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Efficacy and Safety of Anal High-Grade Squamous Intraepithelial Lesion Treatment Modalities: A Systematic Review

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ABSTRACT

Background: There is compelling evidence that treating high-grade squamous intraepithelial lesions (HSIL), the anal squamous cell cancer (ASCC) precursor, reduces the risk of developing ASCC. Using high-resolution anoscopy (HRA), surgical excision, ablative and topical therapies are widely used to treat HSIL.

Objectives: With ASCC incidence increasing and new guidelines on screening high-risk patients, we sought to evaluate the efficacy and safety of HSIL treatment modalities.

Data Sources: EMBASE, MEDLINE, and Cochrane databases were searched for English-language, original studies specifically on HSIL or anal intraepithelial neoplasia (AIN) treatment from inception until December 31, 2025.

Review Methods: Two reviewers independently reviewed abstracts and full-text articles with a third reviewer for discrepancies. Studies were evaluated for efficacy, recurrence and safety.

Results: Sixty-four original papers were evaluated, of which five were randomised controlled trials (two directly comparing different modalities). Numbers in each study and overall quality were low, and extensive heterogeneity existed in methodology. Side effects were common, but significant complications only occurred with surgical excision and photodynamic therapy.

Conclusions: There is insufficient evidence to clearly identify any gold standard HSIL treatment modality. Regardless of the modality, treatment overall is safe, but recurrence is high. Studies directly comparing modalities with standardisation of methodologies and outcome measures are required, especially in light of increasing incidence of ASCC and up-take of HRA.

1 | Introduction

Anal squamous cell carcinoma (ASCC) is rare, but incidence is high in certain groups, especially HIV-positive men who have sex with men (MSM), in whom rates reach 85/100000—higher than the general Australian population's bowel cancer rate (57/100000) [1, 2]. ASCC incidence and mortality are rising both in Australia and globally [3, 4], and up to 98% of cases in HIV-positive MSM are linked to high-risk HPV, particularly subtype 16 [5].

High-grade squamous intraepithelial lesions (HSIL), including AIN 3 and some AIN 2 (p16 positive), are known precursors to ASCC, with a 5-year cumulative incidence of 3.4%–5.7% in people living with HIV (PLWHIV) [6–8]. HSIL can be detected using high-resolution anoscopy (HRA) with biopsy, following

acetic acid application. While HRA has long been used in some centres, interest has grown following the 2022 ANCHOR trial, which found a 57% reduction in cancer progression among PLWHIV treated for HSIL, prompting early trial termination [9].

New consensus screening guidelines from the International Anal Neoplasia Society (IANS) in 2024 and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) recommend screening high-risk groups including MSM living with HIV (MSMHIV) and trans women over 35, and others based on age and risk factors [10, 11]. Initial screening includes digital anorectal examination (DARE), with anal cytology and/or high-risk HPV (HR-HPV) testing. Those with abnormal results should be referred for HRA and possible HSIL treatment. HR-HPV testing alone has the highest HRA referral rate—up to 75% in MSMHIV [12]. Therefore, there is a growing need for trained high-resolution anoscopists.

HSIL is treated with excisional, ablative, and topical therapies [13]. Following on from the systematic review by Brogden et al. in 2022 [14], prior to the ANCHOR study, this review seeks to provide an evidence-based updated summary focusing on recent advances, efficacy, recurrence, and safety of individual HSIL treatments in the context of growing demand for HRA services, such that practitioners can make an informed decision about which to include in their therapeutic armamentarium.

2 | Methods

This systematic review was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria. The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO), ID CRD420251056641.

2.1 | Search Strategies

A comprehensive search of EMBASE, MEDLINE, and COCHRANE databases identified relevant papers from the inception of the databases until December 31, 2025. Various search strategies were employed, including terms such as HSIL, AIN, SIL, high-grade squamous intraepithelial lesions, anal canal tumour, squamous dysplasia, and treatment, management, therapy and intervention. Two independent reviewers screened the papers using the programme JBI SUMARI. A third-party investigator resolved discrepancies between the two reviewers.

2.2 | Inclusion Criteria

Studies focusing on AIN patients undergoing treatment were included. Only studies involving AIN grades 2 or 3, or HSIL, were considered. Only English-language original studies and not review articles were included.

2.3 | Exclusion Criteria

Studies were excluded if they focused solely on the diagnosis or pathology of AIN, or treatment of LSIL/AIN grade 1, or anal cancer. Animal studies and research on HPV-related intraepithelial neoplasia at non-anal sites were also excluded. Studies that did not examine individual modalities separately were excluded. Studies focusing solely on the treatment of anal warts were also considered beyond the scope of this review.

2.4 | Analysis of Studies

Studies were categorised by treatment modality and appraised for efficacy, side effects, safety, and recurrence rates. Advantages and disadvantages of each modality were also noted. Level of evidence was assessed by the Oxford Centre for Evidence-Based Medicine Levels of Evidence [15]. Risk of bias was assessed using Cochrane tools [16–19] for randomised trials and non-randomised comparative studies (RoB 2 and ROBINS-I V2, respectively, along with robvis figure generator tool).

3 | Results

The initial search yielded 4767 studies, and after 1709 duplicates were removed, 3058 remained. After the first screening stage, 2884 studies were excluded based on titles and abstracts. A total of 174 full-text articles were reviewed, with 110 excluded, leaving a final total of 64 studies (Figure 1). Of these, only 5 were randomised controlled trials (RCT). The remainder included 30 cohort studies, 3 pre-phase III clinical trials, 9 pilot studies and 17 case reports/series. A summary of studies by modality is found in Table 1. Table 2 summarises the advantages, disadvantages, efficacy and safety of each modality. A full summary of all studies is shown in Table S1.

