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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

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Background. Anal high-grade squamous intraepithelial lesions (HSILs) ablation may reduce the incidence of invasive cancer, but few data exist on treatment efficacy and natural regression without treatment.

Methods. An open-label, randomized, multisite clinical trial of human immunodeficiency virus (HIV)–infected adults aged ≥27 years with 1–3 biopsy-proven anal HSILs (index HSILs) without prior history of HSIL treatment with infrared coagulation (IRC). Participants were randomized 1:1 to HSIL ablation with IRC (treatment) or no treatment (active monitoring [AM]). Participants were followed every 3 months with high-resolution anoscopy. Treatment participants underwent anal biopsies of suspected new or recurrent HSILs. The AM participants underwent biopsies only at month 12. The primary end point was complete clearance of index HSIL at month 12.

Results. We randomized 120 participants. Complete index HSIL clearance occurred more frequently in the treatment group than in the AM (62% vs 30%; risk difference, 32%; 95% confidence interval [CI], 13%–48%; $P < .001$). Complete or partial clearance (clearance of ≥1 index HSIL) occurred more commonly in the treatment group (82% vs 47%; risk difference, 35%; 95% CI, 16%–50%; $P < .001$). Having a single index lesion, compared with having 2–3 lesions, was significantly associated with complete clearance (relative risk, 1.96; 95% CI, 1.22–3.10). The most common adverse events related to treatment were mild or moderate anal pain and bleeding. No serious adverse events were deemed related to treatment or study participation.

Conclusion. IRC ablation of anal HSILs results in more clearance of HSILs than observation alone.

Clinical Trials Registration. NCT01164722.

Keywords. HSIL; anal cancer; human papillomavirus; high-grade dysplasia; ablation.

Anal cancer is preceded by high-grade squamous intraepithelial lesions (HSILs), and treatment of HSILs identified by high-resolution anoscopy (HRA)–directed biopsy is advocated to prevent the development of invasive anal cancer [1]. The mainstay of anal HSIL treatment is targeted ablation using infrared coagulation (IRC) or hyfrecation (electrocautery) [1–7]. IRC delivers short pulses of a narrow beam of visible and infrared light transmitted down the rigid quartz glass of the light guide, causing thermal coagulation necrosis [8]. Depth of destruction is controlled with length of pulse. Healing occurs with minimal scarring [9].

An initial retrospective review of IRC ablation of anal HSILs in 68 human immunodeficiency virus (HIV)–infected men followed up for as long as 3.5 years showed that of 165 individual lesions, 72% did not recur during follow-up after a single treatment [2]. However, approximately 65% of treated patients had HSILs diagnosed again within a median of 203 days, primarily reflecting development of new HSILs in untreated areas (metachronous). HSIL recurrence after ablation is higher in HIV-infected than in HIV-uninfected individuals [3].

HSILs may regress without treatment. An observational study of anal HSILs in HIV-infected and HIV-uninfected men who have sex with men found a spontaneous regression rate of anal HSILs to low-grade squamous intraepithelial lesions (LSILs) or normal findings of 23.5 per 100 person-years (95% confidence interval [CI], 15.73–35.02) [10]. Unfortunately, we cannot predict which lesions will persist, regress, or progress. To our knowledge, there are no randomized clinical trial data establishing the relative efficacy of IRC HSIL ablation as compared with no treatment.

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METHODS

General Study Design

We conducted a randomized, open-label trial in HIV-infected participants comparing the 1-year clearance of biopsy-proven intra-anal HSILs treated with IRC with regression of HSILs absent treatment at 7 US AIDS Malignancy Consortium (AMC) trial sites (ClinicalTrials.gov No. NCT01164722). Participants were recruited between 2011 and 2014. All clinicians performing HRA and IRC were certified according to standards developed by the AMC HPV Working Group [4].

Study participants were HIV-infected adults aged ≥27 years with 1–3 anal canal HSILs (index lesions). Each index lesion was ≤15 mm in greatest diameter. Table 1 details other inclusion and exclusion criteria. The institutional review board for each participating site approved the study, and all participants signed informed consent.

At enrollment HRA determined the presence of ≥1 previously identified, biopsy-proven index HSILs. Study participants were randomized 1:1 to HSIL ablation with IRC or active monitoring (AM) using a random permuted block randomization scheme stratified by AMC site that was not shared with investigators. The sample size was not large enough to account for multiple stratification factors. After randomization, only participants randomized to treatment had all index lesions treated with IRC.

