

Identifying Optimal Cervical Cancer Prevention Strategies for HIV-positive
Women in Senegal, West Africa – Quantification of the Natural History of HPV
Among HIV-positive Women and Markov Cohort Cost-Effectiveness Analyses

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Dedication

This thesis is dedicated to Orlo and Marciel for instilling the importance of both informal and formal education, Marguerite for demonstrating that gleeful wildness is appropriate and healthy at any age, and Llyod for inspiring a humbling connection to nature.

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ABSTRACT

Objective. The interaction between human immunodeficiency virus (HIV) and human papillomavirus (HPV) results in an increased burden of cervical cancer among HIV-positive women. This research aims to shed light on the important topic of HIV/HPV co-infection with the goal of informing HPV disease prevention efforts. Specifically, using longitudinal data we estimated the natural history of HPV and cervical cancer among HIV-positive women to inform cost-effectiveness modeling aimed at identifying optimal targeted prevention approaches for this high-risk population.

Methods. In total 1,277 women (45% positive for HIV-1 and/or HIV-2) were followed for an average of two years in Senegal, West Africa between 1994 and 2010. Cytology and HPV DNA testing were performed at approximately 4-month intervals. Competing risk modeling was used to estimate rates for transitioning between three clinical relevant natural history stages (*Normal*, *HPV*, and *HSIL*) for HIV-positive and HIV-negative women separately. Markov cohort modeling was used to simulate the impact of various cervical cancer screening strategies among HIV-positive women. Specifically, we compared the relative cost-effectiveness of six screening strategies (Hybrid Capture 2 HPV testing, rapid HPV testing, cytology, visual inspection with acetic acid (VIA), HPV testing followed by cytology triage, and HPV testing followed by VIA triage) and five screening frequencies using projected life expectancy and incremental cost-effectiveness ratios (ICER). Further, the potential cost-effectiveness of HPV vaccination at the time of HIV diagnosis was simulated under various theoretical effectiveness scenarios. One-way and probabilistic sensitivity analyses were conducted to explore the impact of uncertainty on results.

Results. HIV-positive women had significantly higher rates of progression and lower rates of regression compared to HIV-negative women (i.e. adverse transitions). Among those with HIV infection with multiple HPV types, HPV-16/18, HIV-1, and CD4+ count <200 were associated with adverse transitions. Across a broad range of screening scenarios, VIA was identified as the most cost-effective and contextually feasible screening approach. Compared to no screening, annual VIA resulted in an average

discounted increased life expectancy of 1.7 months and a 40% reduction in cervical cancer incidence with an ICER of I\$1,500 per life year saved. High underlying HPV prevalence among HIV-positive women significantly reduced the cost-effectiveness of HPV testing. HPV vaccination was only cost-effective under optimal vaccine efficacy and/or costing scenarios. Specifically, with costs \geq I\$31 vaccination became dominated when vaccine efficacy fell below approximately 70% and 40% for reducing transitions from *Normal* to *HPV-16/18* and *HPV-Other* states, respectively.

Conclusions. High rates of adverse transitions indicate that targeted screening for the growing population of HIV-positive women in Africa is needed. Based on World Health Organization criterion for cost-effectiveness, targeted VIA screening represents an important prevention opportunity among this high-risk population. With lower vaccine-induced titer levels reported among adult HIV-positive women and a potential corresponding reduction in vaccine efficacy, HPV vaccination costs must be reduced for primary prevention to be cost-effective in comparison to screening. Efforts to implement targeted screening, reduce vaccine costs, develop therapeutic vaccines, and evaluate upcoming HPV antiviral treatments should be made.

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A. DISSERTATION OVERVIEW

A.1 Public Health Challenge

Human papillomavirus (HPV) disproportionately affects women who are seropositive for human immunodeficiency virus (HIV), despite advances in and increased access to HIV treatment. Significant efforts have been made to better understand the complex relationship between HPV and HIV in order to reduce HPV associated morbidity and mortality among HIV-positive women; however, much remains unknown. This research aims to shed light on the important topic of HIV/HPV co-infection with the express goal of informing HPV disease prevention efforts.

The following research is based on three key converging areas of science. First, over the past two decades a series of National Cancer Institute funded studies in Senegal, Africa have examined the impact of cervical HPV infection among HIV-negative and HIV-positive participants. Collectively this research, in concert with other studies conducted throughout the world, has established that cervical HPV infection disproportionately affects women who are HIV-positive. Specifically, HIV-positive women are at increased risk for acquiring cervical HPV and are more likely to have persistent infections which progress to dysplasia and invasive cervical cancer. Second, several key articles published in the past decade have demonstrated that early initiation and continuous use of highly active anti-retroviral therapy (ART) significantly reduces the morbidity and mortality associated with HIV. However, the impact of ART on HPV-associated disease remains unclear. While ART significantly reduces other opportunistic infections, research currently indicates that risk of cervical cancer appears to be largely unaffected by ART use. Further, ART increases life expectancy providing additional time to acquire and develop HPV-associated disease which may lead to actual increases in cervical cancer among HIV-positive women. Third, cervical cancer prevention programs (namely, vaccination and screening) are not generally available in sub-Saharan Africa (SSA). Part of the barrier to implementation of prevention programs is that the most effective and comprehensive strategy for HIV-positive women living in SSA remains unknown.

A.2 Specific Aims

Using data previously collected as part of a series of studies in Senegal the following research questions were examined:

Manuscript I: What is the natural history of cervical HPV infection (i.e. the probability of transitioning between key states of the natural history) among women who are HIV-positive, and how does this compare to women who are HIV-negative?

Aim: Quantitatively summarize and compare the natural history of cervical HPV infection among HIV-negative and HIV-positive women (e.g. the risk of HPV acquisition, and development and duration of various stages of clinical disease).

Manuscript II: What is the optimal cervical cancer screening strategy for HIV-positive women in sub-Saharan Africa in the era of ART?

Aim: Identify optimal cervical cancer screening strategies for HIV-positive women living in Senegal using cost-effectiveness modeling.

Manuscript III: What is the potential impact of HPV vaccination when applied to HIV-positive women in Senegal? Specifically, under what circumstances (if any) does the HPV vaccine yield meaningful benefits among HIV-positive women?

Aim: Explore the potential impact of the HPV vaccine when applied to HIV-positive women in Senegal (varying efficacy and cost).

These aims collectively serve to identify optimal cervical cancer prevention strategies among the high-risk population of HIV-positive women. Results can be used to directly inform public health policy for reducing HPV-associated morbidity and mortality in Senegal, with potential application to the broader area of SSA.

B. GENERAL BACKGROUND

General literature related to this research is summarized below followed by focused literature reviews presented before each manuscript (in Chapters C, D, and E).

B1. Senegal: Brief Contextual Background

This research is based on longitudinal data collected in Senegal, a small West African country externally bounded by the Atlantic Ocean. The majority of data collection occurred in Dakar, the capital of Senegal. Senegal has a population of roughly 14 million, of which 60% reside in rural areas and 94% identify as Islamic [1]. Approximately, one in three married women is in a polygamous relationship [2-4]. Senegal receives millions of dollars of international aid each year to invest in healthcare services, as well as sustainable agriculture and renewable energy. Average life expectancy is estimated as 60 years for both men and women [1]. In 2007 it was estimated that unemployment was 48%, with 54% of the population living below poverty [1]. The 2013 gross national product (GNP) per capita for Senegal was \$1,050 (for reference Sudan has a GNP of \$1,750) [5]. In 2008, there was one physician for every 20,000 people [6].

B2. Human Papillomavirus

B2.1 Epidemiology and pathogenesis of genital HPV

Human papillomavirus (HPV) is one of the most common sexually transmitted infections in the world [7], and is the necessary cause of genital warts and squamous cervical cancer [8-12]. The cervix is the lower, narrow portion of the uterus that connects the body of the uterus with the top of the vagina or birth canal (Figure 1). Additionally, a number of other potentially life-threatening sequelae result from HPV infection, including cancers of the anus, head and neck, penis, vulva, and vagina, as well as recurrent respiratory papillomatosis [13]. In total, it is estimated that 5.2% of cancers diagnosed worldwide are attributable to HPV [14]. For reference, it is estimated that roughly 16.1% of cancers are attributable to infectious agents and 19% of cancers are attributable to smoking [15, 16]. There are over 100 different types of HPV, of which over 40 infect the genital area [17]. HPV types differ in terms of the type of epithelium

they infect, their ability to evade immune detection, resist immune defenses, and their oncogenic effects. Types are hierarchically categorized based on their oncogenic potential: high-risk (HR-HPV) and low-risk (LR-HPV). High-risk types 16 and 18 collectively account for roughly 70% of HPV-related cancers worldwide [11, 12, 18]. There is evidence of geographical variability in the prevalence of HPV infection. For instance, based on data extracted from 194 studies with a cumulative sample of over one million women with normal cytology, the prevalence of HPV infection in women was 19.6% in West Africa compared to the world average of 11.7% [7, 19]. Notably, these are estimates, the veracity of which depends on the methods used to detect HPV and representativeness of the women sampled. There may also be some degree of geographic variability in the distribution of HPV types (although the majority of cervical cancer is attributable to types 16 and 18 throughout the world) [9].

The primary route of genital HPV transmission is sexual contact [20]. Based on epidemiological evidence, genital HPV is thought to be highly transmissible; however, empirical data on transmission are limited [21, 22]. Notably, the prevalence of HR-HPV is consistently higher than LR-HPV [20, 23]. Previously, this pattern was thought to be entirely due to differences in duration of infection as HR-HPV types are more persistent [23, 24]. However, HR-16 is consistently shown to have the highest *incidence* compared to other types [25, 26]. Similarly, estimates of the incidence of HR-18 are high, although less consistently so [25]. These patterns suggest possible differences in transmission by HPV type.

Cervical HPV infection occurs in the basal cells of the stratified epithelium (the only cells in which the HPV virus can replicate) [27]. The virus infects epithelial tissues through micro-abrasions that expose segments of the basement membrane of the cervix. The HPV viral genome is transported to the nucleus of a basal cell by unknown mechanisms. A complex transcriptional cascade then occurs as the host cell begins to divide and become decreasingly differentiated in the upper layers of the epithelium. These host cells release copies of HPV, facilitating further spread of the virus. Pre-cancerous lesions are classified by two schemes: the Bethesda system differentiates between low- and high-grade squamous intraepithelial lesions (LSIL and HSIL,

respectively), while the Richart system differentiates between cervical intraepithelial (CIN) grades 1, 2, and 3 (Figure 2). Both are used to indicate the progressive nature of pre-cancerous lesions, with invasive cervical cancer occurring when poorly differentiated cells break through the dermis of the cervix.

The vast majority of genital HPV infections are asymptomatic, transient, and naturally resolve without treatment [25]. The average length of HPV infection has been estimated to be roughly seven months for men (penile infection) and eight months for women (cervicovaginal infection) [24, 28], although there is evidence that the duration of penile infections may be even shorter [29]. Worldwide, the prevalence of genital HPV infection peaks between age 20 and 30 [20, 23, 25]. Co-infection with multiple HPV types is common; however, estimates for the prevalence of co-infection vary considerably [30-32]. In those cases in which genital HPV infection does not naturally resolve, pre-cancerous cervical lesions may develop, and if left untreated, can subsequently progress to cervical cancer. The squamocolumnar junction is the area in which cervical cancer is most likely to develop (Figure 1). Cervical cancer may take up to 25 years to develop after HPV infection, leaving a large time period in which to intervene (Figure 3) [33].

B2.2 Genital HPV clearance and acquired immunity

Infections can clear completely; however, they may also remain latent but capable of reactivation [34-36]. There is evidence that risk of acquiring a new HPV infection is independent of prior infection with other types (including prior infection with other phylogenetically related types) [37]. However, it has been shown that prior HPV infection may protect against future infection with the *same* HPV type, although the duration and mechanisms of immunity remain unclear [38]. Research efforts aimed at resolving these important issues are hindered by the lack of a correlate for immunity. Essentially, the presence of detectable antibodies does not necessarily equate to acquired functional immunity and the lack of detectable antibodies does not necessarily equate to the absence of prior exposure [39]. In short, while there is evidence of acquired type specific natural immunity, the proportion of women who developed immunity remains unknown, as well as the extent and duration of the protection afforded.

B2.3 Prophylactic HPV vaccines

There are currently three prophylactic HPV vaccines available: a bivalent vaccine (Cervarix/HPV2) which protects against types 16 and 18, a quadrivalent vaccine (Gardasil4/HPV4) which protects against types 6, 11, 16 and 18, and a nonavalent vaccine (Gardasil9/HPV9) which protects against 16, 18, 31, 33, 45, 52, 58, 6, and 11. HPV2 and HPV4 protect against those types that cause approximately 70% of cervical cancer, while HPV9 protects against those types that collectively cause approximately 90% of cervical cancer [9, 11, 40]. More than 99% of people develop an antibody response to those types included in the respective vaccines [41-43]. Notably, the antibody response to the vaccine is higher than that resulting from natural infection [41]. This is unusual as vaccine induced immune responses are typically less than that incurred through natural infection.

As there is no known serologic correlate of immunity, phase II and III clinical trials conducted in the United States (US) used observed HPV-vaccine type-related incident infection and cervical dysplasia as primary outcomes to determine efficacy. Vaccines have been found to be highly efficacious in preventing HPV-vaccine type-related persistent infection (in males and females) and dysplasia (pre-cancerous lesions in females). Efficacy against HPV vaccine-type related CIN2/3 was found to be 93% for HPV2, 98% for HPV4, and >98% for HPV9 [43-45]. Importantly, HPV2 and HPV4 vaccines induce some cross-protection against certain HPV types that are phylogenetically related to those types included in the vaccine [46-50]. Cross-protection has not been observed in early HPV9 trials [43]. HPV vaccines do not have demonstrated therapeutic benefit in treating existing lesions, although there is evidence suggesting that there are some protective effects among those with prior but not current infection (i.e. HPV seropositive but HPV DNA negative). For instance, in the PATRICIA trial vaccine efficacy for the prevention of HSIL in women with no evidence of current or prior HPV-16/18 infection was 94.6%, compared to 68.8% in women with evidence of prior HPV-16/18 infection [50]. The duration of protection afforded by the vaccines remains unknown. A subsample of participants from phase III clinical trials have been followed for up to 8.5 years with no evidence of waning immunity [51].

Based on evidence that the HPV vaccines are safe and immunogenic among HIV-positive patients the Advisory Committee on Immunization Practices (ACIP) currently recommends HPV vaccination for HIV-positive females and males up to the age of 26 in the US [52-54]. However, the efficacy and duration of immunity afforded by vaccination when applied to the HIV-positive population remains unknown (both for those who are vaccinated prior to becoming HIV-positive and those who are vaccinated while HIV-positive), although several efficacy trials are currently underway [55]. The relative benefit of vaccinating HIV-positive women remains unknown given a multitude of competing health risks, as well as limited resources in nations with high HIV endemicity. Due to these gaps in the literature, international recommendations regarding HPV vaccination among those who are HIV-positive have not been made.

Importantly, HPV vaccination is the most expensive publically funded vaccine; therefore, it is cost-prohibitive for many countries to implement mass vaccination campaigns and there is growing need to examine potential targeted vaccination strategies. As the 3-dose vaccine series is costly and involves multiple clinic visits over the course of six months there is also growing interest in exploring the potential to adopt a 2-dose schedule. Recent clinical trials have found that antibody responses in females were non-inferior up to two years after receiving a 2-dose series compared a 3-dose series [56, 57]. However, one study found that after two years of follow-up girls who received a 2-dose series experienced type-specific waning of immunity [56]. Given inconsistent evidence, further research examining the potential application of a 2-dose series is underway as the economic implications are considerable.

B3. Cervical Cancer

B3.1 Epidemiology of cervical cancer

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide, with an estimated 528,000 new cases and 266,000 deaths in 2012 [58]. Cervical cancer disproportionately impacts low resource nations. For instance, approximately 88% of cervical cancer mortality occurs in low-resource countries which have only 5% of global cancer resources [59, 60]. It is estimated

that cervical cancer represents approximately 35% of cancers among Senegalese women [61]. Of cancers that affect women, cervical cancer results in the most years of life expectancy lost (estimated at 29 years per person among HIV-negative women) [62].

The morbidity and mortality associated with cervical cancer can be drastically reduced with the widespread implementation of routine screening as demonstrated in the US. Between 1955 and 1992, cervical cancer incidence and death rates declined by more than 60% due to routine Papanicolaou tests (cervical cytology) [63]. Of those cases that occur, it is estimated that 56% are among women who had never been screened or had not been screened in the 3 years prior to diagnosis [64]. For context, age-standardized mortality rates for cervical cancer are 25.5, 14.5 and 1.7 for Senegal, South Africa, and the US respectively. In Senegal, cervical survival is roughly 33.6% (compared to 69% in the United States) [61]. There are four stages of cervical cancer (I-IV). Staging is based on the size of the cancerous growth, the location of the growth in the cervix, and the presence of metastatic tumors.

B4. Human Immunodeficiency Virus

B4.1 Epidemiology and pathogenesis of HIV

Today there are more than 35 million people living with HIV/AIDS of whom 70% are in sub-Saharan Africa (1 in 20 adults in SSA are HIV-positive), and 50% are women [65]. There are two types of HIV: HIV-1 and HIV-2. Worldwide, the predominant virus is HIV-1, while the relatively uncommon HIV-2 is concentrated in West Africa. HIV-2 is considered to be a more mild type with a longer incubation period and lower transmissibility [66]. Recent data indicates that HIV-2 is slowly dying out, likely due to lower transmissibility and relative geographic isolation. A trend analysis based on 10,321 women in Senegal found that the relative prevalence of HIV-2 dropped from 54.2% in 1990 to 20.9% in 2009 [67]. For each HIV type, additional sub-classifications exist with slight variations in transmissibility, incubation periods, viral loads, death rates, and responsiveness to treatment [66]. HIV is one of the most variable of human pathogens with 800 distinct genome sequences; thus, it quickly mutates and diversifies within hosts [68]. HIV has such great genetic instability that HIV virus particles within a person are

considered to be a “swarm of highly related but non-identical viral genomes termed quasi-species” (page S8) [68].

HIV is distinct in that the direct target of the infection is the immune system itself. At the micro-level, the virus infects human T-lymphocyte cells which are responsible for cell-mediated immune function. T-lymphocytes have a series of CD4+ protein molecules on their surface. HIV particles lock onto CD4+ protein sites through the gp120 molecule which acts like an arm. Once locked onto a CD4+ protein site, the gp41 molecule (a second, harpoon-like arm) pierces the T-lymphocyte. Cell invasion occurs during which HIV genetic codes are absorbed into the T-lymphocyte cell. Essentially, the cell is hijacked and used as a replication facility for the virus. The host T-lymphocyte cell begins to disintegrate and die, with the new HIV particles released into surrounding blood and tissue to eventually repeat the process. Over the course of years, the virus depletes CD4+ T-lymphocytes and opportunistic infections (OIs) arise. OIs are defined as infections that are more frequent or severe as a result of immunosuppression. OIs capitalize on the suppressed immune system, and represent the principal cause of morbidity and mortality for HIV-positive people.

B4.2 Antiretroviral therapy: guidelines, access, and impact

In 1996 a new form of HIV treatment was introduced, broadly termed highly active anti-retroviral therapy (ART). ART is much more effective than previous treatment strategies in reducing the HIV-associated morbidity and mortality as it diminishes HIV viral loads which subsequently results in improved CD4+ counts and immune reconstitution. Successful treatment has led to profound reductions in OIs. Further, as ART significantly reduces viral loads (to the point that patients may have undetectable levels) risk of HIV transmission is significantly reduced [69-71]. However, some research indicates that the use of ART is associated with increased sexual risk behaviors [72-76]. Thus, there remains uncertainty regarding the actual effect of ART on transmission at the population level.

There was growing evidence supporting early initiation of ART (prior to CD4+ counts falling below 350 cell/ μ L) [77]. For instance, uncontrolled viral replication and chronic inflammation resulting from infection have been found to increase risk of HIV

transmission and contribute to the development of serious non-AIDS events (such as cardiovascular disease and various cancers). Early treatment has been shown to reduce both HIV transmission and the development of serious non-AIDS conditions [77, 78]. Additionally, evidence suggests that although CD4+ recovery may occur on treatment, complete functional recovery may not be achieved [79]. This is likely due to the fact that CD4+ count is one indicator of a complex immune system function. Updated World Health Organization (WHO) treatment guidelines recommend initiating ART when CD4+ cell counts drop below 500 cell/ μ L [80]. After initial treatment, continuous ART use is recommended regardless of CD4+ count [81].

B4.3 Epidemiology of HIV in Senegal

Senegal has one of the lowest rates of HIV in Africa, as 1% of those aged 15-49 are HIV seropositive [82]. However, the prevalence of HIV among sex workers, men who have sex with men, and injection drug users was recently estimated to be 20%, 22% and 10% respectively, demonstrating that distinct sub-groups are disproportionately at risk of acquiring HIV [83]. Additionally, there are some geographical differences in HIV prevalence within Senegal, with those areas surrounding Gambia (a country nested within Senegal) disproportionately impacted by HIV. Importantly, the Senegalese government was one of the first in Africa to formally acknowledge HIV and implement an active response to the epidemic. Due to these efforts, HIV incidence has stabilized in the past decade with roughly 2,000 new cases per year and a total of 40,000 prevalent cases [82]. The WHO estimates that 50-56% of those who are HIV-positive have access to ART therapy (CD4 < 350) in Senegal; above the average for SSA at 37% [82, 84]. This represents a large increase in access over the last decade, partially due to concerted efforts to increase the number of physicians qualified to administer anti-retroviral medication. For instance, in 2001 there were 12 physicians qualified to administer ART, this increased eight-fold to 95 in 2005 [85]. However, access to ART alone does not equate to uptake and adherence, important factors necessary for reducing HIV-associated morbidity and mortality.

B4.4 HIV and the development of cancer

Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer are AIDS-defining events (ADEs). ADEs are those clinical events that signal a change in the health status of an HIV-positive individual (particularly with respect to survival). ADEs are used to define the clinical presentation of AIDS in combination with CD4+ count. Importantly, those with HIV are at increased risk of many types of cancer in comparison to the general population [86]. Although it remains unclear whether HIV is itself directly oncogenic, it is hypothesized to contribute to the development of malignancies through several mechanisms (e.g., chronic inflammation, infection by oncogenic viruses, impaired immune surveillance, imbalances between cellular proliferation and differentiation). Incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma have declined in the era of ART; however, risk of cervical cancer and several non-AIDS defining cancers (e.g. cancers of the lung, liver, anus, lip, mouth, pharynx, and skin, as well as Hodgkin lymphoma) have either remained unaffected by ART or increased likely due to extended life expectancy and complex interactions between HIV, immune function, and adverse responses to ART [87-89].

