UCSF Helen Diller Family Comprehensive Cancer Center

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Cervical cancer screening among HIV-infected women in Western Kenya: Evaluation of the safety, acceptability, and efficacy of an alternative ablation method for treatment of precancerous lesions

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
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Protocol Signature Page – Participating Site

Protocol No.: 19405 **Version Date:** 07-25-2019

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I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

Principal Investigator	**Site**
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Signature	Date

Abstract

Title	Cervical cancer screening among HIV-infected women in Western Kenya: Evaluation of the safety, acceptability, and efficacy of an alternative ablation method for treatment of precancerous lesions
Study Description	The purpose of this study is to evaluate the safety, acceptability, and efficacy of Thermocoagulation for treatment of precancerous lesions among HIV-positive women in a screen-and-treat program in Western Kenya. Thermocoagulation is endorsed as an alternative to Cryotherapy for treatment of Visual Inspection with Acetic Acid (VIA) or Human Papillomavirus (HPV)-positive women by the 2018 Kenya national cancer guidelines.[32] Data primary from Western countries demonstrate similar efficacy for the treatment of precancerous lesions between Cryotherapy and Thermocoagulation. Data on safety, acceptability, and efficacy, particularly linked to gold-standard pathology, among HIV-positive women in low-resource settings are scare. Given the demonstrated benefits over cryotherapy including increased portability and availability hence easier implementation, use of thermal coagulation for the treatment of precancerous lesions in low resource settings could significantly improve access to treatment compared with cryotherapy. This study seeks to fill a critical data gap by evaluating the efficacy of thermocoagulation among HIV-positive positive women using gold-standard biopsy for disease verification at baseline and follow-up, as indicated. We will also assess the safety and acceptability of this treatment modality among patients and providers.
Study Intervention	Thermocoagulation
Study population	HIV-infected women age 30 – 65 years old enrolled in care at the FACES- supported HIV clinics in Kisumu County in Kenya.

Objectives	Primary Objective: To evaluate the efficacy of thermal coagulation for the treatment of HIV-positive, HPV-positive women by assessing the rate of HPV persistence and CIN2/3 rate at 12 months after treatment. Secondary Objectives: To evaluate the safety of thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya. To evaluate patient satisfaction with thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya. Exploratory Objective: To evaluate provider acceptability of thermal coagulation for the treatment of precancerous cervical lesion within a screen-and-treat program in Western Kenya.
Sample Size	400 HIV-positive participants We seek to enroll 400 participants in order to obtain sufficient numbers of women who have CIN2/3, our outcome of interest. Based on prior studies in this population, we anticipate approximately 35% of HPV-positive women (N ~ 140) will have biopsy-proven CIN2/3

List of Abbreviations

LMIC	Low- and middle-Income countries
VIA	Visual inspection with acetic acid
VAT	Visual assessment for treatment
HPV	Human papillomavirus
HR-HPV	High-risk human papillomavirus
HIV	Human Immunodeficiency Virus
WHO	World Health Organization
CIN2	Cervical intraepithelial neoplasia grade II
CIN2/3	Cervical intraepithelial neoplasia grade II or III
SCJ	Squamo-columnar junction
IARC	International Agency for Research on Cancer
JOOTRH	Jaramogi Oginga Odinga Teaching and Referral Hospital
FACES	Family AIDS Care and Education Services
LEEP	Loop excisional electrosurgical procedure
UCSF	University of California, San Francisco
KEMRI	Kenya Medical Research Institute
AE	Adverse Events
MOH	Ministry of Health
DNA	Deoxyribonucleic Acid
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
NCI	National Cancer Institute

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1 Introduction

1.1 Abstract

Although cervical cancer is preventable, in 2018, an estimated 570,000 new cases will be diagnosed, 90 percent in low- and middle-income countries (LMICs).[1] Women infected with the Human Immunodeficiency Virus (HIV) are at increased risk of cervical cancer due to increased incidence and persistence of the human papillomavirus (HPV) infection, the causative agent.[2] Low-income countries have been unable to implement cytology-based screening programs used in high-income countries due to significant infrastructure and human resource requirements not feasible in these settings.[3] In 2013, the World Health Organization (WHO) recommended cervical cancer screening using Visual Inspection with Acetic Acid (VIA) or HPV testing in LMICs, followed by immediate treatment with cryotherapy without histologic diagnosis.[4] This screen-and-treat strategy decreases loss-to-follow-up, and is associated with a reduction in cervical intraepithelial neoplasia grade 2 and 3 (CIN2/3) and mortality from cervical cancer.[5,8] However, impact on disease burden will not occur until women who screen positive are effectively linked to and receive treatment and appropriate follow-up. Currently, widespread implementation of cryotherapy programs has proven to be difficult given the need for bulky equipment that limits mobility in the field, and need for an ongoing supply of refrigerant gas which is expensive and of unrealizable quality.[6] Recent data primarily among HIV-negative women suggests that thermal coagulation, an alternative treatment method, may be more feasible for implementation in LMICs, with similar efficacy compared to cryotherapy.[6,7] If supported by more research, population-level implementation of thermal coagulation for the treatment of precancerous lesions within LMICs may result in increased access to treatment and hence secondary prevention of cervical cancer.

