MODEL PROFILE
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Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

READER'S GUIDE

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

MODEL PURPOSE

SUMMARY

The purpose of this mathematical model is to study the impact of HPV vaccination accounting for HIV infection dynamics including HIV disease progression by CD4 count and antiretroviral therapy (ART). We created a model that simulates heterosexual HIV transmission and is parameterized to KwaZulu-Natal, South Africa (KZN), a region with high HIV prevalence.

PURPOSE

The model reproduces population-level HIV and HPV disease dynamics and stratifies the population by age, gender, and sexual risk. We model HIV progression by CD4+ T-cell (CD4) count and HIV RNA concentration (viral load). The impact of ART scale-up targeted to HIV-positive persons is also modelled.

HPV progression is modelled by progression through a precancer pathway that leads to cervical cancer. The interaction between HPV and HIV in coinfected subpopulations is modelled by accounting for the increased risk of HPV transmission to an HIV-positive person and the accelerated progression of cervical lesions in HIV-positive women.

Using demographic data from the population under study, the model is calibrated to recapitulate observed patterns of HIV and HPV disease. The population-level impact of HPV vaccination is then assessed by comparing health outcomes in vaccine vs. non-vaccine scenarios.

MODEL OVERVIEW

SUMMARY

There are three key components to the model: 1) Dynamic HPV and HIV transmission, 2) HIV progression and ART scale up, and 3) HPV-related pre-cancer/cancer progression.

PURPOSE

Our dynamic transmission compartmental model examines the impact of HPV vaccination on HIV-positive and HIV-negative women in a high HIV-prevalence setting. Model parameters on transition rates for HIV and HPV disease states were derived by synthesizing relevant findings in the literature. Parameter calibration was performed in order to enhance the model's ability to reflect observed patterns of disease.

BACKGROUND

HPV and HIV infections can interact to increase cervical cancer (CC) risk. The 9-valent HPV (9vHPV) vaccine has high demonstrated effectiveness against HPV types causing 90% of CC. Additionally, one dose of the 9vHPV vaccine has the potential to achieve greater coverage at lower costs than a two-dose schedule. However, the potential impact of single-dose 9vHPV vaccine accounting for HPV-HIV interactions has not been estimated. This model adapts a previously published dynamic compartmental HIV transmission model.

ASSUMPTION OVERVIEW

SUMMARY

This section describes the basic assumptions made by UW's HIV-HPV coinfection model.

BACKGROUND

Compartmental models divide the population under study into various compartments that are characterized by demographic and health-related features. In the present model, this is achieved by stratifying groups according to HIV disease state, HPV disease state, gender, age , and sexual activity.

Maximum likelihood-based calibration is used to calibrate model parameters to various data sources and to infer the value of parameters that cannot be obtained through direct observation.

ASSUMPTION LISTING

In compartmental models, it is assumed that the members within each compartment are homogeneous in nature. As such, the model is not designed to answer questions pertaining to individual-level interventions or health outcomes. However, in the absence of granular individual-level data, the assumption of homogeneity provides for an economical model that can be used to determine the impact of population-level interventions and health outcomes.

Susceptible females can acquire high-risk (HR) HPV infection from a male sexual partner and progress to precancerous lesions categorized as cervical intraepithelial neoplasia, grades 1, 2, or 3 (CIN 1, 2, or 3). HPV infection and CIN1, CIN2, and CIN3 lesions can regress to normal over time and females with CIN3 can develop cervical cancer (categorized in 3 stages: local, regional, and distant). Given the strong connection between HPV infection and cervical cancer incidence, we assume that the pathogenesis of all cervical cancers begins with HPV infection. We assume females who clear their HPV infection can develop low-level natural immunity while males who clear HPV infection do not develop natural immunity. The model estimates the force of HPV infection as a function of sexual mixing (by age and sexual activity), proportion of HPV infected individuals of the opposite sex, and HPV transmission probability, which depends on HIV status and CD4 count if HIV-positive. Once females are infected, the probability of HPV disease progression is governed by age, HIV-status, and CD4 count if infected with HIV.

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HIV-positive females have a higher risk of HPV acquisition and CIN1-2 progression and a lower probability of disease regression and infection clearance. HPV disease progression is inversely related to CD4 count; women at the lowest category CD4 counts are least likely to clear and more likely to experience disease progression.

PARAMETER OVERVIEW

SUMMARY

This section contains the parameters used to inform the natural history model.

BACKGROUND

The UW natural history model is based on data published in the literature. HIV transition rates by CD4 count and viral load level are informed by previous clinical studies. Transition rates for HPV infection and CIN were also informed by existing literature. The transition from CIN3 to cervical cancer was inferred through calibration as this quantity could not be obtained through direct observation.

PARAMETER LISTING OVERVIEW

The parameters used to inform the model follow below:

Population Demographics:

- Population Size – SA 1985 census and scaled to fit KZN's population growth and size profile.

- South Africa's age-specific mortality in 1990, prior to the generalized HIV epidemic. [27] [28]

Sexual History and Sexual Mixing:

- Sexual risk distribution by age and sex. Values are based on Africa Centre data from KwaZulu Natal, South Africa [26]

- Annual number of sexual partnerships by age, gender, and sexual risk. Values are based on Africa Centre data from KwaZulu Natal, South Africa [26] Fertility rate by age and HIV status. Females on ART are assumed to have equal fertility to HIV-negative females. Anderson et al., Ross et al. [12, 29]

- The number of coital acts per partnership by sex, age, and sexual risk group. Values are calibrated to fit age-specific HIV and HPV prevalence data.

