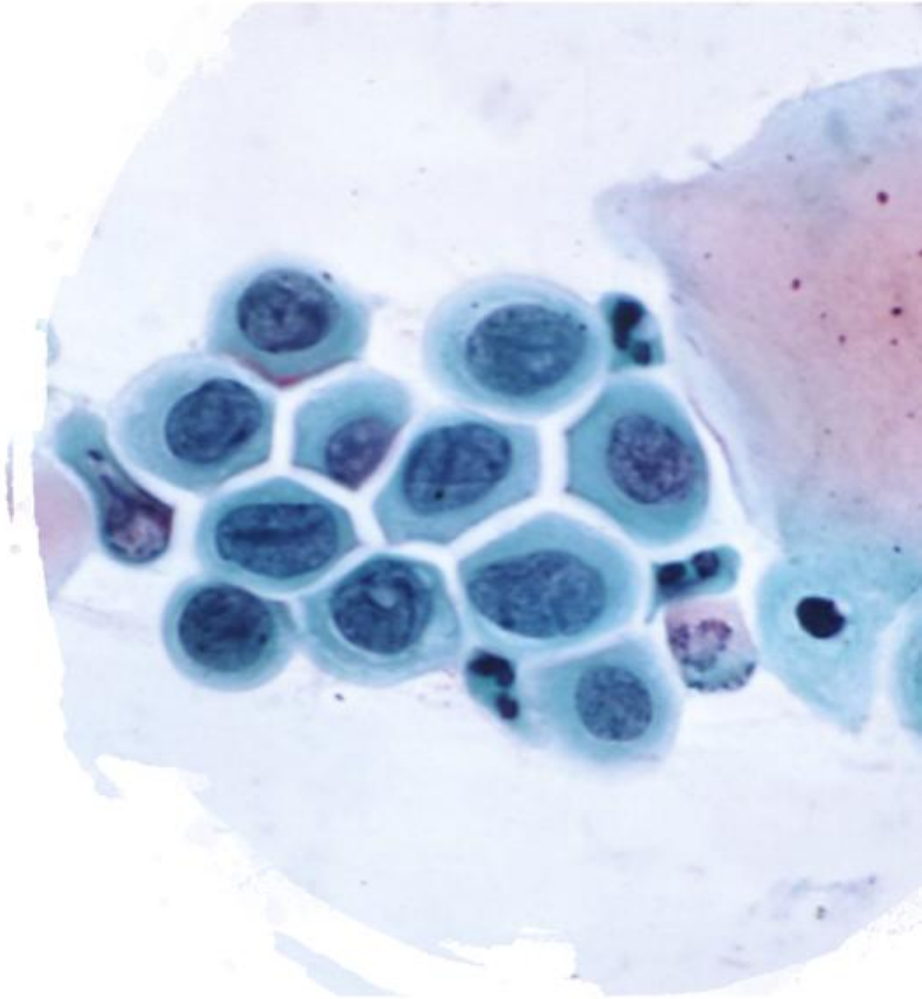
IMMUNOMODULATORS

Anal HSIL, update on treatments

ABLATIVE TREATMENTS
Infrared coagulation
Radiofrecuency
Electrocautery
Trichloroacetic acid
CO2Laser
Photodinamic therapy

IMMUNOMODULATORS
Imiquimod
5Fluorouracil
Cidofovir

ABLATIVE TREATMENTS



ABLATIVE TREATMENTS

HSIL anal management in patients at high risk for anal cancer

- Tissue destruction
- No action against HPV infection
- Applicated by healthcare personnel
- Material
- Most of them→ local anaesthesia
- Localised treatment
- High recurrence rate

Cranston RD *et al*. Sex Transm Dis 2014;41:420–6// Goldstone RN *et al*. Int J Colorectal Dis 2017;32:357–65.// Burgos J *et al* HIV Med 2016;17:524–31.//Chang G *et al*. Dis Colon Rectum 2002;45:453–8. //Gaisa MM *et al*. Cancer 2020;1261470–9.//Burgos J *et al*. J Acquir Immune Defic Syndr 2018;79:612–6.

ABLATIVE TREATMENTS

HSIL anal management in patients at high risk for anal cancer

Ablative Therapies RADIOFREQUENCY ABLATION

- Requires training
- **Requires sedation** + anesthesia
- Duration ≈10 minutes
- Possibility of extense ablation:
  - Circumferential
  - Hemi-circumferential
- AE (pain, stenosis, scar)

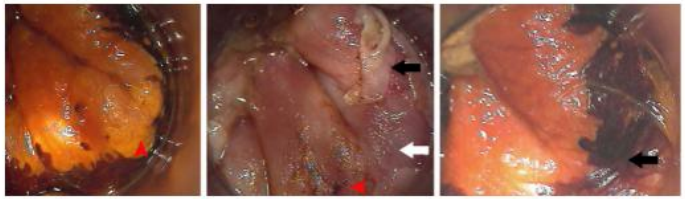
Vergara-Fernandez O *et al*. Outcomes of radiofrequency ablation for anal high-grade squamous intraepithelial lesions. Tech Coloproctol. 2021 ;25:701-707.
Goldstone RN *et al*. A trial of radiofrequency ablation for anal intraepithelial neoplasia. Int J Colorectal Dis. 2017;32:357-365.
Goldstone RN *et al*. Brief Report: Radiofrequency Ablation Therapy for Anal Intraepithelial Neoplasia: Results From a Single-Center Prospective Pilot Study in HIV+ Participants. J Acquir Immune Defic Syndr. 2017 1;76(4):e93-e97.

Int J Colorectal Dis (2017) 32:357–365
DOI 10.1007/s00384-016-2679-2

ORIGINAL ARTICLE

A trial of radiofrequency ablation for anal intraepithelial neoplasia

Robert N. Goldstone[1] · Shirin R. Hasan[2] · Steven Drury[3] · Teresa M. Darragh[4] · Annemieke van Zante[5] · Stephen E. Goldstone[6]



	3 months	6 months	12 months
Effectiveness	60%	90%	100%
Persistence HSIL	3/10	1/10	0/10

Prospective trial (2017)
21 participants (**no HIV+**)
Hemi-circumferential anal canal RFA
3 pulses of 12 j/cm2 (Sedation)
HRA control every 3 months

Individual lesion cure rate after one RFA →88 %
No metachronous lesions at 12 months
Moderate-severe pain 24h

Goldstone RN *et al*. Int J Colorectal Dis. 2017;32:357-365.

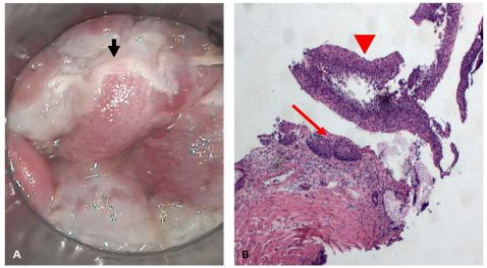
Radiofrequency Ablation Therapy for Anal Intraepithelial Neoplasia: Results From a Single-Center Prospective Pilot Study in HIV+ Participants

Robert N. Goldstone, MD, Shirin R. Hasan, MSc, MS,† and Stephen E. Goldstone, MD‡*

TABLE 2. Safety and Efficacy Results: HSIL Recurrence

	Participant (N = 10) and Lesion (N = 29) Assessments			
	3 mo (N = 10)	6 mo (N = 10)	9 mo (N = 10)	12 mo (N = 10)
Participants with persistent HSIL	3 (30%)	1 (10%)	0 (0%)	0 (0%)
Participants with metachronous HSIL	1 (10%)	0 (0%)	0 (0%)	0 (0%)
Individual index HSIL persistence (N = 29)	7 (24.1%)	1 (3.4%)	0 (0%)	0 (0%)

Data are expressed as n (%).



