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SHORT REPORT

Cancer Therapy and Prevention

Efficacy of thermal ablation for treatment of biopsy-confirmed high-grade cervical precancer among women living with HIV in Kenya

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Abstract

The World Health Organization recommends thermal ablation (TA) as an alternative to cryotherapy within "screen-and-treat" cervical cancer programs in low- and middle-income countries (LMICs), including among women living with HIV (WLWH). Data on TA efficacy among WLWH are limited, however. We conducted a clinical trial to evaluate efficacy of TA for treatment of biopsy-confirmed cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3) among WLWH in Kenya. Nonpregnant HPV-positive WLWH age 25 to 65 years underwent colposcopy-directed biopsy, and same-day treatment with TA, if eligible. Women with biopsy-confirmed CIN2/3 at baseline had colposcopy-directed biopsies at 12 months to determine cure. A total of 376 participants underwent TA during the study period. At baseline, 238 (63.3%) had normal histology, 39 (10.4%) had CIN1, 15 (4.0%) had CIN2, 55 (14.6%) had CIN3, 7 (1.9%) had microinvasive cancer and 22 (5.6%) had indeterminate results. Twelve-month follow-up pathology results are available for 59 of 70 (84.3%) participants with CIN2/3 at baseline. Of these, 39 (66.1%, 95% CI 0.54-0.99) had successful treatment, defined as biopsy-confirmed CIN1 or normal findings, while 20 (33.9%, 95% CI 0.22-0.46) had treatment failure, defined as persistent biopsy-confirmed CIN2 or worse. Treatment failure was 23.1% (95% CI 0.17-0.46) and 39.9% (95% CI 0.23-0.51) among women with CIN2 and CIN3 at baseline, respectively. HIV-positive women with CIN2/3 have high rates of treatment failure at 1-year following thermal ablation. This highlights a significant limitation in the current WHO cervical cancer secondary-prevention strategy and calls for strategies to optimize cervical precancer treatment in this population.

KEYWORDS

CIN2/3, low- and middle-income countries, thermal ablation efficacy, women living with HIV

What's new?

In 2019, the World Health Organization endorsed thermal ablation (TA) as an alternative to cryotherapy for cervical precancer treatment in screen-and-treat programs in low- and

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN2/3, cervical intraepithelial neoplasia grades 2 and 3; HPV, human papillomavirus; LMICs, low- and middle-income countries; PEPFAR, President's Emergency Plan for AIDS Relief; SSA, sub-Saharan Africa; TA, thermal ablation; VIA, visual inspection with acetic acid; WHO, World Health Organization; WLWH, women living with HIV.

middle-income countries (LMICs). Whether TA is more effective among women living with HIV (WLWH), who are at increased risk of cervical cancer in LMICs, however, is unknown. Our study evaluated the efficacy of TA specifically among WLWH with biopsy-confirmed cervical intraepithelial neoplasia grade 2 and 3 (CIN2/3). Treatment failure at 12 months following TA was 23.1% and 39.9% for CIN2 and CIN3, respectively. The findings reveal potentially limited efficacy of TA in WLWH.

1 | BACKGROUND

Cervical cancer incidence and mortality data demonstrate a dire global health inequity. Despite being preventable, in 2020, low- and middle-income countries (LMICs) accounted for 85% of the estimated 570 000 incident cervical cancer cases and 90% of deaths globally.[1] The burden of cervical cancer is particularly pronounced in sub-Saharan Africa (SSA) where HIV is endemic.[2] Women living with HIV (WLWH) have a higher incidence and persistence of human papillomavirus (HPV), the causative agent of cervical cancer, and a six-fold increased risk of developing cervical cancer.[2] As such, cervical cancer prevention among WLWH is an urgent priority.

In 2013, the World Health Organization (WHO) recommend use of cryotherapy for cervical precancer treatment within screen-and-treat programs in LMICs.[3] However, large-scale implementation of cryotherapy is hindered by challenges of transporting bulky gas cylinders and maintaining a consistent supply of refrigerant gas, especially in rural areas.[4] In Malawi, cryotherapy delivery challenges led to only 43.3% of screen-positive women getting treatment in a 5-year period.[4] This led to a search for more feasible treatment options. In 2019, the WHO recommended use of thermal ablation (TA) as an alternative to cryotherapy for use within screen-and-treat programs in LMICs.[5] Similar to cryotherapy, TA does not require anesthesia and can be nurse-administered, ideal for LMICs' primary care settings. TA battery-powered devices are lightweight (2-5 kg) and portable, unlike heavy cryotherapy gas cylinders (15-20 kg), making it more feasible for use in remote clinics.[4] With similar WHO treatment eligibility criteria, TA is increasingly replacing cryotherapy in LMICs' cervical cancer prevention programs.

