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Impact of early treatment programs on HIV epidemics: An immunity-based mathematical model

S.M. Ashrafur Rahman[a,*], Naveen K. Vaidya[b], Xingfu Zou[a]

[a] Department of Applied Mathematics, University of Western Ontario, London, Ontario N6A 5B7, Canada
[b] Department of Mathematics and Statistics, University of Missouri-Kansas City, MO 64110, USA

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ABSTRACT

While studies on pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) have demonstrated substantial advantages in controlling HIV transmission, the overall benefits of the programs with early initiation of antiretroviral therapy (ART) have not been fully understood and are still on debate. Here, we develop an immunity-based (CD4+ T cell count based) mathematical model to study the impacts of early treatment programs on HIV epidemics and the overall community-level immunity. The model is parametrized using the HIV prevalence data from South Africa and fully analyzed for stability of equilibria and infection persistence criteria. Using our model, we evaluate the effects of early treatment on the new infection transmission, disease death, basic reproduction number, HIV prevalence, and the community-level immunity. Our model predicts that the programs with early treatments significantly reduce the new infection transmission and increase the community-level immunity, but the treatments alone may not be enough to eliminate HIV epidemics. These findings, including the community-level immunity, might provide helpful information for proper implementation of HIV treatment programs.

1. Introduction

Prevention of HIV transmission has been one of the prime concerns and challenges for the past three decades. Repeated failure of HIV vaccine development aggravates this challenge further [17,31,34]. On the other hand, the use of early antiretroviral therapy such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) has shown significant effectiveness on reducing HIV transmission [6–8,10,16]. Thus, in the current situation of the vaccine unavailability, the treatment programs with early initiation of therapy constitute promising alternatives for curbing epidemic burden.

A study with 1763 serodiscordant couples from nine countries found 89% reduction of HIV transmission with early initiation of ART [8]. Similarly, a community based cross-sectional study in South Africa estimated about 71.8% reduction of annual risk of HIV transmission with early ART [3]. This risk reduction is mainly attributable to the low level viral load in successfully treated individuals [10]. Some experimental results, however, found that ART could escalate HIV incidence and may worsen the spread of HIV in some cases [35]. Therefore, it is necessary to accurately evaluate the benefits from the early treatment programs, and the mathematical models can help quantify benefits from various potential treatment scenarios.

Several models exist that examine the impact of initiation timing of ART on HIV incidence [5,18,28,30,36]. A comprehensive test-and-treat model among MSM in New York City showed that the cumulative number of new infections can be reduced by 69.1% over 20-year period [36]. Another study showed that the disease progression was reduced higher when ART was initiated at the CD4+ T cell count greater than 350 than at the CD4+ T cell count less than 250 [43]. The dynamical model developed by WHO predicts that annual HIV testing and immediate treatment could reduce HIV incidence and mortality in South Africa to less than 1 case per thousand people per year in five years and HIV prevalence to less than 1% in fifty years [18]. While these models have provided important insights into the effectiveness of treatment programs, none of these existing models takes treatment related alterations of CD4+ T cell counts into account, and thus, can not

* Corresponding author.
E-mail address: srahma33@uwo.ca (S.M.A. Rahman).

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predict overall treatment benefits, including the community-level immunity benefits [2].

As far as HIV dynamics and ART are concerned, CD4 count is one of the most important factors because the CD4 count determines the disease stage, immunity level, and treatment decision, and the treatment greatly affects the patients CD4 count level [15,24,29,39,43]. Measurement of CD4+ T cell count has also an important role in making decisions for screening and prophylaxis for major opportunistic infections, including malaria, severe bacterial infections, *P. jirovecii* pneumonia, and toxoplasmosis [37]. It is thus important to know community-level immunity to formulate guidelines for treatment programs, mainly at the events when outbreaks of other opportunistic diseases occur. In addition, ART usually recovers the CD4+ T cells of infected individuals. This improved immunity tends to reduce the death of infected individuals and prevents the disease progression. Moreover, the timing of ART initiation plays an important role for increased immunity levels and decreased mortality and morbidity [2,4,15]. Therefore, it is critical to include alteration of CD4 count in the HIV models under antiretroviral treatments.

In this study, we develop an immunity-based HIV model that takes CD4 count alterations into account. The model is consistent with the HIV prevalence data from South Africa. We use our model to explore the effects of various ART programs and their initiation timing on HIV transmission dynamics and the community-level immunity. The remaining paper is organized as follows: in Section 2 we develop a mathematical model. Basic properties of the model and stability analysis are presented in Section 3. In Section 4, we estimate parameters and perform data fitting. In Section 5, the results based on our model are presented. Finally, we summarize our findings with discussions in Section 6.

2. Mathematical model

In HIV infection, individual's disease condition is associated primarily with their CD4+ T cell count. In fact, HIV primarily weakens infected individual's immune system by destroying their CD4+ T cells. Therefore, CD4+ T cell count is a crucial marker to measure the strength of the immune system in HIV infected individuals [4,24]. Moreover, a decision as to whether a treatment should begin or not is usually made based on patient's CD4+ T cell count. Current WHO recommendation [1,43] is to start ART when CD4 count falls below 350. Also, individuals having CD4+ T cell count between 350–500 are strongly recommended to start ART, and those having CD4 count greater than 500 are moderately recommended to begin ART [1,43]. These levels of CD4+ T cell count also reflect the patients immunity level: normal (above 500), moderate (350–500), and weak (below 350). Based on these treatment guidelines and immune levels, we divide the total HIV infected population into three compartments (stages) according to their corresponding CD4+ T cell levels. Stage I consists of the individuals with CD4+ T cell count more than 500, stage II with CD4+ T cell count between 350 and 500, and stage III with CD4 count less than 350. Once infected, an individual generally progresses through these stages if they remain untreated. The individual usually regains his CD4+ T cell count after he begins treatment [26]. The amount of CD4+ T cell count recovery depends on the level of CD4+ T cell count at the time the person begins treatment. It could also depend on other factors including the effectiveness of therapies and the presence of drug sanctuary sites [42]. In addition to the regain of CD4+ T cell count, the treatment can also suppress the viral load to an undetectable level. Thus, an infected individual becomes significantly less infectious under treatment [35]. In our model, the treatment can have two consequences: increase in CD4+ T cell count in treated individuals and decrease in HIV transmission by treated individuals.

Table 1
Description of variables of model (2.1).

Variable	Description
S	Number of susceptible
I_1	Number of infected individuals with CD4+ T cell count $>$ 500
I_2	Number of infected individuals with CD4+ T cell count 350–500
I_3	Number of infected individuals with CD4+ T cell count $<$ 350
T_1	Number of treated individuals with CD4+ T cell count $>$ 500
T_2	Number of treated individuals with CD4+ T cell count 350–500
T_3	Number of treated individuals with CD4+ T cell count $<$ 350
N	Total number of individuals

Table 2
Description of parameters of (2.1).

Parameter	Description
Λ	Recruitment rate
λ	Force of infection
β_1	Transmission rate for I_1
β_2	Transmission rate for I_2
β_3	Transmission rate for I_3
β	Transmission rate for treated groups
τ_1	Rate of treatment for I_1
τ_2	Rate of treatment for I_2
τ_3	Rate of treatment for I_3
δ_i	Rate of transfer due to CD4+ T cell decline (i=1,2)
ρ_i	Rate of transfer due to CD4+ T cell increase (i=1,2)
μ_i	Rate of death (i=0,1,...,6)
a	Rate associated with reduction of incidence due to behavioral changes

We consider a homogeneous sexually active (age 15–49 years) population and divide them into seven groups: a susceptible group, S, three infected groups (categorised based on CD4+ T cell count) without treatment, I_1, I_2, I_3 and three infected groups (categorised based on CD4+ T cell count) with treatment, T_1, T_2, T_3. The transmission dynamics are as follows: a susceptible individual moves to the compartment I_1 when he/she comes in successful contact with individual from any of the infected compartments. The individuals of I_1 either get treatment and move to T_1 at the rate of τ_1 or they move to I_2 compartment (due to their CD4+ T cell count declines) at the rate of δ_1. Similarly, individuals move from compartment I_2 to T_2 at the rate of τ_2 (treatment) or to I_3 at the rate of δ_2 (CD4+ T cell decline). The individuals in compartment I_3 get treatment and move to T_3 at the rate of τ_3. Treated individuals gain CD4+ T cell count and move from T_3 to T_2 and from T_2 to T_1 at rates ρ_2 and ρ_1, respectively.