1.2 Background

Despite being a preventable disease through screening and vaccination, cervical cancer is a leading cause of death of women in Sub-Saharan Africa, where 90 percent of the 311,000 deaths in 2018 will occur.[1] In Kenya, cervical cancer accounts for 70-80% of cancers of the genital tract, and is the most common cause of cancer-related death for women, with an estimated 1700 yearly deaths.[8] Cervical cancer is an AIDS-defining malignancy and women infected with the Human Immunodeficiency Virus (HIV) are at increased risk due to increased incidence and persistence of the human papillomavirus (HPV) infection, the causative agent.[2] Compared to HIV-negative women, women with HIV develop precancerous lesions at younger age and have faster progression to cervical cancer, making prevention efforts among this group particularly urgent.[9] While access to the HPV vaccine may play the most significant role in cervical cancer control and elimination, access is currently limited in Sub-Saharan Africa, and its impact on cervical cancer will not be evident for at least twenty years.[10] Therefore, effective cervical cancer screening remains a priority for cancer control in the current generation.

African countries have been unable to implement widespread cytology-based screening programs due to high infrastructure requirements and the need for multiple visits, leading to loss-to-follow-up.[11] In 2013, following significant evidence, the World Health Organization (WHO) recommended cervical cancer screening using Visual Inspection with Acetic Acid (VIA) or high-risk Human Papillomavirus (HR-HPV) testing in low resource settings, followed by immediate treatment with cryotherapy without histopathologic verification.[4] This single-visit strategy decreases loss-to-follow-up in settings where women often overcome significant barriers to reach clinics and is associated with a reduction in CIN2/3 and mortality from cervical

cancer.[4] Studies confirm that the benefit far outweighing the harms of overtreatment.[4] However, while screen-and-treat with cryotherapy has demonstrated high cure rates – 88 percent for CIN1/2, and 77 percent for CIN3, and low rate of adverse events (2.1% with mild pain or cramping, 1.6% with malodorous excessive vaginal discharge, 0.7% with mild bleeding or spotting, and no severe adverse events noted)[12], there are significant barriers to widespread implementation, leading to a need for alternative treatment methods. [6,13] Challenges associated with cryotherapy include bulky equipment limiting mobility, as well as the need for an ongoing supply of refrigerant gas which is expensive and of unrealizable quality in rural areas.[6] An evaluation of 25 health facilities with cryotherapy services in Uganda showed that almost half of them were not operationally owing to lack of gas.[6] In Malawi, over a 5-year period, only 43.3% of women who screened VIA-positive accessed treatment owing to challenges with delivering cryotherapy.[14] This has led to a search of alternative, more easily implementable methods of treatment of cervical pre-cancer in low resource settings.

1.3 Literature Review

Thermal coagulation is an alternative ablative treatment method has increasingly been investigated for use in low resource settings. Thermocoagulation uses heat instead of cold to ablate cervical tissue - the superficial epithelium sloughs off after treatment, and the underlying stroma and glandular crypts are destroyed by desiccation.[15] Similar to cryotherapy, studies support tolerability of thermocoagulation without the use of anesthesia, and the equipment supports self-sterilization.[6,13,16] Compared to cryotherapy, thermal coagulation has several advantages for remote areas. Newer generation battery-powered devices are light and highly portable, weighing only 4.6 kilograms compared to 15-20 kilograms for each cryotherapy gas cylinder.[6] Thermal coagulation also allows for faster treatment – a single application lasting 20 - 40 seconds, compared with the 3-min freeze, 5-min thaw, 3-min freeze cycle for cryotherapy, enabling treatment for more women.[6,16] Widely accepted criteria for eligibility for treatment with thermocoagulation is similar to that for cryotherapy.[6]

Thermal coagulation has been used for treating CIN3 for 3-4 decades, primarily in the United Kingdom.[6] In a systematic review of thirteen primarily European studies on the efficacy of thermal coagulation for treatment of CIN1-3 among 4569 patients, Dolman *et al.* report a 96% (95% CI 92 – 99%) cure rate for CIN1 and 95% (CI 92-98%) for CIN2/3 disease, comparable to published rates for cryotherapy.[16]

In the last few years, several small studies in LMIC have similarly reported comparable results with the use of thermal coagulation for the treatment of precancerous lesions. In Brazil, Naud *et al*. investigated the acceptability, safety and efficacy of thermocoagulation for the treatment of histologically proved CIN2-3.[16] Among 52 women included in the study, 44 (85%) had no evidence of disease one year after thermocoagulation. The rate of no disease at follow-up was similar for women with CIN2 (17/20), 85% and those with CIN3 (27/32), 84%. At follow-up, disease status was evaluated by VIA and cytology, with colposcopy and biopsy as needed.[17] Their study also reported no serious adverse effects following treatment with thermocoagulation. In Malawi, Campbell *et al*. report that 85% of approximately 300 VIA-positive women treated with thermocoagulation had negative VIA at 12-month follow-up, although they had no histological disease verification either at baseline or at follow-up.[18] In Cameroon, Tran *et al*. evaluated the efficacy of thermocoagulation for treatment of biopsy-proven CIN2/3 among women age 30-49 years.[13] Although limited by a small sample size, at 12-months follow-up, using cytology and biopsy to evaluate cure, 70.6% of women had no evidence of disease, comparable to the efficacy rates of cryotherapy within a similar population.[6,19]

In a 2019 updated metanalysis of the efficacy of thermocoagulation for precancerous lesions including 7 studies from LMICs, Randall et al report a pooled estimate of 93.8% (95% CI 90.4 – 95.1).[20] The authors examined the effect of potential modifying factors on the cure rates for thermal ablation for treatment of biopsy-proven CIN2+. Studies restricted to countries in LMICs had a cure rate of 83.6% ((95% CI 78.2 – 88.2%).[20]

