A stigma responsive service delivery model for HPV-based screening among women living with HIV

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Purpose of the Study

The overall goal of the study is to develop and evaluate the effectiveness of a multi-level stigma responsive service delivery model for HPV-based cervical cancer screening.

Aim 1: Work with key stakeholders to develop Elimisha HPV, a multi-level stigma-responsive cervical cancer prevention service delivery model.

Aim 2: Compare cervical cancer prevention outcomes and retention in HIV care in facilities offering Elimisha HPV to facilities providing standard of care HPV-based screening.

Aim 3: Identify individual and facility factors that moderate the effects of Elimisha HPV on cervical cancer prevention and HIV care outcomes.

Background & Significance

HIV and cervical cancer are intersecting public health threats for women in Kenya, where cervical cancer is the most common cancer among women, and reproductive-aged women are five times more likely than other groups to be newly infected with HIV. Women living with HIV (WLWH) are at increased risk for HPV and cervical cancer, with 29% of new cervical cancer cases in Kenya occurring among WLWH. HIV care programs represent high impact settings to target cervical cancer prevention services that can leverage existing infrastructure. Despite increasing calls for integrated services, availability and uptake remain low. In a recent study in western Kenya, only 11% of women enrolled in HIV care reported undergoing cervical cancer screening, suggesting a need to improve implementation and uptake of services.

Molecular testing for HPV is rapidly becoming a more widely available and recommended cervical cancer prevention strategy. As lower cost HPV testing is becoming more widely available in low- and middle-income countries (LMICs), it has been integrated into national and international guidelines for cervical cancer prevention. HPV tests provide a straightforward, actionable result and are more effective at identifying women at high risk for developing cervical pre-cancer and cancer than pelvic exam-based alternatives. Importantly, HPV-based screening can be offered via self-collection, increasing acceptability for women, reducing the staff and space needs, and allowing novel service delivery models. Our team led a five-year cluster-randomized trial of implementation strategies for HPV-self testing, which showed that it was highly acceptable to women living in this region and could be effectively offered by community health volunteers (CHVs). As a result, self-collection for HPV testing has become a standard of care across health facilities in our research site.

HPV and cervical cancer, like HIV, are stigmatized conditions, which influences health care engagement. Stigma and discrimination have been shown to decrease participation in the health care system across multiple disease states. Stigma negatively impacts HIV testing, health care utilization, treatment adherence and overall wellbeing of HIV-positive individuals. Focus group discussions with men and women in Kenya found that cervical cancer is stigmatized because of its anatomic location, its

connection to HPV, and its association with HIV/AIDS. Qualitative studies in South Africa, India and Kenya have shown that cervical cancer stigma was related to the disease's perceived association with promiscuity as well as "marking" from vaginal bleeding and discharge,6 and that providers and women often associated cervical cancer screening with sexually transmitted diseases because of the pelvic exam.36,37 Multiple studies have shown that HPV carries a unique stigma as a sexually transmitted infection, which has negatively impacted cervical cancer prevention strategies, including screening and vaccination.38–41 Our team found that women who did not follow-up after a positive HPV test reported fear of disclosure and shame around their diagnosis.42 Since these factors are known to impact engagement with cervical cancer prevention activities, interventions that comprehensively address the stigmas associated with HPV and cervical cancer are needed to increase screening uptake and maximize the potential benefits of offering screening via self-collection.

WLWH may experience HPV and cervical cancer stigma differently, impacting uptake of health behaviors. Individuals experiencing two stigmatized conditions or states will have different experiences with the conditions than people who have a single condition. The term "intersectional" has been used to describe the combined effects of multiple stigmas, which may impact healthcare access and outcomes. Although the literature around manifestations of intersectional stigma is nascent, some postulate that they are dependent upon the characteristics of the diseases themselves, such that blame for a disease may be potentiated if it is obtained through socially undesirable behavior (e.g., a sexually transmitted infection). Further, research suggests that individuals who report stigma related to one condition may have an increased sensitivity to stigmatizing experiences more broadly, making them more vulnerable to stigma from a second condition. Conversely, people with a stigmatizing condition who report low levels of stigma may be more resilient when faced with a second stigmatizing condition. Most of the research into intersectional stigma explores the experience of people living with HIV; however there has been very little research into intersectionality across HIV, HPV and cervical cancer and how it may impact engagement with prevention activities.

To understand stigma related to HPV, cervical cancer, and HIV, and their intersectional relationship, our team has developed and is finalizing the validation of a measurement tool in western Kenya. A number of instruments have been developed and validated to measure HIV-related stigma at the individual, provider and community levels. However, these instruments do not capture the unique stigmas faced in high HIV prevalence areas or by WLWH related to HPV and cervical cancer. Out team undertook qualitative work to develop a framework for this intersectional stigma that informed an item pool to measure the magnitude and impact of the individual and intersecting stigmas on HIV and cervical cancer prevention behaviors (R21TW011061). The proposed study will leverage this previous work in by using the critical contextual psychometric information collected to inform the development and evaluation of the stigma-responsive service delivery model.

