# Cervical cancer prevention in the context of abating HIV prevalence in Kenya

Gui Liu

A dissertation
submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

University of Washington
2021

Reading Committee:
Ruanne V. Barnabas, Chair
Linda O. Eckert
Rachel L. Winer

Program Authorized to Offer Degree:
Epidemiology

University of Washington

**Abstract**

Cervical cancer prevention in the context of abating HIV prevalence in Kenya

Gui Liu

Chair of the Supervisory Committee:

Ruanne V. Barnabas

Departments of Global Health, Medicine, and Epidemiology

In 2020, the World Health Organization (WHO) launched an initiative to eliminate cervical cancer as a public health problem globally. While high-income countries are expected to achieve this goal in the coming decades, the timeline for elimination will be significantly longer for lower-resourced countries with high HIV burden. In low-and-middle income countries, HIV infection is associated with a 7-fold increase in cervical cancer risk. In Kenya, where HIV prevalence among women is 6%, cervical cancer incidence rate is among the highest in the world. Further, a limited number of studies have shown that human papillomavirus (HPV) infection increases HIV risk, raising the question of whether HPV vaccination could reduce HIV burden. As the country prepares to meet the challenge of cervical cancer elimination, strategies for reducing cervical cancer burden in Kenya will need to account for the synergies between the two diseases. This dissertation aimed to comprehensively quantify the interactions between HIV infection and cervical cancer, and estimate the population-level impact of HPV vaccination on cervical cancer and HIV burden in Kenya.

Using a matched case-control study nested in a randomized control trial of HIV chemoprophylaxis, we evaluated the association between HPV infection and subsequent HIV

acquisition in chapter 2. We found that HPV infections were common among both cases (women who seroconverted) and HIV-negative controls, with infection with one or more HPV types targeted by the nonavalent vaccine detected in 60% of cases and 42% of controls. Adjusting for sexual behaviors and other sexually transmitted infections, women with any HPV infection had 2.6-fold higher risk of HIV acquisition compared to women who were HPV-negative. In particular, infection with a nonavalent vaccine-targeted HPV type increased HIV risk 2.1 times and infection with a quadrivalent-vaccine-targeted type increased HIV risk 1.9 times. These findings suggest that HPV vaccination may reduce HIV incidence.

In chapter 3, we conducted a systematic review and meta-analysis to synthesize the literature on the effect of HIV infection on HPV natural history. We found that relative to HIV-negative women, women living with HIV had significantly higher risk of HPV acquisition, persistence, and progression to cervical precancerous lesions and cancer, with risks increasing as CD4 cell counts decreased. Antiretroviral therapy lowered the risk of HPV acquisition and persistence, and progression to low-grade precancerous lesions, however, its impact on high-grade lesions depended on duration of use.

Finally, in chapter 4, we evaluated the health effects of HPV vaccination in Kenya using a dynamic compartmental model that accounted for the bidirectional interactions between HPV and HIV infections. The model projected that HPV vaccination will reduce cervical cancer incidence by 68-84% and prevent 164,529-326,968 cervical cancer cases over 50 years. The impact of vaccination on cervical cancer burden was greatest and occurred earlier when women aged 15-24 were vaccinated in addition to girls aged 10-14. Further, we found that HPV vaccination will reduce HIV prevalence by 7-11%, averting 23,862-52,951 cases of HIV in men and women over

50 years. Finally, the model projected that HIV prevalence will continue to decline in Kenya, and as a result cervical cancer rates will decline even in the scenario without vaccination.

In conclusion, cervical cancer burden in Kenya can be substantially reduced with HPV vaccination; particularly if the vaccination strategy includes young women aged 15-24. While HPV vaccination had a lesser impact on HIV burden, it should be included as a component of a comprehensive HIV prevention package. Overall, our findings highlighted the importance of accounting for the changing HIV epidemiology in Kenya when considering HPV vaccination strategies.

# Table of Contents

**Acknowledgements**

This dissertation would not have been possible without the support of many people.

First and foremost, I would like to thank my dissertation committee, Ruanne Barnabas, Jared Baeten, Linda Eckert, Peter Gilbert, and Rachel Winer, for their guidance, support, and invaluable feedback, which have challenged me to think deeper and more critically. I especially want to thank Ruanne for her mentorship in the past 4.5 years and for providing me with opportunities to grow as an independent researcher. Her dedication to impactful research and health equity for all is an inspiration.

I would like to also thank the UW Epidemiology Department for their support throughout my PhD process, especially Steve Hawes, Anne Fitzpatrick, and Noel Weiss for their thoughtful feedback on my dissertation aims. At ICRC and DGH, I have been fortunate to work alongside many driven, compassionate, and insightful individuals, all of whom have enhanced my PhD experience and made me a better researcher. Thank you to Cara Bayer, Jennifer Baugh, Connie Celum, Matt Golden, Harald Haugen, Renee Heffron, Rachel Johnson, David Katz, Hannah Leingang, Jai Lingappa, Toni Maddox, Deidra Montoya, Nelly Mugo, Darcy Rao, Allen Roberts, Jen Ross, Monisha Sharma, Kathy Thomas, and Judy Wasserheit.

Many thanks to my epidemiology PhD cohort and friends (from UW and not), including, Joy Castro, Anjali Desai, Hardik Desai, Xinwei Hua, Dorothy Mangale, Kathryn Peebles, Enrique Saldarriaga, Michelle Shin, Val Wanga, and Ni Yu for the comradery, potluck dinners, study sessions, road trips, life advice, and much more. Thanks also to Chue Yang, Aleksey Cherman, Bayley Whitehead, and Frankie Sanchez for making Seattle feel like home.

I am extremely grateful for the unwavering support and encouragement from Eileen Curran, Missy Matz, and the rest of my second family, which have been a comfort during more difficult times. I owe a debt to my brother, Jin, for comic relief and the 24/7 tech support and to my sister, Jie, for keeping me grounded. Finally to my parents: thank you for all of the sacrifices you made over the years working for a better life for your children in a place where you don't know the language, people, or culture. 谢谢爸爸妈妈。

# Chapter 1. Introduction

Cervical cancer is largely preventable, yet it is becoming another indicator of health inequity between high-income and low-income countries. The availability of organized cancer screening programs and human papillomavirus (HPV) vaccination in high-income countries have resulted in significant reductions in cervical cancer incidence and mortality, such that many high-income countries can expect to eliminate cervical cancer as a public health problem in the next 30-40 years.[1-4] However, cervical cancer continues to be one of the most common cancers and the leading cause of cancer deaths among women in sub-Saharan-Africa, where cervical cancer screening coverage is minimal and only one-third of the countries have introduced HPV vaccination.[5-7]

In Kenya specifically, cervical cancer incidence rate was 47 cases per 100,000 women in 2020, which is approximately 5 times higher compared to North American and European regions.[7] Fewer than one in eight Kenyan women had ever been screened for cervical cancer and few girls had been vaccinated against HPV through the national vaccination program, which has been disrupted by the COVID-19 pandemic shortly after its launch in October 2019.[8,9] In addition to the unmet need for cervical cancer prevention, high HIV prevalence among girls and women is a major contributor to the elevated cervical cancer risk. Immunodeficiency caused by HIV infection put women living with HIV at higher risk of developing cervical cancer compared to HIV-negative women.[10-13] In Kenya, one in four incident cervical cancers can be attributed to HIV infection.[11]

On the other hand, efforts to scale up HIV prevention, such as linking people living with HIV to care and antiretroviral therapy (ART) and voluntary male medical circumcision, have been successful in reducing HIV prevalence in Kenya over the last decade.[14,15] As of 2019, HIV prevalence among women aged 15-49 years is approximately 6%, a 20% reduction since 2010.[16,17] While the reduction is promising, the current HIV prevalence still represents considerable disease burden. In addition, adolescent girls and young women (AGYW) aged 15-24 years continue to be

disproportionately infected with HIV.[18] Emerging data point to the elevated HPV prevalence among young women under age 25 as one potential risk factor for HIV acquisition in this population.[19-21]

The World Health Organization (WHO), with the support of member countries and other international organizations, launched an initiative to eliminate cervical cancer as a public health problem globally during the World Health Assembly in August 2020.[22] The strategy to achieve this goal includes increasing HPV vaccination coverage among girls to 90%, as well as scaling up cancer screening and treatment coverage to 70% and 90%, respectively, by 2030.[22] While several mathematical modelling studies have been undertaken to evaluate the impact of cervical cancer prevention strategies in sub-Saharan Africa, few had provided country-level projections that factored in the effect of HIV on cervical cancer epidemiology.[23-28] For resource-constrained countries with significant burden of both cervical cancer and HIV, such as Kenya, context-specific data that takes into account the synergies between the two diseases will be crucial for informing local cervical cancer prevention strategies and resource allocation policy decisions. To address this data gap, this dissertation aims to comprehensively quantify the biological interactions between HPV and HIV infections and, with these data, estimate the health effects of HPV vaccination in Kenya using a dynamic transmission model.

In chapter 2, we evaluate the association between HPV infection and the risk of subsequent HIV acquisition among women. Although HIV prevalence and incidence in sub-Saharan Africa has been declining in the last decade, AGYW aged 14-25 years still face higher HIV risk compared to their male counterparts and people in other age groups.[16] AGYW account for a quarter of the new HIV infections in sub-Saharan Africa even though they represent just 10% of the population.[16,18] HPV, one of the most prevalent sexually transmitted infections, is common among

AGYW shortly after sexual initiation.[21,29] While other sexually transmitted infections have been shown to increase HIV risk, the relationship between HPV infections and HIV acquisition remains unclear.[30] To date, ten studies have evaluated the association between HPV and HIV acquisition among women, but most were limited by small sample size, measurement bias, and confounding.[19,20] Results from the remaining high-quality studies were mixed, with three concluding that HPV infection increased the risk of HIV acquisition while one finding no association. Therefore, in this chapter, we aim to contribute to this body of research by estimating the risk of subsequent HIV acquisition in women with prevalent HPV infection using a case-control study nested in a large randomized controlled trial of HIV chemoprophylaxis for women.[31] The trial had frequent follow-up visits and collected in-depth time-varying sexual behavior data, allowing us to minimize the measurement bias and confounding present in some of the previous studies.

The US Centers for Disease Control and Prevention has classified cervical cancer as an AIDS-defining condition since 1993.[32] While numerous studies have concluded that HIV infection increased the risk of cervical cancer, the strength of the associations varied widely.[12,13] A large number of studies on the impact of HIV on HPV disease progression have also been published, but they have not been synthesized. Thus, in chapter 3, we summarize the effect of HIV on the natural history of HPV infection and cervical cancer development with a systematic review and meta-analysis. Specifically, we aim to estimate the relative risks of HPV acquisition, persistence and progression to precancer lesions and cervical cancer among women living with HIV compared to HIV-negative women. Additionally, the link between HIV and cervical cancer has not been as straightforward as for other AIDS-defining malignancies.[33] Among people living with HIV the United States and European countries, the introduction of effective ART led to almost immediate

declines in the rates of Kaposi Sarcoma and non-Hodgkin Lymphoma, but its effect on cervical cancer rates was not consistent, particularly in the first ten years of introduction.[33-36] These findings suggest that factors other than ART (e.g., CD4 cell count, viral load) may be modifying the association between HIV and cervical cancer. We additionally assess HPV disease progression by CD4 cell count, viral load, and ART use among women living with HIV.

Finally, in chapter 4, we estimate the effect of HPV vaccination strategies on cervical cancer burden using a dynamic, compartmental model of HIV and HPV co-transmission adapted to the Kenyan setting. We parameterized the model with data from chapters 2 and 3 as well as demographic and epidemiological data specific to Kenya. We evaluate the intermediate (30 years) and long term (50 years) reductions in cervical cancer incidence and cumulative number of cases averted across a range of scenarios defined by varying levels of vaccination coverage and strategies. Because we explicitly model the biological interactions between HIV and HPV, we also evaluate the potential impact of HPV vaccination on HIV burden.

# Chapter 2. Prevalent HPV infection increases the risk of HIV acquisition in African women: advancing the argument for HPV immunization

**Prevalent HPV infection increases the risk of HIV acquisition in African women: advancing the argument for HPV immunization**

Gui Liu, MPH;[1,2] Nelly R Mugo, MMed;[2,3] Elizabeth R. Brown, ScD[4,5]; Nyaradzo M Mgodi, MMed[6]; Zvavahera Chirenje, MD;[7] Jeanne M. Marrazzo, MD;[8] Rachel L Winer, PhD;[1,9] Leila Mansoor, PhD;[10] Thesla Palanee-Phillips, PhD;[11,12] Samantha S Siva, MMedSc;[13] Logashvari Naidoo, MBChB;[13] Nitesha Jeenarain;[13] Zakir Gaffoor;[13] Gonasagrie L Nair, MPH;[14] Pearl Selepe, MD;[15] Clemensia Nakabiito, MMed;[16] Baningi Mkhize, MBChB;[12] Brenda Gati Mirembe, MSci;[16] Marthinette Taljaard;[15] Ravindre Panchia, MBBCh;[17] Jared M Baeten, MD;[1,2,18,*] Jennifer E Balkus, PhD;[1,2,4] Florian Hladik, MD;[4,18,19] Connie L Celum, MD;[2] Ruanne V Barnabas, DPhil[1,2,4,18]

[1]Department of Epidemiology, University of Washington, Seattle, USA
[2]Department of Global Health, University of Washington, Seattle, USA
[3]Kenya Medical Research Institute, Nairobi, Kenya
[4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, USA
[5]Department of Biostatistics, University of Washington, Seattle, USA
[6]Clinical Trials Research Centre, University of Zimbabwe, Harare, Zimbabwe
[7]College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe
[8]Department of Medicine/Division of Infectious Diseases, University of Alabama at Birmingham, Alabama, USA
[9]Kaiser Permanente Washington Health Research Institute, Seattle, USA
[10]Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa
[11]Wits Reproductive Health and HIV Institute in Johannesburg, South Africa
[12]Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa
[13]South Africa Medical Research Council, Durban, South Africa
[14]Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa
[15]The Aurum Institute, Klerksdorp, South Africa
[16]Makerere University-John Hopkins University Research Collaboration, Kampala Uganda
[17]Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Soweto, South Africa
[18]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, USA
[19]Department of Obstetrics and Gynecology, University of Washington, Seattle, USA
* Current affiliation: Gilead Sciences, Foster City, USA

Corresponding author contact information:
Gui Liu
Department of Epidemiology
1959 NE Pacific St
Health Sciences Bldg, F-262
Seattle, WA 98195
Email: guiliu@uw.edu

**Abstract**

**Objective** Vaccine-preventable human papillomavirus (HPV) infection is common, especially in sub-Saharan Africa where HIV risk is also high. However, unlike other sexually transmitted infections (STIs), HPV's role in HIV acquisition is unclear. We evaluated this relationship using data from MTN-003, a clinical trial of HIV chemoprophylaxis among cisgender women in sub-Saharan Africa.

**Design** Case-control study

**Methods** We matched 138 women who acquired HIV (cases) to 412 HIV-negative controls. Cervicovaginal swabs collected within 6 months before HIV seroconversion were tested for HPV DNA. We estimated the associations between carcinogenic (high-risk) and low-risk HPV types and types targeted by HPV vaccines and HIV acquisition, using conditional logistic regression models adjusted for time-varying sexual behaviors and other STIs.

**Results** Mean age was 23 (+/- 4) years. Any, high-risk, and low-risk HPV was detected in 84%, 74%, and 66% of cases, and 65%, 55%, and 48% of controls. Infection with ≥2 HPV types was common in cases (67%) and controls (49%), as was infection with nonavalent vaccine-targeted types (60% and 42%). HIV acquisition increased with any (aOR 2.5, 95% CI 1.3-4.7), high-risk (aOR 2.6, 95% CI 1.5-4.6), and low-risk (aOR 1.8, 95% CI 1.1-2.9) HPV. Each additional type detected increased HIV risk by 20% (aOR 1.2, 95% CI 1.1-1.4). HIV acquisition was associated with HPV types targeted by the nonavalent (aOR 2.1, 95% CI 1.3-3.6) and quadrivalent vaccines (aOR 1.9, 95% CI 1.1-3.2).

**Conclusions** HPV infection is associated with HIV acquisition in sub-Saharan African women. In addition to preventing HPV-associated cancers, increasing HPV vaccination coverage may reduce HIV incidence.

**Funding**

University of Washington King K Holmes Endowed Professorship and the National Institutes of Health.

**Keywords:** HIV acquisition, Human Papillomavirus, cervical cancer, adolescent girls and young women

## Introduction

Despite the encouraging decline in global HIV incidence in the past decade, adolescent girls and young women (AGYW) living in sub-Saharan Africa continue to be disproportionately affected by the HIV epidemic.[37] Although they represent only 10% of the population, AGYW aged 14-25 years accounted for 25% of new HIV infections in 2017.[18] Unlike the global HIV incidence trend, the risk of HIV acquisition among AGYW in the highest risk communities has not declined.[38]

AGYW in sub-Saharan Africa experience a number of biological, social, and structural factors that increase their susceptibility to HIV. One highly prevalent biological factor may be human papillomavirus (HPV) infection, which causes cervical cancer and is associated with other anogenital and oropharyngeal cancers.[39,40] HPV is one of the most common sexually transmitted infections,[41] and individuals are highly susceptible shortly after sexual debut.[29] Globally, HPV prevalence is highest among women younger than 25 years compared to older age groups.[21] In Africa specifically, the prevalence of infection with any HPV type is 36% in AGYW.[42]

While the role of other sexually transmitted infections (STIs) in increasing HIV risk is well-established,[30] data on the association between HPV and HIV acquisition is relatively scarce. A meta-analysis of the studies published thus far found a two to three fold increase in the risk of subsequent HIV acquisition among women with an HPV infection.[19,20] However, several of these studies were limited by small sample size, uncontrolled confounding, and misclassification bias related to HPV exposure.[19,20] In nearly half of the nine studies included in the meta-analyses, the time interval between the ascertainment of HPV infection and HIV seroconversion was more than one year. As most HPV infections are transient and clear within one year,[43] the HPV types detected

in those studies are potentially not etiologically relevant to the outcome of HIV seroconversion more than one year later. Further, since both infections are acquired through sexual activity, disentangling behavioral and biological cofactors is not trivial. Consequently, sexual behaviors and coinfection with other STIs were not adequately controlled for in most of the studies.[19,20]

To minimize biases present in previous studies, we estimated the risk of subsequent HIV acquisition in women with HPV infection or cervical precancerous lesions, leveraging data from a randomized controlled trial of pre-exposure prophylaxis (PrEP) against HIV infection, while accounting for the temporal pattern of sexual behaviors and STI coinfections.

## Methods

*Study participants and design*

Our study was nested in the MTN-003 Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, a multicenter randomized placebo-controlled trial in South Africa, Uganda, and Zimbabwe.[31] VOICE aimed to assess the efficacy of HIV oral and topical PrEP in sexually active cisgender women at risk for acquiring HIV. Conducted between 2009 and 2015, VOICE enrolled non-pregnant, contracepting, HIV-uninfected women aged 18-45 years who provided written informed consent. The VOICE study was approved by the institutional review boards and ethics committees at participating institutions. Participants were randomized to receive daily placebo or tenofovir-based PrEP in the forms of oral tablets or vaginal gel. Participants underwent HIV testing monthly with a rapid test, which, if positive, was followed by a confirmatory Western blot. HIV seroconversion was dated at the first positive rapid test. Endocervical and vaginal swabs were collected every six months, though the swabs were not tested for HPV in real time. Additionally,

participants were assessed for other STIs and vaginal infections at enrollment, at annual follow-up visits, and when clinically indicated. Strand displacement amplification of urine samples was used to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (BD ProbeTec; Becton Dickinson). Serological testing was conducted for syphilis. Vaginal fluid swabs were used for rapid tests for bacterial vaginosis and *Trichomonas vaginalis* (BVBlue Test and OSOM, Genzyme), and for wet mount for candidiasis. Wet mount slides were read by local clinical staff or lab staff. Tests for herpes simplex virus type 2 (HSV-2) antibody was conducted using a HSV-2–specific enzyme immunoassay (EIA; Focus Diagnostics) with a cutoff value of <3.5 on stored plasma collected at enrollment and at quarterly follow up visits if they were negative at enrollment.[44] Participants reported their sexual activity in the previous three months using a computer-assisted self-interview platform at enrollment and quarterly during follow-up. Details of the VOICE study procedures were published previously.[31] HPV vaccination was not offered to VOICE participants, as HPV vaccines were not widely available in South Africa, Zimbabwe, and Uganda at the time of study.

To establish a clear temporal relationship between the detection of HPV and HIV acquisition, selection criteria for our case-control analysis were:

1. Having a stored cervical or vaginal swab specimen available for testing, and
2. Cervical or vaginal swab was collected between one to six months before HIV seroconversion.

We excluded swabs collected within one month of HIV seroconversion to minimize the possibility of reverse association, as the detection of HPV infection is increased immediately following HIV seroconversion.[45] Of the 312 participants who seroconverted during the VOICE study, 138 met inclusion criteria. Each case was matched to 3 controls based on study visit, age within five years,

and study site. Using a risk-set sampling method, HIV-negative women who met matching criteria and had a stored cervical or vaginal swab that was collected within six months before the study visit during which cases seroconverted were randomly selected to serve as controls. Our selection criteria were based on the availability of stored cervical swabs. If cervical swabs were not available, we substituted with vaginal swabs. In our final analytic sample, 1% of the specimens tested were from vaginal swabs.

To assess bias in control selection, we compared the baseline characteristics of controls in our study sample to that of VOICE participants overall[31] (Table 1). On average, the participants serving as controls in our study were younger than the VOICE population, thus less likely to be married at the time of enrollment and had fewer children. While 95% of our controls were from South Africa, 81% of VOICE participants were from South Africa, 6% from Uganda, and 13% from Zimbabwe. However, controls in our study were similar to VOICE participants overall in terms of education, condom use, number of male sex partners in the three months before enrollment, and proportion reporting anal sex in the three months before enrollment. We also assessed internal validity by comparing the cases to VOICE participants who seroconverted but were not included in our study (Table 1). At enrollment, the cases and the other VOICE participants who seroconverted were nearly identical in terms of age, country of residence, and the number of live births, but slightly fewer cases had secondary school education or higher (88% vs. 92%). The proportion of cases who were married, use condoms during last vaginal sex, had two or more male sex partners in the past three months, and reported anal sex in the past three months were also similar compared to other VOICE participants who seroconverted.

*Laboratory procedures*

For our nested case-control study, we utilized HIV test results and STI data provided by VOICE. We tested the cervical and vaginal swabs, which were stored at -70C in cryovials containing 400uL phosphate buffered saline, for presence of HPV DNA at the University of Washington (UW) Pathology Laboratory at Harborview Medical Center. HPV DNA was detected using a Luminex-based liquid bead micro array assay with qualitative detection for 37 HPV types.[46] Following the International Agency for Research on Cancer classification scheme, we defined HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 as high-risk types and HPV 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 81, 82, 82 subtype (IS39), 83, 84, and 89 (CP6108) as low-risk types.[40] The women were considered positive for HPV if either the cervical or vaginal swabs tested positive for HPV DNA.

*Statistical analysis*

We examined HPV infection in several ways: infection with any HPV type, infection with any of the high-risk types, infection with any of the low-risk types, and infection with any high-risk type other than HPV 16 and 18. We additionally defined the exposure as infection with either of the types targeted by the bivalent vaccine (HPV 16 or 18), infection with any type targeted by the nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58), and infection with any type targeted by the quadrivalent vaccine (HPV 6, 11, 16, 18) to examine the association of vaccine-preventable HPV types on HIV risk. We also evaluated dose-response relationship between HIV acquisition and the number of HPV types detected by examining the latter as a categorical variable as well as a continuous variable.

A priori, we considered the following covariates as potential confounders: demographics (age, country of residence, and education attainment), sexual behaviors (condom use, number of recent sex partners, having a current primary partner, the participant or her partner having a concurrent relationship outside of their partnership, and having transactional sex in the past year), any recent history of STIs (syphilis, gonorrhea, chlamydia, or trichomoniasis), HSV-2 positivity, and any recent history of other vaginal infections (bacterial vaginosis or candidiasis). Participants' study product assignment in VOICE was considered a confounder if assignment was different by case or control status in our analysis. Data on demographic covariates were extracted from enrollment questionnaires. Sexual behavior data were extracted from quarterly behavioral questionnaires. We used data provided at any time between three months before the cervical or vaginal swab collection visit and the HIV seroconversion visit in cases. If participants answered multiple behavioral questionnaires during that time, we used data from the questionnaire closest to swab collection visit. Similarly, we considered participants to have had a recent history of STI or other vaginal infections if they were diagnosed with a STI between three months before the cervical or vaginal swab collection visit and the HIV seroconversion visit in cases.

We conducted univariate comparisons by case and control status on the covariates listed above using analysis of variance tests for continuous variables and chi-square tests for categorical variables. Using conditional logistic regression models, we estimated odds ratios and 95% confidence intervals (CI) quantifying the association between HPV infection and HIV acquisition. Because controls were matched to cases based on study visit (i.e., follow-up time in study), the resulting effect measures from the conditional logistic regression approximate the incidence rate

ratio. We performed data management and analyses in R (Version 4.0.3) and SAS 9.4 (SAS Institute, Cary, NC).

**Results**

Cases and controls were on average 23 years old at enrollment, with standard deviation of four years (Table 2). While most participants (93%) had at least some secondary school education, the controls were more likely than cases to have attended university or college (p=0.02). The vast majority of the women in the case-control study were enrolled at South African sites (Table 2). Although cases were more likely to have been randomized to the vaginal PrEP and placebo arms and the controls to the oral PrEP and placebo arms, randomization assignment was not significantly different by case status.

Time-varying sexual behaviors, STIs, and other vaginal infections are also described in Table 2. Approximately 4% of cases and controls had a history of transactional sex in the past year. Over 90% of the women in our sample reported having a primary partner in the past three months. However, cases were significantly less likely to have a primary partner compared to controls (94% vs. 98%, p=0.020). While the average number of sex partners in the past three months was the same between cases and controls, cases were more likely to report that their primary partners were non-monogamous (p=0.006) and that they themselves had sex partners other than their primary partner (p=0.033). About 66% of both cases and controls reported using condoms the last time they had sex. Compared to controls, cases had a higher prevalence of recent STI (31% vs 23%, p=0.051), higher seroprevalence of HSV-2 (58% vs 46%, p=0.014), and similar prevalence of other vaginal infections (7% vs 5%, p=0.448).

The prevalence of HPV infection was high in our study sample regardless of HIV status (Table 3), with infection with any HPV type detected in 84% of cases and 65% of controls ($p<0.001$). The prevalence of any high-risk HPV infection was 74% among cases and 55% among controls ($p<0.001$). Cases were also more likely to be positive for HPV infection with any low-risk type compared to controls (66% vs 48%, $p<0.001$). However, the prevalence of infection with either HPV 16 or 18 was not significantly different by case or control status. Infection with multiple HPV types was also common in our study (67% in cases and 49% in controls, $p<0.001$). Cases had an average of three HPV types detected whereas controls had an average of 1.9 types detected ($p<0.001$).

Adjusting for age, education, condom use, number of sex partners, having a current primary partner, the participant and her partner having concurrent relationships outside of their partnership, and having transactional sex in the past year, STIs, HSV-2, and other vaginal infections, women with any HPV infection had 2.6 times higher risk of HIV seroconversion compared to women with no HPV infection (95% CI 1.4 – 4.9, Table 3). Risk of HIV seroconversion was also 2.7 times higher with a high-risk HPV infection (95% CI 1.5-4.9) compared to no high-risk HPV infection and 1.8 times higher with a low-risk HPV infection (95% CI 1.1-2.9) compared to no low-risk infection. For vaccine-preventable HPV infections specifically, we found that HIV acquisition was associated with infection with any of the types targeted by the nonavalent vaccine (aOR 2.2, 95% CI 1.3-3.7) and the quadrivalent vaccine (aOR 2.0, 95% CI 1.2–3.3), but not the bivalent vaccine after adjusting for covariates (aOR 1.6, 95% CI 0.9-2.8). The risk of HIV seroconversion was elevated with infection with a single HPV type (aOR 1.9, 95% CI 0.9-4.2) and increased with the number of HPV types detected (aOR 2.2, 95% CI 1.1-4.6 for two to three types and aOR 4.1, 95%

CI 1.9-8.7 for four or more types; (Figure1)). With each additional HPV type detected, HIV risk increased by 20% (aOR 1.2, 95% CI 1.1-1.4).

**Discussion**

In this case-control study of young women at risk for HIV, infection with any HPV type, high-risk HPV types, and low-risk HPV types were associated with increased risk of HIV infection during follow-up, after adjusting for sexual behaviors and recent history of other STIs. Infection with HPV types targeted by the nonavalent and the quadrivalent HPV vaccines also significantly increased HIV acquisition. We additionally found that the risk of HIV acquisition increased with the number of HPV types detected.

These findings are consistent with previous epidemiological studies and meta-analyses on this topic that controlled for confounding.[19,20,47,48] However, our findings disagreed with those from a similar case-control study conducted by Gallagher et al,[49] which found that HPV infections, regardless of type groupings, were not associated with HIV acquisition.[49] The high prevalence of HSV-2 among both cases and controls (>80%) in that study could have masked the effect of HPV on HIV acquisition, as HSV-2 is strongly associated with HIV acquisition.[50] In contrast, 58% and 46% of the cases and controls in our study were positive for HSV-2.

We additionally found that infection with any HPV types included in the nonavalent vaccine and the quadrivalent vaccine was associated with a two-fold increase in HIV acquisition. HPV vaccination is highly efficacious in reducing cervical cancer risk and is being implemented in an increasing number of countries.[51] Our results suggest that HPV vaccination, particularly with the

nonavalent vaccine, could potentially have the added benefit of protecting women from HIV infection.

Vaccination with the bivalent vaccine, however, may not impact HIV acquisition, as infection with HPV 16 and/or 18 did not significantly increase HIV risk. One potential explanation is that with the relatively lower prevalence of HPV 16/18 in this population, our power was limited to detect a statistically significant association. However, it is also possible that HPV 16 and 18 are less likely than other types to activate a mucosal T-cell response and increase cervical vulnerability to HIV infection. HPV 16/18 infections are the most likely to persist and progress to cervical cancer,[52] and the ability of HPV 16/18 to persist may be correlated with adeptness to evade the immune system. Cytotoxic T lymphocyte responses to HPV oncoproteins E6 and E7 were less likely to be detected in HPV positive women with squamous intraepithelial neoplasia (SIL) than in HPV positive women without SIL, which suggests that persistent HPV infections were less likely to generate target cells for HIV infection.[53] Consistent with this explanation, previous epidemiological studies found no association between abnormal Pap results and HIV infection.[48]

Infection with multiple HPV types was common in our study sample, as well as in the general population of women.[42] We found that concurrent infection with multiple HPV types significantly increased HIV risk. Specifically, the risk of HIV acquisition increased by 20% with each additional HPV type detected. This confirms a previous finding of a dose-response relationship between HPV infection and HIV acquisition among South African women.[47] In that study, relative to no HPV infection, infection with two HPV types was associated with two-fold increase in HIV acquisition and infection with more than four HPV types was associated with almost a six-fold increase in

HIV acquisition.[47] Since both our study and the South African study adjusted for sexual behaviors, the positive association implies this finding is due to an increased biological susceptibility to HIV among women with multiple HPV infections rather than confounding. As individual HPV infections progress and regress independently of each other,[54] having multiple infections may prolong periods of susceptibility to HIV infection.

Our study contributes to the still limited body of research on the effect of HPV infection and HIV acquisition. With a relatively large sample size, the ability to adjust for important time-varying confounders, and short interval between ascertainments of HPV and HIV infections, our study addressed some of the limitations of previously published studies and provided additional evidence of a potential biological interaction between HPV and HIV infections. However, further studies, particularly ones capturing the incidence and clearance of HPV infections, are required to definitively establish causality.

Our study has several limitations. As with many observational studies assessing the association between STIs and HIV acquisition, residual confounding by unmeasured sexual behaviors is possible.[55] The significant associations we observed could potentially be the result of a time lag between HPV and HIV acquisitions from HPV and HIV co-infected partners, because HIV has a lower per-coital act transmission probability compared to HPV.[56,57] Since we do not have data on the HPV and HIV status of the participants' partners, we cannot definitively eliminate this explanation. However, we were able to adjust for having partners beside the primary partner to control for concurrent partnerships that could have led to HPV infection and HIV acquisition. Although 312 women acquired HIV over the course of the VOICE study, we were only able to

include 138 women who had stored cervical or vaginal swab specimens collected one to six months before HIV seroconversion, which could limit internal validity. However, we found that demographic and behavioral characteristics at baseline were similar between cases and controls and the overall VOICE population and between cases and the other VOICE participants who acquired HIV but were not included. Ascertainment of STI and vaginal infections in VOICE was done at the enrollment visit, annually, and at presentation of symptoms, which could have led some women with asymptomatic STIs or vaginal infections between enrollment and the annual visits to be misclassified as negative. Residual confounding by unmeasured or misclassified STI may have biased the associations away from the null.

In August 2020, the World Health Organization announced an ambitious initiative to eliminate cervical cancer as a public health problem in all countries.[22] The initiative has a strong focus on increasing the coverage of HPV vaccination in sub-Saharan African countries, which bear almost 70% of the global HIV burden and have the highest cervical cancer incidence rates in the world.[22,37,58] In countries with high burden of both HPV and HIV infections, wide-spread implementation of HPV vaccination with the nonavalent or the quadrivalent vaccines may have the dual benefit of concurrently reducing risk for HIV and cervical cancer among women.

**Acknowledgement**

The authors gratefully acknowledge the immense contribution of the late Dr. Gita Ramjee to MTN-003 and the field of HIV prevention for women.

Author's contributions: conceptualization – GL, RVB, NRM, ERB, JEB, FH; data acquisition – NMM, ZMC, JMM, LM, TPP, SSS, LN, NJ, ZG, GLN, PS, CN, BM, BGM, MT, RP; formal analysis – GL; data interpretation – all authors; drafting – GL, RVB; reviewing and editing – all authors. All authors approve the final version to be published.

The authors declare no conflict of interest. This research was funded by the University of Washington King K Holmes Endowed Professorship in STDs and AIDS. Funding for the VOICE Study was through a grant to the Microbicide Trials Network from the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The data has not been previously presented.

**Table 1.** Baseline demographic characteristics and sexual behaviors among HIV-negative controls compared to VOICE participants overall.

| | Controls (n = 412) | VOICE participants (n = 5029)[14] | Cases (n = 138) | VOICE participants who seroconverted, but were not included (n=174) |
|---|---|---|---|---|
| **Mean age (SD)** | 23.6 (3.9) | 25.5 (5.1) | 23.2 (4.1) | 23.2 (4.1) |
| **Some secondary school education or higher** | 95% | 92% | 88% | 92% |
| **Country** | | | | |
| South Africa | 391 (95%) | 4077 (81%) | 131 (95%) | 165 (95%) |
| Uganda | 12 (3%) | 322 (6%) | 4 (3%) | 5 (3%) |
| Zimbabwe | 9 (2%) | 630 (13%) | 3 (2%) | 4 (2%) |
| **Currently married** | 34 8% | 1052 (21%) | 7 (5%) | 5 (3%) |
| **Mean number of live births (SD)** | 1.2 (0.9) | 1.5 (1.1) | 1.2 (0.9) | 1.2 (0.9) |
| **Condom use during last vaginal sex** | 325/373 (87%) | 3766/4420 (85%) | 109/126 (87%) | 137/161 (85%) |
| **≥2 male sex partners in the past 3 months** | 92/410 (22%) | 1104/4991 (22%) | 39/137 (28%) | 43/173 (25%) |
| **Anal sex in the past 3 months** | 70/407 (17%) | 868/4991 (17%) | 27/136 (20%) | 38/171 (22%) |

Abbreviation: SD, standard deviation

**Table 2**: Demographic characteristics and sexual behaviors of cases and controls at enrollment and during follow-up.

| | Case (N=138) | Control (N=412) | Total (N=550) | p-value* |
|---|---|---|---|---|
| ***Characteristics at enrollment*** | | | | |
| **Mean age (SD)** | 23.2 (4.1) | 23.6 (3.9) | 23.5 (4.0) | 0.353 |
| **Education** | | | | 0.022 |
| No schooling | 3 (2.2%) | 1 (0.2%) | 4 (0.7%) | |
| Primary | 13 (9.4%) | 20 (4.9%) | 33 (6.0%) | |
| Secondary | 113 (81.9%) | 356 (86.4%) | 469 (85.3%) | |
| College/University | 9 (6.5%) | 35 (8.5%) | 44 (8.0%) | |
| **Country** | | | | 1.000 |
| South Africa | 131 (94.9%) | 391 (94.9%) | 522 (94.9%) | |
| Uganda | 4 (2.9%) | 12 (2.9%) | 16 (2.9%) | |
| Zimbabwe | 3 (2.2%) | 9 (2.2%) | 12 (2.2%) | |
| **Study product** | | | | 0.067 |
| Oral FTC/TDF | 27 (19.6%) | 89 (21.6%) | 116 (21.1%) | |
| Oral placebo | 22 (15.9%) | 98 (23.8%) | 120 (21.8%) | |
| Oral TDF | 21 (15.2%) | 75 (18.2%) | 96 (17.5%) | |
| Vaginal placebo | 40 (29.0%) | 79 (19.2%) | 119 (21.6%) | |
| Vaginal TFV gel | 28 (20.3%) | 71 (17.2%) | 99 (18.0%) | |
| ***Time-varying sexual behaviors, STIs, and vaginal infections*** | | | | |
| **Had transactional sex in the past year** | | | | 0.422 |
| Yes | 6 (4.4%) | 18 (4.4%) | 24 (4.4%) | |
| No | 131 (95.6%) | 392 (95.6%) | 523 (95.6%) | |
| **Had a primary partner in the past 3 months** | | | | **0.020** |
| Yes | 130 (94.2%) | 403 (98.1%) | 533 (97.1%) | |
| No | 8 (5.8%) | 8 (1.9%) | 16 (2.9%) | |
| **Mean number of sex partners in the past 3 months** | 1.4 (0.7) | 1.4 (2.4) | 1.4 (2.1) | 0.980 |
| **Primary partner has other partners** | | | | **0.006** |
| Yes | 99 (71.7%) | 282 (68.4%) | 381 (69.3%) | |
| No | 20 (14.5%) | 101 (24.5%) | 121 (22.0%) | |
| Don't know | 19 (13.8%) | 29 (7.0%) | 48 (8.7%) | |
| **Had other partners besides primary partner** | | | | **0.033** |
| Yes | 35 (26.3%) | 84 (20.7%) | 119 (22.1%) | |
| No | 100 (73.5%) | 337 (82.0%) | 437 (79.9%) | |
| **Condom used at last sex** | | | | 0.987 |
| Yes | 84 (66.1%) | 249 (66.2%) | 333 (66.2%) | |
| No | 43 (33.9%) | 127 (33.8%) | 170 (33.8%) | |
| **Positive for syphilis, gonorrhea, chlamydia, or trichomoniasis** | | | | 0.051 |
| Yes | 42 (31.3%) | 93 (22.9%) | 135 (25.0%) | |
| No | 92 (68.7%) | 313 (77.1%) | 405 (75.0%) | |
| **Positive for herpes simplex virus 2** | | | | 0.014 |
| Yes | 80 (58.0%) | 189 (45.9%) | 269 (48.9%) | |
| No | 58 (42.0%) | 223 (54.1%) | 281 (51.1%) | |
| **Positive for bacterial vaginosis or candidiasis** | | | | 0.448 |

| | | | | |
|---|---|---|---|---|
| Yes | 9 (6.5%) | 20 (4.9%) | 29 (5.3%) | |
| No | 129 (93.5%) | 392 (95.1%) | 521 (94.7%) | |

Abbreviation: SD, standard deviation; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TFV, tenofovir

* Estimated from analysis of variance tests for continuous variables and chi-square tests for categorical variables.

**Table 3.** Crude and adjusted associations between HPV types detected and HIV acquisition.

| | Prevalence | | | Crude OR (95% CI) | Adjusted OR[1] (95% CI) |
|---|---|---|---|---|---|
| | Cases (n = 138) | Controls (n = 412) | P-value[2] | | |
| **Any HPV**[3] | 116 (84.1%) | 269 (65.3%) | <0.001 | 3.0 (1.8-5.2) | 2.6 (1.4-4.9) |
| **High-risk HPV**[4] | 102 (73.9%) | 227 (55.1%) | <0.001 | 2.5 (1.6-4.0) | 2.7 (1.5-4.9) |
| **Low-risk HPV**[5] | 91 (65.9%) | 196 (47.6%) | <0.001 | 2.1 (1.4-3.2) | 1.8 (1.1-2.9) |
| **HPV 16 or18** | 34 (24.6%) | 73 (17.7%) | 0.098 | 1.5 (1.0-2.4) | 1.6 (0.9-2.8) |
| **Non-HPV 16/18 high risk HPV**[6] | 94 (68.1%) | 201 (48.8%) | <0.001 | 2.4 (1.6-3.7) | 2.6 (1.5-4.4) |
| **Nonavalent vaccine HPV**[7] | 83 (60.1%) | 173 (42.0%) | <0.001 | 2.2 (1.5-3.4) | 2.2 (1.3-3.7) |
| **Quadrivalent vaccine HPV**[8] | 50 (36.2%) | 90 (21.8%) | 0.001 | 2.0 (1.3-3.1) | 2.0 (1.2-3.23 |
| **Number of HPV types detected**[9] | 3.0 (2.6) | 1.9 (2.1) | <0.001 | 1.3 (1.1-1.4) | 1.2 (1.1-1.4) |

Abbreviations: OR, odds ratio; HPV, human papillomavirus

[1] Adjusted for age, education, study product arm, having transactional sex in the past year, having a primary partner in the past 3 months, number of sex partners in the past 3 months, having partners other than the primary partner, the primary partner having other partners, condom use at last sex, STI, and vaginal infections. 59 observations were dropped from adjusted conditional logistic regressions for HPV infections due to missing data on covariates. 72 observations were dropped from the adjusted conditional logistic regression for abnormal Pap results due to missing data on Pap results and covariates.

[2] Estimated from chi-square tests comparing prevalence by case-control status. P-value for number of HPV types detected was estimated using analysis of variance test.

[3] Defined as infection with any of the 37 HPV types.

[4] Defined as infection with any of the following: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68.

[5] Defined as infection with any of the following: HPV 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 81, 82, 82 subtype (IS39), 83, 84, and 89 (CP6108).

[6] Defined as infection with any of the following: HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68.

[7] Defined as infection with any of the following: HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58.

[8] Defined as infection with any of the following: HPV 6, 11, 16, or 18.

[9] Data entered under the Prevalence columns represent mean number of HPV types detected and standard deviation

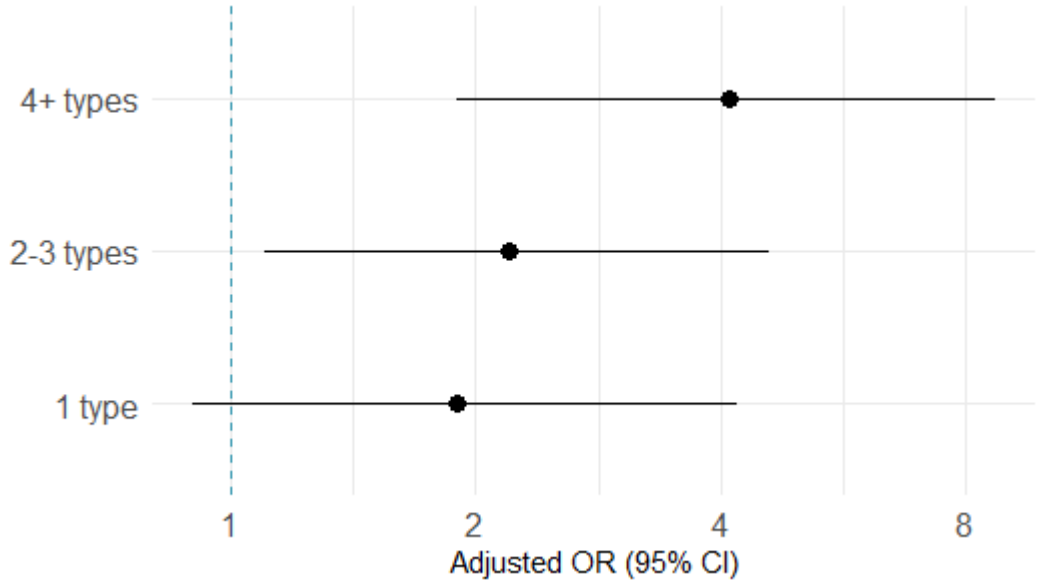



**Figure 1.** Associations between the number of HPV types detected and HIV acquisition. Odds ratios and 95% CI compared number of HPV types detected to no HPV infection and were adjusted for age, education, study product arm, having transactional sex in the past year, having a primary partner in the past 3 months, number of sex partners in the past 3 months, having partners other than the primary partner, the primary partner having other partners, condom use at last sex, STI, and vaginal infections. The dotted line vertical line indicate null.

# Chapter 3. HIV-positive women have higher risk of HPV infection, precancerous lesions, and cervical cancer: A systematic review and meta-analysis

Published citation: Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS. 2018 Mar 27;32(6):795-808. doi: 10.1097/QAD.0000000000001765.

**HIV-positive women have higher risk of HPV infection, precancerous lesions, and cervical cancer: A systematic review and meta-analysis**

**Short title: Impact of HIV on HPV and cervical cancer**

Gui LIU, MPH[1§], Monisha SHARMA, ScM, PhD[2], Nicholas TAN, BS[2], and Ruanne BARNABAS, MBChB, DPhil[1,2,3,4]

[1]Department of Epidemiology, University of Washington, Seattle, WA USA
[2]Department of Global Health, University of Washington, Seattle, WA USA
[3]School of Medicine, University of Washington, Seattle, WA USA
[4]Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[§]Corresponding author:
Gui Liu
Department of Epidemiology
University of Washington
1959 NE Pacific Street
Health Sciences Building, F-262
1-206-520-3800
guiliu@uw.edu

Funding: This work is funded by the National Cancer Institute [U01 CA199334]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Abstract**

**Objectives:** HIV-positive women have higher human papillomavirus (HPV) prevalence and cervical cancer (CC) incidence than HIV-negative women, partly due to HIV's modifying effect on HPV pathogenesis. We synthesized the literature on the impact of HIV on HPV natural history.

**Design:** Systematic review and meta-analysis

**Methods:** We searched the literature for studies evaluating HPV acquisition and persistence or precancer progression by HIV status. Data on HPV natural history by HIV status, CD4+ cell counts, viral load, and antiretroviral therapy (ART) were summarized using fixed effect models.

**Results:** Overall, 38 of 1845 abstracts identified met inclusion criteria. HIV-positive women had higher HPV acquisition (relative risk [$RR_{pooled}$]=2.64, 95% confidence interval [CI] 2.04-3.42) and lower HPV clearance (hazard ratio [$HR_{pooled}$]=0.72, 95% CI 0.62-0.84) than HIV-negative women. HPV acquisition was higher with declining CD4 and was lower in those virally suppressed on ART. HIV was associated with higher incidence of low-grade squamous intraepithelial lesions (LSIL) ($RR_{pooled}$=3.73, 95% CI 2.62-5.32) and high-grade squamous intraepithelial lesions (HSIL) ($HR_{pooled}$=1.32, 95% CI 1.10-1.58), largely due to increased HPV persistence. ART lowered progression from normal cytology to LSIL ($HR_{pooled}$=0.65, 95% CI 0.52-0.82), but not HSIL. CC incidence was associated with HIV positivity (RR=4.1, 95% CI 2.3-6.6), but not with ART.

