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Mathematical insights in evaluating state dependent effectiveness of HIV prevention interventions

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Abstract

Mathematical models have been used to simulate HIV transmission and to study the use of pre-exposure prophylaxis (PrEP) for HIV prevention. Often a single intervention outcome over 10 years has been used to evaluate the effectiveness of PrEP interventions. However, different metrics express a wide variation over time and often disagree in their forecast on the success of the intervention. We develop a deterministic mathematical model of HIV transmission and use it to evaluate the public-health impact of oral PrEP interventions. We study PrEP effectiveness with respect to different evaluation methods and analyze its dynamics over time. We compare four traditional indicators, based on cumulative number or fractions of infections prevented, on reduction in HIV prevalence or incidence and propose two additional methods which estimate the burden of the epidemic to the public-health system. We investigate the short and long term behavior of these indicators and the effects of key parameters on the expected benefits from PrEP use. Our findings suggest that public-health officials considering adopting PrEP in HIV prevention programs can make better informed decision by employing a set of complementing quantitative metrics.

Keywords

HIV transmission; HIV prevalence or incidence; PrEP interventions; ODE model

1 Introduction

In 2010, evidence from two different randomized clinical trial suggested that pre-exposure prophylaxis (PrEP) products based on antiretroviral drug Tenofovir taken orally as a pill (oral PrEP) or applied topically in the form of gel (vaginal microbicides) can help prevent HIV. First, the CAPRISA 004 trial demonstrated a 39% (95%CI, 6% to 60%) overall

decrease in HIV incidence among women in the VMB arm of the trial who were advised to use the product before and after each sex act [4]. Later, the Global iPrEx trial of a daily use of a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) demonstrated a 43.8% efficacy (95%CI, 15% to 63%) to reduce HIV acquisition among men-who-have sex with men (MSM) [5]. Although these products await confirmation from another trial to move toward licensure or label change there is already a broad discussion on what will be population-level benefits from wide-scale PrEP use in high prevalence settings.

Mathematical models have been used to simulate HIV transmission and to study the use of chemoprophylaxis among MSM [3, 6]. Deterministic mathematical models of HIV heterosexual transmission stratified by gender have been analyzed in [1, 2, 7–10]. Often a single intervention outcome based on cumulative number or fractions of infections prevented, on reduction in HIV prevalence or incidence has been used to evaluate the effectiveness of PrEP interventions. These indicators express a wide variation over time and often disagree in their forecast on the success of the intervention ([2, 10]). Therefore, the conclusions of many modeling studies are significantly influenced by the choice of the evaluation method and the period of evaluation. In particular, it has been pointed out that indicators based on prevented infections tend to show mixed results over time due to their sensitivity to changes in population dynamics [1].

In this paper, we develop a deterministic mathematical model of HIV transmission to evaluate the public-health impact of oral PrEP interventions, compare PrEP effectiveness with respect to different evaluation methods and analyze its dynamics over time. We compare four traditional evaluation methods including relative reduction in HIV prevalence and incidence which avoid the ambiguity associated with commonly used indicators based on the absolute number of prevented infections. We consider two additional methods which estimate the burden of the epidemic to the public-health system. We then investigate the short term and long term behavior of these indicators and the effects of key parameters on the expected benefits from PrEP use. The effects of demographic, behavioral, and epidemic parameters on the PrEP impact are studied in a multivariate sensitivity analysis.

2 Model Description and Analysis

In our models (see Fig. 1) the population is divided into two major classes, PrEP users (superscript p , S^p+I^p) and those that do not use PrEP ($S+I$), and further stratified according to their HIV status into susceptible (S , S^p) and infected (I , I^p). Individuals who develop AIDS are accumulated in non-sexually active class A. Individuals join the community (reaching sexual maturity) and departure from the sexually active population at constant rates (Λ , μ). A proportion k of the new recruits start using PrEP. PrEP users are assumed to strictly follow the prescribed regimens. The model which assumes that PrEP reduces both susceptibility and infectiousness of the users (“dual-protection” model) is formulated by the following system of differential equations:

$$\frac{dS^p}{dt} = k\Lambda - (1 - \alpha_s)\beta \frac{S^p I}{N} - (1 - \alpha_s)(1 - \alpha_i)\beta \frac{I^p S^p}{N} - \mu S^p$$

$$\frac{dS}{dt} = (1 - k)\Lambda - \beta \frac{IS}{N} - (1 - \alpha_i)\beta \frac{I^p S}{N} - \mu S \quad (1)$$

$$\frac{dI^p}{dt} = (1 - \alpha_s)\beta \frac{IS^p}{N} + (1 - \alpha_s)(1 - \alpha_i)\beta \frac{I^p S^p}{N} - (\mu + d)I^p$$

$$\frac{dI}{dt} = \beta \frac{IS}{N} + (1 - \alpha_i)\beta \frac{I^p S}{N} - (\mu + d)I.$$

Since the differential equations for these four compartments are independent from the AIDS class (A), we do not include it in our ODE system. Here $N = S^p + S + I^p + I$ represents the sexually active population and α_s (α_i) measures the efficacy of PrEP in reducing susceptibility (infectiousness) of PrEP users. The cumulative HIV acquisition risk per year β is calculated based on the HIV risk per act (b_a) with a HIV-positive partner and the average number of sex acts per year (n):

$$\beta = 1 - (1 - b_a)^n.$$

Cumulative acquisition risk (β) is an increasing function with respect to HIV-acquisition risk per act b_a and average number of sexual acts per year n .

PrEP is introduced at time ($t = 0$) in a population with $N(0) = 1,000,000$ and HIV-prevalence (P). We assume that PrEP is initially adopted by a fraction k_1 of the individuals and that the initial fraction of HIV-positive individuals is reduced by θ as a result of pre-enrollment HIV screening:

$$S^p(0) = k_1(1 - P)N(0)$$

$$S(0) = (1 - k_1)(1 - P)N(0)$$

$$I^p(0) = (1 - \theta)k_1PN(0)$$

$$I(0) = (1 - (1 - \theta)k_1)PN(0).$$

The initial distribution of the epidemic classes may not be critical for the asymptotic behavior of the system but it is essential for the impact indicators calculated over fixed periods of time after the start of the intervention. To isolate the impact of the choice of the evaluation method we simplify the intervention schedule and assume instantaneous uptake of PrEP at predetermined level ($k = k_1$).

Clinical trials in HIV prevention are usually designed to evaluate the efficacy of the tested products in reducing susceptibility (α_s) only. Although a reduction in infectiousness (α_i) is plausible it is not verifiable since all HIV positive participants are immediately withdrawn from the product. Moreover, the biomedical products currently in testing, are based on antiretroviral drugs and are not recommended for use by infected individuals due to the risk of drug resistance development. Therefore, the majority of the modelers assume uni-directional PrEP protection ($\alpha_i = 0$) which means that using PrEP has no effect on the infectiousness or that infected individuals do not take PrEP anymore. This scenario may also represent the idea of control of the PrEP usage by the HIV-positive individuals since fast removal of the infected users from PrEP is the equivalent of setting $\alpha_i = 0$. To address that possibility we consider a “single-protection” model in which the variable P is removed from the baseline model as follows:

$$\frac{dS^p}{dt} = k\Lambda - (1 - \alpha_s)\beta \frac{S^p I}{N} - \mu S^p$$

$$\frac{dS}{dt} = (1 - k)\Lambda - \beta \frac{SI}{N} - \mu S \quad (2)$$

$$\frac{dI}{dt} = \beta \frac{SI}{N} + (1 - \alpha_s)\beta \frac{S^p I}{N} - (\mu + d)I$$

with initial conditions:

$$S^p(0) = k_1(1 - P)N(0)$$

$$S(0) = (1 - k_1)(1 - P)N(0)$$

$$I(0) = PN(0).$$

In our analysis HIV epidemics are simulated in presence and in absence of PrEP. If PrEP is not available the “no intervention” model is reduced to the following system:

$$\frac{dS}{dt} = \Lambda - \beta \frac{SI}{N} - \mu S \quad (3)$$

$$\frac{dI}{dt} = \beta \frac{SI}{N} - (\mu + d)I$$

with $S(0) = (1 - P)N(0)$ and $I(0) = PN(0)$.

