Research Article

Adding Education to "Test and Treat": Can We Overcome Drug Resistance?

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Recent mathematical modelling has advocated for rapid "test-and-treat" programs for HIV in the developing world, where HIV-positive individuals are identified and immediately begin a course of antiretroviral treatment, regardless of the length of time they have been infected. However, the foundations of this modelling ignored the effects of drug resistance on the epidemic. It also disregarded the heterogeneity of behaviour changes that may occur, as a result of education that some individuals may receive upon testing and treatment. We formulate an HIV/AIDS model to theoretically investigate how testing, educating HIV-positive cases, treatment, and drug resistance affect the HIV epidemic. We consider a variety of circumstances: both when education is included and not included, when testing and treatment are linked or are separate, when education is only partly effective, and when treatment leads to drug resistance. We show that education, if it is properly harnessed, can be a force strong enough to overcome the effects of antiretroviral drug resistance; however, in the absence of education, "test and treat" is likely to make the epidemic worse.

1. Introduction

The HIV/AIDS epidemic is the greatest public-health crisis in modern history [1]. Currently, 33 million people are infected with HIV or AIDS, 68% of whom are in developing countries [2]. In 2013, 1.5 million people died of AIDS-related causes [3]. HIV is particularly prevalent in developing and low-income countries, who have few resources to combat the disease. Only 10% of global healthcare research goes to developing countries, where 90% of the world's poorest populations live [4]. HIV stigmatization, discrimination, and inadequate education pose additional social challenges that are hindering countries from advancing in HIV prevention [5].

A primary weapon in the fight against HIV is antiretroviral (ARV) treatment [6]. ARVs have the ability to significantly prolong the life of an infected individual but must be taken according to strict drug regimens for the remainder of their lives [7]. Failure to properly adhere to such medication is responsible for the development of drug resistance, which

can render ARVs less effective [8]. Furthermore, resistant strains can subsequently be transmitted to newly infected individuals, who will not respond to treatment [9]. A variety of mathematical models are in agreement that the prevalence of drug resistance will increase in resource-constrained countries as a result of preexposure prophylaxis [10–12], although other studies have suggested that the development of resistance may be offset by the number of infections averted in the first place [13].

The recent "test-and-treat" proposal aims to scale up existing treatment in developing countries by way of large-scale testing of individuals and then rapid treatment of infected individuals [14]. However, this proposal was based on a deeply flawed mathematical model, one that did not take ARV drug resistance into account and which conflated multiple compartments [15]. Subsequent modelling by Granich and colleagues continues to ignore the effect of resistance [16]. New modelling is urgently needed to examine a broader range of options for the test-and-treat program.

Education is a key tool in disease management that is often overlooked [17]. It requires investment in people, rather than investment in biomedical interventions, but it has the potential to lead to enormous benefits for relatively low cost. Indeed, behavioural interventions have been solely responsible for the near-eradication of guinea worm disease [18]. When people living with HIV navigate the structural challenges of their ecosocial context environment, social capital may be an essential element for the attainment of optimal health [19]. A review of 83 studies of the impact of education on sexual risk behaviours, pregnancy, and STI rates illustrated that 42% found that the programs significantly delayed the initiation of sex among one or more groups for at least six months, 29% reduced the frequency of sex, 35% decreased the number of sexual partners, and 48% increased condom use [20]. Home-based counselling has been shown to be associated with an uptake in testing [21, 22].

Conversely, a lack of information can have a severe impact on worsening the disease. For example, 60% of gay men attending an STD clinic in urban South Africa were unaware that anal sex was a risk factor for HIV [23], while a lack of knowledge about HIV/AIDS, its transmission, and health risks has been correlated with an increase in unprotected sex [24].

However, education needs to be culturally specific, to avoid the pitfall of the developed world dictating to low-income countries [25]. The Global Campaign for Education has estimated that 7 million cases of HIV/AIDS could be avoided in the next decade if every child received a basic education [26]. Educational initiatives include basic information about HIV risk factors, lifestyle counselling for infected individuals, reduction in risky behaviour, and information on prevention [20]. Tying education to both testing and treatment would have immense benefit for people in developing countries.

Previous mathematical models have used deterministic compartmental models to assess sexual behaviour and behaviour change [27], including issues of multiple ongoing partners [28], postdiagnosis behaviour [29], migration patterns of infected individuals [30], and circumcision [31] and in response to the introduction of a potential vaccine [32].

In this paper, we develop a model to study HIV dynamics in a variety of circumstances: both when education is included and not included, when testing and treatment are linked or are separate, when education is only partly effective, and when treatment leads to drug resistance. The main goal is to evaluate these programs and to find the parameters that play a major role in controlling the disease.

2. The Model

We define an HIV-positive educated individual to be one who reduces her probability of transmission, relative to noneducated individuals, due to awareness of the disease's effects. A drug-resistant individual is one for whom treatment has occurred but has failed, resulting in a higher probability of transmission than treated individuals; educated drug-resistant individuals will have a lower transmission probability than noneducated drug-resistant individuals.

The model classifies the sexually active population into eight classes: susceptible (S), HIV positive with unknown status (I), HIV positive with known status and uneducated (I_n), HIV positive with known status and educated (I_e), infected uneducated under treatment (I_{nt}), infected educated under treatment (I_{et}), uneducated with drug resistance (I_{nr}), and educated with drug resistance (I_{er}). Thus, the total sexually interacting adult population is given by $N(t) = S(t) + I(t) + \sum_{i \in F} I_i(t)$, where $F = \{n, e, nt, et, er, nr\}$. It is assumed that susceptible individuals are recruited into the population at a rate Λ and there is a constant natural death rate μ in all classes. Susceptible individuals gain infection following contact with HIV-infected individuals at a rate λ given by

$$\lambda(t) = \frac{\beta\left(I(t) + \sum_{i \in F} \eta_i I_i(t)\right)}{N(t)}, \tag{1}$$

where $\beta = qc$, the product of probability of transmission and the number of sexual partners; η_i are the modification parameters, which ensure that individuals in different cases have different infectivity based on their status; η_{nt} and η_{et} are small due to treatment [33].

We follow the assumption in Bhunu et al. [34] that $\eta_n > 1$ and $\eta_e < 1$. Specifically, this means that risk behaviour increases if an individual is uneducated and tests HIV positive, while risk behaviour decreases if an individual is educated and HIV positive. The former condition occurs in the truly uneducated, who may see their HIV-positive status as a death sentence and thus do not care who they infect. Unprotected sex has been correlated with having less knowledge about HIV/AIDS, its transmission, and health risks [24, 35–37]. The latter assumes that "education" consists of messaging that is at least partly successful, in terms of lowering risky contact. For the same reason, $\eta_{nt} > \eta_{et}$.

We ignore the contribution of AIDS patients in the transmission since their death rate is high and their capability of making new sex partners is low. Also, we assume that infected individuals discover their status at rate σ_k, a proportion p of whom is educated immediately.

Treatment is provided at rates σ_t and σ_{et}, depending on whether the infected individuals are educated or not. Infected individuals may stop treatment at rates r_c or r_{ec}. Uneducated treated individuals may become drug resistant at rate σ_r, while educated treated individuals become drug resistant at rate σ_{re}; we assume that access to education results in better adherence to medication and less resistance, so that $\sigma_{re} < \sigma_r$. Subsequent education is provided at a rate ρ_e before treatment, while treated individuals receive education at rate ρ_{te}. Treatment decreases the progression to AIDS from the rate γ to the rate γ_t. Thus, the dynamics of the testing, educating, and treating programs is given by the following system of ODEs:

$$S'(t) = \Lambda - (\lambda + \mu) S,$$

$$I'(t) = \lambda S - (\mu + \gamma + \sigma_k) I,$$

$$I'_n(t) = (1 - p) \sigma_k I + r_c I_{nt} - (\mu + \gamma + \sigma_t + \rho_e) I_n,$$
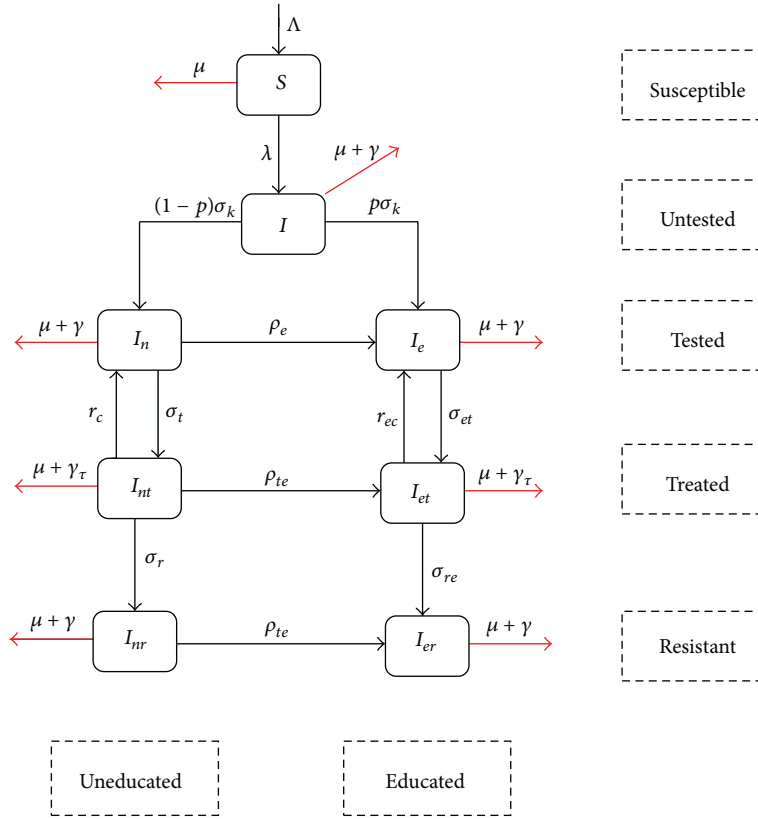
FIGURE 1: The full model: test and treat with education and drug resistance. Sexually active people are either susceptible or infected. Infected individuals are classified depending on knowing their status, being educated, being treated, and being drug resistant or not. We assume that the rate of appearance of new sexually active people is constant.

$$
\begin{aligned}
I_e'(t) &= p\sigma_k I + \rho_e I_n + r_{ec} I_{et} - (\mu + \gamma + \sigma_{et}) I_e, \\
I_{nt}'(t) &= \sigma_t I_n - (\mu + \gamma_t + \sigma_r + r_c + \rho_{te}) I_{nt}, \\
I_{et}'(t) &= \rho_{te} I_{nt} + \sigma_{et} I_e - (\mu + \gamma_t + \sigma_{re} + r_{ec}) I_{et}, \\
I_{nr}'(t) &= \sigma_r I_{nt} - (\mu + \gamma + \rho_{te}) I_{nr}, \\
I_{er}'(t) &= \sigma_{re} I_{et} + \rho_{te} I_{nr} - (\mu + \gamma) I_{er},
\end{aligned}
\tag{2}
$$

with parameters described in Table 1. The model is illustrated in Figure 1.