B5. HPV/HIV Co-infection

B5.1 Overview

There is significant evidence of a synergistic interaction between HIV and HPV, resulting in high HPV-related morbidity and mortality among HIV-positive populations [90]. There are two main theoretical explanations for this interaction [91]. The first explanation maintains that HIV causes systemic immune dysfunction, such that it is incapable of detecting and/or responding to new HPV infections (importantly, this may also lead to the reactivation of latent HPV infections). The second explanation maintains that HIV actually enhances HPV infection by interacting with HPV infected cells. To date, there is evidence to support both of these theories and there is no clear prevailing etiological explanation for this interaction.

HIV-positive women are at increased risk of HPV infection when compared to the general population [3, 92, 93]. For instance, one study found that among HIV-positive

women the odds of developing incident HPV detection were 8.8 times greater than in HIV-negative women [94]. HIV-positive women are more likely to be infected with multiple HPV-types [95-98]. For instance, among 148 South African HIV-positive women, 80% were infected with multiple oncogenic HPV types [97]. Infection with multiple types may be due to the fact that HIV-positive women experience more persistent infection (meaning the infection is less likely to clear and the duration of the infection is therefore longer) [92, 99, 100]. This provides additional time for clinical disease to develop and to transmit the infection. Some studies have found that HIV-positive women have higher HPV viral loads than the general population [93, 101, 102]. The biological mechanism for this remains unclear, but higher viral load is hypothesized to lead to higher transmissibility and extended duration of infection. Overall, studies have shown that HIV-positive women are 1.5 to 8 times more likely to have cervical cancer than HIV-negative women [3, 88, 103-106]. Further, cervical cancer has been observed to occur at an earlier age among HIV-positive women. For instance, in South Africa the mean age at time of diagnosis was 55.2 and 39.8 years for HIV-negative and HIV-positive women respectively [107]. HIV-positive women are also more likely to present with more advanced cancer, particularly when CD4+ count are below 200 [108, 109].

B5.2 The Role of ART, CD4+ count, HIV viral load, age, and HPV type

With the introduction of ART, the morbidity and mortality associated with many opportunistic infections (OIs) has been greatly reduced. However, for reasons that remain unclear, HPV continues to disproportionately affect those who are receiving treatment [90, 103, 110]. At the population level, ART does not appear to reduce incidence of cervical cancer among those who are HIV-positive [88, 106, 111, 112]. However, some observational studies have demonstrated protective effects of ART during earlier stages of HPV natural history, namely with regard to decreased incident pre-cancerous lesions and increased regression [113-118]. For instance, Ahdieh-Grant et al. found that among a cohort of 312 HIV-positive women incident regression increased over time after ART initiation ($p_{\text{trend}} = 0.002$) [113]. Nonetheless, the authors note that the majority of cervical lesions among HIV-positive women did not regress to normal during follow-up, even among those on ART. Similarly, among 714 HIV-positive women, those on ART were

40% more likely to have observed regression from pre-cancerous lesions (after adjustment for CD4+ count) [116].

The fact that ART appears to have little, if any, impact on cervical cancer is illustrative of a recent paradigm shift regarding OIs. In the past, OIs were thought to occur only after the immune system was significantly impaired. With the introduction of ART, it was hypothesized that OIs would become rare as treatment restored immune function. However, research on meningitis, tuberculosis, and HPV indicate that some OIs establish themselves far earlier in the natural history of HIV. In the case of HPV, this observation is somewhat intuitive as the virus is naturally capable of evading the immune system even among those who are HIV-negative. In other words, immune suppression is not necessary for the development of cervical cancer, but an impaired immune system does lead to increased risk and earlier development of cervical cancer. There are two broad explanations for the presence of OIs early in the natural history of HIV infection (which are not mutually exclusive). First, there are biological interactions between some OIs and HIV which have yet to be fully understood. Second, CD4+ count is an imperfect surrogate for immune function. While CD4+ count may be high early in the natural history of HIV (or due to ART) there could be additional indices of immune function that are impaired.

The effect of CD4+ count (independent of ART) on the natural history of HPV appears to be complicated and not yet fully understood. Overall CD4+ count appears to be inversely associated with HPV prevalence, persistence, and pre-cancerous lesions [3, 112, 119-122]. For instance, Delmas et al. found that among 485 HIV-positive women, those with CD4+ counts <200 had approximately twice the prevalence and incidence of pre-cancerous lesions compared to women with CD4+ counts > 500 [119]. Similarly, in a cohort study of 774 HIV-positive women followed for 5.5 years it was shown that incidence of pre-cancerous lesions and risk of progression were greater for those with CD4+ < 500 [112]. Notably, in this study ART was not independently associated with incidence outcomes. Some research has indicated that progression from pre-cancerous lesions to anogenital cancer is independent of CD4+ count [123, 124]. Evidence that women with high CD4+ counts remain at increased risk to HPV infection (compared to

HIV-negative women) may indicate that HIV directly interacts with HPV. This would support the theory that there is a synergist interaction between these two agents.

However, CD4+ count may simply be an incomplete measure of immune function.

HIV plasma viral load is the least understood of these factors and warrants additional research. Several studies have shown a positive association between HIV viral load and the development of clinical HPV-related disease [3, 122, 125, 126]. For instance, among a cohort of 627 women in Senegal, Hawes et al. found a significant positive association between HIV viral load and the development of high-grade squamous intraepithelial lesions (HSIL) [122]. This association was not significant after adjustment for CD4 count. Based on longitudinal data with over 1,800 HIV-positive women, Strickler et al. found evidence of a positive interaction between HIV viral load and HPV infection [126]. Using data from the AIDS Clinical Trials Group, a simulation model aimed at identifying the population level impact of ART found that HIV viral load was marginally associated with prevalent HPV infection (independent of CD4 count) [127]. As HIV viral load is inversely related to CD4+ count, any association between viral load and HPV-related cervical disease simply underscores the importance of ART.

There may be differences in the distribution of HPV types when comparing HIV-positive and HIV-negative women. For instance, a study of approximately 1,200 women in India found that HPV 18 and 16 were the predominant types among all women with prevalent infection; however, among HIV-positive women 53% of oncogenic HPV infections were from types other than 16 and 18 [128]. Differences in the distribution of HPV types have been demonstrated at various stages of clinical cervical disease as well. Based on a meta-analysis of 20 studies throughout the world Clifford et al. found that among women with HSIL, HPV-16 was less common in HIV-positive women, and types considered to be low-risk were more common (Figure 4) [96]. Notably, HIV-positive women were far more likely to be infected with multiple HPV types than HIV-negative women (41.4% verse 6.7% respectively) [96]. Thus, distributional differences may be driven by the increased prevalence of infection with multiple types, and it unknown which type(s) actually caused the development of HSIL. Additionally, based on the analysis of 164 cervical cancer cases in two SSA countries, it was found that type 16 was

less frequent than reports in the rest of the world (49.4% vs. 62.6%), and 18 and 45 were roughly two times more frequent (19.3% vs. 9.4% and 10.3% vs. 5.6% respectively) [129]. Based on this ecological study, the authors of the study posit that the high prevalence of HIV in SSA may drive these geographic HPV type distributional differences. Notably, some research indicates that HIV-negative and HIV-positive populations have similar distributions of HPV [130]. In summary, findings are inconsistent and based on studies which have important methodological limitations. Thus, it is unknown what impact any distributional differences have on HPV-related disease among those who are HIV-positive. Nonetheless, implications in terms of vaccine effectiveness could be profound as vaccines are type specific.

In HIV-negative populations, prevalence of HPV is strongly dependent on age (peaking in the early 20's) which is primarily due to age-related sexual behaviors and acquired immunity. Importantly, data suggests that age is not as strongly associated with HPV prevalence among HIV-positive women, likely due to increased persistence, infection with multiple types, and sexual practices in SSA. For instance, in a cross-sectional study of 498 HIV-positive women in Kenya (age 18 to 55), HR-HPV positivity did not vary significantly by age [118]. Further, based on an analysis of 282 HIV-positive in Cameroon (age 19 to 68), Atashili et al, found that women aged 26 to 59 tended to have a slightly higher prevalence of cervical pre-cancerous lesions than other women, although this was notably non-significant [131]. Among women with CD4+ counts >200, there were no prevalence differences by age. The authors of this study posit that there is little value to age-targeted screening among HIV-positive women.

B6. Decision Modeling: Methodology, Application and Impact

B6.1 Decision modeling in epidemiology

Decision modeling is broadly used to compare the advantages and disadvantages of various policies or interventions. It is undertaken to inform decision-making and/or identify gaps in knowledge that merit future research initiatives. The application of decision modeling to inform public health decision making and future research has grown over the past decade. For example, decision modeling has informed the development of

vaccination recommendations, cervical screening guidelines, colon cancer screening guidelines, environmental regulations, newborn screening practices, consumer product standards, strategies for the use of mass media for public health promotion, legal codes for smoking detectors, measures to increase the safety of blood transfusions and much more. Cost effectiveness analysis (CEA) is a type of decision modeling which provides a systematic, quantitative approach for identifying efficient ways to allocate finite resources. Both the WHO and the World Bank utilize CEA to prioritize and inform practices in resource-limited settings.

B6.2 Overview of the methodology

Decision modeling is a mathematical approach to synthesizing scientific knowledge regarding a certain process of interest (in this case the natural history of HPV) and is used to project key outcomes among a simulated population. In essence, cost-effectiveness models incorporate population behaviors and characteristics, disease rates, and other factors to simulate at the aggregate level how a given intervention may affect a population. Building a deterministic Markov cohort decision model involves four primary steps, outlined briefly below.

- 1.) Epidemiologic data are synthesized and used as key input data for the model. This data is often used to simulate the disease process of interest within a given population.
- 2.) Based on epidemiological data, the natural disease history for a population is simulated by creating 'states'. States categorize an individual's status with regard to the disease of interest. The model then simulates a fixed cohort passing to and from disease states as they age, develop outcomes, or exit the model due to other causes (e.g. death). For instance, in models for AIM II and AIM III women transition back and forth between four key types of states: uninfected, infected with HPV, various stages of HPV-related clinical disease, and death. Synthesized data (from step 1) is used to estimate the probability of transitioning between each state for a given time interval (referred to as the cycle length).
- 3.) Based on the simulated natural history process (from Step 2), key outcomes are compared to observed data to ensure consistency with the epidemiologic data (this

step is referred to as validation and is used to assess consistency of model outcomes with regard to the synthesized data used to construct the model).

4.) Fourth, key interventions of interest are imposed on the simulated cohort. For example, different cervical cancer screening strategies can be simulated and compared using this model to project their potential benefits. Strategies are then compared to identify the optimal strategy using cost-effectiveness ratios. Briefly, cost estimates are based on the financial costs related to screening, diagnosis, and treatment. Effectiveness is measured by either life years or quality-adjusted life years. The strategies are then ranked in order of cost and compared using an incremental cost-effectiveness ratio (ICER). An ICER is calculated using the difference in cost divided by the difference in effectiveness, and represents the cost of an additional unit of effectiveness (e.g. a year of life) that is obtained when implementing a more effective treatment strategy rather than the less effective treatment strategy. Strategies that are more costly and less effective than another are considered 'strongly dominated', while strategies that have higher incremental cost-effectiveness ratios than the next more effective strategy are considered to be 'dominated through extension'. Dominated strategies are not cost-effective relative to other interventions.

Decision modeling allows researchers to: 1) directly compare the effectiveness of various interventions; 2) vary when and how often the interventions are used; and 3) vary assorted population parameters so that the model can be applied to several distinct contextual settings (e.g. the same model can be adapted to identify the best strategy for different populations). Conceptually, decision modeling essentially simulates the unobserved counter-factual (i.e. using observed data we project the unobserved outcomes of various interventions or treatment). Decision modeling can be used to estimate outcomes beyond those reported in research studies, provide insight into key gaps in the literature, identify factors that drive the cost or effectiveness of various intervention strategies, and may be amended as new information emerges.

B7. Conclusion

This research is explicitly directed at informing recommendations for how to best reduce HPV-associated morbidity and mortality among HIV-positive women in Senegal. Specifically, this research aims to: 1) quantify and compare the natural history of cervical HPV infection among HIV-negative and HIV-positive women, 2) use decision modeling to identify optimal cervical cancer screening strategies for HIV-positive women, and 3) examine the potential impact of targeted HPV vaccination on reducing cervical cancer among HIV-positive women. Five primary factors highlight the significance of this research. First, in low resource nations cervical cancer is a leading cause of death for women. Second, cervical cancer disproportionately affects HIV-positive women. Third, HIV is concentrated in SSA. Fourth, cervical cancer among those who are HIV-positive may further increase as earlier initiation of ART and improved ART coverage result in increased life expectancy. Fifth, cervical cancer is essentially entirely preventable but optimal prevention strategies in the context of SSA and among the high-risk population of HIV-positive women remain unknown. Collectively, this research is of significant applied public health importance and directly addresses several gaps in the literature as discussed in further detail in the following chapters.

C. MANUSCRIPT I: A Comparison of the Natural History of HPV Infection and Cervical Abnormalities HIV-positive and HIV-negative Women in Senegal, Africa

C1. Summary

Background. There is evidence of an interaction between human immunodeficiency virus (HIV) and human papillomavirus (HPV) resulting in increased HPV-associated morbidity and cancer mortality among HIV-positive women. This study aims to determine how the natural history of cervical HPV infection differs by HIV status.

Methods. A total of 1,277 women (45% were positive for HIV-1 and/or HIV-2) were followed for an average of two years in Senegal, West Africa between 1994 and 2010. Cytology (with a sub-sample of histology) and HPV DNA testing were performed at approximately 4-month intervals. Competing risk modeling was used to estimate rates for transitioning between three natural history stages: *Normal*, *HPV*, and *HSIL*.

Results. HIV-positive women had significantly higher rates of progression and lower rates of regression compared to HIV-negative women (i.e. adverse transitions). Notably, HIV-positive women had a 2.57 (95% CI: 1.69-3.91; $P < 0.0001$) times higher rate of progression from *HPV* to *HSIL* than HIV-negative women. Among HIV-positive women, infection with multiple HPV types, HPV-16/18, HIV-1, and CD4+ count <200 were associated with adverse transitions.

Conclusions. High rates of adverse transitions indicate that targeted screening for the growing population of HIV-positive women in Africa is needed.

C2. Background

Human papillomavirus (HPV) is the necessary cause of squamous cervical cancer [132], is highly transmissible, and generally acquired near closely after sexual debut [133, 134]. Persistent infection can lead to the development of pre-cancerous lesions which, in the absence of treatment or an effective immune response, can progress to cancer. Approximately 40 genotypes infect the genital tract and are classified hierarchically based on oncogenic potential with high-risk types 16 and 18 accounting for roughly 70% of cervical cancer [11]. There is evidence of an interaction between human

immunodeficiency virus (HIV) and HPV, with HIV-positive women at increased risk for detection of HPV, pre-cancerous cervical lesions, and cervical cancer compared to HIV-negative women [3, 90-92, 96, 99, 103, 122, 135]. Studies have shown that HIV-positive women are 1.5 to 8 times more likely to have cervical cancer than HIV-negative women [3, 88, 103-106]. Although there is no definitive etiological explanation for this interaction, systemic immunosuppression is likely a contributing factor [91].

Despite numerous studies describing the increased burden of HPV and cervical disease among HIV-positive women, few have longitudinally examined the natural history within a single study population and provided direct comparisons to HIV-negative women. Thus, estimates for the probability of transitioning between each natural history stage (i.e. progression and regression) are limited, as well as our understanding of the point at which the natural history of HPV diverges for HIV-positive and HIV-negative women. This study was undertaken to estimate and compare the probability of transitioning between three clinically relevant natural history stages (*Normal*, *HPV*, and *HSIL*) for HIV-positive and HIV-negative women using data from multiple cohort studies conducted in Senegal, West Africa.

C3. Materials and Methods

C3.1 Study population

Data from six cohort studies conducted from 1994 to 2010 in Senegal were used for the present analysis (Table 2). Protocols for each study have been described elsewhere [3, 67, 122, 136-141]. All studies screened women age ≥ 15 presenting at outpatient clinics for participation in longitudinal research with HIV testing at baseline, as well as cervical cytology and HPV DNA sampling roughly every four months for two years. Recruitment occurred at two infectious disease clinics, two family planning clinics, and two sexually transmitted disease clinics serving commercial sex workers (CSWs) in or around Dakar. Studies were approved by the University of Washington and Senegalese Human Subject Review Boards. Consent was obtained from each subject. Data were de-identified and shared variables across the six studies were identified and pooled for analysis.

C3.2 HIV serology and lymphocyte testing

Blood samples were tested for antibody to HIV-1 and HIV-2 using an enzyme-linked immunosorbent assay (ELISA; Genetic Systems, Seattle, WA, USA) or a microwell plate enzyme immunoassay (HIV 1/2 EIA; Sanofi Diagnostics Pasteur, Paris, France). HIV-1 and HIV-2 infections were distinguished by a peptide-based assay, although the assay varied by study (Genie II, Genetic Systems; Multispot, Sanofi Diagnostics Pasteur; Immunocomb II, bispot, Organics, Yavne, Israel). For HIV-positive women, peripheral blood was analyzed with a FACSCCount analyzer (Becton Dickinson Biosciences, San Jose, CA, USA) to determine number of CD4+ cells per microliter.

C3.3 Cytologic and histologic testing

Until 1998 conventional Pap smears were used and evaluated locally in Dakar; thereafter, the Thin Prep monolayer cell preparation system (Cytoc Corp., Boxborough, MA) was used and evaluated by a cytopathologist in Seattle, USA. Results were classified according to the Bethesda system (atypical squamous cells of undetermined significance - ASCUS, low-grade squamous intraepithelial lesion - LSIL, high-grade squamous intraepithelial lesions - HSIL) [142]. All slides obtained prior to 1998, those classified as LSIL or worse, and a random subset of negative slides, were re-read in Seattle.

Protocols for all six parent studies called for colposcopically-directed biopsies and treatment for women with evidence of HSIL or invasive cervical cancer (ICC). However, subject participation for biopsy/treatment was low in earlier studies, in part, due to delays resulting from samples being sent to and re-read in Seattle. With adjustments to study practices and improved communication with participants regarding the importance of monitoring and treatment, colposcopy follow-up in later studies was vastly improved. Representative hemotoxylin-eosin-stained slides were prepared from paraffin-embedded biopsy specimens and reviewed by a blinded study cytopathologist. World Health Organization pathology criteria and terminology were used to classify specimens [137].

C3.4 HPV DNA detection and typing

Polymerase chain reactions (PCRs) assays for detection of HPV DNA were performed, although lab methods evolved over time with expansion of type specific probes (Table 2). Testing was initially performed by use of HPV L1 consensus primers,

HPV type-specific oligonucleotide probes, and a generic probe [143]. This method yielded type-specific identification of HPV 6/11, 16, 18, 31/33/35/39, 45/56, and 51/52. With new probes available in 1998, HPV detection and typing analyses were performed via a PCR-based reverse-line strip test method (Roche Molecular Systems, Alameda, CA) with probes for types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and 84 [144]. In 2000, a Luminex-based testing approach was adopted with additional probes for 61, 62, 64, 67, 69, 70, 71, 72, 81, IS39, and CP6108 [145].

C3.5 Natural history stage classification

In combination with HPV DNA results, cervical histology was used when available, with cytology in all other cases, to classify women at each visit as: *Normal* (defined as HPV-negative), *HPV* (defined as HPV-positive with one or more type in the absence of HSIL), or *HSIL* (defined as HPV-positive with one or more type with the presence of HSIL). Due to a demonstrated lack of reproducibility for cytologic and histologic interpretations of low-grade lesions (i.e. ASCUS, LSIL, and CIN1), these results were not used to inform stage classifications [146]. As transitions to ICC were not examined due to small numbers and possible HSIL treatment effects, these results were excluded.

C3.6 Statistical analyses

The natural history of HPV is multi-directional and non-linear such that women may transition to any other stage (i.e. participants are at risk of more than one mutually exclusive event). Therefore, competing risk modeling was used to estimate cumulative incidence functions and the probability of a specific transition over time [147]. To reduce the complexities arising from interval censoring, follow-up time was set as the midpoint between the visit at which the event of interest or censoring occurred and the preceding visit, an approach which has been used previously in infectious disease research [148]. For each transition, analyses were conducted up to the point at which the cumulative incidence function plateaued and/or there were sparse data.

At each visit, natural history stage was classified as either incident (i.e. the stage differed from the preceding visit) or prevalent (i.e. the baseline visit or the stage was the same as the preceding visit). As HPV can be transient, restricting analyses to women with

incident classification to eliminate left-censoring can actually produce bias. For example, eliminating women who are classified as *Normal* throughout follow-up (prevalent classification), leads to overestimation of the probability of transitioning from *Normal* to *HPV* as only women with prior HPV detection who become HPV-negative during follow-up contribute to incident *Normal*. Thus, to bound results, analyses were calculated separately for prevalent and incident natural history stages. To identify factors influencing the natural history of HPV among HIV-positive women, the following exploratory analyses were conducted: age (≤ 25 vs. > 25), CD4+ count (< 200 vs. ≥ 200), HPV type (16/18 vs. others), HIV type (1 vs. 2), and concurrent infection with multiple HPV types (> 1 vs. 1 type). These analyses were restricted to transitions from *Normal* and *HPV* due to limited numbers for *HSIL*. For HPV-16/18 type specific analyses, women were classified based on the presence of either one of both of these types [149]. Women dually infected with HIV-1 and HIV-2 were removed from HIV type specific analyses due to small numbers (n=52).

Gray's method was used to test for statistical differences in cumulative incidence functions [150]. Robust variances were used when multiple observations from the same woman were included when estimating a transition. Schoenfeld residuals were examined to assess the proportional hazards assumption. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC) and STATA 13 software (StataCorp, College Station, TX).

C4. Results

C4.1 Subject characteristics (Table 3)

Of the 1,277 women, the majority were in their thirties, Muslim, with no more than a primary school education. Fifty-percent were married, 40% of whom were in a polygamous relationship. Forty-five percent of the sample was HIV-positive, of which two-thirds were infected with HIV-1. Antiretroviral therapy (ART) was reported by 27% of the HIV-positive sample. Twenty-five percent were classified as having AIDS (defined as either a CD4+ count less than 200 (cells/ μ L) recorded at any point during follow-up or an AIDS defining event). Median CD4+ count recorded during follow-up was 416

cells/ μ L. HIV-positive women were slightly less likely to be married, had a lower level of education, and were more likely to report using contraception than HIV-negative women. HIV-positive women were also more likely to be commercial sex workers (CSWs), although this was common in both groups due to recruitment from two clinics targeting this population. Most women were followed for over two years, with clinic visits approximately every four months.