2.1 Modeling Assumptions

Several important assumptions are incorporated into the model:

- The HIV prevalence in the whole population is representative for the HIV prevalence among each gender, i.e., the chance to have a HIV-positive partner is proportional to the total HIV prevalence.
- Individuals are assumed to have a fixed number of sex acts per year.
- Sexual behavior of an individual does not change if he/she starts using PrEP but sexual activity stops once AIDS is developed.
- The use of PrEP reduces both HIV susceptibility and infectiousness and by this reduces the HIV acquisition risk per sex act.
- We assume perfect adherence to PrEP: individuals who start using PrEP continue to follow the prescribed regimen indefinitely. However, the scenario with no reduction of infectiousness due to PrEP ($\alpha_i = 0$) is equivalent to immediate withdrawal from PrEP after HIV acquisition.
- The use of other HIV prevention measures including condom use, male circumcision, and ARV treatments are not considered separately in our model. Their effects on HIV transmission are aggregated in the HIV acquisition risk per act.

2.2 Equilibrium Analysis

The “no intervention” model (3), has two steady states: infection free equilibrium $\left(\frac{\Lambda}{\mu}, 0\right)$ and endemic equilibrium $\left(\frac{1}{\beta - d}\Lambda, \frac{\beta - (\mu + d)}{(\mu + d)(\beta - d)}\Lambda\right)$ when $\beta > (\mu + d)$. They exchange stability when the basic reproduction number $R_0 = \frac{\beta}{\mu + d}$ crosses the threshold of one. In epidemiology, the *basic reproduction number* (some-times called *basic reproductive rate* or *basic reproductive ratio*) of an infection is the mean number of secondary infections a typical single infected individual will cause in a population with no immunity to the disease in the absence of interventions to control the infection. It is often denoted by R_0 . This metric is useful because it helps determine whether or not an infectious disease will spread through a population. In general, if $R_0 > 1$ then the infection free steady state is unstable and the infection persists in the population while if $R_0 < 1$ then the infection free steady state is stable and the infection may be eradicated. That is exactly the case for the HIV epidemic modeled by the “no intervention” model (3). A simple application of the Dulac criterion ensures that model (3) does not generate nontrivial periodic solution.

The “single-protection” model (2) has an infection free steady state $\left(\frac{k}{\mu}\Lambda, \frac{1-k}{\mu}\Lambda, 0\right)$. The “dual-protection” model (1) has an infection free steady state $\left(\frac{k}{\mu}\Lambda, \frac{1-k}{\mu}\Lambda, 0, 0\right)$. However,

the positive steady states for these two models, when exist, are too complicated to be expressed explicitly.

2.3 Model Parametrization

We used demographic and HIV prevalence data representative for the sexually active population (15–49 years old) in South Africa for the period between 2001 and 2011 provided by the Statistical Institute of South Africa [27] to parameterize our models in the scenario without PrEP.

First, we estimate the recruitment rate in the sexually active population (Λ). We base our calculations on the approximated number of 15-year olds

$\left(\frac{\text{population aged 15 to 19}}{5} = \frac{5175400}{5} = 1035100\right)$ and the total population size (27,172,400) aged 15 to 49, in year 2011. In our model without PrEP, we assume initial total sexually active population to be $N = 10^6$. Therefore, we scale the estimated entrance rate to obtain the recruitment of the sexually active population (Λ) in our model: $\Lambda = 10^6 \cdot \frac{1035100}{27172400} \approx 38094$ which we use in the epidemic simulations.

Next, we fit the projected HIV prevalence $\frac{I}{S+I}$ by the model without PrEP to the 2001–2011 prevalence data from South Africa [27]. We use the Matlab built-in function

‘fminsearch’ to do the data fitting, with error measurement $\frac{\sum_{i=1}^n |ps_i - p_i|}{n}$, where ps_i represents the HIV prevalence from model simulation, p_i represents the HIV prevalence from data, and n represents the number of data points. Starting with initial parameter values borrowed from published studies: $b_a = 0.0038$ ([24]), $n = 80$ ([25,26]), $\mu = 1/35$ ([23]), and $d = 1/10$ ([21, 22]), we obtain the following parameter set which fits best the prevalence data from year 2001 to year 2011: $b_a = 0.0030$, $n = 65.8494$, $\mu = 0.0250$, and $d = 0.1302$ (with error of data fitting=0.0737). Fig. 2 shows the HIV prevalence data and the best-fitting estimates obtained by the “no intervention” model for the period 2001–2011 (Fig. 2(a)) as well as its long-term projections (Fig. 2(b)).

2.4 Epidemic projections

We present the epidemic dynamics obtained by the “dual-protection” model (1) using the baseline parameter values from Table 1 in Fig. 3(a) and compare them with the projections of the “single-protection” (2) and “no intervention” (3) models in Fig. 3(b).

We observe that all simulations approach steady states after a period of 200 years. A 50% efficacious PrEP which reduce both susceptibility and infectiousness of its users will stabilize on disease-free equilibrium if PrEP is used consistently by 20% of the all sexually active individuals. A uni-directional PrEP protection, simulated by the “single-protection” model, will not be enough to eliminate HIV from the South African population but will reduce the infected population significantly. However, it is not straightforward to evaluate the population level impact of PrEP from the long-term epidemic projections. Therefore, it is very important to find biologically reasonable metrics to quantify the effectiveness of PrEP

interventions. We introduce several indicators and study their behavior under different scenarios over various time periods. We also compare the indicators readings for different interventions to understand how the choice of metric and/or duration affects the relative public-health impact of PrEP projected with mathematical models.

3 Effectiveness Indicators

The impact of PrEP in our analysis is evaluated by the quantitative indicators described in Table 2. The first four indicators are widely used in modeling studies to evaluate the impact of interventions over fixed periods $[0, T]$. The cumulative and the fractional indicators measure the intervention effectiveness based on the infections prevented in scenarios with PrEP compared to scenarios without PrEP. The prevalence and incidence indicators measure the reduction of the projected HIV prevalence and incidence due to PrEP. We propose the last two evaluation methods based on the reduction of the number of infected individuals as they are closely related to the economic burden of the HIV epidemic on the public health system at community and state level since the money allocated for HIV treatment is proportional to the size of the infected population.

Predictions of mathematical models based on quantitative indicators are often used to estimate the effectiveness of novel interventions and to compare the expected benefits from different prevention options. The analytical conclusions in favor of specific option are usually based on evaluations of the indicators over a few fixed periods of intervention time, most likely 10 years but almost certainly between 5 and 30 years. However, all indicators vary over time and may express different preferences when used to decide between comparable prevention programs. We illustrate the idea with a comparison of the indicator dynamics for two hypothetical PrEP interventions. Intervention 1 assumes no control of the PrEP use by HIV-positive individuals ($\theta = 0$) and 50% PrEP efficacy in reducing both susceptibility and infectiousness ($\alpha_s = \alpha_i = 0.5$) while Intervention 2 requires a negative HIV test as a condition for prescribing PrEP ($\theta = 1$) and better PrEP efficacy in reducing infectiousness ($\alpha_s = 0.5$, $\alpha_i = 0.9$). Each of the incidence, prevalence and fractional indicators shows increasing effectiveness of both interventions over 50 years after initiation of PrEP (Fig. 4) with more benefits attributed to Intervention 1 initially but higher impact of Intervention 2 in a long-term. However, they disagree on the timing when the advantage of the Intervention 1 ends. For instance, a preference to Intervention 2 is given after 17 years of PrEP use if based on reduction in HIV incidence and after 22 years if based on reduction in HIV prevalence. The public-health impact of Intervention 1 measured in terms of cumulative fraction of prevented infections remains higher compared to Intervention 2 for up to 32 years which is substantially longer than the evaluation periods used in the majority of the quantitative analyses. Therefore, if PrEP is evaluated over periods between 17 and 32 years the choice of quantitative indicator is critical. We take a closer look at the key drivers of those discrepancies in the indicators' dynamics.

