MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **13**, Number **1**, February **2016**

doi:10.3934/mbe.2016.13.171

pp. **171–191**

MODELLING HIV SUPERINFECTION AMONG MEN WHO HAVE SEX WITH MEN

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(Communicated by James Watmough)

Abstract. Superinfection, a phenomenon that an individual infected by one HIV strain is re-infected by the second heterologous HIV strain, occurs in HIV infection. A mathematical model is formulated to examine how superinfection affects transmission dynamics of drug sensitive/resistant strains. Three reproduction numbers are defined: reproduction numbers R_r and R_s for drug-resistant and drug-sensitive strains, respectively, and the invasion reproduction number R_s^r. The disease-free equilibrium always exists and is locally stable when the larger of R_s and R_r is less than one. The drug resistant strain-only equilibrium is locally stable when $R_r > 1$ and $R_s^r < 1$. Numerical studies show that as the superinfection coefficient of the sensitive strain increases the system may (1) change to bistable states of disease-free equilibrium and the coexistence state from the stable disease-free equilibrium under no superinfection; (2) experience the stable resistant-strain only equilibrium, the bistable states of resistant-strain only equilibrium and the coexistence state, and the stable coexistence state in turn. This implies that superinfection of the sensitive strain is beneficial for two strains to coexist. While superinfection of the resistant strain makes resistant strain more likely to be sustained. The findings suggest that superinfection induces the complicated dynamics, and brings more difficulties in antiretroviral therapy.

1. **Introduction.** After the detection of the first acquired immunodeficiency syndrome(AIDS) patient, human immunodeficiency virus(HIV) spread at an alarming rate worldwide. Antiretroviral therapy (ART) has become an important measure to control the epidemic since ART can extend the life expectancy of HIV-infected individuals and reduce their infectousness [45, 20, 41, 8]. However, poor adherence may accelerate the development of drug resistance during life long treatment [4, 10, 31]. In the clinic, HIV resistance can result from the transmission of drug-resistant mutants to susceptible individuals or from the acquisition of mutations generated during treatment. In recent years, a number of clinical studies

2010 *Mathematics Subject Classification.* Primary: 92D30; Secondary: 34D20.
Key words and phrases. HIV, superinfection, mathematical model, drug resistance, MSM.

indicated that individuals can be re-infected by another HIV virus type after infection by one HIV virus type, and this phenomenon is called as superinfection [1, 17, 16, 23, 29, 33, 30, 7, 27, 34, 36, 11, 15, 18, 13]. Superinfection is prone to happen in areas where there are different HIV subtypes, such as Sub-Saharan Africa, Asia and South Africa. In fact, there are already some superinfection cases occuring in these areas [36, 11, 15]. Up to now, over 50 superinfection cases have been reported by more than 120 articles since 2002 [27]. In the men who have sex with men (MSM) group, two superinfection cases have been recorded [34, 13]. Meanwhile, there are studies indicating that individuals who have been infected with drug-sensitive strains can be re-infected by drug-resistant strains [23, 34], and individuals who have been infected with drug-resistant strains can also be re-infected by drug-sensitive strains [17, 34].

Several studies have investigated the transmission dynamics of drug resistant strains [5, 38, 3, 44, 32, 19, 28]. By studying the transmission model and using a statistical approach, Blower et al. [5] obtained two different results when increasing the usage of ART in San Francisco. Vardavas et al. [38] employed a stochastic formulation to examine the drug-resistant population dynamics, and investigated whether the transmitted resistant strain would exceed the threshold given by WHO. Baggaley et al. [3] studied the impact of antiretroviral therapy (ART) for different treatment strategies. Using a statistical approach, Wilson et al. [44] studied the antiretroviral allocation strategies in KwaZulu-Natal. Sharomi et al. [32] proposed a deterministic model including wild and drug-resistant strains and studied the dynamics of these two strain types. And the competitive exclusion phenomenon happens when reproduction number of resistant strain is larger than that of wild strain. Li et al. [19] studied the stability of HIV model with drug resistance. Raimundo et al. [28] showed that a Hopf bifurcation may occur and individuals infected with drug-resistant strains have some important effects on HIV epidemic.

All these models assumed that susceptibles can be infected both by individuals infected with drug-sensitive strains and individuals infected with drug-resistant strains. But infected individuals can not be further infected by any other virus strains. To the author's best knowledge, no mathematical model has been formulated to describe the phenomenon of superinfection in HIV dynamics. There are many challenges to investigating and accessing effect of superinfection on transmission dynamics of drug-sensitive/resistant strains. The purpose of this study is to propose a mathematical model to examine impact of superinfection on transmission dynamics. By considering this superinfection phenomenon, we can study the transmission dynamics of drug resistance more precisely. Whether superinfection will increase the prevalence of drug resistant strains and whether drug resistant strains will replace drug sensitive strains? All these questions will be investigated in this study.

2. **Model formulations.**

We formulate a deterministic mathematical model with superinfection based on the model proposed by Blower et al. [5], which contains two kinds of HIV strains, drug sensitive strains and drug resistant strains. The underlying structure of the model comprises classes of individuals who are high-risk susceptibles (S), individuals infected with drug sensitive strains (I_s), individuals infected with drug resistant strains (I_r), individuals infected with both drug-sensitive strains and drug-resistant strains (I_{sr}), effectively treated individuals with drug sensitive strains (T_s), treated individuals with drug resistant strains (T_r) and treated

individuals with both drug sensitive and drug resistant strains(T_{sr}). The high-risk population size is represented by N, i.e., $N = S + I_s + I_r + I_{sr} + T_s + T_{sr} + T_r$. Susceptibles can be primary infected by both drug sensitive strains (I_s, I_s, T_s, T_{sr}) and drug resistant strains $(I_r, I_{sr}, T_r, T_{sr})$ at rates of $\lambda_1(t)$ and $\lambda_2(t)$, respectively. What's more, it is supposed that individuals in classes I_r and T_r can be re-infected by infected individuals with drug sensitive strains (I_s, I_{sr}, T_s, T_{sr}) at rates $\lambda_3(t)$ and $\lambda_6(t)$, respectively. Meanwhile, individuals in classes I_s and T_s can be re-infected by infected individuals with drug resistant strains $(I_r, I_{sr}, T_r, T_{sr})$ at rates $\lambda_5(t)$ and $\lambda_4(t)$, respectively, where