Stigma reduction interventions have had a positive effect on both HIV stigma and health outcomes, mainly through increased engagement in care and quality of life. It is paramount that interventions are designed by and for the populations they would affect. Some interventions developed for high-resource settings have not been as successful in LMICs.60,61 There are contextual factors in Kenya that influence stigma and cervical cancer screening, such as lack of knowledge and fear of disclosure of an HPV result to a partner, which may require specialized and culturally-tailored stigma reduction interventions.

Larger social-contextual factors such as poverty, low literacy, lack of treatment availability and cultural and gender norms may also impact the feasibility and acceptability of these interventions. Interventions to address stigma in LMICs have sought to impact drivers of stigma, including peer navigators and video-assisted counseling, and interventions to mitigate harmful effects of stigma, including case management and psychosocial support through support groups64 or family therapy. Interventions that work at multiple levels are more successful than those that target only one aspect of stigma or one population. Recognition of the global disparity in cervical cancer outcomes, especially among WLWH, has led to a drive for low-cost and effective screening and treatment strategies that are feasible and sustainable in LMICs. While the technology and infrastructure to provide these strategies is essential to addressing the gaps in cervical cancer control, interventions must be delivered in a way that is patient-centered and reflective of health beliefs and social influences, including stigma. We propose to address these needs with Elimisha HPV, a multi-level, stigma- responsive service delivery model for cervical cancer prevention for high HIV prevalence settings.

Design & Procedures

This study will be conducted at twelve government-supported outpatient facilities/selected community units offering HIV care and HPV-based cervical cancer screening in Kisumu County in western Kenya, an area with a high HIV prevalence and low coverage of cervical cancer screening services. For Aim 2, the twelve facilities will be randomized to usual care (control) or to receive Elimisha HPV (intervention).

To accomplish the goal of the study, our team will complete study activities described below by study aims.

Aim 1: Collect and incorporate key stakeholder feedback to finalize the components of Elimisha HPV and develop implementation strategies to address potential barriers to introduction.

Primary Outcomes for Aim 1 will be a finalized model for Elimisha HPV, with:
Clearly defined components and the necessary accompanying tools (video, fliers, brochures, etc.)
Training materials
Data collection forms
Evaluation strategy
We will also define strategies to identify, recruit, and train peer navigators who will deliver health messaging in a way that minimizes stigma (based on qualitative data).

Study activities for Aim 1

Phase 1 – Formative research
We will engage key stakeholders through in-depth-interviews (IDIs) and focus group discussions (FGDs) to evaluate the acceptability and perceived effectiveness of the stigma-responsive service delivery model, identifying facets that may need to be adapted and potential barriers to implementation.

We will recruit key stakeholders from our network of partnerships in the region, and augment our potential participant pool with snowball sampling. We anticipate approximately:
25 IDIs with facility managers and clinicians, and members of the County Health Management Team, including the reproductive health coordinator and county health director, and Focus group discussions (FGD) with Community Health Volunteers (CHVs), peer navigators and women living with HIV (WLWH), separately, for a total of three FGD each consisting of approximately ten participants. We may conduct more FGDs with smaller numbers of participants depending on language and convenient location for participants.

Semi-structured IDI and FGD guides will be tailored to each group and focus on their role in cervical cancer screening and HIV care. Questions will explore experiences with cervical cancer and HPV-based screening, stigmatizing attitudes, internalized stigma, and anticipated stigma. We will then present the findings from prior work and solicit feedback on the educational intervention and all components of the delivery model, including organizational readiness and any anticipated implementation challenges. For WLWH, we will also explore decision-making around screening for cervical cancer, experiences at diagnosis and treatment, experiences with the healthcare system, and experiences in the workplace and broader community.

We anticipate that clinicians and facility managers will prefer English for the interviews, however for CHVs, peer navigators and WLWH, FGD guides will be also translated into the local language, Kiswahili or Luo. FGDs will be offered in participant's language choice. We may need to split groups off into multiple FGDs as necessary to accommodate language preferences.

IDIs and FGDs will be audio-recorded, transcribed, and then translated into English as necessary.

Phase 2 – Finalizing intervention (tool development)
In addition to data collection in Aim 1, we will also develop and refine our intervention to be implemented and evaluated in Aim 2. We will use data collected through the IDIs and FGDs to develop:
Educational scripts for CHVs
Adapt the video developed in the pilot.
Visual aids for both CHVs and peer navigators
Graphics and culturally tailored brochures
Standardized scripts and training for CHVs in patient-centered care, stigma responsive delivery and privacy
Strategy and training for a network of peer-navigator
Description of Intervention

Elimisha HPV is a multi-level stigma-responsive cervical cancer prevention service delivery model that incorporates stigma-responsive education, peer navigation and a patient-centered delivery strategy, addressing drivers while mitigating harms from stigma.

The following is further detail on each component described above.

Educational Materials

To increase understanding of HPV-based screening and personal risk perception, and decrease fears of the screening procedure, we have developed and are piloting the following stigma-responsive educational materials.

A brief video portraying a woman overcoming her hesitancy and fears to undergo HPV-based screening. This five-minute video shows an interaction between a woman and a health care provider who briefly describes the screening procedure and addresses her concerns. She is then shown post-treatment describing her experience to a friend and encouraging her to get screened. Based on videos that have been shown to reduce HIV-related stigma in similar settings, we will show this video on tablets to women after they receive basic information on screening.