Prospective trial

10 participants (**9 HIV+**)

Circumferential anal RFA (sedation)

3 pulses of 12 j/cm2

HRA control every 3 months

All participants HSIL free by 12 months

No serious AEs occurred

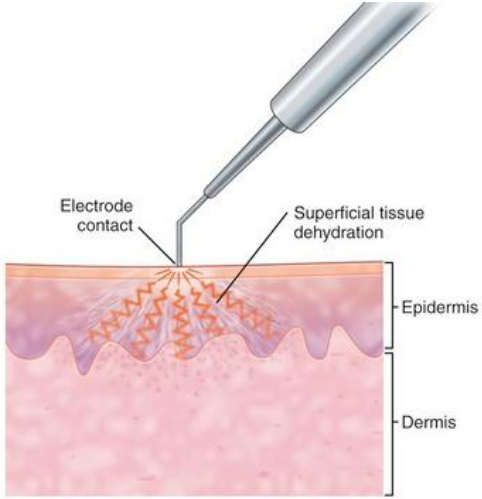
***Average Anal pain peak level after RFA→ 7**

Goldstone RN *et al.* Int J Colorectal Dis. 2017 Mar;32(3):357-365

Ablative Therapies ELECTROCAUTERY

Ablative Therapies Electrocautery

- Electricity heat destruction tissue
- Easy (minimal training)
- Economically affordable (widespread)
  - 1500 €



Marks DK *et al*. J Acquir Immune Defic Syndr. 2012;59: 259-65.
Richel *et al.* Lancet Oncol. 2013 ;14:346-53.
Burgos J *et al*. HIV Med 2016;17:524–31.
Gaisa MM *et al.* Cancer. 2020 1;126:1470-1479.
Fuertes I *et al.* Int J STD AIDS. 2021 May

Ablative Therapies ELECTROCAUTERY

Marks DK *et al*. J Acquir Immune Defic Syndr. 2012;59: 259-65.
Richel *et al.* Lancet Oncol. 2013 ;14:346-53.
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Fuertes I *et al.* Int J STD AIDS. 2021 May

Ablative Therapies Electrocautery

- Local anaesthesia required (most cases)
- Duration 10-15 minutes
- Does not allow extensive treatment
- Frequent AE's: bleeding, local pain (mild and self-limited)
- Risk of HPV inhalation

Electrocautery Ablation of High-Grade Anal Squamous Intraepithelial Lesions in HIV-Negative and HIV-Positive Men Who Have Sex With Men

Douglas K. Marks, BS and Stephen E. Goldstone, MD

Ablative Therapies
ELECTROCAUTERY

RETROSPECTIVE (2012)
232 MSM (132 HIV+)
Follow-up ≈18 months

	HSH NO VIH	HSH VIH
No HSIL after 1st session	85%	**75%**
Recurrence (+ML)	53%	**61%**
No HSIL at last visit	83%	**69%**

Marks DK *et al*. J Acquir Immune Defic Syndr. 2012. 1;59:25965.

DOI: 10.1111/hiv.12352
HIV Medicine (2016), **17**, 524–531

ORIGINAL RESEARCH

The effectiveness of electrocautery ablation for the treatment of high-grade anal intraepithelial neoplasia in HIV-infected men who have sex with men*

J Burgos,[1] A Curran,[1] S Landolfi,[2] J Navarro,[1] N Tallada,[2] A Guelar,[3] M Crespo,[1] I Ocaña,[1] E Ribera[1] and V Falcó[1]

RETROSPECTIVE
83 MSM-HIV
ELECTROCOAGULATION
Mean follow-up 12m

Best responses after 2-4 sessions

Complete Response 32.5%

Partial response 33.7%

No response 33,7%

Recurrence (12m) 25%

Total response ≈ 50%

Burgos J *et al*. HIV Med. 2016;17:524-31.

Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

Open-label, randomised trial

156 MSM-HIV with anal dysplasia (any grade)

Electrocautery 46 patients

Imiquimod 54 patients

5-fluorouracil 48 patients

CUMULATIVE RECURRENCE

	All patients	Imiquimod	Flurouracil	Electrocautery
24 weeks	22% (11/50)	19% (3/16)	38% (5/13)	14% (3/21)
48 weeks	46% (22/48)	47% (7/15)	50% (6/12)	43% (9/21)
72 weeks	67% (30/45)	71% (10/14)	58% (7/12)	68% (13/19)

Data are % (n/N).Cumulative recurrence rates at weeks 24, 48, and 72 after treatment. Of the 54 patients initially responding to treatment, 50 patients returned for a follow up high resolution anoscopy 24 weeks after treatment. An additional two and three patients were lost to follow up at the 48-week and 72-week visits.

Table 3: **Cumulative recurrence rates**

Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

Open-label, randomised trial

156 MSM-HIV with anal dysplasia (any grade)

1sesión/4 semanas
Máximo 5 sesiones

Electrocautery 46 patients

Imiquimod 54 patients

5-fluorouracil 48 patients

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	Intra-anal lesions			Peri-anal lesions		
	Imiquimod	Fluorouracil	Electrocautery	Imiquimod	Fluorouracil	Electrocautery
Complete response						
n/N	9/41	7/42	16/34	9/9	4/7	3/4
% (95% CI)	22% (12–37)	17% (8–31)	47% (31–63)	100% (73–100)	57% (25–84)	75% (29–97)
Partial response						
n/N	6/41	7/42	3/34	..	..	..
% (95% CI)	15% (7–29)	17% (8–31)	9% (2–24)	..	..	..
No response						
n/N	26/41	28/42	15/34	0/9	3/7	1/4
% (95% CI)	63% (48–76)	67% (51–79)	44% (29–61)	0% (0–28)	43% (16–75)	25% (3–71)

Assessment of response by localisation. The cumulative number of peri-anal and intra-anal lesions exceeded the total number of patients, because some patients had both peri-anal and intra-anal lesions. For intra-anal lesions, groups differed significantly in complete response (p=0·0080) and overall (complete+partial) response (p=0·045). For peri-anal lesions, groups did not differ significantly in response (p=0·36).

Table 4: **Response to treatment (per protocol) for peri-anal and intra-anal lesions separately**

EC best results in terms of effectiveness for intra-anal HSIL

Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

	Imiquimod (n=53)		Fluorouracil (n=48)		Electrocautery (n=45)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Any side-effect, highest grade	25 (47%)	23 (43%)	31 (65%)	13 (27%)	34 (76%)	8 (18%)
Pain	20 (38%)	17 (32%)	25 (52%)	7 (15%)	19 (42%)	8 (18%)
Itching	8 (15%)	2 (4%)	5 (10%)	1 (2%)	1 (2%)	0 (0%)
Bleeding	16 (30%)	0 (0%)	19 (40%)	0 (0%)	31 (69%)	0 (0%)
Slimy stool	2 (4%)	1 (2%)	1 (2%)	1 (2%)	3 (7%)	0 (0%)
Urge	2 (4%)	1 (2%)	22 (46%)	4 (8%)	5 (11%)	1 (2%)
Incontinence	2 (4%)	0 (0%)	3 (6%)	1 (2%)	0 (0%)	0 (0%)
Diarrhoea	2 (4%)	1 (2%)	3 (6%)	2 (4%)	3 (7%)	0 (0%)
Flatulence	1 (2%)	0 (0%)	5 (10%)	2 (4%)	0 (0%)	0 (0%)
Influenza-like symptoms	6 (11%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Fatigue	6 (11%)	1 (2%)	2 (4%)	0 (0%)	1 (2%)	0 (0%)

Data are number (%). Severity of side-effects that occurred in at least 5% of participants in one treatment group. Difference between the three treatment groups in side-effects of grades 3–4 was p=0·019 (χ^2 test). Two patients (one in the imiquimod group and one in the electrocautery group) were not available for evaluation of side-effects.

Table 6: Side-effects

Electrocautery: **higher percentage of mild AEs** but **lower percentage of severe AEs**

Original Article

Electrocautery Ablation of Anal High-Grade Squamous Intraepithelial Lesions: Effectiveness and Key Factors Associated With Outcomes

Michael M. Gaisa, MD, PhD [1]; Yuxin Liu, MD, PhD[2]; Ashish A. Deshmukh, PhD, MPH[3]; Kimberly L. Stone, MPH[4]; and Keith M. Sigel, MD, PhD [4]

Ablative Therapies
ELECTROCAUTERY

RETROSPECTIVE
330 HIV with “de novo” anal HSIL
88% MSM
12 months after ablation
≈ 45% local recurrence
≈ 60% overall recurrence

Factors related to poorer response →

Multiple HSILs
HIV detectable CV
Current smoking
Initial / Persistent HPV-16 and/or 18 infection

Gaisa MM *et al.* Cancer. 2020.1;126:1470-9.

Ablative Therapies
INFRARED COAGULATION

- Short pulses of visible and infrared light → necrosis
  - 1.5mm deep lesions
  - Easy to use
- Requires local anaesthesia
- Frequent local side effects: pain and bleeding
- IRC2100™Infrared Coagulation System©: 9000€

Stier EA et al. Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: an AIDS malignancy consortium pilot study. J Acquir Immune Defic Syndr 2008; 47:56–61
Cranston RD, et al. A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. *Int J STD AIDS*. 2008;19:118–120.

Infrared Coagulator Treatment of High-Grade Anal Dysplasia in HIV-Infected Individuals

An AIDS Malignancy Consortium Pilot Study

Elizabeth A. Stier, MD, Stephen E. Goldstone, MD,† J. Michael Berry, MD,‡ Lori A. Panther, MD,§ Naomi Jay, PhD,‡ Susan E. Krown, MD,‖ Jeannette Lee, PhD,¶ and Joel M. Palefsky, MD‡*

Ablative Therapies
INFRARED COAGULATION

- Prospective 2008
- 18 HIV+ patients (44 anal HSILs)
- 11 HPV16+ /No change in HPV type after IR
- **65% complete response after 12m**

TABLE 2. Adverse Events

	Grade			
	1 = Mild	2 = Moderate	3 = Severe	Total
Anal/rectal bleeding	11	1	0	12
Anal/rectal pain	4	6	0	10
Flatulence	2	0	0	2
Fecal incontinence	2	0	0	2
Anal mucous discharge	1	0	0	1

Stier EA *et al*. J Acquir Immune Defic Syndr 2008; 47:56–61

ORIGINAL CONTRIBU

Treatment o
Neoplasia W
Care Popula

Stephen
Joseph S.