- Sexual mixing by age and sexual risk group. The mixing parameter varies from random to assortative, calibrated to fit age-specific HIV incidence and prevalence data.

HIV:

- HIV prevalence from 1990 to 2011. HIV prevalence for 2012 was gathered from a study of Home HIV testing and counseling for HIV in KZN - SA DoH [34], Barnabas et al. [3]

- HIV age-specific prevalence and incidence data - Barnabas et al. [3], Shisana et al. [13], Barnighausen et al. [33]
  HIV prevalence (%) by sex over time in KwaZulu Natal [26]

- HIV-associated mortality. Values are estimates are from observational studies of untreated HIV-positive persons. Persons age 0 to 4 and older than 50 are assumed to have greater mortality as observed. Newell et al. [30], Badri et al. [31], Adler et al. [8]

- Probability of HIV transmission by viral load - Quinn et al., Boily et al. [15, 32]

- The duration of time in each CD4 and viral load stage by sex.

- Proportion of births from HIV-positive females that results in mother-to-child transmission. The rate decreases linearly from 2004 to 2005 and from 2005 to 2008. Bobat et al. [5], Rollins et al. [7], Horwood et al. [6]

- ART coverage over time [35]

HPV and Cervical Cancer:

- HPV prevalence in women and men in South Africa [37]

- HPV prevalence in women without CIN2/3 [40]

- CIN2/3 prevalence by HIV status [40]

- Cervical cancer mortality by stage and HIV status [38, 39]

Component Overview

Summary

This section describes the components of our natural history model.

Overview

There are three key components to the model: 1) Dynamic HPV and HIV transmission, 2) HIV progression and ART scale up, and 3) HPV-related pre-cancer/cancer progression.

Component Listing

Dynamic HPV and HIV transmission: Our model simulates the transmission of HPV and HIV across the population, which is divided into various compartments based on health states (ex. HPV-Infected, HIV-positive, CD4 count etc.) and demographic factors (age, gender, sexual risk level). The rate of infection that a susceptible compartment is subject to depends on: a) the mixing patterns corresponding to the gender, age, and sexual risk level used to describe the compartment, b) the prevalence of infection in other compartments that interact with the susceptible compartment.

HIV progression and ART scale up: HIV progression is simulated by modelling the rate of progression through HIV disease states as described by CD4 count and viral load level. ART scale-up is modelled by representing the rate of ART uptake as a function of time and CD4 count to reflect the reported clinical criteria for ART uptake. In the model, ART uptake reduces the probability of HIV transmission and attenuates a HIV-positive person's rate of progression through the HPV and cervical pre-cancer pathway.

HPV-related pre-cancer/cancer progression: HPV progression is simulated by modelling the rate of progression through HPV disease states. The HPV disease pathway consists of three cervical pre-cancer lesion stages: CIN1, CIN2, and CIN3. The transitions between these stages are modelled as a reversible process to reflect the possibility of spontaneous pre-cancer lesion clearance. Meanwhile, the transition from CIN3 to cervical cancer (CC) is modelled as an irreversible process. The CC associated mortality rate increases with the severity of the cancer, which is described by local, regional, and distant cervical cancer stages in the model.

Further details about the model can be found below:

HIV Natural History:

The natural history of HIV infection is modeled in stages defined by CD4 count and viral load as shown in Figure S1. When a person becomes HIV-infected, s/he enters the acute stage characterized by a short duration and high probability of HIV transmission. The person then progresses through stages of CD4 count and viral load at rates ν^d and ω^v, respectively, where d represents the current CD4 count and v represents the current viral load. The parameters ν^d and ω^v are based on an analysis of disease progression using data from the Partners HSV/HIV and Partners PrEP studies. The average life expectancy from infection to death for untreated persons is 10.7 years.

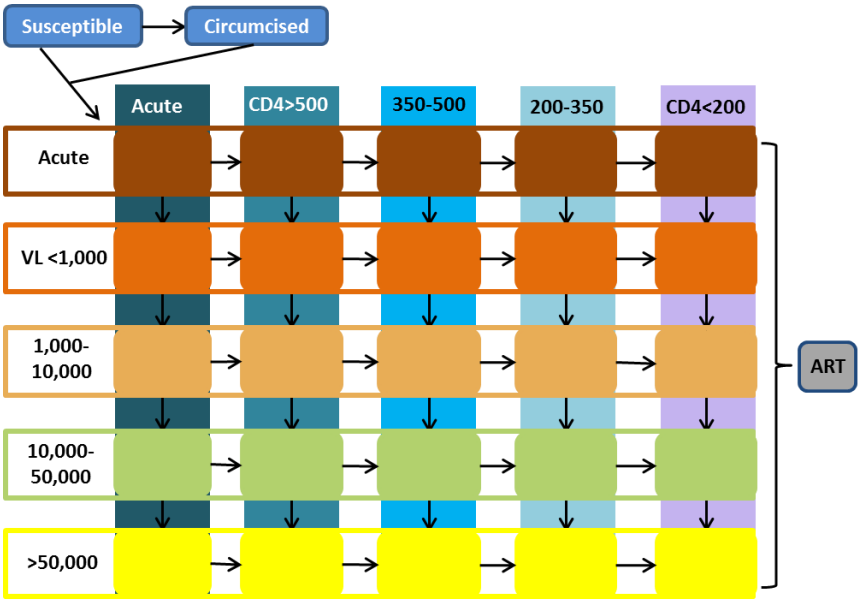

Figure S1. Model transition diagram. A diagram of the natural history of HIV infection. All movement is in one direction except for enrollment in and dropout from interventions from ART.

