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Impact of Tenofovir gel as a PrEP on HIV infection: A mathematical model

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AUTHOR-HIGHLIGHTS

- We develop a novel mathematical model to study Tenofovir gel as a PrEP.
- The model prediction has an excellent agreement with the data from South Africa.
- We quantify effectiveness of the Tenofovir gel against HIV transmission.
- The outcome of Tenofovir gel as PrEP highly depends on its adherence and coverage.
- Tenofovir gel can serve as a strong weapon to fight against the HIV epidemics.

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ABSTRACT

Pre-exposure prophylaxis (PrEP) has been considered as one of the promising interventions for HIV infection as experiments on various groups and sites have reported its significant effectiveness. This study evaluates the effectiveness of Tenofovir gel, one of the widely used PrEPs for women, through a mathematical model. Our model has excellent agreement with the experimental data on the use of Tenofovir gel as a PrEP in South African women. Using our model, we estimate both male-to-female and female-to-male transmission rates with and without Tenofovir gel protection. Through these estimates we demonstrate that the use of Tenofovir gel as a PrEP can significantly reduce the reproduction numbers, new infections, and HIV prevalence in South Africa. Our results further show that the effectiveness of Tenofovir gel largely depends on the level of adherence to the gel and the proportion of women under gel coverage. Even though Tenofovir gel alone may not be able to eradicate the disease as indicated by our estimates of the reproduction numbers, together with other interventions, such as condom use, it can serve as a strong weapon to fight against HIV epidemics.

1. Introduction

During the last three decades, HIV/AIDS—with 55 million infections and 16 million deaths (Cohen et al., 2012)—has been one of the major threats to human beings. Despite remarkable progress on HIV treatments, elimination of HIV/AIDS is still out of reach, and approximately two-and-a-half million people get infected every year (CDC Fact Sheet, 2012; Hallett et al., 2011). Thus, the prevention of new infections remains a great challenge.

A vaccine is presumably the ideal means of protecting the general (healthy) population (Reynell and Trkola, 2012). However, in the case of HIV, such vaccines have not been developed. In 1994, the placebo-controlled phase 3 trial of the rgp120 HIV vaccine showed only 6% effectiveness (Adamczyk et al., 2005). In 2007, the two HIV vaccine trials (HVTN 502 and Merck V520-023) were suspended due to the issues of safety and efficacy (NIAD Statement, 2007). The trial of the *RV 144 HIV* vaccine that induces humoral and cellular immune responses reported only 31% efficacy (Rerks-Ngarm et al., 2009). While more vaccine trials are currently underway (Kang, 2012), no successful HIV vaccine is available at present.

In the absence of a successful vaccine, drug-oriented interventions can be an alternate strategy for reducing infection burden. Recently, remarkable progress has been reported on the use of Pre-Exposure Prophylaxis (PrEP) (Cardo et al., 1997; Cohen, 2010; Connor et al., 1994; Guay et al., 1999; Kashuba et al., 2012; Shaffer et al., 1999). PrEP is the administration of low-level antiretrovirals, such as Tenofovir/TDF (Tenofovir disoproxil fumarate) and Truvada/TDF-FTC (TDF co-formulated with emtricitabine) to the susceptible population, usually, before their exposure

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to potential HIV sources. The oral TDF and TDF-FTC showed protection against HIV-1 infection in heterosexual couples by 67% and 75%, respectively (Baeten et al., 2012). The studies (CDC Fact Sheet, 2012; Grant et al., 2010) also found TDF-FTC to reduce infection by 62% among uninfected heterosexually active men and women, and 44% of infection among men and trans-women who had sex with men. In addition to the use of Tenofovir (alone or in combination with other drugs) as an oral intake, Tenofovir has also been considered as a potential gel (a coitally related vaginal gel to be used by women) for preventing new infections (Karim et al., 2010). A large cohort study (Karim et al., 2010) on 889 heterosexual women with multiple partners has confirmed the profound impact of Tenofovir gel in reducing HIV infections, and its success has gained much attention around the world (BBC News, 2010; News, 2010; Times, 2010).

Tenofovir gel is safe, without any renal toxicity, which is one of the most important safety concerns of TDF (Schaaf et al., 2003). The gel has the advantage of being less of a burden due to the method of its application as it is used only within ± 12 h of sexual acts, unlike the other forms of TDF, which require daily use (CDC Fact Sheet, 2012; Grant et al., 2010; Karim et al., 2010). According to Karim et al. (2010), the gel is used by inserting it into vagina for two times in a 24-h period; one dose within 12 h before sex and another, as soon as possible, within 12 h after sex (Karim et al., 2010). In addition, the unique advantage of this formulation is that women at risk can use it without their partners' knowledge (Times, 2010), avoiding any potential objections from the partner. Better understanding of the effectiveness of Tenofovir gel can be helpful for proper implementation of this gel to gain optimal benefits in preventing HIV burden.

In this study, we develop a mathematical model to quantitatively understand the effectiveness of Tenofovir gel for women in the control of HIV infection. Using our model and survey data from South Africa, we estimate the male-to-female and female-to-male transmission rates both with and without the use of Tenofovir gel. With these estimates we predict the role of Tenofovir gel in reducing reproduction numbers and new infections. We also evaluate the role of adherence and coverage in the success of Tenofovir gel when it is used as a PrEP against HIV epidemic.