However, high-quality data on the efficacy of thermal ablation for treatment of cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3)—the precancerous lesion most likely to progress to cervical cancer—among WLWH are lacking. Available TA efficacy data are primarily from high-income countries with low HIV prevalence, and where desktop-based rather than handheld thermal ablation devices have been used for treatment.[6,7] In a 2019 meta-analysis of available TA efficacy evidence from 23 studies, the cure rate for CIN2/3 was 93.9%.[6] However, only five studies included WLWH. Two of these studies were done in SSA[8,9] and neither used biopsy-confirmed disease—the gold standard, to define cervical precancer cases or to evaluate cure. Instead, visual inspection with acetic acid (VIA) which is known to be highly subjective and nonspecific,[10] was used. The lack of robust TA efficacy data among WLWH in LMICs led the WHO to issue a conditional recommendation, citing "low-to moderate evidence" in this population.[5] To address this gap in the literature, we evaluate the efficacy of thermal ablation for treatment of biopsy-confirmed CIN2/3 among WLWH in Kenya, a low- and middle-income country in SSA.

2 | METHODS

We conducted a single-arm clinical trial at Lumumba Sub-County Hospital within a President's Emergency Plan for AIDS Relief (PEPFAR)-supported HIV clinic in Western Kenya. Between August 2019 to December 2021, WLWH age 25 to 65 years were offered cervical cancer screening using careHPV, which tests for DNA of 14 high-risk HPV types. HPV-positive, nonpregnant women without a history of cervical cancer or precancer treatment were eligible to participate. Per study protocol, all HPV-positive women eligible for ablation were offered TA on the same day regardless of whether a lesion was seen on VIA. Women were considered candidates for TA per the WHO criteria—if, following application of acetic acid, the squamocolumnar junction was fully visualized, cervical lesions, if present, covered less than 75% of the cervix, and there was no endocervical component of the lesion or suspicion for cancer.[3] Ineligible women were referred for excision or other evaluation by a gynecologist. Prior to ablation, all women underwent colposcopically directed biopsies of abnormal lesions, or in the absence of lesions on colposcopy, a random biopsy at 6 or 12 o'clock for disease status ascertainment. The Liger device (Cure Medical Global, USA) was used for TA, applying either a single flat probe for type 1 transformation zone, or nipple shaped probe for type 2 transformation zone, heated to 100°C. Treatment lasted 20 seconds per application, with multiple applications if needed to cover the lesion, as previously described.[11] Cervical biopsies were read by a registered pathologist at the University of Nairobi using the WHO three-tiered CIN classification.[12] Women with microinvasive cancer at baseline were referred for care, and those with indeterminate results were offered repeat screening. Participants CIN2/3 at baseline had 12 months follow-up with and repeat colposcopy, with biopsies of visible lesions or a random biopsy if no lesion was present to assess cure.

Data were analyzed using Stata version 13.1 (StataCorp, College Station, TX). Treatment efficacy was defined as the proportion with CIN2/3 at baseline who had biopsy-confirmed CIN1 or normal pathology at follow-up. Univariate analysis was performed to investigate the association between treatment efficacy at follow-up and clinical and demographic variables at baseline. The Wilcoxon Rank-Sum test was

used to investigate the relationship between CD4 count at baseline and CIN2/3 persistence.

3 | RESULTS

Three hundred and seventy-six participants were consented and enrolled in the study (Figure 1). At baseline histology 238 (63.3%) participants had normal findings on pathology, 39 (10.4%) had CIN1, 70 (18.4%) had CIN2/3, 7 (1.9%) had microinvasive cervical cancer, while 22 (5.9%) had indeterminate results. Participants with microinvasive disease were referred for treatment. Of the 70 participants with CIN2/3 at baseline, 59 (84.3%) were seen at 12-month follow-up with histology available, while 11 (15.7%) were either lost to follow-up or had no histology available.

