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INCREASING SURVIVAL TIME DECREASES THE COST-EFFECTIVENESS OF USING "TEST & TREAT" TO ELIMINATE HIV EPIDEMICS

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Abstract. Treating HIV-infected individuals reduces their viral load, consequently increasing their survival time and decreasing their infectivity. It has been proposed that universal testing and treatment (i.e., universal "test & treat") could lead to HIV elimination and would be extremely cost-effective. It is now being debated whether to use a universal "test and treat" approach in the "real-world" as a prevention strategy to control HIV epidemics. However current modeling predictions of the impact, and cost-effectiveness, of universal "test & treat" strategies are based on an unrealistically short survival time for treated individuals. Here we use mathematical modeling and a longer, more realistic, survival time. We model the potential impact of a universal "test & treat" strategy in South Africa. Our results show that increasing the length of the survival time on treatment, although beneficial to individuals, reduces the probability of eliminating HIV and decreases the cost-effectiveness of using universal "test & treat" strategies. Therefore our results show that individual-level benefits and public health benefits will conflict when using "test & treat" strategies to reduce HIV transmission.

1. **Introduction.** Treating HIV-infected individuals reduces their viral load, consequently increasing their survival time and decreasing their infectivity. Hence treatment has both a therapeutic and preventative impact; but currently it is only used for therapeutic purposes. It was predicted over a decade ago, in a modeling study by Blower et al. that the widespread treatment in San Francisco (that was occurring for therapeutic purposes) would substantially reduce HIV incidence rates in that city over the next 10 years [1]. Empirical data has shown this occurred [6]. Based on this modeling, Blower and Farmer argued that treatment should be considered as an HIV prevention tool (albeit as an unconventional tool) because of their effect on reducing transmission [2]. In 2003 Velasco-Hernandez and colleagues were the first to propose that treatment could potentially be used to eliminate HIV epidemics [24]. Their modeling showed that it was theoretically possible that treatment could eliminate an HIV epidemic, but it was only likely to occur if there were also substantial reductions in risk behavior [24]. More recently, Granich and colleagues

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at the World Health Organization (WHO) have used modeling to predict the impact of treatment on reducing the HIV epidemic in South Africa; we subsequently refer to this model as the WHO model [14, 27]. Granich et al. concluded that universal testing and treatment (i.e., "test & treat") could - within a decade - lead to HIV elimination and would be extremely cost-effective. It is now being debated whether to use a universal "test and treat" approach in the "real-world" as a prevention strategy to control HIV epidemics [14, 4, 7, 10, 13, 18, 20]. However the WHO's modeling predictions are based on unrealistically short survival times for treated individuals [14, 27]. Here we show that increasing the length of the survival time on treatment, although beneficial to individuals, decreases the cost-effectiveness of using "test & treat" to eliminate HIV epidemics.

We investigate, as did Granich et al. at the WHO in their original [14] and their subsequent analyses [15], the impact and cost-effectiveness of a universal "test & treat" strategy in South Africa. This strategy is based on annual HIV testing for the entire South African population ($\approx$ 30 million adults aged between 15 and 49 years) and providing immediate treatment for all HIV-infected adults regardless of their CD4 cell count (i.e., their need for treatment). Currently, in resource-constrained countries HIV-infected individuals are not eligible for treatment until their CD4 cell count has reached a threshold of 350 cells/μL; this generally occurs 5-7 years after infection. Under a "test & treat" strategy all HIV-infected individuals are eligible for treatment regardless of their CD4 cell count. In South Africa 20% of the adult population are infected with HIV. Consequently, under a "test and treat" strategy 5 million adults would need treatment; currently only $\approx$ 1 million adults are receiving treatment and this is for therapeutic purposes.

Previously we have developed a transmission model that, like the WHO model [14], specifies the transmission dynamics of an HIV epidemic driven by heterosexual transmission [27]. However in contrast to the WHO's model [14, 15], our model includes a more realistic representation of the natural history of HIV infection. In addition, our model includes the development (under treatment) and subsequent transmission of drug-resistant strains of HIV; the WHO model is based on the implicit assumption that treated individuals would not develop drug resistance. We have described our model in detail previously [27]. We have also validated our model using historical prevalence data [21, 22]. Here, in order to directly compare our results with those of the WHO, we use a simplified version of our published model. Specifically we remove the components relating to the development and transmission of resistance. To investigate the effect of increasing the length of the survival time on treatment on the cost-effectiveness of a universal "test & treat" strategy we compared the survival time used by the WHO in their modeling study with a longer more realistic survival time based on clinical data. The WHO assumed, as did Dodd et al. in a different modeling study [7], the survival time of a treated individual once they have reached the current treatment initiation threshold (i.e., once their CD4 cell count has fallen to 350 cells/μL) is only $\approx$ 6 years longer than the survival time of an untreated individual with a CD4 count of 350 cells/μL [14, 15]. However, clinical data show this survival time on treatment is unrealistically short; HIV-infected individuals who begin treatment at the current treatment initiation threshold can survive for several decades [19]. In our analyses we refer to the survival time used by the WHO [14, 15] and Dodd et al. [9] as the short survival time. Based on clinical data we assumed treated individuals have a 60% chance of surviving an additional 20 years or more after their CD4 cell count

has fallen to 350 cells/μL [19]. We refer to this survival time as the long survival time.

