Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ ____12 July 2019_____

Glavdia Greatchens Delva Date

Grant proposal

Establishing a Cervical Cancer Prevention and Treatment Program for Human Immunodeficiency Virus (HIV)-positive adolescent girls and women receiving care at Hôpital Foyer Saint Camille, Haiti

By

Glavdia Greatchens Delva
MPH

The Rollins School of Public Health, Emory University
Executive MPH

Prevention Science Track

_____ [Chair's signature]
A.D. McNaghten, PhD
Committee Chair

_____ [Member's signature]
Taylor Gregory, MD
Thesis Field Advisor

Degree: Master of Science in Public Health

Department: Executive MPH

Committee Chair: A.D. McNaghten, PhD

Committee Members:

1. A.D. McNaghten, PhD, Committee Chair
2. Gregory Taylor, MD, Field Thesis Advisor

Grant proposal

Establishing a Cervical Cancer Prevention and Treatment Program for Human Immunodeficiency Virus (HIV)-positive adolescent girls and women receiving care at Hôpital Foyer Saint Camille, Haiti

By

Glavdia Greatchens Delva

Doctor in Medicine

Université Notre Dame d'Haiti (UNDH)
2000-2008

Thesis Committee Chair: A.D. McNaghten, PhD.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Executive MPH
2019

Abstract

Grant proposal

Establishing a Cervical Cancer Prevention and Treatment Program for Human Immunodeficiency Virus (HIV)-positive adolescent girls and women receiving care at Hôpital Foyer Saint Camille, Haiti

By

Glavdia Greatchens Delva

Cervical cancer is the fourth leading cause of cancer-related mortality in women worldwide, with more than 600,000 cervical cancer cases reported yearly, of which 90% occur in low and middle-income countries. In developed countries, 33% of females aged 9 to 26 years old received all recommended doses of human papillomavirus (HPV) vaccination, while only 2.7% females aged 9 to 26 years old completed the full HPV vaccine doses in low-and middle-income countries (LMICs). The scaling-up of HPV vaccination at a rate of 10% per year in low-middle-countries, would reach an estimated 163 million girls, and could avert 3.3 million cervical cancer cases, 2.4 million deaths, and 9.5 million disability-adjusted life years (DALYs) over their lifetimes. HPV vaccination coupled with at least three screening tests in their lifetimes reaching a 70% coverage, could reduce by 60% women lifetime risk of cervical cancer.

Haiti has the highest incidence of cervical cancer in the Western Hemisphere, with an annual aged-standardized incidence and mortality rate estimated at 87.3 and 48.1 per 100,000 women, respectively. An estimated 3.64 million Haitian women aged 15 years and older are at risk of developing cervical cancer each year. The prevalence of cervical cancer is even higher among women infected with the Human Immunodeficiency Virus (HIV) living in Haiti. HPV vaccines have not yet been integrated in the national vaccination program. Low government investment in healthcare, poor health infrastructure, lack of funding, and absence of nationally organized primary and secondary HPV prevention programs are the main barriers to address the high incidence of morbidity and mortality related to cervical cancer in the country.

This Grant Proposal is in response to a call for proposals for optimizing management of coinfections and comorbidities in people living with HIV in order to address the global burden of HPV-associated cancers in LMICs. This proposal will implement an integrative approach encompassing HPV vaccination for HIV-positive female adolescents aged 9 to 26 years old, and “See, Diagnose, and Treat”, point-of-care (POC) molecular testing methods for screening, and treatment of pre-cancerous and cancerous cervical lesions in HIV-positive females seeking care at the HIV primary care unit at Hôpital Foyer Saint Camille (HFSC), a health facility located in the northern area of Port-au-Prince in Haiti, and less than two miles from two major urban slums.

This proposal is a five-year project that will bring innovative approaches to address access barriers, support adoption of improved tools for preventing cervical cancer and managing the disease at the pre-cancer stage. The project will involve multistage implementation, starting by improving the infrastructure, building capacity and establishing a training program on primary and secondary cervical cancer prevention for healthcare providers, patients and the community. The implementation phase will focus on identifying HIV-positive women at risk of cervical cancer and providing them with early detection and treatment including clinical and laboratory diagnostic services. This Cervical Cancer Prevention and Treatment Program will contribute to reducing the morbidity and mortality due to cervical cancer for HIV-positive females seeking care at HFSC.

Grant proposal

Establishing a Cervical Cancer Prevention and Treatment Program for Human Immunodeficiency Virus (HIV)-positive adolescent girls and women receiving care at Hôpital Foyer Saint Camille, Haiti

By

Glavdia Greatchens Delva

Doctor in Medicine

Université Notre Dame d'Haiti (UNDH)
2000-2008

Thesis Committee Chair: A.D. McNaghten, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
In partial fulfillment of the requirements for the degree of
Master of Public Health
in Executive MPH
2019

Table of Contents

Chapter I: Introduction

Introduction and Rationale

Global burden of cervical cancer

Cervical cancer, one of the most preventable cancers, is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality in women worldwide, with more than 600,000 cervical cancer cases reported yearly, of which 90% occur in low and middle-income countries (Torre et al., 2017). Despite many efforts to implement cervical cancer screening and human papillomavirus (HPV) vaccination, more than 250,000 women still die from cervical cancer each year worldwide, which represents one death every two minutes, making this disease one of the greatest threats to women in modern history (World Health Organization, 2018).

In order to curtail the incidence and prevalence of cervical cancer, many developed countries have adopted the World Health Organization (WHO) guidelines for cervical cancer prevention by implementing strategies like primary prevention in the form of HPV vaccination targeting females aged 9 to 26 years old, and secondary prevention consisting of routine screening and treatment of precancerous lesions leading to cervical cancer. According to the Centers for Disease Control and Prevention (CDC), in 2017, 49% of adolescents aged 13 to 17 years old in the United States received the full coverage for HPV vaccination, and 66% of them received the first dose (Centers for Disease Control and Prevention, 2019; Walker et al., 2018). Globally, 118 million females aged 9 to 26 years old have been targeted to receive full coverage of HPV, representing the 70% coverage recommended to alleviate the global burden of cervical cancer. While 33% of adolescents

aged 9 to 26 years old received all recommended doses of HPV vaccination in developed countries, only 2.7% females aged 9 to 26 years old completed the full HPV vaccine doses in low-and middle-income countries (LMICs), where the global burden of cervical cancer resides (Campos, Sharma, et al., 2017).

Problem Statement

Women infected with the Human Immunodeficiency Virus (HIV) living in Haiti are at great risk of cervical cancer because of the lack of effective strategies for the prevention of HPV infection, and detection and treatment of pre-cancerous cervical lesions. The incidence of precancerous and cancerous cervical lesions is four to five times higher in HIV-positive females due to the persistence of HPV infection, leading to cervical lesions and later cervical cancer in the absence of treatment (Ghebre et al., 2017).

In Haiti, HIV-positive women are at higher risk of HPV infection due to their immune-compromised status and they are 2 to 12 times more likely to develop cervical precancerous lesions that lead to cervical cancer than HIV-negative women (Chirenje, 2005). Although access to antiretroviral therapy has improved the life expectancy of adolescents and women living with HIV, cervical cancer remains the greatest risk-related morbidity and mortality for Haitian women because of the following barriers:

1. There is no National Strategic plan and interventions for cervical cancer prevention and treatment are limited to a handful of health facilities.
2. There has been no HPV vaccination campaign specifically targeting adolescents and women living with the Human Immunodeficiency Virus (HIV) in Haiti.

3. The lack of health infrastructure, human, and financial resources impairs the implementation of integrated programs to link HIV and cervical cancer prevention and treatment in primary care services (Mapanga et al., 2018).

There is a need to integrate HPV vaccination and cervical cancer screening programs into already existing HIV services for prevention, early detection and treatment of cervical cancer in HIV-positive females in Haiti.

Purpose Statement

The purpose of this grant is to bring innovative approaches to integrate HIV care services with cervical cancer primary and secondary prevention, implementing HPV vaccination, a "See, Diagnose, and Treat" approach, point-of-care (POC) molecular testing for screening, and treatment of cervical lesions in HIV-positive females seeking care at the HIV primary care unit at Hôpital Foyer Saint Camille (HFSC). The HPV vaccination program will target HIV-positive females aged 9 to 26 years old. In addition, sexually active HIV-positive females aged 18 years and older will be screened for cervical cancer and, if applicable, benefit from the "See, Diagnose, and Treat" approach and point-of-care (POC) HPV molecular testing.

This innovative approach will:

1. Address access barriers to Cervical Cancer Prevention and Treatment for HIV-positive females in low-resource settings.
2. Support the adoption of improved tools for preventing cervical cancer and managing the disease at the pre-cancer stage.

3. Reduce morbidity and mortality due to cervical cancer for HIV-positive females seeking care at Hôpital Foyer Saint Camille (HFSC).

Research Questions

In addition to addressing the affordability and accessibility barriers for Cervical Cancer Prevention and Treatment for HIV-positive females seeking care at Hôpital Foyer Saint Camille, this project will seek to examine the following research questions:

1. What is the cost-benefit of implementing cervical cancer services for HIV-positive females?
2. What is the effectiveness of the current HPV vaccines in HIV-positive females aged 9 to 26 years in Haiti?

Significance Statement

This Cervical Cancer Prevention and Treatment Program will contribute to reducing the morbidity and mortality due to cervical cancer for HIV-positive females seeking care at HFSC. After five years of implementation, this project will achieve full coverage of cervical cancer prevention, screening, and treatment services for HIV-positive females receiving care at Hôpital Foyer Saint Camille. The ultimate aims of this project are to decrease mortality and morbidity related to cervical cancer in this population, improve the quality of life of HIV-positive females, and overcome the economic burden to access cervical cancer prevention, care and treatment for the most vulnerable populations.

This project will be an opportunity to report complete and accurate cervical cancer and HPV vaccination surveillance data to the National Cancer Registry. The impacts and health

outcomes from this project will catalyze more investments to extend the Cervical Cancer Prevention and Treatment Program to include HIV-negative adolescents and women.

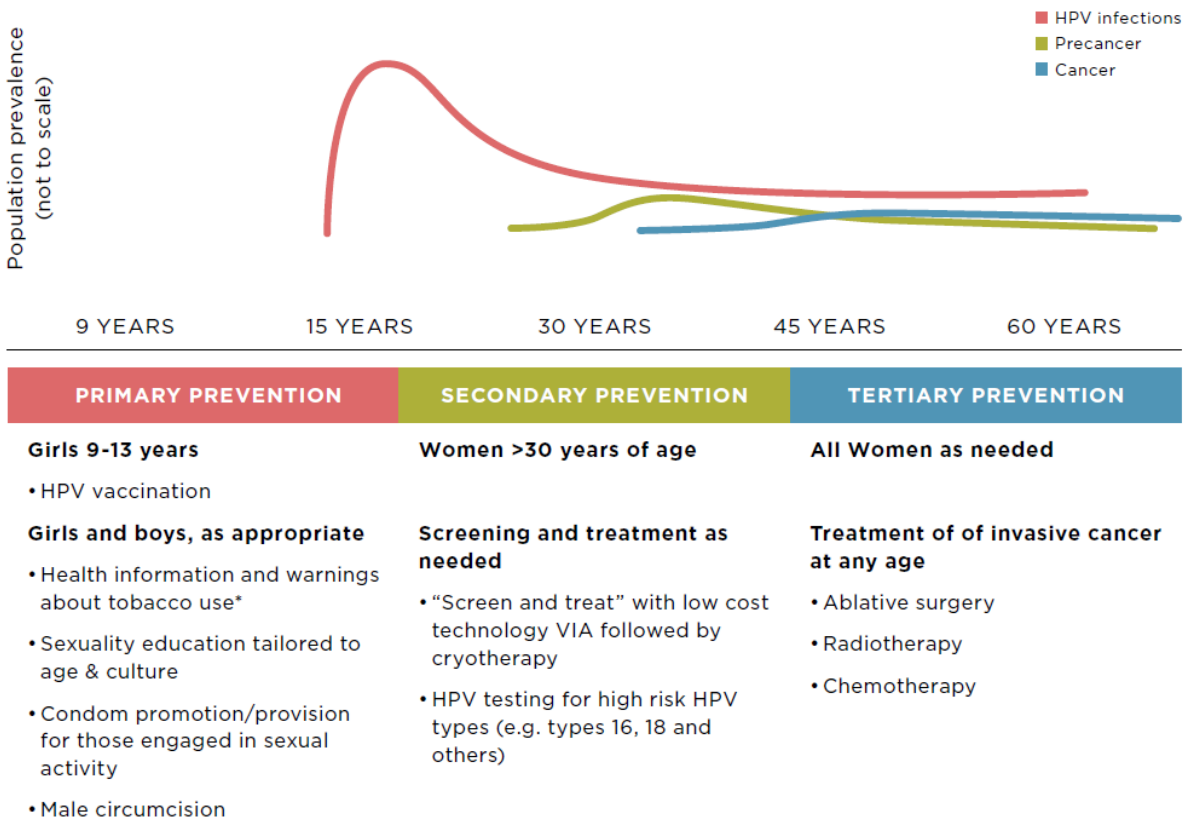
Public health framework for intervention

The WHO proposed an effective public health framework that comprises multiple effective interventions to prevent, detect, and treat cervical cancer across the life course, including vaccines for preadolescent and adolescent girls to prevent most HPV infections and methods to screen women for precancerous lesions, which can be treated effectively in the clinic to prevent the progression to invasive cancer (Figure 1).

WHO's comprehensive approach to cervical cancer prevention and control includes:

1. Introduction and scaling-up of HPV vaccination
2. Introduction and expanding coverage of screening and treatment of precancerous lesions
3. Prompt management of invasive cancers
4. Access to palliative care and monitoring using a standard set of indicators and tools to eliminate cervical cancer.

Figure 1. A comprehensive strategy for eliminating cervical cancer as a public health problem



Source: (World Health Organization, 2016)

Definition of terms

Catchment area: The geographic area from which a facility's clients are drawn.

Cervical cancer prevention and treatment program: A cervical cancer prevention and treatment program comprises an organized set of activities aimed at preventing and reducing morbidity and mortality from cervical cancer. The program provides a plan of action with details on what work is to be done, by whom and when, as well as information about what means or resources will be used to implement the program. The achievement of the program is assessed periodically using a set of measureable indicators. A

comprehensive program includes the principal evidence-based interventions needed to reduce the high and unequal burden imposed on women and health systems in less developed countries by cervical cancer.

Colposcopy: The examination of the cervix, vagina and vulva with an instrument that provides strong light and magnifies a field, allowing specific patterns in the epithelial (surface) layer and surrounding blood vessels to be examined.

Cost-effectiveness analysis: Describes an activity or procedure that produces an adequate beneficial effect on a disease or condition in relation to its cost (in money, equipment, or time).

Coverage: The proportion of all targeted persons who attend a given service in a specified time.

Cryotherapy: By applying a highly cooled metal disc (cryoprobe) to the cervix and freezing the abnormal areas (along with normal areas) covered by it, cryotherapy eliminates precancerous areas on the cervix by freezing (i.e., it is an ablative method).

Endocervical curettage (ECC): Some surface cells are gently scraped from the endocervical canal with a special thin instrument or spatula; this is a simple procedure that takes just a few minutes.

Epidemiology: Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems.

Evaluation: The systematic and objective assessment of the relevance, adequacy, progress, efficiency, effectiveness and impact of a course of action, in relation to objectives and taking into account the resources and facilities that have been deployed.

Financial costs: Actual monetary flows of the buyer, such as the Ministry of Health. Does not include the value of resources already paid for such as personnel time and donated goods.

Guideline: A recommended, standardized plan that provides direction to operationalize policy or strategy.

Human papillomavirus (HPV): Human papillomavirus (HPV) is the most common sexually-transmitted infection (STI). Cervical cancer is caused by high-risk types of HPV; the two high-risk HPV types that most commonly cause cervical cancer are types 16 and 18, which together are responsible for approximately 70% of cervical cancer cases in all countries worldwide.