3.1 Indicator Expressions

To utilize the calculation of the cumulative indicators we need to keep track of the cumulative number of new infections. For this reason we add two equations to the “dual-protection” model (1):

$$\frac{d(I_{New}^p)}{dt} = (1 - \alpha_s)\beta \frac{S^p I}{N} + (1 - \alpha_s)(1 - \alpha_i)\beta \frac{S^p I^p}{N} \quad (4)$$

$$\frac{d(I_{New})}{dt} = \beta \frac{SI}{N} + (1 - \alpha_i)\beta \frac{SI^p}{N},$$

and add an equation to the “single-protection” model (2):

$$\frac{d(I_{New})}{dt} = \beta \frac{SI}{N} + (1 - \alpha_s)\beta \frac{S^p I}{N} \quad (5)$$

with initial conditions $I_{New}(0) = I_{New}^p(0) = 0$, and $I_{New}(0) = 0$ respectively. These new variables (I_{New}^p and I_{New}) represent cumulative HIV infections in PrEP users and non-users, respectively.

If PrEP is not available, the “no intervention” model becomes:

$$\frac{dS}{dt} = \Lambda - \beta \frac{SI}{N} - \mu S$$

$$\frac{dI}{dt} = \beta \frac{SI}{N} - (\mu + d)I \quad (6)$$

$$\frac{d(I_{New})}{dt} = \beta \frac{SI}{N}$$

with initial conditions $S(0) = (1 - P)N(0)$, $I(0) = PN(0)$, and $I_{New}(0) = 0$.

We proceed with analysis of the behavior of the indicators assuming “dual protection”. For the remainder of the paper we use $[]$ to denote variables from the model without PrEP (6) and $[]_{DP}$ for variables from the “dual-protection” model with PrEP (4). Using these notations, the qualitative indicators have the following expressions:

$$C_I(T) = \int_0^T \left(\left[\frac{d}{dt} I_{New}(t) \right] - \left[\frac{d}{dt} I_{New}^p(t) + \frac{d}{dt} I_{New}(t) \right]_{DP} \right) dt$$

$$F_I(T) = \frac{\int_0^T \left(\left[\frac{d}{dt} I_{New}(t) \right] - \left[\frac{d}{dt} I_{New}^p(t) + \frac{d}{dt} I_{New}(t) \right]_{DP} \right) dt}{\int_0^T \left[\frac{d}{dt} I_{New}(t) \right] dt}$$

$$P_I(T) = 1 - \frac{\left[\frac{I^P(T) + I(T)}{S^P(T) + S(T) + I^P(T) + I(T)} \right]_{DP}}{\left[\frac{I(T)}{S(T) + I(T)} \right]}$$

$$aI_I(T) = 1 - \frac{\left[\frac{\int_T^{T+1} \left[\frac{d}{dt} I_{New}^P(t) + \frac{d}{dt} I_{New}(t) \right] dt}{S^P(T) + S(T)} \right]_{DP}}{\left[\frac{\int_T^{T+1} \frac{d}{dt} I_{New}(t) dt}{S(T)} \right]}$$

$$\hat{C}_I(T) = [I(T)] - [I^P(T) + I(T)]_{DP}$$

$$\hat{F}_I(T) = \frac{[I(T)] - [I^P(T) + I(T)]_{DP}}{[I(T)]} = 1 - \frac{[I^P(T) + I(T)]_{DP}}{[I(T)]}.$$

Since integral evaluated on derivative function can be simplified, previous expressions of the indicators are equivalent to the following:

$$C_I(T) = [I_{New}(T)] - [I_{New}^P(T) + I_{New}(T)]_{DP}$$

$$F_I(T) = \frac{[I_{New}(T)] - [I_{New}^P(T) + I_{New}(T)]_{DP}}{[I_{New}(T)]} = 1 - \frac{[I_{New}^P(T) + I_{New}(T)]_{DP}}{[I_{New}(T)]}$$

$$P_I(T) = 1 - \frac{\left[\frac{I^P(T) + I(T)}{S^P(T) + S(T) + I^P(T) + I(T)} \right]_{DP}}{\left[\frac{I(T)}{S(T) + I(T)} \right]}$$

$$aI_I(T) = 1 - \frac{\left[\frac{I_{New}^P(T+1) + I_{New}(T+1) - (I_{New}^P(T) + I_{New}(T))}{S^P(T) + S(T)} \right]_{DP}}{\left[\frac{I_{New}(T+1) - I_{New}(T)}{S(T)} \right]}$$

$$\hat{C}_I(T) = [I(T)] - [I^P(T) + I(T)]_{DP}$$

$$\hat{F}_I(T) = \frac{[I(T)] - [I^p(T) + I(T)]_{DP}}{[I(T)]} = 1 - \frac{[I^p(T) + I(T)]_{DP}}{[I(T)]}.$$

From these expressions we can see that the indicators F_I , P_I , aI_I , and $\hat{F}_I$ are dimensionless and attain value in $[0, 1]$, and they do not depend on the population size. The other two indicators C_I and $\hat{C}_I$ measure changes in population group sizes, and are not dimensionless.

3.2 Initial Dynamics of the Indicators

To understand the practical value of the qualitative indicators we examine their short, intermediate and long term dynamics. We begin with indicator approximations shortly after the start of the intervention. Using the initial conditions defined above we obtained the following expressions associated with the initial indicators' behavior (details can be found in the Appendix):

$$C_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1 \beta P(1 - P)N(0)dt$$

$$F_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1$$

$$P_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1 \beta(1 - P)dt$$

$$aI_I \approx (1 - \alpha_s k_1)[1 - (1 - \theta)\alpha_i k_1]\{1 - (1 - \alpha_s k_1)k_1[1 - (1 - \theta)\alpha_i k_1]\}k_1 \beta P dt$$

$$\hat{C}_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1 \beta P(1 - P)N(0)dt$$

$$\hat{F}_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1 \beta(1 - P)dt.$$

Here we assume $dt = 1$ for the approximation for aI_I because the definition of the incidence indicator is on annual basis.

Note that the expression for the fractional indicator (F_I) depends only on the PrEP efficacy (α_s, α_i) and factors related to the implementation of the intervention at its start such as initial coverage (k_1) and the introductory control of the PrEP usage by HIV-positive individuals (θ) but not on the demographic, behavioral and epidemic parameters. Therefore, fractional indicator represents a metric of the “immediate impact of PrEP” on the HIV epidemic, which is independent of the specific population and the status of the HIV epidemic in it. This metric accounts for the effects of the reduced susceptibility (α_s) of the fraction k_1 of the population which initially uses PrEP combined with the reduced infectiousness (α_i) of a

limited fraction $(1-\theta)k_1$ of the infected population when in contact with partners unprotected by PrEP $(1 - \alpha_s k_1)$. Clearly, if PrEP provides uni-directional protection ($\alpha_i = 0$) or none of the infected individuals is using PrEP ($\theta = 1$) then the “immediate impact of PrEP” is given by the product of PrEP efficacy and coverage ($\alpha_s k_1$). The initial behavior of all other indicators depend on the HIV prevalence (P) at the time of PrEP introduction as well as on the cumulative HIV-acquisition risk (β). Moreover, the cumulative (C_I) and reduction ($\hat{C}_I$) indicators also depend on the initial population size ($N(0)$), which is consistent with the fact that only indicators C_I and $\hat{C}_I$ measure changes on population group sizes, and are not dimensionless.