The five randomised controlled trials had lower risk of bias, with one study in particular being of "Low" risk [20]. Potential concerns in other studies included completer analysis [21], imbalanced arms despite randomisation [22–24], limited reporting of randomisation process or CONSORT-style reporting [23] and unclear blinding of assessors of histopathological outcomes [24]. The non-randomised comparative papers had less favourable risk of bias ratings. Concerns included a lack of confounder identification or adjustment [25, 26], channelling bias [27, 28], incomplete data [26] and subjective outcome criteria [26]. A summary of risk of bias assessments is detailed in Figures S1 and S2.

Figures S3–S11 show individual forest plots for studies comparing two or more treatment arms, with respect to HSIL clearance (no histological/macroscopic evidence of disease at first follow-up after prescribed course of treatment) and HSIL recurrence (new disease in a patient for whom clearance had previously been obtained)—where these data were readily available.

A narrative synthesis of individual treatment modalities is as follows.

3.1 | Topical Therapy

Topical therapy involves patient or clinician-applied creams to the perianus and anal canal. Except for trichloroacetic acid

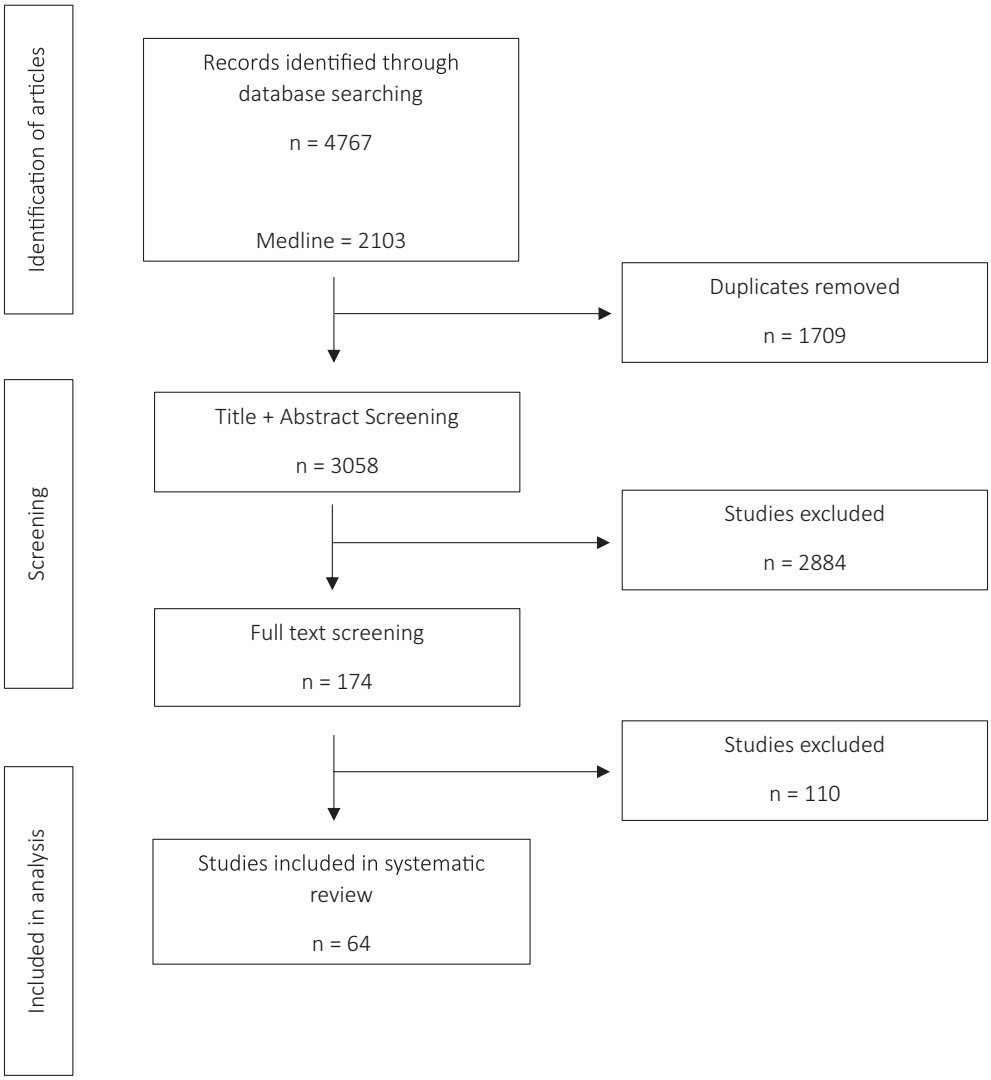

FIGURE 1 | PRISMA Table outlining selection of studies used in final analysis.

(TCA), these agents are mainly used to downstage extensive disease, as an option for those unfit for ablation, or during delays to definitive treatment.

3.1.1 | 5-Fluorouracil (5-FU)

5% 5-Fluorouracil (5-FU), also known commercially as Efudex, is a pyrimidine analog that inhibits DNA synthesis and is commonly used topically for the treatment of non-melanoma skin cancers. It has also been used for anal and perianal AIN, particularly in MSMHIV [29, 30]. Two cohort studies and one RCT were reviewed.

One study found that nightly 5-FU over 20 weeks led to a surface area reduction of HSIL in 55% of 11 patients [30]. It also reduced HPV 16 and other HR-HPV DNA loads, regardless of clinical response [30]. Efficacy varies: Snyder reported 27% histologic downgrading; another study using 5-FU twice weekly for 16 weeks in 46 patients showed 39% complete (CR) and 17% partial responses (PR) (57% total), though 50% of complete responders recurred within 6 months [29, 30].