The individuals in stage I (I_1 & T_1) have the highest immunity and those in stage III (I_3 & T_3) have the lowest immunity. Incorporation of immunity level, including the effects by treatments, is a novel feature of our model, which can track the number of individuals that are in different immunity levels and can predict the community-level immunity under ART programs.

The infectivity of individuals at different stages are different [9]. The rate of transmission by HIV infected individuals without treatment is high during acute infection (few months), decreases to a low level that continues for a long period (usually 6–7 years), and then increases slightly during the last 2–3 years [23]. Therefore, we take different transmission rates, β_1, β_2, and β_3 for I_1, I_2, and I_3 compartments, respectively. Since the viral load of individuals in all treated compartments usually remains low with a low transmission probability [8,35], we do not distinguish infectivity of different compartments of treated groups, and take the same transmission rate β for all T_1, T_2, and T_3. The definition and symbols of the model variables are summarized in Tables 1 and 2. The flow of the population in these transmission dynamics is shown in Fig. 1.

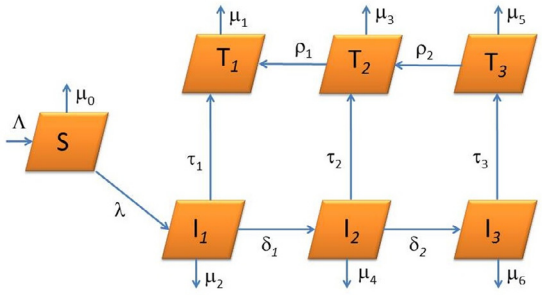

Fig. 1. Schematic diagram of infection.

Following the assumptions discussed above, the infection dynamics can be modeled by the following system of ODEs :

$$\begin{aligned}
\dot{S} &= \Lambda - (\lambda + \mu_0)S \\
\dot{I_1} &= \lambda S - (\tau_1 + \delta_1 + \mu_2)I_1 \\
\dot{I_2} &= \delta_1 I_1 - (\tau_2 + \delta_2 + \mu_4)I_2 \\
\dot{I_3} &= \delta_2 I_2 - (\tau_3 + \mu_6)I_3 \\
\dot{T_1} &= \tau_1 I_1 + \rho_1 T_2 - \mu_1 T_1 \\
\dot{T_2} &= \tau_2 I_2 + \rho_2 T_3 - (\rho_1 + \mu_3)T_2 \\
\dot{T_3} &= \tau_3 I_3 - (\rho_2 + \mu_5)T_3
\end{aligned} \tag{2.1}$$

where the force of infection, λ, is given by

$$\lambda = \frac{\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)}{N} e^{-a(I_1+I_2+I_3+T_1+T_2+T_3)},$$

and

$$N = S + I_1 + I_2 + I_3 + T_1 + T_2 + T_3.$$

The exponential term in λ represents 'behavioral changes' due to media or social awareness [32]. When the number of infected individuals is small, this term has negligible effect and the effect increases as the number of infected individual increases.

3. Model analysis

3.1. Well-posedness

The model (2.1) has seven coupled equations. Following [33] it can be shown that $S(t) \geq 0$. Similarly, we can show that all other state variables are also non-negative as long as the initial values are non-negative.

By adding all the equations of (2.1), the total population N satisfies

$$\dot{N} \leq \Lambda - \mu N,$$

where

$$\mu = \min\{\mu_0, \mu_1, \mu_2, \mu_3, \mu_4, \mu_5, \mu_6\}.$$

By comparison, it implies that $\lim_{t\to\infty} N \leq \Lambda/\mu$. Therefore, the total population is bounded. This suggests that the biologically feasible region of the model is given by

$$\Gamma = \{(S, I_1, I_2, I_3, T_1, T_2, T_3) : S, I_1, I_2, I_3, T_1, T_2, T_3 \geq 0, N \leq \Lambda/\mu\}.$$

3.2. Basic reproduction number

The basic reproduction number, denoted by $\Re_o$, of a model is defined as the total number of secondary infections caused by a typical infected individual in a completely susceptible population [12]. Using the next generation matrix approach [40], the new infection and the transfer matrices of our model are given by

$$F = \begin{pmatrix} \beta_1 & \beta_2 & \beta_3 & \beta & \beta & \beta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \alpha_1 & 0 & 0 & 0 & 0 & 0 \\ -\delta_1 & \alpha_2 & 0 & 0 & 0 & 0 \\ 0 & -\delta_2 & \alpha_3 & 0 & 0 & 0 \\ -\tau_1 & 0 & 0 & \alpha_4 & -\rho_1 & 0 \\ 0 & -\tau_2 & 0 & 0 & \alpha_5 & -\rho_2 \\ 0 & 0 & -\tau_3 & 0 & 0 & \alpha_6 \end{pmatrix},$$

where

$$\alpha_1 = \tau_1 + \delta_1 + \mu_2, \alpha_2 = \tau_2 + \delta_2 + \mu_4, \alpha_3 = \tau_3 + \mu_6, \alpha_4 = \mu_1,$$
$$\alpha_5 = \rho_1 + \mu_3, \alpha_6 = \rho_2 + \mu_5.$$

Then we get $\Re_o$ as follows:

$$\begin{aligned}
\Re_o = \rho(FV^{-1}) &= \frac{\beta_1}{\alpha_1} + \frac{\beta_2\delta_1}{\alpha_2\alpha_1} + \frac{\beta_3\delta_2\delta_1}{\alpha_3\alpha_2\alpha_1} \\
&+ \frac{\beta}{\alpha_5}\left(\frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\right) \\
&+ \frac{\beta}{\alpha_6}\left(\frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\right) + \frac{\beta}{\mu_1}\left(\frac{\tau_1}{\alpha_1}\right. \\
&\left. + \frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2}\frac{\rho_1}{\alpha_5} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\frac{\rho_1}{\alpha_5}\right).
\end{aligned} \tag{3.1}$$

3.3. Stability analysis

The model (2.1) has a unique disease free equilibrium (DFE), $E_0 = (\Lambda/\mu_0, 0, 0, 0, 0, 0, 0)$, and also an endemic equilibrium (EE), E^*. The existence of endemic equilibrium is given in the following sub-section. The stability analysis of these equilibria can reveal whether the disease can survive or not. Following [40], it is easy to prove the following local stability result:

Theorem 3.1. *If $\Re_o < 1$, the DFE, E_0, is locally asymptotic stable, and if $\Re_o > 1$, E_0 is unstable.*

We can further prove that, E_0 is globally asymptotically stable:

Theorem 3.2. *If $\Re_o < 1$, the DFE, E_0, is globally asymptotically stable.*

Proof. Let us consider the auxiliary function

$$L = c_1 I_1 + c_2 I_2 + c_3 I_3 + c_4 T_1 + c_5 T_2 + c_6 T_3, \tag{3.2}$$

where $c_i, i = 1...6$ are constants to be determined. Taking the derivative of L, with respect to t, along the trajectories of (2.1),