2. **Structure of transmission model.** Our transmission mode [27] includes three stages: primary infection, asymptomatic with a CD4 count above 350 cells/μL and symptomatic with a CD4 count below 350 cells/μL. A flow diagram of our model is shown in Figure 1.

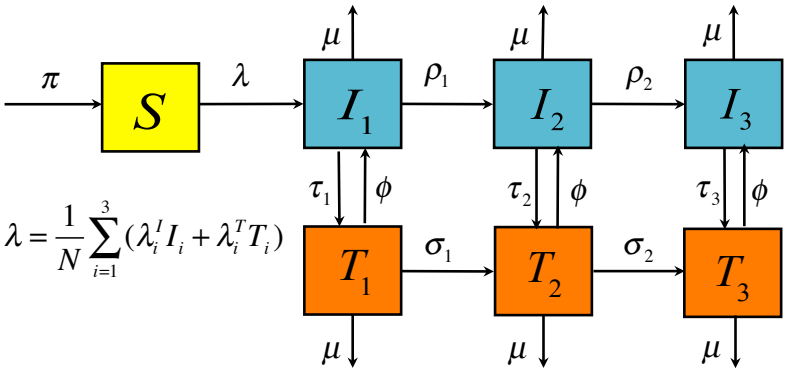

FIGURE 1. Flow diagram for the HIV treatment model specified by equations 1-7. Individuals enter the sexually active population at a rate π and leave the sexually active population at a per capita rate μ. The S class represents susceptible individuals, I_j represent individuals who are infected with HIV and untreated, while the T_j class represents HIV-infected individuals who are on treatment. Individuals in class I_j are treated at a per capita rate τ_j and subsequently give up treatment at a per capita rate ϕ. The parameters λ_j^T and λ_j^T represent the transmission rates respectively for treated and untreated individuals in the j-th class, and N is the size of the sexually active population.

We model viral loads to be highest in primary infection, lower in the asymptomatic stage and to increase again in the symptomatic stage; viral load determines infectivity at each stage of infection [16]. We assume HIV-infected individuals spend $\approx$ 2 months in primary infection, $\approx$ 7.5 years in the asymptomatic stage and $\approx$ 3.5 years in the symptomatic stage [27]. In contrast, the natural infection of HIV in the WHO model has four stages [14, 15]. They assume that HIV-infected individuals have the same infectivity (i.e., viral load), and also spend the same amount of time ($\approx$ 2.75 years), in each of the four stages. Following the WHO model [14], our model is deterministic and based on the following assumptions: (i) individuals can only become infected with HIV through sexual transmission (vertical transmission is not included); (ii) the probability/risk of male-to-female transmission is equal to the probability/risk of female-to-male transmission; (iii) HIV-infected individuals can be treated in any of the three stages; (iv) the model is homogeneous (i.e., every individual in the model is assumed to be at the same risk for acquiring HIV

regardless of their gender, age and/or level of sexual activity) and (v) the earlier an individual receives treatment the longer they will survive.

The model that we use in this current analysis (which is a simplified version of a model we have previously published [27]) is specified by the following seven equations:

$$\frac{dS}{dt} = \pi - \sum_{i=1}^{3}(\lambda_i^I I_i + \lambda_i^T T_i)\frac{S}{N} - \mu S \tag{1}$$

$$\frac{dI_1}{dt} = \sum_{i=1}^{3}(\lambda_i^I I_i + \lambda_i^T T_i)\frac{S}{N} + \phi T_1 - (\tau_1 + \rho_1 + \mu)I_1 \tag{2}$$

$$\frac{dI_2}{dt} = \rho_1 I_1 + \phi T_2 - (\tau_2 + \rho_2 + \mu)I_2 \tag{3}$$

$$\frac{dI_3}{dt} = \rho_2 I_2 + \phi T_3 - (\tau_3 + \rho_3 + \mu)I_3 \tag{4}$$

$$\frac{dT_1}{dt} = \tau_1 I_1 - (\phi + \sigma_1 + \mu)T_1 \tag{5}$$

$$\frac{dT_2}{dt} = \tau_2 I_2 + \sigma_1 T_1 - (\phi + \sigma_2 + \mu)T_2 \tag{6}$$

$$\frac{dT_3}{dt} = \tau_3 I_3 + \sigma_2 T_2 - (\phi + \sigma_3 + \mu)T_3 \tag{7}$$

Individuals join the sexually active population at a rate π and leave the sexually active population at a per capita rate μ.