Side effects (SEs) are common (73%–85%), typically including local irritation and urgency. One study reported 48% with moderate to severe symptoms such as anal pain and proctitis. Serious adverse events have not been reported. Treatment discontinuation due to side effects was low (4%), though dose reduction occurred in 11%–55% of cases [29, 30].

The strongest evidence comes from a randomised controlled trial (RCT) of 148 MSMHIV comparing 5-FU, imiquimod, and monthly electrocautery over 4 months, with follow-up to 72 weeks. 5-FU had the lowest response rate (30% overall), but also the lowest recurrence (58% vs. 71% for imiquimod and 68% for electrocautery, not statistically significant). Side effect rates were similar across groups [20].

3.1.2 | Imiquimod

Imiquimod is an immune response modifier that induces cytokine release, especially interferons, leading to antiviral and antitumor effects. It is self-administered and used for AIN and condyloma [21].

TABLE 1 | Summary of studies by treatment modality.

Modality	Number of original papers	Highest quality of evidence[a]	Years published (range)	Types of articles (*n*, range)
Topical				
5-Fluorouracil	4	1b (Richel, 2013)	2010–2016	1 RCT ($n=48$[b]) 1 cohort[c] ($n=25$[b]) 1 pilot study ($n=46$) 1 case series ($n=11$)
Imiquimod	11	1b (Fox, 2010) 1b (Richel, 2013)	2004–2021	2 RCT ($n=54$–64) 3 cohort[d] ($n=19$–44) 3 cohort[c] ($n=11$–67) 1 pilot study ($n=9$) 2 case series ($n=10$–28)
Cidofovir	3	1b (Burgos 2025)	2016–2025	1 RCT ($n=30$[b]) 1 cohort[d] ($n=23$) 1 pilot study ($n=17$)
Trichloroacetic acid	4	2a (Burgos, 2024)	2009–2024	4 cohort[c] ($n=54$–260)
Sinecatechins	1	1b (Burgos, 2025)	2025	1 RCT ($n=36$[b])
Ablative				
Radiofrequency ablation	5	4 (Goldstone, 2023)	2014–2023	1 cohort[c] ($n=12$) 3 pilot studies (n-10-51) 1 phase I trial ($n=13$)
Electrocautery	11	1b (Richel, 2013) 1b (Burgos, 2025)	2002–2025	2 RCT ($n=36$–46[b]) 3 cohort[d] ($n=37$–83) 6 cohort[c] ($n=91$–330)
Laser	4	4 (Fuertes, 2022)	1993–2022	1 cohort[c] ($n=456$[b]) 1 pilot study ($n=48$) 2 case series ($n=11$–16)
Infrared coagulation	11	1b (Goldstone, 2019)	2005–2021	1 RCT ($n=60$[b]) 1 cohort[d] ($n=98$) 8 cohort[c] ($n=56$–96) 1 pilot study ($n=18$)
Photodynamic therapy	3	4 (van der Snoek, 2012)	2003–2014	1 cohort[d] ($n=15$) 1 case series ($n=20$) 1 case report ($n=1$)
Argon plasma coagulation	1	3 (de Pokomandy, 2018)	2018	1 pilot study ($n=20$)
Cryotherapy	2	3 (Siegenbeek, 2018)	2017–2019	1 cohort[c] ($n=64$) 1 case report ($n=1$)
Other				
Surgical excision	5	4 (Brown, 1999)	1994–2002[b]	2 cohort[d] ($n=27$–37) 1 cohort[c] ($n=34$) 2 case reports ($n=1$)
Endoscopic therapy	7	4 (Borch-Johnsen, 2024) 4 (Lajin, 2022)	2016–2024	1 cohort[c] ($n=37$[b]) 1 case series ($n=3$) 5 case reports ($n=1$)
Novel therapies	4	3 (Cavallari, 2021)	2012–2023	1 RCT ($n=20$) 2 phase I/II trials ($n=19$–56) 1 case report ($n=1$)

[a]According to the Oxford Centre for Evidence-Based Medicine (OCEBM) categorisation [15].
[b]Number of participants in relevant arm of study comparing modalities.
[c]Retrospective cohort study.
[d]Prospective cohort study.

TABLE 2 | Advantages, disadvantages, efficacy and safety of treatment modalities.

Modality	Advantages	Disadvantages	Efficacy (range)[a] (%)	Recurrence (range) (%)	Significant complications	Side-effects
Topical						
5-Fluorouracil	Widely available	Low response compared to imiquimod and EC	CR: 17–39 PR: 13–17	50 at 6 months—58 at 16 months	Nil	Common: itch, urgency, anal pain
Imiquimod	Good efficacy for perianal disease	Potential systemic side-effects	CR: 4–24 PR: 6–29	71 at 18 months—39 at 36 months	Nil	Common: irritation, pain with defecation Systemic side-effects uncommon
Cidofovir	Minimal systemic absorption	Resistance possible	CR: 26–63 PR: 6–30	30 at 3 months 25–37 at 12mo	Nil	Common: itch and discomfort
Trichloroacetic acid	Good efficacy Does not require special equipment	Requires multiple rounds of treatment	CR: 34–36 PR: 28–40	12mth cumulative 12–28	Nil	Rare: itch, mild discomfort
Sinecatechins	Good efficacy with reduced side-effects	Requires prolonged adherence	CR: 9	41 at 48wk	Nil	Common: Itch
Ablative						
Radiofrequency ablation	Ablates the entire canal Reduced metachronous disease	Unable to be used for perianal disease	CR: 58–71 at 12 months–(60 at 18 months)	29–40 at 12 months	Nil	Common: post defecation pain, bleeding, discharge, transient incontinence
Electrocautery	Equipment cheap and widely used	More difficult to control depth of ablation	CR: 21–56 PR: 15–34	25–60 52 weeks 68 at 76 weeks	Nil	Common: mild bleeding, discomfort
Laser	Precise, reduced damage to surrounding tissue	Minimal evidence	CR: 25–50	N/A	Nil	Uncommon and mild
Infra-red coagulation	—	Specialised equipment	CR: 49.9–87.5 PR: 67–81	13 at 30mo– 91 at 17 months	Nil	Common: pain and light bleeding
Photodynamic therapy	—	Significant complications	CR: 28 PR: 16	64	Anal stenosis, facial hyperpigmentation	Common: significant pain, rectal bleeding, purulent discharge
Argon plasma coagulation	—	Expensive	Overall 45	35 within 2 years	Nil	Common: pain