Ordinary Differential Equations:

The model simulates a population from ages 0 to 79 in five-year age-groups, capturing vertical transmission and aging. The system of ODE's describes the states $X_{a,r}^{g,d,v}(t)$ with the following indices:

- g refers to gender
- $g = 0$ for males; $g = 1$ for females
- d refers to disease state defined by CD4 cell count, and treatment and circumcision status
- $d = 0$ for HIV-negative; $d = 1$ for acute infection; $d = 2$ for CD4 >500 cells/μL; $d = 3$ for CD4 500-350 cells/μL; $d = 4$ for CD4 350–200 cells/μL; $d = 5$ for CD4 <200 cells/μL; $d = 6$ for HIV-negative, circumcised, and no PrEP; $d = 7$ for HIV-negative, circumcised, and on

PrEP; $d = 8$ for HIV-negative, uncircumcised, and on PrEP; $d = 9$ for HIV-positive on ART

- v refers to disease state defined by viral load
- $v = 0$ for HIV-negative; $v = 1$ for acute infection; $v = 2$ for VL<1,000 copies/mL; $v = 3$ for VL 1,000-10,000 copies/mL; $v = 4$ for VL 10,000-50,000 copies/mL; $v = 5$ for VL>50,000 copies/mL; $v = 6$ for HIV-positive and on ART
- a refers to age group
- $a = 0$ for ages 0 to 4; $a = 1$ for ages 5 to 9; … ; $a = 11$ for ages 55 to 59
- r refers to sexual risk group defined by number of sexual partnerships per year
- $r = 0$ for low risk; $r = 1$ for medium risk; $r = 2$ for high risk
- h refers to HPV disease type
- s refers to HPV disease state; 0 = No precancer(h = 1) , infected (h >= 2); 1 = CIN1 (if h > 1); 2 = CIN2; 3 = CIN3; 4 = Cervical Cancer (Local); 5 = Cervical Cancer (Regional); 6 = Cervical Cancer (Distant); 7 = Hysterectomy; 8 = Vaccinated; 9 = Immune

The ODEs for the nine HIV disease states are:

$$\frac{dX_{a,r}^{g,0,0}(t)}{dt} = b_{r,0}^{g,0}(t) + \sigma_{a,r}^{g,0} X_{a,r}^{g,7,0}(t) - \left(\mu_a^g + \lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)\right) X_{a,r}^{g,0,0}(t)$$

$$\begin{aligned}\frac{dX_{a,r}^{g,1,v}(t)}{dt} = {} & b_{r,0}^{g,1}(t) + \lambda_{a,r}^{g,0} X_{a,r}^{g,0,0}(t) + \psi_0 \lambda_{a,r}^{1,0}(t) X_{a,r}^{1,6,v}(t) \\ & + \psi_0 \psi_1 \lambda_{a,r}^{1,1}(t) X_{a,r}^{1,7,0}(t) + \psi_1 \lambda_{a,r}^{g,1}(t) X_{a,r}^{g,9,6}(t) + \sigma_{a,r}^{g,1}(t) X_{a,r}^{g,9,6} \\ & - \left(\mu_a^g + \alpha_a^{g,1} + \nu_1 + \pi_{a,r}^{g,1,v}(t)\right) X_{a,r}^{g,1,v}(t)\end{aligned}$$

$$\begin{aligned}\frac{dX_{a,r}^{g,2,v}(t)}{dt} = {} & (\nu_1 + \omega_{v-1}) X_{a,r}^{g,1,v}(t) + \sigma_{a,r}^{g,2} X_{a,r}^{g,9,6}(t) \\ & - \left(\mu_a^g + \alpha_a^{g,2} + \nu_2 + \omega_v + \pi_{a,r}^{g,2,v}(t)\right) X_{a,r}^{g,2,v}(t)\end{aligned}$$

$$\begin{aligned}\frac{dX_{a,r}^{g,3,v}(t)}{dt} = {} & (\nu_2 + \omega_{v-1}) X_{a,r}^{g,2,v}(t) + \sigma_{a,r}^{g,3} X_{a,r}^{g,9,6}(t) \\ & - \left(\mu_a^g + \alpha_a^{g,3} + \nu_3 + \omega_v + \pi_{a,r}^{g,3,v}(t)\right) X_{a,r}^{g,3,v}(t)\end{aligned}$$

$$\begin{aligned}\frac{dX_{a,r}^{g,4,v}(t)}{dt} = {} & (\nu_3 + \omega_{v-1}) X_{a,r}^{g,3,v}(t) + \sigma_{a,r}^{g,4} X_{a,r}^{g,9,6}(t) \\ & - \left(\mu_a^g + \alpha_a^{g,4} + \nu_4 + \omega_v + \pi_{a,r}^{g,4,v}(t)\right) X_{a,r}^{g,4,v}(t)\end{aligned}$$

$$\frac{dX_{a,r}^{g,5,v}(t)}{dt} = (\nu_4 + \omega_{v-1})X_{a,r}^{g,4,v}(t) + \sigma_{a,r}^{g,5}X_{a,r}^{g,9,6}(t) - \left(\mu_a^g + \alpha_a^{g,5} + \nu_5 + \omega_v + \pi_{a,r}^{g,5,v}(t)\right)X_{a,r}^{g,5,v}(t)$$

$$\frac{dX_{a,r}^{g,6,0}(t)}{dt} = b_{r,1}^{g,0}(t) + \sigma_{a,r}^{g,0}X_{a,r}^{g,6,0}(t) - \left(\mu_a^g + \psi_0\lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)\right)X_{a,r}^{g,6,0}(t)$$