- Prospect
- **IRC** vs N
- HSIL /Co
- Follow u

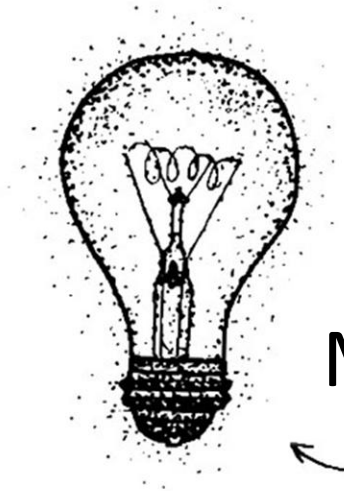
Persisten

Progressi

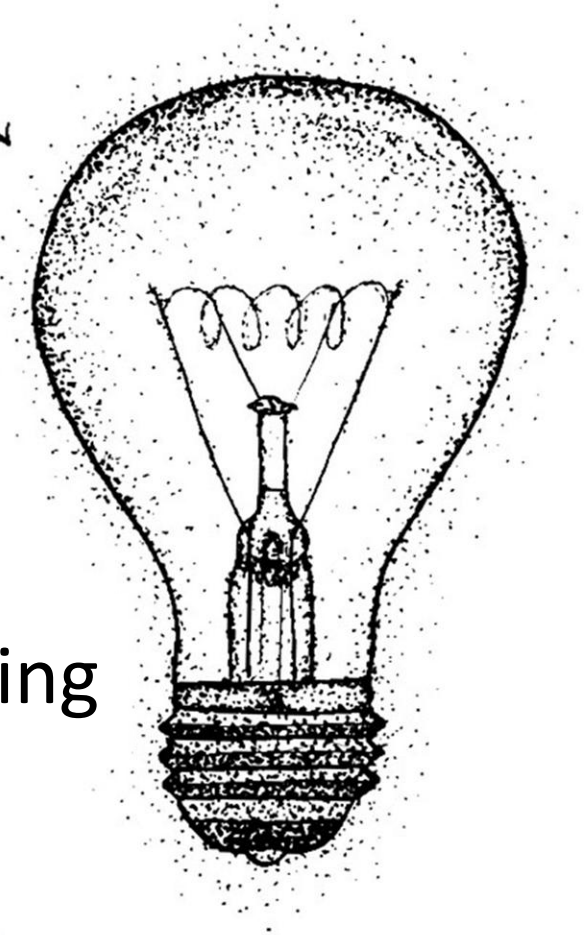
Weis SE, et al. Dis

2 estudios

IRC



Monitoring



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Naomi Jay,[5]
Wilkin[3]

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9;68(7):1204-1212.

ORIGINAL CONTRIBUTION

Treatment of High-Grade Anal Intraepithelial Neoplasia With Infrared Coagulation in a Primary Care Population of HIV-Infected Men and Women

Stephen E. Weis, D.O. [1,2] • Isabel Vecino, M.D. [1] • Janice M. Pogoda, Ph.D. [3]
Joseph S. Susa, D.O. [4]

- **Prospective cohort study** (n=124 PLWHIV)
- **IRC** vs **Not treatment** (voluntarily)
- HSIL /Condylomas
- Follow up ≈ 15 months

	Infrared coagulation	Untreated
Persistence HSIL	**26%**	88%
Progression SCCA	**0%**	**5%**

Weis SE, et al. Dis Colon Rectum. 2012 Dec;55(12):1236-43.

Clinical Infectious Diseases
MAJOR ARTICLE

A Randomized Clinical Trial of Infrared Coagulation Ablation Versus Active Monitoring of Intra-anal High-grade Dysplasia in Adults With Human Immunodeficiency Virus Infection: An AIDS Malignancy Consortium Trial

Stephen E. Goldstone,[1] Shelly Y. Lensing,[2] Elizabeth A. Stier,[3] Teresa Darragh,[4] Jeannette Y. Lee,[2] Annemieke van Zante,[4] Naomi Jay,[5] J. Michael Berry-Lawhorn,[5] Ross D. Cranston,[6] Ronald Mitsuyasu,[7] David Aboulafia,[8] Joel M. Palefsky,[4] and Timothy Wilkin[9]

- **Open-label, randomised, multicentric clinical trial**
- **IRC** vs **active monitoring**
- 120 HIV ≥27 years with 1-3 anal HSILs

	Infrared coagulation	Active monitoring
HSIL clearance 12 months	**63%**	**30%**

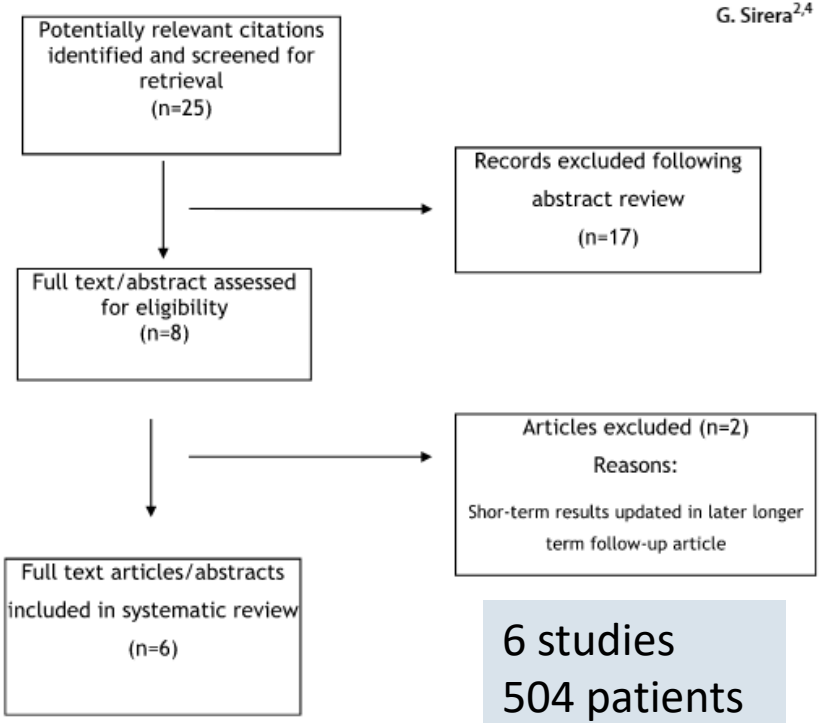
Goldstone SE *et al*. Clin Infect Dis. 2019 Mar 19;68(7):1204-1212.

Techniques in Coloproctology (2019) 23:707–712
https://doi.org/10.1007/s10151-019-02041-7

REVIEW

Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review

J. Corral[1,2] · D. Parés[1,2,3] · F. García-Cuyás[1,2] · B. Revollo[2,4] · S. Videla[2,5] · A. Chamorro[2,4] · M. Piñol[1,2] · B. Clotet[2,3,6] · G. Sirera[2,4]



Study	Year	Patients included	Data analysis	Study	Level of evidence[a]
Stier et al. [12]	2008	18	Prospective	Clinical series	2C
Cranston et al. [13]	2008	68	Retrospective	Clinical series	2C
Goldstone et al. [14]	2011	96	Retrospective	Clinical series	2C
Weis et al. [15]	2012	146	Prospective	Clinical series	2C
Sirera et al. [16]	2013	56	Retrospective	Clinical series	2C
Goldstone et al. [17]	2018	120	Prospective	Randomized, open-label trial	1B

[a]According to Oxford CEBM classification [18]

6 studies
504 patients

Corral J, Parés D, García-Cuyás F, Revollo B, Videla S, Chamorro A, Piñol M, Clotet B, Sirera G. Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review. Tech Coloproctol. 2019 Aug;23(8):707-712.

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REVIEW

Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review

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Study	HSIL at last follow up	Duration follow-up	Developed SISCCA *N* (0%)
Stier et al. [12]	38%	12 m	0/18 (0%)
Cranston et al. [13]	36%	4.7 m	0/68 (0%)
Goldstone et al. [14]	HIV+ 18%	HIV+ 69 m	0/96 (0%)
	HIV− 10%	HIV− 48 m	
Weis et al. [15]	Treated 13%	Treated 1.3 y	0/102 (0%)
	Untreated 93%	Untreated 1.8 y	2/42 (4.8%)
Sirera et al. [16]	12.50%	25 m	0/56 (0%)
Goldstone et al. [17]	Treated 29%	Treated 2 y	0/51 (0%)
	Untreated 72%	Untreated 1 y	0/57 (0%)

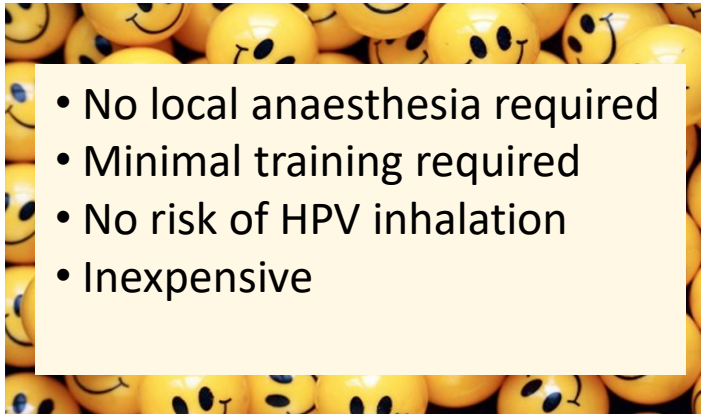
Persistence of anal HSIL in HIV patients after IRC
13%-38%

Corral J, Parés D, García-Cuyás F, Revollo B, Videla S, Chamorro A, Piñol M, Clotet B, Sirera G. Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review. Tech Coloproctol. 2019 Aug;23(8):707-712.