The initial rate of change of the indicators can be approximated as:

$$C'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta P(1 - P)N(0)$$

$$P'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta(1 - P)$$

$$aI'_I \approx (1 - \alpha_s k_1)[1 - (1 - \theta)\alpha_i k_1]\{1 - (1 - \alpha_s k_1)k_1[1 - (1 - \theta)\alpha_i k_1]\}k_1\beta P$$

$$\hat{C}'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta P(1 - P)N(0)$$

$$\hat{F}'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta(1 - P).$$

Notice that initially $C'_I \approx \hat{C}'_I$ and $P'_I \approx \hat{F}'_I$. We study the sensitivity of the initial rate of change of the reduction indicators ($\hat{C}_I$ and $\hat{F}_I$) to some of the intervention (θ , k_1) and epidemic (P) parameters by bifurcation simulations (Fig. 5). These bifurcation parameters were chosen because they are easier to evaluate at community levels compared to HIV-acquisition risk and PrEP efficacy. The graphs in Fig. 5, (a) and (b) demonstrate that the growth of both indicators accelerates if more people start on PrEP (larger k_1) but decelerates if the control of the PrEP usage by infected individuals is more effective (larger θ). The initial rate of change is more sensitive to k_1 than to θ but it is clear that the growth rate of both indicators at the time of PrEP introduction expresses qualitatively similar behavior with respect to the intervention parameters (θ , k_1). In contrast, the graphs presenting the dependence on the initial HIV prevalence show serious discrepancies (Fig. 5(c)). The initial growth rate of the reduction indicator ($\hat{C}_I$) increases when the HIV prevalence ranges from 0 to 50% which includes all realistic values observed so far, particularly in Sub-Saharan Africa (Fig. 5(c)). In comparison, the increase in HIV prevalence within the same range implies smaller growth rate of the fractional reduction indicator $\hat{F}_I$.

3.3 Asymptotic behavior of the indicators

In resource-constrained settings, it is unrealistic to expect the HIV epidemic will die out without additional intervention. Therefore, in the following, we assume that the basic reproduction number of the “no intervention” model is $R_0 > 1$. The asymptotic HIV

prevalence in this case is given by: $\left[\frac{I}{S+I}\right] = 1 - \frac{\mu+d}{\beta} = 1 - \frac{1}{R_0}$.

We want to point out that if the PrEP intervention is strong enough to cause the eradication of HIV in the population, i.e., the HIV epidemic approaches the disease-free equilibrium with the “dual-protection” model, then the asymptotic behavior of all indicators is well determined: i) the cumulative indicator will grow to infinity; ii) the reduction indicator will

stabilize at $\left[\frac{I}{S+I}\right] = \frac{R_0 - 1}{\beta - d} \Lambda$ and iii) all other indicators will approach one. Unfortunately, PrEP intervention alone is unlikely to be sufficient to eradicate HIV. In that case we show that the asymptotic behavior of the indicators can be expressed in terms of the asymptotic proportion (p) of the HIV-positive subpopulation which have been infected while using PrEP (details are presented in Appendix), where p is defined as follows:

$$p = \left[\frac{I^p}{I^p + I} \right]_{DP}.$$

Expressions for the asymptotic values of four of the indicators:

$$P_I = 1 - \frac{R_0 - \frac{1 - \alpha_s(1-p)}{(1-\alpha_s)(1-\alpha_i p)}}{R_0 - 1}$$

$$aI_I = 1 - \frac{R_0 \frac{(1-\alpha_s)(1-\alpha_i p)}{1-\alpha_s(1-p)} - 1}{R_0 - 1}$$

$$\hat{C}_I = \left[\frac{R_0 - 1}{\beta - d} - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \right] \Lambda$$

$$\hat{F}_I = 1 - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{R_0 - 1} \frac{\beta - d}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d}$$

and the asymptotic rate of growth of the cumulative indicator:

$$C'_I = (\mu + d) \left[\frac{R_0 - 1}{\beta - d} - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \right] \Lambda = (\mu + d) \hat{C}_I.$$

show that they are independent of the initial HIV prevalence (P) and the control on the PrEP use by HIV-positive individuals (θ) which have been of critical importance for the initial dynamics of the indicators. Cumulative indicators ($\hat{C}_I$ and C_I) depend indirectly on the population size (N) which determines the entry rate in the population (Λ). Notice that

$C'_I = (\mu + d)\hat{C}_I$ so the value of the reduction indicator is proportional to the annual number of new infections prevented due to PrEP use in a long term. The rest of the indicators are not influenced by the population size (N). Although recruitment parameters such as k and Λ are not explicitly present in some of the expressions above they may affect the asymptotic proportion of PrEP users among infected subpopulation (p).

Therefore, a good approximation of p is important for the evaluation of the asymptotic levels of the indicators. Boundedness of the prevalence indicator $P_I < 1$ and positivity of the annual incidence indicator both imply that

$$p < \frac{(1 - \alpha_s)[R_0 - 1]}{(1 - \alpha_s)\alpha_i R_0 + \alpha_s}.$$

This provides a rough approximation for p . We study the variation of p when the reduction in susceptibility and infectiousness range from 0 to 100 % (Fig. 6(a)) for intervention coverage ($k = 0.1$) which is not sufficient to eradicate HIV even if the PrEP protection against HIV is perfect ($\alpha_s = \alpha_i = 1$). It shows that p depends greatly on the reduction in susceptibility (α_s) and very little on the reduction in infectiousness (α_i). It is clear that the fraction of infections which occur when using PrEP (p) ranges from zero, in case that PrEP provides complete protection against HIV ($\alpha_s = 1$) and no PrEP users ever get infected, to the level of the PrEP coverage (k) in case that PrEP is completely ineffective ($\alpha_s = 0$) and infections are proportionally distributed among PrEP users and non-users.

Our next goal is to examine and compare the long-term behavior of the indicators (specifically those expressed as ratios) for a fixed PrEP intervention (Fig. 6(b)). Although qualitatively similar the trajectories of the indicators show some important differences. First, some indicators such as the reduction in HIV prevalence and the reduction in the infected fraction start at zero while others such as the fraction of prevented infections and the reduction in HIV incidence initiate at positive values. Therefore, it is not surprising that the indicators reach a specific threshold of 20% at times varying from 3 to 11 years after the introduction of PrEP. The times needed to report 50% effectiveness are even farther apart. It takes the intervention 24 years and 33 years to reduce in half the expected HIV incidence and HIV prevalence, respectively. However, almost 90 years are necessary to reduce the cumulative number of new infections by 50%, i.e., such reduction is infeasible over traditionally used evaluation periods of up to 30 years.

4 Evaluation of the public-health impact PrEP

The initial and asymptotic behavior of the indicators are useful in understanding what drives the observed differences in their projections. However, from a public health perspective it is more important to analyze the indicators values over more practical time intervals. Although

no fixed standards exist, the majority of the quantitative studies assume that preventive interventions are implemented for 10 years when their effectiveness is evaluated. The same period is recommended by the World Health Organizations as an evaluation period when cost-effectiveness analyses are conducted [28]. Longer periods are investigated in few studies but always up to 30 years.

In this section we explore the dependence of the indicator readings over 10 and 30 years on key epidemic and intervention parameters. Clearly, the impact of PrEP is positively correlated with both reductions in susceptibility (α_s) and infectiousness (α_i) regardless of what indicator is used to quantify it (Fig. 7). The slopes of the contour plots in the PrEP efficacy parameter space show that if the susceptibility efficacy (α_s) is relatively low (up to 30 %) all indicators are equally dependent of both α_s and α_i . However, with the increase of the PrEP protection against HIV the influence of the reduction of infectiousness decreases significantly. The prevalence indicator (P_I) projects the least effectiveness over 10 years of PrEP use. It predicts that more than 70 % and 55% PrEP efficacy is needed to achieve 20% reduction in HIV prevalence with unidirectional ($\alpha_i = 0$) and bi-directional ($\alpha_i = \alpha_s$) interventions, respectively. In comparison, 20% reduction in the expected HIV infections is possible with 65% effective uni-directional and 55% bi-directional PrEP while 20% reduction in HIV incidence is feasible even if less than 45% effective uni-directional and 30% bi-directional PrEP is used over 10 years. The order of predicted effectiveness by the prevalence and the fractional indicators is reversed over an evaluation period of 30 years. More than half of the parameter space results in more than 50% reduction in HIV prevalence (P_I), an unreachable threshold as a reduction in expected infections (F_I).