The S class represents susceptible individuals, the I_i class represents individuals who are infected with HIV and not on treatment and the T_i class represents HIV-infected individuals on treatment. Subscripts (i) indicate untreated and treated HIV-infected individuals in the primary stage of infection ($i = 1$), asymptomatic stage with a CD4 count above 350 cells/μL ($i = 2$), and symptomatic stage with a CD4 count below 350 cells/μL ($i = 3$). Individuals in class I_i are treated at a per capita rate τ_i and subsequently give up treatment at a per capita rate ϕ. The parameters λ_i^I and λ_i^T represent the transmission rates respectively for treated and untreated individuals in the i-th class by the equations $\lambda_i^I = c\beta_i^I$ and $\lambda_i^T = c\beta_i^T$; where c is the average number of new sex partners per individual per year, and β_i^I and β_i^T are the per-partnership probability of transmitting HIV for untreated and treated individuals, respectively. N is the size of the sexually active population. Treated and untreated HIV-infected individuals in the i-th stage of infection progress to the next stage of infection at respective rates ρ_i and σ_i. Parameter descriptions and values are provided in Table 1.

3. **Reproduction numbers.**

The concept of the Basic Reproduction Number (R_0) is used to characterize infectious disease dynamics [8]. R_0 is defined as the average number of new infections one infected individual generates during their lifetime; assuming the entire population is susceptible and no biomedical and/or behavioral interventions are in place. Given that R_0 is greater than one, an epidemic can be expected to occur. The Control Reproduction Number (R_C) is similar to R_0 however it is calculated based on the assumption that biomedical and/or behavioral interventions are available. If interventions can reduce the value of R_C to below one it can be concluded that - theoretically - it is possible to eliminate the

TABLE 1. Model parameters with descriptions and values.

Parameter	Description	Value
π	Rate of joining the sexually active population	$582,000$ yr^{-1}
$e^{-50\mu}$	Probability of an HIV-negative individual surviving 50 years or more	70%
$1/\rho_1$	Mean duration: primary infection I_1	2 months
$1/\rho_2$	Mean duration: chronic infection I_2	7.3 years
$1/\rho_3$	Mean duration: symptomatic infection I_3	3.5 years
$1-e^{-\phi}$	Probability of interrupting treatment per year	2%
τ_i	Per capita treatment rate: infection stage I_i	1.0 yr^{-1}
$1/\sigma_1$	Mean duration of treamtent in stage T_1	2 months
$\frac{1}{\sigma_2}+\frac{1}{(\rho_2+\tau_2)}-\frac{1}{\rho_2}$	Mean life-years gained through early treratment versus treatment at 350 cells/μL	6 years
$e^{\sigma_3(t+\rho_3-1/(\rho_3+\tau_3))}$	Probability of gaining more than $t=6$ or 20 years of addition life, if treatment is inititated at 350 cells/μL	62%
λ_1^I	Transmission rate: primary infection I_1	0.51 yr^{-1}
λ_2^I	Transmission rate: chronic infection I_2	0.11 yr^{-1}
λ_3^I	Transmission rate: symptomatic infection I_3	0.15 yr^{-1}
ζ	Reduction in infectivity due to treatment	86%
λ_i^T	Transmission rate: treatment stage T_i	$(1-\zeta)\lambda_i^I$

disease. We computed the R_0 for the transmission model in the absence of treatment (i.e., for the model specified by equations (1) through (4) setting $\tau_i = 0$ and $\lambda_i^T = 0$ for $i = 1, 2, 3$). We calculated R_0 (analytically) as the spectral radius (i.e., maximum modulus of the eigenvalues) of the next generation matrix FV^{-1} [8, 23],

where F and V are given by the following expressions:

$$F = \begin{bmatrix} \lambda_1^I & \lambda_2^I & \lambda_3^I \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \rho_1 + \mu & 0 & 0 \\ -\rho_1 & \rho_2 + \mu & 0 \\ 0 & -\rho_2 & \rho_3 + \mu \end{bmatrix}.$$

Note that FV^{-1} has only one nonzero eigenvalue with corresponding eigenvector $e_1 = [1, 0, 0, 0]^T$. R_0 may be straightforwardly expressed as:

$$R_0 = \frac{\lambda_1^I}{\rho_1 + \mu} + \frac{\lambda_2^I \rho_1}{(\rho_1 + \mu)(\rho_2 + \mu)} + \frac{\lambda_3^I \rho_1 \rho_2}{(\rho_1 + \mu)(\rho_2 + \mu)(\rho_3 + \mu)}$$