Brochures to portray the screening process. We found that women wanted to individually review the details of screening with more culturally appropriate images. We have created a culturally tailored step-by-step instruction guide for screening that will be distributed individually to all women when they are receiving the educational messaging.

Communication Norms

We will refine the educational content and develop simplified scripts for CHVs, remove stigmatizing language and focus on positive motivators for screening.

We will review the entire curriculum, scripts, and video to focus on the benefits of screening, emphasize the social support and the positive outcome of cervical cancer prevention. Messaging focused on HPV as a sexually transmitted disease leads to marking and association with negative attributes such as promiscuity and uncleanliness, which are drivers of stigma, reduce risk perception, and increase hesitancy to screen. Shame and embarrassment from an HPV infection may lead to avoidance of follow-up. As the only method of preventing HPV is childhood vaccination, these messages do not lead to actionable outcomes, and are therefore of limited value in settings where HPV- and cervical cancer are stigmatized. Messaging that addresses gender norms and associates screening with self-efficacy and empowerment facilitates screening.

Streamlined education scripts for CHVs and clinical staff that minimize stigmatizing aspects of HPV and focus on actionable outcomes of screening. These scripts will be loaded onto mSaada, the cell-phone-based app for HPV-testing, accompanied by an extensive “frequently asked questions” searchable feature that we developed for a prior study, providing additional support for CHVs and facility staff to avoid inadvertently spreading misinformation or stigmatizing messaging.

Workforce Optimization

We will implement two components to address stigma facilitators arising from provider-related factors: Peer navigator support for women who delayed screening or treatment. We will develop a network of women who have successfully completed the screening and treatment cascade to provide psycho-social

and logistical support to women who have declined screening or who have tested positive for HPV, but not followed up for treatment. We will also engage peer navigators in health facilities on treatment days, to support women with questions or concerns around treatment.

Additional training for CHVs in patient-centered care and establishment of accountability systems for lapses in privacy, feelings of CHV disrespect or distrust. We will adapt a participatory curriculum that was used to train CHVs in HIV care, and is now available online. We will adopt the training sessions focused on increasing CHV self-efficacy, helping patients manage stigma and disclosure, assisting patients in coping with the impact an HIV (or HPV) diagnosis, and increasing the core competencies of communication, interpersonal relationship building, advocacy and professional conduct. Training will take approximately two full days. In Aim 1, we will work with key stakeholders to develop a monitoring and evaluation strategy for the professionalism goals that arise from this training.

Aim 2: Compare cervical cancer prevention outcomes and retention in HIV care in facilities offering Elimisha HPV compared to facilities providing standard of care outreach, education, and screening strategies.

* All materials used for the intervention such as the videos, scripts, consent forms, etc. will be submitted to the IRB for review prior to use in Aim 2.

Outcomes for Aim 2:

To determine the impact of this intervention on cervical cancer screening uptake and treatment, we will carry out a 6-12-month c-RCT in government-supported health facilities/selected community units and compare the following metrics between the intervention and control arms:

Activity 1: Health Facility Identification

In partnership with the County Health Management Team, the study team identified twelve level 2, 3 or 4 health facilities in Kisumu County as potential study sites.

All facilities provide HIV-care along with general outpatient care, management of childhood and adult illnesses, family planning, antenatal care, maternal child health, and cervical cancer screening. There are approximately 45 government-supported level 3 or 4 facilities in Kisumu County, with the majority sharing similar population characteristics (rural and peri-urban, within 1 hour from Kisumu City by public transportation).

We will exclude level 5 and 6 health facilities (county and referral hospitals) because their size, limited number, central location, and availability of specialty services.

Randomization: The 12 study facilities will be randomized to either control or intervention arms. One community unit from within each facility will be included in the study. We will employ a restricted randomization (stratification or covariate-constrained) to achieve baseline comparability of study arms in terms of age distribution, (Rural/Urban) and availability of treatment. We anticipate the

socioeconomic status and HIV prevalence rates will be relatively consistent across the health facilities. We will use a Stata package created by our team to implement the chosen strategy.

The unit of randomization is the facility as the intervention (video, CHV training and peer support) is offered at the facility/community unit level. We have worked with the MoH to identify similar facilities across the region, hoping to minimize differences that may bias the result. We will collect quantitative and observational data to document any differences that result, as we understand that process may be imperfect.

Activity 2: Study Assignment Preparation

After randomization of facilities, we will work with facilities in the control and intervention arms to ensure standardized processes for study-related activities and implementation of Elimisha HPV.

Cervical Cancer Prevention Training:

In order to ensure standardized processes for the basic components of HPV-based screening, facility managers, providers and CHVs in all study facilities (intervention and control) will attend a half-day sensitization on cervical cancer and HPV-based screening (self-collection).
Following this, all CHVs in the study will undergo a half-day training to understand the cell-phone-based tracking system for HPV-testing and results notification (mSaada). Training in education and outreach strategies will take place after randomization.