HPV Test: DNA or serology test to determine active HPV infection.

Indicator: A variable that measures one aspect of a program that is directly linked to the program objectives; markers that help measure change by showing progress toward objectives.

Infrastructure: The items required to support provision of quality services in the designated cervical cancer screening and treatment services at the facility (e.g., handwashing area, washroom, physical layout of the facility, examination room, and communication equipment).

Investment costs: Initial expenditures used in preparation for an intervention. These include implementation costs plus purchase of capital goods, such as cryotherapy and LEEP machines and transport purchases.

Loop Electrosurgical Excision Procedure (LEEP): The removal of abnormal areas from the cervix and the entire transformation zone, using a loop made of thin wire powered by an electrosurgical unit; the loop tool cuts and coagulates at the same time; this is followed by use of a ball electrode to complete the coagulation.

Monitoring: The continuous oversight of an activity to assist in its supervision and to see that it proceeds according to plan; it involves the specification of methods to measure activity, use of resources, and response to services against agreed criteria.

Pap smear: Papanicolaou test, carried out to evaluate the presence of abnormal cervical cells.

Pathology: The study of disease and its effect on body tissue.

Post-treatment follow-up screening: A visit which uses a screening test to determine the success of a previous treatment for precancerous lesions.

Precancerous lesion: Non-invasive lesion with a predictable likelihood of becoming malignant.

Primary prevention of cervical cancer: Actions to avoid exposure to the principal causes of a disease; in the case of cervical cancer, prevention of HPV infection.

Rescreening: A screening visit attended by a woman after a previous negative result on a screening test. This visit is part of routine preventive care and should be conducted within the recommended interval for screening.

Screening: A public health intervention provided to an asymptomatic target population; it is not undertaken to diagnose a disease, but to identify individuals with increased probability of having either the disease itself or a precursor of the disease.

Secondary prevention of cervical cancer: A level of preventive medicine that focuses on early diagnosis, use of referral services, and rapid initiation of treatment to stop the progress of disease processes or of a disability.

Service utilization: The key indicator benchmarks that the facility is tracking (e.g., the number of monthly screenings and treatment rate of precancerous lesions identified).

Target population: A group of people identified as intended clients for a particular health-care service; in this case, the population of women targeted for the cervical cancer prevention and treatment programs.

Treatment of invasive cervical cancer: Includes chemotherapy, radiation, and radical hysterectomy.

Treatment of precancerous lesions: Includes cryotherapy, LEEP, conization, and in some situations, simple hysterectomy.

VIA: Visual inspection of the cervix with the application of 3–5% acetic acid.

Chapter II: Review of the literature

Introduction

Women infected with HIV have a higher prevalence of infection with human papillomavirus (HPV) and are likely to develop persistent infection with multiple HPV types, resulting in higher incidence and prevalence of cervical intraepithelial neoplasia (CIN) lesions and a more likely rapid progression to invasive cervical cancer (Chirenje, 2005). The incidence of precancerous and cancerous cervical lesions is four to five times higher in HIV-infected females due to the persistence of HPV infection, leading to cervical lesions and later cervical cancer in the absence of treatment (Ghebre et al., 2017).

Body of Review of the literature

A thorough review of the literature is indispensable to addressing the affordability and barriers for HPV prevention in HIV-positive females aged 9 to 26 years old and cervical cancer screening and treatment in women seeking care at Hôpital Foyer Saint Camille. This literature review will also be led by the research questions which examine the cost-benefit of implementing cervical cancer services for HIV-positive females at HFSC and the effectiveness of the current HPV vaccines on HIV-positive females aged 9 to 26 years in Haiti.

The WHO guidelines for Screen-and-Treat for cervical cancer prevention recommend providing cervical cancer screening following the diagnosis of HIV in sexually active adolescents aged 9 to 26 years old and women (World Health Organization, 2013). During the World Health Assembly in May 2018, the WHO Director General, Dr. Tedros Adhanom Ghebreyesus, made a call to action for the elimination of cervical cancer globally

by 2069 (World Health Organization, 2018). This call requires countries to adopt specific strategies to scale up HPV vaccines and cervical cancer screening in low-resource settings. In order to implement the WHO guidelines, LMICs have to overcome many barriers, such as insufficient government financial investment in health systems, poor public health system infrastructure, difficulty procuring HPV vaccines and screening supplies, and weak commodity and procurement systems. In line with the WHO calls for accelerating cervical cancer services in LMICs, GAVI, the Vaccine Alliance, an international public-private partnership for equal access to vaccines, has created opportunities for low-resource countries to access HPV vaccines at $4.50 per dose. As of July 2019, through this initiative, six LMICs have introduced the HPV vaccines in their national vaccine programs.

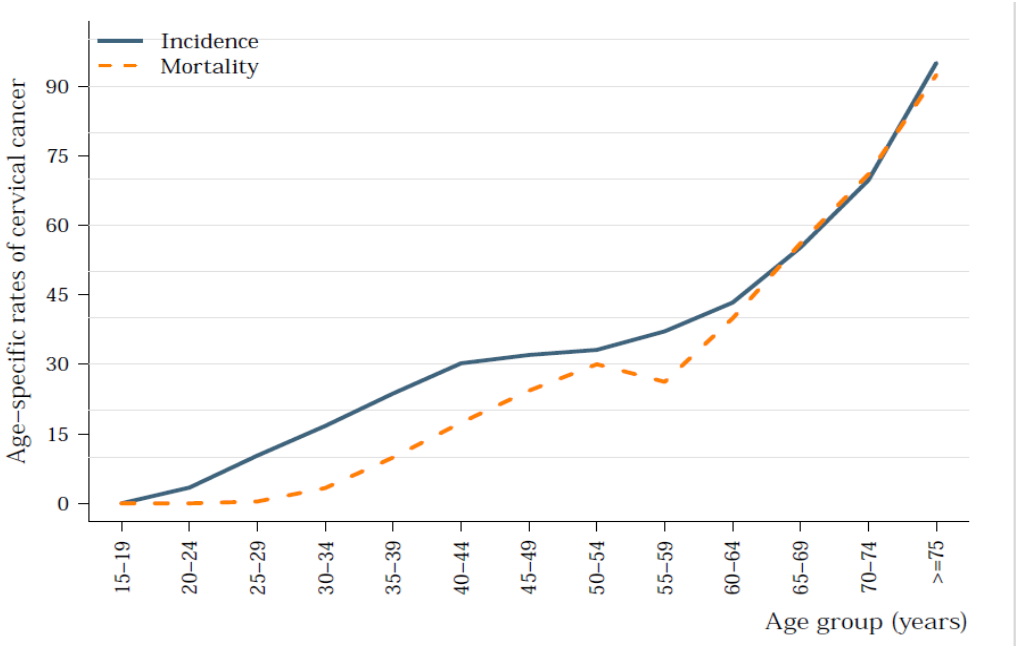
Despite those initiatives, millions of women living in LMICs do not have access to cervical cancer prevention and treatment programs including vaccination, screening, diagnosis and treatment, particularly HIV-positive women living in LMICs who are most at risk of developing cervical cancer.

Cervical Cancer in Haiti

According to the Pan American Health Organization, Haiti had the highest incidence of cervical cancer in the Western Hemisphere, with an annual aged-standardized incidence and mortality rates estimated at 87.3 and 48.1 per 100,000 women, respectively (Luciani et al., 2008). Since then, the morbidity and mortality related to cervical cancer have not been improved. The latest International Agency for Research on Cancer (IARC) report indicates that cervical cancer is the second most frequent cancer among women in Haiti and the first most frequent cause of cancer among women between 15 and 44 years of age;

annual aged-standardized incidence and mortality rates are estimated at 17.1 and 12.5 per 100,000 women respectively (IARC, 2019).

Figure 2: Comparison of age-specific cervical cancer incidence and mortality rates in Haiti (estimates for 2018)



Data source: Haiti: Human Papillomavirus and Related Cancers, Fact Sheet 2018 (IARC, 2019). Data accessed on 09 July 2019

In Haiti, 3.64 million women aged 15 years and older are at risk of developing cervical cancer, and every year, 835 Haitian women are diagnosed with cervical cancer and 563 die from the disease (IARC, 2019).

Human papillomavirus (HPV) vaccination

In developed countries, 33% of females aged 9 to 26 years old received all recommended doses of human papillomavirus (HPV) vaccination, while only 2.7% females aged 9 to 26 years old completed the full HPV vaccine doses in LMICs. The scaling-up of HPV vaccination at a rate of 10% per year in low-middle-countries, would reach an estimated 163 million girls, and could avert 3.3 million cervical cancer cases, 2.4 million deaths, and 9.5 million disability-adjusted life years (DALYs) over their lifetimes (Campos, Sharma, et al., 2017). HPV vaccination coupled with at least three screening tests in their lifetimes reaching a 70% coverage, could reduce women's lifetime risk of cervical cancer by 60% (Goldie et al., 2008).

Although the Haitian Ministry of Health and Population (MSPP) has declared cervical cancer prevention a priority since 2012, few initiatives for primary and secondary prevention services have been carried out. The first HPV vaccination campaign was launched in Haiti in 2009 and 2010, at the initiative of Partners in Health/Zanmi Lasante, a non-profit organization providing health services in the Central Plateau region of Haiti. During this campaign, 27,000 girls aged 10 to 12 years old were vaccinated for HPV and 80% of them completed all three doses (Mandigo et al., 2015). The second HPV vaccination campaign in 2018 resulted in the vaccination of 2,500 girls in Southern Haiti. There has been no HPV vaccination campaign specifically targeting HIV-positive adolescents and women in Haiti.

Cervical Cancer Screening and Treatment Program

Cytology has been long recommended as the front-line test for HPV screening in women. Although cytology-based screening has proven effective in decreasing cervical cancer

incidence rates in many countries (Gradissimo et al., 2017), the implementation of Pap smear-based screening services can be challenging in low-resource healthcare facilities. The scarcity of pathologists capable of performing the Pap-smear cytology leads to long delays in the return of results. For these reasons, the WHO guidelines recommend a screen-and-treat approach using visual inspection with acetic acid for countries that do not have cervical cancer screening programs in place or where resources for Papanicolaou (Pap) or human papillomavirus testing are limited. Some low-income countries have significantly reduced their incidence of cervical cancer through the introduction of low-cost cervical cancer screening and treatment methods. In India, for instance, visual inspection with acetic acid (VIA) screening programs have been proven to effectively reduce cervical cancer mortality by approximately 30% (Van Dyne et al., 2019). VIA is attractive because of its feasibility in low resources settings and its capacity to yield an immediate on-site result so that screening and treatment can occur at a single visit. The sensitivity of VIA for detection of precancerous and cancerous lesions is in range of 56% to 96% with an average of 77% and specificity ranges from 74 to 94% with an average of 86%. Unfortunately, this screening test has a high sensitivity and can lead to overtreatment (Kuhn et al., 2017). Incorporating HPV testing in VIA screening can lead to substantial improvements in specificity while maintaining adequate sensitivity, which can reduce overtreatment. This improvement in specificity will be beneficial for HIV-positive women – a population known to have very high prevalence of HPV infection (Kuhn & Denny, 2017).

Access to antiretroviral therapy has improved the life expectancy of adolescents and women living with HIV. However, women living with HIV in Haiti continue to face high mortality due to cervical cancer because there is no national cervical cancer prevention and

treatment program. A non-profit organization providing screen-and-treat cervical cancer services in Haiti found a prevalence of HIV of 15.4% among women treated for cancerous cervical lesions (DeGennaro et al., 2019).

New Point-of-Care (POC) technologies for HPV DNA testing

Since 2010, the WHO has encouraged the introduction of primary HPV serologic and DNA testing for the monitoring of HPV vaccine impact, and monitoring of changes in the prevalence of HPV types (World Health Organization, 2010). A European randomized clinical trial found that HPV testing as a primary screening tool will provide an additional 60–70% protection against invasive cervical cancer compared to cytology-based screening programs (Ronco et al., 2014). New Point-of-Care (POC) technologies developed for HPV DNA testing have been proven to be highly sensitive to detect precancerous and cancerous lesions. In resource-limited clinical settings, the use of POC diagnostic platforms for HPV testing have the potential for enhancing the scaling-up of a cervical cancer program, by reducing lab processing time to approximately 1 hour per sample and running in a non-batch mode, which may facilitate a same-day see-and-treat approach (Einstein et al., 2014). Moreover, the POC HPV DNA technologies are less costly than traditional molecular platforms, they do not required highly skilled laboratory technologists and advanced laboratory settings. The HPV detection and typing results can be available for clinical decisions in a timely fashion. Their practicability make them easy to implement in any remote laboratory. For the above-mentioned reasons, the utilization of molecular POC technologies have become the alternative for early and rapid disease diagnosis, including

cancer screening and infectious disease detection. A modeling analysis of the cost-effectiveness of HPV testing suggested that the initial cost of a POC HPV test and supporting infrastructure in LMICs could be high but can still provide good value for public health dollars in the long term (Campos, Tsu, et al., 2017). Henceforth, many low-income countries are implementing molecular assays for the detection of high-risk HPV as part of the implementation of "See-and-treat" programs because of practicability and short turn-around-time for diagnosis of cervical cancer for clinical decisions.

There is a need for baseline epidemiologic monitoring of HPV-associated cancers in HIV-positive females in Haiti in order to evaluate 1) the effectiveness of the current HPV vaccines on HIV-positive females in Haiti, 2) the most appropriate HPV vaccines for this population, and 3) to measure the impact of HPV vaccines on cervical cancer in the future.

HPV and Cervical Cancer

It is estimated that approximately 35 types of HPV can infect the human genital tract. Of these, 13 types are designated as high risk because of their association with cervical cancer (Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). HPV16 and HPV18 are associated with approximately 70% of low- and high-grade cervical intraepithelial lesions (HSIL) leading to invasive cancer. Also, some HPV types are more common in women of African descent such as 35, 39, 56, 58, and 68 that are not covered by the current vaccines. HPV16, for instance, is less prevalent in African American compared with Caucasian women with HIV and cervical precancerous lesions independent of immune status (Keller et al., 2018). A meta-analysis of high-risk HPV-type distribution in 19,883 HIV-positive women found that HPV 16/18, but also HPV 45 and HPV 33 tend to be more prevalent in

women infected with HIV (Clifford et al., 2017). In Haiti, the epidemiology of circulating HPV types has not yet been established in order to decide the most appropriate HPV vaccines for the population.

Cost-benefit

A systematic review of cost-effectiveness of cervical cancer screening methods in LMICs found that once in a lifetime cervical cancer screening using the HPV testing strategy to be the most effective. An one-visit VIA screening followed by immediate results and treatment if positive is a more cost-effective screening strategy than cytology in LMICs. Bruni et al. argued that "VIA screening strategy alone or combined with HPV testing can reduce cervical cancer incidence at a cost per life saved below the studied country's GDP per capita, which demonstrates the economic feasibility of saving tens of thousands of lives per year" (Bruni et al., 2016).

A study comparing the costs and cost-effectiveness of conventional cytology (Pap), visual inspection with acetic acid (VIA) and HPV DNA testing for detecting cases of CIN2+ among HIV-infected women currently taking antiretroviral treatment at a public HIV clinic in Johannesburg, South Africa found that the average cost per procedure was US $3.67 for VIA, and that VIA was least sensitive but most cost-effective at US $17.05 per true CIN2+ case detected (Lince-Deroche et al., 2015).

Summary of Current Problem and Study Relevance

The literature review reveals that comprehensive cervical cancer prevention, screening and treatment programs in low-income countries are scarce, which results in higher mortality

related to cervical cancer among women, particularly among HIV-infected women. In Haiti, as for many low-income countries, poor government investment in healthcare contributes to poor health infrastructure, lack of funding, and absence of nationally organized primary and secondary HPV prevention programs to address the high incidence of morbidity and mortality of cervical cancer (Zahedi et al., 2014). The lack of infrastructure, human and financial resources impairs the implementation of integrated programs to link HIV and cervical cancer primary care in the management of HIV-infected women living in developing countries (Sankaranarayanan et al., 2013).