All indicators increase with coverage $k = k_1$ (Fig. 8). The prevalence and fractional indicators, in contrast to the incidence indicator, are sensitive to changes in the transmission rate (β) with increasing influence of β on the fraction of prevented infection for larger evaluation periods. The maximum PrEP effectiveness over 10 years of PrEP use is predicted for complete coverage (k) and modest level of the transmission rate (β) while over 30 years it is achieved for the lowest possible β .

5 Sensitivity Analysis

Finally, we explore the sensitivity of the indicators to changes in each parameter. Using the algorithm presented in [29] we calculate the Partial Rank Correlation Coefficients (PRCC) which evaluate the monotonicity of the model outcomes (indicators) in terms of the model parameters. Values of *PRCC* closer to ± 1 , imply stronger correlation between the output indicator and the input parameter while the sign of the coefficients determines if the outcomes grow or decrease with an increase of the input parameters.

We study separately the sensitivity of the indicators to the parameters (b_a , n , μ , and d) which we fitted using data from South Africa. In our analysis we choose 1000 random parameters combinations of those input parameters sampled uniformly from their corresponding ranges: [0.0015, 0.0045] for b_a , [32.9247, 98.7741] for n , [0.0125, 0.0375] for μ , and [0.0651, 0.1953] for d . Each range is chosen as $[0.5, 1.5] \times (\text{baseline parameter value in Table 1})$. The rest of the parameters are fixed on their baseline values in Table 1. For each parameter set

we simulate the models with “dual-protection” and no intervention and calculate PRCC matrix of all six indicators C_I , F_I , P_I , aI_I , $\hat{C}_I$, and $\hat{F}_I$ for the first 10 years (standard analysis) as well as for the 100 years (long-term analysis). Similarly, we investigate the indicators’ sensitivity to the remaining epidemic and intervention parameters (α_s , α_i , P , k_1 ($k = k_1$), and θ), uniformly sampled from their corresponding ranges: [0.25, 0.75] for α_s , [0.25, 0.75] for α_i , [0.083, 0.249] for P , [0.1, 0.3] for k_1 , and [0.25, 0.75] for θ . Results are presented in Fig. 9.

Correlations for 10-year intervention suggest that from the fitted parameters the indicators are most sensitive to the factors (b_a and n) which determine the transmission rate β . However, their influence over time decreases. C_I and $\hat{C}_I$ are still positively correlated to the two factors while the rest of the indicators are negatively correlated to the two factors over 100 years, both dependencies are weak. The intervention outcomes are split into two groups with respect to their correlation with the HIV induced mortality (d): the cumulative indicators being negatively correlated while the rest being positively correlated with d . Similar discrepancy is observed with respect to the influence of the initial HIV prevalence P over 10 years but the correlations are reversed (positive - for the the cumulative indicators and negative for the rest). Interestingly, in that case the difference between the indicators disappears in a long term. Note that although P appears in the initial conditions only, it continues to have strong influence on all the cumulative and reduction indicators for more than 10 years while its impact on the fraction of prevented infection gets even stronger over time.

Among the intervention parameters, PrEP coverage (k) and PrEP efficacies per act (α_s and α_i) express strong positive correlation with all the indicators in a short term. It remains significant in a long term for all outcomes. This confirms that PrEP coverage and protection level are critical to the intervention success regardless which qualitative metric is used. In contrast, the influence of the initial control on the PrEP use by HIV-positive individuals (θ) reduces substantially in time.

The prevalence (P_I) and the annual incidence (aI_I) indicators express almost the same sensitivity to all parameters. Therefore they should have consistent projections when evaluating the impact of the intervention.

6 Conclusions

Precise evaluation of the expected public-health impact of biomedical interventions for HIV preventions becomes increasingly important with more prevention options entering the pipeline toward licensure. The practice shows that even if the products are effective in reducing the individual risk of acquisition (individual efficacy) the benefits from general usage (population effectiveness) may be limited by variety of epidemic, behavioral and intervention factors. In this paper we analyzed different evaluation metrics of population effectiveness of pre-exposure prophylaxis (PrEP) interventions. We compare four traditional indicators, based on cumulative number or fractions of infections prevented, on reduction in HIV prevalence or incidence with other two metrics based on the reduction in infected subpopulation.

We demonstrated that the quantitative indicators have distinct dynamical profile shortly after the start of PrEP intervention which modifies substantially over time. As a result, when calculated over a fixed period of time these indicators may project significantly different PrEP effectiveness and therefore influence the decision if particular products are potentially good enough for implementation. In general, new prevention methods need to prove their effectiveness in randomized clinical trial (RCT), i.e., to demonstrate that the observed efficacy is significantly larger than zero (positive 95% confidence interval), before applying for licensure. In reality, developers and public-health officials try to avoid PrEP products with low efficacy because the controlled environments of the clinical trials are difficult to be replicated at community level. Another concern is that the availability of PrEP may affect sexual behavior and encourage risk-sex practices. Therefore, minimal efficacy thresholds of 20% or higher are often included in the design of RCTs and similar levels of effectiveness is expected when interventions are modeled at population level [5, 30,31]. Other studies imply that 50% biological efficacy is needed to guarantee significant public-health impact. The question remains what does 20% or 50% PrEP effectiveness mean? We have shown the widely used evaluation metrics may disagree over practical intervals of time (Fig. 6). A reduction in HIV incidence at pre-specified levels seems most realistic as an intervention goal but it is not easy to be estimated in the population. In contrast, a reduction in HIV prevalence is easier to be recorded but more difficult to be achieved in a short term. The reduction in the number of new HIV infections, which is the most popular public-health metric, projects strong PrEP effectiveness initially but grows slower than the other indicators over time.

Moreover, if used to compare the impact of PrEP interventions different indicators may give preference to different options (Fig. 4). We recommend that public-health officials who consider PrEP to be integrated in HIV prevention programs should base their decision on a complex of quantitative metrics. Although is specifically focused on HIV prevention, the same theoretical approach may be extended to model other infectious diseases, such as malaria, cholera, and tuberculosis [11,12] or evaluate the impact of interventions, such as male circumcision, vaccination or quarantine strategies [13, 16–19]. The proposed metrics comparison may be useful when the influence of different behaviour factors, such as sexual disinhibition, smoking or drinking on the epidemics dynamics is studied [14, 15].

Presented results, assuming perfect adherence and instantaneous uptake, are likely to give optimistic views of the potential impact of a PrEP intervention. Although, overall self-reported adherence in the concluded clinical trials is high it is unclear how consistently PrEP will be used in real settings. That will depend among other things on the delivery system (e.g. coital or daily use, oral, topical or slow release ring), individual preferences, availability, acceptability and cost of the product [32, 33]. Perfect adherence and other simplifying assumptions allowed us to support our observations on the indicators and their simulated dynamics with analytical expressions which were easier to be interpreted. We believe that more complex and realistic modeling setup will be more useful in projecting benefits due to PrEP use but it is unlikely to resolve the differences between the interventional outcomes reported in this paper.

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Appendix

8.1 Approximations of the Indicators at the Start of the Intervention

Based on the initial conditions for the two models, we can obtain the approximate behavior of the indicator at the start of the intervention. To facilitate this, we let $I_T(0) = I(0) + I^p(0)$ and $S_T(0) = S(0) + S^p(0)$. Recall that $N(0) = S(0) + I(0)$ when there is no PrEP user and $N(0) = S(0) + S^p(0) + I(0) + I^p(0)$ when there are PrEP users.