3. Submodels

Since the model is complicated, we decided to break it into simplified, yet significant, special cases describing the following programs: testing and obligatory education, testing only, testing with limited education, test and treat without education, and test and treat with obligatory education. These submodels deal with a variety of limiting cases.

3.1. Testing and Obligatory Education.

In this submodel, in which no treatment is adopted, we assume that testing is available for the whole population and free education is

provided immediately, consisting of important information about HIV such as high-risk behaviour, transmission modes, and methods of risk reduction for those who test positive.

It should be noted that this is a limiting case and that, obviously, testing every single person is unrealistic. However, we examine this case partly because it is the goal of the "test-and-treat" program, partly because limiting cases give us insights into the extremities of the model and partly because new at-home self-testing packages have recently been made available cheaply [38], thus increasing the likelihood that HIV testing may vastly increase in the future.

3.1.1. The Model. If $p = 1$, then $I_n = I_{nt} = I_{nr} = 0$. Moreover, if $\sigma_{et} = 0$, then $I_{et} = I_{er} = 0$. As a result, (2) is reduced to

$$
\begin{aligned}
S'(t) &= \Lambda - (\lambda + \mu) S, \\
I'(t) &= \lambda S - (\mu + \gamma + \sigma_k) I, \\
I_e'(t) &= \sigma_k I - (\mu + \gamma) I_e,
\end{aligned}
\tag{3}
$$

with $\lambda = \beta[I + \eta_e I_e]/N$ and $N = S + I + I_e$. The model is illustrated in Figure 2(a).

3.1.2. The Equilibria. Note that, with $I = I_e = 0$, (3) has the disease-free equilibrium (DFE) $(S^*, I^*, I_e^*) = (\Lambda/\mu, 0, 0)$.

TABLE 1: Parameter definitions.

Variable	Definition	Sample value	Range	Units	Reference
$S(t)$	Susceptible population at time t	(state variable)	—	People	—
$I(t)$	Infected population at time t who do not know their status	(state variable)	—	People	—
$I_n(t)$	Uneducated infected population at time t who know their status	(state variable)	—	People	—
$I_e(t)$	Infected, educated population at time t who know their status	(state variable)	—	People	—
$I_{nt}(t)$	Infected, uneducated, and treated population at time t	(state variable)	—	People	—
$I_{et}(t)$	Infected, educated, and treated population at time t	(state variable)	—	People	—
$I_{nr}(t)$	Infected, uneducated, and drug-resistant population at time t	(state variable)	—	People	—
$I_{er}(t)$	Infected, educated, and drug-resistant population at time t	(state variable)	—	People	—
Λ	Recruitment rate	29	25–35	Year^{-1}	[34]
β	Transmission rate	0.5	0.05–0.95	Year^{-1}	[34]
σ_k	Rate of knowing one's status	0.55	0.1–1	Year^{-1}	Assumed
p	The proportion of HIV-positive individuals who are educated immediately upon knowing their status	0.75	0–1	—	Assumed
σ_t	The rate of providing treatment for uneducated people	0.1125	0.1–4	Year^{-1}	[34]
σ_{et}	The rate of providing treatment for educated people	0.1125	0.1–4	Year^{-1}	Assumed
σ_r	The rate at which uneducated people become drug resistant	$0.1 \times \sigma_{et}$	—	Year^{-1}	Assumed
σ_{re}	The rate at which educated people become drug resistant	$0.5 \times \sigma_r$	—	Year^{-1}	Assumed
η_n	Modifying transmission parameter for uneducated people	1.685	1–2.37	—	[9]
η_e	Modifying transmission parameter for educated people	0.343	0.186–1	—	[9]
η_{nt}	Modifying transmission parameter for uneducated and treated people	0.18	0.174–0.186	—	[9]
η_{et}	Modifying transmission parameter for educated and treated people	0.092	0.01–0.174	—	[9]
r_c	The rate at which uneducated people stop their treatment	0.125	0.1–0.15	Year^{-1}	Assumed
r_{ec}	The rate at which educated people stop their treatment	0.0505	0.1–0.15	Year^{-1}	Assumed
ρ_e	The rate of providing late education for nontreated HIV-positive individuals	1	0–2	Year^{-1}	Assumed
ρ_{et}	The rate of providing late education during or after treatment	1	0–2	Year^{-1}	Assumed
μ	Natural mortality rate	0.02	0.015–0.025	Year^{-1}	[34]
γ	Rate of progression to AIDS for nontreated or drug-resistant individuals	0.1	0.05–0.15	Year^{-1}	[34]
γ_t	Rate of progression to AIDS for treated individuals	0.0875	0.05–0.125	Year^{-1}	Assumed

Setting the right-hand side of (3) to zero and solving for S, I and I_e, we have the endemic equilibrium (EE)

$$S^* = \frac{\Lambda}{\lambda^* + \mu},$$

$$I^* = \frac{\Lambda \lambda^*}{(\lambda^* + \mu)(\mu + \gamma + \sigma_k)}, \quad (4)$$

$$I_e^* = \frac{\sigma_k \Lambda \lambda^*}{(\lambda^* + \mu)(\mu + \gamma + \sigma_k)(\mu + \gamma)},$$

with

$$\lambda^* = \frac{\beta(\mu + \gamma + \eta_e \sigma_k) - (\mu + \gamma)(\mu + \gamma + \sigma_k)}{(\mu + \gamma + \sigma_k)}. \quad (5)$$

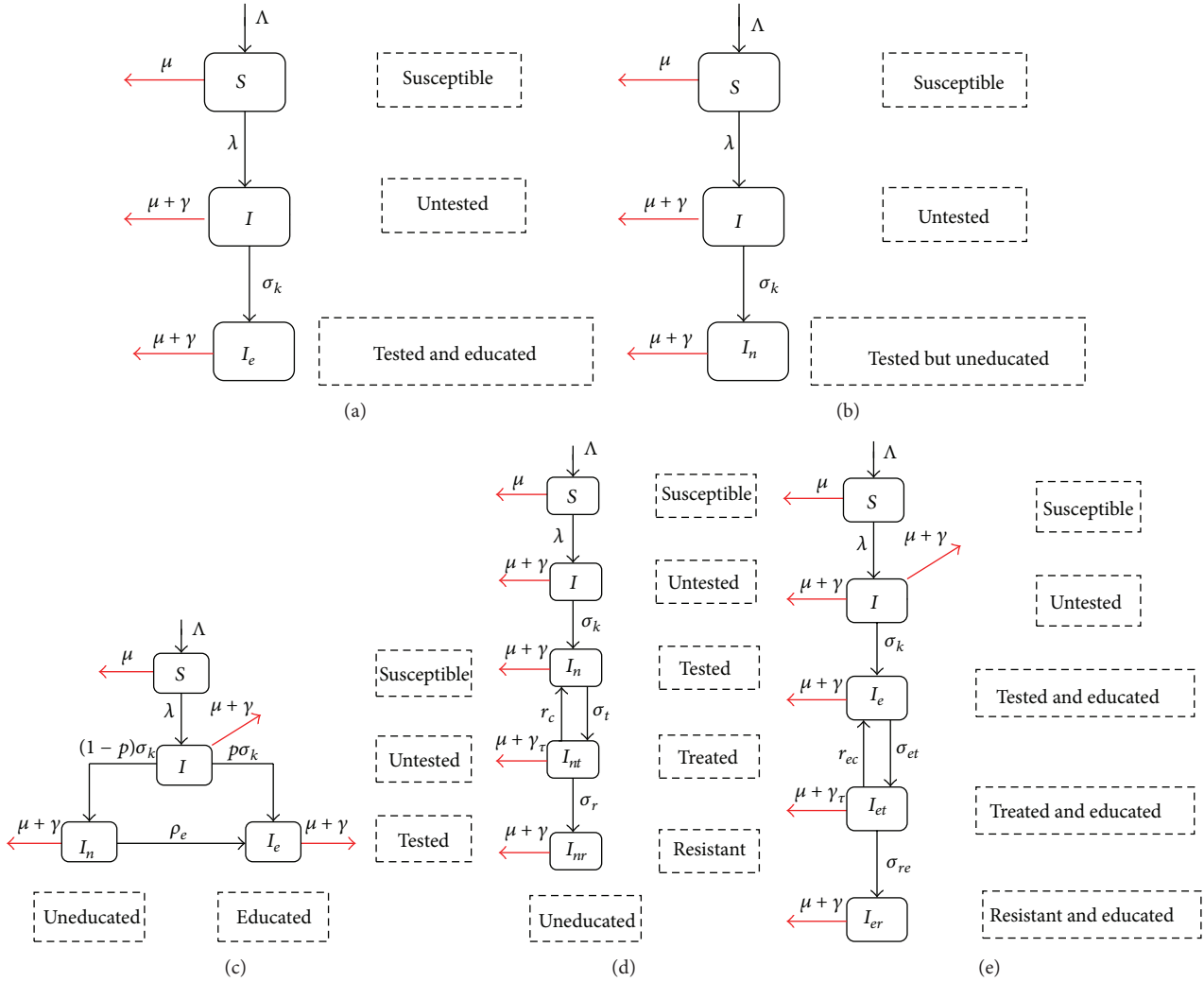*3.1.3. Local and Global Stability.* For the DFE, we have the Jacobian matrix

FIGURE 2: The five submodels. (a) Testing with obligatory education. (b) Testing only. (c) Test and treat with limited education. (d) Test and treat with drug resistance. (e) Test and treat with drug resistance and obligatory education.

$$J = \begin{bmatrix} -\mu & -\beta & -\eta_e\beta \\ 0 & \beta - (\mu + \gamma + \sigma_k) & \eta_e\beta \\ 0 & \sigma_k & -(\mu + \gamma) \end{bmatrix}, \quad (6)$$

which has the characteristic polynomial (s is the variable),

$$(s + \mu)(s^2 + a_1 s + a_0) = 0, \quad (7)$$

where

$$\begin{aligned} a_1 &= 2\mu + 2\gamma + \sigma_k - \beta, \\ a_0 &= (\mu + \gamma)(\mu + \gamma + \sigma_k) - \beta(\mu + \gamma + \eta_e\sigma_k). \end{aligned} \quad (8)$$

When $a_0 = 0$, we have $a_1 > 0$. As a result, all the eigenvalues of J are negative under the condition $a_0 > 0$, which is

equivalent to

$$R_{0e} \equiv \frac{\beta(\mu + \gamma + \eta_e\sigma_k)}{(\mu + \gamma)(\mu + \gamma + \sigma_k)} < 1. \quad (9)$$

Here, R_{0e} is the basic reproduction number [39].

Thus we have proved the following theorem.

Theorem 1. *For $R_{0e} < 1$, the DFE is locally asymptotically stable, and for $R_{0e} > 1$, the DFE is unstable.*

Note that $R_{0e} < 1$ implies $\lambda^* < 0$. As a result, we have the following corollary.

