



## A novel cervical cancer screen-triage-treat demonstration project with HPV self-testing and thermal ablation for women in Malawi: Protocol for a single-arm prospective trial

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### ARTICLE INFO

**Keywords:**  
Cervical cancer  
Screening  
Self-collection  
HPV testing  
Thermal ablation

### ABSTRACT

Cervical cancer is the leading cause of cancer mortality among Malawian women, despite being preventable through screening and preventive therapy. In 2004, Malawi implemented a national screening program, using visual inspection with acetic acid (VIA) and cryotherapy, but its success has been limited due to equipment and human resources challenges. Since the development of that program, new technologies for screening and treatment that are less resource-intensive and more scalable have become available. GeneXpert systems provide fast, accurate HPV results and are increasingly available in low-income countries. Self-collection for human papillomavirus (HPV) testing is a validated method for screening and improves uptake. Thermal ablation provides an alternative ablative treatment that is simpler to use than cryotherapy and can be performed with portable devices. Meanwhile, urine HPV testing methods provide promising options for primary screening. We designed a single-arm prospective study to investigate a novel HPV screen-triage-treat strategy among 1250 women in Lilongwe, Malawi. Our proposed strategy consists of (1) Xpert HPV testing of self-collected samples, (2) VIA and colposcopy for HPV-positive women, and (3) thermal ablation for HPV-positive/ablation-eligible women. We will collect cervical biopsies, Pap smears, and endocervical samples to validate the HPV results and VIA/colposcopy findings against endpoints of high-grade cervical intraepithelial neoplasia or cancer (CIN2+). We will evaluate same-day completion of our algorithm, its performance in triaging women for treatment, and 24-week treatment efficacy of thermal ablation. We will also explore the performance of HPV and methylation tests in urine samples, as compared to provider- and self-collected cervicovaginal samples.

### 1. Introduction

Cervical cancer is the most common cancer and the leading cause of cancer mortality among women in Malawi [1]. Globally, 90% of cervical cancer deaths occur in low-income countries [2]. Cervical cancer is largely a preventable disease, and the disproportionate burden in low-income countries reflects the unequal implementation of cervical

cancer screening and preventive treatment across the globe. In sub-Saharan Africa (SSA), poor access to cervical cancer prevention strategies is compounded by the high prevalence of HIV infection, which increases susceptibility to cervical cancer [3]. In Malawi, 11% of women 15–50 years old are living with HIV [4].

In 2004, Malawi introduced a national screening program using visual inspection with acetic acid (VIA) for primary screening and cryotherapy for VIA-positive lesions [5]. However, as of 2015, the

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<https://doi.org/10.1016/j.conctc.2022.100903>

Received 18 June 2021; Received in revised form 20 December 2021; Accepted 7 February 2022

Available online 9 February 2022

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### Abbreviations

CI	confidence interval
CIN	cervical intraepithelial neoplasia
DNA	deoxyribonucleic acid
ECC	endocervical curettage
GDP	gross domestic product
HIV	human immunodeficiency virus
HPV	human papillomavirus
hr-HPV	high-risk human papillomavirus
IDI	in-depth interviews
NPV	negative predictive value
PPV	positive predictive value
RNA	ribonucleic acid
SCJ	squamocolumnar junction
UNC	University of North Carolina
VIA	visual inspection with acetic acid
WHO	World Health Organization

percentage of women who had been screened at least once was 27%, far below the program's goal of 80% [6]. Furthermore, only 43% of screen-positive women had received treatment. Barriers to successful implementation of this screening program in Malawi revolve around resource requirements. VIA screening requires a private examination room, pelvic examination table, and a trained provider. The need for a pelvic examination may also introduce individual-level barriers related to embarrassment or privacy concerns. Meanwhile, for cryotherapy, the health system must constantly resupply cryogas and address maintenance issues. In 2015, only 32 of the 130 health facilities that offered screening services had cryotherapy machines, 22 of which (69%) were functional [6]. Context-appropriate prevention strategies are urgently needed.

Self-sampling, GeneXpert® human papillomavirus (HPV) testing, and thermal ablation are promising strategies for addressing barriers to cervical cancer prevention in Malawi. We designed a single-arm prospective trial to evaluate the feasibility and performance of a same-day HPV-based screen-triage-treat algorithm that combines these three innovations among 1250 women in Malawi.