R_0 can be understood biological as the sum of several Basic Reproduction Numbers where each term in the summation specifies the Basic Reproduction Number for each infected stage I_i weighted by the probability that an individual progresses to this stage before dying. Previously, we have derived an expression for the Control Reproduction Number (R_C) [27]:

$$R_C = L_1 + L_2 + L_3$$

R_C can be understood biological as the sum of several Control Reproduction Numbers where L_i specifies the Control Reproduction Number for each infected stage I_i and T_i weighted by the probability that an individual progresses to these stages before dying. The L_i are given as follows:

$$\begin{aligned}
L_1 &= r_1^{II}\alpha_1^I + r_1^{IT}\alpha_1^T \\
L_2 &= r_1^{II}\left(\frac{\rho_1}{\tau_1 + \rho_1 + \mu}\right)\left(r_2^{II}\alpha_2^I + r_2^{IT}\alpha_2^T\right) \\
&\quad + \; r_2^{IT}\left(\frac{\sigma_1}{\phi + \sigma_1 + \mu}\right)\left(r_2^{TI}\;\alpha_2^I + r_2^{TT}\alpha_2^T\right) \\
L_3 &= r_1^{IT}\left(\frac{\sigma_1}{\phi + \sigma_1 + \mu}\right) r_2^{TI}\left(\frac{\rho_2}{\tau_2 + \rho_2 + \mu}\right)\left(r_3^{II}\alpha_3^I + r_3^{II}\alpha_3^T\right) \\
&\quad + r_1^{II}\left(\frac{\rho_1}{\tau_1 + \rho_1 + \mu}\right) r_2^{II}\left(\frac{\rho_2}{\tau_2 + \rho_2 + \mu}\right)\left(r_3^{II}\alpha_3^I + r_3^{IT}\alpha_3^T\right) \\
&\quad + r_1^{IT}\left(\frac{\sigma_1}{\phi + \sigma_1 + \mu}\right) r_2^{TT}\left(\frac{\sigma_2}{\phi + \sigma_2 + \mu}\right)\left(r_3^{TI}\alpha_3^I + r_3^{TT}\alpha_3^T\right) \\
&\quad + r_1^{II}\left(\frac{\rho_1}{\tau_1 + \rho_1 + \mu}\right) r_2^{IT}\left(\frac{\sigma_2}{\phi + \sigma_2 + \mu}\right)\left(r_3^{TI}\alpha_3^I + r_3^{TT}\alpha_3^T\right)
\end{aligned}$$

where,

$$\alpha_i^I = \frac{\lambda_i^I}{\tau_i + \rho_i + \mu}, \quad \alpha_i^T = \frac{\lambda_i^T}{\phi + \sigma_i + \mu}, \quad \text{for} \quad i = 1, 2, 3$$

and

$$\begin{aligned}
r_i^{TI} &= \left(\frac{\phi}{\phi + \sigma_i + \mu}\right)\sum_{k=0}^{\infty} g_i^k = \left(\frac{\phi}{\phi + \sigma_i + \mu}\right)\left(\frac{1}{1 - g_i}\right), \\
r_i^{IT} &= \left(\frac{\tau_i}{\tau_i + \rho_i + \mu}\right)\sum_{k=0}^{\infty} g_i^k = \left(\frac{\tau_i}{\tau_i + \rho_i + \mu}\right)\left(\frac{1}{1 - g_i}\right), \\
r_i^{II} &= r_i^{TT} = \sum_{k=0}^{\infty} g_i^k = \frac{1}{1 - g_i}, \quad \text{and} \quad g_i = \left(\frac{\tau_i}{\tau_i + \rho_i + \mu}\right)\left(\frac{\phi}{\phi + \sigma_i + \mu}\right)
\end{aligned}$$

The g_i terms give the probability that an individual in class I_i begins treatment and subsequently gives it up (or vice versa). Similarly, the r_i^{TI} represent the sum of the probabilities for all possible paths an individual may take from T_i to I_i by successively giving up and then resuming treatment (and vice versa r_i^{IT}).

4. **Using the Control Reproduction Number to determine if elimination is possible.** For both the long survival time on treatment and the short survival time on treatment we calculated the effect of a universal "test and treat" strategy on reducing the value of the R_C. To make these calculations we used a range of parameter values for: (i) the CD4 cell count level at which treatment is initiated (range: 100 cells/μL to 800 cells/μL) and (ii) the frequency at which the population is tested for HIV (range: 6 months to 4 years). For both survival times, we assumed there would be additional survival benefits for HIV-infected individuals who began treatment before their CD4 cell count fell to the current treatment initiation threshold of 350 cells/μL. Following the WHO [14, 15], we assumed that if individuals began treatment immediately after they became infected they could gain a maximum of 6 years before they reached the threshold. To make our calculations we also assumed that treatment, by reducing viral load, reduces infectivity by 86%. The recent HPTN 052 clinical trial has shown that treating the HIV-infected partner in a discordant couple reduces the probability of transmission by 96% [5]. However trial results are unlikely to be replicated in the "real-world" due to lower adherence to treatment, and because of other factors such as the presence of other sexually transmitted diseases. Consequently, we used a value of 86%. The remaining parameter values used to calculate R_C are given in the Legend for Figure 2.