2. Methods

2.1. Data

We obtained our data from the CAPRISA (Centre for the AIDS Programme of Research in South Africa) study (Karim et al., 2010). In this study, 889 healthy women were selected and divided into two subgroups: 445 women were prescribed with Tenofovir gel and 444 women with Placebo gel. The number of new infections and the incidence rates were reported cumulatively during the study period of two-and-a-half years. From the given incidence rate (Karim et al., 2010) in the unit of percent women-year (i.e. the number of new infections, in one year, per 100 susceptible women), we calculate the cumulative new infections as follows: the cumulative total number of new infections is $W_0 T\alpha$, where W_0 is the number of susceptible women participants, T is the duration in the study (in year), and α is the incidence rate given in Karim et al. (2010). In the group using Tenofovir gel, for example, after 6 months ($\frac{1}{2}$ year) the incidence rate was 6.0% women-year. With the initial recruited (445) women, the total number of infections is calculated as $445 \times \frac{1}{2} \times 6.0$. In the same way the total number of infections after 24 months (2 years) is calculated as $445 \times 2 \times 5.6$, where the cumulative incidence rate is 5.6% women-year. The data obtained from our calculations are given in Table 1.

Table 1
Data obtained from our calculation based on CAPRISA study (Karim et al., 2010).

Months of follow-up:	6	12	18	24	30
Cumulative HIV infections: (in Tenofovir gel arm)	13	23	35	50	62
Cumulative HIV infections: (in Placebo gel arm)	25	47	68	83	101

Initial recruitment: Tenofovir gel arm = 445 women, Placebo gel arm = 444 women.

2.2. Mathematical model

We develop an HIV dynamic model in which we divide the total population into two groups: a general group and a study group. The general group consists of male and female subgroups. Consistent with the experimental study (Karim et al., 2010), all the individuals in the study group are female, and the study group is subdivided into the Tenofovir subgroup (individuals receiving Tenofovir gel) and the Placebo sub-group (individuals receiving Placebo gel). In this study, the individuals in the general group receive neither Tenofovir nor Placebo gels. Each subgroup is further divided into susceptible (S) and infected (I) subgroups. We assume, for simplicity, that the transmission occurs through heterosexual contact only. The susceptible women using Tenofovir gel (S_d) or Placebo gel (S_c) become infected (I_d or I_c, respectively) through effective contact with infected males (I_m) from the general population. Similarly, susceptible females (S_f) of the general population group become infected (I_f) through contact with infected males, I_m. Here, the study group constitutes only 1% of the total population, and the contribution by the infected females in the study group (less than 0.2% of the whole population) to the new infection is negligible compared to that by the infected females in the general group. Therefore, we assume that the susceptible males get infected only by the infected females of the general group, and ignore the terms for the new infection due to females in the study groups. Note, however, that we also investigated our model by including the study population in the equations of the general population, and found no change in the results. The definition and symbols are summarized in Tables 2–4. The schematic diagram showing the transmission in this dynamics is given in Fig. 1.

The transmission rate from infected female to susceptible male is denoted by β_m. Similarly, the transmission rates from infected male to susceptible females in the general subgroup, the Tenofovir subgroup, and the Placebo subgroup are denoted by β_f, β_d, and β_c, respectively. These transmission rates are given by

$$\beta_i(t) = \beta_{i0} c_{if}(t), \quad i = m, f, d, c,$$

where β_{i0} is the corresponding transmission rate per sexual act, and $c_{if}(t)$ is the average number of sexual acts at time t. As seen in the data (Karim et al., 2010) the coital frequency for the study group decreases approximately linearly. Thus, we fit a linear curve to this coital frequency data (Karim et al., 2010) to obtain $c_{if}(t) = c_f(t) = 7.25 - 0.17t$, $i = d, c$, where t is in months. Thus, we have

$$\begin{aligned} \beta_d &= \beta_{d0} c_f(t), \\ \beta_c &= \beta_{c0} c_f(t). \end{aligned} \tag{2.1}$$

Since the coital frequency data for the general population groups are not available, the transmission rates β_m and β_f are assumed to be constant. We consider only the sexually active population group (age 15–49 years) in this network, and individuals crossing this age group leave our study at the rate of μ_l. We assume that there is no vertical transmission, and newly matured populations (turning 15 years old) are recruited to the susceptible male and female subgroups of the general population at constant rates Λ_m and Λ_f, respectively. The natural death rate and disease death rate are denoted by μ and ν, respectively. Since no additional subjects

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Table 2
Description of variables with initial values of model (2.2).

Parameter	Description	Initial value	Source
S_m	Susceptible male in GP	33,631	Karim et al. (2010), Welz et al. (2007)
I_m	Infected male in GP	5248	Karim et al. (2010), Welz et al. (2007)
S_f	Susceptible female in GP	31,674	Karim et al. (2010), Welz et al. (2007)
I_f	Infected female in GP	10,446	Karim et al. (2010), Welz et al. (2007)
S_d	Susceptible female under TG	445	Karim et al. (2010)
I_d	Infected female under TG	0	Karim et al. (2010)
S_c	Susceptible female under PG	444	Karim et al. (2010)
I_c	Infected female under PG	0	Karim et al. (2010)

GP=General population, TG=Tenofovir gel group, PG=Placebo gel group.

Table 3
Fixed parameter values estimated from demographic data.

Parameter	Description	Value (per month)	Source
Λ_m	Recruitment rate of S_m	173	Statistics South Africa (2010)
Λ_f	Recruitment rate of S_f	187	Statistics South Africa (2010)
μ	Natural death rate	6.67×10^{-4}	Day and Gray (2008)
μ_l	Rate of leaving from the network due to age	2.38×10^{-3}	Estimated
ν	Disease induced death rate	6.1×10^{-3}	Vaidya and Wu (2011)

Table 4
Estimated parameter values.

