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Extensive cervical lesion and treatment outcomes in women with HIV/HPV co-infection

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Abstract

Background Cervical cancer is a common cancer worldwide, with > 85% of deaths occurring in Lower- and Middle-Income Countries where resources for screening programs are limited. Women living with HIV (WLHIV) are at increased risk. HPV test-and-treat is a screening strategy where women with HPV are offered ablative treatment of the cervix to reduce the risk of invasive cancer. WLHIV tend to have more extensive cervical lesions, necessitating more specialised surgical treatments.

Method ACTG A5282 was a randomised, open-label, Phase 2 trial conducted in seven countries that compared a cytology-based screening strategy to HPV test-and-treat for cervical cancer prevention in WLHIV. Women with cervical lesions inappropriate for ablative treatment were assigned to Arm C and underwent colposcopy and directed biopsies. Loop electro-excision procedure was performed if high-grade lesions (bHSIL) were present on cervical biopsies. Women were followed 26 weeks later for repeat evaluations. The Clopper-Pearson exact method was used to construct the 95% confidence interval for the proportion of WLHIV with lesions inappropriate for cryotherapy. Logistic regression models were used to assess the factors associated with these lesions.

Results Of 1046 women screened, 156 (88%) were Black/Non-Hispanic, with a median age of 36 years; 80% were on ART, and 73% had an HIV-1 RNA < 200 copies/mL. On cervical colposcopy, 17% (179/1046, 95% CI 14.9–19.4%) had cervical lesions inappropriate for cervical ablation. Among 428 (44%) women with High-risk HPV (hrHPV) detected, 112 (26%, 95% CI 22.2%, 30.5%) had cervical lesions inappropriate for ablative therapy. hrHPV was found more commonly among women having lesions inappropriate for ablative therapy as compared to lesions appropriate for ablative therapy (70% vs 54%, $p < .001$). Among 128 women with extensive cervical lesions undergoing colposcopic biopsies, 43 (34%) had bHSIL detected. Among women undergoing LEEP treatment of bHSIL, 24% had bHSIL detected 26 weeks later.

Conclusion Cervical lesions inappropriate for ablative therapy were common among WLHIV. This has implications for cervical cancer programs as these lesions can only be optimally treated with surgical therapies such as loop electroexcision procedures, and the capacity for this procedure should be increased to maximise cervical cancer prevention outcomes.

Keywords HPV, Women, Co-infection, HIV care continuum, Cervical cancer, Cytology

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Introduction

Cervical cancer is the fourth most common cancer in women worldwide, with most of the burden of disease in low- and middle-income countries (LMIC) [1]. It is the third most common cancer in Africa, with an estimated annual incidence of 26.2/100 000 population in Africa in 2020 [2], and is the leading cancer cause of death in African women. Persistent human papillomavirus (HPV) infection is the cause of cervical cancer and its precursor lesions. Women living with Human Immunodeficiency Virus (WLHIV) are at a higher risk of persistent HPV infection and cervical cancer precursors. They are six times more likely to develop cancer of the cervix than women without HIV [3, 4]. Cervical cancer is largely preventable with primary prevention through HPV vaccination and active screening to diagnose and treat cervical cancer precursors. As it will take decades to see the full reduction of HPV-related cancers from widespread HPV vaccine programs, there is an urgent need to strengthen secondary cervical cancer prevention programs for WLHIV.

Cervical cancer screening programs have traditionally relied on cytology-based methods as the primary screening test. Molecular tests for high-risk HPV (hrHPV) types have gained widespread acceptance as a primary screen. The HPV-based test-and-treat strategies have been studied since the early 2000s and have been found to be effective in preventing cervical intraepithelial precursor lesions from progressing to high-grade lesions or cervical cancer [5, 6]. These studies also showed that complications from ablative therapy were minor, with no differences in frequency between those with and without HIV. In LMIC, same-day methodologies are attractive because of attrition along the cervical cancer prevention cascade [7–9]. Many LMICs have adopted a "screen-and-treat" approach. This approach typically uses visual inspection after applying acetic acid (VIA). When lesions are detected, ablative therapy with either cryotherapy or thermoablation is performed, and close follow-up is recommended. VIA effectiveness is limited by suboptimal specificity and a requirement for rigorous quality control processes largely because of its subjective nature [10, 11]. The WHO has developed and endorsed an HPV-based test-and-treat strategy [12–15] and criteria for ablative treatment [16], which includes estimating the proportion of the cervix involved and whether there is endocervical extension. However, women with extensive cervical lesions are ineligible for ablative treatment and require care by physicians capable of more specialised excisional procedures that are not feasible in a screen-and-treat approach. Although these criteria are well established, little is known about ineligibility rates for ablative therapy among WLHIV.