**Conclusions**: HIV-positive women have higher risk of acquiring HPV, with risk inversely associated with CD4 count. ART lowered HPV acquisition, increased clearance, and reduced precancer progression, likely via immune reconstitution. While some of our results are limited by small number of studies, our study can inform screening guidelines and mathematical modeling for CC prevention.

**Key words**: HIV, human papillomavirus, HIV/HPV coinfection, precancerous lesions, cervical cancer, antiretroviral therapy

## Introduction

Cervical cancer (CC) is the fourth most common cancer in women worldwide and the most common cancer among women in sub-Saharan Africa.[59] Sub-Saharan Africa has high dual burden of human papillomavirus (HPV) and HIV infection.[60,61] HIV is associated with higher rates of HPV acquisition, decreased clearance of HPV and precancerous lesions, and increased risk of CC.[62,63] Compared to HIV-negative women, CC mortality in HIV-positive women is ~2-times higher.[64,65] With increasing life expectancy of HIV-positive women on antiretroviral treatment (ART), there is a growing need for CC prevention, particularly in low resources settings.[66] In the United States, CC screening programs have been highly effective in reducing CC incidence and HPV vaccines have been shown to reduce the prevalence of HPV 16 and 18-attributable precancer lesions.[67,68] However, availability of HPV vaccines and CC screening is extremely limited in developing settings, although efforts to scale up screening are ongoing in Zambia.[69,70] CC screening coverage in the last 3 years among eligible women is less than 6% in Kenya and 23% in South Africa.[71]

CC screening is not without harm and research on the optimal screening interval for HIV-positive women is still emerging.[72] In September 2015, the recommended CC screening interval for HIV-positive women with normal cytology was changed from annually to every 3 years in the United States.[73] A better understanding of the impact of HIV on HPV natural history can help inform CC screening and prevention policies for HIV-positive women.

Further, although many studies have evaluated the relationship between HIV and HPV pathogenesis the findings have not been synthesized. While ART decreases the incidence of other

AIDS-related cancers, its relationship with CC is unclear.[72,74,75] We conducted a systematic review and meta-analysis to synthesize the literature on HPV natural history in HIV-positive women. Specifically, we evaluate the risk of HPV incidence, persistence, and progression to cervical lesions and cancer among HIV-positive women compare to HIV-negative women. We additionally assess these relationships by CD4+ cell counts, HIV viral load (VL), and ART use.

## Methods

### Study objectives

We sought to assess the interactions between HIV and HPV on the 1) incidence of HPV infection; 2) persistence/clearance of HPV infection; 3) progression from HPV infection to low-grade squamous intraepithelial lesion (LSIL); 4) progression from LSIL to high-grade squamous intraepithelial lesion (HSIL); 5) regression from LSIL; 6) regression from HSIL; and 7) progression to invasive CC. HPV pathogenesis in HIV-positive women was compared to HIV-negative women. We assess the modifying effect of CD4 count, HIV VL, and ART on interactions between HIV and HPV.

### Inclusion/exclusion criteria

Eligible studies examined the acquisition, persistence, or clearance of HPV or the incidence, progression, and regression of cervical lesions by HIV status, CD4 count, HIV VL, and ART using cohort or case-control study design. Studies assessing HPV incidence were included only if they adjusted for confounders identified in previous literature (e.g. age, number of sex partners, etc.) or identified in their data; however we did not restrict on specific confounders (Appendix Table 3). Studies grouping LSIL and HSIL together were only included if proportions of LSIL and HSIL

were reported. If >85% of lesions detected were LSIL, we considered the estimates to approximate LSIL natural history.

**Search strategy**

Following PRISMA guidelines, we conducted a systematic search on PubMed, Embase, Global Health Database, reference list of eligible papers, and conference abstracts (Appendix tables 1 and 2).[76] Search terms included HIV, HPV, cervical lesion, and disease progression. We included only primary research articles, but did not restrict on language or publication date. Additional details about the search strategy are available in the Appendix.

**Study quality assessment**

We assessed the risk of bias (low, moderate, high) in studies using modified criteria for non-randomized observational studies across five domains: study population, detection of outcome and exposure, bias related to study design, statistical analysis, and disclosure of conflict of interest.[77,78] See Appendix Figures 1 and 2 for detailed study quality assessment.

**Statistical analysis**

When possible, effects by HIV status, CD4 count, and ART use were pooled using fixed effect models with inverse variance weighting (SAS 9.4). We combined estimates with the same measures of association (e.g. relative risk, odds ratio, or hazard ratio). We quantified heterogeneity with $I^2$. When the number of studies in a meta-analysis is small, $I^2$ was sometimes a negative value and set to zero.

## Results

The search was conducted on 5/19/2017 and yielded 1845 studies. We excluded 1726 studies after screening abstracts (Figure 1). Primary reasons for exclusions were ineligible study design and HPV infection site. We further excluded 81 studies after reading the full text. Overall, 38 studies were included (Table 1). Most studies were prospective cohort (n=34); the remaining were retrospective cohort (n=2), nested case-control (n=1), and case-crossover (n=1). Most were conducted in North America (n=18) or Africa (n=13). The US (n=15) and South Africa (n=7) were the most frequently represented countries. One study was conducted in Asia and six in Europe. Half of studies included HIV-negative women as the comparison group (n=23). Papanicolaou (Pap) smear was most commonly used to collect cervical specimens and polymerase chain reaction using L1 consensus primers was most common method for genotype detection.

The majority of studies had low risk of bias in selection of study population (79%), ascertainment of exposure and outcome variables (76%), and statistical analysis (71%) (Appendix figures 2 and 3). Only 32% had low risk of study design-specific bias, due to incomplete ascertainment of ART use or high loss to follow-up.

### HPV incidence

Twelve studies assessed HPV incidence,[63,79-89] seven included HIV-negative women as reference.[63,79,80,84,86,89] HIV-positive women had higher risk of acquiring infection with any HPV ($RR_{pooled}$ 2.64, 95% CI 2.04-3.42), as well as high risk (HR) HPV, HPV 16, and HPV 18 ($RR_{pooled}$ 2.35, 95% CI 1.64-3.37; $RR_{pooled}$ 3.05, 95% CI 1.71-5.42; $RR_{pooled}$ 2.55, 95% CI 1.17-5.60, respectively) (Figure 2a).

*CD4 count*

Four studies found that CD4 count modified HPV acquisition in HIV-positive women.[63,81,86,89] Women with high CD4 count (>500 cells/mm$^3$) were at greater risk of infection compared to HIV-negative women, and risk dramatically increased with declining CD4 count (Figure 2b).[63,86,89] One study found the risk of HPV infection decreased by 18% with every 100-cell increase in CD4 (OR 0.82, 95% CI 0.70-0.96).[81] Two studies found higher CD4 count did not significantly reduce HPV incidence (Appendix Table 3).[83,84]

*ART*

Three of the four studies that ascertained ART use from medical records or self-reports found no association between ART and HPV incidence (Appendix Table 3);[83,86,88] while one study found ART reduced HPV 16 and 18 incidence by 72% (RR 0.28, 95% CI 0.09-0.86) but not any HPV incidence (RR 0.79, 95% CI 0.28–2.23).[82] One study comparing effective ART (defined as reducing HIV VL by >90% or to undetectable), to no treatment found that effective ART decreased incidence of any HPV by 36% (OR 0.64, 95% CI 0.46-0.88) but the impact on HR HPV incidence was not statistically significant (OR 0.62, 95% CI 0.38-1.02).[85]

*HIV VL*

Two studies evaluated the role of HIV VL on HPV acquisition.[63,84] Compared to HIV-negative women, the risk of any HPV infection was 3.29 times (95% CI 2.18-4.95) higher among HIV-positive women with VL>10,000 copies/mL and 2.31 times (95% CI 1.49-3.58) higher among those with VL<10,000 copies/mL.[84] Further, HPV acquisition was higher with increasing VL

among women with CD4 >200 cells/mm$^3$ (Figure 2b), although no pattern in HPV acquisition by VL was observed in women with CD4 <200 cells/mm$^3$.[63]

*HPV Reactivation*

One study found that new HPV infections were detected in women who reported no sexual activity in the last 18 months, indicating potential reactivation of latent infections. The rate of potential reactivations was 1.4-4.4 times higher among HIV-positive compared to HIV-negative women.[63]

**HPV persistence and clearance**

Two studies evaluated clearance among women with incident HPV infection.[63,90] HIV-positive women were 28% less likely than HIV-negative women to clear infection with any HPV ($HR_{pooled}$ 0.72, 95% CI 0.62-0.84; Figure 3a). Eleven studies evaluated clearance of incident and prevalent HPV infections together[80,83-85,87,90-95] and found HIV-positive women were 41-46% less likely to clear any HPV infection ($HR_{pooled}$ 0.54, 95% CI 0.48-0.60; $RR_{pooled}$ 0.59, 95% CI 0.49-0.71) and 36-44% less likely to clear HR HPV infection ($HR_{pooled}$ 0.56, 95% CI 0.45-0.69; $RR_{pooled}$ 0.64, 95% CI 0.52-0.78) (Figure 3b).[80,84,90,91] However, pooled effects based on two studies indicate that HPV 16 and 18 clearance were not statistically different by HIV status ($RR_{pooled}$ 0.88, 95% CI 0.49-1.59; $RR_{pooled}$ 1.14, 95% CI 0.80-1.61, respectively);[80,87] while the pooled effects based on three studies indicate that HIV-positive women had lower clearance of both types compared to HIV-negative women ($HR_{pooled}$ 0.61, 95% CI 0.47-0.80 for HPV 16; $HR_{pooled}$ 0.48, 95% CI 0.31-0.72 for HPV 18) (Figure 3b).[79,91,95]

Women with low CD4 count (<200 cells/mm$^3$) had much lower likelihood of HPV clearance compared to women with higher CD4 count (Figure 3c) or HIV-negative women.[84,90,92,93,95] However, two studies found no difference in HPV clearance by CD4 count (Appendix Table 5).[83,84] In one study, clearance rates did not differ by HIV VL (RR 0.77, 95% CI 0.51-1.16) but another found that every one log increase in VL resulted in a 23% reduction in likelihood of clearance (HR 0.77, 95% CI 0.64-0.91).[84,85] ART did not impact clearance of any HPV infection, regardless of adherence or effectiveness (Appendix Table 5).[83,85,91] However, one study found clearance of HR HPV infection other than HPV 16 or 18 was higher among women on ART compared to those not on ART (HR 2.20, 95% CI 1.22-3.98).[91]

**Progression to LSIL**

Eight studies evaluated progression to LSIL from normal cytology[75,95-101] and one study evaluated progression to LSIL from normal cytoloy or atypical squamous cells of undetermined significance (ASCUS).[81] Among women with normal cytology at baseline, HIV-positive women had 3.73 times higher risk of progression to ASCUS or LSIL compared to HIV-negative women (95% CI 2.62-5.32; Figure 4a).[96-98,102] Among HIV-positive women, LSIL incidence in those with persistent HPV infection (detected at ≥2 visits 3-12 months apart) was 11 times higher with HPV 16/18 (95% CI 1.4-88.7) and 8.9 times higher with non-HPV 16/18 types (95% CI 1.2-66.2), compared to women without persistent HPV.[97] In one study, CD4 count and ART were no longer associated with LSIL incidence after adjusting for persistent HPV infection (Appendix Table 6).[97]

LSIL risk was >30% lower in women on ART ($HR_{pooled}$ 0.65, 95% CI 0.52-0.82 and $RR_{pooled}$ 0.67, 95% CI 0.45-1.00; Figure 4b).[75,97,100-102] Risk of LSIL decreased with CD4 count gains after ART

initiation (Figure 4c).[102] Controlling for CD4 count, women on ART had 34% lower risk of LSIL incidence compared to those not on ART (RR 0.66, 95% CI 0.47-0.92).[102]

**Progression to HSIL**

Ten studies assessed progression to HSIL,[62,75,92,98,103-108] seven compared progression by HIV status.[92,98,103-106,108] HIV-positive women had higher risk of developing HSIL compared to HIV-negative women ($HR_{pooled}$ 1.32, 95% CI 1.10-1.58; Appendix figure 3).[92,103-105] Two studies found persistence of HPV and LSIL were stronger predictors of progressing to HSIL than HIV status alone.[103,108] Risk of progression to HSIL from HPV infection with normal cytology was 3 times higher among HIV-positive compared to HIV-negative women;[92,103] risk of progression from LSIL to HSIL was not significantly different by HIV status.[98,104,105,108]

Two studies in HIV-positive women with LSIL or normal cytology did not find an association between ART and HSIL incidence ($OR_{pooled}$ 0.88, 95% CI 0.69-1.12) (Appendix Figure 3).[62,75] However, the risk of progression to HSIL was 34% lower among women initiating ART before LSIL diagnosis and 36% lower among women on ART for ≥2 years.[62,105] Risk of progression was higher in women with lower CD4 count at HSIL diagnosis regardless of ART use.[75] CD4 count, HIV status, and VL were not associated with HSIL incidence after adjusting for persistent HR HPV infection (Appendix Table 6).[104,107]

**LSIL regression**

Eight studies evaluated LSIL regression;[75,99,105,106,109-112] three compared regression by HIV status.[105,106,109] The likelihood of regression was 33% lower among HIV-positive women ($HR_{pooled}$

0.67, 95% CI 0.56-0.82; Figure 5a) and varied by age, CD4 count, ART, and treatment of lesions.[105,109] One study found that for women not on ART, lower CD4 count was associated with reduced LSIL regression (Figure 5b).[103] Likelihood of regression from LSIL was 2.29 times higher among women receiving ART compared to those not on treatment (95% CI 1.56-3.37; Figure 5c).[75,111] Longer duration ART use was associated with increased LSIL regression.[105]

**HSIL regression**

One study evaluating HSIL regression in 173 HIV-positive and negative women with HSIL in Senegal found that HIV-positive women were 43% less likely to regress from HSIL to normal cytology (HR 0.57, 95% CI 0.26-1.29) and equally as likely to regress from HSIL to HPV infection (HR 1.06, 95% CI 0.71–1.59).[92] Among HIV-positive women, likelihood of HSIL regression was 65% lower in women with HPV 16/18 compared to women infected with other types (HR 0.35, 95% CI 0.23-0.54).[92]

**Progression to cervical cancer**

CC incidence was assessed in two studies.[12,62] In the US, the age-standardized CC incidence among HIV-positive women from cohorts in North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) was 4.1 times (95% CI 2.3-6.6) higher than expected in Surveillance, Epidemiology, and End Results registry for the general population.[12] A case-control study nested in NA-ACCORD, which compared HIV-positive women to HIV-negative women, found that relative risk of CC increased with decreasing CD4 count (Appendix Figure 4).[12] Further, among HIV-positive women on ART, CD4 reconstitution halted in CC cases 3 years after initiating ART and 60 months before CC diagnosis, while matched controls (women who never developed

CC) continued to gain CD4 cells.[12] A nested case-control study of the Swiss HIV Cohort Study found that ART was not associated with lower CC incidence, regardless of duration (Appendix Table 9).[62]

**Discussion**

HIV infection was associated with higher incidence of and reduced clearance of HPV infection. Women with low CD4 count and high HIV VL had elevated risk of HPV acquisition, but risk was reduced among ART-adherent women. Low CD4 count was also associated with decreased HPV clearance. While ART reduced LSIL incidence, its impact on HSIL incidence depended on the duration of use. HIV-positive women have lower likelihood of LSIL regression, and ART and high CD4 count were associated with increased LSIL regression. In contrast, HSIL regression was not associated with HIV status. However, the study that examined HSIL regression had a small sample size and should be interpreted with caution.

While the relative risk of acquiring HPV 16/18 was higher among HIV-positive women, HPV 16/18 clearance was not found to differ by HIV status. This may be due to a lack of power or it may be that HPV 16 and 18 are better at evading the host immune system and are less impacted by HIV-associated immunosuppression.[113,114] Studies have found that HPV 16 in particular is more weakly associated with the immune system compared to other types.[115,116] This is consistent with studies that find HIV-positive women have a greater diversity of HPV types in normal cytology and low-grade lesions, but the relative prevalence of HPV 16 and 18 increases with severity of lesions and CC and the proportion of CC attributable to HPV 16/18 is similar between HIV positive and negative women.[114,117]

HIV was also associated with higher LSIL and HSIL incidence, although the relative impact on HSIL was smaller. This suggests that immunosuppression related to HIV infection may play a greater role earlier in the course of HPV natural history, namely acquisition, persistence, and progression to low-grade lesions, while later stage carcinogenicity may be less dependent on immune function. This is consistent with cohort studies that find that, although HIV-positive women have a high burden of abnormal cytology, the vast majority of lesions are low-grade, with only a small increased prevalence in HSIL.[103,118] Therefore, HIV-positive women may be at risk for overtreatment in screening programs as they have a high prevalence of low-grade lesions that infrequently progress to HSIL. The US has recently changed CC screening guidelines in HIV-positive women from annual screening to every 3 years after 3 consecutive normal screens.[73]

CD4 cell count in HIV-positive women is inversely associated with risk of HPV infection and cervical lesion progression. Further, several studies showed that women with high CD4 count (>500 cells/$mm^3$) had similar risk of HPV disease progression as HIV-negative women. Similar associations between immunosuppression and HPV risk have been observed in HIV-negative populations with impaired immune system.[119-122] A meta-analysis of cancer incidence in HIV-positive persons and transplant recipients found both groups were at higher risk of cancers with infectious etiology compared to the general population.[122] The destruction of CD4 cells by HIV may increase the likelihood of HPV establishing infection.[123] Recent evidence also suggests that immunosuppression leads to higher probability of HPV reactivation, potentially due to incomplete clearance of HPV DNA.[124]

HPV persistence likely plays an important role in the interactions between HIV and HPV. HIV-positive women with persistent HPV infection have dramatically higher incidence of precancerous lesions compared to those infected with HPV for <6 months.[94,97,104] Studies find after controlling for HPV persistence, CD4 count and ART use are no longer associated with increased risk of HPV disease progression. This is likely because HIV acts through HPV persistence to increase risk of precancerous lesions. Women infected with HPV for longer have a greater chance of developing cellular changes that lead to precancer or cancer.

The effect of ART on HPV-related disease is less clear. An equal number of studies find ART is associated with reduced HPV disease progression and find no association between ART and HPV pathogenesis. The equivocal results may be due to changes in ART regimens over time or varying durations of ART use. The majority of studies showing no effect of ART used cohorts formed in the early days of ART. Due to high toxicity of the older ART drugs, healthier HIV-infected individuals likely delayed treatment initiation and had poor adherence. Therefore, the women who were on ART likely already had more advanced HIV disease at treatment initiation. Studies show that HIV disease state at ART initiation significantly impacts morbidity and mortality.[125-127] Further, many studies finding no association approximated ART use with medical records or self-report. Studies using more accurate measures of ART adherence (e.g. viral suppression), found ART reduces HPV disease progression. One study found significantly lower incidence of HPV infection and cervical lesions in women who were virologically suppressed on ART compared to women who not on ART or not virologically suppressed.[85] A study showed CC cases had higher odds of CD4 decline on ART prior to CC diagnosis compared to controls who did not subsequently develop CC, which may indicate a disruption in ART use prior to the development of CC.[128] A

longer duration on ART is also associated with reduced HSIL incidence,[62,105] which may indicate immune system recovery.[129]

In addition to the limitations of including studies that ascertained ART status through self-reports and chart reviews, another potential limitation of this review is the heterogeneity of studies included. While majority of studies were longitudinal, variation in analysis, effect measures, and exposures definition limited our ability to perform quantitative analysis. Additionally, due to small number of studies eligible for some objectives, we could not use $I^2$ to quantify heterogeneity in many cases. High loss to follow up was an issue for some of the studies we included. While this limitation was ameliorated with survival analysis methods that censored individuals lost to follow up, effect estimates may be biased in studies that did not address this limitation in their analysis. The magnitude and direction of bias would depend on whether the lost to follow up was differential by HIV, ART, CD4 or VL status.

This review identified gaps in the research on HPV and cervical pre-cancer among HIV-positive women. There is a lack of studies investigating impact of ART on HPV disease progression using objective measures of adherence (e.g. viral suppression). Due to influence of HIV-related disease severity, evaluating HPV progression in by nadir CD4 count would be useful. Further, studies comparing HPV progression between HIV-positive women on ART with HIV-negative women can provide insight into CC risk of virally suppressed HIV-positive women. Finally, accurate estimates of CC incidence by HIV status are needed; national cancer registries do not currently document HIV status of CC cases.

## Competing interests

The authors have no competing interests to declare.


## Acknowledgement

The authors would like to thank the CISNET Cervical Cancer Modelling Consortium and UW librarian, Sarah Safranek, for her guidance in designing the search strategy for abstracts.

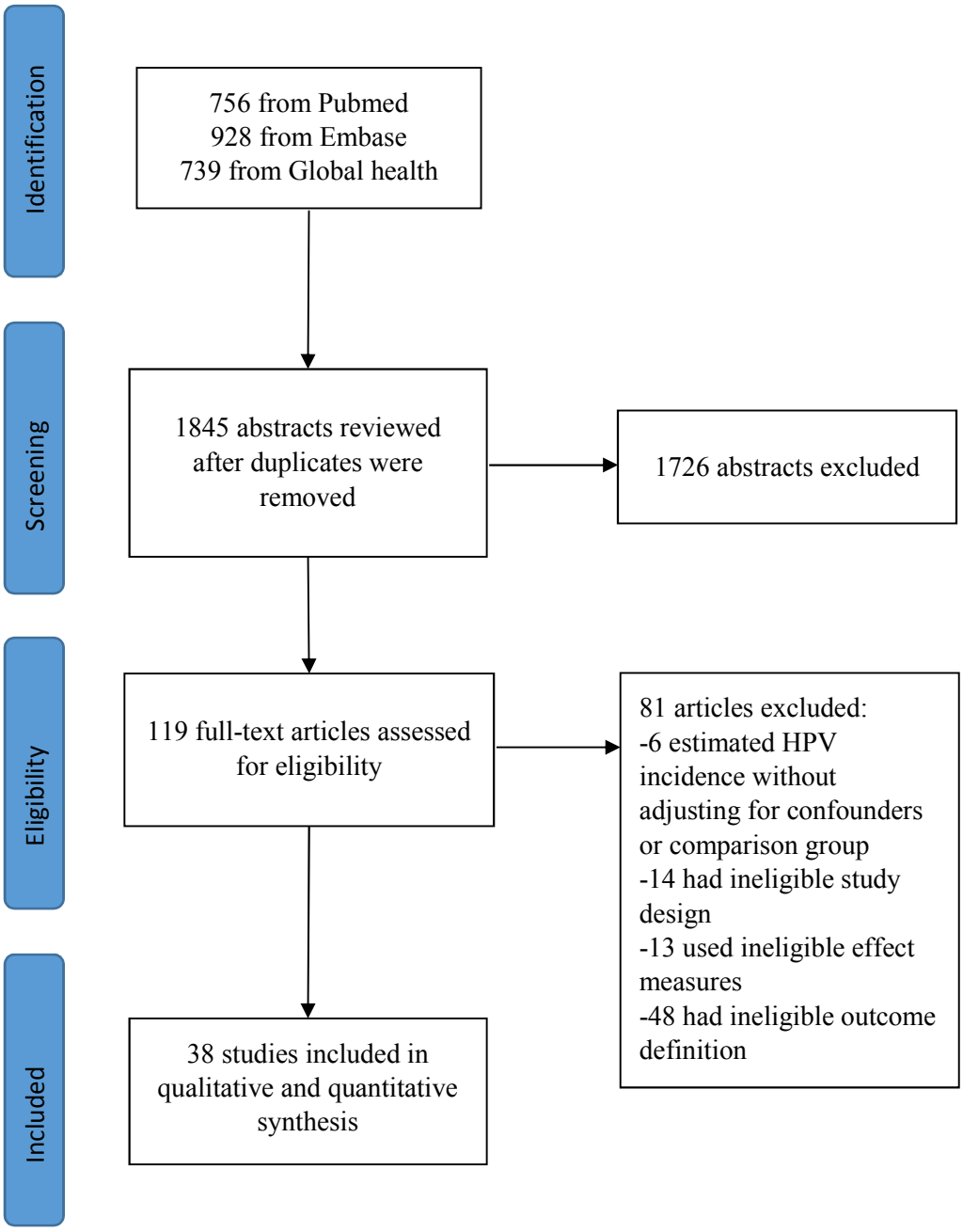

## Authors' contributions

All authors have contributed to the conception and design of the study. GL and MS acquired, analyzed, and interpreted the data. GL, MS, and RB drafted the manuscript and revised it critically for intellectual content. All authors approved the final version to be published.

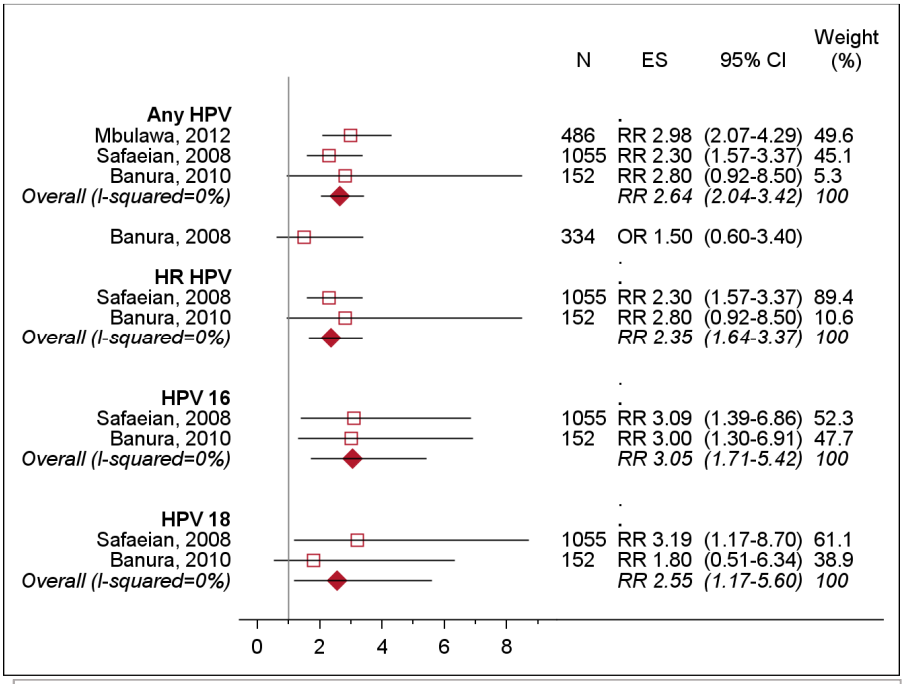
## Supplemental digital content

Appendix.docx

**Figure 1**. Flow chart of the systematic review process.



A




B

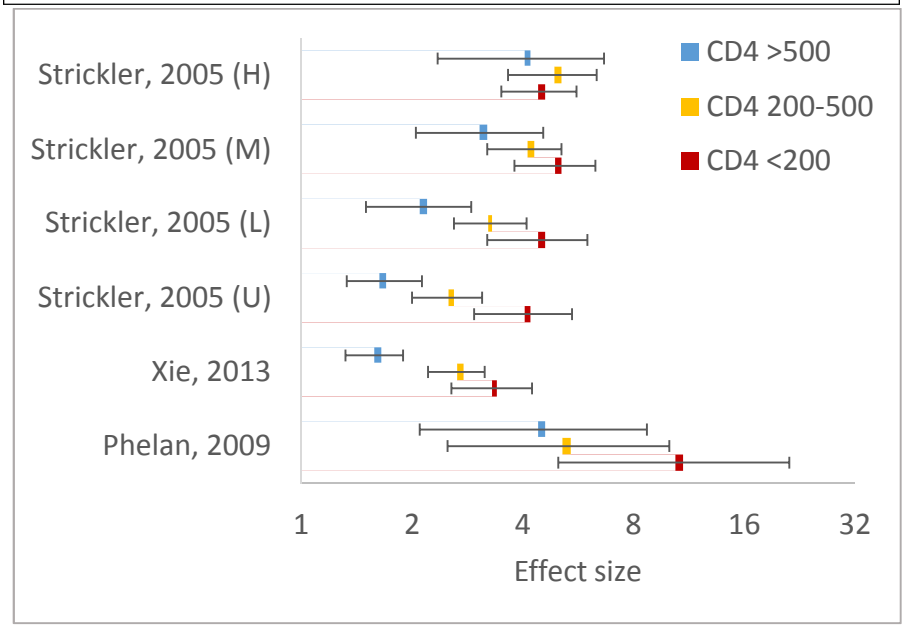
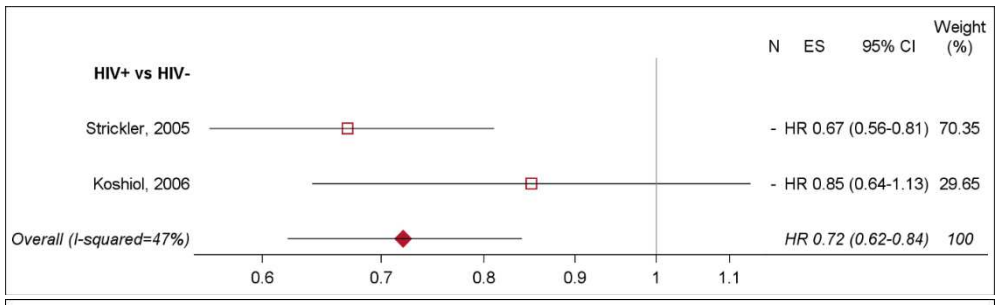
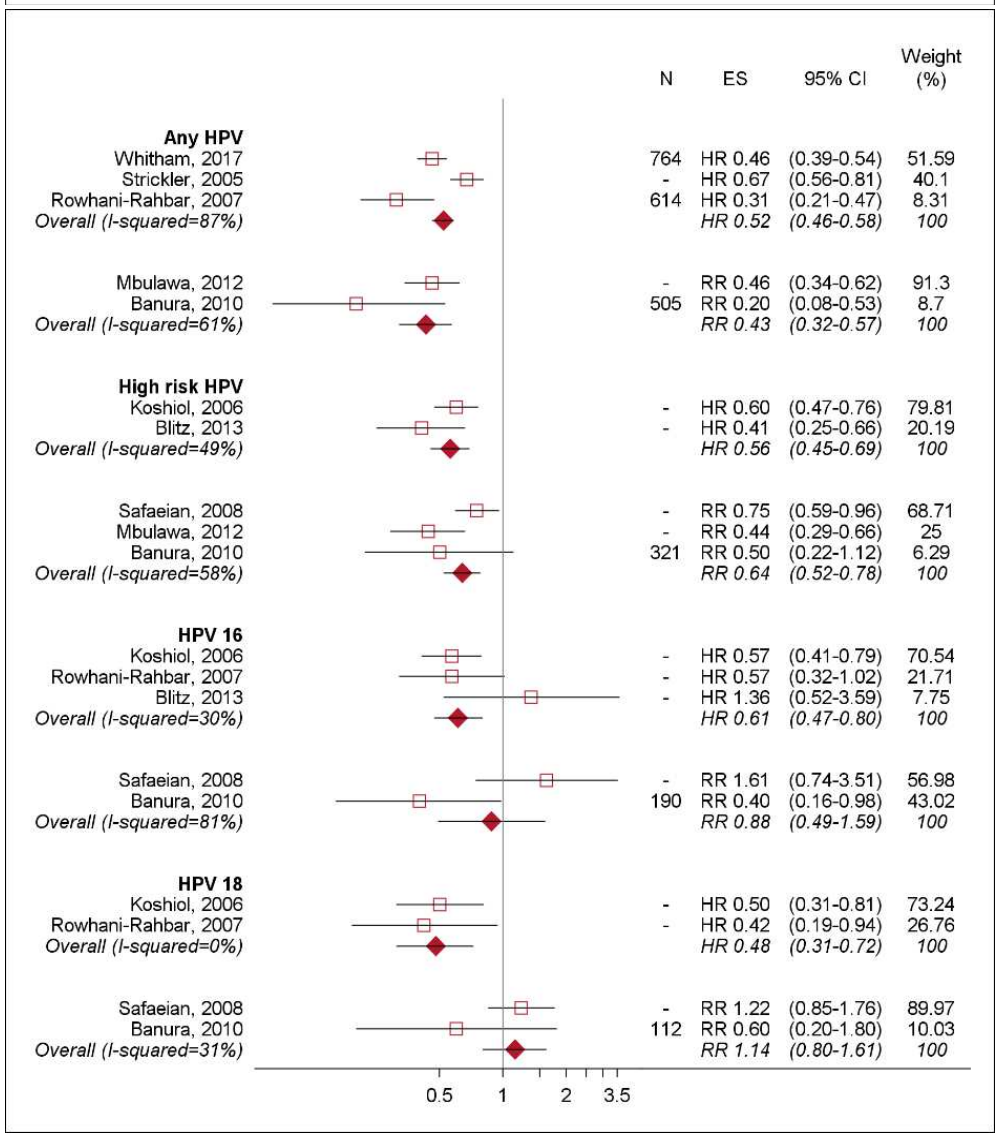



**Figure 2.** HPV incidence among HIV-positive women compared to HIV-negative women. N, sample size; ES, effect size. **A)**. Incidence of HPV infection by HPV type. Banura, 2008 was not included in calculating the overall effect because it reported odds ratio; other studies reported relative risk. **B)**. Relative incidence of any HPV infection, by CD4 count. The effect estimates from Strickler et al, 2005 were stratified HIV RNA load; U = undetectable (<4,000 copies/mL), L = low (4,000-20,000 copies/mL), M = moderate (20,001-100,000 copies/mL), and H = high (>100000 copies/mL). Effect size was measured in odds ratios in Phelan et al, 2009 and hazard ratios in Xie et al, 2003 and Strickler et al, 2005. Effect estimates from Mbulawa et al 2012, Denny et al, 2008, and Mane et al, 2016 were not included in the figure. Mbulawa et al, 2012 used a different CD4 cutoff (>350 vs. <350) and Denny et al, 2008 and Mane et al, 2016 evaluated CD4 as a continuous variable.

A


N ES 95% CI Weight (%)
HIV+ vs HIV-
Strickler, 2005 - HR 0.67 (0.56-0.81) 70.35
Koshiol, 2006 - HR 0.85 (0.64-1.13) 29.65
Overall (I-squared=47%) HR 0.72 (0.62-0.84) 100
0.6 0.7 0.8 0.9 1 1.1

B


N ES 95% CI Weight (%)
Any HPV
Whitham, 2017 764 HR 0.46 (0.39-0.54) 51.59
Strickler, 2005 - HR 0.67 (0.56-0.81) 40.1
Rowhani-Rahbar, 2007 614 HR 0.31 (0.21-0.47) 8.31
Overall (I-squared=87%) HR 0.52 (0.46-0.58) 100
Mbulawa, 2012 - RR 0.46 (0.34-0.62) 91.3
Banura, 2010 505 RR 0.20 (0.08-0.53) 8.7
Overall (I-squared=61%) RR 0.43 (0.32-0.57) 100
High risk HPV
Koshiol, 2006 - HR 0.60 (0.47-0.76) 79.81
Blitz, 2013 - HR 0.41 (0.25-0.66) 20.19
Overall (I-squared=49%) HR 0.56 (0.45-0.69) 100
Safaeian, 2008 - RR 0.75 (0.59-0.96) 68.71
Mbulawa, 2012 - RR 0.44 (0.29-0.66) 25
Banura, 2010 321 RR 0.50 (0.22-1.12) 6.29
Overall (I-squared=58%) RR 0.64 (0.52-0.78) 100
HPV 16
Koshiol, 2006 - HR 0.57 (0.41-0.79) 70.54
Rowhani-Rahbar, 2007 - HR 0.57 (0.32-1.02) 21.71
Blitz, 2013 - HR 1.36 (0.52-3.59) 7.75
Overall (I-squared=30%) HR 0.61 (0.47-0.80) 100
Safaeian, 2008 - RR 1.61 (0.74-3.51) 56.98
Banura, 2010 190 RR 0.40 (0.16-0.98) 43.02
Overall (I-squared=81%) RR 0.88 (0.49-1.59) 100
HPV 18
Koshiol, 2006 - HR 0.50 (0.31-0.81) 73.24
Rowhani-Rahbar, 2007 - HR 0.42 (0.19-0.94) 26.76
Overall (I-squared=0%) HR 0.48 (0.31-0.72) 100
Safaeian, 2008 - RR 1.22 (0.85-1.76) 89.97
Banura, 2010 112 RR 0.60 (0.20-1.80) 10.03
Overall (I-squared=31%) RR 1.14 (0.80-1.61) 100
0.5 1 2 3.5

C

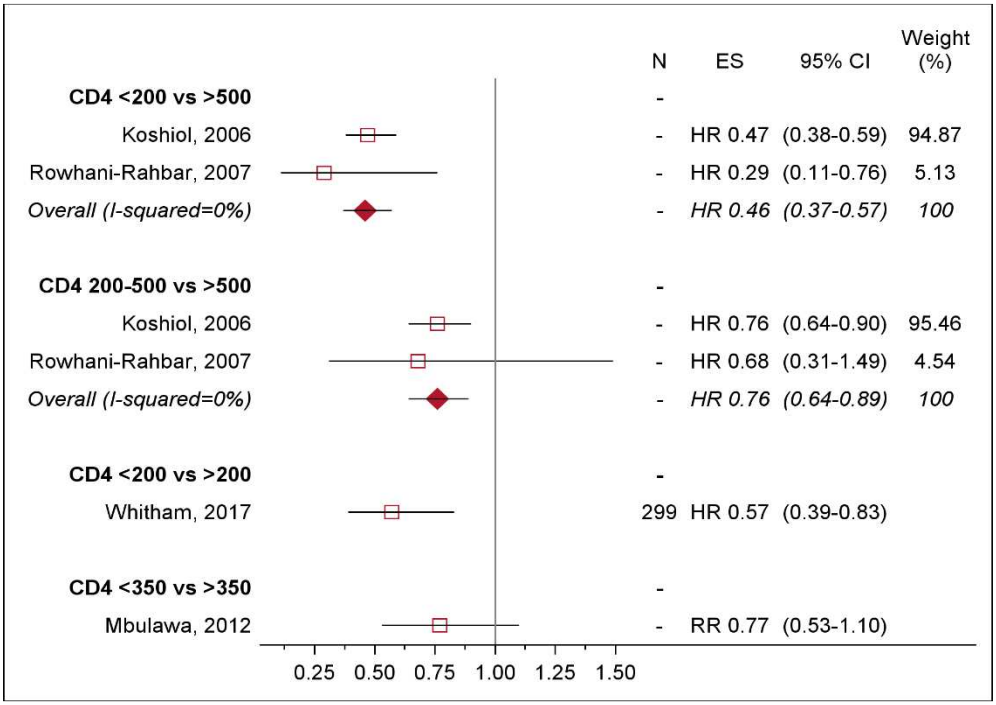



**Figure 3.** Clearance of newly detected and prevalent HPV infections by HIV status and CD4 count. N: sample size, ES: effect size. N= "-" Indicates that the study did not report sample size associated with their estimates. **A)**. Clearance of newly detected HPV infection among HIV-positive women compared to HIV-negative women. **B)**. Clearance of prevalent and newly detected HPV infection among HIV-positive women compared to HIV-negative women, by HPV type. **C).** Clearance of HPV infection among HIV-positive women by CD4 count. Estimates from Mane et al, 2016 and Ahdieh et al, 2000 were not included in the forest plot. Mane et al, 2016 evaluated CD4 count as a continuous variable. And Ahdieh et al, 2000 used HIV-negative women was their reference group. The populations for Whitham et al, 2017 and Rowhani-Rahbar et al, 2007 overlapped.

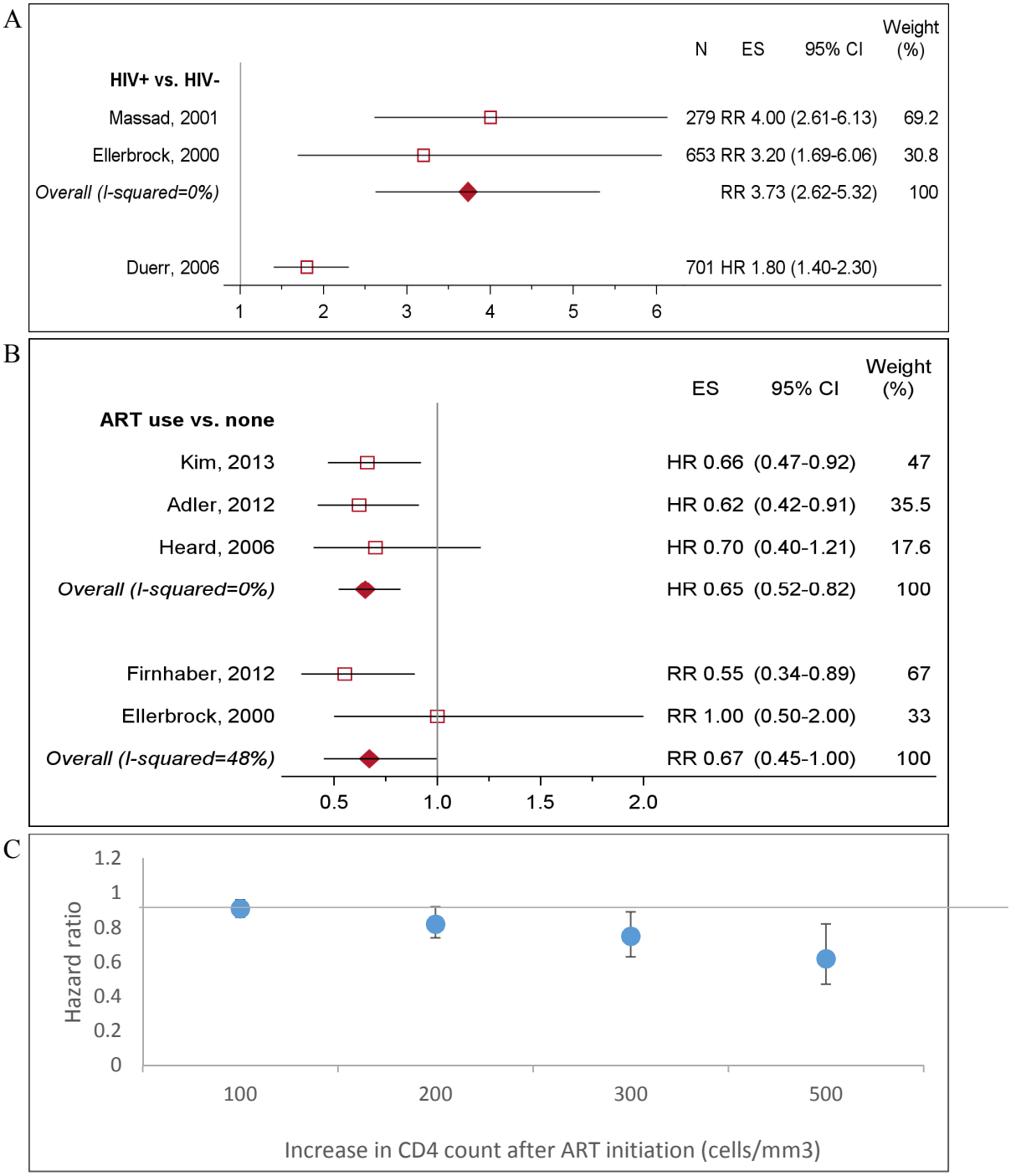
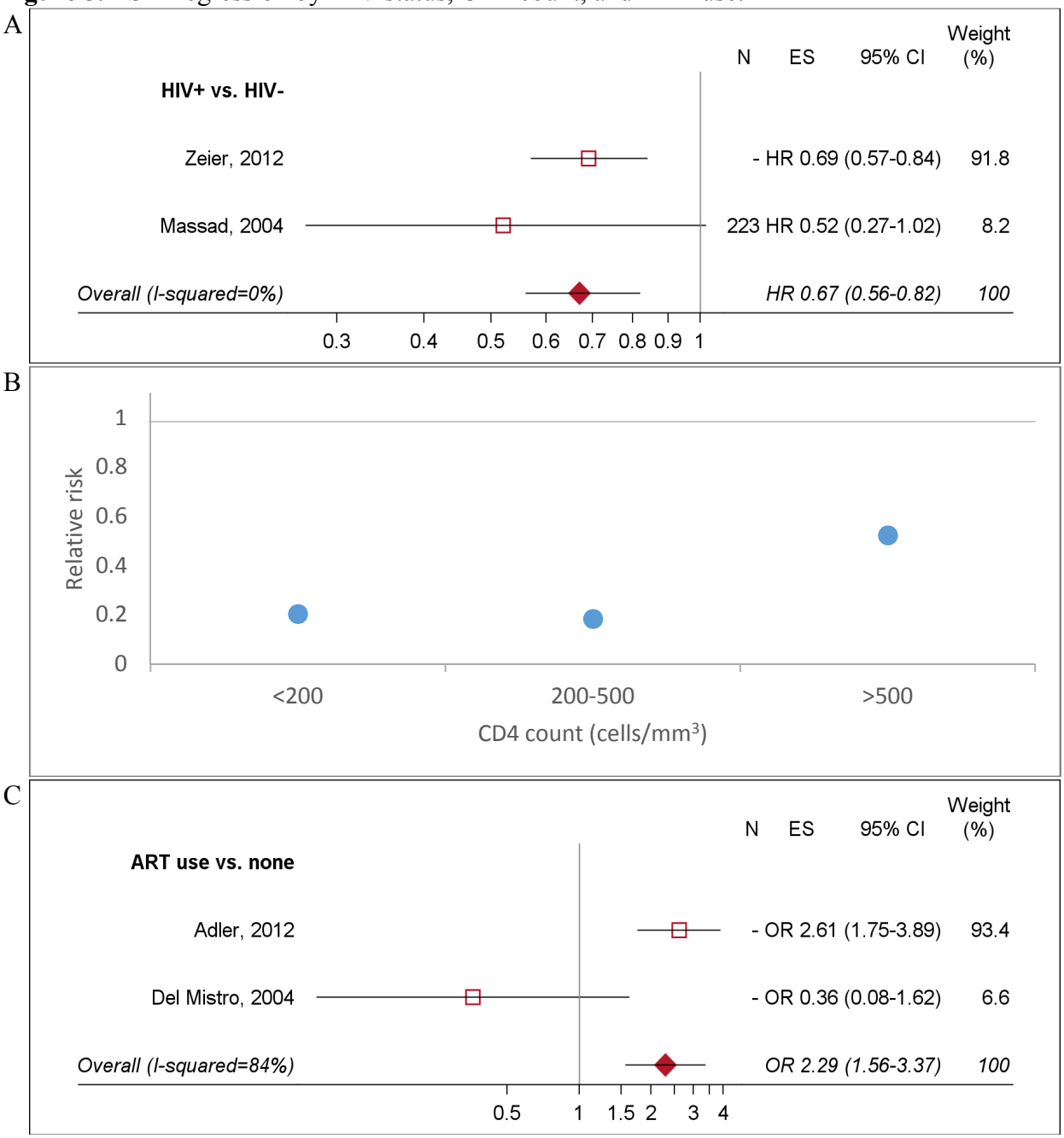



**Figure 4.** LSIL incidence by HIV status and ART use. N: Sample size, ES: effect size. A). LSIL incidence among HIV-positive women compared to HIV-negative women. Duerr et al, 2006 reported its effect size in hazard ratios, and was not included in calculating the overall estimate. B). LSIL incidence among HIV-positive women on ART compared to HIV-positive women not on ART. Estimates from Adler et al, 2012, Firnhaber et al, 2012, and Ellerbrock et al, 2000 adjusted for CD4 count. C). LSIL incidence by absolute increase in CD4 count after ART initiation. Data extracted from Kim, 2013.

