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ORIGINAL RESEARCH

Mathematical Analysis of a Model for Assessing the Impact of Antiretroviral Therapy, Voluntary Testing and Condom Use in Curtailing the Spread of HIV

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Abstract This paper presents a deterministic model for evaluating the impact of anti-retroviral drugs (ARVs), voluntary testing (using standard antibody-based and a DNA-based testing methods) and condom use on the transmission dynamics of HIV in a community. Rigorous qualitative analysis of the model show that it has a globally-stable disease-free equilibrium whenever a certain epidemiological threshold, known as the *effective reproduction number* ($\mathcal{R}_{\text{eff}}$), is less than unity. The model has an endemic equilibrium whenever $\mathcal{R}_{\text{eff}} > 1$. The endemic equilibrium is shown to be locally-asymptotically stable for a special case. Numerical simulations of the model show that the use of the combined testing and treatment strategy is more effective than the use of the standard ELISA testing method with ARV treatment, even for the use of condoms as a singular strategy. Furthermore, the universal strategy (which involves the use of condoms, the two testing methods and ARV treatment) is always more effective than the combined use of the standard ELISA testing method and ARVs.

Keywords HIV · Nucleic acid amplification testing (NAAT) · ARVs · Condoms · Standard testing · Reproduction number · Stability

Introduction

Since its emergence in the 1980s, the human immunodeficiency virus (HIV), the causative agent of the acquired immune deficiency syndrome (AIDS), continues to pose an unprecedented threat to global health and human development. Currently, 33 million people are estimated to be living with HIV/AIDS [40], and more than 25 million people have died

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from HIV-related illnesses during the last 20 years. AIDS is now the leading cause of death in sub-Saharan Africa and the fourth-leading cause of death globally [23]. In addition to being a serious public health menace, HIV/AIDS has far reaching consequences to all social and economic sectors of society. It exacerbates poverty, reduces educational opportunities, devastates the workforce, creates large numbers of orphans, and exerts tremendous pressure on already limited health and social services [2,9,14,36,39,43,44]. Another more troubling aspect of HIV disease is the fact that a sizable proportion (about 25% in North America) of those infected with the virus are not aware of their HIV status [6,25]. Thus, these individuals continue to unknowingly transmit the virus to others (in addition to not being able to benefit from clinical care to reduce morbidity and mortality).

Control measures against the spread of HIV are wide and varied. They include preventive measures (such as the use of condoms, public health education and counselling about safer sex practices, sterilization of needles in health care delivery, voluntary HIV testing) and the use of therapeutic agents. The currently available anti-HIV therapeutic measure is based on using anti-retroviral therapy, especially the highly-active anti-retroviral therapy (HAART), which is known to significantly reduce viral load in treated individuals [13,25,29,30,34]. Unfortunately, HAART is still not widely accessible in many resource-poor nations, where HIV prevalence is the highest (an estimated 5.2 million people in low-and middle-income countries were receiving life-saving HIV treatment at the end of 2009 [38]).

The purpose of this study is to use mathematical modelling to gain insight into the impact of voluntary testing, the use of condoms and the use of anti-retroviral drugs in curtailing the spread of HIV in a community. Two different testing methods, namely a standard antibody test (such as the *Enzyme Linked Immuno Absorbent Assay* (ELISA)) and a DNA-based test, known as the *Nucleic Acid Amplification Testing* (NAAT), will be considered. Unlike the standard antibody test (which typically detect antibodies in the blood after a minimum of three to four weeks of infection), NAAT can detect early infection (within the first few days of occurrence) [1,31,37].

The model to be developed in this study incorporates some of the well-known properties of HIV disease. These notably include the staged-progression aspect, where a typical HIV-infected individual passes through several infection stages, being highly infectious during the pre-antibody phase (characterized by high viremia with over 10 million viral copies per ml), maintaining low infectivity during the asymptomatic phase and becoming highly infectious as s/he progresses toward AIDS (i.e., the AIDS stage of HIV infection) [10,13,15,16,18,22,26,30]. These stages are sometimes categorized into four groups namely, acute sero-conversion stage (less than 28 days of infection), early infection stage (less than 170 days of infection but prior to development of symptoms), established infection stage (after 170 days of infection) and the AIDS stage (characterized by the presence of clinical symptoms of AIDS and very reduced level of CD4 count) [1]. Another important aspect of HIV disease is the fact that HIV RNA levels are positively correlated with infectiousness [28,34].

In addition to developing a reasonably realistic model for HIV spread, this study also contributes by including numerous anti-HIV strategies and carrying out rigorous qualitative analysis of the resulting model. The paper is organized as follows. The model is formulated in "Model Formulation" section, and rigorously analysed in subsequent subsections. Numerical simulations are reported in third section.

Model Formulation

A deterministic compartmental modelling approach is used to design the model as follows. The total population at time t, denoted by $N(t)$, is sub-divided into 10 mutually-exclusive compartments of susceptible individuals ($S(t)$), newly-infected individuals unaware of their status in the acute sero-conversion stage ($I_1^u(t)$; less than 28 days of infection), infected individuals unaware of their HIV status in the asymptomatic stage ($I_2^u(t)$; 28–170 days of infection), infected individuals unaware of their HIV infection status in the established (pre-AIDS) stage ($I_3^u(t)$), infected individuals unaware of their status in the AIDS stage of infection ($A_u(t)$), treated individuals ($T(t)$), and (corresponding) infected individuals aware of their infection status (due to positive HIV diagnosis) at the aforementioned infection stages, denoted by I_1^k, I_2^k, I_3^k and A_k, respectively. Thus,

$$N(t) = S(t) + I_1^u(t) + I_2^u(t) + I_3^u(t) + A_u(t) + I_1^k(t) + I_2^k(t) + I_3^k(t) + A_k(t) + T(t).$$

The susceptible population is increased by the recruitment of new sexually-active individuals (at a rate Π). Susceptible individuals acquire infection, following effective contact with untreated infected individuals, at a rate λ, where

$$\lambda = \frac{\beta}{N}\left[I_1^u + \eta_2 I_2^u + \eta_3 I_3^u + \eta_4 A_u + r\left(I_1^k + \eta_2 I_2^k + \eta_3 I_3^k + \eta_4 A_k\right)\right]. \tag{1}$$

In (1), β is the effective contact rate and the modification parameters $\eta_i (i = 2, 3, 4)$ are estimated as follows. The average transmission rate per coital act during the primary infection stage (i.e, less than 28 days of infection) is estimated to be 0.0082 [42]. Assuming that an infected individual in this stage of infection has an average of six sexual acts per month, it follows that the transmission rate in the primary infection stage is $\beta = 0.0082 \times 6 \times 12 = 0.59$ per year. For the second stage of infection (i.e., 28–170 days of infection), it is assumed that the average transmission rate per coital act is 0.0035. This gives a transmission rate of $\beta = 0.252$ per year (so that, $\eta_2 = 0.43$). For the third stage of HIV infection (i.e., from 170 days of infection to the onset of clinical symptoms of AIDS), the transmission rate per act is 0.007 [42], so that (by using an average of 3 acts per month) $\beta = 0.0252$ per year (hence, $\eta_3 = 0.043$). Finally, following [42], the per coital transmission probability in the AIDS stage is assumed to be 0.0028. Using an estimate of 3 acts per month, it follows that the transmission rate in this stage is $\beta = 0.1$ per year (thus, $\eta_4 = 0.17$). It should be mentioned that, in the above, it is assumed that individuals in the pre-AIDS and AIDS stages have reduced number of sexual acts in comparison to those in the primary and early infection stages (the justification for this assumption is that individuals in the pre-AIDS and AIDS stages are too sick to engage in active sexual activity). In summary, these estimates (for η_i; $i = 1, 2, 3$) show that the rate of HIV transmission is the highest during the primary infection stage ($\beta = 1$). It decreases during the second infection stage to $\beta = 0.252$, and further decreases to $\beta = 0.0252$ in the pre-AIDS stage. The transmission rate then increases to $\beta = 0.1$ in the AIDS stage. These estimates are consistent with the conclusions drawn in numerous HIV modelling studies, such as those reported in [19,42] (it should, however, be mentioned that some studies, such as that reported in [35], show that HIV transmission rate is the highest during the AIDS stage of infection).