Advancing Clinical Therapeutics Globally (ACTG) A5282 was a randomised, open-label, Phase 2 clinical trial that compared a cytology-based screening strategy to HPV test-and-treat to prevent bHSIL in WLHIV. The results of the main study were described in a publication [17]. A subset of women who were screened were not eligible for randomisation as they had extensive lesions inappropriate for ablative treatment (referred to as cervical lesions inappropriate for ablative therapy). These women were assigned to a separate arm and followed up for 26 weeks. In this manuscript, we describe this subset of women.

Methods

Study design

Advancing Clinical Therapeutics Globally (ACTG) A5282 was a randomised, open-label, Phase 2 clinical trial conducted at 13 sites in seven countries that compared a cytology-based screening strategy to HPV test-and-treat for prevention of bHSIL in WLHIV. The detailed inclusion and exclusion criteria and results for the randomised comparison arms are described elsewhere [17].

The women screened for the study underwent cervical hrHPV testing, cervical cytology and colposcopy (see Fig. 1: Study Design). Women with hrHPV detected and cervical lesions appropriate for cervical ablation or no cervical lesions seen were eligible for the randomised portion of the study (Arms A and B). A subset of women ineligible for randomisation was assigned and followed in an open-label, non-randomised arm of the study (Arm C). This arm included two groups of women: women with or without HPV who had cervical lesions inappropriate for ablative therapy (lesions extending more than 3 mm into the endocervical canal or lesions covering more than 75% of the cervix) and women who were HPV negative with visible cervical lesions and/or HSIL on cytology at screening. The objective of Arm C was to estimate the proportion of WLHIV with cervical lesions inappropriate for ablative therapy, evaluate possible factors associated with these lesions, and further describe the presence of cervical bHSIL 26 weeks after study entry. This study is registered in ClinicalTrials.gov as trial number NCT01315353.

Study procedures

All participants provided informed consent and underwent a gynecologic speculum exam to collect cervical swabs for hrHPV, as well as cervical cytobrush and wooden spatula for conventional cytology in all arms of the study. Real-time hrHPV testing was performed locally using the Abbott assay. This provided three separate results (HPV 16, HPV 18, other hrHPV including 31/33/35/39/45/51/52/56/58/59/66/68).