(Continues)

TABLE 2 | (Continued)

Modality	Advantages	Disadvantages	Efficacy (range)[a] (%)	Recurrence (range) (%)	Significant complications	Side-effects
Excisional						
Surgical excision	Enables histologic evaluation	Significant complications	n/a	30–41	Stenosis, Incontinence, SSG breakdown	Common: pain, bleeding, infection
Endoscopic therapy	Good for proximal disease Enables histologic evaluation Minimal side-effects	Unable to be used for perianal disease Specialist training and equipment	n/a	0	Nil	Nil significant

Abbreviations: CR, complete response; PR, partial response.
[a]Response after one episode or cycle of treatment. Encompassing anal canal and perianal disease and in all cohorts (HIV positive and negative).

The strongest evidence comes from three studies in PLWHIV. Fox et al.'s double-blinded RCT of 53 MSMHIV with anal canal HSIL found a 43% overall response (OR) with imiquimod used thrice weekly (14% CR, 29% PR), vs. one CR in the placebo group [21]. A second RCT using the same regimen reported 30% OR (24% CR, 6% PR): electrocautery was superior (68% CR) but imiquimod outperformed 5-FU [20]. Another retrospective cohort study found a response rate of 97% in the imiquimod group versus 73% in electrocautery ablation, the latter requiring more re-treatment (3% vs. 23%) and having more frequent side effects [25].

One study ($n = 44$) used imiquimod five times per week for 16 weeks (extending to 32 if no response), finding 45% OR at 16 weeks (20% CR, 25% PR) and 59% OR at 32 weeks, suggesting extended dosing rather than increased frequency may improve response [31]. Another study of 95 MSMHIV using suppositories thrice weekly found a 46% OR but only 4% CR, likely due to the inclusion of patients with ≥ 2 intra-anal lesions [32].

Notably, both Fox and van der Snoek reported 100% CR in perianal HSIL at 16 weeks, suggesting intra-anal delivery reduces efficacy. Condyloma response is significantly higher, with one study reporting 100% resolution [32, 33].

Recurrence ranges from 71% at 18 months [34] to 39% at 36 months [21]. One study found 26% recurrence at the same site and 55% at untreated sites, often in the anal canal, linked to new HR-HPV types [35]. Kreuter et al. showed reduced HPV subtype diversity and sustained HR-HPV DNA volume reduction post-treatment [35, 36], suggesting recurrence may be linked to new infections in some instances.

Anal imiquimod is safe [37, 38] but SE are common (up to 91%) but usually mild, including local irritation, pain with defecation, and burning. Systemic effects (fatigue, mood swings, flu-like symptoms) occurred in < 11% [31]. Most tolerate treatment well (90% rated as acceptable), and discontinuation is rare. SE are more prolonged than with electrocautery due to longer treatment duration [20, 32].

3.1.3 | Cidofovir

Cidofovir, a synthetic nucleotide analogue active against HPV, has been used in laryngeal HPV disease [39] but is not widely accessible for AIN, with topical formulation currently only available via compounding pharmacy. Two small prospective studies in PLWHIV assessed self-administered cidofovir 1% gel (three times weekly). Treatment was well tolerated in both groups, with itch and discomfort being common; no serious adverse events or discontinuations were reported.

Sendagorta et al. ($n = 16$) found a 63% CR and 6% PR at 12 weeks, with 30% recurrence at 24 weeks [40]. Another study of 23 MSMHIV with persistent HSIL post-ablation (≥ 2 quadrants) reported 39% CR and 30% PR, with 25% recurrence at 12 months [39].

3.1.4 | Trichloroacetic Acid

Topical 85% trichloroacetic acid (TCA) is a clinician-applied treatment long used for AIN and condyloma [41]. Applied to

individual lesions using the wooden end of a cotton swab until whitening, it is inexpensive, easy to use, needs no special equipment or local anaesthetic, and has no systemic effects or plume production [27]. It does, however, require HRA guidance and is sometimes difficult to source, has a short shelf life, and usually requires multiple treatments.

The best evidence comes from two observational studies by Burgos et al., comparing electrocautery (ECA) and TCA in MSMHIV [27, 28], showing TCA to be significantly more effective ($p = 0.004$). In the larger 2024 study [28] ($n = 227$ ECA, $n = 260$ TCA), after one cycle of treatment, TCA had a 73% OR (34% CR, 39% PR), compared to 62% OR (30% CR, 32% PR) for ECA; effects were greater in the propensity score matched cohort. TCA was more effective than electrocautery in smokers, large and multifocal disease, and HPV 16 infection. SE's were common but similar between groups. Bleeding was more common with ECA; itching with TCA.