Results of the R_C analysis are shown in the color-coded plots in Figure 2. Figure 2A is based on the long survival time and Figure 2B is based on the short survival time. Colors indicate the magnitude of the R_C at that particular pair of parameter values; dark blue is the lowest and dark red is the highest. In each plot the Y-axis shows the frequency (in years) of population-level HIV testing and the X-axis shows the treatment initiation threshold in terms of the CD4 cell count in cells/μL. The dotted black curve in each plot delimits the threshold at which R_C equals one; to the right of the line elimination is (theoretically) possible, and to the left of the line elimination is not possible.

It can be seen that under either survival time a universal "test & treat" strategy could (theoretically) lead to HIV elimination in South Africa (Figure 2). However it can also be seen that the length of the survival time on treatment has a significant impact on the probability of elimination using a "test & treat" strategy. The probability of elimination if treated individuals have a long survival time (Figure 2A) is considerable less than if treated individuals have a short survival time (Figure 2B). This can be seen as the area to the right of the dotted black line is considerably smaller in Figure 2A than in Figure 2B. The longer the survival time on treatment, the higher the treatment initiation threshold needs to be in order to achieve elimination and/or the more frequently the population would need to be tested (compare Figure 2A with Figure 2B). If a universal "test & treat" strategy based on annual testing is used, the treatment initiation threshold would need to be at least $\approx$ 625 cells/μL (using the long survival time) but only $\approx$ 400 cells/μL (using the short survival time) (Figure 2). Therefore the longer the survival time on treatment the earlier in the asymptomatic period that individuals will need to be put on treatment in order to eliminate HIV.

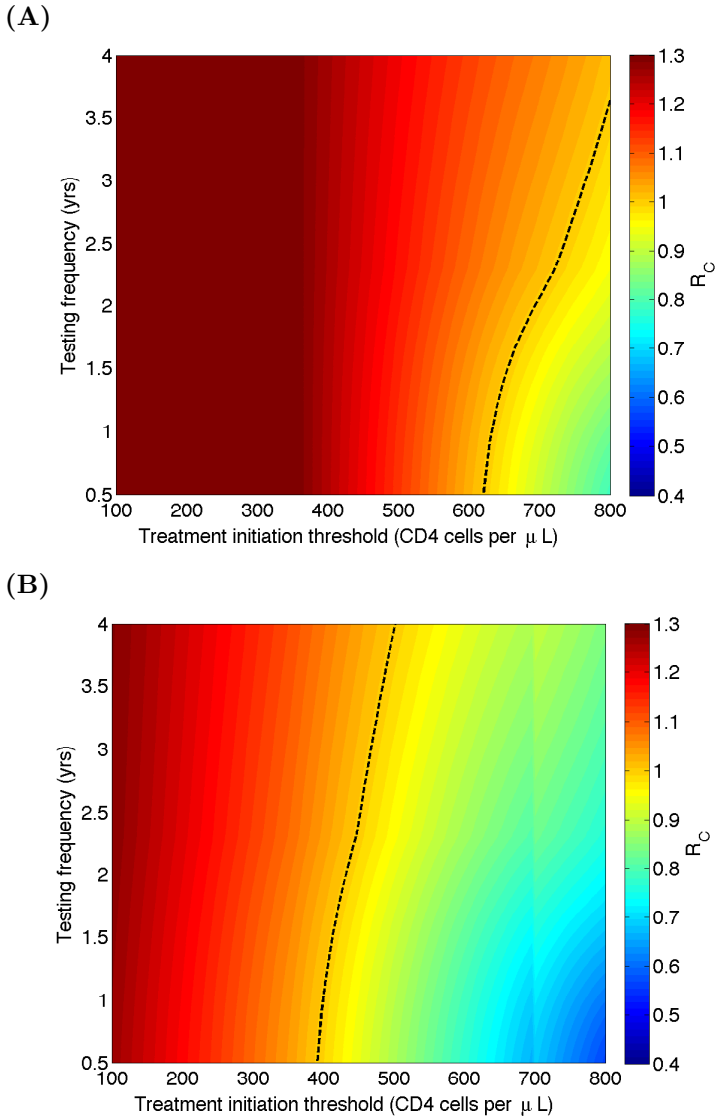

FIGURE 2. The Control Reproduction Number (R_C) is dependent on the average population-level testing frequency for HIV (years between tests) and the treatment initiation threshold in terms of the CD4 cell counts. The dashed black line corresponds to the threshold $R_C = 1$; below this threshold (i.e., $R_C < 1$) elimination is (theoretically) possible. The average treatment-induced reduction in infectivity is 86%. Panels represent the average additional life years that HIV-infected individuals gain through treatment initiated at a CD4 count of 350 cells/μL: **(A)** realistic survival time (25 additional years) and **(B)** short survival time (6 additional years).