$$\begin{aligned}
\lambda_1(t) &= \frac{\beta_s(I_s + \varepsilon_{T_s}T_s)}{N} + \frac{\beta_{sr}p(I_{sr} + \varepsilon_{T_{sr}}T_{sr})}{N},\\
\lambda_2(t) &= \frac{\beta_r(I_r + \varepsilon_{T_r}T_r)}{N} + \frac{\beta_{sr}(1-p)(I_{sr} + \varepsilon_{T_{sr}}T_{sr})}{N},\\
\lambda_3(t) &= \frac{\beta'_s(I_s + \varepsilon_{T_s}T_s)}{N} + \frac{\beta'_{sr}p(I_{sr} + \varepsilon_{T_{sr}}T_{sr})}{N},\\
\lambda_4(t) &= \frac{\beta'_r(I_r + \varepsilon_{T_r}T_r)}{N} + \frac{\beta''_{sr}(1-p)(I_{sr} + \varepsilon_{T_{sr}}T_{sr})}{N}.
\end{aligned}$$

Since there is some fitness cost for the drug resistant strains[5, 21], when individuals infected with drug sensitive strains are re-infected by drug resistant strains, the probability for these drug resistant strains to survive and reproduce is very small. We then simply assume that before treatment individuals infected with drug sensitive strains cannot be re-infected by drug resistant strains, that is $\lambda_5(t) = 0$. In contrast, if treatment is introduced, the survival ability for drug resistant strains is much greater than that of drug sensitive strains. Thus, we suppose that after treatment individuals infected with drug resistant strains cannot be re-infected by drug sensitive strains, that is $\lambda_6(t) = 0$.

Individuals in class I_{sr} or class T_{sr} can transmit both drug sensitive and drug resistant strains with probability p and $1 - p$, respectively. Parameters β_s and β_r denote the transmission coefficients (including the transmission probability per high risk behavior and the frequency of high risk behaviors per year) for individuals with drug sensitive and drug resistant strains. Parameter β'_s and β'_{sr} denote the transmission coefficients for class I_r re-infected by drug sensitive strains through contacts with individuals in classes I_s and I_{sr}, respectively. Parameter β'_r and β''_{sr} denotes the transmission coefficient for class T_s re-infected by drug resistant strains through contacts with individuals in classes I_r and I_{sr}, respectively. Here, we assume $\beta'_s = \alpha_1\beta_s, \beta'_{sr} = \alpha_1\beta_{sr}$, $\beta'_r = \alpha_2\beta_r, \beta''_{sr} = \alpha_2\beta_{sr}$. $\alpha_i > 1 (i = 1, 2)$ denotes that superinfection is more likely to happen than primary infection and $\alpha_i < 1 (i = 1, 2)$ denotes that superinfection is less likely to happen than primary infection. HIV infected individuals may have different transmission probabilities per high-risk behavior due to antiretroviral therapy or various contact rates due to behavior changes, at the same time, we then introduce a modification factor for each class with antiretroviral treatment to represent the differences from the baseline value for individuals without antiretroviral treatment, denoted by $\varepsilon_{T_s}, \varepsilon_{T_r}$ and $\varepsilon_{T_{sr}}$, respectively.

Suppose that individuals enter into the susceptible class at a rate U and exit at a constant rate μ(due to natural death or stopping high risk behaviors). Individuals in each infected class incur disease-related death at rates, denoted by $v^I_s, v^I_r, v^I_{sr}, v^T_s, v^T_r, v^T_{sr}$, respectively. σ denotes the treatment coverage rate. And the

rate of resistance development for treated individuals from T_s to T_{sr} and T_{sr} to T_r are the constants r_1 and r_2, respectively. The flow diagram is shown in figure 1, and the definitions of all parameters are described in table 1.

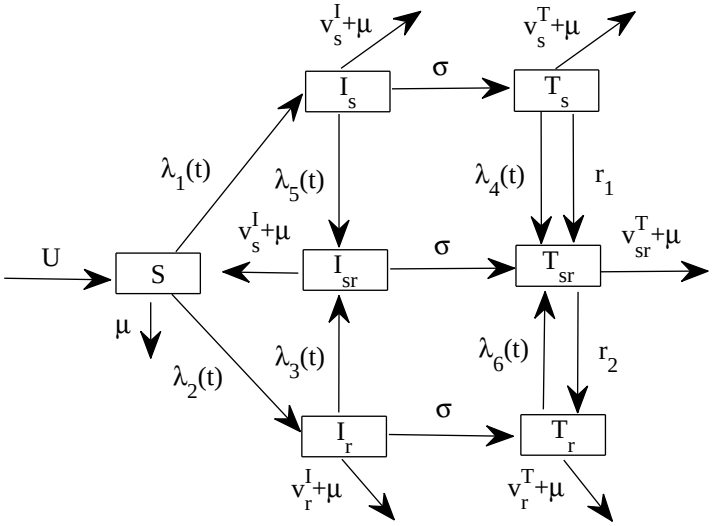

FIGURE 1. Flow diagram of the model.

The model equations are as follows.

$$\begin{cases} S' &= U-\lambda_1(t)S-\lambda_2(t)S-\mu S,\\ I_s' &= \lambda_1(t)S-\lambda_5(t)I_S-\sigma I_s-(v_s^I+\mu)I_s,\\ I_r' &= \lambda_2(t)S-\lambda_3(t)I_r-\sigma I_r-(v_r^I+\mu)I_r,\\ I_{sr}' &= \lambda_3(t)I_r+\lambda_5(t)I_S-\sigma I_{sr}-(v_{sr}^I+\mu)I_{sr},\\ T_s' &= \sigma I_s-\lambda_4(t)T_s-r_1T_s-(v_s^T+\mu)T_s,\\ T_{sr}' &= \lambda_4(t)T_s+\lambda_6(t)T_r+\sigma I_{sr}+r_1T_s-r_2T_{sr}-(v_{sr}^T+\mu)T_{sr},\\ T_r' &= \sigma I_r+r_2T_{sr}-\lambda_6(t)T_r-(v_r^T+\mu)T_r. \end{cases} \tag{1}$$

For convenience, we introduce the following notations, $\omega_1 = \sigma + v_s^I + \mu, \omega_2 = \sigma + v_r^I + \mu, \omega_3 = \sigma + v_{sr}^I + \mu, \omega_4 = r_1 + v_s^T + \mu, \omega_5 = r_2 + v_{sr}^T + \mu, \omega_6 = v_r^T + \mu$.