Control Arm

CHVs in control arms will undergo training to understand and deliver standard health messaging around HPV-based screening and treatment with thermocoagulation, counseling about self-collection and counseling about results and follow-up with women.
Control facilities will be equipped with the outreach and educational materials that have been used in HPV-based screening in Kisumu previously.
Intervention Arm

Community Health volunteers (CHVs)

CHVs in the intervention facilities will undergo training to understand stigma, including HIV-related stigma and intersectional stigma. As part of their training, they will complete the validated stigma measurement instrument and work with trained stigma experts to understand how their scores may impact the way they offer services.

Training will also include patient-centered care, with a focus on communication and ensuring privacy.

Following this, they will be trained on the study protocol, to use the educational materials, including the scripts, brochures, and videos.

At the end of the training, CHVs will complete a test of understanding of both basic HPV screening and the study protocol to demonstrate their comprehension of the study.

CHVs in both control and intervention facilities will complete a pre- and post-training survey to assess to assess attitudes and knowledge regarding HPV testing and treatment, results counseling, and communication (respect, confidentiality). They will also complete this survey approximately 6-9 months from start of participation.

Peer navigators

Peer navigators will be identified, recruited, and trained using the training materials and curriculum developed in Aim 1, with a similar focus on counseling and motivational interviewing techniques. As part of their training, they will complete the validated stigma measurement instrument and work with trained stigma experts to understand how their scores may impact the way they offer services.

Activity 3: Screening to Treatment Cascade

We anticipate approaching/registering approximately 12,000 women for HPV screening during routine Community Health Volunteer (CHV) household visits in selected Community Units (CU) in Kisumu County (100 per CHV; 10 CHVs per community unit selected; 12 facilities). Some women may come to the facility solely to undergo HPV screening, having heard about it from outreach campaigns or others in the community. These women include WLWH, who would benefit from cervical cancer screening (aged 30-65 years overall, 25-65 for WLWH; intact uterus and cervix).

The screening to treatment cascade includes HPV-based cervical cancer screening of women, receipt of results and treatment for women who screen positive for HPV16/18.
Data for women who screen for HPV will be collected via clinical records and the mSaada mobile App. Prior to CHVs entering data into mSaada App used for clinical purposes (App tracking HPV screening to treatment cascade of steps), women will provide a brief verbal consent. We will access de- identified data from the MOH for secondary analysis.

Description of mSaada App

The mSaada app is designed for use by CHVs and other MOH staff on cell phones or tablets. CHVs will access the mSaada App on smartphones that have already been provided to the CHVs by the county MOH through Living Goods. These phones currently are used to access eCHIS, the county electronic health record. mSaada App will be installed on their phones.

The mSaada App facilitates HPV sample and case management. All data is stored on an encrypted server. mSaada has the capability to send automatic text messages which may be used to provide results for women who opt in. Women who undergo screening may opt for any type of results notification. The available options for results notification include a home visit, phone call or text message. In prior work, we have found that leaving results with the woman's health facility led to low numbers of women

returning for results, so we are not offering that option. For women who do not have phones, or do not wish to have their results transmitted by phone, they can opt for a home visit.

We have worked with the County Health Management Team in designing the current and prior studies, and have decided that women should not be excluded from the study or discouraged from HPV screening if they do not have their own phones. This aligns with the current cervical cancer screening register (MOH 412) which allows for an alternate proxy phone number. Women may opt for a home visit, regardless of whether they have a phone or not. Women without access to phones can choose a home visit or, if they feel they have access to a phone through someone whom they trust with their health information, can choose for a phone call or text message.

Control and intervention facilities – standard of care strategies under Kenya medical guidelines
Standard strategy for HPV-based cervical cancer screening:
CHVs in the control and intervention arms will offer HPV-testing via self-collection to all eligible women in their catchment population using a standard of care model. CHVs will offer HPV self-collection at a home-visit. If a client does not feel comfortable with self-collection, the CHV can offer to assist with self-collection or can suggest that the client go to a facility to have a health care provider do a clinician-collected screening.
CHVs will lead conduct outreach and education activities, individual and/or group counseling about HPV-testing, instructions about self-collection, and processing of the specimens using the Ampfire System with reflex testing for HPV16/18.
Within two weeks, laboratory results will be available for health facilities. CHVs or other facility staff may record results in the facility register and notify women via text, phone call or home visit.

Standard strategy for treatment for women who test positive on HPV-based test:
Women who test positive for HPV16/18 will be referred to a facility for visual inspection with acetic acid, followed by treatment with thermocoagulation or cryotherapy as indicated, the current standard of care.
Women with lesions not amenable to treatment with thermocoagulation may undergo loop electrosurgical excision procedure (LEEP) at the same visit or be referred for further evaluation.
Women with lesions suspicious for cancer will undergo biopsy and have follow-up with the gynecologist at the district hospital for treatment planning.
Women who are delayed in seeking follow-up (greater than three months since notification of diagnosis) will receive additional text message reminders and home visits, per protocol.
For women with a positive HPV test, pre-cancer treatment is provided by providers in MOH facilities. When MOH provider finds lesions suspicious of cancer, they provide the woman with linkages to higher facility where further management can be done.

The study will cover the cost of a biopsy and pathology reading for women with lesions suspicious of cancer.

Standard processes for HPV-based cervical cancer screening program in Kisumu, Kenya

For cervical cancer screening standard of care, MoH-supported facilities are increasingly transitioning from cervical cancer screening with Visual Inspection with Acetic Acid (VIA) to HPV-based screening, and Kisumu East facilities have had high-risk HPV screening available using the AmpfireTM testing system (Atila Biosystems, Menlo Park) since October 2021.