Corollary 2. *(1) If $R_{0e} < 1$, then the DFE is the only equilibrium. (2) For $R_{0e} > 1$, then the DFE and the EE coexist.*

In the following theorem, we will prove global stability for the DFE.

Theorem 3. *The DFE is a globally asymptotically stable equilibrium of model system (3) provided $R_{0e} < 1$.*

Proof. We utilize Theorem 2 in [40]. Consider $F(X, 0) = [K - \mu X]$,

$$A = \begin{bmatrix} \beta - (\mu + \gamma + \sigma_k) & \eta_e \beta \\ \sigma_k & -(\mu + \gamma) \end{bmatrix},$$

$$\widetilde{G}(X, Y) = \begin{bmatrix} \beta (I + \eta_e I_e) \left(1 - \dfrac{S}{N}\right) \\ 0 \end{bmatrix} \geq 0, \tag{10}$$

for all $(X, Y) \in \{(S, I, I_e) \in \mathbb{R} : N \leq \Lambda/\mu\}$. As a result, the conditions of Theorem 2 [40] are satisfied, and the result follows. □

It follows that R_0 is a transcritical bifurcation and is thus a useful threshold parameter. See [41] for more discussion.

We will now study the stability of the EE. We utilize Theorem 4 in [40]. Note that, for

$$\beta = \frac{(\mu + \gamma)(\mu + \gamma + \sigma_k)}{(\mu + \gamma + \eta_e \sigma_k)} \equiv \beta_c, \tag{11}$$

the Jacobian matrix for the DFE has zero as an eigenvalue, with left eigenvector

$$u_1 = -\frac{\beta}{\mu} \left[\frac{(\mu + \gamma)}{\sigma_k} + \eta_e \right] u_3,$$

$$u_2 = \frac{(\mu + \gamma)}{\sigma_k} u_3, \tag{12}$$

and $u_3 > 0$ free. Also, it has right eigenvector

$$v_1 = 0,$$

$$v_2 = \frac{(\mu + \gamma)}{\eta_e \beta} v_3 \tag{13}$$

and $v_3 > 0$ free. Moreover,

$$b \equiv \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta} (E_0, \beta_0) = v_2 (u_2 + \eta_e u_3) > 0, \tag{14}$$

where E_0 is the DFE. This implies that (i) or (iv) in Theorem 4 [40] are applicable. However, for $\beta < \beta_c$, E_0 is locally asymptotically stable and we have no other positive equilibria. As a result, (iv) is the only applicable case. This means that, when β changes from $\beta < \beta_c$ to $\beta > \beta_c$, E_0 changes from stable to unstable and the EE changes from negative to positive and locally asymptotically stable.

Thus we have proved the following.

Theorem 4. *For $R_{0e} > 1$ but close to 1, the unique EE is locally asymptotically stable.*

Remark 5. Note that $\partial R_{0e}/\partial \sigma_k < 0$ because $\eta_e < 1$, which means that if obligatory education is provided, then rapid testing will reduce R_{0e} and thus potentially control the disease.

We have found the DFE and EE for a simple system representing testing and obligatory education. The local and global stability for the DFE and local stability for the EE have been proven. Moreover, the value of the basic reproduction number and the critical rate of transmission are calculated.

As a result, testing and obligatory education is a way of reducing the spread of the disease, so long as effective education is provided to everyone who tests positive. However, obligatory education is not realistic and may be expensive. We thus relax the obligatory education requirement in the next two sections, in order to explore this further.

3.2. Testing Only. In this submodel, we examine a possible program that provides testing for the whole population with the aim of more knowledge about the prevalence of HIV, but without any treatment or education for HIV-positive cases.

If $p = 0$, then $I_e = I_{et} = I_{er} = 0$. Moreover, if $\sigma_t = 0$, then (2) becomes

$$S'(t) = \Lambda - (\lambda + \mu) S,$$

$$I'(t) = \lambda S - (\mu + \gamma + \sigma_k) I, \tag{15}$$

$$I_n'(t) = \sigma_k I - (\mu + \gamma) I_n,$$

with

$$\lambda = \frac{\beta [I + \eta_n I_n]}{N} \tag{16}$$

and $N = S + I + I_n$. This model is illustrated in Figure 2(b).

Similar to the previous case, the equilibria are given by (4), but with

$$\lambda^* = \frac{\beta (\mu + \gamma + \eta_n \sigma_k) - (\mu + \gamma)(\mu + \gamma + \sigma_k)}{(\mu + \gamma + \sigma_k)}. \tag{17}$$

Also, we have the same results for stability but with the basic reproduction number and the critical rate of transmission given by

$$R_{0n} = \frac{\beta (\mu + \gamma + \eta_n \sigma_k)}{(\mu + \gamma)(\mu + \gamma + \sigma_k)},$$

$$\beta_c = \frac{(\mu + \gamma)(\mu + \gamma + \sigma_k)}{(\mu + \gamma + \eta_n \sigma_k)}. \tag{18}$$

Remark 6. Note that $\partial R_{0n}/\partial \sigma_k \geq 0$ because $\eta_n > 1$. This means that if testing is provided without education, then rapid testing and knowing one's status will not control the disease. Comparing this to Remark 5, it is clear that any testing program should be supported with education.

We have found the DFE and EE for a simple model representing the testing-only program and an eradication threshold R_{0n}. The local and global stability for the DFE and local stability for the EE are similar to the previous section. However, if testing is provided without education, then rapid testing and knowledge of one's HIV status will not control the disease. It follows that testing without education is likely to increase the prevalence of the disease; thus any testing program should be supported with education.

3.3. Testing with Education versus Testing without Education.
Mathematically, the only difference between Sections 3.1 and 3.2 is that the risk behaviour parameter $\eta_e < 1$ is replaced by $\eta_n > 1$ to show the difference in behaviour between educated and uneducated HIV-positive cases. While testing and providing education is a scenario that reduces HIV prevalence, the testing-only program may increase risky behaviour for HIV-positive cases, which will increase HIV prevalence.

3.4. Testing with Limited Education.
In this submodel, we examine a program that provides testing for everyone, but education of positive cases is not available for everybody due to cost or infrastructure limitations.

3.4.1. The Model.
Assume $p \in [0, 1]$ and $\sigma_t = \sigma_{et} = 0$. Then $I_{nt} = I_{et} = I_{nr} = I_{er} = 0$, so (2) becomes

$$S^* = \frac{\Lambda}{\lambda^* + \mu}, \tag{20}$$

$$I^* = \frac{\Lambda \lambda^*}{(\lambda^* + \mu)(\mu + \gamma + \sigma_k)}, \tag{21}$$

$$I_n^* = \frac{(1 - p)\sigma_k \Lambda \lambda^*}{(\lambda^* + \mu)(\mu + \gamma + \sigma_k)(\mu + \gamma + \rho_e)}, \tag{22}$$

$$I_e^* = \frac{p\sigma_k \Lambda \lambda^* (\mu + \gamma + \rho_e) + \rho_e (1 - p)\sigma_k \Lambda \lambda^*}{(\lambda^* + \mu)(\mu + \gamma + \sigma_k)(\mu + \gamma + \rho_e)(\mu + \gamma)}, \tag{23}$$

$$\lambda^* = \frac{\beta(\mu + \gamma + \rho_e)(\mu + \gamma + p\eta_e \sigma_k) + \eta_n \beta(1 - p)\sigma_k(\mu + \gamma) + \rho_e(1 - p)\sigma_k}{(\mu + \gamma)(\mu + \gamma + \sigma_k) + (1 - p)\sigma_k(\mu + \gamma) + p\sigma_k(\mu + \gamma + \rho_e)}$$

$$- \frac{(\mu + \gamma)(\mu + \gamma + \sigma_k)(\mu + \gamma + \rho_e)}{(\mu + \gamma)(\mu + \gamma + \sigma_k) + (1 - p)\sigma_k(\mu + \gamma) + p\sigma_k(\mu + \gamma + \rho_e)}. \tag{24}$$

Note that (20)–(23) include the DFE $(S^*, I^*, I_e^*) = (\Lambda/\mu, 0, 0, 0)$ when $\lambda^* \leq 0$ and the endemic equilibrium when $\lambda^* > 0$.

3.4.3. Local and Global Stability.
Similar to Section 3.1.3, the DFE has the Jacobian matrix

$$J$$

$$= \begin{bmatrix} -\mu & -\beta & -\eta_n \beta & -\eta_e \beta \\ 0 & \beta - (\mu + \gamma + \sigma_k) & \eta_n \beta & \eta_e \beta \\ 0 & (1 - p)\sigma_k & -(\mu + \gamma + \rho_e) & 0 \\ 0 & p\sigma_k & \rho_e & -(\mu + \gamma) \end{bmatrix}. \tag{25}$$

$$S'(t) = \Lambda - (\lambda + \mu)S,$$

$$I'(t) = \lambda S - (\mu + \gamma + \sigma_k)I,$$

$$I_n'(t) = (1 - p)\sigma_k I - (\mu + \gamma + \rho_e)I_n, \tag{19}$$

$$I_e'(t) = p\sigma_k I + \rho_e I_n - (\mu + \gamma)I_e,$$

with $\lambda = \beta[I + \eta_n I_n + \eta_e I_e]/N$ and $N = S + I + I_n + I_e$. See Figure 2(c).

We will calculate the equilibria for this system and analyze their stability. Also, we will express the basic reproduction number for this system in terms of the basic reproduction numbers of the testing-only program and the testing with obligatory education program.

3.4.2. The Equilibria.
Similar to Section 3.1.2, we have

The linear stability of the DFE is obtained using the next-generation matrix [42]. Define the nonnegative matrix

$$F \equiv \begin{bmatrix} \beta & \eta_n \beta & \eta_e \beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{26}$$

and the nonsingular matrix

$$V \equiv \begin{bmatrix} \mu + \gamma + \sigma_k & 0 & 0 \\ -(1 - p)\sigma_k & \mu + \gamma + \rho_e & 0 \\ -p\sigma_k & -\rho_e & \mu + \gamma \end{bmatrix}. \tag{27}$$

The reproduction number is

$$R_{0ne} = \rho\left(FV^{-1}\right) = \frac{\beta\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right) + \eta_n\beta\left(1 - p\right)\sigma_k\left(\mu + \gamma\right) + \eta_e\beta\sigma_k\left((1 - p)\rho_e + p\left(\mu + \gamma + \rho_e\right)\right)}{\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right)\left(\mu + \gamma + \sigma_k\right)}. \tag{28}$$

As a result, we have the following theorem.

Theorem 7. *For $R_{0ne} < 1$, the DFE is locally asymptotically stable and for $R_{0ne} > 1$ the DFE is unstable.*

Note that $\lambda^* < 0$ when $R_{0ne} < 1$, so we have the following corollary.