As examples, we will provide the approximation computation for the prevalence indicator,

cumulative indicator, and fractional indicator. Recall that $P_I = 1 - \frac{\left[\frac{I^p + I}{S^p + S + I^p + I} \right]_{DP}}{\left[\frac{I}{S + I} \right]}$. We will

first estimate $\left[\frac{I}{S + I} \right]$ and $\left[\frac{I^p + I}{S^p + S + I^p + I} \right]_{DP}$ separately:

$$\begin{aligned} \left[\frac{I}{S + I} \right] &\approx \frac{I(0) + \left(\frac{dI}{dt} \right)(0) dt}{I(0) + S(0) + \left(\frac{dI}{dt} + \frac{dS}{dt} \right)(0) dt} \\ &= \frac{I(0) + \left[\beta \frac{S(0)I(0)}{N(0)} - (\mu + d)I(0) \right] dt}{I(0) + S(0) + [\Lambda - \mu S(0) - (\mu + d)I(0)] dt} \\ &= \frac{PN(0) + [\beta P(1 - P)N(0) - (\mu + d)PN(0)] dt}{N(0) + [\Lambda - \mu(1 - P)N(0) - (\mu + d)PN(0)] dt} \\ &= \frac{P + [\beta P(1 - P) - (\mu + d)P] dt}{1 + \left(\frac{\Lambda}{N(0)} - \mu - dP \right) dt}; \end{aligned}$$

$$\begin{aligned} \left[\frac{I^p + I}{S^p + S + I^p + I} \right]_{DP} &\approx \frac{I_T(0) + \left(\frac{dI^p}{dt} + \frac{dI}{dt} \right)(0) dt}{N(0) + \left(\frac{dS^p}{dt} + \frac{dS}{dt} + \frac{dI^p}{dt} + \frac{dI}{dt} \right)(0) dt} \\ &= \frac{I_T(0) + \left\{ [I_T(0) - \alpha_i I^p(0)] [S_T(0) - \alpha_s S^p(0)] \frac{\beta}{N(0)} - (\mu + d)I_T(0) \right\} dt}{N(0) + [\Lambda - \mu N(0) - dI_T(0)] dt} \\ &= PN(0) \left(1 + \left\{ (1 - P)N(0) [1 - (1 - \theta)k_1 + (1 - \alpha_i)(1 - \theta)k_1] [1 - k_1 + (1 - \alpha_s)k_1] \cdot \frac{\beta}{N(0)} - (\mu + d) \right\} dt \right) \cdot \frac{1}{N(0) + (\Lambda - \mu N(0) - dPN(0)) dt} \\ &= \frac{P + \left\{ [1 - (1 - \theta)k_1 \alpha_i] (1 - \alpha_s k_1) \beta P(1 - P) - (\mu + d)P \right\} dt}{1 + \left(\frac{\Lambda}{N(0)} - \mu - dP \right) dt}. \end{aligned}$$

Then by the expression of prevalence indicator, we have:

$$\begin{aligned}
 P_I &\approx 1 - \frac{\frac{P + \{[1 - (1 - \theta)k_1\alpha_i](1 - \alpha_s k_1)\beta P(1 - P) - (\mu + d)P\}dt}{1 + \left(\frac{\Lambda}{N(0)} - \mu - dP\right)dt}}{\frac{P + [\beta P(1 - P) - (\mu + d)P]dt}{1 + \left(\frac{\Lambda}{N(0)} - \mu - dP\right)dt}} \\
 &= 1 - \frac{P + \{[1 - (1 - \theta)k_1\alpha_i](1 - \alpha_s k_1)\beta P(1 - P) - (\mu + d)P\}dt}{P + [\beta P(1 - P) - (\mu + d)P]dt} \\
 &= 1 - \frac{1 + \{[1 - (1 - \theta)k_1\alpha_i](1 - \alpha_s k_1)\beta(1 - P) - (\mu + d)\}dt}{1 + [\beta(1 - P) - (\mu + d)]dt} \\
 &\approx (-\{[1 - (1 - \theta)k_1\alpha_i](1 - \alpha_s k_1)\beta(1 - P) - (\mu + d)\}dt) \\
 &\quad \{1 - [\beta(1 - P) - (\mu + d)]dt\} \\
 &\approx -\{[1 - (1 - \theta)k_1\alpha_i](1 - \alpha_s k_1)\beta(1 - P) - (\mu + d)\}dt + \\
 &\quad [\beta(1 - P) - (\mu + d)]dt \\
 &= [\alpha_s + (1 - \theta)\alpha_i - (1 - \theta)\alpha_s \alpha_i k_1]k_1\beta(1 - P)dt = \\
 &\quad [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta(1 - P)dt.
 \end{aligned}$$

Thus, the slope at which the prevalence indicator increases at the beginning of the intervention can be approximated by

$$P'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta(1 - P).$$

By the expression of cumulative indicator, we have:

$$\begin{aligned}
 C_I &\approx [I_{\text{New}}(0) + \frac{d}{dt}I_{\text{New}}(0)dt] - [I_{\text{New}}(0) + \frac{d}{dt}I_{\text{New}}(0)dt + I_{\text{New}}^p(0) + \frac{d}{dt}I_{\text{New}}^p(0)dt]_{DP} \\
 &= [0 + \beta \frac{S(0)I(0)}{N(0)}dt] \\
 &\quad - [0 + (\beta \frac{S(0)I(0)}{N(0)} + (1 - \alpha_i)\beta \frac{S(0)I^p(0)}{N(0)})dt + 0 + ((1 - \alpha_s)\beta \frac{S^p(0)I(0)}{N(0)} + (1 \\
 &\quad - \alpha_s)(1 - \alpha_i)\beta \frac{S^p(0)I^p(0)}{N(0)})dt]_{DP} \\
 &= dt\beta(1 - P)PN(0) - dt[\beta(1 - k_1)(1 - P)(1 - (1 - \theta)k_1)PN(0) + (1 - \alpha_i)\beta(1 \\
 &\quad - k_1)(1 - P)(1 - \theta)k_1PN(0) + (1 - \alpha_s)\beta k_1(1 - P)(1 - (1 - \theta)k_1)PN(0) + (1 \\
 &\quad - \alpha_s)(1 - \alpha_i)\beta k_1(1 - P)(1 - \theta)k_1PN(0)] \\
 &= dt\beta(1 - P)PN(0) \cdot \{1 - [(1 - k_1)(1 - (1 - \theta)k_1) + (1 - \alpha_i)(1 - k_1)(1 - \theta)k_1 \\
 &\quad + (1 - \alpha_s)k_1(1 - (1 - \theta)k_1)) + (1 - \alpha_s)(1 - \alpha_i)k_1(1 - \theta)k_1]\} \\
 &= dt\beta(1 - P)PN(0) \cdot \{1 - [(1 - \alpha_s k_1)(1 - (1 - \theta)k_1) + (1 - \alpha_s k_1)(1 - \alpha_i)(1 \\
 &\quad - \theta)k_1]\} = dt\beta(1 - P)PN(0)\{1 - (1 - \alpha_s k_1)(1 - \alpha_i(1 - \theta)k_1)\} \\
 &= dt\beta(1 - P)PN(0)\{1 - [1 - \alpha_s k_1 - \alpha_i(1 - \theta)k_1 + \alpha_s k_1 \alpha_i(1 - \theta)k_1]\} \\
 &= [\alpha_s + (1 - \theta)\alpha_i - (1 - \theta)\alpha_s \alpha_i k_1]k_1\beta P(1 - P)N(0)dt \\
 &= [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)]k_1\beta P(1 - P)N(0)dt.
 \end{aligned}$$