Ablative therapies
Trichloroacetic Acid

- Topical Ablative Treatment
- TCA 80%
- 4-5 touches
- Applicated by healthcare personnel

Ablative therapies
TRICHLOROACETIC ACID



Ablative therapies
TRICHLOROACETIC ACID

ORIGINAL STUDY

Topical Application of Trichloroacetic Acid Is Efficacious for the Treatment of Internal Anal High-Grade Squamous Intraepithelial Lesions in HIV-Positive Men

Ross D. Cranston, MD, FRCP, Jonathan R. Baker, PA-C,† Yimeng Liu, MPH, MS,‡ Lu Wang, MS,‡ Esther Elishaev, MD,§ and Ken S. Ho, MD**

Retrospective
98 HSIL (72 MSM-HIV patients)

Response 78.6% → LSIL or normal
49.0% Respond after 1 session
27.6% Respond after 2 sessions

15.1% local recurrence
AEs not formally recorded

Cranston RD *et al*. Sex Transm Dis. 2014 Jul;41(7):420-6.

Efficacy of Trichloroacetic Acid in the Treatment of Anal Intraepithelial Neoplasia in HIV-Positive and HIV-Negative Men Who Have Sex With Men

Jasmeet Chadha Singh, MD, Victoria Kuohung, MD,† and Joel M. Palefsky, MD‡*

Ablative therapies
TRICHLOROACETIC ACID

- Retrospective
- 54 MSM (65% HIV+) / 55 lesions (35% LSIL)
- **Response 71% of HSIL**
- **Relapse 6 months**
  - 67% in non-HIV
  - **75% in HIV**
- 5% local discomfort

Predictors of poorer response ➡ **>40 years**
≥3 HSIL

Singh JC *et al*. J Acquir Immune Defic Syndr. 2009 Dec 1;52(4):474-9

Retrospective
2-4 treatment sessions

Effectiveness of Trichloroacetic Acid vs. Electrocautery Ablation for the Treatment of Anal High-Grade Squamous Intraepithelial Lesion in HIV-Infected Patients

Joaquin Burgos, MD, PhD, Mario Martin-Castillo, MD,† Stefania Landolfi, MD,‡ Maria C. Dinares, MD,‡ Judith Villar, MD, PhD,‡§ Jordi Navarro, MD,* Esteve Ribera, MD, PhD,* Vicenç Falcó, MD, PhD,* and Adria Curran, MD, PhD**

	ELECTROCAUTERY	TCA
HSH-VIH	182	56
Complete Response	33.5%	**60.7%**
Partial Response	28.0%	23.2%
Good tolerability	80.6% (more **bleeding**)	82.6% (more **itching**)
Recurrence 12m	**14.6%**	27.6%

Burgos J *et al*Effectiveness of Trichloroacetic Acid vs. Electrocautery Ablation for the Treatment of Anal High-Grade Squamous Intraepithelial Lesion in HIV-Infected Patients. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):612-616.

Ablatives therapies
CO2 LASER

- Superficial vaporisation of the epithelium
- Wavelength of 10.600nm
- High precision
- Minimal damage to adjacent tissues
- Expensive

- Applicated by healthcare personnel
- No local anaesthesia required (intraanal)
- Risk of HPV inhalation
- Requires eye protection

unpublished data

Ablatives therapies CO2 LASER

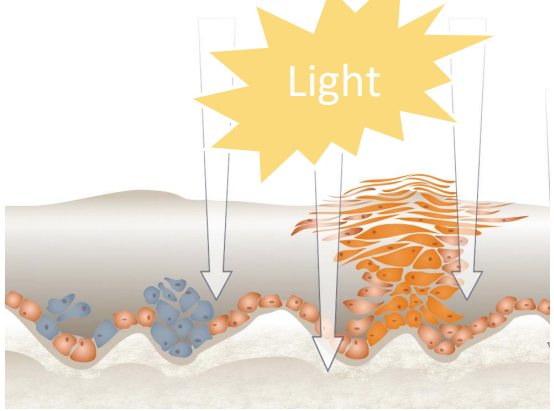
- Single-arm, clinical trial (2021)
- 52 HIV+ (98% MSM)
  - 72 no previously treated HSILs
  - No local anesthesia

Short term response Per Protocol	48 patients
Complete Response	**50.0%**
Partial response	20.8%
No response	29.1%

AEs Grade 1→ 24.5%
AEs Grade 2→ 6.1%

- **69.4% → NO symptoms during or after the procedure**

Ablative Therapies
PHOTODYNAMIC THERAPY



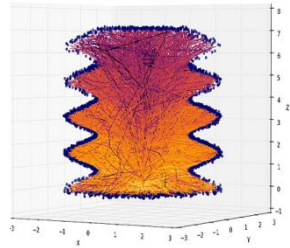
- Prospective 15 MSM-HIV AIN3
- **Complete Response 28%**
- **Partial Response 14%**
- No Response 6%
- AE: severe pain, stenosis (1 case)

- Ablation by application of a light source to a previously photosensitised area
- Photosensitisation can be systemic or topical

- Uniform application
- **Significant local AEs**: 1 stenosis out of 15 patients, severe pain, suppuration...

van der Snoek EM *et al.* Photodynamic therapy with systemic meta-tetrahydroxyphenylchlorin in the treatment of anal intraepithelial neoplasia, grade 3. 2012 Lasers Surg Med 44(8):637–644.

Ablative Therapies
PHOTODYNAMIC THERAPY



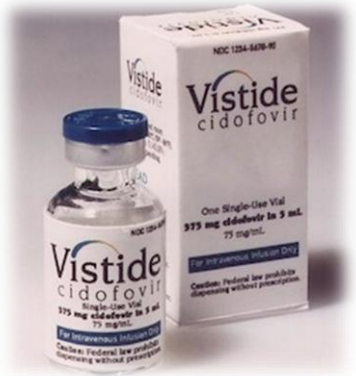
Proyect ClearPap

- H.La Paz Dr. Jesús Manuel Muñoz
- Device for the treatment of HSIL by application of PDT
- ClearPap is able to overcome the current limitations of PDT.
- Applies and diffuses light homogeneously throughout the cavity for increased therapy efficacy
- Synergistic effect between therapy and drug action and increased immune response with relief of AEs

IMMUNOMODULATORY THERAPIES

HSIL anal management in patients at high risk for anal cancer

INMUNOMODULATORS

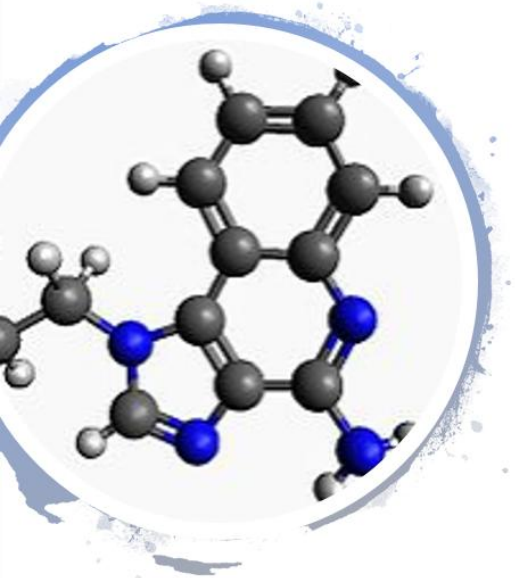


INMUNOMODULATORS

- Stimulate/suppress the immune system
- Actvity against HPV infection
- Self-applied / Outpatient
- Full mucosal treatment
- Local and systemic AEs
- Expensive, patient's expens
- Not for use in pregnant women

HSIL anal management in patients at high risk for anal cancer

HSIL anal management in patients at high risk for anal cancer



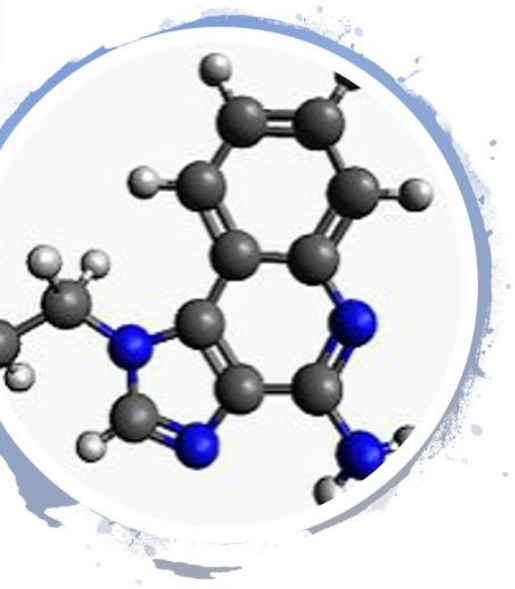
IMMUNOMODULATORY THERAPIES

Imiquimod

- Activates Toll like Receptor 7
  - Activation of innate and cellular immune pathways
  - Antiviral, antitumoural and immunoregulatory effects
- Off-label use for management of anogenital dysplasia
- Available in 3.75 and 5% cream
  - studies carried out with 5% dosage
- Can be provided in suppositories

IMMUNOMODULATORY THERAPIES

Imiquimod



Fox PA, Nathan M, Francis N, Singh N, Weir J, Dixon G, Barton SE, Bower M**. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod**. AIDS. 2010 Sep 24;24(15):2331-5.