We have defined four core service-delivery delivery strategies that are necessary for the sustainability of HPV- based screening in a resource-constrained setting such as Kenya. These are all components that we have evaluated and found to be feasible and acceptable strategies to offer the WHO-recommended strategy adopted by the Kenya MoH within the infrastructure capacity of government-supported outpatient facilities.

These core elements of HPV-based screening in Kisumu will be available in all study facilities.

EDUCATION: CHV-led outreach, education, and service delivery. CHV-led services are a core part of Kenya's community-plan, and have been effectively deployed to offer education and screening with HPV self- collected specimens. Elimisha HPV will provide CHVs additional support to address identified gaps through the components described below.

HPV testing via self-collection. Self-collected HPV testing has similar sensitivity and specificity as clinician- collected HPV testing, is preferable to women and addressed many logistical and cultural barriers to pelvic exams. We have found it to be highly feasible and acceptable among women in western Kenya.

Text-messages with testing results and health messaging options for women. Text messages were found to be acceptable, providing privacy and the ability to review message content. The Duke team developed and tested the mSaada platform for patient tracking, CHV counseling support and text messaging in this setting. Basic mSaada components have been picked up by the Kisumu County Health Management team to provide the basic infrastructure support for CHV-led HPV testing.

Treatment with thermocoagulation offered within HIV care facilities, per WHO and Kenya guidelines.

Intervention facilities/selected community units

Elimisha HPV: a multi-level stigma-responsive delivery model for HPV-based cervical cancer screening (intervention):
Health facilities/selected community units in the intervention arm will offer HPV-testing using the Elimisha HPV model.
During regular visits to households in the community, CHVs who have been trained in patient-centered care will:
Introduce the option of HPV self-collection. At this time, CHVs will counsel women on the importance of treatment, and that CHVs may carry out home visits or phone calls to help the woman navigate the follow-up process.
Provide individual or group education (if more than one eligible women is in the household) using standardized scripts.

Show a brief educational video to the client, if appropriate.
Share educational materials to address women's questions.
Provide instructions with graphics that describe the self- sampling procedure.

Peer navigators

One of the Elimisha HPV stigma reduction strategies includes the linking of a peer navigator with a woman who has declined screening or has delayed seeking follow-up care. At the time of initial screening, the CHV will ask the woman if she agrees to have a peer navigator reach out to her in the event that she declines screening or delays seeking follow-up care. The CHV will document the woman's response in the mSaada app, whether she agrees or not.

In summary for women who provide verbal assent to peer navigation,
A peer navigator will be linked with a woman who decline screening, and will reach out within the following week.
A peer navigator will reach out to women who are delayed in seeking follow-up care to offer to discuss their own experience with screening and treatment, and answer any questions about treatment process.

Laboratory processing time and notification of results will be the same as in control facilities.

Activity 4: Follow-up administration of stigma measurement tool

In the pilot and validation of the stigma scales, we found that the range of stigma scores (0-3, with three representing higher levels of stigma) was impacted by education and preferred language. We are carrying out this study to determine the impact of the intervention on stigma scores, which will be reflected in the difference between the control and intervention arms (an outcome measure).

Control and Intervention Facilities

We will ask CHVs and peer navigators participating in the study to complete the stigma scale (validated instrument to measure HPV, HIV, and cervical cancer-related stigma) prior to their training (mentioned in activity 2) and the end of their aim 2 participation.

In months 6-12 of the c-RCT, the study team will recruit women who were registered by CHVs in mSaada as eligible for cervical cancer screening to complete a survey that includes the stigma scale and feedback on CHV household visits.

Per facility/selected community unit, we will randomly select 67 women (around 804 women in total) to complete the survey (either at the facility or in the community for the convenience of the participant).
Women will be considered eligible for the survey if they were registered by a CHV in mSaada.
Instruments have been translated and the stigma scale is validated into Luo and will be self-administered or administered orally with computer-assisted answer entry to ensure confidentiality.
The survey will take about 30-60 minutes to complete.

We will review information from the health records that the CHV recorded including whether the CHV offered to show a video about HPV; HPV test results; and information on any follow-up appointments related to the HPV screening.

Aim 3: Employ a convergent mixed methods design to identify and contextualize the ways in which individual and facility characteristics moderate the effects of Elimisha HPV on cervical cancer prevention and HIV care outcomes

Primary Outcomes for Aim 3

Understand the factors that are related to the success of the delivery model, so programs will have more information to contextualize the strategy to their resources and population. This will be the first time the validated stigma measurement tool for HPV, HIV and cervical cancer stigma is used to evaluate an intervention, providing a key metric in understanding mechanisms of the intervention's effect. Factors at the patient, community health volunteer and peer navigator level; factors at the health facility level; and factors at the County Health Management Team level.

Study activities for Aim 3:

Qualitative Data Collection
We will explore the patient, provider, and facility experience with Elimisha HPV through IDIs with key stakeholders in both arms.