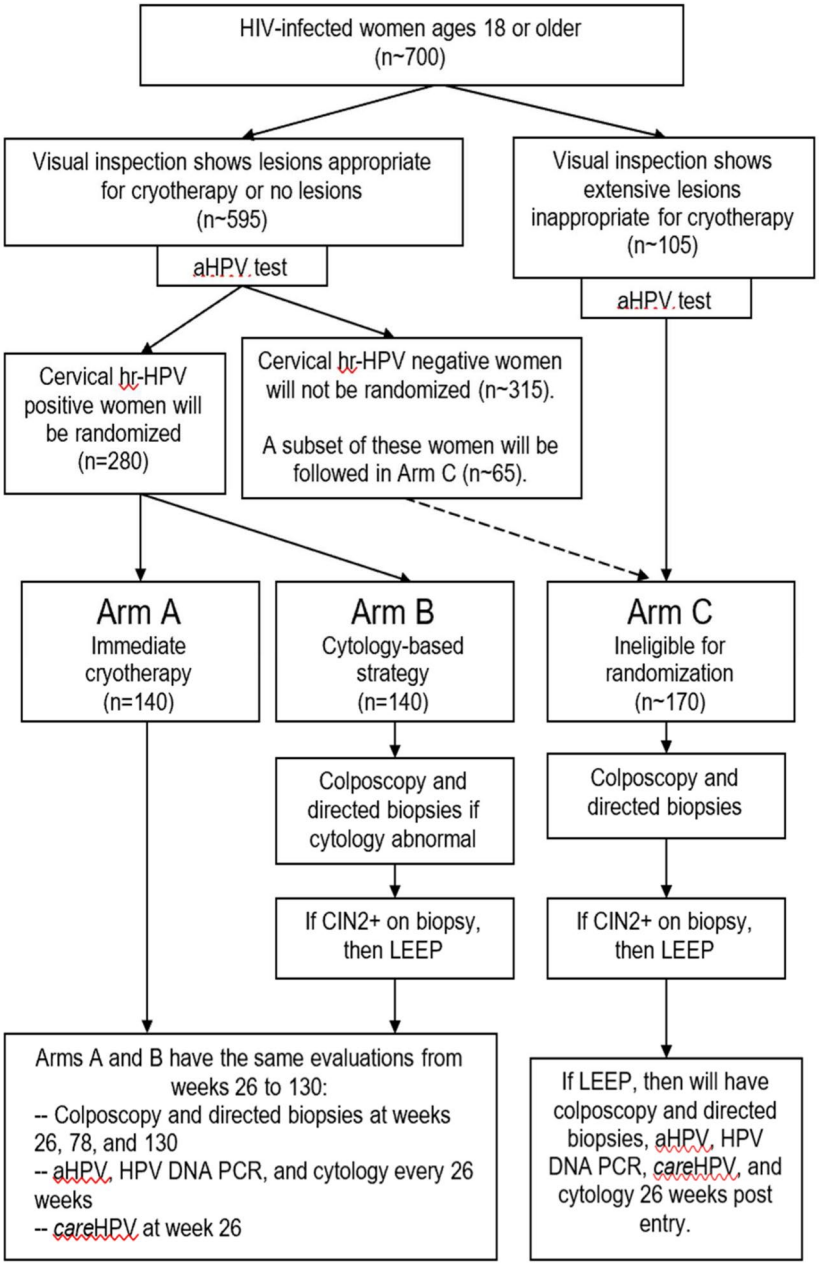

Fig. 1 Study design

Women underwent cervical colposcopy, which involved applying 5% acetic acid to the cervix to assess for the presence of cervical lesions suggestive of squamous intraepithelial lesions or cancer and to assess suitability for ablative therapy. Blood for haematology, plasma HIV-1 RNA level, and CD4 + T-cell count were collected at baseline. Pregnancy testing was conducted at baseline, whenever pregnancy was suspected, and prior to the loop electrical excision procedure (LEEP).

Participants in Arm C had colposcopy and directed biopsies at study entry and were followed for 26 weeks in the study. If bHSIL was detected at baseline, the participant underwent LEEP. All women were followed 26 weeks after enrollment for hrHPV testing, cervical cytology, and cervical colposcopy with directed biopsies. Women diagnosed with cervical cancer during the study were referred for treatment. A sociodemographic

and sexual history questionnaire was administered at study entry and 26 weeks follow-up.

Adverse events were ascertained during clinical assessments and graded using the Division of AIDS Table for Grading the Severity of Adult Adverse Events Version 1.0, December 2004 and Addendum 1-Female Genital Grading Table for Use in Microbicide Studies (available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.)

Statistical considerations

The objectives of this analysis were to estimate the proportion of WLHIV with cervical lesions inappropriate for cryotherapy and evaluate risk factors associated with these lesions. Baseline factors used in this analysis were age, CD4 count, plasma HIV-1 RNA, antiretroviral therapy (ART) use, HPV types detected, sexual history and recent sexual activity. The Clopper-Pearson method was used to construct a two-sided 95% confidence interval (CI) for the proportion. Logistic regression was used to evaluate associations between factors and cervical lesions inappropriate for ablative therapy. An odds ratio with its corresponding Wald's 95% CI from logistic regression as an estimate of association was also provided. Two-sided tests were performed using a 5% level of significance. We also described bHSIL at baseline and 26 weeks post-enrollment.