Once infected individuals are made aware of their infection status (by positive HIV diagnosis), it is assumed that these individuals (who are moved to the class of individuals who know their positive HIV infection status) will reduce their risky behaviour by a factor of r. Marks et al. [24,25] estimated that knowledge of HIV status resulted in 57% reduction in unprotected sex (so that, $r \simeq 0.43$). Condom use is modelled in terms of reduction in the

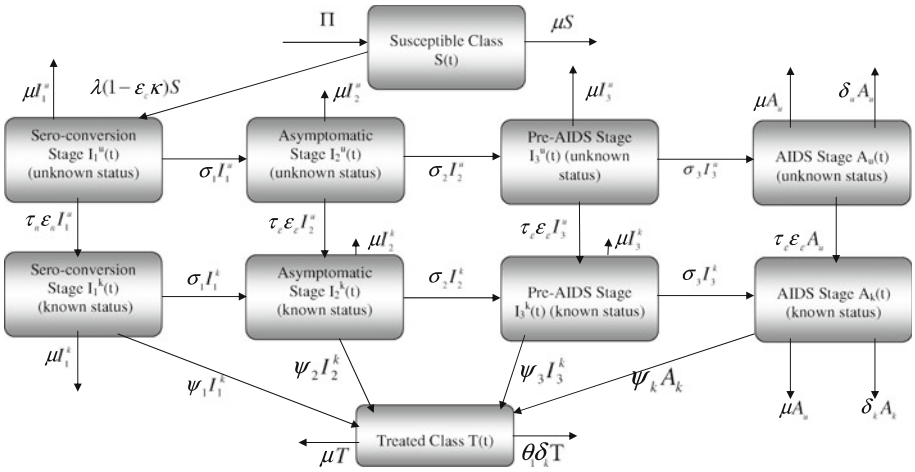

Fig. 1 Schematic diagram of the model (2)

infection rate, λ, by a factor of $(1 - \epsilon_c\kappa)$, where $0 < \epsilon_c < 1$ is the condom efficacy and $0 < \kappa < 1$ is the fraction of sexually-active individuals that use condoms consistently and correctly (condom compliance). It is assumed that newly-infected individuals are unaware of their infection status until they are detected either by NAAT or the standard antibody test.

It is assumed that individuals unaware of their infection status progress from the acute sero-conversion stage (I_1^u) to the asymptomatic stage (I_2^u), at a rate σ_1. Progression from the asymptomatic stage (I_2^u) to the pre-AIDS stage (I_3^u) occurs at a rate σ_2. Finally, pre-AIDS individuals progress to the AIDS stage at a rate σ_3. Individuals that are unaware of their infection status in the I_1^u class are tested (using NAAT) at a rate τ_n, with efficacy ϵ_n $(0 < \epsilon_n < 1)$. Those that are positively diagnosed move to the corresponding I_1^k class. Standard (ELISA) testing is used for individuals in the I_2^u, I_3^u and A_u classes at a rate τ_ϵ, with efficacy ϵ_ϵ $(0 < \epsilon_\epsilon < 1)$; and those positively identified move to their corresponding I_k class. Individuals aware of their infection status progress through the various infection stages at the same rate $(\sigma_i;\ i = 1, 2, 3)$ as those who are not (in other words, it is assumed that knowledge of HIV infection status does not alter the progression rate among untreated infected individuals).

Individuals aware of their status in the infection stages I_1^k, I_2^k, I_3^k and A_k are treated at rates ψ_1, ψ_2, ψ_3 and ψ_k, respectively. It is assumed, for mathematical tractability, that these (treated) individuals do not transmit infection. Further, natural mortality occurs in all epidemiological classes at a rate μ (i.e., $1/\mu$ represents the average duration of acquisition of sexual partners), and individuals in the AIDS stage suffer an additional disease-induced death (at rates δ_u and δ_k, for individuals unaware or aware of their status, respectively). It is assumed that treated individuals eventually succumb to the disease (at a reduced disease-induced rate $\theta_1\delta_k$, with $0 < \theta_1 < 1$).

Putting the aforementioned formulations and assumptions together, it follows that the model for HIV transmission, in the presence of the two testing methods, condom use and ARVs, is given by the following system of differential equations (a schematic description of the model is given in Fig. 1, and the variables and parameters of the model are described in Table 1):

Table 1 Description of model variables and parameters

Variable	Description
$S(t)$	Susceptible individuals
$I_1^u(t)$	Infected individuals unaware of their status in acute sero-conversion stage
$I_2^u(t)$	Infected individuals unaware of their status in the asymptomatic stage
$I_3^u(t)$	Infected individuals unaware of their status in the pre-AIDS stage
$A_u(t)$	Infected individuals unaware of their status in the AIDS stage
$I_1^k(t)$	Infected individuals aware of their status in acute sero-conversion stage
$I_2^k(t)$	Infected individuals aware of their status in the asymptomatic stage
$I_3^k(t)$	Infected individuals aware of their status in the pre-AIDS stage
$A_k(t)$	Infected individuals aware of their status in the AIDS stage
$T(t)$	Treated individuals
$N(t)$	Total population

Parameter	Description	Value/range	Reference
Π	Recruitment rate into the susceptible population	2000 $(\text{year})^{-1}$	[33]
β	Effective contact rate	3 $(\text{year})^{-1}$	Assumed
r	Reduction in risky behaviour amongst diagnosed individuals	0.43	[24,25]
$\frac{1}{\mu}$	Average duration of acquisition of sexual partners	30 years	
$\sigma_1, \sigma_2, \sigma_3$	Progression rates	13, 2.6, $\frac{1}{15}$ $(\text{year})^{-1}$	[15,18]
η_2, η_3, η_4	Modification parameters	0.43, 0.043, 0.17	Estimated using the ranges in [42]
τ_n	Rate of administration of NAAT testing	Variable	
ϵ_n	Efficacy of NAAT testing	0.99	[31]
κ	Condom compliance	0.7 $(\text{year})^{-1}$	[7]
ϵ_c	Efficacy of condom use	0.6	[3]
τ_ϵ	Rate of administration of standard (ELISA) testing	Variable	
ϵ_ϵ	Efficacy of standard testing	0.96	[31]
θ_1	Modification parameter	0.001	Assumed
δ_u, δ_k	Disease-induced mortality rates	0.47, 0.04 $(\text{year})^{-1}$	[15]
$\psi_1, \psi_2, \psi_3, \psi_k$	Treatment rates $(I_1^k, I_2^k, I_3^k, A_k)$	Variable	

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi - (1-\epsilon_c\kappa)\lambda S - \mu S,\\
\frac{dI_1^u}{dt} &= (1-\epsilon_c\kappa)\lambda S - \sigma_1 I_1^u - \tau_n\epsilon_n I_1^u - \mu I_1^u,\\
\frac{dI_2^u}{dt} &= \sigma_1 I_1^u - \sigma_2 I_2^u - \tau_\epsilon\epsilon_\epsilon I_2^u - \mu I_2^u,\\
\frac{dI_3^u}{dt} &= \sigma_2 I_2^u - \sigma_3 I_3^u - \tau_\epsilon\epsilon_\epsilon I_3^u - \mu I_3^u,\\
\frac{dA_u}{dt} &= \sigma_3 I_3^u - \tau_\epsilon\epsilon_\epsilon A_u - \mu A_u - \delta_u A_u,
\end{aligned}
$$

$$\begin{aligned}
\frac{dI_1^k}{dt} &= \tau_n \epsilon_n I_1^u - \sigma_1 I_1^k - \psi_1 I_1^k - \mu I_1^k,\\
\frac{dI_2^k}{dt} &= \sigma_1 I_1^k + \tau_\epsilon \epsilon_\epsilon I_2^u - \sigma_2 I_2^k - \psi_2 I_2^k - \mu I_2^k,\\
\frac{dI_3^k}{dt} &= \sigma_2 I_2^k + \tau_\epsilon \epsilon_\epsilon I_3^u - \sigma_3 I_3^k - \psi_3 I_3^k - \mu I_3^k,\\
\frac{dA_k}{dt} &= \sigma_3 I_3^k + \tau_\epsilon \epsilon_\epsilon A_u - \psi_k A_k - \mu A_k - \delta_k A_k,\\
\frac{dT}{dt} &= \psi_1 I_1^k + \psi_2 I_2^k + \psi_3 I_3^k + \psi_k A_k - \mu T - \theta_1 \delta_k T. \qquad (2)
\end{aligned}$$

The model (2) is a modification of the model presented in [1], in that it accounts for four HIV infection stages (as against the three infection stages considered in [1]). Furthermore, this study provides a rigorous mathematical analysis of the model (this is not given in [1]).

Basic Properties of the Model

To be epidemiologically meaningful, it is important to prove that the solutions of the basic model (2), with positive initial data, will remain positive for all time $t > 0$.