Corollary 8. *(1) If $R_{0e} < 1$, then the DFE is the only equilibrium. (2) If $R_{0e} > 1$, then the DFE and the EE coexist.*

Note that

$$R_{0ne} = pR_{0e} + (1 - p)R_{0n}$$
$$- \frac{(1 - p)\sigma_k\beta\rho_e\left(\eta_n - \eta_e\right)}{\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right)\left(\mu + \gamma + \sigma_k\right)}. \tag{29}$$

For $p = 1$, we have $R_{0ne} = R_{0e}$ and for $p = 0$ and $\rho_e = 0$ (i.e., no education), we have $R_{0ne} = R_{0n}$. Note also that the third term in (29) is always negative with absolute value less than or equal to $(1 - p)R_{0n}$. So we have the following corollary.

Corollary 9. *If $R_{0e}, R_{0n} < 1$, then $R_{0ne} < 1$.*

For global stability of the DFE, we have the following theorem.

Theorem 10. *The DFE is a globally asymptotically stable equilibrium of model system (19) provided $R_{0ne} < 1$.*

Proof. As in Theorem 3, we utilize Theorem 2 in [40]. Consider $F(X, 0) = [K - \mu X]$,

$$A = \begin{bmatrix} \beta - (\mu + \gamma + \sigma_k) & \eta_n\beta & \eta_e\beta \\ (1 - p)\sigma_k & -(\mu + \gamma + \rho_e) & 0 \\ p\sigma_k & \rho_e & -(\mu + \gamma) \end{bmatrix}, \tag{30}$$

$$\widetilde{G}(X, Y) = \begin{bmatrix} \beta\left(I + \eta_n I_n + \eta_e I_e\right)\left(1 - \dfrac{S}{N}\right) \\ 0 \\ 0 \end{bmatrix} \geq 0,$$

for all $(X, Y) \in \{(S, I, I_n, I_e) \in \mathbb{R} : N \leq \Lambda/\mu\}$. As a result, the conditions of Theorem 2 [40] are satisfied, and the result follows. $\square$

Now let us study the stability of the EE utilizing Theorem 4 in [40]. For

$$\beta = \frac{\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right)\left(\mu + \gamma + \sigma_k\right)}{(1 - p)\sigma_k\sigma\left[\eta_n\beta\left(\mu + \gamma\right) + \eta_e\beta\rho_e\right] + \left(\mu + \gamma + \rho_e\right)\left[\beta\left(\mu + \gamma\right) + \eta_e\beta p\sigma_k\right]} \equiv \beta_c, \tag{31}$$

the Jacobian matrix for the DFE has zero as an eigenvalue, with left eigenvector

$$u_1$$
$$= -\frac{\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right)\left(\mu + \gamma + \sigma_k\right)}{\mu\left(1 - p\sigma_k\right)\left(\rho_e + \left(p/\left(1 - p\right)\right)\left(\mu + \gamma + \rho_e\right)\right)}u_4,$$
$$u_2 = \frac{\left(\mu + \gamma + \rho_e\right)\left(\mu + \gamma\right)}{\left(1 - p\sigma_k\right)\left(\rho_e + \left(p/\left(1 - p\right)\right)\left(\mu + \gamma + \rho_e\right)\right)}u_4, \tag{32}$$
$$u_3 = \frac{\left(\mu + \gamma\right)}{\rho_e + \left(p/\left(1 - p\right)\right)\left(\mu + \gamma + \rho_e\right)}u_4$$

and $u_4 > 0$ free. Also, it has the right eigenvector

$$v_1 = 0,$$
$$v_2 = \frac{\left(\mu + \gamma\right)}{\eta_e\beta}v_4,$$

$$v_3 = \frac{\eta_n\beta\left(\mu + \gamma\right) + \eta_e\beta\rho_e}{\eta_e\beta\left(\mu + \gamma + \rho_e\right)}v_4 \tag{33}$$

and $v_4 > 0$ free. Moreover,

$$b \equiv \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial_{x_i}\partial_\beta}\left(E_0, \beta_0\right) = v_2\left(u_2 + \eta_n u_3 + \eta_e u_4\right) \tag{34}$$
$$> 0,$$

where E_0 is the DFE. So (iv) is the only applicable case in Theorem 4 in [40]. This implies that when β changes from $\beta < \beta_c$ to $\beta > \beta_c$, E_0 changes from stable to unstable and the EE changes from negative to positive and locally asymptotically stable.

We have thus proved the following.

Theorem 11. *For $R_{0ne} > 1$ but close to 1, the unique EE is locally asymptotically stable.*

Remark 12. Note that when p is close to one, $\partial R_{0ne}/\partial \sigma_k < 0$ and $\partial R_{0ne}/\partial \rho_e < 0$. This means that any testing should be provided with subsequent education to reduce R_{0ne} and hence control the disease.

$$p > 1 - \frac{1 - R_{0e}}{R_{0n} - R_{0e} - (\sigma_k \beta \rho_e (\eta_n - \eta_e) / (\mu + \gamma + \rho_e) (\mu + \gamma) (\mu + \gamma + \sigma_k))}. \tag{35}$$

If $\rho_e \to 0$, this inequality becomes $p > 1 - ((1 - R_{0e})/(R_{0n} - R_{0e}))$. This implies a critical value for early education to

We end this section with the following remark in which a formula for critical value of early education is given explicitly, when late education rate is given and fixed.

Remarks. One can prove that $R_{0ne} < 1$ if and only if

control HIV in the absence of treatment. Note also that, if early education is fixed, then the late education threshold is given by

$$\rho_e > \frac{(\mu + \gamma)^2 (\mu + \gamma + \sigma_k) [pR_{0e} + (1 - p) R_{0n} - 1]}{(1 - p) \sigma_k \beta (\eta_n - \eta_e) + (\mu + \gamma) (\mu + \gamma + \sigma_k) - (pR_{0e} + (1 - p) R_{0n})}. \tag{36}$$

Figure 3 illustrates R_{0ne} as a function of two variables, showing that $R_{0ne} > 1$ always for our sample parameter values. We have also explicitly found critical values for education parameters, such that any higher education implies disease control.

We have established local and global stability for the DFE and local stability for the EE. Moreover, the value of the basic reproduction number and the critical rate of transmission are calculated. In addition, the basic reproduction number is expressed in terms of the basic reproduction numbers of the two previous programs: testing only and testing with obligatory education.

We have shown that if sufficient education is provided, then the disease can be controlled. We found a critical value of early education to control HIV in the absence of treatment, although this value may not be reached in practice. As a result, any testing program accompanied by partial education of some tested individuals should be supported with subsequent education for individuals who did not receive education at the time.

3.5. Test and Treat without Education. In this submodel, we examined the test-and-treat program taking into account the possibility of the prevalence of drug-resistant cases, but in the absence of education. This is equivalent to the Granich model [14], but with drug resistance included.

3.5.1. The Model. Setting $p = 0$, system (2) is reduced to

$$S'(t) = \Lambda - (\lambda + \mu) S,$$

$$I'(t) = \lambda S - (\mu + \gamma + \sigma_k) I,$$

$$I_n'(t) = \sigma_k I + r_c I_{nt} - (\mu + \gamma + \sigma_t) I_n, \tag{37}$$

$$I_{nt}'(t) = \sigma_t I_n - (\mu + \gamma_t + \sigma_r + r_c) I_{nt},$$

$$I_{nr}'(t) = \sigma_r I_{nt} - (\mu + \gamma) I_{nr},$$

with $\lambda = \beta[I + \eta_n I_n + \eta_{nt} I_{nt} + \eta_{nr} I_{nr}]/N$ and $N = S + I + I_n + I_{nt} + I_{nr}$. See Figure 2(d).

3.5.2. The Equilibria. Setting $f_1 = \mu + \gamma + \sigma_k$, $f_2 = \mu + \gamma + \sigma_t$, $f_3 = \mu + \gamma_t + \sigma_r + r_c$, and $f_4 = \mu + \gamma$, then the equilibria for system (37) satisfy

$$S^* = \frac{\Lambda}{\lambda^* + \mu},$$

$$I^* = \frac{\Lambda \lambda^*}{(\lambda^* + \mu) f_1},$$

$$I_n^* = \frac{\sigma_k \Lambda \lambda^* f_3}{(\lambda^* + \mu) f_1 [f_2 f_3 - r_c \sigma_t]}, \tag{38}$$

$$I_{nt}^* = \frac{\sigma_t \sigma_k \Lambda \lambda^*}{(\lambda^* + \mu) f_1 [f_2 f_3 - r_c \sigma_t]},$$

$$I_{nr}^* = \frac{\sigma_r \sigma_t \sigma_k \Lambda \lambda^*}{(\lambda^* + \mu) f_1 f_4 [f_2 f_3 - r_c \sigma_t]},$$

with

$$\lambda^* = \frac{\beta \varphi_n - \theta_n}{\psi_n}, \tag{39}$$

where

$$\varphi_n = f_4 [f_2 f_3 - r_c \sigma_t + \eta_n \sigma_k f_3 + \eta_{nt} \sigma_t \sigma_k] + \eta_{nr} \sigma_r \sigma_t \sigma_k,$$

$$\theta_n = f_4 f_1 [f_2 f_3 - r_c \sigma_t],$$

$$\psi_n = f_4 [f_2 f_3 - r_c \sigma_t + \sigma_k f_3 + \sigma_t \sigma_k] + \sigma_r \sigma_t \sigma_k. \tag{40}$$
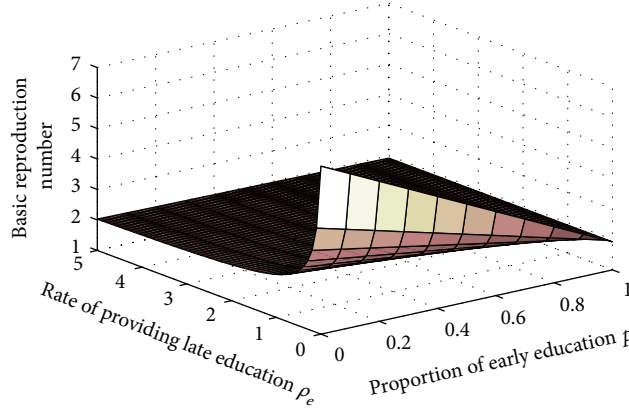
FIGURE 3: The basic reproduction number for the model of testing with limited education (29) as a function of two variables: the rate of late education before treatment (ρ_e) and proportion of early education (p). It is clear that this program does not eradicate the disease since $R_{0ne} > 1$ always. Thus education alone is insufficient.