A study using a model-based approach to synthesize population, demographic, and epidemiological data from 50 LMICs, predicts that more than 44 million women living in LMICs would be diagnosed with cervical cancer and half of them would die without strategic interventions to avert the morbidity and mortality related to cervical cancer (Campos, Sharma, et al., 2017). The same study analyzed the health and economic impact of scaling-up the coverage of HPV vaccination and cervical cancer screening in LMICs. The study found that in low-income and lower-middle-income tier 1 countries, a ten-year comprehensive HPV vaccination and screening program, with a scaling up at a rate of 10% per year, would reach an estimated 163 million girls, and could avert 3.3 million cervical cancer cases, 2.4 million deaths, and 9.5 million disability-adjusted life years (DALYs) over their lifetimes. Globally, the same program would prevent 5.2 million cervical cancer cases, 3.7 million deaths, and 22.0 million DALYs over their lifetimes, for the cost of US $3.2 billion (Campos, Sharma, et al., 2017). Vaccination alone could reduce cervical cancer mortality by 40% over the lifetime; and vaccination coupled with at least three screening tests, reaching a 70% coverage, could reduce women’s lifetime risk of cervical cancer by

60% (Goldie et al., 2008; Kim et al., 2016). There is an urgent need to develop and implement an effective public health strategy to address gaps in infrastructure, human and financial resources in order to reduce the burden of HPV-related cancers in women infected with HIV in developing countries.

The main strength of this review of literature is that implementing cervical cancer primary and secondary prevention programs is feasible in low resources countries, despite of poor public infrastructure. The review demonstrates that the lack of public health infrastructure can make it challenging to treat advanced cervical neoplasms, but does not impede the implementation of HPV vaccination, and cervical cancer screening and cryotherapy treatment, which have proven to provide significant benefits with relatively low infrastructure or training requirements (Parkhurst et al., 2013).

The main weakness of this literature review is the scarcity of cervical cancer and HPV vaccination surveillance data from the National Cancer Registries in LMICs. This evidence stresses the importance of increasing accurate and quality surveillance data on cervical cancers in developing countries for informing cancer policies and further cancer research on HPV vaccines.

Chapter III: Methodology

Funding Agency

The Unitaid is an international organization based in Geneva and hosted by the WHO. Since its establishment in 2006, the organization has invested in cutting-edge health solutions to accelerate the end of major diseases and maximize the effectiveness of the

global health response by catalyzing equitable access to better health products in LMICs. In partnership with WHO, PEPFAR, and the Global Fund, the organization invests in innovative researches and identifies new affordable and effective health solutions with potential to alleviate the burden of HIV/AIDS, tuberculosis and malaria, and to improve access to diagnostics and treatment for HIV co-infections such as hepatitis C and human papillomavirus (HPV).

Since its establishment, Unitaid has received about US $3 billion in contributions mainly from France, the United Kingdom, Norway, the Bill & Melinda Gates Foundation, Brazil, Spain, the Republic of Korea, and Chile.

Through calls for proposals, Unitaid finances short-term grants that bring health innovations into practice to fast-track access and reduce costs of more effective medicines, technologies and systems to achieve maximum impact.

Over the last decade the organization's investments played a key role in reducing the price of antiretroviral treatment for HIV, scaling up the use of a new tool that tests for drug-resistant tuberculosis, and increasing access to quality antimalarial drugs and new diagnostic techniques.

Description of the Grant Announcement

With the ultimate goal of "Preventing deaths from cervical cancer", the Unitaid has announced a Call for Proposals for interventions: "Optimizing management of coinfections and comorbidities in people living with HIV".

Context

As called upon by WHO in the World Health Assembly in May 2018, the Unitaid seeks to accelerate access and scale use of optimal tools for cervical cancer secondary prevention in LMICs.

The objective of this call for proposals is to identify projects that can address access barriers, catalyze the market for, and support adoption of improved tools for managing the disease at the pre-cancer stage, thereby reducing the increasing death toll due to cervical cancer in LMICs in general, and in particular in HIV-coinfected women.

Under this call, Unitaid is soliciting proposals for the following interventions with a view to advancing innovative cervical cancer screening and treatment tools, enabling the paradigm change for screening and treatment programs in LMICs:

- Catalyzing a market for optimal products for cervical cancer screening and treatment in LMICs by addressing access barriers (market entry, affordability) for the most promising new technologies (molecular tests, other new tests and self-collector devices, point-of-care (POC) treatment devices);
- Supporting introduction of these products in selected early-adopter countries through integrated approaches, and identifying the most effective delivery channels to support future scale-up and maximize impact and value-for-money.

The complete solicitation announcement can be found at https://unitaid.org/call-for-proposal/preventing-deaths-from-cervical-cancer/#en

The grant review process

The grant proposal underwent a three-step review:

- The first review was initiated after completion of the first draft of the document.

- The second review was performed after addressing the first reviewers' comments to completing a second grant proposal draft.
- The third review was carried out during and after the thesis defense.

The reviewers are public health professionals working in the field of infectious disease including HIV, Hepatitis, and Tuberculosis, and cancer treatment. They are from the Centers for Disease Control and Prevention (CDC), University of Maryland-Baltimore, and the National Institutes of Health (NIH). Each reviewer was individually asked to perform an in-depth review of the overall grant proposal at every step. The reviews took approximately 5 to 15 days and include the reviewers' written comments and recommendations to improve the quality of the thesis document.

Grant proposal reviewers

Paul Denis Leger, MD, MPH. Paul Denis Leger, MD (Vanderbilt 2017), MPH (Quisqueya, Haiti).

Dr. Leger is a Fellow in Hematology and Oncology at the National Institutes of Health, Bethesda, MD. Paul has 19 years of experience in clinical research in HIV/AIDS and Oncology. After completing a residency in Internal Medicine at the State University Hospital in Port-au-Prince, Haiti in 2001, Paul joined the GHESKIO Centers, where he went on to play a pivotal role in the scale-up of antiretroviral therapy in Haiti. Furthermore, he was involved in Caribbean, Central and South American research initiatives to address treatment challenges in the region.

After the devastating earthquake of 2010, he relocated to the United States to pursue advanced training in clinical medicine, research, and leadership development. At

Vanderbilt University, Nashville, TN, he conducted research focusing on identifying associations between human genetic variants and clinically relevant antiretroviral drug response phenotypes. His work has been published in peer-reviewed journals and has helped to change HIV/AIDS treatment policy and guidelines.

Dr. Leger was selected as a reviewer for this grant proposal because of his extensive experience in HIV/AIDS clinical research and his strong interest with recent innovations in precision medicine for the treatment of cancers with an emphasis on genomics and molecular genetics.

Gregory Taylor, MD. Dr. Taylor has Medical Degree from the University of Maryland School of Medicine Baltimore, and Bachelor in Science in Biology from Virginia Technology Blacksburg, Virginia. Dr. Taylor has been involved in the care of HIV infected patients at the University of Maryland for the past two decades in both direct patient care and research venues. His previous and current research include studies into tobacco related pathology in HIV infected patients including women. In addition, Dr. Taylor has performed research on the effects of HPV related disease in the HIV infection patient population. These studies have involved both laboratory, epidemiologic, and interventional clinical components.

This grant proposal is performed under Dr. Taylor mentorship. He is also one of the reviewers of this grant. Dr. Taylor is selected as mentor and reviewer for this project because of his experience in HIV care and treatment, cervical cancer prevention, screening

and treatment in HIV-positive women and his research studies on HPV-related cancers in HIV-positive patients.

Astride Jules, MD, MPH. Dr. Astride Jules is a Haiti-trained pediatrician and a US-trained family medicine physician with a keen interest in public health. She obtained her master of public health degree at Vanderbilt University School of Medicine in 2009 through the prestigious Fulbright Scholarship. After obtaining her MPH, she remained at Vanderbilt University as a post-graduate fellow to continue her research work on the complications of HIV and influenza infection in children under 5 years old. In 2015, she started a family medicine residency at Meharry Medical College and completed her training at the University of Maryland Medical Center in 2019.

A passionate patient advocate, Dr. Jules strongly believes that public health research is essential for improving patient outcomes. Her research interests span birth defects in pregnant women exposed to medications in the first trimester to influenza-related complications in children under five years old.

Macarthur Charles, MD, PhD, MS. Dr. Charles is a physician trained in internal medicine and infectious disease at the Weill Cornell Medical College. Dr. Charles' public health work has focused on his native Haiti for the past 15 years. As a fellow in infectious disease at Cornell, he led a project, through a collaboration with the Haitian NGO GHESKIO, to help implement one of the first large scale urban antiretroviral therapy programs in Haiti in 2004. This pioneering experience provided the basis for the

countrywide expansion of antiretroviral therapy. Dr. Charles subsequently helped establish the first molecular laboratory in the country to perform HIV testing for early infant diagnosis and viral load.

Dr. Charles played a key role in strengthening the Haiti public health system after the 2010 earthquake. As the lead medical officer at the GHESKIO center in Port-au-Prince, he supervised a team of health professionals in the care of patients with tuberculosis (TB), HIV, and cholera. Dr. Charles joined CDC in 2013 as a TB Advisor in Haiti, a role in which he worked with key stakeholders to support rapid TB diagnosis, active case finding through innovative approaches, and management of patients with multidrug resistant TB. Some of the achievements include implementing the TB diagnostic network, establishing the first biosafety level 3 laboratory at the National Public Health Lab, and developing guidelines for the management of MDR-TB.

A passionate supporter for technology transfer and public health workforce development in resource-limited settings, Dr. Charles has mentored many public health professionals and has published over two dozen manuscripts in peer-reviewed journals. Dr. Charles has been asked to review this grant proposal based on his experience in technologies transfer and health innovations to fast-track access to health services in low-income settings.

A.D. McNaghten, PhD, MHSA. Dr. McNaghten is the Chief of the Capacity Building Branch in the Centers for Disease Control and Prevention's (CDC) Division of HIV/AIDS Prevention (DHAP). The Capacity Building Branch provides technical assistance and training to the HIV prevention workforce to support the implementation of science- and

evidence-based initiatives and strategies to prevent the transmission of HIV and reduce HIV-related health disparities, illness and death.

Dr. McNaghten previously was an Associate Research Professor and is now an Adjunct Associate Professor in the Department of Epidemiology at Emory University's Rollins School of Public Health. She has over 20 years of experience in HIV epidemiology and prevention research. She has served as a Principal Investigator and Project Officer for several international and domestic projects monitoring disease progression, laboratory data, and prescription and impact of antiretroviral therapies among persons with HIV. She was previously the Principal Investigator on a CDC-funded randomized trial of HIV testing and counseling interventions conducted in 36 outpatient departments in three African countries. She was the Team Lead for DHAP's Behavioral and Clinical Surveillance Branch's Clinical Outcomes Team and the Principal Investigator for the population-based Medical Monitoring Project. She has also served as the CDC Surveillance Officer for CDC-Zimbabwe and consulting Surveillance Officer for the African region. Dr. McNaghten previously worked as an Epidemiologist with the Council of State and Territorial Epidemiologists. In that role, she provided technical assistance to health departments and community based organizations in the use of epidemiologic data for HIV prevention planning.

Dr. McNaghten received her M.H.S.A. and Ph.D. from Ohio University.

Protection of human subjects

This project will be implemented primarily to improve health service delivery through cervical cancer prevention and treatment services according to the WHO guidelines.

Moreover, the project will collect cervical tissue material from women at the time of colposcopy. This tissue will be preserved and used later for further HPV molecular genotyping testing in order to characterize HPV types. Therefore, we will request Institutional Review Board (IRB) review and approval from HFSC and the University of Maryland.

During the formative needs assessment as well as during the final evaluation, human subjects will be invited to participate either via focus groups or interviews or surveys. In order to align with the NIH requirements, we will ensure that the project team obtains the approval from the HFSC IRB committee prior to the activities; we will ensure that written informed consent and/or assent for minors is obtained from all participants. Although the project plans to support health services for female adolescents aged 9 to 26 years old, we will not interview adolescents under 18 years old. Epidemiologic and demographic data related to individuals will be coded before any analysis for report and dissemination. All data will be kept confidential both during their collection, analysis, and dissemination.

Chapter IV: Incorporation of reviewers' comments

Reviewer 1: Dr. Paul Denis Leger

This is a very interesting and well documented project addressing a critical public health topic for the developing world. Haiti has one of the highest incidence of cervical cancer of the world (94 cases per 100,000 inhabitants compared to 6.5 cases per 100,000 inhabitants in the US). While the introduction of HPV vaccine and screening with Pap smear has contributed to significantly decrease the incidence of cervical cancer in the developed

world, cervical cancer has remained the major cause of cancer related death in Haiti with an estimated 1500 deaths annually. Because of limited financial resources dedicated to public health, limited health infrastructure and very few trained professionals in the field, no progress has been made in cervical cancer control in Haiti. Below are a few comments to improve the project of Dr. Delva.

Comment 1: Any reason for not including young male adolescents infected with HIV in the targeted intervention group to be vaccinated?

Response to comment 1: The call for proposal requests to conduct activities aiming at reducing mortality due to cervical cancer in HIV-positive women. I recognize that there is a need for HPV vaccination for HIV-positive young male adolescents. However, to stay aligned with the request for proposals and because of the high-risk of cervical cancer, only HIV-positive females will be targeted.

Comment 2: It is not clear what intervention would be performed on adolescents and what intervention on HIV-infected women. Based on the current language, it seems adolescents age 9-26 years would be offered Pap smear as well. Please clarify.

Response to comment 2: I clarified in the document that HPV vaccination intervention will be provided to HIV positive females aged 9 to 26 years old. Screening for cervical cancer will be carried out for HIV-positive women aged 18 years and older and sexually active.

Comment 3: Any reason for not including adolescents aged 9 to 26 year-old as recommended by ACIP?

Response to comment 3: There is no specific reason not to include adolescents from 9 to 26 years old. Adolescent's age range will be updated as per the ACIP recommendation.

HIV-positive adolescents and women aged 18 years and older and sexually active will be screened for cervical cancer as well.

Comment 4: Do you have a contingency plan to reach out patients with negative VIA but positive high risk HPV if they don't return to the clinic?

Response to comment 4: Community liaisons at HFSC will reach out to patients with negative VIA but positive high risk HPV if they don't return to the clinic. This contingency plan has been added to the proposal.

Comment 5: You specified that this project presents minimal risk for the beneficiaries as no human material would be collected. However the project will collect cervical tissue material from colposcopy for molecular HPV genotype testing. I think it would be appropriate to change to language to include full IRB approval from HFSCA and University of Maryland if you intend to collect data for publication.

Response to comment 5: This section has been updated.

Comment 6: What is your plan to share the results of your intervention with the rest of the world? A plan for publication would be appropriate.

Response to comment 5: A plan for publication has been added to the proposal.

Reviewer 2: Dr. Astride Jules

This is a great project carefully designed taking into consideration the reality of a resource-limited setting. This project implementation will be a great asset in improving the health status of the Haitian population. Please see my comments bellow:

Comment 1: Per the ASCCP guidelines screening for HPV related lesions in HIV infected women less than 21 is recommended only when they are sexually active you need to specify

which population will benefit from the screening because it is not clear that patients 9-26 not sexually active will benefit only from the vaccine.

Response to comment 1: I have updated the intervention for this population according to the ASCCP guidelines. I specify in the proposal that cervical cancer screening will be provided to sexually active women aged 18 years old and older.

Comment 2: In reference to comment 1, in the chart specify that visual inspection with acetic acid will be done to women either 21 or more and those less than 21 but sexually active.

Response to comment 2: This section has been updated accordingly.

Comment 3: Please use the term vaccination appropriately instead of immunization since vaccination is referred to the response of the host to the vaccine that would have been evaluated with specific testing.

Response to comment 3: Updates have been made throughout the document to use the term vaccination instead of immunization.

Comment 4. Page 12, objective 2.1 Please delete the between by and June.

Response to comment 4: This section has been updated accordingly.

Comment 5. Page 19, please replace infections disease by infectious diseases.

Response to comment 4: Updates will be made accordingly.