Lemma 1 *Let the initial data* $S(0) > 0, I_1^u(0) \geq 0, I_2^u(0) \geq 0, I_3^u(0) \geq 0, A_u(0) \geq 0, I_1^k(0) \geq 0, I_2^k(0) \geq 0, I_3^k(0) \geq 0, A_k(0) \geq 0$ *and* $T(0) \geq 0$. *Then, the solutions* $(S, I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k, T)$ *of the model* (2) *are non-negative for all* $t > 0$. *Furthermore,*

$$\limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu}.$$

Proof Let $t_1 = \sup\{t > 0 : S, I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k, T > 0\}$. Thus, $t_1 > 0$. It follows from the first equation of the differential equation system (2) that

$$\frac{dS(t)}{dt} = \Pi - [(1 - \epsilon_c \kappa)\lambda(t) + \mu]S(t),$$

which is equivalent to,

$$\frac{d}{dt}\left[S(t)\exp\left\{\int_0^t (1 - \epsilon_c\kappa)\lambda(u)du + \mu t\right\}\right] = \Pi \exp\left\{\int_0^t (1 - \epsilon_c\kappa)\lambda(u)du + \mu t\right\}.$$

Thus,

$$S(t_1)\exp\left\{\int_0^{t_1} (1-\epsilon_c\kappa)\lambda(u)du + \mu t_1\right\} - S(0) = \int_0^{t_1} \Pi \exp\left\{\int_0^x (1 - \epsilon_c\kappa)\lambda(v)dv + \mu x\right\} dx,$$

so that,

$$\begin{aligned}
S(t_1) = S(0)\exp\left\{-\int_0^{t_1} (1 - \epsilon_c\kappa)\lambda(u)du + \mu t_1\right\} + \exp\left\{-\int_0^{t_1} (1 - \epsilon_c\kappa)\lambda(u)du + \mu t_1\right\}\\
\times \int_0^{t_1} \Pi \exp\left\{\int_0^x (1 - \epsilon_c\kappa)\lambda(v)dv + \mu x\right\} dx > 0.
\end{aligned}$$

Similarly, it can be shown that $I_1^u(0) > 0, I_2^u(0) > 0, I_3^u(0) > 0, A_u(0) > 0, I_1^k(0) > 0, I_2^k(0) > 0, I_3^k(0) > 0, A_k(0) > 0$ and $T(0) > 0$ for all $t > 0$. Thus, all solutions of the model, with non-negative initial data, remain non-negative for all $t > 0$.

Adding all the equations of the basic model (2) gives,

$$\frac{dN(t)}{dt} = \Pi - \mu N(t) - \delta_u A_u(t) - \delta_k[A_k(t) + \theta_1 T(t)]. \tag{3}$$

Noting that $0 < A_u(t) \leq N(t), 0 < A_k(t) \leq N(t)$ and $0 < T(t) \leq N(t)$, it follows from (3) that

$$\Pi - (\mu + \delta_u + \delta_k + \theta_1\delta_k)N(t) \leq \frac{dN(t)}{dt} < \Pi - \mu N(t).$$

Thus,

$$\frac{\Pi}{\mu + \delta_u + \delta_k + \theta_1\delta_k} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu},$$

so that $\limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu}$, as required. □

Local Stability of Disease-Free Equilibrium (DFE)

Since the model (2) monitors human populations, it is assumed that the variables and associated parameters are non-negative for all $t \geq 0$. The DFE of the model (2) is given by

$$\mathcal{E}_0 = \left(S^*, I_1^{u*}, I_2^{u*}, I_3^{u*}, A_u^*, I_1^{k*}, I_2^{k*}, I_3^{k*}, A_k^*, T^*\right) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0\right). \tag{4}$$

Consider the biologically-feasible region

$$\mathcal{D} = \left\{\left(S, I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k, T\right) \in \mathbb{R}_+^{10} : N \leq \frac{\Pi}{\mu}\right\}.$$

The following steps are taken to establish the positive invariance of $\mathcal{D}$ (i.e., solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t > 0$). The rate of change of total population, obtained by adding all the equations of the model (2), is given by

$$\frac{dN}{dt} = \Pi - \mu N - \delta_u A_u - \delta_k A_k - \theta_1\delta_k T. \tag{5}$$

Since the right hand-side of (5) is bounded by $\Pi - \mu N$, a standard comparison theorem can be used to show that $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$. Thus, $\mathcal{D}$ is positively-invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (2) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed [16].

The linear stability of $\mathcal{E}_0$ is studied using the next generation operator technique in [8,41]. The associated non-negative matrix, H, for the new infection terms, and the non-singular M-matrix, V, for the remaining transfer terms, are, respectively, given by

$$H = \begin{pmatrix} \beta p & \beta\eta_2 p & \beta\eta_3 p & \beta\eta_4 p & \beta r p & \beta r\eta_2 p & \beta r\eta_3 p & \beta r\eta_4 p & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_1 & k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\sigma_2 & k_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_3 & k_4 & 0 & 0 & 0 & 0 & 0 \\ -m_1 & 0 & 0 & 0 & k_5 & 0 & 0 & 0 & 0 \\ 0 & -m_2 & 0 & 0 & -\sigma_1 & k_6 & 0 & 0 & 0 \\ 0 & 0 & -m_2 & 0 & 0 & -\sigma_2 & k_7 & 0 & 0 \\ 0 & 0 & 0 & -m_2 & 0 & 0 & -\sigma_3 & k_8 & 0 \\ 0 & 0 & 0 & 0 & -\psi_1 & -\psi_2 & -\psi_3 & -\psi_k & k_9 \end{pmatrix},$$

where,

$$p = 1 - \epsilon_c\kappa, \quad m_1 = \tau_n\epsilon_n, \quad m_2 = \tau_\epsilon\epsilon_\epsilon, \quad k_1 = \mu + \sigma_1 + \tau_n\epsilon_n,$$
$$k_2 = \sigma_2 + \mu + \tau_\epsilon\epsilon_\epsilon, \quad k_3 = \sigma_3 + \mu + \tau_\epsilon\epsilon_\epsilon, \quad k_4 = \mu + \delta_u + \tau_\epsilon\epsilon_\epsilon, \quad k_5 = \mu + \sigma_1 + \psi_1,$$
$$k_6 = \mu + \sigma_2 + \psi_2, \quad k_7 = \mu + \sigma_3 + \psi_3, \quad k_8 = \mu + \delta_k + \psi_k \quad \text{and} \quad k_9 = \mu + \theta_1\delta_k.$$

It follows that the *effective reproduction number*, denoted by $\mathcal{R}_{\text{eff}}$, is given by

$$\mathcal{R}_{\text{eff}} = \rho(HV^{-1}) = \frac{p\beta \sum_{i=1}^{3} A_i}{\prod_{i=1}^{8} k_i}, \tag{6}$$

where ρ denotes the spectral radius, and

$$A_1 = m_2 r\sigma_1 k_5\{\eta_4\sigma_3\sigma_2[k_7k_6 + k_4(k_3 + k_6)] + k_4k_8[\eta_2k_3k_7 + \eta_3\sigma_2\,(k_6 + k_3)]\},$$
$$A_2 = m_1 r k_4 k_3 k_2[(\eta_3k_8 + \eta_4\sigma_3) + k_7k_8(k_6 + \eta_2\sigma_1)],$$
$$A_3 = k_5k_6k_7k_8[\sigma_2\sigma_1(\eta_4\sigma_3 + \eta_3k_4) + k_3k_4(k_2 + \eta_2\sigma_1)].$$

The threshold quantity, $\mathcal{R}_{\text{eff}}$, measures the average number of new secondary cases generated by a single infected individual in a population where the aforementioned anti-HIV control measures are implemented. It is worth stating that, in (6), β is the infection rate and $\frac{1}{k_i}$ $(i = 1, \ldots, 8)$ represent the respective mean duration in the infection classes $(I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k)$. An associated epidemiological threshold is the *basic reproduction number* ($\mathcal{R}_0$), obtained in a similar way by considering the model (2) in the absence of any anti-HIV intervention (i.e., $\kappa = \epsilon_c = \tau_n = \epsilon_n = \tau_\epsilon = \epsilon_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0$), is given by

$$\mathcal{R}_0 = \frac{\beta A_3}{\prod_{i=1}^{8} k_i},$$

where A_3 is as defined earlier (but with the aforementioned intervention-related parameters set to zero). The threshold quantity $\mathcal{R}_0$ measures the average number of new infections generated by a single infected individual in a completely susceptible population.

Using Theorem 2 of [41], the following result is established.

Lemma 2 *The DFE, $\mathcal{E}_0$, of the system (2), given by (4), is locally-asymptotically stable (LAS) if $\mathcal{R}_{\text{eff}} < 1$, and unstable if $\mathcal{R}_{\text{eff}} > 1$.*

The epidemiological implication of Lemma 2 is that HIV can be eliminated from the community when $\mathcal{R}_{\text{eff}} < 1$, provided the initial sizes of the sub-populations of the model (2) are in the basin of attraction of $\mathcal{E}_0$. In other words, an influx of small number of infected individuals into the community will not generate large outbreaks if $\mathcal{R}_{\text{eff}} < 1$. To ensure that disease elimination is independent of the initial population sizes of the state variables of the model, a global asymptotic stability result (of the DFE) is established below.