3.5.3. Local and Global Stability. For the DFE, we have the Jacobian matrix

$$
J = \begin{bmatrix}
-\mu & -\beta & -\eta_n\beta & -\eta_{nt}\beta & -\eta_{nr}\beta \\
0 & \beta - f_1 & \eta_n\beta & \eta_{nt}\beta & \eta_{nr}\beta \\
0 & \sigma_k & -f_2 & r_c & 0 \\
0 & 0 & \sigma_t & -f_3 & 0 \\
0 & 0 & 0 & \sigma_r & -f_4
\end{bmatrix}. \tag{41}
$$

Set

$$
F \equiv \begin{bmatrix}
\beta & \eta_n\beta & \eta_{nt}\beta & \eta_{nr}\beta \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix},
$$

$$
V \equiv \begin{bmatrix}
f_1 & 0 & 0 & 0 \\
-\sigma_k & f_2 & -r_c & 0 \\
0 & -\sigma_{nt} & f_3 & 0 \\
0 & 0 & -\sigma_r & f_4
\end{bmatrix}. \tag{42}
$$

Then

$$
R_{0nt} = \rho\left(FV^{-1}\right)
$$
$$
= \frac{\beta\left(f_3 f_2 f_4 - f_4\sigma_t r_c + \eta_n\sigma_k f_3 f_4 + \eta_t\sigma_t\sigma_k f_4 + \eta_{nr}\sigma_r\sigma_t\sigma_k\right)}{f_1 f_4\left(f_2 f_3 - r_c\sigma_t\right)}, \tag{43}
$$

the basic reproduction number.

We have proved the following theorem.

Theorem 13. *For $R_{0nt} < 1$, the DFE is locally asymptotically stable. For $R_{0nt} > 1$, the DFE is unstable.*

It is clear that $R_{0nt} < 1$ implies $\lambda^* < 0$. So we have the following corollary.

Corollary 14. *(1) If $R_{0nt} < 1$, then the DFE is the only equilibrium. (2) If $R_{0nt} > 1$, the DFE and the EE coexist.*
Now we will prove the global stability for the DFE.

Theorem 15. *The DFE is a globally asymptotically stable equilibrium of model system (50) provided $R_{0nt} < 1$.*

Proof. Again, we utilize Theorem 2 in [40]. Consider $F(X, 0) = [K - \mu X]$,

$$
A = \begin{bmatrix}
\beta - (\mu + \gamma + \sigma_k) & \eta_e\beta & \eta_{nt}\beta & \eta_n\beta \\
\sigma_k & -(\mu + \gamma + \sigma_t) & r_c & 0 \\
0 & \sigma_t & -(r_c + \sigma_r + \mu + \gamma_t) & 0 \\
0 & 0 & \sigma_r & -(\mu + \gamma)
\end{bmatrix},
$$

$$
\widetilde{G}(X, Y) = \begin{bmatrix}
\beta\left(I + \eta_e\left(I_n + I_{nr}\right) + \eta_{nt}I_{nt}\right)\left(1 - \dfrac{S}{N}\right) \\
0 \\
0 \\
0
\end{bmatrix} \geq 0, \tag{44}
$$

for all $(X, Y) \in \{(S, I, I_e, I_{et}, I_{er}) \in \mathbb{R} : N \leq \Lambda/\mu\}$. So the conditions of Theorem 2 [40] are satisfied, and the global stability follows from this theorem. □

For the stability of the EE, the previous technique is used here (applying Theorem 4 in [40]).

Note that

$$\beta = \frac{\theta}{\varphi} \equiv \beta_c \tag{45}$$

is equivalent to $R_{0nt} = 1$. The Jacobian matrix for the DFE has zero as an eigenvalue, with left eigenvector

$$
\begin{aligned}
u_1 &= -\frac{\beta}{\mu}\left[u_2 + \eta_n u_3 + \eta_{nt} u_4 + \eta_{nr} u_5\right], \\
u_2 &= \frac{\beta}{\sigma_k \sigma_r \sigma_t}\left[f_2 f_3 - r_c \sigma_t\right] u_5, \\
u_3 &= \frac{f_3 f_4}{\sigma_r \sigma_t} u_5, \\
u_4 &= \frac{f_4}{\sigma_r} u_5
\end{aligned}
\tag{46}
$$

and $u_5 > 0$ free. Also, it has right eigenvector

$$
\begin{aligned}
v_1 &= 0, \\
v_3 &= \left(\frac{\beta \sigma_t}{f_2 f_3 - r_c \sigma_t}\left(\frac{\eta_n r_c}{f_2} + \frac{\eta_{nr} \sigma_r}{f_4} + \eta_{nt}\right) + \frac{\eta_n \beta}{f_2}\right) v_2, \\
v_4 &= \frac{\beta f_2}{f_2 f_3 - r_c \sigma_t}\left(\frac{\eta_n r_c}{f_2} + \frac{\eta_{nr} \sigma_r}{f_4} + \eta_{nt}\right) v_2, \\
v_5 &= \frac{\eta_{nr} \beta v_2}{f_4} v_2
\end{aligned}
\tag{47}
$$

and $v_2 > 0$ free. Moreover,

$$
\begin{aligned}
b &\equiv \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(E_0, \beta_c) \\
&= v_2\left(u_2 + \eta_e u_3 + \eta_{nt} u_4 + \eta_e u_5\right) > 0,
\end{aligned}
\tag{48}
$$

where E_0 is the DFE. The positivity of b follows because $v_2, u_2, u_3, u_4, u_5 > 0$. This implies that (i) or (iv) in Theorem 4 [40] is applicable. However, for $\beta < \beta_0$, E_0 is locally asymptotically stable and we have no other positive equilibria, which means that (iv) is the only applicable case. This means that, when β changes from $\beta < \beta_0$ to $\beta > \beta_0$, E_0 changes from stable to unstable and the EE changes from negative to positive and locally asymptotically stable.

As a result, we have proved the following theorem.

Theorem 16. For $R_{0nt} > 1$ but close to 1, the unique EE is locally asymptotically stable.

Remarks. (1) Note that $\partial R_{0nt}/\partial \sigma_k > 0$ and $\partial R_{0nt}/\partial \sigma_t > 0$ because $\eta_n > 1$, which means that test and treat without

education may make the disease worse, as more people know their status and as more people receive treatment.

(2) Note that Section 3.2 is a special case of this section when $\sigma_t = r_c = 0$. The reason that we examined that case explicitly is that the result in Section 3.2 was used to rewrite the basic reproduction number in Section 3.4 (29).

As a result, test and treat without education will exacerbate the disease when drug resistance is taken into account. In the next section, we include education.

3.6. Test and Treat with Drug Resistance and Obligatory Education.

In this submodel, we examined the test-and-treat program, supported by obligatory education for HIV-positive cases, while including the effects of drug resistance.

3.6.1. The Model.
Setting $p = 1$, but $\sigma_{et} \neq 0$, system (2) is reduced to

$$
\begin{aligned}
S'(t) &= \Lambda - (\lambda + \mu)S, \\
I'(t) &= \lambda S - (\mu + \gamma + \sigma_k)I, \\
I_e'(t) &= \sigma_k I + r_{ec} I_{et} - (\mu + \gamma + \sigma_{et})I_e, \\
I_{et}'(t) &= \sigma_{et} I_e - (\mu + \gamma_t + \sigma_{re} + r_{ec})I_{et}, \\
I_{er}'(t) &= \sigma_{re} I_{et} - (\mu + \gamma)I_{er},
\end{aligned}
\tag{49}
$$

with $\lambda = \beta[I + \eta_e I_e + \eta_{et} I_{et} + \eta_{er} I_{er}]/N$ and $N = S + I + I_e + I_{et} + I_{er}$. See Figure 2(e).

We will analyse this system in a similar way as the previous models. Let $g_1 = \mu + \gamma + \sigma_k$, $g_2 = \mu + \gamma + \sigma_{et}$, $g_3 = \mu + \gamma_t + \sigma_{re} + r_{ec}$, and $g_4 = \mu + \gamma$.

3.6.2. The Equilibria.
For system (49), we have the equilibria

$$
\begin{aligned}
S^* &= \frac{\Lambda}{\lambda^* + \mu}, \\
I^* &= \frac{\Lambda \lambda^*}{(\lambda^* + \mu)g_1}, \\
I_e^* &= \frac{\sigma_k \Lambda \lambda^* g_3}{(\lambda^* + \mu)g_1[g_2 g_3 - r_{ec}\sigma_{et}]}, \\
I_{et}^* &= \frac{\sigma_{et}\sigma_k \Lambda \lambda^*}{(\lambda^* + \mu)g_1[g_2 g_3 - r_{ec}\sigma_{et}]}, \\
I_{er}^* &= \frac{\sigma_{re}\sigma_{et}\sigma_k \Lambda \lambda^*}{(\lambda^* + \mu)g_1 g_4[g_2 g_3 - r_{ec}\sigma_{et}]},
\end{aligned}
\tag{50}
$$

with

$$\lambda^* = \frac{\beta\varphi - \theta}{\psi}, \tag{51}$$

where

$$\varphi = g_4 \left[g_2 g_3 - r_{ec}\sigma_{et} + \eta_e \sigma_k g_3 + \eta_{et}\sigma_{et}\sigma_k \right]$$
$$+ \eta_{er}\sigma_{re}\sigma_{et}\sigma_k,$$
$$\theta = g_1 g_4 \left[g_2 g_3 - r_{ec}\sigma_{et} \right], \tag{52}$$
$$\psi = g_4 \left[g_2 g_3 - r_{ec}\sigma_{et} + \sigma_k g_3 + \sigma_{et}\sigma_k \right] + \sigma_{re}\sigma_{et}\sigma_k.$$

This includes the DFE $(S^*, I^*, I_e^*, I_{et}^*, I_{er}^*) = (\Lambda/\mu, 0, 0, 0, 0)$ when $\lambda^* \le 0$ and the endemic equilibrium, when $\lambda^* > 0$.

3.6.3. Local and Global Stability. For the DFE, we have the Jacobian matrix

$$J = \begin{bmatrix} -\mu & -\beta & -\eta_e\beta & -\eta_{et}\beta & -\eta_{er}\beta \\ 0 & \beta - g_1 & \eta_e\beta & \eta_{et}\beta & \eta_{er}\beta \\ 0 & \sigma_k & -g_2 & r_{ec} & 0 \\ 0 & 0 & \sigma_{et} & -g_3 & 0 \\ 0 & 0 & 0 & \sigma_{re} & -g_4 \end{bmatrix}. \tag{53}$$

The linear stability of the DFE follows from the next-generation matrix with

$$F \equiv \begin{bmatrix} \beta & \eta_e\beta & \eta_{et}\beta & \eta_{er}\beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$
$$V \equiv \begin{bmatrix} g_1 & 0 & 0 & 0 \\ -\sigma_k & g_2 & -r_{ec} & 0 \\ 0 & -\sigma_{et} & g_3 & 0 \\ 0 & 0 & -\sigma_{re} & g_4 \end{bmatrix}, \tag{54}$$

$$R_{0et} = \rho\left(FV^{-1}\right)$$
$$= \frac{\beta\left(g_2 g_3 g_4 - g_4\sigma_{et}r_{ec} + \eta_e\sigma_k g_3 g_4 + \eta_{et}\sigma_{et}\sigma_k g_4 + \eta_{er}\sigma_{re}\sigma_{et}\sigma_k\right)}{g_1 g_4\left(g_2 g_3 - \sigma_{et}r_{ec}\right)}. \tag{55}$$

We have proved the following theorem.