C4.2 Progression and regression (Table 4)

Of 1,054 cases of *Normal*, 56.4% were incident. HIV-positive *Normal* women had a 1.62 times higher rate of *HPV* detection than HIV-negative women (95% CI: 1.35-1.95). The 24-month predicted probability of *HPV* detection for HIV-positive women was 0.66 and 0.83 for prevalent and incident classification of *Normal*, respectively, compared to 0.49 and 0.67 for HIV-negative women (Figure 5A). Women identified as incident *Normal* had a 1.64 times higher rate of *HPV* detection than prevalent cases (95% CI: 1.38-1.95). HIV-positive *Normal* women also had a 1.60 times higher rate of progression to *HSIL* than HIV-negative women, although this association was not significant (95% CI: 0.76-3.36). The 24-month predicted probability of *HSIL* for HIV-positive women was 0.04 and 0.07 for prevalent and incident classification of *Normal*, respectively, compared to 0.02 and 0.04 for HIV-negative women (Figure 5B). Women identified as incident *Normal* had a slightly increased rate of progression to *HSIL* than prevalent cases, although this was not significant.

Of 1,233 cases of *HPV* detection, 39.7% were incident. HIV-positive women had a 0.47 times lower rate of regression from *HPV* to *Normal* than HIV-negative women (95% CI: 0.39-0.56). The 24-month predicted probability of regression to *Normal* for HIV-positive women was 0.57 and 0.79 for prevalent and incident *HPV* detection, respectively, compared to 0.83 and 0.96 for HIV-negative women (Figure 5C). Women with incident *HPV* detection had a 1.85 times higher rate of regression to *Normal* than women with prevalent detection (95% CI: 1.58-2.16). HIV-positive women with *HPV* had a 2.57 times higher rate of progression to *HSIL* than HIV-negative women (95% CI: 1.69-3.91). The 24-month predicted probability of progression to *HSIL* for HIV-positive women was 0.18 and 0.20 for incident and prevalent *HPV* detection, respectively,

compared to 0.07 and 0.09 for HIV-negative women (Figure 5D). Those with prevalent *HPV* detection had a slightly increased rate of progression to *HSIL* than incident cases, although this was not significant.

Of 168 cases of *HSIL*, 62.5% were incident. HIV-positive women had a 0.59 times lower rate of regression from *HSIL* to *Normal* than HIV-negative women (95% CI: 0.26-1.65). The 12-month predicted probability of regression to *Normal* for HIV-positive women was 0.10 and 0.14 for prevalent and incident *HSIL*, respectively, compared to 0.17 and 0.23 for HIV-negative women (Figure 5E). Women with incident *HSIL* had a 1.39 times higher rate of regression to *Normal* than women with prevalent classification, although this association was not significant. HIV-positive and HIV-negative women with *HSIL* had a similar rate of regression to *HPV* (relative rate = 1.18, 95% CI: 0.78-1.78). For HIV-positive women the 12-month predicted probability of regression to *HPV* ranged from 0.70 and 0.73 for incident and prevalent *HSIL*, respectively, compared to 0.65 and 0.68 for HIV-negative women (Figure 5F). Those with prevalent *HSIL* had a slightly increased rate of regression to *HPV* than incident cases, although this was not significant.

C4.3 Potential effect modifiers (Table 5)

HIV-positive women with CD4+ counts <200 had a 3.31 times higher rate of transitioning from *Normal* to *HSIL* than women with higher CD4+ counts (95% CI: 1.10-9.93). Low CD4+ count was also associated with a higher rate of progression from *HPV* to *HSIL* (2.23, 95% CI: 1.27-3.92), and lower rate of regression from *HPV* to *Normal* (0.54, 95% CI: 0.36-0.81).

HIV-positive *Normal* women with HPV-16/18 had a 4.67 times higher rate of progression to *HSIL* than those infected with other HPV types (95% CI: 1.11-19.60). Similarly, those with HPV-16/18 infection had a higher rate of progressing from *HPV* to *HSIL* (2.05, 95% CI: 1.23-3.42) and a lower rate of regression to *Normal* (0.36, 95% CI: 0.26-0.49) compared to those infected with other HPV types. HPV type-specific differences in associations for the other transitions examined were non-significant.

HIV-positive women classified as *Normal* were more likely to transition to *HPV* with the detection of multiple types than a single type (1.99, 95% CI: 1.48-2.69). HIV-positive

women *Normal* were also more likely transition to *HSIL* with the detection of multiple types than a single type, although this association was not statistically significant (2.07, 95% CI: 0.51-8.45). Further, women with multiple *HPV* types had a higher rate of progression to *HSIL* (2.29, 95% CI: 1.37-3.84) than those with a single *HPV* type. HIV-positive women with multiple *HPV* types also had a 0.36 times lower rate of regression from *HPV* to *Normal* than women with a single *HPV* type (95% CI: 0.26-0.49).

Among *Normal* HIV-positive women, those age ≤ 25 years had a 1.51 times higher rate of incident *HPV* detection than those > 25 (95% CI: 1.09-2.08). Age associations for the other transitions examined were non-significant.

Among *Normal* HIV-positive women, those with HIV-1 had a 1.85 times higher rate of incident *HPV* detection than those with HIV-2 (95% CI: 1.35-2.53). Similarly, women with HIV-1 had a 1.83 times higher rate of progression from *HPV* to *HSIL* compared to women with HIV-2 (95% CI: 0.93-3.59). Women with HIV-1 also had a lower rate of regression from *HPV* to *Normal* than those with HIV-2 (0.74, 95% CI: 0.56-0.96). In contrast, those with HIV-1 had a lower rate of progression from *Normal* to *HSIL* (0.41, 95% CI: 0.16-1.04). Mutual adjustment for baseline age and CD4+ count (as surrogate measures of duration and severity of HIV infection), did not affect these findings.

C5. Discussion

Cervical cancer is the fourth most common cause of cancer death affecting women worldwide [58], disproportionately impacting low resource nations (most notably in sub-Saharan Africa where HIV is endemic) [58, 60]. As HIV-positive women are at increased risk of cervical cancer, understanding the distinct natural history within this population is essential for informing targeted prevention efforts. This study found that HIV-positive women had higher rates of incident *HPV* detection and progression to *HSIL*, as well as lower rates of regression from *HSIL* and *HPV* infection when compared to HIV-negative women. The most notable difference between HIV-positive and HIV-negative women was the more than doubled rate of progression from *HPV* to *HSIL*. True transition probabilities likely lie between the incident and prevalent curves as a function of age and sexual activity.

While analyses of potential effect modifiers should be interpreted with caution due to limited sample sizes, overall results suggest that HIV-positive women with baseline CD4+ counts <200 (cells/ μ L), infection with HPV-16/18, or concurrent infection with multiple HPV types had higher rates of progression and lower rates of regression. Data on ART were limited for several studies included in the analysis; therefore, the impact of baseline CD4+ count was examined to capture some of these treatment effects. Although some studies suggest that ART and improved CD4+ counts may reduce adverse transitions [151-153], the impact on cervical cancer incidence not been demonstrated [154]. Consistent with other research [97, 98], this study found increased incident detection of multiple HPV types in HIV-positive women compared to HIV-negative women, but also demonstrated that infection with multiple types increased progression and decreased regression. This is particularly important as >1 type was present in 71% of visits in which HIV-positive women had HPV detection, in comparison to 28% among HIV-negative women.

Evidence regarding the role of HIV type on the natural history of HPV is conflicting [3, 122, 141, 155-159], with some research indicating that HIV-2 is more strongly associated with HPV-related disease than HIV-1. In contrast, the present analysis found HIV-1 to be more strongly associated with adverse transitions than HIV-2 (with the notable exception of a lower probability of transitioning from *Normal* to *HSIL*). HIV-1 has a shorter incubation period, higher transmissibility, and more rapid development of immunosuppression compared to HIV-2 [66, 139]. Thus, it is biologically plausible that women with HIV-1 are at greater risk due to more severe immunosuppression. However, longer survival among women with HIV-2 [160] may result in higher lifetime risk due to extended time to develop cervical cancer. Dissimilar findings may be a function of methodological approaches with case-control and cross-sectional research detecting effects of differential survival, and longitudinal research involving short-term follow-up, such as the present analysis, detecting effects of differential immunosuppression.

This study has several limitations. The present analysis focused on three stages of natural history: *Normal* (defined as HPV-negative), *HPV* (defined as HPV-positive with one or more type and the absence of *HSIL*), or *HSIL* (defined as HPV-positive with one

or more type and the presence of HSIL). Importantly, if a woman went from HPV-positive with type 16 to HPV-positive with type 18 in consecutive visits this was classified as a continuation of the *HPV* stage. This situation was unusual as many women had multiple HPV types such that one type was persistent during consecutive *HPV* visits. With varying protocols across studies, clinic visits in which biopsies were not indicated, and limited participant follow-up, histology was only available for 10% of all clinic visits. In the absence of histology, cytology was used to inform classification of women into natural history stages. Misclassification resulting from cytology likely leads to undetected cervical abnormalities (e.g. false negatives), such that some women are classified as *HPV* when in fact they are *HSIL*. Thus, progression to *HSIL* may be underestimated while regression from *HSIL* may be overestimated. However, it is important to note that histology is an imperfect gold standard with demonstrated low reproducibility [146]. A number of screening and diagnostic technologies were utilized in these studies with validity improving over time, which may produce time-varying misclassification. However, the overall performance of HIV typing and PCR detection of HPV DNA have been demonstrated to be high throughout these studies, such that the likelihood of substantial time-varying misclassification is small. Estimates of natural regression from *HSIL* may be overestimated due to biopsy or treatment effects, yet participant follow-up for treatment was low in earlier studies, thus these effects are likely minimal. While most clinic visits occurred in four month intervals there were cases with longer lapses between visits, increasing the interval censoring and the possibility of missed transitions between visits. Further, this sample is largely comprised of women in their thirties who may have been previously infected with HPV, such that a positive HPV test represents incident DNA detection rather than incident infection (i.e. reactivation effects).

This study has a number of strengths, most notably a large longitudinal sample to directly compare HIV-positive and HIV-negative women. These data allowed for the examination of the impact of HIV type, as both HIV-1 and HIV-2 are endemic to West Africa. HPV-16 and HPV-18 were tested for in each study included in the analysis; therefore, we were able to examine the roles of these highly oncogenic types separate

from other types. Further, this sample is diverse and includes both Muslim women in polygamous marriages as well as registered CSWs. As CSW are estimated to represent roughly 25% of new HIV cases in Africa, this population is particularly relevant for co-infection research [161]. Finally, factors known to impact HPV natural history are minimal in this sample (e.g. oral contraception use, smoking, prior cervical cancer screening/treatment, and HPV vaccination).

C6. Conclusion

Findings suggest that targeted prevention programs for HIV-positive women are needed. However, cost-effectiveness analyses specific to the HIV-positive population in sub-Saharan Africa should be developed as the relative impact of screening and vaccination strategies may be different for this high-risk group than the general population. For instance, given the high prevalence of HPV among HIV-positive women, HPV testing as a stand-alone strategy may be inefficient for identifying women for targeted follow-up. The importance of identifying optimal targeted prevention strategies is further highlighted by modeling evidence suggesting that cervical cancer among HIV-positive women may increase in the future due to extended life expectancy resulting from ART [154, 162].

D. MANUSCRIPT II: Identifying Optimal Cervical Cancer Screening Approaches for HIV-positive Women in Senegal, West Africa - A Markov Cohort Cost-Effectiveness Model

D1. Summary

Background. Cervical cancer prevention strategies specific to the high-risk population of HIV-positive women in sub-Saharan Africa remain limited due, in part, to uncertainty regarding optimal approaches. This paper examines the cost-effectiveness of screening strategies relevant to Senegal, West Africa.

Methods. Using Markov cohort modeling with a 4-month cycle over a 15-year time horizon, we examined the relative cost-effectiveness of six screening strategies (Hybrid Capture 2 HPV testing, rapid HPV testing, cytology, visual inspection with acetic acid (VIA), HPV testing followed by cytology triage, and HPV testing followed by VIA triage) and five screening frequencies using projected life expectancy and incremental cost-effectiveness ratios (ICER). One-way and probabilistic sensitivity analyses were conducted to explore the impact of uncertainty on results.

Results. In base case analyses, VIA was the most cost-effective strategy examined. Compared to no screening, annual VIA resulted in a discounted increased life expectancy of 1.7 months and a 40% reduction in cervical cancer incidence with an ICER of I\$1,500 per life year saved. When accounting for uncertainty, VIA and cytology emerge as the most likely to be cost-effective. High underlying HPV prevalence among HIV-positive women significantly reduces the cost-effectiveness of HPV testing.

Conclusions. Cost-effective strategies for targeted cervical cancer screening among HIV-positive women represent an important prevention opportunity among this high-risk population.

D2. Background

Human papillomavirus (HPV) is the necessary cause of squamous cervical cancer [132], is highly transmissible, and generally acquired closely after sexual debut [133, 134]. Persistent infection can lead to the development of pre-cancerous lesions which, in

the absence of treatment or an immune response, can progress to cancer. High-risk HPV types 16 and 18 are estimated to account for 70% of cervical cancer [11]. Women with human immunodeficiency virus (HIV) infection are at an increased risk for detection of HPV, pre-cancerous cervical lesions, and cervical cancer compared to HIV-negative women [3, 90-92, 96, 99, 103, 122, 135]. Cervical cancer is the leading cause of cancer mortality among women in sub-Saharan Africa (SSA) [58] where 70% of the global HIV burden is concentrated [65].

Cervical cancer is entirely preventable yet disproportionately impacts developing regions with limited access to prevention services. Several studies and pilot projects have demonstrated the feasibility of implementing cervical cancer screening and treatment in low-resource settings [163], although significant economic and infrastructural challenges remain [164]. While screening with cytology has been widely adopted in developed nations resulting in major declines in cervical cancer incidence over the past 60 years, significant laboratory, equipment, and clinical expertise requirements have limited the capacity to establish cytology in low-resource settings [164, 165]. Further, cytology has low reproducibility and sensitivity in comparison to other strategies, necessitating frequent screening to achieve high effectiveness [146, 165]. As such, a substantial effort has been made to identify and evaluate screening strategies that are more contextually relevant for the high-risk setting of SSA. Hybrid Capture 2 (HC2) HPV testing is highly sensitive and reproducible with the potential for self-collection of samples [166], yet requires significant investment in laboratory equipment and technician expertise [164]. Both cytology and HPV testing involve laboratory processing time leading to delays in obtaining results and an additional clinic visit if treatment is needed. Visual inspection with acetic acid (VIA) may be most suitable to low-resource settings as it involves naked eye inspection of the cervix (yielding immediate results), and requires little clinical expertise and no laboratory equipment for processing samples. However, inter-observer differences in subjectively determining positivity, concerns regarding over treatment, and the potential for small lesions to remain undetected may reduce the effectiveness of VIA [164]. The more recently developed careHPV™ test offers the benefits of standard HPV testing, but yields rapid results (roughly two hours of processing time), mobile battery

operated processing equipment, and minimal technical training [164, 167]. Both VIA and rapid HPV testing can be implemented as part of a same day ‘screen and treat’ approach, minimizing losses to follow-up and delayed treatment. Immediate treatment with cryotherapy has minimal infrastructure requirements and can be provided by nurses and midwives [164]. In contrast, surgical treatment with conization or loop electrosurgical excision procedure (LEEP) require significant infrastructure and technical training, and are further limited by the lack of pathology services in SSA settings [168].

Importantly, the performance of test and treatment modalities can be reduced when applied to HIV-positive women adding further uncertainty regarding optimal cervical cancer prevention strategies for this high-risk population. The United States (US) President’s Emergency Plan for AIDS Relief (PEPFAR) has provided support for limited efforts to initiate cervical cancer screening programs for HIV-positive women in some countries, such as Ethiopia, Tanzania, and Zambia [169]. PEPFAR-supported interventions include VIA screening and treatment with cryotherapy or LEEP, although the impact of these modalities on morbidity and mortality among this population has not been clearly demonstrated.

In summary, despite demonstrated successes in both research and pilot projects working to overcome challenges and identify contextually relevant approaches, no SSA country has currently successfully implemented a national population-based cervical cancer screening program. Thus, there is a pressing need for a targeted approach to best allocate resources to high-risk populations, such as HIV-positive women, and inform the eventual implementation of comprehensive population-based screening paradigms [170]. As there are no published cost-effectiveness analyses for cervical cancer screening specific to HIV-positive women in Africa, there is uncertainty regarding the most optimal and contextually relevant approach. Given the distinct natural history of HPV among HIV-positive women, as well as varying test and treatment attributes, it is important to quantitatively compare the potential impact of screening strategies to understand how these factors collectively impact HPV-associated morbidity and mortality. To address this gap in the literature, we constructed a simulation model to examine the relative cost-effectiveness of cytology, VIA, HC2 HPV testing, rapid HPV testing, rapid HPV DNA

testing followed by cytology triage, and rapid HPV DNA testing followed by VIA triage among HIV-positive women in Senegal, West Africa.

D3. Materials and Methods

A Markov cohort model was developed to simulate the natural history of HPV and the development of cervical cancer among HIV-positive women, with screening and treatment scenarios overlaid to determine the relative cost, life expectancy, and cost-effectiveness of each strategy. A 4-month cycle was used as the natural history of HPV is transient such that a short interval is needed to capture clinically relevant transitions (in other words the model simulates time in 4-month iterations). A 15-year time horizon was used, with women entering the model at time of HIV diagnosis (to simulate a point-of-care approach for initiation of screening while leveraging existing HIV care infrastructure). Five screening frequencies were examined (baseline only, baseline and five year screening, baseline with five and ten year screenings, triennial, and annual) resulting in one, two, three, six, and fifteen total screens.

D3.1 Input data (Table 6)

Using data described previously [171], competing risk modeling was used to estimate natural history transition probabilities. Briefly, 575 HIV-positive women were followed for an average of two years in Senegal between 1994 and 2010. Cytology (with histology in a sub-sample of women) and HPV DNA testing were performed at approximately 4-month intervals. At each visit, women were classified into one of five mutually exclusive natural history states: Normal (defined as HPV-negative), HPV-16/18 (defined as HPV-positive with at least type 16 and/or 18), HPV-Other (defined as HPV-positive with the absence of types 16/18), CIN2/3-16/18 (defined as HPV-16/18 with the presence of CIN2/3), and CIN2/3-Other (defined as HPV-Other with the presence of CIN2/3). These five health states, combined with invasive cervical cancer (ICC) and death, comprise the underlying natural history model (Figure 6). Baseline screening data from Senegal were used to populate states at the beginning of the model (i.e. initial vector parameterization). Death from other causes among HIV-positive women was estimated from the literature with a wide-range of heterogeneity in the underlying study samples to conservatively

account for uncertainty in this parameter given the role of competing risks, as well as access and adherence to anti-retroviral treatment (ART) [81, 172-174].

Estimates for screening test performance were derived from the literature specific to HIV-positive women using histology as the gold standard, with multiple sources forming a range and the midpoint used as a base estimate. Estimates specific to rapid HPV testing among HIV-positive women were limited; thus, the relative performance of rapid testing compared to HC2 among HIV-negative women was used to calculate estimates of validity for the present analysis.

Given established feasibility for implementation in low-resource settings [175, 176], cryotherapy was the primary treatment for pre-cancerous lesions. Cases in which women were ineligible for cryotherapy given the size of the lesion were assumed to be referred for LEEP, with the proportion requiring LEEP estimated from literature specific to HIV-positive women in SSA [177-179]. Due to lack of chemotherapy and radiation availability within Senegal and the broader area of SSA, we assumed hysterectomy-only treatment for cancer. A proportion of women with late stage cervical cancer were assumed to present with symptoms (independent of available screening initiatives), consistent with other models. Estimates of treatment effectiveness were established from the literature specific to HIV-positive women, with multiple sources informing a base and range for sensitivity analyses. Studies in which pre-cancer recurrence was established after approximately one year of follow-up were given greater weight for estimation of treatment effectiveness, as longer follow-up may lead to detection of disease resulting from new infections as opposed to recurrence (leading to an underestimate of effectiveness). As the underlying natural history model accounts for newly acquired and reactivated infections at the aggregate level, inclusion of estimates of effectiveness from studies with extensive follow-up could lead to double counting of recurrence. All follow-up treatment was simulated to occur within the same 4-month cycle as screening.

For the base analysis, participation in follow-up testing and treatment was assumed to be 100%. Sensitivity analyses exploring the impact of less than perfect retention for strategies involving multiple visits (ex: referral for LEEP or cytology followed by treatment) were conducted, with retention estimates based on literature specific to HIV-

positive women in SSA. For strategies employing a same day ‘screen and treat’ approach retention rates were held at 100% to capture the benefits of averted losses to follow-up.

In the absence of costs for screening and treatment specific to Senegal, estimates were established from literature specific to low-resource nations in SSA, with multiple sources forming a range and the midpoint used as a base estimate. All sources included direct medical costs including staff, supplies, equipment, and specimen transport. Additionally, some sources also incorporated estimates of women’s traveling and time costs (notably, these additional costs represented a small fraction of estimates for a given test/procedure). Costs specific to rapid HPV testing in SSA were unavailable; thus, the relative cost of rapid testing compared to VIA in other low resource nations was used to calculate estimated costs for the present analysis. Costs in the literature were expressed in either US or international dollars (I\$). I\$ are a hypothetical currency in which national currencies are transformed into a common currency, the US dollar, based on price differences between countries. I\$ have the same purchasing power as US dollars in the US. To standardize estimates and account for inflation, costs were updated to 2013 international dollars using Senegalese purchasing power parity (PPP) exchange rates and consumer price index (CPI) deflators.