Results

Study population

Between April 2012 and May 2014, the study screened 1120 participants from 13 clinical research sites, and 1046 women had one or more cervical cancer screening results. See Fig. 2 for the distribution of participants in different arms and subgroups. See Table 1 for the characteristics of the screening population in the main study and the baseline characteristics of the Arm C cohort. Briefly, for the arm c cohort, the median CD4 + count was 568 cells/mm3 (Q1, Q3: 391, 728), with 68% (114/167) having nadir CD4 + count > 200 cells/mm3.

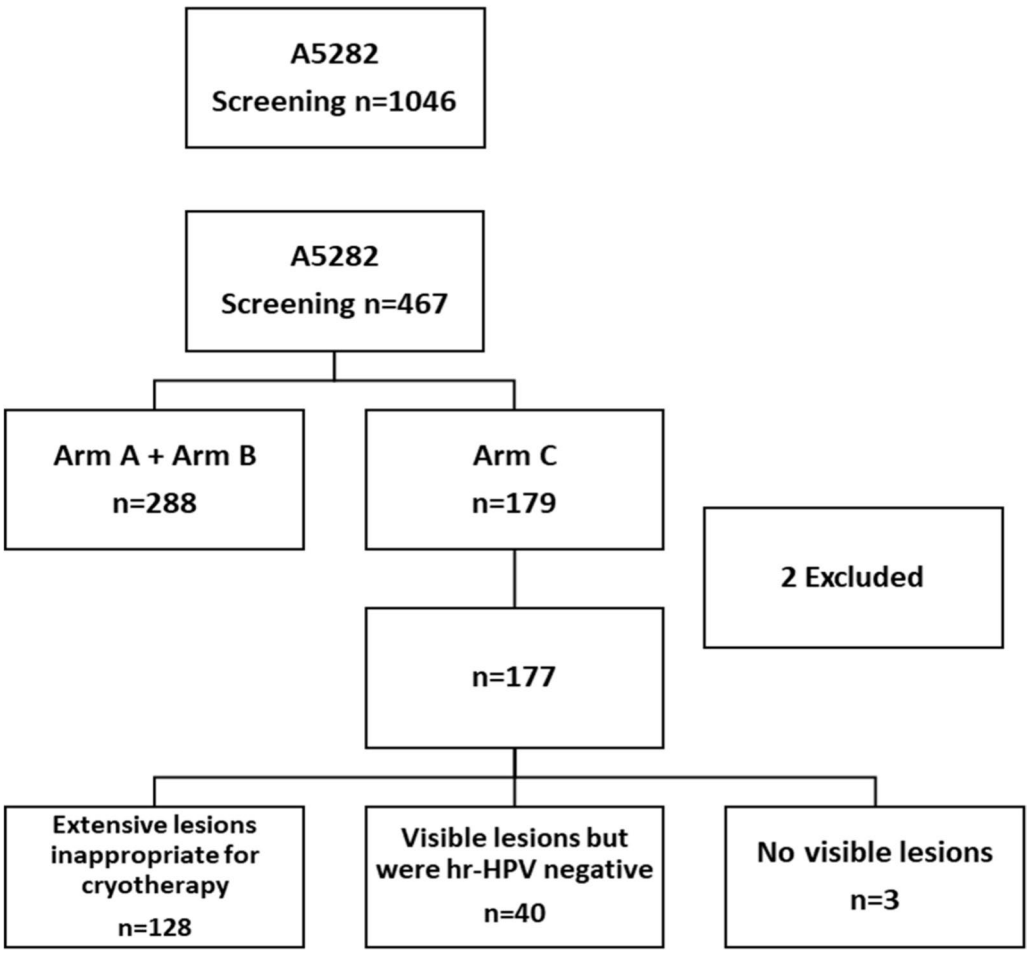

Fig. 2 Arm C study population

Table 1 Characteristics of study participants

Characteristic		Total screened (n = 1046)	Arm C: lesions inappropriate for cryo (n = 128)	Arm C: hr-HPV negative w/lesions or HSIL (n = 49)
Age (years)	Median (Q1, Q3)	37 (32, 42)	36 (30, 42)	38 (33, 42)
Race/Ethnicity	Black Non-Hispanic	747 (71%)	113 (88%)	43 (88%)
	Hispanic (Regardless of Race)	58 (6%)	0 (0%)	6 (12%)
	Asian, Pacific Islander	320 (31%)	15 (12%)	0 (0%)
CD4 count (cells/mm^3)	Median (Q1, Q3)	530 (387, 716)	573 (381, 734)	555 (415, 718)
HIV-1 RNA (copies/mL)	< 200	660 (68%)	92 (72%)	37 (76%)
On ART at screening	NO	209 (20%)	27 (21%)	8 (16%)
History of prior cervical cytology tests	Yes	711 (68%)	89 (70%)	30 (63%)
	No	56 (32%)	38 (30%)	18 (38%)
	Unknown	2	1	1
Age of first vaginal sex (years)	< 20	816 (78%)	99 (78%)	37 (77%)
	≥ 20	230 (22%)	28 (22%)	11 (23%)
	Not indicated	2	1	1
Lifetime number of vaginal sex partners	1	157 (15%)	21 (17%)	6 (13%)
	2–5	732 (70%)	90 (71%)	32 (67%)
	> 5	157 (15%)	16 (13%)	10 (21%)
	Not indicated	2	1	1
Abbott hr-HPV results				
HPV 16		99 (10%)	23 (20%)	0
HPV 18		52 (5%)	15 (13%)	0
Other hr-HPV		359 (37%)	66 (58%)	0
hr-HPV		428 (44%)	83 (72%)	0
Cytology results				
NILM		337 (35%)	43 (34%)	24 (51%)
ASCUS/LSIL		525 (54%)	43 (34%)	16 (34%)
HSIL		107 (11%)	41 (32%)	7 (15%)
Missing		77	1	2
Colposcopy	No lesions seen	523 (50%)		
	Lesions seen, approp for cryo	271 (26%)		
	Lesions seen, not approp for cryo	178 (17%)		