Theorem 17. *For $R_{0et} < 1$, the DFE is locally asymptotically stable. For $R_{0et} > 1$, the DFE is unstable.*

It is clear that $R_{0et} < 1$ implies $\lambda^* < 0$. So we have the following corollary.

Corollary 18. *(1) If $R_{0et} < 1$, then the DFE is the only equilibrium. (2) If $R_{0et} > 1$, the DFE and the EE coexist.*

The proofs of the following two theorems are similar to those in Section 3.5.3.

Theorem 19. *The DFE is a globally asymptotically stable equilibrium of model system (50) provided $R_{0et} < 1$.*

Theorem 20. *For $R_{0et} > 1$ but close to 1, the unique EE is locally asymptotically stable.*

Remarks. (1) Note that $\partial R_{0et}/\partial\sigma_k < 0$ and $\partial R_{0et}/\partial\sigma_{et} < 0$ because $\eta_e < 1$, which means that if obligatory education is provided, then the test-and-treat program will reduce R_{0et} and theoretically control the disease. For the dependence of R_{0et} on both treatment and drug resistance rates, see Figure 4.

(2) Note that Section 3.1 is a special case of this section. However, the results from Section 3.1 were used to rewrite the basic reproduction number in Section 3.4 (29).

4. Full Model Analysis

We now turn to the full model. Using the next-generation matrix with

$$F \equiv \begin{bmatrix} \beta & \eta_n\beta & \eta_e\beta & \eta_t\beta & \eta_{et}\beta & \eta_{er}\beta & \eta_{nr}\beta \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V \tag{56}$$

$$\equiv \begin{bmatrix} h_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -(1-p)\sigma_k & h_2 & 0 & -r_c & 0 & 0 & 0 \\ -p\sigma_k & -\rho_e & h_3 & 0 & -r_{ec} & 0 & 0 \\ 0 & -\sigma_t & 0 & h_4 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_{te} & -\rho_{te} & h_5 & 0 & 0 \\ 0 & 0 & 0 & -\sigma_r & 0 & h_6 & 0 \\ 0 & 0 & 0 & 0 & -\sigma_{re} & -\rho_{te} & h_7 \end{bmatrix},$$

we have

$$R_0 = \rho\left(FV^{-1}\right) = \frac{\beta\Psi}{\Phi}, \tag{57}$$

where

$$\Psi = h_6 h_7 h_4 h_2 h_5 h_3 - h_6 h_7 h_4 h_2 \sigma_{te} r_{ec} - h_6 h_7 \sigma_t r_c h_5 h_3$$
$$+ h_6 h_7 \sigma_t r_c \sigma_{te} r_{ec} + \eta_n q\sigma_k h_4 h_6 h_7 h_5 h_3$$
$$- \eta_n q\sigma_k h_4 h_6 h_7 \sigma_{te} r_{ec} + \eta_e \sigma_k h_6 h_7 ph_2 h_4 h_5$$
$$- \eta_e \sigma_k h_6 h_7 p\sigma_t r_c h_5 + \eta_e \sigma_k h_6 h_7 \rho_e qh_4 h_5$$
$$+ \eta_e \sigma_k h_6 h_7 r_{ec}\sigma_t q\rho_{te} + \eta_{nt}\sigma_t q\sigma_k h_6 h_7 h_5 h_3$$
$$- \eta_{nt}\sigma_t q\sigma_k h_6 h_7 \sigma_{te} r_{ec} + \eta_{et}\sigma_k h_6 h_7 \sigma_{te} ph_2 h_4$$
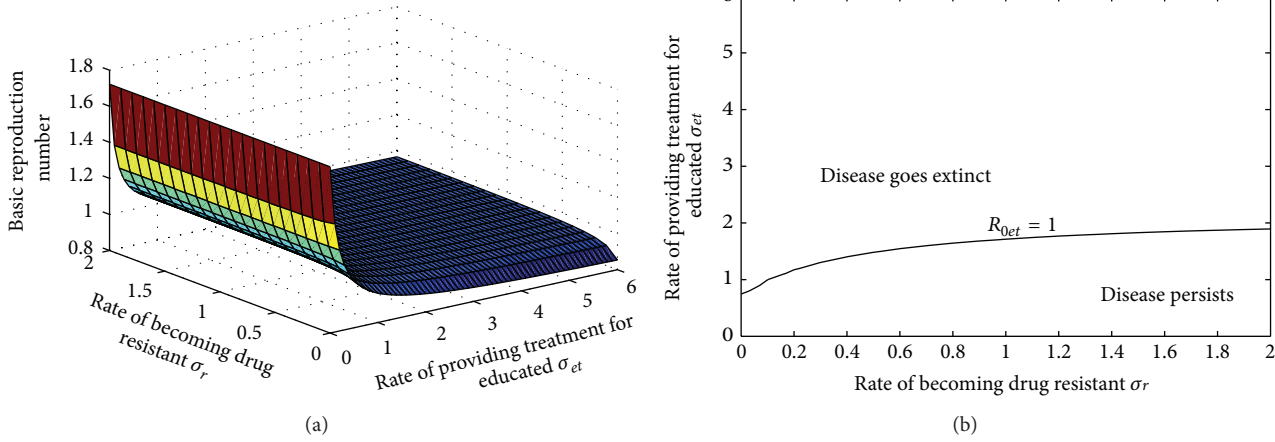
FIGURE 4: (a) The basic reproduction number for the test and treat with drug resistance and obligatory education model (55) as a function of two variables: the rate of becoming drug resistant σ_r and the rate of providing treatment for educated individuals σ_{et}. (b) The projection of the surface $R_{0et} = 1$ on the plane (σ_r, σ_{et}). With sufficient education, the disease can be controlled.

$$
\begin{aligned}
&- \eta_{et}\sigma_k h_6 h_7 \sigma_{te} p \sigma_t r_c + \eta_{et}\sigma_k h_6 h_7 \sigma_{te} \rho_e q h_4 \\
&+ \eta_{et}\sigma_k h_6 h_7 \sigma_t q \rho_{te} h_3 + \eta_{er}\sigma_r \sigma_t q \sigma_k h_7 h_5 h_3 \\
&- \eta_{er}\sigma_r \sigma_t q \sigma_k h_7 \sigma_{te} r_{ec} + \eta_{nr}\sigma_k \sigma_{re} h_6 \sigma_{te} p h_2 h_4 \\
&- \eta_{nr}\sigma_k \sigma_{re} h_6 \sigma_{te} p \sigma_t r_c + \eta_{nr}\sigma_k \sigma_{re} h_6 \sigma_{te} \rho_e q h_4 \\
&+ \eta_{nr}\sigma_k \sigma_{re} h_6 \sigma_t q \rho_{te} h_3 + \eta_{nr}\sigma_k \rho_{te} \sigma_r \sigma_t q h_5 h_3 \\
&- \eta_{nr}\sigma_k \rho_{te} \sigma_r \sigma_t q \sigma_{te} r_{ec}, \\
\Phi = {}& h_1 h_6 h_7 \left(h_4 h_2 h_5 h_3 - h_4 h_2 \sigma_{te} r_{ec} - \sigma_t r_c h_5 h_3 \right. \\
&\left. + \sigma_t r_c \sigma_{te} r_{ec} \right).
\end{aligned}
\tag{58}
$$

Here

$$
\begin{aligned}
h_1 &= \mu + \gamma + \sigma_k, \\
h_2 &= \mu + \gamma + \sigma_t + \rho_e, \\
h_3 &= \mu + \gamma + \sigma_{et}, \\
h_4 &= \mu + \gamma_t + \sigma_r + r_c + \rho_{te}, \\
h_5 &= \mu + \gamma_t + \sigma_{re} + r_{ec}, \\
h_6 &= \mu + \gamma + \rho_{te}, \\
h_7 &= \mu + \gamma.
\end{aligned}
\tag{59}
$$

We thus have the following result.

Theorem 21. *For $R_0 < 1$, the DFE for the full model is locally asymptotically stable. For $R_0 > 1$, the DFE is unstable.*

The analysis of the full model is limited, due to the complexity of the model. While we were able to determine the local stability of the DFE, the remaining analysis is restricted to the submodels we examined above. However, we will supplement this with numerical simulations.

5. Numerical Simulations

The data used for the simulations are given in Table 1. Note that the value of the modification parameters is calculated using the transmission values for different classes given in Table S2 [9], in which the values represent $\eta_i \beta$ for $i = n, e, nt, et$. We calculated the mean value of $\widetilde{\beta}_m = 0.086$. We then used the endpoints of the ranges given for $\widetilde{\beta}$ in Table S2 [9] and solved $\widetilde{\eta}\widetilde{\beta}_m = \widetilde{\beta}$. The values for $\widetilde{\eta}$ are used as endpoints to construct ranges for η_i for $i = n, e, nt, et$. Finally, $\sigma_r = 1/L$, where L is the time spent under treatment before becoming drug resistant, with a range 6.5–8.6 in Table S11 [9].

We start by investigating the sensitivity analysis of R_{0ne} to parameters. This covers the various testing cases, with varying degrees of education, but without treatment.

5.1. Sensitivity Analysis. Due to the degree of uncertainty in the parameter values, we examined a range of parameter values to investigate the dependence of R_{0ne} on parameter variation for testing with partial education. We use Latin hypercube sampling and partial rank correlation coefficients (PRCCs) to identify which parameters R_{0ne} is most sensitive to [43]. Latin hypercube sampling is a statistical sampling method that evaluates sensitivity of an outcome variable to all input variables. PRCCs measure the relative degree of sensitivity to each parameter, regardless of whether the parameter has a positive or negative influence on the outcome variable. Figure 5(a) plots PRCCs for each input parameter for the testing with limited education model. This demonstrates that R_{0ne} is most sensitive to variations in transmissibility, β, the degree of modification for transmission among educated individuals, η_e, and the rate of progress to AIDS, γ. Note that the sensitivity analysis is for the case of testing with limited education, not the full model.