## 2. Study rationale

The World Health Organization (WHO) now recommends high-risk HPV (hr-HPV) screening strategies where feasible [7]. In a pooled analysis comparing VIA and HPV test performance, HPV testing showed higher sensitivity for the detection of cervical intraepithelial neoplasia (CIN) 2+ and cancer than VIA (0.95 vs 0.69), with no significant difference in specificity [8]. HPV testing for primary screening has resulted in greater reductions in cervical cancer incidence and mortality than VIA or Pap smear for primary screening, including in low-resource settings [9]. The Xpert HPV assay (Cepheid, Inc., Sunnyvale, CA) seems well-suited for SSA, since GeneXpert machines have been introduced widely in the region for tuberculosis diagnosis [10]. Xpert HPV tests perform similarly to other commercially available HPV DNA tests [11–17]. Further, Xpert provides results in 1–2 h, allows for non-batched testing, and does not require highly skilled lab personnel to operate [11].

Xpert HPV testing has similar clinical performance for CIN2+ or high-grade squamous intraepithelial lesion (HSIL) detection on self-collected and provider-collected samples [18–20]. Self-collection reduces barriers to screening because it is less human resource-intensive and potentially more acceptable to women [21]. In multiple settings, providing the option of self-collection has resulted in increased screening uptake [22].

Urine sampling may present an even less invasive and equally effective strategy for primary HPV testing [23–28], but has not yet been validated with the Xpert HPV assay. Beyond DNA testing, methylation changes in human genes and the HPV virus are strongly correlated with the development of CIN and invasive cervical cancer [29–31]. Methylation tests, such as the S5 methylation classifier, could be used for primary screening or added in sequence with HPV DNA testing to improve specificity of screening [32]. However, validation data on methylation testing, especially on self-collected cervicovaginal and urine samples, are still limited.

Thermal ablation provides a less resource-intensive ablative treatment than cryotherapy. It does not require a constant supply chain for cryogas, and treatment duration is 20–40 s, unlike cryotherapy which requires two applications of 3 min each with a thaw period of 5 min in between [33]. Thermal ablation achieves a cure rate of 94% for CIN2+ [33]. However, in a recent meta-analysis of 34 studies, only three studies were performed in Africa and only two of those included HIV-positive participants [33]. Since that analysis, a randomized controlled trial in Zambia showed that cryotherapy, thermal ablation, and loop excision had comparable effectiveness for resolution of positive HPV/VIA status [34]. Even with the relatively limited data on thermal ablation use in Africa, the Malawi Ministry of Health has introduced thermal ablation, due to the implementation challenges with cryotherapy [5].

Cervical cancer prevention programs need to be adapted for the setting. We propose a same-day screen-triage-treat algorithm combining Xpert HPV testing of self-collected samples and thermal ablation for HPV-positive/ablation-eligible women. This strategy has yet to be validated in resource-limited settings, and high HIV prevalence. Missed treatment (undertreatment of CIN2+ cases) and unnecessary treatment (overtreatment due to false positive tests) occur with any cervical cancer screening algorithm, and are yet to be robustly quantified for HIV-infected women. We aim to understand the performance of our proposed same-day screen-triage-treat algorithm, the utility of VIA triaging for treatment among HPV-positive women, the effectiveness of thermal ablation particularly in HIV-infected populations, and the performance of novel tests – including urine HPV testing and methylation testing – as screening methods. In this paper, we describe the study design and discuss the significance of the study.

## 3. Methods

### 3.1. Study objectives

To address the study aims, we specified the following:

#### 3.1.1. Primary objectives

1. To assess completion of a novel HPV-based cervical cancer same-day screen-triage-treat strategy among women in Lilongwe, Malawi, using self-collected vaginal brush sampling for hr-HPV testing, followed by VIA and thermal ablation for HPV-positive/ablation-eligible (by colposcopy) women;
2. To determine the 24-week efficacy of thermal ablation among women with CIN2/3.

#### 3.1.2. Secondary objectives

1. To evaluate the performance of the strategy by estimating overtreatment for women who are HPV-positive/VIA-positive/ablation-eligible women and undertreatment (missed treatment for CIN2+ cases) among HPV-positive/VIA-negative women;
2. To explore women's experiences with the proposed ICC screen-triage-treat strategy, including acceptability of self-collection;
3. To compare Xpert HPV testing and S5 methylation testing in urine samples with performance in provider- and self-collected cervicovaginal samples

### 3.2. Study design

This is a prospective single-arm study of a novel cervical cancer same-day screen-triage-treat algorithm in 1250 women (625 HIV-negative and 625 HIV-positive) in Lilongwe, Malawi.