we have

$$\begin{aligned}\dot{L} &= c_1\dot{I}_1 + c_2\dot{I}_2 + c_3\dot{I}_3 + c_4\dot{T}_1 + c_5\dot{T}_2 + c_6\dot{T}_3\\ &= c_1(\lambda S - \alpha_1 I_1) + c_2(\delta_1 I_1 - \alpha_2 I_2) + c_3(\delta_2 I_2 - \alpha_3 I_3)\\ &\quad + c_4(\tau_1 I_1 + \rho_1 T_2 - \alpha_4 T_1)\\ &\quad + c_5(\tau_2 I_2 + \rho_2 T_3 - \alpha_5 T_2) + c_6(\tau_3 I_3 - \alpha_6 T_3)\\ &\le c_1\frac{\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)}{N}S - c_1\alpha_1 I_1 + c_2\delta_1 I_1\\ &\quad - c_2\delta_2 I_2\\ &\quad + c_3\delta_2 I_2 - c_3\alpha_3 I_3 + c_4\tau_1 I_1 + c_4\rho_1 T_2 - c_4\alpha_4 T_1\\ &\quad + c_5\tau_2 I_2 + c_5\rho_2 T_3 - c_5\alpha_5 T_2 + c_6\tau_3 I_3 - c_6\alpha_6 T_3\\ &\le c_1(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3))\\ &\quad + (c_2\delta_1 - c_1\alpha_1 + c_4\tau_1)I_1\\ &\quad + (c_3\delta_2 - c_2\alpha_2 + c_5\tau_2)I_2 + (-c_3\alpha_3 + c_6\tau_3)I_3 - c_4\alpha_4 T_1\\ &\quad + (-c_5\alpha_5 + c_4\rho_1)T_2 + (c_5\rho_2 - c_6\alpha_6)T_3\\ &= (\Re_0 - 1)[\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)], \end{aligned} \tag{3.3}$$

where

$$\begin{aligned}c_1 &= \frac{\beta_1}{\alpha_1} + \frac{\beta_2\delta_1}{\alpha_2\alpha_1} + \frac{\beta_3\delta_2\delta_1}{\alpha_3\alpha_2\alpha_1}\\ &\quad + \frac{\beta}{\alpha_4}\left(\frac{\tau_1}{\alpha_1} + \frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2}\frac{\rho_1}{\alpha_5} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\frac{\rho_1}{\alpha_5}\right)\\ &\quad + \frac{\beta}{\alpha_5}\left(\frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\right) + \frac{\beta}{\alpha_6}\left(\frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\right),\\ c_2 &= \frac{\beta_2}{\alpha_2} + \frac{\beta_3\delta_2}{\alpha_3\alpha_2} + \frac{\beta\tau_3\delta_2}{\alpha_2\alpha_3\alpha_6} + \frac{\beta\rho_1(\tau_2\alpha_3\alpha_6 + \rho_2\tau_3\delta_2)}{\alpha_2\alpha_3\alpha_4\alpha_5\alpha_6}\\ &\quad + \frac{\beta(\tau_2\alpha_3\alpha_6 + \rho_2\tau_3\delta_2)}{\alpha_2\alpha_3\alpha_5\alpha_6},\\ c_3 &= \frac{\beta_3}{\alpha_3} + \frac{\beta\tau_3}{\alpha_3\alpha_6} + \frac{\beta\rho_1\rho_2\tau_3}{\alpha_3\alpha_4\alpha_5\alpha_6} + \frac{\beta\rho_2\tau_3}{\alpha_3\alpha_5\alpha_6},\ c_4 = \frac{\beta}{\alpha_4},\\ c_5 &= \frac{\beta}{\alpha_5} + \frac{\beta\rho_1}{\alpha_4\alpha_5},\\ c_6 &= \frac{\beta}{\alpha_6} + \frac{\beta\rho_1\rho_2}{\alpha_4\alpha_5\alpha_6} + \frac{\beta\rho_2}{\alpha_5\alpha_6}.\end{aligned}$$

Therefore, $\dot{L} \le 0$ when $\Re_o < 1$ with the equality holding only when state variables regarding infection are zero. By [21], all positive solutions approach $\mathcal{M}$, the largest invariant subset of the set $\{\frac{dL}{dt} = 0\}$. Since $\frac{dL}{dt}$ is zero only at disease free state and in the disease free state the solution always approaches to E_0, $\mathcal{M} = \{E_0\}$ is a singleton set. Thus, the equilibrium E_0 is globally attractive. By virtue of the Theorem 3.1, E_0 is globally asymptotically stable. □

3.4. Persistence of the disease

In the previous section, we proved that if $\Re_o < 1$ then the disease dies out regardless of its initial size of outbreak. On the other hand, when $\Re_o > 1$ the DFE becomes unstable. Due to the nonlinearity along with the exponential term in the force of infection, λ, the model posed an extreme complexity to the stability analysis of the endemic equilibrium. However, we are able to show that the infectious populations I_1, I_2, I_3, T_1, T_2 and T_3 will remain persistent for $\Re_o > 1$.

Theorem 3.3. *Assume that $\Re_0 > 1$. Then the disease is uniformly persistent in the sense that there exists an $\eta > 0$ such that for every positive solution of (2.1), there holds*

$$\liminf_{t\to\infty} I_i(t) > \eta, \quad \liminf_{t\to\infty} T_i(t) > \eta, \quad i = 1, 2, 3.$$

Moreover, there exists an endemic equilibrium in this case.

Proof. We apply a theorem in [38] to prove the uniform persistence. To this end, let

$$U = (S, I_1, I_2, I_3, T_1, T_2, T_3), \quad \bar{U} = (I_1, I_2, I_3, T_1, T_2, T_3),$$

$$X = \Big\{U \in \mathcal{R}^7_+ | U_i \ge 0, i = 1...7,$$

$$\text{where } U_i \text{ is the i'th component of } U\Big\},$$

$$X_0 = \Big\{U \in X | U_i > 0, i = 2..7\Big\},$$

$$Y = X/X_0 = \Big\{U \in X | U_i = 0, \text{for some } \ i = 2...7\Big\}.$$

Now we show that the system (2.1) is uniformly persistent with respect to (X_0, Y). Since Y contains a single equilibrium E_0, it is sufficient to show that $W^s(E_0) \cap X_0 = \phi$, where $W^s(E_0)$ denotes the stable manifold of E_0. Suppose this is not true. Then there is a solution $(S, I_1, I_2, I_3, T_1, T_2, T_3) \in X_0$ of (2.1) such that

$$\lim_{t\to\infty}(S(t), I_1(t), I_2(t), I_3(t), T_1(t), T_2(t), T_3(t)) \to (\Lambda/\mu, 0, 0, 0, 0, 0, 0).$$

Then for any $\xi > 0$, we have

$$\frac{\Lambda}{\mu} - \xi \le S \le \frac{\Lambda}{\mu} + \xi,$$
$$0 \le U_i \le \xi, i = 2...7$$

for large t. It follows from the system (2.1) that

$$\begin{aligned}\begin{pmatrix}\dot{I}_1\\ \dot{I}_2\\ \dot{I}_3\\ \dot{T}_1\\ \dot{T}_2\\ \dot{T}_3\end{pmatrix} &= \begin{pmatrix}\lambda S\\ 0\\ 0\\ 0\\ 0\\ 0\end{pmatrix} + \begin{pmatrix}-\alpha_1 & 0 & 0 & 0 & 0 & 0\\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0\\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0\\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0\\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2\\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6\end{pmatrix}\\ &\quad \times \begin{pmatrix}I_1\\ I_2\\ I_3\\ T_1\\ T_2\\ T_3\end{pmatrix},\\ &\ge \begin{pmatrix}\beta_1\tilde{S}(\xi) - \alpha_1 & \beta_2\tilde{S}(\xi) & \beta_3\tilde{S}(\xi) & \beta\tilde{S}(\xi) & \beta\tilde{S}(\xi) & \beta\tilde{S}(\xi)\\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0\\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0\\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0\\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2\\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6\end{pmatrix}\\ &\quad \times \begin{pmatrix}I_1\\ I_2\\ I_3\\ T_1\\ T_2\\ T_3\end{pmatrix},\\ &\equiv \tilde{J}(\xi)\bar{U},\end{aligned}$$

where,

$$\tilde{S}(\xi) = \frac{\Lambda/\mu_0 - \xi}{\Lambda/\mu_0 + 7\xi},$$

Table 3
HIV prevalence data from South Africa [44].