Treatment Arm

IRC was performed under HRA guidance after infiltration with local anesthetic, as described elsewhere [2]. Briefly, the IRC tip was placed in direct contact with the lesion and treated with 1.5-second pulses of infrared light sequentially applied to the entire lesion. Necrotic tissue was debrided with sharp and blunt dissection to the level of the submucosal vessels. This was repeated until all index HSILs were completely removed.

Treatment arm (TA) participants were seen every 3 months for digital anorectal examination, anal cytology, and HRA with biopsy of areas with suspected HSILs. After ablation, HSILs were characterized in 2 ways: at the site of the original index lesion (recurrence) or at a new site (metachronous). Biopsy-proven recurrent or metachronous HSILs were treated with IRC within 4 weeks of diagnosis. Participants were followed up for 24 months after baseline treatment. At 12 and 24 months, TA participants underwent biopsy at index lesion sites (even if no lesion was seen) and sites with lesions suspected of being new HSILs. All treated participants completed a symptom diary for 10 days after treatment.

AM Arm

Study participants in the AM arm were examined by means of digital anorectal examination, anal cytology, and HRA every 3 months. Anal biopsy specimens were obtained only for lesions suspected of possible progression to invasive cancer, to prevent possible treatment effect from multiple biopsies. At 12 months after enrollment, AM arm participants underwent biopsy at index lesion sites (even if no lesion was seen) and sites with lesions suspected of being new HSILs. Study participants in the AM arm with HSILs at 12 months could cross over to IRC treatment for an additional 12 months, undergoing HRA every 3 months with ablation of metachronous or recurrent HSILs.

Anal biopsy specimens were interpreted at local site laboratories and classified as no evidence of intraepithelial lesion or cancer, LSIL (anal intraepithelial neoplasia grade 1), HSIL (anal intraepithelial neoplasia grade 2 or 3), or invasive cancer.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• HIV-infected adults aged ≥27 y with 1–3 anal canal HSILs (index lesions)	• History of anal cancer
	• Prior treatment of anal HSILs with IRC at any time or treatment of anal HSILs by any means other than IRC within 2 months before enrollment
• Each index lesion was ≤15 mm in greatest diameter[a]	
• Within 90 d of enrollment:	
CD4 cell count ≥200 /μL	• Concurrent perianal HSIL, perianal condyloma, or vulvar HSIL or condyloma requiring treatment
Absolute neutrophil count >750 /μL	
Hemoglobin ≥9.0 g/dL	
	• LSIL or condyloma covering >25% of the anal canal circumference
Platelet count ≥75/μL	
INR and aPTT ≤ ULN (as defined by each site's local laboratory)	• Ongoing use of anticoagulant therapy other than aspirin or nonsteroidal anti-inflammatory medications
	• Treatment for an acute infection or other serious medical illness within 14 d before study entry; cancer requiring systemic therapy
	• Concurrent immunomodulatory therapy
	• History of HPV vaccination (added after protocol implementation)

Abbreviations: aPTT, activated partial thromboplastin time; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; INR, international normalized ratio; IRC, infrared coagulation; LSIL, low-grade squamous intraepithelial lesion; ULN, upper limit of normal.

[a]The initial protocol specified a maximum lesion greatest diameter of 10 mm, but this was increased to 15 mm after enrollment began.

A single pathologist (T. D.) reviewed biopsy specimens centrally. Discordant interpretations were reviewed and adjudicated with a second central pathologist (A. v. Z.). The central pathology interpretation was used for analysis. If a biopsy specimen was not available for central review (for 4 follow-up biopsy specimens through 12 months), the local histology result was used.

The primary end point was complete index lesion clearance (CILC) at month 12. In the TA, CILC was defined as no biopsy-proven HSIL at the site of all index lesions from the time of the initial treatment through month 12. In the AM arm, CILC was defined as regression of all index HSILs to LSILs or normal findings at month 12. Partial index lesion clearance (PILC) was defined as resolution of ≥1 (but not all) index lesions at month 12. CILC through month 24 was also evaluated from those continuing in the study in the TA, and for those in the AM arm who crossed over to IRC treatment at 12 months.

Statistical Analysis

The primary study population was the full analysis set based on intention to treat, including all participants who were randomized and completed the baseline visit. All participants not attending the month 12 visit or participants without ≥1 biopsy sample at month 12 were considered failures for the primary end point of 12-month CILC. Month 24 responses were based on evaluable participants.