Our innovative algorithm consists of self-collected vaginal brush for hr-HPV testing, followed by VIA for HPV-positive women, and thermal ablation for HPV-positive/VIA-positive/ablation-eligible women. We will perform VIA and colposcopy on every 10th HPV-negative women to assess for possible under-diagnosis from HPV testing of self-collected samples. Cervical colposcopy will be used to determine final eligibility for thermal ablation for all HPV-positive women. Additional samples will be collected for women who undergo a colposcopy examination to correlate with clinical findings: colposcopy-directed cervical biopsy for women with any visible lesions, Pap smear for women with no visible lesions, and endocervical curettage (ECC) for all women.

Enrollment will last up to 24 weeks, with a maximum of three follow-up visits. For women who are HPV-negative and not randomly selected for VIA and colposcopy, study participation will complete after the Week 0 visit. All women who undergo a colposcopy examination at the Week 0 visit will return for a Week 4 visit to receive their pathology or cytology results from the initial visit. Participants who underwent thermal ablation at the initial visit will return at Week 24 for follow-up provider-collected sample for HPV testing, colposcopy-directed cervical biopsy or Pap smear, and ECC. Participants will receive results from these specimens at the Week 28 visit, which will be the final study visit.

All participants will give an informed consent prior to participation. This study is approved by the University of North Carolina (UNC) Institutional Review Board and the National Health Sciences Research Committee in Malawi and is registered in [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04092257).

### 3.3. Study population, location, and personnel

The study will be conducted at UNC Project-Malawi's Tidziwe Centre clinic in Lilongwe, Malawi. Malawi has a population of 18.1 million with a GDP per capita of \$516 USD [35]. The estimated HIV prevalence among women aged 15–49 years old is 11% [4]. The annual number of new cases of cervical cancer in Malawi is 4163 and there are 2879 deaths attributed to cervical cancer per year [1].

UNC Project-Malawi is a collaboration between the University of North Carolina at Chapel Hill (UNC-CH) and the Malawi Ministry of Health. It has been operational in Malawi since 1990 and has been active in NIAID network research since 2001. This research site is among the largest, most productive, and most comprehensive HIV clinical research sites in the world.

### 3.4. Eligibility and recruitment

Participants will be recruited from outpatient clinics, particularly those that provide sexual and reproductive health services and HIV care services, in Lilongwe, Malawi. Study staff will provide educational talks about cervical cancer and the study in the clinic waiting areas. Women interested in the study will be booked for screening at the UNC Project Malawi research clinic and undergo informed consent before any study procedures are conducted. Women will be screened to see if they meet the study eligibility criteria (Table 1). Of the 1250 participants, we will recruit 625 who are HIV-positive and 625 HIV-negative. Positive HIV status will be established by positive results on a rapid HIV test and a second confirmatory method (different rapid test, plasma HIV-1 RNA viral load, or Bio-Rad Geenius assay).

### 3.5. Study procedures by visit

#### 3.5.1. Week 0 procedures

At the screening/enrollment visit, women will complete urine

**Table 1**  
Inclusion and exclusion criteria for study participation.

Inclusion Criteria	Exclusion Criteria
<b>Female</b>	Current or prior history of cervical, vaginal or vulvar cancer or dysplasia
<b>25–50 years old at study enrollment</b>	Current symptomatic sexual transmitted infection requiring treatment (may enroll after successful treatment)
<b>Able and willing to provide written informed consent</b>	Prior HPV vaccination
	Participants with known allergy to acetic acid
	Participants with a history of total hysterectomy
	Participants who are pregnant or plan on becoming pregnant during the study period
	Participants who are less than 12 weeks postpartum
	Participants with other illnesses that would limit compliance with study requirements or in the opinion of the investigator or designee, have a problem that would make participation in the study unsafe, or complicate interpretation of study findings

pregnancy testing, HIV testing, and a baseline questionnaire for socio-demographic data and cervical cancer risk factors. Urine collected will also be sent for hr-HPV and S5 methylation testing. For HIV-positive women, we will collect a blood sample for HIV-1 RNA viral load and CD4 count (Table 2).

Women will be counseled on how to self-collect a cervicovaginal brush, and they will be provided with illustrated instructions that have been validated in groups with low-literacy [36]. Further follow up study procedures will be based on HPV results (Fig. 1). Time stamps will be collected at multiple points to track average times for all steps, including self-collection, specimen transport, Xpert testing, result transport, VIA, and thermal ablation.