Year :	1990	1991	1992	1993	194	1995	1996	1997	1998	1999	2000	2001
Prev.:	0.3	0.6	1.1	2.0	3.3	5.0	7.0	9.2	11.3	13.2	14.9	16.2
Year :	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Prev. :	17.1	17.8	18.3	18.5	18.7	18.8	18.9	18.9	18.9	18.8	18.9	

and

$$\tilde{J}(0) = \begin{pmatrix} \beta_1 - \alpha_1 & \beta_2 & \beta_3 & \beta & \beta & \beta \\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0 \\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0 \\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0 \\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2 \\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6 \end{pmatrix}. \quad (3.4)$$

Note that $\tilde{J}(0)$ is equal to $(F - V)$, has at least one eigenvalue with positive real part when $\Re_\circ > 1$ [40]. Since $\xi > 0$ is arbitrary, one can make ξ small enough so that $s(\tilde{J}(\xi))$ is positive, where $s(A)$ is the largest real part of the eigenvalues of A. Then there exist solutions of the linear system

$$\dot{\bar{U}} = \tilde{J}(\xi)\bar{U},$$

that grow exponentially. By comparison, the solutions U become unbounded as $t \to \infty$. This is a contradiction to the fact that the solutions of the system (2.1) are ultimately bounded. Therefore, $W^s(E_0) \cap X_0 = \phi$. Following Theorem 4.6 [38], it can be concluded that the system (2.1) is uniformly persistent with respect to (X_0, Y).

Furthermore, the system (2.1) is dissipative, therefore, by Theorems 3.3 in [20], it implies that system (2.1) has an endemic equilibrium (i.e. all components are positive). This completes the proof of the theorem. □

4. Data fitting and parameter estimation

4.1. Data

We used the World Bank data for HIV prevalence in South Africa [44]. The yearly adult HIV prevalence data from 1990 to 2012 were considered. The 'adult prevalence' is defined as the percentage of adult infected individuals among the 15–49 years old population. The data are given in Table 3.

4.2. Parameter values and initial conditions

HIV mortality is primarily attributed to CD4+ T cell counts and disease stage; the mortality is higher in patients with low CD4+ T cell counts. An individual with successful treatment can have almost a normal life due to high level of CD4 count maintenance [2]. Following the previous studies [4,5,27] we estimated the mortality rates of the individuals in different compartments as $\mu_0 = 0.0288$, $\mu_2 = 0.0888$, $\mu_4 = 0.1368$, $\mu_6 = 0.3108$, $\mu_1 = 0.0408$, $\mu_3 = 0.0528$ and $\mu_5 = 0.1752$.

HIV infected individuals, if remained untreated, are highly infectious during the first few months (stage I) [9]. Then the infectivity declines and remains low during the asymptotic period for about 6–7 years (stage II), followed by an increase to a higher level during stage III. To represent these different infectiousness for I_1, I_2, and I_3, we set $\beta_1 = m_1\beta_2, \beta_3 = m_2\beta_2$, and estimate the constants m_1, m_2. On the other hand, the treated individuals have little contribution in transmission. The reduction of transmission due to treatment could reach as high as 96% [8]. Following this result, we considered $\beta = 0.04 \times \beta_2$. Since treatment is usually not given to individuals with higher CD4+ T cell counts, we take $\tau_1 = 0$, and $\tau_2 = 0$ for data fitting.

Table 4
Values of the estimated parameters.

Parameters	Estimated value (per year*)
β_2	0.082
m_1	12.57
m_2	4.54
ρ_1	0.57
ρ_2	0.82
δ_1	0.33
δ_2	0.34
τ_3	0.11
a	2.4744e-7(*per number)
$\beta_1 = m_1\beta_2, \beta_3 = m_2\beta_2$	

The population [13,44] corresponding to the year 1990 is taken as the initial value as the data begins at the year 1990. According to Day et al. [11] and Dorrington et al. [13], 37.08 million people lived in South Africa in 1990, among which 45% were adult (15–49 years). Using HIV prevalence data [44] and CD4+ T cell count distribution among HIV positive individuals [3] we calculated the initial population for our model to be $S(0) = 17.94$ million, $I_1(0) = 0.0163$ million, $I_2(0) = 0.009$ million, and $I_3(0) = 0.011$ million. Since there were no treatments available for HIV infected individuals in South Africa in 1990, the initial populations in treatment compartments are taken to be zero.

4.3. Data fitting

We fit the model (2.1) to the data (Table 3) to estimate nine parameters $\delta_1, \delta_2, \rho_1, \rho_2, \tau_3, m_1, m_2, a$, and β_2. With certain initial guesses of these parameters, we solve the model (2.1) using the MATLAB built-in functions 'ode45'. Then implementing the solutions to the MATLAB routine 'fmincon', we estimate the parameters that correspond to the minimum of the following error function

$$E = \sum_{i=1}^{i=23} \left(\frac{I_1(t_i) + I_2(t_i) + I_3(t_i) + T_1(t_i) + T_2(t_i) + T_3(t_i)}{N(t_i)} \times 100 - P(t_i) \right)^2,$$

where $I_1(t_i)$, $I_2(t_i)$, $I_3(t_i)$, $T_1(t_i)$, $T_2(t_i)$, $T_3(t_i)$, $N(t_i)$ are numerically computed model solutions at time t_i and $P(t_i)$ is the HIV prevalence data at time t_i.

5. Results

5.1. Model fit to the data

We obtained some of the model parameters from the primary literature [2,4,5,26,27], and estimated the remaining nine parameters by fitting the model to the data (Table 3) [44]. The model solution using the best parameter estimates along with the data is shown in Fig. 2. The model fits the data very well. The set of parameter values that generates the best fit is given in Table 4.

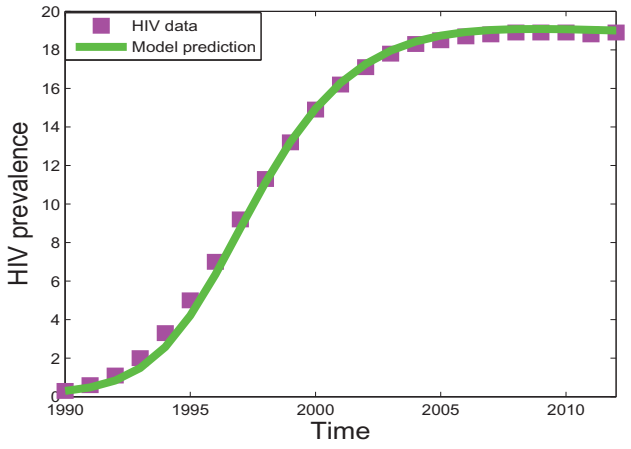

Fig. 2. Data fitting result. The solid green curve shows the yearly adult prevalence of HIV infections predicted by the model and squares are the data (Table 3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

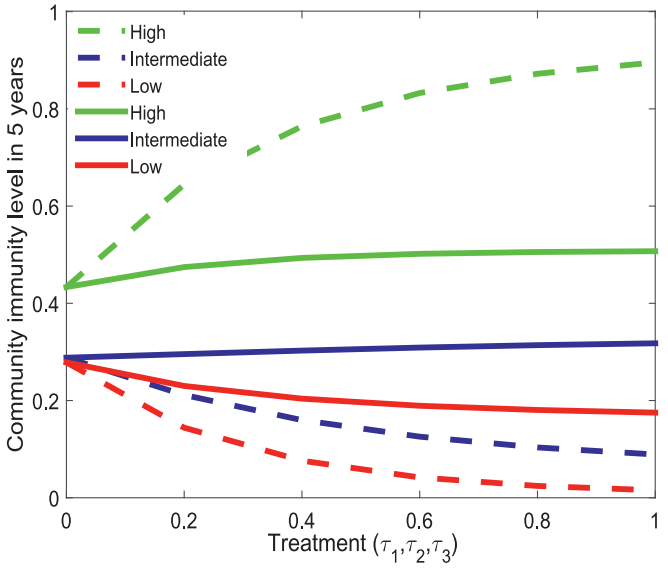

Fig. 3. Community-level immunity in 5 years under treatment program. Solid curves show the immunity levels predicted by the model that ignores recovery of CD4+ T cells and dashed curves show the prediction of our model. The values of the parameters used for this graph are listed in Table 4.