D3.2 Calibration –

In the absence of estimates of cervical cancer risk specific to HIV-positive populations, the natural history model was calibrated to 2012 GLOBOCON estimates for Senegal [61] with a multiplier ranging from two to eight to capture the relative effect of HIV as reported in the literature [3, 88, 103-106, 180, 181]. The Nelder-Mead direct-search algorithm [182, 183] with 10,000 initial value combinations was employed to minimize sums of squares between simulation outcomes and calibration targets. Natural history estimates which best optimized model fit and were biologically relevant were selected (e.g. risk of progression to cancer was greater for HPV-16/18 than other types, with HPV-16/18 accounting for approximately 70% of cervical cancer) [11, 130]. Inputs for the base analysis were calibrated for a five-fold increase in cervical cancer risk with the top ten percent of best fitting estimates for two- to eight-fold increases forming the lower and upper bounds, respectively, for sensitivity analyses. To assess internal validity

of the natural history model, outputs were compared to reported HPV and CIN2/3 prevalence from studies used to estimate natural history transitions with high agreement observed [3]. Model outputs were also compared to literature from the broader area of SSA to assess external validity. Specifically, prevalence of HPV [92, 93], HR-16/18 [184], and high-grade lesions [185], as well as HPV-16/18 positivity among women with high-grade lesions [96], were compared with high agreement observed between study results and model output. Lastly, the model was reviewed by Senegalese clinicians providing care to HIV-positive women to ensure face-validity of key inputs, outputs, and assumptions. Calibration was conducted using R Studio 3.1 (Boston, MA, USA).

D3.3 Analysis

The relative performance of each screening strategy was measured using incremental cost-effectiveness ratios (ICERs) which represent the cost of an additional unit of effectiveness that is obtained when implementing a more effective strategy rather than a less effective strategy. Strategies that were more costly and less effective than another (i.e. strongly dominated) and strategies with a higher ICER than a more effective alternate strategy (i.e. weakly dominated) were eliminated. Based on World Health Organization recommendations, strategies with ICERs less than Senegal's 2013 per capita Gross Domestic Product (GDP) were considered 'very cost-effective' (approximately I\$1,050) and strategies less than three times the per capita GDP were considered 'cost-effective' (approximately I\$3,150) [5, 186]. One-way sensitivity analyses were conducted to assess the influence of uncertainty in key parameters on results. To simultaneously account for uncertainty in all input parameters, a probabilistic sensitivity analysis with 50,000 samples from uniform distributions was conducted with results displayed in a cost-effectiveness acceptability curve (CEAC) representing the Bayesian probability that a given screening strategy will be cost-effective across varying levels of willingness-to-pay thresholds. Future costs and life years were discounted at an annual rate of 3%. Markov cohort cost-effectiveness modeling was conducted in TreeAge Pro 2015 (Williamstown, MA, USA). IRB approval was not necessary for this study as the existing data do not meet the criterion for human subjects' research.

D4. Results

D4.1 Base-case analysis (Table 7)

With no screening, discounted fifteen year costs per woman and life expectancy were I\$66 and 9.55 years, respectively (costs accrued under a no screening paradigm are the result of women seeking medical care given presentation of cervical cancer symptoms). VIA was 'very cost-effective' for all screening frequencies examined, except for annual screening. Specifically, annual VIA resulted in a discounted increased life expectancy of 1.7 months with an ICER of I\$1,500 per life year saved (remaining below the threshold for 'cost-effective'). Cervical cancer incidence and mortality were reduced by 40% and 70%, respectively, with annual VIA when compared to no screening. Cytology, rapid HPV testing, and rapid HPV testing followed by either VIA or cytology triage remained dominated for all screening frequencies examined. HC2 was not dominated; however, the ICERs far exceeded the willingness-to-pay threshold.

VIA and cytology consistently resulted in fewer false-positives than other strategies. While rapid HPV testing followed by VIA or cytology triage resulted in the highest number of false-positives test results, the second round of screening following a positive HPV test lead to a substantial reductions in unnecessary referrals to treatment (approximately a 65% reduction compared to VIA). Notably, HC2 and rapid HPV as stand-alone testing strategies resulted in the highest number of unnecessary treatment referrals (approximately 20% greater than VIA), likely a function of high underlying HPV prevalence among HIV-positive women.

D4.2 Sensitivity analyses (Table 8)

One-way sensitivity analyses with three screenings (i.e. baseline, five and ten year testing) revealed that estimates of incremental cost-effectiveness were most influenced by retention in care, progression to cervical cancer, cervical cancer mortality in the absence of treatment, and the potential impact of ART. Results were less sensitive to discounting, death from other causes, and pre-cancer treatment effectiveness, with no meaningful impact on relative cost-effectiveness. Of note, the limited impact of discounting on results is partially a function of the 15 year time horizon used for present analysis (i.e. discounting becomes more influential as the time horizon is extended (data not shown)).

Potential losses to follow-up were considered for strategies involving follow-up visits (e.g. cytology) and treatment referrals requiring LEEP as opposed to same-day treatment with cryotherapy. Overall, as retention is reduced, both the costs and effects for each strategy decrease as well. Specifically, as retention in care fell below 70% the cost of VIA exceeded that of cytology (as fewer women successfully follow-up with treatment after a positive cytology result, reducing total costs); however, costs decline at a faster rate than effects such that cytology becomes more competitive on a relative scale. For instance, with 50% retention in care, three VIA screens resulted in an ICER of I\$1100 per life year saved in comparison to I\$640 for cytology. Notably, the impact of less than perfect retention in care on effectiveness is attenuated as screening frequency increases with the opportunity to address any missed follow-up during a future visit.

Strategies became more cost-effective with accelerated progression to cervical cancer. Specifically, under a maximum progression scenario, three VIA screens resulted in an ICER of I\$414 per life year saved. In contrast, with minimum progression the ICER for annual VIA was I\$475 per life year saved (remaining below the threshold for ‘cost-effective’).

With increasing cervical cancer mortality given the absence of treatment, screening becomes more cost-effective (as the impact of screening on cervical cancer death increases and the ICER becomes smaller). Under a maximum cervical cancer mortality scenario, the ICER for three VIA screenings is I\$653, in comparison to I\$1,056 under a minimum cervical cancer mortality scenario.

Given evidence that higher CD4+ counts are associated with improved clearance of infection, regression from pre-cancers lesions, and treatment effectiveness [151-153, 171, 187, 188], we examined the potential impact of ART access and adherence. Specifically, maximum progression and death inputs with minimum regression inputs were used to simulate the potential effects of low ART coverage, while minimum progression and death inputs with maximum regression inputs were used to simulate high ART coverage. The ICERs for three VIA screens under low and high ART coverage scenarios were I\$237 and I\$2,298, respectively. Similar to the impact of cervical cancer mortality, the

impact of screening increases under a maximum progression scenario, resulting in smaller ICERs.

When accounting for uncertainty in all inputs simultaneously (i.e. initial vector parameterization, natural history transitions, death from other causes, death from cervical cancer, treatment effectiveness, screening performance, and costs), VIA and cytology were probabilistically the most likely cost-effective screening strategies (Figure 7). Cytology emerged as a cost-effective strategy in 16-28% of iterations when examining results beyond a willingness-to-pay threshold of I\$600. Base estimates for test performance were similar for VIA and cytology; however, the upper ranges for cytology sensitivity and specificity slightly exceed that of VIA. Similarly, plausible ranges for cost of VIA and cytology overlap. In those cases in which cytology was more cost-effective than VIA, inputs from upper bounds of test performance and lower bounds for cost were selected. Collectively these two factors drive the emergence of cytology as a potentially cost-effective strategy.

D5. Discussion

The objective of this model was to provide insight into the potential impact of existing cervical cancer screening tools in the high-risk population of HIV-positive women in Senegal. As HIV-positive women are at an increased risk of cervical cancer it is critical to explore potential prevention strategies while collectively accounting for the distinct natural history, screening performance, treatment effectiveness, and competing risks factors within this population. Markov cohort modeling provides an important tool for quantitatively and simultaneous accounting for these factors. When accounting for a wide range of all input parameters, this simulation model found that VIA and cytology are ‘very cost-effective’ with ICERs below I\$1,050 per life year saved. Results were largely driven by relative differences in costs as effects on life expectancy were similar across the screening strategies examined. Notably, the impact of screening, as measured by life expectancy, is averaged across the simulated cohort such that the discounted increased life expectancy of 1.7 resulting from annual VIA yields approximately 2,830 additional life years among the estimated 20,000 HIV-positive women in the Senegal.

Importantly, VIA may be more contextually suitable for lower-resource settings given minimal infrastructural and technical expertise requirements. Mexico's national cytology program was largely ineffective over several decades despite the fact that they had considerably greater resources and existing medical infrastructure than Senegal and much of SSA [189-191]. Limited quality control, lack of equipment maintenance, and poor reporting of results to patients were identified as significant contributors to sub-optimal outcomes. Successful implementation of a cytology screening program requires significant and sustained quality control measures, including regular independent re-reading of samples, staff trainings, and laboratory inspections. Further, a key assumption of cost-effectiveness analyses is that given the funding, all necessary components of an intervention can be purchased. While tangible items required for the screening strategies examined can be purchased and shipped to areas within SSA, this assumption is unlikely to be met in terms of the labor force required for cytology, specifically trained and qualified cytotechnologists. VIA can be implemented with limited technical expertise by a wide range of medical providers (including nurses and midwives); however, the processing of cytology results requires specialized laboratory technicians, a labor force which would have to be developed with additional funds in advance. These factors should be considered when interpreting the emergence of cytology as a cost-effective strategy in probabilistic sensitivity analyses and during policy decision-making.

HPV testing strategies remained consistently dominated (i.e. more costly and less effective than alternate strategies) or far exceeded the willingness-to-pay threshold. This is likely a function of the lower specificity of HPV testing in comparison to cytology and VIA, and high underlying HPV prevalence among HIV-positive women. For instance, one study from which data were used to inform estimates of natural history found that roughly 67% of HIV-positive women had prevalent HPV detection in comparison to 25% of HIV-negative women [3]. Essentially, given high HPV positivity among HIV-positive women, HPV DNA testing results in the majority of women referred for costly follow-up testing and/or treatment, such that the test functionally does little in terms of focusing resources on those who are at greatest risk. Recalibrating HPV testing positivity cut-points specifically for an HIV-positive population may improve overall test performance

and should be investigated [192]. However, improved specificity results in diminished sensitivity, the effects of which should be simulated to determine optimal trade-offs. Further, genetic markers of proliferative lesions, including p16 and mRNA coding for the viral E6 and/or E7 proteins, could be used in combination with HPV testing to improve test performance [193]. The resulting costs and application to HIV-positive populations have not been established in the literature, but warrant consideration.

This analysis has several limitations. Estimates of cervical cancer risk may be misestimated due to both the unknown relative increase in risk among HIV-positive women and uncertainty regarding incidence in the general population. GLOBOCAN predictions incorporate methods to overcome the likely underreporting of cervical cancer by using a combination of cancer registry, autopsy, and published research data, algorithms to weight data quality, and extrapolation of data from geographically linked areas; however, uncertainty remains [58]. To address this limitation, a wide range of multipliers were used, with sensitivity analyses demonstrating that results remained robust across a number of cancer risk scenarios. Much of the literature on screening performance among HIV-positive women was specific to low-resource settings, which both increases the face-validity of the model to the current context of screening in SSA but also yields lower estimates of validity than that obtained in developed settings. Further, estimates of costs are subject to probable extensive situational heterogeneity as they are largely dependent on transportation, labor, and scaling factors [169, 194]. Therefore, literature specific to any low-resource SSA countries was included yielding a wide range for cost estimates to conservatively represent uncertainty in these parameters. Possible increases in HIV transmission due to inflammation and bleeding following cryotherapy and LEEP were not examined. To date, no study has examined potential transmission implications resulting from treatment [195]; however, as one study reported that half of HIV-positive women had sex during the month after treatment against medical recommendation [135], the potential for increased HIV transmission is not trivial and highlights the need for comprehensive education and risk communication specific to HIV-positive women and their partners. Finally, the present model is ageless in that screening initiation is assumed to occur at the time of HIV diagnosis with mortality and

natural history estimates averaged across age. This approach was taken for several reasons. First, evidence suggests that in contrast to observed patterns in HIV-negative women, age is not strongly associated with the natural history of HPV among HIV-positive women, likely due to increased persistence and infection with multiple types [118, 131, 171]. Second, there is likely significant heterogeneity in age at the time of HIV diagnosis. For instance, testing strategies often target high-risk populations (such as commercial sex workers) which may overlook key sub-populations (such as married women in polygamous relationships) resulting in heterogeneity in age at time of HIV diagnosis. The average age of the underlying cohort used to estimate natural history transitions was 34 years. Importantly, among those diagnosed in their teens or early twenties potentially delaying initial screening until their 30's should be considered to optimized resources and outcomes, especially in circumstances when a one lifetime screening approach is adopted.

The internal validity of this model is likely enhanced as natural history estimates were derived from a single Senegalese study population with a large sample of HIV-positive women using methods that specifically yield transition probabilities. However, the broader exchangeability of these parameters should be considered when generalizing findings. For instance, transitions from *Normal* to *HPV* are a function of both biological and behavioral factors (i.e. the biological risk of transmission given exposure and the more behaviorally driven risk of exposure given sexual behavior which may vary geographically). Further, of the Senegalese sample used to estimate natural history parameters, the median CD4+ count at baseline was 416 cells/ μ L with 27% of women reporting use of ART [171]. There is evidence that higher CD4+ counts are associated with improved clearance of infection, regression from pre-cancers lesions, and treatment effectiveness [151-153, 171, 187, 188]. However, at the population level any protective effects of ART and improved CD4+ counts on cervical cancer incidence have yet to be clearly demonstrated [154]. Additionally, there is evidence that cervical cancer among HIV-positive women may increase in the future due to extended life expectancy resulting from ART (providing greater time to acquire HPV and develop cancer) [154, 162]. Sensitivity analyses exploring the potential impact of ART coverage were conducted

demonstrating that VIA remained a ‘cost-effective’ strategy across a wide range of natural history inputs. Importantly, given the demonstrated stability of findings in one-way and probabilistic sensitivity analyses, there may be a reasonable foundation upon which to generalize findings to SSA nations with similar economic and social characteristics. Additional research examining relative cost-effectiveness among key sub-populations (e.g. urban and rural areas, commercial sex workers) should be conducted.

D6. Conclusion

Cervical cancer remains a key public health challenge despite major advancements in screening and treatment options. Several research and demonstration projects have established the feasibility of cervical cancer screening in low-resource settings, yet infrastructural, training, and financial demands have prevented wide-scale implementation of population-based screening programs in much of the high-risk setting of SSA. This research is the first comprehensive comparison of multiple screening strategies among this high-risk population. Results demonstrate that cervical cancer screening among HIV-positive women is cost-effective, such that they are an ideal population for targeted screening to both reduce preventable disease and prioritize limited resources.

E. MANUSCRIPT III: Potential Cost-Effectiveness of Targeted HPV Vaccination in HIV-positive Women in Senegal, West Africa: A Theoretical Exploratory Analysis

E1. Summary

Background. Cervical cancer prevention strategies specific to the high-risk population of HIV-positive women in sub-Saharan Africa remain limited due to, in part, uncertainty regarding optimal approaches. This paper examines the potential cost-effectiveness of targeted HPV vaccination among adult HIV-positive women in Senegal, West Africa.

Methods. Using Markov cohort modeling with a 4-month cycle over a 15-year time horizon, we examined the relative cost-effectiveness of vaccination for several scenarios based on various estimates of potential vaccine effectiveness and cost using projected life expectancy and incremental cost-effectiveness ratios (ICER). Specifically, vaccination at the time of HIV diagnosis was examined under various theoretical effectiveness scenarios, with comparison to visual inspection with acetic acid (VIA) screening (at baseline, year five, and year ten). One-way sensitivity analyses were conducted to explore the impact of uncertainty on results.

Results. HPV vaccination was only cost-effective under optimal vaccine efficacy and/or costing scenarios. Specifically, with costs \geq \$31 vaccination became dominated when vaccine efficacy fell below approximately 70% and 40% for reducing transitions from *Normal* to *HPV-16/18* and *HPV-Other* states, respectively.

Conclusions. With lower vaccine-induced titer levels reported among adult HIV-positive women and a potential corresponding reduction in vaccine efficacy, HPV vaccination costs must be reduced for primary prevention to be cost-effective in comparison to screening. Efforts to implement targeted screening, reduce vaccine costs, develop therapeutic vaccines, and evaluate upcoming HPV antiviral treatments should be made for this high-risk population.

E2. Background

Human papillomavirus (HPV) is the necessary cause of squamous cervical cancer [132], is highly transmissible, and generally acquired closely after sexual debut [133,

134]. Approximately 40 genotypes infect the genital tract with types classified hierarchically based on their oncogenic potential. Persistent infection can lead to the development of pre-cancerous lesions which, in the absence of treatment or an immune response, can progress to cancer. Women with human immunodeficiency virus (HIV) infection are at a significantly increased risk for detection of HPV, pre-cancerous cervical lesions, and cervical cancer compared to HIV-negative women [3, 90-92, 96, 99, 103, 122, 135]. Cervical cancer is the leading cause of cancer mortality among women in sub-Saharan Africa (SSA) [58], an area with only 5% of global cancer resources and 70% of the global HIV burden [65].

There are currently three prophylactic HPV vaccines available: a bivalent vaccine which protects against types 16 and 18 (Cervarix, GSK), a quadrivalent vaccine which protects against types 6, 11, 16, and 18 (Gardasil, Merck & Co.), and the recently approved nonavalent which protect against types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9, Merck & Co.). The bivalent and quadrivalent vaccines protect against those types that collectively cause 70% of cervical cancer (HPV types 16 and 18), while the nonavalent affords extended protection against types collectively attributable to 90% of cervical cancer [9, 11, 40]. Additionally, the quadrivalent and nonavalent vaccines protect against HPV types 6 and 11 which cause over 90% of anogenital warts [10]. All three HPV vaccines have been shown to be safe and elicit strong immune responses with subsequent demonstrated reductions in cervical HPV infection and cervical intraepithelial neoplasia (CIN) pre-cancerous lesions [43-45, 196, 197]. The duration of protection remains unknown, although participants from early phase III clinical trials are being actively followed with no evidence of waning immunity 8.5 years post-vaccination [51]. Notably, the bivalent and quadrivalent vaccines elicit cross-protection to other HPV types that are phylogenetically related to those included in the vaccine [47, 198]. However, early evidence indicates that the nonavalent vaccine does not induce protective effects for non-vaccine HPV types [43].

While many developed nations now recommend routine HPV vaccination for adolescent boys and girls prior to sexual debut, implementation of vaccination in low-resource settings presents significant financial and infrastructural challenges. The HPV

vaccine is a three-dose series and is the most expensive publically funded vaccine at roughly \$300 in the United States. Thus, it is cost-prohibitive for many countries to implement mass vaccination campaigns although recent efforts to subsidize HPV vaccination costs by GAVI hold promise in terms of expanding access in low-resource high-risk settings. However, the GAVI subsidized series costs \$15, which far exceeds the average cost of vaccines included in WHO-UNICEF Global Immunization program [199]. While GAVI covers the full cost of HPV vaccines for initial demonstration programs that are required as part of a successful application for GAVI support, countries that implement national HPV vaccination programs must meet a co-financing requirement. Further, GAVI support is only available to the “poorest countries” with a Gross National Income (GNI) per capita less than \$1,580. Forty-nine countries meet this criterion, of which 20 have been approved for demonstration projects to assess their capacity to successfully administer a vaccine to adolescent girls. Senegal is eligible for GAVI assistance and is currently implementing a demonstration program as part of the application process. In addition to financial obstacles, the infrastructure of existing vaccination programming is largely designed for point-of-care administration to infants and mothers, and young school-aged children as a population of convenience. As such, infrastructure specific to vaccinating adolescent girls in low-resource settings is limited. Due to these challenges there is growing interest in identifying possible populations for targeted vaccination efforts to both reduce cost and maximize benefits.

HIV-positive women may be a key population for targeted vaccination as they are at an increased risk of cervical cancer and vaccination has the potential to be incorporated into existing HIV care services. The safety and immunogenicity of the HPV vaccine in HIV-positive populations has been demonstrated in several clinical trials with seroconversion rates $\geq 90\%$ [53, 200-204]. However, some studies have found lower vaccine-induced antibody titer levels in HIV-positive participants compared to HIV-negative controls [53, 201, 204]. The effect of reduced titer levels in HIV-positive women remains unknown as there is no known correlate for immunity (i.e. the lowest level of immune response required to sufficiently confer immune protection remains unknown) [205]. HPV vaccine efficacy for clinical outcomes (i.e. incident HPV infection

and clinical disease) has not been established in HIV-positive populations, although several clinical trials are currently underway [55]. Despite the lack of demonstrated efficacy, both Australia and the United States currently recommend HPV vaccination for HIV-positive women. Importantly, GAVI funding for HPV vaccination is specific to adolescent girls, such that vaccine costs for HIV-positive adult women will likely exceed that of the subsidized series. Across a wide range of theoretical levels for vaccine efficacy and cost, we examined the potential impact of targeted HPV vaccination among adult HIV-positive women in Senegal, West Africa. Specifically, we used Markov cohort simulation model to estimate the relative cost-effectiveness of vaccination in comparison to screening with visual inspection to inform public health practice and resource allocation in resource limited settings.

E3. Materials and Methods

A Markov cohort model was developed to simulate the natural history of HPV and the development of cervical cancer among HIV-positive women, with vaccination overlaid to determine relative cost, life expectancy, and cost-effectiveness. A 4-month cycle was used as the natural history of HPV is transient such that a short interval is needed to capture clinically relevant transitions. A 15-year time horizon was used, with women entering the model at time of HIV diagnosis (to simulate a point-of-diagnosis approach for vaccination). Additionally, in prior analyses using this model [206], six cervical cancer screening strategies were evaluated with visual inspection with acetic acid (VIA) identified as the most cost-effective. This analysis includes VIA screening (at baseline, year 5, and year 10) for comparative purposes.

E3.1 Input data (Table 9)

Using data described previously [171], competing risk modeling was used to estimate natural history transition probabilities. Briefly, 575 HIV-positive women were followed for an average of two years in Senegal between 1994 and 2010. Cytology (with histology in a sub-sample of women) and HPV DNA testing were performed at approximately 4-month intervals. At each visit, women were classified into one of five mutually exclusive natural history states: Normal (defined as HPV-negative), HPV-16/18 (defined as HPV-

positive with at least type 16 and/or 18), HPV-Other (defined as HPV-positive with the absence of types 16/18), CIN2/3-16/18 (defined as HPV-16/18 with the presence of CIN2/3), and CIN2/3-Other (defined as HPV-Other with the presence of CIN2/3). These five health states, combined with invasive cervical cancer (ICC) and death, comprise the underlying natural history model (Figure 8). Baseline screening data from Senegal were also used to populate states at the beginning of the model (i.e. initial vector parameterization). Death from other causes among HIV-positive women was estimated from the literature with a wide-range of heterogeneity in the underlying study samples to conservatively account for uncertainty in this parameter given the role of competing risks, as well as access and adherence to anti-retroviral treatment (ART).