All HPV-positive women and every 10th consecutive HPV-negative woman will undergo VIA and colposcopy using Mobile ODT EVA system. During the speculum examination, the provider will collect a cervical brush for hr-HPV and S5 methylation testing (as comparison for urine sample testing). If lesion is seen with VIA and/or colposcopy, study clinicians will collect 2–4 cervical biopsies; otherwise, they will collect Pap smear. ECC will be collected for all women undergoing colposcopy to assess for endocervical dysplasia or cancer. VIA and thermal ablation will be performed by trained research nurses as per the Malawi national cervical cancer control program guidelines, and/or study clinicians comprised of a clinician, a medical officer and gynecologists, who will also perform colposcopy, cervical biopsies or Pap smear and ECC.

HPV-positive women will be treated with thermal ablation if the following criteria are met at colposcopy: 1) cervical lesions are not suspicious for invasive cervical cancer; 2) cervical lesions are located entirely on the ectocervix; 3) cervical lesions are no more than 2–3 mm into the endocervical canal; 4) the entire squamocolumnar junction (SCJ) can be visualized; and 5) all visible lesions are deemed appropriate for thermal ablation by the treating provider. Trained study nurses and clinicians will perform thermal ablation using a TC Thermocoagulator (Liger Medical HTU-110, Lehi UT), a second-generation, FDA-approved handheld and battery-operated thermal ablation device that can treat around 30–60 women per battery charge and which takes 20–40 s per treatment [37].

#### 3.5.2. Week 4

Participants who had cervical biopsy or Pap smear and ECC collected at Week 0 will return at Week 4 for pathology or cytology results. Women who underwent thermal ablation will be evaluated for any post-treatment adverse events during this visit. Referrals will be made as needed, including for HPV-positive women who did not receive treatment and were found to have HSIL or CIN2+.

**Table 2**  
Schedule of study procedures.

Study Visit	Screening & Enrollment	Week 4	Week 24	Week 28
Women who will attend the study visit	All women	Women who had cervical biopsy or cervical pap smear, and ECC done at Screening & Enrollment	Women who had CIN1+ at Screening & Enrollment and underwent thermal ablation	Women who attended the Week 24 Visit
Evaluations				
Informed consent	X			
Baseline survey	X			
Urine pregnancy testing	X	X	X	
HIV-1 rapid test	X			
HIV-1 confirmatory test	X <sup>a</sup>			
CD4 <sup>+</sup> T cell count	X <sup>b</sup>			
HIV-1 RNA (plasma)	X <sup>b</sup>			
Self-collected vaginal brush	X			
hr-HPV testing of self-collected samples	X		X	
hr-HPV and S5 methylation testing of urine sample	X			
hr-HPV testing and S5 methylation testing of provider-collected cervical brush	X <sup>c</sup>		X	
VIA	X <sup>c</sup>			
Colposcopy, cervical biopsy or Pap smear, and ECC	X <sup>c,d</sup>		X	
Thermal ablation	X <sup>e</sup>			
Thermal ablation-related adverse events evaluation		X		
Interval medical history		X		
Provide results and any referrals		X		X
Enroll for IDIs	X	X		

<sup>a</sup> Performed for women with initial rapid HIV positive result.

<sup>b</sup> For women who are HIV-positive.

<sup>c</sup> For women who are hr-HPV positive on self-collected sample and for every 10th woman who is hr-HPV negative.

<sup>d</sup> Cervical biopsy and ECC if lesion seen at colposcopy; Pap smear and ECC if no lesion seen at colposcopy.

<sup>e</sup> For women who are HPV-positive, VIA-positive, and ablation-eligible (judged at colposcopy).

### 3.5.3. Week 24

All women who had CIN1-3 and underwent thermal ablation will be asked to return for a follow-up visit at Week 24 post-treatment to assess for resolution of CIN and HPV clearance. For this visit assessment, provider-collected brush for Xpert HPV testing and colposcopy-directed biopsy (for women with lesions) or Pap smear (for women without lesions) and ECC will be collected.

### 3.5.4. Week 28

Week 28 visit will be the final study visit. Women will receive their testing results from Week 24 and be referred as necessary if they have persistent or new abnormalities.

## 3.6. Qualitative interview procedures

Up to 30 women with different screening outcomes (HPV-negative, HPV-positive/VIA-negative and HPV-positive/VIA-positive) will be recruited for in-depth interviews (IDIs) about their experiences with the proposed screen-triage-treat strategy. The IDIs will be conducted in the local language, Chichewa, in private rooms at UNC Project-Malawi. Interviews will cover prior knowledge of cervical cancer, experience with the self-sampling, understanding of the results, and intention to share their screening experience with others. Additionally, the interviewer will ask women to provide quantitative ratings of their privacy, embarrassment, discomfort, pain, and confidence during the screening and treatment procedures.