5.2. Community-level immunity

The immunity of individual is divided into three levels: high, intermediate, and low. The immunity level is high if CD4+ T cells count of the individual is above 500, intermediate if the count falls between 350 and 500, and low if the count is below 350. According to our model setting, individuals belonging to stage I (I_1 & T_1) have the high immunity level whereas individuals at stage II and stage III have intermediate and low immunity levels, respectively. The fraction of individuals in the community at each immunity level can be used as health indicators of the community and are important for public health management to control other opportunistic diseases. We define these fractions as community levels of immunity which we investigate under various HIV treatment programs. Our model predicts that in the presence of CD4+ T cell recovery, the high, intermediate and low immunity levels can reach to 90%, 8%, and 2%, respectively in 5 years. However, when recovery rates are considered to be absent ($\rho_1 = \rho_2 = 0$), those immunity levels become 51%, 32%, and 17%, respectively (Fig. 3). These estimates thus show the significant effect of recovery of CD4+ T cells on immunity levels.

5.3. HIV transmission

Our estimates show that the value of m_1 and m_2 are 12.57 and 4.54 indicating β_1 is about 13 times higher and β_3 is about 5 times higher than β_2. These estimates are consistent with the experimental results which found m_1 between 7 and 26 and m_2 between 2 and 6 [23,35,41]. These results show that HIV-infected individuals in stages I and III have more contribution than stage II to the transmission of HIV, thus implying that individuals in these groups (I & III) can be potential targets for treatment as prevention of HIV transmission. With these transmission rates, our model predicts that the total new infections generated in 5 years by the individuals in the stages I, II, and III are 1.89 million, 0.11 million, and 0.47 million, respectively, without treatment, while they reduce to 0.58 million, 0.029 million, and 0.11 million, respectively, with treatment.

5.4. CD4 count loss and recovery

The disease progression rates estimated by our model are $\delta_1 = 0.33$ and $\delta_2 = 0.34$. That is, an HIV infected individual, if untreated, takes about 3 years, on average, to progress from stage I to stage II, and 3 years from stage II to stage III. These progression rates are in agreement with the experimental results [22,24,29]. Our estimates of CD4+ T cell count recovery rates, $\rho_1 = 0.57, \rho_2 = 0.82$, show that with treatment HIV patients can recover CD4+ T cell count to the level of above 350 within 1 year on average and to the level of above 500 within the next 2 years on average. This finding of CD4+ T cell recovery rates is in agreement with the experimental results [26] in which the median of CD4+ T cell count is found to be increased from 180 to 350 in about 15 months and from 350 to 500 in about 21 months after initiation of ART.

5.5. Outcomes of treatment program

In this section, we predict the outcomes of various treatment programs on the HIV epidemic. We particularly focus on single group and multiple group treatment programs. For the purpose of demonstration, we presented our simulation for the treatment rate from 0 to 1 per year. However, our simulation can be easily extended beyond to higher treatment rates. For longer term, our qualitative results do not change.

5.5.1. Single group treatment program

We estimated the total new infections generated during the five year period from 2015 to 2020 as a function of treatment rates τ_1, τ_2, τ_3 (Fig. 4), implemented one at a time (single group). Note that in our model, the treatment rate τ_i, $(i = 1, 2, 3)$ per year means on average the individuals stay untreated for $1/\tau_i$ years during their lifespan in I_i class. As expected, the results show that treatment can reduce infections significantly. However, it is important to note that treatment (at the rate 1/year) at stage I can reduce the total number of new infections by 50% and 45% more than those at stage II and stage III, respectively. More importantly, treatment at stage I alone is more effective on reducing new infections than treatments at stages II and III combined (Fig. 4 a,b).

The effect of treatment on disease death is also remarkable. However, in contrast to the effect seen in preventing new infections, treatments at the different stages are not significantly different in preventing disease death during this 5 year period (Fig. 5a). Almost 30% of disease death can be reduced by implementing any

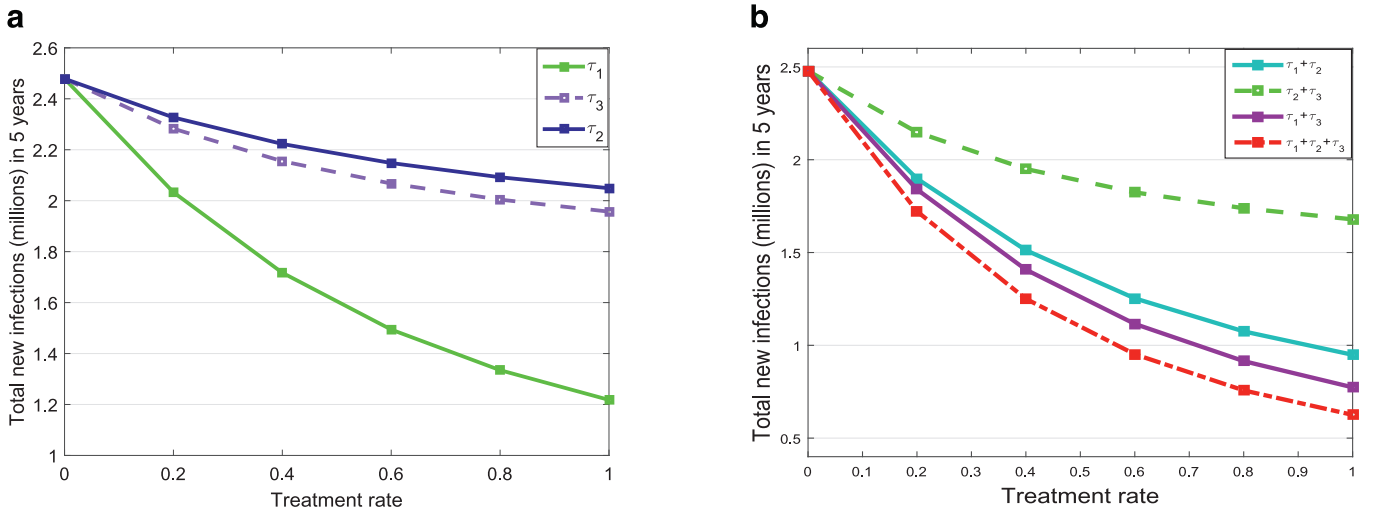

Fig. 4. Total new infections in a five year period (calculated as the integral of the total infection terms for five years) with (a) single group treatment program, (b) multi-group treatment program. The values of the parameters used for these graphs are listed in Table 4.

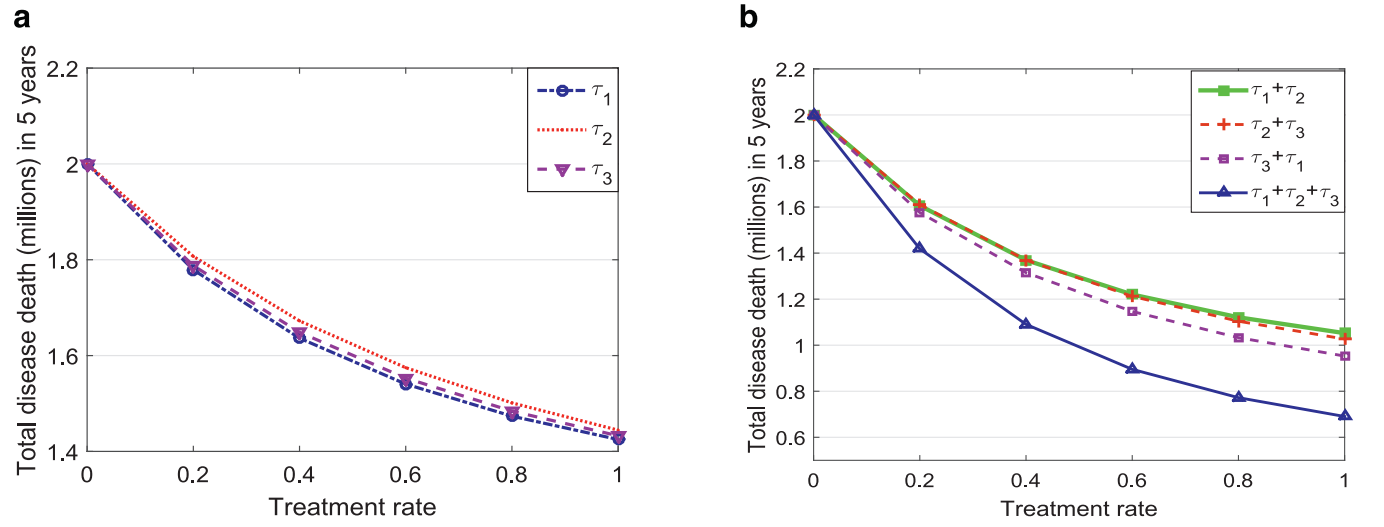

Fig. 5. Total AIDS death in a five year period (calculated as the integral of the total infection terms for five years) with (a) single group treatment program, (b) multi-group treatment program. The values of the parameters used for these graphs are listed in Table 4.

of the single group treatment programs (i.e. τ_1 or τ_2 or $\tau_3 = 1$). This result is important as it predicts that the early treatment strategy might not be significantly beneficial in preventing deaths.