Thus the disease is reliably controlled only for sufficiently small transmissibility, low modification of transmission for educated, and a high rate of progress to AIDS. It should be noted that variations in β and η_e will change R_{0ne} from
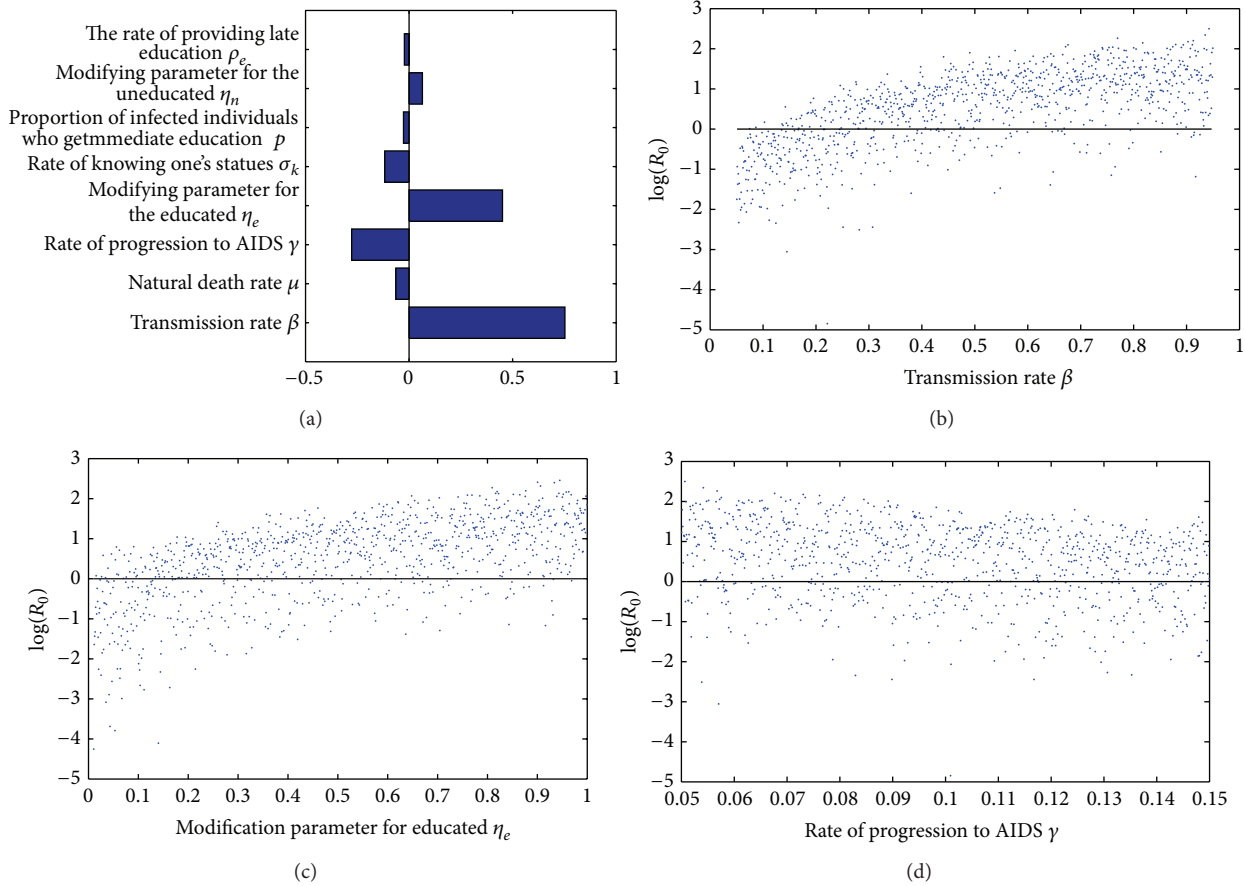
FIGURE 5: Sensitivity analysis for the testing with limited education model. (a) Partial rank correlation coefficients indicate that transmissibility, the modification parameter for educated individuals and the rate of progress to AIDS have the greatest effect on R_{0ne}. Parameters with PRCC > 0 will increase R_{0ne} when they are increased, while parameters with PRCC < 0 will decrease R_{0ne} when they are increased. (b)–(d) Monte Carlo simulations for 1000 runs drawn from parameter ranges using Latin Hypercube Sampling. If β or η_e is sufficiently small, then the disease can be controlled.

values greater than one to small values, resulting in significant dependence of R_{0ne} on these parameters in Figure 5. Note that β has more effect on the outcome in practice, but we have little control over the transmissibility. However, with education, the coefficient η_e can be decreased.

It should be noted that this sensitivity analysis restricts p to the range 0.85–1, which means that we are starting with a population for whom a large proportion receive education immediately after knowing their status. If p is reduced significantly below this, then eradication is not possible.

5.2. The Impact of Education on Testing with Limited Education.
In the testing with limited education model (19), we considered three scenarios.

(1) Early versus late education: we compare the effect of early education ($p = 0.75$, $\rho_e = 0.25$) and late education ($p = 0.25$, $\rho_e = 0.75$) by comparing the percentage of infected in all classes after 10 years. See Figure 6(a). We used the formula % $= e^{-rL}$ to change percentages to rates, where L is the average period of time spent in the class to be educated [9]. The

impact of education is essentially unchanged whether it occurs early or late.

(2) The impact of education on average testing: we examined the effect of education by comparing the infected classes in the model (19) with education ($p = 0.75$, $\rho_e = 1$) and the infected classes without education ($p = 0$, $\rho_e = 0$) after 10 years with average testing ($\sigma_k = 0.55$ as in the table). See Figure 6(b). It is clear that education reduces the percentage of infected in all classes.

(3) The impact of education on rapid testing: we examined the effect of education by comparing the infected classes in the model (19) with education ($p = 0.75$, $\rho_e = 1$) and the infected classes without education ($p = 0$, $\rho_e = 0$) after 10 years for rapid testing ($\sigma_k = 1$). See Figure 6(c). It is clear that education reduces the percentage of infected in all classes.

5.3. The Impact of Education on Different Test-and-Treat Scenarios.
In the full model (2), we considered the following scenarios.
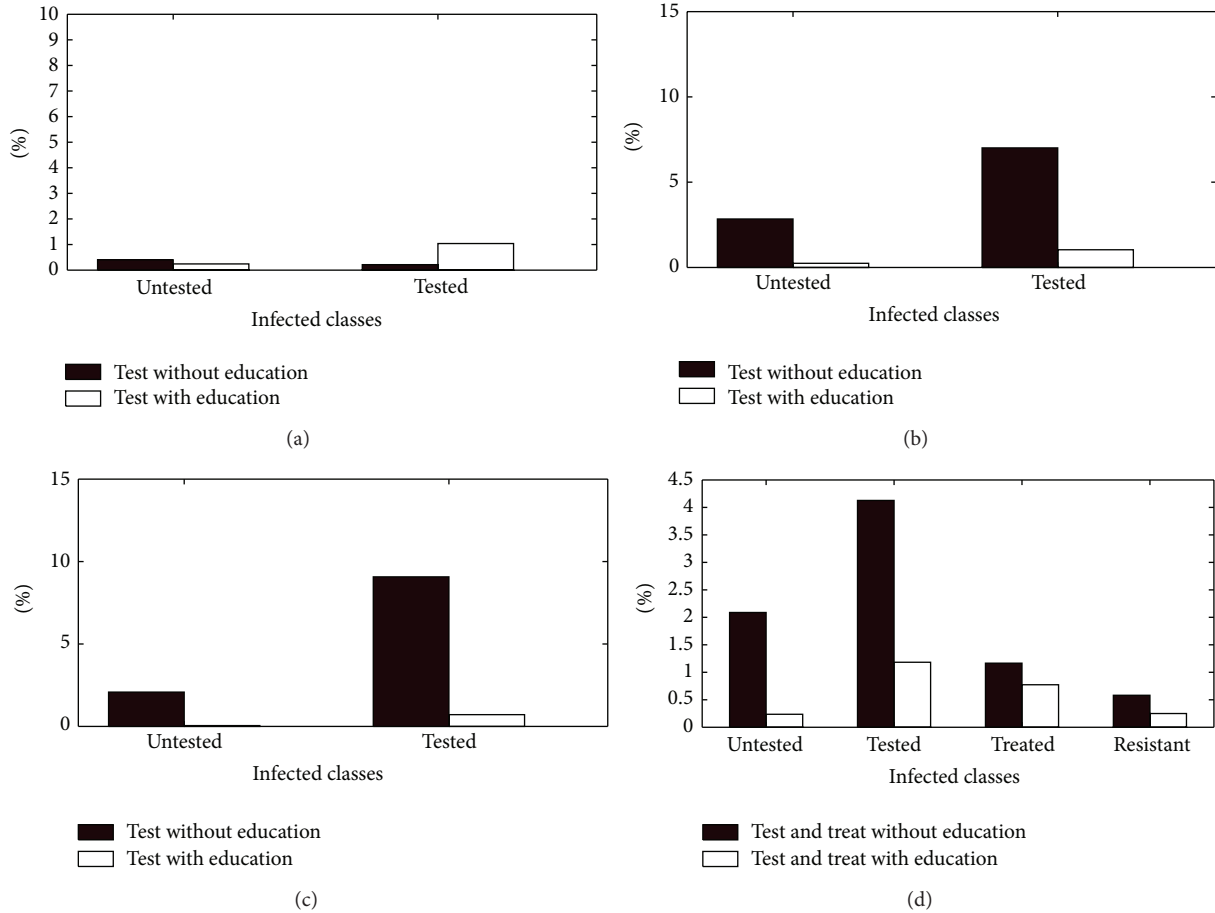
(a)

(b)

(c)

(d)

FIGURE 6: The effects of education on the number of infected individuals (total population started with is 1450) after 10 years. (a) Comparison between percentage of infected in different classes when early education ($p = 0.75$, $\rho_e = 0.25$) and late education ($p = 0.25$, $\rho_e = 0.75$) are considered in the limited-education model (19). (b) Comparison between percentage of infected individuals in different classes when average testing is provided ($\sigma_k = 0.55$), in the absence of education ($p = 0$, $\rho_e = 0$) and when partial education is provided ($p = 0.75$, $\rho_e = 1$) in the limited-education model. (c) Comparison between percentage of infected individuals in different classes when rapid testing is adopted ($\sigma_k = 1$), in the absence of education ($p = 0$, $\rho_e = 0$) and when limited education is provided ($p = 0.75$, $\rho_e = 1$) in the limited-education model. (d) Comparison between percentage of infected in different classes in the absence of education and when limited education is provided ($p = 0.75$, $\rho_e = 1$, and $\rho_{et} = 1$) in the full model. Here low treatment is considered ($\sigma_t = \sigma_{et} = 0.125$).

(1) The impact of education on average testing and late treatment: in this part, we examined the impact of education when late treatment is adopted. In the model (2), we considered $\sigma_t = \sigma_{et} = 0.125$, assuming that infected individuals spend eight years (on average) before starting treatment. Then we compared the percentage of people infected after 10 years in the absence of education and in the cases $p = 0.75$, $\rho_e = 1$, and $\rho_{et} = 1$.

We also illustrated a time-series solution for model (2) with and without education. It is clear from Figure 8 that, without education, rapid testing and early treatment need at least 20 years more than the same scenario with education and costs more, due to the higher number of cases to be treated.

(2) The impact of education on average testing and early treatment: in this part, we studied the impact of

education when early treatment is adopted. In model (2), we considered $\sigma_t = \sigma_{et} = 4$, corresponding to the infected waiting only three months (on average) before starting treatment. Then we compared the percentage of people infected after 30 years in the absence of education and in the cases $p = 0.75$, $\rho_e = 1$, and $\rho_{et} = 1$. Figure 7(a) shows the importance of supporting any treatment program with education to reduce the number of infected in all classes, especially in the drug-resistant class.

