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Impact of population recruitment on the HIV epidemics and the effectiveness of HIV prevention interventions

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Abstract

Mechanistic mathematical models are increasingly used to evaluate the effectiveness of different interventions for HIV prevention and to inform public-health decisions. By focusing exclusively on the impact of the interventions, the importance of the demographic processes in these studies is often underestimated. In this paper, we use simple deterministic models to assess the effectiveness of pre-exposure prophylaxis (PrEP) in reducing the HIV transmission and to explore the influence of the recruitment mechanisms on the epidemic and effectiveness projections. We employ three commonly used formulas that correspond to constant, proportional and logistic recruitment and compare the dynamical properties of the resulting models. Our analysis exposes substantial differences in the transient and asymptotic behavior of the models which result in 47% variation in population size and more than 6 percentage points variation in HIV prevalence over 40 years between models using different recruitment mechanisms. We outline the strong influence of recruitment assumptions on the impact of HIV prevention interventions and conclude that detailed demographic data should be used to inform the integration of recruitment processes in the models before HIV prevention is considered.

Keywords

Mathematical modeling; HIV prevention; Pre-exposure prophylaxis; Population recruitment

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1 Introduction

In the last decade the HIV research focus moved toward development of prevention strategies and interventions. The field celebrated effective treatment options which almost eliminated mother-to-child transmission (Becquet et al. 2009), proven reduction of male risk through circumcision (Gray et al. 2007; Bailey et al. 2007; Auvert et al. 2005), as well as the advances in the treatment as prevention for serodiscordant couples (Cohen et al. 2011). Recently, significant attention and hope is associated with the growing number of promising options for pre-exposure prophylaxis (PrEP) which when applied topically, in the form of gels, or taken as a daily pill (oral PrEP) substantially reduce the risk of HIV acquisition (Karim et al. 2010; Grant et al. 2010; Baeten et al. 2012; Thigpen et al. 2012; Choopanya et al. 2013).

Mathematical models have been extensively employed to provide insights into the effectiveness and cost-effectiveness of different prevention programs (Abbas et al. 2007; Cremin et al. 2013; Desai et al. 2008; Dimitrov et al. 2010, 2011, 2012; Grant et al. 2010; Zhao et al. 2013; Supervie et al. 2010; Nichols et al. 2013; Juusola et al. 2012). Although focused on the intervention characteristics, such as efficacy mechanisms, roll out schedule, projected adherence and coverage these analyses necessarily model the demographic processes in the population such as births, sexual maturation, mortality and migration. In a recent article we argued that modeling efforts related to demographics deserve more attention (Dimitrov et al. 2014).

In this paper we compare some common modeling assumptions related to population recruitment and investigate their influence on the epidemic dynamics and projected effectiveness of PrEP use. Almost all models of HIV prevention interventions that have appeared in the scientific literature use either constant recruitment, assuming that a fixed number of individuals are joining the population per unit time (Wilson et al. 2008; Supervie et al. 2010; Sorensen et al. 2012; Kato et al. 2013; Dimitrov et al. 2013b; Abbas et al. 2013) or proportional recruitment, in which the number of “newcomers” is proportional to the population size (Vickerman et al. 2006; Granich et al. 2009; Bacaer et al. 2010; Cox et al. 2011; Eaton and Hallett 2014). In this study, we additionally consider logistic recruitment assuming that the number of people who join the population increases with population size but saturates at specific level driven by resource limitations. We modify a model (Zhao et al. 2013), previously used to project the impact of daily regimens of oral PrEP, to study the population dynamics and compare the efficacy of PrEP interventions under different recruitment assumptions. We demonstrate the impact of the recruitment assumptions using simple extensions of the classical SI model some of which have been already analyzed (Korobeinikov 2006; Hwang and Kuang 2003; Berezovsky et al. 2005). However, the comparison we present here is instrumental in understanding the importance of population recruitment which remain valid even when more complex models are employed.

The paper is organized as follows. In the next two sections population models in absence and presence of PrEP intervention are formulated, their asymptotic behavior is analyzed and compared under different recruitment assumptions. In Section 4, the influence of the recruitment assumptions on the projected intervention impact is investigated through

numerical simulations. The efficacy of the PrEP intervention is estimated by various metrics using HIV epidemics simulated in the absence of PrEP as a baseline. The paper concludes with a brief discussion.

2 Modeling HIV epidemics in absence of PrEP

We first study the impact of three different assumptions about the recruitment rate on the population dynamics in the absence of PrEP. We consider the following model:

$$\begin{aligned}\frac{dS}{dt} &= f(N) - \beta \frac{SI}{N} - \mu S \\ \frac{dI}{dt} &= \beta \frac{SI}{N} - (\mu + d)I.\end{aligned}\quad (1)$$

with $S(0) = (1-P)N_0$ and $I(0) = PN_0$, where P is the initial HIV prevalence in the initial population of size N_0 . Here, the total population N is divided into two major classes, susceptibles (S) and infected (I). Frequency-dependent transmission is assumed and the cumulative HIV acquisition risk per year β is calculated based on the HIV risk per act (β_a) with a HIV-positive partner and the average number of sex acts per year (n):

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

Individuals join the population, i.e., become sexually active, at a rate $f(N)$. We explore the effects of the following three different recruitment types: $f_C(N) = \Lambda$, $f_P(N) = rN$, and

$f_L(N) = rN(1 - \frac{N}{K})$ corresponding to constant, proportional to size and logistic entrance rate, respectively. The values of the parameters have been identified from the literature or by fitting the simulated HIV dynamics to available empirical data. All model parameters are described in Table 1.

We are primarily interested in the projections of HIV prevalence which is estimated and reported periodically in the scientific literature as statistical data. Therefore, we focus on the

dynamics of the fractions of susceptible ($s = \frac{S}{N}$) and infected ($i = \frac{I}{N} = 1 - s$) individuals projected by the model (1).

The following propositions describe the asymptotic behavior of the model (1) without PrEP under different recruitment mechanisms. They summarize results that have been presented in published studies (Korobeinikov 2006; Hwang and Kuang 2003; Berezovsky et al. 2005).

Proposition 1 All solutions of Model (1) with non-negative initial conditions and constant recruitment $f_C(N) = \Lambda$ are non-negative and bounded with total population size

$$N(t) \leq \max\{N_0, \frac{\Lambda}{\mu}\}.$$

If the basic reproduction number $R_0 = \frac{\beta}{\mu+d} < 1$, then the model has a unique disease-free equilibrium $E_{df} = (\frac{1}{\mu}\Lambda, 0)$ which is globally stable (see Fig.1a, Region 1). When $R_0 > 1$, the disease-free equilibrium (E_{df}) is unstable and the model possesses a unique endemic equilibrium $E^* = (\frac{1}{\beta-d}\Lambda, \frac{1}{(\beta-d)} \cdot (R_0 - 1)\Lambda)$ which is globally stable (Region 2).

Proposition 2 All solutions of Model (1) with non-negative initial conditions and proportional recruitment $f_H(N) = rN$ are non-negative.

The unique steady state, $E_{ext} = (0, 0)$, of the model corresponds to population extinction. A solution of (1) either approaches E_{ext} or the population size grows unbounded under endemic or disease-free conditions, depending on parameter values as follows (see Fig. 1b):

- When $r < \mu$, all solutions are bounded and the population compartments $(S(t), I(t)) \rightarrow (0, 0)$. The extinction steady state (E_{ext}) is stable and the population goes extinct even in the absence of HIV (Region 3);
- When $r > \mu$ and $\beta < r + d$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(s(t), i(t)) \rightarrow (1, 0)$ which corresponds to a disease-free equilibrium prevalence (Region 1);
- When $\mu < r < \mu + d$ and $r + d < \beta < \frac{(\mu+d)d}{\mu+d-r}$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(s(t), i(t)) \rightarrow (\frac{r}{\beta-d}, 1 - \frac{r}{\beta-d})$. Endemic equilibrium prevalence (Region 2);
- When $\mu < r < \mu + d$ and $\beta > \frac{(\mu+d)d}{\mu+d-r}$, all solutions are bounded, $(S(t), I(t)) \rightarrow (0, 0)$ with population fractions $(s(t), i(t)) \rightarrow (\frac{r}{\beta-d}, 1 - \frac{r}{\beta-d})$. The extinction steady state (E_{ext}) is stable where population extinction is caused by HIV (Region 4);
- When $r > \mu + d$ and $\beta > r + d$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(s(t), i(t)) \rightarrow (\frac{r}{\beta-d}, 1 - \frac{r}{\beta-d})$. Endemic equilibrium prevalence (Region 2);

Proposition 3 All solutions of Model (1) with non-negative initial conditions and logistic recruitment $f_L(N) = rN(1 - \frac{N}{K})$ are non-negative. The model has three possible steady states: population extinction $E_{ext} = (0, 0)$, disease-free $E_{df} = (\frac{r-\mu}{r}K, 0)$ and endemic $E^* = \frac{r-\mu-d(1-\frac{1}{R_0})}{r}K(\frac{1}{R_0}, \frac{R_0-1}{R_0})$ which exchange stability as follows (see Fig.1c):

- When $r < \mu$, the disease free (E_d) and the endemic (E^*) equilibria do not exist. The extinction steady state (E_{ext}) is globally stable. The population goes extinct even in the absence of HIV (Region 3);
- When $r > \mu$ and $\beta < \mu + d$, the endemic equilibrium (E^*) does not exist. The disease-free steady state (E_d) is globally stable, while the extinction steady state (E_{ext}) is unstable (Region 1);
- When $\mu < r < \mu + d$ and $\mu + d < \beta < \frac{(\mu + d)d}{\mu + d - r}$ all three equilibria exist. The endemic steady state (E^*) is globally stable, while the extinction (E_{ext}) and the disease-free (E_d) equilibria are unstable (Region 2);
- When $\mu < r < \mu + d$ and $\beta > \frac{(\mu + d)d}{\mu + d - r}$, the endemic equilibrium (E^*) does not exist. The extinction steady state (E_{ext}) is globally stable, while the disease-free (E_d) equilibrium is unstable. The population goes extinct under the pressure of HIV (Region 4);
- When $r > \mu + d$ and $\beta > \mu + d$ all three equilibria exist. The endemic steady state (E^*) is globally stable, while the extinction (E_{ext}) and the disease-free (E_d) equilibria are unstable (Region 2);

Table 2 summarizes and compares the long-term dynamics of the model (1) under various recruitment assumptions. It shows that different recruitment mechanisms support different epidemic outcomes. Population always survives under constant recruitment while extinction, both independent of HIV and under HIV pressure, is possible when the proportional or the logistic recruitment is assumed. Furthermore, the shape and size of the biologically relevant regions of disease free and endemic conditions are different for different mechanisms. Notice that even when all models stabilize at endemic equilibrium the HIV prevalence under the the logistic and the constant recruitment is greater compared to under the proportional recruitment (see Fig. 1d). Moreover, assuming the endemic equilibrium is stable, the asymptotic HIV prevalence is completely independent of the recruitment rate assumed under constant/logistic mechanism, which is not case for the model with proportional recruitment. It should be noted however, that under logistic recruitment, the existence conditions of the endemic equilibrium are dependent on the recruitment rate. Finally, unbounded projections, implying unlimited population growth, are featured under the proportional recruitment only.