Parameter	Description	Value (per month)
β_f	Transmission rate from I_m to S_f	0.0785
β_{d0}	Per act transmission rate from I_m to S_d	0.0047
β_{c0}	Per act transmission rate from I_m to S_c	0.0085
β_d	Transmission rate from I_m to S_d	0.0219[a]
β_c	Transmission rate from I_m to S_c	0.0396[a]
$\beta_m=\beta_f/2.3$	Transmission rate from I_f to S_m	0.0341

[a] Calculated by using (3.1).

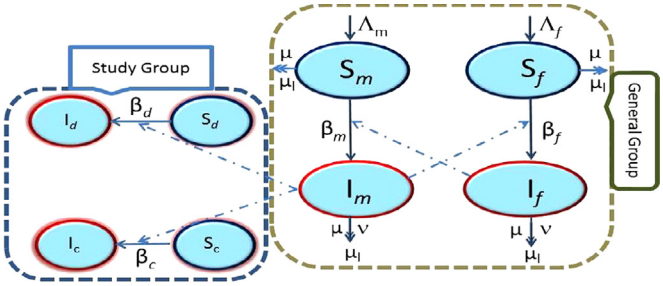

Fig. 1. Transfer diagram of infection. The solid arrows between the compartments indicate transfer of individuals while dashed-dotted arrows indicate cause of transfer of individuals.

were enrolled in the study group and only one individual died from this group, we do not include any birth/death term in the model for these sub-groups. With these assumptions, the dynamics of infection can be modeled by the following ODE system:

$$\dot{S_m} = \Lambda_m - \frac{\beta_m I_f S_m}{S_f + I_f} - (\mu + \mu_l) S_m,$$

$$\dot{I_m} = \frac{\beta_m I_f S_m}{S_f + I_f} - (\mu + \mu_l + \nu) I_m,$$

$$\dot{S_f} = \Lambda_f - \frac{\beta_f I_m S_f}{S_m + I_m} - (\mu + \mu_l) S_f,$$

$$\dot{I_f} = \frac{\beta_f I_m S_f}{S_m + I_m} - (\mu + \mu_l + \nu) I_f,$$

$$\dot{S_d} = -\frac{\beta_d I_m S_d}{S_m + I_m},$$

$$\dot{I_d} = \frac{\beta_d I_m S_d}{S_m + I_m},$$

$$\dot{S_c} = -\frac{\beta_c I_m S_c}{S_m + I_m},$$

$$\dot{I_c} = \frac{\beta_c I_m S_c}{S_m + I_m}, \tag{2.2}$$

where dots represent the derivatives with respect to time t.

2.3. Parameter values and initial conditions

For the CAPRISA study (Karim et al., 2010), the women were selected from rural (Vulindlela) and urban (eThekwini) sites of South Africa. The total population in the rural site in 2007 was 90,000 (Karim et al., 2010). Taking the similar proportion for the population in the network from the urban site, we use the total population in our study to be 180,000 (Karim et al., 2010). According to Statistics South Africa (2010) (STATSSA), 45% of the total population belongs to the age group 15–49, among which 48% are male and 52% are female. Among the total population, 12% belong to the age group 10–14 (Statistics South Africa, 2010), which helps us to estimate $\Lambda_m = 173$/month and $\Lambda_f = 187$/month. As mentioned above we assume that the recruitment only added to the susceptible subgroups of the general group. Using the male HIV prevalence (13.5%, Welz et al., 2007) and the female HIV prevalence (24.8%, Karim et al., 2010) at the study site, we calculate the initial population in the general subgroups as $S_m(0) = 33,631$, $I_m(0) = 5248$, $S_f(0) = 31,674$, and $I_f(0) = 10,446$. The average life time of HIV infected individuals without any treatment is 13.5 years (8–19 years, Vaidya and Wu, 2011), yielding $\nu = 0.074$ per year. The other (non-HIV) death rate of 15–49 age group in South Africa has been recorded as 8 per 1000 per 1 year (Day and Gray, 2008), giving $\mu = 0.008$ per year. Moreover, individuals leave the study after 35 years (15–49 years), which yields $\mu_l = 1/35$ per year. The female-to-male transmission rate is usually smaller than the male-to-female transmission rate (Nicolosi et al., 1994; Padian et al., 2009). Nicolosi et al. (1994) found that the ratio between male-to-female and female-to-male transmission rates is 2.3; we therefore take $\beta_m = \beta_f/2.3$. The three

transmission rates, β_f, β_{d0} and β_{c0}, are estimated from fitting our model to the data.

2.4. Data fitting

The HIV infection data corresponding to the Tenofovir and the Placebo groups are given in Table 1. We fix several parameters by estimating them from the demographic data (Table 3), and consider only β_f, β_{d0}, and β_{c0} as free parameters during the data fitting process. We solve the ODE system (2.2) using ode45, an ODE solver in MATLAB. We further use the MATLAB function 'fmincon' to estimate free parameters by minimizing the following error function:

$$J=\sum_{i=1}^{N}\left[(I_d(t_i)-\hat{I}_d(t_i))^2+(I_c(t_i)-\hat{I}_c(t_i))^2\right],$$

where $I_d(t_i)$ and $I_c(t_i)$ are the model solutions at time t_i; $\hat{I}_d(t_i)$, $\hat{I}_c(t_i)$ are data at time t_i; and N is the total number of data points for each group.

3. Results

3.1. Effect of gel on transmission rates

In model-fitting we have three free parameters β_f, β_{d0}, β_{c0}. The estimated parameters are given in Table 4, and the fitted curves are shown in Fig. 2. The model fits the data very well. To simplify the discussion, we approximate the average transmission rates β_d and β_c by

$$\beta_d \approx \frac{\beta_{d0}}{D}\int_0^D c_f(t)\,dt,$$
$$\beta_c \approx \frac{\beta_{c0}}{D}\int_0^D c_f(t)\,dt, \qquad (3.1)$$

where D is the duration of the study period (here $D=30$ months). The values of the estimated parameters are $\beta_f=0.0785$, $\beta_{d0}=0.0047$, and $\beta_{c0}=0.0085$ (Table 4). By using (3.1), we obtain $\beta_d=0.0219$ and $\beta_c=0.0396$.