3. Dynamics analysis.

3.1. Stability of disease-free equilibrium.

Setting the right side of the model (1) equal to 0, it is easy to compute the disease-free equilibrium (DFE)

$$E_0 : (S^0, I_s^0, I_r^0, I_{sr}^0, T_s^0, T_{sr}^0, T_r^0) = (\frac{U}{\mu}, 0, 0, 0, 0, 0, 0).$$

The basic reproduction number R_0, the average number of secondary cases generated by a single primary case in a fully susceptible population during its average infectious period[9, 40], is a threshold parameter for the infectious disease and can help determine whether an infectious disease will spread through a population. Using the next-generation matrix method [40], we get the basic reproduction number, which is calculated as $R_0 = \max\{R_s, R_r\}$, where

$$R_s = \frac{\beta_s}{\omega_1} + \frac{\beta_s \varepsilon_{T_s} \sigma}{\omega_1 \omega_4} + \frac{\beta_{sr} p \varepsilon_{T_{sr}} r_1 \sigma}{\omega_1 \omega_4 \omega_5}, \quad R_r = \frac{\beta_r}{\omega_2} + \frac{\beta_r \varepsilon_{T_r} \sigma}{\omega_2 \omega_6}.$$

Obviously, R_s is the average number of secondary cases generated by a single primary case infected with drug sensitive strains and R_r is the average number of secondary cases generated by a single primary case infected with drug resistant strains. Either R_s or R_r is independent of superinfection terms. From [40] we obtain the following theorem.

Theorem 3.1. *When $R_0 < 1$, the DFE E_0 of system (1) is locally asymptotically stable, but is unstable when $R_0 > 1$.*

Theorem 3.2. *In the absence of superinfection (i.e. $\beta_s' = \beta_r' = \beta_{sr}' = \beta_{sr}'' = 0$), the DFE E_0 of system (1) is globally asymptotically stable whenever $R_0 < 1$.*

Proof. It is obvious that when $\beta_s' = \beta_r' = \beta_{sr}' = \beta_{sr}'' = 0$, E_0 is locally stable when $R_0 < 1$. So we only need to verify that E_0 is globally attractive. Since $S(t) \leq N(t)$, we have

$$\begin{aligned}
I_s' &\leq \beta_s(I_s + \varepsilon_{T_s} T_s) + \beta_{sr} p \varepsilon_{T_{sr}} T_{sr} - \omega_1 I_s, \\
I_r' &\leq \beta_r(I_r + \varepsilon_{T_r} T_r) + \beta_{sr}(1-p)\varepsilon_{T_{sr}} T_{sr} - \omega_2 I_r, \\
T_s' &\leq \sigma I_s - \omega_4 T_s, \\
T_{sr}' &\leq r_1 T_s - \omega_5 T_{sr}, \\
T_r' &\leq \sigma I_r + r_2 T_{sr} - \omega_6 T_r.
\end{aligned}$$

Now we get the comparison system

$$\left\{\begin{array}{rcl}
x_1' &=& \beta_s(x_1 + \varepsilon_{T_s} x_3) + \beta_{sr} p \varepsilon_{T_{sr}} x_4 - \omega_1 x_1, \\
x_2' &=& \beta_r(x_2 + \varepsilon_{T_r} x_5) + \beta_{sr}(1-p)\varepsilon_{T_{sr}} x_4 - \omega_2 x_2, \\
x_3' &=& \sigma x_1 - \omega_4 x_3, \\
x_4' &=& r_1 x_3 - \omega_5 x_4, \\
x_5' &=& \sigma x_2 + r_2 x_4 - \omega_6 x_5.
\end{array}\right. \tag{2}$$

Considering the following subsystem

$$\left\{\begin{array}{rcl}
x_1' &=& \beta_s(x_1 + \varepsilon_{T_s} x_3) + \beta_{sr} p \varepsilon_{T_{sr}} x_4 - \omega_1 x_1, \\
x_3' &=& \sigma x_1 - \omega_4 x_3, \\
x_4' &=& r_1 x_3 - \omega_5 x_4.
\end{array}\right. \tag{3}$$

Obviously, when $R_s < 1$, $x_1 \to 0, x_3 \to 0, x_4 \to 0$ as $t \to \infty$. Thus, we can get the limit system

$$\left\{\begin{array}{rcl}
x_2' &=& \beta_r(x_2 + \varepsilon_{T_r} x_5) - \omega_2 x_2, \\
x_5' &=& \sigma x_2 + r_2 x_4 - \omega_6 x_5.
\end{array}\right. \tag{4}$$

And, when $R_r < 1$, $x_2 \to 0, x_5 \to 0$. Thus, the disease-free equilibrium of system (2) is globally asymptotically stable when $R_0 < 1$. By the comparison theorem [14, 42] we can get that the solutions of system (1) satisfy that $I_s(t) \leq 0, I_r(t) \leq 0, I_{sr}(t) \leq 0, T_s(t) \leq 0, T_r(t) \leq 0, T_{sr}(t) \leq 0$ Thus, E_0 is globally attractive. Combining with the local stable result, it follows that E_0 is globally asymptotically stable. □

Note that here we only prove the DFE E_0 of system (1) is globally asymptotically stable for $R_0 < 1$ in the absence of superinfection. When considering superinfection, it is difficult to prove its stability due to complexity, but we will show that the coexistent state may be feasible for $R_0 < 1$.