Richel O, de Vries HJC, van Noesel CJM, et al. **Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial.** Lancet Oncol 2013; 14: 346–353.

van der Snoek EM, den Hollander JC and van der Ende ME. **Imiquimod 5% cream for five consecutive days a week in an HIV-infected observational cohort up to 32 weeks in the treatment of high-grade squamous intraepithelial lesions: Table 1.** Sex Transm Infect 2015;91: 245–247.

Kaspari M, Gutzmer R, Kaspari T, et al**. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma.**
Br J Dermatol 2002; 147: 757–759.

Wieland U, Brockmeyer NH, Weissenborn SJ, et **al.Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men**. Arch Dermatol 2006; 142: 1438–1444.

Salas-Márquez C, Repiso-Jiménez JB, Padilla-España L,et al. **Imiquimod anal tampons treatment of anal intraepithelial neoplasia**. J Eur Acad Dermatol Venereol 2018; 32: e334–e336.

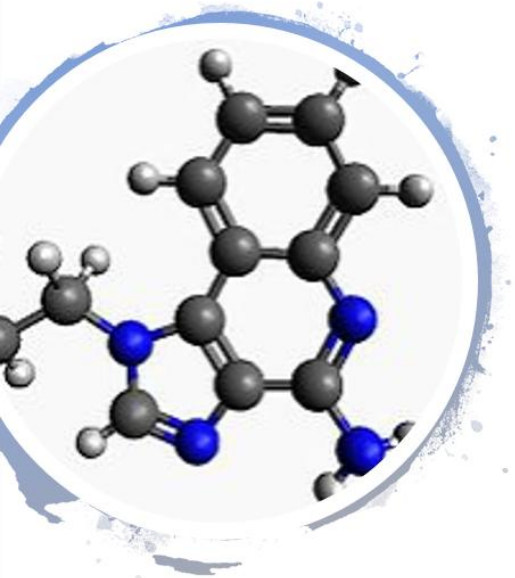
Willems N, Libois A, Nkuize M, et al**. Treatment of anal dysplasia in HIV-positive men who have sex with men in a large AIDS reference centre.** Acta Clin Belg 2017;72: 29–35.

Santorelli C, Leo CA, Baldelli F, et al. **Response to imiquimod 5% cream as treatment for condyloma and anal intraepithelial neoplasia in HIV-positive and HIVnegative**
patients. Sex Transm Infect 2017; 93: 229.

Fuertes I, Bastida C, Lopez-Cabezas C, Rodríguez-Carunchio L, Ordi J, Mallolas J, Cranston RD, Blanco JL. **The effectiveness and tolerability of imiquimod suppositories to treat extensive intra-anal high-grade squamous intraepithelial lesions/warts in HIV-infected individuals**. Int J STD AIDS. 2019 Oct;30(12):1194-1200.

A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod

Paul A. Fox[a], Mayura Nathan[b], Nicholas Francis[c], Naveena Singh[d], Justin Weir[c], Glen Dixon[c], Simon E. Barton[a] and Mark Bower[a]



Double blind randomized placebo controlled study

64 HIV+ MSM (53 completed)

Imiquimod (28) 3 x per week **x 4 months**

Placebo (25) 3 x per week **x 4 months**

Anal cytology, HRA and biopsy at 6 months

- Imiquimod: 4 resolved, 8 LSIL (43%)
- Placebo: 1 resolved (4%)

Overall **63% response** during follow up to 36 months

benefit of prolonged or repeated treatments

Fox PA *et al*. AIDS. 2010 Sep 24;24(15):2331-5.

Review article

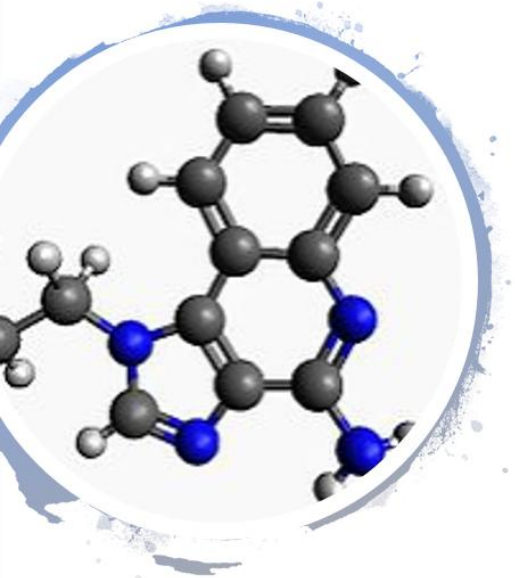
INTERNATIONAL JOURNAL OF STD & AIDS

Intra-anal use of imiquimod: what is the clinical evidence?

International Journal of STD & AIDS
0(0) 1–7

DOI: 10.1177/0956462419855828
journals.sagepub.com/home/std
SAGE

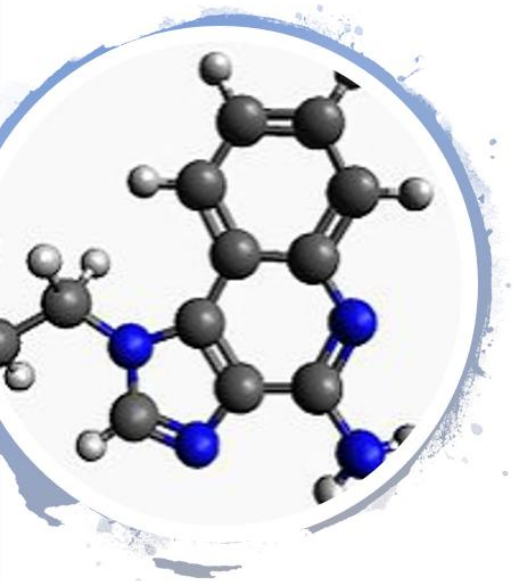
Ioannis D Gkegkes[1,2], Christos Iavazzo[3] and Apostolos P Stamatiadis[1]



- **14 studies** (3 randomized controlled trials, 5 retrospective studies, 4 prospective studies, and 2 case reports)
- **422 patients**, (**66.6% HIV+** infection)
- HSILs (50%) / Warts (45%)
- Mean duration of imiquimod 14.8 weeks
  - range: 8–24
- Dosage of imiquimod ranged between 5.2 - 15 mg
  - Self-applied imiquimod cream 83.6%
  - Suppositories 4%
  - Anal tampons 6.6%
- Common AE were (minor) pain, itching, and burning sensation

Gkesgkes et al. Int J STD AIDS. 2019;30:1018-1024.

HSIL anal management in patients at high risk for anal cancer



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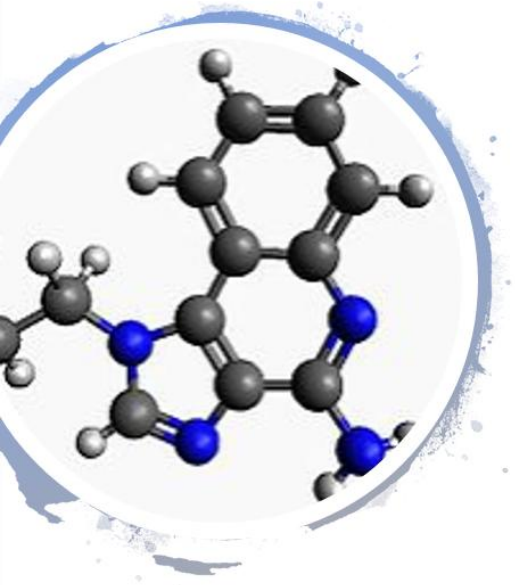
journals.sagepub.com/home/std
SAGE

Ioannis D Gkegkes[1,2], Christos Iavazzo[3] and Apostolos P Stamatiadis[1]

	HSIL	WARTS
Complete Response	**35%**	**67%**
Partial Response	**20.9%**	**-**
Recurrence	**15%**	**19.8%**

Good option, especially in case of both extensive and circumferential intra-anal HSIL

IMMUNOMODULATORY THERAPIES
Imiquimod



- Intra-anal treatment with imiquimod better tolerated than perianal treatment
- Better response in perianal HSIL

Richel O, *et al*. Lancet Oncol 2013; 14: 346–353.
Wieland U *et al.* Arch Dermatol 2006; 142: 1438–1444.