$$\frac{dX_{a,r}^{g,7,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t)X_{a,r}^{g,5,0}(t) - \left(\sigma_{a,r}^{g,0} + \mu_a^g + \psi_0\psi_1\lambda_{a,r}^{g,1}(t)\right)X_{a,r}^{g,7,0}(t)$$

$$\frac{dX_{a,r}^{g,8,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t)X_{a,r}^{g,0,0}(t) - \left(\sigma_{a,r}^{g,0} + \mu_a^g + \psi_1\lambda_{a,r}^{g,1}(t)\right)X_{a,r}^{g,8,0}(t)$$

$$\frac{dX_{a,r}^{g,9,6}(t)}{dt} = \sum_{v=1}^{5}\sum_{d=1}^{5}[\pi_{a,r}^{g,d,v}(t)X_{a,r}^{g,d,v}(t) - \left(\sigma_{a,r}^{g,d} + \mu_a^g\right)X_{a,r}^{g,9,6}(t)]$$

The equation variables are:

$b_{r,c}^{g,d}(t)$	The number of births that are HIV-negative ($d = 0$), HIV-positive ($d = 1$), uncircumcised ($c = 0$), or circumcised ($c = 1$)
$\sigma_{a,r}^{g,d}$	The dropout rate from PrEP ($d = 0$) or ART ($d = 1, \ldots, 5$)
μ_a^g	The background mortality
$\lambda_{a,r}^{g,d}(t)$	The force of infection for HIV-negative persons on PrEP ($d = 1$) or off PrEP ($d = 0$)
$\pi_{a,r}^{g,d,v}(t)$	The coverage of PrEP ($d = 0$), ART ($d = 1, \ldots, 5$), circumcision ($d = 6$), condom use among HIV-negative persons ($d = 7$), condom use among PrEP users ($d = 8$), and condom use among ART users ($d = 9$)
$\alpha_a^{g,d}$	The HIV-associated mortality
ν_d	The rate of progressing from CD4 state d to $d + 1$
ω_d	The rate of progressing from VL state v to $v + 1$
ψ_d	The reduction in HIV transmission due to circumcision ($d = 0$), PrEP ($d = 1$), ART ($d = 2$), or condom use ($d = 3$)

HPV Natural History

The system of ODE's describes the states $X_{a,r}^{g,d,v,h,s}(t)$ with the following indices:

- g refers to gender
- $g = 0$ for males; $g = 1$ for females
- d refers to disease state defined by CD4 cell count, and treatment and circumcision status
- $d = 0$ for HIV-negative; $d = 1$ for acute infection; $d = 2$ for CD4 >500 cells/μL; $d = 3$ for CD4 500-350 cells/μL; $d = 4$ for CD4 350–200 cells/μL; $d = 5$ for CD4 <200 cells/μL; $d = 6$ for HIV-negative, circumcised, and no PrEP; $d = 7$ for HIV-negative, circumcised, and on PrEP; $d = 8$ for HIV-negative, uncircumcised, and on PrEP; $d = 9$ for HIV-positive on ART
- v refers to disease state defined by viral load
- $v = 0$ for HIV-negative; $v = 1$ for acute infection; $v = 2$ for VL<1,000 copies/mL; $v = 3$ for VL 1,000-10,000 copies/mL; $v = 4$ for VL 10,000-50,000 copies/mL; $v = 5$ for VL>50,000 copies/mL; $v = 6$ for HIV-positive and on ART
- a refers to age group
- $a = 0$ for ages 0 to 4; $a = 1$ for ages 5 to 9; … ; $a = 11$ for ages 55 to 59
- r refers to sexual risk group defined by number of sexual partnerships per year
- $r = 0$ for low risk; $r = 1$ for medium risk; $r = 2$ for high risk
- h = 0 for HPV-negative, h = 1 for HPV-positive
- s refers to HPV disease state; 0 = No precancer(h = 1) , infected (h >= 2); 1 = CIN1 (if h > 1); 2 = CIN2; 3 = CIN3; 4 = Cervical Cancer (Local); 5 = Cervical Cancer (Regional); 6 = Cervical Cancer (Distant); 7 = Immune; 8 = Vaccinated

The ODEs for the HPV disease states are:

$$\frac{dX_{a,r}^{g,d,v,0,0}(t)}{dt} = r_a X_{a,r}^{g,d,v,1,7} - \left(ж_d \lambda_{HPV}{}_{a,r}^{g,d,v}(t) + V \cdot u(t - t_v)\right) X_{a,r}^{g,d,v,0,0}(t)$$

$$\frac{dX_{a,r}^{g,d,v,1,0}(t)}{dt} = ж_d [\lambda_{HPV}{}_{a,r}^{g,d,v}(t) X_{a,r}^{g,d,v,0,0}(t) + \xi_a \lambda_{HPV}{}_{a,r}^{g,d,v}(t) X_{a,r}^{g,d,v,1,7} + \phi_V \lambda_{HPV}{}_{a,r}^{g,d,v}(t) X_{a,r}^{g,d,v,1,8} u(t - t_v)] + k_{0,1}^a X_{a,r}^{g,d,v,1,1} + k_{0,2}^a X_{a,r}^{g,d,v,1,2} - (k_{1,0}^a + k_{2,0}^a) X_{a,r}^{g,d,v,1,0}$$

$$\frac{dX_{a,r}^{g,d,v,1,1}(t)}{dt} = ע_{1,2}^d k_{1,0}^a X_{a,r}^{g,d,v,1,0} + ע_{1,2}^d k_{1,2}^a X_{a,r}^{g,d,v,1,2} + ע_{1,3}^d k_{1,3}^a X_{a,r}^{g,d,v,1,3} - (ת_{2,1}^d k_{2,1}^a + ת_{2,1}^d k_{3,1}^a + k_{7,1}^a) X_{a,r}^{g,d,v,1,1}$$