Global Stability of DFE

Theorem 1 *The DFE of the model (2), given by (4), is globally-asymptotically stable (GAS) in $\mathcal{D}$ whenever $\mathcal{R}_{\text{eff}} \leq 1$.*

Proof Consider the Lyapunov function

$$\mathcal{M} = f_1 I_1^u + f_2 I_2^u + f_3 I_3^u + f_4 A_u + f_5 I_1^k + f_6 I_2^k + f_7 I_3^k + f_8 A_k,$$

where,

$$\begin{aligned}
f_1 &= \frac{k_1k_2k_3k_4k_5k_6k_7k_8\mathcal{R}_{\text{eff}}}{p\beta},\\
f_2 &= k_1k_5\left[k_6k_7k_8(\eta_2k_3k_4+\eta_3\sigma_2k_4+\eta_4\sigma_2\sigma_3)+rm_2k_8(\eta_2k_3k_4k_7+\eta_3\sigma_2k_4k_6+\eta_3\sigma_2k_3k_4)\right.\\
&\quad \left.+r\eta_4m_2\sigma_2\sigma_3(k_6k_7+k_4k_6+k_3k_4)\right],\\
f_3 &= k_1k_2k_5k_6\left[k_8(\eta_3k_4k_7+\eta_4\sigma_3k_7+r\eta_3m_2k_4)+r\eta_4m_2\sigma_3(k_4+k_7)\right],\\
f_4 &= k_1k_2k_3k_5k_6k_7(\eta_4k_8+r\eta_4m_2),\\
f_5 &= k_1k_2k_3k_4r(k_6k_7k_8+\eta_2\sigma_1k_7k_8+\eta_3\sigma_1\sigma_2k_8+\eta_4\sigma_1\sigma_2\sigma_3),\\
f_6 &= k_1k_2k_3k_4k_5r(\eta_2k_7k_8+\eta_3\sigma_2k_8+\eta_4\sigma_2\sigma_3),\\
f_7 &= k_1k_2k_3k_4k_5k_6r(\eta_3k_8+\eta_4\sigma_3),\\
f_8 &= k_1k_2k_3k_4k_5k_6k_7r\eta_4,
\end{aligned}$$

with Lyapunov derivative given by (where a dot represents differentiation with respect to t)

$$\begin{aligned}
\dot{\mathcal{M}} &= f_1\dot{I}_1^u + f_2\dot{I}_2^u + f_3\dot{I}_3^u + f_4\dot{A}_u + f_5\dot{I}_1^k + f_6\dot{I}_2^k + f_7\dot{I}_3^k + f_8\dot{A}_k,\\
&= \frac{k_1k_2k_3k_4k_5k_6k_7k_8S\lambda\mathcal{R}_{\text{eff}}}{\beta} - \frac{k_1^2k_2k_3k_4k_5k_6k_7k_8I_1^u\mathcal{R}_{\text{eff}}}{p\beta},\\
&\quad -\frac{k_1^2k_2k_3k_4k_5k_6k_7k_8I_1^u\mathcal{R}_{\text{eff}}}{p\beta} - \frac{k_1k_2k_3k_4k_5k_6k_7k_8N\lambda}{\beta},\\
&= \frac{k_1k_2k_3k_4k_5k_6k_7k_8S\lambda\mathcal{R}_{\text{eff}}}{\beta} - \frac{k_1k_2k_3k_4k_5k_6k_7k_8N\lambda}{\beta},
\end{aligned}$$

$$
\begin{aligned}
&= \frac{k_1k_2k_3k_4k_5k_6k_7k_8N\lambda}{\beta}\left(\frac{S\mathcal{R}_{\text{eff}}}{N}-1\right),\\
&\leq \frac{k_1k_2k_3k_4k_5k_6k_7k_8N\lambda}{\beta}(\mathcal{R}_{\text{eff}}-1) \quad \text{since } S\leq N \text{ in } \mathcal{D},\\
&\leq 0 \text{ for } \mathcal{R}_{\text{eff}}\leq 1.
\end{aligned}
$$

Thus, $\dot{\mathcal{M}}\leq 0$ if $\mathcal{R}_{\text{eff}}\leq 1$ with $\dot{\mathcal{M}}=0$ if and only if $I_1^u=I_2^u=I_3^u=A_u=I_1^k=I_2^k=I_3^k=A_k=0$. It follows, from the LaSalle's Invariance Principle [21], that $I_1^u\to 0$, $I_2^u\to 0$, $I_3^u\to 0$, $A_u\to 0$, $I_1^k\to 0$, $I_2^k\to 0$, $I_3^k\to 0$ and $A_k\to 0$ as $t\to\infty$. Further, substituting $I_1^u=I_2^u=I_3^u=A_u=I_1^k=I_2^k=I_3^k=A_k=0$ in the first and last equations of the model (2) shows that $S\to\frac{\Pi}{\mu}$ and $T\to 0$ as $t\to\infty$. Thus, $(S,I_1^u,I_2^u,I_3^u,A_u,I_1^k,I_2^k,I_3^k,A_k,T)\to(\frac{\Pi}{\mu},0,0,0,0,0,0,0,0,0)$ as $t\to\infty$. Further, since $\mathcal{D}$ is positively-invariant, it follows that the DFE, $\mathcal{E}_0$, is GAS in $\mathcal{D}$ if $\mathcal{R}_{\text{eff}}\leq 1$. □

An alternative proof for Theorem 1, using a comparison theorem argument, is given in Appendix A.

Existence and Stability of Endemic Equilibrium Point (EEP)

The existence of possible endemic equilibria of the model (that is, equilibria where the disease is endemic) is explored as follows. Let,

$$
\mathcal{E}_1=\left(S^{**},I_1^{u**},I_2^{u**},I_3^{u**},A_u^{**},I_1^{k**},I_2^{k**},I_3^{k**},A_u^{**},T^{**}\right)
$$

represents an arbitrary endemic equilibrium of the model (2). Further, let

$$
\lambda^{**}=\frac{\beta}{N^{**}}\left[I_1^{u**}+\eta_2I_2^{u**}+\eta_3I_3^{u**}+\eta_4A_u^{**}+r\left(I_1^{k**}+\eta_2I_2^{k**}+\eta_3I_3^{k**}+\eta_4A_k^{**}\right)\right]. \tag{7}
$$

Solving the equations in the model (2) at steady-state, in terms of $\lambda^{**}S^{**}$, gives

$$
\begin{aligned}
&I_1^{u**}=B_1\lambda^{**}S^{**},\ I_2^{u**}=B_2\lambda^{**}S^{**},\ I_3^{u**}=B_3\lambda^{**}S^{**},\ A_u^{**}=B_4\lambda^{**}S^{**},\\
&I_1^{k**}=B_5\lambda^{**}S^{**},\ I_2^{k**}=B_6\lambda^{**}S^{**},\ I_3^{k**}=B_7\lambda^{**}S^{**},\ A_k^{**}=B_8\lambda^{**}S^{**},\\
&T^{**}=B_9\lambda^{**}S^{**},
\end{aligned} \tag{8}
$$

with,

$$
\begin{aligned}
&B_1=\frac{p}{k_1},\ B_2=\frac{\sigma_1B_1}{k_2},\ B_3=\frac{\sigma_2B_2}{k_3},\ B_4=\frac{\sigma_3B_3}{k_4},\ B_5=\frac{m_1B_1}{k_5},\\
&B_6=\frac{1}{k_6}(\sigma_1B_5+m_2B_2),\ B_7=\frac{1}{k_7}(\sigma_2B_6+m_2B_3),\ B_8=\frac{1}{k_8}(\sigma_3B_7+m_2B_4),\\
&B_9=\frac{1}{k_9}(\psi_1q_1B_5+\psi_2q_2B_6+\psi_3q_3B_7+\psi_kq_kB_8).
\end{aligned}
$$

Using (8) in (7), and simplifying, gives

$$
B_{10}(\lambda^{**})^2-\lambda^{**}C_1=0, \tag{9}
$$

where,

$$
C_1=\mathcal{R}_{\text{eff}}-1 \quad \text{and} \quad B_{10}=\sum_{i=1}^{9}B_i.
$$

The positive endemic equilibrium of the model (2) can then be obtained by solving for λ^{**} in (9) and substituting the result into (8). Clearly, $\lambda^{**} = 0$ is a solution of (9), which corresponds to the DFE ($\mathcal{E}_0$). For $\lambda^{**} \neq 0$, the quadratic (9) can be simplified to

$$B_{10}\lambda^{**} - C_1 = 0. \tag{10}$$

Since all the model parameters are non-negative, it follows that $B_{10} > 0$ and $C_1 > 0$ for $\mathcal{R}_{\text{eff}} > 1$. Thus, the linear equation (10) has a unique positive solution, given by $\lambda^{**} = \frac{C_1}{B_{10}}$, whenever $\mathcal{R}_{\text{eff}} > 1$. The components of this solution are obtained by substituting the unique value of λ^{**} into (8). Since $\mathcal{R}_{\text{eff}} < 1$ implies that $C_1 < 0$, it follows that, for $\mathcal{R}_{\text{eff}} < 1$, $\lambda^{**} < 0$ (which is epidemiologically meaningless). Similarly, if $\mathcal{R}_{\text{eff}} = 1$, the coefficient $C_1 = 0$, so that $\lambda^{**} = 0$ (which corresponds to the DFE, $\mathcal{E}_0$). Hence, the model has no positive solution whenever $\mathcal{R}_{\text{eff}} \leq 1$. These results are summarized below.