The demographic and clinical characteristics of participants with less than CIN2 at baseline (n = 299) are compared to those with CIN2 or worse (n = 77) in Table 1. The mean age was 39.9 years among those with less than CIN2, and 40.5 years among those with CIN2 or worse. The mean CD4 cell count did not differ between the groups and was greater than 400 cell/mm^3 and both groups had ~97% HIV viral suppression at baseline. Compared to participants with <CIN2, participants with CIN2 or worse were more likely to be VIA positive (11.3% vs 0.9%, $P < .0001$) and to require more than 1 probe application to treat their lesion (27.3% vs 17.1%, $P = .003$).

The mean time to follow-up was 14.4 months (SD 2.3). Among the 59 (84.3%) participants with CIN2/3 at baseline who were seen at follow-up, 39 (66.1%, 95% CI 0.54-0.99) had successful treatment, with follow-up pathology of CIN1 or less, while 20 (33.9%, 95% CI 0.22-0.46) had treatment failure, defined as CIN2 or worse on pathology (Table 2). Treatment failure was 23.1% (95% CI 0.17-0.46) and 39.9% (95% CI 0.23-0.51) among women with CIN2 and CIN3 at baseline, respectively. The 3 participants with CIN2 at baseline who failed treatment all progressed to CIN3 at 12 months. Of the 17 with CIN3 at baseline who failed treatment, 2 had CIN2 at follow-up while 15 had persistent CIN3. In univariate analysis, no demographic or clinical variables were significantly associated with CIN2/3 treatment failure at follow-up (data not shown). While not statistically significant, compared to those with baseline CD4 count <200 cell/mm,[3] participants with CD4 greater than 200 were less likely to have treatment failure, OR 0.6 (95% CI 0.11-3.34). Participants who had a detectable viral load had 1.2 increased odds of treatment failure compared to those with viral suppression (95% CI 0.11-32.01), and those with CIN3 had 1.95 increased odds of treatment failure compared to those with CIN2 at baseline (95% CI 0.47-8.1).