3 Modeling HIV epidemics in the presence of PrEP

Next, we investigate the influence of the different recruitment mechanisms on the asymptotic dynamics of models that include PrEP interventions by considering the following system of differential equations:

$$\begin{aligned} \frac{dS^p}{dt} &= k f(N) - (1 - \alpha_s) \beta \frac{S^p I}{N} - \mu S^p \\ \frac{dS}{dt} &= (1 - k) f(N) - \beta \frac{S I}{N} - \mu S \\ \frac{dI}{dt} &= \beta \frac{S I}{N} + (1 - \alpha_s) \beta \frac{S^p I}{N} - (\mu + d) I \end{aligned} \quad (2)$$

with initial conditions:

$$\begin{aligned} S^p(0) &= k(1 - P)N_0 \\ S(0) &= (1 - k)(1 - P)N_0 \\ I(0) &= PN_0, \end{aligned}$$

where P is the initial HIV prevalence, N_0 is the initial population size, and k is the coverage of PrEP among susceptible individuals. Here, the population is divided into three major classes, according to their HIV and PrEP status: susceptible individuals who do not use PrEP (S); susceptible PrEP users (S^p) and infected individuals (I). A constant proportion k of the new recruits are assumed to start using PrEP. The same proportion of the susceptible individuals start on PrEP initially. Since PrEP provides imperfect protection against HIV, some of the PrEP users become infected. The risk of drug-resistance emergence among infected PrEP users has been discussed in the HIV prevention community (Dimitrov et al. 2012, 2013a; Supervie et al. 2010, 2011) and wide-scale PrEP interventions will likely include periodic HIV screening of all prescribed users. Therefore, we assume that PrEP users stop using the product after acquiring HIV and all infected individuals accumulate in the compartment (I).

Again, we explore the effects of the three different recruitment formulas: $f_C(N) = \Lambda$, $f_P(N) = rN$, and $f_L(N) = rN(1 - \frac{N}{K})$ corresponding to constant, proportional to size and logistic entrance rate.

The basic reproduction number of model (2) is given by

$$R_0 = (1 - k)R_0(S) + kR_0(S^p) \triangleq (1 - k)\frac{\beta}{\mu + d} + k\frac{(1 - \alpha_s)\beta}{\mu + d} = \frac{(1 - \alpha_s k)\beta}{\mu + d}.$$

Proposition 4 All solutions of Model (2) with non-negative initial conditions and constant recruitment $f_C(N) = \Lambda$ are non-negative and bounded. If $R_0 < 1$ then the model has unique

disease-free equilibrium $E_{df} = (\frac{k}{\mu}\Lambda, \frac{1 - k}{\mu}\Lambda, 0)$ which is locally stable (See Fig. 2(a), Region

1). Further, if $R_0 < \frac{\mu}{\mu + d}$ then E_{df} is globally stable. If $R_0 > 1$ then E_{df} is unstable and the model possesses unique endemic equilibrium E^* which is locally stable (Region 2) and satisfies:

$$E^* = \left(\frac{\Lambda(\Lambda - dI^*)}{\mu}, \frac{k}{\Lambda + ((1 - \alpha_s)\beta - d)I^*}, \frac{\Lambda(\Lambda - dI^*)}{\mu}, \frac{1 - k}{\Lambda + (\beta - d)I^*}, I^* \right),$$

where I^* is a solution of

$$F(I) \triangleq \beta - d - \mu - \frac{\beta \mu I}{\Lambda - dI} - \frac{\alpha_s \beta k \Lambda}{(1 - \alpha_s) \beta I + \Lambda - dI} = 0$$

in the interval $(0, \frac{\Lambda}{d})$. The HIV prevalence associated with E^* is $i_{\text{const}}^* = \frac{\mu I^*}{\Lambda - dI^*}$.

Proposition 5 All solutions of Model (2) with non-negative initial conditions and proportional recruitment $f_L(N) = rN$ are non-negative.

The unique steady state $E_{\text{ext}} = (0, 0, 0)$ of the model implies population extinction. A solution of (2) either approaches E_{ext} or the population size grows unbounded under endemic or disease-free conditions, depending on different parameter values as follows (see Fig.2(b)):

- When $r < \mu$, all solutions are bounded and $(S^p(t), S(t), I(t)) \rightarrow (0, 0, 0)$. the extinction steady state (E_{ext}) is stable and the population goes extinct even in the absence of HIV (Region 3);
- When $r > \mu$ and $\beta < \frac{r+d}{1 - \alpha_s k}$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(p(t), i(t)) \rightarrow (k, 0)$ corresponding to disease-free equilibrium prevalence (Region 1);
- When $\mu < r < \mu + d$ and $\frac{r+d}{1 - \alpha_s k} < \beta < \bar{\beta}$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(p(t), i(t)) \rightarrow (p_{\text{lin}}^*, i_{\text{lin}}^*)$. Endemic equilibrium prevalence (Region 2);
- When $\mu < r < \mu + d$ and $\beta > \bar{\beta}$, all solutions are bounded and $(S^p(t), S(t), I(t)) \rightarrow (0, 0, 0)$. The extinction steady state (E_{ext}) is stable where population extinction is caused by HIV (Region 4);
- When $r > \mu + d$ and $\beta > \frac{r+d}{1 - \alpha_s k}$, the extinction steady state (E_{ext}) is unstable and the population size grows unbounded with population fractions $(p(t), i(t)) \rightarrow (p_{\text{lin}}^*, i_{\text{lin}}^*)$. Endemic equilibrium prevalence (Region 2);

Here, $\bar{\beta}$ is the solution of the equation (8) derived in A. 5. As before $p = \frac{S^p}{N}$ and $i = \frac{I}{N}$ represent the fractions of susceptibles PrEP users and infected individuals projected by the model (2) and $(p_{\text{lin}}^*, i_{\text{lin}}^*)$ is the corresponding endemic equilibrium of the fractional model (4)-(5) derived in A.5.

Proposition 6 All solutions of Model (2) with non-negative initial conditions and logistic

recruitment $f_L(N) = rN(1 - \frac{N}{K})$ are non-negative and bounded. The model has three possible equilibria corresponding to population extinction $E_{\text{ext}} = (0, 0, 0)$, disease-free

$E_{\text{df}} = (k \frac{r - \mu}{r} K, (1 - k) \frac{r - \mu}{r} K, 0)$ and endemic

$E^* = (S^{p*}, S^*, I^*) = (p_{\log}^* N^*, (1 - p_{\log}^* - i_{\log}^*) N^*, i_{\log}^* N^*)$, where $(p_{\log}^*, i_{\log}^*, N^*)$ is the equilibrium of the fractional model (9) derived in A.6. These steady states exchange stability as follows (see Fig. 2(c)):

- When $r < \mu$, the disease free (E_d) and the endemic (E^*) equilibria do not exist. The extinction steady state (E_{ext}) is globally stable. The population goes extinct even in the absence of HIV (Region 3);
- When $r > \mu$ and $\beta < \frac{\mu+d}{1-\alpha_s k}$, the endemic equilibrium (E^*) does not exist. The disease-free steady state (E_d) is locally stable, while the extinction steady state (E_{ext}) is unstable (Region 1);
- When $\mu < r < \mu + d$ and $\frac{\mu+d}{1-\alpha_s k} < \beta < \bar{\beta}$, the endemic steady state (E^*) is stable, while the extinction (E_{ext}) and disease-free (E_d) equilibria are unstable (Region 2);
- When $\mu < r < \mu + d$ and $\beta > \bar{\beta}$, the endemic equilibrium (E^*) does not exist. The extinction steady state (E_{ext}) is stable, while the disease-free (E_d) is unstable. The population extincts under the pressure of HIV (Region 4);
- When $r > \mu + d$ and $\beta > \frac{\mu+d}{1-\alpha_s k}$, the endemic steady state (E^*) is stable, while the extinction (E_{ext}) and disease-free (E_d) equilibria are unstable (Region 2);

Moreover, the HIV prevalence associated with Model (2) under logistic and constant recruitment is the same, i.e., $i_{\log}^* = i_{\text{const}}^*$. The results on the stability of the endemic equilibrium (E^*) are only verified numerically.

Similar to the case without PrEP, different recruitment mechanisms yield a difference in the boundedness of the solutions and support different sets of epidemic outcomes with unequal HIV prevalence separated by different parameter conditions. The addition of PrEP does not change the shape of the regions with alternative epidemic outcome but rather complicates their boundary conditions. Notice that if the endemic equilibria are stable for the models under logistic and constant recruitment, the asymptotic HIV prevalence projected by those two models is the same, while the HIV prevalence under the proportional recruitment is lower compared to models with constant/logistic recruitment (Fig. 2d). Our analysis shows that, assuming the endemic equilibrium is stable, the asymptotic HIV prevalence under constant and logistic mechanisms is independent of the recruitment rate (for proof see A.6), but not if the proportional mechanism is employed. However, the existence conditions of the endemic equilibrium under logistic recruitment is dependent on the recruitment rate.

