Test-and-treat approach to HIV/AIDS: A primer for mathematical modeling

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Abstract

The public benefit of treatment-as-prevention has induced a need to justify goodness for the public, and mathematical modeling studies played a key role in designing and evaluating the test-and-treat strategy for controlling HIV/AIDS. Here we briefly and comprehensively review the essence of contemporary understanding of treatment-as-prevention policy through mathematical modeling approaches and identify key pitfalls that have been identified to date. While the decrease in HIV incidence is achieved with certain coverages of diagnosis, care and continued treatment, HIV prevalence is not necessarily decreased and sometimes the test-and-treat is accompanied by increased long-term cost of antiretroviral therapy (ART). To confront with the complexity of assessment for this policy, the elimination threshold or the effective reproduction number has been proposed for its use in determining the overall success to anticipate eventual elimination. Since the publication of original model in 2009, key issues of test-and-treat modeling studies, including theoretical problems surrounding the sexual partnership network, detailed transmission dynamics and heterogeneous risk groups, have been identified. To explicitly design country-specific control policy, quantitative modeling approaches to each single setting with differing epidemiological context area required through collaboration among clinicians, public health practitioners, laboratory technologists, epidemiologists and mathematical modelers.

Background

Whereas the treatment of diseases has been conducted to expect individual benefit, e.g. aiming for eventual cure, in medical facilities, its use for directly transmitted infectious diseases can sometimes offer public benefits. Such treatment for the public interest is represented by the so-called "test and treat" approaches to HIV/AIDS [1] and another well-known radical approach may be the eradication therapy of *Helicobacter pylori* infection in the stomach. The very first test-and-treat model by Granich and his colleagues has excellently resulted in forming a landmark of global health policy [2], assisting the world to be motivated to universally or at least radically screen HIV infected individuals in the population and promote their treatment, not only for their suppression from progression of HIV infection but also for the public benefit. Nevertheless, the public benefit has also induced a need to justify goodness for the public, because "treatment as prevention" is no longer an individual interest but something to be ensured by the public or governmental organizations for its preventive performance [1].

The very first model of test-and-treat [2] has been repeatedly criticized for its practical utility, controversies and oversimplified model structure, and a number of alternative mathematical approaches have been proposed to assess the population impact of test-and-treat strategy in both quantitative and qualitative manners. It is valuable to overview mathematical approaches to test-and-treat strategy of HIV/AIDS for both general and expert readers as a primer. The present short review aims to briefly share the essence of contemporary understanding of the treatment-as-prevention.

What is test-and-treat?

In the simplest manner, the test-and-treat strategy is mathematically captured by a four-compartmental model system (Figure 1). While HIV infected individuals are at risk of developing AIDS in a matter of some 10 years since infection, diagnosis of HIV in advance of AIDS could bring infected individuals under antiretroviral therapy (ART). Effective ART in preventing infected individuals from their pathophysiological progression to AIDS has been established and continuously improved over time [3]. In theoretical sense, ART at the population level is considered to offer three different types of impact, i.e., (i) reduced opportunity of secondary transmission [4,5], (ii) reduced infectiousness per contact [6,7], and (iii) individual impact including extended life expectancy [8], and reduced risks of AIDS and AIDS death [3,9]. Considering these benefits, Granich et al. [2] have shown that substantial herd immunity (or to be more precise "indirect population effect" of mass treatment; hereafter we use "herd immunity" for simplicity) could be attained by a combination of universal testing and expanded ART among all infected individuals, helping to curb the HIV epidemic, assuming that a high adherence level is maintained for decades.