Lemma 3 *The model (2) has a unique positive endemic equilibrium, given by $\mathcal{E}_1$, whenever $\mathcal{R}_{\text{eff}} > 1$, and no positive equilibrium otherwise.*

The local stability of the unique EEP, $\mathcal{E}_1$, will now be explored for the special case where the disease-induced mortality is negligible (i.e., $\delta_u = \delta_k = 0$). Setting $\delta_u = \delta_k = 0$ in the model (2) gives

$$\frac{dN(t)}{dt} = \Pi - \mu N(t). \tag{11}$$

Hence, it follows from (11) that $N(t) \to \frac{\Pi}{\mu} = N^*$ as $t \to \infty$. Further, using the substitution $S = N^* - I_1^u - I_2^u - I_3^u - A_u - I_1^k - I_2^k - I_3^k - A_k - T$ (and noting that $\delta_u = \delta_k = 0$) in the model (2) gives the following reduced model:

$$\begin{aligned}
\frac{dI_1^u}{dt} &= p\lambda\left(N^* - I_1^u - I_2^u - I_3^u - A_u - I_1^k - I_2^k - I_3^k - A_k - T\right) - k_1 I_1^u,\\
\frac{dI_2^u}{dt} &= \sigma_1 I_1^u - k_2 I_2^u,\\
\frac{dI_3^u}{dt} &= \sigma_2 I_2^u - k_3 I_3^u,\\
\frac{dA_u}{dt} &= \sigma_3 I_3^u - k_{41} A_u,\\
\frac{dI_1^k}{dt} &= m_1 I_1^u - k_5 I_1^k,\\
\frac{dI_2^k}{dt} &= \sigma_1 I_1^k + m_2 I_2^u - k_6 I_2^k,\\
\frac{dI_3^k}{dt} &= \sigma_2 I_2^k + m_2 I_3^u - k_7 I_3^k,\\
\frac{dA_k}{dt} &= \sigma_3 I_3^k + m_2 A_u - k_{81} A_k,\\
\frac{dT}{dt} &= \psi_1 I_1^k + \psi_2 I_2^k + \psi_3 I_3^k + \psi_k A_k - k_{91} T,
\end{aligned} \tag{12}$$

where $k_{41} = k_4|_{\delta_u=0}$, $k_{81} = k_8|_{\delta_k=0}$ and $k_{91} = k_9|_{\delta_k=0}$. It can be shown, using the above approach, that the system (12) has a unique endemic equilibrium, given by $\mathcal{E}_2 = \mathcal{E}_1|_{\delta_u=\delta_k=0}$, whenever $\mathcal{R}_c = \mathcal{R}_{\text{eff}}|_{\delta_u=\delta_k=0} > 1$. Further, the following result holds (see Appendix B for the proof):

Theorem 2 *The unique endemic equilibrium,* $\mathcal{E}_2$, *of the reduced model* (12), *is LAS whenever* $\mathcal{R}_c > 1$.

The epidemiological implication of Theorem 2 is that HIV will persist in the community if the reproduction threshold ($\mathcal{R}_c$) exceeds unity.

Numerical Simulations

The model (2) is simulated using the parameter values given in Table 1 (unless otherwise stated). Some of the parameter values are obtained from the literature (such as in [6,7,15,18,24,25,31]). In particular, the stage progression parameters are estimated as follows. Since the period for the acute sero-conversion stage (I_1) is less than 28 days of infection [1], the average duration in this stage is set at $\frac{1}{\sigma_1} = \frac{4}{52}$ (so that, $\sigma_1 = 13$ per year). Similarly, the average duration in the second infection stage (I_2) is approximately 20 weeks (28–170 days [1]). Thus, $\frac{1}{\sigma_2} = \frac{20}{52}$ (so that, $\sigma_2 = 2.6$ per year). The duration in the third (I_3) stage is assumed to be 15 years [1] (thus, $\sigma_3 = \frac{1}{15}$ per year). It should be stated that although the model is parameterized using data largely from resource-rich countries, it is robust enough to allow for the evaluation of scenarios for resource-poor nations (by using appropriate parametrization).

First of all, the model (2) is simulated to evaluate the effect of condom use, as a single anti-HIV intervention. Comparisons are made with the following three different effectiveness levels of the combined testing (standard ELISA and NAAT) and treatment strategy:

(i) low effectiveness level of the combined testing and treatment strategy: $\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.4$;
(ii) medium effectiveness level of the combined testing and treatment strategy: $\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.6$;
(iii) high effectiveness level of the combined testing and treatment strategy: $\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 1$.

The aforementioned effectiveness levels, chosen arbitrarily, are used to address the problem of the uncertainty in the estimate of the values of the parameters related to the testing and treatment rates.

Using the low effectiveness level of the combined testing and treatment strategy, it is shown that the combination of the two testing methods and treatment is more effective (saves more new cases) than the use of condoms as a singular anti-HIV strategy followed by the use of only the standard ELISA testing method with ARV treatment (Fig. 2a). Using the medium effectiveness level of the combined testing and treatment strategy, it is also shown that the combination of the two testing methods and treatment is more effective than the use of the only the standard testing method with ARVs followed by the condom use as a singular strategy (Fig. 2b). Similar trends were observed for high effectiveness level of the combined testing and treatment strategy (Fig. 2c). It should, however, be mentioned that the use of condoms as a singular anti-HIV intervention is marginally more effective than the low effectiveness level of the standard testing and ARV strategy (but this situation is reversed if the effectiveness of the standard testing and ARV strategy is increased to medium or high levels).

Figure 3 shows simulation results comparing the effect of the combined use of standard testing and ARVs against a universal strategy (that entails the use of condoms, the two testing methods and ARVs). Here, too, the aforementioned three effectiveness levels of the combined

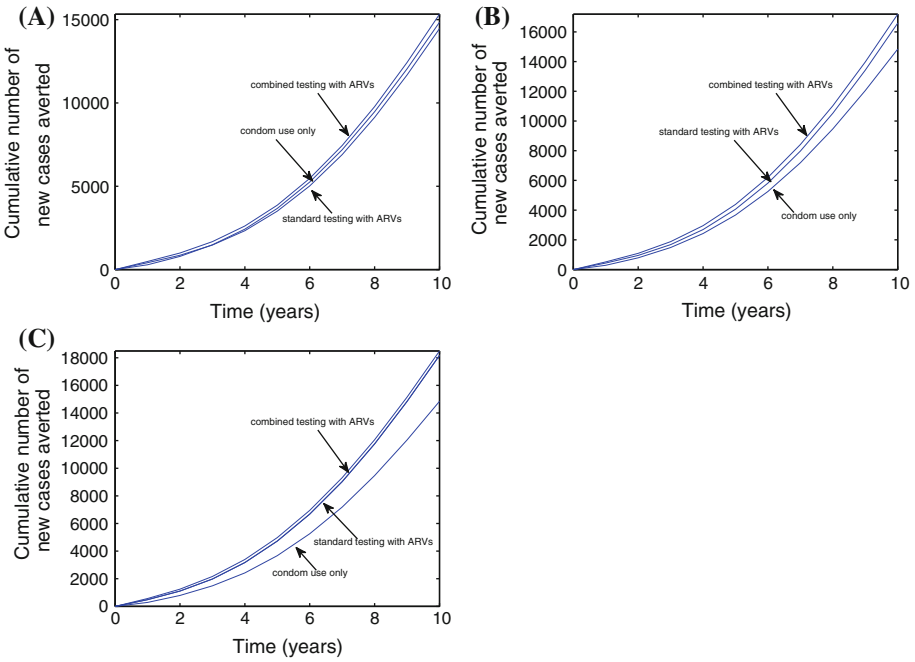

Fig. 2 Cumulative number of cases averted using condoms only and various effectiveness levels of the combined testing and ARVs intervention strategy. **a** Low effectiveness level of the combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.4$; so that, $\mathcal{R}_{\text{eff}} = 0.64$ and $\mathcal{R}_0 = 2.65$), **b** moderate effectiveness level of the combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.6$; so that, $\mathcal{R}_{\text{eff}} = 0.61$), and **c** high effectiveness level of the combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 1$; so that, $\mathcal{R}_{\text{eff}} = 0.58$). All other parameters are as given in Table 1

testing and treatment strategy are used. The universal strategy saves more cases than any of the three effectiveness levels of the combined testing and treatment strategy (see Fig. 3a–c).