	Colpo not performed/Missing	74		

Eighty percent of participants were on ART at screening, 137 (77%) at study entry, most commonly 3TC, TDF, EFV (taken by 62/137-45.3%participants). Seventy-three percent of participants (129/177) had a plasma HIV-1 RNA < 200 copies/mL.

Extensive cervical lesions

Among 1046 women with screening data, 17% (178/1046) had lesions inappropriate for cervical ablation 95% CI [14.9%, 19.4%]. In addition, 523/1046 (50%) had no lesions seen by colposcopy at screening, 26% (271/1046) had lesions appropriate for ablative therapy, and 74/1046 (7%) had no colposcopy results. Among 428 (44%) women with hrHPV detected, 112 [26%, 95% CI 22.2%, 30.5%] had lesions inappropriate for ablative therapy. Among 99 women with HPV 16, 36 (36%) had lesions inappropriate for ablative therapy. Cervical hrHPV was found more commonly among women with cervical lesions inappropriate for cervical ablation as compared to women with lesions appropriate for cervical ablation (70% vs 54%, p < 001). See Table 2 for details. Current CD4 cell count and HIV viral suppression were not associated with the detection of cervical lesions inappropriate for cervical ablation.

Table 2 Risk factors for extensive cervical lesions

Risk factor	No cervical lesions	Cervical lesions appropriate for cryo	Extensive cervical lesions inappropriate for cryo	p-value (extensive lesions vs. lesions appropriate for cryo
hrHPV	154 (30%)	137 (54%)	112 (70%)	<.001
HPV16	23 (5%)	37 (14%)	36 (23%)	0.046
HPV18	15 (3%)	15 (6%)	20 (13%)	0.019
Other hrHPV	131 (26%)	117 (46%)	89 (56%)	0.056
Median CD4 count	520	536	528	0.23
Plasma HIV-1 RNA < 40 copies/mL	346 (71%)	181 (69%)	107 (62%)	0.15

bHSIL outcomes among women with extensive cervical lesions

179 (2 were subsequently found to be ineligible) women were enrolled into the non-randomised arm (Arm C). This arm included 128 women with extensive cervical lesions inappropriate for ablative therapy and 49 women having other cervical lesions or HSIL cytology but no hrHPV detected (see Table 1 for characteristics of these groups).