5. **Using the transmission model to determine if elimination is possible.** An analysis of R_C does not provide any information on how long it would take to eliminate HIV. Previous modeling of using treatment to eliminate HIV has shown it could take 50 to 100 years [24]. In addition, an analysis of R_C does not provide any information as to: (i) how quickly incidence will be reduced, (ii) how many individuals will need to be treated and (iii) costs. Therefore we conducted numerical analyses of our transmission model. We used demographic and epidemiologic data from South Africa to parameterize our model; all model parameter values are given in the Legend of Figure 3. We simulated a "test & treat" strategy with annual testing and generated two scenarios: one using the short survival time and one using the long survival time. To determine if elimination had occurred we used the WHO definition of elimination: less than 1 new HIV infection occurring per thousand individuals per year [14, 9].

The predicted impact of an annual "test & treat" strategy on incidence in South Africa is shown in Figure 3. It can be seen that the shorter the survival time the greater the reduction in incidence; compare dotted blue line (short survival time) with the solid blue line (long survival time) in Figure 3A. If the survival time is short the incidence rate is almost at the elimination threshold after 40 years, ≈ 1.5 new HIV infections per 1,000 individuals, and continuing to decrease (dotted blue line in Figure 3A). If a long survival time is used, after 40 years, the incidence rate is twice as high, ≈ 3 new HIV infections per 1,000 individuals (solid blue line in Figure 3A). In both scenarios, as the result of the "test & treat" strategy, all of the HIV-infected individuals in the population are on treatment; consequently all of the transmission that is occurring is from these treated individuals. Therefore the longer the individuals survive on treatment, the lower and slower the reduction in incidence.

The numbers requiring treatment over 40 years for both survival time scenarios is shown in Figure 3B. The greater the survival time the more individuals require treatment and the longer they require it; compare dotted blue line (short survival time) with the solid blue line (long survival time) in Figure 3B. The results show that substantial differences occur very quickly in the number of individuals requiring treatment; and the difference between the two scenarios diverges considerably over time. After 40 years, ≈ 2.1 million individuals would need treatment if the survival time on treatment is short (dotted blue line in Figure 2B) versus ≈ 4.3 million (solid blue line in Figure 3B) if the survival time is long.

6. **How much would a "test & treat" strategy in South Africa cost?** We calculated treatment costs in United States (US) dollars. Following the WHO [15], we used annual per person treatment costs of $751 per year for first-line regimens and a discount rate of 3.5% per year.

Discounted annual (Figure 4A) and cumulative (Figure 4B) cost curves for South Africa were calculated using the model generated predictions for the numbers on treatment shown in Figure 3B. In Figure 4A and 4B the dotted blue line represents the scenario based on the short survival time, and the solid blue line represents the scenario based on the long survival time (Figure 4A and 4B). Not surprisingly, the longer the survival time the greater the annual, and cumulative, treatment costs. After 40 years the annual treatment costs of a universal "test & treat" strategy would be nearly twice as high, if the survival time was long than if the survival time was short (Figure 4A). Cumulative treatment costs are $\approx$ $78 billion (long survival