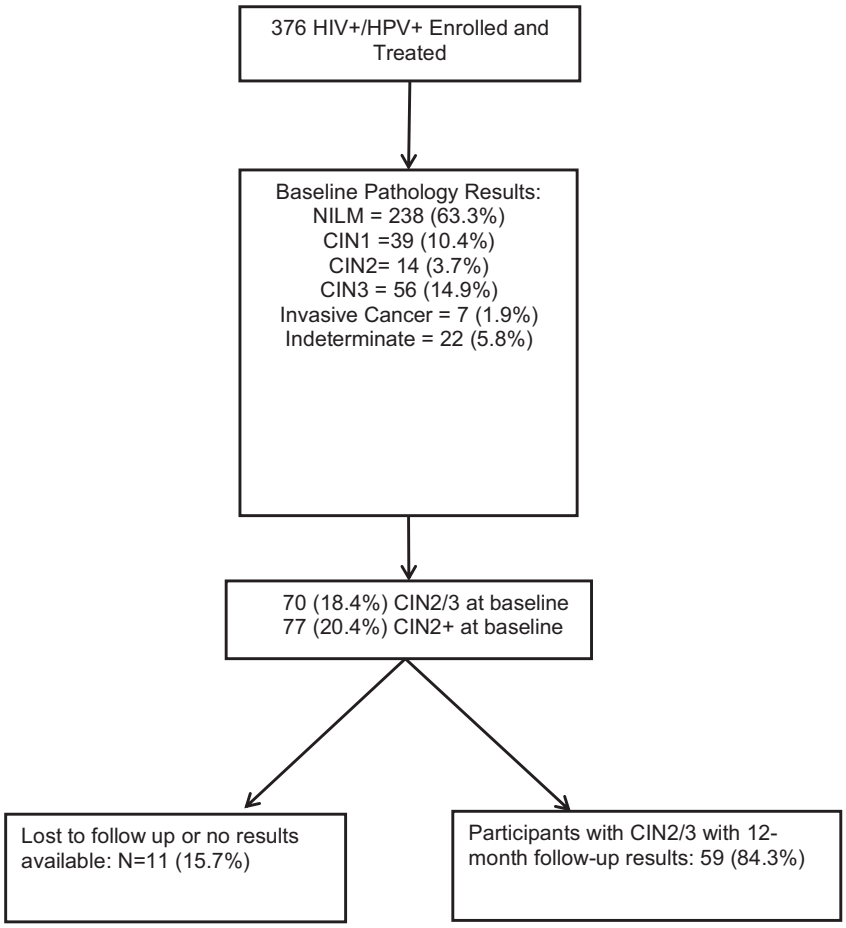

FIGURE 1 Participant enrollment flowchart

TABLE 1 Baseline demographics and clinical characteristics of HPV+/HIV+ women in Kenya who underwent thermal ablation by baseline pathology diagnosis

Characteristic value[a]	<CIN2 at baseline (N = 299)	≥CIN2 at baseline[b] (N = 77)	*P*
Age (mean, SD) year	(39.9, 8.61)	(40.5, 8.22)	.557
Marital status, n (%)			
Single	34 (11.4%)	6 (7.8%)	.367
Married	136 (48.5%)	38 (49.3%)	
Widowed	81 (27.1%)	16 (20.8%)	
Divorced	48 (16.0%)	17 (22.1%)	
Highest education level attended, n (%)			
None	0 (0.0%)	0 (0.0%)	.231
Primary	153 (52.4%)	42 (56.7%)	
Post-primary/vocation	2 (0.7%)	0 (0.0%)	
Secondary	101 (34.6%)	23 (31.1%)	
Post-secondary	36 (12.3%)	9 (12.2%)	
Employment status, n (%)			
Employed	240 (80.3%)	64 (83.1%)	.571
Not employed	59 (19.7%)	13 (16.9%)	
Daily household income, n (%)			
<500 Kshs	191 (63.9%)	51 (66.2%)	.691
≥500 Kshs	108 (36.1%)	26 (33.8%)	
Parity (mean, SD)	(3.3, 2.04)	(3.3, 2.81)	.799
Age at first sexual intercourse (mean, SD)	(17.6, 3.26)	(17.6, 2.74)	.899
Number of sexual partners (mean, SD)	(3.8, 3.24)	(4.0, 3.30)	.608
CD4 count (mean, SD)	(442.9, 311.31)	(460.7, 276.05)	.708
Virally suppressed, n (%)			
Yes	282 (97.6)	70 (97.2)	.863
No	7 (2.4)	2 (2.8)	
Currently using contraception, n (%)			
Yes	124 (41.5%)	28 (36.4%)	.109
No	175 (58.5%)	48 (62.3%	
Do not know	0 (0.0%)	1 (1.3%)	
Method of contraception, n (%)			
Implant	64 (36.5%)	14 (29.2%)	.477
Injectable	49 (28.0%)	15 (31.2%)	
Condoms	47 (26.9%)	16 (33.3%)	
Pills	10 (5.7%)	1 (2.1%)	
Other	5 (2.9%)	2 (4.2)	
Prior cervical cancer screening, n (%)			
Yes	217 (72.6%)	48 (62.3%)	.214
No	79 (26.4%)	28 (36.4%)	
Do not know	3 (1.0%)	1 (1.3%)	
VIA result at screening, n (%)			
Positive	2 (0.9)	7 (11.3)	<.0001
Negative	233 (99.1)	55 (88.7)	
Number of TA probe applications, n (%)			
1	248 (82.9)	56 (72.7)	.003
>1	51 (17.1)	21 (27.3)	

[a]*t*-Test, chi-square or Fischer's exact test.
[b]14 CIN2, 56 CIN3 and 7 invasive cancer.

TABLE 2 Efficacy of thermal ablation for treatment of biopsy-confirmed CIN2/3 at 12 months among HIV-positive women in Kenya

Baseline pathology	Treatment success[a] (cure), N (%, 95% CI)	Treatment failure,[b] N (%, 95% CI)
CIN2 or 3 (N = 59)	39 (66.1%, 0.54, 0.782)	20 (33.9%, 0.22, 0.46)
CIN2 (N = 13)	10 (76.9%, 0.54,0.998)	3 (23.1%, 0.17–0.46)
CIN3 (N = 46)	29 (63.04%, 0.49, 0.77)	17 (39.9%, 0.23,0.51)

[a]Regression to CIN1 or normal pathology on 12-month biopsy.
[b]Persistence of CIN2 or higher on 12-month biopsy.

