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AN IMMUNITY BASED HIV MODEL TO ILLUSTRATE IMPACT OF EARLY TREATMENT PROGRAM

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ABSTRACT:

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.

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. 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. 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. Similarly, a community based cross-sectional study in South Africa estimated about 71.8% reduction of annual risk of HIV transmission with early ART. This risk reduction is mainly attributable to the low-level viral load in successfully treated individuals . Some experimental results, however, found that ART could escalate HIV incidence and may worsen the spread of HIV in some cases. 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.

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

2. PRELIMINAY CONCEPTS

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 . 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 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.

We consider a homogeneous sexually active (age 15-49 years) population and divide them into seven groups: a susceptible group, S, three infected groups (categorized based on CD4+ T cell count) without treatment, I1, I2, I3 and three infected groups (categorized based on CD4+ T cell count) with treatment, T1, T2, T3. The transmission dynamics are as follows: a susceptible individual moves to the compartment I1 when he/she comes in successful contact with individual from any of the infected compartments. The individuals of I1 either get treatment and move to T1 at the rate of $\tau 1$ or they move to I2 compartment (due to their CD4+ T cell count declines) at the rate of $\delta 1$. Similarly, individuals move from compartment I2 to T2 at the rate of $\tau 2$ (treatment) or to I3 at the rate of $\delta 2$ (CD4+ T cell decline). The individuals in compartment I3 get treatment and move to T3 at the rate of $\tau 3$. Treated individuals gain CD4+ T cell count and move from T3 to T2 and from T2 to T1 at rates $\rho 2$ and $\rho 1$, respectively. The individuals in stage I (I1 & T1) have the highest immunity and those in stage III (I3 & T3) 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. 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. Therefore, we take different transmission rates, $\beta 1$, $\beta 2$, and $\beta 3$ for I1, I2, and I3 compartments, respectively. Since the viral load of individuals in all treated compartments usually remains low with a low transmission probability. we do not distinguish infectivity of different compartments of treated groups, and take the same transmission rate β for all T1, T2, and T3.

$$S' = \Lambda - (\lambda + \mu 0)\, S$$
$$I'1 = \lambda S - (\tau 1 + \delta 1 + \mu 2)\, I1$$
$$I'2 = \delta 1 I1 - (\tau 2 + \delta 2 + \mu 4)\, I2$$
$$I'3 = \delta 2 I2 - (\tau 3 + \mu 6)\, I3$$
$$T'1 = \tau 1 I1 + \rho 1 T2 - \mu 1 T1$$
$$T'2 = \tau 2 I2 + \rho 2 T3 - (\rho 1 + \mu 3)\, T2$$
$$T'3 = \tau 3 I3 - (\rho 2 + \mu 5)\, T3$$

where the force of infection, λ, is given by

$$\lambda = \beta + \beta 2 + \beta 3$$

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

Table 1: Description of variables of model

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 amount<350-500
I_3	number of infected individuals with CD4+T cell count>350
T_1	number of treated individuals with CD4+T cell amount>500
T_2	number of treated individuals with CD4+T cell amount <350-500 T_3 number of treated individuals with CD4+T cell count>350
N	total number of individual

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,,….,6)
a	rate associated with reduction of incidence due to beha vioral changes

The model has seven coupled equations. Following 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
$N^{\cdot} \leq \Lambda - \mu N$
$\mu = \min\{\mu 0, \mu 1, \mu 2, \mu 3, \mu 4, \mu 5, \mu 6\}$.
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
$\Gamma = \{(S, I1, I2, I3, T1, T2, T3) : S, I1, I2, I3, T1, T2, T3 \geq 0, N \leq \Lambda/\mu\}$ . .

Basic reproduction number

The basic reproduction number, denoted by R0, of a model is defined as the total number of secondary infections caused by a typical infected individual in a completely susceptible population. Using the next generation matrix approach, the new infection and the transfer matrices of our model are given by
$\alpha 1 = \tau 1 + \delta 1 + \mu 2$, $\alpha 2 = \tau 2 + \delta 2 + \mu 4$, $\alpha 3 = \tau 3 + \mu 6$, $\alpha 4 = \mu 1$, $\alpha 5 = \rho 1 + \mu 3$, $\alpha 6 = \rho 2 + \mu 5$.

Stability analysis

The model (2.1) has a unique disease free equilibrium (DFE), $E0 = (\Lambda/\mu 0, 0, 0, 0, 0, 0, 0)$, 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 [48], it is easy to prove the following local stability result:

Theorem 3.1.

If $R0 < 1$, the DFE, E0, is locally asymptotic stable, and if $R0 > 1$, E0 is unstable.
We can further prove that, E0 is globally asymptotically stable: Theorem 3.2. If $R0 < 1$, the DFE, E0, is globally asymptotically stable. Proof Let us consider the auxiliary function
$L = c1I1 + c2I2 + c3I3 + c4T1 + c5T2 + c6T3$,
where ci, 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
previous studies [6, 8] 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 $\mu 5 = 0.1752$.