**Figure 5.** LSIL regression by HIV status, CD4 count, and ART use.




N: Sample size, ES: effect estimate. N= "-" Indicates that the study did not report sample size associated with their estimates. **A)**. LSIL regression among HIV-positive women compared to HIV-negative women. **B)**. LSIL regression among HIV-positive women compared to HIV-negative women, by CD4 count. Data extracted from Six et al, 1998. Confidence intervals for these estimates were not included in the study. C). LSIL regression among HIV-positive women on ART compared to HIV-positive women not on ART. Data from Ahdieh-Grant et al, 2004 was not included in the figure. Because LSIL regression was not observed in any of the HIV-positive women not on ART, the study could not obtain an estimate for the effect of ART use on LSIL regression.

# Chapter 4. Impact of multi-age cohort human papillomavirus vaccination on cervical cancer incidence among Kenyan girls and women: A mathematical modeling evaluation of HPV vaccination strategies in the context of moderate HIV prevalence

Impact of multi-age cohort human papillomavirus vaccination on cervical cancer incidence among Kenyan girls and women: A mathematical modeling evaluation of HPV vaccination strategies in the context of moderate HIV prevalence

Gui Liu, MPH;[1,2] Cara Bayer, MS;[2] Darcy Rao, PhD;[2] Monisha Sharma, PhD;[2] Nelly Mugo MD, MPH;[2,3] Elizabeth A Bukusi, MMed, MPH, PhD;[2,3] Maricianah Onono; Betty W Njoroge;[3] and Ruanne V Barnabas, MBChB, DPhil[1,2,4,5]

1Department of Epidemiology, University of Washington, Seattle, USA
2Department of Global Health, University of Washington, Seattle, USA
3Kenya Medical Research Institute, Nairobi, Kenya
4Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, USA
5Department of Obstetrics and Gynecology, University of Washington, Seattle, USA

Corresponding author
Gui Liu
Department of Epidemiology
University of Washington
1959 NE Pacific Street
Health Sciences Building, F-262
1-206-520-3800
guiliu@uw.edu

**Acknowledgement**
We thank Drs. Anne Korir and Max Parkins at Elodret Cancer Registry and Nairobi Cancer Registry for providing data and their insights regarding cervical cancer burden in Kenya. This work is funded by the National Cancer Institute (U01 CA199334) and the Bill and Melinda Gates Foundation (OPP1188693). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Partial support for this research came from a Eunice Kennedy Shriver National Institute of Child Health and Human Development research infrastructure grant, P2C HD042828, to the Center for Studies in Demography & Ecology at the University of Washington.

**Abstract**

**Introduction**

Cervical cancer incidence is high among Kenyan women due in part to HIV, which increases cervical cancer risk. Human papillomavirus (HPV) vaccination is a cost-effective prevention against cervical cancer, but its impact is dependent on vaccination coverage and HIV prevalence. As HPV is associated with HIV acquisition, HPV vaccination may also decrease HIV burden. We evaluated the impact of HPV vaccination scale-up strategies in the context of changing HIV epidemiology in Kenya.

**Methods**

Using a dynamic, compartmental mathematical model of HIV and HPV transmission validated for Kenya, we evaluated the health effects of vaccination in the following scenarios: 1) single-age cohort vaccination of girls aged 10 at 90% coverage, 2) routine vaccination of girls aged 10-14 at 90% coverage, 3) routine and moderate coverage (50%) of multi-age cohort catch-up (MAC) vaccination of women aged 15-24, 4) routine and high coverage (80%) of MAC vaccination, and 5) routine and vaccination of women aged 15-44 at 80% coverage (HPV-FASTER). We assumed Kenya meets the UNAIDS 90-90-90 goals for HIV treatment. The model outcomes were the 1) changes in annual cancer incidence and HIV prevalence, and, 2) the cumulative cases of cervical cancer and HIV averted, relative to no HPV vaccination from 2021-2070.

**Results**

By 2070, cervical cancer incidence was reduced by 68% with 164,529 cervical cancer cases averted with single-age cohort vaccination. Routine vaccination reduced cancer incidence by 75% and averted 206,115 cancer cases. Moderate and high-coverage MAC vaccination and HPV-FASTER reduced cancer incidence by 80%, 82%, and 84% averting 254,930, 278,690, and

326,968 cancer cases, respectively. The reduction in HIV prevalence in women due to vaccination was 7.6% with single-age vaccination, 8.9% with routine vaccination, 10.0% with moderate MAC, 10.6% with high-coverage MAC, and 11.0% with HPV-FASTER, corresponding to 15,609, 20,570, 27,568, 31,145, and 34,981 cases of HIV averted. If UNAIDS goals for HIV treatment were met, cervical cancer incidence will decline from 44.3 to 27.3 per 100,000 between 2020 and 2070 without HPV vaccination due to HIV prevalence decrease among women from 6.5% to 0.3%.

**Conclusions**

HPV vaccination has the potential to substantially decrease cervical cancer burden in Kenya, particularly if multiple age cohorts are vaccinated. While HPV vaccination may have modest impact on HIV prevalence, it has a role in a comprehensive HIV prevention package that includes sexual and reproductive health services. To achieve elimination of cervical cancer in Kenya, screening and treatment of pre-cancers will be required in addition to widespread vaccination.

**Keywords** HPV vaccination, HIV, cervical cancer, math model

## Introduction

With the advances in primary and secondary cervical cancer prevention in high-income countries (HICs), cervical cancer is increasingly an indicator of global health disparities. Approximately 90% of the estimated 604,000 new cervical cancer cases and 342,000 deaths due to cervical cancer in 2020 occurred in low- and middle-income countries.[7] While the majority of cervical cancers are prevented in HICs, cervical cancer is one of the most common cancers and cause of cancer deaths among Kenya women.[60,130] Due to inequitable access to vaccines against human papillomavirus (HPV) infection and other cervical cancer prevention services, cervical cancer incidence rate is more than 5 times higher in Kenya compared to the United States and other HICs.[7,131]

HIV infection among women is an important contributing factor to the high burden of cervical cancer in Kenya.[11,114] Women living with HIV (WLHIV) have significantly higher risk of HPV infection and a six-fold higher risk of cervical cancer compared to HIV-uninfected women.[20,132,133] In addition, HPV infection is associated with HIV acquisition.[19,20] As of 2020, HIV prevalence among Kenyan adult women was 6%; representing almost 900,000 WLHIV who are at elevated risk for cervical cancer compared to the general population.[16]

HPV vaccines are safe, durable, and highly efficacious in preventing infection with the most oncogenic HPV types and the sequelae associated with these infections.[134-136] Further, vaccines are cost-effective cervical cancer prevention strategies in countries across a range of income levels, including Kenya.[137,138] HPV vaccination can result in net positive health savings, even after accounting for opportunity cost to other health services.[138] To accelerate the impact of HPV vaccination at the population level, the World Health Organization (WHO) recommends multi-age

cohort vaccination of girls 9 – 15 years old.[139] However, Kenya and many other LMIC are vaccinating a single age cohort (girls aged 9 or 10) due to limited vaccine supply and funding, resulting in only a fraction of eligible girls vaccinated each year.[6] Encouragingly, investment priorities of local ministries of health and international donors may shift in response to WHO's initiative to eliminate cervical cancer as a public health problem globally.[22]

A crucial component to the success of this initiative is increasing HPV vaccination coverage in LMIC.[22] However, vaccination implementation will need to be tailored to each country, as the population-level impact of vaccination on cervical cancer rates varied depending on the age group targeted for vaccination and the baseline level of cervical cancer risk.[4,23] In addition, in high HIV-burden countries, prevention of HIV could independently reduce cervical cancer incidence and mortality.[140] In this modeling study, we aimed to evaluate the population-level impact of different HPV vaccination strategies on cervical cancer burden in Kenya, while accounting for the effect of the changing HIV epidemiology and scale-up of HIV prevention. As a secondary objective, we also evaluated the impact of HPV vaccination on HIV burden, as our model captures the increased risk of HIV acquisition among women with an HPV infection.[19,20] Data from our study could help inform public health decision making in Kenya and other countries with similar levels of cervical cancer and HIV.

## Methods

### *Model description*

We adapted a previously published compartmental, dynamic model of heterosexual HPV and HIV transmission to the Kenyan setting.[26] The model simulates demographic dynamics, HIV infection

and progression, HPV infection and progression to cervical cancer, and the interactions between HIV and HPV infections. Births, deaths, population growth, and age composition over time in the model are parameterized using the Kenya-specific fertility and non-HIV mortality rates from United Nations Population Division (UNPD) (Tables S2 and S4).[141] We modelled male and female populations aged 0-79 in five-year age groups and with age- and sex-specific sexual behaviors.

Susceptible individuals in the model population acquire HIV through heterosexual contact or, to a lesser extent, through mother-to-child transmission. We assume women with an HPV infection have higher probability of HIV acquisition compared to those without an HPV infection.[19,20] HIV disease progression is characterized by decreasing CD4 cell count and increasing HIV RNA (viral load). People living with HIV have higher mortality rates compared to HIV-uninfected individuals, with mortality rates increasing as CD4 counts decreases. People living with HIV initiate antiretroviral therapy (ART) according to the historical CD4 count-based eligibility criteria in Kenya.[142] We assume an increasing proportion of people on ART are virally suppressed over time (Supplemental Appendix 2, p128). The ART coverage/viral suppression levels in the model parallel the historical coverage levels observed in Kenya (Supplemental Appendix 2 Table S12 and Figure S2). Additionally, we assume that 72.9% of men and women living with HIV are virally suppressed by 2030, achieving the UNAIDS 90-90-90 goals. Coverage of male circumcision also follows historical trends in Kenya (Supplemental Appendix 2 Table S13 and Figure S3), and is assumed reach at least 90% in all ages by 2030.

We model oncogenic HPV infection in two groupings: infection with an HPV type targeted by vaccines (HPV 16, 18, 31, 33, 45, 52, and 58) and infection with other oncogenic HPV types (HPV

35, 39, 51, 56, 59 and 68) (Supplemental Appendix 2 Figure S1). Acquisition and progression of these two infections are independent of each other and can occur simultaneously. While men can only be HPV-infected or susceptible, women in the model have additional HPV-associated states including cervical intraepithelial neoplasia grades (CIN) 1 to 3 and cervical cancer. Further, women who clear HPV infection benefit from temporary immunity against reinfection with the same HPV type (either vaccine-targeted or non-vaccine-targeted type). WLHIV will have higher probability of HPV acquisition, persistence, progression to CIN and reduced regression from CIN.[20,133] Specifically, HPV acquisition and CIN progression increased with decreasing CD4 count while HPV clearance and CIN regression decreased with decreasing CD4 count. We modelled a constant cervical cancer screening coverage of 7.4% in women without HIV and 12.3% in WLHIV across all scenarios, as observed.[8]

Demographic and sexual behavior parameters are based on data from UNPD and Kenya DHS. We parameterized the model using epidemiological and clinical parameters, including HIV and HPV transmission probabilities and CIN progression rates, to fit to HIV, HPV, and cervical cancer epidemiology in Kenya. We calibrated the model by fitting to age- and sex-specific HIV prevalence from 2003 and 2008-2009 Kenya Demographics and Health Surveys and 2007 and 2012 Kenya AIDS Indicator Surveys.[8,143-145] We estimated HIV prevalence and 95% confidence intervals from DHS using the survey procedures in SAS (V9.4, Cary NC). We fit to age- and HIV-status specific HPV prevalence estimated observational studies in Kenya.[146,147] Additionally, we fit the overall and age-specific cancer incidence rates to GLOBOCAN 2012 estimates.[148] We validated the model outputs against 2018 Kenya Population-based HIV Impact Assessment (PHIA) and GLOBOCAN 2020.[7,17] To represent uncertainty around select influential parameters,

specifically HIV transmission probability, HPV transmission probability, and the risk of HIV acquisition among women infected with HPV relative to HPV-uninfected women, we varied the parameters within expected ranges. We ran 100 iterations, with the model randomly selecting a value from the specified range for these three parameters at each iteration. For the outcome estimates, we reported the median and the interquartile range of the 100 iterations, as these represent the best fit of the model output to observed data. Model dynamics are governed by a system of ordinary differential equations that are solved in MATLAB using a 4th-order Runge-Kutta numerical method. Detailed description of model processes, calibration, and parameters is included in Supplemental Appendix 2.

*HPV vaccination scenarios*

We modeled the impact of quadrivalent HPV vaccine on cervical cancer incidence over 50 years, with vaccination beginning in 2021. Specific scenarios are as follows:

1. No vaccination. This serves as the reference for evaluating the impact of vaccination strategies described below.
2. Single age cohort vaccination. Girls aged 10 years are vaccinated at 90% coverage. This scenario reflects Kenya's vaccination strategy in 2019.
3. Routine vaccination. Girls aged 9-14 are vaccinated at 90% coverage. This scenario represents the vaccination strategy proposed by the WHO to eliminate cervical cancer.[22]
4. Moderate multiple age catch-up (MAC) vaccination. Routine vaccination of girls aged 9-14 at 90% coverage, with one year of MAC vaccination for women aged 15-24 years at 50% coverage.

5. High coverage MAC vaccination. Routine vaccination of girls aged 9-14 at 90% coverage, with one year of MAC vaccination for women aged 15-24 years at 80% coverage.
6. HPV-FASTER. Routine vaccination of girls aged 9-14 at 90% coverage, with one year of vaccination for women aged 15-44 at 80% coverage. This scenario reflects the strategy proposed by Bosch et al based on clinical trial data showing high vaccine efficacy among mid-adult women up to aged 45.[149]

We assume the nonavalent vaccine provides lifelong protection and prevents 90% of cervical cancers.[150] Only girls and women in the HPV susceptible and immune compartments will benefit from vaccination, consistent with clinical trial data demonstrating low vaccine efficacy in recipients with detectable HPV infection at the time of vaccination.[151] Cervical cancer screening, ART coverage, and male circumcision prevalence are the same across all scenarios.

*Outcomes*

To determine vaccination impact on cervical cancer, we estimated yearly age-standardized cervical cancer incidence rates between 2021-2070 all scenarios. We used WHO 2000-2025 Standard Population distribution as weights for age-standardization.[152] We measured the impact of vaccination as incidence rate ratios by dividing incidence rates from scenarios 2-5 by the rate from the no vaccination scenario in the same year. We also estimated cumulative number of cervical cancer cases averted 30 and 50 years after vaccination introduction. To assess whether HPV vaccination had any impact on HIV burden, we estimate yearly relative reduction in HIV prevalence, with the no vaccination scenario as reference: $\frac{HIV_{no\ vaccination} - HIV_{vaccination}}{HIV_{no\ vaccination}} * 100$. We

also estimate the cumulative number of HIV cases averted after 30 years and 50 years of vaccination.

## Results

### *Model fit*

Model predictions demonstrated good fit to epidemiological data for HIV prevalence (Figures 1, Supplemental Appendix 2 Figures S6-7), HPV prevalence (Supplemental Appendix 2 Figure S8), and to GLOBOCAN-estimated cervical cancer incidence rates (Figure 2). The model HIV estimates were validated against sex- and age-specific HIV prevalence from 2018 Kenya PHIA survey[17] (Figure 1) and cervical cancer incidence rates were validated against GLOBOCAN 2020[7] (Supplemental Appendix 2 Figures S9 and S10), with good visual agreement for both comparisons.

### *Vaccine impact on cervical cancer*

The model-estimated cervical cancer incidence in 2020 was 44.3 per 100,000 women (IQR 34.6-50.2, Figure 3a), corresponding to 6,143 (IQR 4,848-6,935) new cases of cervical cancer (Supplemental Appendix 2 Figure S12). Without vaccination, cervical cancer incidence rate was 31.7 per 100,000 women (IQR 23.3-37.8) in 2050 and 27.3 per 100,000 women (IQR 19.7-32.7) in 2070. Due to increased population size, 13,061 (IQR 10,085-15,222) and 16,528 (IQR 13,432-19,229) new cases of cervical cancer were expected in those years (Supplemental Appendix 2 Figure S5a).

By 2050, single age cohort vaccination of 10-year-old girls at 90% coverage was predicted to decrease cervical cancer incidence rate, relative to no vaccination, by 22% (RR 0.78, IQR 0.77-

0.78), averting 21,342 cases (IQR 18,235-25,311) of cervical cancer over 30 years (Table 1, figure 3b). With routine vaccination of girls aged 10-14 years at 90% coverage, cervical cancer incidence was reduced by 33% (RR 0.67, IQR 0.67-0.68) and 35,038 cancer cases (IQR 29,501-41,407) were averted. Cervical cancer incidence was reduced by 45% (RR 0.55, IQR 0.54-0.55) with moderate (50% coverage) MAC for women aged 15-24 and 51% (RR 0.49, IQR 0. 0.48-0.49) with high-coverage (80%) MAC, averting 57,370 (IQR 47,396-66,759) and 68,310 (IQR 55,612-79,092) cases of cervical cancer, respectively. The HPV-FASTER strategy reduced cervical cancer reduced by 63% (RR 0.37, IQR 0.36-0.38) and 98,783 cases (IQR 77,219-114,567) were averted.

By 2070, relative to no vaccination, incidence rate ratio was 0.32 (IQR 0.31-0.32) with single age cohort vaccination, 0.25 (IQR 0.25-0.25) with routine vaccination, 0.20 (IQR 0.20-0.20) with moderate MAC vaccination, 0.18 (IQR 0.17-0.18) with high-coverage MAC vaccination, and 0.16 (IQR 0.15-0.16) with HPV-FASTER; representing 68%, 75%, 80%, 82%, and 84% reduction in cancer risk, respectively (Figure 3b). Over 50 years, single age cohort vaccination is expected to prevent 164,529 (IQR 139,946-197,108) cases of cervical cancer, while 206,115 (IQR 173,778-247,221) cases were averted with routine vaccination, 254,930 (IQR 212,510-303,618) with moderate MAC vaccination, 278,690 (IQR 229,763-330,529) cases with high-coverage MAC vaccination, and 326,968 (IQR 262,991-383,806) cases with HPV-FASTER (Table 1).

*Vaccine impact on HIV*

HIV prevalence was 6.1% (IQR 4.4-7.5) among women and 2.9% (IQR 2.1-3.6) among men in 2020. If the UNAIDS 90-90-90 goals are achieved, prevalence among women and men is predicted to decrease to 1.0% (IQR 0.7-1.3) and 0.5 (IQR 0.3-0.7) in 2050 and to 0.3% (IQR 0.2-0.4) and 0.2% (IQR 0.1-0.2) in 2070, with little difference between scenarios (Table 2, figure 4a). In 2050,

HIV prevalence in both women and men was reduced by 5.4% or less in all scenarios relative to no vaccination (Table 2). However, among women, 7,596 cases (IQR 5,018-12,627) of HIV were averted with single age cohort vaccination, 11,370 cases (IQR 7,548-18,702) with routine vaccination, 17,183 cases (IQR 11,570-27,740) with moderate MAC vaccination, 20,116 cases (IQR 13,533-32,301) with high-coverage MAC vaccination, and 23,626 cases (IQR 15,811-37,286) with HPV-FASTER (Table 2). Because pre-vaccination HIV burden among men was lower compared to women, the number of HIV cases averted among men was also proportionately lower even though the percent reductions in HIV prevalence were similar (Table 2).

Relative to no vaccination, HIV prevalence among women in 2070 was reduced by 7.6% (IQR 6.1-9.1) with single age cohort vaccination, 8.9% (IQR 7.1-10.6) with routine vaccination, 10.0% (IQR 8.1-12.0) with additional moderate MAC vaccination, 10.6% (IQR 8.7-12.7) with high-coverage MAC vaccination, and 11.0% (IQR 8.9-13.2) with HPV-FASTER; relative reductions in men were similar (Supplemental Appendix 2 Figure S13). Cumulative number of HIV cases averted in women after 50 years of vaccination was 15,609 (IQR 9,916-27,192) with single age cohort vaccination, 20,570 (IQR 13,284-35,553) with routine vaccination, 27,568 (IQR 18,298-46,725) with moderate MAC vaccination, 31,145 (IQR 20,691-52,430) with high-coverage MAC vaccination, and 34,981 (IQR 23,224-57,825) with HPV-FASTER (Table 2). The number of cases of HIV infections averted over 50 years in men were approximately half of that in women (Table 2).

**Discussion**

Overall, HPV vaccination has the potential to substantially mitigate cervical cancer risk in Kenya in the next 50 years, particularly if the vaccination strategy included older adolescents and young women. Compared to no vaccination, cervical cancer risk in 2070 was three times lower with single age cohort vaccination of 10-year-old girls and was up to 5.7 times lower with MAC vaccination of women aged 15-24. Additionally, MAC vaccination could further prevent 90,401 to 114,161 cases of cervical cancer in addition to the cases prevented through single age cohort vaccination. The total cumulative cervical cancer cases averted by 2070 was almost double in the MAC scenarios compared to the single age cohort vaccination scenario.

Because MAC vaccination and HPV-FASTER led to more people in the overall population vaccinated and higher vaccination coverage in older age groups, the impact of vaccination on cervical cancer incidence is realized earlier. With MAC vaccination and HPV-FASTER, 23-30% of the cumulative cases of cervical cancers averted had been prevented in 2050, compared to 13% with single age cohort vaccination. These findings are consistent with post-vaccination HPV surveillance data from European and North American countries, which show that population-level HPV prevalence declined more rapidly and to a greater extent with multiple age cohort vaccination (up to age 19 or 26) than with single age cohort vaccination.[153] While the HPV-FASTER strategy resulted in the greatest reduction of cervical cancer in our analysis, this strategy has been found to be not cost-effective in settings with high coverage of cervical cancer screening.[154] However, the logistics and cost-effectiveness of implementing HPV-FASTER in settings with low screening coverage has not been evaluated.

While the WHO strongly recommends routine vaccination of girls 9-14 years old, its recommendation for vaccinating young women 15 and older is more tentative, leaving countries to decide whether to vaccinate young women.[155] One concern regarding vaccinating this population is the reduced vaccine effectiveness in young women due to more previous HPV infection exposures compared to girls aged 9-14.[156] To accurately reflect vaccine efficacy in our model, only girls and women who are susceptible to HPV infection (i.e., negative for the types targeted by the vaccine) are conferred protection from HPV vaccination. The additional reduction in cervical cancer cases and incidence rates in the MAC vaccination scenarios compared to single age cohort and routine vaccination scenarios demonstrate that older adolescents and young women can indeed benefit from HPV vaccination and expanding eligibility to this age group can lead to population-level reduction in cancer burden. While we found a greater and earlier impact with MAC vaccination compared to routine and single age cohort vaccination, the difference between the two catch-up scenarios are moderate. Relative to the moderate catch-up scenario, the high-coverage catch-up scenario results in an additional 23,760 cases of cervical cancers averted over 50 years. This is likely because the proportion women vaccinated in the moderate catch-up scenario scales up to same level as in the high-coverage catch-up scenario within 10 years of vaccine introduction (Supplemental Appendix 2 Table S17 and Figure S12).

We modelled bidirectional interactions between HIV and HPV infections, such that HIV infection increased the risk of HPV acquisition and progression and HPV infection increased subsequent HIV acquisition. Kenya has made marked progress in HIV prevention, leading to a steady decline in HIV prevalence in the last two decades.[16] In 2018, 69% of all Kenyan adults living with HIV are on treatment and virally suppressed and 92% of men are circumcised.[17] We assume that Kenya

will continue their current trajectory of ART coverage and male circumcision, resulting in 72.9% of people with HIV virally suppressed and at least 90% of all men circumcised by 2030, achieving the UNAIDS 90-90-90 goals. Under these assumptions, the model predicted that HIV prevalence among both men and women will decrease drastically to less than 0.5%. Due to the decline in HIV burden, the model also projected a 38% decline in cervical cancer incidence rates without HPV vaccination from 44.3 per 100,000 women in 2020 to 27.3 per 100,000 women in 2070. Our findings are in line with those of Hall et al, which projected a 32% decline in cervical cancer incidence due to ART and male circumcision in Tanzania.[140] Conversely, while women with HPV infection were assumed to have on average 2 times higher risk of acquiring HIV compared to women who are HPV-negative, HPV vaccination had minimal impact on the overall HIV burden, reducing HIV prevalence by only 1.8-9.9% in 2070. This is likely because vaccinated populations could still acquire infection with oncogenic HPV types not targeted by the nonavalent vaccine. However, the cumulative number of HIV infections prevented as a result of vaccination was not trivial, with up to 27,812 cases averted in women and 14,693 cases averted in men. Although men were not vaccinated, they indirectly benefited from the reduced HIV burden in women. These findings support a role for HPV vaccination in the comprehensive HIV prevention package that includes sexual and reproductive health services.[157]

Of note, we found that even in the highest coverage scenario (90% of 9-14-year-old girls and 80% of 15-44-year-old women vaccinated), cervical cancer elimination, defined as incidence of ≤4 per 100,000, will not be achieved in Kenya in the next 50 years. The nonavalent vaccine prevents 90% of cervical cancers,[150] but additional interventions will need to be implemented to prevent cancers caused by other oncogenic HPV types not targeted by the quadrivalent vaccine in order to lower

the incidence rate below the threshold of 4 per 100,000 women. This is consistent with other modeling studies have indicated that cervical cancer elimination in LMICs, such as Kenya, may not be achievable even in the next century with vaccination alone.[4,23] Additional investment in secondary prevention will be necessary to accelerate cervical cancer elimination in Kenya. Based on the 2012 KAIS,[8] we assume that 7.4% of HIV-negative women and 12.3% of WLHIV women receive one cervical cancer screening in their lifetime at age 35. Increasing screening coverage and the frequency of screening would prevent cancer among unvaccinated women and prevent cervical cancer caused by HPV types not targeted by the vaccine.

A strength of our model is that HIV and HPV transmissions occur dynamically, allowing the model to capture herd effects from interventions. This enabled us to estimate the total, population-level effect of vaccination on cervical cancer in Kenya. In addition, we explicitly modelled the biological interactions between HIV and HPV infections, which made it possible to isolate the effect of HPV vaccination on cervical cancer from that of HIV prevention. Accurate projection of vaccination impact will be important as Kenya plans to meet the challenge of cervical elimination amidst changing HIV epidemiology. Further, while the convergence of evidence that HPV infection increased the risk of HIV acquisition prompted questions regarding the effectiveness of HPV vaccination for HIV prevention, clinical trials to investigate these questions were not recommended due to ethical and financial concerns.[158,159] However, our model was able to estimate HPV vaccination impacts on HIV burden while circumventing the ethical and financial issues associated with observational studies or randomized controlled trials.

Our study has some limitations. Sexual behavior patterns, including condom use and mixing, are highly influential in producing age- and/or sex-specific disease trends that matches epidemiological data. For simplicity, we assumed these parameters are static over time. However, our projections of future HIV and cervical cancer burden would be affected if changes in future sexual behavior patterns occur. Similarly, our predictions regarding the benefit of multi-age cohort vaccination among young women aged 15-24 could be affected if sexual behaviors in this population change in the future. Due to a lack national-level cervical cancer incidence data in Kenya, we calibrated our model to the overall and age-specific cervical cancer incidence rates estimated by GLOBOCAN.[7] These rates were based on two regional cancer registries in Eldoret and Nairobi, and may not be representative of the overall cancer incidence in Kenya. Further, vaccination coverage in our model scales up to the specified level immediately in all vaccination scenarios. For example, in the high-coverage MAC scenario, 90% of girls aged 10-14 and 80% of women aged 15-24 are vaccinated within the first year of vaccine introduction. In reality, such high coverage, especially among older adolescents and adult women, may be difficult to achieve rapidly, as had been demonstrated in Australia and the United States.[160,161] If scale-up of vaccination is gradual, the incremental health benefits from vaccinating young adult women may also be delayed. Finally, although HPV vaccination commenced in 2021 in our model, actual program roll-out in Kenya may be delayed due to the impact of the COVID-19 pandemic on health care budget and personnel.[162,163] However, because the pandemic has not affected Kenya as severely as other countries, international organizations, such as the World Bank, expect relatively quick recovery in Kenya after the pandemic is under control.[164,165] Assuming Kenya's healthcare system recover to pre-pandemic condition, our results will still be relevant if the vaccine program is delayed by one or two years.

In conclusion, cervical cancer burden in Kenya can be substantially reduced with quadrivalent HPV vaccination. The reduction in cancer incidence is greater and occurs earlier when multiple age cohorts are included in the vaccination strategy. However, even in our most optimistic scenario, the cervical cancer elimination threshold is not reached. Concurrent scale-up of cervical precancer screening and treatment coverage will be needed to eliminate cervical cancer as a public health problem in Kenya.

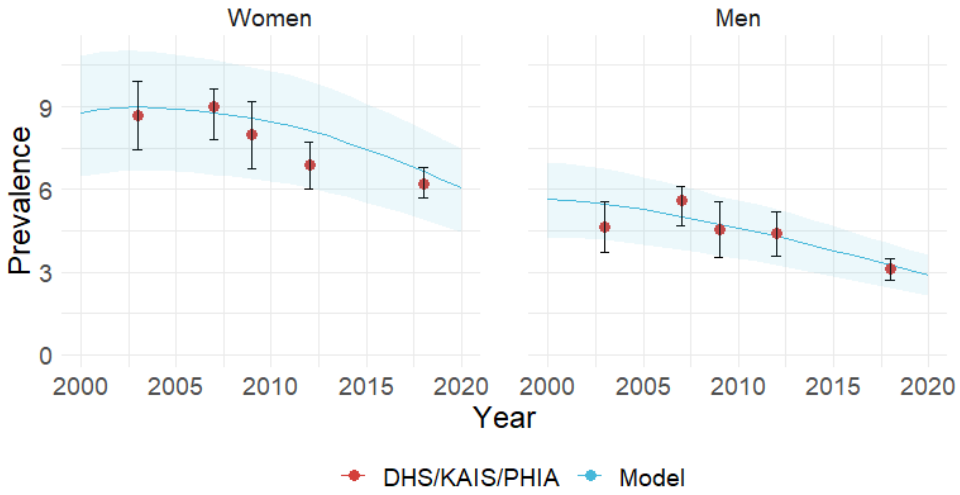



**Figure 1.** Model estimated HIV-prevalence among men and women between 2000-2020 (blue line) compared to data from 2003 and 2008-2009 Demographic and Health Survey (DHS), 2007 and 2012 Kenya AIDS Indicator Survey (KAIS), and 2018 Population-based HIV Impact Assessment (PHIA).

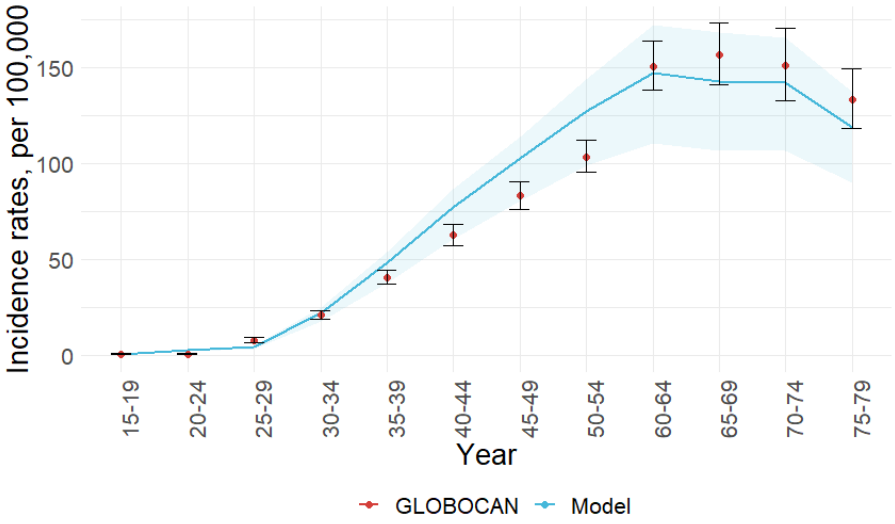



**Figure 2.** Model estimated age-specific cervical cancer incidence rates (blue line) compared to Globocan 2012 estimates (red dots).

**Table 1.** Cervical cancer incidence rates, HIV prevalence, and vaccine impact on cervical cancer in 2050 and 2070.

| | CC rates, per 100,000 | Rate Ratio | Cumulative cancer cases averted |
|---|---|---|---|
| **2050** | | | |
| **No vaccination** | 31.7 (23.3-37.7) | Reference | Reference |
| **Single age cohort** | 24.5 (18.1-29.2) | 0.78 (0.77-0.78) | 21342 (18235-25311) |
| **Routine** | 21.3 (15.8-25.3) | 0.67 (0.67-0.68) | 35038 (29501-41407) |
| **Moderate MAC** | 17.4 (12.9-20.6) | 0.55 (0.54-0.55) | 57370 (47396-66759) |
| **High coverage MAC** | 15.5 (11.5-18.3) | 0.49 (0.48-0.49) | 68310 (55612-79092) |
| **HPV-FASTER** | 11.9 (9.0-13.8) | 0.37 (0.36-0.38) | 98783 (77219-114567) |
| **2070** | | | |
| **No vaccination** | 27.3 (19.7-32.8) | Reference | Reference |
| **Single age cohort** | 8.5 (6.1-10.4) | 0.32 (0.31-0.32) | 164529 (139946-197108) |
| **Routine** | 6.7 (4.8-8.2) | 0.25 (0.25-0.25) | 206115 (173778-247221) |
| **Moderate MAC** | 5.4 (3.9-6.5) | 0.20 (0.20-0.20) | 254930 (212510-303618) |
| **High coverage MAC** | 4.8 (3.5-5.8) | 0.18 (0.17-0.18) | 278690 (229763-330529) |
| **HPV-FASTER** | 4.2 (3.2-5.0) | 0.16 (0.15-0.16) | 326968 (262991-383806) |

**Table 2.** HPV vaccination impact on HIV burden among women and men in 2050 and 2070.

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | **HIV prevalence** | **% reduction** | **Cumulative HIV cases averted** | **HIV prevalence** | **% reduction** | **Cumulative HIV cases averted** |
| **2050** | | | | | | |
| **No vaccination** | 1.04 (0.70-1.38) | Reference | Reference | 0.53 (0.36-0.71) | Reference | Reference |
| **Single age** | 1.01 (0.69-1.34) | 2.4 (1.9-3) | 7596 (5018-12627) | 0.52 (0.35-0.69) | 2.2 (1.7-2.5) | 3491 (2320-5622) |
| **Routine** | 1.00 (0.68-1.33) | 3.4 (2.7-4.1) | 11370 (7548-18702) | 0.51 (0.35-0.68) | 3.1 (2.5-3.7) | 5352 (3597-8609) |
| **Moderate MAC** | 0.99 (0.68-1.31) | 4.5 (3.6-5.4) | 17183 (11570-27740) | 0.51 (0.35-0.67) | 4.3 (3.5-5.1) | 8192 (5630-13000) |
| **High MAC** | 0.98 (0.68-1.30) | 5.1 (4.1-6.2) | 20116 (13533-32301) | 0.5 (0.35-0.67) | 4.9 (4.0-5.8) | 9620 (6636-15268) |
| **HPV-FASTER** | 0.97 (0.67-1.30) | 5.4 (4.4-6.6) | 23626 (15811-37286) | 0.5 (0.34-0.67) | 5.3 (4.3-6.2) | 10945 (7651-17366) |
| **2070** | | | | | | |
| **No vaccination** | 0.31 (0.19-0.46) | Reference | Reference | 0.16 (0.10-0.24) | Reference | Reference |
| **Single age** | 0.29 (0.18-0.42) | 7.6 (6.1-9.1) | 15609 (9916-27192) | 0.15 (0.10-0.22) | 7.4 (5.9-8.9) | 8253 (5156-13666) |
| **Routine** | 0.29 (0.18-0.41) | 8.9 (7.1-10.6) | 20570 (13284-35553) | 0.15 (0.09-0.22) | 8.6 (6.9-10.3) | 10944 (6959-18009) |
| **Moderate MAC** | 0.28 (0.18-0.41) | 10.0 (8.1-12.0) | 27568 (18298-46725) | 0.15 (0.09-0.21) | 9.8 (8.0-11.7) | 14604 (9596-23731) |
| **High MAC** | 0.28 (0.18-0.40) | 10.6 (8.7-12.7) | 31145 (20691-52430) | 0.15 (0.09-0.21) | 10.4 (8.5-12.4) | 16444 (10870-26697) |
| **HPV-FASTER** | 0.28 (0.18-0.40) | 11.0 (8.9-13.2) | 34981 (23224-57825) | 0.15 (0.09-0.21) | 10.8 (8.8-12.8) | 17970 (12023-29161) |

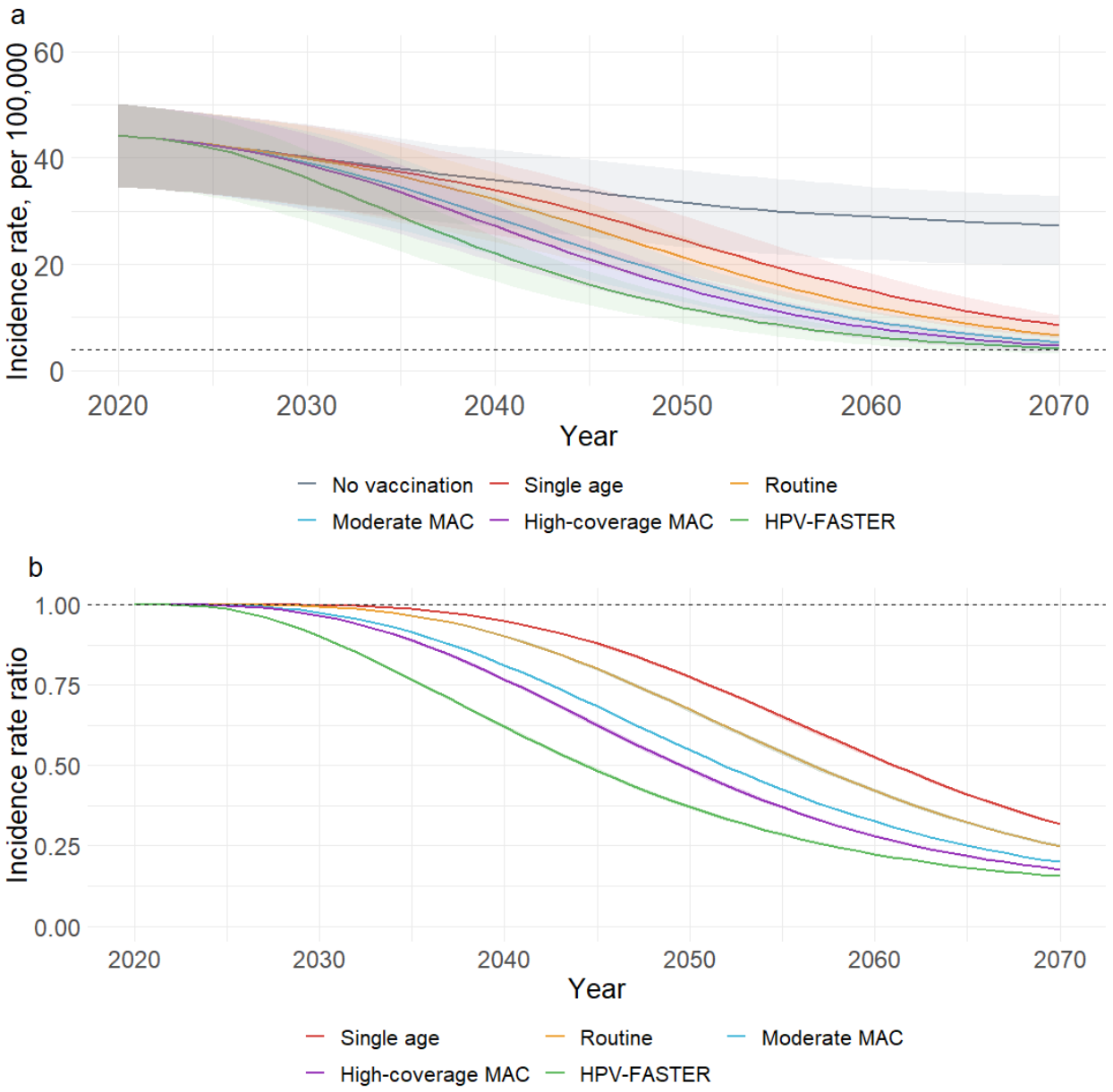



**Figure 4**. HPV vaccination impact on cervical cancer outcomes. A). Yearly age-standardized cervical cancer incidence rates from 2020-2070 by model scenario. Dashed lines indicate cancer elimination threshold of 4 per 100,000 women. Subplot b). Yearly incidence rate ratios compared to no vaccination. The dotted horizontal line indicate null.

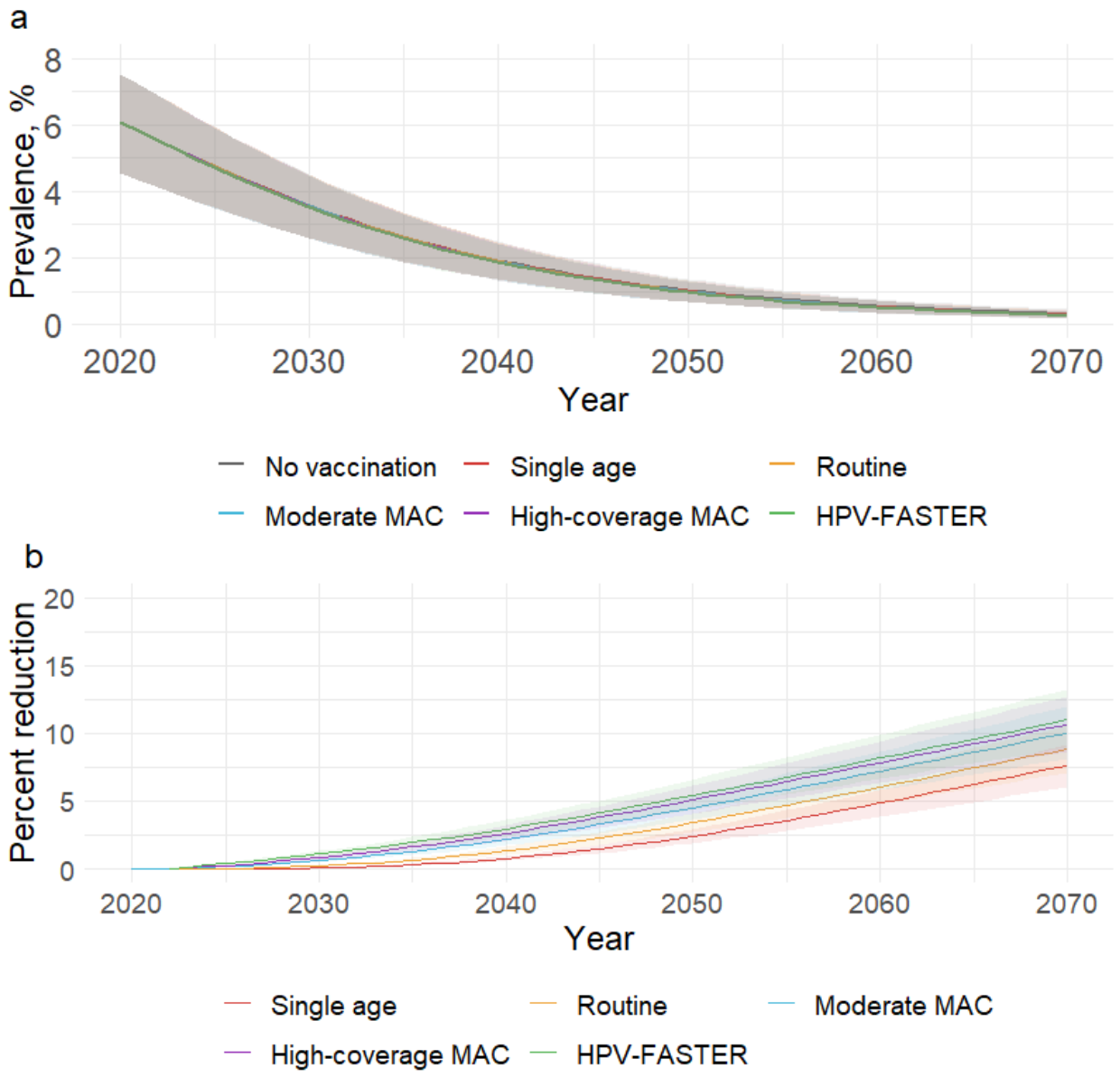



**Figure 5.** HPV vaccination impact on HIV burden in women. Subplot a) HIV prevalence among women over time by scenario. Because HIV prevalence was similar in all scenarios, lines for scenarios overlap almost completely. Subplot b) percent reduction in HIV prevalence relative to no vaccination.

# Chapter 5. Discussion

Eliminating cervical cancer as a public health problem will be more challenging in LMICs than in high-income countries, due to higher current level of cervical cancer risk, and in some LMICs, HIV. This work of this dissertation addressed a data gap in cervical cancer prevention research for LMICs with significant HIV prevalence using Kenya as a case study. By quantifying the bidirectional interactions between HIV and HPV infections and modeling these interactions in detail, we can more accurately represent the future trajectory of cervical cancer burden in Kenya, where HIV epidemiology is changing due to effective HIV control in the past decades.[16] The country-specific data generated by this work could be used to inform local cervical cancer prevention policies.