Enroll 20-24 women and 7-10 CHVs and peer navigators, with the option to recruit more if new themes are emerging in the IDIs. Interview guides will probe understanding of health messaging, emotional response to the various educational tools, and perceived impact of the intervention on screening and follow-up decision-making, including any unintended negative experiences in either the control or intervention arms.

Interview 10-12 facility supervisors and MoH clinical personnel to explore facility-level barriers and facilitators to HPV-based screening and other components of Elimisha HPV. Topics to be explored with facility supervisors will include ways in which the service delivery model impacted cervical cancer screening acceptability and accessibility, potential positive and negative impacts on workflow and staffing models and ideas to improve the model for maximum scalability, sustainability, and effectiveness.

In addition, we will solicit feedback from key stakeholders in the County Health Management Team for brief semi-structured interviews.

Interviews will be conducted by experienced qualitative interviewers in the language of preference for the participant, and audio recorded onto an MP3 file. These files will first be transcribed directly in the language of the interview and then will be translated into English.

Our planned qualitative and quantitative activities in Aim 3 may elucidate the contribution of experienced stigma or discrimination at the community level as well as the moderating effect of stigma on our primary outcomes.

Selection of Subjects

Aim 1 Participants

Key stakeholders (Aims 1)
Key stakeholders in decisions about, implementation of and service delivery for cervical cancer and HIV care programs.

We will enroll approximately 25 stakeholders.

Inclusion criteria:
Age 18 or older
Must be one of the following:
Facility manager, clinician (nurses, medical officers, and clinical officers) providing HIV and reproductive health care services to women in government-supported facilities in Kisumu County
Community Health Volunteer (CHV)
HIV-peer navigator or a woman attending these facilities, including a woman living with HIV (WLWH) and/or woman who has completed HPV testing and treatment of the cervix.
Agree to be audio recorded
Exclusion criteria:
Does not understand the study purpose and details
Is not willing to sign an informed consent
Aim 2 Participants

Women located in catchment areas of each community unit (Aim 2)
CHVs will register at the facility level/selected community unit and collect data for approximately 6,000 screened for HPV. As data from women's screening will be utilized for this analysis, women screened for HPV will provide brief verbal consent documented in mSaada App used to track clinical information related to HPV screening.

Women eligible for cervical cancer screening per the Kenya Ministry of Health guidelines include:
Women living with HIV (WLWH) will be between the age of 25 and 65
All other women will be between the age of 30 and 65
All women should have an intact uterus and cervix
HPV testing (self-collected and provider-assisted) and follow-up care post-testing is offered through the County Health Management Team under the Kenya guidelines. Since screening and treatment are clinical activities and not research activities, women will not sign an informed consent for HPV screening or treatment.

Women registered within the 12 community units participating in the study (Aim 2)
For Aim 2, activity 4, we will enroll approximately 804 randomly selected women, (67 per community unit in each of 12 facilities).

Inclusion criteria:
A Community Health Volunteer (CHV) has registered the woman in the mSaada App (electronic HPV-based cervical cancer screening tracking tool) during the study period
Is eligible for cervical cancer screening per the Kenya Ministry of Health guidelines include:
Women living with HIV (WLWH) will be between the age of 25 and 65
All other women will be between the age of 30 and 65
All women should have an intact uterus and cervix

Exclusion criteria:
Does not understand the study purpose and details
Is not willing to provide informed consent

CHVs working through government-supported health facilities (Aim 2)

We have worked in partnership with the Ministry of Health to determine the implementation strategy, which will utilize the community unit. Each community unit is structured to have about 10 CHVs, each of whom serve about 100 households.] We will select one community unit (CU) from each facility then invite all CHVs assigned to that CU to participate in the study. We expect to enroll approximately 120-150 CHVs. This will ensure that CHVs are evenly spread across the facilities and are covering roughly the same number of household/eligible women. We feel this model in which we work with the community unit in partnership with the ministry is more likely to represent sustainability.

We will work with CHV supervisors to approach CHVs for study participation and possible enrollment into the study for training and participation in the stigma-responsive service delivery model. Since study outcomes may appear to reflect CHV job performance, we will explain this as part of the informed consent and emphasize the voluntary nature of participation in the study. For both optimization of study activities and to avoid any coercion, CHVs will be able to decline participation without impact on their position in the facility.

Inclusion criteria:
Age 18 or older
Must be a Community Health Volunteer (CHV) at government-supported facilities in Kisumu County
Exclusion criteria:
Does not understand the study purpose and details
Is not willing to sign an informed consent

HIV-peer navigators (Aim 2)
Approximately 60 (10 per intervention health facility) HIV-peer navigator or a woman attending these facilities, including a woman living with HIV (WLWH).

Inclusion criteria:
Age 18 or older
Must have complete HPV screening and treatment in the past
Must be interested in getting trained as a peer navigator
Exclusion criteria:
Does not understand the study purpose and details
Is not willing to sign an informed consent

Aim 3 Participants
Participants will be purposively recruited from each study arm to achieve a sample with heterogeneous demographic and clinical characteristics (e.g., age, HIV and HPV status).

Women attending government-supported health facilities (Aim 3)
We will enroll approximately 24 women with the option to recruit more if new themes are emerging in the IDIs.