The transmission rate from infected males to females under Tenofovir gel, β_d, is 45% smaller than that to females under Placebo gel, β_c, i.e., the relative effectiveness of Tenofovir gel over Placebo gel is 45%. This result is consistent with the findings of the CAPRISA study (Karim et al., 2010), in which 39–50% relative effectiveness of Tenofovir gel compared to Placebo gel were found.

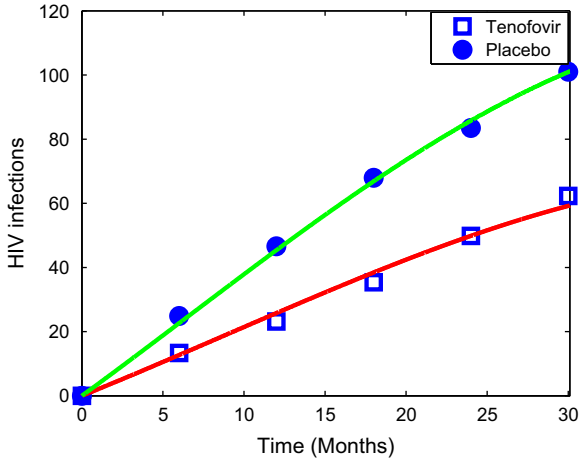

Fig. 2. Data fitting with β_f, β_{d0}, and β_{c0} as variable parameters. The solid green curve shows the simulation of cumulative infection of Tenofovir gel user (I_d) while dots are the corresponding data. The red curve predicts the cumulative infection of Placebo gel user (I_c) while squares are the corresponding data. The predictions fit the data very well. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

We estimate the transmission rate β_d to be 72% smaller than β_f, indicating that the use of Tenofovir gel as a PrEP is 72% effective on reducing HIV transmission. It is worth noting that β_c is also 50% smaller than β_f. This indicates that Placebo gel itself provides protection against HIV infection. Though Placebo gel has no antiviral activity, a plausible explanation for this protection is that it forms a physical barrier for HIV to reach the target cell. This is consistent with the findings by Lai et al. (2009) that the barrier at vaginal mucosa prevents the virus from reaching the target cells (CD4+ T cells) lying beneath the epithelial cell layer. The reduction of infection in the Placebo gel group may also be due to the fact that they received comprehensive counseling to minimize the risk of infection (Karim et al., 2010). The results suggest that the net magnitude of the gel efficacy has to be interpreted carefully.

3.2. Reproduction numbers and effects of Tenofovir gel

We define the *male reproduction number*, $\mathfrak{R}_0^m$, by the average number of new male infections generated by an infected female individual in her entire life when she is introduced into an entirely susceptible male population; and the *female reproduction number*, $\mathfrak{R}_0^f$, is defined by the average number of new female infections generated by an infected male individual in his entire life when he is introduced into an entirely susceptible female population. Furthermore, we define *the basic reproduction number*, $\mathfrak{R}_0$, by the average number of secondary infections of the same-sex generated by a typical infected individual in his/her entire life when he/she is introduced into an entirely susceptible population. These numbers measuring the secondary same-sex individuals are important to study the sex-focused interventions such as the female-focused Tenofovir gel considered in this study.

From our model, the male and female reproduction numbers can be obtained as

$$\mathfrak{R}_0^m=\frac{\beta_m S_m(0)}{(\mu+\nu+\mu_l)S_f(0)}, \qquad \mathfrak{R}_0^f=\frac{\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)}.$$

Similarly, the basic reproduction number in the absence of interventions is given by

$$\mathfrak{R}_0=\mathfrak{R}_0^m\mathfrak{R}_0^f. \qquad (3.2)$$

Using our estimates, we obtain $\mathfrak{R}_0$ to be 31.53, with $\mathfrak{R}_0^m=3.93$ and $\mathfrak{R}_0^f=8.02$. This shows that women are much more vulnerable to the infection, consistent with many experimental findings (Baral et al., 2013; Hader et al., 2001). The basic reproduction numbers with and without interventions are summarized in Table 5. Note that the female-to-male transmission rate is not affected by the use of Tenofovir gel because only susceptible women, after having been tested for eligibility, use this gel as an intervention. Thus the gel has no effect on the male reproduction number ($\mathfrak{R}_0^m$), and it remains the same ($\mathfrak{R}_0^m=3.93$), whether the women use the gel or not. Importantly, by the use of Tenofovir gel, $\mathfrak{R}_0^f$ is reduced from 8.02 to 2.23, and the resulting $\mathfrak{R}_0$ is reduced from 31.53 to 8.82.

Table 5
Effect of gel on HIV infection and reproduction numbers.

Transmission rates (β s)	New infections male (T_m) (in 1 year)	New infections female (T_f) (in 1 year)	Basic repr. number ($\mathfrak{R}_0$)	Male repr. number ($\mathfrak{R}_0^m$)	Female repr. number ($\mathfrak{R}_0^f$)
$\beta_f=0.0785$	3786	4847	31.53	3.93	8.02
$\beta_d=0.0219$	3311	1399	8.80	3.93	2.23

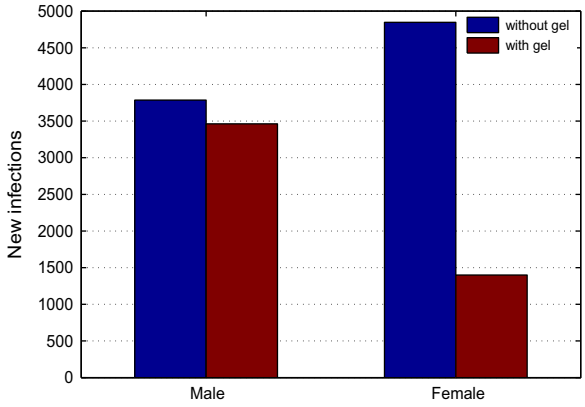

Fig. 3. Comparison chart of new infection in 1 year with or without Tenofovir gel intervention.