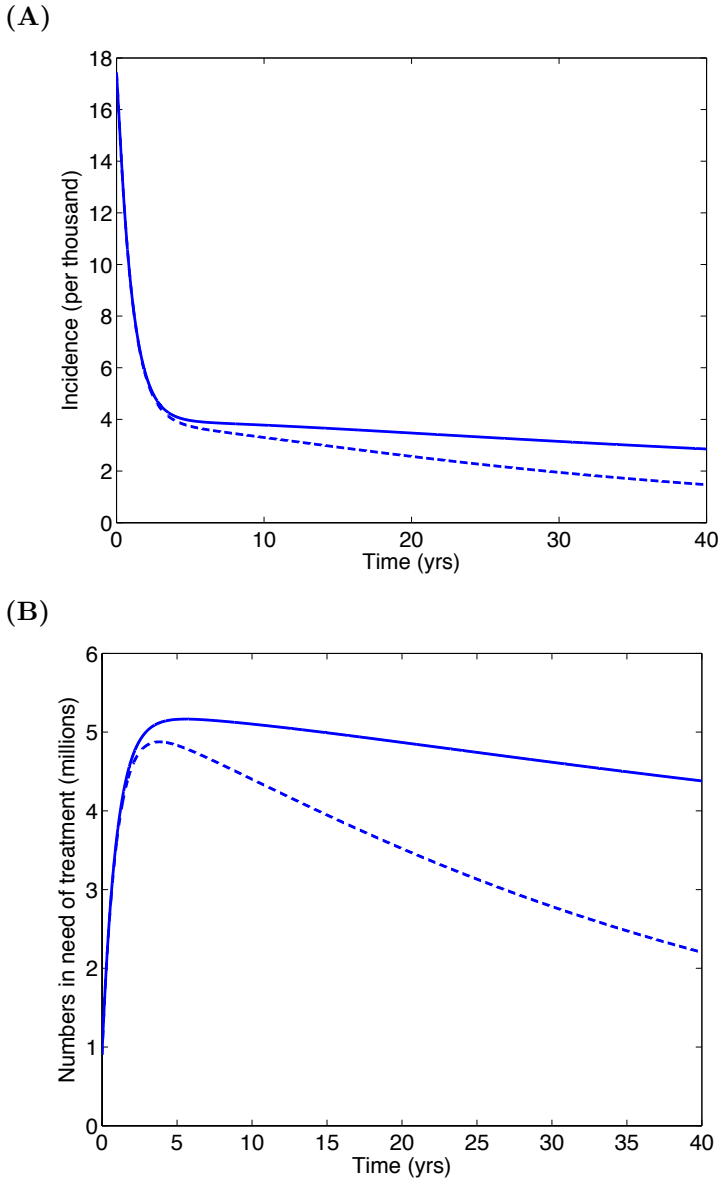

FIGURE 3. Predictions for South Africa generated from our transmission model if a universal "test & treat" (with annual testing) strategy is implemented and there is a 62% probability of surviving an additional 6 years (dashed curve) or 20 years (solid curve) when treatment is initiated at a CD4 count of 350 cells/μL. The average treatment-induced reduction in infectivity is 86%. Panels show **(A)** annual incidence over time and **(B)** number of individuals on treatment over time.

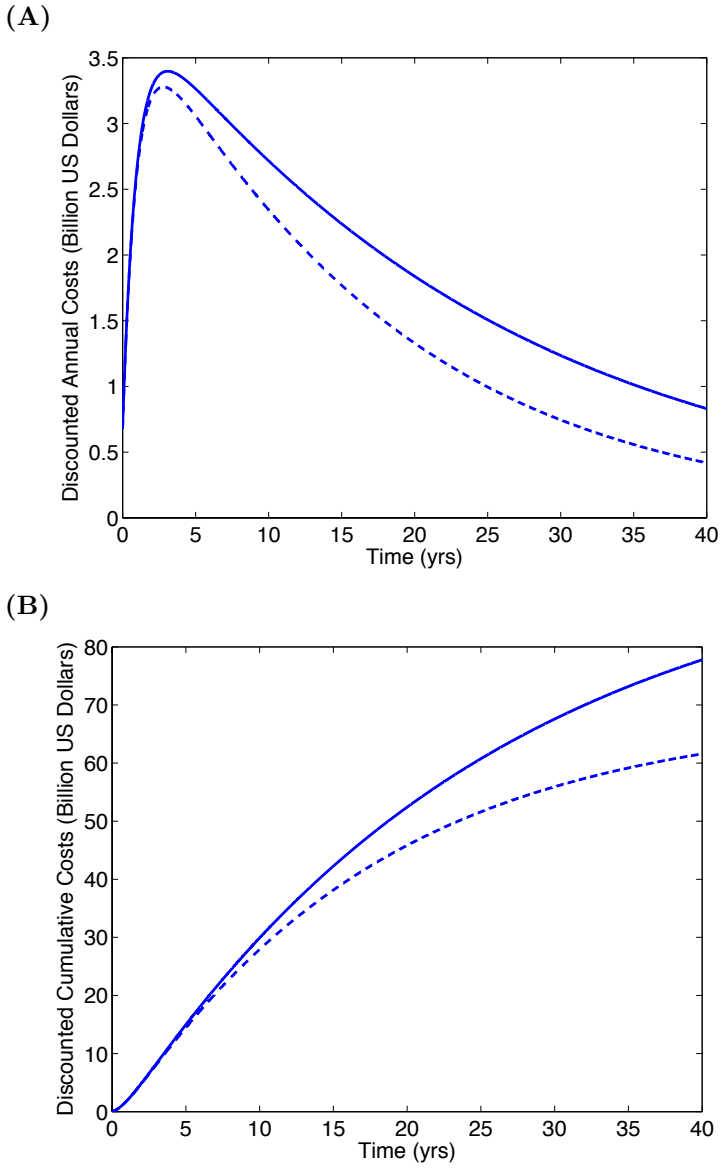

FIGURE 4. Comparison of costs of a universal "test and treat" strategy in South Africa (with annual testing) if there is a 62% probability of surviving an additional 6 years (dashed curve) or 20 years (sold curve) when treatment is initiated at a CD4 count of 350 cells/μL. Costs are discounted by 3.5% annually, following Granich et al. [15]. The average treatment-induced reduction in infectivity is 86%. Panels show **(A)** discounted annual treatment costs over time and **(B)** discounted cumulative treatment costs over time.