Data on safety and efficacy of thermocoagulation among HIV-positive women in low resources settings are limited. A 2016 Nigerian study among VIA-positive, HIV-positive women treated with thermocoagulation reported a cure rate of 81.7% (95% CI 74.7 – 88.6%), with cure defined as negative VIA at 12-month follow-up,.[21] In a metanalysis of LMIC studies including 155 HIV-positive women, 120 (84% - confidence interval not reported) were without evidence of dysplasia at follow-up, the majority assessed by VIA.[20]

While limited, current data suggests that thermocoagulation is comparable to cryotherapy for treatment of precancerous lesions in HIV-positive women. The 2018 Kenya National Cancer Guidelines recommend the use of either Cryotherapy or Thermocoagulation for treatment of precancerous lesions among both HIV-positive and HIV-negative women.[22] The WHO has convened a Guideline Development Group to review the evidence for thermocoagulation and is expected to make a recommendation.[20]

1.4 Study Rationale

Despite significant progress in developing feasible and context-appropriate cervical cancer screening tools for low resource settings, impact on disease burden will not occur until all women who screen positive for precancerous cervical lesions are linked to treatment.[6] Despite cryotherapy being WHO-recommended for use in screen-and-treat programs in LMICs, wide-scale implementation has proven challenging. Given the demonstrated benefits over cryotherapy, use of thermal coagulation for the treatment of precancerous lesions in low resource settings could significantly increase access to treatment compared with cryotherapy, potentially closing this important effectiveness gap in screening programs in low-resource settings.

Data on the safety, acceptability, and efficacy of thermocoagulation for treatment of precancerous lesions is limited, however, particularly among HIV-positive women who face disproportional burden of cervical cancer. From this study, we will provide crucial data on the safety, acceptability, and efficacy of thermocoagulation for treatment of CIN2/3 among HIV-positive women by supporting gold-standard biopsy verification at baseline and at 12-months follow-up after treatment. We will also evaluate provider acceptability of this new treatment method, a crucial aspect of widespread uptake. This data will inform national cervical cancer programs as well as inform policy and guideline development within the national government and the World Health Organization for this high-risk group of women in urgent need of prevention strategies.

We seek to investigate the safety, acceptability, and effectiveness of thermal coagulation for the treatment of biopsy-proven CIN2/3 among HIV-positive women in Western Kenya. We also seek to evaluate provider acceptability of thermocoagulation as a treatment method for precancerous lesions.

1.5 Anticipated Application of Study Results

The results from this study will we will provide crucial data on the safety, acceptability, and efficacy of thermocoagulation for treatment of CIN2/3 among HIV-positive women by supporting gold-standard biopsy verification at 12-months after treatment. If proven safe and efficacious, given the benefits over cryotherapy, there is potential for widespread adoption of thermal coagulation within screen-and-treat programs which may vastly improve access to treatment of precancerous lesions within Kenya and other LMICs, and support the goal of prevention, and elimination, of cervical cancer. This data will inform national cervical cancer programs as well as inform policy and guideline development within the national government and the World Health Organization for this high-risk group of women in urgent need of prevention strategies.

2 Study Objectives

2.1 Hypothesis

We hypothesize that the efficacy of thermal coagulation for the treatment of CIN2/3 among HIV-infected women will be similar to reported rates of cryotherapy among this population.

2.2 Primary Objective

To evaluate the efficacy of thermal coagulation for the treatment of HIV-positive, HPV-positive women by assessing rates of HPV persistence and CIN2/3 rate at 12 months after treatment

- Endpoints:
    - Proportion of women with no evidence of cervical dysplasia at 12-month follow-up based on colposcopy and biopsy.
    - Proportion of women with persistent HPV at 12-month follow-up

2.3 Secondary Objectives

To evaluate patient safety of thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya.

- Endpoints:
    - Average pain score immediately after treatment
    - The rate of AEs reported at 4-6 week follow-up

To evaluate patient satisfaction with thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya.

- Endpoint: Proportion of participants who answer ‘yes’ to satisfaction questions at 4-6 week follow-up.

2.4 Exploratory Objective

To evaluate provider acceptability of thermal coagulation for the treatment of precancerous cervical lesion within a screen-and-treat program in Western Kenya.

- Endpoint: Healthcare providers satisfaction scores on a validated Usability Likert Scale administered via a questionnaire.

3 Study Design

3.1 Characteristics

We will prospectively enroll four hundred HIV-positive women to undergo cervical cancer screening at FACES-supported MOH clinics in Kisumu County. After informed consent, clinical and demographic information will be collected, and participants will undergo cervical cancer screening using HPV testing. Women who previously screened positive for HPV (within the last 3 months) but have not undergone treatment will also be eligible for recruitment. Women with a positive HPV test will be evaluated for treatment with thermal coagulation, per WHO standards of ablative treatment. Per the WHO and Kenya Ministry of Health guidelines, women who will be candidates for thermal coagulation if the squamocolumnar junction is fully visualized, the cervical lesion covers less than 75% of the cervix, and there is no endocervical component or suspicion of cancer.[8] Women who are not candidates for ablation will be referred to nearby a referral facility. All participants with a positive HPV test will undergo directed biopsy just prior to treatment for disease ascertainment but proceed to have same-day treatment, according to the WHO guidelines for screen & treat.

At 12-months after treatment, all participants treated at baseline will undergo repeat colposcopy, directed biopsy for those with cervical abnormalities or those with CIN2/3 at baseline, as well as provider collected HPV testing for persistence. Twenty-five percent of women with normal colposcopy will have a random biopsy at 6 or 12-O'Clock to confirm the absence of disease. Pain will be assessed immediately following treatment using a visual analog scale (VAS). The presence and severity of AEs will be assessed 4-6 weeks following treatment via a phone call, or in person visit, if warranted. Healthcare providers offering thermal ablation for the treatment of precancerous lesions will be surveyed at 4-6 week follow-up to evaluate provider acceptability and satisfaction with this treatment method.