Inclusion criteria:
Will have completed an HPV screening test at one of the intervention or control facilities
Agree to be audio recorded

Exclusion criteria:
Does not understand the study purpose and details
Is not willing to provide informed consent
Community Health Volunteers (CHVs) and Peer Navigators (Aims 3)
We will enroll approximately 10 CHVs and peer navigators with the option to recruit more if new themes are emerging in the IDIs.

Inclusion criteria:
Participated as a CHV or peer navigator at one of the facilities participating in the study
Agree to be audio recorded

Exclusion criteria:
Does not understand the study purpose and details
Is not willing to sign an informed consent
Facility managers (Aim 3)
We will enroll approximately 12 facility managers.

Inclusion criteria:
Age 18 or older
A manager at one of the facilities participating in the study
Agree to be audio recorded

Exclusion criteria:
Does not understand the study purpose and details

Is not willing to sign an informed consent

Risk/Benefit Assessment

Risks:
There are two potential risks of the study: loss of confidentiality, discomfort with questions.

Loss of confidentiality
There is always risk associated with loss of confidentiality for participants in a study. However, this risk of loss of confidentiality will be minimized through rigorous training of study personnel, use of study identifiers to make data de-identified unless linked to personal identifiers, restricting access to identifiable data, and publishing only aggregate (not individual-level) statistical summaries that limit re-identification of participants.

Discomfort with questions
There is also the possibility that some questions might upset or create discomfort in participants if topics are considered sensitive. Women may be upset by questions about personal experiences with cervical cancer screening and stigma-related questions. Research staff will look for signs of discomfort and assure participants that they are not being judged, that answers will be kept confidential, and that they can refused to answer any question.

Benefits:
For women attending facilities there are no direct benefits for taking part in the study. However, women receiving the intervention may be more likely to complete HPV testing and follow-up with treatment if HPV +. WLWH may be more likely to attend follow-up HIV care and receive consistent refills of ART.

For stakeholders (clinicians, facility managers), there are no direct benefits for taking part in the study. However, they may feel a sense of satisfaction in helping inform a process that may improve future cancer screening and treatment programs, provide faster care to patients, improve patient follow-up care, and reduce deaths from this disease in the future.

There are no direct benefits for taking part in the study. However, CHVs and peer navigators participating in the intervention may increase their level of knowledge and skill regarding HPV screening and treatment as well as using stigma-responsive language.

Data Analysis & Statistical Considerations

Aim1
Data Analysis for Aim 1: Data collection, analysis and intervention development will happen iteratively, so that stakeholder interviews will be modified to build upon what has been learned. Dr. Huchko and the research team will conduct a Rapid Qualitative Analysis, first writing succinct summaries for each piece of data collected, outlining issues relevant to each domain of inquiry (e.g., testing experience,

prior screening, experience with other cancers or sexually transmitted infections), and identifying newly emerging research questions that might be explored in subsequent qualitative data collection (Aim 3). The team may use NVivo software to apply these themes to the textual data using thematic analysis. An analytic report will be written to triangulate data and summarize how the findings inform the overall structure of the service delivery model.

Aim 2

Sample Size and Power Calculations for Aim 2: The Aim 2 sample size for women who will complete the stigma survey will be determined by the population of registered women by each CHV in the 12 community units. We will seek to enroll a random sample of women within the community unit served by CHVs in both the control and intervention communities. We have chosen the community unit rather than the facility register as the source of data given the availability of digital mapping data for each community completed in Kisumu County in April 2023. We will divide the total number of women registered in each community unit eligible for screening by 67 and use that number to determine the rate at which women are approached. For example, if there are 3 community units, with a total of 250 age-eligible women, 250/67 is approximate every 4th woman. If a woman is not able to be reached or declines to participate in the survey, we will approach the next woman on the list.

For Aim 2a, we based our power estimates on the difference in HPV screening uptake rates between intervention and control arms, using data from our previous studies in this region to estimate screening uptake, intracluster correlation (ICC), and coefficient of variation of cluster sizes.120 In a cluster-RCT to evaluate HPV-based testing strategies, the population screening coverage in the control arm was 37% compared to 57% in the intervention arm.

For this study, we assume an average of 1,000 women of screening age registered per facility, with a coefficient of variation of catchment area sizes of 0.31 and an intracluster correlation estimation of 0.043 using the formula for binary outcomes.121 With six communities per arm, we would have 90% power to determine an intervention effect as small as 20%, assuming 5% type I error. This number of participants is feasible, given the population size and the numbers of women reached in our c- RCT in a neighboring county.

For Aim 2b, we based our power calculation on HPV prevalence and treatment uptake rates seen in our previous study. Assuming 23% HPV prevalence and 37%-57% screening rate, we will have between 85 and 131 women in each community eligible for treatment. Using the same parameters as above, we would have greater than 90% power to see a 21% difference in treatment rates between control and intervention arms, conservatively assuming a 40% treatment uptake in the control arm20 and the same ICC as above.

For Aim 2c, based on prior data20, we assume that 40% of the sample will be WLWH and that in control 65% of WLWH will attend follow-up care and receive consistent refills of ART. In this case, we have greater 90% power to detect a 18% difference in rates of follow-up between control and intervention arms.