To achieve such indirect effect and individual treatment series by HIV screening and treatment at a population level, it is essential to ensure that three key tasks are achieved, i.e., (i) finding HIV infected individuals, (ii) maintaining HIV care and monitoring CD4-positive T cell count and (iii) ensuring adherence and successful ART to suppress viral load. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has introduced the concept of an HIV treatment cascade to identify and fill gaps in the continuum of services for testing, care and effective treatment. Following the 21st International AIDS Conference in Durban, South Africa, the UNAIDS report

has led to a global slogan of "90-90-90" by 2020 that aims to achieve targets, which are that 90% of people living with HIV know their HIV infection, 90% of people who know their HIV infection are accessing treatment and 90% of people on treatment has enjoyed suppressed viral loads [10]. By the year 2030, UNAIDS is even aiming to achieve 95-95-95 at a global level. From a variety of countries, care cascade of the HIV/AIDS has been estimated and evaluated (e.g. Figure 2 [11]), helping the country to point out the ongoing weakness of interventions. For instance, the case study of the United States in 2011 indicates that the diagnostic coverage is close to reach 90%, while more than half of diagnosed individuals are not continuously engaged in care, and thus, their viral level is not brought under control by ART (Figure 2). The critical point of the USA cascade in 2011 would thus be a need to ensure continued provision of care for diagnosed HIV infected individuals.

To date, a part of published empirical evidence indicated that widespread ART has led to reductions in nearly all aspects of HIV/AIDS. For instance, expanded ART in Canada has been shown to be associated with decreased morbidity, mortality and HIV transmission, demonstrating that the combination of HIV testing and ART programs in Canada has had a promising and profound population impact [12]. On the other hand, while the reduced infectiousness has been shown to decrease HIV incidence, the ART certainly increases the life expectancy of people living with HIV/AIDS (PLWHA) and can sometimes increase the prevalence of HIV over time [13]. A more recent study has indicated that even the reduction in HIV incidence is not necessarily promised by test-and-treat program, especially if a part of 90-90-90 goal is not satisfied [14]. The importance of comprehensively understanding the pros and cons of treatment-as-prevention strategy is increasingly recognized. Here we introduce a simple mathematical model, based on Figure 1, to understand such controversy in the next section.

Transmission dynamics of HIV under treatment-as-prevention

Here we consider a simple mathematical model to understand how test-and-treat influences the population dynamics of HIV/AIDS. First, we divide the population into susceptible individuals, infected individuals without AIDS (*H*) and those who have been diagnosed as AIDS (*A*). Population *H* and *A* are further divided into undiagnosed (H_u and A_u) and diagnosed (H_d and A_d) groups. Four compartments of HIV infected individuals have been schematically illustrated in Figure 1. At least in this model, we assume that all diagnosed individuals are brought to be under ART.

Susceptible individuals experience infection with a rate $\lambda(t)$ which is a function of infectious individuals H_u, A_u, H_d and A_d. We assume that ART reduces one's infectiousness on a whole from β to $\varepsilon\beta$ where parameter ε takes a value between zero and one, and the value $1-\varepsilon$ represents the relative reduction in the transmissibility. Such reduction may not only be attributed to direct effectiveness of treatment, but also caused by awareness of infection status and reduced frequency of risky sexual intercourse. Without treatment, infected individuals are assumed to develop AIDS with a progression rate ρ. HIV infected individuals under ART progresses to AIDS with a far smaller rate $\gamma\rho$ where the value of $1-\gamma$ would be between zero and one and $\frac{1}{\gamma\rho}-\frac{1}{\rho}$ scales the average gain of the extended time without AIDS. In addition to the natural death rate, μ, AIDS patients experience a higher mortality rate than HIV infected individuals, because of disease induced death rate δ.

Parameter α represents the rate of diagnosis among HIV infected individuals, and $1/\alpha$ gives the average waiting time for diagnosis.

The model is written as the system of ordinary differential equations.

$$\frac{dH_u}{dt} = \lambda(t)\big(1 - H_u(t) - A_u(t) - H_d(t) - A_d(t)\big) - (\alpha + \rho + \mu)H_u(t),$$

$$\frac{dA_u}{dt} = \rho H_u(t) - (\mu + \delta)A_u(t),$$

$$\frac{dH_d}{dt} = \alpha H_u(t) - (\gamma\rho + \mu)H_d(t),$$

$$\frac{dA_d}{dt} = \gamma\rho H_d(t) - (\mu + \delta)A_d(t),$$

where the force of infection $\lambda(t)$ is given by

$$\lambda(t) = \beta H_u(t) + \varepsilon\beta H_d(t).$$

It should be noted that the transmission rate β reflects not only the infectiousness per contact but also the rate of sexual contact per unit time. To understand the concept of treatment-as-prevention in the simplest manner, the model presented here has ignored gender and details of sexual partnership. Since AIDS patients are aware of their own infection status, we do not account for the infectiousness of AIDS patients for simplicity.