Several studies (Granich et al., 2009; Nyabadza and Mukandavire, 2011), in which the sexes were not distinguished, estimate that the basic reproduction number ($\Re_0$) of HIV infection in South Africa ranges from 4.5 to 7.0. In our model, we consider the male and female populations separately. For such a model, similar to vector-borne disease models, one faces a choice of either using $\Re_0 = \Re_0^m \Re_0^f$ (as in (3.2)), or $\Re_0 = \sqrt{\Re_0^m \Re_0^f}$ to define the basic reproduction number. The former is more biologically intuitive and tractable, while the latter is based on the next generation approach (van den Driessche and Watmough, 2002) and is mathematically more rigorous. For our model, if we adopt the latter, meaning that we account for both male and female-borne "generations", we would obtain $\Re_0 = \sqrt{\Re_0^m \Re_0^f}$ by calculating the spectral radius of the next generation matrix. Using the values of $\Re_0^m$ and $\Re_0^f$ above, we then obtain $\Re_0 = \sqrt{31.5} \approx 5.61$, which is consistent with previous studies (Granich et al., 2009; Nyabadza and Mukandavire, 2011).

While the use of Tenofovir gel is significantly effective on reducing the basic reproduction number, $\Re_0$ still remains quite large (> 1) even under the Tenofovir gel intervention. Therefore, additional interventions (e.g. condom use) are needed to achieve the desired result $\Re_0 < 1$, the condition for eradication of the disease from the community (Diekmann et al., 1990; van den Driessche and Watmough, 2002). Assuming that other additional interventions can reduce the transmission rates β_m and β_f by fraction q, i.e. $\beta_m \to (1-q)\beta_m$ and $\beta_f \to (1-q)\beta_f$, we obtain that

$$\Re_0 = \frac{\beta_m \beta_f (1-q)^2}{(\mu+\nu+\mu_l)^2}$$

with other interventions only, while

$$\Re_0 = \frac{\beta_m \beta_d (1-q)^2}{(\mu+\nu+\mu_l)^2}$$

with a combination of other interventions and Tenofovir gel. This implies that to satisfy the condition $\Re_0 < 1$, we require

$$q > 1 - \frac{(\mu+\nu+\mu_l)}{\sqrt{\beta_m \beta_f}} = 0.82$$

with other interventions only, and

$$q > 1 - \frac{(\mu+\nu+\mu_l)}{\sqrt{\beta_m \beta_d}} = 0.66$$

if Tenofovir gel is added to other interventions. Thus, addition of Tenofovir gel to other interventions significantly reduces the level of other interventions required for successful eradication of the disease (requirement of at least 82% effectiveness vs. requirement of only 66% effectiveness).

3.3. Effect of Tenofovir gel on new infections

In this section, we consider the base-case, i.e. all susceptible women in the general population group use the gel with 72% adherence, and present the sensitivity of the coverage and adherence in a later section. We also assume that only susceptible women, after having been tested, are eligible (CDC Fact Sheet, 2012) to use Tenofovir gel. We note that there might be some women on continued gel use from an unknown time of infection to the time of diagnosis. We ignore this time lag by assuming a frequent testing scenario, in which the proportion of unidentified infected women who are on continued gel is small.

Using the estimated transmission rates, we now calculate the total number of new infections. The total number of new infections of male and female, $T_m(t)$ and $T_f(t)$, respectively, can be obtained by integrating the infection terms of the model (2.2), and are given by

$$T_m(t) = \int_0^t \frac{\beta_m I_f(s) S_m(s)}{S_f(s)+I_f(s)}\, ds,$$

$$T_f(t) = \int_0^t \frac{\beta_f I_m(s) S_f(s)}{S_m(s)+I_m(s)}\, ds.$$

With the estimated parameters the total number of new male and female infections, in one year, are $T_m(12) = 3786$ and $T_f(12) = 4847$, respectively. By using Tenofovir gel the total male and female infections can be reduced to 3311 and 1399, respectively (Fig. 3 and Table 5). This result showing 71% reduction in the women's infection due to Tenofovir gel is remarkable, and highlights the potential of Tenofovir gel to be used as a PrEP. Compared to Placebo gel (Karim et al., 2010), Tenofovir gel is 44% more effective on reducing new infections consistent with the trial study (Karim et al., 2010). As mentioned earlier, Tenofovir gel is used by susceptible females only, and, as expected, male infection is reduced by 15% only.

We also calculate the probability of transmission per act from males to females (Boily et al., 2009) in the general population, the Tenofovir population, and the Placebo population as 0.24%, 0.08%, and 0.16%, respectively. These transmission probabilities are consistent with those found in previous studies (Boily et al., 2009; Hughes et al., 2012; Pinkerton, 2008).