A crucial component of the WHO cervical cancer elimination strategy is increasing the coverage of HPV vaccination.[22] Using a dynamic transmission model that accounted for the bidirectional interactions between HIV and HPV, we estimated that HPV vaccination has the potential to reduce cervical cancer incidence by 63-78% to 6-10 cases per 100,000 women in the next 50 years. Compared to previous models of HPV vaccination in LMIC that did not account for HIV, our model predicted a larger impact on cervical cancer in Kenya.[4,23] For example, models from the WHO Cervical Cancer Elimination Modelling Consortium estimated that cervical cancer incidence in sub-Saharan Africa will only decline by approximately 40% and remain at 15 per 100,000 women 50 years after vaccine introduction.[23] However, because a significant proportion of cervical cancer is attributed to HIV infection in these regions (24% in Kenya and 20% in sub-Saharan Africa overall), the influence of HIV prevention on cervical cancer cannot be ignored.[11] Our model also projected that HPV vaccine impact on cervical cancer was more pronounced (e.g., greater percent reduction in incidence and lower incidence rate) and occurred earlier with catch-up vaccination for young women aged 15-24 compared to single age cohort vaccination of 10-

year-old girls or routine vaccination of 10-14 year-old girls. These results are consistent with real world data that demonstrate that catch-up vaccination for AGYW aged 15-24 was associated with greater and earlier reductions in the population-level prevalence of vaccine-preventable HPV infections and HPV-associated diseases.[153]

Our findings support the implementation of routine HPV vaccination for girls aged 10-14 with short-term catch-up vaccination for young adult women up to age 24 in Kenya to accelerate cervical cancer burden reduction. Although we have not evaluated cost-effectiveness in our model, previous studies have shown that HPV vaccines are cost-effective in almost all countries, regardless of income level.[137,138,166] As a GAVI-eligible country, Kenya currently pays $4.50 or less for each dose of HPV vaccine. Adjusting for the expenses of vaccine delivery and opportunity costs to other health services, vaccinating 90% of girls up to age 15 is cost-effective in Kenya even if the vaccines cost 5 times more.[138] This suggests that incorporating a catch-up vaccination program for young women aged 15-24 may also be fiscally achievable. All of the above health economic analyses assumed that girls are vaccinated according to the 2-dose regimen currently recommended by WHO. Evidence that one dose of HPV vaccine may confer similar protection as two doses are emerging, and several clinical trials are ongoing to definitively evaluate one-dose HPV vaccine efficacy.[167-171] If efficacious, a one-dose regimen could further attenuate the cost of a high-coverage HPV vaccination program. Additionally, the global supply of HPV vaccines may soon increase with new HPV vaccines being developed by Chinese and Indian manufacturers, potentially further reducing the price per dose of HPV vaccines.[172]

Similar to other modeling studies, we found that cervical cancer elimination in Kenya would not be attainable in the next 50 years with HPV vaccination alone.[4,23,27] This points to a need for a more robust cervical cancer screening program to prevent cancers caused by HPV types

not targeted by the vaccine. Although the Kenyan Ministry of Health recommends cervical cancer screening for HIV-negative women every 5 years and women living with HIV every 2 years, only 7.4% of HIV-negative women and 12.3% of women living with HIV had ever been screened.[8,173] Reasons for the low uptake include lack of awareness about HPV and cervical cancer, discomfort with screening procedures, stigma surrounding cervical cancer and its association with HIV, financial costs, and lack of health care capacity.[174-179] More recently developed methods in detecting and treating cervical precancerous lesions, such as self-collection of cervical samples, point-of-care HPV tests, and affordable and rapid treatment with thermal ablation, could reduce screening anxiety and financial burden on women and the health care system but would need to be scaled up.[180-182] Additional work is needed to increase cervical cancer awareness and reduce stigma. More intense screening is needed for women living with HIV, as they have higher risk of cervical cancer. Integration of routine cervical cancer screening with HIV care could improve screening uptake and efficiency, and therefore reduce cancer incidence and deaths in this population.[183,184]

While our model demonstrated that HPV vaccination was highly effective at reducing cervical cancer burden in Kenya, its impact on HIV prevalence was modest. Based on the results from chapter 2 and previously published literature, we assumed that HIV acquisition was on average 2 times higher among women with an HPV infection.[19,20] Given this assumption, the model projected that HPV vaccination will reduce HIV prevalence by at most 11% after 50 years even in the highest coverage scenario. These results are as expected, since women in the model could still be infected with HPV types not targeted by the vaccine. Clinical trials of treatment for other sexually transmitted infections have similarly found moderate effect on HIV acquisition.[185,186] However, the number of HIV infections averted with HPV vaccination (more

than 50,000 among men and women) is not trivial, making a case for including HPV vaccination as part of a comprehensive HIV prevention package in settings with high HPV prevalence. HPV vaccination may have greater impact on HIV burden when combined with other HIV prevention strategies, such as pre-exposure prophylaxis against HIV, treatment for other sexually transmitted infections, and condom use.[187]

In addition to HPV vaccination, we also modelled the scale-up of two HIV interventions, ART and male circumcision. We assume that coverage of these interventions meet the targets set by Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO: 72.9% of all people living with HIV on ART and virally suppressed and 90% of men circumcised.[188,189] Under these assumptions, the model predicted that HIV prevalence will decrease to <0.5% in 2070, and as a result future cervical cancer incidence rates will fall by 38% in the scenario without vaccination. The HIV interventions reduced cervical cancer rates via two mechanisms: ART and male circumcision reduced population-level HIV incidence in the model and ART lowered the risk of HPV acquisition and progression among women living with HIV.[63,190] These findings emphasize the importance of HIV control measures in Kenya, especially the provision of ART for all people living with HIV. A consistent finding from the literature review in chapter 3 was that the degree of immunosuppression was associated with the risk of HPV acquisition and progression to cervical cancer, highlighting the need for early HIV diagnosis and treatment. As of 2018, 17% of women and 27% of men living with HIV in Kenya did not know their status.[17] Additional research is needed on strategies to reach people with undiagnosed HIV and to engage them in care.

In conclusion, the results of this dissertation demonstrated the value of considering the synergies between HIV and HPV infections when evaluating the population-level impact of cervical cancer prevention. HPV vaccination is an effective strategy for reducing cervical cancer

burden in Kenya in the context of shifting HIV epidemiology, but existing measures for HIV prevention must also be maintained and scaled up to meet UNAIDS treatment goals. By modeling HIV and HPV epidemics specific to the local context, we contributed data to the development of impactful cervical cancer prevention strategies tailored to Kenya.

**Supplemental appendix 1: PRISMA checklist, detailed search methods, risk of bias assessment, and additional results for Chapter 3**

Appendix to:

**HIV-positive women have higher risk of HPV infection, precancerous lesions, and cervical cancer: A systematic review and meta-analysis**

Gui Liu, MPH, Monisha Sharma, ScM, PhD, Nicholas Tan, BS, and Ruanne Barnabas, MBChB, DPhil

**Table A1. PRISMA checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3-4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4, appendix |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Appendix |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4, appendix |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4 |

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4, appendix |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Appendix |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5, appendix |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 5, appendix |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5-9, Table 1, appendix |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 5-9, appendix |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Appendix |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9-11 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 11 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

**Table A2.** Systematic review search strategies and search terms. The strategies and terms for each database searched are listed separately.

**Pubmed**:

Filter: NOT reviews

| Search | Terms used |
|---|---|
| **#1** | (Disease Progression[mh] OR natural history[mh] OR progress*[tw] OR persist*[tw] OR clear*[tw] OR pathogenesis[tw] OR natural history[tw]) |
| **#2** | (Papillomaviridae[mh] OR Cervical Intraepithelial Neoplasia[mh] OR Uterine Cervical Neoplasms[mh] OR HPV[tw] OR human papillomavirus[tw] OR Uterine Cervical Dysplasia[mh] OR squamous intraepithelial lesion[tw] OR Cervical intraepithelial neoplasia[tw] OR CIN[tw] OR SIL[tw]) |
| **#3** | (hiv[mh] OR hiv infections[mh] OR AIDS[mh] OR hiv[tw] OR human immunodeficiency virus[tw] OR AIDS[tw] OR acquired immunodeficiency[tw]) |
| **#4** | #1 AND #2 AND #3 AND #4 |

**Embase**:

Filters: NOT NLM, NOT reviews, NOT letters

| Search | Terms used |
|---|---|
| **#1** | 'hiv'/exp OR 'hiv' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' OR 'aids'/exp OR 'aids' OR 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' |
| **#2** | 'papillomaviridae'/exp OR 'hpv' OR 'human papillomavirus' OR 'uterine cervix cancer'/exp OR 'uterine cervix dysplasia'/exp OR 'uterine cervix cancer' OR 'uterine cervix dysplasia' OR 'squamous intraepithelial lesion' OR 'cervical intraepithelial neoplasia' OR 'cervical cancer’ |
| **#3** | 'disease course'/exp OR 'disease course' OR 'progress*' OR 'persist*' OR 'virus pathogenesis'/exp OR 'clear*' OR 'natural history' |
| **#4** | #1 AND #2 AND #3 |

**Global Health Database**

| Search | Terms used |
|---|---|
| **#1** | HIV OR "'human immunodeficiency virus" OR AIDS OR "acquired immune deficiency syndrome" |
| **#2** | hpv OR "human papillomavirus" OR "uterine cervix cancer" OR "uterine cervix dysplasia" OR "squamous intraepithelial lesion" OR HSIL OR LSIL OR SIL OR "cervical intraepithelial neoplasia" OR CIN OR "cervical cancer" |
| **#3** | "disease course" OR "progress*" OR "persist*" OR "virus pathogenesis" OR "clear*" OR "natural history" |
| **#4** | #1 AND #2 AND #3 |

**Risk of bias assessment**

We assessed the quality of eligible studies using modified criteria for non-randomized observational studies. We determined the level of risk of bias in the studies across 5 domains: study population, detection of outcome and exposure, bias related to study design, statistical analysis, and conflict of interest disclosure. The level of risk in each domain was rated low, moderate, or high. We then summarized the overall risk of bias across all studies. Below are the criteria for bias assessment in each domain:

- Study population:
    - Use appropriate population for the study question(s)
    - Explicitly define the study population and state the eligibility criteria
    - Describe the sources and methods of participant selection (for cohort studies) or case ascertainment and control selection (for case-control studies).
- Exposure and outcome detection:
    - Use valid and reliable methods to ascertain exposure and outcome status.
    - Include only participants whose exposure occurred prior to outcome
    - Outcome assessors blinded to participants' exposure status or outcome was ascertained by multiple assessors
- Design-specific biases:
    - Address issues such as recall bias and social desirability bias if the exposure or outcome was ascertained in interviews or questionnaires
    - Address differential loss to follow up
    - Address misclassification of exposure or outcome
    - Address high lost to follow up or missing data
- Statistical analysis:
    - Use appropriate analysis methods for the type of data collected
    - Assess and control for confounding within the study's data or control for confounders found in previous research
    - Conduct sensitivity analysis
- Conflict of interest:
    - Explicitly state conflict of interest
    - Identify funding sources

Overall quality of the included studies and quality assessment of individual studies are presented below. Overall, risk of bias in the selection of study population was low in 79% of the studies. Majority of the studies used appropriate source population to investigate their study objective and explicitly stated recruitment methods and eligibility criteria. Risk of bias in the ascertainment of exposure and outcome variables was low in 76% of the studies. The remaining 24% had moderate risk of bias, largely due to reliance on ascertainment of ART use using self-reports or medical chart review. 68% of the studies had moderate to high risk of study design-specific bias. This was mainly due to high loss to follow up and the use of potentially inappropriate proxies to determine ART use. Participants in these studies were considered to be on ART if they self-reported ART use or had documented prescriptions of ART. Previous studies have shown that indirect measures of ART use can be unreliable and may not correlate with actual use.[191] Studies were considered to have high risk of design-specific bias if they had high

proportion of participants lost to follow up. 71% of the studies had low risk of bias in the statistical analysis domain. Majority of the studies used appropriate time-to-event analysis methods and adequately controlled for confounders, however about a third of the studies did not account for follow up time or control for confounders. In the conflict of interest domain, 34% of the studies had low risk of bias, while 66% had moderate risk of bias. The lack of declaration of conflict of interest was the main reason for rating of higher risk of bias. However, studies may not declare conflict of interest if not required to do so by the journals. Therefore, not declaring conflict of interest does not necessarily mean that the results are biased.

**Figure A1.** A Summary of risk of bias in study population selection, detection of exposure and outcome, study design, statistical analysis, and conflict of interest declaration in the studies included in the systematic review and meta-analysis.

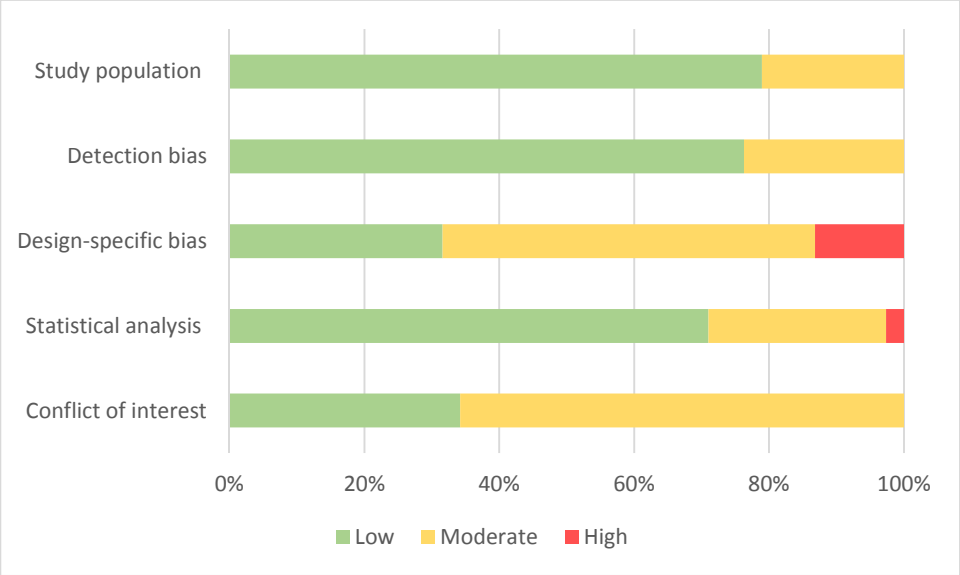
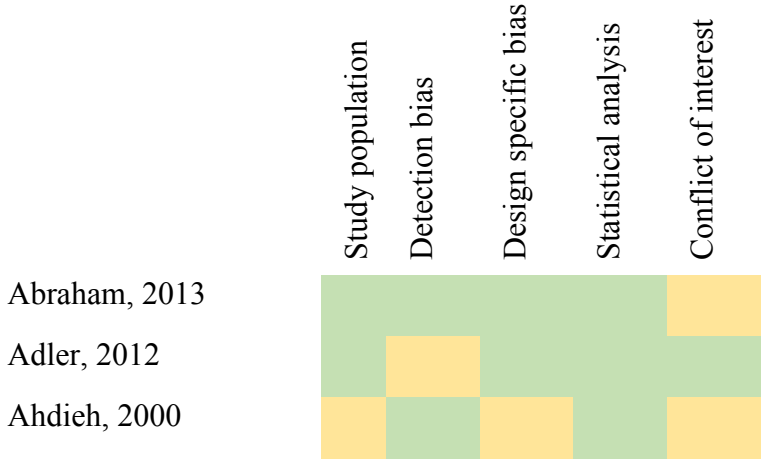
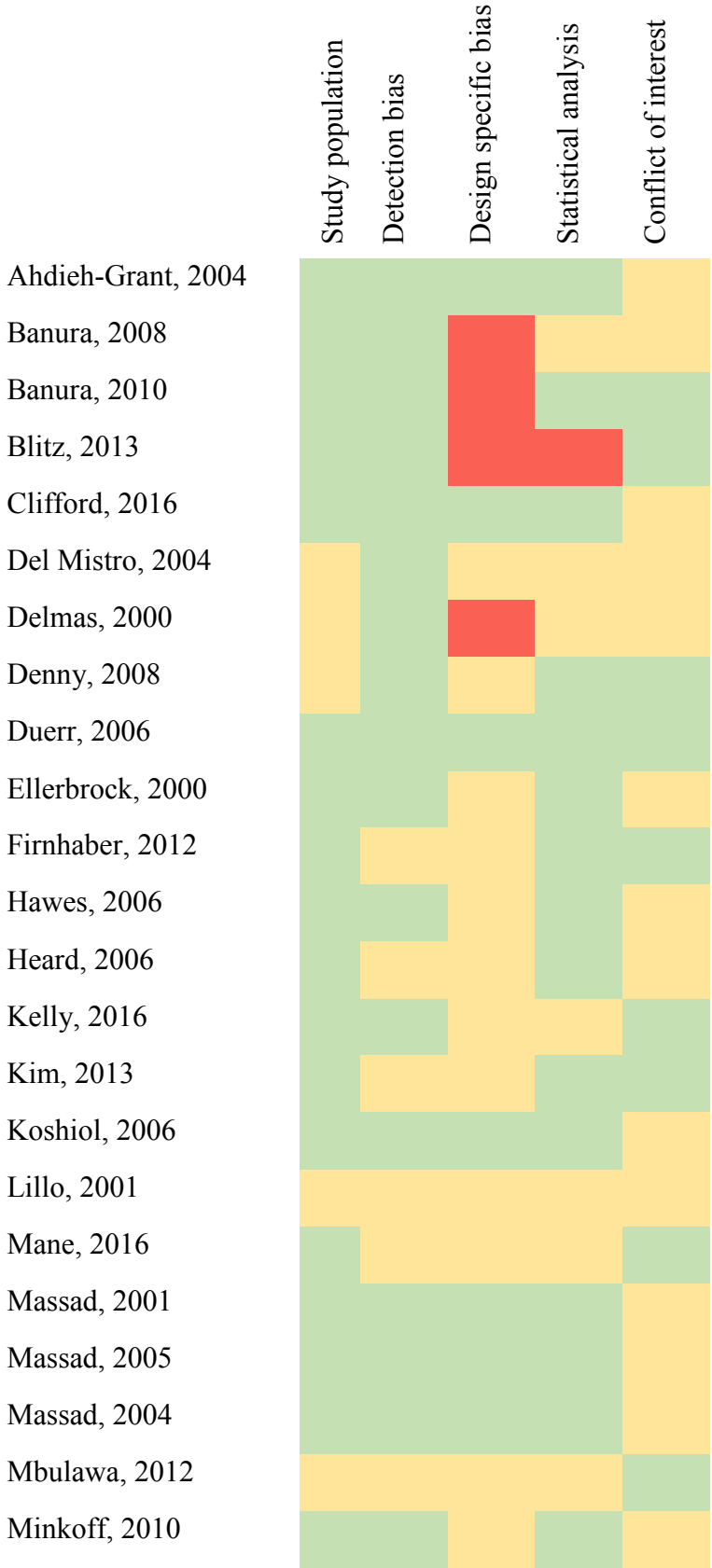
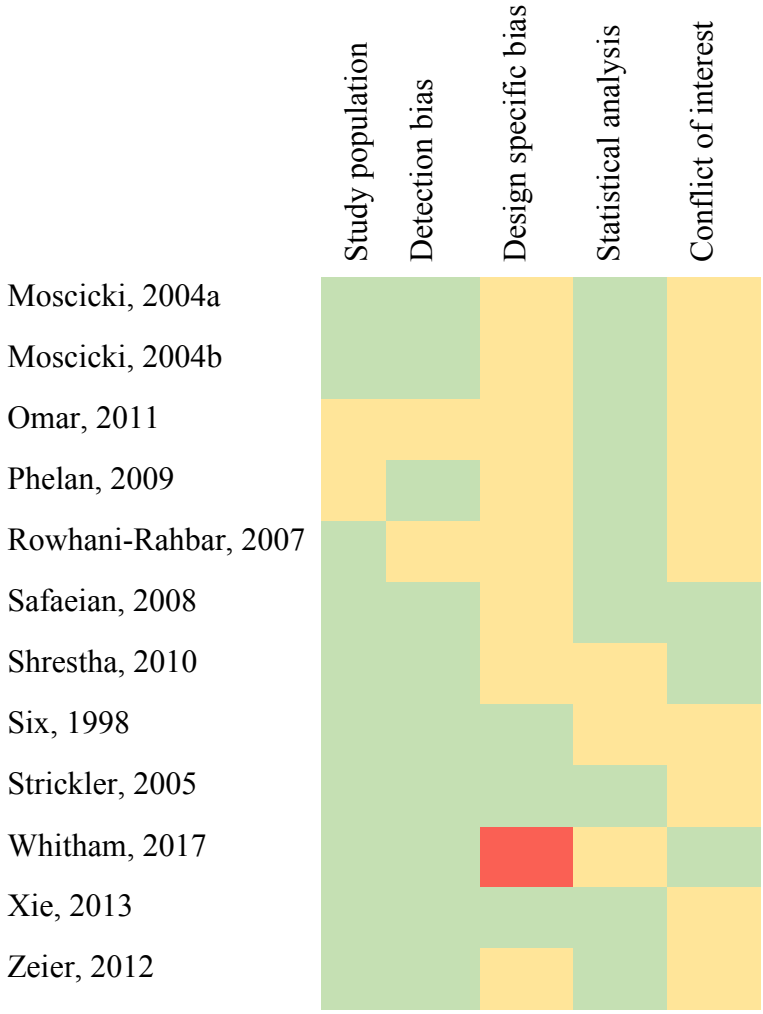



**Figure A2.** Risk of bias in study population selection, detection of exposure and outcome, study design, statistical analysis, and conflict of interest declaration in individual studies.



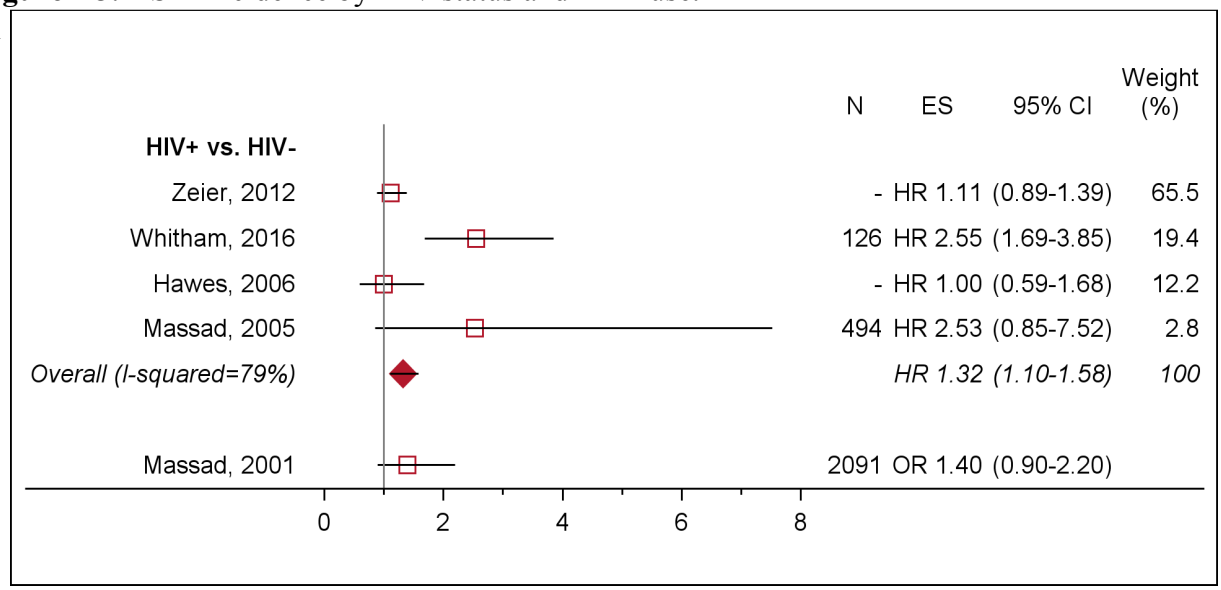

Study population
Detection bias
Design specific bias
Statistical analysis
Conflict of interest
Ahdieh-Grant, 2004
Banura, 2008
Banura, 2010
Blitz, 2013
Clifford, 2016
Del Mistro, 2004
Delmas, 2000
Denny, 2008
Duerr, 2006
Ellerbrock, 2000
Firnhaber, 2012
Hawes, 2006
Heard, 2006
Kelly, 2016
Kim, 2013
Koshiol, 2006
Lillo, 2001
Mane, 2016
Massad, 2001
Massad, 2005
Massad, 2004
Mbulawa, 2012
Minkoff, 2010



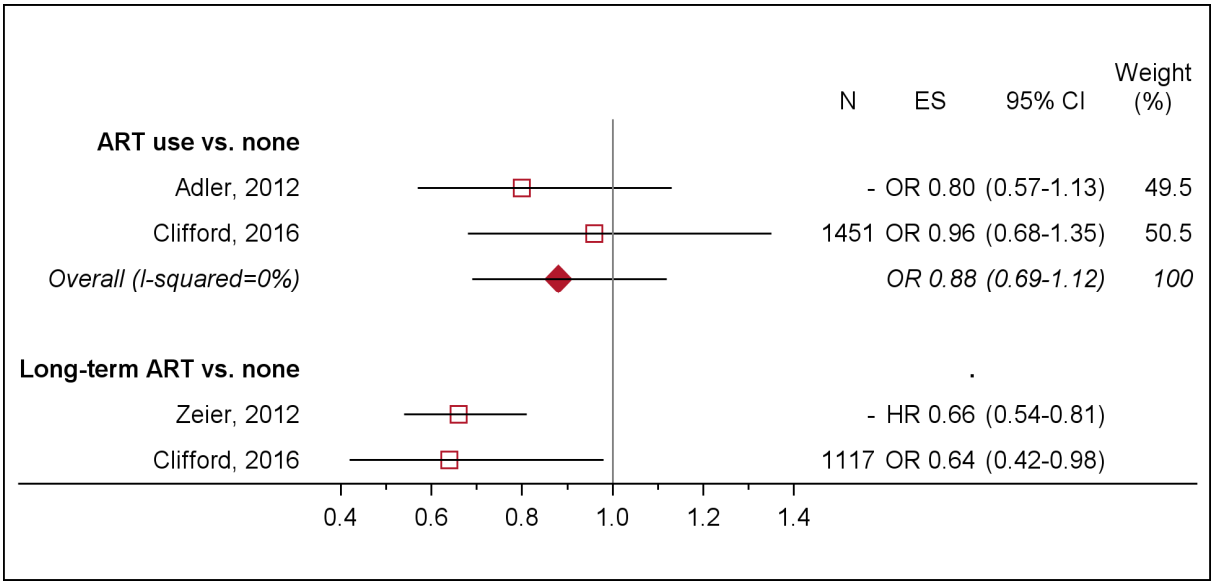

Green indicates low risk of bias, yellow indicates moderate risk of bias, and red indicates high risk of bias.

**Figure A3**. HSIL incidence by HIV status and ART use.

A

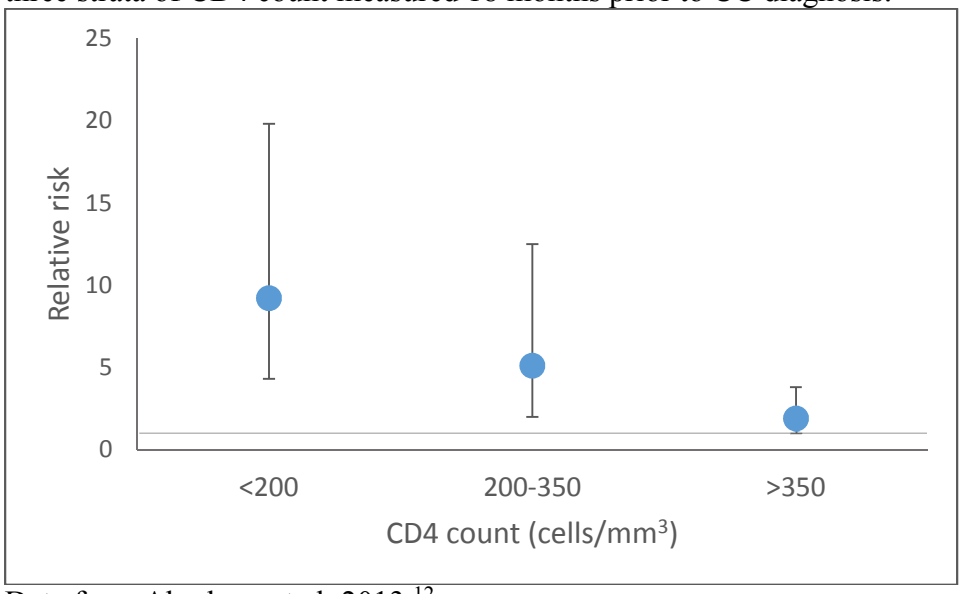



B




N: sample size, ES: effect size. N= "-" Indicates that the study did not report sample size associated with their estimates. A). HSIL incidence among HIV-positive women compared to HIV-negative women. Massad et al, 2001 was not included in calculating the overall estimate as it reported odds ratio. Data from Moscicki et al, 2004 were not included in the figure, as the authors did not obtain an effect estimate for the comparison between HIV-positive women and HIV-negative women. Data from Six et al, 1998 were also not included in the figure, as the authors estimated CD4-stratified RR rather than an overall estimate for HIV-positive women. B). HSIL incidence among HIV-positive women on ART compared to HIV-negative women not on ART. A summary estimate was not calculated for long-term ART use, as the two studies reported different measures of association.

**Figure A4.** CC incidence among HIV-positive women compared to HIV-negative women across three strata of CD4 count measured 18 months prior to CC diagnosis.




Data from Abraham et al, 2013.[12]

Data extracted from included studies.

We collected data from the included studies using a modified data extraction form based on the template provided by Cochrane Training.[192] From each study, we extracted the following information: first author's name, publication year, study design, year and location of data collection, sample size, age of study population, cervical specimen collection method and interval, tests used for detecting and typing HPV, duration of follow-up, proportion lost to follow up, HIV disease characteristics (ART use, CD4 count, and viral load), statistical methods used, confounders, and outcome measures related to the objectives of the systematic review and meta-analysis.

**Table A3. Risk estimates of HPV incidence by HIV status, CD4 count, ART use, and viral load. Estimates must adjust for confounders to be included in the systematic review and meta-analysis.**

| Study | N | CD4 | HPV type | Comparison groups | Risk estimates (95% CI) | Adjusted confounders |
|---|---|---|---|---|---|---|
| **Banura, 2008** | 334 | N/A | Any HPV | HIV+ vs HIV- | OR 1.5 (0.6-3.4) | Age |
| **Banura, 2010** | 380 | N/A | Any HPV | HIV+ vs HIV- | RR 2.8 (0.9 – 8.3) | Age, number of lifetime partners |
| | | | High risk HPV | HIV+ vs HIV- | RR 2.1 (0.9 – 5.1) | |
| | | | HPV 16-related | HIV+ vs HIV- | RR 3.0 (1.3 – 6.9) | |
| | | | HPV 18-related | HIV+ vs HIV- | RR 1.8 (0.5 – 6.2) | |
| **Mbulawa, 2012** | 486 | N/A | Any HPV | HIV+ vs HIV- | RR 2.98 (2.07–4.29) | HPV type-specific detection rate |
| | | | Any HPV | VL <10,000 copies/mL vs HIV- | RR 2.31 (1.49-3.58) | |
| | | | Any HPV | VL >10,000 copies/mL vs HIV- | RR 3.29 (2.18-4.95) | |
| | | | Any HPV | CD4 <350 vs ≥350 cells/mL | RR 1.05 (0.74–1.51) | |
| | | | High risk HPV | VL <10,000 copies/mL vs HIV- | RR 2.58 (1.41-4.70) | |
| | | | High risk HPV | VL >10,000 copies/mL vs HIV- | RR 4.12 (2.27-7.46) | |
| **Safaeian, 2008** | 1055 | N/A | High risk HPV | HIV+ vs HIV- | RR 2.30 (1.57-3.37) | Age, number of lifetime partners |
| | | | HPV 16 | HIV+ vs HIV- | RR 3.09 (1.39-6.85) | |
| | | | HPV 18 | HIV+ vs HIV- | RR 3.19 (1.17-8.71) | |
| **Phelan, 2009** | 219 | N/A | Any HPV | CD4 >500 cells/mL vs HIV- | OR 4.6 (2.3−8.9) | HIV/CD4, age, crack use, number of male partners in last 10 years |
| | | | Any HPV | CD4 200-500 cells/mL vs HIV- | OR 5.4 (2.8−10.3) | |
| | | | Any HPV | CD4 <200 cells/mL vs HIV- | OR 10.9 (5.5−21.7) | |
| | | N/A | Any HPV | CD4 200-500 vs >500 cells/mL | OR 1.2 (0.7–2.0) | |
| | | | Any HPV | CD4 <200 vs >500 cells/mL | OR 2.0 (1.1–3.6) | |
| | | | Any HPV | Any ART vs no ART | OR 1.5 (1.0-2.3) | |
| **Xie, 2013** | 2386 | N/A | Any HPV | CD4 >500 cells/mL vs HIV- | HR 1.65 (1.39–1.96) | Age, race, smoking, number of male partners in last 6 months |
| | | | Any HPV | CD4 200-500 cells/mL vs HIV- | HR 2.76 (2.33–3.27) | |
| | | | Any HPV | CD4 <200 cells/mL vs HIV- | HR 3.40 (2.66–4.34) | |
| | | N/A | High risk HPV | CD4 >500 cells/mL vs HIV- | HR 1.62 (1.31-2.00) | |
| | | | High risk HPV | CD4 200-500 cells/mL vs HIV- | HR 2.49 (2.04–3.03) | |
| | | | High risk HPV | CD4 <200 cells/mL vs HIV- | HR 3.82 (3.01–4.86) | |
| **Denny, 2008** | 400 | Med: 248 | Any HPV | Every 100-cell increase in CD4 | OR 0.82 (0.70–0.96) | Factors not listed |
| **Mane, 2016** | 215 | Med: 386 | Any HPV | Every 100-cell increase in CD4 | OR 1.29 (0.99–1.67) | Age, CD4, ART |
| | | | Any HPV | ART vs none | OR 4.46 (0.92–21.59) | |
| **Lillo, 2001** | 163 | Mean: 350 | Any HPV | HAART vs other ART and no ART | RR 0.79 (0.28–2.23) | CD4, HIV viral load, gynecologic treatment |
| | | | HPV 16 and 18 | HAART vs other ART and no ART | OR 0.28 (0.09–0.86) | |
| **Shresta, 2010** | 373 | Med 516 | HPV 16 | Post-HAART vs pre-HAART | RR 1.13 (0.30-4.24) | All non-time varying confounders |
| | | | HPV 18 | Post-HAART vs pre-HAART | RR 0.67 (0.23-1.95) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Minkoff, 2011** | 286 | N/A | Any HPV | Adhere vs pre-HAART | OR 0.69 (0.51-0.94) | Time-varying SIL treatment, CD4, age, number of partners in the past 6 months, smoking, race/ethnicity |
| | | | Any HPV | Non-adhere vs pre-HAART | OR 1.03 (0.83-1.29) | |
| | | | Any HPV | Adhere vs non-adhere | OR 0.67 (0.47-0.96) | |
| | | | Any HPV | Effective vs pre-HAART | OR 0.64 (0.46–0.88) | |
| | | | Any HPV | Ineffective vs pre-HAART | OR 1.00 (0.78–1.29) | |
| | | | Any HPV | Effective vs ineffective | OR 0.63 (0.44–0.92) | |
| | | | High risk HPV | Adhere vs pre-HAART | OR 0.49 (0.30-0.82) | |
| | | | High risk HPV | Non-adhere vs pre-HAART | OR 1.01 (0.72-1.42) | |
| | | | High risk HPV | Adhere vs non-adhere | OR 0.49 (0.28-0.86) | |
| | | | High risk HPV | Effective vs pre-HAART | OR 0.62 (0.38–1.02) | |
| | | | High risk HPV | Ineffective vs pre-HAART | OR 0.92 (0.64–1.34) | |
| | | | High risk HPV | Effective vs ineffective | OR 0.67 (0.38–1.19) | |
| **Strickler, 2005** | | | Any HPV | VL <4000 copies, CD4 <200 vs HIV- | HR 4.2 (3.1-5.6) | CD4 and viral load. Adjusting for demographics and behavioral variables did not change results |
| | | | Any HPV | VL <4000 copies, CD4 200-500 vs HIV- | HR 2.6 (2.1-3.2) | |
| | | | Any HPV | VL <4000 copies, CD4 >500 vs HIV- | HR 1.7 (1.4-2.2) | |
| | | | Any HPV | VL 4000-20000 copies, CD4 <200 vs HIV- | HR 4.6 (3.4-6.2) | |
| | | | Any HPV | VL 4000-20000 copies, CD4 200-500 vs HIV- | HR 3.3 (2.7-4.2) | |
| | | | Any HPV | VL 4000-20000 copies, CD4 >500 vs HIV- | HR 2.2 (1.6-3.0) | |
| | | | Any HPV | VL 20001-100000 copies, CD4 <200 vs HIV- | HR 5.1 (4.0-6.5) | |
| | | | Any HPV | VL 20001-100000 copies, CD4 200-500 vs HIV- | HR 4.3 (3.4-5.3) | |
| | | | Any HPV | VL 20001-100000 copies, CD4 >500 vs HIV- | HR 3.2 (2.2-4.7) | |
| | | | Any HPV | VL >100000 copies, CD4 <200 vs HIV- | HR 4.6 (3.7-5.8) | |
| | | | Any HPV | VL >100000 copies, CD4 200-500 vs HIV- | HR 5.1 (3.9-6.6) | |
| | | | Any HPV | VL >100000 copies, CD4 >500 vs HIV- | HR 4.2 (2.5-6.8) | |

**Table A4. Risk estimates of** HPV infection incidence that did not adjust for any confounders. These estimates were excluded from the systematic review and meta-analysis.

| Study | HPV type | Comparison groups | Risk estimate (95% CI) |
|---|---|---|---|
| **Ahdieh, 2001** | HPV 16/18/31/45 | HIV+ vs HIV- | RR 1.8 (1.3–2.7) |
| | HPV 16 | HIV+ vs HIV- | RR 1.5 (0.8–3.0) |
| | HPV 18 | HIV+ vs HIV- | RR 2.2 (1.1–4.7) |
| | Other high risk | HIV+ vs HIV- | RR 2.1 (1.5–2.9) |
| | Low risk | HIV+ vs HIV- | RR 2.7 (2.0–3.6) |
| **Blitz, 2013** | Any high risk | HIV+ vs HIV- | HR 2.28 (1.09-4.77) |
| | HPV 16 | HIV+ vs HIV- | HR 2.03 (0.75-5.52) |
| | Non-HPV 16/18 high risk | HIV+ vs HIV- | HR 1.56 (0.73-3.32) |
| **Branca, 2003** | Any HPV | HIV+ vs HIV- | OR 8.8 (1.2-64.6) |
| **Minkoff, 2001** | Any HPV | HIV+ vs HIV- | RR 2.66 (1.59-4.44) |
| **Safaeian, 2008** | High risk HPV | HIV+ vs HIV- | RR 2.47 (1.75-3.45) |
| | HPV 16 | HIV+ vs HIV- | RR 2.71 (1.13-6.06) |
| | HPV 18 | HIV+ vs HIV- | RR 3.23 (1.06-9.13) |
| **Sun, 1997** | Any HPV | HIV+ vs HIV- | RR 1.22 |

**Table A5. Risk estimates of HPV clearance by HIV status, CD4 count, ART use, and viral load.**

| Study | HPV type | Comparison groups | Risk estimates (95% CI) |
|---|---|---|---|
| **Banura, 2010** | Any HPV | HIV+ vs HIV- | RR 0.2 (0.1 – 0.7) |
| | High risk HPV | HIV+ vs HIV- | RR 0.5 (0.2 – 1.0) |
| | HPV 16-related | HIV+ vs HIV- | RR 0.4 (0.2 – 1.2) |
| | HPV 18-related | HIV+ vs HIV- | RR 0.6 (0.2 – 1.8) |
| **Mbulawa, 2012** | Any HPV | HIV+ vs HIV- | RR 0.46 (0.34-0.62) |
| | Any HPV | CD4 <350 vs ≥350 cells/mm$^3$ | RR 0.77 (0.53–1.10) |
| | Any HPV | VL <10,000 vs >10,000 copies/mL | RR 0.77 (0.51-1.16) |
| | High risk HPV | HIV+ vs HIV- | RR 0.44 (0.29–0.65) |
| **Koshiol, 2006** | High risk HPV | HIV+ vs HIV- | HR 0.60 (0.47-0.76) |
| | HPV 16-related | HIV+ vs HIV- | HR 0.57 (0.41-0.78) |
| | HPV 18-related | HIV+ vs HIV- | HR 0.50 (0.31-0.82) |
| | High risk HPV* | HIV+ vs HIV- | HR 0.85 (0.64-1.13) |
| | HPV 16-related* | HIV+ vs HIV- | HR 0.92 (0.62-1.35) |
| | HPV 18-related* | HIV+ vs HIV- | HR 0.81 (0.45-1.46) |
| | Any HPV | CD4 200-500 vs >500 cells/mm$^3$ | HR 0.76 (0.64–0.90) |
| | Any HPV | CD4 <200 vs >500 | HR 0.47 (0.37–0.58) |
| | Low risk HPV | HIV+ vs HIV- | HR 0.63 (0.45–0.88) |
| **Blitz, 2003** | High risk HPV | HIV+ vs HIV- | HR 0.41 (0.25-0.65) |
| | High risk HPV | CD4 200-500 vs >500 cells/mm$^3$ | HR 1.35 (0.76-2.41) |
| | High risk HPV | CD4 <200 vs >500 cells/mm$^3$ | HR 1.13 (0.53-2.42) |
| | High risk HPV | ART use vs non-use | HR 1.5 (0.84-2.68) |
| | HPV 16 | HIV+ vs HIV- | HR 1.36 (0.52–3.62) |
| | HPV 16 | CD4 200-500 vs >500 cells/mm$^3$ | HR 2.80 (1.06–7.36) |
| | HPV 16 | CD4 <200 vs >500 cells/mm$^3$ | HR 2.97 (.78–11.28) |
| | HPV 16 | ART use vs non-use | HR 0.69 (0.28–1.70) |
| | Non-16/18 high risk HPV | HIV+ vs HIV- | HR 0.32 (0.19-0.55) |
| | Non-16/18 high risk HPV | ART use vs non-use | HR 2.20 (1.22–3.98) |
| **Whitham, 2017** | Any HPV | HIV+ vs HIV- | HR 0.46 (0.39-0.54) |
| | Any HPV | CD4 <200 vs >200 cells/mm$^3$ | HR 0.57 (0.39-0.83) |
| **Minkoff, 2011** | Any HPV | Adhere vs pre-ART | OR 1.28 (0.99–1.66) |
| | Any HPV | Non-adhere vs pre-ART | OR 1.05 (0.86–1.29) |
| | Any HPV | Adhere vs non-adhere | OR 1.22 (0.91–1.64) |
| | Any HPV | Effective vs pre-ART | OR 1.16 (0.88–1.52) |
| | Any HPV | Ineffective vs pre-ART | OR 1.12 (0.89–1.41) |
| | Any HPV | Effective vs ineffective | OR 1.03 (0.75–1.42) |
| **Ahdieh, 2000** | Any HPV | HIV+ CD4 <200 vs HIV- | HR 0.10 (0.04-0.28) |
| | Any HPV | HIV+ CD4 >200 vs HIV- | HR 0.29 (0.17-0.48) |
| **Moscicki, 2004** | Any HPV | HIV- vs HIV+ | HR 1.38 (0.99-1.93) |
| | Any HPV | HIV- vs HIV+ CD4 >500 | HR 1.60 (1.11–2.29) |
| **Rowhani-Rahbar, 2007** | Any HPV | HIV+ vs HIV- | HR 0.31 (0.21–0.45) |
| | Any HPV | CD4 <200 vs >500 | HR 0.29 (0.11–0.76) |
| | Any HPV | CD4 200-500 vs >500 | HR 0.68 (0.31-1.48) |
| | Any HPV | Order magnitude increase in VL | HR 0.77 (0.64–0.91) |
| | HPV 16 | HIV+ vs HIV- | HR 0.57 (0.32–1.02) |
| | HPV 18 | HIV+ vs HIV- | HR 0.42 (0.19–0.95) |
| **Safaeian, 2008** | High risk HPV | HIV+ vs HIV- | RR 0.75 (0.59-0.96) |
| | HPV 16 | HIV+ vs HIV- | RR 1.61 (0.74-3.51) |
| | HPV 18 | HIV+ vs HIV- | RR 1.22 (0.85-1.77) |
| **Strickler, 2005** | Any HPV* | HIV+ vs HIV- | HR 0.67 (0.56-0.81) |
| **Mane, 2016** | Any HPV | ART vs none | OR 2.16 (0.74–6.27) |
| | Any HPV | Every 100-cell increase in CD4 | OR 1.05 (0.85–1.31) |

*Clearance of incident infections

**Table A6. Risk estimates of progression to LSIL by HIV status, CD4 count, ART use, and viral load**

| Study | SIL | Comparison groups | Risk estimate (95% CI) |
|---|---|---|---|
| **Duerr, 2006** | ASCUS | HIV+ vs HIV- | HR 1.8 (1.4-2.3) |
| | ASCUS | CD4 <200 vs >500 | HR 1.9 (1.2-2.9) |
| | ASCUS | CD4 200-500 vs >500 | HR 1.1 (0.8-1.5) |
| | ASCUS | HIV+: high or intermediate risk HPV vs none | HR 3.1 (2.2-4.3) |
| | ASCUS | HIV+: low risk HPV vs none | HR 1.8 (1.3-2.5) |
| **Ellerbrock, 2000** | LSIL | HIV+ vs HIV- | RR 3.2 (1.7-6.1) |
| | LSIL | HIV+: persistent HPV16/18 vs no | RR 11.0 (1.4-88.7) |
| | LSIL | HIV+: persistent HPV other than 16/18 vs no | RR 8.9 (1.2-66.2) |
| | LSIL | HIV+: Baseline CD4 | RR 1.3 (0.9-2.1) |
| | LSIL | HIV+: ART (last 6 months) vs no | RR 1.0 (0.5-2.0) |
| **Massad, 2001** | ASCUS+ | HIV+ vs HIV- | OR 1.7 (1.0-2.8) |
| | ASCUS+ | CD4<200 vs. CD4>200 or HIV- | OR 2.0 (1.5-2.6) |
| | ASCUS+ | RNA>4000 vs. RNA<4000 or HIV- | OR 2.3 (1.7-3.3) |
| | ASCUS+ | HIV+ vs HIV- | RR 2.4 (1.9-3.0) |
| | LSIL | HIV+ vs HIV- | RR 4.0 (2.6-6.1) |
| | LSIL | HPV-, CD4 >200, RNA <4000 vs HPV-, HIV- | RR 1.2 (0.5-2.6) |
| | LSIL | HPV-, CD4 >200, RNA >4000 vs HPV-, HIV- | RR 3.8 (2.0-7.0) |
| | LSIL | HPV-, CD4 <200, RNA >4000 vs HPV-, HIV- | RR 9.0 (4.4-18.2) |
| | LSIL | HPV+, HIV- vs HPV-, HIV- | RR 1.9 (0.8-4.5) |
| | LSIL | HPV+, CD4 >200, RNA <4000 vs HPV-, HIV- | RR 2.1 (1.0-4.5) |
| | LSIL | HPV+, CD4 >200, RNA >4000 vs HPV-, HIV- | RR 4.3 (2.2-8.7) |
| | LSIL | HPV+, CD4 <200, RNA <4000 vs HPV+, HIV- | RR 4.4 (1.3-14.4) |
| | LSIL | HPV+, CD4 <200, RNA >4000 vs HPV+, HIV- | RR 7.9 (3.9-16.1) |
| **Denny, 2008** | LSIL | HIV+: high risk HPV+ vs high risk HPV- | HR 3.09 (1.94–4.93) |
| | LSIL | CD4 201–500 vs <200 | HR 0.75 (0.45–1.26) |
| | LSIL | CD4 >500 vs <200 | HR 0.43 (0.20–0.93) |
| **Delmas, 2000** | LSIL | Baseline CD4 <200 vs >500 | RR 1.9 (1.0-3.7) |
| | LSIL | Baseline CD4 200-500 vs >500 | RR 1.6 (0.9-2.8) |
| | LSIL | Untreated: CD4 <200 vs >500 | RR 1.7 (0.8-3.5) |
| | LSIL | Untreated: CD4 200-500 vs >500 | RR 1.3 (0.6-2.8) |
| | LSIL | On ART: CD4 200-500 vs >500 | RR 1.9 (1.0-3.6) |
| | LSIL | On ART: CD4 <200 vs >500 | RR 2.9 (1.1-8.0) |
| **Firnhaber, 2012** | LSIL | ART vs none | RR 0.55 (0.34-0.90) |
| **Adler, 2012** | LSIL | ART vs none | HR 0.62 (0.42-0.91) |
| | LSIL | CD4 <200 vs >500 | HR 1.73 (1.15-2.61) |
| | LSIL | CD4 200-350 vs >500 | HR 1.61 (1.12-2.30) |
| | LSIL | CD4 350-500 vs >500 | HR 1.45 (1.0-2.11) |
| **Kim, 2013** | LSIL | ART vs old ART | HR 0.46 (0.31–0.69) |
| | LSIL | ART vs any ART | HR 0.35 (0.19–0.63) |
| | LSIL | ART vs no ART | HR 0.66 (0.47–0.92) |
| | LSIL | ART vs others | HR 0.47 (0.33–0.68) |
| | LSIL | 100-cell increase in CD4 | HR 0.91 (0.86–0.96) |
| | LSIL | 200-cell increase in CD4 | HR 0.82 (0.74–0.92) |
| | LSIL | 300-cell increase in CD4 | HR 0.75 (0.63–0.89) |
| | LSIL | 500-cell increase in CD4 | HR 0.62 (0.47–0.82) |
| **Heard, 2006** | LSIL | ART vs none | HR 0.7 (0.4-1.2) |
| | LSIL | CD4 <200 vs >500 | HR 1.3 (0.7-2.4) |
| | LSIL | CD4 200-500 vs >500 | HR 0.9 (0.6-1.4) |