In the absence of diagnosis and treatment, the basic reproduction number, R_0, the average number of secondary cases generated by a single primary case in a fully susceptible population, is given by linearizing the abovementioned system nearby the disease-free equilibrium, and we get

$$R_0 = \frac{\beta}{\rho+\mu}.$$

In the presence of diagnosis and treatment, the effective reproduction number, R_c, the average number of secondary cases generated by a single primary case under test-and-treat policy is similarly derived as

$$R_c = \frac{\beta}{\alpha+\rho+\mu} + \frac{\varepsilon\beta}{\gamma\rho+\mu}\frac{\alpha}{\alpha+\rho+\mu}.$$

To assess the test-and-treat strategy, a number of important and different epidemiological metrics have been quantified, e.g. common indicators include (i) the effective reproduction number, (ii) the incidence and prevalence given as the solution of the above mentioned system and (iii) the cost-effectiveness ratio as informed by the model outcome.

Different screening approaches would lead to different population outcomes. Such differing patterns of screening could arise in many ways, e.g. different frequency of HIV testing in the population, the use of advanced molecular techniques to detect those in the window period, targeted testing of high risk groups and different HIV infection stage (e.g. time since infection) to start treatment. Granich et al. [2] compared the cost of the so-called “opt-in” and “opt-out” strategies of testing. Opt-in strategy assumes that every infected individual presents to health services and starts ART at CD4+ count 350 cell/mL. Opt-out strategy assumes yearly universal voluntary testing of all individuals in the population, which is followed by immediate ART upon diagnosis of HIV infection. The study has shown that the cost of opt-in strategy will continue to increase whereas the cost of opt-out strategy would eventually decrease with a success of controlling HIV/AIDS at the population level.

The suggested opt-out strategy is expected to eliminate HIV within 10 years and the reality on that point has been subject to debate. Granich et al. [2] and Kretzschmar et al. [15] mathematically derived the elimination threshold and studied the conditions of treatment which makes the elimination of HIV feasible, such as the frequency of testing, test coverage or an initiation time of the ART. Figure 3 shows a simulation result of epidemic scenarios using the abovementioned equation system.

Sensitivity of the effective reproduction number and PLWHA as a function of the rate of diagnosis α is examined. Given that the rate of diagnosis is greater than a certain threshold to lead to $R_c<1$, the test-and-treat is proven to successfully control the HIV epidemic. The successful control endorses the global slogan of 90-90-90 strategy, targeting high enough diagnosis and treatment coverage to ensure substantial public benefit of HIV/AIDS.

Important pitfalls of test-and-treat are mainly seen in its long-term effects. For instance, the prevalence of HIV infection is not necessarily promised to decrease. Shafer et al. [16] estimated the population impact of ART in the future accounting for the change in the turnover rate of sexual partnership under ART. The model expected that ART will reduce the HIV incidence, while the HIV prevalence may be increased. Figure 4 compares two simple scenarios, i.e., long term dynamics with and without test-and-treat policy, comparing HIV incidence and prevalence. Meeting certain mathematical conditions (especially, with large α and ε), both HIV incidence and prevalence would decrease with time. Nevertheless, HIV prevalence in the presence of test-and-treat could exceed that without any control if the relative transmissibility of infected individuals under treatment is not sufficiently small. With the increased HIV prevalence, it follows that testing every year and immediate treatment upon diagnosis is not necessarily the most cost-efficient strategy and could even increase long-term ART costs [17]. Theoretically, such controversial increase can be avoided by reducing the transmissibility for those who are diagnosed, for example, by ensuring high effectiveness of treatment, or by reducing the frequency of risky sexual intercourse after awareness of the infection state. Increase in HIV prevalence also indicates that the impact of test-and-treat should not be assessed by only a single epidemiological indicator, and multiple aspects of the epidemiology have to be carefully examined, especially using the effective reproduction number or elimination threshold.