4 Public-health impact of PrEP interventions

The asymptotic behavior of the models described in the previous section is informative for the ability of the PrEP intervention to alter the course of the HIV epidemic in the long term. However, in reality the efficacy of PrEP is evaluated over specific initial period (up to 50

years) often by different quantitative metrics. We have demonstrated in previous work that the choice of evaluation method may influence the conclusions of the modeling analyses (Zhao et al. 2013). Here, we quantify the impact of PrEP interventions using four indicators borrowed from published modeling studies (see Table 4) and compare the influence of the recruitment mechanisms on the impact projected with each indicator. The fractional indicator (F_I) measures the intervention efficacy as the proportion of the expected infections in the scenario without PrEP prevented when PrEP is used. The prevalence (P_I) and incidence (aI_I) indicators measure the reduction in the projected HIV prevalence and incidence due to PrEP use, respectively. The last indicator ($\hat{F}_I$) estimates the reduction of the number of infected individuals at any given time and correlates with 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 absolute number of infected individuals.

To track the cumulative number of new infections over time, we add the following equation to model (1):

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

and similarly to model (2):

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

Numerical solutions of the models are obtained under different recruitment mechanisms $f(N)$ keeping all the remaining parameters the same. We assume that the annual influx of people in the population is 1,000,000 initially which is the approximate number of 15-year olds in 2001 in the Republic of South Africa. We calculate the corresponding parameter values to ensure comparable recruitment for each mechanism. As a result, $\Lambda = 10^6$ is used for the

model with constant recruitment, $r = \frac{10^6}{N_0}$ for the model with proportional recruitment and

$r = \frac{10^6 K}{N_0(K - N_0)}$ with $K = 9 \times 10^7$ for the model with logistic recruitment, where $N_0 = 27,172,431$ is the initial population size representative for the 15-49 year-old population in South Africa (see Table 5). The resulting population dynamics over 200 years under scenarios with and without PrEP are presented in Figure 3. Note that with identical initial recruitment and using the same values for all other parameters, the population dynamics substantially diverge over the simulated period. In the absence of PrEP, the population suffers the smallest decrease in size (33%) under the constant recruitment scenario because the disease-related mortality does not impact the influx of newly susceptible people (Figure 3 (a),(c),(e)). In comparison, the population loses 94% and almost 100% over 200 years under the logistic and proportional recruitment scenarios. In addition to the population size, the proportion of infected individuals is affected as well. Assuming an initial HIV prevalence of 16.6%, the models predict that the HIV prevalence will raise to 24% with

constant, 29% with logistic and 49% with proportional recruitment (Figure 3 (g)). The results do not change qualitatively if 20% of the population use PrEP. Naturally, for all recruitment methods the projected number of susceptible individuals is larger compared to the scenario without PrEP. However, the model with constant recruitment also projects smaller number of infected individuals versus the scenario without PrEP while the other methods show substantial increase in infected individuals due to the fact that healthier population size is preserved when PrEP is used. The relative order of the projected population size by recruitment mechanism remains the same (Figure 3 (b),(d),(f)). However, the dynamics predicted with logistic recruitment (dashed black lines) tend to stay closer to those with constant recruitment (solid blue lines) which was not the case when PrEP is not used. PrEP leads to significant reduction in HIV prevalence under all recruitment scenarios. Although the model with proportional recruitment is still most pessimistic on a long term with respect to HIV prevalence (18%), the other two mechanisms result in comparable projections of 13%. Note, that the infected proportion under constant recruitment remains smaller for at least 150 years compared to logistic recruitment, but after that the projections reverse (Figure 3 (h)).

The impact of the recruitment on the projected PrEP efficacy is investigated in Figure 4. The choice of recruitment mechanisms shows no substantial impact over the initial period of 20-30 years but results in up to 18% difference in predicted reduction in HIV prevalence and incidence in longer term (Figure 4 (a),(b)). The model using proportional recruitment is most optimistic predicting 64% reduction in HIV prevalence and 68% in HIV incidence, respectively, over 200 years. Conversely, the model with constant recruitment projects largest fraction of infection prevented (Figure 4 (c)). Interestingly, the same indicator projects negative overall PrEP impact of the models with proportional and logistic recruitment after 102 and 130 years. It is the result of the critical decline in population size under the scenario without PrEP which limits the number of HIV infections in the long term.

Finally, we simulated the HIV epidemics by fitting the models with different recruitment rates to 10-year demographic and epidemic data representative for the Republic of South Africa (Africa 2012). Parameters values (Table 6) were determined to minimize a least square error between projected population and data (the number of susceptible and infected individuals) in the absence of PrEP following the approach proposed in a previous study (Zhao et al. 2013). The relative short duration of the fitted period did not allow for significant difference in the “best fit” parameters across models. As a result, the predictions of HIV dynamics and PrEP effectiveness with that “best fit” parameter sets (see Figure 5 and Figure 6 in the Appendix), were qualitatively similar to the simulations with fixed parameter sets (Fig. 3 and 4).

5 Discussion

Mathematical models are frequently used to estimate the expected efficacy of different interventions for HIV prevention under various epidemic settings. In this study, we demonstrated that the modeling assumptions regarding population recruitment can have a strong influence on the projected course of the HIV epidemic and as a result can impact the projected success of any planned interventions. We considered models equipped with three

distinct recruitment mechanisms (constant, proportional, and logistic) and studied their behavior. Our analysis showed that the three models possess qualitatively different dynamic characteristics. The susceptible and infected populations stabilize in size to their respective equilibria under any feasible combination of parameters when constant recruitment is assumed. This model supports only two long-term outcomes corresponding to a disease-free and an endemic equilibrium, respectively. In comparison, the proportional and the logistic recruitment support four long-term outcomes including a disease free equilibrium, an endemic equilibrium, an equilibrium corresponding to population extinction under the pressure of HIV and an equilibrium corresponding to population extinction in absence of HIV. The parameter conditions where the transitions between asymptotic states occur (i.e., the bifurcation points) are the same for these two models but different from those for the model with the constant recruitment. On the other hand, the constant and the logistic model share an endemic fractional equilibrium which is different from the proportional model, i.e., they project different HIV prevalence in the long term. Somewhat unexpected, the recruitment rate has no influence on the asymptotic HIV prevalence when endemic equilibrium is reached under the constant and the logistic mechanisms while being of importance if the proportional mechanism is employed.

As a result, the simulations of HIV epidemics with the three models over 200 years show large discrepancies in the population size and HIV prevalence under identical initial conditions and forces of infection. The projected HIV prevalence varies from 24%, under constant recruitment, to 49%, under proportional recruitment. In addition, a significant difference in the reduction in HIV prevalence and incidence (almost 20%) is predicted when 50% effective PrEP is used by 20% of the population. Over the entire simulated period, the proportional recruitment provides the most optimistic estimates of the PrEP effectiveness in terms of a prevalence reduction while the constant recruitment predicts a larger fraction of infections prevented.

The models that we used to illustrate the importance of the recruitment mechanisms were purposely simple as to allow us for a more comprehensive analytical work. However, we believe that the same or even stronger impact of the choice of a recruitment treatment exists for compartmental models with higher level of complexity because the integration of the demographic processes such as births, sexual maturation and immigration remains the same. As a result, the differences in population size and distribution, which arise from the decision regarding recruitment, propagate into the epidemic dynamics and affect the intervention effectiveness.

It can be argued that, regardless of the differences in the dynamic behavior, all three models agree in their efficacy projections over 20-30 years, which is the usual period over which the interventions are evaluated. However, often the models are run for extended periods (till endemic equilibrium is reached) in order to simulate “mature” epidemics and the intervention is introduced afterward (Boily et al. 2004; Abbas et al. 2007). The key message of this analysis is that the way the recruitment is incorporated in the models impacts the HIV epidemic and may have a significant effect on the projected efficacy of different HIV interventions. Demographic data, including statistics on births and age-specific mortality, should be used to inform the modeling mechanisms before HIV prevention is considered.

Our future research plans include exploring the importance of population recruitment and departure within both, compartmental and individual-based, modeling frameworks.

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Appendix

A Proofs of main results

A.1 Proof of Proposition 1

Positivity and boundedness of the solutions can be easily proved. Then periodic solutions

can be excluded by Dulacs Criteria. Let $P(S, I) := \frac{dS}{dt}$ and $Q(S, I) := \frac{dI}{dt}$, then

$$\frac{\partial}{\partial S} \frac{P}{SI} + \frac{\partial}{\partial I} \frac{Q}{SI} = -\frac{\Lambda}{S^2 I} < 0.$$

Model (1) with constant recruitment $f_C(N)$ has two possible steady states $E_{df} = (\frac{1}{\mu}\Lambda, 0)$ and

$E^* = (\frac{1}{\beta-d}\Lambda, \frac{1}{\beta-d}(R_0 - 1)\Lambda)$, where $R_0 = \frac{\beta}{\mu+d}$. Notice that E^* (positive steady state) exists if and only if $R_0 > 1$.

The eigenvalues of the Jacobian evaluated at E_{df} are $\lambda_1 = -\mu < 0$ and $\lambda_2 = (\mu + d)(R_0 - 1)$ which implies that E_{df} is locally stable when $R_0 < 1$ and unstable when $R_0 > 1$.

For the eigenvalues of the Jacobian evaluated at E^* it is true that

$\lambda_1 + \lambda_2 = (\mu + d)(1 - R_0 - \frac{\mu}{\mu + d}) < 0$ and $\lambda_1 \times \lambda_2 = (\mu + d)[\beta(R_0 - 1)^2 + \mu R_0(R_0 - 1)] > 0$ which implies that E^* is locally stable when exists.

Finally by the Poincaré-Bendixson theorem we have the following results:

- when $R_0 < 1$, E_{df} is globally stable and E^* does not exist;
- when $R_0 > 1$, E^* is globally stable and E_{df} is unstable.

A.2 Proof of Proposition 2

The positivity of the solutions of Model (1) with proportional recruitment $f_P(N)$ can be easily proved. The equation for the total population size

$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = rN - \mu S - (\mu + d)I = (r - \mu)N - dI \leq (r - \mu)N$ implies that $N(t) \rightarrow 0$ extinction if $r < \mu$. It is clear that the extinction occurs even in the absence of HIV ($I = 0$)

when the first equation of Model (1) becomes $\frac{dS}{dt} = (r - \mu)S$. Next we study the case when $r > \mu$.