Sample size was based on the assumption that CILC would be achieved in 50% of study participants in the TA and 20% in the AM arm by the primary end point. With 60 participants in each arm, we had 91.3% power to detect this difference between arms at a 1-sided α level of .025.

For the primary analysis, the percentages of participants with CILC were compared according to arm across sites, using a stratified Mantel-Haenszel test at a 1-sided α level of .025. Lesion-level responses were compared according to arm, with adjustment for clinical site in a generalized estimating equations binary model for relative risk (RR) that accounted for clustering of lesions within participants. Using RR regression, we explored predictors of CILC after adjusting for extent of disease, HIV treatment status, and other participant characteristics. We used Kaplan-Meier methods to analyze time to HSIL detection (in index or metachronous lesions) after IRC treatment.

RESULTS

Cohort Characteristics

Between May 2011 and June 2014, a total of 176 participants were screened with 121 randomized. One participant withdrew from observation immediately before any procedures were performed and was excluded from the analysis (Figure 1). The most common reason for screen failure was no HSIL (42%). Ultimately, 120 participants were enrolled, divided evenly between TA and AM arm. Seventy-one participants (59%) were enrolled from a single site (S.E.G. site). Table 2 describes participant characteristics. Most were white, non-Hispanic men receiving antiretroviral therapy (ART) (90%), with good viral suppression and immune reconstitution. Although most characteristics were similar between arms, significantly more Hispanic participants were randomized to treatment, and significantly more with >1 HSIL index lesion were randomized to the AM arm. At 12 and 24 months, cytology showed Atypical Squamous Cells-cannot exclude HSIL (ASC-H) or HSIL in 7 and 5 participants, respectively, and histology showed HSIL in all participants.

Response to Treatment and Spontaneous Regression

At 12 months, 52 of 60 (participants 87%) in the TA and 57 of 60 (95%) in the AM arm returned and had evaluable biopsy specimens (Figure 1). During the 12-month follow-up, 32 TA participants (53%) underwent a single ablation, and 18 (30%) and 9 (15%) had 2 and 3 treatments, respectively. In no participants did the lesions progress to cancer. Table 3 presents the index lesion response rate at 12 months. Overall, 37 (62%) TA participants had CILC (no index lesion recurrence), compared with 18 (30%) in the AM arm, for an absolute difference of 32% (95% CI, 13–48%; $P < .001$). Forty-nine participants (82%) in the TA and 28 (47%) in the AM arm had CILC or PILC, for an absolute difference of 35% (95% CI 16–50%; $P < .001$). In subsequent central pathological review, 4 participants in the TA and 5 in the AM arm did not have HSILs confirmed at baseline; when these participants were excluded, the absolute difference, (33%; 95% CI, 13%–50%) was unchanged. Overall study results did not change significantly when only the local versus central pathology results were used (absolute difference, 34% vs 32%, respectively).

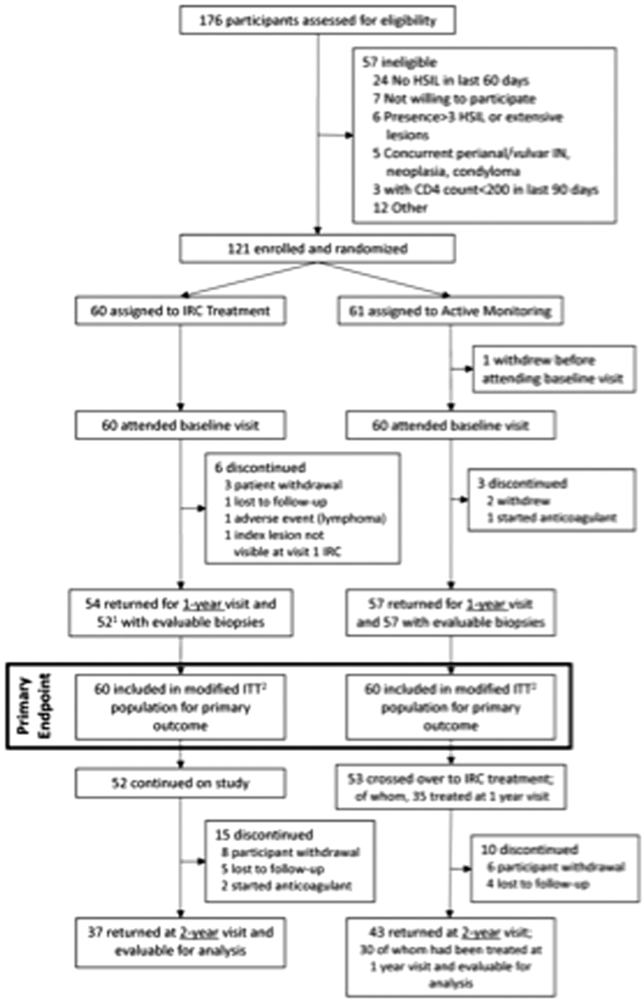
When response or regression rate was examined on the index lesion level, TA participants had significantly superior outcome (63% vs 42%, respectively; $P = .001$). (Table 3) Metachronous lesions were identified through 12 months in 25 (47%) of TA participants and at 12 months in 12 (21%) of the AM-arm participants ($P = .004$). The disease-free rate, defined as absence of index or metachronous HSIL at 12 months, was 71% in TA participants and 28% in AM arm participants, for an absolute difference of 43% (95% CI, 22%–59%; $P < .001$).