Estimates for VIA screening performance were derived from the literature specific to HIV-positive women using histology as the gold standard, with multiple sources forming a range and the midpoint used as a base estimate. Given established feasibility for implementation in low-resource settings [175, 176], cryotherapy was assumed to be the primary treatment for pre-cancerous lesions. Cases in which women were ineligible for cryotherapy given the size of the lesion were assumed to be referred for LEEP, with the proportion requiring LEEP estimated from literature specific to HIV-positive women in SSA [177-179]. Due to lack of chemotherapy and radiation availability within Senegal and the broader area of SSA, we assumed hysterectomy-only treatment for cancer. A proportion of women with late stage cervical cancer were assumed to present with symptoms (independent of available screening initiatives). Estimates of pre-cancer treatment effectiveness were established from the literature specific to HIV-positive women, with multiple sources informing base and range for sensitivity analyses. Studies in which recurrence was established within one year of follow-up were given greater weight for estimation of treatment effectiveness, as longer follow-up may lead to detection of disease resulting from new infections as opposed to recurrence (leading to an underestimate of effectiveness). As the underlying natural history model accounts for newly acquired and reactivated infections at the aggregate level, inclusion of estimates of effectiveness from studies with extensive follow-up could also lead to double counting of recurrence. All follow-up treatment was assumed to occur within the same 4-month cycle

as screening. As VIA can be implemented as a same day ‘screen and treat’ approach, retention in follow-up care was assumed to be 100%.

In the absence of data specific to Senegal we used previously published estimates of screening and treatment costs for low-resource nations in SSA, with multiple sources forming a range and the midpoint used as a base estimate. All sources included direct medical costs including staff, supplies, equipment, and specimen transport. Additionally, some sources also incorporated estimates of women’s traveling and time costs (notably, these additional costs represented a small fraction of estimates for a given test/procedure). Estimates of vaccination costs are based on literature reporting plausible theoretical ranges as the majority of low-resource African countries do not offer HPV vaccination or have existing infrastructure specific to vaccinating older adolescent girls, and the price is dependent on negotiations, scaling, and the role of international aid programs. Costs in the literature were expressed in either US or international dollars (I\$). I\$ are a hypothetical currency in which national currencies are transformed into a common currency, the US dollar, based on price differences between countries. I\$ have the same purchasing power as US dollars in the US. To standardize estimates and account for inflation, costs were updated to 2013 international dollars using Senegalese purchasing power parity (PPP) exchange rates and consumer price index (CPI) deflators.

As vaccine efficacy among HIV-positive women is currently unknown, the present analysis examined HPV vaccination as an exploratory analysis across a broad range of inputs. With the assumption that the vast majority of women will acquire HPV prior to HIV diagnosis (given that HPV is both common and highly transmissible), as an upper bound vaccine efficacy (VE) was estimated based on observed protective effects in HIV-negative women with likely prior or current HPV infection (i.e. adult, HPV seropositive, or HPV DNA positive women) (Table 10). Protective effects have been observed in this population for both vaccine and non-vaccine HPV types; thus, separate estimates of efficacy were applied to transitions for exiting *Normal* to *HPV-16/18* states and *Normal* to *HPV-Other* states. Due to limited vaccine type specific efficacy data among this population, vaccination was simulated generically. No therapeutic benefits were assumed for those infected with HPV at baseline of the simulation. Upper bound estimates of

efficacy were reduced incrementally to collectively capture uncertainty, as well as the likely effects of reactivation and reduced vaccine efficacy in HIV-positive women. Vaccination uptake was set at 100% with complete coverage for all three-doses, with duration of immunity varied from 10 to 15 years.

E3.2 Calibration

In the absence of estimates of cervical cancer risk specific to HIV-positive populations, the natural history model was calibrated to 2012 GLOBOCON estimates for Senegal [61] with a multiplier ranging from two to eight to capture the relative effect of HIV as reported in the literature [3, 88, 103-106, 180, 181]. The Nelder-Mead direct-search algorithm [182, 183] with 10,000 initial value combinations was employed to minimize sums of squares between simulation outcomes and calibration targets. Natural history estimates which best optimized model fit and were biologically relevant were selected (e.g. risk of progression to cancer was greater for HPV-16/18 than HPV-Other with HPV-16/18 accounting for approximately 70% of cervical cancer) [11, 130]. Inputs for the base analysis were calibrated for a five-fold increase in cervical cancer risk with the top ten percent of best fitting estimates for two- to eight-fold increases forming the lower and upper bounds, respectively, for sensitivity analyses. To assess internal validity of the natural history model, outputs were compared to reported HPV and CIN2/3 prevalence from studies used to estimate natural history transitions with high agreement observed [3]. Model outputs were also compared to literature from the broader area of SSA to assess external validity. Specifically, prevalence of HPV [92, 93], HR-16/18 [184], and high-grade lesions [185], as well as HPV-16/18 positivity among women with high-grade lesions [96] were compared with high agreement observed between study results and model output. Lastly, the model was reviewed by Senegalese clinicians providing care to HIV-positive women to ensure face-validity of key inputs, outputs, and assumptions. Calibration was conducted using R Studio 3.1 (Boston, MA, USA).

E3.3 Analysis

The relative performance of each prevention strategy was measured using incremental cost-effectiveness ratios (ICERs) which represent the cost of an additional unit of effectiveness that is obtained when implementing a more effective strategy rather than a

less effective strategy. Strategies that were more costly and less effective than another (i.e. strongly dominated) and strategies with a higher ICER than a more effective alternate strategy (i.e. weakly dominated) were eliminated. Based on World Health Organization recommendations, strategies with ICERs less than Senegal's 2013 per capita Gross Domestic Product (GDP) were considered 'very cost-effective' (approximately I\$1,050) and strategies less than three times the per capita GDP were considered 'cost-effective' (approximately I\$3,150) [5, 186]. One-way sensitivity analyses and tornado plots were conducted to assess the influence of uncertainty in key parameters on results. Future costs and life years were discounted at an annual rate of 3%. Markov cohort cost-effectiveness modeling was conducted in TreeAge Pro 2015 (Williamstown, MA, USA). IRB approval was not necessary for this study as the existing data do not meet the criterion for human subjects' research.

E4. Results

E4.1 Base analysis (Table 11)

With no screening or vaccination, discounted fifteen year costs per woman and life expectancy were I\$66 and 9.55 years, respectively (costs accrued under a no screening paradigm are the result of women seeking medical care given presentation of cervical cancer symptoms). With duration of immunity extending for 15 years, vaccination coupled with VIA screening was 'very cost-effective' for all vaccine efficacy (VE) scenarios examined with vaccine costs set at I\$5, and under an optimal VE scenario (i.e. transitions to *HPV-16/18* states and *HPV-Other* states reduced by 80% and 50%, respectively) with vaccine costs set at \leq I\$31. With costs \geq I\$31 and VE reduced to account for likely diminished effectiveness among adult HIV-positive women, vaccination alone became dominated through extension with a higher incremental cost-effectiveness ratio than VIA screening. Specifically, with costs \geq I\$31 vaccination was dominated when VE fell below approximately 70% and 40% for reducing transitions to *HPV-16/18* and *HPV-Other* states, respectively (or similar combinations of strata specific VE that yield the same overall reductions in transitions). Overall, vaccination becomes dominated through extension when costs exceed I\$38, I\$24, I\$15, and I\$7 for each of the

four levels of VE examined, respectively. Domination through extension applies when a strategy is less costly but also less effective than an alternative strategy, to such a degree that the cost per life year saved is greater than a more costly and more effective option. Similar patterns in relative cost-effectiveness remained when duration of immunity was reduced to 10 years.

E4.2 Sensitivity analyses (Table 12)

One-way sensitivity analyses with duration of immunity and vaccine costs set at 15 years and I\$31, respectively, revealed that estimates of cost-effectiveness were most influenced by death from other causes, discounting, and the specificity of VIA. However, relative cost-effectiveness remained stable across several input parameters such that vaccination with optimal efficacy coupled with VIA screening remained ‘very cost-effective’ (except with maximum discounting and death from other causes in which ICERs slightly exceeded the WTPT for ‘very cost-effective’). Vaccination with minimal efficacy remained dominated by extension when varying all inputs examined. Notably, with the maximum specificity of VIA (89%) vaccination becomes dominated even with optimal VE, highlighting the costly implications of false-positives. Reductions in the initial prevalence of HPV (i.e. increased initial parameterization for *Normal*) lead to increased cost-effectiveness of vaccination as a greater proportion of women could immediately benefit from vaccination.

When examining the impact of uncertainty using tornado plots (Figure 9), vaccine costs, VE for HPV-16/18, the specificity of VIA, and death from other causes emerge as the most consistently influential input variables. VE for transitions to *HPV-Other* states, retention in follow-up LEEP care, VIA sensitivity, and cryotherapy effectiveness were less influential.

E5. Discussion

The objective of this simulation model was to provide insight into the potential impact of HPV vaccination in the high-risk population of HIV-positive women in Senegal. This model found that vaccination was only a cost-effective option under optimal vaccine efficacy and/or costing scenarios. Results were largely driven by relative

differences in costs as the impact on life expectancy of the cervical cancer prevention strategies examined was minimal due to high rates of all-cause mortality among HIV-positive women in SSA. Recent efforts to subsidize HPV vaccination cost hold promise; however, GAVI funding for HPV vaccination is specific to adolescent girls such that vaccine costs for HIV-positive adult women will likely exceed that of the subsidized series. Importantly, efforts to develop vaccines with less dependence on cold-chain storage and distribution are underway, which, if successful, could greatly reduce the cost and infrastructural requirements for HPV vaccination [207].

We used reported vaccine efficacy among previously HPV infected patients to provide a theoretical upper bound for the relative impact of vaccination among HIV-positive women. This literature is extremely limited with significant heterogeneity in methodology (e.g. vaccine type, dosage, endpoints, and underlying study population with regards to age and prior infection). These analyses were post-hoc, with limited statistical power, and significant variability in reported estimates. In light of these factors, the potential impact of vaccination was modeled generically (in other words, differences in efficacy for bivalent, quadrivalent and nonavalent vaccines were not examined due to a lack of data). Further, previously HPV infected HIV-negative women likely present over estimates of efficacy as they are immunocompetent and capable of mounting an immune response such that they became seropositive. HIV-positive women may be less capable of both mounting and maintaining an immune response; thus, the capacity to extrapolate effects observed in previously HPV infected HIV-negative samples to HIV-positive women remains unknown. For instance, vaccination of HIV-positive individuals against Hepatitis A, Hepatitis B, Hepatitis C, influenza, pneumococcus, diphtheria, pertussis, tetanus, haemophilus influenza, and cholera elicit lower immune responses than in HIV-negative individuals [208-228]. Further, HPV-16/18 titer levels among those with HIV have been shown to be 23% to 70% lower than HIV-negative controls [52, 53]. Importantly, responses among those on ART often remain sub-optimal relative to HIV-negative individuals, although they have in some cases been shown to improve with larger and/or more frequent vaccine doses [203, 208]. Finally, the potential impact of reactivation on HPV vaccination efficacy is largely unknown as no therapeutic benefits

have been demonstrated; however, vaccine-induced immune responses could improve immune responses to reactivation. These factors should be considered when interpreting results.

There are several limitations to this analysis. The present model does not account for indirect protective effects of vaccination (i.e. reduced HPV transmission to sexual partners), which may result in an underestimate of vaccine cost-effectiveness. However, the assumption that indirect effects could result from vaccinating HIV-positive women is largely determined by two factors: the underlying prevalence of HIV and the presumption that there are in fact meaningful protective effects to pass on. Less than 1% of Senegalese women are HIV-positive and HPV vaccine efficacy among this population remains unknown [82]. Further, vaccine effectiveness is examined at an aggregate level; however, given prior HPV exposure at the time of vaccination, CD4+ count, and ART use there may be underlying heterogeneity within the HIV-positive population which should be considered when generalizing results [53]. For instance, based on evidence that vaccine induced titers levels may be greater among those on ART [202], delaying vaccination could be considered among women with low CD4+ counts at the time of diagnosis until immune reconstitution has been achieved with treatment. The present model is also ageless and assumes HPV vaccination at time of HIV diagnosis (i.e. a point-of-care approach). There is sparse literature reporting the average age at time of HIV diagnosis, with the majority of literature regarding HIV testing focusing on CD4+ count and other indicators of disease progression at time of diagnosis. The average age of the underlying cohort used to estimate natural history transitions was 34 years. Estimates of life expectancy for HIV-positive women in SSA are highly varied. Based on an analysis of fourteen multinational HIV-positive cohort studies, it was found that life expectancy is highly dependent on CD4+ count at time of ART initiation, as well as continued access and adherence to ART, with an average life expectancy in those with HIV approximately two-thirds that of HIV-negative controls [229, 230]. ART coverage in Senegal is currently estimated at approximately 50% [65] and testing strategies target high-risk populations (such as commercial sex workers) which may overlook key sub-populations (such as married women in polygamous relationships) resulting in heterogeneity in age at

time of HIV diagnosis. Given these factors, the impact of the time horizon chosen for present analysis was examined (results not shown) with vaccination becoming more cost-effective with an extended time horizon; however, there were no meaningful changes to relative comparisons of cost-effectiveness. Lastly, the present cost-effectiveness model is based on the inclusion of factors directly related to cervical cancer with the assumption that all background variables are held constant (referred to as the steady-state assumption). In reality, there are many dynamic variables that can impact results across time and space (such as civil unrest, natural disasters, global warming and changes in economic stability).

E6. Conclusion

With lower vaccine-induced titer levels reported among adult HIV-positive women and a potential corresponding reduction in vaccine efficacy, HPV vaccination costs must be reduced for primary prevention to be cost-effective in comparison to screening. Efforts to implement targeted screening, reduce the cost of HPV vaccination, develop therapeutic vaccines, and evaluate upcoming HPV antiviral treatments should be made for this high-risk population.

F. CONTRIBUTIONS AND CONCLUSIONS

This research involves the synthesis of epidemiologic data and methodologies from several public health disciplines. Key contributions are discussed below.

Quantifying the natural history of HPV among women in the high-risk setting of SSA, using a large sample and providing direct comparisons between HIV-positive and HIV-negative women, represents a major contribution to the field. HIV-positive women were found to depart from their HIV-negative counterparts at each stage of the natural history, providing unique insight in the pathophysiology of HPV among HIV-positive women and evidence that sustained prevention measures are needed. Importantly, natural history estimates provide the foundation for simulation modeling such that this work directly supports the development of simulation models. Estimates are presented in two formats (unadjusted in AIM I and stratified by HPV type in AIM II). These data allow other research teams from around the world to create cervical cancer prevention models tailored to different settings and different sub-populations of HIV-positive women. With independent teams constructing models based on different assumptions, model structures, and background target populations comes a more robust understanding of cost-effective prevention.

With clear evidence that HIV-positive women are at an increased risk of cervical cancer the following research questions were addressed: given high competing risks among HIV-positive women (i.e. high overall mortality) can cervical cancer interventions yield meaningful effects, and if so, what is the optimal strategy based on cost-effectiveness and the context of medical care infrastructure within Senegal and the more general low resource setting of SSA. This research demonstrated that cervical cancer screening can yield meaningful improvements in life expectancy such that VIA screening is ‘very cost-effective’ based on WHO criterion. For instance, the discounted average increased life expectancy of 1.7 resulting from annual VIA yields approximately 2,830 additional life years among the estimated 20,000 HIV-positive women in the Senegal. This analysis represents the first cost-effectiveness analysis of cervical cancer screening among HIV-positive women in Africa, with comprehensive comparisons of several

different screening strategies. This model was developed for the context of Senegal; however, given the demonstrated stability of findings in sensitivity analyses and sound biological exchangeability of natural history estimates, there may be a reasonable foundation upon which to generalize findings to SSA nations with similar economic and social characteristics.

With ongoing efforts to expand HPV vaccine coverage and subsidize costs for adolescent girls in low resource settings, the potential application to HIV-positive women is of growing interest. This research demonstrated that targeted HPV vaccination among HIV-positive women was only cost-effective in comparison to screening under optimal vaccine efficacy and costing scenarios. Given lower vaccine-induced titer levels reported among adult HIV-positive women and a potential corresponding reduction in vaccine efficacy, vaccination costs must be reduced for primary prevention to be cost-effective.

Importantly, the simulation model developed for AIM II and AIM III uses a conditional framework in that cost-effectiveness is examined within a specific disease (cervical cancer). With increased computational capacities, the field of decision analysis is now developing approaches for examining cost-effectiveness across diseases and populations. This represents a major methodological advancement in that head-to-head comparisons across models can be made. When accounting for high competing risks among this population, it is possible that while cervical cancer screening is cost-effective, other interventions are more cost-effective (for example, efforts to expand HIV testing, manage chronic tuberculosis, etc.). This methodological advancement represents an exciting opportunity with great potential to effect change and better optimize resource allocation. Efforts to work collaboratively with other decision modeling teams will be made to address this limitation and advance the field.

In summary, this research capitalizes on extensive existing data from Senegal, uniquely examines both primary and secondary prevention strategies, and provides a platform for future research endeavors. Key findings indicate that efforts should be made to implement targeted screening, reduce the cost of HPV vaccination, develop therapeutic vaccines, and evaluate upcoming HPV antiviral treatments for this high-risk population.

Table 1. Abbreviations

ADE	AIDS defining event
AIDS	acquired immune deficiency syndrome
AIS	adenocarcinoma <i>in situ</i>
ART	anti-retroviral therapy
ASCUS	atypical squamous cells of undetermined significance
CDC	Centers of Disease Control and Prevention
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CIN	cervical intraepithelial neoplasia
CPI	consumer price index
CSW	commercial sex worker
GDP	gross domestic product
EGL	external genital lesions
HC2	Hybrid Capture 2
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR-HPV	high-risk HPV
HSIL	high-grade squamous intraepithelial lesion
ICC	invasive cervical cancer
ICER	incremental cost-effectiveness ratios
ITT	intention-to-treat
LEEP	loop electrosurgical excision procedure
LR-HPV	low-risk HPV
LSIL	low-grade squamous intraepithelial lesion
OIs	opportunistic infections
PCR	polymerase chain reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PPP	purchasing power parity
RCT	randomized controlled trials
SSA	sub-Saharan Africa
SVA	single visit approach
TVC	total vaccinated cohort (regardless of HPV-seropositivity)
US	United States
VC	vaccine cost
VE	vaccine efficacy
VIA	visual inspection with acetic acid
WHO	World Health Organization
WTPT	willingness-to-pay threshold

Table 2. Overview of studies included in the analysis

No.	Study Title	Study duration	Inclusion criteria	Study sample*	Type-specific HPV DNA detection	Relevant references
1	Natural history of cervical neoplasia in HIV-1 and HIV-2	1994 - 1999	Age \geq 15	755 (291 HIV+)	12 types up to 1998 27 types thereafter	[3, 122, 136]
2	Control of HIV-1 by HIV-2 associated immune responses	2000 - 2006	Age \geq 15 ART naïve	121 (119 HIV+)	38 types	[139]
3	Epidemiology of HIV-1/HIV-2 dual infection	2001 - 2005	Age \geq 15 HIV-1/2+ On ART	7 (7 HIV+)	38 types	[140]
4	Developing new approaches for cervical cancer control	2002 - 2007	Age \geq 15	3 (3 HIV+)	38 types	[137]
5	Antiretroviral therapy for HIV-2 infection in Senegal	2005 - ongoing	Age \geq 16 HIV-2+ On ART	4 (4 HIV+)	38 types	[138]
6	HIV-associated DNA hyper-methylation in cervical cancer	2005 - 2010	Age \geq 18	387 (151 HIV+)	38 types	[67, 141]

* Sample size for the present study differs from the total samples reported in prior publications due to missing HIV status and/or the lack of longitudinal cytology/histology and HPV DNA data.

Table 3. Baseline characteristics of pooled study sample

Characteristic	HIV- (n = 702)	HIV+ (n = 575)	Total N = 1,277
Age (years)			
Median	34	35	34
Interquartile range	27-44	29-41	28-42
Age at sexual debut (years)			
Median	17	17	17
Interquartile range	15-19	15-19	15-19
Lifetime sex partners (%)			
None	0.6	0.2	0.4
One	45.5	31.2	39.0
2-5	25.2	32.8	28.6
6-10	1.7	1.9	1.8
>10	27.0	33.9	30.2
Religion (%)			
Muslim	85.5	88.9	87.1
Christian	14.1	10.6	12.4
Other/None	0.4	0.5	0.5
Marital status (%)			
Married (monogamy)	34.4	24.8	30.1
Married (polygamy)	25.5	14.3	20.5
Never married	15.4	9.4	12.7
Separated/divorced	20.4	32.2	25.7
Widowed	4.3	19.3	11.0
Education (%)			
None	42.6	50.5	46.1
Primary School	30.1	32.9	31.4
Secondary School	24.3	15.5	20.4
University	3.0	1.1	2.1
Follow-up duration (days)			
Median	780	808	791
Interquartile range	368-1,155	386-1,330	377-1,213
Interval between clinic visits (days)			
Median	139	134	136
Interquartile range	122-232	119-238	120-236
Commercial sex worker (%)	24.8	32.5	28.3
Cigarette use (% , ever)	15.4	19.5	17.2
Contraception use (% , ever)	46.9	37.1	42.5
Alcohol consumption (% , ever)	9.0	14.6	11.5

Table 3. continued...

Characteristic	HIV- (n = 702)	HIV+ (n = 575)	Total N = 1,277
<i>HIV-positive subsample</i>			
HIV-subtype (%)			
HIV-1	-	68.0	-
HIV-2	-	23.0	-
Dual infection	-	9.0	-
CD4+ count (cells/ μ L)			
Median	-	416	-
Interquartile range	-	257-633	-
ART use (% , ever)	-	27.2	-
AIDS ^a (%)	-	24.0	-

a: Classified by a defining event or CD4+ count < 200 recorded at any time during follow-up.