We analyze the following fractional form of Model (1) with proportional recruitment $f_P(N)$:

$$\begin{aligned}\frac{dS}{dt} &= [r - (\beta - d)s](1 - s) \\ \frac{dN}{dt} &= [r - \mu - d(1 - s)]N \\ i &= 1 - s.\end{aligned}$$

Notice that the first equation is independent of N which allow us to study $s(t)$ directly in the biologically feasible region $\{0 \leq s \leq 1\}$. Since $s(0) \in (0, 1)$, then $\lim_{t \rightarrow \infty} s(t) = 1$ (and $\lim_{t \rightarrow \infty} i(t) = 0$) if:

$$\begin{aligned}& -\beta < d \text{ or} \\ & -\beta > d \text{ and } \frac{r}{\beta - d} \geq 1.\end{aligned}$$

Combined, these two cases imply that if $\beta < r + d$ then each solution of the fractional model approaches disease-free equilibrium. Under this condition the population size grows unbounded. Alternatively, if $\beta > r + d$ all solutions of the fractional model approach the

endemic equilibrium with $\lim_{t \rightarrow \infty} s(t) = \frac{r}{\beta - d}$ and $\lim_{t \rightarrow \infty} i(t) = 1 - \frac{r}{\beta - d}$. The equation for the population size $N(t)$ implies that in this case the population extinction under HIV pressure will be caused if $(\mu + d - r)\beta > (\mu + d)d$. Therefore the population is endangered only if $r < \mu$

$$+ d \text{ and } \beta < \frac{(\mu + d)d}{\mu + d - r}.$$

A.3 Proof of Proposition 3

The region $\{S \geq 0, I \geq 0, S + I \leq K\}$ is positive invariant under the model (1) with logistic recruitment which can be checked by determining the sign of the derivatives on the

boundary. Given $S + I > K$ in $\{S \geq 0, I \geq 0\}$, we have $\frac{dN}{dt} = rN(1 - \frac{N}{K}) - \mu N - dI \leq -\mu N$ and thus the total population will decrease below carrying capacity. Therefore we consider only the region $\{S \geq 0, I \geq 0, S + I \leq K\}$.

Periodic solutions in the region $\{S \geq 0, I \geq 0, S + I \leq K\}$ can be excluded by Dulac's Criteria.

Let $P(S, I) := \frac{dS}{dt}$ and $Q(S, I) := \frac{dI}{dt}$, then

$$\frac{\partial}{\partial S} \left(\frac{P}{SI} \right) + \frac{\partial}{\partial I} \left(\frac{Q}{SI} \right) = -\frac{r}{K} \left(\frac{1}{S} + \frac{1}{I} \right) - \frac{r}{S^2} \left(1 - \frac{S+I}{K} \right) < 0.$$

The model has three possible steady states:

1. Extinction equilibrium $E_{ext} = (0, 0)$ which always exist;
2. Disease-free equilibrium $E_{df} = (\frac{r - \mu}{r}K, 0)$ which exists for $r > \mu$ and

3.

Endemic equilibrium $E^* = \frac{r - \mu - d(1 - \frac{1}{R_0})}{r} K(\frac{1}{R_0}, \frac{R_0 - 1}{R_0})$, where $R_0 = \frac{\beta}{\mu + d}$. It exist if $R_0 > 1 \Leftrightarrow \beta > \mu + d$ and $r > \mu + d(1 - \frac{1}{R_0})$. The later is equivalent to $\beta(\mu + d - r) < (\mu + d)d$ which is true if:

$$- r > \mu + d \text{ or}$$

$$- r < \mu + d \text{ and } \beta < \frac{(\mu + d)d}{\mu + d - r}$$

Similar to Proposition 2, we can show that if $r < \mu$ then the population go extinct ($N(t) \rightarrow 0$) and all solutions approach the extinction equilibrium E_{ext} . Next we assume that $r > \mu$.

Eigenvalues of the Jacobian matrix at E_{df} are $-(r - \mu) < 0$ and $\beta - (\mu + d)$. It implies that when exists E_{df} is stable when $R_0 < 1 \Leftrightarrow \beta < \mu + d$, and unstable otherwise.

Eigenvalues of the Jacobian matrix at E^* satisfy

$$\lambda_1 + \lambda_2 = -[r - \mu - d(1 - \frac{1}{R_0})] - (1 - \frac{1}{R_0})(\beta - d) < 0 \text{ and}$$

$$\lambda_1 \cdot \lambda_2 = [r - \mu - d(1 - \frac{1}{R_0})][\beta - (\mu + d)] > 0. \text{ It implies that } E^* \text{ is stable when exists.}$$

The proof will be completed when the local stability of the extinction equilibrium E_{ext} is analyzed. We follow an approach similar to one often used in the analysis of ratio-dependent population models (Hews et al. 2010). To avoid singularity at (0, 0) it is studied through the

modified model in terms of the fraction of susceptibles $s = \frac{S}{N}$ and total population size N

(note that infected fraction satisfies $i = \frac{I}{N} = 1 - S$):

$$\begin{aligned} \frac{dS}{dt} &= [r(1 - \frac{N}{K}) + (d - \beta)s](1 - s) \\ \frac{dN}{dt} &= [r(1 - \frac{N}{K}) - \mu - d(1 - s)]N. \end{aligned} \quad (3)$$

It possesses two steady states $E_1 = (1, 0)$, $E_2 = (\frac{r}{\beta - d}, 0)$ corresponding to E_{ext} .

The Jacobian matrix at E_1 has an eigenvalue $r - \mu > 0$ which implies that E_1 is unstable.

Eigenvalues of the Jacobian matrix at E_2 are $\lambda_1 = d + r - \beta$ and $\lambda_2 = -\frac{\mu + d}{\beta - d}(\beta - d - R_0 r)$. It implies that E_2 is stable if $\beta > d + r$ and $\beta > d + R_0 r$. As a result E_{ext} is stable if $\beta > \max\{d + r, d + R_0 r\}$ and unstable otherwise. Then,

– when $R_0 < 1$ ($\beta < \mu + d$), E_{ext} is unstable since $\beta < d + r$. In this case endemic (E^*) equilibrium does not exist while the disease-free (E_{df}) steady state is stable;

– when $R_0 > 1$ ($\beta > \mu + d$), E_{00} is stable if $\beta > d + R_0 r$, i.e., when endemic (E^*) equilibrium does not exist. In this case the disease-free (E_{df}) steady state is unstable;

Finally the global stability results in the Proposition follow by Poincaré-Bendixson theorem.

A.4 Proof of Proposition 4

Positivity and boundedness of solutions can be easily proved. Then $\frac{dS^p}{dt} \leq k\Lambda - \mu S^p$ implies $\limsup_{t \rightarrow \infty} S^p \leq \frac{k\Lambda}{\mu}$ and $\frac{dS}{dt} \leq (1-k)\Lambda - \mu S$ implies $\limsup_{t \rightarrow \infty} S \leq \frac{(1-k)\Lambda}{\mu}$. Therefore

$\frac{dN}{dt} = \frac{dS^p}{dt} + \frac{dS}{dt} + \frac{dI}{dt} = \Lambda - \mu N - dI \geq \Lambda - (\mu + d)N$ implies $\liminf_{t \rightarrow \infty} N \geq \frac{\Lambda}{\mu + d}$. Then in the

long term we have $\frac{S}{N} \leq \frac{(1-k)(\mu + d)}{\mu}$, and $\frac{S^p}{N} \leq \frac{k(\mu + d)}{\mu}$, which implies

$$\begin{aligned} \frac{dI}{dt} \leq I & \left[\beta \frac{(1-k)(\mu + d)}{\mu} + (1 - \alpha_s) \beta \frac{k(\mu + d)}{\mu} \right. \\ & \left. - (\mu + d) = I \frac{(\mu + d)^2}{\mu} \left[\beta \frac{1-k}{\mu + d} + (1 - \alpha_s) \beta \frac{k}{\mu + d} - \frac{\mu}{\mu + d} \right] \right] \\ & = I \frac{(\mu + d)^2}{\mu} \left(R_0 - \frac{\mu}{\mu + d} \right). \end{aligned}$$

. Now if $R_0 < \frac{\mu}{\mu + d}$, then because of the positivity of the solution, we know $\lim_{t \rightarrow \infty} I = 0$. Then combining this result with the equations

in Model (2), implies that $\lim_{t \rightarrow \infty} S^p = \frac{k\Lambda}{\mu}$ and $\lim_{t \rightarrow \infty} S = \frac{(1-k)\Lambda}{\mu}$. Thus, global stability of the

infection-free steady state $E_{df} = (\frac{k\Lambda}{\mu}, \frac{(1-k)\Lambda}{\mu}, 0)$ under condition $R_0 < \frac{\mu}{\mu + d}$ is proved. For local stability of E_0 , we consider the corresponding eigenvalues $\lambda_1 = -\mu < 0$, $\lambda_2 = -\mu < 0$ and $\lambda_3 = (\mu + d)(R_0 - 1)$. Therefore, E_{df} is stable when $R_0 < 1$ and unstable when $R_0 > 1$.

Now we consider E^* . By setting $F(I) = 0$ and dividing by $\Lambda^2 (\mu + d)$, we obtain that F^* is a root of:

$$\hat{F}(I) \triangleq (R_0 - 1) + \left((d - (1 - \alpha_s)\beta) - (\mu + d - (1 - \alpha_s)\beta) \frac{\beta}{\mu + d} - d(R_0 - 1) \right) \frac{I}{\Lambda} - (d - \beta)(d - (1 - \alpha_s)\beta) \frac{I^2}{\Lambda^2}$$

Substituting in iN where $i := \frac{I}{N}$, and $N = \frac{\Lambda}{\mu + di}$ into $\hat{F}(I) = 0$ we notice that F^* is also a root of:

$$\overline{F}(iN) \triangleq \mu(\mu + d)(1 - R_0) + \beta(\mu + d\alpha_s k - (\beta - \mu - d)(1 - \alpha_s))i + (1 - \alpha_s)\beta^2 i^2$$

Now substituting back in for I and $N = \frac{\Lambda - dI}{\mu}$, we notice that F^* is a root of:

$$\bar{F}(I) = \mu(\mu + d)(1 - R_0) + \beta(\mu + d\alpha_s k - (\beta - \mu - d)(1 - \alpha_s)) \frac{I}{N} + (1 - \alpha_s)\beta^2 \frac{I^2}{N^2}$$

Now we have $\hat{F}(0) = (R_0 - 1)$ and $\hat{F}'(\frac{\Lambda}{d}) = -\frac{(1 - \alpha_s)\beta^2 \mu}{d^2(\mu + d)} < 0$.