3.2 Study Population

HIV-infected women age 30 – 65 years old enrolled in care at the FACES- supported HIV clinics in Kisumu County in Kenya.

3.3 Sample Size and Power Calculation

The study sample size is calculated based on the primary objective.

We seek to enroll 400 participants in order to obtain sufficient numbers of women who have CIN2/3, our outcome of interest. Based on prior studies in this population, we anticipate approximately 35% of HPV-positive women (N ~ 140) will have biopsy-proven CIN2/3.[24] The study design is a non-inferiority trial using results from the only study using standard cryotherapy in a similar population[19] to establish the non-inferiority boundary. We

will compare the efficacy rate in our study using thermocoagulation to the non-inferiority boundary established using the efficacy rate and lower 95% confidence bound from this cryotherapy treatment publication from a similar population.[19]

The efficacy results of cryotherapy in the De Vuyst paper were 77.2% (95% CI: 66.4-85.9%).[19] Using 77.2% with a non-inferiority margin of 10% which is at the limit of the confidence bound and is closest to the null effect.[24] Using this margin, the new treatment method is hypothesized to be at least as good as cryotherapy. Based on this non-inferiority margin, a sample size of 140 women with CIN2/3 achieves 90% power in using a one-sided test with a significance level of 0.025. Based on this sample size, power of 90%, and significance of 0.025, the minimal detectable effect size (the actual difference between cryotherapy and thermocoagulation) is 0.0102.

We will leverage the robust HIV-care infrastructure at FACES in which patients are seen at every one to three months, and the presence of an established patient tracing system (including home visits) to reduce loss-to-follow-up. Assuming a 14% loss to follow-up, which would result in a sample size of 120, we are still be powered for our non-inferiority margin of 10% with a minimal detectable effect size of 0.0184, with 80% power and an alpha of 0.025. Sample size and non-inferiority calculations used NCSS PASS software and G-Power software.

3.4 Study Site

This study will take place at the Family AIDS Care & Education Services (FACES)-supported Ministry of Health (MOH) clinics in Kisumu County in Kenya. At FACES, cervical cancer screening using VIA or HPV testing is offered to sexually active women enrolled in care between 18 and 65 years of age, according to the Kenya Ministry of Health guidelines. Women who screen positive are offered treatment onsite when available or referred to a nearby tertiary center.

3.5 Risks and Benefits

3.5.1 Potential Risks

We anticipate that the potential risks to participants in the study will be minimal. Study subjects may feel discomfort or embarrassment during the pelvic exam. There may be minimal discomfort during self-collection of HPV specimens. Participants may be at risk for psychological or emotional discomfort at different stages of the study if they have a diagnosis of CIN2/3 and learn about the potential risk of cervical cancer. Participants may risk some discomfort and mild spotting after the colposcopy and biopsy. We anticipate that this will be minimal, as exams will be performed by trained clinicians, and thermal coagulation would ablate the biopsied area with the tissue desiccation, hence stopping any bleeding. Other mechanisms to achieve hemostasis at bleeding sites including use of Silver Nitrate sticks will be available to study clinicians. Women who are not eligible for thermocoagulation due to large lesions will be referred to a nearby tertiary facility for further care, per clinic protocol. Following treatment for abnormal screening, women will have vaginal discharge for a few days for which they will be provided anticipatory guidance. During the 12-month follow-up visit, all treated women will have repeat screening with colposcopy and biopsy as needed, as well as repeat HPV-testing with provider collection. Twenty-five percent of women who have normal colposcopy results will have a random biopsy for ascertainment of cure after treatment. This may not have been performed in a routine clinical visit and may be associated with slight discomfort, but the risk to the patient will

be minimized by adequate training of clinicians, and anticipatory guidance provided to the patient. We believe that the benefit of reducing verification bias in performing these biopsies will strengthen the study results and prove a strong case for implementing this treatment method on a large scale.

3.5.2 Protection Against Risks

To reduce the likelihood of participants experiencing psychological discomfort, we will make every effort to create a secure and trustworthy environment. Study staff that counsel participants and carry out examinations will undergo training on culturally sensitive ways to reduce discomfort and embarrassment during the pelvic exam, including providing a private area for women to undress for pelvic exams, providing a clean sheet to cover the woman during exams and obtaining verbal consent prior to each step of the procedure. To assist participants who may experience psychological discomfort when learning of a diagnosis of cervical dysplasia, we will ensure access to experienced counselors who work at FACES. When diagnosed with early-stage cervical cancer during this study will be navigated through the referral process to ensure adequate care by a gynecologist oncologist at the referral facility. All study staff will be thoroughly trained in the study protocol, study procedures, good clinical practices and protection of human subjects prior to starting the study. All exams will be performed gently and, in a way that most minimizes discomfort, bleeding or anxiety in the participants.