Risk Factors for CILC (Absence of Index Lesion)

In multivariable analysis (Table 4), the only factors significantly associated with CILC after adjustment for ART were being in the TA (RR, 2.22; 95% CI, 1.49–3.29), undergoing treatment at 1 trial site (with S. E. G.) (RR, 1.47; 95% CI, 1.03–2.09) and having a single index HSIL (RR, 1.96; 95% CI, 1.22–3.10). There was no significant difference in spontaneous regression rates across trial sites (data not shown).

24-Month End-point Results

Thirty-five participants in the AM arm underwent IRC ablation of persistent index and metachronous lesions at 12 months, and 30 (86%) were evaluable at 24 months. Twenty-five participants had a single treatment, 2 had 2 treatments, and 3 required 3 treatments. Of these, 25 participants (83%) had CILC at



[1] Both in evaluable participants had 2 index lesions at enrollment and at month 12 one biopsy site was benign and one biopsy site was not evaluable. These participants were considered failures for the primary outcome.
[2] Modified intention-to-treat (ITT) included all randomized participants who attended baseline visit.

Figure 1. Participant disposition flow diagram. The modified intention-to-treat (ITT) analysis included all participants who attended the baseline visit. Both participants categorized as not evaluable had 2 index lesions at enrollment, and at 12 months, 1 biopsy site was benign and 1 was not evaluable; for both participants, the result was considered a failure for the primary outcome. Abbreviations: HSILs, high-grade squamous intraepithelial lesions; IRC, infrared coagulation.

24 months, and 41 of 51 treated index lesions (80%) did not recur. The disease-free rate was 80% (24 of 30) at study completion. None of these results significantly differed from what was seen in TA participants at 12 months ($P > .05$).

Among the 30 TA participants who returned at 24 months, 25 (83%) achieved CILC, and of the 51 HSILs treated, CILC was achieved in 41 (80%). Of 16 AM arm participants with no HSIL at 12 months, 11 returned at 24 months, with the index HSIL recurring in 4 of them by month 24.

Probability of HSIL-free Survival

Kaplan-Meier probability of HSIL recurrence is shown in Figure 2. It is estimated that with a single IRC treatment 63.5% (standard deviation, 6.4%) of participants will remain HSIL free at 6 months, a rate falling to 52.5% (6.7%) at 12 months and 42.1% (7.1%) by 24 months. The probabilities of HSIL-free survival in AM-arm participants who crossed over to treatment at 12 months were 87.5% (5.9%) at 6 months after treatment and 63.5% (9.6%) at 12 months. The Kaplan-Meier curves were not significantly different (log-rank test, $P = .13$).