For Aim 2d, we will compare the difference in stigma scores between subsets of women in the intervention and control arms. Using the stigma scale initially validated on our current study (R21 TW011061) we will estimate intersectional HIV-HPV-Cervical Cancer stigma scores and compare enrollment arms. Assuming an ICC of 0.01, a sample of 67 women per community (approximately 800 total) would provide 90% power at a two-tailed type I error rate of 5% to detect a 0.30 standardized mean change in stigma difference between intervention and control.119 Given the size of the communities and the ability to recruit women successfully for similar surveys in these settings in the past, we do not anticipate difficulty in obtaining this sample size.

Analysis Plan for Aim 2: The analyses will employ the intention-to-treat principle, wherein all outcomes are analyzed by assigned study arm, regardless of whether women in the intervention arm were exposed to all or part of Elimisha HPV or underwent screening or whether women in the control arm inadvertently was exposed to health messages from the intervention facilities.

In Aim 2a-2c outcomes are binary. Binomial regression modeling with log-link (or modified Poisson regression115 if binomial regression does not converge) will be used to regress individual-level outcomes on intervention arm in order to estimate the relative effect of the intervention on screening uptake and accessing treatment, which we will report as risk ratios. Clustering by facility will be accounted for using the generalized estimating equations (GEE) approach. To correctly estimate the standard error (SE) of the intervention effect, we will use the Fay-Graubard approach.116 Appropriate methods will be used to account for the restricted randomization approach used in the c-RCT design phase; for example, adjustment for stratification factors if stratification is used. Secondary analyses will adjust for individual-level covariates including age, parity, number of children at home, prior screening and education level. Because of baseline comprehensive record keeping in both arms, we expect that missing outcome data patterns will be comparable across study arms, i.e., that outcomes are “missing at random” conditional on treatment arm. Under this assumption, the GEE analyses will provide unbiased intervention effect estimates. Sensitivity analyses will be used to test these assumptions.118 Since the outcome in Aim 2c will only be aggregated at the cluster level, all individual-level covariates will be aggregated to the cluster level. Hence, the analysis will not need to be adjusted for clustering and simple log- binomial regression will be fit.

For Aim 2d, levels of stigma related to cervical cancer, HPV and HIV will be measured using the validated stigma scale from our prior study. Scores on each scale will be compared between a subset of women in control and intervention arms. Linear mixed effects modeling will be used and will include the following fixed effects: intervention-arm indicator, follow-up time point indicator, their interaction (to allow different intervention effects at each follow-up time point). Two random effects will be included to account for the clustered design and for repeated measures on each woman.

Aim3: Measurements and Analysis Plan

Quantitative Analysis Plan: Quantitative data for Aim 3 will come from the c-RCT. At baseline, we will collect data on both facility-level and individual-level characteristics thought to be associated with the Aim 2 outcomes, as well as potentially leading to differential treatment effects (Table 3). We will assess for effect modification by including each of these predictors separately in the GEE statistical models

described in Aim 2 as a main effect and interaction with intervention arm. We will use forest plots to visually display the intervention effects separately by each level of the effect modifier. These exploratory results will be used to tailor the intervention in the future, as well as providing evidence others can use to inform their HPV screening interventions.

Qualitative Data Analysis Plan for Aim 3:
Transcripts will be managed and analyzed using a Framework Approach to coding, in which key conceptual domains are derived from both the existing literature and the qualitative data gathered for the study. NVivo qualitative data analysis software will be used as a tool for coding and analysis. As a first step, the research team will develop a preliminary coding structure based on the literature and topics included in the interview guides, apply this coding to a sample of initial transcripts, and will then refine it with input from the investigative team.

In the next step, transcripts will be reviewed again, and a more detailed, second-level coding structure will be developed. A detailed analytical report will interpret key findings of the coding scheme, using direct quotations to illustrate themes and second-level codes. The study team will review the transcripts throughout the study and seek participation until we have reached saturation.

Quantitative and Qualitative Data Integration:
We will use the Pillar Integration Process to integrate quantitative and qualitative data in four sequential stages (listing, matching, checking, and pillar building) after it has been analyzed independently.124 We will first list raw quantitative and qualitative data (i.e., means, frequencies, selected quotes) as well as coded or grouped data (GEE model results and forest plots, themes, sub-themes,) in a joint display table. We will then horizontally match the quantitative data and qualitative data that reflect similar content, patterns or parallels, adding data and codes not previously listed, and further refining categories. We will then cross-check data in the columns of the joint display table for completeness and appropriate matching. Finally, in the pillar building stages, findings in the quantitative and qualitative columns will be compared to identify patterns, insights, and possible explanations to build inferences from the findings as a whole. Integrated themes based on these inferences will be documented and described.

Data & Safety Monitoring

Adverse Event Reporting. This clinical trial of an implementation strategy will not incur any F.D.A. defined adverse or serious adverse events. However, under oversight of the Duke and Kenya Medical Research Institute's ethical review boards, we will consider protocol violations and lapses in confidentiality as adverse events that would need to be reported within 10 days to the appropriate Institutional Review Board. The primary risk to participants in this study is loss of confidentiality. Field staff will be trained to complete descriptions of protocol violations or any unexpected adverse events that will then be sent electronically to both the U.S. Principal Investigator and the site Principal Investigator.