3.5.3 Potential Benefits

The research question in the Primary Objective will directly benefit study participants by identifying women with abnormal cervical cancer screening results and offering treatment to prevent progression to cancer. Previously, women who screened positive for precancerous lesions were referred for care, some of whom are lost to follow-up in navigating the referral process. In enrolling in the study, all eligible women will access immediate treatment in the clinic instead of referral. During screening, some women with potential early-stage cancer may be identified and will be referred for appropriate evaluation and treatment to a gynecologist oncologist at the referral site. Study staff will support these participants through the referral process to ensure they are seen by a Gynecologist Oncologist. The research questions in the Secondary Objectives will not directly benefit individual patients but will contribute to the knowledge of safety and acceptability of this method of treatment for precancerous lesions that may enable widespread adoption of this technique if proved safe and effective. The Exploratory Objective will evaluate provider acceptability of Thermocoagulation thereby providing crucial insights into potential limitations for widespread provider acceptability of this treatment method. All participants may also gain knowledge about cervical cancer screening and prevention from spending more time with study staff and study clinicians. According to KEMRI regulations, participants will only be reimbursed for their transportation expenses related to participation in the study. Hence, for study-specific visits, women will be reimbursed a rate set by KEMRI. Women participating in the study during a scheduled visit will be reimbursed a meal voucher only.

4 Participant Eligibility, Recruitment, and Enrollment

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

1. Age 30-65 years.
2. Enrolled in HIV care at FACES-supported clinics in Kisumu County.
3. Able to understand a written informed consent document, and willing to sign it.
4. Speaks a language that the consent form and data collection instruments are written in.

4.1.2 Exclusion Criteria

1. Has a history of cervical cancer.
2. Has received any treatment for cervical precancer after screening positive for precancer.
3. Has evidence of cervical infection.
4. Pregnant women are excluded from this study.

4.2 Recruitment and Enrollment

Women receiving care at FACES-supported HIV- clinics will be considered for recruitment into the study. At these clinics, patients are introduced to cervical cancer screening as part of an HIV education session when they enroll in care. Information about cervical cancer and the opportunity for screening is reinforced as part of a general daily health talk given while patients are waiting to be seen for their routine HIV care, and then reinforced through individualized counseling during their clinical visit. Women willing to undergo cervical cancer screening will be screened consecutively for their study eligibility and asked about their willingness to participate in the study.

Screening and informed consent for participation in the study will take place in a private gynecologic exam room prior to a pelvic exam. Women who previously screened positive for HPV (within the last 3 months) but have not undergone treatment will also be eligible for recruitment. Those who screen positive and are eligible for thermal ablation will be offered treatment and will form the study group

Participant Registration

A written, signed, informed consent form (ICF) must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected.

5 Study Procedures and Assessments

5.1 HPV Self-Testing

In this study, cervical cancer screening will be done using HPV testing via self-sampling.

HPV testing at baseline will be performed using patient self-collected samples. After providing informed consent, participants will be provided with visual and verbal instructions for HPV self-collection and offered a private area to perform self-collection before returning the kit to the health provider. During self-collection, women will be instructed to proceed to a designated private area with the collection brush and tube. While inside the collection area, she will undress from the waist down. She will then open the cap of the collection tube and lay both the tube and the cap aside on a flat surface. Next, they will open the case of the collecting brush, holding it from the plastic end that is the handle. She will then squat or stand in a comfortable position with her legs and thighs wide open. With one hand holding the plastic handle of the collection brush, she will use the other hand to open the outside of her vagina and gently insert the tip of the brush into her vagina. While holding the brush steady, she will gently advance the brush, with a slight left or right rotation for easy penetration until she feels resistance (at the cervix). At this point, she will turn the brush left or right five times to collect cells from the cervix. She will then remove the brush from her vagina and insert it into the collection tube until it reaches the bottom of the container. While holding the tube firmly with one hand, she will break off the handle of the brush with her other hand at the scored line against the mouth of the tube. She will then replace the lid of the collection tube and dispose of the brush handle in a rubbish container. A sanitizer for cleaning hands will be available for use before and after collection.

We will use the CareHPV™ system which tests for DNA of 14 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).[25] The self-collected samples will be placed in a cool area within the FACES laboratory and tests will be run in batches of 90, per the manufacturer's instructions, by a trained laboratory technician. Women who screen positive for HR-HPV will be offered a pelvic exam and treatment per the WHO recommendation.[4] Visual inspection with acetic acid will be performed at the time of the pelvic exam to determine eligibility for thermal ablation based on the size of the lesion and other characteristics, as recommended by the WHO and Ministry of Health.[4] A HPV-positive woman will be considered a candidate for thermal coagulation if the squamocolumnar junction is fully visualized, the cervical lesions takes up less than 75% of the cervix, there is no endocervical component of the lesion, and the lesion is not suspicious for cancer. Women who do not meet these criteria will be referred to a tertiary facility for appropriate care.

5.2 Pelvic Exam

Study examinations will take place in a private room equipped with a gynecologic exam bed in the FACES clinic. Participants will be placed in a dorsal lithotomy position. The external genitalia will be examined to look for any evidence of infection or genital ulcer disease. After introduction of a sterile speculum, the clinician will use a swab to wipe away cervical mucus or blood and assess for evidence of cervicitis.[26] In the case of concern for cervical infection, routine testing and treatment will be performed and screening deferred until treatment is complete.[8]

5.3 Visual Inspection with Acetic Acid

In this study, VIA will be performed on all HPV positive women to assess for eligibility for ablative treatment in a process referred to visual assessment for treatment (VAT).[6] After identification of the cervical anatomy, including the squamocolumnar junction, the clinician will apply 5% acetic acid to the cervix. After one minute, the clinician will examine the cervix again to interpret results of the VIA according to the following criteria:

VIA will be defined as negative if the following findings are present:[26]

1. Circumferential identification of the squamocolumnar junction (SCJ)
2. No aceto-white or faint, ill-defined white lesions at the SCJ or aceto-white lesions far away from the SCJ

VIA will be defined as positive if the following findings are present, as established by the International Agency for Research on Cancer (IARC):[8,26]

1. Raised, thickened, a well-defined, opaque aceto-white lesion at or close to the SCJ
2. Large circumferential aceto-white lesions covering the external os
3. Pre-existing condyloma or leukoplakia which turns intensely white after application of acetic acid

The WHO criteria for cryotherapy will be used to assess for eligibility for thermal coagulation – namely, if the squamocolumnar junction is fully visualized, the cervical lesion covers less than 75% of the cervix, and there is no endocervical component or suspicion of cancer.[4] These criteria for the use of thermal coagulation widely accepted and is used in other studies and clinical settings.