## 3.7. Quality assurance procedures

For quality assurance, study clinicians comprised of a clinician (AV), a medical officer (LM) and gynecologists (LC, FS, FL) will be certified through the National Cancer Institute-funded AIDS Malignancy Consortium (AMC) 099 study before performing colposcopy in the study. During colposcopy, images of the cervix will be captured and stored through the Mobile ODT EVA system. De-identified images will be internally reviewed by a gynecologist (JHT) who is involved in the study but not performing any of the study colposcopies, to ensure quality and consistency across colposcopists. If discrepancies in colposcopy are noted, the gynecologist will discuss the images with the colposcopists on a weekly basis as needed. Two local pathologists certified by the AMC studies will review all study pathology samples and will discuss a set proportion (at least 10%) of slides with a UNC Chapel Hill pathologist.

## 3.8. Participant retention plan

Once a participant is enrolled, study staff will make every effort to retain the participant for the protocol-specified duration of follow-up, thereby minimizing potential biases associated with loss to follow-up. Participants will be enrolled in the study only if they demonstrate understanding through the comprehension assessment conducted during the informed consent process, including what will be expected of them during study participation. For each missed visit, a study community nurse or educator will make every effort to contact the participant by phone or physical tracing except when the participant withdraws consent or the visit is not feasible due to unplanned relocation. To facilitate adherence and mitigate participants' expenses for the study-related visits, we will provide transport reimbursement, in accordance with guidelines from the Malawi National Health Sciences Research Committee.

## 3.9. Statistical considerations

### 3.9.1. Sample size

Our sample size of 1250 women who participate in the Week 0 visit will give us sufficient power to calculate 95% confidence intervals (CIs) for the proportion of women who complete each step of the screen-