Adverse Events

Through 12 months of follow-up, 11 serious adverse events occurred (grade 3–5) among 9 participants, with none deemed study related. (Table 5) Adverse events at least possibly related to study procedures were observed in 87% of TA participants and 7% of AM-arm participants, with anal pain (mild or moderate) in 48 (80%) and bleeding (mild

Table 2. Participant Demographics and Disease Characteristics

Characteristic	IRC Treatment (n = 60)	AM Arm (n = 60)	*P* Value[a]
Male sex, No. (%)	54 (90)	58 (97)	.14
Race/ethnicity, No. (%)			
Non-Hispanic white	36 (60)	42 (70)	.05
Non-Hispanic black	7 (12)	7 (12)	
Hispanic[b]	16 (27)	6 (10)	
Other	1 (2)	5 (8)	
Age, mean (range), y	49.0 (25–78)	50.5 (27–67)	.37
ART, No. (%)	54 (90)	54 (90)	>.99
Undetectable HIV viral load, No. (%)	35 (59)	42 (71)	.18
Detectable viral load, median (range), copies/mL	412 (77–1830)	300 (82–1948)	.56
CD4 cell count, median (IQR), cells/μL			
Baseline	669 (501–816)	620 (514–736)	.34
Nadir	271 (106–395)	300 (153–438)	.38
History of AIDS diagnosis, No. (%)	20 (33)	19 (32)	.85
History of HSIL, No. (%)	29 (48)	29 (48)	>.99
Prior HSIL treatment, No. (%)[c]	21/29 (72)	24/29 (83)	.34
Baseline No. of lesions, No. %[d]			
1	41 (68)	32 (53)	.03
2	17 (28)	19 (32)	
3	2 (3)	9 (15)	

Abbreviations: AM, active monitoring; ART, antiretroviral therapy; HIV, human immunodeficiency; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; IRC, infrared coagulation.

[a] *P* values determined with χ^2 test or Wilcoxon rank sum test for categorical or continuous data, and with stratified (by site) Mantel-Haenszel test for number of lesions.

[b] Although the 4 categories of race/ethnicity did not significantly differ overall by arm, the difference between Hispanic and non-Hispanic participants was statistically significant (*P* = .02).

[c] Of those with a history of high-grade dysplasia.

[d] Identified by local pathologist.

or moderate) in 47 (78%) of TA participants. Six serious adverse events in 6 participants (3 in each arm) were identified during the second year, and none were related to study participation (Table 5).

DISCUSSION

We performed the first randomized, prospective trial comparing treatment with IRC to AM in HIV-infected participants with limited anal canal HSILs. At 1 year after randomization,

Table 3. 12-Month Response at Participant and Lesion Levels[a]

	Participants or Lesions, % [95% CI] (No./Total No.)			
Response	IRC Treatment	AM Arm	Risk Difference (95% CI), %	*P* Value[b]
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

Abbreviations: AM, active monitoring; CI, confidence interval; CILC, complete index lesion clearance; HSIL, high-grade squamous intraepithelial lesion; IRC, infrared coagulation; PILC, partial index lesion clearance.

[a] There was no index lesion HSIL recurrence after the initial ablation in IRC arm or regression of index lesion to normal or low-grade squamous intraepithelial lesions absent treatment in the AM arm. All results are at the participant level except for Index lesion level clearance (bottom row).

[b] *P* values determined with on stratified (by site) Mantel-Haenszel test or generalized estimating equation relative risk model with adjustment for site (lesion-level analysis).

[c] Cross-sectional estimate at 1 point in time in returning evaluable participants.

[e] Cumulative estimate in returning evaluable participants.

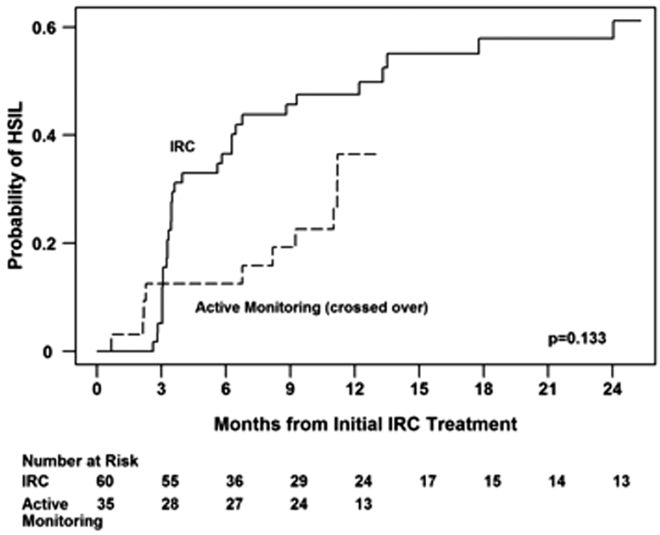
Table 4. Predictors of 12-Month CILC at the Participant Level