The population corresponding to the year 1990 is taken as the initial value as the data begins at the year 1990. According to Day et al and Dorrington et al., 37.08 million people lived in South Africa in 1990, among which 45% were adult (15-49 years). Using HIV prevalence data and CD4+ T cell count distribution among HIV positive individuals we calculated the initial population for our model to be S(0) = 17.94 million, I1(0) = 0.0163 million, I2(0) = 0.009 million, and I3(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.

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. Following the previous studies. We estimated the mortality rates of the individuals in the different compartments as $\mu 0 = 0.0288$, $\mu 2 = 0.0888$, $\mu 4 = 0.3168$, $\mu 6 = 0.1368$, $\mu 1 = 0.0408$, $\mu 3 = 0.0528$ and $\mu 5 = 0.1752$.

HIV infected individuals, if remained untreated , are highly infectious during the first few months. Then the infectivity declines and remains low during the asymptotic period for about 6-7 years, followed by an increase to higher level during stage III. To represent these different infectiousness for I1 ,I2, I3, we set $\beta 1 = m1\ \beta 2$, $\beta 3 = m2\ \beta 2$, and estimate the constants m1,m2. 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%. 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.

The population [9, 3] corresponding to the year 1990 is taken as the initial value as the data begins at the year 1990. According to Day et al. [17] and Dorrington et al. [19], 37.08 million people lived in South Africa in 1990, among which 45% were adult (15-49 years). Using HIV prevalence data [53] and CD4+ T cell count distribution among HIV positive individuals [5] we calculated the initial population for our model to be S(0) = 17.94 million, I1(0) = 0.0163 million, I2(0) = 0.009 million, and I3(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 $\delta 1$, $\delta 2$, $\rho 1$, $\rho 2$, $\tau 3$, m1, m2, a, and $\beta 2$. 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

$$E = \sum_{i=231=1} (I1(ti)+I2(ti)+I3(ti)+T1(ti)+T2(ti)+T3(ti)N(ti)\times 100-P(ti))2$$

where I1(ti), I2(ti), I3(ti), T1(ti), T2(ti), T3(ti), N(ti) are numerically computed model solutions at time ti and P(ti) is the HIV prevalence data at time ti

5. RESULTS

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

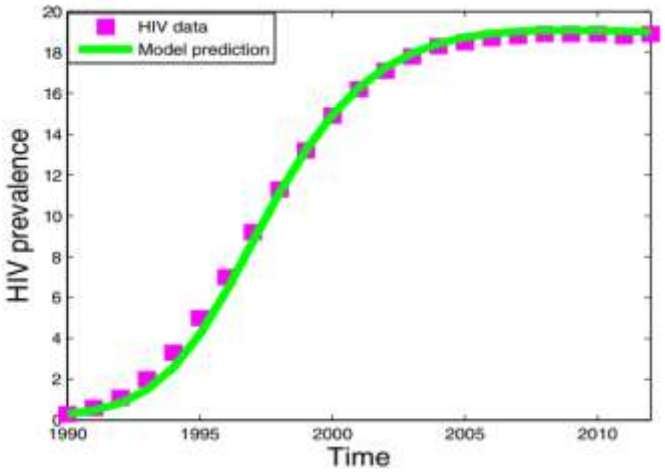

Figure 2: Data fitting result. The solid green curve shows the yearly adult prevalence of HIV infections predicted by the model and squares are the data (Table 3).

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 (I1 & T1) 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 (Figure 3). These estimates thus show the significant effect of recovery of CD4+ T cells on immunity levels.

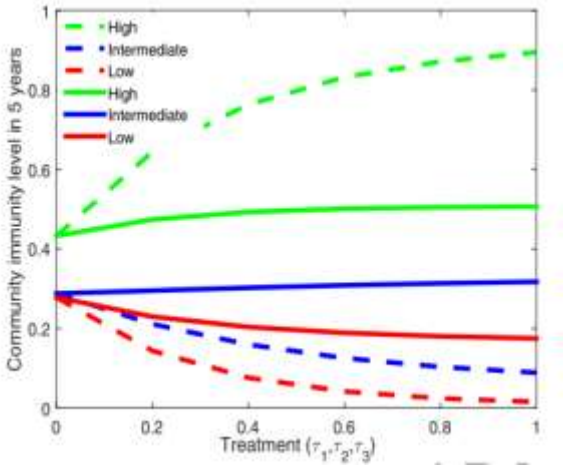

Figure 3: Community-level immunity in 5 years under treatment program. Solid curves show the immunity levels predicted by the model that ignores recovery of CD4+ T cells and dashed curves show the prediction of our model. The values of the parameters used for this graph are listed.

5.3. HIV transmission

Our estimates show that the value of m1 and m2 are 12.57 and 4.54 indicating $\beta 1$ is about 13 times higher and $\beta 3$ is about 5 times higher than $\beta 2$. These estimates are consistent with the experimental results

which found m1 between 7 and 26 and m2 between 2 and 6. 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. 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 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.

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