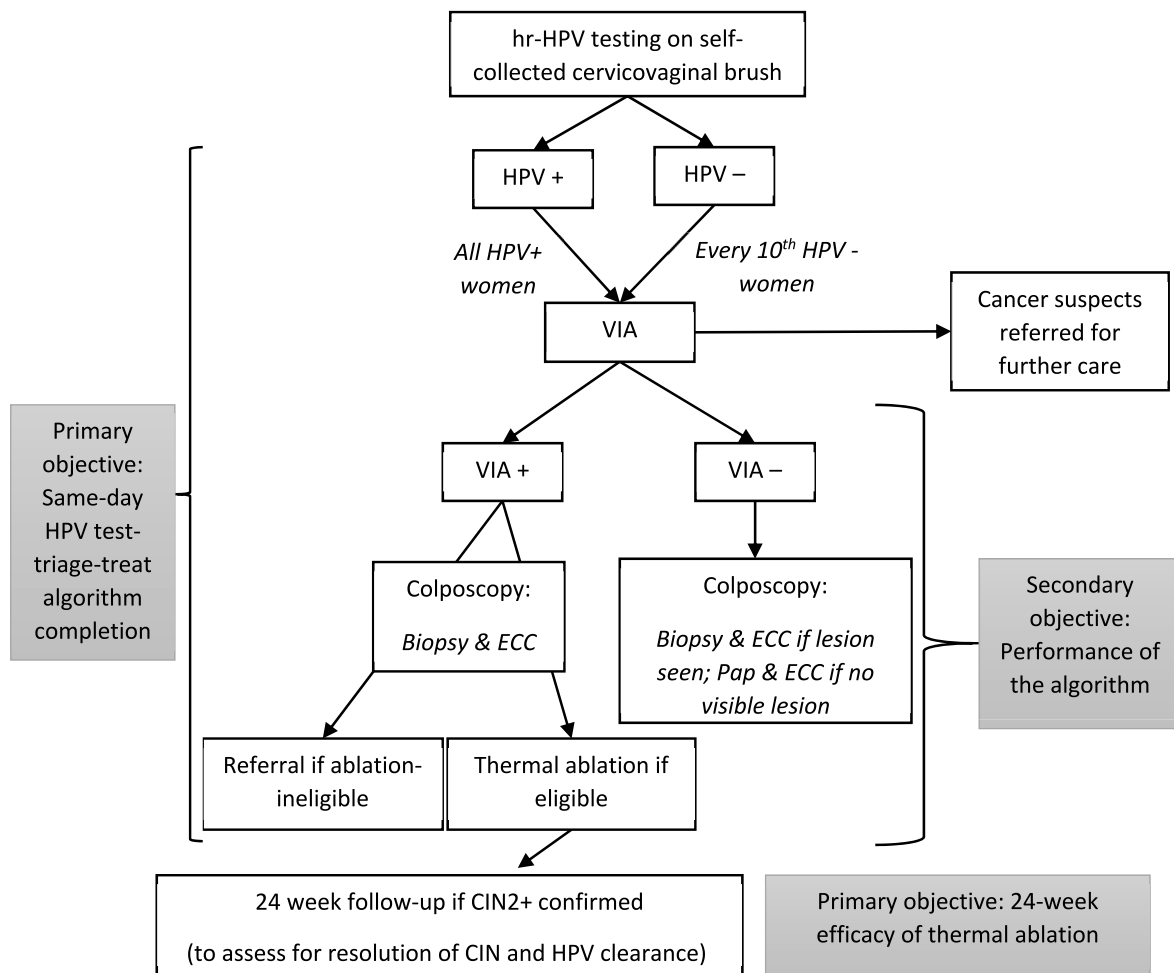


Fig. 1. Screen-triage-treat algorithm.

trriage-treat algorithm.

We expect to have sufficient sample size to measure the efficacy of thermal ablation for treating CIN2/3 within  $\pm 8\%$  both for the overall sample and the HIV-positive sub-group. Based on prior studies done among HIV-positive women in SSA, we assume that at least 50% ( $n = 313$ ) of the 625 HIV-positive women will be positive for hr-HPV [3] and that at least 20% of these 313 women will have CIN2/3 [38,39] which gives us at least 63 HIV-positive women with CIN2/3 in our cohort. Among HIV-negative women, we assume that at least 20% ( $n = 125$ ) of the 625 HIV-negative women will be positive for hr-HPV [40,41] and that at least 10% of these women will have CIN2/3 [41], which gives us at least 13 HIV-negative women with CIN2/3 in our cohort. We assume that 5% of the 76 women with CIN 2/3 will be lost-to-follow-up for 24 weeks visit based on prior experience from studies at UNC Project-Malawi. Therefore, we will be able to determine the 24-week efficacy of thermal ablation among approximately 72 women, including 60 HIV-positive women, with CIN2/3. This sample size of 72 CIN2/3 women, 60 of whom are HIV-positive, is comparable with other studies included in a meta-analysis that evaluated the efficacy of thermal ablation for treating CIN2/3 [33]. Assuming treatment efficacy of 90% over 24-weeks follow-up, we should have  $>95\%$  confidence to measure the efficacy within  $\pm 8\%$  both for the overall sample and the HIV-positive sub-group.

For determining HPV clearance after thermal ablation, we expect that 438 women (313 HIV-positive and 125 HIV-negative) will be positive for hr-HPV and that essentially all of these women will meet criteria for thermal ablation. This sample size provides 99.9% power to detect a difference between hr-HPV positivity pre- and post-treatment, assuming

100% HPV positivity pre- and 35% HPV positivity at 24 weeks post-treatment. We assume that 35% will still be hr-HPV-positive based on a recent systematic review of HPV persistence post-cryotherapy [42]; no such estimates are available for thermal ablation.

Formal power calculations were not done for any study objectives besides the ones related to same-day completion and thermal ablation cure rates, because the other objectives are primarily descriptive.

For the qualitative interviews, up to 30 women will be recruited. We expect to reach thematic saturation with this sample size, based on research in qualitative interviews showing that few new themes are established after the first 18 interviews [43]. We expect significant overlap in themes between the HPV-positive and HPV-negative groups.

### 3.9.2. Data analysis plan

For completion of the algorithm, we will calculate the following proportions with corresponding 95% CIs for the two primary outcomes: a) the proportion of HPV-positive women who had VIA performed on the same-day of HPV testing, and b) the proportion of HPV-positive/ablation-eligible (by colposcopy) women who had thermal ablation performed on the same-day of HPV testing. We will also calculate the median time needed to complete the proposed HPV testing, VIA triage, and treatment cascade.

For 24-week efficacy of thermal ablation, we will compare the rate of CIN2/3 resolution to historic cure rates for CIN 2/3 with cryotherapy. We will also determine the 24-week efficacy for CIN1 and HPV clearance.