		Univariate Analysis		Multivariable Model[b]	
Predictor	Participants, No.	CILC, No. (%)	*P* Value[a]	RR (95% CI)	*P* Value
Study arm					
IRC treatment	60	37 (62)	<.001	2.22 (1.49–3.29)	<.001
AM arm	60	18 (30)		1	
Clinical site					
S.E.G. site	71	39 (55)	.02	1.47 (1.03–2.09)	.03
Other 5 sites	49	16 (33)		1	
Age, y					
25–49	60	25 (42)	.36	…	…
50–78	60	30 (50)		…	
Sex					
Male	112	51 (46)		…	…
Female	8	4 (50)	>.99	…	
Race					
White	92	42 (46)	.94	…	…
Nonwhite	28	13 (46)		…	
Ethnicity					
Hispanic or Latino	22	14 (64)	.07	…	…
Non-Hispanic or non-Latino	97	41 (42)		…	
Nadir CD4 cell count, cells/μL					
≥200	78	35 (45)	.77	…	…
<200	42	20 (48)		…	
AIDS diagnosis					
Yes	39	16 (41)	.46	…	…
No	81	39 (48)		…	
History of HSIL					
Yes	58	27 (47)	.88	…	…
No	62	28 (45)		…	
Prior treatment for HSIL					
Yes	45	23 (51)	.37	…	…
No	75	32 (42)		…	
ART					
Yes	108	54 (50)	.006	4.95 (0.77–31.60)	.09
No	12	1 (8)		1	
Baseline CD4 cells/μL					
≥500	93	41 (44)	.48	…	…
<500	27	14 (52)		…	
Baseline CD8 cells/μL					
≥847 (median)	57	26 (46)	.85	…	…
<847	57	27 (47)		…	
Detectable HIV viral load					
No	77	36 (47)	.77	…	…
Yes	41	18 (44)		…	
No. of index lesions					
1	73	42 (58)	.001	1.96 (1.22–3.10)	.005
2–3	47	13 (28)		1	
Sum of greatest diameters, mm					
0 to <9	61	33 (54)	.06	…	…
≥9	59	22 (37)		…	
Total	120	55 (46)		…	

Abbreviations: AM, active monitoring; ART, antiretroviral therapy; CI, confidence interval; CILC, complete index lesion clearance; HIV, human immunodeficiency; HSIL, high-grade squamous intraepithelial lesion; IRC, infrared coagulation; RR, relative risk.

[a] *P* values determined with χ^2 test.

[b] Variables significant at $P < .10$ in univariate analyses were considered in the multivariable generalized estimating equations binary model for RR, which adjusted for clinical site and accounted for clustering of lesions within participant; the final multivariable model included only variables that were significant at $P < .10$ after adjustment for other variables in the model. Ethnicity and sum of greatest diameters did not meet inclusion criterion after adjustment for treatment, site, ART, and number of index lesions.



* Active monitoring arm participants were not treated for the first 12 months. Those with HSIL at month-12 could then be treated and followed for recurrence for an additional 12 months.

Figure 2. Kaplan-Meir Probability of high-grade squamous intraepithelial lesion (HSIL) diagnosis after initial infrared coagulation (IRC) treatment for IRC arm and active monitoring (AM) arm after crossover to IRC treatment. Those in the AM arm were not treated for the first 12 months. Those with HSILs at month 12 could then be treated and followed up for recurrence for an additional 12 months.

participants in the TA were significantly more likely to have clearance of their index lesions, more likely to have achieved PILC, and more likely to be free of HSILs (either index or metachronous) than those in the AM arm.

Our observed response rates are consistent with those reported in prior retrospective cohort studies of ablative therapy. In 2005, Goldstone et al [2] reported the first series of HSIL ablation in HIV-infected participants, demonstrating that

Table 5. Treatment-related Adverse Events and Non–treatment-related Serious Adverse Events

	Participants, No. (%)			
	IRC Treatment		AM Arm	
Adverse Events[a]	Grade 1–2	Grade 3–5	Grade 1–2	Grade 3–5
Treatment related				
Anal pain	48 (80)	0	3 (5)	0
Postoperative hemorrhage/anal hemorrhage	47 (78)	0	0	0
Non–treatment related				
Anxiety	0	0	0	11 (2)
Fracture	0	0	0	1 (2)
Aortic valve disease	0	0	1 (2)	0
Pericardial effusion	0	1 (2)	0	0
Other cardiac disorder (coronary heart disease)	0	1 (2)	0	0
Thromboembolic event	0	1 (2)	0	1 (2)
Retinal vascular disorders	0	0	0	1 (2)
Other neoplasms (basal cell carcinoma)	0	0	0	1 (2)
Other neoplasms (lymphoma)	0	1 (2)	0	0
Other infections (*Salmonella* poisoning)	0	1 (2)	0	0

Abbreviations: AM, active monitoring; IRC, infrared coagulation.