Reviewer 3: Dr. Macarthur Charles

Summary comments: This is a well-structured grant proposal to tackle cervical cancer prevention, detection, and treatment among HIV-positive adolescent girls and women in Haiti. The background is well written and presents a cogent justification why the

intervention is both necessary and long overdue. Data on cervical cancer rates in Haiti are sparse but according to PAHO, Haiti has the highest rates of cervical cancer in the Western hemisphere. There is no cervical cancer strategy in Haiti. The HPV vaccine has only been given under limited pilot initiatives. The approach the candidate proposes is based on the WHO screen and treat guidelines. However, the candidate will introduce point-of-care HPV diagnosis using the GeneXpert platform, which is already available in Haiti. The candidate hopes this project will contribute to reduce mortality due to cervical cancer, to strengthen the national cancer registry, and to expand the approach to other areas of Haiti under the guidance of the Ministry of Health.

My specific comments/suggestions:

Comment 1: Provide more detail on the GeneXpert platform and what HPV subtypes are detected.

Response to comment 1: More detail has been added to describe GeneXpert and the high-risk subtypes.

Comment 2: Are there any data on the prevalence of HPV and its subtypes in HIV-positive Haitian women in Haiti? How will the candidate's study provide more information on this aspect?

Response to comment 2: There are limited data on the prevalence of HPV in HIV-positive women in Haiti and no prevalence study has been conducted yet. However, an unpublished evaluation conducted in a large urban clinic showed high-risk HPV carriage rates of 62% among HIV-positive women (personal communication).

Comment 3: The candidate should outline the steps on how she will go about including the HPV vaccine in the current vaccination schedule for adolescent girls at Hôpital Foyer Saint Camille.

Response to comment 3: Information education sessions on cervical cancer prevention, diagnosis, and treatment will be held daily at HFSC. In order to target female adolescents eligible for HPV vaccination, a nurse focal point will identify all adolescent girls 9-26 years old daily, ask them (18 and above) or their parents (10-17 years old) if they are interested in the HPV vaccination. If they agree, the nurse will record their demographic information in a specific register, and refer them for HPV vaccination.

At the national level, a workshop with the Ministry of Health, GAVI and other key stakeholders such as Partners In Health and GHESKIO, will be convened to develop a national strategic plan on cervical cancer prevention, diagnosis, and treatment. This national strategic plan will be based on the WHO recommendations outlined in the Toolkit for Cervical Cancer Prevention and Control Programs (World Health Organization, 2019). It will include HPV vaccination of adolescent girls 9-26 years old as a key prevention intervention and the “See, Diagnose, and Treat” approach.

Comments 4: Format the document: Uniform font size throughout; spelling and grammatical errors to address throughout. Follow track changes in the text.

Response to comment 4: Addressed in the text.

Reviewer 4: Dr. Gregory Taylor

I looked over the draft and am most impressed by the professionalism in the draft and all the hard work. Overall it looks great. I have added some thoughts (in green letter).

Comment 1: Reference the HPV types that are more common in women of African descent such as 35, 39, 56, 58, and 68 that are not covered by the current vaccines.

Response to comment 1: These references have been added to the second draft of the proposal.

Comment 2: Will the HPV molecular testing results be compared to the HPV types covered in the available HPV vaccine?

Response to comment 2: The HPV genotyping results will be compared with the HPV types covered by the current HPV vaccines. This information has been updated in the proposal.

Comment 3: "Would also use HPV detected to measure effectiveness of vaccine, especially if some patients only receive 1 or 2 doses of HPV vaccines".

Response to comment 3: This clarification has been made in the document.

Comment 4: Do you think it is possible to do a digital photo if Aceto white areas seen, and store them so as to use for comparison after ablative therapy?

Response to comment 4: Taking photo of Aceto white areas seen during VIA is feasible. This intervention will done after patient' informed consent. This section has been update in the proposal.

Comment 5: "I'm confused here, are you doing pathology analysis of the samples or a see and treat protocol? If just doing see and treat, then no endocervical curettage and biopsy would be done for diagnosis. If see and treat then would state that a LEEP cone would be done if the lesions extend into the endocervical canal.

Response to comment 5: The project uses the "See-and-Treat" protocol for cervical cancer screening. Doing endocervical curettage and biopsy will be costly and require a skilled

physician and pathologist. This part has been updated in the protocol according to the comments.

Comment 6: "would look for all 14 high risk HPV types if feasible."

Response to comment 6: Updates have been made accordingly.

Comment 7: You will need to say how this would help i.e. if a lesion is still seen will it not be removed if HPV negative.

Response to comment 7: If a lesion is seen at colposcopy, it will be removed regardless the HPV results. This section has been update in the document.

Comment 8: You may want to say that HPV detection will help us develop a model to determine the value of concurrent HPV testing with see and treat.

Response to comment 8: I agree. Update has been made in the proposal, as suggested.

Comment 9: You will need to state what you will do, and or how you will proceed with and analysis patients who are lesion+/HPV- and No Lesion /HPV+.

Response to comment 9: Patient with visible lesions at colposcopy with undergo LEEP or Cryotherapy. Patient with no visible lesions at colposcopy and with HPV testing positive will have follow-up visit in 3 to 6 months. This clarification has been made in the document.

Comment 10: Consider calculation of predictive values of concurrent HPV testing. Also using the above strategy what your end point is? Is it recurrence of lesion or HPV detection in one year?

Response to comment 10: Calculation of predictive values of concurrent HPV testing in comparison with VIA and colposcopy. The endpoint of this strategy is the recurrence of lesion. Update has been made in the document accordingly.

Comment 11: Explore the possibility of implementing HPV detection as a less invasive and cost effective method for screening and prevention of HPV and expanding these strategies into the non-HIV infected population.

Response to comment 11: I agree. This section has be updated.

Reviewer 5: Dr. A.D. McNaghten

Comment 1: HIV and HPV should both be defined the first time they are used in the Executive Summary.

Response to comment 1: This section has been revised.

Comment 2: WHO refers to "screen-and-treat" and "screen, diagnose and treat" as approaches. I suggest using one of these to match WHO.

Response to comment 2: The cervical cancer secondary prevention approach will be "Screen, Diagnose-and-Treat". Updates have been in the entire document.

Comment 3: I assume this is adolescent girls versus adolescents in general. That should be specified throughout the proposal.

Response to comment 3: The HPV vaccination program will target HIV-positive adolescent girls and young women aged 9 to 26 years old according to the Advisory Committee on Vaccination Practices (ACIP) for HPV vaccination for HIV-positive population. Updates will be made throughout the document.

Comment 4: Your proposal indicates the program would be for all women, not limited to HIV+ women.

Response to comment 4: In line with the call for proposals, the project will focus primarily on HIV-positive women.

Comment 5: The primary target age for vaccination is 9-14. Why 10 instead of 9? Is it because studies cited in this proposal use age 10?

Response to comment 5: I have changed the primary target age for vaccination to 9-26.

Comment 6: The program you are proposing is actually screening for precancerous lesions and providing treatment to prevent cancer, as well as identifying cancerous lesions.

Response to comment 6: The comment is correct. Clarification will be made in the document.

Comment 7: Clarify that the HPV vaccination intervention will target adolescents 9 to 26 years old. And then screening will be more than 20 years old HIV-positive women.

Response to comment 7: Clarification will be made in the document

Comment 8: You need to use consistent language and consistently present the proposed activities throughout this proposal, and also consistently define the population(s) the activities are targeted to. You frequently refer to cervical cancer services, which doesn't emphasize the prevention focus of your proposed program and sounds more like you are dealing with women who have already developed cervical cancer. From what I can tell, you want to focus on cervical cancer prevention through HPV vaccination and the screening and treatment ("see-and-treat") of pre-cancerous lesions (or is it a "see, diagnose and-treat" because of the POC molecular testing?).

Response to comment 8: The entire document has been updated to improve consistency in language and in the proposed activities.

Comment 9: The proposal has very limited detail about the HPV molecular testing.

Response to comment 9: More details have been added regarding the HPV molecular testing.

Comment 10: I don't think the barriers preventing access have been defined. It sounds more like a service that has not been available versus one that is available but not accessible.

Response to comment 10: The document has been updated to define barriers preventing access.

Comment 11: Clarify how HPV vaccines will be integrated in the routine vaccine program. Describe the patient flow?

Response to comment 11: Information education sessions on cervical cancer prevention, diagnosis, and treatment will be held daily at HFSC. In order to target adolescents eligible for HPV vaccination, a nurse focal point will identify all adolescent girls 9-26 years old daily, ask them (18 and above) or their parents (10-17 years old) if they are interested in the HPV vaccination. When a patient agrees to be vaccinated, the nurse will provide specific information to the patient, record the patient's demographic information in the HPV vaccine patient register, administer the HPV vaccine, and schedule an appointment for the patient the patient to return within 3-6 months.

Comment 12: How you will do the cost benefit analysis? Where will the baseline information be collected? Please provide further details of this part in the project.

Response to comment 12: The costing analysis will be performed using the WHO C4P-ST Excel data analysis tool. Data requirements for this analysis include service costs (HPV vaccination, Screening, Diagnosis, and Treatment) and non-service costs (Microplanning, Training, Communication, Monitoring and Evaluation, and other activities). A "Master Price List" is included as a worksheet within the C4P-ST tool to facilitate cost data collection. The cost data will be obtained through publicly available data and/or by working

with stakeholders and partners in Haiti. The C4P-ST tool allows cost comparison for different strategies either at the intervention level or at the health facility level.

Comment 13: Describe the proposed role of the University of Maryland in the project.

Response to comment 13: The University of Maryland will provide hands-on training in colposcopy, LEEP, and cryotherapy procedures for HFSC staff.

Chapter V: Grant Proposal

Executive Summary

This Grant Proposal is in response to a call for proposals for optimizing management of coinfections and comorbidities in people living with the human immunodeficiency virus (HIV) in order to address the global burden of Human papillomavirus (HPV)-associated cancers in low- and middle-income countries (LMICs). This proposal will implement an integrative approach encompassing HPV vaccination for females aged 9-26 years of age, and “See, Diagnose, and Treat”, and point-of-care (POC) molecular testing methods for screening, and treatment of pre-cancerous and cancerous cervical lesions in HIV-positive sexually active HIV-positive women aged 18 years and older at the HIV primary care unit at Hôpital Foyer Saint Camille (HFSC), a health facility located in the northern area of Port-au- Prince in Haiti, and less than two miles from two major urban slums.

This proposal is a five-year project that will bring innovative approaches to address access barriers, support adoption of improved tools for preventing cervical cancer and managing the disease at the pre-cancer stage. It will be a multistage implementation, starting by improving the infrastructure, building capacity and establishing a training program on primary and secondary cervical cancer prevention for health care providers, patients and the community. The implementation phase will focus on identifying HIV-positive women at risk of cervical cancer and provide them with early detection and treatment including clinical and laboratory diagnostic services. The results will contribute to reducing the mortality and morbidity due to cervical cancer for HIV-positive females seeking care at Hôpital Foyer Saint Camille (HFSC). Through the proposed activities, Hôpital Foyer Saint Camille will have the capacity to provide high quality and affordable HPV-associated

services including HPV vaccination and “See, Diagnose, and Treat” cervical cancer prevention and treatment services for HIV-positive women.

Project narrative

Currently, females infected with the Human Immunodeficiency Virus (HIV) receiving care at Hôpital Foyer Saint Camille do not receive cervical cancer prevention and treatment services as part of the HIV/AIDS care service package. During the five years of implementing this project, all HIV-infected females aged 9 to 26 years old at Hôpital Foyer Saint Camille will receive full coverage of HPV vaccination, and HIV-positive women aged 18 years and older will be screened for cervical precancerous and cancerous lesions, and they will also receive treatment to prevent cervical cancer. Achieving this goal will contribute to decreasing mortality, improving quality of life, and overcoming some of the economic barriers women face in Haiti.

Problem statement

Women infected with the Human Immunodeficiency Virus (HIV) living in Haiti are at great risk of cervical cancer because of the lack of effective strategies for the prevention, detection, and treatment of pre-cancerous cervical lesions.

Background

Significance

Cervical cancer, one of the most preventable cancers, is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality in women worldwide, with more than 600,000 cervical cancer cases reported yearly, of which 90% occur in low and middle-income countries (Torre et al., 2017). Despite many efforts to implement cervical cancer screening and human papillomavirus (HPV) vaccination, more than 250,000 women still die from cervical cancer each year worldwide, which represents one death every two minutes, making this disease one of the greatest threats to women in modern history (World Health Organization, 2018).

In order to curtail the incidence and prevalence of cervical cancer, many developed countries have adopted the World Health Organization (WHO) guidelines for cervical cancer prevention by implementing strategies like primary prevention in the form of HPV vaccination targeting female adolescents aged 9 to 26 years old, and secondary prevention consisting of routine screening and treatment of precancerous lesions. According to the Centers for Disease Control and Prevention (CDC), in 2017, 49% of adolescents aged 13 to 17 years old in the United States received the full coverage for HPV vaccination, and 66% of them received the first dose (Centers for Disease Control and Prevention, 2019;

Walker et al., 2018). Globally, 118 million females aged 9 to 26 years old have been targeted to receive full coverage of HPV, representing the 70% coverage recommended to alleviate the global burden of cervical cancer. While 33% of females aged 9 to 26 years old received all recommended doses of HPV vaccination in developed countries, only 2.7% females aged 9 to 26 years old completed the full HPV vaccine doses in low-and middle-income countries (LMICs), where 56% of the global burden of cervical cancer resides (Campos, Sharma, et al., 2017). A study using a model-based approach to synthesize population, demographic, and epidemiological data from 50 LMICs, has predicted that more than 44 million women living in LMICs would be diagnosed of cervical cancer and half of them would die, without strategic interventions to avert the morbidity and mortality related to cervical cancer (Campos, Sharma, et al., 2017). The same study analyzed the health and economic impact of scaling-up the coverage of HPV vaccination and cervical cancer screening in LMICs. The study found that in low-income and lower-middle-income tier 1 countries, a ten-year comprehensive HPV vaccination and screening program, with a scaling up at a rate of 10% per year, would reach an estimated 163 million girls, and could avert 3.3 million cervical cancer cases, 2.4 million deaths, and 9.5 million disability-adjusted life years (DALYs) over their lifetimes. Globally, the same program would prevent 5.2 million cervical cancer cases, 3.7 million deaths, and 22.0 million DALYs over their lifetimes, for the cost of US $3.2 billion (Campos, Sharma, et al., 2017). Vaccination alone could reduce cervical cancer mortality by 40% over their lifetime; and vaccination coupled with at least three screening tests, reaching a 70% coverage, could reduce women's lifetime risk of cervical cancer by 60% (Goldie et al., 2008; Kim et al., 2016).

During the World Health Assembly (WHA) in May 2018, the WHO Director General, Dr. Tedros Adhanom Ghebreyesus, made a call to action for the elimination of cervical cancer globally by 2069 (World Health Organization, 2018). This call requires countries to adopt specific strategies to scaling HPV vaccines and cervical cancer screening in low resource settings. Unfortunately, in order to implement the WHO guidelines, LMICs have to overcome many barriers, such as insufficient government financial investment in health systems, poor public health system infrastructure, difficulty procuring HPV vaccines and screening supplies, and weak commodity and procurement systems. In line with the WHO calls for accelerating cervical cancer services in LMICs, GAVI, the Vaccine Alliance, an international public-private partnership for equal access to vaccines, has created opportunities for low-resource countries to access HPV vaccines at $4.50 per dose. As of July 2019, through this initiative, six LMICs have introduced the HPV vaccines in their national vaccine programs.