$$\frac{dX_{a,r}^{g,d,v,1,2}(t)}{dt} = k_{2,0}^a X_{a,r}^{g,d,v,1,0} + ת_{2,1}^d k_{2,1}^a X_{a,r}^{g,d,v,1,1} + ע_{2,3}^d k_{2,3}^a X_{a,r}^{g,d,v,1,3} - (ת_{3,2}^d k_{3,2}^a + k_{7,2}^a) X_{a,r}^{g,d,v,1,2}$$

$$\frac{dX_{a,r}^{g,d,v,1,3}(t)}{dt} = ת_{3,1}^d k_{3,1}^a X_{a,r}^{g,d,v,1,1} + ת_{3,2}^d k_{3,2}^a X_{a,r}^{g,d,v,1,2} - (ע_{1,3}^d k_{1,3}^a + ע_{2,3}^d k_{2,3}^a + k_{4,3}^a) X_{a,r}^{g,d,v,1,3}$$

$$\frac{dX_{a,r}^{g,d,v,1,4}(t)}{dt} = k_{4,3}^a X_{a,r}^{g,d,v,1,3} - (k_{5,4}^a + \zeta_4) X_{a,r}^{g,d,v,1,4}$$

$$\frac{dX_{a,r}^{g,d,v,1,5}(t)}{dt} = k_{5,4}^a X_{a,r}^{g,d,v,1,4} - (k_{6,5}^a + \zeta_5) X_{a,r}^{g,d,v,1,5}$$

$$\frac{dX_{a,r}^{g,d,v,1,6}(t)}{dt} = k_{6,5}^a X_{a,r}^{g,d,v,1,5} - \zeta_6 X_{a,r}^{g,d,v,1,6}$$

$$\frac{dX_{a,r}^{g,d,v,1,7}(t)}{dt} = \sum_{s=1}^{3} [k_{7,s}^a X_{a,r}^{g,d,v,1,s}] - (ж_d \xi_a \lambda_{HPV}{}_{a,r}^{g,d,v}(t)) X_{a,r}^{g,d,v,1,7}$$

$$\frac{dX_{a,r}^{g,d,v,1,8}(t)}{dt} = [V \cdot X_{a,r}^{g,d,v,0,0}(t) - ж_d \phi_V(a) \lambda_{HPV}{}_{a,r}^{g,d,v}(t) X_{a,r}^{g,d,v,1,8}] \, u(t - t_v)$$

The equation variables are:

$\lambda_{HPV}{}_{a,r}^{g,d,v}(t)$	The force of infection for HPV-negative persons
$ж_d$	HPV acquisition risk multiplier for HIV-positive individuals with CD4 count d
ξ_a	HPV acquisition risk reduction multiplier for individuals with natural HPV immunity
$\phi_V(a)$	HPV acquisition risk reduction multiplier for individuals vaccinated against HPV
$k_{s',s}^{a}$	Rate of progressing from HPV/CIN state s to s'
ζ_s	Cervical cancer-associated mortality for persons at stage s
r_a	Rate of waning natural immunity
$п_{s',s}^{d}$	Progression rate multiplier from HPV/CIN stage s to s' for HIV-positive individuals with CD4 count d
$ע_{s,s'}^{d}$	Regression rate multiplier from HPV/CIN stage s' to s for HIV-positive individuals with CD4 count d
t_v	The year that vaccination begins
V	Vaccination rate
$u(t-t_v)$	The Heaviside step function

Demography:

At each iteration, the force of infection and the number of births are calculated and then used to evaluate the ODEs along with mortality and disease progression. The numbers of incident infections, HIV-related deaths, and individuals entering CD4≤200 cells/μL are also calculated to determine QALYs.

Births:

The number of births, $b_{r,c}^{g,d}(t)$, determines how many newborns enter the population of gender g, disease state d, sexual risk group r, and circumcision status c ($c = 0$ for uncircumcised; $c = 1$ for circumcised males). For simplicity, we assume only neonatal circumcision (the circumcision level is increased over time such that 10% of males are circumcised by 2013, as currently observed in KZN and shown in Figure S2 [3, 4]), that infected births enter the acute stage,

and that women age 15–49 give birth. Fertility rates are stratified by age and stage of disease. Births from uninfected mothers, $bS(t)$, and from HIV-positive mothers, $bI(t)$, are:

$$bS(t) = \sum_{a=3}^{9}\sum_{r=0}^{2}\left[\gamma_a^0 X_{a,r}^{1,0,0}(t) + \gamma_a^9 X_{a,r}^{1,9,6}(t)\right]$$

$$bI(t) = \sum_{a=3}^{9}\sum_{r=0}^{2}\sum_{d=1}^{5}\sum_{v=1}^{5}\gamma_a^d X_{a,r}^{1,d,v}(t) + \sum_{a=3}^{9}\sum_{r=0}^{2}\gamma_a^9 X_{a,r}^{1,9,6}(t)$$

HIV-negative births for uncircumcised males, $b_{r,0}^{0,0}(t)$, are:

$$b_{r,0}^{0,0}(t) = 0.5 * \phi_{0,r}^{0,0} * \Big(bS(t) + \big(1-\eta(t)\big)bI(t)\Big) * \big(1-\pi_{0,r}^{1,5}(t)\big)$$