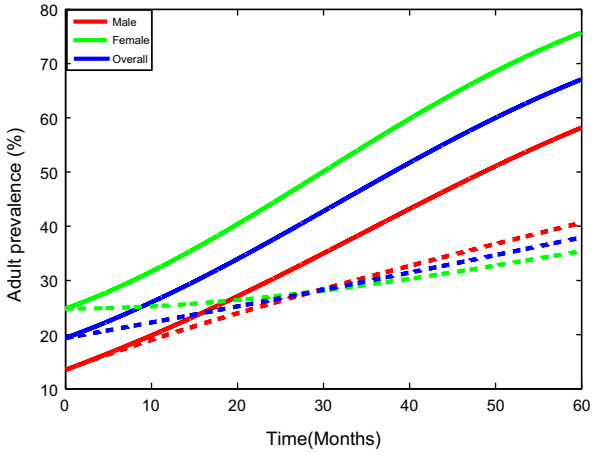

Fig. 4. HIV prevalence (see Section 3.4 for definitions) of male, female and overall population with and without Tenofovir gel interventions over 5 years. The top three (solid line) curves represent prevalence with no gel while the bottom three (dashed line) curves represent prevalence with gel. The blue color represents overall prevalence while red and green represent male and female prevalence respectively. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

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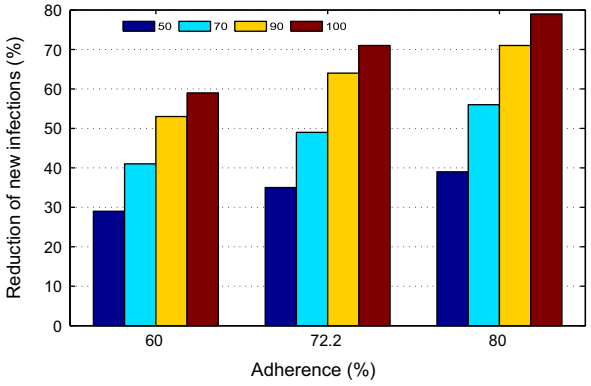

Fig. 5. Reduction of female infections (in 1 year) with respect to adherence and coverage. The reduction rate increases with adherence and coverage. The adherence level 72.2% was observed in the study group (Karim et al., 2010).

3.4. Effect of Tenofovir gel on HIV prevalence

HIV prevalence is defined as the proportion of HIV infected individuals in the total population. More precisely, male, female and overall prevalence are defined by (no. of HIV positive men/total no. of men) $\times$ 100%, (no. of HIV positive women/total no. of women) $\times$ 100%, and (no. of HIV positive individuals/total population) $\times$ 100%, respectively. In the absence of interventions, both male and female prevalences increase over time as shown by the 5 year HIV dynamics (Fig. 4). However, these HIV prevalence patterns can be altered by the use of Tenofovir gel as a PrEP. The overall HIV prevalence as well as the male and female prevalences can drastically be reduced by Tenofovir gel. In a 5-year period, the use of Tenofovir gel as a PrEP reduces the overall, the male, and the female prevalences by 44%, 15% and 61%, respectively.

3.5. Adherence to Tenofovir gel application

As seen above, the use of Tenofovir gel significantly reduces the transmission rate. If r represents the reduction of transmission rate due to the gel, then

$$(1-r)\beta_f = \beta_d. \tag{3.3}$$

Using our estimates of β_f and β_d, we obtain $r=0.721$ ($\sim 72\%$). In this section, we further highlight that r primarily depends on two factors, the effectiveness (ε) of Tenofovir gel and the adherence (a) to its application. The Tenofovir gel is prescribed as two doses within a 24-h period of a sexual act; one dose of the gel within 12 h before sex and another as soon as possible, within 12 h after sex (Karim et al., 2010). Since the average number of sexual acts for the study group is 5 per month (i.e. ≈ 1/week) (Karim et al., 2010), we may reasonably assume that the use of gel in the 24 h period of one sexual act does not affect the next sexual act. Assuming that the reduction rate r increases linearly with the adherence level, for a simple case we take $\varepsilon a = r = 0.721$. Using the adherence level of 72.2%, reported in the trial study (Karim et al., 2010), we find that the gel efficacy is 99.86%, and use these values for the base-case computation.

We now evaluate the sensitivity of adherence on the reproduction numbers, new infections, and the prevalence. Note that in our simple model of $\varepsilon a = r$, the sensitivity of the adherence level is equivalent to the sensitivity of the efficacy. When the adherence level is changed from 72.2% to 60% and to 80%, female infections are reduced by 59% and 79%, respectively, in 1 year under 100% coverage (Fig. 5). Similarly, for 60% and 80% adherence levels, the basic reproduction number is changed to 12.61 and 6.31, respectively, and the female reproduction number is changed to 3.21 and 1.61, respectively. In these adherence levels (60% and 80%), the overall HIV prevalence reaches 44.37% and 33.46%, respectively, at the end of 5 years.

Note that this effect depends on the gel coverage of susceptible female population. Thus, we further evaluate how changes in the coverage affect this outcome. Let us assume that a fraction c of the susceptible women are under the gel coverage, i.e. these women are infected at the rate of β_d, while the remaining fraction, $1-c$, of the susceptible women are infected at the rate of β_f. As mentioned earlier, only susceptible women use Tenofovir gel; so it does not affect the infectivity of infected women to transmit the virus to susceptible men. Therefore, the gel does not affect the female-to-male transmission rate, β_m, or the male reproduction number, $\mathfrak{R}_0^m$. However, the gel affects $\mathfrak{R}_0^f$, which is given by

$$\mathfrak{R}_{0c}^f = \frac{(1-c)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)} + \frac{c\beta_d S_f(0)}{(\mu+\nu+\mu_l)S_m(0)},$$

for the coverage c. By using (3.3), the above formula becomes

$$\mathfrak{R}_{0c}^f = \frac{(1-c)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)} + \frac{c(1-\varepsilon a)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)},$$

and the corresponding basic reproduction number, from (3.2), is given by

$$\mathfrak{R}_{0c} = \mathfrak{R}_0^m \mathfrak{R}_{0c}^f.$$

As seen in Fig. 6, $\mathfrak{R}_{0c}$ decreases as the level of adherence and/or the coverage increases, and it becomes less than one if the product of the adherence and coverage levels is greater than 0.97 (Fig. 6). The coverage also significantly affects the new infections (Fig. 5) and the disease prevalence (Fig. 7). For example, at 80% adherence level, if the coverage is increased from 70% to 90%, the reduction of yearly new infections increases from 56% to 71% of that of the case without the Tenofovir gel (Fig. 5). Similarly, at 100% adherence level, when the coverage is increased from 60% to 80%, the male prevalence, the female prevalence, and the overall prevalence are reduced by 6%, 15%, and 11%, respectively (Fig. 7).