time) versus ≈ $61 billion (short survival time). Since the short survival time reflects the modeling study by the WHO and the long survival time presents the realistic survival time [19], our results show the WHO has underestimated annual costs (after 40 years) by 50% and cumulative costs by ≈ 22%.

7. **Conclusion.** Public health interventions designed for controlling sexually transmitted diseases (STDs) often aim to target prevention tools to individuals in behavioral core groups, because these individuals disproportionally contribute to transmission. It was first shown in modeling studies conducted by Hethcote and Yorke that strategies based on targeting core groups have the potential to cause a substantial reduction in transmission of STDs [17]. It has been suggested that if treatment is going to be used for HIV prevention purposes (and resources are limited) the conventional approach should be taken and treatment should be targeted to behavioral core groups [9]. However a strategy based on using conventional prevention tools directly benefits uninfected individuals in the core group, but is not likely to lead to any significant "loss of benefit" to individuals who are outside the core group. Treatment should be regarded as an unconventional prevention tool because it provides at least two "benefits": (i) a potential "preventive benefit" for uninfected individuals in the community and (ii) most importantly, a "survival benefit" for the infected individuals who receive treatment. If treatment is regarded as a conventional prevention tool and behavioral core groups are preferentially targeted, the number of HIV infections prevented would be maximized. However, such a strategy will ensure that infected individuals outside the core group will suffer a substantial loss in "survival benefits". Hence targeting behavioral core groups would be the most effective way to reduce transmission, but would be extremely unethical in terms of treatment equity. In addition, it is very unlikely to be feasible; while such a targeting strategy is easy to implement in a mathematical model it is impossible to implement in a large-scale in the "real-world". We suggest that targeting the sickest AIDS patients (as has been done in Haiti [11]) would optimize both therapeutic and preventive goals. This targeting strategy would be ethical, feasible and epidemiologically sound.

Our results show that increasing the length of the survival time, although beneficial to individuals, (i) reduces the probability of eliminating HIV and (ii) decreases the cost-effectiveness of using universal "test & treat" strategies. Our results show that individual-benefits and public health benefits will conflict when using "test & treat" strategies to reduce HIV transmission. The development of more effective therapies will greatly benefit individuals by increasing their life expectancy. However, it is extremely important to realize that the development of more effective therapies will decrease the impact and the cost-effectiveness of "test & treat" strategies. Notably the long survival time on treatment that we have evaluated is based on current clinical data and is the realistic survival time, the short survival time we have investigated is that used in previous modeling studies by the WHO and others [14, 15, 9]. The predictions made by the WHO are now being used to formulate global health policy. The purpose of our analysis is to show that modeling predictions based on using unrealistic assumptions regarding survival time lead to significantly overestimating the epidemiological benefits, and substantially underestimating the costs, of a universal "test and treat" strategy. Taken together our results show that previous modeling predictions by the WHO [14, 15] and by Dodd

et al. [9] have substantially overestimated both the impact and cost-effectiveness of a "test & treat" strategy.

"Test & treat" could be extremely beneficial and significant in reducing transmission if it is widely used, viral suppression rates are high, and drug resistance does not develop [12]. We stress that it is essential to base modeling predictions on the impact, and costs, of "test & treat" on current clinical data. It is critical to obtain correct estimates of cost-effectiveness to make informed decisions when choosing among preventions and for developing evidence-based health policies. We recommend that any modeling results that are used as a foundation for health policy decisions should always be carefully examined. Uncertainty and sensitivity analysis should be used to determine the robustness of results [3]. In addition, assumptions that are made to construct health policy models should be made transparent enough to permit policy makers to understand them. Modeling results should always be interpreted with caution. We recommend that models should never be used as the sole basis for making health policy decisions; many other, often more important factors that are not included in the modeling framework, need to be considered [7]. However models can be useful in bringing to light new issues that need to be considered. Our results have shown that individual-benefits and public health benefits may sometimes conflict, and that could occur with using a "test & treat" strategy to reduce transmission. As more effective drugs are developed that increase survival time further they will be of great benefit to millions of individuals infected with HIV. However it is important to realize that more effective drugs may also decrease the cost-effectiveness of "test & treat".

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