Assume $R_0 > 1$, then $\hat{F}(0) > 0$ and also $\beta > d$. Since $\hat{F}(0) > 0$, $\hat{F}'(\frac{\Lambda}{d}) < 0$ and $\hat{F}$ is a second order polynomial, we have existence of a unique endemic equilibrium.

Assume $R_0 < 1$. Since

$$\mu + d\alpha_s k - (\beta - \mu - d)(1 - \alpha_s) \geq \mu + d\alpha_s k - \alpha_s k(\mu + d) \left(\frac{1 - \alpha_s}{1 - \alpha_s k} \right) \geq \alpha_s k(\mu + d) \left(1 - \frac{1 - \alpha_s}{1 - \alpha_s k} \right) > 0,$$

we have that $\bar{F}(I) > 0$ for all $I \in (0, \frac{\Lambda}{d})$ and therefore we have no solution F^* .

Therefore when $R_0 < 1$, there is only the disease-free equilibrium, E_{df} and whenever $R_0 > 1$ there is both the disease-free equilibrium, E_{df} and the endemic equilibrium, E^* .

Now we analyze the stability of the endemic equilibrium, E^* . Because of the complexity of the expressions, we will not express the positive steady state explicitly. Now assume that

$$R_0 = \frac{(1 - \alpha_s k)\beta}{\mu + d} > 1.$$

The Jacobian of the system is:

$$J = \begin{pmatrix} -\frac{(I+S)(1-\alpha_s)}{N^2}\beta I - \mu & \frac{(1-\alpha_s)}{N^2}\beta S^p I & -\frac{(S^p+S)(1-\alpha_s)}{N^2}\beta S^p \\ \frac{1}{N^2}\beta S I & -\frac{S^p+I}{N^2}\beta I - \mu & -\frac{S^p+S}{N^2}\beta S \\ \frac{I-(I+S)\alpha_s}{N^2}\beta I & \frac{I+S^p\alpha_s}{N^2}\beta I & \frac{(S^p+S)(S+S^p(1-\alpha_s))}{N^2}\beta - (\mu+d) \end{pmatrix}.$$

Using

$$P = \begin{pmatrix} 1 & -1 & -1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

we see that the Jacobian is similar to

$$H = P^{-1}JP = \begin{pmatrix} -\mu & 0 & -d \\ \frac{1}{N^2}\beta SI & -\frac{1}{N}\beta I - \mu & -\frac{1}{N}\beta S \\ \frac{I-(I+S)\alpha_s}{N^2}\beta I & \frac{\alpha_s}{N}\beta I & \frac{(S^p-I)(1-\alpha_s)+S}{N}\beta - (\mu+d) \end{pmatrix}.$$

Rewriting H evaluated at the endemic equilibrium using $p^* := \frac{S^{P^*}}{N^*}$, $s^* := \frac{S^*}{N^*}$, $i^* := \frac{I^*}{N^*}$, $N^* = \frac{\Lambda}{\mu+di^*}$ and $i^* + p^* + s^* = 1$, we obtain:

$$H = \begin{pmatrix} -\mu & 0 & -d \\ \beta s^* i^* & -\beta i^* - \mu & -\beta s^* \\ ((s^* + i^*)(1 - \alpha_s) - s^*)\beta i^* & \alpha_s \beta i^* & -(1 - \alpha_s)\beta i^* \end{pmatrix}$$

where $s^* = \frac{1}{\alpha_s \beta}(\mu + d - (1 - i^*)(1 - \alpha_s)\beta)$.

We have the characteristic polynomial:

$$f(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C$$

Where

$$\begin{aligned} A &= (2 - \alpha_s)\beta i + 2\mu, \\ B &= (1 - \alpha_s)(\beta i^* + di^* + 2\mu)\beta i^* + \mu(\beta i^* + \mu) + \alpha_s(\beta - d)\beta s^* i^* \\ C &= ((1 - \alpha_s)(d\beta i^{*2} + d\mu i^* + \mu(\beta i^* + \mu)) + \alpha_s\mu(\beta - d)s^*)\beta i^*. \end{aligned}$$

Clearly if $R_0 > 1$, then $\beta > d$, which implies that $A > 0$, $B > 0$ and $C > 0$. Also we have that

$$\begin{aligned}
AB - C = & 3\mu^2\beta i^* \\
& + 2\mu^3 + \alpha_s^2\mu\beta^2 i^{*2} \\
& + \alpha_s\mu(\beta \\
& \quad - d)\beta i^* s^* \\
& + \alpha_s(2 \\
& \quad - \alpha_s)(\beta \\
& \quad - d)\beta^2 i^{*2} s^* \\
& + (1 - \alpha_s)(\mu d i^* \\
& + \beta^2 i^{*2} + 6\mu\beta i^* \\
& + 4\mu^2)\beta i^* \\
& + (1 - \alpha_s)^2(\mu \\
& + (\beta + d)i^*)\beta^2 i^{*2} > 0.
\end{aligned}$$

Therefore by the Routh-Hurwitz Criteria, the endemic equilibria, E^* is locally stable.

A.5 Proof of Proposition 5

We analyze the fractional model associated with proportional recruitment:

$$\frac{dp}{dt} = kr - rp - [(1 - \alpha_s)\beta - d]pi \triangleq X(p, i) \quad (4)$$

$$\frac{di}{dt} = [\beta - (d+r) - \alpha_s\beta p - (\beta - d)i]i \triangleq Y(p, i) \quad (5)$$

$$s = 1 - p - i \quad (6)$$

$$\frac{dN}{dt} = [r - \mu - di]N. \quad (7)$$

Notice that the first two equations of the system (4) - (7) are decoupled from the rest which allow us to study the reduced system (4) and (5).

Positivity of solutions for the fractional system can be easily checked. Further,

$$\begin{aligned}
\frac{dp}{dt} + \frac{di}{dt} &= kr - rp - \beta pi \\
&+ \alpha_s pi \\
&+ d pi \\
&+ (\beta - d)i \\
&- ri - \alpha_s \beta pi \\
&- (\beta - d)i^2 \\
&= kr - r(p \\
&+ i) - \beta pi \\
&- (\beta - d)pi \\
&+ (\beta - d)i \\
&- (\beta - d)i^2 \\
&= kr - r(p \\
&+ i) - \beta pi \\
&+ (\beta - d)i[1 - (p+i)].
\end{aligned}$$

Then at $p + i = 1$, $\frac{d(p+i)}{dt} = -r + kr - \beta pi = -r(1 - k) - \beta pi < 0$ implies that $(p + i)(t) \rightarrow 1$ for $t > 0$ given that $(p + i)(0) = 1$.

The periodic solutions for the reduced system, and therefore for the transformed system, can be excluded by Dulac's Criteria: $\frac{\partial}{\partial p}(\frac{X}{pi}) + \frac{\partial}{\partial i}(\frac{Y}{pi}) = -\frac{kr}{p^2 i} - \frac{\beta - d}{p} < 0$, when given $\beta - d > 0$.

For the reduced system, there are possibly several steady states: $E_1 = (k, 0)$ (always exists) and $E_2 = (p_{lin}^*, i_{lin}^*) := (p^*, i^*)$ (positive steady state, existence depends on parameter values).

For E_1 , we have eigenvalues $\lambda_1 = -r < 0$ and $\lambda_2 = (1 - \alpha_s k)\beta - (d + r)$. Therefore if $(1 - \alpha_s k)\beta < (d + r)$, then E_1 is locally stable; if $(1 - \alpha_s k)\beta > (d + r)$, then E_1 is unstable.

For E_2 , we have $Ap^{*2} + Bp^* + C = 0$ and $i^* = 1 - \frac{\alpha_s \beta p^* + r}{\beta - d}$, with $A = \alpha_s \beta [(1 - \alpha_s)\beta - d]$, $B = -[(\beta - d - r)((1 - \alpha_s)\beta - d) + (\beta - d)r]$, and $C = (\beta - d)kr$. If further $0 < p^* < 1$ and $0 < i^* < 1$, then (p^*, i^*) exists as a positive steady state.

Notice that $p^* \in (0, \frac{\beta - (d+r)}{\alpha_s \beta})$ and $i^* \in (0, \frac{\beta - (d+r)}{\beta - d})$. So we assume that $\beta > d + r$. Denote $F(p) = Ap^2 + Bp + C$, then we have the following results for $F(p)$ over

$$(0, \frac{\beta - (d+r)}{\alpha_s \beta}): F(0) = (\beta - d)kr > 0, \text{ and}$$

$F(\frac{\beta - (d+r)}{\alpha_s \beta}) = -\frac{(\beta - d)r}{\alpha_s \beta} [(1 - k\alpha_s)\beta - (d+r)]$. Now if $(1 - k\alpha_s)\beta > d + r$, then $F(0) > 0$ and $F(\frac{\beta - (d+r)}{\alpha_s \beta}) < 0$ implies a unique solution of $F(p) = 0$ over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$, because $F(p)$ is a parabolic function.

Now consider the case when $(1 - k\alpha_s)\beta < d + r (\Rightarrow (1 - \alpha_s)\beta - d < r)$. If $(1 - \alpha_s)\beta > d$, then $F(0) > 0$ and $F(\frac{\beta - (d+r)}{\alpha_s \beta}) > 0$ implies no solution of $F(p) = 0$ over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$, because $F(p)$ is linear or concave down. If $(1 - \alpha_s)\beta < d$, then $F(p)$ is concave up and attains its

minimum at $\hat{p} = \frac{\beta - (d+r)}{2\alpha_s \beta} + \frac{(\beta - d)r}{2\alpha_s \beta [(1 - \alpha_s)\beta - d]} > \frac{\beta - (d+r)}{2\alpha_s \beta} + \frac{(\beta - d)r}{2\alpha_s \beta r} > \frac{\beta - (d+r)}{\alpha_s \beta}$.

Therefore if $(1 - \alpha_s)\beta > d$, then $F(0) > 0$ and $F(\frac{\beta - (d+r)}{\alpha_s \beta}) > 0$ implies no solution of $F(p) = 0$ over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$, because $F(p)$ is decreasing over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$.

Therefore if $\beta > d + r$, we have a unique solution of $F(p) = 0$ over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$ when $(1 - k\alpha_s)\beta > d + r$ and no solution over $(0, \frac{\beta - (d+r)}{\alpha_s \beta})$ when $(1 - k\alpha_s)\beta < d + r$.