Overtreatment will be calculated as the proportion of HPV-positive/VIA-positive/ablation-eligible women who would have been treated

with thermal ablation based on their HPV and VIA triage results alone (without colposcopy), and were found to have no CIN2+ on baseline cervical biopsy or ECC. This proportion will represent the women with no lesions or low-grade lesions (CIN1) who would have been unnecessarily treated if we based the decision to treat on HPV and VIA triage alone. Undertreatment will be calculated as the proportion of women with CIN2+ or HSIL on baseline biopsy or Pap smear who were not treated or referred in our algorithm due to a negative HPV and/or VIA result. This proportion will represent the women with CIN2+ or HSIL who were missed by our algorithm. For undertreatment, we will also evaluate the proportion of women who underwent thermal ablation and were found to be ECC positive for endocervical CIN2+, and therefore needed to be referred for further management since thermal ablation does not adequately treat endocervical dysplasia. This sub-set analysis of HPV-negative women undergoing VIA will allow us to control for potential verification bias. As all women will not be referred for verification by colposcopy, using only the histology results on HPV-positive women to estimate disease burden could lead to biased inference. To correct for this verification bias, we will utilize the colposcopy results among the random sub-set of HPV-negative women to employ the maximum likelihood method proposed by Zhou [44].

For qualitative interviews, we will perform thematic analysis, with two researchers coding each interview and using consensus to create the codebook.

For the novel urine testing methods, we will compare sensitivity, specificity, and positive and negative predictive values (PPV and NPV) for CIN2+ detection between the sample types, with CIN2+ based on histology results from the Week 0 visit. Again, our comparison samples are from provider-collected cervical brush and self-collected cervico-vaginal brush. Since methylation testing has been described as a possible method for triaging HPV-positive women, we will calculate the number of women who would be recommended for further evaluation and possible treatment per CIN2+ case detected, with and without the methylation triage.

Finally, we will use multivariable logistic regression to evaluate risk factors for CIN2+ among our population. Possible risk factors are collected on the baseline questionnaire (e.g. age, age at first sexual intercourse, number of sexual partners) and the laboratory testing performed at Week 0 (e.g. HIV-1 RNA load, CD4<sup>+</sup> cell count).

### 3.10. Current status

Recruitment and enrollment was paused for opening in March 2020 due to the uncertainties around conducting studies during the COVID-19 pandemic. However, the Malawi government continued cervical cancer screening services with some adjustments made in response to COVID-19. With personal protective equipment now readily available in-country, and clear guidance from the Malawi NHSRC on conduct of research during COVID-19 pandemic, the study opened to enrolment on June 24, 2020 and will continue till end February 2022.

## 4. Discussion

Our study will address the feasibility and performance of HPV-based screen-triage-treat strategy for cervical cancer prevention in a resource-limited setting, with one of the highest rates of cervical cancer related deaths in the world [2]. Malawi's national cervical cancer control program has been making strides, with resultant increase in screening coverage from 9.3% to 26.5% over a five-year period [6]. However, this coverage is suboptimal to reduce the burden of cervical cancer in the country. There are significant barriers to scaling up VIA and cryotherapy in Malawi. These include limited access to screening services and preventive therapy hampered by performance of the VIA-based screening and supplies for cryotherapy for screen-positive women [6, 45]. Context-appropriate and scalable solutions are urgently needed to mitigate the impact of cervical cancer.

HPV testing is highly reproducible and addresses concerns about reliability of VIA-based screening [8]. The advent of Xpert HPV testing addresses many of the barriers to implementing an HPV-based screening strategy in resource-limited countries including Malawi [11]. Additionally, Xpert testing has been validated with self-collected samples, with a high sensitivity for CIN2+ detection [18]. Self-collection reduces provider burden and has been shown to increase screening uptake, possibly due to better acceptability among women. Self-collected samples are highly stable for transport [46], which improves the feasibility of community-based screening in countries like Malawi with majority rural population [4].

Before HPV-based primary screening can be scaled-up, there are several questions that need to be addressed. The performance of our proposed algorithm – involving Xpert testing of self-collected samples and thermal ablation for HPV-positive/ablation-eligible women – has not been validated in Malawi. Using HPV testing as the primary screening instead of VIA introduces an extra wait-time step because Xpert results take 1–2 h. In the national cervical cancer control program, of the 939 women for whom cryotherapy treatment was postponed, 500 (53.2%) never received treatment [6]. Same-day screen-and-treat improves treatment rates by minimizing loss-to-follow-up. It is crucial to demonstrate that same-day completion of the screen-and-treat algorithm is still feasible with the incorporation of Xpert HPV testing. Our study will address the feasibility, and since we are tracking time points for each step, provide insight into where women might be the most likely lost to follow up. However, we understand the limitation which could come about due to selection bias of our study population, which could represent already motivated women to undergo screening.