5.4 Baseline Colposcopy and Cervical Biopsy

All women with a positive HPV screening test will undergo a colposcopy exam followed by a directed biopsy of abnormal areas using a punch biopsy forceps. If there are no abnormal areas, a random biopsy will be performed at 6 or 12 O'clock. Colposcopy exam will be done in accordance with the International Federation for Cervical Pathology and Colposcopy (IFCPC) guidelines, including sequential evaluation using a green filter and acetic acid.[27] During the cervical biopsy, the study clinician will use a biopsy forceps to obtain a rice-grain-sized cervical specimen, either at the site of abnormality or at random quadrants. The specimen(s) will be placed in a container with formalin, labeled and stored while awaiting transportation to pathology.

5.5 Thermocoagulation

Treatment of positive screening results will be performed using the Liger Thermocoagulator device.[28] Eligibility for ablative treatment with the thermal coagulator is similar to the WHO-recommended criteria for cryotherapy, as described above.[4,13] The Liger thermocoagulator device is a second-generation, hand-held, battery powered, rechargeable device that was developed by Liger Medical in Utah USA specifically for use in low resource settings. Previous generations of this device have been used for treatment of precancerous lesions in multiple studies both in Sub-Saharan Africa and in Europe.[6,7,13,17,18,29]

The cordless, rechargeable device has two components, the detachable probe that comes in different sizes to match lesion size, and is heated once in contact with the cervix, and the hand-held portion that contains the battery and control mechanism with automated timing. Once activated, the tip of the probe, in contact with the cervix heats up to 100 ºC over approximately four seconds. Once at this temperature, an inbuilt timer starts for a recommended treatment length of 20 seconds. If the lesion is larger than the probe, or the transformation zone is not fully covered by the probe, several overlapping applications are performed to cover the entire lesion.[17]

This temperature and length of treatment induce tissue necrosis to a depth of just over 5 mm, which is necessary to destroy close to 100% of CIN3 lesions.[6] While there is no consensus in the literature about the optimal thermoablation temperature and application time, Prendiville *et al*. compared the depth of tissue damage produced by the Liger thermocoagulator applied for 20, 30, or 45 seconds at 90 ºC, 100 ºC, and 120 ºC on a tissue model.[30] They found that a depth of more than 5 mm was achieved for all application durations at both 100 ºC and 120 ºC, supporting the choice of 100 ºC for 20 seconds setting.[30]

This setting has been used for treatment of precancerous lesions in many studies including a recent study in Brazil among women with biopsy-proven CIN2/3, in which 85% (17/20) of those with CIN2 and 84% (27/32) with CIN3 had no evidence of disease at 12-month follow-up.[17] Studies on thermocoagulation so far confirm patient tolerability with no local anesthesia or analgesics, similar to cryotherapy.[6,13,17,18,31]

Once treatment is complete, for sterilization, the manufacturer recommends one of two methods. The detachable probe can be rinsed with mild detergent and water, and then soaked for 20-60 minutes with ~ 2.5% glutaraldehyde solution (Cydex) or 0.5% Chlorine solution.[28] Alternatively, the probe can be decontaminated with alcohol and re-heated to 100 ºC for sterilization before reuse, as viral proteins are denatured at temperatures above 60 ºC.[15,17,28]

5.6 Post-treatment Pain Assessment

Pain will be assessed using a visual analog scale (VAS) immediately following treatment.

5.7 4-6 Week Follow-up

5.7.1 Adverse Events Evaluation

Adverse events will be evaluated at 4-6 weeks following treatment with a follow-up phone call or in-person visit (based on patient preference, distance from the clinic, and symptom severity) at which time a woman's subjective assessment of symptoms and duration will be obtained and recorded in a study questionnaire. Adverse events will be graded using the Division of AIDS Table for Grading Severity of female genital symptoms in which Grade 0 is normal, 1 is mild, 2 is moderate and 3 is severe symptoms. Women who elect a phone-call evaluation and report grade 2 or 3 symptoms will be asked to present for an in-person evaluation. Transport reimbursement will be provided for all study visits.

5.7.2 Provider Acceptibility Evaluation

At 4-6 week follow up, providers will be surveyed using a Provider Acceptability survey, modified from the System Usability Scale to evaluate provider acceptability and satisfaction with the use of thermal coagulation for treatment of precancerous lesions.[32]

5.8 12 Month Follow-up Exam

At approximately 12-months after treatment, all participants treated at baseline will undergo repeat colposcopy, biopsy for those with CIN2/3 at baseline or those with suspicious lesions on colposcopy, as well as provider collected HPV-collection for persistence. Twenty-five percent of women with normal colposcopy will have a random biopsy at 6 or 12-O'Clock for ascertainment and avoidance of verification bias.

5.9 Medical Record Data Collection

Individual participant data, including demographic and clinical information, will be collected from paper and electronic medical record at FACES and recorded into study-specific data collection forms. Participants will be enrolled in FACES for HIV-care and have regular laboratory monitoring of CD4+ counts and viral loads.