Despite those initiatives, millions of women living in LMICs do not have access to cervical cancer prevention and treatment programs including vaccination, screening, diagnosis and treatment, particularly HIV-positive women living in LMICs who are most at risk of developing cervical cancer. The incidence of precancerous and cancerous cervical lesions is four to five times higher in HIV-infected females due to the persistence of HPV infection, leading to cervical lesions and later cervical cancer in the absence of treatment (Ghebre et al., 2017). A study using population-based cancer registry data from 15 states in the US found a relative risk (RR) of cervical cancer of 68.6 (95% CI: 59.7 to 78.4) among HIV-positive women, and an elevated risk of all HPV-associated in situ cancer of RR = 8.9 (95% CI: 8.0 to 9.9) among women living with HIV in comparison to the general population

(Chaturvedi et al., 2009). The WHO guidelines for cervical prevention recommend providing cervical cancer screening following the diagnosis of HIV in sexually active adolescents aged 9 to 26 years old and women (World Health Organization, 2013). Cytology has been long recommended as the front-line test for HPV screening in women. Although cytology-based screening has proven effective in decreasing cervical cancer incidence rates in many countries (Gradissimo & Burk, 2017), the implementation of Pap smear-based screening services can be challenging in low-resource healthcare facilities due to the scarcity of pathologists capable of performing the Pap-smear cytology leading to long delay in the return of results. A European randomized clinical trial found that HPV testing as a primary screening tool will provide an additional 60-70% protection against invasive cervical cancer compared to cytology-based screening programs (Ronco et al., 2014). New Point-of-Care (POC) technologies developed for HPV DNA testing have been proven to be highly sensitive to detect precancerous and cancerous lesions. In resource-limited clinical settings, the use of POC diagnostic platforms for HPV testing have the potential for enhancing the scaling-up of a cervical cancer program, by reducing lab processing time to approximately 1 hour per sample and running in a non-batch mode, which may facilitate a same-day see-and-treat approach (Einstein et al., 2014). Moreover, the POC HPV DNA technologies are less costly than traditional molecular platforms, and they do not required high skilled laboratory technologist and advanced laboratory settings. The HPV detection and typing results can be available for clinical decisions in a timely fashion. Their practicability make them easy to implement in any remote laboratory. For the above-mentioned reasons, the utilization of molecular POC technologies has become the alternative for early and rapid disease diagnosis, including cancer screening and

infectious disease detection. As Campos at al. model projections suggested, the initial cost of a POC HPV test and supporting infrastructure in LMICs can be high but still provide good value for public health dollars in the long term (Campos, Tsu, et al., 2017). Henceforth, many low-income countries are implementing molecular assays for the detection of High Risk HPV as part of the implementation of “See-and-treat” programs because of practicability and short turn-around-time for diagnosis of cervical cancer for clinical decisions.

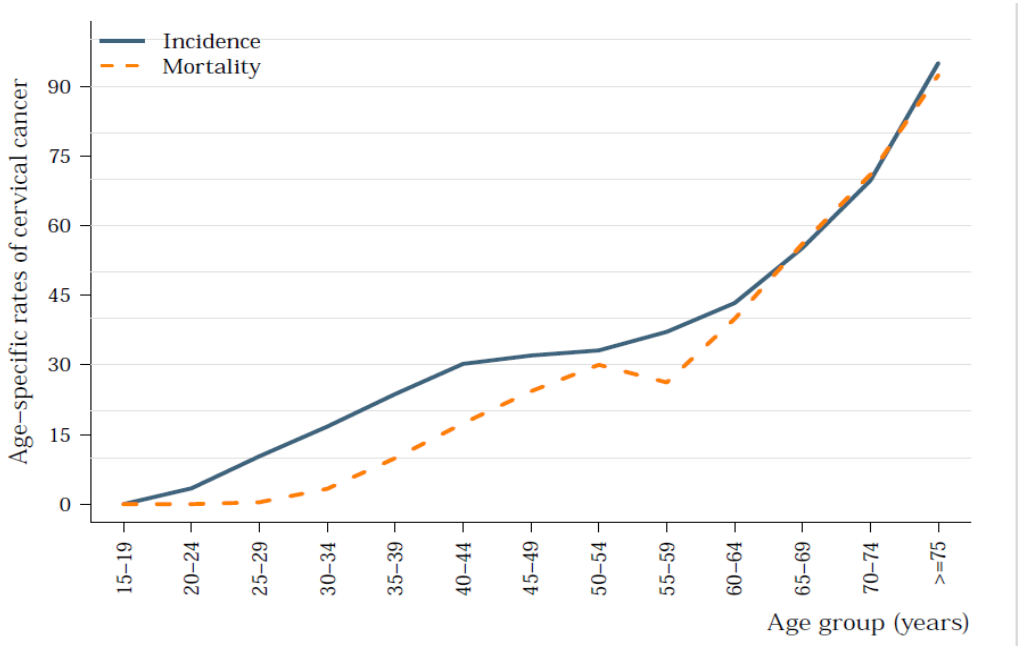
Since 2010, the WHO has encouraged the introduction of primary HPV serologic and DNA testing for the monitoring of HPV vaccine impact, and monitoring of changes in the prevalence of HPV types (World Health Organization, 2010). Despite the WHO recommendations, comprehensive cervical cancer programs in low-income countries are scarce, which results in higher mortality related to cervical cancer among women, particularly among HIV-infected women. The lack of infrastructure, human and financial resources impairs the implementation of integrated programs to link HIV and cervical cancer primary care in the management of HIV-infected women living in developing countries (Sankaranarayanan et al., 2013). There is an urgent need to develop and implement an effective public health strategy to address gaps in infrastructure, human and financial resources in order to reduce the burden of HPV-related cancers in women infected with HIV in developing countries.

Cervical Cancer in Haiti

According to the Pan American Health Organization, in (year) Haiti had the highest incidence of cervical cancer in the Western Hemisphere, with an annual aged-standardized

incidence and mortality rates estimated at 87.3 and 48.1 per 100,000 women, respectively (Luciani & Andrus, 2008). Since then, the morbidity and mortality related to cervical cancer have not been improved. The latest International Agency for Research on Cancer (IARC, Figure 1) report indicates that cervical cancer is the second most frequent cancer among women in Haiti and the first most frequent cause of cancer among women between 15 and 44 years of age; and an annual aged-standardized incidence and mortality rates estimated at 17.1 and12.5 per 100.000 women, respectively (IARC, 2019).

Figure 1. Comparison of age-specific cervical cancer incidence and mortality rates in Haiti (estimates for 2018)



Data source: Haiti: Human Papillomavirus and Related Cancers, Fact Sheet 2018 (IARC, 2019). Data accessed on 09 July 2019.

In Haiti, 3.64 million women aged 15 years and older are at risk of developing cervical cancer, and every year, 835 Haitian women are diagnosed with cervical cancer and 563 die from the disease (IARC, 2019). Although the Haitian Ministry of Health and Population (MSPP) has declared cervical cancer prevention a priority since 2012, few initiatives for primary and secondary prevention services have been carried out. The first ever HPV vaccination campaign was launched in Haiti in 2009 and 2010, at the initiative of Partners in Health/Zanmi Lasante, a non-profit organization providing health services in the Central Plateau region of Haiti. During this campaign, 27,000 girls aged 10 to 12 years old were vaccinated for HPV and 80% of them completed all three doses (Mandigo et al., 2015). The second HPV vaccination campaign was conducted in 2018 in Southern Haiti, and 2,500 girls were vaccinated during this campaign. There has been no HPV vaccination campaign targeting specifically adolescents and women infected with the Human Immunodeficiency Virus (HIV) living in Haiti, the most affected by cervical cancer. Access to a cervical cancer prevention and treatment program is also lacking for this population. Although access to antiretroviral therapy has improved the life expectancy of women living with HIV in Haiti, the prevalence of cervical cancer in this group of population remains very high. A non-profit organization providing screen-and-treat cervical services in Haiti has found a prevalence of HIV of 15.4% among women treated for cancerous cervical lesions (DeGennaro et al., 2019).

It is estimated that approximately 35 types of HPV can infect the human genital tract. Of these, 13 types are designated as high risk because of their association with cervical cancer (Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). HPV16 and HPV18 are associated with approximately 70% of low- and high-grade cervical intraepithelial lesions

(HSIL) leading to invasive cancer. Also, there are HPV types that are more common in women of African descent such as 35, 39, 56, 58, and 68 that are not covered by the current vaccines. HPV16, for instance, is less prevalent in African American compared with Caucasian women with HIV and cervical precancerous lesions independent of immune status (Keller et al., 2018). A meta-analysis of high-risk HPV-type distribution in 19,883 HIV-positive women found that HPV 16/18, but also HPV 45 and HPV 33 tend to be more prevalent in women infected with HIV (Clifford et al., 2017). In Haiti, the epidemiologic monitoring of circulating HPV types has not yet been performed in order to decide the most appropriate HPV vaccines for the population. There are limited data on the prevalence of HPV in HIV-positive women in Haiti and no prevalence study has been conducted yet. However, an unpublished evaluation conducted at a large HIV clinic - GHESKIO Centers- in Port-au-Prince, Haiti, showed that 62% of HIV-positive women had high-risk HPV (Riviere, 2010) (Table 1). In addition, 42% of the women had abnormal Pap smear results, with 7% having high-grade squamous intraepithelial lesions. A review of medical records at HFSC showed that 122 HIV-positive women had Pap smears performed. Among those women, 43% had abnormal results, with 7% showing high-grade lesions. There is a need for baseline epidemiologic monitoring of HPV-associated cancers in HIV-positive females in Haiti in order to evaluate the most appropriate HPV vaccines for this population and to measure the impact of HPV vaccines on cervical cancer in the future.

Table 1. Cervical cancer screening results across HIV treatment groups.

	Early HAART	Deferred HAART
	221 (52.37)	201 (47.63)
Cervical cancer screening results		
High Risk HPV DNA	129 (58.37)	131 (65.17)
PAP results		
WNL	119 (53.85)	105 (52.24)
ASCUS	29 (13.12)	20 (9.95)
LSIL	52 (23.53)	46 (22.89)
HSIL	15 (6.79)	15 (7.46)

Source: Unpublished data: (Riviere, 2010)

In 2016, Haiti allocated 0.83% of its GDP from public funds for health, and the government expenditure per capita on health was $9 per year (IHME et al., 2018). As for many low-income countries, poor government investment in healthcare undoubtedly contributes to poor health infrastructure, lack of funding, and absence of nationally organized primary and secondary HPV prevention programs to address the high morbidity and mortality of cervical cancer (Zahedi et al., 2014).

This Grant Proposal is for a five-year project that will bring innovative approaches to address access barriers, and support the adoption of improved tools for preventing cervical cancer and managing the disease at the pre-cancer stage. This project will reduce morbidity and mortality due to cervical cancer for HIV-positive females seeking care at Hôpital Foyer Saint Camille (HFSC), a healthcare facility providing care, education and food support to children and women exposed or infected with HIV and their affected families. Given that cervical cancer incidence is higher among HIV-positive women, our project will primarily

target this group of this population, but the services arising from this project will not be limited to HIV-positive patients only.

Goals and Objectives

This Grant Proposal identifies three ultimate goals to carry out activities through the use of innovative and affordable technologies and approaches to support the Cervical Cancer Prevention and Treatment Program at the HIV primary care unit at Hôpital Foyer Saint Camille (HFSC), a health facility located in the northern area of Port-au- Prince in Haiti, at less than two miles from two major urban slums.

Goal 1. This project will design an integrated HPV prevention program to provide HPV vaccination to HIV-positive females aged 9 to 26 years old seeking care at Hôpital Foyer Saint Camille.

Objective 1.1. By March 2020 develop a strategic plan based on the WHO guidelines adapted to integrate HPV services within the HIV care and treatment program at Hôpital Foyer Saint Camille.

Objective 1.2. By June 2020, 80% females aged 9 to 26 years receiving care at HFSC will have received the first dose of the HPV vaccine.

Objective 1.3. By the end of the project, 80% females aged 9 to 26 years receiving care at HFSC will have received all recommended doses of the HPV vaccine.

Goal 2. This project will implement an integrative approach a one visit “See, Diagnose, and Treat”, and point-of-care (POC) molecular testing methods for screening, detecting, diagnosing and treating pre-cancerous and cancerous cervical lesions in sexually active

HIV-positive women aged 18 years and older receiving care at Hôpital Foyer Saint Camille.

Objective 2.1. By January 2021, strengthen the HFSC laboratory capacity to perform HPV molecular testing to support the diagnosis of cervical cancer.

Objective 2.2. By June 2021, 100% of HIV-positive women will be screened for cervical cancer using the "See, Diagnose-and-Treat" approach.

Objective 2.3. By the end of the project, 100% of specimens collected from women with a suspicion of HPV infection will be tested for HPV by molecular testing.

Goal 3. This proposal intends to use the model of the Cervical Cancer Prevention and Treatment Program implemented at Hôpital Foyer Saint Camille to promote the scaling-up of the integrated cervical cancer approach to provide access to Cervical Cancer Prevention and Treatment Program for sexually active HIV-positive women aged 18 years and older in Haiti.

Objective 3.1. By January 2023, analyze cost-benefit of the integrated approach for the Cervical Cancer Prevention and Treatment Program for HIV-positive women at HFSC.

Objective 3.2. By January 2024, promote the introduction of the integrated approach for the Cervical Cancer Prevention and Treatment Program through discussion, partnership and collaboration with the Haitian Ministry of Health and key stakeholders involved in the care of HIV-positive women in Haiti.

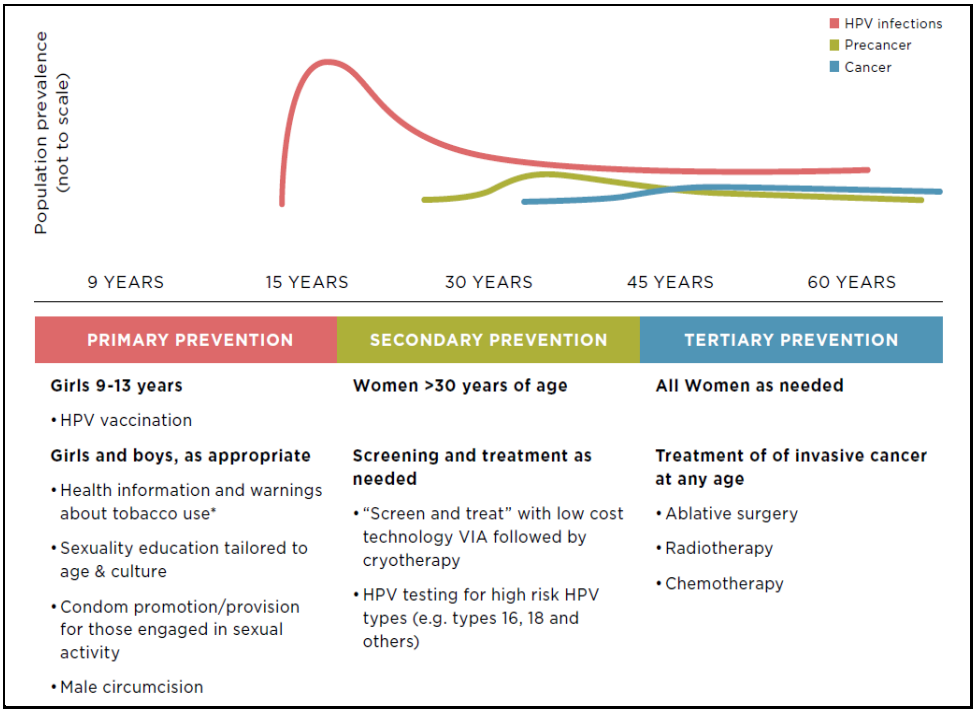
Intervention framework

The interventions framework will follow the WHO recommended programmatic interventions over the life course to prevent HPV infection and cervical cancer a including vaccines for adolescent girls to prevent most HPV infections and methods to screen women for precancerous lesions, which can be treated effectively in the clinic to prevent the progression to invasive cancer (Figure 2).

This approach to cervical cancer prevention and control includes:

1. Introduction and scaling-up of HPV vaccination;
2. Introduction and expanding coverage of screening and treatment of cervical precancerous lesions; and
3. Prompt referral of invasive cancers for surgery.