**Table A7. Risk estimates of progression to HSIL from normal cytology or LSIL by HIV status, CD4 count, ART use, and viral load.**

| Study | Comparison groups | Risk estimates (95% CI) | Baseline condition |
|---|---|---|---|
| **Whitham, 2016** | From normal to HSIL: HIV+ vs HIV- | HR 1.53 (0.73-3.21) | Normal cytology, HPV- |
| | From HPV to HSIL: HIV+ vs HIV- | HR 2.55 (1.69-3.86) | Normal cytology, HPV+ |
| | CD4<200 vs >200 | HR 2.86 (0.95-8.58) | Normal cytology, HPV- |
| | HPV 16/18 vs others | HR 4.62 (1.10-19.42) | Normal cytology, HPV- |
| | Multiple HPV vs single HPV | HR 2.33 (1.40-3.88) | Normal cytology, HPV+ |
| **Massad, 2001** | HIV+ vs HIV- | OR 1.4 (0.9-2.2) | Prevalent or incident LSIL |
| | HPV+ vs HPV- | OR 1.6 (1.2-2.1) | |
| | CD4<200 vs. CD4>200 or HIV- | OR 1.1 (0.9-1.4) | |
| | RNA>4000 (vs. RNA<4000 or HIV-) | OR 1.3 (1.1-1.7) | |
| **Adler, 2012** | HAART vs none | OR 0.80 (0.57-1.14) | Prevalent or incident LSIL |
| | CD4 <200 vs >500 | OR 2.50 (1.67-3.73) | |
| | CD4 201-350 vs >500 | OR 1.89 (1.36-2.62) | |
| | CD4 351-500 vs >500 | OR 1.84 (1.31-2.59) | |
| **Zeier, 2012** | HIV+ vs HIV- | HR 1.11 (0.88-1.38) | Prevalence LSIL |
| | HAART use before LSIL vs none | HR 0.66 (0.54-0.81) | |
| | HAART use after LSIL vs none | HR 0.90 (0.67-1.20) | |
| **Massad, 2005** | HIV+ vs HIV- | HR 2.53 (0.85–7.50) | Prevalent LSIL, negative colposcopy |
| | HIV+: high risk HPV+ vs no HPV | HR 2.56 (1.13–5.80) | |
| | HIV+: low risk HPV+ vs no HPV | HR 1.41 (0.61–3.26) | |
| | CD4 >500 vs <200 | HR 0.74 (0.31–1.76) | |
| | CD4 200-500 vs <200 | HR 0.31 (0.15–0.63) | |
| | HIV RNA >70000 vs <10000 | HR 1.19 (0.52–2.71) | |
| | HIV RNA 10000-70000 vs <10000 | HR 1.32 (0.61–2.85) | |
| **Moscicki, 2004** | HIV+ vs HIV- | Not retained in model | HSIL negative |
| | HAART vs none | Not retained in model | |
| | HIV+: HPV 16-related types vs none | HR 3.69 (1.06–12.80) | |
| | HIV+: HPV 18-related types vs none | HR 4.49 (1.16–17.42) | |
| | HIV+: multiple high risk types vs none | HR 3.69 (1.07–12.71) | |
| | HIV+: low risk HPV types vs none | HR 2.44 (0.41–14.41) | |
| **Six, 1998** | CD4 >500 vs HIV- | 1 | Prevalent LSIL |
| | CD4 <500 vs HIV- | Undefined, denom = 0 | |
| **Clifford, 2016** | Baseline CD4 >500 vs 350-500 | OR 0.89 (0.62-1.26) | CIN 2/3-negative |
| | Baseline CD4 200-350 vs 350-500 | OR 1.51 (1.04-2.18) | |
| | Baseline CD4 <200 vs 350-500 | OR 1.72 (1.16-2.54) | |

| | | | |
|---|---|---|---|
| | Baseline CD4: every 100 cell increase | OR 1.10 (1.04-1.16) | |
| | Nadir CD4 200-350 vs >350 | OR 1.57 (1.09-2.25) | |
| | Nadir CD4 50-200 vs >350 | OR 2.20 (1.55-3.11) | |
| | Nadir CD4 <50 vs >350 | OR 2.20 (1.47-3.30) | |
| | Nadir CD4 every 100-cell increase | OR 1.15 (1.08-1.22) | |
| | Ever cART use vs never | OR 0.96 (0.68-1.35) | |
| | >2 years cART use vs never | OR 0.64 (0.42-0.98) | |
| | <2 years cART use vs never | OR 1.25 (0.86, 1.81) | |
| **Hawes, 2006** | High risk HPV-: HIV+ vs HIV- | HR 3.0 (0.7-13.3) | Normal cytology |
| | High risk HPV+: HIV+ vs HIV- | HR 3.0 (1.6-5.6) | |
| | HIV+, high risk HPV+ vs HIV-, high risk HPV- | HR 11.5 (2.7-49.0) | |
| | HIV-: high risk HPV+ vs high risk HPV- | HR 4.3 (1.0-18.1) | |
| | HIV+ vs HIV- | HR 1.0 (0.6-1.7) | |
| | CD4 200-500 vs >500 | HR 1.6 (0.5-4.9) | |
| | CD4 <200 vs >500 | HR 1.7 (0.5-5.6) | |
| | Per order of magnitude increase in RNA | HR 1.0 (0.8-1.4) | |
| **Kelly, 2006** | HIV+: high risk HPV persistence vs HPV- or HPV-cleared | OR 7.90 (3.11-20.07) | CIN 2/3-negative |
| | HIV+: HPV 16/18 persistence vs HPV- or HPV-cleared | OR 5.25 (2.14-12.91) | |

**Table A8. Risk estimates of regression from LSIL by HIV status, CD4 count, ART use, and viral load.**

| Study | Comparison groups | Risk estimates (95% CI) |
|---|---|---|
| **Delmas, 2000** | CD4 <200 vs >500 | RR 0.5 (0.2-1.4) |
| **Adler, 2012** | HAART vs none | OR 2.61 (1.75–3.89) |
| | CD4 <200 vs >500 | OR 0.96 (0.56–1.66) |
| | CD4 201-350 vs >500 | OR 1.09 (0.71–1.66) |
| | CD4 351-500 vs >500 | OR 0.67 (0.41–1.09) |
| **Zeier, 2012** | HIV+ vs HIV- | HR 0.69 (0.57-0.85) |
| | HIV-unknown vs HIV- | HR 1.09 (0.89-1.34) |
| | Pre-LSIL ART vs none | HR 1.71 (1.29-2.27) |
| | Post-LSIL ART vs none | HR 0.77 (0.61-0.97) |
| | CD4 >350 vs <200 | HR 1.00 (0.75-1.33) |
| | CD4 200-349 vs <200 | HR 0.77 (0.56-1.05) |
| **Six, 1998** | CD4 <200 vs HIV- | RR 0.21 |
| | CD4 200-500 vs HIV- | RR 0.19 |
| | CD4 >500 vs HIV- | RR 0.52 |
| **Massad, 2004** | HIV+ vs HIV- | HR 0.52 (0.27-1.03) |
| | CD4 200-500 vs <200 | HR 1.39 (0.74- 2.60) |
| | CD4 >500 vs <200 | HR 1.33 (0.56-3.12) |
| | HIV RNA >20000 vs <20000 | HR 0.56 (0.31-1.02) |
| | HAART vs none | HR 1.32 (0.71-2.50) |
| | HIV+: high risk HPV+ vs none | HR 0.32 (0.18–0.56) |
| | HIV+: low risk HPV+ vs none | HR 0.22 (0.09–0.51) |
| **Del Mistro, 2004** | HAART vs none | OR 0.36 (0.08–1.62) |
| | Non-HAART vs none | OR 0.05 (0.01–0.46) |
| | Misc ART vs none | OR 0.07 (0.01–0.54) |
| | Baseline CD4 | OR 0.996 (0.99–1.00) |
| **Ahdieh-Grant, 2004** | Not on HAART: CD4 >500 vs <200 | RR 3.00 (1.21-7.41) |
| | Not on HAART: CD4 350-499 vs <200 | RR 2.21 (0.85-5.72) |
| | Not on HAART: CD4 200-349 vs <200 | RR 1.92 (0.74-4.99) |
| | HAART vs none | Undefined, denom=0 |
| **Omar, 2011** | CD4 | Data not shown |

**Table A9. Risk estimates of ICC incidence by HIV status, ART use, and CD4 count.**

| Study | Comparison groups | Risk estimates (95% CI) |
|---|---|---|
| **Clifford, 2016** | Ever cART use vs never | OR 0.62 (0.15-2.54) |
| | >2 years cART use vs never | OR 0.34 (0.05-2.26) |
| | <2 years cART use vs never | OR 0.97 (0.20-4.66) |
| **Abraham, 2013** | CD4 >350 18 months before diagnosis vs HIV- | RR 1.9 (1.0–3.8) |
| | CD4 200-350 18 months before diagnosis vs HIV- | RR 5.1 (2.0–12.5) |
| | CD4 <200 18 months before diagnosis vs HIV- | RR 9.2 (4.3–19.8) |
| | CD4 <200 at diagnosis vs HIV- | RR 8.4 (4.6–15.3) |
| | CD4 200-350 at diagnosis vs HIV- | RR 5.8 (2.3–14.6) |
| | CD4 >350 at diagnosis vs HIV- | RR 1.7 (0.9–3.2) |

References reviewed but not included in the synthesis and meta-analysis:


1. Adachi A, Fleming I, Burk RD, Ho GY, Klein RS. Women with human immunodeficiency virus infection and abnormal Papanicolaou smears: a prospective study of colposcopy and clinical outcome. Obstet Gynecol. 1993;81(3):372-7.
2. Adler D, Wallace M, Bennie T, Abar B, Sadeghi R, Meiring T, et al. High Risk Human Papillomavirus Persistence Among HIV-infected Young Women in South Africa. Int J Infect Dis. 2015;33:219-21.
3. Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. J Infect Dis. 2001;184(6):682-90.
4. Almonte M, Albero G, Molano M, Carcamo C, García PJ, Pérez G. Risk factors for human papillomavirus exposure and co-factors for cervical cancer in Latin America and the Caribbean. Vaccine. 2008;26(Supplement 11):L16-L36.
5. Anastos K, Hoover DR, Burk RD, Cajigas A, Shi Q, Singh DK, et al. Risk factors for cervical precancer and cancer in HIV-infected, HPV-positive Rwandan women. PLoS One. 2010;5(10):e13525.
6. Appleby P, Beral V, Newton R, Reeves G. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. J Natl Cancer Inst. 2000;92(22):1823-30.
7. Atashili J, Smith JS, Adimora AA, Eron J, Miller WC, Myers E. Potential impact of antiretroviral therapy and screening on cervical cancer mortality in HIV-positive women in sub-Saharan Africa: a simulation. PLoS One. 2011;6(4):e18527.
8. Bekolo CE, O'Bryan G, Tchago FE, Nangue C, Bekoule PS, Kollo B. Integrating cervical cancer screening with HIV care in Cameroon: Comparative risk analysis of cervical disease in HIV-infected women receiving antiretroviral therapy to women in the general population. PLoS One. 2016;11(2).
9. Belafsky P, Clark RA, Kissinger P, Torres J. Natural history of low-grade squamous intraepithelial lesions in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr Hum Retrovirol. 1996;11(5):511-2.
10. Berrebi A, Badiou W, Duclusaud A. [Frequency, persistence and recurrence of HPV lesions of the uterine cervix in HIV-seropositive women]. Gynecol Obstet Fertil. 2008;36(5):521-4.
11. Branca M, Garbuglia AR, Benedetto A, Cappiello T, Leoncini L, Migliore G, et al. Factors predicting the persistence of genital human papillomavirus infections and PAP smear abnormality in HIV-positive and HIV-negative women during prospective follow-up. Int J STD AIDS. 2003;14(6):417-25.
12. Brogly SB, Watts DH, Ylitalo N, Franco EL, Seage GR, 3rd, Oleske J, et al. Reproductive health of adolescent girls perinatally infected with HIV. Am J Public Health. 2007;97(6):1047-52.
13. Calore EE, Pereira SM, Cavaliere MJ. Progression of cervical lesions in HIV-seropositive women: a cytological study. Diagn Cytopathol. 2001;24(2):117-9.
14. Cardillo M, Hagan R, Abadi J, Abadi MA. CD4 T-cell count, viral load, and squamous intraepithelial lesions in women infected with the human immunodeficiency virus. Cancer. 2001;93(2):111-4.
15. Chen YMA, Chen M, Jen I, Law MG, Bhatia K, Sharp GB. Cancer incidence in a nationwide HIV/AIDS patient cohort in Taiwan in 1998-2009. Top Antivir Med. 2014;22:357-8.
16. Cubie HA, Seagar AL, Beattie GJ, Monaghan S, Williams AR. A longitudinal study of HPV detection and cervical pathology in HIV infected women. Sex Transm Infect. 2000;76(4):257-61.

17. Drogoul-Vey MP, Marimoutou C, Robaglia-Schlupp A, Beerli M, Gastaut JA, Cau P, et al. Determinants and evolution of squamous intraepithelial lesions in HIV-infected women, 1991-2004. AIDS Care. 2007;19(8):1052-7.
18. Dryden-Peterson S, Medhin H, Kebabonye-Pusoentsi M, Seage GR, Suneja G, Kayembe MKA, et al. Cancer incidence following expansion of HIV treatment in Botswana. PLoS One. 2015;10(8).
19. D'Souza G, Fakhry C, Sugar EA, Seaberg EC, Weber K, Minkoff HL, et al. Six-month natural history of oral versus cervical human papillomavirus infection. Int J Cancer. 2007;121(1):143-50.
20. D'Souza G, Palefsky JM, Zhong Y, Minkoff H, Massad LS, Anastos K, et al. Marijuana use is not associated with cervical human papillomavirus natural history or cervical neoplasia in HIV-seropositive or HIV-seronegative women. Cancer Epidemiol Biomarkers Prev. 2010;19(3):869-72.
21. Eckert LO, Watts DH, Koutsky LA, Hawes SE, Stevens CE, Kuypers J, et al. A matched prospective study of human immunodeficiency virus serostatus, human papillomavirus DNA, and cervical lesions detected by cytology and colposcopy. Infect Dis Obstet Gynecol. 1999;7(3):158-64.
22. El Midaoui A, Niemiec T, Maciejewski J, Firlag-Burkacka E, Kalinowska M. Natural history of human papillomavirus infection in HIV-infected women. HIV and AIDS Review. 2005;4(4):11-7.
23. Ene L, Voinea C, Stefanescu C, Sima D, Duiculescu D, Mehta SR. Cervical HPV infection in Romanian women infected with HIV during early childhood. Int J STD AIDS. 2016;27(12):1079-85.
24. Fife KH, Wu JW, Squires KE, Watts DH, Andersen JW, Brown DR. Prevalence and persistence of cervical human papillomavirus infection in HIV-positive women initiating highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2009;51(3):274-82.
25. Firnhaber C, Goeieman B, Faesen M, Levin S, Williams S, Rameotshela S, et al. Prospective one year follow up of HIV infected women screened for cervical cancer using visual inspection with acetic acid, cytology and human papillomavirus testing in Johannesburg South Africa. PLoS One. 2016;11(1).
26. Firnhaber C, Goeieman B, Mao L, Faesen M, Levin S, Williams S, et al. One-year follow-up of HIV+ women screened with VIA, Cytology and HPV in South Africa. Top Antivir Med. 2015;23:36.
27. Fontaine J, Hankins C, Money D, Rachlis A, Pourreaux K, Ferenczy A, et al. Human papillomavirus type 16 (HPV-16) viral load and persistence of HPV-16 infection in women infected or at risk for HIV. J Clin Virol. 2008;43(3):307-12.
28. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001;285(13):1736-45.
29. Ghartey J, Kovacs A, Burk RD, Stewart Massad L, Minkoff H, Xie X, et al. Genital tract HIV RNA levels and their associations with human papillomavirus infection and risk of cervical precancer. J Acquir Immune Defic Syndr. 2014;66(3):316-23.
30. Gichangi PB, Bwayo J, Estambale B, De Vuyst H, Ojwang S, Rogo K, et al. Impact of HIV infection on invasive cervical cancer in Kenyan women. AIDS. 2003;17(13):1963-8.
31. Gingelmaier A, Grubert T, Kaestner R, Mylonas I, Weissenbacher T, Bergauer F, et al. High recurrence rate of cervical dysplasia and persistence of HPV infection in HIV-1-infected women. Anticancer Res. 2007;27(4a):1795-8.
32. Heard I, Bergeron C, Jeannel D, Henrion R, Kazatchkine MD. Papanicolaou smears in human immunodeficiency virus-seropositive women during follow-up. Obstet Gynecol. 1995;86(5):749-53.
33. Heard I, Cubie HA, Mesher D, Sasieni P. Characteristics of HPV infection over time in European women who are HIV-1 positive. BJOG. 2013;120(1):41-9.
34. Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. AIDS. 1998;12(12):1459-64.

35. Hensel M, Goetzenich A, Hanhoff N, Wolf E, Knechten H, Mosthaf F. Cancer incidence in HIV-positive patients in Germany: A nation-wide survey from 2000 to 2007. J Clin Oncol. 2009;27(15):e22115.
36. Jalil EM, Bastos FI, Melli PP, Duarte G, Simoes RT, Yamamoto AY, et al. HPV clearance in postpartum period of HIV-positive and negative women: a prospective follow-up study. BMC Infect Dis. 2013;13:564.
37. Kahesa C, Mwaiselage J, Wabinga HR, Ngoma T, Kalyango JN, Karamagi CA. Association between invasive cancer of the cervix and HIV-1 infection in Tanzania: the need for dual screening. BMC Public Health. 2008;8:262.
38. Kalima M, Lishimpi K, Meza JL, Watanabe-Galloway S, Msadabwe SC, Mwaba CK, et al. Observed and expected incidence of cervical cancer in lusaka and the southern and Western provinces of Zambia, 2007 to 2012. Int J Gynecol Cancer. 2015;25(1):98-105.
39. Kang M, Cu-Uvin S. Association of HIV viral load and CD4 cell count with human papillomavirus detection and clearance in HIV-infected women initiating highly active antiretroviral therapy. HIV Med. 2012;13(6):372-8.
40. Kelly HA, Ngou J, Chikandiwa A, Sawadogo B, Gilham C, Omar T, et al. Associations of Human Papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa. PLoS One. 2017;12(3):e0174117.
41. Kim T, Lee K, Lee Y, Lim K, Lee I, Kim M, et al. The risk factors and rate for progression of cervical intraepithelial lesions in HPV 16 or 18 infected women with ASCUS or lsil within one year. Int J Gynecol Cancer. 2015;25(9):840.
42. Kirby TO, Allen ME, Alvarez RD, Hoesley CJ, Huh WK. High-risk human papillomavirus and cervical intraepithelial neoplasia at time of atypical squamous cells of undetermined significance cytologic results in a population with human immunodeficiency virus. J Low Genit Tract Dis. 2004;8(4):298-303.
43. Konopnicki D, Manigart Y, Gilles C, Barlow P, de Marchin J, Feoli F, et al. Sustained viral suppression and higher CD4+ T-cell count reduces the risk of persistent cervical high-risk human papillomavirus infection in HIV-positive women. J Infect Dis. 2013;207(11):1723-9.
44. Koshiol J, Schroeder J, Jamieson DJ, Marshall SW, Duerr A, Heilig CM, et al. Smoking and time to clearance of human papillomavirus infection in HIV-seropositive and HIV-seronegative women. Am J Epidemiol. 2006;164(2):176-83.
45. Kravchenko J, Akushevich I, Sudenga SL, Wilson CM, Levitan EB, Shrestha S. Transitional probability-based model for HPV clearance in HIV-1-positive adolescent females. PLoS One. 2012;7(1):e30736.
46. Lehtovirta P, Paavonen J, Heikinheimo O. Risk factors, diagnosis and prognosis of cervical intraepithelial neoplasia among HIV-infected women. Int J STD AIDS. 2008;19(1):37-41.
47. Lofgren SM, Tadros T, Herring-Bailey G, Birdsong G, Mosunjac M, Flowers L, et al. Progression and regression of cervical pap test lesions in an urban AIDS clinic in the combined antiretroviral therapy era: A longitudinal, retrospective study. AIDS Res Hum Retroviruses. 2015;31(5):508-13.
48. Massad LS, Xie X, D'Souza G, Darragh TM, Minkoff H, Wright R, et al. Incidence of cervical precancers among HIV-seropositive women. Am J Obstet Gynecol. 2015;212(5):606.e1-8.
49. Minkoff H, Ahdieh L, Massad LS, Anastos K, Watts DH, Melnick S, et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. AIDS. 2001;15(16):2157-64.

50. Minkoff H, Feldman J, DeHovitz J, Landesman S, Burk R. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. Am J Obstet Gynecol. 1998;178(5):982-6.
51. Minkoff H, Feldman JG, Strickler HD, Watts DH, Bacon MC, Levine A, et al. Relationship between smoking and human papillomavirus infections in HIV-infected and -uninfected women. J Infect Dis. 2004;189(10):1821-8.
52. Montejano R, Arribas JR, Bernardino JI, Martin-Carbonero L, Montes ML, Moreno V, et al. A descriptive study of cancer incidence in a cohort of HIVinfected patients followed since 1986. J Int AIDS Soc. 2016;19:148-9.
53. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu JH, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. J Infect Dis. 2004;190(8):1413-21.
54. Mwakigonja AR, Torres LM, Mwakyoma HA, Kaaya EE. Cervical cytological changes in HIV-infected patients attending care and treatment clinic at Muhimbili National Hospital, Dar es Salaam, Tanzania. Infect Agent Cancer. 2012;7:3.
55. Odida M, Sandin S, Mirembe F, Kleter B, Quint W, Weiderpass E. HPV types, HIV and invasive cervical carcinoma risk in Kampala, Uganda: A case-control study. Infect Agent Cancer. 2011;6(1).
56. Olaitan A, Mocroft A, McCarthy K, Phillips A, Reid W, Johnson M. Cervical abnormality and sexually transmitted disease screening in human immunodeficiency virus-positive women. Obstet Gynecol. 1997;89(1):71-5.
57. Paramsothy P, Jamieson DJ, Heilig CM, Schuman PC, Klein RS, Shah KV, et al. The effect of highly active antiretroviral therapy on human papillomavirus clearance and cervical cytology. Obstet Gynecol. 2009;113(1):26-31.
58. Parkin DM, Nambooze S, Wabwire-Mangen F, Wabinga HR. Changing cancer incidence in Kampala, Uganda, 1991-2006. Int J Cancer. 2010;126(5):1187-95.
59. Patrelli TS, Gizzo S, Peri F, Franchi L, Volpi L, Esposito F, et al. Impact of Highly Active Antiretroviral Therapy on the Natural History of Cervical Precancerous Lesions: A 17-Year Institutional Longitudinal Cohort Study. Reprod Sci. 2013;21(7):837-45.
60. Patrelli TS, Gizzo S, Peri F, Franchi L, Volpi L, Esposito F, et al. Impact of highly active antiretroviral therapy on the natural history of cervical precancerous lesions: A 17-year institutional longitudinal cohort study. Reprod Sci. 2014;21(7):837-45.
61. Pavan MVS, Teja MP, Sree AD, Babu KM, Sriharsha M, Babu SC, et al. Prevalance and incidence of most common communicable diseases in ART patients. International Journal of Research and Development in Pharmacy and Life Sciences. 2015;4(4):1641-6.
62. Perksanusak T, Sananpanichkul P, Chirdchim W, Bhamarapravatana K, Suwannarurk K. Colposcopy Requirement of Papanicolaou Smear after Atypical Squamous Cells of Undetermined Significance (ASC-US) by Follow-up Protocol in an Urban Gynaecology Clinic, a Retrospective Study in Thailand. Asian Pac J Cancer Prev. 2015;16(12):4977-80.
63. Petry KU, Scheffel D, Bode U, Gabrysiak T, Kochel H, Kupsch E, et al. Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions. Int J Cancer. 1994;57(6):836-40.
64. Robinson WR, Luck MB, Kendall MA, Darragh TM. The predictive value of cytologic testing in women with the human immunodeficiency virus who have low-grade squamous cervical lesions: a substudy of a randomized, phase III chemoprevention trial. Am J Obstet Gynecol. 2003;188(4):896-900.
65. Rohner E, Bütikofer L, Maskew M, Chen YMA, Friedman R, G DS, et al. Global burden of cervical cancer in HIV-positive women on antiretroviral therapy. Top Antivir Med. 2016;24(E-1):251.

66. Rowhani-Rahbar A, Hawes SE, Sow PS, Toure P, Feng Q, Dem A, et al. The impact of HIV status and type on the clearance of human papillomavirus infection among Senegalese women. J Infect Dis. 2007;196(6):887-94.
67. Ruche Gl, Leroy V, Mensah-Ado I, Ramon R, You B, Bergeron C, et al. Short-term follow up of cervical squamous intraepithelial lesions associated with HIV and human papillomavirus infections in Africa. Int J STD AIDS. 1999;10(6):363-8.
68. Samuel M, Bailey A, Hoey M, Campbell L, Taylor C. Grade of cervical intraepithelial neoplasia (CIN) is not related to the degree of immunosuppression in a multi-ethnic cohort of HIV-infected women undergoing colposcopy. HIV Med. 2009;10:24.
69. Schuman P, Ohmit SE, Klein RS, Duerr A, Cu-Uvin S, Jamieson DJ, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. J Infect Dis. 2003;188(1):128-36.
70. Singh N, Bansal B, Singh U, Qureshi S, Tripathi AK. Comparative study of preinvasive and invasive lesions of the cervix in HIV-positive and HIV-negative women. Clinical Cancer Investigation Journal. 2015;4(1):39-42.
71. So KA, Kim MJ, Lee KH, Lee IH, Kim MK, Lee YK, et al. The impact of high-risk HPV genotypes other than HPV 16/18 on the natural course of abnormal cervical cytology: A Korean HPV cohort study original article purpose. Cancer Res Treat. 2016;48(4):1313-20.
72. Suardi E, Bai F, Comi L, Pandolfo A, Rovati M, Barco A, et al. Factors associated with HPV-DNA clearance in a cohort of HIV-positive patients: Role of cART and gender. J Int AIDS Soc. 2014;17(4):142.
73. Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC, Jr. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med. 1997;337(19):1343-9.
74. Syrjänen K, Shabalova I, Naud P, Kozachenko V, Derchain S, Zakharchenko S, et al. Risk estimates for persistent high-risk human papillomavirus infections as surrogate endpoints of progressive cervical disease critically depend on reference category: analysis of the combined prospective cohort of the New Independent States of the Former Soviet Union and Latin American Screening Studies. Int J STD AIDS. 2011;22(6):315-23.
75. Thorsteinsson K, Storgaard M, Katzenstein TL, Ladelund S, Ronsholt FF, Johansen IS, et al. Prevalence and distribution of cervical high-risk human papillomavirus and cytological abnormalities in women living with HIV in Denmark - the SHADE. BMC Cancer. 2016;16(1):866.
76. Van Doornum GJ, Prins M, Juffermans LH, Hooykaas C, van den Hoek JA, Coutinho RA, et al. Regional distribution and incidence of human papillomavirus infections among heterosexual men and women with multiple sexual partners: a prospective study. Genitourin Med. 1994;70(4):240-6.
77. Vernon SD, Reeves WC, Clancy KA, Laga M, St Louis M, Gary HE, Jr., et al. A longitudinal study of human papillomavirus DNA detection in human immunodeficiency virus type 1-seropositive and -seronegative women. J Infect Dis. 1994;169(5):1108-12.
78. Videla S, Darwich L, Canadas MP, Paredes R, Tarrats A, Castella E, et al. Epidemiological data of different human papillomavirus genotypes in cervical specimens of HIV-1-infected women without history of cervical pathology. J Acquir Immune Defic Syndr. 2009;50(2):168-75.
79. de Vuyst H, Alemany L, Lacey C, Chibwesha CJ, Sahasrabuddhe V, Banura C, et al. The burden of human papillomavirus infections and related diseases in sub-Saharan Africa. Vaccine. 2013;31(Suppl. 5):F32-F46.

80. Yamada R, Sasagawa T, Kirumbi LW, Kingoro A, Karanja DK, Kiptoo M, et al. Human papillomavirus infection and cervical abnormalities in Nairobi, Kenya, an area with a high prevalence of human immunodeficiency virus infection. J Med Virol. 2008;80(5):847-55.
81. Zhang YX, Xiong Y, Gui XE, Rong YP, Cai HB, Ma L. [Analysis of cervical HPV infection in HIV positive Chinese women]. Zhonghua Fu Chan Ke Za Zhi. 2012;47(3):185-90.

**Supplemental appendix 2: Technical details for the mathematical model in Chapter 4**

## I. Model overview

The deterministic, compartmental model was parameterized to represent transmission and progression of HIV and oncogenic human papillomavirus (or high-risk HPV (hrHPV)) in Kenya, which has an HIV prevalence of 4.5% in 2019.[16] The model was adapted from a previously published model fitted to KwaZulu-Natal, South Africa.[26] The primary objective of the current modeling study is to evaluate population-level impact of HPV vaccination on cervical cancer outcomes, while taking into account the changing HIV epidemiology and scaling-up of HIV prevention in Kenya.

Because the data we use to inform the model are not stratified by gender modality, our model population represents a primarily cisgender, heterosexual population in Kenya. Men and women infected with hrHPV may clear the infection, and infections in women may progress through stages of precancerous lesions to cervical cancer (Figure S1). HIV progression is tracked by CD4+ cell count and HIV RNA concentration (viral load), and infected individuals may achieve viral suppression with antiretroviral therapy (ART) beginning in 2005 (Figure S1). A key feature of our model is representation of the bidirectional interactions between HIV and HPV, whereby HIV infection increases the probability of HPV acquisition and the rate of disease progression and HPV infection increases the probability of HIV acquisition. We calibrate the model to fit to HIV, HPV, and cervical cancer epidemiology in Kenya.

Model dynamics are governed by a system of differential equations that are solved in MATLAB using a $4^{th}$-order Runge-Kutta numerical method. The model simulates events in discrete time with two-month intervals. At each time step, differential equations are evaluated to estimate the number of persons in each demographic, infection, disease, or treatment compartment for the following time step. The dynamic nature of our transmission model captures population-level effects such as herd immunity.

This work was facilitated through the use of advanced computational, storage, and networking infrastructure provided by the Hyak supercomputer system at the University of Washington.

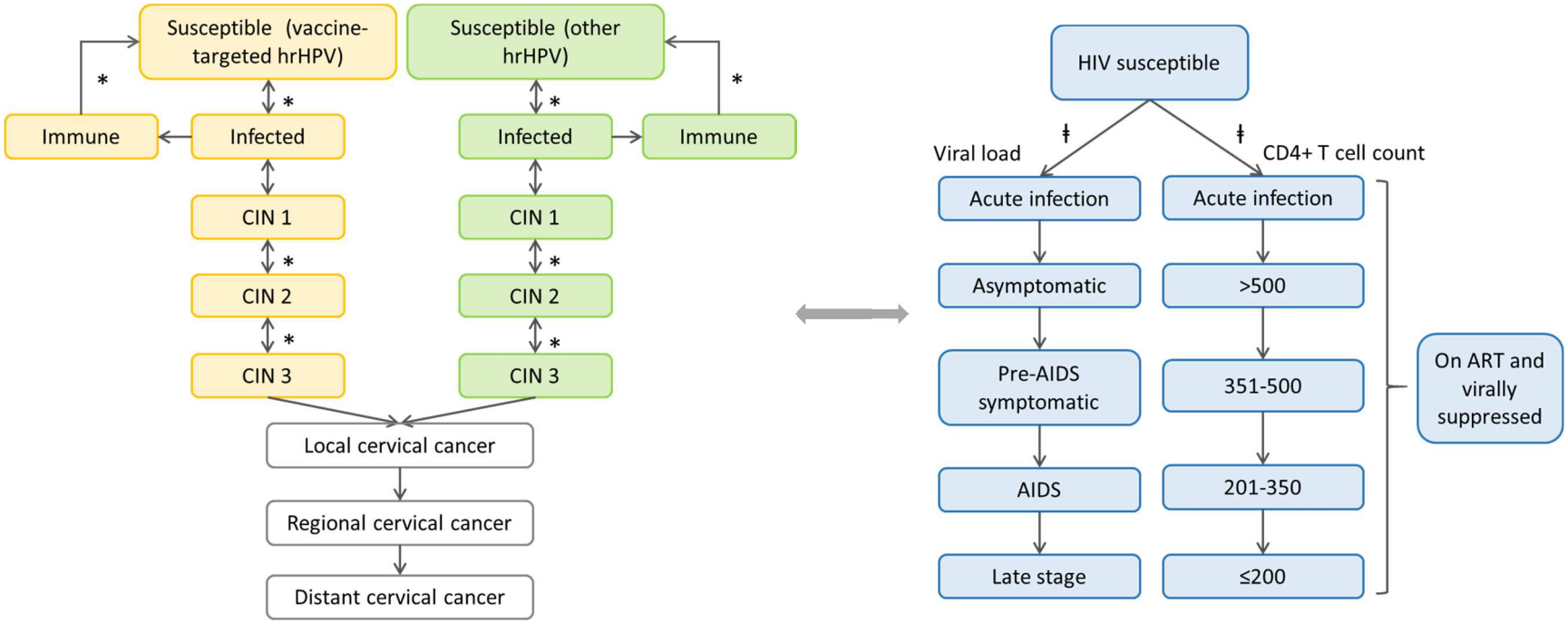



**Figure S1.** Model schematic illustrating HPV progression and HIV progression. We model HPV infection with high-risk HPV (hrHPV) types targeted by HPV vaccines (HPV 16, 18, 31, 33, 45, 52, and 58) and other high risk, non-vaccine targeted types (HPV 35, 39, 51, 56, 59 and 68). Arrows with * indicate processes that are affected by HIV infection, and arrows with ǂ indicated processes affected by HPV infection.

**II. Modules and parameter values**

a. Demography

We model a dynamic, open population of males and females aged 0 to 79 in Kenya in 5-year age groups. To allow HPV transmission dynamics and cervical cancer to equilibrate before introducing HIV in 1980, we initialize the model in 1925. The sex- and age-specific distribution of our initial population in 1925 is based data from United Nations Population Division (UNPD), which estimates Kenya population by sex and age starting in 1950.[141] We fit exponential distributions for each sex and age group to extrapolate backwards to 1925 (Table S1).

At each two-month time step, the model calculates the number of births and deaths based on fertility and mortality rate inputs. The initial fertility rates are based on UNPD-estimated rates for 1960.[141] We then scale down fertility rates to produce population distributions consistent with UNPD estimates from 1950-2020 as well as Kenya Census data from 2009 and 2019.[141,193,194] We assume fertility rates for women living with HIV (WLHIV) with CD4 count of <500 cells/mm$^3$ are 0.41-0.58 of women without HIV and the rates for WLHIV on ART or had CD4 >500 cells/mm3 are the same as women without HIV (Table S2).[195,196] We further scale down fertility rates after 2020 to fit projected population estimates.

To age the population, one-fifth of each compartment moves to the next age group annually. Persons leave the population due to death or aging past 79. To model deaths, we apply age- and sex-specific mortality rates estimated by UNPD (Table S3).[141] We assume linear changes in rates between 1950, 1985, 2010, and 2020, which are the years for which rates are available. After initializing HIV in 1980, we model background and HIV-specific mortality separately. To estimate background mortality rates not related to HIV, we subtract HIV-specific mortality[197,198] from UNPD-estimated mortality rates.

**Table S1. Initial population size.** The population distribution by sex and 5-year age groups is projected backward from UNPD estimates for Kenya in 1950.

| Age Group | Initial Population Size | | Source |
|---|---|---|---|
| | **Male** | **Female** | UNPD[141] |

| | | |
|---|---|---|
| **0 – 4** | 237966 | 240166 |
| **5 – 9** | 143534 | 145291 |
| **10 – 14** | 110242 | 110999 |
| **15 – 19** | 99096 | 97339 |
| **20 – 24** | 91121 | 86235 |
| **25 – 29** | 84685 | 75947 |
| **30 – 39** | 80170 | 68470 |
| **35 – 39** | 78914 | 63502 |
| **40 – 44** | 79282 | 61809 |
| **45 – 49** | 76761 | 63348 |
| **50 – 54** | 68455 | 62295 |
| **55 – 59** | 52798 | 53896 |
| **60 – 64** | 39427 | 45400 |
| **65 – 69** | 27875 | 36647 |
| **70 – 74** | 16553 | 25006 |
| **75 – 79** | 7905 | 14683 |
| **TOTAL** | **1294783** | **1251034** |

**Table S2. Baseline fertility rates per 1000 women by age.** These fertility rates are applied from 1925-1970, then scaled down thereafter. Age groups not shown in this table have fertility rates of 0.

| Age Group | HIV Uninfected | Source |
|---|---|---|
| **15 – 19** | 0.182 | |
| **20 – 24** | 0.379 | |
| **25 – 29** | 0.365 | |
| **30 – 34** | 0.306 | UNPD[141] |
| **35 – 39** | 0.219 | |
| **40 – 44** | 0.119 | |
| **45 – 49** | 0.042 | |

**Table S3. UNPD-estimated age- and sex-specific background mortality rates for 1950, 1985, 2000, and 2020.[141]** We assume linear changes in background mortality between the years. These rates do not include deaths caused by HIV, which are estimated separately.

| | 1925-1950 | | By 1985 | | By 2000 | | By 2020 | | Source |
|---|---|---|---|---|---|---|---|---|---|
| **Age Group** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | |
| **0 – 4** | 0.103 | 0.088 | 0.047 | 0.040 | 0.071 | 0.062 | 0.036 | 0.027 | |
| **5 – 9** | 0.009 | 0.009 | 0.003 | 0.002 | 0.004 | 0.003 | 0.001 | 0.001 | |
| **10 – 14** | 0.005 | 0.005 | 0.002 | 0.002 | 0.003 | 0.002 | 0.001 | 0.001 | |
| **15 – 19** | 0.006 | 0.006 | 0.003 | 0.002 | 0.004 | 0.003 | 0.001 | 0.001 | |
| **20 – 24** | 0.009 | 0.007 | 0.004 | 0.003 | 0.006 | 0.005 | 0.002 | 0.001 | UNPD[141] |
| **25 – 29** | 0.010 | 0.008 | 0.005 | 0.004 | 0.009 | 0.009 | 0.003 | 0.002 | |
| **30 – 34** | 0.011 | 0.009 | 0.006 | 0.005 | 0.012 | 0.012 | 0.004 | 0.003 | |
| **35 – 39** | 0.012 | 0.010 | 0.007 | 0.006 | 0.016 | 0.016 | 0.005 | 0.004 | |
| **40 – 44** | 0.014 | 0.012 | 0.009 | 0.007 | 0.019 | 0.017 | 0.007 | 0.005 | |
| **45 – 49** | 0.016 | 0.013 | 0.011 | 0.008 | 0.023 | 0.018 | 0.009 | 0.006 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **50 – 54** | 0.020 | 0.016 | 0.015 | 0.010 | 0.027 | 0.019 | 0.012 | 0.008 |
| **55 – 59** | 0.025 | 0.020 | 0.019 | 0.013 | 0.033 | 0.022 | 0.016 | 0.010 |
| **60 - 64** | 0.035 | 0.030 | 0.028 | 0.020 | 0.044 | 0.028 | 0.024 | 0.015 |
| **65- 69** | 0.050 | 0.045 | 0.042 | 0.032 | 0.061 | 0.040 | 0.036 | 0.024 |
| **70 - 74** | 0.075 | 0.071 | 0.066 | 0.054 | 0.091 | 0.061 | 0.056 | 0.039 |
| **75 - 79** | 0.116 | 0.110 | 0.108 | 0.091 | 0.138 | 0.096 | 0.089 | 0.066 |

b. Sexual behavior

In our model, sexual activity begins in the 10-14 age group. In each sexually active age group, we divide the population into low-, medium-, or high-risk groups with variable rates of partnership formation. The distribution of these risk groups by sex and age is based on self-reported sexual behaviors data from 15-54 year old respondents in the 2014 Kenya Demographic and Health Survey (DHS),[199] and is calculated as the percentage of the cohort who reported 0-1 partner (low risk), 2-4 partners (moderate risk), or ≥5 partners (high risk) in the past year. We then calibrate risk group distribution for ages 15-54 to fit to observed HIV and HPV data. Individuals aged 10-14 are assumed to be predominately low risk, while the risk distribution for ages 55 and older is extrapolated from the 50-54 age group (Table S4).

Similarly, while the initial sexual partnership inputs are based the 2014 Kenya DHS data,[199] we calibrate the yearly partner change rates in each risk group by sex and age to fit to observed disease data (Table S5). This approach partially compensates for reporting biases and the lack of partnership concurrency in our model. Our compartmental model structure is not equipped to represent concurrent partnerships. Therefore using the number of sex partners as reported would underestimate the rate of HPV and HIV transmission.

Using methods similar to other models, patterns of sexual contact in our model are characterized by age and sexual risk groups.[200] The degree of mixing is defined by the parameter, $\epsilon$ ($\epsilon_\alpha$ for mixing by age and $\epsilon_r$ for mixing by risk group), which ranged from 0, indicating completely assortative (like-with-like), to 1, indicating random mixing that is proportional to compartment size. Based on studies that show

that Kenyan women are on average 4-7 years younger than their male partners,[201] we assume an age mixing matrix with $\epsilon_\alpha = 0.2$. For mixing by risk group, we assume $\epsilon_r = 0.3$.

Because we model heterosexual contact with no concurrency, the modeled number of partnerships must be the same for men and women. However, the observed data we used to inform these parameters are subject to selection and response biases, resulting in imbalances. To correct this, we adjust contact rates such that the number of partners for men in a given age and risk group equals the number of partners for women in the same age and risk groups.

**Table S4. Proportion of individuals in low, medium, and high risk groups by sex and age.** The risk group distribution for those older than 55 is extrapolated from the 50-54 age group.

| | Males | | | Females | | | Source |
|---|---|---|---|---|---|---|---|
| **Age Group** | **Low-Risk** | **Medium-Risk** | **High-Risk** | **Low-Risk** | **Medium-Risk** | **High-Risk** | |
| **10 – 14** | 0.972 | 0.026 | 0.002 | 0.972 | 0.026 | 0.002 | |
| **15 – 19** | 0.779 | 0.216 | 0.004 | 0.757 | 0.234 | 0.009 | |
| **20 – 24** | 0.564 | 0.424 | 0.012 | 0.595 | 0.377 | 0.028 | |
| **25 – 29** | 0.611 | 0.365 | 0.023 | 0.635 | 0.354 | 0.010 | 2014 Kenya DHS[199] |
| **30 – 34** | 0.656 | 0.331 | 0.013 | 0.689 | 0.301 | 0.010 | / calibrated |
| **35 – 39** | 0.717 | 0.275 | 0.008 | 0.730 | 0.263 | 0.007 | |
| **40 – 44** | 0.732 | 0.262 | 0.006 | 0.781 | 0.213 | 0.005 | |
| **45 – 49** | 0.807 | 0.188 | 0.005 | 0.826 | 0.169 | 0.005 | |
| **50 – 54** | 0.891 | 0.106 | 0.004 | 0.891 | 0.106 | 0.004 | |
| **55 – 79** | 0.891 | 0.106 | 0.004 | 0.891 | 0.106 | 0.004 | |

**Table S5. Average number of partners in each risk group by sex and age.** Estimates for those older than 55 is extrapolated from the 55-60 age group.

| | Males | | | Females | | | Source |
|---|---|---|---|---|---|---|---|
| **Age Group** | **Low-Risk** | **Medium-Risk** | **High-Risk** | **Low-Risk** | **Medium-Risk** | **High-Risk** | |
| **10 – 14** | 0.03 | 0.00 | 0.00 | 0.03 | 0.01 | 0.00 | |
| **15 – 19** | 0.23 | 2.45 | 5.41 | 0.50 | 2.45 | 6.41 | |
| **20 – 24** | 0.87 | 2.58 | 9.78 | 0.87 | 2.58 | 11.08 | |
| **25 – 29** | 0.87 | 2.33 | 11.10 | 0.90 | 2.33 | 10.15 | 2014 Kenya DHS[199] |
| **30 – 34** | 0.93 | 2.11 | 10.15 | 0.95 | 2.11 | 9.76 | / calibrated |
| **35 – 39** | 0.93 | 2.08 | 9.67 | 0.93 | 2.08 | 9.67 | |
| **40 – 44** | 0.93 | 2.06 | 8.28 | 0.93 | 2.06 | 8.28 | |
| **45 – 49** | 0.93 | 2.00 | 7.35 | 0.93 | 2.00 | 7.35 | |
| **50 – 54** | 0.92 | 1.90 | 7.03 | 0.92 | 1.90 | 7.03 | |
| **55 – 79** | 0.92 | 1.85 | 2.50 | 0.92 | 1.85 | 2.50 | |

c. Natural history

*i. HIV*

HIV begins in 1980 in our model with an initial prevalence of 0.5% in ages 15-54 and 0.2% in other age groups. HIV infection occurs either through mother-to-child transmission or heterosexual contact. We model mother-to-child transmission rates that decrease over time to reflect improvements in services for pregnant women living with HIV (Table S6).[202,203] The force of HIV infection is estimated as a function of sexual mixing (by age and sexual risk group), HIV prevalence in the opposite sex, male circumcision, and HIV viral load. The risk of HIV transmission is highest during the acute stage of infection. Risk decreases during the asymptomatic phase of HIV infection before increasing in the pre-AIDS symptomatic and AIDS stages.[204-207] We base HIV transmission per act in the asymptomatic stage on literature[57] and apply risk multipliers across the other stages of infection (Tables S6). We assume male-to-female transmission probability is equal to female-to male transmission probability across all viral load stages. As a proxy for decreased sexual activity due to advanced disease during late-stage HIV, we reduce HIV per-act transmission to be 10% of the AIDS rate.[207] We assume that women with an HPV infection have between 1.6-2.2 times higher risk of acquiring HIV.[19,20]

The transition rates between CD4 count stages and viral load stages are based on literature describing the average duration in each CD4 and viral load stage by sex and age (Tables S7).[205,208-210] Individuals can go on ART when this intervention is introduced in the model in 2005. We assume that people on ART are virally suppressed. HIV-associated mortality rates with untreated HIV are estimated from studies of untreated persons living with HIV and depend on CD4 cell count and age (Table S8).[198,211,212] As a results of these combination of disease progression and mortality rates, untreated women have a longer average life expectancy than untreated men. In addition, children under five have the highest HIV-specific mortality, and adults >50 years have HIV mortality rates two times that of persons aged 5-

49.[197,213] HIV-associated mortality for people on ART treatment is relative to background mortality, and decreases over time to reflect improvement in baseline health among persons initiating treatment.[214-216] From 2004 to 2011, HIV-associated mortality among people with HIV on ART is 1.5 times the background rate. This rate decreases to 1.4, 1.25, and 1.15 times the background mortality rate in 2011, 2015, and 2016, respectively.