Among 128 women with extensive lesions inappropriate for ablative therapy who entered Arm C, 43 (34%) had bHSIL detected on colposcopy; one participant had cervical cancer detected and had a total abdominal hysterectomy at week 20 of the study. Among 115 with available hrHPV results, 83 (72%) had hrHPV detected. Among the 83 women with extensive lesions and hrHPV detected, 36 (43%) had bHSIL. Among the subset of 23 women with HPV 16 and extensive lesions, 14 (61%) had bHSIL. Among 43 participants with lesions not appropriate for ablative therapy with bHSIL, 32 were treated with LEEP prior to the follow-up assessment at 26 weeks; seven received LEEP at a later time point. Of those who had LEEP prior to the week 26 visit, 25 had a follow-up biopsy at week 26 and six (24%) had bHSIL.

Other Arm C participants

There were 49 women who were hrHPV negative who either had HSIL cytology or visible cervical lesions. See Table 1 for the characteristics of these participants. bHSIL was diagnosed in five (10%) at baseline; all of the bHSIL was morphologically cervical intraepithelial neoplasia grade 2.

Predictors of CIN2 + among 128 participants screened with cervical lesions inappropriate for ablative therapy in Arm C

The association of selected baseline characteristics with bHSIL among participants screened with lesions inappropriate for ablative therapy is shown in Tables 2 and 3. At baseline, detection of HPV 16 and non-16/18 hrHPV

Table 3 Associations with week 26 CIN2 +

Characteristic	Univariate Analysis: OR (95% CI) of CIN2 +	p-value	Multivariable Analysis: OR (95% CI) of CIN2 +	p-value
ART Use at screening	0.7 (0.2, 2.8)	0.638		
CD4 < 500 cells/mm3	1.3 (0.4, 4.5)	0.696		
HIV RNA ≥ LLQ	2.1 (0.7, 6.7)	0.201		
Age < 20 years at first vaginal sex	6.9 (0.8, 57.9)	0.074		
With > 1 lifetime vaginal sex partner	0.3 (0.1, 1.0)	0.046	0.3 (0.1, 0.8)	0.023
With ≥ 2 years (104 weeks) of ART at entry	0.8 (0.3, 2.6)	0.724		
Week 26 Abbott HPV 16	3.0 (0.5, 17.3)	0.219		
Week 26 Abbott HPV 18	N/A*	N/A*		
Week 26 Abbott Other hr-HPV	3.1 (0.8, 12.0)	0.109		
Week 26 Abbott hr-HPV	5.8 (1.1, 30.6)	0.036	3.5 (1.0, 12.0)	0.044
Week 26 Less Often Condom Use during vaginal sex	0.9 (0.3, 3.0)	0.890		
Week 26 Not using condom during last vaginal sex	1.6 (0.4, 6.3)	0.515		
Week 26 With > 1 vaginal sex partner in last 6 months	N/A*	N/A*		

* No OR (95% CI) and p-value provided due to convergence issues

were both associated with bHSIL ($p < 0.01$). The prevalence of HPV 16 was 37% among women having bHSIL and 92% for any hrHPV detected. At week 26, a one-lifetime vaginal sex partner was less likely to develop bHSIL (odds ratio 0.3; 95% CI 0.1–0.8; $P = 0.023$). hrHPV was also associated with the development of bHSIL (odds ratio 3.5; 95% CI 1.0–12.0; $P = 0.044$).

Safety

Among women in Arm C, there were four grade 3 events: 3 instances of cervical bleeding and one instance of cervical inflammation. No deaths or pregnancies occurred during the study follow-up.

Discussion

The WHO recommends a screen and treat or a screen triage and treat approach for cervical cancer prevention for women in LMIC. DNA testing for HPV is the preferred screening methodology over either VIA or cytology, and only those with HPV will have a visual inspection. While ablation is readily available and can be performed by non-physicians, it is not the optimal treatment for women with extensive cervical lesions. Our study provides important estimates for planning screen-and-treat programs. Previously, it was estimated that the non-randomised arm of the study would include 170 women based on a study in Zambia, which demonstrated that approximately 20% of women presenting for cervical cancer screening had lesions inappropriate for ablative therapy [18]. Our study demonstrated that if screening with VIA alone, 17% of women would have extensive cervical lesions requiring excisional therapy. If screening with hrHPV testing alone, our study suggests that 26% will have extensive cervical lesions requiring excisional therapy. This suggests that screen-and-treat programs for women living with HIV should have readily available LEEP services.