HIV-negative births for circumcised males, $b_{r,1}^{0,0}(t)$, are:

$$b_{r,1}^{0,0}(t) = 0.5 * \phi_{0,r}^{0,0} * \Big(bS(t) + \big(1-\eta(t)\big)bI(t)\Big) * \pi_{0,r}^{1,5}(t)$$

HIV-negative births for females, $b_{r,0}^{1,0}(t)$, are:

$$b_{r,1}^{1,0}(t) = 0.5 * \phi_{0,r}^{1,0} * \Big(bS(t) + \big(1-\eta(t)\big)bI(t)\Big)$$

HIV-positive births for males and females, $b_{r,0}^{g,1}(t)$, are:

$$b_{r,0}^{g,1}(t) = 0.5 * \phi_{0,r}^{g,0} * \eta(t)bI(t)$$

The equation variables are:

$\phi_{a,r}^{g,d}$	The proportion of individuals in age a, gender g, and treatment status d ($d = 0$, no treatment; $d = 1$, PrEP; $d = 2$, ART) that is born into sexual risk group r
$\eta(t)$	The proportion of births from HIV-positive females that result in vertical transmission
$\pi_{0,r}^{1,5}(t)$	The proportion of HIV-negative males that is circumcised at birth
γ_a^d	The annual fertility rate for females by age and disease state

Each birth is multiplied by 0.5 given an assumed gender ratio at birth of 1:1. The proportion of births from HIV-positive mothers that result in infection, $\eta(t)$, decreases linearly from 34% in 2004 to 20.2% in 2005, then to 7.1% in 2008 [5-7]. The proportion of circumcised HIV-negative males, $\pi_{0,r}^{1,5}(t)$, remains at 10% from 1990 to 2013 [3].

Mortality:

People leave the population due to death or aging past age 79. Mortality is represented by mortality caused by HIV, $\alpha_a^{g,d}$, and all other background mortality, μ_a^g. Mortality caused by HIV varies by stage of disease and age (individuals 0 to 4 years old and 50 to 79 years old are assumed to have elevated risks of death), and individuals on ART are assumed to have no disease-induced mortality [8, 9]. The background mortality rate is estimated to be the population mortality rate in 1990, prior to the generalized HIV epidemic.

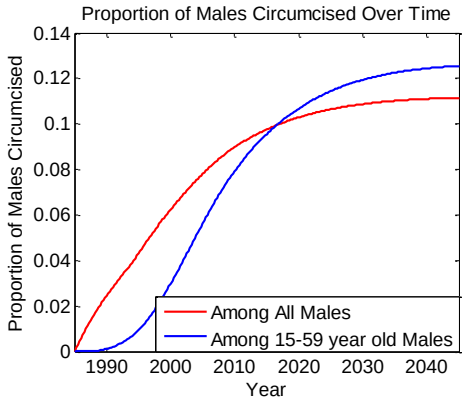

Figure S2. Circumcision prevalence in males. Proportion of males circumcised over time. Note that circumcision among 15 to 59-year-old males surpasses the overall rate because uncircumcised males are less likely to acquire HIV, and thus have lower mortality.

Disease Transmission:

HIV

Disease transmission is governed by the force of infection, $\lambda_{a,r}^{g,d}(t)$, which determines the number of people who are infected at each time-step.

For HIV

$$:\lambda_{a,r}^{g,d}(t) = \sum_{a'=0}^{15}\sum_{r'=0}^{2}\left[c_{g,a,r}^{*a',r'}(t)\rho_{g,a,r}^{a',r'}(t) * \frac{-(\sum_{d'=1}^{9}\sum_{v'=1}^{5}\ln(1-\beta^{g,r,v'})\psi_3 X_{a',r'}^{g',d',v'}(t)) + \ln(1-\beta^{g,r,6})\psi_3\psi_4 X_{a',r'}^{g',9,6}(t)}{\sum_{d'=1}^{9}\sum_{v'=0}^{6} X_{a',r'}^{g',d',v'}(t)}\right]$$

The equation variables are:

$c_{g,a,r}^{*a',r'}(t)$	The number of partners from age a' and sexual risk group r' that an individual has per year
$\rho_{g,a,r}^{a',r'}(t)$	The mixing matrix which describes the distribution of partners from each age and sexual risk group
$\beta^{g,r,v'}$	The probability of HIV transmission per partnership between an HIV-positive person of stage v' and HIV-negative person of risk group r

The overall force of infection for a specific age-group is the sum of the risk of acquiring HIV from all possible partners.

HPV

Disease transmission is governed by the force of infection, ${\lambda_{HPV}}_{a,r}^{g,d}$, which determines the number of people who are infected at each time-step.

$$\lambda_{HPV}{}_{a,r}^{g,d}(t) = \sum_{a'=0}^{15}\sum_{r'=0}^{2}\left[c_{g,a,r}^{*a',r'}(t)\rho_{g,a,r}^{a',r'}(t) * \frac{-(\sum_{s'=0}^{8}\sum_{d'=0}^{9}\sum_{v'=1}^{5}\ln(1-\beta_{HPV}^{g,r}) X_{a',r'}^{g',d',v',1,s'}(t)}{\sum_{v'=1}^{5}\sum_{s'=0}^{8}\sum_{d'=0}^{9}\sum_{h'=0}^{1} X_{a',r'}^{g',d',v',h',s'}(t)}\right]$$

The equation variables are:

$c_{g,a,r}^{*a',r'}(t)$	The number of partners from age a' and sexual risk group r' that an individual has per year
$\rho_{g,a,r}^{a',r'}(t)$	The mixing matrix which describes the distribution of partners from each age and sexual risk group
$\beta_{HPV}^{g,r}$	The probability of HPV transmission per partnership between an HPV-positive person and an HPV-negative person of risk group r