Predictor demographic variables will include participant age, gravidity, parity, history of cervical cancer screening, marital status, and the number of current and previous sexual partners. Clinical variables include current WHO status, CD4+ count levels, previous sexually transmitted infections, contraceptive use, and ongoing use of antiretroviral therapy.

6 Data Quality and Management

6.1 Staff Training

Study exams will be carried out by clinical officers and nurses who have undergone training in HPV testing, speculum exam, VIA, specimen collection, colposcopy, and biopsy. The training will be based on the International Agency for Research on Cancer (IARC), Kenya Ministry of Health (MOH) and WHO curricula and will contain didactic lectures, discussions, review of cervical photographs, and hands-on experience. [33,8,34,35]

Several providers at FACES have already undergone training for cervical cancer screening and treatment based on cryotherapy and thermocoagulation. Additional, specific training and demonstration regarding the use of the Liger thermocoagulator will be performed by the Principal Investigator, a U.S trained Gynecologist, using instructional material, including demonstration videos, from the manufacturer. All providers will be observed performing several treatment cases to ensure competency. All study staff will undergo training in Good Clinical Practices, informed consent, participant confidentiality, and study-specific procedures.

After satisfactory completion of training, including an examination and proctored procedures, staff will receive certification. Periodic training and assessment sessions will be done throughout the study. Lab technicians will be oriented in the proper handling, storage, and transport of laboratory specimens.

6.2 Secure Data Storage and Study Files

The study will be conducted within existing clinic settings at the FACES clinics in Nyanza Province. Participant data will be collected from the participant's electronic and paper records into study-specific forms. Study-specific forms will be stored in locked file cabinets within the clinic. Data from study-specific forms will be entered into a web-based, secure data storage

platform (ODK or RedCap), with labeling by unique study ID only. A file correlating study ID and medical file number will be kept in a separate password-protected excel computer file and accessible only to the core research team. Additionally, all study computers are password protected and kept in locked offices within the clinics.

The PI is responsible for ensuring the accurate capture of study data. The information collected on study-specific forms shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant. All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

7 Statistical Analysis Plans

Statistical analysis for all study objectives will be carried out using STATA and SPSS software.

7.1 Primary Objective

To evaluate the efficacy of thermal coagulation for the treatment of HIV-positive, HPV-positive women by assessing rates of HPV persistence and CIN2/3 at 12 months after treatment

Four hundred HIV-positive women with positive HPV testing will undergo colposcopy-directed biopsy for disease ascertainment prior to same-day treatment with thermal coagulation. At 12-months after treatment, all participants will undergo repeat HPV testing for persistence, and those who are HPV-positive will undergo repeat colposcopy, and biopsy as indicated for abnormal results, or random biopsy for 25% of those with normal colposcopy. We will define cure as a normal biopsy result or normal colposcopy among those who do not receive a biopsy.

Statistical Analysis: We will report the proportion of women with no evidence of cervical dysplasia at 12-months (primary outcome) follow-up, including 95% confidence intervals. We will extrapolate the rate of disease among those with normal colposcopy based on the rate of disease among the 25% in this group who will receive biopsy, and this will be incorporated in calculating persistence. We will perform a logistic regression to examine predictors of treatment success, using clinical and demographic variables as predictor variables. We will also report the rate of persistence of HPV at follow-up and compare with rates reported in the literature in this same population. We will compare efficacy rates for clearance of CIN2/3 to historical results following cryotherapy treatment in similar settings. A one-sample exact test will be used to compare the obtained efficacy proportion to that of historical controls.

We will leverage the robust infrastructure of the FACES in which patients are seen every one-to three months, and there is an established patient tracing system (including home visits) to reduce loss-to-follow-up. With a loss-to-follow-up rate of 10%, we will still be powered to answer this objective. Prior studies at this clinic have been able to achieve > 90% follow-up rate.[36] While limited by the lack of randomization to cryotherapy versus thermocoagulation, this study will provide pilot results that may enable a future randomized study evaluation of these two treatment methods.

7.2 Secondary Objectives

To evaluate the safety of thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya.

Statistical Analysis: We will calculate the average pain score immediately after treatment, as reported using the visual analog scale with confidence intervals. We will determine the proportion of women who experience grade 2 and 3 AEs, and severe adverse events (SAEs) during follow-up and calculate confidence intervals. Rates of AEs and SAEs will be compared to published rates for cryotherapy amongst this population (2.1% with mild pain or cramping, 1.6% with malodorous excessive vaginal discharge, 0.7% with mild bleeding or spotting, and no severe adverse events).[12] We will use one sample proportion test to compare proportions.

To evaluate patient satisfaction with thermal coagulation for the treatment of abnormal cervical lesions within a screen-and-treat program among HIV-positive women in Western Kenya.

Statistical Analysis: We will evaluate patient satisfaction with thermocoagulation by determining the proportion of participants answering yes to satisfaction questions at the 4-6 week follow-up.

7.3 Exploratory Objective

To evaluate provider acceptability of thermal coagulation for the treatment of precancerous lesions within a screen-and-treat program in Western Kenya.

Statistical Analysis: Healthcare providers offering thermocoagulation for treatment of precancerous lesions will be surveyed to evaluate provider acceptability and satisfaction with this treatment method using a modified System Usability Scale. The System Usability Scale is a widely used measure of product usability, using a Likert scale, rated from 1-5 in order of agreement with statements related to usability, acceptability, and satisfaction.[32] A one-way frequency table will be used to describe and summarize responses to questions on acceptability and satisfaction based on a Likert scale. Higher ratings will signify higher acceptability and satisfaction. Descriptive statements of challenges associated with this treatment method or safety concerns will also be elicited and reported in summary form.