Figure 2. WHO-recommended strategy for cervical cancer prevention and treatment



Source: (World Health Organization, 2016)

Target population for intervention

HPV vaccination

The HPV vaccination program will target HIV-positive female adolescents and young women aged 9 to 26 years old according to the Advisory Committee on Vaccination Practices (ACIP) for HPV vaccination for HIV-positive population.

Cervical cancer screening and treatment

The target population for the "See, Diagnose, and Treat", and point-of-care (POC) HPV molecular testing are sexually active HIV-positive female adolescents aged 18 years old and older.

Strategic Approach

To achieve the goals and specific objectives of this project, we will carry-out activities that will contribute to the elimination of cervical cancer as a public health problem, as called upon by the World Health Assembly in May 2018.

Goal 1. This project will implement an integrated HPV prevention program to provide HPV vaccination to HIV-positive females aged 9 to 26 years old and cervical cancer screening and treatment services for sexually active women aged 18 years and older seeking care at Hôpital Foyer Saint Camille.

Expected Outcome

The expected outcome for this intervention is to equip Hôpital Foyer Saint Camille with an operational plan for implementing HPV vaccination and cervical cancer services.

Goal 1 Strategy

WHO recommends that girls between 9 and 14 years of age receive two doses of HPV vaccine in all countries. Until now, HPV vaccine has not been included in the national vaccination program of Haiti due to lack of adequate commodity and supply chain system to maintain the cold chain and absence of a strategic plan for universal introduction of the HPV vaccines. The HIV/AIDS program at HFSC has thus far focused only on treatment of HIV-positive adults and children, and education and support of affected families. The HIV/AIDS program at HFSC consists of a cohort of approximately 1,000 women and their children. A cervical cancer prevention and treatment program is not part of the health care package. There is a need for HPV-related prevention, care and treatment.

Process: Situational Analysis

To address this gap, we will conduct a survey to assess the need for a cervical cancer prevention and treatment program and evaluate the facility infrastructure, health services organization and human and financial resources available at the hospital. We will also conduct interviews with key leaders in the community living in the hospital catchment area and focus group sessions with HIV-positive patients receiving care and treatment at the hospital. To identify the most effective strategy to help HIV-positive females at HFSC gain access to and the Cervical Cancer Prevention and Treatment Program, we will gather insights from 1) the needs assessment findings, 2) a thorough review of scientific literature on HPV vaccination and cervical cancer programs in resource-limited settings from PubMed and other online web science databases, and 3) a review of the WHO, CDC and the BETHESDA guidelines for cervical cancer

prevention. This process will contribute to collecting sufficient information on resources required to design and implement an HPV prevention and a same day "See, Diagnose-and-Treat" cervical cancer program, supported by POC molecular HPV detection adapted for low-resource settings like Hôpital Foyer Saint Camille. The plan will take into consideration the social, cultural, and economic context of the community.

Data collection

The data collected from patients' records and through the survey, interviews, and focus groups will help identify opportunities and challenges for implementing HPV prevention and treatment programs at the hospital; also, it will help assess knowledge, cultural beliefs, perceptions, and attitudes towards cervical cancer.

Activities

Our strategy will include the following activities:

1. Perform a Situational Assessment for cervical cancer prevention and treatment services for HIV-positive females receiving care at HFSC.
2. Conduct a training needs assessment for cervical cancer prevention, care and treatment for healthcare providers at HFSC.
3. Prepare an operational plan for implementing the Cervical Cancer Prevention and Treatment Program at HFSC.
4. Initiate discussions with the Haitian Ministry of Health and the GAVI, the Vaccine Alliance representatives in Haiti to support full coverage HPV vaccination for

HIV-positive females aged 9 to 26 years old visiting the hospital or living in its catchment area.

5. Recruit project staff to support the implementation of the Cervical Cancer Prevention and Treatment Program at HFSC.
6. Conduct training for healthcare providers in the hospital on the proper use of the WHO guidelines for HPV vaccination and Cervical Cancer Prevention and Treatment Program.
7. Reinforce the commodity system at the hospital by procuring equipment and supplies for the program.
8. Place order for materials and equipment for project implementation.
9. Establish collaboration between HFSC and the University of Maryland- Baltimore to support the implementation of Cervical Cancer Prevention and Treatment Program.

Goal 2. This project will implement an integrative approach a one visit "See, Diagnose, and Treat", and point-of-care (POC) molecular testing methods for screening, detecting, diagnosing and treating pre-cancerous and cancerous cervical lesions in HIV-positive women.

Expected Outcome

At the end of the second year of the project, Hôpital Foyer Saint Camille will have full capacity to provide in one visit, HPV vaccines to HIV-positive women aged 9 to 26 years old, high quality cervical cancer prevention and treatment services including

HPV point-of-care (POC) molecular testing to HIV-positive female adolescents and women seeking care at the Hôpital.

Goal 2 Strategy

The ICO/IARC HPV Latin America report estimates a yearly incidence of 835 cervical cancer cases yearly and a crude mortality rate of 10% in Haiti (IARC, 2019). Although the Haitian Ministry of Health (MSPP) declared cervical cancer prevention a national priority, and formed a committee in 2014 to review national cervical cancer screening guidelines, barriers to access health services such ineffective health infrastructure, lack of trained healthcare professionals, and absence of a cervical cancer surveillance system have impeded the implementation of an effective cervical cancer screening program. However, with the recent WHO guidelines and technological advancements of cost-effective cervical cancer screening methods and tools, implementing cervical cancer programs in low-income settings is feasible.

Our proposal seeks to promote a one visit “See, Diagnose, and Treat” approach using the VIA method as baseline cervical cancer screening for HIV-positive women at the HFSC. This approach will be using the flow chart detailed in Figure 3, which is a modified HPV WHO screening algorithm that incorporates VIA, POC HPV molecular testing, colposcopy, loop electrosurgical excision procedure (LEEP) or cryotherapy.

The one-visit “See, Diagnose, and Treat” approach consists of the following steps:

1. A VIA will be performed by a trained nurse or physician using inexpensive materials such as vaginal speculum, vinegar and a light source. Digital photos will be also taken

and stored if Aceto-white areas are seen during the VIA procedure. This will be useful for comparison after ablative therapy.

2. Patients who are VIA-negative will be scheduled to return for follow-up screening in 12 months.
3. Women who are VIA-positive will immediately undergo colposcopy. At the same time, a cervical sample will be taken by inserting a clean brush 1-1.5 cm into the cervix to perform POC HPV molecular testing.
4. Immediately after or while performing the colposcopy, women with visible lesions at colposcopy, regardless of the HPV results, will undergo Cryotherapy or LEEP.
5. Patients with high suspicion of invasive cervical cancer lesions will be referred for surgery.
6. The follow-up visits will be scheduled at 3-6 months for HIV-positive women with HPV positive results with no cervical lesions at colposcopy.
7. Women who are HPV-negative, VIA negative and with no cervical lesions at colposcopy will be rescreened every year.
8. The follow-up visits will be scheduled at 12 months after LEEP or Cryotherapy.
9. The end point of this algorithm is the recurrence of cervical lesions.

   Steps 1 to 4 are inexpensive procedures that can be performed in the outpatient settings along with the colposcopy procedure.

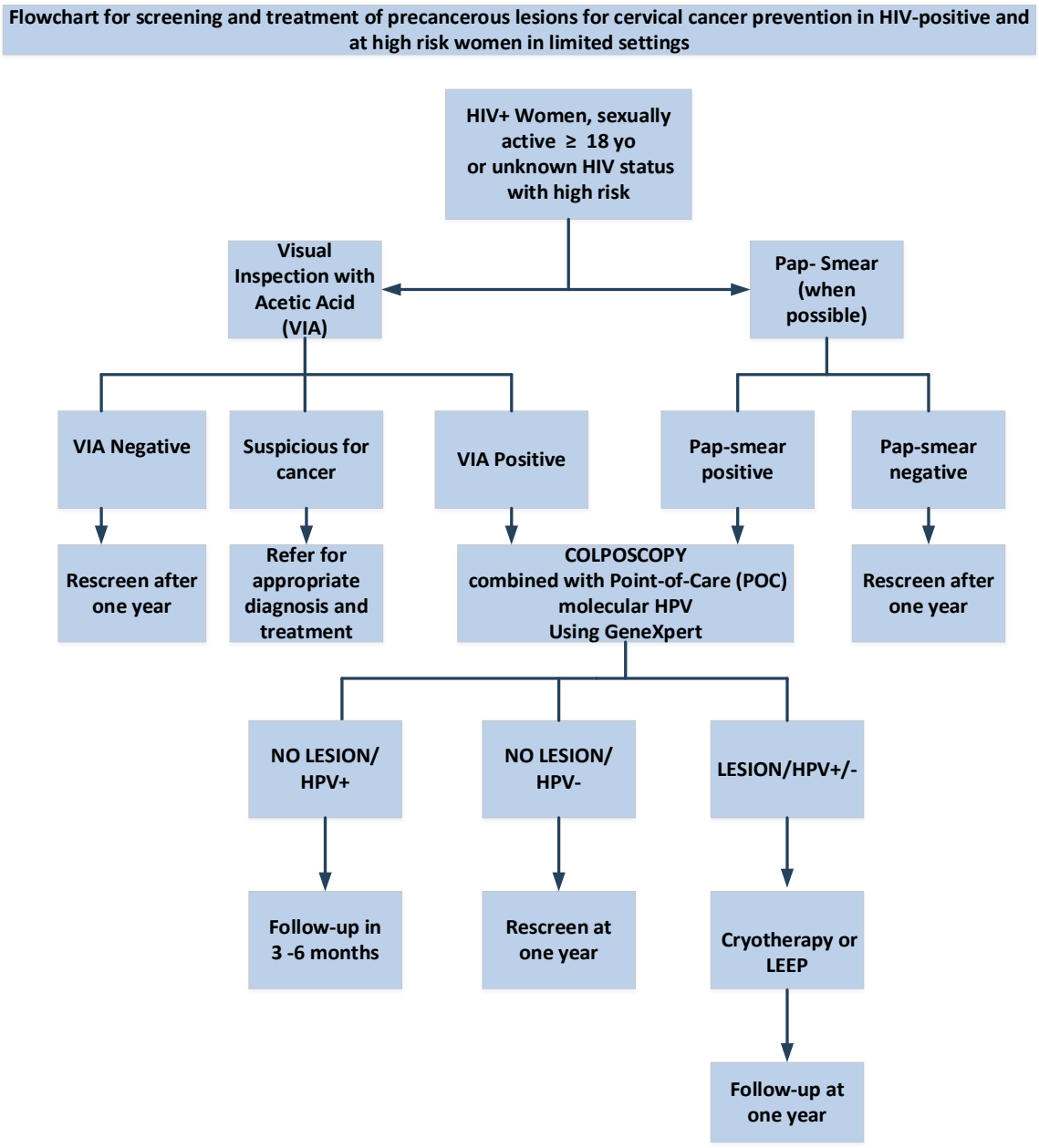
This project will also use POC HPV molecular testing methods for screening HPV infections and High Risk HPV typing for sexually active HIV-positive females aged 18 years and older seeking care at the HIV primary care unit at Hôpital Foyer Saint

Camille. HFSC has acquired a sixteen-module GeneXpert® equipment (Cepheid, Sunnyvale, CA) that is currently being used only for the molecular detection of *M. tuberculosis* complex and its drug sensitivity to rifampin. This machine also has the capability to perform a large spectrum of POC molecular testing for various infectious diseases, such as Chlamydia, Gonorrhea and HPV. This is an opportunity to strengthen the existing laboratory capacity at HFSC to perform HPV testing from cervical samples collected during the colposcopy. This proposal will support training for laboratory technologists on the HPV Xpert assay. This assay can detect high-risk HPV types, such as HPV 14, 16, 18 and HPV 45 in 60 minutes, and provide HPV results in one hour (60 minutes) so that care providers can classify patients based on the high-risk HPV genotypes in a timely fashion. Cervical fluid specimens will be stored for further detection of all 14 high risk HPV.

The integration of molecular testing to the screening algorithm will help diagnose HPV infection and classify the circulating genotypes of HPV in HIV women at HFSC. Knowing the circulating genotype of HPV is crucial for 1) determining HPV-type specific prevalence among the population, 2) for the evaluation of vaccine effectiveness, especially if some patients only receive 1 or 2 doses, and 3) for monitoring and scaling-up the vaccination program. For this project, the HPV genotyping will support not only the epidemiologic monitoring of HPV infections, but also the follow-up of treated patients. Moreover, the HPV genotyping results will be compared to the HPV types covered in the available HPV vaccines.

The adjuvant molecular HPV detection to “See and Treat’” will help develop a model to determine the value of concurrent HPV testing with “See, Diagnose, and Treat”.

Figure 3. Proposed flowchart for screening, diagnosing, and treating precancerous lesions for cervical cancer prevention in HIV-positive and in high-risk women in resource-limited settings



Activities

To achieve the aforementioned goals we will undertake the following activities:

1. In collaboration with the University of Maryland-Baltimore (UMB) team, develop training program on primary and secondary cervical cancer prevention for health care providers, patients and the community to implement a "See-and-Treat protocol for routine screening of HPV infections.
2. Facilitate training sessions between UMB and HFSC.
3. Launch the HPV vaccination program at HFSC.
4. Conduct training for laboratory technicians to strengthen HFSC capacity for Point-of-Care (POC) molecular HPV detection
5. Pilot the integrated routine Cervical Cancer "See, Diagnose, and Treat" services at Hôpital Foyer Saint Camille for HIV-positive Women.
6. Full implementation of the Cervical Cancer "See, Diagnose, and Treat" services for HIV-positive women living in the catchment area of Hôpital Foyer Saint Camille.
7. Establish a hospital referral network to refer women diagnosed with advanced cervical cancer lesions for surgery.

Plan for integration HPV vaccination and cervical cancer services in HIV care and treatment at HFSC

Information education sessions on cervical cancer prevention, diagnosis, and treatment will be held daily at HFSC. A nurse will identify all HIV-positive females 9-26 years old daily, ask them and/or their parents or guardians (for those under 18 years old) if they are interested in the HPV vaccination and cervical cancer screening. Informed

consent, including potential risk and benefit of the intervention, will be discussed with the patient and, if he/she agrees, the inform consent form will be signed. An assent form will be signed for those under 18 years old. The nurse will record the patient's demographic information in an HPV register and administer the HPV vaccination. The second dose of the vaccine will be scheduled within 6-12 months of the first dose. For patients who do not return for the follow-up visit or who are lost to follow-up, a community liaison at HFSC will reach out to patients.

At the national level, a workshop with the Ministry of Health, GAVI and other key stakeholders such as Partners In Health and GHESKIO, will be convened to develop a national strategic plan on cervical cancer prevention, diagnosis, and treatment. This national strategic plan will be based on the WHO recommendations outlined in the Toolkit for Cervical Cancer Prevention and Control Programs (World Health Organization, 2019). It will include HPV vaccination of HIV-positive females 9-26 years old as a key prevention intervention and the "See, Diagnose, and Treat" approach for sexually active HIV-positive women aged 18 years and older.

Goal 3. The proposal intends to use the Hôpital Foyer Saint Camille model to promote the scaling-up of the integrated cervical cancer approaches to overcome barriers preventing access to Cervical Cancer Prevention and Treatment Program for HIV-positive females **aged 9 to 26 years old and** sexually active HIV-positive women aged 18 years and older **in Haiti.**

3.1. By January 2023, analyze cost-benefit of the integrated approach for Cervical Cancer Prevention and Treatment Program for HIV-positive women at HFSC.

3.2. By January 2024, perform epidemiologic monitoring of circulating HPV types in sexually active HIV-positive females 18 years and older.

3.3. By January 2024, promote the introduction of the integrated approach for Cervical Cancer Prevention and Treatment Program through discussion, partnership and collaboration with the Haitian Ministry of Health and key stakeholders involved in HIV and women care and in Haiti.

Expected Outcome

Following the evidence generated from the project, the Haitian Ministry of Health and its partners will adopt policies and public health interventions for implementing the "See, Diagnose, and Treat" approach for cervical cancer screening, diagnosis, and treatment in Haiti.