Whether to include a VIA triage for treatment after an HPV-positive result is still a point of debate [47–49]. Performing VIA following an HPV-positive result may result in lower sensitivity compared to HPV testing alone, while there are concerns that HPV screen-and-treat strategies could lead to overtreatment. The rates of missed treatment (undertreatment) and unnecessary treatment (overtreatment) of HPV-based screen-and-treat strategy, have not been robustly studied, particularly in resource limited settings. By collecting pathology samples from all HPV-positive women, we have the opportunity to determine rates of overtreatment and undertreatment of the proposed strategy using histologic outcomes as gold standard. These analyses will provide preliminary essential data of the utility of VIA triaging for treatment following an HPV-positive result.

Meanwhile, thermal ablation requires fewer resources than cryotherapy and is simple enough to be operated by mid-level providers such as nurses. Newer battery-powered, hand-held thermocoagulator devices are promising for outreach clinics targeting hard-to-reach populations. For these reasons, the Malawi government already endorsed thermal ablation as an alternative ablative treatment for the national cervical cancer control program. However, data for thermal ablation efficacy are limited in settings with high HIV prevalence and are not typically defined histologically, but rather based on subsequent negative VIA result, which is not a robust indicator of the absence of CIN2/3 [50]. Including a substantial group of HIV-positive women in our study allows us to provide insight on our research questions in HIV-infected populations. In particular, thermal ablation efficacy evidence in HIV-infected women is solely needed. Our study will also provide a unique experience for using thermal ablation among nurses, who form a substantial number of available trained providers for Malawi's national cervical cancer control program. With the capacity for histologic diagnosis from baseline and follow-up visits, our study will provide robust data for thermal ablation efficacy, particularly among HIV-positive women.

Our study will also contribute to the small but growing body of evidence for urine HPV and methylation testing in low-income countries. We will be able to include comparisons between three different samples and measurements for 625 HIV-positive women, a high-risk group that so far has not been included in urine screening studies for cervical cancer

prevention. Urine tests may provide less-invasive options for primary screening or triaging.

For the HIV-negative women, our ability to investigate thermal ablation efficacy is limited by a relatively small sample size, since we expect that only 13 women will have CIN2/3 due to the lower expected prevalence among HIV-negative women. Additionally, for women who are VIA-negative, we will not initially collect cervical biopsies, even if their self-collected sample was positive for HPV, which may underestimate our CIN2+ endpoint. However, cytology and ECC performed on HPV-positive/VIA-negative women will likely identify any high-grade cervical dysplasia not noted on VIA or colposcopy, and we will refer these women for appropriate evaluation and treatment, including cervical biopsy.

If successful, our approach is arguably the most broadly-scalable strategy to optimize cervical cancer screening in high-burden countries like Malawi where screening is largely inadequate. Cervical cancer should not remain a leading cause of cancer death since it is largely preventable with vaccination and screening. Due to implementation challenges, HPV vaccination is not readily available in Malawi. Even if widespread HPV vaccination of girls is achieved in Malawi, millions of Malawian females will still be vulnerable to cervical cancer since only girls aged 9–13 years will be eligible for vaccination and a subsequent decline in hr-HPV incidence will not occur for decades [51]. Our study results will help inform national cervical cancer control programs across SSA on how to utilize innovations like self-collection, Xpert HPV testing, and thermal ablation to reduce the risk for cervical cancer among their populations.

## Funding

This work was supported by the U.S. National Institutes of Health, Bethesda, MD, USA [grant number: NIH R21CA236770], UNC Lineberger Comprehensive Cancer Center Tier 2 Stimulus Award, Chapel Hill, NC, USA, Tier 2 Stimulus Award, and U.S. Agency for International Development, Washington, DC, USA [grant number: AID-OAA-A-11-00012].

The study funders were not involved in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The NIH funders did influence study design by stipulating that cervical biopsies could not be obtained for HPV-positive/VIA-negative women.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We acknowledge the research team members for their commitment and preparatory work to see the study open to enrollment. We thank Fannie Kachale, Twambilire Phiri, Dr. Alinafe Mbewe, and Dr. Jonathan Ngoma, for their support. We would like to also thank Dr. Siobhan O'Connor, Dr. Jobiba Chinkhumba, Dr. Groesbeck Parham, Dr. Mina Hosseini-pour, Rob Krysiak, Gerald Tegha, Simon Nicholas and UNC Project-Malawi management for their support. We also acknowledge Rovers for donating the physician-collection brushes for this study.

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