3.2. **Existence and stability of boundary equilibrium.** Before establishing the existence and stability of the boundary equilibrium, we introduce another reproduction number, invasion reproduction number. The invasion reproduction number for one strain may govern whether the strain can successfully invade the system at the other strain-only equilibrium. It is the expected number of secondary infections produced by one infectious individual containing one strain,introduced into a population where the other strain is at equilibrium[26, 22, 6]. The computation method is given in [26, 22, 6]. The invasion reproduction number of drug sensitive strains in this article can be described in the following process. Firstly, it is supposed that there is no individual infected with drug sensitive strains and solving the system for drug resistant strain-only equilibrium. Secondly, one individual infected with drug sensitive strains is introduced, and R_s^r denotes the number of secondary infections produced by this infected individual.

Note that there is no drug sensitive strain-only equilibrium as long as the rate of emergence of drug resistant variants r_1 is larger than zero. However, the system does have the drug resistant strain-only equilibrium. Using the similar method proposed in [39], we can get the existence and stability of the drug resistant strain-only equilibrium and we have the following theorem.

Theorem 3.3. *The resistant strain-only equilibrium* $E_r = (S_r^*, 0, I_r^*, 0, 0, 0, T_r^*)$ *exists whenever* $R_r > 1$*, and* E_r *is locally asymptotically stable when* $R_s^r < 1$*, where*

$$\begin{aligned} R_s^r = & \frac{\beta_s S_r^*}{\omega_1 N_r^*} + \frac{\beta_s \varepsilon_{T_s} \sigma S_r^*}{\omega_1 N_r^*} \frac{1}{\beta_r'(I_r^* + \varepsilon_{T_r} T_r^*)/N_r^* + \omega_4} + \frac{\beta_{sr}' p I_r^*}{\omega_3 N_r^*} + \frac{\beta_{sr}' p \varepsilon_{T_{sr}} \sigma I_r^*}{\omega_3 \omega_5 N_r^*} \\ & + \frac{\beta_{sr} p \varepsilon_{T_{sr}} \sigma S_r^*}{\omega_1 \omega_5 N_r^*} \frac{\beta_r'(I_r^* + \varepsilon_{T_r} T_r^*)/N_r^* + r_1}{\beta_r'(I_r^* + \varepsilon_{T_r} T_r^*)/N_r^* + \omega_4}, \end{aligned}$$

and $S_r^* = \frac{U - \omega_2 I_r^*}{\mu}$, $I_r^* = \frac{U(R_r - 1)}{(1 + \frac{\sigma_r}{\omega_4})\mu + \omega_2(R_r - 1)}$, $T_r^* = \frac{\sigma_r I_r^*}{\omega_4}$.

Proof. Solving the system at the steady state, we have

$$\begin{aligned} S^* =& \frac{U}{\lambda_1^* + \lambda_2^* + \mu}, \\ I_s^* =& \frac{\lambda_1^* U}{\omega_1(\lambda_1^* + \lambda_2^* + \mu)}, \\ I_r^* =& \frac{\lambda_2^* U}{(\lambda_3^* + \omega_2)(\lambda_1^* + \lambda_2^* + \mu)}, \\ I_{sr}^* =& \frac{\lambda_2^* \lambda_3^* U}{\omega_3(\lambda_3 + \omega_2)(\lambda_1^* + \lambda_2^* + \mu)}, \\ T_s^* =& \frac{\sigma \lambda_1^* U}{\omega_1(\lambda_4^* + \omega_4)(\lambda_1^* + \lambda_2^* + \mu)}, \\ T_{sr}^* =& \frac{\sigma \lambda_3^* \lambda_2^* U}{\omega_3 \omega_5(\lambda_3^* + \omega_2)(\lambda_1^* + \lambda_2^* + \mu)} + \frac{(\lambda_4^* + r_1)\sigma \lambda_1^* U}{\omega_1 \omega_5(\lambda_4^* + \omega_4)(\lambda_1^* + \lambda_2^* + \mu)}, \\ T_r^* =& \frac{\sigma \lambda_2^* U}{\omega_6(\lambda_3^* + \omega_2)(\lambda_1 + \lambda_2 + \mu)} + \frac{r_2 \sigma \lambda_3^* \lambda_2^* U}{\omega_3 \omega_5 \omega_6(\lambda_3^* + \omega_2)(\lambda_1^* + \lambda_2^* + \mu)} \\ & + \frac{r_2(\lambda_4^* + r_1)\sigma \lambda_1^* U}{\omega_1 \omega_5 \omega_6(\lambda_4^* + \omega_4)(\lambda_1^* + \lambda_2^* + \mu)}. \end{aligned} \tag{5}$$

At the steady state, λ_1 and λ_2 satisfy that

$$\begin{aligned}\lambda_1^* =&\frac{\beta_s(I_s^*+\varepsilon_{T_s}T_s^*)}{N^*}+\frac{\beta_{sr}p(I_{sr}^*+\varepsilon_{T_{sr}}T_{sr}^*)}{N^*},\\ \lambda_2^* =&\frac{\beta_r(I_r^*+\varepsilon_{T_r}T_r^*)}{N^*}+\frac{\beta_{sr}(1-p)(I_{sr}^*+\varepsilon_{T_{sr}}T_{sr}^*)}{N^*},\\ \lambda_3^* =&\alpha_1\lambda_1^*,\\ \lambda_4^* =&\alpha_2\lambda_2^*.\end{aligned} \tag{6}$$