- Smoking as a predictor of worse response

Fuertes I *et al*. Int J STD AIDS. 2019 Oct;30(12):1194-1200.
Harvey G *et al*. Clin Exp Dermatol. 2019;44(4):e140–4.

Original research article

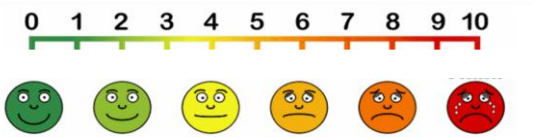
INTERNATIONAL JOURNAL OF STD & AIDS

The effectiveness and tolerability of imiquimod suppositories to treat extensive intra-anal high-grade squamous intraepithelial lesions/ warts in HIV-infected individuals

Irene Fuertes[1,*], Carla Bastida[2,*], Carmen Lopez-Cabezas[2], Leonardo Rodriguez-Caruncho[2], Jaume Ordi[3,4], Josep Mallolas[5], Ross D Cranston[5] and Jose Luis Blanco[5]

TOLERABILITY:

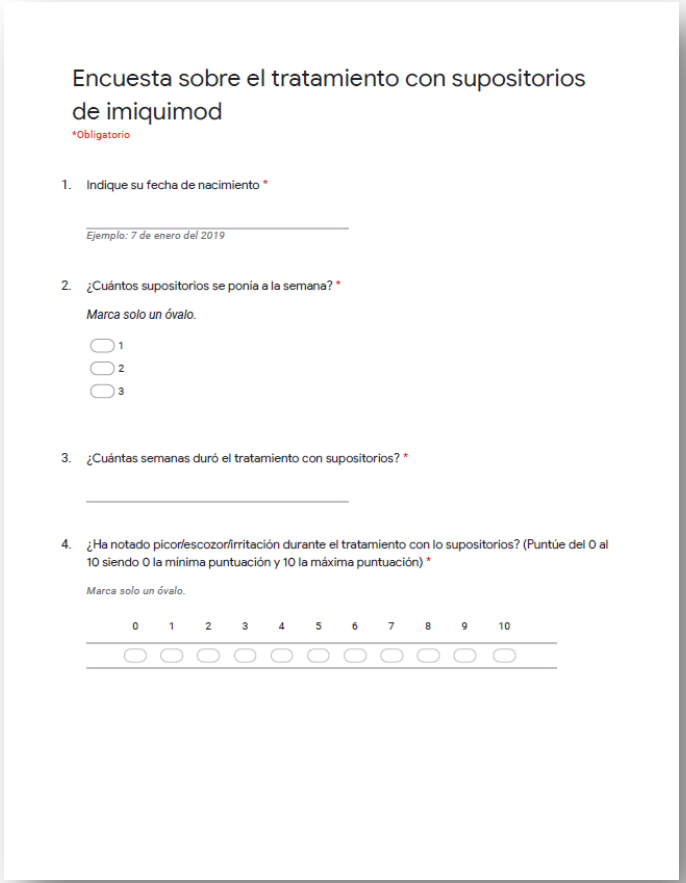
Anonymous online survey (20 questions)



GOOD
Symptoms < 3
No reduction / No interruption of treatment because of AE

BAD
Symptoms >7
Reduction / Interruption of treatment because of AE

ACCEPTABLE
Symptoms 3-7
No reduction /No interruption of treatment because of AE



Encuesta sobre el tratamiento con supositorios de imiquimod

*Obligatorio

1. Indique su fecha de nacimiento *

Ejemplo: 7 de enero del 2019

2. ¿Cuántos supositorios se ponía a la semana? *

Marca solo un óvalo.

1
2
3

3. ¿Cuántas semanas duró el tratamiento con supositorios? *

4. ¿Ha notado picor/escozor/irritación durante el tratamiento con lo supositorios? (Puntúe del 0 al 10 siendo 0 la mínima puntuación y 10 la máxima puntuación) *

Marca solo un óvalo.

0 1 2 3 4 5 6 7 8 9 10

Fuertes I *et al*. Int J STD AIDS. 2019 Oct;30(12):1194-1200

TOLERABILITY

GOOD
57,1% (n=36)

ACCEPTABLE
33,3% (n=21)

>90%

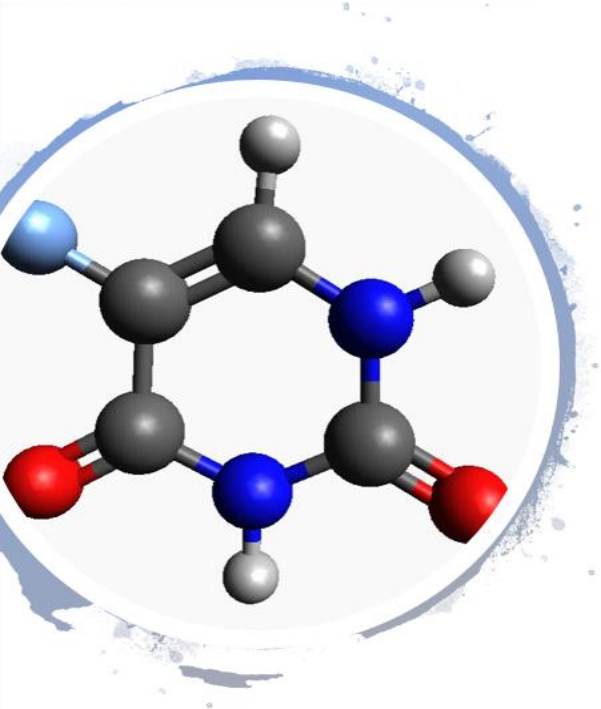
BAD
9,5% (n=6)

RESULTS:

Adverse Events	Total patients = 63
Local AE pain, itching, and burning sensation	39,7% (n=25)
Severe	11,1% (n=7)
Moderate	28,6% (n=18)
Sistemic AE	20,7% (n=13)
Severe	4,8% (n=3)
Need for analgesia to mitigate AE	15,9% (n=10)
Reduction of treatment because of AE	14,3% (n=9)
Interruption of treatment because of AE	9,5% (n=6)

Fuertes I *et al*. Int J STD AIDS. 2019;30(12):1194-1200

IMMUNOMODULATORY THERAPIES
5 FLUOROURACIL



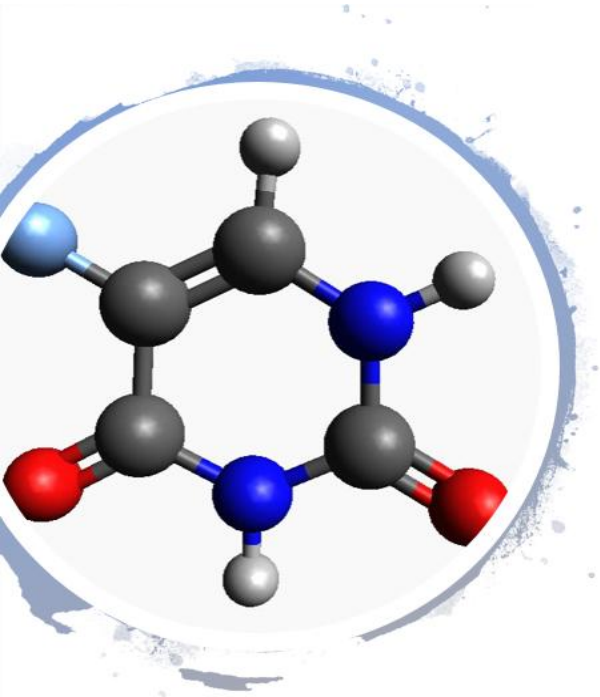
Potent antimetabolite (group of fluoropyrimidines)

Antitumoral effect

Formulated in petrolatum (3-5%)

No suppositories

IMMUNOMODULATORY THERAPIES
5 FLUOROURACIL



Richel *et al.* Br J Dermatol. 2010;163:1301-7

THERAPEUTICS

BJD
British Journal of Dermatology

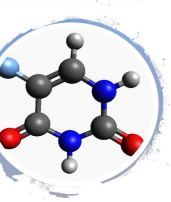
Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men

O. Richel, U. Wieland,* H.J.C. de Vries,† N.H. Brockmeyer,‡ C. van Noesel,§ A. Potthoff,‡ J.M. Prins and A. Kreuter‡

- Open prospective pilot study
- 46 patients
- 76% →multifocal disease/74% → HSIL

ITT analysis 5-Flu 46 patients		
Response	Complete	39%
	Partial	17%
No response		37%
Recurrence		50% (of CR group)
AE		85% (just 2 discontinued)

Treatment led to a significant decrease of HPV16-DNA load and high-risk HPV-DNA load in all patients



Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

Open-label, randomised trial

156 MSM HIV with anal dysplasia (any grade!!)

Electrocautery 46 patients

Imiquimod 54 patients

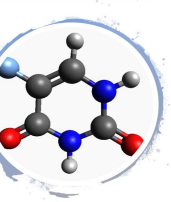
5-fluorouracil 48 patients

CUMULATIVE RECURRENCE

	All patients	Imiquimod	Flurouracil	Electrocautery
24 weeks	22% (11/50)	19% (3/16)	38% (5/13)	14% (3/21)
48 weeks	46% (22/48)	47% (7/15)	50% (6/12)	43% (9/21)
72 weeks	67% (30/45)	71% (10/14)	58% (7/12)	68% (13/19)

Data are % (n/N).Cumulative recurrence rates at weeks 24, 48, and 72 after treatment. Of the 54 patients initially responding to treatment, 50 patients returned for a follow up high resolution anoscopy 24 weeks after treatment. An additional two and three patients were lost to follow up at the 48-week and 72-week visits.