Goal 3 Strategy

Currently there is no data available on the incidence and prevalence of cervical cancer from the Haiti National Cancer Registry (IARC, 2019). This project will be an opportunity to report completed and accurate cervical cancer and HPV vaccination surveillance data to the National Cancer Registry. The evidence generated from project will serve to convince the Haitian Ministry of Health to adopt policies for implementing the "See, Diagnose, and Treat" approach for cervical cancer screening, diagnosis and treatment in Haiti. This approach has the advantages of using low cost medical equipment to perform colposcopy evaluation for treating pre-cancerous and cancerous cervical lesions at one office visit. This avoids patient loss to follow-up and noncompliance and decreases expenses related to medical visits, time and diagnosis.

We will evaluate the benefits and sustainability of the cervical cancer prevention program implementation in order to promote its scaling-up nationwide. Therefore, through collaboration with the Ministry of Health and Population in Haiti, we will promote the integrated model implemented at Hôpital Foyer Saint Camille to convince stakeholders of the need to introduce the program nation-wide. We will support the Ministry of Health to identify the appropriate strategy to provide Cervical Cancer Prevention and Treatment to the most vulnerable women in the population.

Activities:

1. Collect quantitative and qualitative data for scaling up cervical cancer prevention in other major health facilities in the country.
2. Conduct a cost-benefit analysis of the project implementation.
3. Dissemination of the project achievements to national and international stakeholders through meetings, conferences and publications.
4. Report completed and accurate cervical cancer and HPV vaccination surveillance data to the National Cancer Registry.
5. Prepare a report for funders and recommendations to the Haitian Ministry of Health and Population to adopt policies for implementing the “See, Diagnose, and Treat” approach for cervical cancer screening, diagnosis and treatment in Haiti.
6. Explore the possibility of implementing HPV detection as a less invasive and cost-effective method for screening and prevention of HPV and expanding these strategies into the non-HIV infected population.

Research Methodology

Cost-Benefit Analysis

The Cost-Benefit Analysis (CBA) analysis will estimate the equivalent money value of the benefits and costs of establishing cervical cancer prevention program for HIV-positive women at HFSC. The evidence generated from this analysis will serve to evaluate they it is worthwhile to scale-up the project and to convince the Haitian Ministry of Health to adopt policies for implementing the "See, Diagnose, and Treat" approach for cervical cancer in Haiti. The benefits and costs will be expressed in terms of US dollars and the inflation rate in Haiti at the time of the analysis. The costing analysis will be performed using the WHO C4P-ST Excel tool.

The C4P-ST tool will be customized to estimate cost comparison for different strategies either at the intervention level or at the health facility level. The parameters in Table 3 below will be taken into consideration during the analysis

Table 3. Cost per procedure

	Costs with No Interventions	Costs with Interventions
HPV Vaccines		
Personnel		
Supplies		
Total		
VIA		
Personnel		
Supplies		
Equipment		
Total		
Colposcopy/LEEP/Cryotherapy		
Personnel		
Supplies		
Equipment		
Total		
HPV DNA and Genotyping		
Personnel		
Supplies		
Equipment		
Lab/transport		
Total		

The benefits will be calculated using the DALYs for HPV vaccination coverage, cervical cancer screened, diagnosed and treated for cervical cancer in low income countries (Campos, Sharma, et al., 2017). The benefits and costs will be expressed in terms of US dollars and the inflation rate in Haiti at the time of the analysis The benefit-cost ration will be analysed for each intervention will be compared with the total costs of the intervention: Benefit-cost ratio (B / C) and net benefit (B – C). The benefit-cost ratio is found by dividing the intervention's net benefits by its net cost. A ratio greater than $1, suggests that the intervention produces more benefits than it costs. In contrast, a negative ratio comes from a negative numerator or denominator and infers that the benefits have negative costs or negative benefits, respectively (Pan American Health Organization, 2014).

Participants

All HIV-positive females aged 18 years and older will be asked to provide written informed consent to participate before screening with all three methods (HPV vaccine, VIA, HPV molecular testing, and colposcopy). In addition, parents or guardians of HIV-positive females under 18 years old will be asked to provide written informed consent.

Procedures

A positive VIA will undergo colposcopy. Cervical tissue material will be collected from colposcopy for molecular HPV DNA and genotype testing. HPV DNA and genotyping results will be received later and will not be used to determine whether LEEP or Cryotherapy treatment would be done.

Data management

Baseline demographic and clinical data such as age, marital status, education level, smoking habits, current method of contraception, pregnancy history, knowledge about HPV, HPV vaccine and related cervical cancer, cytology results, HIV viral load, CD4 T-cell count, and clinical findings will be collected during the situational assessment using mixed methods including survey and focus groups. Data requirements for the cost analysis are listed in Table 4 below and will include service costs (HPV vaccination, Screening, Diagnosis, and Treatment) and non-service costs (Microplanning, Training, Communication, Monitoring and Evaluation, and other activities). A "Master Price List" is included as a worksheet within the C4P-ST tool to facilitate cost data collection. The unit costs data for supplies and equipment will be obtained from facility expenditure records and through publicly available data and/or by working with stakeholders and partners in Haiti.

Table 4. Resources to provide HPV vaccination and cervical cancer screening services.

Resource	**Number**	**Details**
Personnel		
Staff nurse	1	Retrieve the day's supplies, set up the rooms. Assisted with VIA/colposcopy/LEEP/Cryotherapy.
Laboratory technologist	1	Perform Pap and HPV DNA/genotyping sample collection, provided screening results.
Medical officer	1	Review all results, provided instruction on whether to call back the women for follow up, and assisted in provision of results as needed. Performed colposcopy/LEEP/Cryotherapy.
Counselor	1	Assist in calling back women and scheduling HPV vaccination and return visits if needed.
Supplies		Gloves, masks, linen savers, cotton swabs, paper towels, hand washing/sanitizing supplies, pens/pencils, forms, files, sanitary towels, acetic acid, paper towels.

Furnishings		One room for screening and one for VIA/colposcopy/LEEP/Cryotherapy procedures contain desks, chairs, examination beds, trolleys, and other medical furnishings.
Other equipment		Speculum, metal receiving dishes, colposcopy machine, punch forceps, digital camera for VIA, monitor for VIA quality control.
Laboratory		
HPV DNA analysis		Sample collection kit, GeneXpert reagent kits.

Epidemiologic monitoring of circulating HPV types in the target

Study intervention

This monitoring of circulating HPV genotyping will be a cross-sectional study using cervical specimen and/or tissue material collected during colposcopy for molecular HPV DNA and genotype testing.

Methods and materials

Viral DNA will be extracted from cervical samples using the QIAamp MinElute virus spin kit (Qiagen, CA), according to in the manufacturer's brochure and as described in the literature (Bansal et al., 2014). To detect HPV-DNA, real-time polymerase chain reaction (RT-PCR) assay will be performed on an ABI 7500 instrument (Applied Biosystems, CA, USA) at the University of Maryland-Baltimore. A positive control (cloned HPV-DNA) and a negative control (nuclease-free deionized water) will be included in each PCR amplification. HPV DNA positivity will be detected by agarose gel electrophoresis.

Real-time PCR-based kits (Qiagen, CA) and Sanger sequencing method (Genewiz, NJ) will be used to identify the genotype(s) in the samples which test positive for HPV DNA.

Participants

HIV-positive aged 18 years and older will be ask to provide written consent to participate before screening with all three methods (VIA, HPV molecular testing and Colposcopy.

Procedures

A positive VIA will undergo colposcopy. Cervical tissue material will be collected from colposcopy for molecular HPV DNA and genotype testing. HPV DNA and genotyping results will be received later and will not be used to determine whether LEEP or Cryotherapy treatment would be done.

Data management

Demographic and clinical characteristics of HIV-positive women data will be collected from medical records and laboratory logbooks.

Statistical analysis

Data analysis will be performed using SPSS V.20, Stata 13, or the latest version of R to analyze the characteristics above-mentioned. Descriptive statistical analysis and other appropriate statistical tests of associations (odds ratios, chi-square and confidence intervals) will also be calculated. Calculation of predictive values of current HPV testing will be done in comparison with VIA and colposcopy. Patient demographic and clinical characteristics including age, marital status, education level, smoking habits, current method of contraception, pregnancy history, knowledge about HPV, HPV vaccine and related cervical cancer, cytology results, HIV viral load, CD4 T-cell count, and clinical

findings will be analyzed using frequency distributions. Crude association between HPV positivity and each of the previously mentioned characteristics will be assessed using the chi-squared test. Significance level will be considered as P <0.05 and unadjusted odds ratios (OR) will be reported with their corresponding 95% confidence intervals (CI).

Dissemination, notification, and reporting of results

A report will be prepared every month to inform the HIV program at HFSC on the circulating HPV, and the same report will be provided to the National Cancer Registry. The HPV vaccine effectiveness evaluation will be performed annually on the first cohort of HIV patients receiving the HPV vaccines during the first year of the project. The results will be disseminated to HFSC supervisory board, the Ministry of Health and stakeholders. Conference abstracts and manuscripts will be developed for submission to national or international conferences and scientific journals.

Project Approach: Theory of Change

Problem statement	Women infected with the Human Immunodeficiency Virus (HIV) living in Haiti are at great risk of cervical cancer because of the lack of effective strategies for the prevention, detection, and treatment of pre-cancerous cervical lesions.	
Outputs	**Outcomes**	**Goals**
1. Health care providers are trained on the HPV vaccination schedule. 2. An operation plan is developed for cervical cancer services in HIV-infected women.	1.1. Hôpital Foyer Saint Camille will have a functioning HPV prevention program. 1.2. Hôpital Foyer Saint Camille will be provided with HPV vaccines, supplies and equipment to maintain the cold chain	1. This project will design an integrative HPV prevention program to provide HPV vaccination and cervical cancer services to HIV-positive female adolescents and women seeking care at Hôpital Foyer Saint Camille.

1. 100% Health care providers trained on "See, Diagnose, and Treat" cervical cancer services. 2. 100% HIV-positive women are screened or treated using the "See, Diagnose, and Treat" cervical cancer protocol. 3. HIV-negative access to low-cost cervical cancer services.	2.1 At the end of the project, Hôpital Foyer Saint Camille will have full capacity to provide high quality and affordable "See, Diagnose, and Treat" cervical cancer services including clinical care and HPV Point-of-Care molecular testing.	2. In response to the Request for Application, this proposal will strengthen Hôpital Foyer Saint Camille's capacity to provide a HPV Vaccination and "See, Diagnose, and Treat" cervical cancer services for HIV-positive women.
3.1. Complete and accurate cervical cancer and HPV vaccination surveillance data are reported to the National Cancer Registry. 3.2. The "See, Diagnose, and Treat" approach is presented to national and international stakeholders through meetings, conferences and publications.	3.1 Following the evidence generated from project, the Haitian Ministry of Health will adopt policies for implementing the "See, Diagnose, and Treat" approach for cervical cancers screening, diagnosis and treatment in Haiti.	3. The proposal intends to use the Hôpital Foyer Saint Camille Model to promote the scaling-up of integrated cervical cancer approaches to overcome barriers preventing access to cervical cancer services for disadvantaged female adolescents and women in Haiti.

Innovation and Affordability

a) The implementation of Pap smear-based screening services can be challenging in low-resource healthcare facilities such as Hôpital Foyer Saint Camille due to the scarcity of pathologists capable of performing the Pap-smear cytology leading to long delays in the return of results. In addition, limited health budgets constitute a major challenge to sustain this procedure in the long-term. To overcome these barriers we propose an innovative and

affordable “See, Diagnose, and Treat” intervention for routine screening and treatment of HPV infections and cervical abnormalities for HIV infected women in particular. The “See, Diagnose, and Treat” procedure, combined with POC HPV molecular testing, colposcopy and treatment of the cervical lesions in one visit, have proven to improve patient compliance and reduce treatment costs, and emotional stress and anxiety for the women (Ebisch et al., 2016). Therefore, through this project we will reinforce the existing clinical and laboratory capacity to efficiently provide one-day screening, detection, diagnosis, and treatment for cervical cancer for HIV positive women. This project is innovative because it will build on existing capacity and use inexpensive medical supplies and equipment like vinegar, colposcope, speculum and a light source, to make the Cervical Cancer Prevention and Treatment Program affordable and accessible for any low-income woman living in Haiti. While reducing the procedure’s cost to the lowest sustainable price, this approach will alleviate unreasonable financial burden on the hospital, the donors, individuals, or other payers. In turn, HIV positive females aged 9 to 26 years and sexually active HIV-positive females aged 18 years and older visiting HFSC will have access to the Cervical Cancer Prevention and Treatment Program as recommended by the WHO guidelines.

Expected Impact

A statistical modelling study predicts that the implementation of HPV-based screening twice per lifetime at age 35 to 45 years in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert a total of 12.5-13.4 million cases in the next 50 years (Simms et al., 2019). After five years of implementing this project, we expect achieving full coverage of HPV vaccination and services for female adolescents aged 9 to

26 years old and HIV-positive women receiving care at Hôpital Foyer Saint-Camille. Achieving this goal will positively impact the lives of women and their families by decreasing mortality and morbidity related to cervical cancer for our target population, improve their quality of life, and overcoming the economic burden to access cervical cancer prevention, care and treatment the most vulnerable populations.

This initiative will contribute to catalyze more investments for HPV vaccination and cervical cancer screen-and-treat programs in low-income health facilities in Haiti in order to mitigate the burden of cervical cancer while maximizing public health and economic impact the health system general.

Timeline

Project Phases	Activities	YEAR 1				YEAR 2				YEAR 3				YEAR 4				YEAR 5			
		Q1 2020	Q2 2020	Q3 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Q1 2023	Q2 2023	Q3 2023	Q4 2023	Q1 2024	Q2 2024	Q3 2024	Q4 2024
GOAL 1: This project will design an integrative HPV prevention program to provide HPV vaccination and cervical cancer services to HIV-positive adolescents and women seeking care at hospital Foyer Saint Camille.																					
Expected Outcome: Hospital Foyer Saint Camille will have an operational plan for implementing cervical cancer cervices.																					
1. Planning	Sign Grant award with																				
	Recruit project staff																				
	Develop Situation Assessment tools																				
	Develop annual work plan																				
	Develop scope of work for the consultant																				
2. Pre-Implementation Phase	Perform Situation Assessment																				
	Perform Formative needs assessment																				
	Data collection and analysis																				
	Initiate discussion with key stakeholders including MoH, UMB, GAVI																				
	Prepare operational plan																				
	Develop a procurement plan and procure necessary project equipment and materials																				
	Design HPV vaccination program Develop the "Same-day See-and-Treat" protocol																				
	Signature collaborative agreement between partners/stakeholders																				
GOAL 2: This project will catalyze the implementation of an integrated cervical cancer program encompassing HPV vaccination, "Same Day See-and-Treat, and point-of-care (POC) molecular testing																					
Expected Outcome: Hospital Foyer Saint Camille will have full capacity to provide HPV vaccines high quality and affordable "same-day" cervical cancer services including clinical care and HPV point-of-care (POC) molecular testing to adolescents and women seeking care at the Hospital.																					
3. 1. Implementation Phase I	Development of training program on primary and																				
	Conduct training sessions																				
	Launch the HPV vaccination program at HFSC																				
	Pilot the integrated routine Cervical Cancer "Same day See and-Treat" services																				
3.2. Implementation Phase II	Full implementation of the Cervical Cancer "Same-day See-and Treat" services																				
	Establish a hospital referral network to refer for surgery																				
4. Monitoring and Evaluation	Perform Mid-project Monitoring and evaluation																				
	Collect quantitative and qualitative for cost-benefit analysis																				
	Project bi-annual performance review																				
GOAL 3: The proposal intends to use the Hospital Foyer Saint Camille Model to promote the scaling-up of the integrated cervical cancer approaches to overcome barriers preventing access to cervical cancer services for disadvantaged adolescents and women in Haiti																					
Expected Outcome: Following the evidence generated from project, the Haitian Ministry of Health and its patners will adopt policies and public health interventions for implementing the "same-day" approach for cervical cancers screening, diagnosis and treatment in Haiti																					
5.Surveillance	Provide quarterly data HPV vaccination and Cervical cancer trends to the national Cancer Registry																				
	Analyze Cervical Cancer trends and make appropriate programmatic decisions																				
6. Reporting and Scaling-up	Develop donor report and share recommendations with the Haitian Ministry of health																				
	Dissemination of the project achievements through workshop, conferences, meetings and publications																				
	Initiate discussion with the MoH and key stakeholders to advocate and identifying the most effective delivery channels to provide HPV vaccination to the most at risk adolescents and cervical cancer services to the most vulnerable women in the population																				

Organizations

Hôpital Foyer Sainte Camille, Haiti

Hôpital Foyer Sainte Camille has established its HIV/AIDS program in 2005 with the objective of providing care to children and women exposed or infected with HIV. Its catchment area includes Cité Soleil and Canaan, two major slums north of Port-au-Prince, the capital of Haiti. The program focuses on the treatment of HIV-positive women and children and provides education and food support for affected families. The program also provides care to HIV-positive children and adolescents living in orphanages.