Conclusions

A deterministic model is designed and used to monitor the impact of voluntary HIV testing (based on the use of a standard antibody-based and a DNA-based testing methods), condom use and the use of ARVs in curtailing the spread of HIV in a population. Rigorous qualitative analysis of the model reveals that it has a globally-asymptotically stable disease-free equilibrium whenever a certain threshold quantity is less than unity. Furthermore, the model has a unique endemic equilibrium when the threshold quantity exceeds unity. The endemic equilibrium is shown to be locally-asymptotically stable for a special case. Numerical simulations of the model, using a reasonable set of parameter values, show the following:

(i) The combined testing and treatment strategy is more effective than the use of the standard ELISA testing method with ARV treatment. The use of condoms as a sole anti-HIV strategy is marginally more effective than the low effectiveness level of the standard testing and ARV strategy (this situation is reversed if the effectiveness of the standard testing and ARV strategy is increased to medium or high levels).

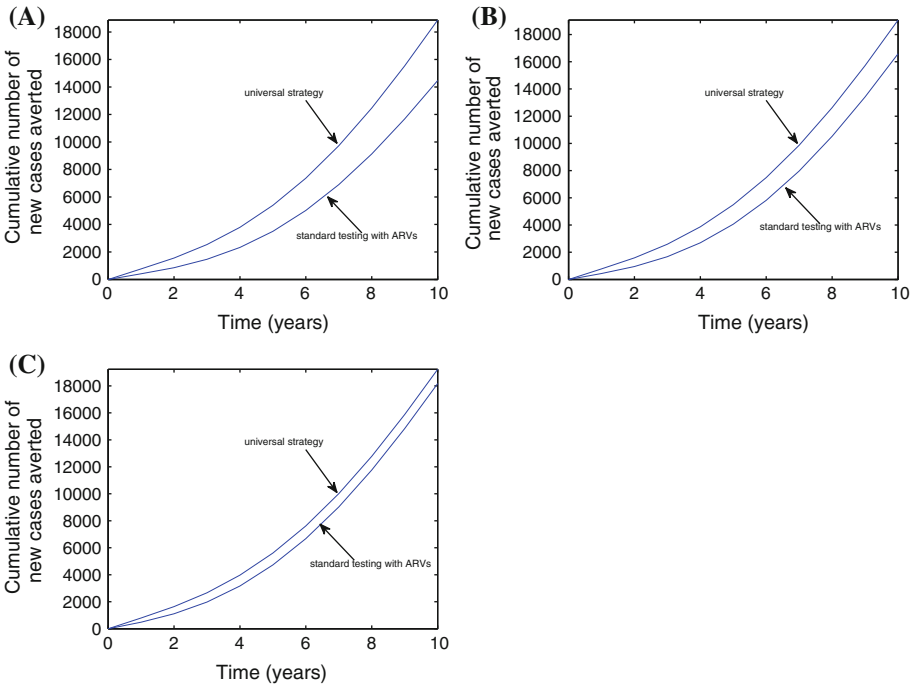

Fig. 3 Cumulative number of cases averted using a combined standard testing and ARVs and a universal strategy. **a** Low effectiveness level of the combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.4$), **b** moderate effectiveness level of the combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 0.6$), and **c** high effectiveness of the level combined testing and treatment strategy ($\tau_n = \tau_\epsilon = \psi_1 = \psi_2 = \psi_3 = \psi_k = 1$). All other parameters are as given in Table 1

(ii) The universal strategy is always more effective than the combined use of the two testing methods and ARVs (regardless of the effectiveness level of the latter strategy).

Overall, this study shows that the prospects of effectively controlling the spread of HIV using the interventions considered in this study are bright (particularly if they are used in combination). It is worth stating, however, that the simulation results presented in this study are sensitive to the choices of parameter and initial values used in the simulations. The uncertainties associated with the parameters related to the testing and treatment rates are accounted for by considering three (arbitrarily chosen) effectiveness levels of the combined testing and treatment strategy (a more detailed uncertainty analysis, based on Latin hypercube sampling [4,5,27,32] for example, can be applied if more data (related to the testing and treatment rates) becomes available).

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Appendix A: Alternative Proof for Theorem 1

Proof It should be noted, first of all, that the equations for the infected components in the model (2) can be written in terms of

$$\begin{pmatrix} \frac{dI_1^u}{dt} \\ \frac{dI_2^u}{dt} \\ \frac{dI_3^u}{dt} \\ \frac{dA_u}{dt} \\ \frac{dI_1^k}{dt} \\ \frac{dI_2^k}{dt} \\ \frac{dI_3^k}{dt} \\ \frac{dA_k}{dt} \\ \frac{dT}{dt} \end{pmatrix} = (H - V) \begin{pmatrix} I_1^u \\ I_2^u \\ I_3^u \\ A_u \\ I_1^k \\ I_2^k \\ I_3^k \\ A_k \\ T \end{pmatrix} - p\beta \left(1 - \frac{S}{N}\right) U \begin{pmatrix} I_1^u \\ I_2^u \\ I_3^u \\ A_u \\ I_1^k \\ I_2^k \\ I_3^k \\ A_k \\ T \end{pmatrix},$$

where,

$$U = \begin{pmatrix} 1 & \eta_2 & \eta_3 & \eta_4 & r & r\eta_2 & r\eta_3 & r\eta_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and H and V are as defined in "Local Stability of Disease-Free Equilibrium" section.

Since $S \leq N$ (for all $t \geq 0$) in $\mathcal{D}$, it follows that

$$\begin{pmatrix} \frac{dI_1^u}{dt} \\ \frac{dI_2^u}{dt} \\ \frac{dI_3^u}{dt} \\ \frac{dA^u}{dt} \\ \frac{dI_1^k}{dt} \\ \frac{dI_2^k}{dt} \\ \frac{dI_3^k}{dt} \\ \frac{dA^k}{dt} \\ \frac{dT}{dt} \end{pmatrix} \leq (H - V) \begin{pmatrix} I_1^u \\ I_2^u \\ I_3^u \\ A_u \\ I_1^k \\ I_2^k \\ I_3^k \\ A_k \\ T \end{pmatrix}. \tag{A.1}$$

Using the fact that the eigenvalues of the matrix $H - V$ all have negative real parts, it follows that the linearized differential inequality system (A.1) is stable whenever $\mathcal{R}_{\text{eff}} < 1$. Consequently, $(I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k, T) \to (0,0,0,0,0,0,0,0,0)$ as $t \to \infty$. It follows, by comparison theorem [20], that $(I_1^u, I_2^u, I_3^u, A_u, I_1^k, I_2^k, I_3^k, A_k, T) \to (0,0,0,0,0,0,0,0,0)$. Substituting $I_1^u = I_2^u = I_3^u = A_u = I_1^k = I_2^k = I_3^k = A_k = T = 0$ into the first equation of the model (2) gives $S(t) \to \frac{\Pi}{\mu}$ as $t \to \infty$. Thus,

$$\begin{aligned}&\left(S(t), I_1^u(t), I_2^u(t), I_3^u(t), A_u(t), I_1^k(t), I_2^k(t), I_3^k(t), A_k(t), T(t)\right)\\ &\to \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0\right)\end{aligned}$$

as $t \to \infty$ and $\mathcal{R}_{\text{eff}} < 1$. Hence, $\mathcal{E}_0$ is GAS in $\mathcal{D}$ if $\mathcal{R}_{\text{eff}} < 1$. □