In relation to the population impact, the HIV infection stage at the start of treatment has attracted researchers' attentions [18], because the population impact of ART would be maximize if infected individuals are diagnosed at the very early stage of infection. In addition, at a late infection-age of HIV, the frequency of sexual contact is smaller than those in earlier stages [19].

Future considerations

While many mathematical modeling studies exist, all have certainly agreed that increased diagnostic testing coupled with ART would induce a certain level of herd immunity to the population. Mathematical modeling studies have found that model assumptions, especially many properties of the sex partner network, would have a profound impact on the incidence and prevalence, and incorporating local behavioral data is considered to be critical [17].

Due to the need to satisfy high diagnostic coverage and treatment, it is essential to first uncover the care cascade at each country level and locality. Depending on risk populations, the diagnostic coverage may greatly differ due to different awareness of risky behavior. Understanding the transmission dynamics in the present day including the proportions of diagnosed, those followed-up and those adhered to HIV, the topical question to answer may be to see if the effective reproduction number is achieved to be the less than the value of one and if the elimination threshold was met. Country-specific case studies have to be conducted to confront with this task and understand the pros and cons with varying transmission dynamics by country. Depending on the epidemiological context and the coverages of

cascade achieved, the optimal frequency of HIV testing is known to vary: opt-out strategy with HIV testing every year is not always optimal [17].

Second, long-term epidemiological impact has yet to be explored in detail, preferably along with empirical datasets. In the presence of continued effort of test-and-treat approaches, HIV prevalence (or the number of PLWHA) and their life expectancy are expected to increase. These observations are likely to lead to ageing of infected individuals. Moreover, the aged infected individuals are more and more likely to experience chronic diseases. Nevertheless, the failure to maintain high coverage of care and adherence to ART could lead to dramatic resurgence of the incidence and the surge of ART costs. Another critical issue in the context of long-term impact is the emergence of drug resistant HIV, especially in resource-limited countries with a struggle to maintaining adherence. Dose adherence remains to be the key issue in such settings and continued monitoring of drug sensitivity would be critical [20].

Not only leveraging the infrastructure and capacity for scaling up ART in resource limited settings, but the scale-up of diagnostic and treatment coverages of heterogeneous risk populations that are hard to reach are likely to be key issues at practical settings [21]. Depending on epidemiological contexts of sexual mixing, transmission dynamics (incidence/prevalence) and heterogeneous risk groups, realistic quantitative approaches need to be sought supported by collaborations among clinicians, public health practitioners, epidemiologists and mathematical modelers.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HN conceived of the short review. KN constructed the model, performed simulations and drafted the basis of manuscript as bullet points. HN wrote the original version of the manuscript. XS and AI gave comments on earlier version of the manuscript. All authors reviewed, revised and approved the final version of the manuscript.

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Figures

Figure 1 - Flow chart of a simple compartmental model

Variable H_u [H_d] is a fraction of undiagnosed [diagnosed] HIV-infected individuals without AIDS, A_u [A_d] is a fraction of previously undiagnosed [diagnosed] AIDS cases.

Figure 2 - HIV care continuum in the United States, 2011

Estimated percentages of persons living with HIV infection are shown [11]. In 2011, an estimated 1.2 million persons were living with HIV infection in the United States.

Figure 3 - Test-and-treat with high screening rate may lead to the elimination of HIV

When the rate of diagnosis is greater than a certain threshold value, test-and-treat can successfully control HIV epidemic. Parameter values are $\mu=1/60$, $\rho=1/10$, $\gamma=1/3$, $\beta=0.15$, $\delta=1/2$ and $\varepsilon=0.3$.