While the test and treat strategies have been shown to be more effective than the cytology-based strategy, the finding that 17% of women were ineligible for ablative therapy has important programmatic implications. Most screening and ablative therapy is performed by mid-level practitioners, and excisional therapy requires referral to an advanced practitioner. Currently, the President's Emergency Plan For AIDS Relief (PEPFAR) program does not routinely collect aggregate data on screen-and-treat treatment eligibility or outcomes of screening, including onward referral; thus, programmatic data on the suitability of the approach is lacking. In some sites, this information is collected clinically [19] and likely provides an important quality assurance mechanism. This conclusion has been shared with the agencies overseeing the PEPFAR program.

Screen-and-treat programs provide cervical treatments without obtaining histology. If screening with VIA, our data suggests that 34% of women with extensive cervical lesions would have cervical HSIL. If screening with HPV DNA testing, 43% of women with hrHPV and extensive cervical lesions would be expected to have cervical HSIL. The high prevalence of HSIL in these women justifies proceeding directly to excisional therapy (e.g. screen and LEEP) without obtaining cervical biopsies. Detection of HPV was the only characteristic that appeared to be associated with the detection of extensive cervical lesions. We did not find evidence that immune suppression was associated with the presence of these lesions.

Studies are ongoing to evaluate the possibility of same-day screening and treatment to improve uptake. This implies a need for further implementation research on point-of-care tools for easy diagnosis to ensure speedy diagnosis and immediate referral for care. Until primary prevention with the HPV vaccine is well established, a multipronged approach for effective screening and treatment of HPV and HPV-related early lesions will be critical for reducing morbidity, saving lives, and substantially reducing the cost and burden of disease on the health system.

The effectiveness of LEEP in the clearance of HSIL is known to be better than ablative therapy, especially in WLHIV [20]. We observed that 24% of women with cervical HSIL and extensive cervical lesions treated with LEEP had cervical HSIL detected 26 weeks later. Studies done in women without HIV have shown that the risk of recurrent or persistent HSIL after LEEP treatment is around 10% and is increased in patients with positive margins. However, some studies indicate that hrHPV post-treatment predicts treatment failure more accurately than margin status [21, 22]. A study done in WLHIV in Kenya reported similar findings, indicating that hrHPV detection was more likely to be associated with the recurrence of HSIL. Recurrence or persistence after LEEP tends to be higher (19%) in WLHIV after 12 or 24 months of follow-up [11, 20, 23]. Optimal excisional treatment and monitoring post-excision for extensive cervical lesions for WLHIV still need to be determined [24].

Our study identified a small subset of women with lesions that were HPV negative, of whom approximately 10% had cervical HSIL at screening. The numbers were too small to make inferences about their outcomes but repeated HPV screening may be helpful for this population.

Limitations

There were missing data that limited the completeness of our analysis. We did not have a complete study follow-up, and some women (25%) did not undergo treatments for cervical HSIL as required by the study (either did not go for treatment or went later than recommended). We did not have a central pathology review to ensure the appropriateness of cervical HSIL diagnoses. The colposcopic impression was subjective, and no centralised quality assurance program supported this determination.

Conclusion

In summary, we found that WLHIV were commonly found to have lesions inappropriate for ablative therapy, especially among women with hrHPV detected. These women required excisional therapy at screening, and HPV testing alone was inadequate for optimal treatment. Women with these lesions had a high prevalence of cervical HSIL and generally responded well to LEEP therapy. These data underscore the importance of improving and sustaining access to LEEP services to reduce cervical cancer among WLHIV.

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Author contributions
RM, TW, CG and CF were involved in the designed the sub-group analysis and drafted the manuscript. HC conducted the statistical analysis. All authors were involved in drafting and reviewing the manuscript and approved the final version. All authors vouch for the accuracy and completeness of the data, data analyses, and interpretations, as well as adherence to the study protocol. All authors shared the final responsibility for deciding to submit for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The trial was approved by each site's institutional review board or ethics committee. Each participant signed informed consent forms prior to being enrolled in the study. This study is registered in ClinicalTrials.gov [NCT01315353].

Consent for publication
All authors shared the final responsibility and consent for submitting for publication.

Competing interests
The authors declare no competing interests.

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