Table 4. Hazard ratios for HIV+ and HIV- Senegalese women

Initial Health Stages	Transition Health Stages						
	Total	HPV			HSIL		
n		Hazard ratio	P-value	n	Hazard ratio	P-value	
<i>Normal</i>	1054	503		28			
HIV+	484	289	1.62	<0.0001	17	1.60	0.21
HIV-	570	214	ref.	-	11	ref.	-
Incident Classification	594	295	1.64	<0.0001	18	1.69	0.17
Prevalent Classification	460	208	ref.	-	10	ref.	-
			<i>Normal</i>		<i>HSIL</i>		
<i>HPV</i>	Total	n	Hazard ratio	P-value	n	Hazard ratio	P-value
	1233	752			122		
HIV+	602	296	0.47	<0.0001	83	2.57	<0.0001
HIV-	631	456	ref.	-	39	ref.	-
Incident Classification	489	321	1.85	<0.0001	50	0.87	0.46
Prevalent Classification	744	431	ref.	-	72	ref.	-
			<i>Normal</i>		<i>HPV</i>		
<i>HSIL</i>	Total	n	Hazard ratio	P-value	n	Hazard ratio	P-value
	168	24			113		
HIV+	106	13	0.59	0.21	76	1.18	0.45
HIV-	62	11	ref.	-	37	ref.	-
Incident Classification	105	16	1.39	0.43	69	0.92	0.68
Prevalent Classification	63	8	ref.	-	44	ref.	-

*Note: Transition numbers (by row) do not sum to the total provided as women remained in the same state for the duration of follow-up or transitioned to cervical cancer. Transitions to cancer were not examined due to extremely limited sample sizes.

Table 5. Univariate analyses of potential effect modifiers, HIV+ women

Initial Health Stages	Transition Health Stages						
	Total	HPV			HSIL		
		n	Hazard ratio	P-value	n	Hazard ratio	P-value
<i>Normal</i>							
CD4+ count < 200	48	27	1.31	0.22	4	3.31	0.03
CD4+ count ≥ 200	412	257	ref.	-	13	ref.	-
HPV - 16/18	26	23	0.96	0.86	3	4.67	0.04
HPV - Other	200	183	ref.	-	5	ref.	-
HPV - Multiple Types	67	60	1.99	<0.0001	3	2.07	0.31
HPV - Single Type	272	146	ref.	-	5	ref.	-
Age ≤ 25	68	46	1.51	0.01	1	0.39	0.37
Age > 25	414	242	ref.	-	16	ref.	-
HIV-1	316	205	1.85	<0.0001	8	0.41	0.06
HIV-2	130	65	ref.	-	9	ref.	-
			<i>Normal</i>		<i>HSIL</i>		
	Total	n	Hazard ratio	P-value	n	Hazard ratio	P-value
<i>HPV</i>							
CD4+ count < 200	101	32	0.54	0.003	22	2.23	0.005
CD4+ count ≥ 200	466	257	ref.	-	56	ref.	-
HPV - 16/18	170	29	0.36	<0.0001	30	2.05	0.0059
HPV - Other	449	178	ref.	-	41	ref.	-
HPV - Multiple Types	306	63	0.36	<0.0001	48	2.29	0.0016
HPV - Single Type	313	144	ref.	-	23	ref.	-
Age ≤ 25	87	46	1.26	0.22	13	1.13	0.73
Age > 25	514	249	ref.	-	70	ref.	-
HIV-1	425	192	0.74	0.03	63	1.83	0.08
HIV-2	131	82	ref.	-	12	ref.	-

*Transition numbers (by row) do not sum to total as some women remained in the same state for the duration of follow-up. HPV-type specific analyses from transitions from *Normal* (the initial state) were conducted based on the type acquired, while analyses of transitions from *HPV* (the initial state) were conducted based on what type women had while HPV+.

Table 6. Key model parameters for base-case and sensitivity analyses

Parameter	Base	Minimum	Maximum	References
Natural history, 4-month				
<i>Progression</i>				
Normal to HPV-16/18	0.0247	0.0159	0.0385	[171]
Normal to HPV-Other	0.1548	0.1323	0.1847	[171]
Normal to CIN2/3-16/18	0.0026	0.0008	0.0089	[171]
Normal to CIN2/3-Other	0.0041	0.0016	0.0106	[171]
HPV-16/18 to CIN2/3-16/18	0.0439	0.0291	0.0674	[171]
HPV-Other to CIN2/3-Other	0.0226	0.0163	0.0316	[171]
HPV-16/18 to HPV-Other	0.1053	0.0786	0.1445	[171]
HPV-Other to HPV-16/18	0.0465	0.0358	0.0607	[171]
CIN2/3-16/18 to ICC Early	0.1065	0.0335	0.1680	[171, 231] ^a
CIN2/3-Other to ICC Early	0.0160	0.0084	0.0440	[171, 231] ^a
ICC Early to ICC Late ^b	0.1517	0.1062	0.1972	[231, 232]
<i>Regression</i>				
HPV-16/18 to Normal	0.0536	0.0388	0.0748	[171]
HPV-Other to Normal	0.1252	0.1074	0.1474	[171]
CIN2/3-16/18 to HPV-16/18	0.4000	0.3500	0.4500	[171] ^a
CIN2/3-Other to HPV-Other	0.4500	0.4000	0.5000	[171] ^a
CIN2/3-16/18 to Normal	0.0050	0.0010	0.0100	[171] ^a
CIN2/3-Other to Normal	0.0582	0.0273	0.1268	[171]
<i>Mortality</i>				
Other causes	0.0125	0.0050	0.0200	[81, 172-174]
Early ICC ^b	0.0431	0.0302	0.0561	[231, 233]
Late ICC ^b	0.1216	0.0852	0.1581	[231, 234]
Symptoms of Late ICC	0.4200	0.2600	0.6600	[231, 232]

Table 6. continued...

Parameter	Base	Minimum	Maximum	References
Screening validity				
Rapid HPV, sensitivity	0.82	0.74	0.90	[167, 235, 236]
Rapid HPV, specificity	0.64	0.51	0.77	
HC2, sensitivity	0.90	0.84	0.95	[135, 237-240]
HC2, specificity	0.64	0.51	0.77	
Cytology, sensitivity	0.73	0.53	0.93	[231, 237, 238, 240-244]
Cytology, specificity	0.73	0.49	0.96	
VIA, sensitivity	0.75	0.63	0.87	[135, 237, 238, 240, 242, 244-246]
VIA, specificity	0.70	0.51	0.89	
Treatment effectiveness, %				
Pre-cancer treatment	80.0	60.0	90.0	[125, 135, 187, 188, 239, 247-260]
Retention in care	100.0	50.0	100.0	[177-179, 248, 261-263]
Costs, 2013 I\$				
Rapid HPV DNA testing	24	5	42	[264]
HC2 HPV DNA testing	22	12	31	[194, 265-267]
Cytology	10	4	16	[194, 265-268]
VIA	5	2	8	[169, 265-267, 269]
Cryotherapy	53	15	90	[169, 265-267, 269]
LEEP	164	47	280	[265-267]
Hysterectomy	540	324	755	[265-267]
Palliative care	200	121	280	[270, 271]

a: Estimated using statistical calibration with initial values from the Senegal data.

b: Variation assumed to be $\pm 30\%$ of the base-case value.

Table 7. Cost-effectiveness of cervical cancer screening strategies in HIV+ Senegalese women

Strategy	Cost 2013 I\$	Life years	ICER*	Cancer incidence	Cancer death	False positives ^a	False negatives ^a	Over referral to treatment ^a
Baseline screening								
No screening	66	9.555	reference	0.071941	0.048573	-	-	-
VIA	101	9.606	681	0.066442	0.040406	554	22	554
Cytology	106	9.606	dom	0.066562	0.040465	498	24	498
Rapid HPV/VIA triage	123	9.603	dom	0.067278	0.040824	862	35	199
Rapid HPV/cytology	126	9.603	dom	0.067384	0.040878	842	37	179
HC2	140	9.609	14,863	0.065592	0.039999	666	9	666
Rapid HPV	144	9.607	dom	0.066035	0.040209	665	16	665
Baseline and 5 year screening								
VIA	110	9.628	610	0.064400	0.034034	780	30	780
Cytology	117	9.627	dom	0.064574	0.034124	702	32	702
Rapid HPV/VIA triage	140	9.624	dom	0.065603	0.034664	1,215	47	280
Rapid HPV/cytology	144	9.624	dom	0.065754	0.034743	1,187	49	252
HC2	164	9.631	15,153	0.063142	0.033384	938	12	938
Rapid HPV	169	9.629	dom	0.063802	0.033724	937	21	937
Baseline, 5, and 10 year screening								
VIA	119	9.631	698	0.062716	0.030744	962	36	962
Cytology	127	9.630	dom	0.062936	0.030851	866	39	866
Rapid HPV/VIA triage	154	9.627	dom	0.064224	0.031487	1,498	56	346
Rapid HPV/cytology	158	9.627	dom	0.064412	0.031580	1,464	59	311
HC2	182	9.635	17,110	0.061120	0.029969	1,156	14	1,156
Rapid HPV	188	9.633	dom	0.061961	0.030376	1,155	25	1,155
Baseline and triennial screening								
VIA	150	9.652	873	0.058424	0.025095	1,523	54	1,523
Cytology	162	9.651	dom	0.058756	0.025227	1,371	59	1,371
Rapid HPV/VIA triage	202	9.647	dom	0.060696	0.026002	2,372	85	547
Rapid HPV/cytology	208	9.647	dom	0.060977	0.026115	2,317	88	493
HC2	244	9.656	21,183	0.055982	0.024130	1,832	21	1,832
Rapid HPV	253	9.654	dom	0.057274	0.024639	1,830	39	1,830

Table 7. continued...

Strategy	Cost 2013 I\$	Life years	ICER*	Cancer incidence	Cancer death	False positives^a	False negatives^a	Over referral to treatment^a
Baseline and annual screening								
VIA	273	9.693	1,500	0.042742	0.014773	3,637	115	3,637
Cytology	300	9.692	dom	0.043430	0.014933	3,271	124	3,271
Rapid HPV/VIA triage	388	9.688	dom	0.047476	0.015876	5,653	180	1,304
Rapid HPV/cytology	402	9.687	dom	0.048065	0.016014	5,520	188	1,174
HC2	489	9.698	41,195	0.037716	0.013604	4,380	45	4,380
Rapid HPV	509	9.695	dom	0.040366	0.014220	4,372	82	4,372

*Incremental cost-effectiveness ratios were not presented for those strategies that were dominated (i.e. more costly and less effective than another).

a: per 1,000 women screened over the course of 15 years (women may experience false positives, false negatives, and over referrals to treatment more than once in those scenarios in which screening is recurrent).

Table 8. One-way sensitivity analyses for cost-effectiveness of cervical cancer screening strategies in HIV+ Senegalese women

Input variable	Incremental cost-effectiveness ratio					
	VIA	Cytology	Rapid HPV/ VIA	Rapid HPV/ Cytology	HC2	Rapid HPV
Base case	698	dom	dom	dom	17,110	dom
Retention						
Minimum, 0.5	1,100	640	dom	dom	dom	41,447
Base, 1.0	698	dom	dom	dom	17,110	dom
Progression to cervical cancer						
Minimum, 16/18: 0.0335, Other: 0.0084	1,425	dom	dom	dom	41,229	dom
Maximum, 16/18: 0.1680, Other: 0.0440	414	dom	dom	dom	11,206	dom
Discounting						
Minimum, 0.00	508	dom	dom	dom	13,722	dom
Maximum, 0.05	852	dom	dom	dom	19,791	dom
Death – other causes						
Minimum, 0.005	555	dom	dom	dom	14,563	dom
Maximum, 0.020	872	dom	dom	dom	20,144	dom
Pre-cancer treatment effectiveness						
Minimum, 0.6	772	dom	dom	dom	20,236	dom
Maximum, 0.9	666	dom	dom	dom	16,255	dom
Cervical cancer mortality						
Minimum, Early: 0.0302, Late: 0.0561	1,056	dom	dom	dom	25,037	dom
Maximum, Early: 0.0852, Late: 0.1581	653	dom	dom	dom	15,544	dom
Potential impact of ART uptake						
Low ART: Maximum progression/death, minimum regression	237	dom	dom	dom	6,906	dom
High ART: Minimum progression/death, maximum regression	2,298	dom	dom	dom	82,378	dom

*Based on three total screens (baseline with five and ten year screenings)

Table 9. Model parameters for base-case and sensitivity analyses

Parameter	Base	Minimum	Maximum	References
Initial vector, %^a				
Normal	34.86	27.89	41.83	[171]
HPV-16/18	14.87	11.89	17.84	[171]
HPV-Other	42.91	34.33	51.49	[171]
CIN2/3-16/18	2.39	1.91	2.87	[171]
CIN2/3-16/18	3.59	2.87	4.30	[171]
ICC	0.69	0.55	0.83	[171]
Natural history, 4-month risk				
<i>Progression</i>				
Normal to HPV-16/18	0.0247	0.0159	0.0385	[171]
Normal to HPV-Other	0.1548	0.1323	0.1847	[171]
Normal to CIN2/3-16/18	0.0026	0.0008	0.0089	[171]
Normal to CIN2/3-Other	0.0041	0.0016	0.0106	[171]
HPV-16/18 to CIN2/3-16/18	0.0439	0.0291	0.0674	[171]
HPV-Other to CIN2/3-Other	0.0226	0.0163	0.0316	[171]
HPV-16/18 to HPV-Other	0.1053	0.0786	0.1445	[171]
HPV-Other to HPV-16/18	0.0465	0.0358	0.0607	[171]
CIN2/3-16/18 to ICC Early	0.1065	0.0335	0.1680	[171, 231] ^b
CIN2/3-Other to ICC Early	0.0160	0.0084	0.0440	[171, 231] ^b
ICC Early to ICC Late ^c	0.1517	0.1062	0.1972	[231, 232]
<i>Regression</i>				
HPV-16/18 to Normal	0.0536	0.0388	0.0748	[171]
HPV-Other to Normal	0.1252	0.1074	0.1474	[171]
CIN2/3-16/18 to HPV-16/18	0.4000	0.3500	0.4500	[171] ^b
CIN2/3-Other to HPV-Other	0.4500	0.4000	0.5000	[171] ^b
CIN2/3-16/18 to Normal	0.0050	0.0010	0.0100	[171] ^b
CIN2/3-Other to Normal	0.0582	0.0273	0.1268	[171]

Table 9. continued...

Parameter	Base	Minimum	Maximum	References
Natural history, 4-month risk				
<i>Mortality</i>				
Other causes	0.0125	0.0050	0.0200	[81, 172-174].
Early ICC ^c	0.0431	0.0302	0.0561	[231, 233]
Late ICC ^c	0.1216	0.0852	0.1581	[231, 234]
Symptoms of Late ICC	0.4200	0.2600	0.6600	[231, 232]
Vaccine efficacy, %				
HPV-16/18 states	-	0.0	80.0	[272-276]
HPV-Other states	-	0.0	50.0	
Screening/treatment performance				
VIA, sensitivity	0.75	0.63	0.87	[135, 237, 238, 240, 242, 244-246]
VIA, specificity	0.70	0.51	0.89	
Pre-cancer treatment	0.80	0.60	0.90	[125, 135, 187, 188, 239, 247-260]
Costs, 2013 I\$				
VIA	5	2	8	[169, 265-267, 269]
Cryotherapy	53	15	90	[169, 265-267, 269]
LEEP	164	47	280	[265-267]
Hysterectomy	540	324	755	[265-267]
Palliative care	200	121	280	[270, 271]
HPV vaccination	31	5	57	[265, 266, 268, 277-279]

a: Variation assumed to be $\pm 20\%$ of the base-case value.

b: Estimated using statistical calibration with initial values from the Senegal data.

c: Variation assumed to be $\pm 30\%$ of the base-case value.

Table 10. Selected outcomes, HPV vaccine trials among HIV-negative women with prior HPV

Study	Study design, vaccine type	Age, follow-up	Inclusion criteria	Vaccine Efficacy	Main conclusions
Lehtinen et al.[272]	RCT, doubled-blinded, Bivalent (N=17,402)	15-25, 48 mo. (median)	Women with ≤ 6 lifetime sex partners, TVC	60.7% reduction in HPV-16/18 CIN2+ (80.1% vs. 33.2% in 15-17 and 21-25 year olds) 33.1% reduction in total CIN2+ (44.0% vs. 8.9% in 15-17 and 21-25 year olds)	Effectiveness in adult women which reduced with increasing age (i.e. inversely associated)
Castellsague et al.[273]	RCT, double-blinded, Quadrivalent (N= 3,819)	24-45, 48 mo. (median)	Women at least 5 years free of cervical disease or genital warts	66.9% reduction in persistent infection (6 mo.), CIN or EGL among HPV-6/11/16/18 seropositive and DNA-negative women 47.2% reduction in persistent infection (6 mo.), CIN or EGL among ITT sample	Effectiveness in adult women, seropositivity is an underestimate of prior exposure likely producing over estimates of VE
Szarewski et al. [274]	Sub-analysis of RCT, double-blinded, Bivalent (N= 3,489)	15-25, 39 mo. (median)	HPV-16/18 seropositive and DNA-negative women	49.7% reduction in HPV-16/18 infection 87.8% reduction in HPV-16/18 CIN1+ 88.5% reduction in HPV-16/18 CIN2+ 67.2% reduction in total CIN1+ 68.8% reduction in total CIN2+	Effectiveness in women with serological indications of prior infection
Joura et al. [275]	Retrospective analysis of RCT, double-blinded, Quadrivalent (N= 1,350)	15-26, 16 mo. (median)	Women who received treatment for cervical pre-cancer	74.2% reduction in HPV-6/11/16/18 CIN1+ 61.3% reduction in HPV-6/11/16/18 CIN2+ 48.3% reduction in total CIN1+ 64.9% reduction in total CIN2+	Effectiveness in women with prior treatment for cervical pre-cancer
FUTURE II Study Group[276]	Sub-analysis of two RCTs, double-blinded, Quadrivalent (N= 3,489)	15-26, 36 mo. (median)	Women with ≤ 4 lifetime sex partners and no genital	10.6% reduction in HPV-16/18 CIN2+ or AIS among women who were HPV-16/18 seronegative, DNA positive at baseline 1.2% reduction in HPV-16/18 CIN2+ or AIS among women who were HPV-16/18 seropositive, DNA positive at baseline	No meaningful effectiveness in women with evidence of former or current infection at baseline

RCT, randomized controlled trials; CIN, cervical intraepithelial neoplasia; EGL, external genital lesions; ITT, intention-to-treat; TVC, total vaccinated cohort (regardless of HPV-seropositivity); VE, vaccine efficacy; AIS, adenocarcinoma *in situ*

Table 11. Vaccination in HIV+ Senegalese women, exploratory cost-effectiveness analysis of efficacy

Strategy	Cost 2013 I\$				Life Years	ICER				Cancer Incidence	Cancer Death
	VC-5	VC-15	VC-31	VC-57		VC-5	VC-15	VC-31	VC-57		
<i>Duration of immunity - 15 years</i>											
VE - 80% HPV-16/18, 50% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	dom	ref.	ref.	ref.	0.071941	0.048573
Vaccination	57	67	83	109	9.590	ref. ^b	39	498	ex. dom	0.049864	0.037723
VIA	119	119	119	119	9.631	dom	ex. dom	866	698	0.062716	0.030744
Vaccination & VIA	114	124	140	166	9.653	907	907	985	2,191	0.044536	0.024347
VE - 60% HPV-16/18, 30% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	Dom	ref.	ref.	ref.	0.071941	0.048573
Vaccination	62	72	88	114	9.577	ref. ^b	285	ex. dom	ex. dom	0.058228	0.041739
VIA	119	119	119	119	9.631	Dom	ex. dom	698	698	0.062716	0.030744
Vaccination & VIA	118	128	144	170	9.645	819	819	1,763	3,612	0.051231	0.026651
VE - 40% HPV-16/18, 20% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	dom.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	66	76	92	118	9.569	ref. ^b	694	ex. dom	ex. dom	0.063541	0.044360
VIA	119	119	119	119	9.631	ex. dom	698	698	698	0.062716	0.030744
Vaccination & VIA	120	130	146	172	9.640	769	1,263	3,078	6,026	0.055623	0.028200
VE - 20% HPV-16/18, 10% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	ref.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	68	78	94	120	9.561	386	ex. dom	ex. dom	dom	0.068057	0.046615
VIA	119	119	119	119	9.631	727	698	698	698	0.062716	0.030744
Vaccination & VIA	122	132	148	174	9.635	768	3,171	7,016	13,264	0.059414	0.029553

VE, vaccine efficacy; VC, vaccine cost; dom, dominated; ex.dom, dominated by extension. VIA occurs at baseline, year five, and year 10 of the simulation

a: per 1,000 women screened

b: strategy become more cost-effective than no active screening

Table 11. continued...