The yearly death avoidance (YDA) (number of individuals' lives saved per year) increases as the treatment rate increases (Fig. 6a–d). The YDA also increases over time. In the first year, treatment at stage III has the highest YDA followed by treatment at stage II and stage I. After 3 years, however, a reverse order is observed, showing that the early treatment is beneficial in saving lives in a long run (or in the later part of the epidemic). On increasing treatment rates from 0.20 to 0.40 in any stage, the YDA can be increased by 1.5 fold in the 5th year (Fig. 6a, b). Similarly, an increase in treatment from 0.20 to 0.80 results in YDA twice as large in the 5th year (Fig. 6a, d).

We predict 10-year HIV prevalence under the single group treatment program. The prevalence can be reduced from 19% to 11%, 17% and 18% by treating individuals at stages I, II and III, respectively. These results show that treatment program at stage II and III are less effective compared to stage I, to reduce the prevalence. We also observe the similar effect on the basic reproduction number, $\Re_0$. Treatment at stage I can reduce R_0 as much as 66% (from 3.3 to 1.1) while there is negligible effect of treatments at stages II and III on $\Re_0$. Unfortunately, even with the rate up to 1/year, single group treatment programs do not bring $\Re_0$ below 1 indicating that it may be harder to eliminate the disease with the single group treatment program alone (Theorem 3.2).

We also carried out simulation study to identify whether the single disease treatment program is effective to maintain high level of the community-level immunity. Our results show that the high level immunity could reach up to 68%, 66%, and 53% in 5 years with treatment focused at stage I, stage II, and stage III, respectively. While early treatment (stage I) seems to maintain a higher level of community-level immunity, the benefit obtained with the early treatment does not seem significantly high.

5.5.2. Multi-group treatment program

We found that almost 80% of new infections can be reduced by universal treatment, i.e. by treating individuals in all stages (Fig. 4b), which is almost twice as much as that achieved from any single group treatment. Only 30% reduction of new infections can be achieved by treatment at both stages II and III combined. With treatment programs combining stages I and II, or stages I and III, the total new infections can be reduced by 60% and 68%, respectively.

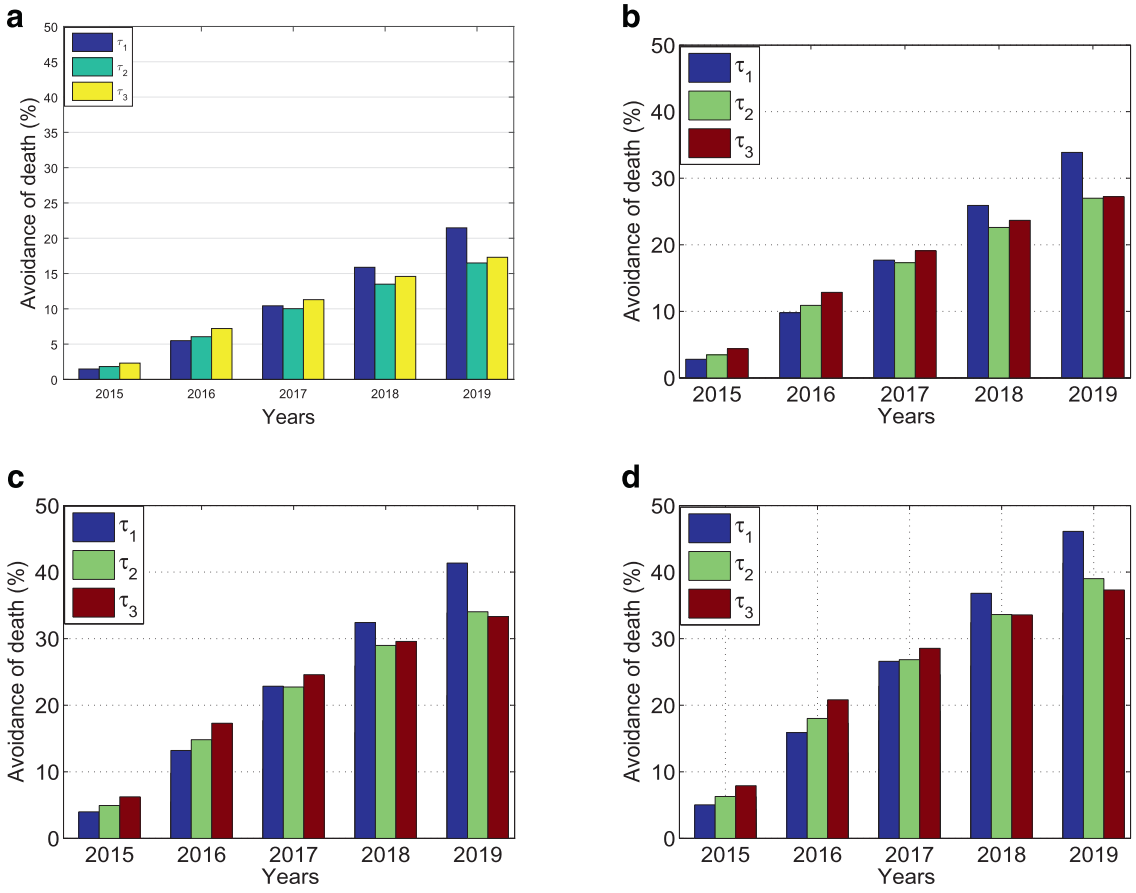

Fig. 6. Yearly death avoidance (YDA) by single group treatment program, (a) treatment rate 0.20, (b) treatment rate 0.40, (c) treatment rate 0.60, (d) treatment rate 0.80. The values of the parameters used for these graphs are listed in Table 4.

With a treatment program focused on any two stages combined, the disease death can be reduced by almost 50% in 5 years. In this case, the YDA can be achieved up to about 35% at 20% treatment level. When all the three stages are included in the treatment program (universal treatment) the disease death can be reduced by 65% in 5 years (Fig. 5b). This reduction is twice as much as that achieved from any single group treatment program (Fig. 5a,b). By increasing the universal treatment rate to 0.80 the YDA can be achieved up to 85% (Fig. 7d).

With universal treatment, HIV prevalence can be reduced from 19% to 11% in 10 years (Fig. 8b). The long term prevalence under the universal treatment program predicted by our model shows that at least 50 years are required to reduce the prevalence to below 5% (Fig. 8 c), indicating that treatment alone might not be an efficient way for reducing the current HIV prevalence in a relatively short time period.

We also computed $\Re_0$ under various treatment combinations. With treatment at stage II and stage III combined (i.e. $\tau_2 = \tau_3 = 1$), $\Re_0$ reduces from 3.30 to 2.67. The other treatment combinations (stage I and stage II or stage I and stage III, or stages I, II, and III) can reduce $\Re_0$ from 3.30 to 0.85 (Fig. 9b). Importantly, the multiple group treatment programs can reduce $\Re_0$ to below 1. However, to reduce R_0 to below 1, a high treatment rate is required (Fig. 9b). The region in treatment-parameter space where $\Re_0 < 1$ is shown in Fig. 10. Since treatment at stage II and stage III combined do not reduce $\Re_0$ to less than 1, we did not include this graph.