3.6. Sensitivity analysis

To determine the robustness of our parameter estimates, we performed a sensitivity analysis by varying the fixed parameters by $\pm 20\%$. We found that the estimations were insensitive to the change in most of the parameters. The most sensitive parameters are the initial values of the male and female prevalence. The sensitivity of the estimated parameters subject to the fixed parameters is provided in Table 6. When we vary the male and female initial prevalence randomly between 10% and 30%, the estimated transmission rate β_{d0} varies between 0.0032 and 0.0060. Similarly, β_f varies between 0.0652 and 0.0869, and β_{c0} varies between 0.0073 and 0.0110. The sensitivity analysis shows that our estimation is robust.

4. Discussion

Tenofovir gel is one of the candidates with the highest potential for pre-exposure prophylaxis to provide protection to uninfected women who are at high risk of HIV infection. This is not a vaccine, but using it regularly or according to prescribed guidelines it may provide vaccine-like protection. The experimental data has revealed the significant effects of Tenofovir gel on protecting vulnerable women from HIV infection (Karim et al., 2010). Thus Tenofovir gel has been thought to be an important potential PrEP in the absence of effective HIV vaccines as in the current situation. It is not yet well understood how much impact Tenofovir gel can have on population-level HIV dynamics when it is distributed as a PrEP to susceptible women in the community. Here, we developed

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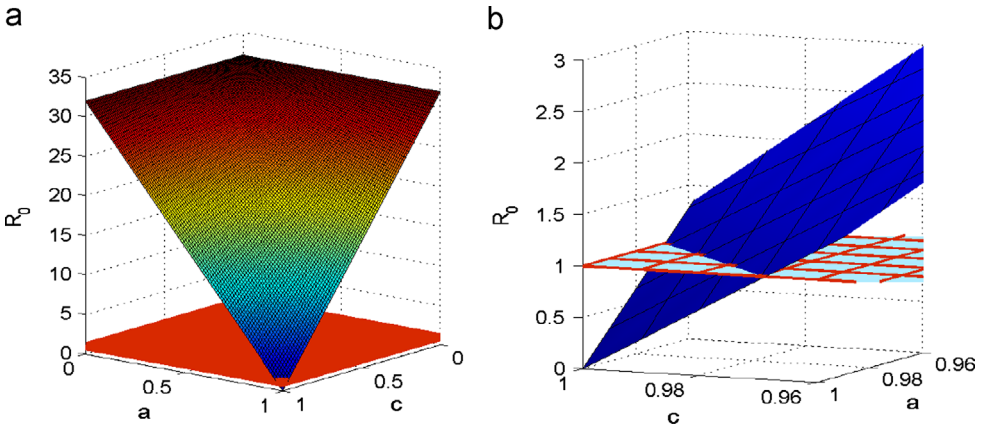

Fig. 6. Impact of adherence and coverage on $\Re_0$. (a) Full image; (b) highlighted area where $\Re_0$ passes through 1.

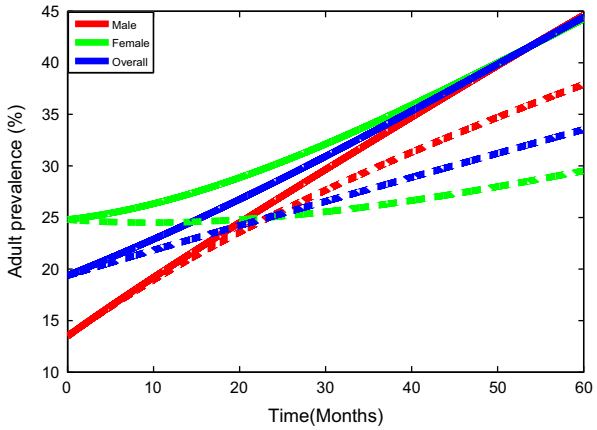

Fig. 7. Impact of coverage on prevalence. The top three (solid line) curves represent prevalence with 60% gel coverage while the bottom three (dashed line) curves represent prevalence with 80% gel coverage. The blue color represents overall prevalence while red and green represent male and female prevalence, respectively. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

a mathematical model to better understand the possible implications of Tenofovir gel as a PrEP against an HIV epidemic. Our model is consistent with the experimental data on the use of Tenofovir gel as a PrEP in South Africa (Fig. 2).

This study provides the HIV transmission rates from male-to-female and from female-to-male with and without the use of Tenofovir gel. We found that Tenofovir gel can reduce the male-to-female transmission rate by 72%. As a result, yearly women infections can be reduced by almost 80% (Fig. 5) when Tenofovir gel is used as a PrEP. Given the nature of the gel application, i.e. only susceptible women use it, it is expected that the gel does not have direct impact on the female-to-male transmission rate. However, the male population also receives a benefit of 15% annual infection reduction due to indirect female protection. These annual reductions of male and female infections also reflect on the long-term prevalence (Fig. 4). By implementing the gel as a PrEP over the 5-year period, the male and female prevalence can be reduced by 15% and 61%, respectively, with 44% reduction in the overall prevalence. As demonstrated by our results, these remarkable effects of Tenofovir gel on reducing infection rates, new infections, and prevalence further highlight the potential of Tenofovir gel for its broader use as a PrEP.