Other studies report side effects to be relatively common (ranging between 5% and 36%) but with no reported serious complication [27, 28, 41, 42].

Earlier studies [41, 42] showed 71%–78% clearance with varied methodology. One reported 49% clearance with a single treatment [42], and another [41] required, on average, two to achieve clearance.

Recurrence rates varied widely due to inconsistent definitions. One study reported 72% recurrence at 6 months, though this included new lesions [41]; another cited 15% recurrence at the original site, 22% at adjacent sites, and 32% at other sites [42]. Cumulative 12-month recurrence was 12%–28% [27, 28].

3.1.5 | Sinecatechins

Sinecatechins, a green-tea–derived topical extract rich in catechins, exert antiviral, anti-inflammatory, antioxidant, and pro-apoptotic effects that help clear HPV-associated lesions. The TreatAIN open-label RCT comparing electrocautery, topical cidofovir 1% or topical sinecatechins 10% in PLWHIV found no statistically significant difference in treatment efficacy; however, sinecatechins (33%, $p < 0.001$) had a significantly lower side effect profile than ECT and cidofovir (97.2% and 85.7%, respectively) [24].

3.2 | Ablative Therapy

HRA-guided ablative therapies are best for discrete, low-volume HSIL. Choice tends to depend on anoscopist's experience and local practice.

Whilst modalities were not directly compared, insight into the use of ablative treatments as a whole comes from a retrospective analysis of 727 MSM treated with a combination of laser, infrared coagulation and electrocautery over 14 years. Kaplan–Meier predicted recurrence 1 year after first ablation was 53% and 49% for MSMHIV and HIV negative patients, respectively. Median time to recurrence was 6.8 and 6.9 months, and median number of recurrences was ≤ 2 and ≤ 1 for MSMHIV and HIV negative patients respectively [43].

3.2.1 | Radiofrequency Ablation

Radiofrequency ablation (RFA) uses a probe emitting radiofrequency energy to induce coagulative necrosis. Its broad, less precise tip makes it suitable for treating large areas, and it is used in Barrett's oesophagus. Circumferential RFA (cRFA) is used in anal canal disease and targets the entire squamocolumnar junction (SCJ) identified at HRA. The technique is useful as most recurrences occur in untreated areas, despite effective targeted RFA [44].

Most RFA evidence comes from Goldstone's cohort studies. The highest quality data is from a prospective, dual-centre study of 48 PLWHIV and HIV negative patients with HSIL within 3 cm proximal to the SCJ. Patients were followed three-monthly, with new HSILs treated as needed. At 18 months, 60% had no recurrence; Kaplan–Meier analysis showed a 40% recurrence probability at 6–30 months [45]. This and most studies on RFA, report efficacy in terms of time to recurrence and time to disease clearance, rather than response rate after a one-off treatment. A smaller study ($n = 21$ without HIV) using hemi-circumferential RFA showed 71% efficacy after one treatment; 29% had recurrence within, and 33% outside, the treated area by 12 months [46]. Two other studies showed only early persistence or recurrence at the treatment site, suggesting SCJ-wide treatment is particularly effective for metachronous disease [44, 47].

RFA appears safe, with no major adverse events reported [48]. One study showed no changes in manometry or endoanal ultrasound findings and even improved sexual function post-treatment [47].

Side effects were very common and include post-defecation pain (85%), bleeding (91%), discharge, frequency, and transient incontinence, typically resolving in 2–3 weeks [44–47].

3.2.2 | Electrocautery

Electrocautery (EC) is a commonly used modality employing electrical current to necrose lesions down to the level of the submucosal vessels. A portable, low-energy hyfrecator is frequently used in the outpatient setting, as it does not require grounding and is less expensive than the standard electrocautery unit used in the operating theatre. A sweeping, 'paintbrush' technique is used to remove char until the lesion is fully ablated [13]. The technique is a popular choice for surgeons and new units because of availability and familiarity with the equipment, and it was the main modality used in the ANCHOR study [9].

Four original retrospective studies examining EC alone and one comparing EC, 5-FU, and imiquimod were evaluated. There was considerable variation in treatment protocols and definitions of response and recurrence. OR ranged between 39% and 62% [49–51]. One small early study ($n = 37$) reported persistence/

recurrence as high as 79% in PLWHIV, though 0% in HIV negative patients [52]. When multiple episodes of EC are considered, Burgos ($n = 83$ MSMHIV) reported 33% CR and 34% PR, with 18% requiring more than one round of treatment and 25% recurrence at a mean of 12 months. Fuertes ($n = 91$) reported 56% CR and 15% PR at 18 months, requiring a mean of 1.5 sessions of electrocautery, with 25% recurrence (23% metachronous, 2% local) [53].

In Richel's study comparing EC to 5-FU and imiquimod, EC had a CR of 53%, better than 5-FU ($p = 0.08$) and imiquimod ($p = 0.10$). Recurrence at 72 weeks was 68%, similar to the other modalities [20]. EC resulted in fewer overall side-effects but a longer duration of side-effects and more bleeding compared with imiquimod and 5-FU [20].

No serious adverse events such as anal stenosis were recorded in any studies [20, 49–53].

3.2.3 | Laser

Lasers, particularly CO_2 lasers, are commonly used for treating AIN, mainly for ablation and occasionally excision. CO_2 lasers are used preferentially over diode lasers. Laser can be applied via handpiece, with fibre attachment for precise work in the anal canal, or mounted on a microscope with a micromanipulator, depending on operator preference. The CO_2 laser emits infrared light (10 600 nm), strongly absorbed by tissue water, causing superficial vaporisation with minimal thermal injury. Its long wavelength limits scattering, enhancing precision and reducing collateral damage [54].