Strategy	<u>Cost 2013 I\$</u>				Life Years	<u>ICER</u>				Cancer Incidence	Cancer Death
	VC-5	VC-15	VC-31	VC-57		VC-5	VC-15	VC-31	VC-57		
<i>Duration of immunity - 10 years</i>											
VE - 80% HPV-16/18, 50% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	dom.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	58	68	84	110	9.589	ref. ^b	54	517	ex. dom	0.054398	0.038169
VIA	119	119	119	119	9.631	dom.	ex. dom	847	698	0.062716	0.030744
Vaccination & VIA	115	125	141	167	9.652	906	906	1,021	2,243	0.048928	0.024770
VE - 60% HPV-16/18, 30% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	dom.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	63	73	89	115	9.577	Ref ^b	301	ex. dom	ex. dom	0.060959	0.042009
VIA	119	119	119	119	9.631	dom.	ex. dom	698	698	0.062716	0.030744
Vaccination & VIA	118	128	144	170	9.645	819	819	1,808	3,682	0.053951	0.026918
VE - 40% HPV-16/18, 20% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	dom.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	66	76	92	118	9.569	ref.	ex. dom	ex. dom	ex. dom	0.065185	0.044523
VIA	119	119	119	119	9.631	ex. dom	698	698	698	0.062716	0.030744
Vaccination & VIA	120	130	146	172	9.640	769	1,301	3,139	6,127	0.057282	0.028364
VE - 20% HPV-16/18, 10% HPV-Other											
No screening/vaccination	66	66	66	66	9.555	ref.	ref.	ref.	ref.	0.071941	0.048573
Vaccination	68	78	94	120	9.561	401	ex. dom	ex. dom	dom	0.068807	0.046689
VIA	119	119	119	119	9.631	725	698	698	698	0.062716	0.030744
Vaccination & VIA	122	132	148	174	9.635	798	3,232	7,127	13,457	0.060178	0.029629

VE, vaccine efficacy; VC, vaccine cost; dom, dominated; ex.dom, dominated by extension. VIA occurs at baseline, year five, and year 10 of the simulation

a: per 1,000 women screened

b: strategy become more cost-effective than no active screening

Table 12. One-way sensitivity analyses, cost-effectiveness of cervical cancer prevention strategies in HIV+ Senegalese women

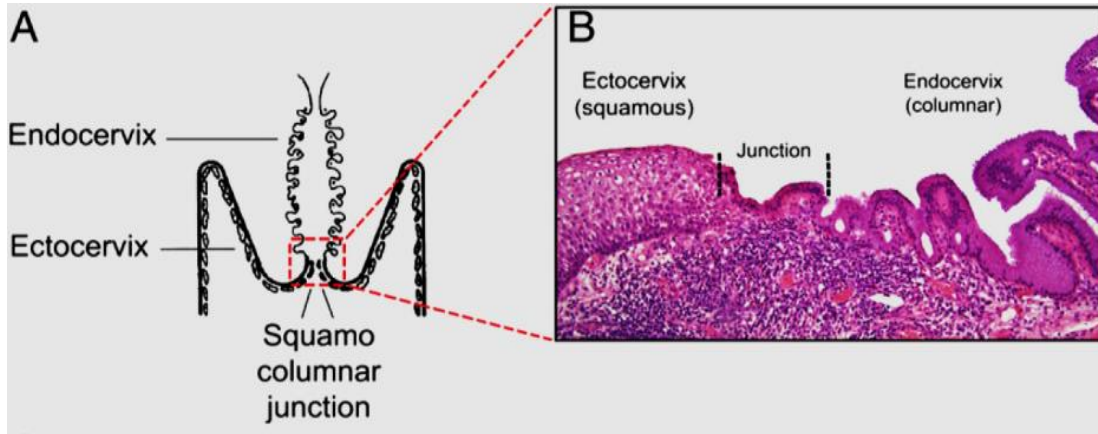
Input variable	Incremental cost-effectiveness ratio (life expectancy)					
	VE – 80% HPV-16/18, 50% HPV-Other			VE – 20% HPV-16/18, 10% HPV-Other		
	Vaccination	VIA	Vaccination & VIA	Vaccination	VIA	Vaccination & VIA
Base case	498 (9.590)	866 (9.631)	985 (9.653)	ex. dom (9.561)	698 (9.631)	7,016 (9.635)
Death – other causes						
Minimum, 0.0050	305 (11.105)	ex. dom (11.157)	740 (11.185)	ex. dom (11.068)	555 (11.157)	5,317 (11.162)
Maximum, 0.0200	753 (8.355)	968 (8.388)	1,392 (8.405)	ex. dom (8.333)	872 (8.388)	9,213 (8.391)
Discounting						
Minimum, 0	255 (11.643)	ex. dom (11.699)	685 (11.729)	ex. dom (11.603)	508 (11.699)	4,875 (11.705)
Maximum, 0.05	711 (8.522)	967 (8.557)	1,324 (8.574)	ex. dom (8.500)	852 (8.557)	8,850 (8.560)
Initial parameterization, Normal						
Minimum, 27.89%	536 (9.588)	822 (9.631)	1,017 (9.652)	ex. dom (9.561)	697 (9.631)	7,194 (9.635)
Maximum, 41.83%	464 (9.592)	913 (9.631)	955 (9.653)	ex. dom (9.562)	698 (9.631)	6,846 (9.636)
VIA cost						
Minimum, I\$2	499 (9.590)	642 (9.631)	985 (9.653)	ex. dom (9.561)	577 (9.631)	7,015 (9.635)
Maximum, I\$8	497 (9.590)	ex. dom (9.631)	1,053 (9.653)	ex. dom (9.561)	818 (9.631)	7,016 (9.635)
VIA screening uptake						
Minimum, 60%	498 (9.590)	738 (9.608)	742 (9.634)	ex. dom (9.561)	581 (9.608)	5,699 (9.613)
Base, 100%	498 (9.590)	866 (9.631)	985 (9.653)	ex. dom (9.561)	698 (9.631)	7,016 (9.635)
VIA sensitivity						
Minimum, 63%	498 (9.590)	930 (9.628)	978 (9.650)	ex. dom (9.561)	724 (9.628)	6,959 (9.632)
Maximum, 87%	498 (9.590)	814 (9.634)	994 (9.655)	ex. dom (9.561)	675 (9.634)	7,077 (9.638)
VIA specificity						
Minimum, 51%	498 (9.590)	ex. dom (9.631)	1,381 (9.653)	ex. dom (9.561)	1,086 (9.631)	7,026 (9.635)
Maximum, 89%	ex. dom (9.590)	309 (9.631)	974 (9.653)	ex. dom (9.561)	309 (9.631)	7,005 (9.635)
Retention in follow-up LEEP care						
Minimum, 60%	498 (9.590)	880 (9.629)	984 (9.651)	ex. dom (9.561)	702 (9.629)	6,989 (9.634)
Base, 100%	498 (9.590)	866 (9.631)	985 (9.653)	ex. dom (9.561)	698 (9.631)	7,016 (9.635)

Table 12. continued...

Input variable	Incremental cost-effectiveness ratio (life expectancy)					
	VE – 80% HPV-16/18, 50% HPV-Other			VE – 80% HPV-16/18, 50% HPV-Other		
	Vaccination	VIA	Vaccination & VIA	Vaccination	VIA	Vaccination & VIA
Pre-cancer treatment effectiveness						
Minimum, 60%	498 (9.590)	ex. dom (9.626)	1,008 (9.648)	ex. dom (9.561)	772 (9.626)	6,920 (9.630)
Maximum, 90%	498 (9.590)	800 (9.633)	997 (9.655)	ex. dom (9.561)	666 (9.633)	7,067 (9.637)

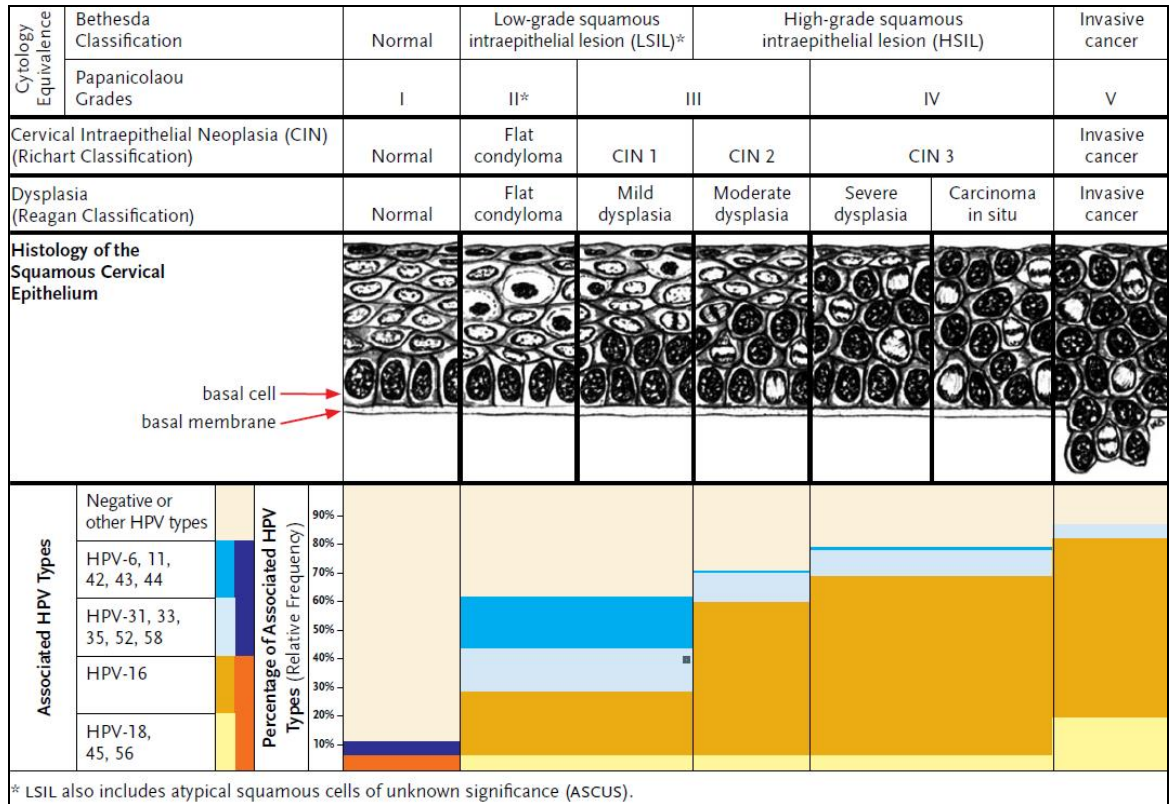
VE, vaccine efficacy; dom, dominated; ex.dom, dominated by extension. Duration of immunity set at 15 years. VIA was set to occur at baseline, year five, and year 10 of the simulation. Vaccine cost set to I\$31.

Figure 1. Visual of the cervix



Source: Herfs et al. 2012 [280]

Figure 2. Cervical clinical disease and classification schemes



Source: Bratcher J, Palefsky J. 2008. Anogenital HVP Infection & Associated Neoplasia in HIV+ Men and Women. The PRN Notebook.

Figure 3. The natural history of cervical cancer

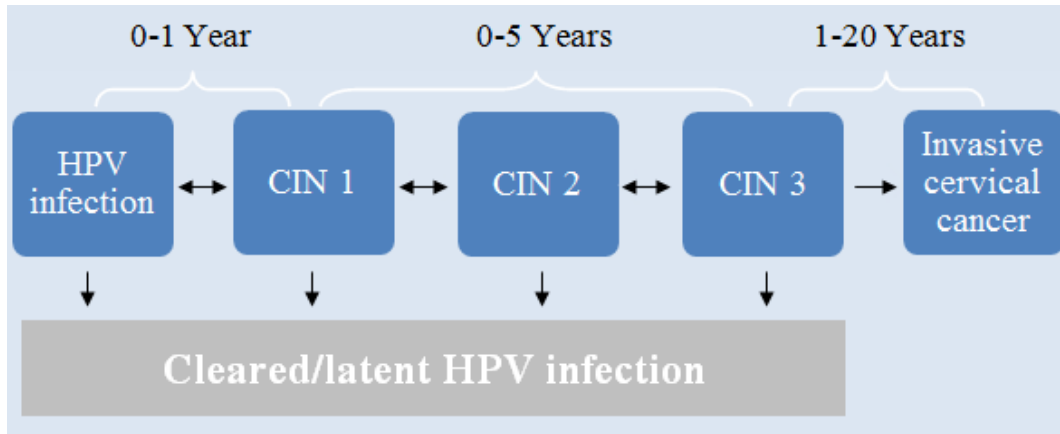
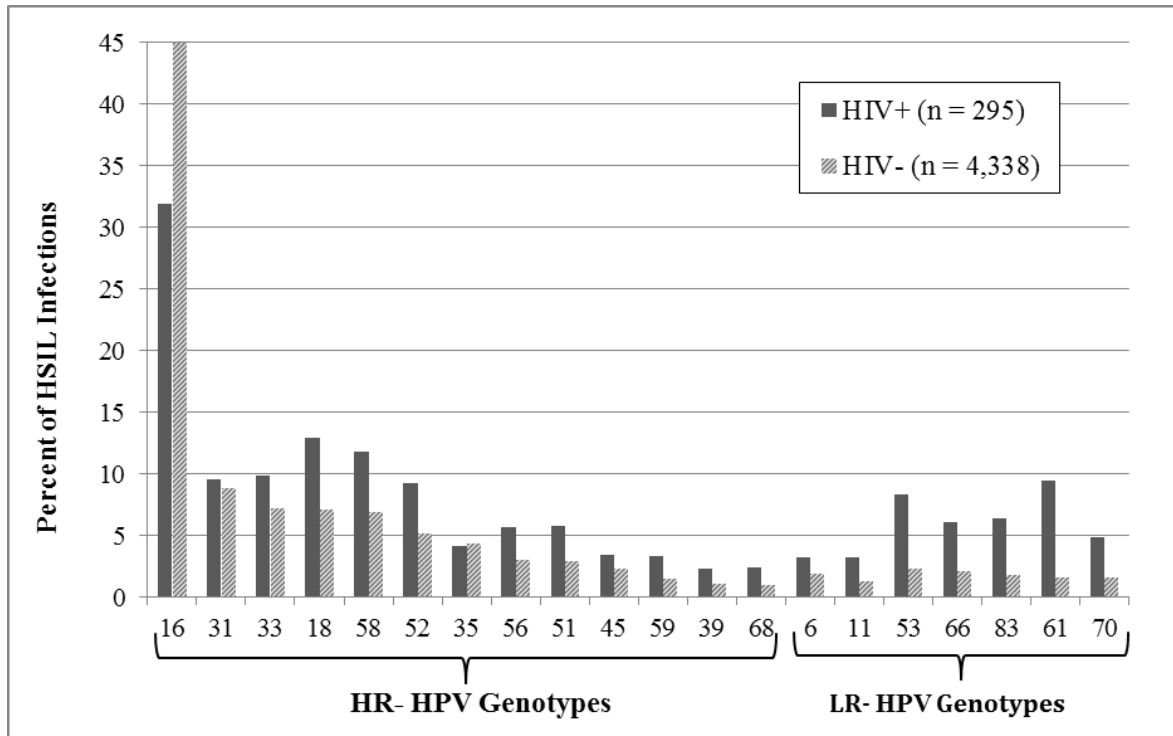
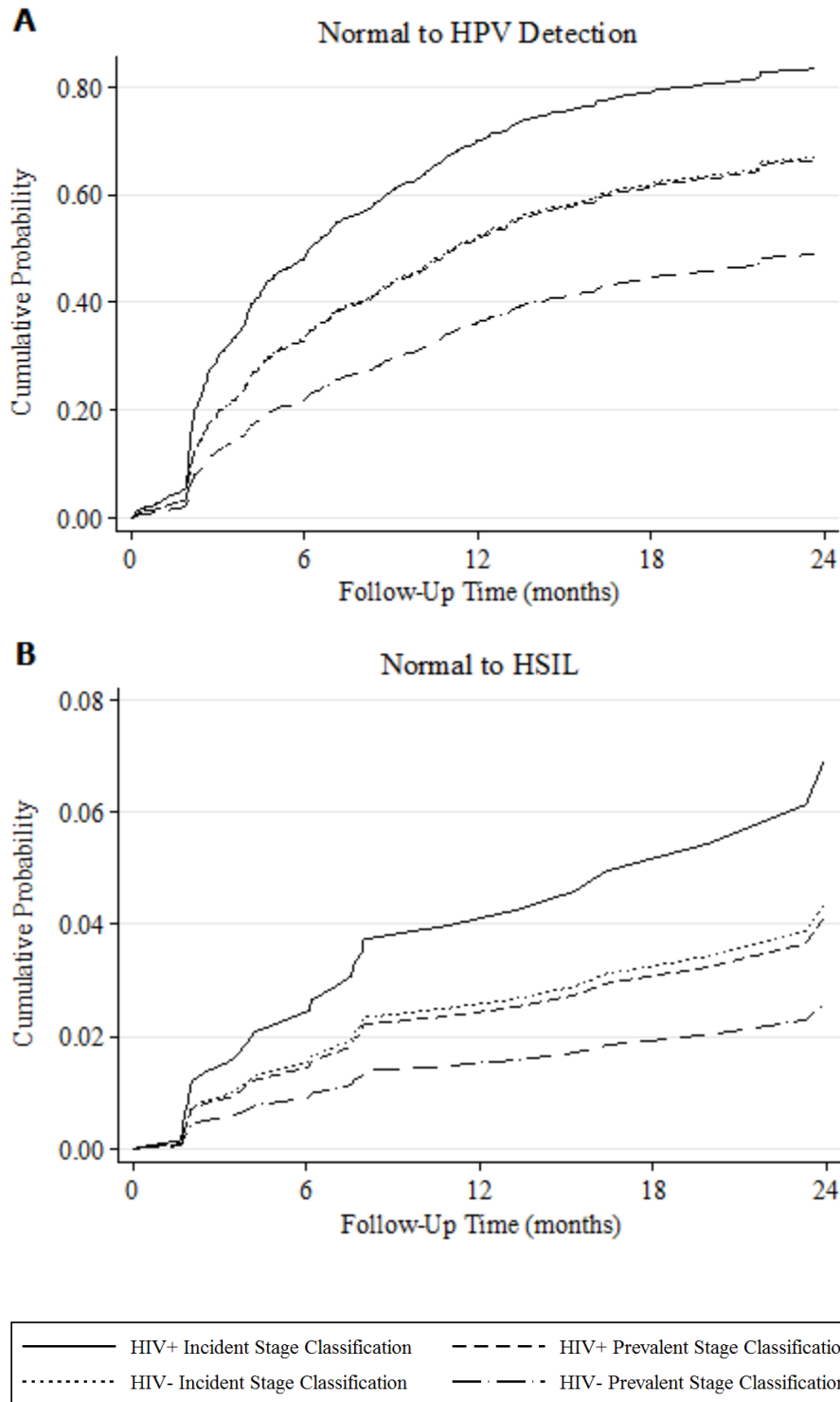


Figure 4. HPV type distributions among women with high-grade squamous intraepithelial lesions

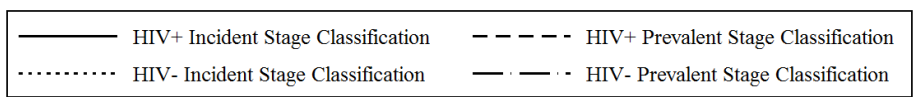
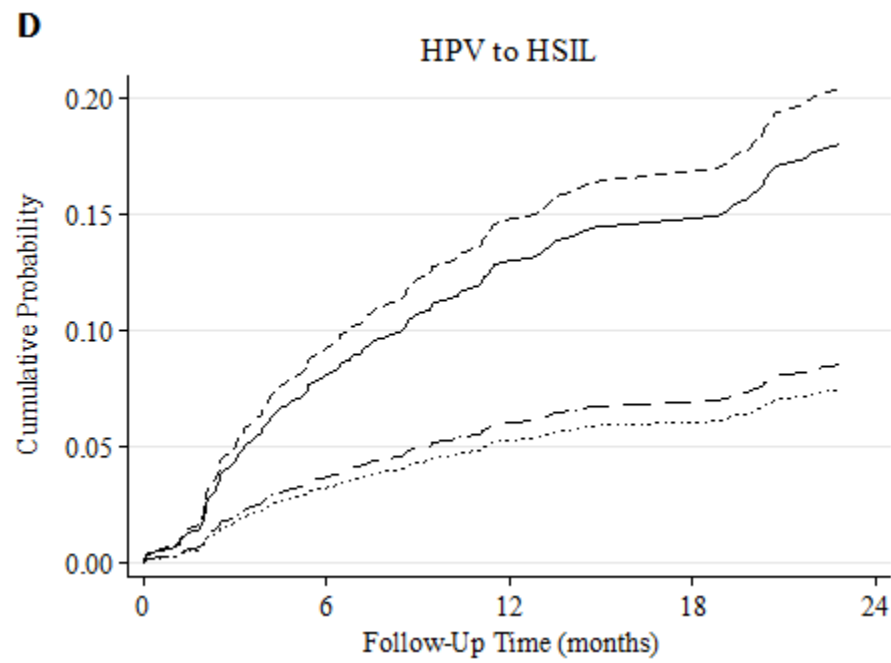
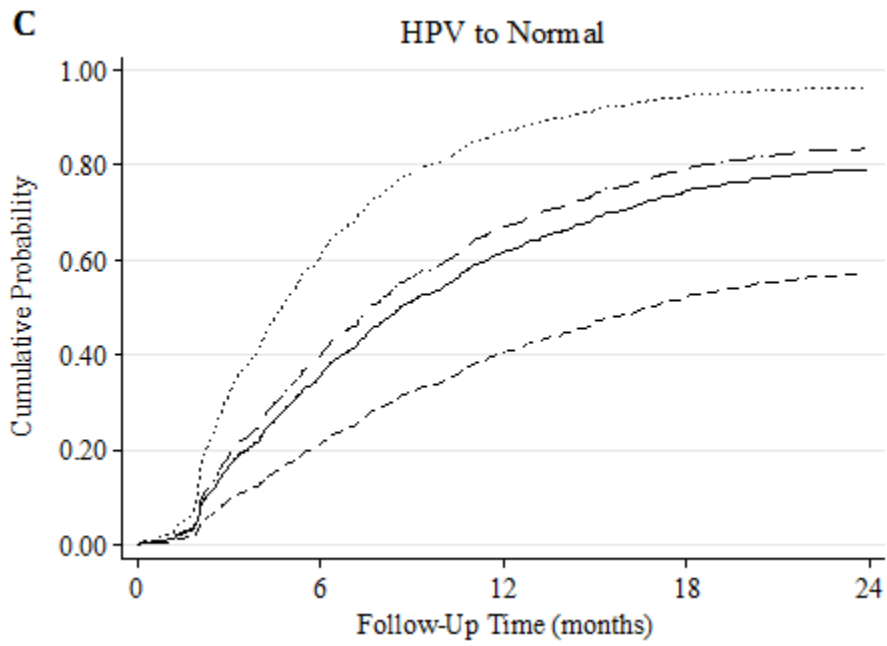


Source: Adapted from Clifford et al.[96]

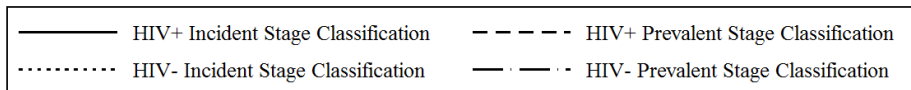
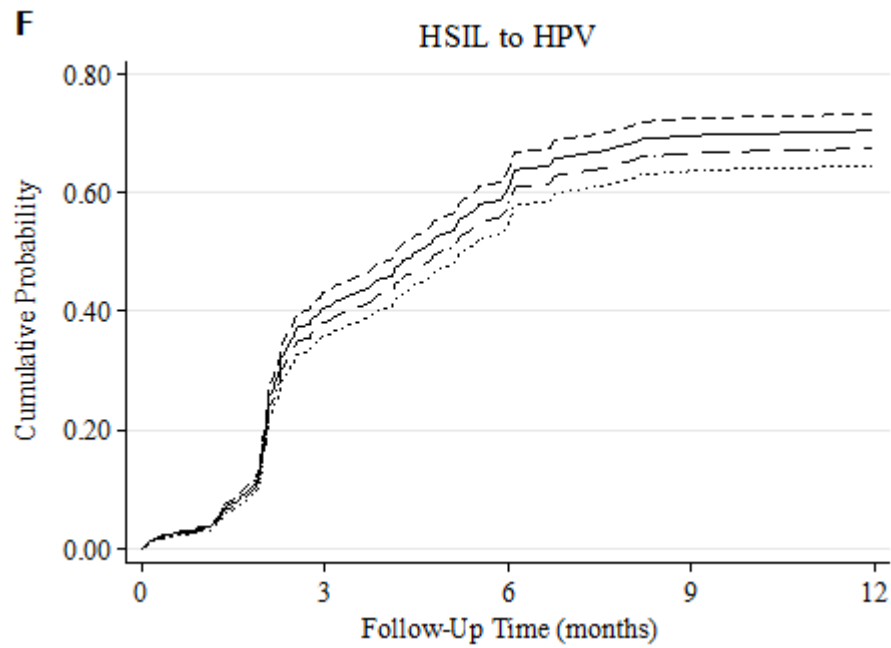
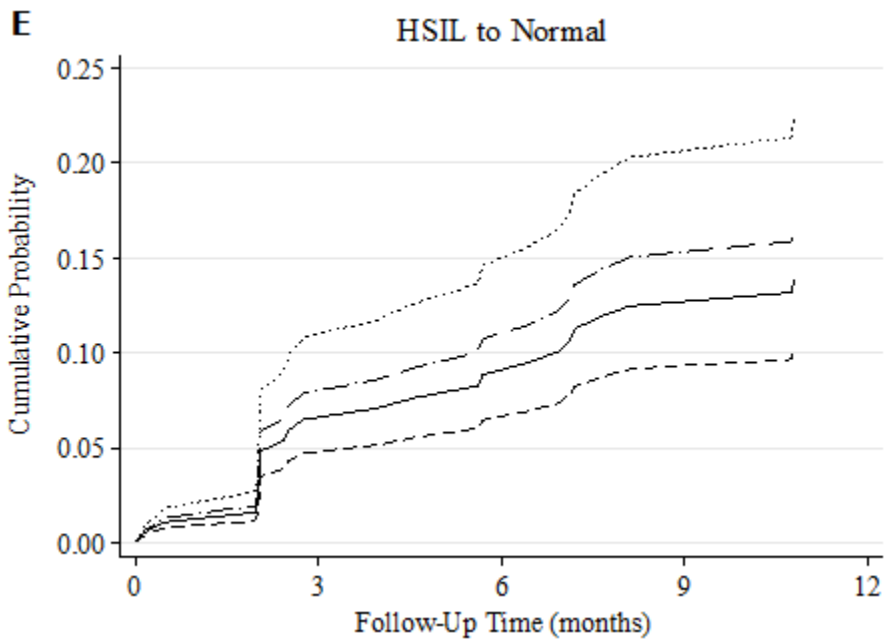
Figure 5. Predicted cumulative probabilities for HIV+ and HIV-Senegalese women*



*Note different x and y axis scaling between figures.