We defined and calculated the male (female) reproduction number, $\Re_0^m$ ($\Re_0^f$), as well as the basic reproduction number ($\Re_0$). Without intervention, our estimates provide $\Re_0 = 31.53$ for the Vulindlela and eThekwini regions of South Africa. This high value of $\Re_0$ reflects the devastating impact of the HIV/AIDS epidemic in South Africa. Our estimation shows that the female reproduction number ($\Re_0^f$) is twice that of the male reproduction number ($\Re_0^m$), indicating that women are particularly vulnerable to HIV infection as mentioned previously (Baral et al., 2013; Hader et al., 2001). With the use of Tenofovir gel as a PrEP by susceptible women, both $\Re_0$ and $\Re_0^f$ can be brought down significantly to 8.80 and 2.23, respectively. However, despite the use of Tenofovir gel, $\Re_0$ still remains greater than 1, implying that the use of Tenofovir gel alone will not be able to eliminate the disease. A partial explanation for the lack of strength of Tenofovir gel to eradicate disease could be that Tenofovir gel does not reduce the male transmission rate (or male reproduction number), and the infection of women is governed by the infected male population. Thus our results suggest that a combination program incorporating Tenofovir gel as a PrEP into other additional interventions, such as condom protection, may result in the successful eradication of HIV/AIDS.

Our results support the hypothesis that adherence and coverage are key for the success of Tenofovir gel as a PrEP. The individual protection depends on the adherence level while overall impact depends on the coverage of susceptible women by Tenofovir gel. Both adherence and coverage have a positive effect on the reduction of infections, reproduction numbers, and prevalence (Figs. 5–7). These observations suggest that the adherence and coverage must be taken into account while evaluating the outcomes of Tenofovir gel as a PrEP. Moreover, HIV prevention programs with Tenofovir gel as a PrEP need to be designed aiming at a higher level of adherence and coverage. For example, to increase the adherence level, an alternate form of Tenofovir gel, such as an intravaginal ring (IRV) (Mesquita et al., 2012), can be suggested. Similarly, an optimal coverage can be achieved by identifying women at high risk and bringing them under gel coverage.

One of the interesting findings of our study is that Placebo gel also shows some effectiveness against HIV infection, as opposed to the general expectation that Placebo gel has negligible effect. To understand this in detail, we also considered the model with $\beta_f = \beta_c$ assuming that Placebo gel has no effect. Interestingly, we found that the model with $\beta_f = \beta_c$ provides significantly worse fit ($p = 0.0025$, F-test) to the data compared to our original model. This surprising effect could be due to the fact that though Placebo gel does not contain any anti-viral agent, it may form a physical barrier against HIV reaching the target cell (Lai et al., 2009). It may also be due to the fact that the study group under Placebo gel received comprehensive counseling to minimize the risk of infection. The results suggest that the net effectiveness of Tenofovir gel has to be interpreted carefully.

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Table 6
Sensitivity of the estimated parameters on the fixed parameters.

Fixed parameters	Base-value	Changes (%)	Changes in β_f (%)	Changes in β_{d0} (%)	Changes in β_{c0} (%)
Λ_m	$173\ m^{-1}$	± 20	0.01	0.37	0.47
Λ_f	$187\ m^{-1}$	± 20	0.01	0.37	0.47
μ	$6.67 \times 10^{-4}\ m^{-1}$	± 20	± 0.03	0.37	0.47
μ_l	$2.38 \times 10^{-3}\ m^{-1}$	± 20	-0.08	0.38	0.48
ν	$6.1 \times 10^{-3}\ m^{-1}$	± 20	± 2.48	0.45	0.54
Initial male-prevalence	13.5%	± 20	± 13.97	± 22.39	± 22.27
Initial female-prevalence	24.8%	± 20	± 7.65	± 2.26	± 2.35

While this study offers some valuable insights into the implication of Tenofovir gel as a PrEP on HIV dynamics, we identify several limitations of our study. Our estimates are based on limited data sets from South Africa. We assumed that the adherence of gel increases the protection linearly, which may not be the case for each individual. The drug concentration and its efficacy might also play a role in determining the overall effects on transmission. Our model further assumes that only susceptible women use Tenofovir gel (CDC Fact Sheet, 2012). However, there might be some infected women on continued gel from the time of infection to the time of diagnosis. To the best of our knowledge, there is no clear evidence about the effects of gel on the transmission from women to men. If these unknowingly infected women continue gel use, which may provide additional protection not accounted for in our study, then the benefits of Tenofovir gel can be expected to be more than those found in this study. In this case, we have underestimated the benefit from Tenofovir gel. While these infected women on the continued gel use can be ignored in some regions with frequent testing facilities as in our computation, the model needs to be improved to include this group in the regions with poor resources. Finally, we acknowledge that the women in the experimental study (Karim et al., 2010) benefited from supplementary care, including education, counseling, and motivation; our estimates of the benefits from Tenofovir gel might have been affected by these. Further studies with more data sets may help achieve a deeper understanding of the actual benefit of Tenofovir gel as a PrEP.

In summary, Tenofovir gel as a PrEP for women can be an effective tool to fight against HIV infection. In the absence of a successful vaccine, Tenofovir gel can be used as a PrEP to provide significant direct protection to women, and indirectly to men, from HIV infection. In combination with other interventions, Tenofovir gel as a PrEP has the potential to eradicate HIV/AIDS, the most devastating current human epidemic. A strategic and prudent use of this gel is required to obtain the optimal impact.

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