[a]The table lists treatment-related adverse events occurring in ≥5% of participants in either arm for grades 1–2 and in any participants for grades 3–5. When a participant had multiple occurrences of a specific adverse event, the most severe is shown. All serious adverse events are listed; none were treatment related. There were no grade 5 adverse events.

within 1 year of their first ablation, HSILs recurred in almost two-thirds of patients. Moreover, they reported long-term results of HSIL ablation by any method (IRC, electrocautery, or laser) in 456 HIV-infected participants, and the Kaplan-Meier–adjusted probability of recurrent HSIL at 1 year was 53%, similar to our data [1]. In a prospective trial, Richel et al [11] reported a slightly lower recurrence rate of 43% at 48 weeks in 46 HIV-infected patients treated with cautery ablation, but participants could have LSILs or HSILs involving the canal or perianal skin. LSILs and perianal HSILs have lower recurrence rates than anal canal HSILs, which could account for their improved results [12, 13].

We report spontaneous HSIL regression in almost one-third of participants without treatment. HSIL regression was documented in a retrospective Australian study of 574 HIV-infected and HIV-uninfected participants, in whom about 25% demonstrated spontaneous regression during approximately 1 year of follow-up [10]. When only HIV-infected participants were considered, regression occurred in approximately 20%. Our data found a higher rate of regression, which could be related to our enrolling participants with relatively limited disease. Biopsy of lesions, especially when small, could also contribute to HSIL regression.

Compared with the AM arm, metachronous HSILs developed in more than twice as many TA participants, which could reflect the fact that AM arm participants had lesions biopsied only at 12 months, whereas in the TA, biopsies were performed whenever lesions were identified. Metachronous HSILs could have regressed before biopsy in AM arm participants. It is also possible that treatment could cause a host or viral response, with development of additional metachronous lesions. Irrespective of this difference, TA participants were significantly more likely year than those in the AM arm to be disease free at 1 year.

We identified multiple factors affecting response. As in other series, our data document that having a single lesion significantly improved response [1, 3]. There is a significant learning curve related to HRA, and more experience increases the ability to identify HSILs [14, 15]. Similarly, our data suggest that procedural experience may affect treatment outcome. One site (S. E. G.) had a significantly higher CILC rate than other sites. The investigator at this site (S. E. G.) has the longest experience with HSIL ablation, which could translate to improved outcome. Although receipt of ART significantly improved CILC in univariate analysis and had an almost 5-fold RR of achieving CILC in multivariable analysis, this effect was not statistically significant, perhaps because 90% of participants received ART.

We did not identify clinical factors predictive of HSIL regression without treatment. Future studies should evaluate possible predictors of regression that were not tested for such as human papillomavirus types or other biomarkers in addition to clinical characteristics.

No participants' lesions progressed to anal cancer, which is encouraging but not unexpected. We did not enroll participants with large-volume disease. Moreover, participants were observed for only 1 year before being offered treatment. This short observation period in only 60 participants with limited disease was probably not sufficient to identify progression. An ongoing clinical trial that will include >5000 HIV-infected adults with anal HSILs randomized to treatment or AM will address this question (ANCHOR study; ClinicalTrials.gov No. NCT02135419).

Spontaneous regression occurred in AM arm participants, and waiting 1 year to treat those with limited disease did not reduce the CILC rate once participants were treated. It might be reasonable to adjust the treatment algorithms so that individuals with limited disease (and especially those with a single small HSIL) could be observed closely for a year to determine whether spontaneous regression occurs. Persistent HSILs could then be treated. Even if not all lesions regress, PILC resulting in fewer HSILs could facilitate ablative therapy with less recurrence and diminished morbidity. Even when complete regression occurs, individuals must continue follow-up. In approximately 15% of those with CILC achieved at 1 year, the index lesion recurred during the second year.