Next, we can show that E_2 is stable when it exists. Notice that the existence of E_2 requires $(1 - \alpha_s k)\beta > (d + r)$, when E_1 is unstable. Also, we have

$$kr - rp^* - [(1 - \alpha_s)\beta - d]p^* i^* = 0 \Rightarrow -r - [(1 - \alpha_s)\beta - d]i^* = -\frac{kr}{p^*}; -[(1 - \alpha_s)\beta - d]p^* = -\frac{kr - rp^*}{i^*},$$

and

$$\beta - (d+r) - \alpha_s \beta p^* - (\beta - d)i^* = 0.$$

And we have the following Jacobian matrix for E_2 :

$$J(E_2) = \begin{vmatrix} -r - [(1 - \alpha_s)\beta - d]i^* & -[(1 - \alpha_s)\beta - d]p^* \\ -\alpha_s \beta i^* & -(\beta - d)i^* + \beta - (d+r) - \alpha_s \beta p^* - (\beta - d)i^* \end{vmatrix}.$$

Then

$$J(E_2) = \begin{vmatrix} -\frac{kr}{p^*} & -\frac{kr - rp^*}{i^*} \\ -\alpha_s \beta i^* & -(\beta - d)i^* \end{vmatrix}.$$

The corresponding eigenvalues satisfy

$$\lambda_1 + \lambda_2 = -\frac{kr}{p^*} - (\beta - d)i^* < 0,$$

and

$$\lambda_1 \cdot \lambda_2 = \frac{kr}{p^*}(\beta - d)i^* - \alpha_s \beta(kr - rp^*).$$

Furthermore,

$$\begin{aligned} \lambda_1 \cdot \lambda_2 &= \frac{kr}{p^*}(\beta - d)(1 - \frac{\alpha_s \beta p^* + r}{\beta - d}) - \alpha_s \beta(kr - rp^*) \\ &= \frac{r}{p^*}[k(\beta - d - \alpha_s \beta p^* - r) - \alpha_s \beta(k - p^*)p^*] \\ &= \frac{r}{p^*}[\alpha_s \beta p^{*2} - 2\alpha_s \beta kp^* + k(\beta - d - r)]. \end{aligned}$$

Therefore, $\lambda_1 \cdot \lambda_2 > 0$ since $f(p^*) = \alpha_s \beta p^{*2} - 2\alpha_s \beta kp^* + k(\beta - d - r) > 0$. We know that $f(p^*)$ attains the minimum value $f(k)$ at $p^* = k$. Now it is sufficient to show that $f(k) > 0$. Since $(1 - \alpha_s k)\beta > (d + r) \Rightarrow \beta - d - r > \alpha_s k\beta$, then

$$f(k) = \alpha_s \beta k^2 - 2\alpha_s \beta k^2 + k(\beta - d - r) = k(\beta - d - r) - \alpha_s \beta k^2 > k\alpha_s k\beta - \alpha_s \beta k^2 = 0.$$

Thus, we have proven that E_2 is stable when it exists, i.e., require $(1 - \alpha_s k)\beta > (d + r)$. Further since $(1 - \alpha_s k)\beta > (d + r)$ implies $\beta > d$ (no periodic solutions) and E_1 is unstable, then E_2 is globally stable when it exists.

If $(1 - \alpha_s k)\beta < (d + r)$, then E_1 is stable and E_2 does not exist. Further $\beta > d$ implies no periodic solutions, therefore we conclude that E_1 is globally stable provided that $(1 - \alpha_s k)\beta < (d + r)$ and $\beta > d$.

Now, for the original system, similar to Proposition 2, we can show that the unique steady state $E = (0, 0, 0)$ is globally stable if $r < \mu$. Next we will study the cases when $r > \mu$. We know that when $\beta > d$, $E_1 = (k, 0)$ is globally stable when $(1 - k)\beta + k(1 - \alpha_s)\beta < d + r$, while $E_2 = (p^*, i^*)$ is globally stable when $(1 - k)\beta + k(1 - \alpha_s)\beta > d + r$. Then by (6), the total population $N(t)$ either approaches 0 when $r - \mu - d \lim_{t \rightarrow \infty} i(t) < 0$, or blows up when $r - \mu - d \lim_{t \rightarrow \infty} i(t) > 0$. Similarly by (7), the infected population $I(t)$ either approaches 0 when $\beta(1 - \lim_{t \rightarrow \infty} p(t) - \lim_{t \rightarrow \infty} i(t)) + (1 - \alpha_s)\beta \lim_{t \rightarrow \infty} p(t) - (\mu + d) < 0$, or blows up when $\beta(1 - \lim_{t \rightarrow \infty} p(t) - \lim_{t \rightarrow \infty} i(t)) + (1 - \alpha_s)\beta \lim_{t \rightarrow \infty} p(t) - (\mu + d) > 0$. Thus, periodic solutions for (2) do not exist when $\beta > d$.

Further, if $r > \mu + d$, then $r - \mu - d \lim_{t \rightarrow \infty} i(t) > 0$ and the population grows unbounded. Now assume that $\mu < r < \mu + d$. Substituting in $i^* = 1 - \frac{\alpha_s \beta p^* + r}{\beta - d}$ and p^* into the above we derive conditions for population extinction. We obtain

$$\beta(1 - p^* - i^*) + (1 - \alpha_s)\beta p^* - (\mu + d) = 0$$

which yields $p^* = \frac{(\mu + d)(\beta - d) - r\beta}{d\alpha_s\beta}$. Then substituting the expression for p^* into the equation $Ap^{*2} + Bp^* + C = 0$ and dividing out $\beta - d$ gives us the following conditions for population extinction: if $\beta > \bar{\beta}$ there is population extinction and if $\beta < \bar{\beta}$ the population grows unbounded, where $\bar{\beta}$ is a solution to the equation:

$$a\beta^2 + b\beta + c = 0 \quad (8)$$

with

$$\begin{aligned} a &= (r - \mu)(1 - \alpha_s)(r - \mu - d) \\ b &= d((r - \mu)(\mu + d)(1 - \alpha_s) + (r - \mu)\mu + d(r\alpha_s k - \mu)) \\ c &= \mu d^2(\mu + d). \end{aligned}$$

Whenever $\mu < r < \mu + d$, we see that $a < 0$ and $c > 0$. Therefore by Descartes' rule of signs,

there is exactly one positive solution, namely, $\bar{\beta} = \frac{-b - \sqrt{b^2 - 4ac}}{2a}$. Moreover we have

$$\bar{\beta} > \frac{r + d}{1 - \alpha_s k}.$$

A.6 Proof of Proposition 6

The invariance of the biologically feasible region can be easily proved. Given $S^p + S + I > K$ in $\{S^p = 0, S = 0, I = 0\}$, we have $\frac{dN}{dt} = rN(1 - \frac{N}{K}) - \mu N - dI \leq -\mu N$ and thus the total population will decrease below carrying capacity. Therefore we consider only the region $\{S^p = 0, S = 0, I = 0, S^p + S + I = K\}$. Then similar to Proposition 2, we can show that the extinction steady state E_{ext} is globally stable if $r < \mu$.

We analyze the fractional model associated with logistic recruitment:

$$\begin{aligned} \frac{dp}{dt} &= kr(1 - \frac{N}{K}) - r(1 - \frac{N}{K})p - ((1 - \alpha_s)\beta - d)pi \\ \frac{di}{dt} &= ((\beta - d)(1 - i) - r(1 - \frac{N}{K}) - \alpha_s\beta p)i \\ \frac{dN}{dt} &= (r(1 - \frac{N}{K}) - \mu - di)N. \end{aligned} \quad (9)$$

From now on, we assume $r > \mu$. For the eigenvalues for E_{df} , we have $\lambda_1 + \lambda_2 = -r < 0$, $\lambda_1 \cdot \lambda_2 = \mu(r - \mu) > 0$ and $\lambda_3 = (\mu + d)(R_0 - 1)$. Therefore E_{df} is stable when $R_0 < 1$ and unstable when $R_0 > 1$.

Next, we prove that when $\mu < r < \mu + d$, the extinction steady state is stable if $\beta > \bar{\beta}$ and unstable if $\beta < \bar{\beta}$, where $\bar{\beta}$ is a solution of Equation (8); and that the positive steady state also exists if $\beta < \bar{\beta}$. Furthermore when $r > \mu + d$, we prove that the positive steady state exists if $R_0 > 1$.

For Model (9), there are possibly several steady states: $E_1 = (k, 0, 0)$ (always exists), $E_2 = (p^*, i^*, 0)$ (existence depends on parameter values), $E_3 = (k, 0, \frac{r - \mu}{r}K)$, and $E_4 = (p_{log}^*, i_{log}^*, N^*)$ (existence depends on parameter values). Notice that E_3 is equivalent with $E_{df} = (k \frac{r - \mu}{\mu}K, (1 - k) \frac{r - \mu}{\mu}K, 0)$ for (2), and E_4 is equivalent with the positive steady state E^* for (2) when it exists, while E_1 and E_2 are both corresponding to $E_{ext} = (0, 0, 0)$ for Model (2). Let us assume that $r > \mu$.

For E_1 , we have eigenvalues $\lambda_1 = -r < 0$, $\lambda_2 = (1 - \alpha_s k)\beta - (d + r)$, and $\lambda_3 = r - \mu > 0$. So E_1 is unstable.

For E_2 , we have $Ap^{*2} + Bp^* + C = 0$ and $i^* = 1 - \frac{\alpha_s \beta p^* + r}{\beta - d}$, with $A = \alpha_s \beta [(1 - \alpha_s)\beta - d]$, $B = -[(\beta - d - r)[(1 - \alpha_s)\beta - d] + (\beta - d)r]$, and $C = (\beta - d)kr$. If further $0 < p^* < 1$ and $0 < i^* < 1$, then $(p^*, i^*, 0)$ exists as a steady state. This is similar to the case $E_2 = (p^*, i^*)$ in Proposition 5 (with proportional recruitment) when taking $N^* = 0$. We obtain that E_2 is stable whenever $\mu < r < \mu + d$ and $\beta > \bar{\beta}$ and unstable otherwise.

For $E_4 = (p_{log}^*, i_{log}^*, N^*) := (p^*, i^*, N^*)$, we have $Ap^{*2} + Bp^* + C = 0$,

$$i^* = \frac{\beta - \mu - d - \alpha_s \beta p^*}{\beta}, N^* = \frac{r - \mu - di^*}{r}K, \text{ with } A = \alpha_s(1 - \alpha_s)\beta, B = -[(1 - \alpha_s)(\beta - \mu -$$

$d) + \mu + k\alpha_s d]$, and $C = kd \frac{\beta - \mu - d}{\beta} + k\mu$. Therefore, positive steady states may exist but are too complicated to be expressed explicitly.