4 | DISCUSSION

In our study, evaluating the efficacy of TA for treatment of biopsy-confirmed high-grade cervical precancer (CIN2/3) among HPV-positive WLWH in Kenya, the rates of CIN2/3 treatment failure at 12 months are high. Treatment failure was highest for women with CIN3 at baseline, with over a third found with CIN2 or worse at 12 months. At baseline, all women were enrolled in HIV care and on antiretroviral therapy with good disease control as evidenced by a mean CD4 count of 473 cell/mm^3 and with over 95% having HIV viral suppression. To the best of our knowledge, this is the first study to report the efficacy of TA for treatment of CIN2/3 in HPV-positive WLWH from SSA with rigorous disease status ascertainment at both baseline and follow-up.

Thermal ablation was endorsed by the WHO in 2019 for use within screen-and-treat programs in LMICs, including among WLWH, in part to address challenges with implementation of cryotherapy. Previous TA efficacy studies, primarily from high-income, low HIV prevalence countries and using desktop-based devices, report high CIN2/3 efficacy rates.[7,13,14] In the largest systematic review, TA had 93.8% efficacy for treatment of biopsy-confirmed CIN2/3.[6] However, generalizability of these results to WLWH in SSA are limited due to the lack of rigorous efficacy data from this population.

Our findings of high CIN2/3 treatment failure rates align with recent TA efficacy studies using hand-held devices, which also assessed disease status in WLWH through histology or other objective criteria.[15-17] In a 2023 study reporting 3.5-year treatment outcomes from a cohort of WLWH in India, among 32 HPV+ WLWH with biopsy-confirmed CIN2/3 who received TA and had follow-up, 9 (28%) had persistent CIN2+ at follow-up.[15] Although data on the impact of HIV control on CIN treatment outcome was not reported, persistent HPV infection following TA was significantly associated with recurrent CIN2/3 (OR 138.2, 95% CI 20.3-3300.2). In a 2020 study reporting pilot results of an ongoing randomized trial in Zambia, treatment success following TA, defined as type-specific HPV clearance at 6 months was 44% in WLWH, compared to 83% in HIV-negative women.[16] Despite the limitation of no histological diagnosis at baseline for direct comparison, the high persistent HPV rates post-TA observed in WLWH is a known risk factor of CIN2/3 treatment failure,[18] and suggests TA's limitation in WLWH. Among HIV-negative women in SSA, higher than previously reported TA failure rate for women with biopsy-confirmed CIN2/3 was demonstrated in a study from Cameroon in which 29.4% with biopsy-confirmed CIN2/3 had persistent disease 12 months after thermal ablation.[17] In our study, the presence of occult endocervical lesions and first sexual activity before 15 years of age were significantly associated with treatment failure. Our results are also consistent with prior randomized trials using histology diagnosis from South Africa[19] and Kenya[20] that demonstrate 27% to 30% CIN2/3 recurrence in WLWH at 12 to 24 months following cryotherapy, further demonstrating limitations of ablation in WLWH. The association of high HIV viral load and low CD4 cell counts with CIN2/3 treatment failure, which is suggested in our results, has been observed in other studies.[20]

The demonstrated high CIN2/3 treatment failure rate in WLWH is concerning as TA is increasingly the main precancer treatment method used in SSA where access to excision is limited. Without robust follow-up, which is often lacking in many LMICs, many treated women are at risk of progression to invasive cancer where curative options are limited or unavailable. As such, studies aimed at understanding the causes of CIN2/3 treatment failure following TA in WLWH are urgently needed. This includes the impact of TA treatment duration on depth of tissue necrosis and hence treatment adequacy, appropriate patient selection for TA in screen and treat programs, the impact of probes type used on treatment efficacy, among other factors. The WHO guidelines recommend a minimum of 20 to 30 seconds per TA treatment application,[5] and prior studies primarily in HIV-negative women suggest no difference in cure rates by treatment length.[6] Among women undergoing hysterectomy for benign conditions, the mean depth of tissue destruction following TA ranged from 2.6 mm (100°C for 20 seconds) to 3.5 mm (120°C for 30 seconds).[21] However, the maximal depth of CIN2/3 lesions in under-screened women in LMICs may be deeper, as was demonstrated in a study in Peru where 10.3% of cone excision specimens for CIN3 had depth ≥3.5 mm.[22] This suggests that the depth of necrosis following 20 or 30 seconds TA treatment may not achieve sufficient therapeutic depth in certain women, and this may contribute to the high recurrence observed. There are no published studies on the depth of CIN2/3 necrosis based on duration of TA among WLWH in SSA.