Appendix B: Proof of Theorem 2

Proof Let $\mathcal{R}_c > 1$, so that the unique EEP of the reduced model (12), given by $\mathcal{E}_2$, exists. The proof of Theorem 2 is based on using the technique in [17] (see also [11,12]), which employs a Krasnoselskii sub-linearity trick. Assume, first of all, that the linearization of the system (12), around the equilibrium $\mathcal{E}_2$, has solution of the form:

$$\bar{\mathbf{Z}}(t) = \bar{\mathbf{Z}} e^{\tau t}, \tag{B.1}$$

with $\bar{\mathbf{Z}} = (Z_i)$ and $\tau, Z_i \in \mathbb{C}$ $(i = 1, \ldots, 10)$. Substituting a solution of the form (B.1) into the linearized system of (12), around the unique endemic equilibrium $\mathcal{E}_2$, gives the following system of linear equations

$$\begin{aligned}
\tau Z_1 &= (p_1 - p_2 - k_1)Z_1 + (p_1\eta_2 - p_2)Z_2 + (p_1\eta_3 - p_2)Z_3 + (p_1\eta_4 - p_2)Z_4\\
&\quad + (p_1 r - p_2)Z_5 + (p_1 r\eta_2 - p_2)Z_6 + (p_1 r\eta_3 - p_2)Z_7 + (p_1 r\eta_4 - p_2)Z_8\\
&\quad + (p_1 - p_2)Z_9,\\
\tau Z_2 &= \sigma_1 Z_1 - k_2 Z_2,\\
\tau Z_3 &= \sigma_2 Z_2 - k_3 Z_3,\\
\tau Z_4 &= \sigma_3 Z_3 - k_{41} Z_4,\\
\tau Z_5 &= m_1 Z_1 - k_5 Z_5,\\
\tau Z_6 &= \sigma_1 Z_5 + m_2 Z_2 - k_6 Z_6,\\
\tau Z_7 &= \sigma_2 Z_6 + m_2 Z_3 - k_7 Z_7,\\
\tau Z_8 &= \sigma_3 Z_7 + m_2 Z_4 - k_{81} Z_8,\\
\tau Z_9 &= \psi_1 Z_5 + \psi_2 Z_6 + \psi_3 Z_7 + \psi_k Z_8 - k_{91} Z_9,
\end{aligned} \tag{B.2}$$

where,

$$p_1 = \frac{p\beta S^{**}}{N^*}, \quad p_2 = Q_1 + Q_2,$$

with,

$$\begin{aligned}
Q_1 &= \frac{p\beta\left[I_1^{u**} + \eta_2 I_2^{u**} + \eta_3 I_3^{u**} + \eta_4 A_u^{**}\right]}{N^*},\\
Q_2 &= \frac{p\beta\left[r\left(I_1^{k**} + \eta_2 I_2^{k**} + \eta_3 I_3^{k**} + \eta_4 A_k^{**}\right)\right]}{N^*}.
\end{aligned}$$

System (B.2) is simplified as follows. Firstly, the negative terms in the last nine equations of system (B.2) are moved to their respective left-hand sides. We then solve for Z_2 from the second, Z_3 from the third and so on. The results are then substituted into the first equation of the system (B.2). Finally, all the negative terms of the first one equation are moved to the left-hand side. These algebraic manipulations result in the following general system:

$$[1 + F_i(\tau)]Z_i = (M\bar{\mathbf{Z}})_i, \quad i = 1, \ldots, 9, \tag{B.3}$$

where,

$$F_1(\tau) = D_1 + \frac{p_2}{k_1}\left[D_2 + D_3 + D_4 + D_5 + D_6 + D_7 + D_8 + \frac{1}{\tau + k_{91}}(\psi_1 D_5 + \psi_2 D_6 + \psi_3 D_7 + \psi_k D_8)\right],$$

$$F_2(\tau) = \frac{\tau}{k_2},\ F_3(\tau) = \frac{\tau}{k_3},\ F_4(\tau) = \frac{\tau}{k_4},\ F_5(\tau) = \frac{\tau}{k_5},\ F_6(\tau) = \frac{\tau}{k_6},\ F_7(\tau) = \frac{\tau}{k_7},$$

$$F_8(\tau) = \frac{\tau}{k_8},\ F_9(\tau) = \frac{\tau}{k_{91}},\ D_1 = \frac{\tau + p_2}{k_1},\ D_2 = \frac{\sigma_1}{\tau + k_2},\ D_3 = \frac{\sigma_2 D_2}{\tau + k_3},$$

$$D_4 = \frac{\sigma_3 D_3}{\tau + k_4},\ D_5 = \frac{m_1}{\tau + k_5},\ D_6 = \frac{m_2 D_2}{\tau + k_6} + \frac{\sigma_1 D_5}{\tau + k_6},\ D_7 = \frac{m_2 D_6}{\tau + k_7},\ D_8 = \frac{m_2 D_4}{\tau + k_8},$$

with,

$$M = \begin{pmatrix} p_1 & \eta_2 p_1 & \eta_3 p_1 & \eta_4 p_1 & r p_1 & r\eta_2 p_1 & r\eta_3 p_1 & r\eta_4 p_1 & p_1 \\ \frac{\sigma_1}{k_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\sigma_2}{k_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\sigma_3}{k_{41}} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{m_1}{k_5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{m_2}{k_6} & 0 & 0 & \frac{\sigma_1}{k_6} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{m_2}{k_7} & 0 & 0 & \frac{\sigma_2}{k_7} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{m_2}{k_{81}} & 0 & 0 & \frac{\sigma_3}{k_{81}} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\psi_1}{k_{91}} & \frac{\psi_2}{k_{91}} & \frac{\psi_3}{k_{91}} & \frac{\psi_k}{k_{91}} & 0 \end{pmatrix}.$$

The notation $M(\bar{Z})_i$ (with $i = 1, \ldots, 9$) denotes the ith coordinate of the vector $M(\bar{\mathbf{Z}})$. It should further be noted that the matrix M has non-negative entries, and the equilibrium $\mathcal{E}_2$ satisfies $\mathcal{E}_2 = M\mathcal{E}_2$. Furthermore, since the coordinates of $\mathcal{E}_2$ are all positive, it follows then that if $\bar{Z}$ is a solution of (B.3), then it is possible to find a minimal positive real number s such that

$$|| \bar{\mathbf{Z}} || \leq s\mathcal{E}_2, \tag{B.4}$$

where, $|| \bar{\mathbf{Z}} || = (|| Z_1 ||, \ldots, || Z_9 ||)$ with the lexicographic order, and $|| \cdot ||$ is a norm in $\mathbb{C}$.

The main goal is to show that $Re(\tau) < 0$. Assume the contrary (i.e., $Re(\tau) \geq 0$). We then need to consider two cases: $\tau = 0$ and $\tau \neq 0$. Assume the first case, $\tau = 0$. Then, (B.2) is a homogeneous linear system in the variables Z_i ($i = 1, \ldots, 9$). The determinant of the system (B.2) corresponds to that of the Jacobian of the system (12) evaluated at $\mathcal{E}_2$, which is given by

$$\triangle = \frac{E\lambda S^{**} p}{N^*} + k_1 k_2 k_3 k_{41} k_5 k_6 k_7 k_{81} k_{91}\left(1 - \frac{S^{**}}{N^*}\mathcal{R}_c\right), \tag{B.5}$$

where,

$$
\begin{aligned}
E = {} & m_2k_5\sigma_1\{\sigma_2\sigma_3k_{41}[k_6k_{12}(q_k+k_{91})]+\sigma_2k_{41}k_{81}(k_3+k_6)\\
& +k_3k_4k_7k_8k_{12}(1+k_{11})+k_3k_4k_8k_{11}(k_7a_2+\sigma_2k_{12}+a_3\sigma_2)\}\\
& +m_1k_2k_3k_{41}\{\sigma_1\sigma_2[\sigma_3(k_{91}+1)+k_8(1+k_{91})]+k_7k_8[k_6+k_{91}(\sigma_1+k_6)+\sigma_1]\}\\
& +k_5k_6k_7k_{81}k_{91}[\sigma_1\sigma_2(\sigma_3+k_{41})+k_3k_{41}(k_2+\sigma_1)].
\end{aligned}
$$

By solving the equations of the model (12), at the endemic steady-state $\mathcal{E}_2$, and using the first equation of (12), it can be shown that

$$\frac{S^{**}}{N^*}=\frac{1}{\mathcal{R}_c}. \tag{B.6}$$

Thus, using (B.6) in (B.5) shows that $\triangle > 0$. Consequently, the system (12) can only have the trivial solution $\bar{\mathbf{Z}}=\bar{\mathbf{0}}$ (which corresponds to the DFE, $\mathcal{E}_0$).