Table 3: **Cumulative recurrence rates**



Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

	Intra-anal lesions			Peri-anal lesions		
	Imiquimod	Fluorouracil	Electrocautery	Imiquimod	Fluorouracil	Electrocautery
Complete response						
n/N	9/41	7/42	16/34	9/9	4/7	3/4
% (95% CI)	22% (12–37)	17% (8–31)	47% (31–63)	100% (73–100)	57% (25–84)	75% (29–97)
Partial response						
n/N	6/41	7/42	3/34	..	..	..
% (95% CI)	15% (7–29)	17% (8–31)	9% (2–24)	..	..	..
No response						
n/N	26/41	28/42	15/34	0/9	3/7	1/4
% (95% CI)	63% (48–76)	67% (51–79)	44% (29–61)	0% (0–28)	43% (16–75)	25% (3–71)

Assessment of response by localisation. The cumulative number of peri-anal and intra-anal lesions exceeded the total number of patients, because some patients had both peri-anal and intra-anal lesions. For intra-anal lesions, groups differed significantly in complete response (p=0·0080) and overall (complete+partial) response (p=0·045). For peri-anal lesions, groups did not differ significantly in response (p=0·36).

Table 4: **Response to treatment (per protocol) for peri-anal and intra-anal lesions separately**

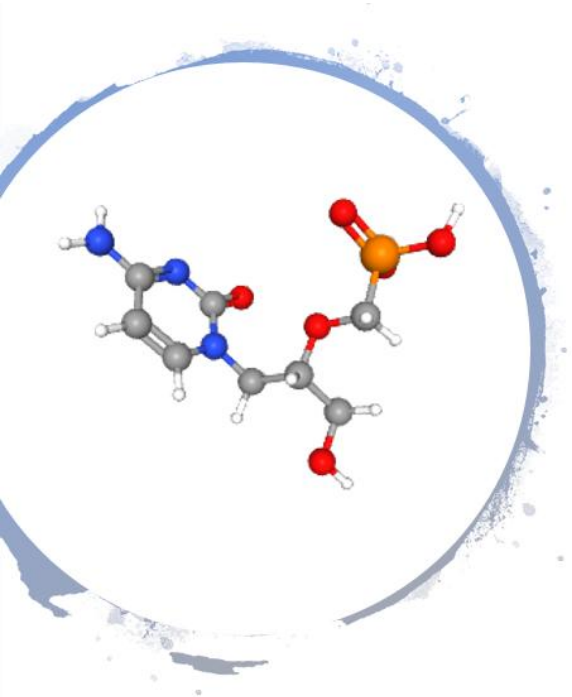
5Fluorouracilo intra-anal and perianal

Poorer efficacy results compared to imiquimod and electrocoagulation

AE 5 FU:
More patients with Grade 1-2 but fewer with Grade 3-4 than imiquimod-treated patients

IMMUNOMODULATORY THERAPIES

Cidofovir

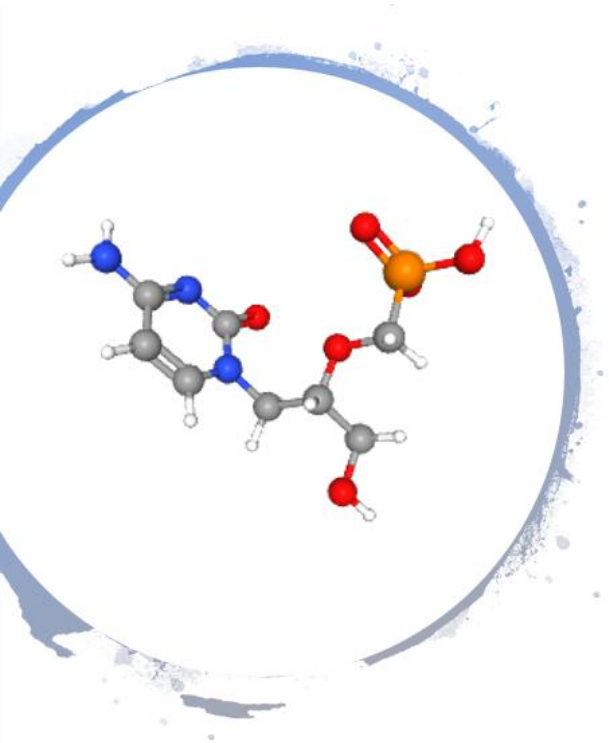


- Cidofovir is a nucleotide analog with activity against a wide range of DNA viruses

  Induces of apoptosis in HPV-infected cells
  Reduces of expression of E6 and E7
  Increases the levels of the tumor suppressor protein p53
  Antiangiogenic effect

- Off-label use for management of anogenital dysplasia
- Field treatment and patient self-application
  - Formulated in cream 1-2%
- Hospital dispensing
  - No cost for the patient

IMMUNOMODULATOR Y THERAPIES CIDOFOVIR



Topical cidofovir to treat high-grade anal intraepithelial neoplasia in HIV-infected patients: a pilot clinical trial

Elena Sendagorta[a], Jose I. Bernardino[b], Mario Álvarez-Gallego[c], Marta Feíto[a], Rosa Feltes[a], Maria J. Beato[d], Jose A. Pérez-Molina[e], Maria Yllescas[f], Mariana Díaz-Almirón[g], Jose R. Arribas[b], Juan González-García[b], Pedro Herranz[a], for the CIDAN12/7412 GESIDA Study Group

- Single-arm, clinical trial
- 17 HIV-infected patients with intraanal HSIL
- Cidofovir 1%cream, 3 times weekly for 4w
- ITT population
  - **62.5% had achieved CR at 12 week**
    - At 24w: 70% remained in CR, 20% recurred HSIL
  - **Local AE in 81% (no discontinuations)**
- Mean number of genotypes between baseline visit and week 12 was significantly reduced

Sendagorta *et al* AIDS. 2016. 2;30;75-82.

ORIGINAL CONTRIBUTION

Health-Related Quality of Life and Sexual Functioning of HIV-Positive Men Who Have Sex With Men Who Are Treated for Anal Intraepithelial Neoplasia

Matthijs L. Siegenbeek van Heukelom, M.D.[1,2,3] • Olivier Richel, M.D., Ph.D.[1,2]
Pythia T. Nieuwkerk, Ph.D.[4] • Henry J. C. De Vries, M.D., Ph.D.[2,3,5]
Jan M. Prins, M.D., Ph.D.[1,2]

Electrocautery 46 patients

Imiquimod 54 patients

5-fluorouracil 48 patients

- Impact of 3 treatment options for anal SIL on **health-related quality of life and sexual functioning** in HIV-positive MSM
- 148 patients → 16 weeks of treatment

- **Imiquimod** group were:
  - **more likely to report pain/discomfort at week 8 than** patients in the EC group.
- **Electrocautery** group were:
  - more likely to report **anxiety/depression and were less satisfied with their overall sex life** at week 16
  - more likely to report pain/discomfort and problems with usual activities at week 20 than patients in the 5FU group.

Dis Colon Rectum. 2016 Jan;59(1):42-47.