**Table S6. Annual HIV transmission rates by route of transmission.**

| Route | Value | Risk multipliers by viral load stages | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | | Acute | Asymptomatic | Pre-AIDS symptomatic | AIDS | Late-stage | |
| **Mother to child** | | | | | | | |
| Before 2004 | 0.42 | | | | | | |
| By 2007 | 0.32 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 202,203 |
| By 2013 | 0.20 | | | | | | |
| **Sexual contact** | 0.0008-0.0012 | 9.0 | 1.0 | 2.5 | 7.0 | 0.7 | 57,204-207,217 |

**Table S7. Average duration of time (in years) spent in each CD4 stage and viral load stage with untreated HIV by sex and age.** We estimate time in the asymptomatic stage such that the total time spent in all viral load stages matches the total time spent in CD4 stages.

| HIV states | Males | | | Females | | | Reference |
|---|---|---|---|---|---|---|---|
| | 0-4 | 5-49 | 50-79 | 0-4 | 5-49 | 50-79 | |
| **CD4 counts** | | | | | | | |
| Acute | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 208,210 |
| ≥501 | 0.25 | 0.25 | 0.25 | 0.93 | 0.93 | 0.29 | |
| 351-500 | 3.56 | 3.56 | 2.85 | 3.71 | 3.71 | 3.34 | |
| 201-350 | 4.67 | 4.67 | 4.51 | 4.68 | 4.68 | 4.23 | |
| ≤200 | 2.13 | 3.70 | 1.85 | 2.13 | 3.70 | 1.85 | |
| **Viral load** | | | | | | | |
| Acute | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 205,209 |
| Asymptomatic | 5.87 | 6.60 | 3.88 | 5.87 | 7.44 | 4.13 | |
| Pre-AIDS symptomatic | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | |
| AIDS | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | |
| Late-stage | 0.83 | 0.83 | 0.83 | 0.83 | 0.83 | 0.83 | |

**Table S8. HIV-specific mortality by CD4 cell count and age.**

| Age Group | Acute | CD4 ≥500 | CD4 350-500 | CD4 200-350 | CD4 ≤200 | Reference |
|---|---|---|---|---|---|---|
| **0 – 4** | 0 | 0.4700 | 0.4700 | 0.4700 | 0.4700 | 197,198,211-213 |
| **5 – 49** | 0 | 0.0035 | 0.0255 | 0.0455 | 0.2655 | |
| **50 – 79** | 0 | 0.0071 | 0.0511 | 0.0911 | 0.5311 | |

*ii. HPV*

The model simulation begins in 1925 with an initial HPV prevalence of 20% among 15-44 year-old men and women. Because we are primarily interested in cervical cancer outcomes, our model represents infection with the HPV types classified as high risk, or oncogenic, by the International Agency for Research on Cancer.[40] Infections are due to either vaccine-targeted hrHPV types (HPV 16, 18, 31, 33, 45, 52, and 58) or non-vaccine-targeted hrHPV types (HPV 35, 39, 51, 56, 59 and 68). Per-coital HPV transmission probability is based on literature[56] then calibrated (Table S9). We assume that transmission probability of non-vaccine-targeted HPV type is higher than vaccine-targeted HPV type to reproduce type distribution of HPV infections in sub-Saharan Africa.[218,219] HPV transmission among women with regional or distant cervical cancer is reduced by 50%. We set that male-to-female and female-to-male transmission probabilities to be equal. However, we assume that men do not develop natural immunity.[220] Women develop partial immunity against reinfection with the same HPV type group (vaccine-type or non-vaccine type) that wanes at an annual rate of 0.024 (Table S9).[221] In our model, women with persistent HPV infection can progress to precancerous lesions (represented as cervical intraepithelial neoplasia (CIN) grades 1, 2, or 3) and cervical cancer (categorized as local, regional, or distant) as shown in Figure S1. CIN 1, 2, and 3 can regress and HPV infection can clear naturally. CIN progression and regression rates were based on data previously described by Tan et al. (Supplement Table S23).[26] The transition rates were defined separately for HPV 16, 18, and other high-risk types. The original data used by Tan et al included additional transitional states. We reweighted transitions by types and consolidated transitions to better match our current HPV type grouping and natural history structure. For reweighting purposes, we assumed the type distribution of CIN2 to be the average of the type distributions for low-grade and high-grade lesions. After the reweighting, transition rates for each infection type (vaccine-targeted or non-vaccine-targeted) are manually calibrated (Table S9).

Individuals with HIV have higher rates of HPV acquisition, immunity waning, and disease progression, and lower rates of HPV clearance and CIN regression.[133] The effect size of HIV on HPV natural history is inversely correlated with CD4 cell count and is represented by risk multipliers on HPV infection acquisition and clearance and CIN progression or regression in HIV-negative women. The risk multipliers are initially based on literature then calibrated to fit to observed data (Table S9). Women on ART have lower risk of HPV infection and cervical precancer lesions compared to untreated women living with HIV and similar HPV prevalence compared to women without HIV.[222,223] However, sub-Saharan Africa women living with HIV continue to have elevated cancer incidence rates despite being on ART.[34,128] Based on these data, we assume women on treatment and virally suppressed have HPV acquisition and disease progression rates comparable to HIV-negative women, but HPV clearance, disease regression rates, and cervical cancer-associated mortality are equivalent to untreated women with high (>500) CD4 count. WLHIV also have higher cervical cancer-associated mortality rates than HIV-negative women,[224] with the mortality rates increasing with decreasing CD4 count (Table S10).[65] The effect of HIV on mortality decreases as cervical cancer progresses.[65]

Because the model does not track infection duration, we use age multipliers as proxies for HPV persistence. The multipliers are applied to both HPV types and scaled up linearly across each age grouping (Table S11). The age multipliers are based on those previously described by Tan et al., 2018 in Supplement Table S25.[26] The multiplier values are the average of the vaccine-type and non-vaccine-type relative risks after rate adjustment.

**Table S9. HPV-related transition rates per year.** Multipliers are relative risks of transitioning between HPV states for women with HIV compared to women without HIV, and depended on CD4 count and ART status. To capture uncertainty related to the values of select influential parameters, we let the probability of vaccine-targeted HPV transmission vary within a range.

| Parameter description | Without HIV | | Multipliers with HIV | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Value | Reference | On ART | CD4 ≥500 | CD4 350-500 | CD4 200-350 | CD4 ≤200 | Reference |
| **Per-partner transmission probability** | | | | | | | | |
| Vaccine-targeted | 0.008-0.014 | [56], calibrated | 1 | 2.14 | 2.39 | 2.54 | 2.78 | [20,225], calibrated |
| Non-vaccine-targeted | 0.016 | Calibrated | | | | | | |
| **HPV to CIN 1** | | | | | | | | |
| Vaccine-targeted | 0.586 | Calibrated | NA | NA | NA | NA | NA | |
| Non-vaccine-targeted | 0.266 | Calibrated | | | | | | |
| **CIN 1 to CIN 2** | | | | | | | | |
| Vaccine-targeted | 0.182 | Calibrated | 1 | 1.05 | 1.47 | 1.89 | 2.31 | Calibrated |
| Non-vaccine-targeted | 0.065 | Calibrated | | | | | | |
| **CIN 2 to CIN 3** | | | | | | | | |
| Vaccine-targeted | 0.169 | Calibrated | 1 | 1 | 1.1 | 1.2 | 1.4 | Calibrated |
| Non-vaccine-targeted | 0.076 | Calibrated | | | | | | |
| **CIN3 to local cancer** | | | | | | | | |
| Vaccine-targeted | 0.002 | Calibrated | NA | NA | NA | NA | NA | |
| Non-vaccine-targeted | 0.001 | Calibrated | | | | | | |
| **Local to regional cancer** | 0.020 | [226] | | | | | | |
| **Regional to distant cancer** | 0.025 | [226] | | | | | | |
| **HPV to immune in women** | | | | | | | | |
| Vaccine-targeted | 1.772 | Calibrated | 0.6 | 0.6 | 0.55 | 0.45 | 0.30 | Calibrated |
| Non-vaccine-targeted | 1.768 | Calibrated | | | | | | |
| **HPV to susceptible in men** | | | | | | | | |
| Vaccine-targeted | 1.238 | Calibrated | 0.6 | 0.6 | 0.55 | 0.45 | 0.30 | Calibrated |
| Non-vaccine-targeted | 1.241 | Calibrated | | | | | | |
| **CIN 1 to HPV** | | | | | | | | |
| Vaccine-targeted | 0.360 | Calibrated | 0.6 | 0.6 | 0.55 | 0.45 | 0.30 | Calibrated |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Non-vaccine-targeted | 0.423 | Calibrated | | | | | | |
| **CIN2 to CIN 1** | | | | | | | | |
| Vaccine-targeted | 0.494 | Calibrated | 0.93 | 0.93 | 0.853 | 0.698 | 0.465 | Calibrated |
| Non-vaccine-targeted | 0.301 | Calibrated | | | | | | |
| **CIN 3 to CIN 2** | | | | | | | | |
| Vaccine-targeted | 0.102 | Calibrated | 1.02 | 1.02 | 0.935 | 0.765 | 0.51 | Calibrated |
| Non-vaccine-targeted | 0.101 | Calibrated | | | | | | |
| **Natural immunity waning** | 0.024 | [221] | 1.42 | 1.42 | 1.57 | 1.97 | 2.83 | Calibrated |
| **Natural immunity protection** | 70% | [227] | NA | NA | NA | NA | NA | |

**Table S10.** Cervical cancer-associated mortality by cancer stage and CD4 cell count among women living with HIV.

| | Local | Regional | Distant | Reference |
|---|---|---|---|---|
| **HIV uninfected** | 0.0624 | 0.1502 | 0.5207 | [65,224] |
| **HIV-positive on ART** | 0.2071 | 0.2418 | 0.5207 | |
| **CD4 ≥500** | 0.2071 | 0.2418 | 0.5207 | |
| **CD4 350-500** | 0.2515 | 0.2936 | 0.5207 | |
| **CD4 200-350** | 0.3052 | 0.3563 | 0.5207 | |
| **CD4 ≤200** | 0.4489 | 0.5240 | 0.5207 | |

**Table S11.** Age multipliers on transition rates.

| Transition rate | 25-49 | 50-69 | 70-79 | Reference |
|---|---|---|---|---|
| **HPV infection to CIN1 progression** | 0.49 | 0.35 | 0.35 | |
| **CIN1 to CIN2 progression** | 1.17 | 1.42 | 1.42 | |
| **CIN2 to CIN3 progression** | 1.79 | 2.54 | 3.04 | |
| **CIN3 to cervical cancer progression** | 10.86 | 25.72 | 30.64 | |
| **HPV infection clearance to immune (females) or susceptible (males)** | 0.79 | 0.51 | 0.45 | |
| **CIN1 to HPV infection regression** | 1.00 | 1.00 | 1.00 | |
| **CIN2 to CIN1 regression** | 1.00 | 1.00 | 1.00 | |
| **CIN3 to CIN2 regression** | 0.77 | 0.27 | 0.14 | |

d. Historical interventions

*i. HIV antiretroviral therapy (ART)*

Beginning in 2005, we model the effects of ART in populations that achieve viral suppression. People living with HIV who initiate ART without achieving viral suppression are assumed to have no benefit from treatment and are not tracked in our model. Populations in the ART/viral suppression compartment have reduced HIV-associated mortality, which also decreases over time as the average CD4 count at ART initiation increases.[214-216,228] Additionally, we assume no onward transmission of HIV with ART.[229,230] And women on ART have the same fertility rates as HIV-negative women.[196]

We define ART coverage as the percentage of all persons with HIV who are on treatment and virally suppressed. Reflecting changes in treatment eligibility policy for Kenya,[142] only people with a CD4 count ≤200 cells/μL are put on ART in 2005. The initiation threshold is subsequently raised to CD4 <250 cells/mm$^3$ in 2007, CD4 ≤350 cells/mm$^3$ in 2011, and to CD4 ≤500 cells/mm$^3$ in 2014. Finally, anyone with HIV regardless of CD4 cell count is eligible for ART from 2016 on, including those with acute infection. Our model recreates the historical ART coverages reported by the Kenya Ministry of Health.[17,231,232] However, due to treatment non-adherence and discontinuation as well as the CD4-based eligibility criteria,[233,234] the proportion of viral suppression among all people living with HIV was likely lower than the reported historical ART coverage levels, especially in the earlier ART eras. To adjust for this, we assume that 43% of people on ART are virally suppressed before 2013.[231] We increase the proportion virally suppressed among people on ART linearly from 43% to 75% between 2013-2015,[231] and from 75% to 90% from 2015 to 2018.[17] The proportions of all people with HIV who are virally suppressed in our model is listed in Table S12 and represented in Figure S2. Given the current trajectory, we assume that Kenya will achieve the Joint United Nations Programme (UNAIDS) on HIV/AIDS 90-90-90 goal to have 72.9% of all people living with HIV virally suppressed by 2030. We do not model

ART discontinuation (i.e., loss of viral suppression). As a results, the cumulative probability of being on ART increases with age.

Trends in HIV-associated mortality on treatment mirror changes to the ART initiation threshold to reflect higher baseline health among persons initiating treatment over time. HIV-associated mortality with treatment is relative to background mortality.[214-216] From 2004 to 2011, HIV-associated mortality among people with HIV on ART is 0.5 times the background rate. This rate decreases to 0.4, 0.25, and 0.15 times the background mortality rate in 2011, 2015, and 2016, respectively.

**Table S12. Proportion of persons living with HIV on ART and virally suppressed Kenya.** We derived the following estimates based on the proportion of viral suppression among people living with HIV on ART reported by the Kenyan Ministry of Health. Because data was not available for 2014, we assume a linear increase in viral suppression from 2013 to 2015. We assume that Kenya will achieve UNAIDS 90-90-90 goal by 2030.

| Year | Female | Male | Reference |
|---|---|---|---|
| **2005** | 2.9 | 2.2 | |
| **2006** | 6.6 | 4.9 | |
| **2007** | 9.2 | 6.8 | |
| **2008** | 12.5 | 9.3 | |
| **2009** | 23.0 | 19.6 | |
| **2010** | 31.4 | 26.7 | 17,232,235 |
| **2011** | 35.3 | 30.0 | |
| **2012** | 38.7 | 32.9 | |
| **2013** | 44.4 | 37.7 | |
| **2015** | 44.8 | 38.0 | |
| **2016** | 54.2 | 46.1 | |
| **2017** | 63.0 | 53.6 | |
| **2030** | 72.9 | 72.9 | |

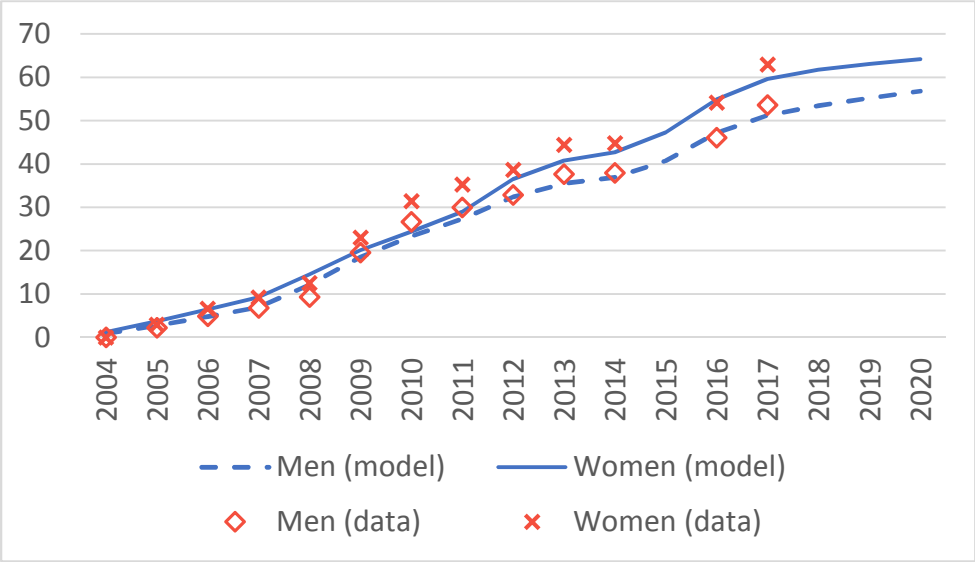



**Figure S2.** ART coverage among men and women in the model (blue), compared to observed data (red).

*ii. Condoms*

Condoms use is initiated in the model in 1995 and stabilized in 2000. Based on data from observational studies and DHS surveys, we assume the condom use varied by sexual risk group, with people in the highest risk group most likely to use condoms.[199,236,237] We specify that condom use was 12% in the low risk group, 25% in the medium risk group, and 35% in the high risk group. We assume condoms reduce HIV acquisition in both males and females by 80%.[238] However, we assume no protection against HPV acquisition with condom use.[239-242]

*iii. Circumcision*

We assume that circumcised HIV-negative men have 55% lower HIV acquisition compared to uncircumcised men,[243] however, HPV acquisition risk is not reduced.[244-247] We also assume no protective effect of circumcision against HPV infection for men with HIV.[248] In addition, while circumcision does not reduce the risk of HIV transmission to female partners,[249,250] we assume that women with circumcised, HPV-infected male partner have 23% lower risk of HPV acquisition.[251]

We model medical circumcision beginning in 1960 for 15-19 and 20-24 age groups to account for the traditional practice of male circumcision as a rite of passage for many young men in Kenya.[252] For this reason, the national prevalence of circumcision was >80% in 2003[144] before the campaigns to scale up circumcision began in 2008.[253] We adjusted the circumcision rate so that the proportion of men circumcised matches the coverage levels reported in 2003, 2008-2009, and 2014 DHS surveys (Table S13).[144,145,199] Circumcision coverage among HIV-negative men in 2000-2020 in the model is illustrated in Figure S3. The model does not track circumcision among men with HIV. We assume circumcision coverage scales up to 90% in all ages by 2030.

**Table S13. Proportion of HIV-negative men who are circumcised.**

| Year | 15-19 | 20-24 | 25-29 | 30-39 | 40-49 | Reference |
|---|---|---|---|---|---|---|
| **2003** | 71.5 | 89 | 88.3 | 89.3 | 83.7 | 144 |
| **2008** | 75.8 | 88.6 | 85.1 | 89.5 | 91.9 | 145 |
| **2014** | 87.1 | 96.5 | 94.6 | 93.4 | 91.9 | 199 |

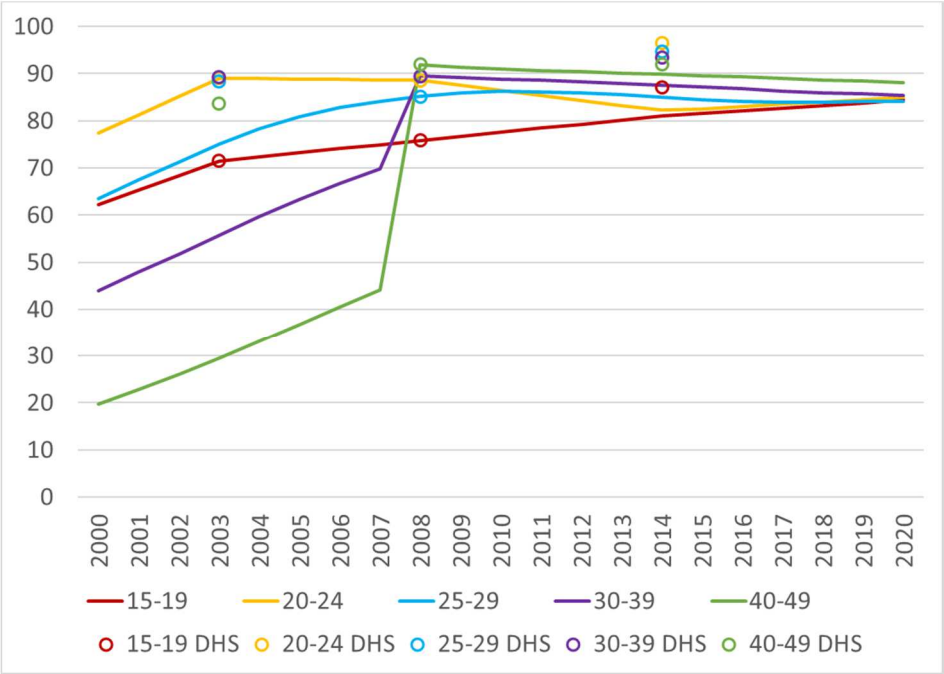



**Figure S3.** Prevalence of male circumcision among HIV-negative men in the model (lines) compared to DHS estimates for the entire Kenyan male population (circles).

*iv. HPV vaccination*

Our model was designed to evaluate the impact of the nonavalent HPV vaccine, in that we group HPV infections into vaccine-targeted types (HPV 16, 18, 31, 33, 45, 52, and 58) and other high-risk HPV types. Under this scheme, the nonavalent vaccine is 100% efficacious against infection with the vaccine-targeted types. However, the quadrivalent or the bivalent vaccine will most likely to be used in Kenya's national HPV vaccination program for the foreseeable future.[172] To estimate the impact of using the quadrivalent vaccine, we adjust the efficacy against vaccine-targeted types by a factor of (0.7/0.9), based on evidence that HPV types 16 and 18 contribute to 70% of cervical cancer cases relative to the 90% attributable to one or more of the types included in the nonavalent vaccine. In this calculation, we do not account for cross-protection against additional HPV types.[254] We assume that the vaccine provides complete, lifelong protection against covered types. The vaccine is ineffective for persons infected with a vaccine-targeted HPV types.

*v. HPV screening and treatment*

Beginning in 2000, we model once-per-lifetime cervical cancer screening for women in the age range of 35-39. Although Kenya policy during this time frame[255] recommended screening every 5 years beginning at age 30, observed data suggest low compliance with this schedule.[256] Informed by consultation with in-country experts, we conservatively assume only one lifetime screen in the model. Based on our analysis of 2014 DHS data, we assume 7.4% screening coverage in HIV-negative women and 12.3% screening coverage among women with HIV. We assume that women are screened using visual inspection with acetic acid (VIA) with a sensitivity of 62%.[257] Of the women who test positive, 72% return for triage using colposcopic biopsy.[258] Those confirmed to have CIN2-3 are treated with cryotherapy, which as an efficacy of 97% in HIV-negative women and 66% in women with HIV.[259,260] Among women confirmed to have cervical cancer after triage, 40% return for hysterectomy treatment.[258] These rates reflect challenges with

follow-up and retention for cervical cancer prevention and treatment, particularly with a multi-visit screening and treatment approach.

Additionally, evidence suggests that 28% of women treated for CIN2-3 have persistent HPV infection, including cases with residual or recurrent CIN.[261] Because this estimate is drawn from studies of primarily HIV-negative women, we used the estimate of 9% treatment failure in HIV-negative women above to calculate the percent of women who would have persistent HPV with successfully treated lesions (18.5%). Lacking data on differential HPV persistence by HIV status, we assume that HPV persistence after lesion clearance is the same among women living with HIV. Women with a successfully treated lesion who also clear HPV are assumed to develop temporary, partial immunity against reinfection with the same modeled HPV type (vaccine-targeted type vs. other hrHPV).

We assume that hysterectomy is 100% effective at treating cervical cancer. We do not account for treatment or recurrence of late-stage cancers that have spread to other organ systems. After hysterectomy, women are assumed to be infertile, unable to acquire or transmit HPV, and to have no increase in mortality due to their prior cancer status. We do not model symptomatic diagnosis of cervical cancer or treatment with other methods such as radiation or chemotherapy. We assume cervical screening and treatment are equally effective for both vaccine-targeted type and other hrHPV. For women infected with both, their disease status is determined by their most advanced HPV type.

**III. Calibration and validation**

*a. Calibration*

The initial model parameter values were based on a previously published version of the model fitted to KwaZulu-Natal, South Africa; the calibration method is discussed in detail in the supplemental appendix to the publication.[26] For this current modeling study, we manually calibrated the parameters to fit to HIV, HPV, and cervical cancer epidemiology in 2000-2020 in Kenya. Our calibration targets are listed in Table

S14. We calibrated the parameters related to demographics to match UNPD-estimated population size from 1950-2070. We based sexual behavior parameters on data reported in the 2014 Kenya DHS,[199] then calibrated these parameters to produce time and age trends in HIV and HPV prevalence that match the observed data. To calibrate sexual behaviors, we assume that people in higher risk groups have more sex partners per year but have fewer coital acts per partnership, reflecting higher partnership formation rate and shorter partnership duration. We calibrate the age-specific number of coital acts per partnership in women. We assume men aged 10-19 have the same number of acts per partnership as women, whereas men aged 20-79 have equal acts to women of the next lowest age group, reflecting age disparities in partnerships.[201]

To reflect higher transmission probability of non-vaccine-targeted types, we calibrate the HPV transmission probability for vaccine-targeted type, then we apply a multiplier on this probability to approximate the transmission probability of non-vaccine-targeted types. We adjust this multiplier so that relative distribution of types matches those observed in studies from sub-Saharan Africa (Table S15. The value for the relative risk of HIV acquisition with HPV infection is randomly selected from a uniform distribution with a minimum of 1.6 and maximum of 2.2.[19] We ran 100 iterations, and report the median and the interquartile range of outcomes.

**Table S14:** Calibration targets.

| | Year | Age | Value | Reference |
|---|---|---|---|---|
| **Total population size** | 2000 | 0-79 | 31890777 | 141 |
| | 2005 | 0-79 | 36547290 | |
| | 2010 | 0-79 | 41942714 | |
| | 2015 | 0-79 | 47765057 | |
| | 2020 | 0-79 | 53627022 | |
| | 2025 | 0-79 | 59981315 | |
| | 2030 | 0-79 | 66449655 | |
| | 2035 | 0-79 | 73026286 | |
| | 2040 | 0-79 | 79469672 | |
| | 2045 | 0-79 | 85669262 | |
| | 2050 | 0-79 | 91575092 | |
| | 2055 | 0-79 | 97174763 | |

| | | | | |
|---|---|---|---|---|
| | 2060 | 0-79 | 102398265 | |
| | 2065 | 0-79 | 107170157 | |
| | 2070 | 0-79 | 111411341 | |
| **Population age distribution, men and women combined** | 2010 | 0-9 | 0.31 | 141 |
| | | 10-19 | 0.23 | |
| | | 20-29 | 0.19 | |
| | | 30-39 | 0.12 | |
| | | 40-49 | 0.07 | |
| | | 50-59 | 0.04 | |
| | | 60-79 | 0.03 | |
| **Population age distribution, men and women combined** | 2020 | 0-9 | 0.31 | 141 |
| | | 10-19 | 0.23 | |
| | | 20-29 | 0.19 | |
| | | 30-39 | 0.12 | |
| | | 40-49 | 0.07 | |
| | | 50-59 | 0.04 | |
| | | 60-79 | 0.03 | |
| **HIV Prevalence, men** | 2003 | 15-19 | 0.004 | 144 |
| | | 20-24 | 0.024 | |
| | | 25-29 | 0.073 | |
| | | 30-34 | 0.066 | |
| | | 35-39 | 0.084 | |
| | | 40-44 | 0.088 | |
| | | 45-49 | 0.052 | |
| | | 15-49 | 0.046 | |
| | 2007 | 15-19 | 0.01 | 143 |
| | | 20-24 | 0.02 | |
| | | 25-29 | 0.07 | |
| | | 30-34 | 0.09 | |
| | | 35-39 | 0.09 | |
| | | 40-44 | 0.10 | |
| | | 45-49 | 0.06 | |
| | | 15-49 | 0.056 | |
| | 2009 | 15-19 | 0.007 | 145 |
| | | 20-24 | 0.015 | |
| | | 25-29 | 0.065 | |
| | | 30-34 | 0.068 | |
| | | 35-39 | 0.104 | |
| | | 40-44 | 0.057 | |
| | | 45-49 | 0.043 | |
| | | 15-49 | 0.046 | |
| | 2012 | 15-19 | 0.009 | 8 |
| | | 20-24 | 0.013 | |
| | | 25-29 | 0.043 | |
| | | 30-34 | 0.066 | |

| | | | | |
|---|---|---|---|---|
| | | 35-39 | 0.05 | |
| | | 40-44 | 0.081 | |
| | | 45-49 | 0.089 | |
| | | 15-49 | 0.044 | |
| **HIV prevalence, women** | 2003 | 15-19 | 0.030 | |
| | | 20-24 | 0.090 | |
| | | 25-29 | 0.129 | |
| | | 30-34 | 0.117 | 144 |
| | | 35-39 | 0.118 | |
| | | 40-44 | 0.095 | |
| | | 45-49 | 0.039 | |
| | | 15-49 | 0.087 | |
| | 2007 | 15-19 | 0.035 | |
| | | 20-24 | 0.074 | |
| | | 25-29 | 0.102 | |
| | | 30-34 | 0.133 | 143 |
| | | 35-39 | 0.112 | |
| | | 40-44 | 0.094 | |
| | | 45-49 | 0.088 | |
| | | 15-49 | 0.09 | |
| | 2009 | 15-19 | 0.03 | |
| | | 20-24 | 0.06 | |
| | | 25-29 | 0.10 | |
| | | 30-34 | 0.11 | 145 |
| | | 35-39 | 0.09 | |
| | | 40-44 | 0.14 | |
| | | 45-49 | 0.06 | |
| | | 15-49 | 0.08 | |
| | 2012 | 15-19 | 0.011 | |
| | | 20-24 | 0.046 | |
| | | 25-29 | 0.079 | |
| | | 30-34 | 0.066 | 8 |
| | | 35-39 | 0.123 | |
| | | 40-44 | 0.106 | |
| | | 45-49 | 0.107 | |
| | | 15-49 | 0.069 | |
| **HPV prevalence, HIV-negative women** | 2005 | 20-24 | 0.29 (0.25-0.52) | |
| | | 25-29 | 0.30 (0.12-0.47) | |
| | | 30-39 | 0.26 (0.13-0.39) | |
| | | 40-49 | 0.24 (0.10-0.39) | 147,262 |
| **HPV prevalence, women with HIV** | 2005 | 20-24 | 0.66 (0.58-0.75) | |
| | | 25-29 | 0.67 (0.56-0.79) | |
| | | 30-39 | 0.57 (0.45-0.71) | |
| | | 40-49 | 0.56 (0.43-0.68) | |
| **Cervical cancer incidence, per 100,00 women** | 2012 | 15-19 | 0.7 | 148 |

| | | | | |
|---|---|---|---|---|
| | | 20-24 | 0.8 | |
| | | 25-29 | 8.0 | |
| | | 30-34 | 21.0 | |
| | | 35-39 | 40.7 | |
| | | 40-44 | 62.7 | |
| | | 45-49 | 83.1 | |
| | | 50-54 | 103.4 | |
| | | 55-59 | 130.3 | |
| | | 60-64 | 150.5 | |
| | | 65-69 | 156.3 | |
| | | 70-74 | 150.7 | |
| | | 75-79 | 133.2 | |
| | | 15-79 | 40.0 | |

**Table S15.** Relative distribution of HPV types (vaccine-targeted vs non-vaccine-targeted) at each stage of HPV infection and progression.

| Criteria | HPV Type | Value | Reference |
|---|---|---|---|
| **HPV** | Vaccine-targeted | 0.4682 | 263,264 |
| | Non-vaccine-targeted | 0.5318 | |
| **CIN1** | Vaccine-targeted | 0.5192 | 263,265 |
| | Non-vaccine-targeted | 0.4808 | |
| **CIN3** | Vaccine-targeted | 0.7371 | 219,263,266 |
| | Non-vaccine-targeted | 0.2629 | |
| **Cervical cancer** | Vaccine-targeted | 0.8578 | 218,263,267,268 |
| | Non-vaccine-targeted | 0.1422 | |

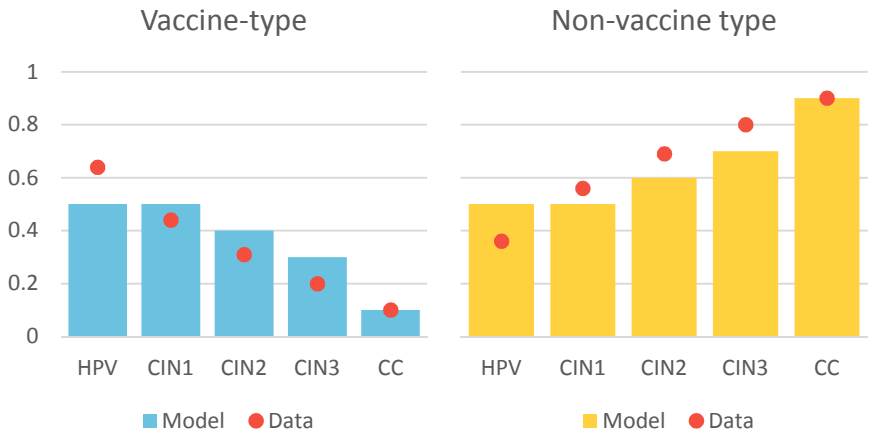



**Figure S4.** Distribution of HPV types at each HPV state in the model compared to data.

*b. Validation*

We validated our HIV natural history module to additional time points and data sources (Table S16). We compared our model HIV output to age- and sex-specific HIV prevalence reported in the Population-based HIV Impact Assessment (PHIA) in 2018, which used a similar sampling method as DHS and KAIS surveys.[17] To validate cervical cancer incidence projection, we compared model output against GLOBOCAN 2020.[7]

**Table S16.** Validation targets.

| | Year | Age | Value | Reference |
|---|---|---|---|---|
| **HIV Prevalence, men** | 2018 | 15-19 | 0.005 | 17 |
| | | 20-24 | 0.006 | |
| | | 25-29 | 0.022 | |
| | | 30-34 | 0.032 | |
| | | 35-39 | 0.043 | |
| | | 40-44 | 0.063 | |
| | | 45-49 | 0.083 | |
| | | 15-49 | 0.031 | |
| **HIV Prevalence, women** | 2018 | 15-19 | 0.012 | 17 |
| | | 20-24 | 0.034 | |
| | | 25-29 | 0.060 | |
| | | 30-34 | 0.095 | |
| | | 35-39 | 0.087 | |
| | | 40-44 | 0.119 | |
| | | 45-49 | 0.106 | |
| | | 15-49 | 0.062 | |
| **Cervical cancer incidence, per 100,00 women** | 2020 | 15-19 | 0.2 | 7 |
| | | 20-24 | 0.38 | |
| | | 25-29 | 3.5 | |
| | | 30-34 | 14.4 | |
| | | 35-39 | 29.1 | |
| | | 40-44 | 50.4 | |
| | | 45-49 | 72.9 | |
| | | 50-54 | 91.4 | |
| | | 55-59 | 109.7 | |
| | | 60-64 | 122.3 | |
| | | 65-69 | 124.7 | |
| | | 70-74 | 114.1 | |
| | | 75-79 | 80.67 | |
| | | 15-79 | 45.7 | |

*c. Comparing model output to data*

*Demographics*

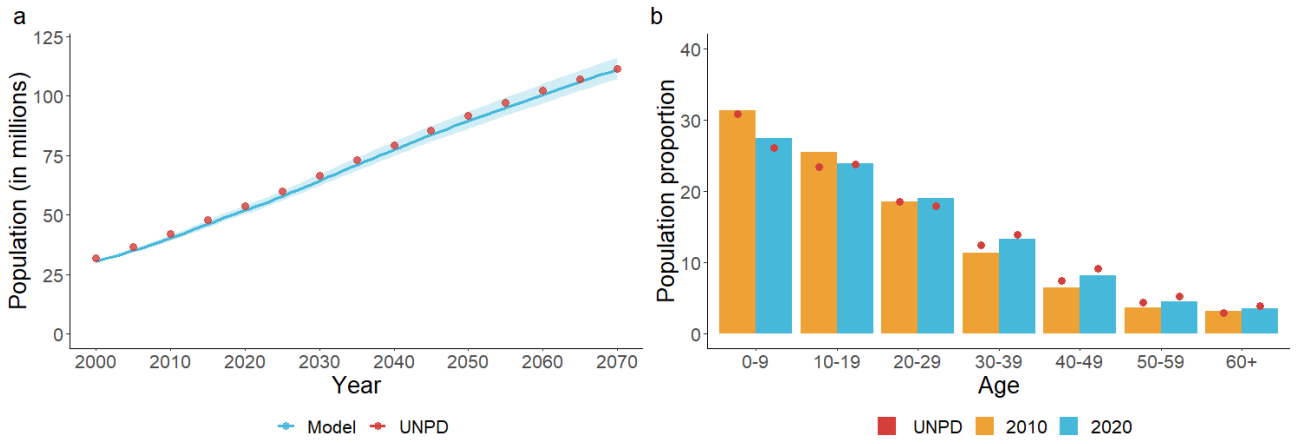



**Figure S5.** A). Model-projected total population size, including men and women, over time (blue line) compared to UNPD estimates for Kenya (red dots). B). Age distribution of model population, in 10-year age groups, in 2010 (yellow) and 2020 (blue) compared to UNPD estimates (red).

*HIV*

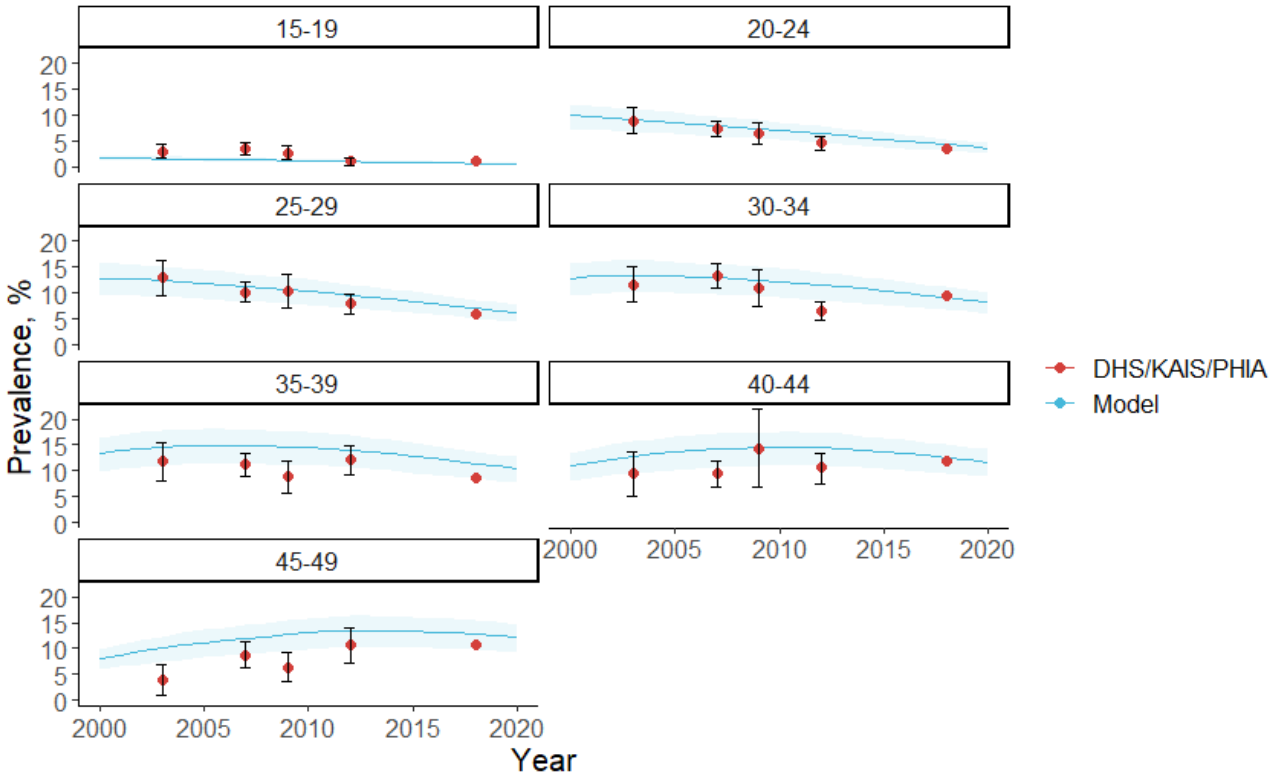


**Figure S6.** Model-estimated HIV prevalence among adult women by 5-year age groups (blue) compared to age-specific 2003 DHS, 2007 KAIS, 2008-2009 DHS, 2012 KAIS, and 2018 PHIA data for the same age groups (red). We calibrated to 2003, 2007, 2008-2009, and 2012 values and validated against the 2018 values.

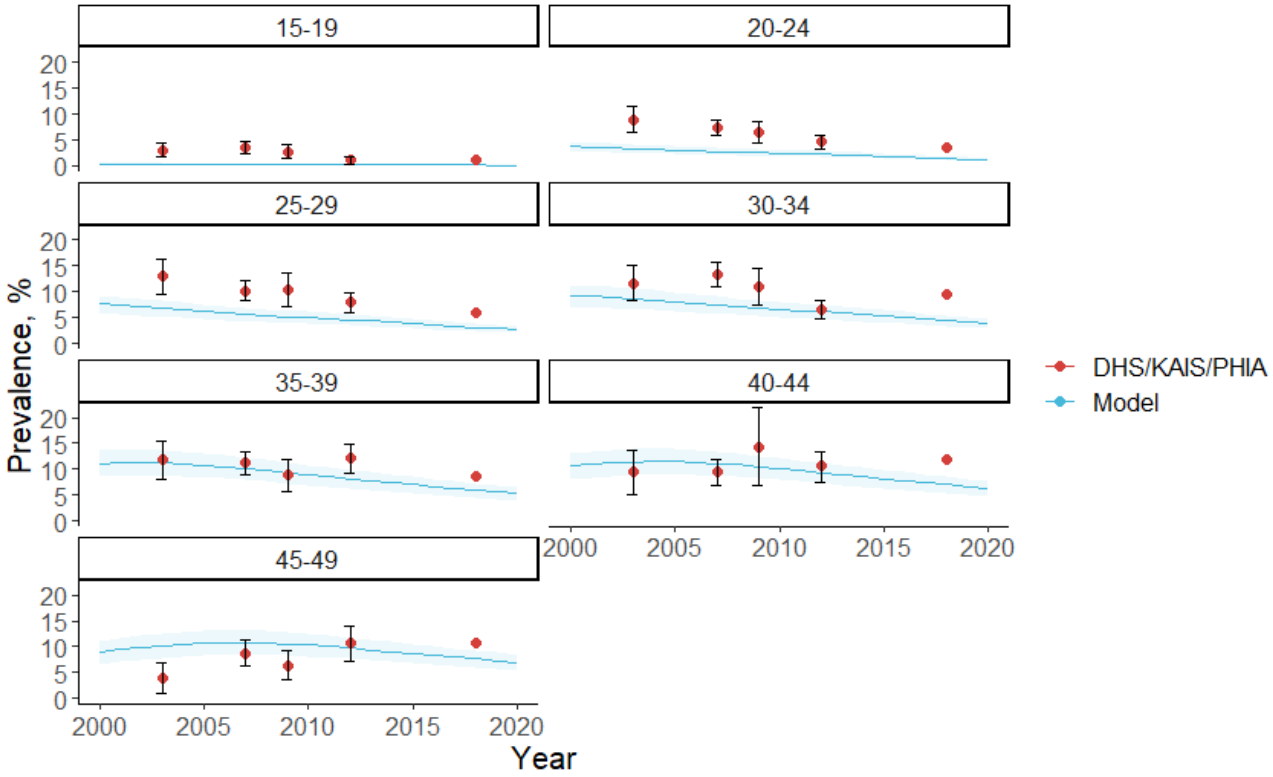



**Figure S7.** Model-estimated HIV prevalence among adult men by 5-year age groups (blue) compared to age-specific 2003 DHS, 2007 KAIS, 2008-2009 DHS, 2012 KAIS, and 2018 PHIA data for the same age groups (red). We calibrated to 2003, 2007, 2008-2009, and 2012 values and validated against the 2018 values.

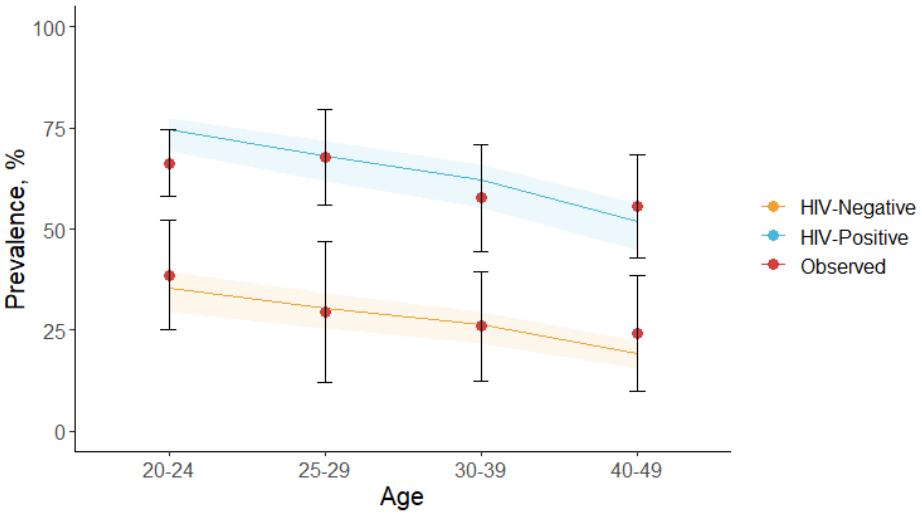


**Figure S8**. Model estimated HPV prevalence by 10-year age group among HIV-negative women (yellow) and women with HIV (blue) compared to estimates from observational studies.[147,262]

*Cervical cancer*

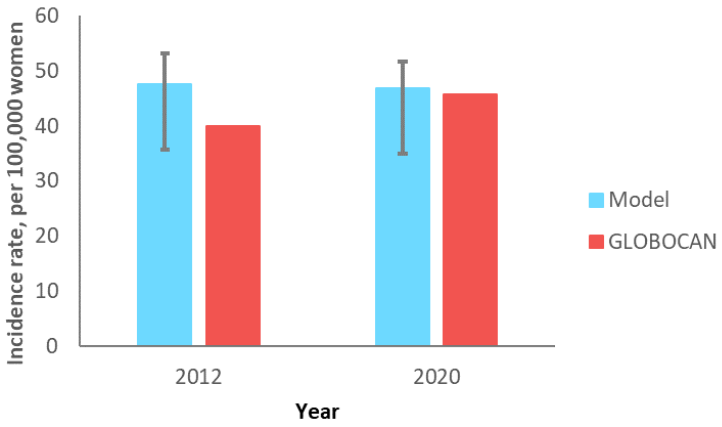



**Figure S9**. Age-standardized cervical cancer incidence rates in 2012 and 2020 for women aged 15-79 (blue) compared to age-standardized estimates for women of the same age from GLOBOCAN (red).

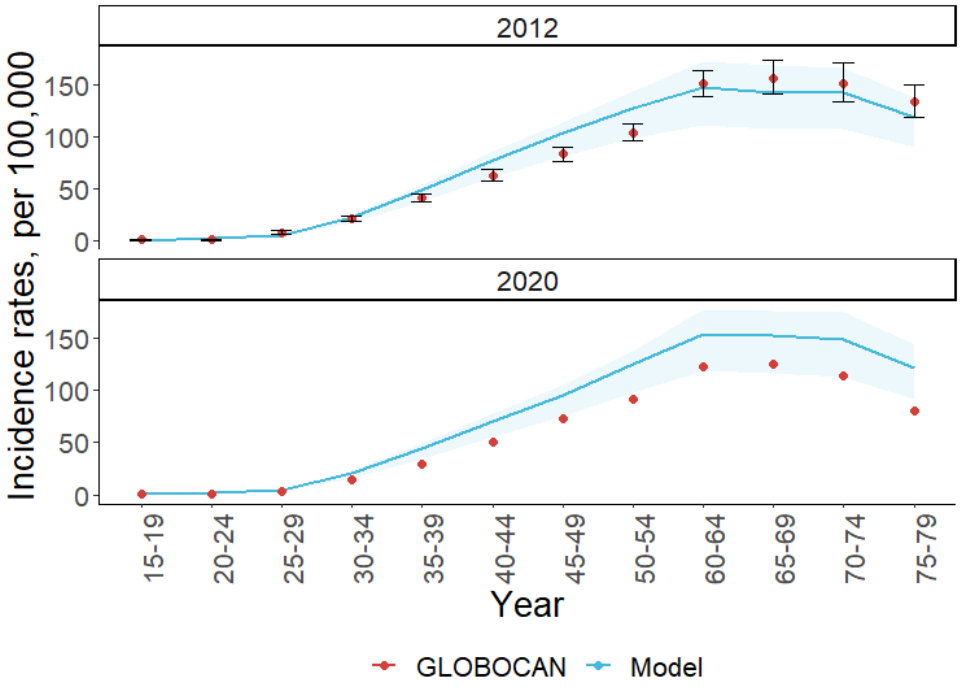



**Figure S10**. Model-estimated age-specific cervical cancer incidence rates (blue), compared to GLOBOCAN estimates (red). We calibrated to 2012 GLOBOCAN data and validated against 2020 GLOBOCAN data.