Thus, the slope at which the cumulative indicator increases at the beginning of the intervention can be approximated by

$$C'_I \approx [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)] k_1 \beta P(1 - P)N(0).$$

By the expression of fractional indicator, we have:

$$\begin{aligned}
F_I &\approx 1 - \frac{[I_{New}(0) + \frac{d}{dt}I_{New}(0) + I_{New}^P(0) + \frac{d}{dt}I_{New}^P(0)]_{DP}}{[I_{New}(0) + \frac{d}{dt}I_{New}(0)]} \\
&= 1 - \left[0 + \left(\beta \frac{S(0)I(0)}{N(0)} + (1 - \alpha_i)\beta \frac{S(0)I^P(0)}{N(0)} \right) dt + 0 + \left((1 - \alpha_s)\beta \frac{S^P(0)I(0)}{N(0)} + (1 - \alpha_s)(1 - \alpha_i)\beta \frac{S^P(0)I^P(0)}{N(0)} \right) dt \right]_{DP} \\
&\quad \cdot \frac{1}{[0 + \beta \frac{S(0)I(0)}{N(0)} dt]} \\
&= 1 - [\beta(1 - k_1)(1 - P)(1 - (1 - \theta)k_1)PN(0) \\
&\quad + (1 - \alpha_i)\beta(1 - k_1)(1 - P)(1 - \theta)k_1PN(0) \\
&\quad + (1 - \alpha_s)\beta k_1(1 - P)(1 - (1 - \theta)k_1)PN(0) \\
&\quad + (1 - \alpha_s)(1 - \alpha_i)\beta k_1(1 - P)(1 - \theta)k_1PN(0)] \\
&\quad \cdot \frac{1}{\beta(1 - P)PN(0)} \\
&= 1 - [(1 - k_1)(1 - (1 - \theta)k_1) \\
&\quad + (1 - \alpha_i)(1 - k_1)(1 - \theta)k_1 \\
&\quad + (1 - \alpha_s)k_1(1 - (1 - \theta)k_1) \\
&\quad + (1 - \alpha_s)(1 - \alpha_i)k_1(1 - \theta)k_1] = [\alpha_s + (1 - \theta)\alpha_i \\
&\quad - (1 - \theta)\alpha_s\alpha_i k_1] k_1 \\
&= [\alpha_s + (1 - \theta)\alpha_i(1 - \alpha_s k_1)] k_1.
\end{aligned}$$

8.2 Asymptotic Approximations of the Indicators

To approximate the asymptotic behavior of indicators, we need to study the steady state of the two models. What is challenging is to study the steady state of the baseline model using PrEP (4). From

$$\frac{d(S^p + S + I^p + I)}{dt} = \Lambda - \mu(S^p + S + I^p + I) - d(I^p + I) = 0$$

we obtain that at steady state,

$$N = \frac{\Lambda - d(I^p + I)}{\mu}.$$

From

$$\frac{d(S^p + I^p)}{dt} = k\Lambda - \mu(S^p + I^p) - dI^p = 0$$

we obtain that at steady state,

$$S^p = \frac{k\Lambda - (d + \mu)I^p}{\mu}.$$

Moreover, from

$$\frac{d(S + I)}{dt} = (1 - k)\Lambda - \mu(S + I) - dI = 0$$

we obtain that at steady state,

$$S = \frac{(1 - k)\Lambda - (d + \mu)I}{\mu}.$$

In the following, let $m = \mu + d$ and $\hat{I} = I^p + I$. Then at steady state,

$$\begin{aligned}
\frac{d(\hat{I})}{dt} &= (1 - \alpha_s)\beta \frac{S^p I}{N} + \beta \frac{SI}{N} + (1 - \alpha_s)(1 - \alpha_i)\beta \frac{S^p I^p}{N} + (1 - \alpha_i)\beta \frac{SI^p}{N} - m\hat{I} \\
&= [I + (1 - \alpha_i)I^p] (1 - \alpha_s)\beta \frac{S^p}{N} + [I + (1 - \alpha_i)I^p] \beta \frac{S}{N} - m\hat{I} \\
&= [I + (1 - \alpha_i)I^p] [S + (1 - \alpha_s)S^p] \frac{\beta}{N} - m\hat{I} \\
&= [I + (1 - \alpha_i)I^p] \left[\frac{(1 - k)\Lambda - mI}{\mu} + (1 - \alpha_s) \frac{k\Lambda - mI^p}{\mu} \right] \frac{\beta}{N} - m\hat{I} \\
&= 0.
\end{aligned}$$

Hence,

$$\beta [I + (1 - \alpha_i)I^p] \left[\frac{(1 - k)\Lambda - mI}{\mu} + (1 - \alpha_s) \frac{k\Lambda - mI^p}{\mu} \right] = m\hat{I} \frac{\Lambda - d\hat{I}}{\mu}.$$

Let $p = \left[\frac{I^p}{I^p + I} \right]_{DP} = \left[\frac{I^p}{\hat{I}} \right]_{DP}$, and assume that $\hat{I} = I^p + I = 0$ at steady state. Then

$$\beta(\hat{I} - \alpha_i p \hat{I}) \left[\frac{(1 - k)\Lambda - m(1 - p)\hat{I}}{\mu} + (1 - \alpha_s) \frac{k\Lambda - mp\hat{I}}{\mu} \right] - m\hat{I} \frac{\Lambda - d\hat{I}}{\mu} = 0$$

$$\beta \hat{I} (1 - \alpha_i p) \left[\frac{(1 - k)\Lambda - m(1 - p)\hat{I}}{\mu} + (1 - \alpha_s) \frac{k\Lambda - mp\hat{I}}{\mu} \right] = m\hat{I} \frac{\Lambda - d\hat{I}}{\mu}$$

$$\beta(1 - \alpha_i p) \left[\frac{(1 - k)\Lambda + (1 - \alpha_s)k\Lambda}{m} - (1 - p)\hat{I} - (1 - \alpha_s)p\hat{I} \right] = \Lambda - d\hat{I}$$

$$\frac{\beta(1 - \alpha_i p)(1 - \alpha_s k)}{\mu + d} \Lambda - \beta(1 - \alpha_i p)(1 - \alpha_s p)\hat{I} = \Lambda - d\hat{I}$$

$$\hat{I} = \frac{\frac{\beta(1 - \alpha_i p)(1 - \alpha_s k)}{\mu + d} - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \Lambda = \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \Lambda.$$

Notice that in the model with no intervention (6), the basic reproduction number is

$R_0 = \frac{\beta}{\mu + d}$, and the endemic steady state is $\left(\frac{1}{\beta - d} \Lambda, \frac{R_0 - 1}{\beta - d} \Lambda \right)$. By the definitions of the

indicators, now we can find the expressions to approximate the asymptotic behavior of $\hat{C}_I$ and $\hat{F}_I$:

$$\hat{C}_I = \left[\frac{R_0 - 1}{\beta - d} - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \right] \Lambda;$$

$$\hat{F}_I = 1 - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{R_0 - 1} \frac{\beta - d}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d}.$$

Now consider the prevalence indicator, we want to find $\left[\frac{I^p + I}{S^p + S + I^p + I} \right]_{DP}$ at the steady state.

$$\begin{aligned} & \frac{dI^p}{dt} + (1 - \alpha_s) \frac{dI}{dt} \\ &= (1 - \alpha_s) \beta \frac{(S^p + S)I}{N} + (1 - \alpha_s)(1 - \alpha_i) \beta \frac{(S^p + S)I^p}{N} \\ & \quad - (\mu + d) [I^p + (1 - \alpha_s)I] \\ &= (1 - \alpha_s) \beta [I + (1 - \alpha_i)I^p] \frac{S^p + S}{N} - (\mu + d) [I^p + (1 - \alpha_s)I] = 0 \end{aligned}$$