Evidence is limited to three studies. In a prospective study of 48 PLWHIV with HSIL treated with single-session CO_2 ablation, 50% achieved CR, and 21% PR. Metachronous lesions developed in 25% [54]. Another audit ($n = 28$) showed 25% were lesion-free at 6 months [55]. Neither study had a sufficiently long follow-up to determine recurrence rates. Across both studies, adverse events were mild and transient; one reported 69% of patients had no symptoms [54].

In an older study using the CO_2 laser for excision (used as a scalpel), of 11 patients with AIN 3, half remained disease-free at 18 months; 20% developed metachronous lesions but were successfully re-treated with no further recurrence over 6–77 months. No significant complications were reported [56].

3.2.4 | Infrared Coagulation

Infrared coagulation (IRC) delivers infrared and visible light in short pulses via a sheathed light guide, causing thermal coagulation necrosis. Pulse length controls tissue depth [22]. It can be used in an outpatient setting, is good for haemostasis, and creates minimal plume [57].

Ten studies, including one RCT, assessed IRC for HSIL. Initial efficacy ranged from 67% to 81% [57–60], while recurrence (reported variably) ranged from 13% to 91% over 6–30 months [58–65].

Evaluation protocols varied. One study using cytology and standard anoscopy (HRA if abnormal) found 87.5% recurrence-free at 30 months, likely underestimating recurrence [63]. Another used HRA for positive cytology post-treatment and found 25% recurrence at a median of 6 months, though cytology is not as sensitive as HRA [61].

Multiple lesions [58, 62] increased recurrence and subsequent treatments reduced recurrence rate [57, 59]. No cases progressed to anal SCC.

The strongest evidence comes from a 2019 RCT (Goldstone et al.), where 120 PLWHIV with 1–3 HSILs were randomised to IRC or monitoring. At 12 months, HSIL clearance was 62% vs. 30% ($p < 0.001$), with no progression to SCC in either group [22].

Mild to moderate pain and bleeding were common, between 4% and 80% of participants across multiple studies, with no reports of severe complications [58, 59, 64].

3.2.5 | Photodynamic Therapy

Photodynamic therapy (PDT) employs light to ablate AIN lesions treated with a photosensitising agent, which can be administered locally or systemically. Red or green light is applied through an anoscopic applicator (wavelength affects tissue penetration depth), facilitating non-thermal ablation [66].

Three studies were identified [66–68]. The highest-quality evidence involves 15 MSMHIV treated with intravenous metatetrahydroxyphenylchlorin and red or green light; CR was 28%, PR was 16%, with 64% recurrence at an average of 8 months [66]. Pain was significant (up to 7.9/10), with frequent rectal bleeding, discharge, and scarring. One patient experienced anal stricturing, others had pain during infusion and one case of facial hyperpigmentation after sun exposure [66]. In a case report, PDT using topical 5-aminolevulinic acid led to complete HSIL resolution at 5 weeks, with minimal side effects and no recurrence at 6 months [67].

3.2.6 | Argon Plasma Coagulation

Argon plasma coagulation (APC) delivers radiofrequency energy via ionised argon gas, producing thermal coagulation and vaporisation to a depth of 2–3 mm with minimal surrounding damage. Widely used in gastrointestinal mucosal disease, its use for HSIL is limited to one study of 20 MSMHIV. OR was 45% after one session but 85% of these had recurred within 12 months, mostly local. After two to three treatments, 65% were HSIL-free at 2 years [69].

APC was safe, with no serious adverse events, though pain lasting a week was common. Treatment was costly [69].

3.2.7 | Cryotherapy

Whilst commonly used for condyloma treatment, cryotherapy is rarely used to treat HSIL. One study utilising a spray gun in up

to five treatments reported overall 34% CR and 26% PR ($n = 58$), with worse efficacy for perianal disease and 68% recurrence. 48% had side effects, mostly pain and mild bleeding, with no major complications [70]. One case report using a nitrous oxide cryoballoon to circumferentially ablate the distal rectum/proximal anal canal in a patient with AIN 3 found no recurrence after two cycles after 24 months [71].

3.3 | Surgical Excision

With modern ablative therapies and concerns about stenosis, surgical excision of HSIL is now mainly reserved for specific indications—most commonly when there is concern lesions may harbour invasive disease. Excision allows histologic assessment and may be curative for T1 ASCC and superficially invasive squamous cell carcinoma of the anus (SISCCA). It is also used for AIN arising from anal fistulas and extensive perianal disease to avoid multiple ablation sessions.

Evidence is limited to two case reports and two prospective studies. Split skin grafts (SSG) and diversion were frequently used. Recurrence or residual disease occurred in 30% in one study ($n = 27$). In another ($n = 34$), 19 had incomplete excisions, of which 12 persisted. Of the 15 with clear margins, two recurred (13%) [72]. Stenosis or incontinence occurred in up to 15%, especially with failed SSG and extensive disease [73]. Case reports using flap or mucosal advancement preserved continence, though long-term data were limited [74, 75], and there is concern about covering residual HSIL with a flap. Occult invasive cancer was found in up to 22%, mostly perianal lesions [73].

3.4 | Endoscopic Treatment

Endoscopic resection techniques, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are established for GI premalignant lesions and have recently been applied to AIN. Since 2016, several case reports and series have described their use with gastroscopes or colonoscopes, often using caps to open anal folds, and with enhanced endoscopic imaging functions [76].