Now we consider the case $\tau \neq 0$. In this case, $Re(F_i(\tau)) \geq 0 (i = 1, \ldots, 9)$ since, by assumption, $Re(\tau) \geq 0$. It is easy to see that this implies $\mid 1 + F_i(\tau) \mid > 1$ for all i. Now, define $F(\tau) = \min \mid 1 + F_i(\tau) \mid$ (for $i = 1, \ldots, 9$). Then, $F(\tau) > 1$. Hence, $\frac{s}{F(\tau)} < s$. The minimality of s implies that $\| \bar{\mathbf{Z}} \| > \frac{s}{F(\tau)}\mathcal{E}_2$. But, on the other hand, taking norms on both sides of the second equation of (B.2), and using the fact that M is non-negative, we obtain

$$F(\tau) \| Z_2 \| \leq M(\| Z \|)_2 \leq s(M \| \mathcal{E}_2 \|)_2 \leq sI_1^{u**}. \tag{B.7}$$

Then, it follows from the above inequality that $\| Z_2 \| \leq \frac{s}{F(\tau)} I_1^{u**}$, which contradicts $Re(F_i(\tau)) \geq 0$. Hence, $Re(\tau) < 0$. Thus, the equilibrium $\mathcal{E}_2$ is LAS if $\mathcal{R}_c > 1$. □

References

1. Alimadad, A., Edwards, M., Feher, B., Gemmrich, S., Gumel, A.B., Langmore, I., Sharomi, O., Strawbridge, E., Steinberg, M., Taylor, D., Yurtseven, O., Zhang, Y.: In: Proceedings of the 10th PIMS Industrial Problem Solving Workshop. Simon Fraser University, Vancouver (2006)
2. Antiretroviral therapy coverage rate in low- and middle-income countries. http://www.aidsportal.org/Article_Details.aspx?ID=3121 (2006). Accessed September 2010
3. Aubert, B., Taljaard, D., Lagrade, E., Sobngwi-Tambekou, J., Sitta, R. et al.: Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med. **2**, e298 (2005)
4. Blower, S.M., Dowlatabadi, H.: Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. Int. Stat. Rev. **62**, 229–243 (1994)
5. Blower, S.M., Aschenbach, A.N., Gershengorn, H.B., Kahn, J.O.: Predicting the unpredictable: transmission of drug-resistant HIV. Nat. Med. **9**(7), 1016–1020 (2001)
6. Centers For Disease Control: Morbidity and mortality weekly report. MMWR **55**, No. RR-14 (2006)
7. Davis, K.R., Weller, S.C.: The effectiveness of condoms in reducing heterosexual transmission of HIV. Fam. Plan. Prospect. **31**(6), 272–279 (1999)
8. Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J.: On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. J. Math. Biol. **28**, 503–522 (1990)
9. Dixon, S., McDonald, S., Roberts, J.: The impact of HIV and AIDS on Africa's economic development. BMJ **324**, 232–234 (2002)
10. Elbasha, E.H., Gumel, A.B.: Theoretical assessment of public health impact of imperfect prophylactic HIV-1 vaccines with therapeutic benefits. Bull. Math. Biol. **68**, 577–614 (2006)
11. Esteva, L., Vargas de León, C.: Influence of vertical and mechanical transmission on the dynamics of dengue disease. Math. Biosci. **167**, 51–64 (2000)
12. Esteva, L., Gumel, A.B., Vargas de León, C.: Qualitative study of transmission dynamics of drug-resistant malaria. Math. Comput. Model. **50**(3–4), 611–630 (2009)

13. Fauci, A.S., Pantaleo, G., Stanley, S., Weissman, D.: Immunopathogenic mechanisms of HIV infection. Ann. Intern. Med. **124**, 654–663 (1996)
14. Fleck, F.: Developing economies shrink as AIDS reduces workforce. BMJ **329**, 129 (2004)
15. Gumel, A.B., Connell McCluskey, C., van den Driessche, P.: Mathematical study of a staged-progression HIV model with imperfect vaccine. Bull. Math. Biol. **68**(8), 2105–2128 (2006)
16. Hethcote, H.W.: The mathematics of infectious diseases. SIAM Rev. **42**, 599–653 (2000)
17. Hethcote, H.W., Thieme, H.R.: Stability of the endemic equilibrium in epidemic models with subpopulations. Math. Biosci. **75**, 205–227 (1985)
18. Hyman, J.M., Li, J., Stanley, E.A.: The differential infectivity and staged progression models for the transmission of HIV. Math. Biosci. **208**, 227–249 (1999)
19. Jacquez, J.A., Koopman, J.S., Simon, C.P., Longini, I.M.: Role of the primary infection in epidemics of HIV infection in gay cohorts. J. Acquir. Immune Defic. Syndr. **7**(11), 1169–1184 (1994)
20. Lakshmikantham, V., Leela, S., Martynyuk, A.A.: Stability Analysis of Nonlinear Systems. Marcel Dekker Inc., New York (1989)
21. LaSalle, J.P.: The Stability of Dynamical Systems. Regional Conference Series in Applied Mathematics. SIAM, Philadelphia (1976)
22. Longini, I., Clark, W., Byers, R.: Statistical analysis of the stages of HIV infections using a Markov model. Stat. Med. **8**, 831–843 (1989)
23. Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J.L.: Global Burden of Disease and Risk Factors. A Co-publication of the World Bank and Oxford University Press, Washington, DC/New York (2006)
24. Marks, G., Crepaz, N., Janssen, R.S.: Meta-analysis of high-risk sexual behaviour in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J. Acquir. Immune Defic. Syndr. **39**(4), 446–453 (2005)
25. Marks, G., Crepaz, N., Janssen, R.S.: Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS **20**, 1447–1450 (2006)
26. McCluskey, C.: A model of HIV/AIDS with staged progression and amelioration. Math. Biosci. **181**, 1–16 (2003)
27. McLeod, R.G., Brewster, J.F., Gumel, A.B., Slonowsky, D.A.: Sensitivity and uncertainty analysis for a SARS model with time-varying inputs and outputs. Math. Biosci. Eng. **3**, 527–544 (2006)
28. Mellors, J., Munoz, A., Giorgi, J., Margolick, J., Tassoni, C. et al.: Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann. Intern. Med. **126**, 946–954 (1997)
29. Mills, E.J. et al.: Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta analysis. JAMA **296**(6), 679–690 (2006)
30. Perelson, A., Nelson, P.: Mathematical analysis of HIV-1 dynamics in vivo. SIAM Rev. **41**, 3–44 (1999)
31. Pilcher, C.D., Fiscus, S.A., Nguyen, T.Q., Foust, E., Wolf, L.: Detection of acute infections during HIV testing in North Carolina. N. Engl. J. Med. **352**(18), 1873–1883 (2005)
32. Podder, C.N., Gumel, A.B., Bowman, C.S., McLeod, R.G.: Mathematical study of the impact of quarantine, isolation and vaccination in curtailing an epidemic. J. Biol. Syst. **15**(2), 185–202 (2007)
33. Porco, T.C., Blower, S.M.: Designing HIV vaccination policies subtypes and cross-immunity. Interfaces **28**(3), 167–190 (1998)
34. Quinn, T.C., Wawer, M.J., Sewankambo, N., et al. for the Rakai Project Study Group: Viral load and heterosexual transmission of human immunodeficiency virus. N. Engl. J. Med. **342**, 921–929 (2000)
35. Rapatski, B.L., Suppe, F., Yorke, J.A.: HIV epidemics driven by late disease stage transmission. J. Acquir. Immune Defic. Syndr. **38**(3), 241–253 (2005)
36. Report on the Global AIDS Epidemic: Executive summary/UNAIDS: a UNAIDS 10th anniversary special edition. http://data.unaids.org/pub/GlobalReport/2006/2006_GR-ExecutiveSummary_en.pdf (2006). Accessed November 2009
37. Simpson, K.N., Biddle, A.C., Leone, P.A., Wolf, L., Williams, D., Kuruc, J., McCoy, S., Miller, W.C., Hightow, L.B., Pilcher, C.D.: Cost effectiveness of screening for acute HIV-infection: the North Carolina STAT program. Private communication to BC CDC (2006)
38. UNAIDS: More than five million people receiving HIV treatment. http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2010/20100719_Vienna_PR_WHO.asp (2010). Accessed September 2010
39. United Nations Department of Economic and Social Affairs/Population Division: The impact of AIDS. United Nations. http://www.un.org/esa/population/publications/AIDSimpact/22_EXEC_SUMMARY_English.pdf (2002). Accessed November 2009
40. U.S. Global Health Policy: The global HIV/AIDS epidemic: fact sheet. http://www.kff.org/hivaids/upload/3030-13.pdf (2009). Accessed 10 November 2009

41. van den Driessche, P., Watmough, J.: Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. **180**, 29–48 (2002)
42. Wawer, M. et al.: Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J. Infect. Dis. **191**, 1403–1409 (2005)
43. WHO: The World Health Report: Changing History. World Health Organization, Geneva (2004)
44. World Bank: Confronting AIDS: Public Priorities in a Global Epidemic. Oxford University Press, New York (1997)