Compared to the single group treatment, with multi-group treatment programs, the community-level immunity can be significantly increased with the high level immunity reaching up to 83%, 75%, and 72% in 5 years with treatment combination at stages I and II, stages I and III, and stages II and III, respectively. Furthermore, with universal treatment, this level can be maintained at 90%.

6. Discussion

Studies show that early ART program can be a successful intervention for HIV transmission. However, appropriate initiation timing of ART still remains unclear. This study takes the modeling approach to examine the HIV infection dynamics under various treatment programs, including the one with early treatment. The model developed here is unique in the sense that it is based on CD4+ T cell count that plays an important role on disease progression, HIV transmission, and treatment decision, and is altered by ART. Our model has an excellent agreement with the HIV prevalence data from South Africa (Fig. 2). The model system is well-posed meaning the solution is bounded as well as non-negative for any non-negative initial values. Using model analysis, we showed that the disease free equilibrium is globally stable when $\Re_0 < 1$ and unstable when $\Re_0 > 1$. Moreover, the model showed the persistence of disease when $\Re_0 > 1$.

We used the model to evaluate benefits of treatment programs targeted to the populations at various CD4 count levels. For the model parameters related to South Africa, we found that early treatment (treatment at stage I) can reduce new infection by 2.5 folds more than from treatments at stage II and stage III (Fig. 4a,b). The treatment at stage I is also much more effective on reducing adult prevalence as well as $\Re_0$ compared to treatments at stage II

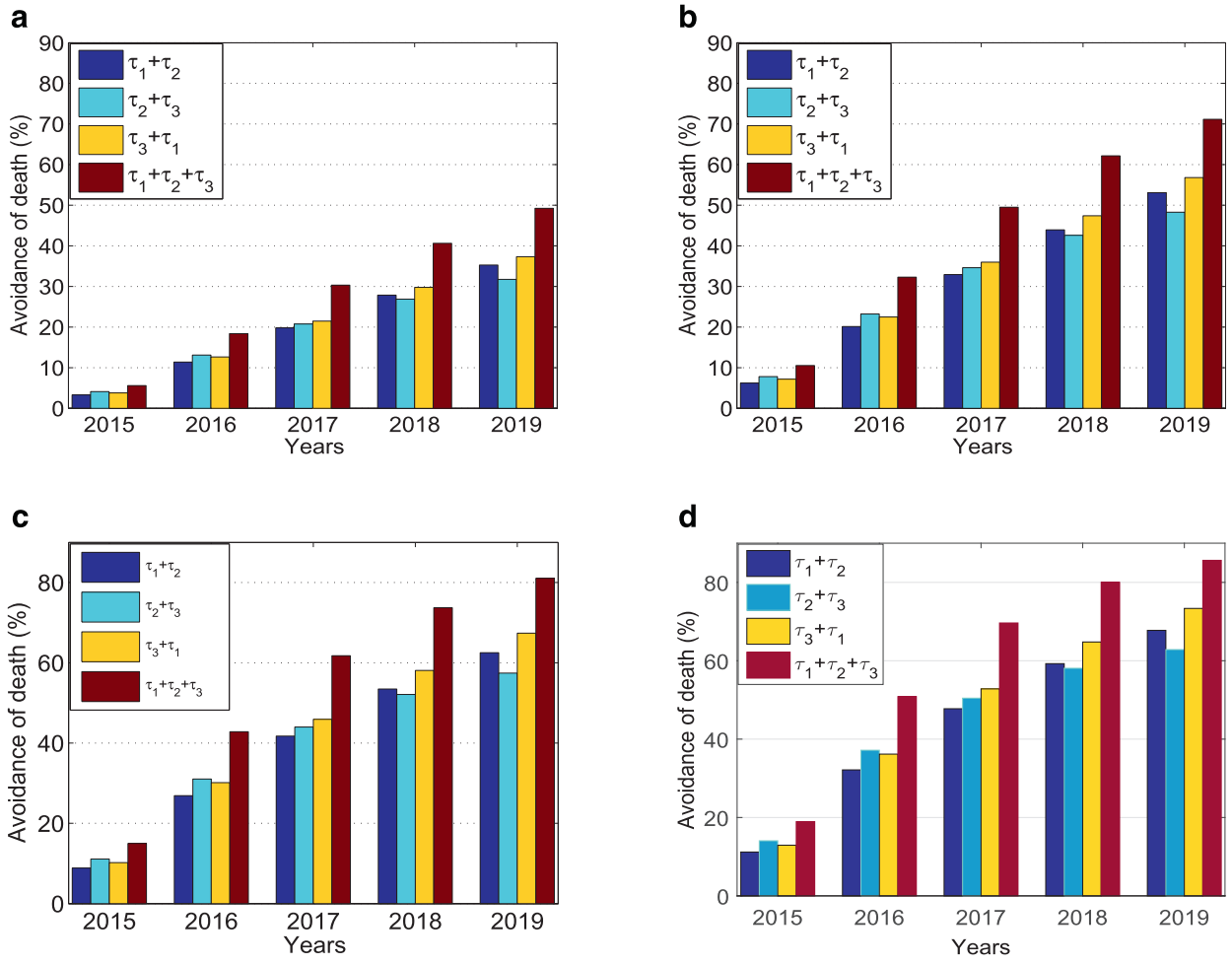

Fig. 7. Yearly death avoidance (YDA) by multi group treatment program, (a) treatment rate 0.20, (b) treatment rate 0.40, (c) treatment rate 0.60, (d) treatment rate 0.80. The values of the parameters used for these graphs are listed in Table 4.

and stage III. Our model predicts that the universal treatment program at rate 0.5/year can reduce the prevalence to less than 3% in 50 years (Fig. 8,c), consistent with a previous study [18], which shows that the universal testing with immediate ART can reduce the prevalence to below 1% in 50 years.

The total disease death decreases in the same manner during the five-year treatment duration for any choice of treatment programs (Fig. 5). However, treatment at stage III is more effective on avoiding deaths in the beginning of the treatment program while the treatment at stage I is more effective on avoiding deaths in the later part of the treatment program (Fig. 6). Since the disease death is higher in stage III, treatment at stage III can save more lives at the beginning of the treatment program. The treatment at stage I causes delay for individuals to progress to the stage III, eventually saving more lives in the long run (i.e., during the later part of the program).

The universal treatment program provides more benefits than the single group or the two groups treatment programs of reducing new infections, disease death, prevalence as well as $\Re_0$ (Fig. 4). Moreover, our model simulations evaluating community-based immunity show that compared to any other treatment programs, the universal treatment program is most effective maintaining about 90% of the infected population with the high level of immunity. Having higher community-level immunity is important for proper management of infectious diseases, including opportunistic diseases.

While the treatment has significant effects on HIV transmission and prevalence, it may not be able to eliminate the disease unless extremely high treatment rate is implemented. Since, this high coverage of ART is highly unlikely, elimination of disease may require additional intervention programs (for example, condom promotion).

While our model (2.1) captures some vital aspect of HIV dynamics under treatment, the model has several limitations. First, the model does not distinguish population by sexes. Second, the model does not address the issues of adherence of ART and the drug resistance. If a patient misses his/her ART doses and/or drug resistance arises, our results may be altered. Third, the model does not distinguish individuals with known and unknown status and assumes that once an individual is HIV positive, he/she is able to begin ART if he/she belongs to the treatment target group. Fourth, as the results of the model depend on the model parameters, uncertainties involved in parameter estimation could affect the results. Finally, this study assumed only the CD4+ T cell count as a marker for disease progression. However, overall immunity can be beyond the CD4 count as the multiple markers of disease progression have been investigated and considered for clinical practices [14,19,25]. For example, HIV RNA level, total lymphocyte count (TLC), psychosocial factors, and chronic immune activation can also be potential markers for the HIV disease progression [14,19]. Including other markers in categorization of the population under investigation could improve the disease dynamics models.