Figure 4 - Test-and-treat could increase HIV prevalence

(a, c) The rate of change in HIV incidence, (b, d) the proportion of the PLWHA (people living with HIV/AIDS). Without test-and-treat policy, the rate of diagnosis was set as $\alpha=0$. Under the test-and-treat policy, $\alpha=0.3$ was adopted. Parameter values are $\mu=1/60$, $\rho=1/10$, $\gamma=1/3$, $\beta=0.15$, $\delta=1/2$ and $\varepsilon=0.3$. The test-and-treat reduces both the incidence and the prevalence in (a) and (b). For panel (c) and (d), $\varepsilon=0.5$ was used instead of $\varepsilon=0.3$ as the relative transmissibility for those who are diagnosed. In this scenario, test-and-treat increases HIV prevalence. Initial values are $H_u=0.15$, $A_u=0.01$, $H_d=0$ and $A_d=0$.

Embedded figures
Figure 1

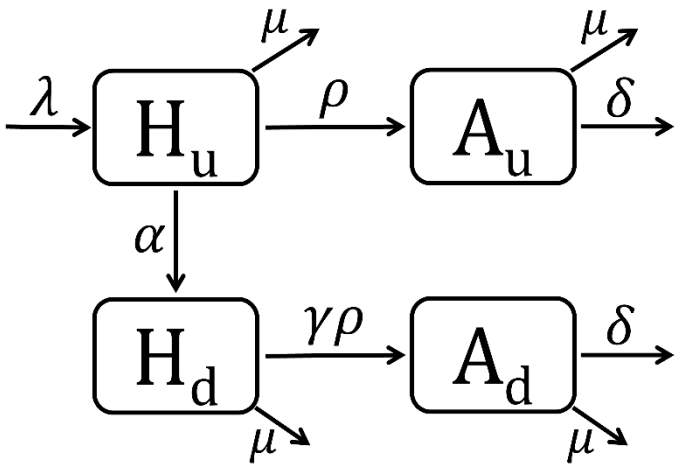


Figure 2

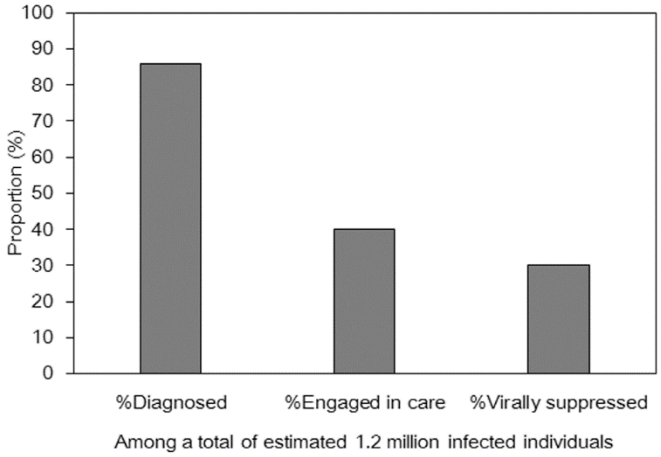


Figure 3

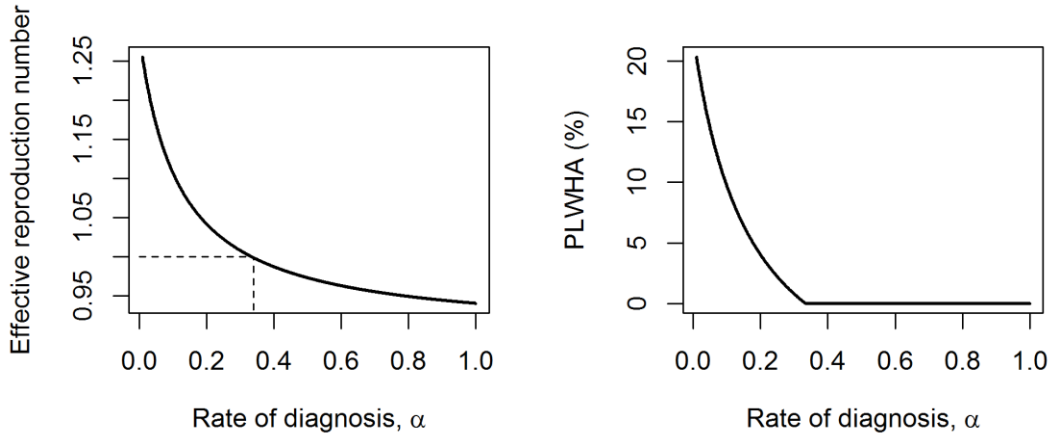
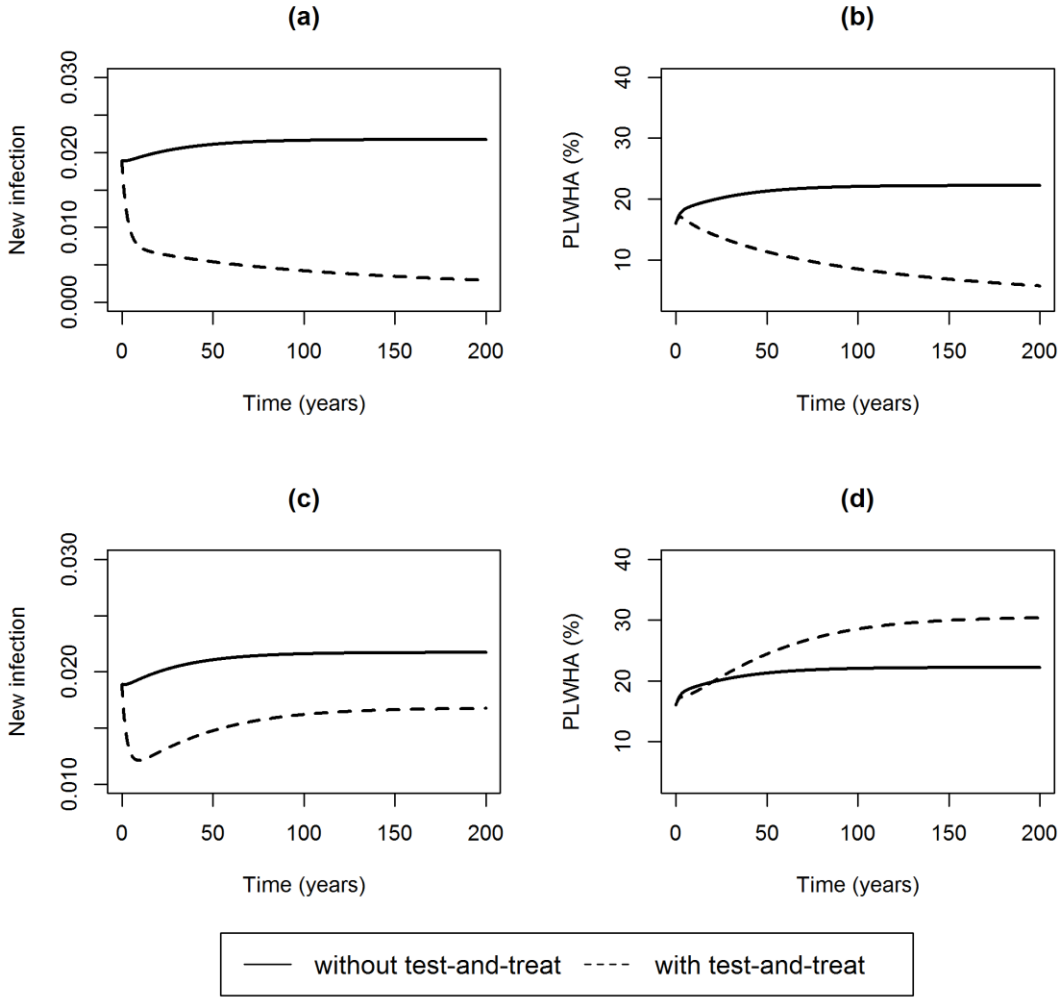


Figure 4


(a)
(b)
(c)
(d)
New infection
PLWHA (%)
Time (years)
0.000
0.010
0.020
0.030
10
20
30
40
0
50
100
150
200
without test-and-treat
with test-and-treat

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