(3) The impact of education on rapid testing and early treatment: in this part, we studied the impact of education when early treatment is adopted, using the same parameters as in the previous scenario except that $\sigma_k = 1$, corresponding to knowing one's status within a year of infection. The differences between Figures 7(a) and 7(b) are slight, whereas the effects of education (white boxes) in each are significant across
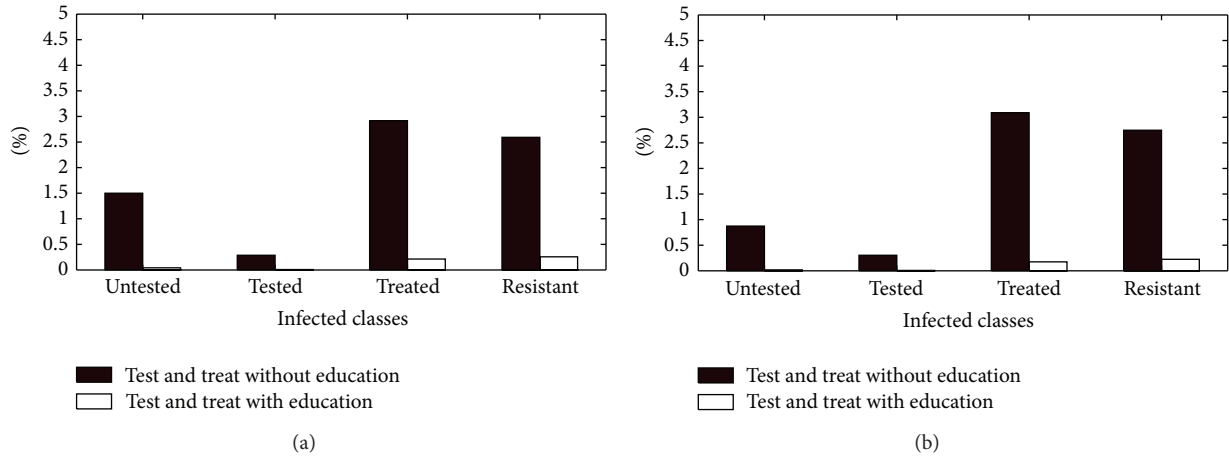
(a)

(b)

FIGURE 7: Comparison between percentage of infected (after 30 years, using model (2)) in different classes in the absence of education (solid boxes) and when the following education parameters are considered: $p = 0.75$, $\rho_e = 1$, and $\rho_{et} = 1$ (white boxes). (a) Early treatment and average testing ($\sigma_t = \sigma_{et} = 4$ and $\sigma_k = 0.55$). (b) Early treatment and rapid testing ($\sigma_t = \sigma_{et} = 4$ and $\sigma_k = 1$). Thus education has a greater effect on drug resistance than rapid testing.
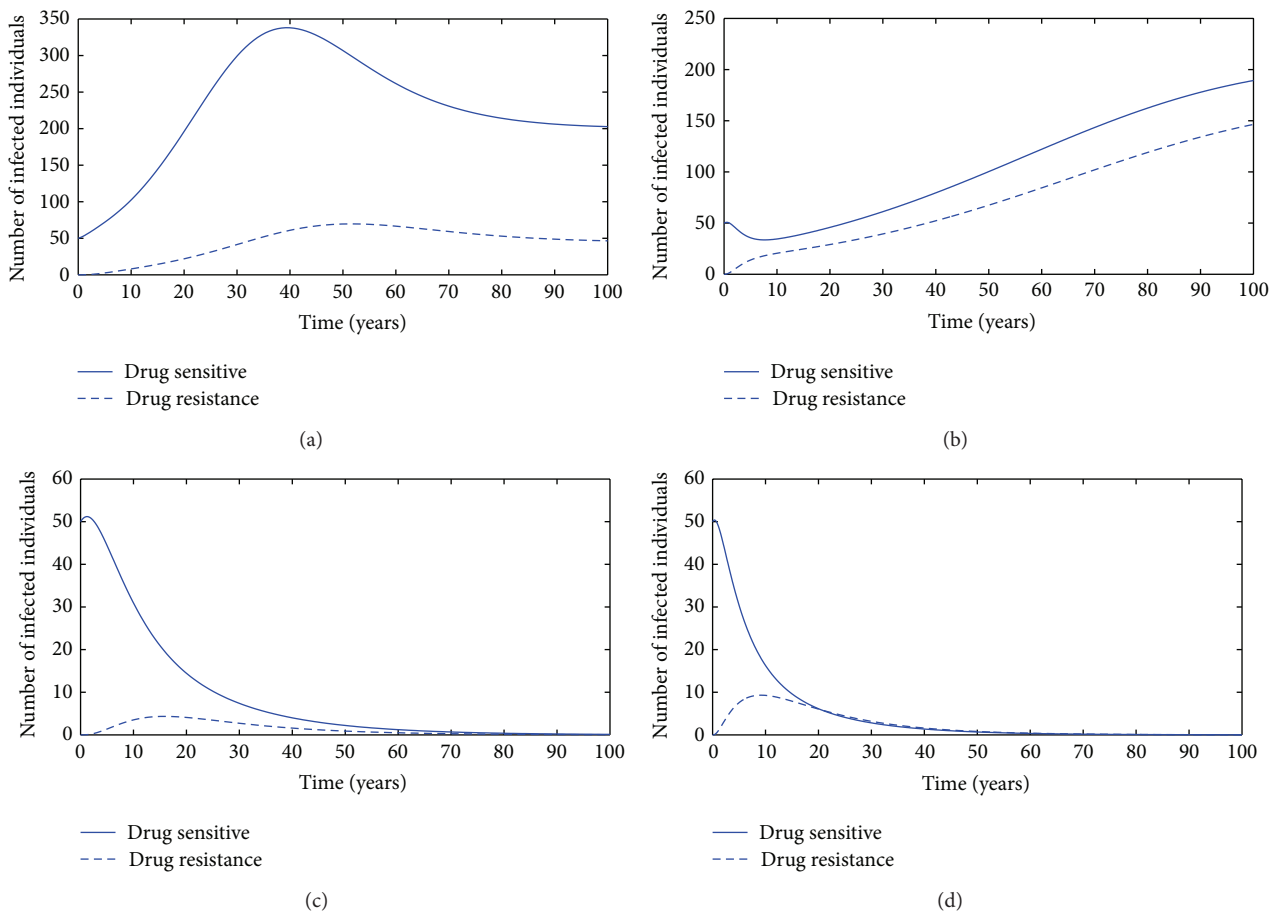

(a)

(b)

(c)

(d)

FIGURE 8: Infected non-drug-resistant (solid curves) and drug-resistant (dashed curves) individuals as a function of time, for the full model. The upper figures are with no education, while the lower figures use education parameters $p = 0.75$, $\rho_e = 1$, and $\rho_{et} = 1$. On the left, treatment parameters considered are $\sigma_t = \sigma_{et} = 0.125$ and $\sigma_k = 0.55$, corresponding to average testing and late treatment. On the right, treatment parameters considered are $\sigma_t = \sigma_{et} = 4$ and $\sigma_k = 1$, corresponding to rapid testing and early treatment. Thus, without education, rapid testing and early treatment are likely to lead to high levels of resistance in the long term.

all classes, especially in the drug-resistant class. This suggests that education has a much greater impact on the outcome than early testing.

It follows that education is important, but also that too rapid treatment may "burn up" the grace period, leading to long-term elevated levels of drug resistance.

6. Discussion

As a disease-management tool, education has the potential to transform societies. If applied correctly, using culturally specific sensitivity, education may be the dividing line between disease management and an epidemic that remains out of control. Here, we measure education's success by its ability to reduce the risk of infection. This may be through behaviour changes such as reduced sexual contact, more protection options such as condoms or altering other risky behaviour. There are, of course, many complexities to education and the means of delivery, but what we see here is the power that it can have to keep HIV in check, if combined with testing.

Treatment is desirable, but overtreatment is not. Specifically, treating HIV-positive individuals too early provides little short-term benefit but has the potential to amplify drug resistance considerably. When the first-line drugs run out, most individuals in the developing world will be unable to afford second-line treatments. This is likely to result in continual use of first-line drugs, even if their net effect may be negative. Without careful safeguards, the current "test-and-treat" program may very well spark an epidemic of drug-resistant virus that will be impervious to future treatment. However, we have shown that education, whether provided at the outset or later, can overcome the effects of drug resistance.

Control of HIV tends to focus on easily measurable scientific outcomes, such as a successful vaccine, microbicide, or drug regimen, which are all aspects of physical sciences. However, the natural sciences have a great deal to offer as well; targeting human behaviour, while less of a measurable outcome, can nevertheless reap enormous rewards. Too often in the scientific literature, HIV is thought of as an abstract problem to be solved, with little regard to human suffering. Conversely, by ignoring human behaviour, many theoretical studies are ignoring a potentially significant variable. As understood in this context, education and the stochasticity of behaviour are not so much "soft" elements of natural science but an important variable missing from many physical science studies.

Our model has some limitations, which should be acknowledged. We focused on HIV-positive individuals, ignoring susceptibles. We conflated different ages and genders, which may have an impact, especially where education is concerned (e.g., education may reach those within the school system much more easily than those outside it). Treatment was also considered uniform for those infected, which is not true in general and often stratifies with socioeconomic status. A major challenge for future research is to include education for the susceptible population, which may be modelled using numerical simulations. We note, however, that educating the infected population can theoretically control the disease; furthermore, with scaled-up testing, reaching such individuals is feasible, whereas reaching susceptible individuals may be more complicated. Furthermore, the assumption that uneducated individuals increase their risk behaviour could be relaxed in such simulations, allowing risk behaviour to either increase or decrease stochastically.

Nevertheless, it is clear that HIV/AIDS educational programs can have a positive impact on the epidemic, especially when social structure and cultural beliefs of the community are considered. Educating those infected with HIV/AIDS may cause behavioural changes and safe sex practices that reduce HIV/AIDS infections. Additionally, treating HIV-positive individuals who change their sexual behaviour and reduce their sexual contacts with other individuals may be an effective tool to control the epidemic. However, treatment must be carefully managed to avoid the prevalence of drug-resistant HIV. Getting tested, knowing one's HIV status, controlled treatment, and changing one's sexual behaviour are all factors that will contribute to a reduction in HIV transmission.

In summary, any testing program should be supported by education. As a strategy, "test and treat" is potentially worthwhile, if the initial focus is "test," if "treat" is carefully managed and if the program can be supplemented with high-quality, culturally specific education. Furthermore, if obligatory education is provided, then the test-and-treat program will theoretically control the disease. As a result, the best program is test and treat with education, even when drug resistance is taken into account. It follows that education is the missing piece from the test-and-treat jigsaw.

Disclosure

For citation purposes, please note that the question mark is part of the author's name.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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