Mixing Matrix:

Using methods similar to other models, the mixing matrix, $\rho_{g,a,r}^{a',r'}(t)$, describes patterns of sexual contact by calculating the proportion of one's sexual partners that come from a specific age and sexual-risk group [10].

$$\rho_{g,a,r}^{a',r'}(t) = \left[\epsilon_a \frac{\sum_{r'=0}^{2}(c_{a',r'}^{g'} \sum_{d'=0}^{9}\sum_{v'=0}^{6} X_{a',r'}^{g',d',v'}(t))}{\sum_{a'=0}^{15}\sum_{r'=0}^{2}(c_{a',r'}^{g'} \sum_{d'=0}^{9}\sum_{v'=0}^{6} X_{a',r'}^{g',d',v'}(t))} + (1-\epsilon_a)\delta_a^{a'}\right] * \left[\epsilon_r \frac{c_{a',r'}^{g'} \sum_{d'=0}^{9}\sum_{v'=0}^{6} X_{a',r'}^{g',d',v'}(t)}{\sum_{r'=0}^{2}(c_{a',r'}^{g'} \sum_{d'=0}^{9}\sum_{v'=0}^{6} X_{a',r'}^{g',d',v'}(t))} + (1-\epsilon_r)\delta_r^{r'}\right]$$

Where	$\delta_r^{r'}$	$= 1.0$	If $r = r'$
		$= 0.0$	If $r \neq r'$
Before 2005:	$\delta_a^{a'}$	$= 0.3$	If $a = a'$
		$= 0.7$	If $a = a' + 1$ (for males) If $a = a' - 1$ (for females)
		$= 0.0$	Otherwise
After 2005:	$\delta_a^{a'}$	$= 0.7$	If $a = a'$
		$= 0.3$	If $a = a' + 1$ (for males) If $a = a' - 1$ (for females)
		$= 0.0$	Otherwise

Mixing patterns vary between random and assortative, as determined by the parameter ϵ. Random mixing ($\epsilon = 1$) is mixing proportional to the relative sizes of all compartments and this method is consistent for both random mixing by risk and by age. However, assortative mixing ($\epsilon = 0$) is among groups with similar characteristics and differs for mixing by risk and age. Assortative mixing by risk ($\epsilon_r = 0$) is defined by the identity matrix $\delta_r^{r'}$, whereas assortative mixing by age ($\epsilon_a = 0$) is defined by an off-diagonal matrix $\delta_a^{a'}$. The off-diagonal pattern results in females of age a being more likely to form partnerships with males of age $a = a' - 1$, which is consistent with reports of such age discrepancies in KZN [11, 12]. Although this off-diagonal method results in some age groups having fewer than 100% of their partnerships, those age-groups are $a = 0$ and $a = 11$, which contribute relatively little to overall HIV transmission. We assume that this tendency for age-gaps diminishes in 2005. Furthermore, ϵ_a and ϵ_r shift from random to assortative over the course of the simulation, given the consistent government campaigns against risky sexual behavior [13].

Per-Partnership Probability of Transmission:

The per-partnership probability of transmission, $\beta^{g,r,d'}$, depends on the sexual risk group of the HIV-negative partner and the disease state of the HIV-positive partner. The probabilities of transmission per partnership are:

$\beta^{0,r,v'} = 1 - (1 - \chi^{v'})^{A_r^0}$	For male HIV-negative partners
$\beta^{1,r,v'} = \left(1 - (1 - \chi^{v'})^{A_r^1}\right)$	For female HIV-negative partners

$\chi^{g,d'}$ is the per-act probability of transmission for an HIV-positive partner of HIV stage d', and the exponent, A_r^g, is the number of coital acts based on the HIV-negative partner's sexual risk group and gender.

The per partnership probability of transmission is calculated in a similar manner for HPV. χ^{HPV} is the per-act probability of transmission for an HPV-positive partner:

$$\beta_{HPV}^{g,r} = 1 - (1 - \chi^{HPV})^{A_r^0}$$
$$\beta_{HPV}^{g,r} = \left(1 - (1 - \chi^{HPV})^{A_r^1}\right)$$

Rate of Partner Change:

Data on sexual behavior and specifically, sexual contact rates, $c_{a,r}^{g}$, are often subject to biases leading to contact rate data that, when assuming solely heterosexual contact, are inconsistent between males and females [14]. We account for this variability by using an adjusted contact rate, $c^{*a'r'}_{g,a,r}(t)$, which equilibrates the reported number of sexual partners by males and females [10]. The adjusted contact rate can be male- or female-driven, as determined by the parameter θ, where $\theta = 1$ for male-driven, $\theta = 0$ for female-driven, and $\theta = 0.5$ when compromised equally. We assume $\theta = 0.5$ given the lack of data to assume otherwise. The adjusted contact rate for females is:

$$c_{1,a,r}^{*a',r'}(t) = c_{a,r}^{1} B_{a,r}^{a',r'}(t)^{-(1-\theta)}$$

For males, the adjusted contact rate is:

$$c_{0,a,r}^{*a',r'}(t) = c_{a,r}^{0} B_{a,r}^{a',r'}(t)^{\theta}$$

The discrepancy between the two populations, $B_{a,r}^{a',r'}(t)$, is defined as:

$$B_{a,r}^{a',r'}(t) = \frac{c_{a,r}^{0}\rho_{0,a,r}^{a',r'}(t) * \sum_{d=0}^{9}\sum_{v=0}^{6} X_{a,r}^{0,d,v}(t)}{c_{a,r}^{1}\rho_{1,a,r}^{a',r'}(t) * \sum_{d=0}^{9}\sum_{v=0}^{6} X_{a,r}^{1,d,v}(t)}$$

Model Calibration:

The model was calibrated to fit HIV prevalence data from South Africa (1990 to 2000) and KwaZulu-Natal (2001 to 2012). The parameters for HIV transmission probability, sexual partnership duration, and sexual mixing were varied individually and final values were chosen by least-squares regression in the HIV prevalence output. HIV transmission probability was varied from 0.00053 to 0.00097 assuming a normal distribution [15], the rate of sexual partnership change was based on a previous study [10] and varied by a factor from 0.5 to 1.5 assuming a normal distribution, and the degree of sexual mixing was varied from 0.1 to 1 [10] assuming a normal distribution.