This study has several limitations. As previously mentioned, more participants with 2 or 3 index lesions were randomized to AM, which could affect results. It is possible that the absolute difference in HSILs is overestimated, given that at baseline the AM group had more HSILs than the treatment group, but in the multivariable model the RR of HSIL clearance was still significant. We enrolled participants with small lesions, which could overestimate response, because small lesions may be more likely than large lesions to resolve with treatment or regress without treatment. The investigators were all fairly experienced in treating HSILs and participants were mostly white, HIV-infected men with limited disease, receiving ART with satisfactory viral suppression and immune reconstitution, making results less generalizable to other providers and populations. The overall strength of this study rests on the fact that it is the first multicenter, prospective, randomized trial powered to determine whether or not HSIL ablation is superior to AM alone in clearing HSILs in HIV-infected individuals.

In conclusion, IRC ablation of anal canal HSILs is more likely to result in complete or partial resolution than AM alone in those with small and few lesions. Although there is treatment-related morbidity, treatment-related serious adverse events were not observed. Spontaneous HSIL regression can occur, and delaying definitive therapy for 1 year in those with limited disease did not affect ultimate outcomes. Future studies should identify more effective treatment options so that more patients can be effectively treated with a single intervention.

Notes

Author contributions. Trial design: S. E. G., S. Y. L., E. A. S., T. D., J. Y. L., N. J., J. M. B. L., R. D. C., R. M., D. A., J. M. P., and T. W.; collection of data: S. E. G., E. A. S., T. D., A. v. Z., N. J., J. M. B. L., R. D. C., R. M., D. A., J. M. P., and T. W.; analysis of data: S. Y. L. and J. Y. L.; interpretation of data: S. E. G., S. Y. L., E. A. S., J. Y. L., J. M. P., and T. W.; manuscript writing: S. E. G. S. Y. L., E. A. S., and T. W.; review of manuscript: S. E. G., S. Y. L., E. A. S., T. D., J. Y. L., A. v. Z., N. J., J. M. B. L., R. D. C., R. M., D. A., J. M. P., and T. W.; and figures and tables: S. Y. L. and J. Y. L.

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References

1. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. Dis Colon Rectum **2014**; 57:316–23.
2. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. Dis Colon Rectum **2005**; 48:1042–54.
3. Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. Dis Colon Rectum **2011**; 54:1284–92.
4. Stier EA, Goldstone SE, Berry JM, 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.
5. Weis SE, Vecino I, Pogoda JM, Susa JS. Treatment of high-grade anal intraepithelial neoplasia with infrared coagulation in a primary care population of HIV-infected men and women. Dis Colon Rectum **2012**; 55:1236–43.
6. Sirera G, Videla S, Piñol M, et al. Long-term effectiveness of infrared coagulation for the treatment of anal intraepithelial neoplasia grades 2 and 3 in HIV-infected men and women. AIDS **2013**; 27:951–959.
7. Cranston RD, Hirschowitz SL, Cortina G, Moe AA. 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**; 19:118–20.
8. Colver G, Cherry G, Dawber R, Ryan T. Tattoo removal using infra-red coagulation. Br J Dermatol **1985**; 112:481–485.
9. Halasz C. Treatment of common warts using infrared coagulator. J Dermatol Surg Oncol **1994**; 20:252–256.
10. Tong WW, Jin F, McHugh LC, et al. Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. AIDS **2013**; 27:2233–43.
11. Richel O, de Vries HJC, van Noesel CJM, Dijkgraaf MGW, Prins JM. 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**; 14:346–53.
12. Johnstone AA, Silvera R, Goldstone SE. Targeted ablation of perianal high-grade dysplasia in men who have sex with men: an alternative to mapping and wide local excision. Dis Colon Rectum **2015**; 58:45–52.
13. Silvera RJ, Smith CK, Swedish KA, Goldstone SE. Anal condyloma treatment and recurrence in HIV-negative men who have sex with men. Dis Colon Rectum **2014**; 57:752–61.
14. Swedish KA, Lee EQ, Goldstone SE. The changing picture of high-grade anal intraepithelial neoplasia in men who have sex with men: the effects of 10 years of experience performing high-resolution anoscopy. Dis Colon Rectum **2011**; 54:1003–7.
15. Hillman RJ, Gunathilake MP, Jin F, Tong W, Field A, Carr A. Ability to detect high-grade squamous anal intraepithelial lesions at high resolution anoscopy improves over time. Sex Health **2016**; 13:177–81.