ESD, using an endoscopic knife to excise lesions to the submucosa, allows en-bloc excision and histological evaluation. Five case reports and a series ($n = 3$) described treatment of 10–30 mm lesions (LSIL and HSIL) with no major complications or recurrence over 3–16 months [76–81].

A 2023 retrospective study compared underwater EMR using near-focus with white light and narrow-band imaging to surgical excision (not ablation) by inspection alone (not HRA) in 80 patients ($n = 37$ endoscopic arm). Endoscopic patients needed more treatments to achieve clearance (median 2 vs. 1), and 10 of 12 surgical patients who underwent endoscopic follow-up had recurrence. Bleeding occurred equally in both groups, but one endoscopic case required transfusion. The technique was limited in distal and perianal disease [26].

3.5 | Novel Therapies

Several novel therapies for AIN have been reported. A 2023 phase I trial of artesunate suppositories, an anti-malarial with antiviral and HPV-targeted cytotoxicity, found 35% CR and 24% PR among 19 HSIL patients by 40 weeks. Non-HPV16 HR-HPV cleared in 50% of complete responders. The treatment was well tolerated, with no serious adverse events [82].

A phase I/II trial of the topical herbal cream arnebia indigo jade pearl (AIJP) showed 58% resolution of HSIL at 12 months, with 6% experiencing moderate side effects [83].

A trial of oral probiotics in MSMHIV with HSIL showed promising trends. At 6 months, the probiotic group exhibited higher dysplasia regression, fewer new lesions, and lower progression rates; HPV clearance was more frequent but not statistically significant. No adverse effects were noted [23].

A case report described complete regression of a large HSIL in a HIV negative man treated with high-dose penicillin for concurrent *Treponema pallidum* infection, suggesting bacterial co-infection may influence HPV-related dysplasia; an area that warrants further study [84].

4 | Discussion

A variety of modalities exist to treat anal HSIL. In total, 64 original papers were examined from the past 32 years, of which 18 (28%) are from the last 5 years, with a majority of these more recent studies being on endoscopic or novel therapies. As experience with treating the disease has progressed, there has been a shift away from excisional management of HSIL, popular in the late 1990s, towards topical and ablative techniques, largely due to high rates of serious complications and precise detection with HRA.

Overall, there is limited high-quality evidence directly comparing treatment modalities, with only five randomised controlled trials (8%), of which only two studies directly compared different modalities. 30 (47%) were cohort studies, a majority single-centre and retrospective. The numbers many trials were low, and considerable variation existed in treatment protocols between studies. Timing of follow-up HRAs to assess efficacy and recurrence was varied and inconsistent. Assessment of treatment response was primarily based on HRA, although some studies employed standard anoscopy or cytology alone or favoured subjective over objective outcome assessment (e.g., proceduralist visualisation rather than routine post-treatment biopsy with blinded histopathologist assessment).

Outcome measures also varied. Most studies defined efficacy in terms of CR (no AIN) or PR (regression to LSIL) at first HRA post-treatment, with recurrence defined as any HSIL on subsequent HRAs. Other studies, particularly those involving RFA and IRC, treated HSIL on subsequent HRAs and defined treatment success in terms of time to recurrence and number of treatments required to become disease-free. This latter method

utilises Kaplan–Meier curves and is probably a better method of assessing response as it recognises HSIL as a chronic condition.

Such heterogeneity of outcome metrics and endpoints precludes pooling of data for meta-analysis, making direct comparison between studies difficult. It also partially accounts for the wide ranges in published efficacy and recurrence rates. Standardisation of outcome measures in terms of disease volume, response, and recurrence needs to occur for future treatment studies. This is likely to be addressed in the COrSIcA Study, currently underway, which aims to define core outcome sets for future AIN treatment studies [85]. Standardised methodologies for treatment studies (timing of post-treatment HRA and assessment of response) also need to occur. Many studies with lower-quality evidence or bias were pilot or feasibility studies, with larger studies planned by authors—we therefore expect higher-quality evidence on HSIL treatment modalities to emerge in the coming years.

Based on the studies assessed, it is not possible to confidently identify any ablative or topical modality that is significantly better than any other. Of the included studies, probably the highest quality evidence comes from Richel's study, finding that electrocautery is more effective than imiquimod or 5-FU, but numbers were low ($n = 156$) and recurrence high [20]. Multiple studies identified imiquimod as especially effective for perianal disease. Although the ANCHOR trial represents the most clinically important study in this field [9], it was excluded from this review as it did not provide separate comparative analyses of individual treatment modalities. In addition, the primary endpoint was progression to ASCC rather than HSIL clearance, which was the outcome of interest for this review.

Another promising modality is TCA, with quality evidence showing high efficacy (some studies suggesting more than EC), easy application and safety, making it a useful modality in resource-limited settings and for anoscopists not comfortable with ablation. Downsides are that it usually requires multiple applications, may not be as useful in bulky lesions, and may be difficult to source. Despite widespread use for HSIL, there is surprisingly limited evidence supporting laser ablation, with few studies and no long-term data to deduce recurrence.

What is true across all studies is that recurrence is high, irrespective of modality. Recurrence was highest in PLWHIV, especially those with low CD4 counts and with greater volume of disease. It may be reasonable to accept that, regardless of recurrence rates, repeated HSIL treatments by whatever modality serve to delay and, at best, prevent eventual progression to ASCC, consistent amongst all treatment studies and in line with the findings from ANCHOR [9]. In this respect, anal HSIL should be managed within a chronic disease framework, comprising: the use of evidence-based, planned care; reorganisation of practice systems and provider roles; improved patient self-management support; increased access to expertise; and greater availability of clinical information [86].