8 Study Management

8.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol-related procedures are performed on any participants.

The Principal Investigator must comply with GCP/ICH guidelines and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

8.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

We will ensure that all procedures conform to US, Kenyan and international ethical standards regarding research involving human subjects.

8.3 Informed Consent

To participate in any study activities, women must be willing and able to participate, be able to sign or mark a consent form, and speak one of the languages into which the consent form and data collection instruments have been translated, including English, D'Luo, and Kiswahili. All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

8.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

8.5 Oversight and Monitoring Plan

Oversight of the trial is provided by the Principal Investigator (PI), Dr. Chemtai Mungo and principal co-investigators Dr. Jackton Omoto and Cirilus Ogollah.

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) will be responsible for monitoring data quality and patient safety for this study.

8.5.1 Data and Safety Monitoring Plan and Procedures

As this trial is categorized as low-risk based on the study design, per the risk-based algorithm in the DSMC, twenty percent of all enrolled subjects and all regulatory documents will be audited remotely once per year as per the HDFCCC National Cancer Institute (NCI)-approved Data and Safety Monitoring Plan (DSMP). The subject data will be remotely audited by the HDFCCC DSMC via the use of a HIPAA compliant system and will be source document verified with the data entered in Red Cap and OnCore.

The Principal Investigator, Dr. Chemtai Mungo will assure that informed consent will be obtained before performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data will be accessible at all times for the Principal Investigator and co-investigators to review. The Principal Investigator and co-investigators will review study conduct - accrual, dropouts, and protocol deviations - on a weekly basis. The Principal Investigator and co-investigators will review AEs individually and in aggregate on a weekly basis. The Principal and Investigator and co-investigators will review serious adverse events (SAEs), in real-time. The Principal Investigator will ensure all protocol deviations, adverse events (AEs), and SAEs are reported to the DSMC and IRB according to the applicable regulatory requirements. Investigators will conduct a continuous review of data and patient safety at the monthly Gynecologic Oncology Site Committee meetings

8.5.2 Adverse Event Monitoring

All clinically significant AEs and all SAEs, whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of an investigational product or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All AEs will be reported according to the Maseno University Ethics Review Committee (MUERC) and UCSF IRB Committee in accordance with AE reporting guidelines.

Adverse events are graded according to the **Common Terminology Criteria for Adverse Events (CTCAE)** as developed and revised by the **Common Therapy Evaluation Program (CTEP)** of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational device or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational device(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational device(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational device(s) or study procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational device(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational device(s) or study procedure.

All clinically significant adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings.

8.5.2.1 Serious Adverse Event Reporting

- An adverse event is defined as a serious adverse event (SAE) according to the following criteria:
- Death.

- Life-threatening (i.e., results in immediate risk of death).
- Requires inpatient hospitalization
- Permanent or significant disability/incapacity.
- An event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six (6) weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last study intervention and is determined to be possibly, probably, or definitely related either to the investigational agent or any research related procedure, the Principal Investigator or his/her designee must notify the DSMC Chair or Vice-Chair within 1 business day. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

8.5.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days.

8.5.4 Management of Risks to Subjects

Expected AEs

Expected AEs associated with the Thermocoagulation include:

- Mild discomfort associated with biopsy collection and treatment
- Mild vaginal discharge for a few days to weeks following treatment

AE Management

- Concerning symptoms will be evaluated in person by a trained clinician, and treatment offered where appropriate
- AEs will be evaluated for whether or not they are attributable to the treatment and reported as such
- All AEs will be followed to conclusion

8.5.5 Interim Data Analysis for Safety and Acceptability

For the safety and acceptability objective, we will perform an interim analysis after enrolling 1/3 of the expected number of women planned (n=133).

We will evaluate the proportion of grade 3 or higher adverse events associated with Thermocoagulation (as graded by the Scale above) with 95% Confidence Intervals. We will compare this proportion of grade 3 or above adverse events to the published literature on cryotherapy in similar settings. The results of the interim analysis will be submitted to the HDFCCC DSMC for review at the next scheduled DSMC meeting.

8.6 Record Keeping and Record Retention

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each participant enrolled in the study. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process. The quality assurance process used by the study team must be reviewed and approved by the HDFCCC DSMC.

Confidentiality throughout the trial is maintained by ensuring all study staff have undergone training in Good Clinical Practices, informed consent, participant confidentiality, and study-specific procedures. Study-specific forms will be stored in locked file cabinets within the clinic. Data from study-specific forms will be entered into a web-based, secure data storage platform (ODK or RedCap), with labeling by unique study ID only. A file correlating study ID and medical file number will be kept in a separate password-protected excel computer file and accessible only to the core research team.

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8.7 Duration of the Study/Project

	March 2019	April-June 2019	Jul-Sep 2019	Oct-Dec 2019	Jan-March 2020	April-June 2020	Jul-Sep 2020	Oct-Dec 2020
Hire and train project coordinator	X							
Develop SOPs, Study Manual, Database	X	X						
Train clinic and lab staff in protocols	X	X						
Participant Enrollment and Specimen Collection		X	X	X	X	X		
Specimen Processing and Evaluation			X	X	X	X		
12-month follow-up study visits						X	X	
Analyze data					X	X	X	
Present data at regional, national, or international meetings							X	X
Write and submit manuscript							X	X

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