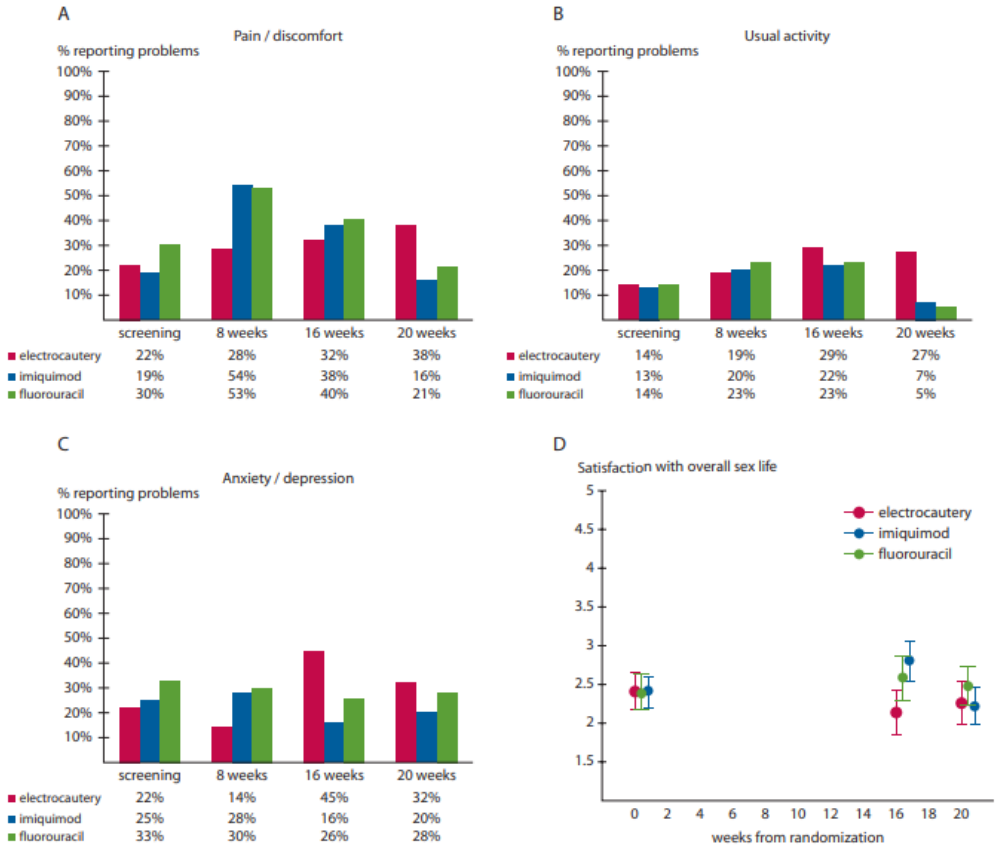


FIGURE 1. A, EQ-5D scores for the dimension pain/discomfort before treatment, during treatment, and after treatment for AIN, per treatment arm. B, EQ-5D scores for the dimension usual activity before treatment, during treatment, and after treatment for AIN, per treatment arm. C, EQ-5D scores for the dimension anxiety/depression before treatment, during treatment, and after treatment for AIN, per treatment arm. AIN = anal intraepithelial neoplasia; before treatment = screening; during treatment = 8, 16 weeks; after treatment = 20 weeks. D, Overall satisfaction with sex life in the past 4 weeks before treatment, during treatment, and after treatment for AIN, per treatment arm (mixed linear model). AIN = anal intraepithelial neoplasia; before treatment = 0 weeks; during treatment = 16 weeks; after treatment = 20 weeks.

ORIGINAL CONTRIBUTION

Health-Related Quality of Life and Sexual Functioning of HIV-Positive Men Who Have Sex With Men Who Are Treated for Anal Intraepithelial Neoplasia

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Jan M. Prins, M.D., Ph.D.[1,2]

Conclusions: All treatment options have a negative impact on aspects of health-related quality of life.

Electrocautery has significantly more negative effects on health-related quality of life and sexual functioning.

Experiencia personal

HSIL anal management in patients at high risk for anal cancer

Electrocautery

Effective

Cheap

Local anaesthesia required

Painful

Poor for extensive lesions and perianal

Better for condyloma

HSIL anal management in patients at high risk for anal cancer

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Imiquimod

Very usefull for extensive intra-anal HSIL and condyloma

Expensive (patient)

Poor adherence

HSIL anal management in patients at high risk for anal cancer

Electrocautery
Effective
Cheap
Local anaesthesia required
Painful
Poor for extensive lesions and peria
Better for condyloma

TCA
Effective
Cheap
No anaesthesia
Possibility of dealing with extensive HSIL
Poor for condyloma

Imiquimod
Very usefull for extensive intra-anal HSIL and condyloma
Expensive (patient)
Poor adherence

HSIL anal management in patients at high risk for anal cancer

Electrocautery
Effective
Cheap
Local anaesthesia required
Painful
Poor for extensive lesions and peria
Better for condyloma

Laser CO2
Effective
Expensive (department)
No anaesthesia
Possibility of dealing with extensive HSIL
Better for condyloma

TCA
Effective
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Very usefull for extensive intra-anal HSIL and condyloma
Expensive (patient)
Poor adherence

5-Fluorouracil
Usefull for extensive intra-anal HSIL
Expensive (patient)
Poor adherence

Making decisions (in brief)

- Avoid invasive treatments
- Make your patient understand the reason for treatment
- Discuss therapeutic possibilities with your patient
- Think of a plan B in case of a poor response to your first attempt
- Explain warning signs to your patient
- Ask for help if you need

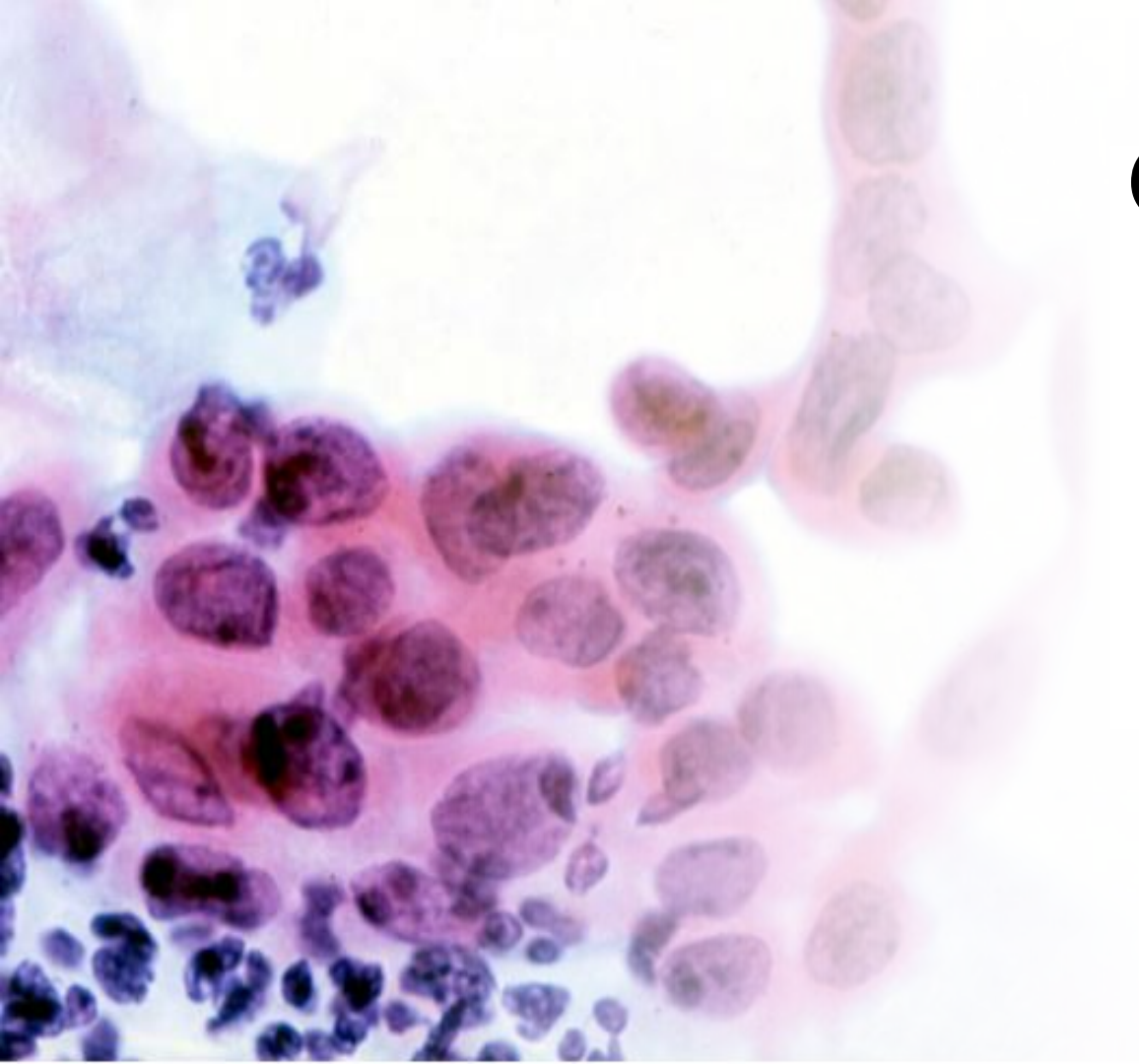
  (other anoscopists/other specialists)
- Prioritise the treatment you manage best

Future of anal HSIL management

Future of anal HSIL management

- Identification of target HSILs to be treated
- Correct selection of HPV vaccination candidates
- Combined treatments

  (ablative + immunomudulator)
- Maintenance treatment
  - New immunomodulators
  - New ablatives
  - Modifications of the microbiota…



Gracias por vuestra atención

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