## IV. Additional results

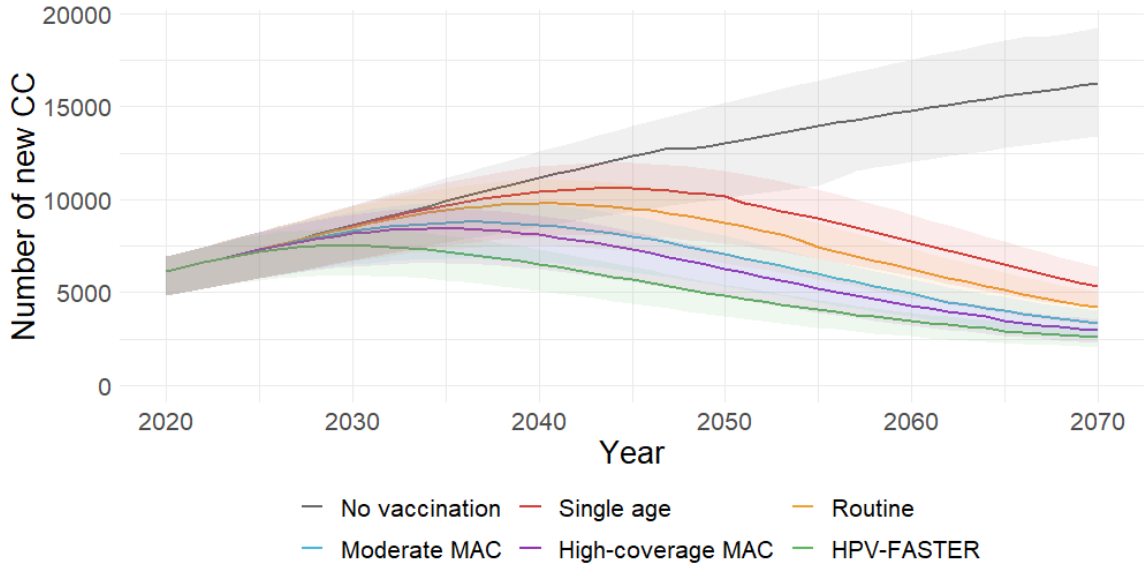



**Figure S11**. Annual number of new cervical cancer cases.

**Table S17.** The proportion of 15-79 year-old women vaccinated in each scenario.

| Year | Single age | Routine | Moderate catch-up | High-coverage catch-up | HPV-FASTER |
|---|---|---|---|---|---|
| **2030** | 25% | 37% | 48% | 55% | 76% |
| **2040** | 43% | 53% | 61% | 66% | 82% |
| **2050** | 57% | 64% | 71% | 75% | 85% |
| **2060** | 67% | 73% | 78% | 81% | 87% |
| **2070** | 76% | 80% | 83% | 83% | 88% |

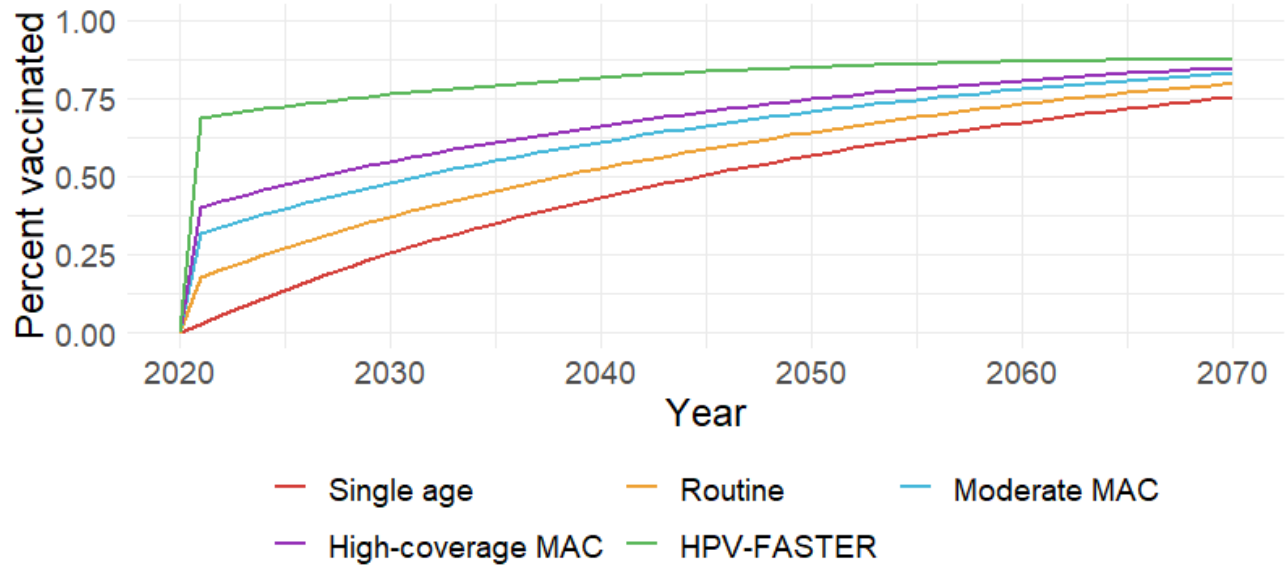



**Figure S12.** The proportion of all girls and women aged 15-79 vaccinated in each scenario.

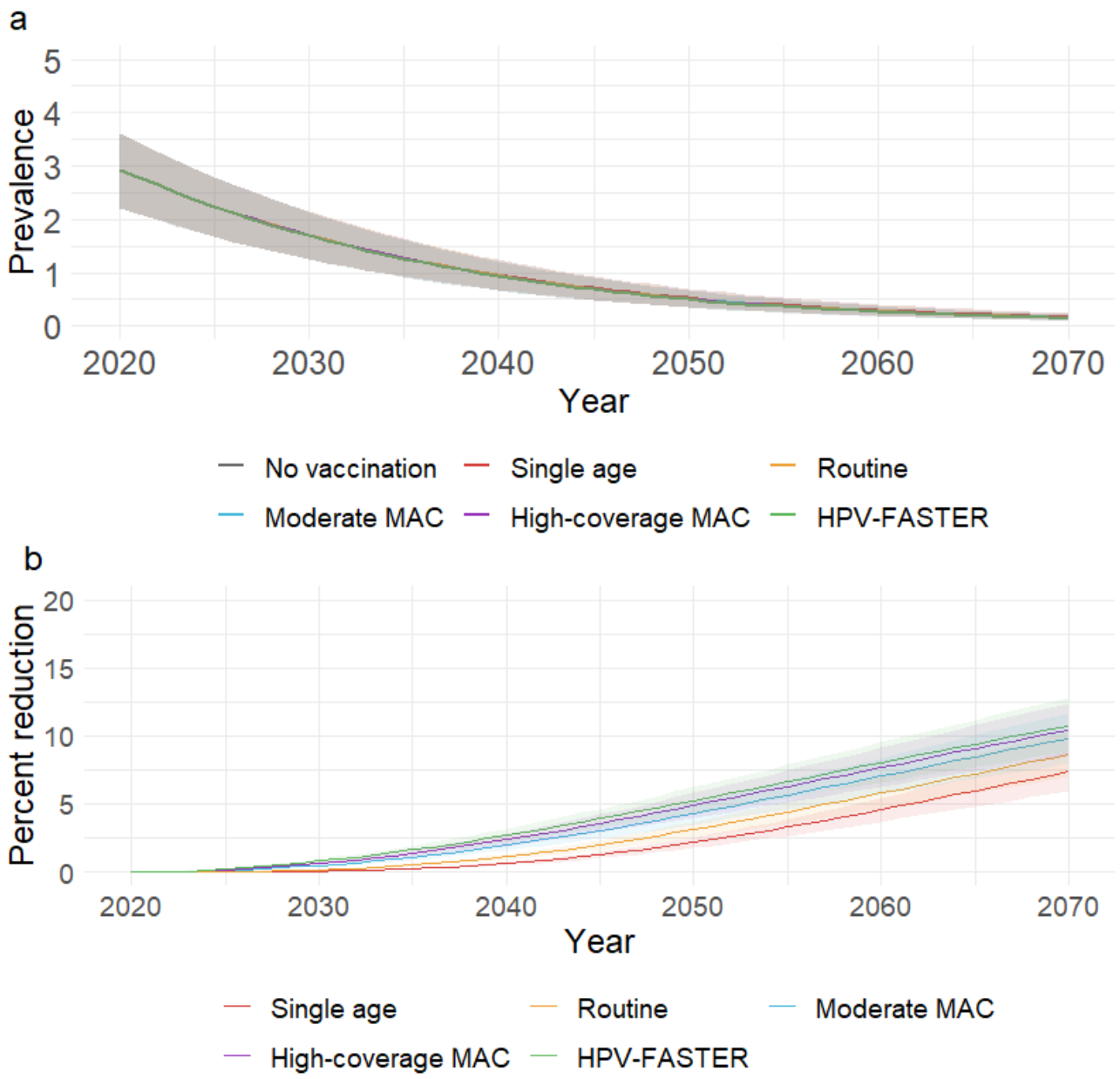



**Figure S13.** HPV vaccination impact on HIV burden in men. Subplot a) HIV prevalence among men over time by scenario. Because HIV prevalence was similar in all scenarios, lines for scenarios overlap almost completely. Subplot b) percent reduction in HIV prevalence relative to no vaccination.

**V. Differential equations**

We use a system of differential equations to estimate changes in population and infection dynamics over each time step. We split the full system of equations into topic-based modules and solve each iteratively

using a 4th-order Runge-Kutta numerical solver in MATLAB. The order is largely historical and based on the work of (Tan et al., 2018)[26]. The modules are:

1. HPV natural history
    a. Progression and clearance of HPV
    b. Progression and regression of precancerous lesions
    c. Development and progression of cervical cancer
    d. Cervical cancer- associated mortality
2. Cervical cancer screening and treatment
    a. Screening
    b. Treatment
3. HPV and HIV transmission
    a. Heterosexual mixing by gender, age, and risk group
    b. Partnership adjustment
    c. HPV infection by type
    d. HIV infection
4. HIV natural history and treatment
    a. CD4 progression
    b. Viral load progression
    c. ART initiation, discontinuation, and scale-up by CD4 count
    d. HIV-associated mortality
5. Demography
    a. Births
    b. Mother-to-child HIV transmission

c. Aging and risk-group redistribution

d. Natural deaths

6. Male circumcision
7. HPV vaccination
    a. School-based regimen
    b. Catch-up regimen

Throughout each simulation, we track population demographics and the number of persons with infection, with progressed disease, or with preventative or therapeutic treatment. We describe these states $X_{g,a,r}^{d,v,h,s,x,p}(t)$ with the following indices (using 1-based indexing):

| Index | Description | Values |
|---|---|---|
| *d* | HIV disease state, CD4 count, circumcision status, and ART status | 1. HIV-negative, uncircumcised<br>2. HIV-negative, circumcised<br>3. HIV-positive, acute infection<br>4. HIV-positive, CD4 > 500 cells/μL<br>5. HIV-positive, CD4 350-500 cells/μL<br>6. HIV-positive, CD4 200-350 cells/μL<br>7. HIV-positive, CD4 ≤ 200 cells/μL<br>8. HIV-positive, on ART |
| *v* | HIV viral load | 1. If ( $2 < d < 8$ ), Acute infection; if ( $d = 1,2$ ), HIV-negative: VL = 0.0<br>2. Asymptomatic: VL = 3.0-4.5 $\log_{10}$<br>3. Pre-AIDS symptomatic: VL = 4.0-5.5 $\log_{10}$<br>4. AIDS: VL = 5.5-7.0 $\log_{10}$<br>5. Late-stage<br>6. On ART and virally suppressed: VL = 0.0 |
| *h* | Vaccine-type HPV precancer or disease state | 1. Susceptible<br>2. Infected<br>3. CIN1<br>4. CIN2<br>5. CIN3<br>6. Cervical cancer or hysterectomy<br>7. Immune |
| *s* | Non-vaccine type HPV precancer or disease state | 1. Susceptible<br>2. Infected<br>3. CIN1<br>4. CIN2<br>5. CIN3<br>6. Cervical cancer or hysterectomy<br>7. Immune |

| | | |
|---|---|---|
| *x* | Cervical cancer or hysterectomy status | 1. If ( *h* = 6 or *s* = 6 ), Cervical cancer, local; else, no cancer or hysterectomy<br>2. Cervical cancer, regional<br>3. Cervical cancer, distant<br>4. Hysterectomy |
| *p* | Vaccination and screening history | 1. Non-vaccinated, non-screened<br>2. Vaccinated<br>3. Screened<br>4. Vaccinated and screened |
| *g* | Gender | 1. Male<br>2. Female |
| *a* | Age | 1. 0-4<br>2. 5-9<br>3. 10-14<br>4. 15-19<br>5. 20-24<br>6. 25-29<br>7. 30-34<br>8. 35-39<br>9. 40-44<br>10. 45-49<br>11. 50-54<br>12. 55-59<br>13. 60-64<br>14. 65-69<br>15. 70-74<br>16. 75-79 |
| *r* | Risk | 1. Low risk<br>2. Medium risk<br>3. High risk |

*V.a. Demography*

| **Equation variables** | |
|---|---|
| $\gamma_a^d(\mathrm{t})$ | The annual fertility rate for females by age *a* and HIV disease stage *d*.<br>Women ages 15-49 bear children. |
| $\eta(t)$ | The proportion of births from HIV-positive females that result in vertical transmission. |
| $b\_s(t)$ | Number of births by HIV-negative women and women on ART. |
| $b\_i(t)$ | Number of births by women living with HIV. |
| $b_{g,a,r}^{d,1,h,s,x,p}(t)$ | Number of infant births of HIV disease stage *d* and gender *g*.<br>We assume an equal gender ratio at birth of 1:1, that all newborns are born as low risk, no vertical transmission of HPV, and that if HIV is vertically transmitted, that infected newborns are born into the acute stage of HIV. |
| $\phi_{g,a,r}$ | Distribution of sexual risk *r* by gender *g* and age *a.* (Currently, the risk distribution derived from male partner data is used for both males and females for simplicity.) |
| $\mu\_bkrd_{g,a}(t)$ | Annual background mortality rate by gender *g* and age *a.* |

***Fertility***

The number of births by HIV status of the mother are calculated as:

*HIV-negative women and women on ART*

$$b\_s(t) = \sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{3}\sum_{p=1}^{4}\sum_{a=4}^{10}\sum_{r=1}^{3}\left[\gamma_a^1(t).X_{g,a,r}^{1,1,h,s,x,p}(t) + \gamma_a^8(t).X_{g,a,r}^{8,6,h,s,x,p}(t)\right]$$

*Women living with HIV*

$$b\_i(t) = \sum_{d=3}^{7}\sum_{v=1}^{5}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{3}\sum_{p=1}^{4}\sum_{a=4}^{10}\sum_{r=1}^{3}\left[\gamma_a^d(t).X_{g,a,r}^{d,v,h,s,x,p}(t)\right]$$

We then compute the number of births by gender and HIV status of the infant as:

*HIV-negative, uncircumcised births*

*For $h = s = x = p = a = r = 1$,*

$$b_{g,a,r}^{1,1,h,s,x,p}(t) = 0.5\left(b\_s(t) + \left(1 - \eta(t)\right)b\_i(t)\right)$$

else,

$$b_{g,a,r}^{1,1,h,s,x,p}(t) = 0$$

*HIV-positive births*

*For $h = s = x = p = a = r = 1$,*

$$b_{g,a,r}^{3,1,h,s,x,p}(t) = 0.5\,\eta(t).b\_i(t)$$

else,

$$b_{g,a,r}^{3,1,h,s,x,p}(t) = 0$$

***Aging***

To age the population, one-fifth of each compartment moves to the next age group while maintaining the same gender, disease state, and sexual risk distribution $\phi_{g,a,r}$:

$$\frac{dX_{g,1,r}^{d,v,h,s,x,p}(t)}{dt} = -\frac{1}{5}\sum_{r=1}^{3} X_{g,1,r}^{d,v,h,s,x,p}(t)\,.\,\phi_{g,a,r} \qquad (for\ a = 1)$$

$$\frac{dX_{g,a,r}^{d,v,h,s,x,p}(t)}{dt} = -\frac{1}{5}\sum_{r=1}^{3} X_{g,a,r}^{d,v,h,s,x,p}(t)\,.\,\phi_{g,a,r} + \frac{1}{5}\sum_{r=1}^{3} X_{g,a-1,r}^{d,v,h,s,x,p}(t)\,.\,\phi_{g,a-1,r} \qquad (for\ a \neq 1)$$

Upon aging to the next five-year group, individuals are re-distributed into the closest unfilled risk group to match observed data on the age distribution of low, medium, and high-risk individuals.

***Mortality***

We compute the number of deaths due to background mortality as:

$$\frac{dX_{g,a,r}^{d,v,h,s,x,p}(t)}{dt} = -\mu\_bkrd_{g,a}(t).X_{g,a,r}^{d,v,h,s,x,p}(t)$$

b. Sexual Behavior

***Mixing matrix***

| Equation variables | |
|---|---|
| $c_{g,a,r}$ | Number of partners a person has per year of gender *g,* age *a,* and sexual-risk group *r* (ie. the partner exchange rate, or contact rate). |
| $\epsilon_a$ | Mixing parameter by age *a.*<br>We assume a mixing pattern that is partially random and partially off-diagonal ($0 < \epsilon_a < 1$), where ($\epsilon_a = 0$) indicates completely off-diagonal mixing, and ($\epsilon_a = 1$) indicates completely random mixing. |
| $\epsilon_r$ | Mixing parameter by sexual-risk group *r.*<br>We assume a mixing pattern that is partially random and partially on-diagonal ($0 < \epsilon_r < 1$), where ($\epsilon_r = 0$) indicates completely on-diagonal mixing, and ($\epsilon_r = 1$) indicates completely random mixing. |
| $\delta_{g,a,a'}$ | Mixing pattern by age.<br>In completely non-random mixing by age, females are most likely to form partnerships with males of the next oldest age group. We represent this pattern using on off-diagonal matrix.<br><br>For males ($g$ = 1) of age *a* mixing with females of age *a'*:<br>= 0.3 if ($a = a'$)<br>= 0.7 if ($a = a' + 1$)<br>except for the following (correct for no sexual activity before age group 3):<br>= 0.0 if ($a = a' = 1$)<br>= 0.0 if ($a = 2$) and ($a'$ = 1)<br>= 0.0 if ($a = 2$) and ($a'$ = 2)<br>= 0.0 if ($a = 3$) and ($a'$ = 2)<br><br>For females ($g$ = 2) of age *a* mixing with males of age *a'*:<br>= 0.3 if ($a = a'$)<br>= 0.7 if ($a = a' - 1$)<br>except for the following (correct for no sexual activity before age group 3):<br>= 0.0 if ($a = a' = 1$)<br>= 0.0 if ($a = 1$) and ($a'$ = 2)<br>= 0.0 if ($a = a' = 2$)<br>= 0.0 if ($a = 2$) and ($a'$ = 3) |
| $\delta_{r,r'}$ | Mixing pattern by risk.<br>Completely non-random mixing by risk confines sexual encounters to individuals within the same risk group. We represent this pattern using an identity matrix.<br>= 1.0 if ($r = r'$)<br>= 0.0 if ($r \neq r'$) |

For a person of gender *g,* age *a,* and sexual-risk group *r,* we use the mixing matrix $\rho_{g,a,a',r,r'}(t)$ to describe the proportion of sexual partners that come from age group *a'* and sexual-risk group *r'*. We assume that mixing is partially random and partially designated by a mixing pattern $\delta_{g,a,a'}$ or $\delta_{r,r'}$. The overall mixing matrix is therefore a weighted average of random mixing proportional to the number of available partnerships of each group, and mixing among groups with similar characteristics. Although an off-diagonal mixing pattern results in the first and last ages groups (ages 10-14 and 75-79) having fewer than 100% of their partnerships, these age groups have relatively few partnerships and contribute marginally to overall infection transmission.

$$\rho_{g,a,a',r,r'}(t) = \left( \epsilon_a \cdot \frac{\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)}{\sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)} + (1-\epsilon_a)\delta_{g,a,a'} \right) \cdot \left( \epsilon_r \cdot \frac{\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)}{\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)} + (1-\epsilon_r)\delta_{g,r,r'} \right)$$

***Rate of partner change***

| **Equation variables** | |
|---|---|
| $c_{g,a,r}$ | Number of partners a person has per year of gender *g,* age *a,* and sexual-risk group *r* (ie. the partner exchange rate, or contact rate).<br>We assume zero partnerships for individuals below the age of sexual debut (age 10). |
| $\theta$ | Gender influence on contact rate adjustment.<br>We assume an adjusted contact rate equally driven by rates reported by males and females (<br>$\theta = 0.5$), where ($\theta = 0$) when completely female-driven, and ($\theta = 1$) when completely male-driven. |
| $\rho_{g,a,a',r,r'}(t)$ | Mixing matrix for a person of gender *g,* age *a,* and sexual-risk group *r* that describes the proportion of sexual partners that come from age group *a'* and sexual-risk group *r'*.<br>We assume a solely heterosexual population and therefore that all contacts are with the opposite gender. |

Bias in observed data leads to contact rates $c_{g,a,r}$ that, when assuming solely heterosexual contact, are inconsistent between males and females. We account for this variability by using an adjusted contact

rate $c^{*}_{g,a,a',r,r'}(t)$ that ensures that the number of partnerships of males of age *a* and risk group *r* with females of age *a'* and risk group *r'* equals the number of partnerships of females of age *a* and risk group *r* with males of age *a'* and risk group *r'*.

We first calculate the discrepancy between reported male and female contacts as:

$$B_{a,a',r,r'}(t) = \frac{c_{1,a,r} \cdot \rho_{1,a,a',r,r'}(t) \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{c_{2,a,r} \cdot \rho_{2,a,a',r,r'}(t) \cdot \sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)}$$

We then compute the adjusted contact rate for females as:

$$c^{*}_{2,a,a',r,r'}(t) = c_{2,a,r} \cdot \rho_{2,a,a',r,r'}(t) \cdot B_{a,a',r,r'}(t)^{\theta} \cdot \left( \frac{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)} \right)^{-(1-\theta)}$$

and for males, an adjusted contact rate of:

$$c^{*}_{1,a,a',r,r'}(t) = c_{1,a,r} \cdot \rho_{1,a,a',r,r'}(t) \cdot B_{a,a',r,r'}(t)^{-(1-\theta)} \cdot \left( \frac{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)} \right)^{\theta}$$

c. Transmission Probabilities

***Per-partnership probability of transmission***

| **Equation variables** | |
|---|---|
| $A_{g,a,r}$ | Number of acts per partnership of gender *g,* age *a,* and sexual-risk group *r*.<br>We assume zero acts for individuals below the age of sexual debut (age 10). |
| $\chi\_HIV_g^{v',x'}$ | Per-act probability of HIV transmission to a person of gender *g* based on the viral load *v'* of the HIV-positive partner.<br>We assume the probability of female-to-male HIV transmission is equal to the probability of male-to-female transmission across all viral load stages ($\chi\_HIV_1^{v'} = \chi\_HIV_2^{v'}$). We reduce HIV per-act transmission as a proxy for decreased sexual activity during late-stage HIV (*v'* = 5), regional or distant cervical cancer (*x'* = 2 or *x'* = 3), or hysterectomy (*x'* = 4). |
| $\chi\_HPV_g^{v',x'}$ | Per-act probability of HPV transmission to a person of gender *g*.<br>We assume the per-act probability of HPV transmission is the same for vaccine-type and non-vaccine-type HPV and across all stages of pre-cancer or cervical cancer. We reduce HPV per-act transmission as a proxy for decreased sexual activity during late-stage HIV (*v'* = 5) or regional or distant cervical cancer (*x'* = 2 or *x'* = 3). We assume no HPV transmission after hysterectomy (*x'* = 4). |

The per-partnership probability of HIV transmission $\beta\_HIV_{g,a,r}^{v',x'}$ is the cumulative risk of acquiring HIV from all sexual acts with a partner. This quantity depends on the per-act probability of HIV transmission and the number of acts per partnership.

We calculate the per-partnership probability of HIV transmission to a male partner:

$$\beta\_HIV_{1,a,r}^{v',x'} = 1 - (1 - \chi\_HIV_1^{v',x'})^{A_{1,a,r}}$$

Similarly, the per-partnership probability of HIV transmission to a female partner:

$$\beta\_HIV_{2,a,r}^{v',x'} = 1 - (1 - \chi\_HIV_2^{v',x'})^{A_{2,a,r}}$$

Likewise, the per-partnership probability of HPV transmission $\beta\_HPV_{g,a,r}^{v',x'}$ depends on the per-act probability of HPV transmission and the number of acts per partnership.

We calculate the per-partnership probability of HPV transmission to a male partner:

$$\beta\_HPV_{1,a,r}^{v',x'} = 1 - (1 - \chi\_HPV_1^{v',x'})^{A_{1,a,r}}$$

Similarly, the per-partnership probability of HPV transmission to a female partner:

$$\beta\_HPV_{2,a,r}^{v',x'} = 1 - (1 - \chi\_HPV_2^{v',x'})^{A_{2,a,r}}$$

***Force of infection***

| **Equation variables** | |
|---|---|
| $c^*_{g,a,a',r,r'}(t)$ | Adjusted yearly contact rate for persons of gender *g,* age *a,* and risk group *r,* with persons of the opposite gender, age *a',* and risk group *r'.* |
| $\beta\_HIV_{g,a,r}^{v',x'}$ | Annual per-partnership probability of HIV transmission from a HIV-positive person with viral load *v'* and cervical cancer stage *x'* to a HIV-susceptible partner with gender *g,* age *a,* and risk group *r.* |
| $\beta\_HPV_{g,a,r}^{v',x'}$ | Annual per-partnership probability of HPV transmission from a HPV-infected person with viral load *v'* and cervical cancer stage *x'* to a HPV-susceptible partner with gender *g,* age *a,* and risk group *r.* |

The force of infection represents the cumulative risk of acquiring HIV or HPV from all possible partners, and depends on the adjusted contact rate, the per-partnership probability of transmission, and the proportion of sexually active persons who are HIV- or HPV-infected.

The force of infection $\lambda\_HIV_{g,a,r}(t)$ determines HIV disease transmission:

$$\lambda\_HIV_{g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c^{*}_{g,a,a',r,r'}(t).\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln(1-\beta\_HIV_{g,a,r}^{v',x'}).\sum_{d'=3}^{8}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right)$$

Similarly, the force of infection $\lambda\_vHPV_{g,a,r}(t)$ determines vaccine-type HPV transmission:

$$\lambda\_vHPV_{g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c^{*}_{g,a,a',r,r'}(t).\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln(1-\beta\_HPV_{g,a,r}^{v',x'}).\sum_{d'=1}^{8}\sum_{h'=2}^{6}\sum_{s'=1}^{7}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right)$$

and $\lambda\_nvHPV_{g,a,r}(t)$ defines non-vaccine-type HPV transmission:

$$\lambda\_nvHPV_{g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c^{*}_{g,a,a',r,r'}(t).\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln(1-\beta\_HPV_{g,a,r}^{v',x'}).\sum_{d'=1}^{8}\sum_{h'=1}^{7}\sum_{s'=2}^{6}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right)$$

d. Natural History and Interventions

***HIV***

| Equation variables | |
|---|---|
| $\mu\_HIV_{g,a}^{d}$ | Annual HIV-associated mortality rate by gender *g*, age *a*, and HIV disease stage *d* for ($3 \leq d \leq 8$). |
| $\lambda\_HIV_{g,a,r}(t)$ | Force of HIV infection for HIV-negative persons by gender *g,* age *a,* and risk *r*. |
| $\rho\_HIV_{g}$ | Reduction in HIV acquisition due to circumcision by gender.<br>Only males receive circumcision ($\rho\_HIV_{2} = 1$). |
| $\psi\_HIV_{g}$ | Reduction in HIV acquisition due to population-level condom use by gender. |
| $\omega^{d}$ | The rate of progressing from HIV stage *d* to stage *d + 1,* for ($3 \leq d \leq 7$). |
| $l^{d}$ | The rate of progressing from viral load stage *v* to *v + 1,* for ($1 \leq v \leq 5$). |
| $P_{g,a}(t)$ | The proportion of HIV-negative persons of gender *g* and age *a* that are circumcised.<br>Only males receive circumcision ($P_{2,a}(t) = 0$). |
| $A_{g,a}^{d}(t)$ | The proportion of persons living with HIV of disease stage *d,* gender *g,* and age *a* that initiate ART. |
| $\sigma_{g,a,r}^{d,v}(t)$ | The proportion of persons who discontinue ART based on the recent distribution of persons initiating ART by gender *g*, age *a,* risk *r,* disease *d,* and viral *v*. |

We calculate changes in HIV status and HIV stage defined by CD4 count, viral load, and treatment status. The HIV-negative population can acquire HIV after sexual debut with a force of infection reduced by circumcision in males and condom use by either gender. We only track circumcision among HIV-negative men. Individuals with HIV infection experience HIV-associated mortality, CD4 and viral load stage

progression, and ART initiation and discontinuation. CD4 and viral load stage are not tracked among persons on treatment.

*HIV-negative, uncircumcised*

$$\frac{dX_{g,a,r}^{1,1,h,s,x,p}(t)}{dt} = -\left(\psi\_HIV_g.\lambda\_HIV_{g,a,r}(t) + P_{g,a}(t)\right)X_{g,a,r}^{1,1,h,s,x,p}(t)$$

*HIV-negative, circumcised*

$$\frac{dX_{g,a,r}^{2,1,h,s,x,p}(t)}{dt} = P_{g,a}(t).X_{g,a,r}^{1,1,h,s,x,p}(t) - \left(\psi\_HIV_g.\rho\_HIV_g.\lambda\_HIV_{g,a,r}(t)\right)X_{g,a,r}^{2,1,h,s,x,p}(t)$$

*HIV-positive, acute infection*

$$\frac{dX_{g,a,r}^{3,1,h,s,x,p}(t)}{dt} = \psi\_HIV_g.\lambda\_HIV_{g,a,r}(t).X_{g,a,r}^{1,1,h,s,x,p}(t) + \psi\_HIV_g.\rho\_HIV_g.\lambda\_HIV_{g,a,r}(t).X_{g,a,r}^{2,1,h,s,x,p}(t) + \sigma_{g,a,r}^{3,1}(t).X_{g,a,r}^{8,6,h,s,x,p}(t) - \left(\mu\_HIV_{g,a}^{3} + \omega^3 + A_{g,a}^{3}(t)\right)X_{g,a,r}^{3,1,h,s,x,p}(t)$$

*HIV-positive, CD4 > 500 cells/μL*

$$\frac{dX_{g,a,r}^{4,v,h,s,x,p}(t)}{dt} = \omega^3.X_{g,a,r}^{3,v,h,s,x,p}(t) + l^{v-1}.X_{g,a,r}^{4,v-1,h,s,x,p}(t) + \sigma_{g,a,r}^{4,v}(t).X_{g,a,r}^{8,6,h,s,x,p}(t) - \left(\mu\_HIV_{g,a}^{4} + \omega^4 + l^v + A_{g,a}^{4}(t)\right)X_{g,a,r}^{4,v,h,s,x,p}(t)$$

*HIV-positive, CD4 350-500 cells/μL*

$$\frac{dX_{g,a,r}^{5,v,h,s,x,p}(t)}{dt} = \omega^4.X_{g,a,r}^{4,v,h,s,x,p}(t) + l^{v-1}.X_{g,a,r}^{5,v-1,h,s,x,p}(t) + \sigma_{g,a,r}^{5,v}(t).X_{g,a,r}^{8,6,h,s,x,p}(t) - \left(\mu\_HIV_{g,a}^{5} + \omega^5 + l^v + A_{g,a}^{5}(t)\right)X_{g,a,r}^{5,v,h,s,x,p}(t)$$

*HIV-positive, CD4 200-350 cells/μL*

$$\frac{dX_{g,a,r}^{6,v,h,s,x,p}(t)}{dt} = \omega^5.X_{g,a,r}^{5,v,h,s,x,p}(t) + l^{v-1}.X_{g,a,r}^{6,v-1,h,s,x,p}(t) + \sigma_{g,a,r}^{6,v}(t).X_{g,a,r}^{8,6,h,s,x,p}(t) - \left(\mu\_HIV_{g,a}^{6} + \omega^6 + l^v + A_{g,a}^{6}(t)\right)X_{g,a,r}^{6,v,h,s,x,p}(t)$$

*HIV-positive, CD4 ≤ 200 cells/μL*

$$\frac{dX_{g,a,r}^{7,v,h,s,x,p}(t)}{dt} = \omega^6.X_{g,a,r}^{6,v,h,s,x,p}(t) + l^{v-1}.X_{g,a,r}^{7,v-1,h,s,x,p}(t) + \sigma_{g,a,r}^{7,v}(t).X_{g,a,r}^{8,6,h,s,x,p}(t) - \left(\mu\_HIV_{g,a}^{7} + \omega^7 + l^v + A_{g,a}^{7}(t)\right)X_{g,a,r}^{7,v,h,s,x,p}(t)$$

*HIV-positive, on ART*

$$\frac{dX_{g,a,r}^{8,6,h,s,x,p}(t)}{dt} = \sum_{d=3}^{7}\sum_{v=1}^{5}\left(A_{g,a}^{d}(t).X_{g,a,r}^{d,v,h,s,x,p}(t) - \sigma_{g,a,r}^{d,v}.X_{g,a,r}^{8,6,h,s,x,p}(t)\right)$$

***HPV***

| **Equation variables** |
|---|

| | |
|---|---|
| $\mu\_HPV_g^{d,h,s,x}$ | Annual cervical cancer-associated mortality rate by gender *g*, HIV disease stage *d*, vaccine-type HPV stage *h,* non-vaccine-type HPV stage *s,* and cervical cancer stage *x* for ($1 \leq x \leq 3$).<br>Only females have cervical cancer-associated mortality ($\mu\_HPV_1^{d,h,s,x} = 0$) and only when ($h = 6$ or $s = 6$). |
| $\lambda\_vHPV_{g,a,r}(t)$ | Force of vaccine-type HPV infection for susceptible persons of gender *g,* age *a,* and risk *r*. |
| $\lambda\_nvHPV_{g,a,r}(t)$ | Force of non-vaccine-type HPV infection for susceptible persons of gender *g,* age *a,* and risk *r*. |
| $ж_d$ | HPV acquisition risk multiplier for HIV-positive individuals with CD4 count ($4 \leq d \leq 7$). |
| $\rho\_HPV_g$ | HPV acquisition reduction multiplier due to circumcision by gender.<br>Only males receive circumcision ($\rho\_HPV_2 = 1$). |
| $\psi\_HPV_g$ | HPV acquisition reduction multiplier due to population-level condom use by gender. |
| $\xi_{g,a}$ | HPV acquisition reduction multiplier by gender and age for individuals with type-specific natural immunity.<br>Only females temporarily develop partial natural immunity ($\xi_{1,a} = 0$). Older women develop stronger natural immunity than young girls. |
| $\phi_a$ | Vaccine-type HPV acquisition reduction multiplier by age for vaccinated individuals.<br>We assume life-long protection with vaccination ($\phi_a$ is equivalent for all vaccinated ages). |
| $k\_v_{g,a}^{h,h'}$ | Transition rate of progressing or regressing from vaccine-type HPV precancer or disease stage *h* to stage *h'*.<br>Only women develop precancerous lesions and cervical cancer ($k\_v_{1,a}^{h,h'} = 0$ except for HPV clearance when $h = 2$ and $h' = 1$). |
| $k\_nv_{g,a}^{s,s'}$ | Transition rate of progressing or regressing from non-vaccine-type HPV precancer or disease stage *s* to stage *s'*.<br>Only women develop precancerous lesions and cervical cancer ($k\_v_{1,a}^{s,s'} = 0$ except for HPV clearance when $s = 2$ and $s' = 1$). |
| $r_g$ | Rate of waning type-specific natural immunity.<br>Only females temporarily develop partial natural immunity ($r_1 = 0$). |
| $\varphi_g^{h,s,x,x'}$ | Progression rate of cervical cancer from stage *x* to stage *x'*.<br>Only women develop cervical cancer ($\varphi_1^{h,s,x,x'} = 0$) and ($\varphi_2^{h,s,x,x'} > 0$ only when *h* or $s = 6$) |
| $\zeta\_v^{d,h,h'}$ | Transition rate multiplier for HIV-positive individuals progressing or regressing from vaccine-type precancer or disease stage *h* to stage *h'* with CD4 count *d.*<br>Transition rate multipliers for HIV-positive individuals are the same for vaccine-type and non-vaccine-type HPV ($\zeta\_v^{d,h,h'} = \zeta\_nv^{d,s,s'}$ when $h = s$ and $h' = s'$). |
| $\zeta\_nv^{d,s,s'}$ | Transition rate multiplier for HIV-positive individuals progressing or regressing from non-vaccine-type precancer or disease stage *s* to stage *s'* with gender *g* and CD4 count *d.*<br>Transition rate multipliers for HIV-positive individuals are the same for vaccine-type and non-vaccine-type HPV ($\zeta\_v^{d,h,h'} = \zeta\_nv^{d,s,s'}$ when $h = s$ and $h' = s'$). |
| $\ell_g$ | Additional multiplier for clearance of vaccine or non-vaccine-type HPV infection.<br>Only applied to males ($\ell_2 = 1$). |

| | |
|---|---|
| $V_{g,a}^{d}$ | The proportion of persons with HIV disease status *d,* gender *g,* and age *a* vaccinated. |

***Vaccine-targeted HPV types and precancer equations***

*Male susceptible*

$$\frac{dX_{1,a,r}^{d,v,1,s,1,1}(t)}{dt} = \ell_1.\zeta\_v^{d,2,1}.k\_v_{1,a}^{2,1}.X_{1,a,r}^{d,v,2,s,1,1}(t) - \left(\text{ж}_d.\rho\_HPV_1.\psi\_HPV_1.\lambda\_vHPV_{1,a,r}(t) + V_{1,a}^{d}\right)X_{1,a,r}^{d,v,1,s,1,1}(t)$$

*Male HPV-infected*

$$\frac{dX_{1,a,r}^{d,v,2,s,1,1}(t)}{dt} = \text{ж}_d.\rho_{HPV1}.\psi_{HPV1}.\lambda_{vHPV1,a,r}(t).X_{1,a,r}^{d,v,1,s,1,1}(t) - \ell_1.\zeta\_v^{d,2,1}.k\_v_{1,a}^{2,1}.X_{1,a,r}^{d,v,2,s,1,1}(t)$$

*Male susceptible, vaccinated*

$$\frac{dX_{1,a,r}^{d,v,1,s,1,2}(t)}{dt} = V_{1,a}^{d}.X_{1,a,r}^{d,v,1,s,1,1}(t) + \ell_1.\zeta\_v^{d,2,1}.k\_v_{1,a}^{2,1}.X_{1,a,r}^{d,v,2,s,1,2}(t) - \phi_a.\text{ж}_d.\rho\_HPV_1.\psi\_HPV_1.\lambda\_vHPV_{1,a,r}(t).X_{1,a,r}^{d,v,1,s,1,2}(t)$$

*Male HPV-infected, vaccinated*

$$\frac{dX_{1,a,r}^{d,v,2,s,1,2}(t)}{dt} = \phi_a.\text{ж}_d.\rho_{HPV1}.\psi_{HPV1}.\lambda_{vHPV1,a,r}(t).X_{1,a,r}^{d,v,1,s,1,2}(t) - \ell_1.\zeta\_v^{d,2,1}.k\_v_{1,a}^{2,1}.X_{1,a,r}^{d,v,2,s,1,2}(t)$$

*Female susceptible*

$$\frac{dX_{2,a,r}^{d,v,1,s,x,[1,3]}(t)}{dt} = \zeta\_v^{d,7,1}.r_2.X_{2,a,r}^{d,v,7,s,x,[1,3]}(t) - \left(\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t) + V_{2,a}^{d} + \mu\_HPV_2^{d,1,s,x}\right)X_{2,a,r}^{d,v,1,s,x,[1,3]}(t)$$

*Female immune*

$$\frac{dX_{2,a,r}^{d,v,7,s,x,[1,3]}(t)}{dt} = V_{2,a}^{d}.X_{2,a,r}^{d,v,7,s,x,[1,3]}(t) + \zeta\_v^{d,2,7}.k\_v_{2,a}^{2,7}.X_{2,a,r}^{d,v,2,s,x,[1,3]}(t) - \left(\zeta\_v^{d,7,1}.k\_v_{2,a}^{7,1} + \xi_{2,a}.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t) + V_{2,a}^{d} + \mu\_HPV_2^{d,7,s,x}\right)X_{2,a,r}^{d,v,7,s,x,[1,3]}(t)$$

*Female HPV-infected*

$$\frac{dX_{2,a,r}^{d,v,2,s,x,[1,3]}(t)}{dt} = \zeta\_v^{d,3,2}.k\_v_{2,a}^{3,2}.X_{2,a,r}^{d,v,3,s,x,[1,3]}(t) + \text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t).X_{2,a,r}^{d,v,1,s,x,[1,3]}(t) + \xi_{2,a}.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t).X_{2,a,r}^{d,v,7,s,x,[1,3]}(t) - \left(\zeta\_v^{d,2,7}.k\_v_{2,a}^{2,7} + \zeta\_v^{d,2,3}.k\_v_{2,a}^{2,3} + \mu\_HPV_2^{d,2,s,x}\right)X_{2,a,r}^{d,v,2,s,x,[1,3]}(t)$$

*Female susceptible, vaccinated*

$$\frac{dX_{2,a,r}^{d,v,1,s,x,[2,4]}(t)}{dt} = \zeta\_v^{d,7,1}.r_2.X_{2,a,r}^{d,v,7,s,x,[2,4]}(t) + V_{2,a}^{d}.X_{2,a,r}^{d,v,1,s,x,[1,3]}(t) - \left(\phi_a.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t) + \mu\_HPV_2^{d,1,s,x}\right)X_{2,a,r}^{d,v,1,s,x,[2,4]}(t)$$

*Female immune, vaccinated*

$$\frac{dX_{2,a,r}^{d,v,7,s,x,[2,4]}(t)}{dt} = \zeta\_v^{d,2,7}.k\_v_{2,a}^{2,7}.X_{2,a,r}^{d,v,2,s,x,[2,4]}(t) + V_{2,a}^{d}.X_{2,a,r}^{d,v,7,s,x,[1,3]}(t) - \left(\zeta\_v^{d,7,1}.k\_v_{2,a}^{7,1} + \phi_a.\xi_{2,a}.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t) + \mu\_HPV_2^{d,7,s,x}\right)X_{2,a,r}^{d,v,7,s,x,[2,4]}(t)$$

*Female HPV-infected, vaccinated*

$$\frac{dX_{2,a,r}^{d,v,2,s,x,[2,4]}(t)}{dt} = \zeta\_v^{d,3,2}.k\_v_{2,a}^{3,2}.X_{2,a,r}^{d,v,3,s,x,[2,4]}(t) + \phi_a.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t).X_{2,a,r}^{d,v,2,s,x,[2,4]}(t) + \phi_a.\xi_{2,a}.\text{ж}_d.\psi\_HPV_2.\lambda\_vHPV_{2,a,r}(t).X_{2,a,r}^{d,v,7,s,x,[2,4]}(t) - \left(\zeta\_v^{d,2,7}.k\_v_{2,a}^{2,7} + \zeta\_v^{d,2,3}.k\_v_{2,a}^{2,3} + \mu\_HPV_2^{d,2,s,x}\right)X_{2,a,r}^{d,v,2,s,x,[2,4]}(t)$$

*Female CIN1*

$$\frac{dX_{2,a,r}^{d,v,3,s,x,p}(t)}{dt} = \zeta\_v^{d,4,3}.k\_v_{2,a}^{4,3}.X_{2,a,r}^{d,v,4,s,x,p}(t) + \zeta\_v^{d,2,3}.k\_v_{2,a}^{2,3}.X_{2,a,r}^{d,v,2,s,x,p}(t) - \left(\zeta\_v^{d,3,4}.k\_v_{2,a}^{3,4} + \zeta\_v^{d,3,2}.k\_v_{2,a}^{3,2} + \mu\_HPV_2^{d,3,s,x}\right)X_{2,a,r}^{d,v,3,s,x,p}(t)$$

*Female CIN2*

$$\frac{dX_{2,a,r}^{d,v,4,s,x,p}(t)}{dt} = \zeta\_v^{d,5,4}.k\_v_{2,a}^{5,4}.X_{2,a,r}^{d,v,5,s,x,p}(t) + \zeta\_v^{d,3,4}.k\_v_{2,a}^{3,4}.X_{2,a,r}^{d,v,3,s,x,p}(t) - \left(\zeta\_v^{d,4,5}.k\_v_{2,a}^{4,5} + \zeta\_v^{d,4,3}.k\_v_{2,a}^{4,3} + \mu\_HPV_2^{d,4,s,x}\right)X_{2,a,r}^{d,v,4,s,x,p}(t)$$

*Female CIN3*

$$\frac{dX_{2,a,r}^{d,v,5,s,x,p}(t)}{dt} = \zeta\_v^{d,4,5}.k\_v_{2,a}^{4,5}.X_{2,a,r}^{d,v,4,s,x,p}(t) - \left(\zeta\_v^{d,5,6}.k\_v_{2,a}^{5,6} + \zeta\_v^{d,5,4}.k\_v_{2,a}^{5,4} + \mu\_HPV_2^{d,5,s,x}\right)X_{2,a,r}^{d,v,5,s,x,p}(t)$$

***Non-vaccine-targeted HPV types and precancer equations***

The non-vaccine-type HPV and precancer equations follow the same pattern as the vaccine-type HPV equations with a few updates. All values of *s* equal the values of *h* in the vaccine-type equations, and *h* equals any value. Vaccination does not depend on non-vaccine-type HPV infection status.