Provided HSIL is treated, HIV control, optimising immunosuppression in transplant recipients, and smoking cessation are probably more important in disease management than modality choice. More research is needed into HPV vaccination as post-treatment adjuvant therapy, with promising evidence from a non-concurrent cohort study suggesting reduced recurrence post ablative treatment [87].

What is clear from the literature is that treatment of HSIL is safe. Despite concerns, significant complications of stenosis and incontinence were only reported for surgical excision and PDT. More effective topical and ablative methods have superseded surgical excision, reserving it for specific indications. The use of PDT cannot be recommended given its mediocre efficacy and recurrence rate. Temporary pain, discomfort, and bleeding are common for all modalities, although patient drop-out due to side effects was low across all studies.

One advantage of having no obviously superior modality is that new HRA providers can use whichever they have experience with or access to, thereby reducing cost and learning curve. Endoscopists are playing a growing role in the diagnosis and management of HSIL, with promising outcomes so far. Ideally, anoscopists would have multiple modalities at their disposal and tailor treatment depending on disease and patient factors. Patient factors that may influence modality include tolerance to side effects and compliance with follow-up (favouring modalities with low recurrence rates). Disease characteristics include location, extent of disease, concern about invasion, and previous treatments.

The major advance since Brodgen's review in 2020 is the publication of ANCHOR, confirming HSIL treatment reduces the risk of ASCC [9, 14]. In the intervening 5 years, there has been no significant research comparing modalities to determine if a superior one exists. Several new studies have been released recently, with more in preparation—these were not included as they fall out of our inclusion period. This is likely to continue as HSIL treatment is an emerging field, and it is rapidly evolving. In particular, multimodal therapy has become more common but was not addressed in this review so as to avoid under-estimating individual treatment effect sizes. There is therefore scope for further regular reviews and meta-analyses as the field develops.

With compelling evidence for benefit in treating HSIL, the focus now lies on high-quality trials with consistent methodologies that directly compare different modalities. Collaboration between existing and new HRA centres is required. Since most studies are in PLWHIV (59% of all papers in this review), assessing modalities in other patient cohorts requires investigation. Studies are needed to determine whether specific modalities are more effective for certain disease patterns, such as perianal versus anal canal disease and recurrent disease. Questions also remain regarding the best approach to treating high-volume disease and multi-zonal disease, as well as the use of combined topical and ablative therapies.

Author Contributions

Matthew Joseph Marino: conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, software, formal analysis, project administration, data curation, supervision, resources. **Sophie Jones:** conceptualization, investigation, writing – original draft, methodology, writing – review and editing, formal analysis, data curation, resources.

Nicholas Reid Caldwell: conceptualization, investigation, methodology, validation, visualization, writing – review and editing, formal analysis, data curation, resources. **Catherine Cartwright:** conceptualization, investigation, writing – original draft, methodology, data curation, resources. **Benedict Blacket:** investigation, writing – original draft, writing – review and editing, validation, methodology, formal analysis, resources, data curation. **Richard Clive Turner:** conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, formal analysis, project administration, data curation, supervision, resources.

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The authors have nothing to report.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Cochrane risk-of-bias (RoB 2) assessment of included randomised controlled trials. **Figure S2:** Cochrane risk-of-bias (ROBINS-I) assessment of included non-randomised multi-arm studies. **Figure S3a:** HSIL clearance comparing imiquimod and fluorouracil for Richel et al. [20]. **Figure S3b:** HSIL recurrence comparing imiquimod and fluorouracil for Richel et al. [20]. **Figure S3c:** HSIL clearance comparing imiquimod and electrocautery for Richel et al. [20]. **Figure S3d:** HSIL recurrence comparing imiquimod and electrocautery for Richel et al. [20]. **Figure S3e:** HSIL clearance comparing fluorouracil and electrocautery for Richel et al. [20]. **Figure S3f:** HSIL recurrence comparing fluorouracil and electrocautery for Richel et al. [20]. **Figure S4:** HSIL clearance comparing imiquimod and placebo for Fox et al. [21]. **Figure S5a:** HSIL clearance comparing infra-red coagulation and active monitoring for Goldstone et al. [22]. **Figure S5b:** HSIL recurrence comparing infra-red coagulation and active monitoring for Goldstone et al. [22]. **Figure S6:** HSIL clearance comparing probiotic and placebo for Cavallari et al. [23]. **Figure S7a:** HSIL clearance comparing electrocautery and cidofovir for Burgos et al. [24]. **Figure S7b:** HSIL recurrence comparing electrocautery and cidofovir for Burgos et al. [24]. **Figure S7c:** HSIL clearance comparing electrocautery and sinecatechins for Burgos et al. [24]. **Figure S7d:** HSIL recurrence comparing electrocautery and sinecatechins for Burgos et al. [24]. **Figure S7e:** HSIL clearance comparing cidofovir and sinecatechins for Burgos et al. [24]. **Figure S7f:** HSIL recurrence comparing cidofovir and sinecatechins for Burgos et al. [24]. **Figure S8:** HSIL clearance comparing electrocautery and imiquimod for Hidalgo-Tenorio et al. [25]. **Figure S9a:** HSIL clearance comparing electrocautery and TCA for Burgos et al. [27] with propensity score matching. **Figure S9b:** HSIL recurrence comparing electrocautery and TCA for Burgos et al. [27]. **Figure S10a:** HSIL clearance comparing electrocautery and TCA for Burgos et al. [28] with propensity score matching. **Figure S10b:** HSIL recurrence comparing electrocautery and TCA for Burgos et al. [28]. **Figure S11:** HSIL clearance comparing endoscopic and surgical resection for Borch-Johnsen et al. [26]. **Table S1:** Summary of all included Studies.