Notice that $i^* \in (0, \frac{r - \mu}{d})$ and $p^* \in \left(\frac{\beta - (\mu + d) - \frac{r - \mu}{d}}{\alpha_s \beta}, \frac{\beta - (\mu + d)}{\alpha_s \beta} \right)$. So we assume that $\beta > \mu + d$ and $r > \mu$ so that E_4 may exist as an endemic steady state. Denote $F(p) = Ap^2 + Bp + C$, then we have the following results for $F(p)$ over $(0, \frac{\beta - (\mu + d)}{\alpha_s \beta})$: Since $A > 0$, $B < 0$, and $C > 0$, we have

$$0 < \frac{-B - \Delta}{2A} < \frac{-B + \Delta}{2A}$$

where

$$\Delta = \sqrt{B^2 - 4AC}. \quad (10)$$

Since $F(0) = \frac{k(\mu + d)(\beta - d)}{\beta} > 0$ and $F\left(\frac{\beta - (\mu + d)}{\alpha_s \beta}\right) = -\frac{\mu(\mu + d)}{\alpha_s \beta}(R_0 - 1) < 0$, then there

is only one solution on the interval $\left(0, \frac{\beta - (\mu + d)}{\alpha_s \beta}\right)$, and we have that when it exists,

$$p^* = \frac{-B - \Delta}{2A}.$$

Also we have that p^* is a solution on the interval if and only if

$$F\left(\frac{\beta - (\mu + d) - \beta \frac{r - \mu}{d}}{\alpha_s \beta}\right) > 0. \text{ That is:}$$

$$\frac{(1 - \alpha_s)\beta^2(r - \mu)^2 + d^3\mu - d\beta(r - \mu)(\beta - \mu)(1 - \alpha_s) + d\beta\mu(r - \mu)}{d^2\alpha_s\beta} + \frac{d^2(r(1 - (1 - k)\alpha_s)\beta + \mu(\mu - \beta(2 - \alpha_s)))}{d^2\alpha_s\beta} > 0.$$

Given $R_0 > 1$ and $r > \mu$, we have $\beta > \frac{\mu + d}{1 - \alpha_s k}$. This provides the following conditions for existence:

$$- r > \mu + d$$

$$- r < \mu + d \text{ and } \beta \leq \frac{(\mu + d)d}{\mu + d - r}$$

$$- \frac{(\mu + d)\mu}{\mu + dk} \leq r < \mu + d \text{ and } \bar{\beta} > \beta > \frac{(\mu + d)d}{\mu + d - r}$$

$$-r < \frac{(\mu+d)\mu}{\mu+dk} \text{ and } \bar{\beta} > \beta > \frac{(\mu+d)d}{\mu+d-r}$$

where $\bar{\beta}$ is a solution to the equation (8). The above conditions reduce to:

$$-r > \mu + d \text{ and } \beta > \frac{\mu+d}{1-\alpha_s k}$$

$$-\mu < r < \mu + d \text{ and } \bar{\beta} > \beta > \frac{\mu+d}{1-\alpha_s k}.$$

Now consider the case when $R_0 < 1 (\Rightarrow \beta < \frac{\mu+d}{1-k\alpha_s})$. $R(p)$ is concave up and attains its

minimum at $\hat{p} = \frac{\beta - (\mu+d)}{2\alpha_s\beta} + \frac{\mu+k\alpha_s d}{2\alpha_s(1-\alpha_s)\beta} > \frac{\beta - (\mu+d)}{\alpha_s\beta}$, since

$$\begin{aligned} & \frac{\beta - (\mu+d)}{2\alpha_s\beta} \\ & + \frac{\mu+k\alpha_s d}{2\alpha_s(1-\alpha_s)\beta} \\ & - \frac{\beta - (\mu+d)}{\alpha_s\beta} \\ & = \frac{\mu+k\alpha_s d - (1-\alpha_s)[\beta - (\mu+d)]}{2\alpha_s(1-\alpha_s)\beta} > \frac{\mu+k\alpha_s d - (1-\alpha_s)[\frac{\mu+d}{1-k\alpha_s} - (\mu+d)]}{2\alpha_s(1-\alpha_s)\beta} \\ & = \frac{(2-\alpha_s - \frac{1-\alpha_s}{1-k\alpha_s})\mu + k\alpha_s(1 - \frac{1-\alpha_s}{1-k\alpha_s})d}{2\alpha_s(1-\alpha_s)\beta} > 0. \end{aligned}$$

Therefore $F(\frac{\beta - (\mu+d)}{\alpha_s\beta}) > 0$ implies no solution of $R(p) = 0$ over

$$\left(\frac{\beta - (\mu+d) - \frac{r-\mu}{d}}{\alpha_s\beta}, \frac{\beta - (\mu+d)}{\alpha_s\beta} \right), \text{ because } R(p) \text{ is decreasing over}$$

$$\left(\frac{\beta - (\mu+d) - \frac{r-\mu}{d}}{\alpha_s\beta}, \frac{\beta - (\mu+d)}{\alpha_s\beta} \right).$$

Thus when $R_0 > 1$, if either $r > \mu + d$ or both $\beta < \bar{\beta}$ and $\mu < r < \mu + d$, we have a unique

solution of $R(p) = 0$ over $\left(\frac{\beta - (\mu+d) - \frac{r-\mu}{d}}{\alpha_s\beta}, \frac{\beta - (\mu+d)}{\alpha_s\beta} \right)$. Also there is no solution over

$\left(\frac{\beta - (\mu+d) - \frac{r-\mu}{d}}{\alpha_s\beta}, \frac{\beta - (\mu+d)}{\alpha_s\beta} \right)$ whenever either $R_0 < 1$ or if $R_0 > 1$ we have both $\mu < r < \mu + d$ and $\beta > \bar{\beta}$.

Now we give partial results for the stability of E_4 . The Jacobian evaluated at E_4 can be expressed as:

$$J = \begin{pmatrix} -\mu - (1 - \alpha_s)\beta i^* & -((1 - \alpha_s)\beta - d)p^* & \frac{r}{K}(-k + p^*) \\ -\alpha_s\beta i^* & -(\beta - d)i^* & \frac{r}{K}i^* \\ 0 & -dN^* & -\frac{r}{K}N^* \end{pmatrix}$$

which has characteristic polynomial

$$f(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C$$

where

$$A = (\beta - d)i^* + (1 - \alpha_s)\beta i^* + \frac{N^*r}{K} + \mu, \\ B = i^*(\beta - d)(i^*\beta(1 - \alpha_s) + \mu) + i^*p^*\alpha_s\beta(d - \beta(1 - \alpha_s)) + \frac{N^*r}{K}(i^*\beta + i^*\beta(1 - \alpha_s) + \mu),$$

and

$$C = \frac{N^*r i^*\beta}{K}(dk\alpha_s + \mu + (i^* - p^*\alpha_s)\beta(1 - \alpha_s)).$$

Given $R_0 > 1$ and $i^* < \frac{r - \mu}{d}$, we have $A > 0$. Substituting in for i^* and p^* we obtain:

$$C = \frac{N^*r i^*\beta}{K}\Delta > 0,$$

where Δ is as in (10). Therefore the equilibrium is locally stable if and only if $AB - C > 0$. We have the following

$$\begin{aligned}
AB - C = & (i^*(1 - \alpha_s)\beta + i^*(\beta - d) + \frac{N^*r}{K} + \mu)(i^*d(\beta p^* \alpha_s - i^*(1 - \alpha_s))) \\
& - \beta k \alpha_s - \mu)) \\
& + \frac{N^*r(i^*\beta + i^*(1 - \alpha_s)\beta + \mu)}{K}(i^*(1 - \alpha_s)\beta + i^*(\beta - d) + \frac{N^*r}{K} + \mu) + i^*\beta \Delta(i^*(1 - \alpha_s)\beta + I^*(\beta - d) + \mu).
\end{aligned}$$

Due to the complexity of the above expression, we have only numerically verified for plausible parameter values, that the equilibrium, E_4 , is locally stable whenever it exists.

Now we show that the HIV prevalence associated with Model (2) under logistic and constant recruitment is the same, i.e., $i_{\text{const}}^* = i_{\text{log}}^*$, whenever both equilibria exist and are stable.

Assume $R_0 = \frac{(1 - \alpha_s k)\beta}{\mu + d} > 1$. We have shown already that with constant recruitment, the infected population, I^* , is a root of:

$$\hat{F}(I) \triangleq AI^2 + BI + C$$

Where

$$\begin{aligned}
A &= -(d - \beta)(d - (1 - \alpha_s)\beta) \frac{1}{\Lambda^2}, \\
B &= \left((d - (1 - \alpha_s)\beta) \left(1 - \frac{\beta}{\mu + d} \right) - \mu \frac{\beta}{\mu + d} - d(R_0 - 1) \right) \frac{1}{\Lambda}, \\
C &= R_0 - 1.
\end{aligned}$$

Next, we calculate I^* . $R_0 > 1$ implies that $\beta > \frac{\mu+d}{1-\alpha_s k} > \mu+d > d$. Thus we have

$$d - (1 - \alpha_s)\beta < d - \frac{(1 - \alpha_s)(\mu+d)}{1 - \alpha_s k} < d - (\mu+d) = -\mu$$

and therefore, $A < 0$ and $C > 0$. By Descartes' rule of signs there is exactly one positive root of $\hat{F}(I)$. Since $I^* > 0$, we must have that

$$I^* = \frac{-B - \sqrt{B^2 - 4AC}}{2A}.$$

The total population is given by $N = \frac{\Lambda - dI}{\mu}$, so that

$$N^* = \frac{\Lambda - dI^*}{\mu}.$$

Therefore, the HIV prevalence under constant recruitment is

$$i_{\text{const}}^* = \frac{I^*}{N^*} = \frac{\mu I^*}{\Lambda - dI^*}.$$

First, notice that Λ factors out of I^* and thus will be absent in the final expression. Substituting in for I^* , we have that after rationalizing the denominator

$$i_{\text{const}}^* = \frac{(1 - \alpha_s)(\beta - \mu - d) - \mu - \alpha_s k d + \Delta_{\text{const}}}{2(1 - \alpha_s)\beta},$$

Where

$$\Delta_{\text{const}} = \sqrt{\frac{\Lambda^2(\mu+d)^2}{\beta^2}(\beta^2 - 4AC)}.$$

We already have shown that the HIV prevalence given logistic growth is

$$i_{\text{log}}^* = 1 - \alpha_s p^* - \frac{\mu+d}{\beta},$$

Where

$$p^* = \frac{-\bar{B} - \Delta_{\log}}{2\bar{A}},$$

$$\Delta_{\log} = \sqrt{\bar{B}^2 - 4\bar{A}\bar{C}},$$

and

$$\bar{A} = \alpha_s(1 - \alpha_s)\beta,$$

$$\bar{B} = -((1 - \alpha_s)(\beta - \mu - d) + \mu + k\alpha_s d),$$

$$\bar{C} = kd\frac{\beta - \mu - d}{\beta} + k\mu.$$

Substituting p^* into $i_{\log}^*$ and simplifying, we obtain

$$i_{\log}^* = \frac{(1 - \alpha_s)(\beta - \mu - d) - \mu - \alpha_s kd + \Delta_{\log}}{2(1 - \alpha_s)\beta}.$$

It can be checked that $i_{\text{const}} = i_{\log}^*$, and therefore $i_{\text{const}}^* = i_{\log}^*$.