Hence,

$$\frac{S^p + S}{N} = \frac{\mu + d}{(1 - \alpha_s) \beta} \frac{1 - \alpha_s \frac{I}{I^p + I}}{1 - \alpha_i \frac{I^p}{I^p + I}} = R_0^{-1} \frac{1}{1 - \alpha_s} \frac{1 - \alpha_s(1 - p)}{1 - \alpha_i p};$$

$$\frac{I^p + I}{N} = 1 - \frac{\mu + d}{(1 - \alpha_s) \beta} \frac{1 - \alpha_s \frac{I}{I^p + I}}{1 - \alpha_i \frac{I^p}{I^p + I}} = 1 - R_0^{-1} \frac{1}{1 - \alpha_s} \frac{1 - \alpha_s(1 - p)}{1 - \alpha_i p}.$$

By the definition of prevalence indicator, the asymptotical behavior of the prevalence indicator can be determined by

$$P_I = 1 - \frac{1 - R_0^{-1} \frac{1}{1 - \alpha_s} \frac{1 - \alpha_s(1 - p)}{1 - \alpha_i p}}{1 - R_0^{-1}} = 1 - \frac{R_0 - \frac{1 - \alpha_s(1 - p)}{(1 - \alpha_s)(1 - \alpha_i p)}}{R_0 - 1}.$$

For the cumulative indicator at the steady state, we have

$$\frac{d}{dt} C_I = \left[\frac{d}{dt} I_{New} \right] - \left[\frac{d}{dt} (I_{New}^p + I_{New}) \right]_{DP}$$

$$\begin{aligned}
\frac{d}{dt}C_I &= [(\mu+d)I] - [(\mu+d)(I^p+I)]_{DP} \\
&= \left(\frac{\beta - (\mu+d)}{\beta - d} - \frac{\beta(1 - \alpha_i p)(1 - \alpha_s k) - (\mu+d)}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \right) \Lambda \\
&= (\mu+d) \left(\frac{R_0 - 1}{\beta - d} - \frac{R_0(1 - \alpha_i p)(1 - \alpha_s k) - 1}{\beta(1 - \alpha_i p)(1 - \alpha_s p) - d} \right) \Lambda.
\end{aligned}$$

We see that the cumulative indicator keep increasing and eventually the rate approaches a constant.

Finally, we look at the annual incidence indicator

$$aI_I(n) = 1 - \frac{\left[\frac{I_{New}^p(n+1) + I_{New}(n+1) - (I_{New}^p(n) + I_{New}(n))}{S^p(n) + S(n)} \right]_{DP}}{\left[\frac{I_{New}(n+1) - I_{New}(n)}{S(n)} \right]_{DP}} = 1 - \frac{\left[\frac{\frac{d}{dt}(I_{New}^p(n+q) + I_{New}(n+s))}{S^p(n) + S(n)} \right]_{DP}}{\left[\frac{\frac{d}{dt}I_{New}(n+r)}{S(n)} \right]_{DP}} \text{ with some } q, s, r \in [0, 1],$$

then at steady state, we have

$$aI_I = 1 - \frac{\left[\frac{\frac{d}{dt}(I_{New}^p + I_{New})}{S^p + S} \right]_{DP}}{\left[\frac{\frac{d}{dt}I_{New}}{S} \right]_{DP}} = 1 - \frac{\left[\frac{(\mu+d)(I^p+I)}{S^p+S} \right]_{DP}}{\left[\frac{(\mu+d)I}{S} \right]_{DP}} = 1 - \frac{\left[\frac{I^p+I}{S^p+S} \right]_{DP}}{\left[\frac{I}{S} \right]_{DP}} = 1 - \frac{R_0 \frac{(1-\alpha_s)(1-\alpha_i p)}{1-\alpha_s(1-p)} - 1}{R_0 - 1}.$$

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Fig. 1.
Flow diagram of a PrEP intervention for the model (1) formulation.

Fig. 2.
 (a) HIV prevalence among sexually active population in South Africa for the period 2001–2011 from data and fitted with the “no intervention” model; (b) Long-term projections of the HIV prevalence based on fitted “no intervention” model.

Fig. 3.

(a) Long-term compartment dynamics of the “dual-protection” model and (b) comparison of the epidemic dynamics projected by the “dual-protection”, “single-protection” and “no intervention” models using baseline parameter values from Table 1.

Fig. 4.

Comparison of the indicators projections for two PrEP interventions over 50-year period.

Intervention 1 assumes that $\theta = 0$ and $\alpha_s = \alpha_i = 0.5$. Intervention 2 assumes that $\theta = 1$, $\alpha_s = 0.5$ and $\alpha_i = 0.9$. All other parameters are fixed on their baseline parameter values from Table 1.

Fig. 5. Initial growth rate of reduction ($\hat{C}_I$) and fractional reduction ($\hat{F}_I$) indicators with respect to (a) θ , (b) k_1 and (c) P . $\hat{C}_I$ is denoted by green solid line, while $\hat{F}_I$ is denoted by blue dashed line. All other parameters are fixed on their baseline parameter values from Table 1.

Fig. 6.

(a) Asymptotic values of the proportion of the HIV-positive individuals who have been infected while using PrEP (p) as a function of the PrEP efficacies (α_s and α_i) assuming 10 % PrEP coverage ($k = k_1 = 0.1$). (b) Long term dynamics of the quantitative indicators based on simulations with “dual-protection” and “no intervention” models using parameters from Table 1.

Fig. 7. Contour plots of the indicators (F_I , P_I , and aI_I) over 10 and 30 years with respect to selected intervention parameters α_i and α_s . All other parameters are fixed at the baseline parameter values from Table 1.

Fig. 8.

Contour plots of the indicators (F_I , P_I , and aI_I) over 10 and 30 years with respect to selected epidemic parameters β and k_1 . All other parameters are fixed at the baseline parameter values from Table 1.

Fig. 9. Partial rank correlation coefficients (PRCC) between model parameters and the quantitative indicators over 10 and 100 years.

Table 1

Parameter description and baseline values

Par.	Description	Value	Ref.
d	HIV carrier's annual rate of progression to AIDS	0.1302	fitted [27]
Λ	Annual rate at which individuals become sexually active	38094	calc. [27]
$\frac{1}{\mu}$	Time (in years) to remain sexually active	$\frac{1}{0.0250}$	fitted [27]
b_a	HIV acquisition risk per act	0.0030	fitted [27]
n	Number of sexual acts per year per individual	65.8494	fitted [27]
β	Cumulative HIV-acquisition risk	$\beta(n, b_a)$	calc.
$N(0)$	Initial sexually active population	10^6	assumed
P	Initial HIV prevalence	0.166	[27]
k_1	Initial PrEP coverage	0.2	assumed
θ	Reduction in the initial fraction of HIV positive individuals as a result of pre-enrollment screening	0.5	assumed
k	Proportion of the new recruits that start using PrEP	$k = k_1$	assumed
α_s	Efficacy of PrEP in reducing susceptibility of PrEP users	0.5	assumed
α_i	Efficacy of PrEP in reducing infectiousness of PrEP users	0.5	assumed

Table 2

Indicator description

Indicator	Name	Description
$C_I(T)$	Cumulative indicator	Cumulative number of infections prevented over the period $[0, T]$ due to the usage of PrEP
$F_I(T)$	Fractional indicator	Fraction of infections prevented over the period $[0, T]$ due to the usage of PrEP
$P_I(T)$	Prevalence indicator	Reduction in HIV-prevalence at time $t = T$ due to the usage of PrEP
$aI_I(T)$	Incidence indicator	Reduction in the annual HIV incidence at time $t = T$ due to the usage of PrEP
$\hat{C}_I(T)$	Reduction indicator	Reduction in the projected number of infections at time $t = T$ due to the usage of PrEP
$F_I^{\hat{}}(T)$	Fractional reduction indicator	Fraction of the projected number of infections at time $t = T$ reduced due to the usage of PrEP