***Cervical cancer equations***

*Female cervical cancer, local*

*(where h=6)*

$$\frac{dX_{2,a,r}^{d,v,6,s,x,p}(t)}{dt} = \zeta\_v^{d,5,6}.k\_v_{2,a}^{5,6}.X_{2,a,r}^{d,v,5,s,x,p}(t)$$

*(where s=6)*

$$\frac{dX_{2,a,r}^{d,v,h,6,x,p}(t)}{dt} = \zeta\_v^{d,5,6}.k\_v_{2,a}^{5,6}.X_{2,a,r}^{d,v,h,6,x,p}(t)$$

*(where h=6 or s=6)*

$$\frac{dX_{2,a,r}^{d,v,h,s,1,p}(t)}{dt} = -\left(\varphi_2^{h,s,1,2} + \mu\_HPV_2^{d,h,s,1}\right)X_{2,a,r}^{d,v,h,s,1,p}(t)$$

*Female cervical cancer, regional (where h=6 or s=6)*

$$\frac{dX_{2,a,r}^{d,v,h,s,2,p}(t)}{dt} = \varphi_2^{h,s,1,2}.X_{2,a,r}^{d,v,h,s,1,p}(t) - \left(\varphi_2^{h,s,2,3} + \mu\_HPV_2^{d,h,s,2}\right)X_{2,a,r}^{d,v,h,s,2,p}(t)$$

*Female cervical cancer, distant (where h=6 or s=6)*

$$\frac{dX_{2,a,r}^{d,v,h,s,3,p}(t)}{dt} = \varphi_2^{h,s,2,3}.X_{2,a,r}^{d,v,h,s,2,p}(t) - \left(\mu\_HPV_2^{d,h,s,3}\right)X_{2,a,r}^{d,v,h,s,3,p}(t)$$

## References


1. Wingo PA, Cardinez CJ, Landis SH, Greenlee RT, Ries LA, Anderson RN, et al. Long-term trends in cancer mortality in the United States, 1930-1998. Cancer. 2003;97(12 Suppl):3133-275.
2. Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, et al. The challenges of organising cervical screening programmes in the 15 old member states of the European Union. European journal of cancer (Oxford, England : 1990). 2009;45(15):2671-8.
3. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. The New England journal of medicine. 2020;383(14):1340-8.
4. Simms KT, Steinberg J, Caruana M, Smith MA, Lew J-B, Soerjomataram I, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. The Lancet Oncology. 2019;20(3):394-407.
5. Louie KS, de Sanjose S, Mayaud P. Epidemiology and prevention of human papillomavirus and cervical cancer in sub-Saharan Africa: a comprehensive review. Tropical medicine & international health : TM & IH. 2009;14(10):1287-302.
6. Bruni L, Saura-Lázaro A, Montoliu A, Brotons M, Alemany L, Diallo MS, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010–2019. Preventive medicine. 2021;144:106399.
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.
8. Kenya Ministry of Health. 2012 Kenya AIDS Indicator Survey (KAIS). Nairobi, Kenya: Ministry of Health 2014.
9. Special feature: immunization and COVID-19 [press release]. Geneva, Switzerland: World Health Organization2021.
10. Ruffieux Y, Muchengeti M, Egger M, Efthimiou O, Bartels L, Olago V, et al. Immunodeficiency and Cancer in 3.5 Million People Living with Human Immunodeficiency Virus: the South African HIV Cancer Match Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021.
11. Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah ASV, et al. Estimates of the global burden of cervical cancer associated with HIV. The Lancet Global Health. 2020.
12. Abraham AG, D'Souza G, Jing Y, Gange SJ, Sterling TR, Silverberg MJ, et al. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. Journal of acquired immune deficiency syndromes (1999). 2013;62(4):405-13.
13. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. Journal of the National Cancer Institute. 2005;97(6):425-32.
14. Kenya Ministry of Health. Kenya HIV Estimates Report. Nairobi: Kenya Ministry of Health; 2018.
15. Borgdorff MW, Kwaro D, Obor D, Otieno G, Kamire V, Odongo F, et al. HIV incidence in western Kenya during scale-up of antiretroviral therapy and voluntary medical male circumcision: a population-based cohort analysis. The lancet HIV. 2018;5(5):e241-e9.
16. UNAIDS. UNAIDS Data Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2020.
17. Kenya Ministry of Health National AIDS & STI Control Program. Kenya Population-based HIV Impact Assessment (KENPHIA) 2018. Nairobi, Kenya: National AIDS & STI Control Program; 2020.
18. UNAIDS. Women and HIV — A spotlight on adolescent girls and young women. Geneva, Switzerland: UNAIDS; 2019.
19. Houlihan CF, Larke NL, Watson-Jones D, Smith-McCune KK, Shiboski S, Gravitt PE, et al. Human papillomavirus infection and increased risk of HIV acquisition. A systematic review and meta-analysis. AIDS (London, England). 2012;26(17):2211-22.
20. Looker KJ, Rönn MM, Brock PM, Brisson M, Drolet M, Mayaud P, et al. Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and meta-analyses of

longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. Journal of the International AIDS Society. 2018;21(6):e25110-e.
21. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet Infectious diseases. 2007;7(7):453-9.
22. WHO. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Heath Organization; 2020.
23. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020;395(10224):575-90.
24. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020;395(10224):591-603.
25. Campos NG, Lince-Deroche N, Chibwesha CJ, Firnhaber C, Smith JS, Michelow P, et al. Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):195-205.
26. Tan N, Sharma M, Winer R, Galloway D, Rees H, Barnabas RV. Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa. Vaccine. 2018;36(32 Pt A):4830-6.
27. Hall MT, Smith MA, Simms KT, Barnabas R, Murray JM, Canfell K. Elimination of cervical cancer in Tanzania: Modelled analysis of elimination in the context of endemic HIV infection and active HIV control. International journal of cancer. 2021.
28. Baussano I, Lazzarato F, Ronco G, Dillner J, Franceschi S. Benefits of catch-up in vaccination against human papillomavirus in medium- and low-income countries. International journal of cancer. 2013;133(8):1876-81.
29. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol. 2003;157(3):218-26.
30. Røttingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sexually transmitted diseases. 2001;28(10):579-97.
31. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2015;372(6):509-18.
32. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 1992;41(Rr-17):1-19.
33. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. Current opinion in HIV and AIDS. 2017;12(1):6-11.
34. Rohner E, Bütikofer L, Schmidlin K, Sengayi M, Maskew M, Giddy J, et al. Cervical cancer risk in women living with HIV across four continents: A multicohort study. International journal of cancer. 2020;146(3):601-9.
35. Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, et al. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013;57(11):1638-47.
36. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148(10):728-36.
37. UNAIDS. Global AIDS update 2019 — Communities at the centre. Geneva, Switzerland: UNAIDS; 2019.

38. Birdthistle I, Tanton C, Tomita A, de Graaf K, Schaffnit SB, Tanser F, et al. Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis. The Lancet Global Health. 2019;7(11):e1521-e40.
39. Gillison ML, Shah KV. Chapter 9: Role of Mucosal Human Papillomavirus in Nongenital Cancers. JNCI Monographs. 2003;2003(31):57-65.
40. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. The Lancet Oncology. 2009;10(4):321-2.
41. Smith JS, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of infection with human papillomavirus in females: a global review. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2008;43(4 Suppl):S5-25, S.e1-41.
42. Ogembo RK, Gona PN, Seymour AJ, Park HS, Bain PA, Maranda L, et al. Prevalence of human papillomavirus genotypes among African women with normal cervical cytology and neoplasia: a systematic review and meta-analysis. PloS one. 2015;10(4):e0122488.
43. Winer RL, Hughes JP, Feng Q, Xi LF, Cherne S, O'Reilly S, et al. Early natural history of incident, type-specific human papillomavirus infections in newly sexually active young women. Cancer Epidemiol Biomarkers Prev. 2011;20(4):699-707.
44. Marrazzo JM, Rabe L, Kelly C, Richardson B, Deal C, Schwartz JL, et al. Tenofovir Gel for Prevention of Herpes Simplex Virus Type 2 Acquisition: Findings From the VOICE Trial. The Journal of infectious diseases. 2019;219(12):1940-7.
45. Wang C, Wright TC, Denny L, Kuhn L. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. The Journal of infectious diseases. 2011;203(4):479-86.
46. Feng Q, Cherne S, Winer RL, Balasubramanian A, Lee SK, Hawes SE, et al. Development and evaluation of a liquid bead microarray assay for genotyping genital human papillomaviruses. Journal of clinical microbiology. 2009;47(3):547-53.
47. Averbach SH, Gravitt PE, Nowak RG, Celentano DD, Dunbar MS, Morrison CS, et al. The association between cervical human papillomavirus infection and HIV acquisition among women in Zimbabwe. AIDS (London, England). 2010;24(7):1035-42.
48. Smith-McCune KK, Shiboski S, Chirenje MZ, Magure T, Tuveson J, Ma Y, et al. Type-specific cervico-vaginal human papillomavirus infection increases risk of HIV acquisition independent of other sexually transmitted infections. PloS one. 2010;5(4):e10094.
49. Gallagher KE, Baisley K, Grosskurth H, Vallely A, Kapiga S, Vandepitte J, et al. The Association Between Cervical Human Papillomavirus Infection and Subsequent HIV Acquisition in Tanzanian and Ugandan Women: A Nested Case-Control Study. The Journal of infectious diseases. 2016;214(1):87-95.
50. Looker KJ, Elmes JAR, Gottlieb SL, Schiffer JT, Vickerman P, Turner KME, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. The Lancet Infectious diseases. 2017;17(12):1303-16.
51. PATH. Global HPV Vaccine Introduction Overview: PATH; 2020 [Available from: https://path.azureedge.net/media/documents/Global_HPV_Vaccine_Intro_Overview_Slides_webversion_2020May.pdf.
52. Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. EClinicalMedicine. 2020;22:100293.
53. Nakagawa M, Stites DP, Palefsky JM, Kneass Z, Moscicki AB. CD4-positive and CD8-positive cytotoxic T lymphocytes contribute to human papillomavirus type 16 E6 and E7 responses. Clin Diagn Lab Immunol. 1999;6(4):494-8.
54. Wentzensen N, Schiffman M, Dunn T, Zuna RE, Gold MA, Allen RA, et al. Multiple human papillomavirus genotype infections in cervical cancer progression in the study to understand cervical cancer early endpoints and determinants. International journal of cancer. 2009;125(9):2151-8.

55. Zetola NM, Bernstein KT, Wong E, Louie B, Klausner JD. Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs. Journal of acquired immune deficiency syndromes (1999). 2009;50(5):546-51.
56. Burchell AN, Richardson H, Mahmud SM, Trottier H, Tellier PP, Hanley J, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. Am J Epidemiol. 2006;163(6):534-43.
57. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet (London, England). 2001;357(9263):1149-53.
58. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 2020;8(2):e191-e203.
59. American Cancer Society. Global cancer facts and figures, 3rd edition. Atlanta: American Cancer Society; 2015.
60. De Vuyst H, Alemany L, Lacey C, Chibwesha CJ, Sahasrabuddhe V, Banura C, et al. The burden of human papillomavirus infections and related diseases in sub-saharan Africa. Vaccine. 2013;31 Suppl 5:F32-46.
61. Bruni L, Barrionuevo-Rosas L, Albero G, Serrano B, Mena M, Gómez D, et al. Human Papillomavirus and Related Diseases in the World. Summary Report 2017. . ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre); 2017.
62. Clifford GM, Franceschi S, Keiser O, Schöni-Affolter F, Lise M, Dehler S, et al. Immunodeficiency and the risk of cervical intraepithelial neoplasia 2/3 and cervical cancer: A nested case-control study in the Swiss HIV cohort study. International journal of cancer. 2016;138(7):1732-40.
63. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. Journal of the National Cancer Institute. 2005;97(8):577-86.
64. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(21):2376-83.
65. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. HIV Infection and Survival Among Women With Cervical Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(31):3749-57.
66. UNAIDS. Global AIDS update 2016. Geneva, Switzerland: UNAIDS; 2016 January 8, 2018.
67. Hariri S, Bennett NM, Niccolai LM, Schafer S, Park IU, Bloch KC, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States - 2008-2012. Vaccine. 2015;33(13):1608-13.
68. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. European journal of cancer (Oxford, England : 1990). 2013;49(15):3262-73.
69. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. The Lancet Global health. 2016;4(7):e453-63.
70. Parham GP, Mwanahamuntu MH, Kapambwe S, Muwonge R, Bateman AC, Blevins M, et al. Population-level scale-up of cervical cancer prevention services in a low-resource setting: development, implementation, and evaluation of the cervical cancer prevention program in Zambia. PloS one. 2015;10(4):e0122169.
71. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. PLoS medicine. 2008;5(6):e132.
72. Habbema D, Weinmann S, Arbyn M, Kamineni A, Williams AE, I MCMdK, et al. Harms of cervical cancer screening in the United States and the Netherlands. International journal of cancer. 2017;140(5):1215-22.
73. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR

Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2009;58(Rr-4):1-207; quiz CE1-4.
74. Dryden-Peterson S, Medhin H, Kebabonye-Pusoentsi M, Seage GR, 3rd, Suneja G, Kayembe MK, et al. Cancer Incidence following Expansion of HIV Treatment in Botswana. PloS one. 2015;10(8):e0135602.
75. Adler DH, Kakinami L, Modisenyane T, Tshabangu N, Mohapi L, De Bruyn G, et al. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. AIDS (London, England). 2012;26(13):1645-52.
76. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
77. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. International journal of epidemiology. 2007;36(3):666-76.
78. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed). 2016;355:i4919.
79. Banura C, Franceschi S, van Doorn LJ, Arslan A, Kleter B, Wabwire-Mangen F, et al. Prevalence, incidence and clearance of human papillomavirus infection among young primiparous pregnant women in Kampala, Uganda. International journal of cancer. 2008;123(9):2180-7.
80. Banura C, Sandin S, Van Doorn LJ, Quint W, Kleter B, Wabwire-Mangen F, et al. Type-specific incidence, clearance and predictors of cervical human papillomavirus infections (HPV) among young women: A prospective study in Uganda. Infectious agents and cancer. 2010;5(1).
81. Denny L, Boa R, Williamson AL, Allan B, Hardie D, Stan R, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstetrics and gynecology. 2008;111(6):1380-7.
82. Lillo FB, Ferrari D, Veglia F, Origoni M, Grasso MA, Lodini S, et al. Human papillomavirus infection and associated cervical disease in human immunodeficiency virus-infected women: effect of highly active antiretroviral therapy. The Journal of infectious diseases. 2001;184(5):547-51.
83. Mane A, Sahasrabuddhe VV, Nirmalkar A, Risbud AR, Sahay S, Bhosale RA, et al. Rates and determinants of incidence and clearance of cervical HPV genotypes among HIV-seropositive women in Pune, India. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2016;88:26-32.
84. Mbulawa ZZ, Marais DJ, Johnson LF, Coetzee D, Williamson AL. Impact of human immunodeficiency virus on the natural history of human papillomavirus genital infection in South African men and women. The Journal of infectious diseases. 2012;206(1):15-27.
85. Minkoff H, Zhong Y, Burk RD, Palefsky JM, Xue X, Watts DH, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. The Journal of infectious diseases. 2010;201(5):681-90.
86. Phelan DF, Gange SJ, Ahdieh-Grant L, Mehta SH, Kirk GD, Shah K, et al. Determinants of newly detected human papillomavirus infection in HIV-infected and HIV-uninfected injection drug using women. Sexually transmitted diseases. 2009;36(3):149-56.
87. Safaeian M, Kiddugavu M, Gravitt PE, Gange SJ, Ssekasanvu J, Murokora D, et al. Determinants of incidence and clearance of high-risk human papillomavirus infections in rural Rakai, Uganda. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1300-7.
88. Shrestha S, Sudenga SL, Smith JS, Bachmann LH, Wilson CM, Kempf MC. The impact of highly active antiretroviral therapy on prevalence and incidence of cervical human papillomavirus infections in HIV-positive adolescents. BMC infectious diseases. 2010;10:295.
89. Xie X, Strickler HD, Xue X. Additive hazard regression models: an application to the natural history of human papillomavirus. Computational and mathematical methods in medicine. 2013;2013:796270.
90. Koshiol JE, Schroeder JC, Jamieson DJ, Marshall SW, Duerr A, Heilig CM, et al. Time to clearance of human papillomavirus infection by type and human immunodeficiency virus serostatus. International journal of cancer. 2006;119(7):1623-9.

91. Blitz S, Baxter J, Raboud J, Walmsley S, Rachlis A, Smaill F, et al. Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. The Journal of infectious diseases. 2013;208(3):454-62.
92. Whitham HK, Hawes SE, Chu H, Oakes JM, Lifson AR, Kiviat NB, et al. A Comparison of the Natural History of HPV Infection and Cervical Abnormalities among HIV-Positive and HIV-Negative Women in Senegal, Africa. Cancer Epidemiol Biomarkers Prev. 2017;26(6):886-94.
93. Ahdieh L, Munoz A, Vlahov D, Trimble CL, Timpson LA, Shah K. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and -seronegative women. Am J Epidemiol. 2000;151(12):1148-57.
94. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. The Journal of infectious diseases. 2004;190(1):37-45.
95. Rowhani-Rahbar A, Hawes SE, Sow PS, Toure P, Feng Q, Dem A, et al. The impact of HIV status and type on the clearance of human papillomavirus infection among Senegalese women. The Journal of infectious diseases. 2007;196(6):887-94.
96. Duerr A, Paramsothy P, Jamieson DJ, Heilig CM, Klein RS, Cu-Uvin S, et al. Effect of HIV infection on atypical squamous cells of undetermined significance. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;42(6):855-61.
97. Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, et al. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. Jama. 2000;283(8):1031-7.
98. Massad LS, Ahdieh L, Benning L, Minkoff H, Greenblatt RM, Watts H, et al. Evolution of cervical abnormalities among women with HIV-1: evidence from surveillance cytology in the women's interagency HIV study. Journal of acquired immune deficiency syndromes (1999). 2001;27(5):432-42.
99. Delmas MC, Larsen C, van Benthem B, Hamers FF, Bergeron C, Poveda JD, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. AIDS (London, England). 2000;14(12):1775-84.
100. Firnhaber C, Westreich D, Schulze D, Williams S, Siminya M, Michelow P, et al. Highly active antiretroviral therapy and cervical dysplasia in HIV-positive women in South Africa. J Int AIDS Soc. 2012;15(2):17382.
101. Heard I, Potard V, Costagliola D. Limited impact of immunosuppression and HAART on the incidence of cervical squamous intraepithelial lesions in HIV-positive women. Antiviral therapy. 2006;11(8):1091-6.
102. Kim SC, Messing S, Shah K, Luque AE. Effect of highly active antiretroviral therapy (HAART) and menopause on risk of progression of cervical dysplasia in human immune-deficiency virus- (HIV-) infected women. Infectious diseases in obstetrics and gynecology. 2013;2013:784718.
103. Hawes SE, Critchlow CW, Sow PS, Toure P, N'Doye I, Diop A, et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus type 1 (HIV-1) and HIV-2. Journal of the National Cancer Institute. 2006;98(2):100-9.
104. Massad LS, Evans CT, Strickler HD, Burk RD, Watts DH, Cashin L, et al. Outcome after negative colposcopy among human immunodeficiency virus-infected women with borderline cytologic abnormalities. Obstetrics and gynecology. 2005;106(3):525-32.
105. Zeier MD, Botha MH, van der Merwe FH, Eshun-Wilson I, van Schalkwyk M, la Grange M, et al. Progression and persistence of low-grade cervical squamous intraepithelial lesions in women living with human immunodeficiency virus. Journal of lower genital tract disease. 2012;16(3):243-50.
106. Six C, Heard I, Bergeron C, Orth G, Poveda JD, Zagury P, et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. AIDS (London, England). 1998;12(9):1047-56.
107. Kelly HA, Sawadogo B, Chikandiwa A, Segondy M, Gilham C, Lompo O, et al. Epidemiology of High-risk Human Papillomavirus and Cervical Lesions in African women living with HIV/AIDS: Effect of Anti-Retroviral Therapy. AIDS (London, England). 2016.

108. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu JH, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. Journal of Infectious Diseases. 2004;190(8):1413-21.
109. Massad LS, Evans CT, Minkoff H, Watts DH, Strickler HD, Darragh T, et al. Natural history of grade 1 cervical intraepithelial neoplasia in women with human immunodeficiency virus. Obstetrics and gynecology. 2004;104(5 Pt 1):1077-85.
110. Ahdieh-Grant L, Li R, Levine AM, Massad LS, Strickler HD, Minkoff H, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. Journal of the National Cancer Institute. 2004;96(14):1070-6.
111. Del Mistro A, Bertorelle R, Franzetti M, Cattelan A, Torrisi A, Giordani MT, et al. Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2004;38(5):737-42.
112. Omar T, Schwartz S, Hanrahan C, Modisenyane T, Tshabangu N, Golub JE, et al. Progression and regression of premalignant cervical lesions in HIV-infected women from Soweto: a prospective cohort. AIDS (London, England). 2011;25(1):87-94.
113. Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. The Journal of infectious diseases. 2001;184(6):682-90.
114. Clifford GM, de Vuyst H, Tenet V, Plummer M, Tully S, Franceschi S. Effect of HIV Infection on Human Papillomavirus Types Causing Invasive Cervical Cancer in Africa. Journal of acquired immune deficiency syndromes (1999). 2016;73(3):332-9.
115. Strickler HD, Palefsky JM, Shah KV, Anastos K, Klein RS, Minkoff H, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. Journal of the National Cancer Institute. 2003;95(14):1062-71.
116. Massad LS, Xie X, Burk RD, D'Souza G, Darragh TM, Minkoff H, et al. Association of cervical precancer with human papillomavirus types other than 16 among HIV co-infected women. American journal of obstetrics and gynecology. 2016;214(3):354.e1-6.
117. Mbulawa ZZA, Coetzee D, Williamson A-L. Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. BMC infectious diseases. 2015;15:459-.
118. Massad LS, Xie X, D'Souza G, Darragh TM, Minkoff H, Wright R, et al. Incidence of cervical precancers among HIV-seropositive women. American journal of obstetrics and gynecology. 2015;212(5):606.e1-8.
119. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(12):3202-9.
120. Brown MR, Noffsinger A, First MR, Penn I, Husseinzadeh N. HPV subtype analysis in lower genital tract neoplasms of female renal transplant recipients. Gynecologic oncology. 2000;79(2):220-4.
121. Dugué PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. Expert review of anticancer therapy. 2013;13(1):29-42.
122. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet (London, England). 2007;370(9581):59-67.
123. Nicol AF, Fernandes AT, Bonecini-Almeida Mda G. Immune response in cervical dysplasia induced by human papillomavirus: the influence of human immunodeficiency virus-1 co-infection -- review. Memorias do Instituto Oswaldo Cruz. 2005;100(1):1-12.
124. Doorbar J. Latent papillomavirus infections and their regulation. Current opinion in virology. 2013;3(4):416-21.
125. Grant PM, Zolopa AR. When to start ART in the setting of acute AIDS-related opportunistic infections: the time is now! Curr HIV/AIDS Rep. 2012;9(3):251-8.
126. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. The Cochrane database of systematic reviews. 2010;2010(3):Cd008272.

127. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet (London, England). 2009;373(9672):1352-63.
128. Rohner E, Sengayi M, Goeieman B, Michelow P, Firnhaber C, Maskew M, et al. Cervical cancer risk and impact of Pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. International journal of cancer. 2017;141(3):488-96.
129. van den Dries L, Claassen MAA, Groothuismink ZMA, van Gorp E, Boonstra A. Immune activation in prolonged cART-suppressed HIV patients is comparable to that of healthy controls. Virology. 2017;509:133-9.
130. Landy R, Pesola F, Castañón A, Sasieni P. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case-control study. British journal of cancer. 2016;115(9):1140-6.
131. Ng'ang'a A, Nyangasi M, Nkonge NG, Gathitu E, Kibachio J, Gichangi P, et al. Predictors of cervical cancer screening among Kenyan women: results of a nested case-control study in a nationally representative survey. BMC public health. 2018;18(Suppl 3):1221.
132. Clifford GM, Franceschi S, Keiser O, Schoni-Affolter F, Lise M, Dehler S, et al. Immunodeficiency and the risk of cervical intraepithelial neoplasia 2/3 and cervical cancer: A nested case-control study in the Swiss HIV cohort study. International journal of cancer. 2016;138(7):1732-40.
133. Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS (London, England). 2018;32(6):795-808.
134. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. The Cochrane database of systematic reviews. 2018;5:Cd009069.
135. Kjaer SK, Nygard M, Dillner J, Brooke Marshall J, Radley D, Li M, et al. A 12-Year Follow-up on the Long-Term Effectiveness of the Quadrivalent Human Papillomavirus Vaccine in 4 Nordic Countries. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018;66(3):339-45.
136. Mugo N, Eckert LO, Odero L, Gakuo S, Ngure K, Celum C, et al. Antibody responses to prophylactic quadrivalent human papillomavirus vaccine at 48 months among HIV-infected girls and boys ages 9-14 in Kenya, Africa. Vaccine. 2021.
137. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-14.
138. Ochalek J, Abbas K, Claxton K, Jit M, Lomas J. Assessing the value of human papillomavirus vaccination in Gavi-eligible low-income and middle-income countries. BMJ global health. 2020;5(10).
139. WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2016 – conclusions and recommendations. Releve epidemiologique hebdomadaire. 2016;91(48):561-82.
140. Hall MT, Smith MA, Simms KT, Barnabas RV, Canfell K, Murray JM. The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: A modelling study. PloS one. 2020;15(5):e0231388.
141. United Nations Department of Economic and Social Affairs. World Population Prospects Geneva, Switzerland: United Nations; 2019 [Available from: https://population.un.org/wpp/Download/Standard/Population/.
142. Kenya Ministry of Health National AIDS & STI Control Program. The Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya. Nairobi: Kenya Ministry of Health 2018 August.
143. Kenya Ministry of Health and Sanitation. 2007 Kenya AIDS Indicator Survey (KAIS). Nairobi, Kenya: Kenya Ministry of Health and Sanitation,; 2009.
144. Central Bureau of Statistics CBSK, Ministry of Health MOHK, Macro ORC. Kenya Demographic and Health Survey 2003. Calverton, Maryland, USA: CBS, MOH, and ORC Macro; 2004.
145. Kenya National Bureau of Statistics - KNBS, National AIDS Control Council/Kenya, National AIDS/STD Control Programme/Kenya, Health MoP, Sanitation/Kenya, Kenya Medical Research Institute. Kenya Demographic and Health Survey 2008-09. Calverton, Maryland, USA: KNBS and ICF Macro; 2010.

146. Luchters SM, Vanden Broeck D, Chersich MF, Nel A, Delva W, Mandaliya K, et al. Association of HIV infection with distribution and viral load of HPV types in Kenya: a survey with 820 female sex workers. BMC infectious diseases. 2010;10:18.
147. Yamada R, Sasagawa T, Kirumbi LW, Kingoro A, Karanja DK, Kiptoo M, et al. Human papillomavirus infection and cervical abnormalities in Nairobi, Kenya, an area with a high prevalence of human immunodeficiency virus infection. Journal of medical virology. 2008;80(5):847-55.
148. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5):E359-86.
149. Bosch FX, Robles C, Díaz M, Arbyn M, Baussano I, Clavel C, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nature Reviews Clinical Oncology. 2016;13(2):119-32.
150. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology. 2010;11(11):1048-56.
151. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England journal of medicine. 2007;356(19):1928-43.
152. Ahmad OB, Boschi Pinto C, Lopez AD. Age Standardization of Rates: A New WHO Standard. GPE Discussion Paper Series: No 31. 2001:10-2.
153. Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boily M-C, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. The Lancet. 2019.
154. Kim JJ, Simms KT, Killen J, Smith MA, Burger EA, Sy S, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLoS medicine. 2021;18(3):e1003534.
155. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017. Releve epidemiologique hebdomadaire. 2017;92(19):241-68.
156. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012;30 Suppl 5:F123-38.
157. World Health Organization. Chapter 4. Health Sector Interventions. 2016. In: Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations – 2016 Update [Internet]. Geneva. Available from: https://www.ncbi.nlm.nih.gov/books/NBK379695/.
158. Rositch AF, Gravitt PE, Smith JS. Growing evidence that HPV infection is associated with an increase in HIV acquisition: exploring the issue of HPV vaccination. Sexually transmitted infections. 2013;89(5):357-.
159. van der Loeff MF, Nyitray AG, Giuliano AR. HPV vaccination to prevent HIV infection: time for randomized controlled trials. Sexually transmitted diseases. 2011;38(7):640-3.
160. Brotherton J, Gertig D, Chappell G, Rowlands L, Saville M. Catching up with the catch-up: HPV vaccination coverage data for Australian women aged 18-26 years from the National HPV Vaccination Program Register. Communicable diseases intelligence quarterly report. 2011;35(2):197-201.
161. Agénor M, Murchison GR, Chen JT, Bowen DJ, Rosenthal MB, Haneuse S, et al. Impact of the Affordable Care Act on human papillomavirus vaccination initiation among lesbian, bisexual, and heterosexual U.S. women. Health services research. 2020;55(1):18-25.
162. Ouma PN, Masai AN, Nyadera IN. Health coverage and what Kenya can learn from the COVID-19 pandemic. J Glob Health. 2020;10(2):020362-.
163. Kenya Ministry of Health. COVID-19 Outbreaks in Kenya. . Nairobi, Kenya: Kenya Ministry of Health 2020.
164. Basra E, Kazungu J, Organi S, Kabia E, Ogero M, Kasera K. Assessing the Indirect Health Effects of the COVID-19 Pandemic in Kenya. Washington, DC: Center for Global Development; 2021.
165. Amid Recession, Sub-Saharan Africa Poised for Recovery [press release]. 2021.

166. Mahumud RA, Alam K, Keramat SA, Ormsby GM, Dunn J, Gow J. Cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review. PloS one. 2020;15(6):e0233499.
167. Whitworth HS, Gallagher KE, Howard N, Mounier-Jack S, Mbwanji G, Kreimer AR, et al. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials. Vaccine. 2020;38(6):1302-14.
168. Baisley KJ, Whitworth HS, Changalucha J, Pinto L, Dillner J, Kapiga S, et al. A dose-reduction HPV vaccine immunobridging trial of two HPV vaccines among adolescent girls in Tanzania (the DoRIS trial) - Study protocol for a randomised controlled trial. Contemporary clinical trials. 2021;101:106266.
169. ClinicalTrials.gov. National Library of Medicine (U.S.). (2000, February 29 – ). The KEN SHE Study on HPV-vaccine Efficacy. Identifier NCT03675256 [Available from: https://clinicaltrials.gov/ct2/show/NCT03675256.
170. ClinicalTrials.gov. National Library of Medicine (U.S.). (2000, February 29 – ). Scientific Evaluation of One or Two Doses of the Bivalent or Nonavalent Prophylactic HPV Vaccines. Identifier NCT03180034 [Available from: https://clinicaltrials.gov/ct2/show/NCT03180034.
171. Kreimer AR, Sampson JN, Porras C, Schiller JT, Kemp T, Herrero R, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. Journal of the National Cancer Institute. 2020;112(10):1038-46.
172. HPV vaccine manufacturers commit to provide enough supply to immunize at least 84 million girls in Gavi countries [press release]. Geneva, Switzerland2020.
173. Kenya Ministry of Health. Kenya National Cancer Screening Guidelines. Nairobi, Kenya: Ministry of Health; 2018.
174. Adewumi K, Nishimura H, Oketch SY, Adsul P, Huchko M. Barriers and Facilitators to Cervical Cancer Screening in Western Kenya: a Qualitative Study. Journal of cancer education : the official journal of the American Association for Cancer Education. 2021.
175. Page CM, Ibrahim S, Park LP, Huchko MJ. Systems-level barriers to treatment in a cervical cancer prevention program in Kenya: Several observational studies. PloS one. 2020;15(7):e0235264.
176. Perehudoff K, Vermandere H, Williams A, Bautista-Arredondo S, De Paepe E, Dias S, et al. Universal cervical cancer control through a right to health lens: refocusing national policy and programmes on underserved women. BMC international health and human rights. 2020;20(1):21.
177. Ragan KR, Buchanan Lunsford N, Lee Smith J, Saraiya M, Aketch M. Perspectives of Screening-Eligible Women and Male Partners on Benefits of and Barriers to Treatment for Precancerous Lesions and Cervical Cancer in Kenya. The oncologist. 2018;23(1):35-43.
178. Rosser JI, Njoroge B, Huchko MJ. Cervical Cancer Stigma in Rural Kenya: What Does HIV Have to Do with It? Journal of cancer education : the official journal of the American Association for Cancer Education. 2016;31(2):413-8.
179. Kemper KE, McGrath CJ, Eckert LO, Kinuthia J, Singa B, Langat A, et al. Correlates of cervical cancer screening among women living with HIV in Kenya: A cross-sectional study. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2021.
180. Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. Sexually transmitted infections. 2017;93(1):56-61.
181. Samwel K, Kahesa C, Mwaiselage J, Gonzalez D, West JT, Wood C, et al. Analytical performance of a low-cost multiplex polymerase chain reaction human papillomavirus genotyping assay for use in Sub-Saharan Africa. Journal of medical virology. 2019;91(2):308-16.
182. Ajenifuja KO, Belinson J, Goldstein A, Desai KT, de Sanjose S, Schiffman M. Designing low-cost, accurate cervical screening strategies that take into account COVID-19: a role for self-sampled HPV typing2. Infectious agents and cancer. 2020;15:61.

183. Davies N, Chersich M, Mullick S, Naidoo N, Makhoba N, Rees H, et al. Integrating Cervical Cancer Screening Into Safer Conception Services to Improve Women's Health Outcomes: A Pilot Study at a Primary Care Clinic in South Africa. Sexually transmitted diseases. 2019;46(2):91-7.
184. Perez-Guzman PN, Chung MH, De Vuyst H, Dalal S, Mutai KK, Muthoni K, et al. The impact of scaling up cervical cancer screening and treatment services among women living with HIV in Kenya: a modelling study. BMJ global health. 2020;5(3):e001886.
185. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. Lancet (London, England). 1999;353(9152):525-35.
186. Gregson S, Adamson S, Papaya S, Mundondo J, Nyamukapa CA, Mason PR, et al. Impact and process evaluation of integrated community and clinic-based HIV-1 control: a cluster-randomised trial in eastern Zimbabwe. PLoS medicine. 2007;4(3):e102.
187. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep. 2011;8(1):62-72.
188. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva, Switzerland: UNAIDS; 2014.
189. World Health Organization. Voluntary medical male circumcision for HIV prevention in 14 priority countries in East and Southern Africa. Geneva, Switzerland: World Health Organization; 2017.
190. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. The New England journal of medicine. 2016;375(9):830-9.
191. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. Journal of acquired immune deficiency syndromes (1999). 2006;43 Suppl 1(Suppl 1):S79-87.
192. The Cochrane Collaboration Effective Practice and Organisation of Care. Data collection form. EPOC Resources for review authors. Oslo, Norway: Norwegian Knowledge Centre for the Health Services; 2013.
193. Kenya National Bureau of Statistics. The 2009 Kenya Population and Housing Census. Nairobi, Kenya: Kenya National Bureau of Statistics; 2010.
194. Kenya National Bureau of Statistics. The 2019 Kenya Population and Housing Census. Nairobi, Kenya: Kenya National Bureau of Statistics; 2020.
195. Ross A, Van der Paal L, Lubega R, Mayanja BN, Shafer LA, Whitworth J. HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. AIDS. 2004;18(5):799-804.
196. Tweya H, Feldacker C, Breeze E, Jahn A, Haddad LB, Ben-Smith A, et al. Incidence of pregnancy among women accessing antiretroviral therapy in urban Malawi: a retrospective cohort study. AIDS and behavior. 2013;17(2):471-8.
197. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet (London, England). 2004;364(9441):1236-43.
198. Badri M, Lawn SD, Wood R. Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study. Lancet (London, England). 2006;368(9543):1254-9.
199. Kenya National Bureau of S, Ministry of HK, National ACCK, Kenya Medical Research I, National Council for P, Development/Kenya. Kenya Demographic and Health Survey 2014. Rockville, MD, USA; 2015.
200. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 1993;342(1300):137-59.
201. Ferry B, Caraël M, Buvé A, Auvert B, Laourou M, Kanhonou L, et al. Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection. AIDS (London, England). 2001;15:S41-S50.
202. Datta P, Embree JE, Kreiss JK, Ndinya-Achola JO, Braddick M, Temmerman M, et al. Mother-to-child transmission of human immunodeficiency virus type 1: report from the Nairobi Study. The Journal of infectious diseases. 1994;170(5):1134-40.

203. Waruru A, Achia TNO, Muttai H, Ng'ang'a L, Zielinski-Gutierrez E, Ochanda B, et al. Spatial-temporal trend for mother-to-child transmission of HIV up to infancy and during pre-Option B+ in western Kenya, 2007-13. PeerJ. 2018;6:e4427.
204. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. The New England journal of medicine. 2000;342(13):921-9.
205. Hubert JB, Burgard M, Dussaix E, Tamalet C, Deveau C, Le Chenadec J, et al. Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection. The SEROCO Study Group. AIDS. 2000;14(2):123-31.
206. Lingappa JR, Hughes JP, Wang RS, Baeten JM, Celum C, Gray GE, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. PLoS One. 2010;5(9):e12598.
207. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. The Journal of infectious diseases. 2008;198(5):687-93.
208. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;53(8):817-25.
209. Lyles RH, Munoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. Multicenter AIDS Cohort Study. The Journal of infectious diseases. 2000;181(3):872-80.
210. Pantazis N, Morrison C, Amornkul PN, Lewden C, Salata RA, Minga A, et al. Differences in HIV natural history among African and non-African seroconverters in Europe and seroconverters in sub-Saharan Africa. PLoS One. 2012;7(3):e32369.
211. Lewden C, Gabillard D, Minga A, Ekouevi DK, Avit D, Konate I, et al. CD4-specific mortality rates among HIV-infected adults with high CD4 counts and no antiretroviral treatment in West Africa. Journal of acquired immune deficiency syndromes (1999). 2012;59(2):213-9.
212. Maduna PH, Dolan M, Kondlo L, Mabuza H, Dlamini JN, Polis M, et al. Morbidity and mortality according to latest CD4+ cell count among HIV positive individuals in South Africa who enrolled in project Phidisa. PLoS One. 2015;10(4):e0121843.
213. Adler WH, Baskar PV, Chrest FJ, Dorsey-Cooper B, Winchurch RA, Nagel JE. HIV infection and aging: mechanisms to explain the accelerated rate of progression in the older patient. Mech Ageing Dev. 1997;96(1-3):137-55.
214. Brinkhof MW, Boulle A, Weigel R, Messou E, Mathers C, Orrell C, et al. Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. PLoS medicine. 2009;6(4):e1000066.
215. Cornell M, Johnson LF, Wood R, Tanser F, Fox MP, Prozesky H, et al. Twelve-year mortality in adults initiating antiretroviral therapy in South Africa. Journal of the International AIDS Society. 2017;20(1):21902.
216. de Coninck Z, Hussain-Alkhateeb L, Bratt G, Ekstrom AM, Gisslen M, Petzold M, et al. Non-AIDS Mortality Is Higher Among Successfully Treated People Living with HIV Compared with Matched HIV-Negative Control Persons: A 15-Year Follow-Up Cohort Study in Sweden. AIDS patient care and STDs. 2018;32(8):297-305.
217. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. The Lancet Infectious diseases. 2009;9(2):118-29.
218. Denny L, Adewole I, Anorlu R, Dreyer G, Moodley M, Smith T, et al. Human papillomavirus prevalence and type distribution in invasive cervical cancer in sub-Saharan Africa. Int J Cancer. 2014;134(6):1389-98.
219. Dartell M, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. Sexually transmitted diseases. 2012;39(3):201-8.

220. Beachler DC, Jenkins G, Safaeian M, Kreimer AR, Wentzensen N. Natural Acquired Immunity Against Subsequent Genital Human Papillomavirus Infection: A Systematic Review and Meta-analysis. J Infect Dis. 2016;213(9):1444-54.
221. Johnson HC, Elfstrom KM, Edmunds WJ. Inference of type-specific HPV transmissibility, progression and clearance rates: a mathematical modelling approach. PLoS One. 2012;7(11):e49614.
222. Kelly H, Weiss HA, Benavente Y, de Sanjose S, Mayaud P. Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. The lancet HIV. 2018;5(1):e45-e58.
223. Suehiro TT, Damke G, Damke E, de Azevedo Ramos PLR, de Andrade Pereira Silva M, Pelloso SM, et al. Cervical and oral human papillomavirus infection in women living with human immunodeficiency virus (HIV) and matched HIV-negative controls in Brazil. Infectious agents and cancer. 2020;15:31.
224. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. Lancet Oncol. 2010;11(2):165-73.
225. Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS. 2018;32(6):795-808.
226. Campos NG, Burger EA, Sy S, Sharma M, Schiffman M, Rodriguez AC, et al. An updated natural history model of cervical cancer: derivation of model parameters. Am J Epidemiol. 2014;180(5):545-55.
227. Rosillon D, Baril L, Del Rosario-Raymundo MR, Wheeler CM, Skinner SR, Garland SM, et al. Risk of newly detected infections and cervical abnormalities in adult women seropositive or seronegative for naturally acquired HPV-16/18 antibodies. Cancer Med. 2019;8(10):4938-53.
228. Lilian RR, Rees K, Mabitsi M, McIntyre JA, Struthers HE, Peters RPH. Baseline CD4 and mortality trends in the South African human immunodeficiency virus programme: Analysis of routine data. South Afr J HIV Med. 2019;20(1):963.
229. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. Jama. 2016;316(2):171-81.
230. Eisinger RW, Dieffenbach CW, Fauci AS. HIV Viral Load and Transmissibility of HIV Infection: Undetectable Equals Untransmittable. Jama. 2019;321(5):451-2.
231. Kenya Ministry of Health. Kenya AIDS Response Progress Report 2016. Available from: http://nacc.or.ke/wp-content/uploads/2016/11/Kenya-AIDS-Progress-Report_web.pdf.
232. Kenya Ministry of Health National AIDS & STI Control Program. Kenya AIDS Response Progress Report, Progress Towards Zero. Nairobi, Kenya: Kenya Ministry of Health; 2014.
233. Karcher H, Omondi A, Odera J, Kunz A, Harms G. Risk factors for treatment denial and loss to follow-up in an antiretroviral treatment cohort in Kenya. Tropical medicine & international health : TM & IH. 2007;12(5):687-94.
234. Zachariah R, Van Engelgem I, Massaquoi M, Kocholla L, Manzi M, Suleh A, et al. Payment for antiretroviral drugs is associated with a higher rate of patients lost to follow-up than those offered free-of-charge therapy in Nairobi, Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;102(3):288-93.
235. Kenya Ministry of Health National AIDS & STI Control Program. AIDS Response Progress Report Nairobi, Kenya: Kenya Ministry of Health 2016.
236. Waithaka M, Bessinger R. Sexual Behavior and Condom Use in the Context of HIV Prevention in Kenya. Population Services International; 2001.
237. Cherutich P, Brentlinger P, Nduati R, Kiarie JN, Farquhar C. Condom use among sexually active Kenyan female adolescents at risk for HIV-1 infection. AIDS and behavior. 2008;12(6):923-9.
238. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002(1):CD003255.
239. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sexually transmitted diseases. 2002;29(11):725-35.
240. Ho GY, Studentsov YY, Bierman R, Burk RD. Natural history of human papillomavirus type 16 virus-like particle antibodies in young women. Cancer Epidemiol Biomarkers Prev. 2004;13(1):110-6.

241. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. Jama. 2001;285(23):2995-3002.
242. Sanchez-Aleman MA, Uribe-Salas FJ, Lazcano-Ponce EC, Conde-Glez CJ. Human papillomavirus incidence and risk factors among Mexican female college students. Sexually transmitted diseases. 2011;38(4):275-8.
243. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database of Systematic Reviews. 2009(2).
244. Albero G, Castellsagué X, Lin H-Y, Fulp W, Villa LL, Lazcano-Ponce E, et al. Male circumcision and the incidence and clearance of genital human papillomavirus (HPV) infection in men: the HPV Infection in men (HIM) cohort study. BMC infectious diseases. 2014;14:75-.
245. Albero G, Villa LL, Lazcano-Ponce E, Fulp W, Papenfuss MR, Nyitray AG, et al. Male circumcision and prevalence of genital human papillomavirus infection in men: a multinational study. BMC infectious diseases. 2013;13:18-.
246. Vanbuskirk K, Winer RL, Hughes JP, Feng Q, Arima Y, Lee S-K, et al. Circumcision and acquisition of human papillomavirus infection in young men. Sexually transmitted diseases. 2011;38(11):1074-81.
247. Tobian AAR, Kong X, Gravitt PE, Eaton KP, Kigozi G, Serwadda D, et al. Male circumcision and anatomic sites of penile high-risk human papillomavirus in Rakai, Uganda. International journal of cancer. 2011;129(12):2970-5.
248. Tobian AA, Kong X, Wawer MJ, Kigozi G, Gravitt PE, Serwadda D, et al. Circumcision of HIV-infected men and transmission of human papillomavirus to female partners: analyses of data from a randomised trial in Rakai, Uganda. The Lancet Infectious diseases. 2011;11(8):604-12.
249. Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. The Lancet Infectious diseases. 2009;9(11):669-77.
250. Lei JH, Liu LR, Wei Q, Yan SB, Yang L, Song TR, et al. Circumcision Status and Risk of HIV Acquisition during Heterosexual Intercourse for Both Males and Females: A Meta-Analysis. PLoS One. 2015;10(5):e0125436.
251. Wawer MJ, Tobian AAR, Kigozi G, Kong X, Gravitt PE, Serwadda D, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. Lancet (London, England). 2011;377(9761):209-18.
252. Shaffer DN, Bautista CT, Sateren WB, Sawe FK, Kiplangat SC, Miruka AO, et al. The protective effect of circumcision on HIV incidence in rural low-risk men circumcised predominantly by traditional circumcisers in Kenya: two-year follow-up of the Kericho HIV Cohort Study. Journal of acquired immune deficiency syndromes (1999). 2007;45(4):371-9.
253. Fleming PJ, Doshi M, Harper GW, Otieno F, Bailey RC. Integration of voluntary male medical circumcision for HIV prevention into norms of masculinity: findings from Kisumu, Kenya. Culture, health & sexuality. 2020:1-13.
254. de Sanjose S, Serrano B, Tous S, Alejo M, Lloveras B, Quiros B, et al. Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58. JNCI Cancer Spectr. 2018;2(4):pky045.
255. Kenya Ministry of Health and Sanitation. National Guidelines for Prevention and Management of Cervical, Breast and Prostate Cancers. Nairobi, Kenya: Kenya Ministry of Health and Sanitation; 2012.
256. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. PLoS Med. 2008;5(6):e132-e.
257. Chung MH, McKenzie KP, De Vuyst H, Richardson BA, Rana F, Pamnani R, et al. Comparing Papanicolau smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. AIDS (London, England). 2013;27(18):2909-19.
258. Khozaim K, Orang'o E, Christoffersen-Deb A, Itsura P, Oguda J, Muliro H, et al. Successes and challenges of establishing a cervical cancer screening and treatment program in western Kenya. International

journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2014;124(1):12-8.
259. Greene SA, De Vuyst H, John-Stewart GC, Richardson BA, McGrath CJ, Marson KG, et al. Effect of Cryotherapy vs Loop Electrosurgical Excision Procedure on Cervical Disease Recurrence Among Women With HIV and High-Grade Cervical Lesions in Kenya: A Randomized Clinical Trial. Jama. 2019;322(16):1570-9.
260. Kuhn L, Wang C, Tsai WY, Wright TC, Denny L. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. AIDS (London, England). 2010;24(16):2553-61.
261. Hoffman SR, Le T, Lockhart A, Sanusi A, Dal Santo L, Davis M, et al. Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review. International journal of cancer. 2017;141(1):8-23.
262. Luchters SMF, Broeck DV, Chersich MF, Nel A, Delva W, Mandaliya K, et al. Association of HIV infection with distribution and viral load of HPV types in Kenya: a survey with 820 female sex workers. BMC infectious diseases. 2010;10(1):18.
263. Bruni L AG, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human Papillomavirus and Related Diseases in South Africa: Summary Report 17 June 2019.
264. Van Aardt MC, Dreyer G, Richter KL, Becker P. Human papillomavirus-type distribution in South African women without cytological abnormalities: a peri-urban study. Southern African Journal of Gynaecological Oncology. 2013;5(sup1):S21-S7.
265. Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(5):1157-64.
266. Van Aardt MC, Dreyer G, Snyman LC, Richter KL, Becker P, Mojaki SM. Oncogenic and incidental HPV types associated with histologically confirmed cervical intraepithelial neoplasia in HIV-positive and HIV-negative South African women. S Afr Med J. 2016;106(6).
267. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-56.
268. van Aardt MC, Dreyer G, Pienaar HF, Karlsen F, Hovland S, Richter KL, et al. Unique human papillomavirus-type distribution in South African women with invasive cervical cancer and the effect of human immunodeficiency virus infection. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015;25(5):919-25.