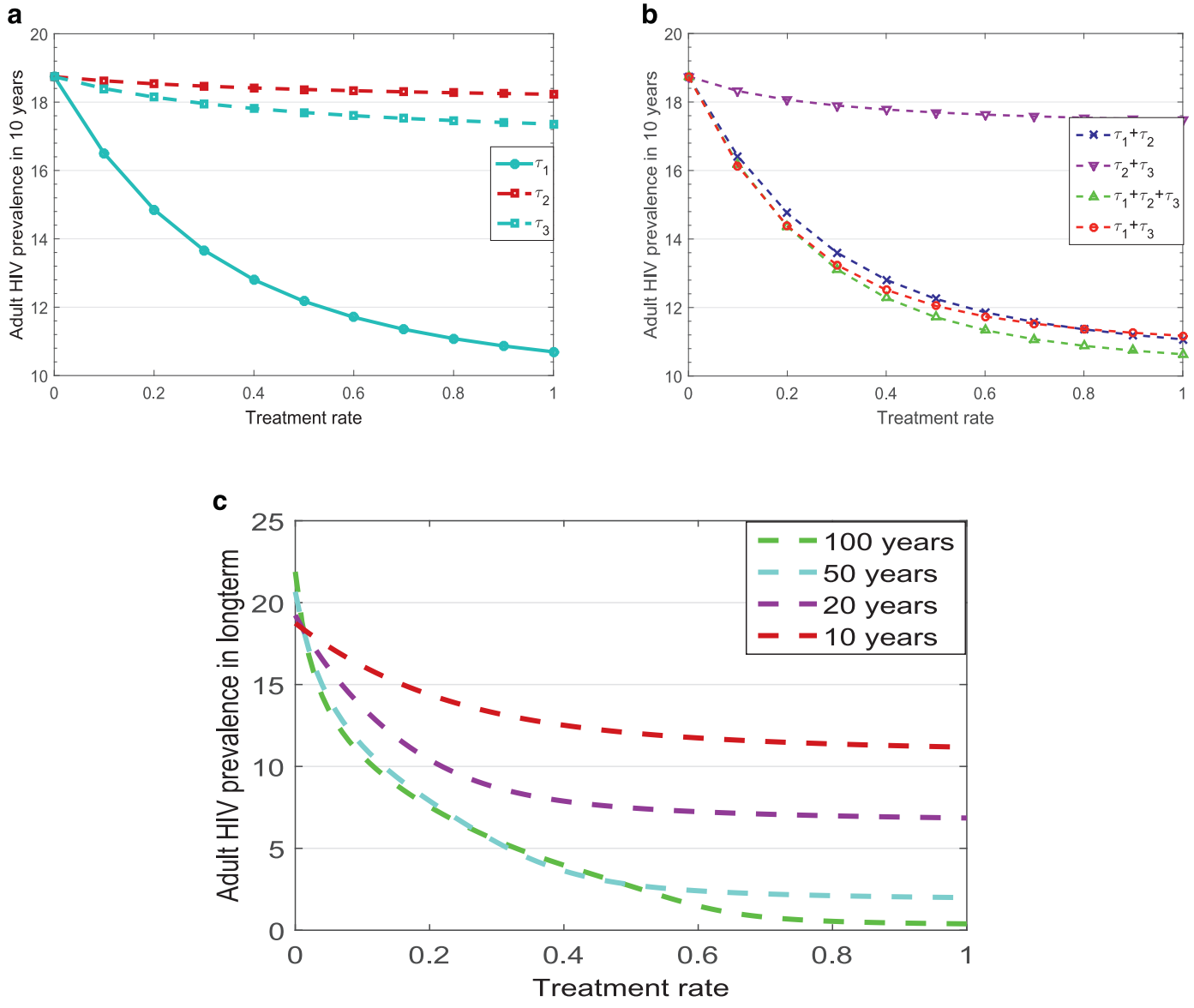

Fig. 8. Model prediction of HIV prevalence under treatment program; (a) prevalence after 10 years with single group treatment program, (b) prevalence after 10 years with multi-group treatment program, (c) long term projections with universal treatment program. The values of the parameters used for these graphs are listed in Table 4.

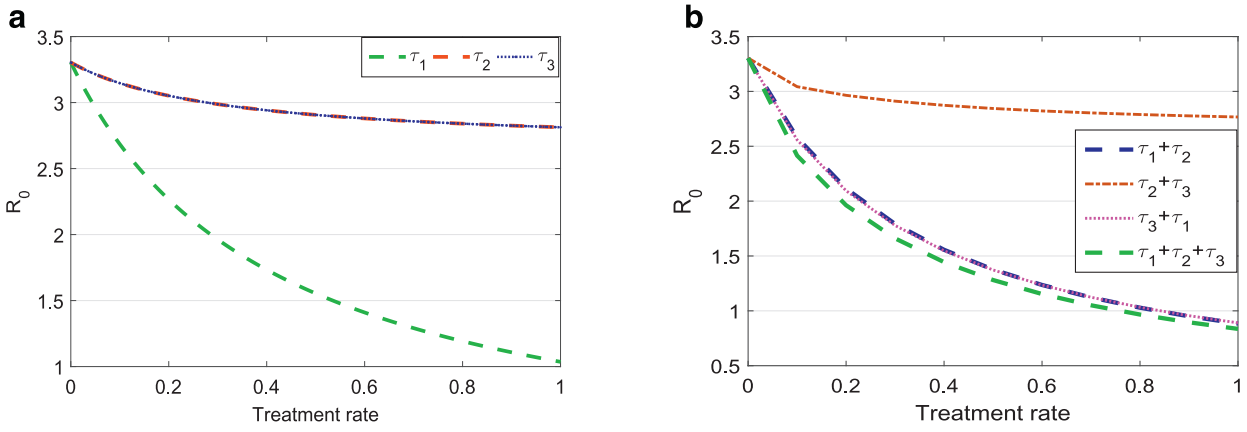

Fig. 9. $\Re_0$ vs. treatment rates, (a) single group treatment program, (b) multi-group treatment program. The values of the parameters used for these graphs are listed in Table 4.

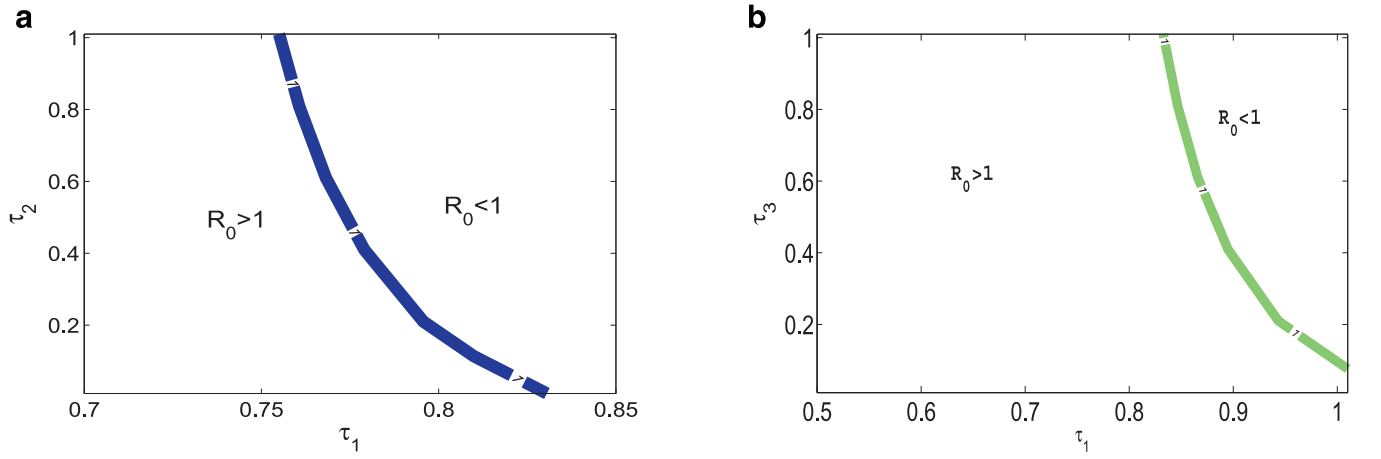

Fig. 10. Region where $\Re_0 < 1$ and $\Re_0 > 1$ (a) in $\tau_1 - \tau_2$ parameter space, (b) in $\tau_1 - \tau_3$ parameter space. The values of the parameters used for these graphs are listed in Table 4.

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