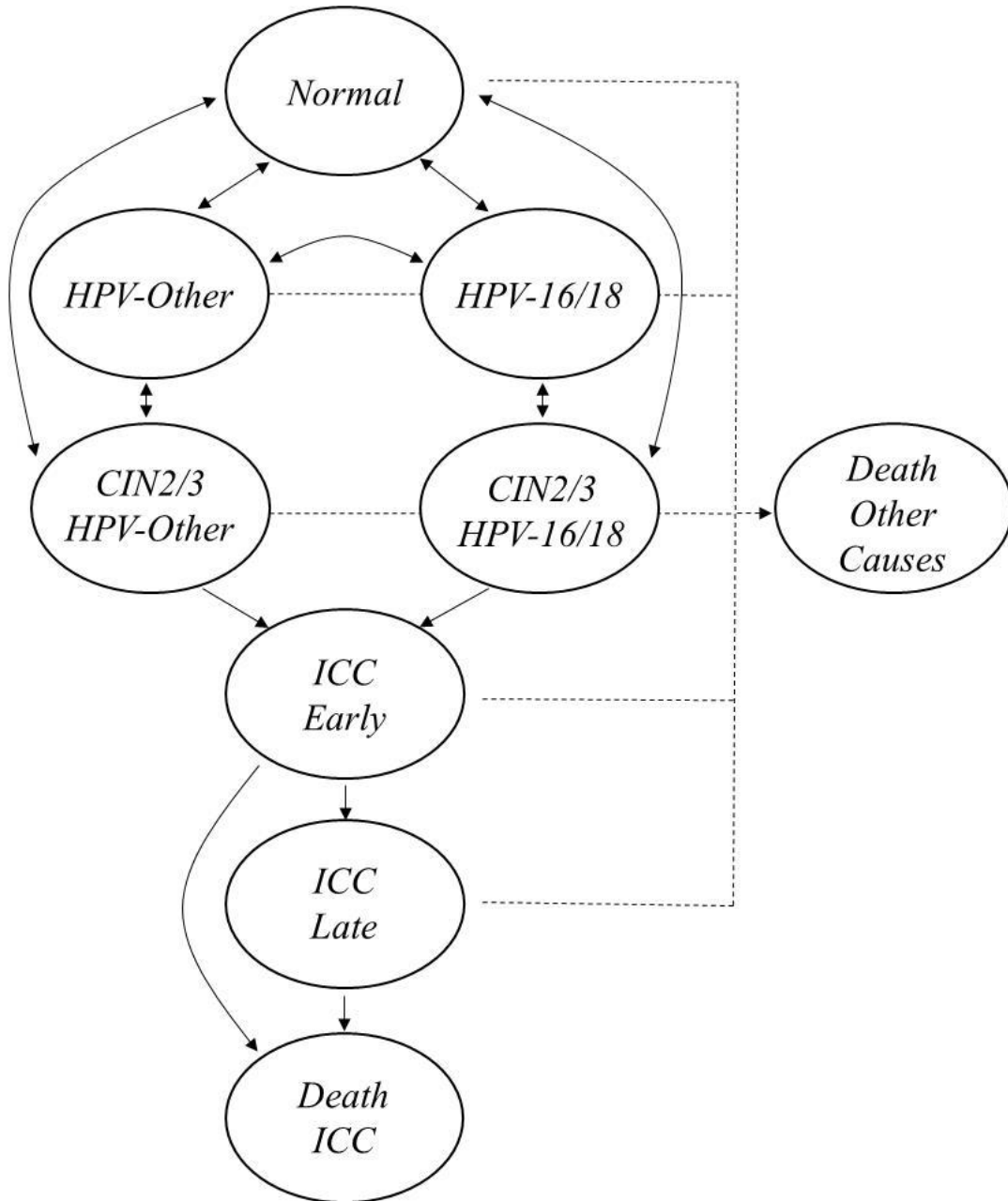


*Note different x and y axis scaling between figures.



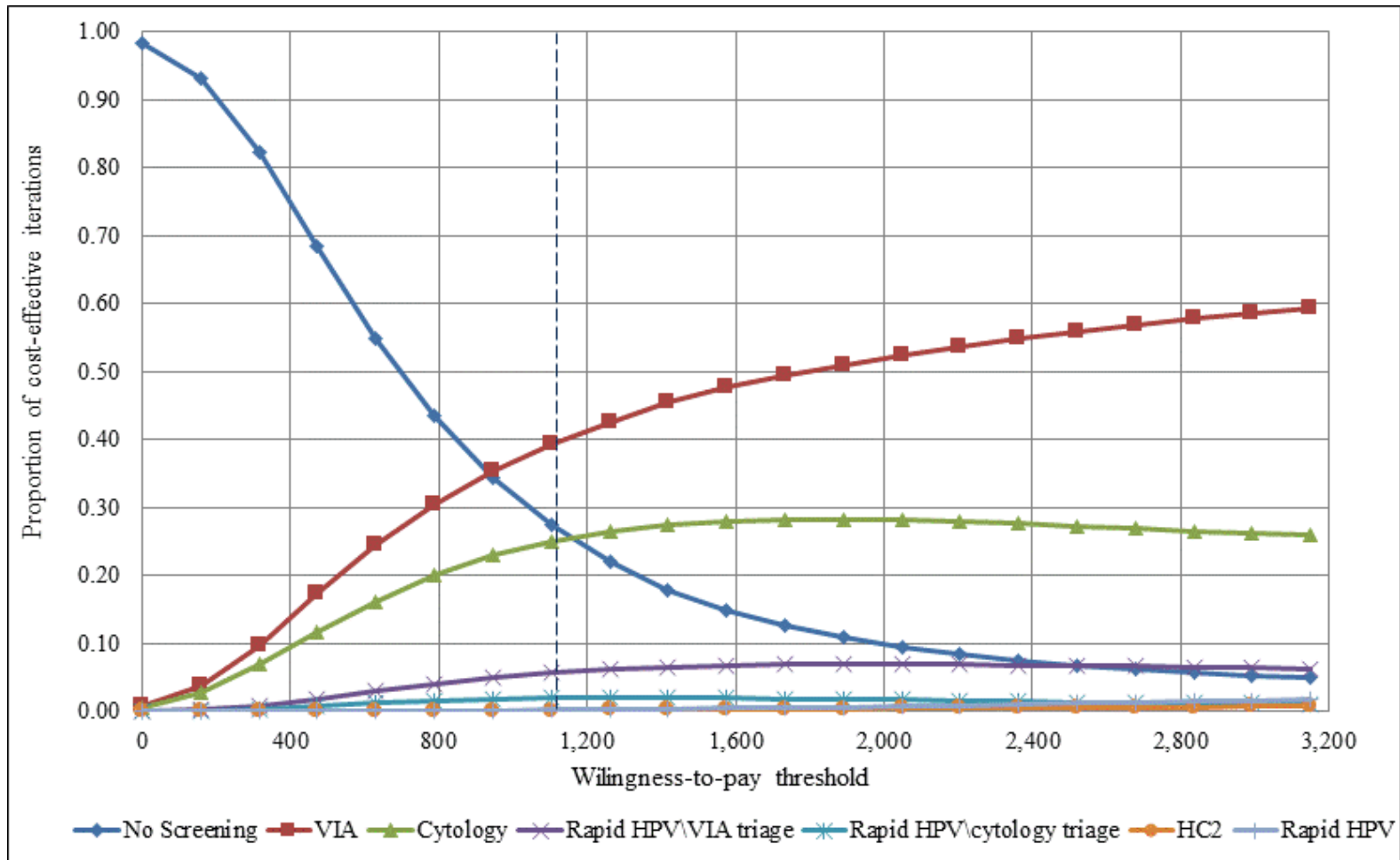
*Note different x and y axis scaling between figures.

Figure 6. Overview of natural history model states and transitions



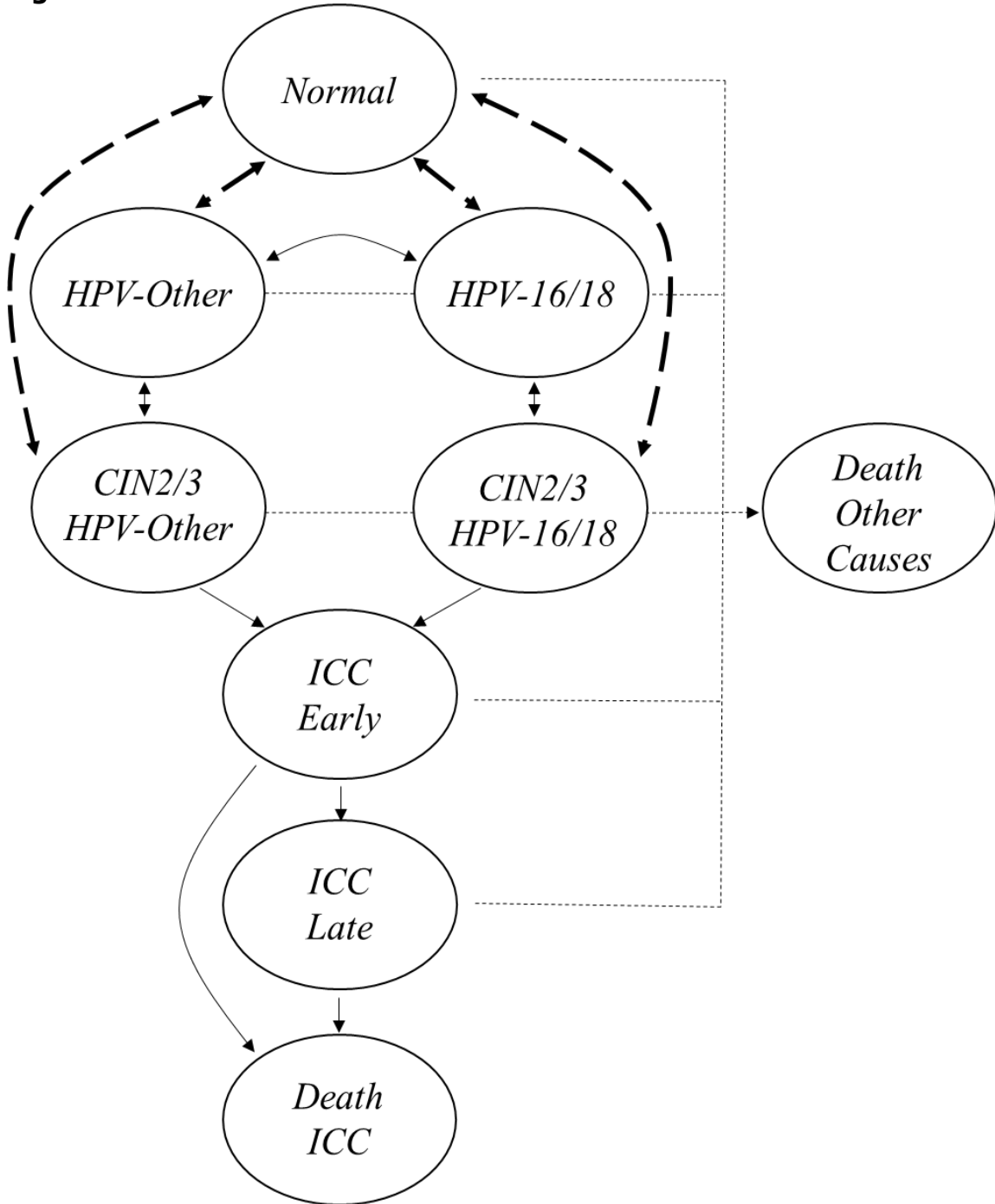
*For all non-death states women may continue to remain within a given state, in addition to transitioning to another state (depicted above).

Figure 7. Cost-effectiveness acceptability curve, cervical cancer screening among HIV+ women



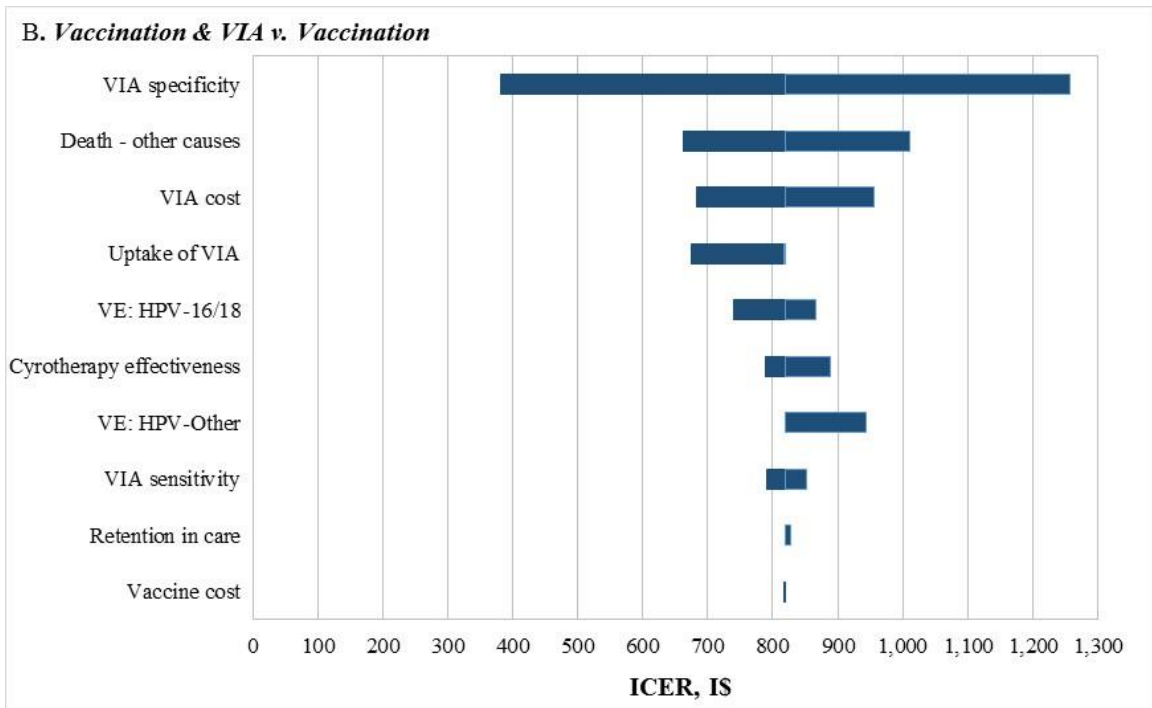
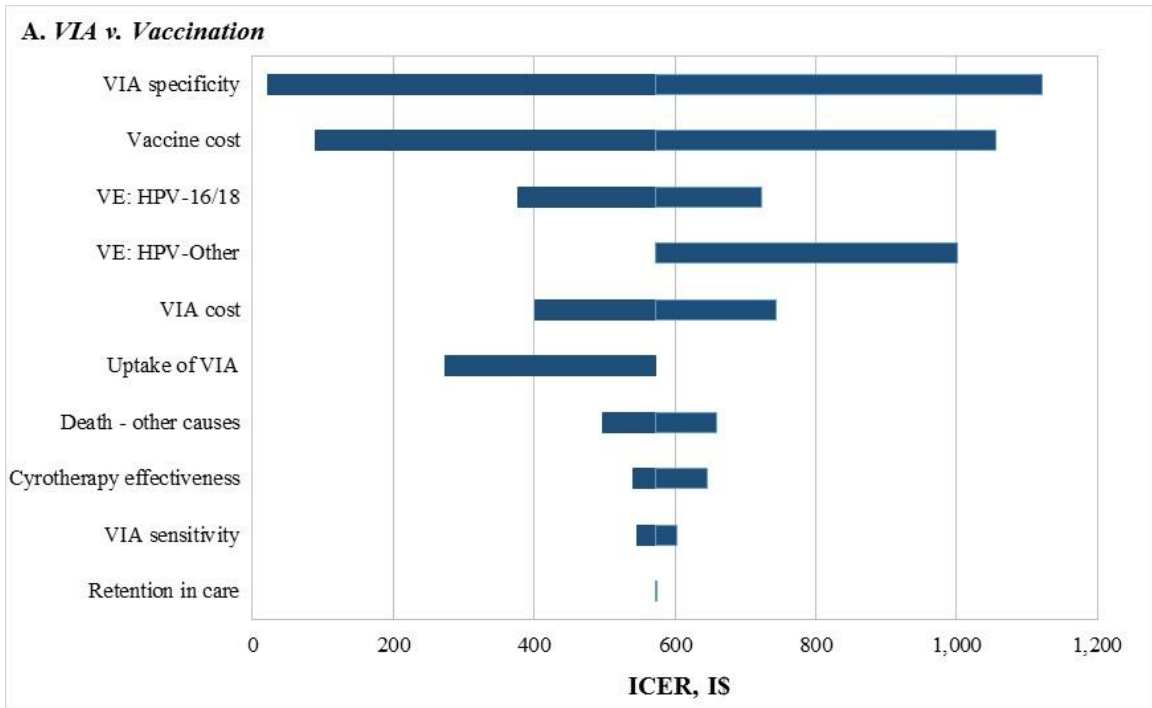
*The willingness-to-pay threshold for ‘very cost-effective’ strategies (I\$1,050) is depicted in the vertical line for reference, with the upper bound for “cost effective” at I\$3,150 (based on WHO criterion).

Figure 8. Overview of model states and transitions

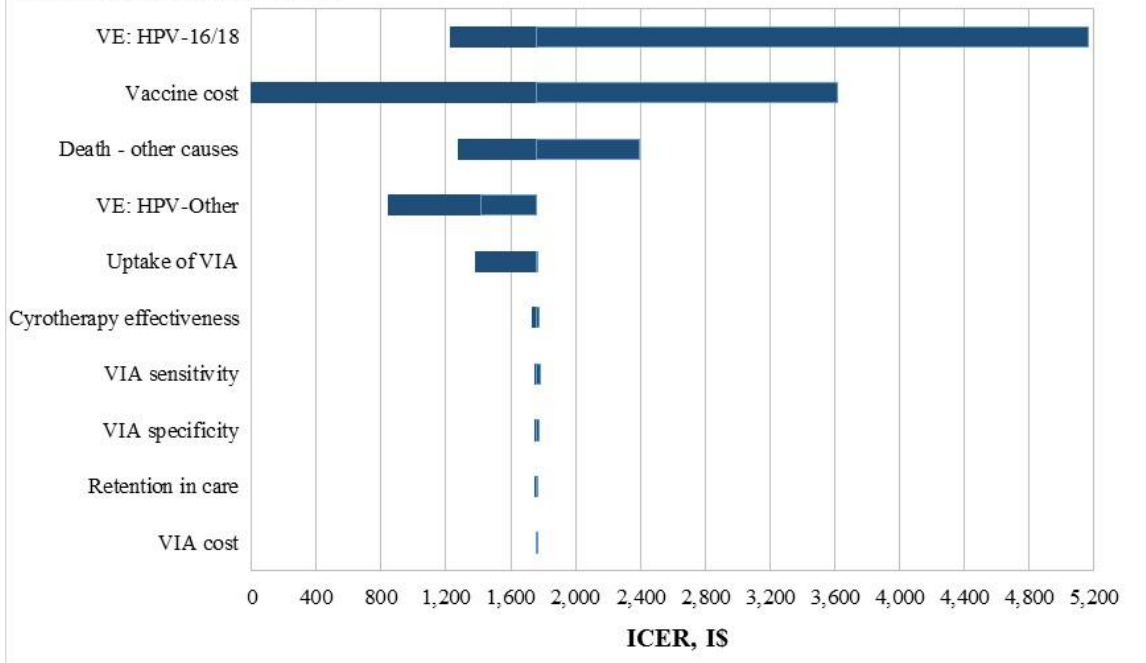


*For all non-death states women may continue to remain within a given state, in addition to transitioning to another state (depicted above). Transitions impacted by the vaccine are in bold, dash lines.

Figure 9. Tornado plots displaying the impact of uncertainty in key input variables



C. Vaccination & VIA v. VIA



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