Population Aging:

To age the population, one-fifth of each compartment enters the next age group of corresponding gender, sexual risk, and disease state. When individuals age, they also change sexual risk; therefore, they redistribute to a set sexual-risk profile, $\phi_{a,r}^{g,d}$, that varies by age, gender, and treatment status. All compartments, except for the youngest and oldest age-groups, experience influx from the prior age and efflux into the next age. The 0 to 4 age-group only receives influx through births while the 55 to 59 age-group exits the population rather than entering the next age. Therefore, each state has a second ODE that occurs at each time step:

$\frac{dX_{0,r}^{g,d}(t)}{dt} = -\frac{1}{5}X_{0,r}^{g,d}(t)$	For $a = 0$
$\frac{dX_{a,r}^{g,d}(t)}{dt} = -\frac{1}{5}X_{a,r}^{g,d}(t) + \frac{1}{5}\sum_{r=0}^{2} X_{a-1,r}^{g,d}(t)\,\phi_{a-1,r}^{g,d}$	For $a \neq 0$

Interventions

ART Treatment Enrollment:

Coverage of ART treatment for HIV-positive persons increases from 0% in 2004 to 35% for persons with CD4 ≤200 cells/μL in 2006 as previously observed in KZN [16], then to 36% coverage for all HIV-positive persons in 2014 as observed in the Home HTC study [3, 4]. ART coverage is modeled to reach the expected ART coverages in 2000, 2006, and 2014, and to reach a steady-state in

approximately 2025. The steady-state ART coverage depends on the scenario being simulated. ART treatment is assumed to reduce the likelihood of HIV transmission by 96% as suggested by recent studies ($\psi_2 = 0.96$), and persons on ART are expected to have the same life expectancy as HIV-negative persons of similar age and gender, and thus, are assumed not to be subject to HIV-associated mortality [9, 17-20]. The annual drop-out rate is 6%, which is equally likely for all individuals regardless of their HIV state prior to treatment. Individuals who drop out of ART return to the infected stages at the same proportion with which they enrolled.

Circumcision:

This model includes a background level of circumcision of 10% as currently observed in KZN [3]. Several studies show that circumcised males have a 60% ($\psi_0 = 0.6$) lower risk of acquiring HIV, but are not at a reduced risk of transmitting HIV [21-23]. Therefore, the model does no track the circumcision status of HIV-positive persons. The ODE for HIV-negative circumcised males is:

$$\frac{dX_{a,r}^{0,6,0}(t)}{dt} = b_{r,1}^{0,0}(t) + \sigma_{a,r}^{0,0} X_{a,r}^{1,7,0}(t) - \left(\mu_a^0 + (1-\psi_0)\lambda_{a,r}^{0,0}(t) - \pi_{a,r}^{0,6,0}(t)\right) X_{a,r}^{0,6,0}(t)$$

Other models have studied the impact of circumcision in-depth to include wound healing periods and sexual activity [24, 25]. However, this model assumes that circumcision is instantaneous.

HPV vaccination:

HPV vaccination begins in 2017 and continues until the end of the simulation in 2100. The HPV vaccine was assumed to confer protection to 90% of oncogenic HPV types and possess a maximum of 80% efficacy (V_{max}) against vaccine-type HPV infections. Vaccine coverage levels of 90%, 70%, and 50% among females aging from the 5-9 age category into the 10-14 age category were modelled. For each of these coverage levels, the effects of waning vaccine immunity were studied by comparing lifelong vaccine efficacy with average vaccine efficacy periods (t_{eff}) of 20, 15, and 10 years after vaccinating at age a_{vax}. Following this period, the efficacy of the vaccine was assumed to wane at a linear rate such that no vaccine efficacy was retained 20 years following the end of the vaccine efficacy period. The model uses the age group of vaccinated compartments as a proxy for the time elapsed since vaccination.

$$\phi_V(a) = V_{max} - \left(\frac{V_{max}}{20} * a * u\left(a - (t_{eff} + a_{vax})\right)\right.$$

OUTPUT OVERVIEW

An output document describes a general output of the model. This document exists to provide an introduction to the types of outputs generated by the model.

SUMMARY

This section describes outputs from the model.

OVERVIEW

The model tracks the prevalence and incidence of HPV, HIV, and their associated outcomes in each compartment for the entire simulated period. This allows for comparisons of population-level health outcomes in the absence and presence of various prevention and intervention strategies. Ultimately, this facilitates the study of the efficacy and cost-effectiveness of said strategies.

OUTPUT LISTING

The results that are currently being produced are:

- Overall HIV prevalence
- Proportion of HIV-positive population on ART
- Population-level distribution of CD4 count and viral load among HIV-positive individuals
- HIV prevalence by age and gender
- HPV prevalence
- CIN 2/3 prevalence by HIV status
- Cervical cancer incidence
- Cervical cancer mortality

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