Data on whether use of the "2-probe technique" may impact TA efficacy in WLWH are also lacking. The 2-probe technique, used in the initial TA studies and associated with high CIN2/3 treatment efficacy rates involves using a conical probe to ablate the lower (distal) endocervical canal, followed by a flat probe to ablate the entire visible transformation zone.[13] Standard guidelines do not currently exist on use of different probes types, and none of the handheld TA devices used in LMICs have a separate endocervical probe. In our study, a single probe with a small nipple was used for Type 2 transformation zones and a flat probe for Type 1 transformation zones. It is unknown whether the use of a separate conical probe to ablate the endocervix would impact recurrence in WLWH, and this can be explored in future studies. Possible reasons this 2-probe technique may be more effective include potentially ablating distant endocervical crypts[23] removed from the transformation zone that harbor HPV-infected or dysplastic cells. In a UK study among HIV-negative women, endocervical crypt

involvement by CIN on pretreatment biopsies was associated with an almost fourfold risk of high-grade cytology recurrence following TA.[24] It has been postulated that crypt involvement by CIN may represent deeper or multifocal disease with a more aggressive potential of CIN associated with high-risk HPV.[23] Our study did not collect data on crypt involvement in pretreatment biopsies to evaluate this association, and it is unknown if endocervical crypt involvement by CIN is more common in WLWH and can help explain the higher CIN2/3 recurrence following TA. Longitudinal studies among WLWH undergoing TA in LMICs can evaluate whether the presence of endocervical crypts impacts CIN2/3 recurrence.

Similarly, studies on the impact of lesion size and the type of transformation zone on TA treatment efficacy in LMICs are needed. The WHO criteria used in our study, recommends TA for Type 1 or Type 2 transformation zone where the TA probe tip will achieve complete ablation of the squamocolumnar junction. Inadequate fidelity to these guidelines in the context of screen-and-treat programs in LMICs which are not led by gynecologists or experienced colposcopists may impact observed efficacy rates.

Our study's strength lies in using gold-standard histology diagnoses at baseline and follow-up to define CIN2/3 cases and ascertain cure, minimizing classification bias. However, limitations include a small sample size hindering identification of predictors of treatment failure, no HPV testing at follow-up inhibiting investigation of impact of HPV persistence on treatment failure, and lack of endocervical biopsies restricting our understanding of observed recurrences' relation to endocervical disease. Our 12-month follow-up rate of 84.3%, consistent with similar studies, could have validity implications due to potential differential loss-to-follow-up.

In conclusion, while hand-held TA devices are increasing access to cervical precancer treatment in LMICs, our results find higher CIN2/3 recurrence rates among WLWH than previously reported. This underscores a limitation of the current secondary prevention strategy in this high-risk group. Programs using TA must ensure robust follow-up protocols to identify and manage treatment failure among WLWH. Urgent research on innovative strategies, including adjuvant therapies to lower recurrence,[25] are needed to optimize treatment outcomes until more effective treatments are available.

AUTHOR CONTRIBUTIONS

Chemtai Mungo and Craig R. Cohen conceptualized the project; Chemtai Mungo, Cirilus Ogollah Osongo, Jeniffer Ambaka and Jackton Omoto led the study implementation; Chemtai Mungo performed analysis and wrote the original draft; Jackton Omoto and Craig R. Cohen aided in interpreting the results and revised the manuscript. All authors discussed the results and commented on the manuscript. The work reported in the paper has been performed by the authors unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

De-identified data are available from the authors upon reasonable request.

ETHICS STATEMENT

The trial was registered under ClinicalTrials.gov identifier: NCT04191967. Ethics approval for the study was obtained from the institutional review boards of Maseno University and the University of California San Francisco. All participants provided written informed consent.

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