By the expressions in Equation (5) and (6) we can obtain

$$\begin{aligned}\lambda_1^* =&\phi_1(\lambda_1^*,\lambda_2^*)=\frac{\beta_s\lambda_1^*U}{N^*\omega_1(\lambda_1^*+\lambda_2^*+\mu)}+\frac{\beta_s\varepsilon_{T_s}\sigma\lambda_1^*U}{N^*\omega_1(\lambda_4^*+\omega_4)(\lambda_1^*+\lambda_2^*+\mu)}\\ &+\frac{\beta_{sr}p\lambda_2\lambda_3^*U}{N^*\omega_3(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}+\frac{\beta_{sr}p\varepsilon_{T_{sr}}\sigma\lambda_3^*\lambda_2^*U}{N^*\omega_3\omega_5(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}\\ &+\frac{\beta_{sr}p\varepsilon_{T_{sr}}(\lambda_4^*+r_1)\sigma\lambda_1^*U}{N^*\omega_1\omega_5(\lambda_4^*+\omega_4)(\lambda_1^*+\lambda_2^*+\mu)},\\ \lambda_2^* =&\phi_2(\lambda_1^*,\lambda_2^*)=\frac{\beta_r\lambda_2^*U}{N^*(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}+\frac{\beta_r\varepsilon_{T_r}\sigma\lambda_2^*U}{N^*\omega_6(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}\\ &+\frac{\beta_r\varepsilon_{T_r}r_2\sigma\lambda_3^*\lambda_2^*U}{N^*\omega_3\omega_5\omega_6(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}+\frac{\beta_r\varepsilon_{T_r}r_2(\lambda_4^*+r_1)\sigma\lambda_1^*U}{N^*\omega_1\omega_5\omega_6(\lambda_4^*+\omega_4)(\lambda_1^*+\lambda_2^*+\mu)}\\ &+\frac{\beta_{sr}(1-p)\lambda_2^*\lambda_3^*U}{N^*\omega_3(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}\sigma\lambda_3^*\lambda_2^*U}{N^*\omega_3^*\omega_5^*(\lambda_3^*+\omega_2)(\lambda_1^*+\lambda_2^*+\mu)}\\ &+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}(\lambda_4^*+r_1)\sigma\lambda_1^*U}{N^*\omega_1\omega_5(\lambda_4^*+\omega_4)(\lambda_1^*+\lambda_2^*+\mu)}.\end{aligned} \tag{7}$$

where $N^*=S^*+I_s^*+I_r^*+I_{sr}^*+T_s^*+T_{sr}^*+T_r^*$. Then, finding the fixed points of the following system

$$x=\phi(x)=\begin{pmatrix}\phi_1(\lambda_1^*,\lambda_2^*)\\ \phi_2(\lambda_1^*,\lambda_2^*)\end{pmatrix},\text{where } x=\begin{pmatrix}\lambda_1^*\\ \lambda_2^*\end{pmatrix}. \tag{8}$$

will yield the equilibrium.

Obviously, we have $\phi_1(0,\lambda_2^*)=0$. We only need to solve the equation $\phi_2(0,\lambda_2^*)=\lambda_2^*$ to find the fixed point. By some calculations, we can get $\lambda_2^*=0$, corresponding to disease-free equilibrium, or $\lambda_2^*=(R_r-1)/(\frac{\sigma}{\omega_2\omega_6}+\frac{1}{\omega_2})$, corresponding to the drug resistant strain-only boundary equilibrium. It is clear that the second root exists if and only if $R_r>1$. Therefore, the drug resistant strain-only boundary equilibrium is feasible if $R_r>1$.

Now we verify the local stability of the boundary equilibrium E_r. The Jacobian matrix of the system (8) is given by

$$J(\lambda_1^*,\lambda_2^*)=\begin{pmatrix}\frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*} & \frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\\ \frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*} & \frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\end{pmatrix}. \tag{9}$$

It is not difficult to verify that ϕ and $J(\lambda_1^*,\lambda_2^*)$ are both non-negative matrixes for all non-negative population densities. From [39], the spectral radius of $\rho(J(\lambda_1^*,\lambda_2^*))$ determines whether the equilibrium point is locally stable or unstable. And we can

get that

$$J(0,\lambda_2^*)=\begin{pmatrix} \frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*}\Big|_{(0,\lambda_2^*)} & \frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(0,\lambda_2^*)} \\ 0 & \frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(0,\lambda_2^*)} \end{pmatrix}, \tag{10}$$

where

$$\begin{aligned}
\frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*}\Big|_{(0,\lambda_2^*)} &= \frac{1}{R_r}\left[\frac{\beta_s}{\omega_1}+\frac{\beta_s\varepsilon_{T_s}\sigma}{\omega_1(\alpha_2\lambda_2^*+\omega_4)}+\frac{\beta'_{sr}p\lambda_2^*}{\omega_2\omega_3}+\frac{\beta'_{sr}p\varepsilon_{T_{sr}}\sigma\lambda_2^*}{\omega_2\omega_3\omega_5}\right.\\
&\quad \left.+\frac{\beta_{sr}p\varepsilon_{T_{sr}}(\alpha_2\lambda_2^*+r_1)\sigma}{\omega_1\omega_5(\alpha_2\lambda_2^*+\omega_4)}\right]\\
&= R_s^r.\\
\frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(0,\lambda_2^*)} &= \frac{\beta_r}{\omega_2R_r}-\frac{\beta_r\omega_2(R_r-1)}{\omega_2^2R_r^2}+\frac{\beta_r\varepsilon_{T_r}\sigma}{\omega_2\omega_6R_r}-\frac{\beta_r\varepsilon_{T_r}\sigma\omega_2\omega_6(R_r-1)}{\omega_2^2\omega_6^2R_r^2}\\
&= \frac{1}{R_r}.
\end{aligned}$$

Thus, whenever $R_r>1$ and $R_s^r<1$, the resistant strain-only equilibrium E_r is locally asymptotically stable. This completes the proof. □

Remark 1. In the absence of superinfection, we can get the existence and stability of boundary equilibrium using the similar method. The drug resistant strain-only boundary equilibrium $E_r=(S^*,0,I_r^*,0,0,0,T_r^*)$ exists whenever $R_r>1$, and E_r is locally asymptotically stable when $R_r>R_s$ (no matter when R_s is larger or smaller than 1). In fact, when $\beta'_s=\beta'_r=\beta'_{sr}=\beta''_{sr}=0$, the Jacobian matrix (10) reads

$$\frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*}\Big|_{(0,\lambda_2^*)} = \left(\frac{\beta_s}{\omega_1}+\frac{\beta_s\varepsilon_{T_s}\sigma_s}{\omega_1\omega_4}+\frac{\beta_{sr}p\varepsilon_{T_{sr}}r_1\sigma}{\omega_1\omega_4\omega_5}\right)\frac{1}{R_r}=\frac{R_s}{R_r}<1.$$

and

$$\frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(0,\lambda_2^*)} = \frac{1}{R_r}<1.$$

Thus, whenever $R_r>1$ and $R_s<R_r$, the drug resistant strain-only equilibrium is locally asymptotically stable in the absence of superinfection.