As of June 2019, the hospital has a cohort of 923 patients, 677 of which are on ART. Over the past 5 years, the funds received through a partnership with CDC-PEPFAR via the International Training and Education Center for Health (I-TECH) and the Catholic Medical Mission Board (CMMB), have helped implement and strengthen the HIV program.

After more than fourteen years of diligent work in the management of patients with HIV and in the prevention and elimination of the transmission of infection from mother to child, HFSC has positively positioned itself to be the successful applicant for this Request for Proposal. If awarded, we will strengthen the existing infrastructures to expand toward an integrated services enabled to provide primary and secondary HPV and Cervical Cancer Program for HIV affected patients and individuals living in HFSC's catchment area.

University of Maryland Baltimore, USA

This proposal will help establish collaboration with the University of Maryland Baltimore, an international partner with experience with cervical cancer management in HIV-positive women. The University of Maryland will provide hands-on training in colposcopy, LEEP,

and cryotherapy procedures for HFSC staff. This collaboration will strengthen the standard of training to the highest level, allowing the staff to provide better quality of care and treatment to the beneficiaries of this project

Evaluation and Dissemination

The project will be evaluated in three phases:

Baseline evaluation: A baseline evaluation will be conducted at the beginning of the project during the situational and needs assessments. The information collected at this phase will contribute to develop the operation plan and collected community insights on perceptions, knowledge, needs and attitudes on HPV infection and Cervical Cancer Prevention and Treatment Program.

Quarterly evaluation: After implementation of the HPV program and Cervical Cancer Prevention and Treatment Program at HFSC, we will conduct quarterly monitoring and evaluation in order to collect epidemiologic data on the HPV vaccination and trends of HPV infection and cervical cancer at HFSC. This project will contribute to report complete and accurate case-based cervical cancer surveillance data to the National Cancer Registry at the Ministry of Health. We will also collect data to assess the effectiveness and challenges related to the project rollout. The collected information will help to adjust the operation plan to better meet the needs of the beneficiaries.

Final evaluation: This phase will consist of the analysis of the project achievements with regards to the set goals and objectives. In addition, we plan to perform a cost-benefit analysis of this project this project and assess the satisfaction level of the beneficiaries. The

information collected through this support the elaboration of the final report and recommendations for further public health interventions.

Sustainability and multiplying impact

This proposal strategy for sustainability includes building capacity and transferring skills to the HFSC healthcare providers to efficiently managing HPV primary and secondary prevention program and provide high quality of care to the patients. The project will also ensure context-specific interventions and build on existing structures to ensure sustainability through the promotion of the adoption of inexpensive interventions to make the Cervical Cancer Prevention and Treatment Program affordable and accessible for any low-income woman living in Haiti. We will catalyze our approach impact through collaboration with the Haitian Ministry of Health, local and global partners (research organizations, government and NGOs) to pilot, and scale up the HPV vaccination and the same-day “See, Diagnose, and Treat” intervention. By using evidence from our project we will collaborate with our partners to carry out advocacy to influence national policy for implementing inexpensive and affordable Cervical Cancer Prevention and Treatment Program nationwide. We will also disseminate our model through networking with donor-funded forums, thematic conferences, publications and university research programs.

Ethical considerations

This project will be implemented primarily to improve health service delivery through Cervical Cancer Prevention and Treatment services according to the WHO guidelines. The project will collect cervical tissue material from women at the time of colposcopy. This

tissue will be preserved and used later for further HPV molecular genotyping testing in order to characterize HPV types. Therefore, we will request Institutional Review Board (IRB) review and approval from HFSC and the University of Maryland.

During the formative needs assessment as well as during the final evaluation, human subjects will be invited to participate either via focus groups or interviews or surveys. In order to align with the NIH requirements, we will ensure that the project team obtains the approval from the HFSC IRB committee prior the activities; we will ensure that written informed consent and/or assent for minors is obtained from all participants. Although the project plans to support health services for females aged 9 to 26 years old, we will not interview adolescents under 18 years old. However, epidemiologic and demographic data related to individuals will be coded before any analysis for report and dissemination. All data will be kept confidential during their collection, analysis, and dissemination.

References

Bansal, D., Elmi, A. A., Skariah, S., Haddad, P., Abu-Raddad, L. J., Al Hamadi, A. H., Mohamed-Nady, N., Affifi, N. M., Ghedira, R., Hassen, E., Al-Thani, A. A., Al-Ansari, A. A., & Sultan, A. A. (2014). Molecular epidemiology and genotype distribution of Human Papillomavirus (HPV) among Arab women in the State of Qatar. *J Transl Med, 12*, 300. doi:10.1186/s12967-014-0300-4

Bruni, L., Diaz, M., Barrionuevo-Rosas, L., Herrero, R., Bray, F., Bosch, F. X., de Sanjose, S., & Castellsague, X. (2016). Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health, 4*(7), e453-463. doi:10.1016/s2214-109x(16)30099-7

Campos, N. G., Sharma, M., Clark, A., Lee, K., Geng, F., Regan, C., Kim, J., & Resch, S. (2017). The health and economic impact of scaling cervical cancer prevention in 50 low- and lower-middle-income countries. *Int J Gynaecol Obstet, 138 Suppl 1*, 47-56. doi:10.1002/ijgo.12184

Campos, N. G., Tsu, V., Jeronimo, J., Mvundura, M., & Kim, J. J. (2017). Estimating the value of point-of-care HPV testing in three low- and middle-income countries: a modeling study. *BMC Cancer, 17*(1), 791. doi:10.1186/s12885-017-3786-3

Centers for Disease Control and Prevention. (2019). *HPV Coverage Data*. USA Retrieved from https://www.cdc.gov/hpv/hcp/vacc-coverage/index.html

Chaturvedi, A. K., Madeleine, M. M., Biggar, R. J., & Engels, E. A. (2009). Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst, 101*(16), 1120-1130. doi:10.1093/jnci/djp205

Chirenje, Z. M. (2005). HIV and cancer of the cervix. *Best Pract Res Clin Obstet Gynaecol, 19*(2), 269-276. doi:10.1016/j.bpobgyn.2004.10.002

Clifford, G. M., Tully, S., & Franceschi, S. (2017). Carcinogenicity of Human Papillomavirus (HPV) Types in HIV-Positive Women: A Meta-Analysis From HPV Infection to Cervical Cancer. *Clin Infect Dis, 64*(9), 1228-1235. doi:10.1093/cid/cix135

DeGennaro, V., Jr., Shafer, M., Kelly, M., Cornely, J. R., & Bernard, J., Jr. (2019). Cervical cancer treatment in Haiti: A vertically-integrated model for low-resource settings. *Gynecol Oncol Rep, 28*, 71-75. doi:10.1016/j.gore.2019.03.009

Ebisch, R. M., Rovers, M. M., Bosgraaf, R. P., van der Pluijm-Schouten, H. W., Melchers, W. J., van den Akker, P. A., Massuger, L. F., & Bekkers, R. L. (2016). Evidence supporting see-and-treat management of cervical intraepithelial neoplasia: a systematic review and meta-analysis. *Bjog, 123*(1), 59-66. doi:10.1111/1471-0528.13530

Einstein, M. H., Smith, K. M., Davis, T. E., Schmeler, K. M., Ferris, D. G., Savage, A. H., Gray, J. E., Stoler, M. H., Wright, T. C., Jr., Ferenczy, A., & Castle, P. E. (2014). Clinical evaluation of the cartridge-based GeneXpert human papillomavirus assay in women referred for colposcopy. *J Clin Microbiol, 52*(6), 2089-2095. doi:10.1128/jcm.00176-14

Ghebre, R. G., Grover, S., Xu, M. J., Chuang, L. T., & Simonds, H. (2017). Cervical cancer control in HIV-infected women: Past, present and future. *Gynecol Oncol Rep, 21*, 101-108. doi:10.1016/j.gore.2017.07.009

Goldie, S. J., Diaz, M., Constenla, D., Alvis, N., Andrus, J. K., & Kim, S. Y. (2008). Mathematical models of cervical cancer prevention in Latin America and the Caribbean. *Vaccine, 26 Suppl 11*, L59-72. doi:10.1016/j.vaccine.2008.05.063

Gradissimo, A., & Burk, R. D. (2017). Molecular tests potentially improving HPV screening and genotyping for cervical cancer prevention. *Expert Rev Mol Diagn, 17*(4), 379-391. doi:10.1080/14737159.2017.1293525

IARC, I. A. f. R. o. C. (2019). *Haiti: Human Papillomavirus and Related Cancers, Fact Sheet 2018*. Retrieved from https://hpvcentre.net/

IHME, & Evaluation, I. f. H. M. a. (2018). Haiti - Government Health expenditure. Retrieved from http://www.healthdata.org/haiti

Keller, M. J., Burk, R. D., Massad, L. S., Eltoum, I. E., Hessol, N. A., Anastos, K., Xie, X., Minkoff, H., Xue, X., Reimers, L. L., Kuniholm, M., D'Souza, G., Colie, C., Aouizerat, B., Palefsky, J. M., & Strickler, H. D. (2018). Racial differences in human papilloma virus types amongst United States women with HIV and cervical precancer. *Aids, 32*(18), 2821-2826. doi:10.1097/qad.0000000000002005

Kim, J., Bell, C., Sun, M., Kliewer, G., Xu, L., McInerney, M., Svenson, L. W., & Yang, H. (2016). Effect of human papillomavirus vaccination on cervical cancer screening in Alberta. *Cmaj, 188*(12), E281-e288. doi:10.1503/cmaj.151528

Kuhn, L., & Denny, L. (2017). The time is now to implement HPV testing for primary screening in low resource settings. *Prev Med, 98*, 42-44. doi:10.1016/j.ypmed.2016.12.030

Lince-Deroche, N., Phiri, J., Michelow, P., Smith, J. S., & Firnhaber, C. (2015). Costs and Cost Effectiveness of Three Approaches for Cervical Cancer Screening

among HIV-Positive Women in Johannesburg, South Africa. *PLoS One, 10*(11), e0141969. doi:10.1371/journal.pone.0141969

Luciani, S., & Andrus, J. K. (2008). A Pan American Health Organization strategy for cervical cancer prevention and control in Latin America and the Caribbean. *Reprod Health Matters, 16*(32), 59-66. doi:10.1016/s0968-8080(08)32405-7

Mandigo, M., Frett, B., Laurent, J. R., Bishop, I., Raymondville, M., Marsh, S., & Kobetz, E. (2015). Pairing community health workers with HPV self-sampling for cervical cancer prevention in rural Haiti. *Int J Gynaecol Obstet, 128*(3), 206-210. doi:10.1016/j.ijgo.2014.09.016

Mapanga, W., Girdler-Brown, B., Feresu, S. A., Chipato, T., & Singh, E. (2018). Prevention of cervical cancer in HIV-seropositive women from developing countries through cervical cancer screening: a systematic review. *Syst Rev, 7*(1), 198. doi:10.1186/s13643-018-0874-7

Pan American Health Organization. (2014). *Cost-Benefit Analysis Methodology*. Retrieved from https://www.paho.org/disasters/index.php?option=com_docman&view=download&alias=2178-smart-hospitals-toolkit-cost-benefit-analysis-cba&category_slug=smart-hospitals-toolkit&Itemid=1179&lang=en

Parkhurst, J. O., & Vulimiri, M. (2013). Cervical cancer and the global health agenda: Insights from multiple policy-analysis frameworks. *Glob Public Health, 8*(10), 1093-1108. doi:10.1080/17441692.2013.850524

Riviere, C. (2010). *A study of HPV and cervical disease in HIV infected women enrolled in an Early versus Standard ART in Haiti.* (Master in Science Masters' Projects), Weill Cornell University,

Ronco, G., Dillner, J., Elfstrom, K. M., Tunesi, S., Snijders, P. J., Arbyn, M., Kitchener, H., Segnan, N., Gilham, C., Giorgi-Rossi, P., Berkhof, J., Peto, J., & Meijer, C. J. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet, 383*(9916), 524-532. doi:10.1016/s0140-6736(13)62218-7

Sankaranarayanan, R., Anorlu, R., Sangwa-Lugoma, G., & Denny, L. A. (2013). Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in sub-Saharan Africa. *Vaccine, 31 Suppl 5*, F47-52. doi:10.1016/j.vaccine.2012.06.066

Simms, K. T., Steinberg, J., Caruana, M., Smith, M. A., Lew, J. B., Soerjomataram, I., Castle, P. E., Bray, F., & Canfell, K. (2019). Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. *Lancet Oncol, 20*(3), 394-407. doi:10.1016/S1470-2045(18)30836-2

Torre, L. A., Islami, F., Siegel, R. L., Ward, E. M., & Jemal, A. (2017). Global Cancer in Women: Burden and Trends. *Cancer Epidemiol Biomarkers Prev, 26*(4), 444-457. doi:10.1158/1055-9965.Epi-16-0858

Van Dyne, E. A., Hallowell, B. D., Saraiya, M., Senkomago, V., Patel, S. A., Agrawal, S., Ghosh, A., Saraf, D., Mehrotra, R., & Dhillon, P. K. (2019). Establishing

Baseline Cervical Cancer Screening Coverage - India, 2015-2016. *MMWR Morb Mortal Wkly Rep, 68*(1), 14-19. doi:10.15585/mmwr.mm6801a4

Walker, T. Y., Elam-Evans, L. D., Yankey, D., Markowitz, L. E., Williams, C. L., Mbaeyi, S. A., Fredua, B., & Stokley, S. (2018). National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2017. *MMWR Morb Mortal Wkly Rep, 67*(33), 909-917. doi:10.15585/mmwr.mm6733a1

World Health Organization. (2010). *Human papillomavirus laboratory manual*. Retrieved from Geneva: https://www.who.int/immunization/hpv/learn/hpv_laboratory_manual__who_ivb_2009_2010.pdf

World Health Organization. (2013). *Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva: World Health Organization* (978-92-4-154869-4). Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK195239/

World Health Organization. (2016). *Towards the Elimination of Cervical Cancer*. Retrieved from https://www.who.int/ncds/un-task-force/background-paper-cervical-cancer-partners-meeting-december2016.pdf

World Health Organization. (2018). *Call for Action: An NCD We Can Overcome*. Retrieved from https://www.who.int/reproductivehealth/DG_Call-to-Action.pdf?ua=1

World Health Organization. (2019). Retrieved from https://www.who.int/ncds/surveillance/data-toolkit-for-cervical-cancer-prevention-control/en/

Zahedi, L., Sizemore, E., Malcolm, S., Grossniklaus, E., & Nwosu, O. (2014). Knowledge, attitudes and practices regarding cervical cancer and screening among Haitian health care workers. *Int J Environ Res Public Health, 11*(11), 11541-11552. doi:10.3390/ijerph111111541

http://apps.who.int/iris/bitstream/handle/10665/94830/9789241548694_eng.pdf;jsessionid=4D90949BAC825E711520EDAE466665FB?sequence=1

https://unitaid.org/call-for-proposal/preventing-deaths-from-cervical-cancer/#en