B Demographic data and simulations for the Republic of South Africa

Age structured population data about the Republic of South Africa for year 2001 and from year 2003 to 2011, in thousands, is presented in Table 5. The data has been adapted from Statistics South Africa (Africa 2012). In the table, T(15-49) refers to total population of individuals from age 15 to 49. Similarly, P(15-49) refers to HIV prevalence among people of age 15 to 49. HIV-T and SUS-T refer to total number of infected and susceptible individuals ages 15 to 49, respectively.

Table 5

Age structured population for the Republic of South Africa.

Age\Year	2001	2003	2004	2005	2006	2007	2008	2009	2010	2011
15-19	4982	5263	4924	4898	4938	4976	5153	5214	5226	5175
20-24	4295	4392	4679	4621	4654	4675	4784	4921	5019	4900
25-29	3935	4100	4292	4211	4271	4336	4367	4424	4519	4598
30-34	3341	3422	3696	3762	3842	3864	3914	3888	4036	4041
35-39	3072	3217	2851	2780	2842	2972	3147	3282	3465	3600
40-44	2619	2794	2537	2483	2428	2400	2390	2443	2524	2613
45-49	2087	2242	2214	2187	2215	2222	2241	2260	2231	2245
T(15-49)	24331	25431	25195	24943	25190	25446	25995	26433	27019	27172
P(15-49)	0.16	0.162	0.162	0.162	0.166	0.165	0.164	0.164	0.165	0.166
HIV-T	3893	4120	4082	4041	4181	41994	4263	4335	4458	4511

Age\Year	2001	2003	2004	2005	2006	2007	2008	2009	2010	2011
SUS-T	20438	21311	21114	20902	21008	21247	21732	22098	22561	22662

Parameter values generated from data fitting are listed in Table 6 and the corresponding simulations using fitted parameter values are presented in Figs. 5 and 6.

Table 6

Parameter values generated from data fitting.

Parameter	Recruitment mechanism		
	constant	proportional	logistic
β	0.196924711	0.196935536	0.196924711
μ	0.029793556	2.93E-02	0.02438153
d	0.119146121	0.11955454	0.125
Λ	996344		
r		0.04095	0.0511875
K			1.13E+08
err	0.044056109	0.044755966	0.043080597

Fig. 5. Population dynamics for models with different recruitment rates: constant (blue —), proportional (red —+—), and logistic (black --). Initial recruitment and parameter values unrelated to recruitment are generated from data fitting (see Table 6).

Fig. 6. PrEP effectiveness over 200 years for models with different recruitment rates: constant (blue —), proportional (red - - -), and logistic (black - - -). Initial recruitment and parameter values unrelated to recruitment are generated from data fitting (see Table 6).

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Fig. 1. Bifurcation diagrams of models employing different recruitment functions in the absence of PrEP : (a) constant; (b) proportional; (c) logistic. Parameter regions in the plane of recruitment rate (Λ or r) and transmission rate (β) correspond to: 1- disease-free equilibrium, 2- endemic equilibrium, 3- population extinction in absence of HIV and 4- population extinction under the pressure of HIV. (d) Absolute difference in equilibrium HIV prevalence projected by models with constant/logistic and proportional recruitment when all other parameters are fixed at values in Table 1.

Fig. 2. Bifurcation diagrams of models in presence of PrEP employing different recruitment functions: (a) constant; (b) proportional; (c) logistic. Parameter regions in the plane of recruitment rate (Λ or r) and transmission rate (β) correspond to: 1- disease-free equilibrium, 2- endemic equilibrium, 3- population extinction in absence of HIV and 4- population extinction under the pressure of HIV. (d) Absolute difference in equilibrium HIV prevalence projected by models with constant/logistic and proportional recruitment when all other parameters are fixed at values in Table 1.

Fig. 3. Population dynamics over 200 years for models with different recruitment rates: constant (blue —), proportional (red - - -), and logistic (black - - -). Initial recruitment and parameter values unrelated to recruitment are kept the same across the models (see Table 1).

Fig. 4. PrEP effectiveness over 200 years projected by models with different recruitment rates: constant (blue —), proportional (red - - -), and logistic (black - - -). Initial recruitment and parameter values unrelated to recruitment are kept the same across the models (see Table 1).

Table 1
Model parameters

Parameter	Description	Baseline Value	Reference
N_0	Initial population size	27,172,431	(Africa 2012)
P	Initial HIV prevalence	16.6%	(Africa 2012)
Λ	Constant recruitment: Fixed number of individuals who become sexually active annually	10^6	(Africa 2012)
r	Proportional and logistic recruitment: Annual rate of individuals who become sexually active as a proportion of the total population	$\frac{\frac{\Lambda}{N_0}}{\frac{\Lambda}{N_0} + \frac{N_0}{K}}$	calculated to ensure comparability
K	Population carrying capacity	9×10^7	assumed
β_a	HIV acquisition risk per act	0.27%	(Boily et al. 2009)
n	Average number of sexual acts per year	80	(Wawer et al. 2005; Kalichman et al. 2009)
β	Annual HIV acquisition risk in partnership with infected individual	19.5%	calculated from β_a and n
μ	Annual departure rate based on background mortality and average time to remain sexually active	2.5%	(UNAIDS 2009)
d	Annual rate of progression to AIDS	12.5%	(Morgan et al. 2002; Porter and Zaba 2004)
k	Proportion of the new recruits using PrEP	20%	assumed
α_s	Efficacy of PrEP in reducing susceptibility per act	50%	(Karim et al. 2010; Baeten et al. 2012)

Table 2

Asymptotic behavior of the epidemic model (1) in the absence of PrEP under different recruitment assumptions.

Recruitment type	Parameter conditions	Epidemic outcome	HIV prevalence at equilibrium	Trajectory
Constant	$\beta < \mu + d$	disease free	0	bounded
	$\beta > \mu + d$	endemic	$1 - \frac{\mu + d}{\beta}$	bounded
Proportional	$r > \mu, \beta < r + d$	disease free	0	unbounded
	$r + d < \beta < \frac{(\mu + d)d}{\mu + d - r}$	endemic	$1 - \frac{r}{\beta - d}$	unbounded
	$\beta > \frac{(\mu + d)d}{\mu + d - r}$	extinction under HIV pressure	-	bounded
	$r < \mu$	extinction in absence of HIV	-	bounded
Logistic	$r > \mu, \beta < \mu + d$	disease free	0	bounded
	$\mu + d < \beta < \frac{(\mu + d)d}{\mu + d - r}$	endemic	$1 - \frac{\mu + d}{\beta}$	bounded
	$\beta > \frac{(\mu + d)d}{\mu + d - r}$	extinction under HIV pressure	-	bounded
	$r < \mu$	extinction in absence of HIV	-	bounded

Table 3

Asymptotic behavior of the epidemic models the in presence of PrEP (2) under different recruitment assumptions.

Recruitment type	Parameter conditions	Epidemic outcome	HIV prevalence at equilibrium	Trajectory
Constant	$\beta < \frac{\mu+d}{1-\alpha_s k}$	disease free	0	bounded
	$\beta > \frac{\mu+d}{1-\alpha_s k}$	endemic	i_{const}^*	bounded
Proportional	$r > \mu, \beta < \frac{r+d}{1-\alpha_s k}$	disease free	0	unbounded
	$\frac{r+d}{1-\alpha_s k} < \beta < \bar{\beta}$	endemic	i_{lin}^*	unbounded
	$\beta > \bar{\beta}$	extinction under HIV pressure	-	bounded
	$r < \mu$	extinction in absence of HIV	-	bounded
Logistic	$r > \mu, \beta < \frac{\mu+d}{1-\alpha_s}$	disease free	0	bounded
	$\frac{\mu+d}{1-\alpha_s k} < \beta < \bar{\beta}$	endemic	i_{log}^*	bounded
	$\beta > \bar{\beta}$	extinction under HIV pressure	-	bounded
	$r < \mu$	extinction in absence of HIV	-	bounded

Table 4

Evaluating the efficacy of PrEP intervention over a period of T years.

Indicator	Description	Formula [*]
$F_K(T)$	Fraction of infections prevented over the period $[0, T]$	$1 - \frac{[I_{New}(T)]p}{[I_{New}(T)]}$
$P_K(T)$	Reduction in HIV-prevalence at time $t = T$	$1 - \frac{[\frac{I(T)}{S^p(T)+S(T)+I(T)}]p}{[\frac{I(T)}{S(T)+I(T)}]}$
$aI_K(T)$	Reduction in the HIV incidence for the period $[T-1, T]$	$1 - \frac{[\frac{I_{New}(T)-I_{New}(T-1)}{S^p(T-1)+S(T-1)}]p}{[\frac{I_{New}(T)-I_{New}(T-1)}{S(T-1)}]}$
$\hat{F}_K(T)$	Proportion reduction in the number of infected at time $t = T$	$1 - \frac{[I(T)]p}{[I(T)]}$

^{*}

$[]$ denotes variables from the model without PrEP (1) while $[]p$ variables from the model with PrEP (2).