In the following we initially examine existence and stability of the positive equilibrium in the absence of superinfection due to the complexity. When superinfection is considered, the existence and stability of E_{sr} is studied by numerical methods.

3.3. **Existence and stability of coexistence state.**

Theorem 3.4. *If $\beta'_s=\beta'_r=\beta'_{sr}=\beta''_{sr}=0$, system (1) has a coexistence equilibrium E_{sr} when $R_s>R_r>1$ or $R_s>1>R_r$, and the coexistence equilibrium E_{sr} is locally asymptotically stable whenever it is feasible.*

Proof. From the first equation of (7) we get $R_sU=N^*(\lambda_1^*+\lambda_2^*+\mu)$ when $\lambda_1^*>0$. Thus, $R_s=1+\left(\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}\right)\lambda_1^*+\left(\frac{1}{\omega_2}+\frac{\sigma_r}{\omega_2\omega_6}\right)\lambda_2^*$. Substitute $N^*(\lambda_1^*+\lambda_2^*)$ by R_sU to the second equation we have $\left(\frac{R_r}{R_s}-1\right)\lambda_2^*+\frac{1}{R_s}\left(\frac{\beta_r\varepsilon_{T_r}r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}\right.$

$+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}r_1\sigma}{\omega_1\omega_4\omega_5}\Big)\lambda_1^*=0$. Thus, λ_1^* and λ_2^* satisfy the following equations.

$$\begin{aligned}\left(\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}\right)\lambda_1^*+\left(\frac{1}{\omega_2}+\frac{\sigma_r}{\omega_2\omega_6}\right)\lambda_2^*=&R_s-1,\\ \frac{1}{R_s}\left(\frac{\beta_r\varepsilon_{T_r}r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}r_1\sigma}{\omega_1\omega_4\omega_5}\right)\lambda_1^*+\left(\frac{R_r}{R_s}-1\right)\lambda_2^*=&0.\end{aligned}$$

By Cramer's rule, the above equation has unique solution when the determinant of coefficient matrix is not zero.

$$d=\begin{pmatrix}\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6} & \frac{1}{\omega_2}+\frac{\sigma_r}{\omega_2\omega_6}\\ \frac{1}{R_s}\left(\frac{\beta_r\varepsilon_{T_r}r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}r_1\sigma}{\omega_1\omega_4\omega_5}\right) & \frac{R_r}{R_s}-1\end{pmatrix},$$

$$d_1=\begin{pmatrix}R_s-1 & \frac{1}{\omega_2}+\frac{\sigma_r}{\omega_2\omega_6}\\ 0 & \frac{R_r}{R_s}-1\end{pmatrix},d_2=\begin{pmatrix}\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6} & R_s-1\\ \frac{1}{R_s}\left(\frac{\beta_r\varepsilon_{T_r}r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}+\frac{\beta_{sr}(1-p)\varepsilon_{T_{sr}}r_1\sigma}{\omega_1\omega_4\omega_5}\right) & 0\end{pmatrix}.$$

Then, $\lambda_1^*=\frac{d_1}{d},\lambda_2^*=\frac{d_2}{d}$. It is easy to get that both d_1/d and d_2/d are positive real numbers if and only if $R_s>R_r$, $R_s>1$. Thus, the coexistence equilibrium E_{sr} exists if and only if $R_s>R_r$, $R_s>1$.

Now we verify the local stability of the coexistence equilibrium E_{sr}. From system (8) we can get the Jacobian matrix at E_{sr} as follows.

$$J(\lambda_1^*,\lambda_2^*)=\begin{pmatrix}\frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*}\Big|_{(\lambda_1^*,\lambda_2^*)} & \frac{\partial\phi_1(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(\lambda_1^*,\lambda_2^*)}\\ \frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_1^*}\Big|_{(\lambda_1^*,\lambda_2^*)} & \frac{\partial\phi_2(\lambda_1^*,\lambda_2^*)}{\partial\lambda_2^*}\Big|_{(\lambda_1^*,\lambda_2^*)}\end{pmatrix},\tag{11}$$

The roots of the following equation give the eigenvalues of matrix $J(\lambda_1^*,\lambda_2^*)$

$$x^2-x\left(\frac{\partial\phi_1}{\partial\lambda_1^*}+\frac{\partial\phi_2}{\partial\lambda_2^*}\right)\Big|_{(\lambda_1^*,\lambda_2^*)}+\left(\frac{\partial\phi_1}{\partial\lambda_1^*}\frac{\partial\phi_2}{\partial\lambda_2^*}-\frac{\partial\phi_1}{\partial\lambda_2^*}\frac{\partial\phi_2}{\partial\lambda_1^*}\right)\Big|_{(\lambda_1^*,\lambda_2^*)}=0.$$

Thus, the eigenvalues are given by

$$x_{1,2}=\frac{L_1\pm\sqrt{L_2^2+4L_3}}{2},$$

where

$$\begin{aligned}L_1=&\left(\frac{\partial\phi_1}{\partial\lambda_1^*}+\frac{\partial\phi_2}{\partial\lambda_2^*}\right)\Big|_{(\lambda_1^*,\lambda_2^{**})}=\frac{R_r+1}{R_s},\\ L_2=&\left(\frac{\partial\phi_1}{\partial\lambda_1^*}-\frac{\partial\phi_2}{\partial\lambda_2^*}\right)\Big|_{(\lambda_1^*,\lambda_2^*)}=1-\frac{1}{R_s}\left(\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}\right)\lambda_1^*\\ &-\frac{R_r}{R_s}+\frac{1}{R_s}\left(\frac{1}{\omega_2}+\frac{\sigma_r}{\omega_2\omega_6}\right)\lambda_2^*,\\ L_3=&\left(\frac{\partial\phi_1}{\partial\lambda_2^*}\frac{\partial\phi_2}{\partial\lambda_1^*}\right)\Big|_{(\lambda_1^*,\lambda_2^*)}=\left[\frac{1}{R_s}\left(\frac{1}{\omega_2}+\frac{1}{\omega_2\omega_6}\right)\lambda_2^*\right]\\ &\left[\frac{R_r}{R_s}-1+\left(\frac{1}{\omega_1}+\frac{\sigma}{\omega_1\omega_4}+\frac{r_1\sigma}{\omega_1\omega_4\omega_5}+\frac{r_1r_2\sigma}{\omega_1\omega_4\omega_5\omega_6}\right)\lambda_1^*\right].\end{aligned}$$

By some calculations we can get the formula of two eigenvalues

$$x_1 = \frac{\frac{R_r+1}{R_s} + \left|\frac{1-R_r}{R_s}\right|}{2} = \frac{R_r}{R_s},$$
$$x_2 = \frac{\frac{R_r+1}{R_s} - \left|\frac{1-R_r}{R_s}\right|}{2} = \frac{1}{R_s}.$$

Thus, the dominant eigenvalue of $J(\lambda_1^*, \lambda_2^*)$ is either $\frac{R_r}{R_s}$ for $R_r > 1$ or $\frac{1}{R_s}$ for $R_r < 1$. Then, whenever $R_s > 1$ and $R_s > R_r$, the dominant eigenvalue is less than one. Thus, the coexistence equilibrium E_{sr} is locally asymptotically stable. This completes the proof. □

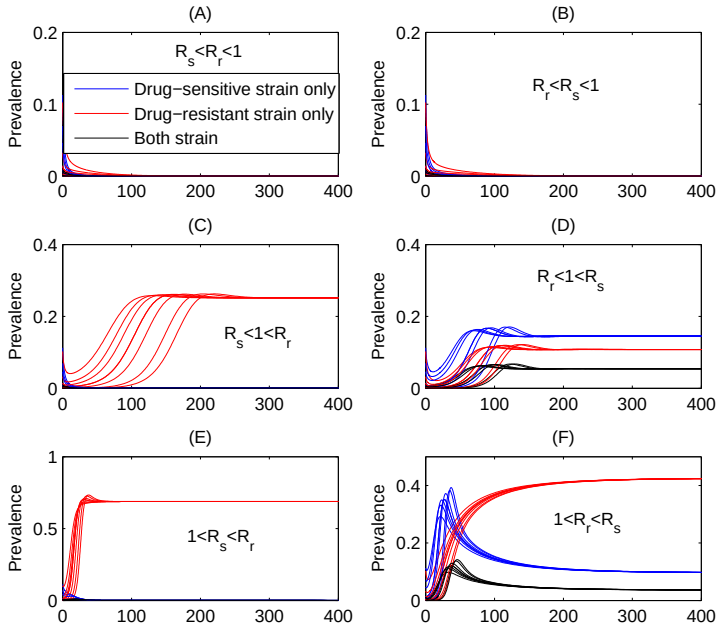

FIGURE 2. Prevalence of infection for drug sensitive/resistant strains in the absence of superinfection. Blue, red and black lines denote the number of cases infected with drug sensitive strains only, drug resistant strains only and both strains, respectively. (A)$\beta_s = 0.1, \beta_r = 0.15, \beta_{sr} = 0.65, p = 0.65$, (B)$\beta_s = 0.16, \beta_r = 0.15, \beta_{sr} = 0.65, p = 0.65$, (C) $\beta_s = 0.156, \beta_r = 0.25, \beta_{sr} = 0.65, p = 0.65$, (D)$\beta_s = 0.35, \beta_r = 0.15, \beta_{sr} = 0.65, p = 0.65$, (E)$\beta_s = 0.4, \beta_r = 0.6, \beta_{sr} = 0.65, p = 0.65$, (F) $\beta_s = 0.6, \beta_r = 0.4, \beta_{sr} = 0.65, p = 0.65$.

4. **Effect of superinfection.** In this part, we will do some numerical simulations to verify our theoretical results obtained above and examine effects of superinfection on the HIV epidemic. All parameters are chosen for the current situation of gay men in China[35, 20, 48]. The disease related death rates are chosen to satisfy that $1/v_s^T \geq 1/v_{sr}^T \geq 1/v_r^T \geq 1/v_r^I \geq 1/v_{sr}^I \geq 1/v_s^I$ [5]. For the superinfection

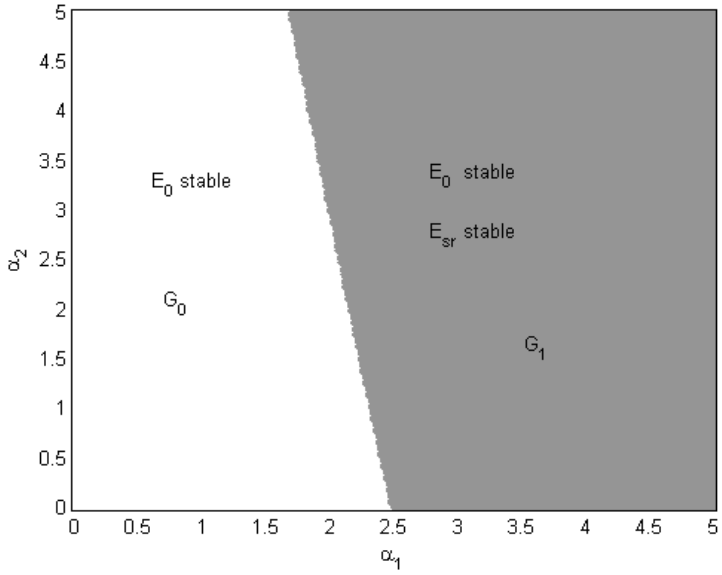

FIGURE 3. Plot of stability of E_0 and E_{sr} in the plane $\alpha_1 - \alpha_2$ when $R_s < 1, R_r < 1, R_s^r < 1$. $\beta_s = 0.14, \beta_r = 0.18, \beta_{sr} = 0.85, p = 0.85$.

rate, there are two different opinions: some studies show that the superinfection rate is similar to the rate of initial infection [33, 7, 24, 25], while others indicate that superinfection is very rare [37, 12]. The study implemented by Redd et al. [30] showed that the superinfection rate was 1.44 per 100 person years which is lower than the primary incidence. In this study, we take different values of the superinfection rate to simulate various situations. Let $\beta_s' = \alpha_1\beta_s$, $\beta_{sr}' = \alpha_1\beta_{sr}$ and $\beta_r' = \alpha_2\beta_r$, $\beta_{sr}'' = \alpha_2\beta_{sr}$ with the changing values of α_1 and α_2. Both α_1 and α_2 vary from 0 to 10. It is supposed that the treatment efficacy is lower for people infected with drug resistant strains. Here, we choose the value of ε_{T_r} and $\varepsilon_{T_{sr}}$ which are no less than ε_{T_s}. Other values of parameter are listed in table 1.

In the absence of superinfection (i.e., $\alpha_1 = \alpha_2 = 0$), we do six groups of simulations with various initial conditions, as shown in figure 2, where blue, red and dark curves denote the number of infected cases infected with drug sensitive strains-only, drug resistant strains-only and both strains, respectively. From figure 2(A) and (B) we can get that when both R_s and R_r are less than one, the disease-free equilibrium is globally asymptotically stable. Figures 2 (C) and (E) indicate that when $R_r > R_s$ and $R_r > 1$ the drug sensitive strain will die out and the drug resistance strain-only boundary equilibrium is stable. Figures 2 (D) and (F) show the stability of the coexistence equilibrium when $R_s > 1 > R_r$ or $R_s > R_r > 1$.

In the presence of superinfection (i.e. $\alpha_1 > 0, \alpha_2 > 0$), we now examine the effects of superinfection on stability of all possible equilibria. We consider the following five scenarios in terms of relation of R_s, R_r and unity.

Firstly, when $R_s < 1, R_r < 1$, we let α_1 and α_2 vary from 0 to 8 with step of 0.02. For each pair of (α_1, α_2), we solve model (1) numerically with sufficiently large initial value ($y_0 = (763240, 100000, 50000, 1000, 10000, 50000, 1000)$) for a sufficiently long time (say, $t = 100,000$). If system (1) converges to the disease-free equilibrium the

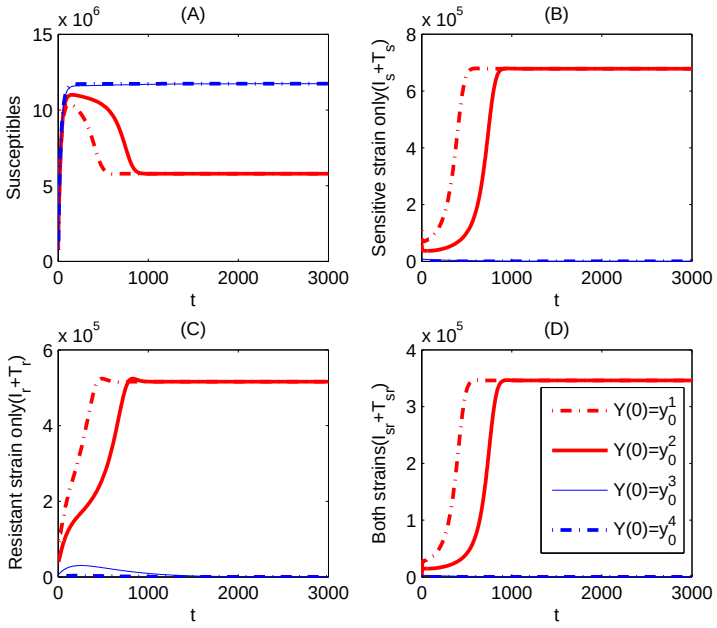

FIGURE 4. Plot of stability of E_0 and E_{sr} for different initial values when $R_s < 1, R_r < 1$. $\beta_s = 0.14, \beta_r = 0.18, \beta_{sr} = 0.85, p = 0.85, \alpha_1 = 4, \alpha_2 = 0.3$, $y_0^1 = (763240, 100000, 50000, 1000, 10000, 50000, 1000)$, $y_0^2 = (763240, 50000, 30000, 1000, 10000, 1000, 10000)$, $y_0^3 = (763240, 10000, 5000, 1000, 1000, 100, 500)$, $y_0^4 = (763240, 1000, 500, 100, 100, 100, 500)$.

coordinate (α_1, α_2) is marked by white color, otherwise if the disease is persistent, i.e. there is a positive number δ, $I_s(t) > \delta, I_r(t) > \delta, I_{sr}(t) > \delta, T_s(t) > \delta, T_{sr}(t) > \delta$ and $T_r(t) > \delta$ for the sufficiently large time t, we mark the coordinate (α_1, α_2) by light grey color. The results are shown in figure 3. If we change the initial value to a sufficiently small value, say, $y_0 = (763240, 1000, 500, 100, 100, 100, 500)$, it is easy to get that system (1) converges to the disease-free equilibrium no matter how α_1 and α_2 vary. Thus, we can obtain that when $(\alpha_1, \alpha_2) \in G_0$, there is only one disease-free equilibrium E_0 which is stable. However, when $(\alpha_1, \alpha_2) \in G_1$, there are two stable equilibria, disease-free equilibrium E_0 and coexistence equilibrium E_{sr}, shown in figure 3. For a given value of α_2, increasing α_1 induces system changes to stabilize at either disease-free equilibrium or the coexistent state from the stable disease-free equilibrium, as shown in figure 3. This implies that superinfection of the sensitive strain is beneficial for two strains to coexist. If we choose $\alpha_1 = 5, \alpha_2 = 0.3$, which lie in G_1, we can get that solutions initiating from different values stabilize at different equilibria. Figure 4 shows that solutions starting from the initial values $y_0^1 = (763240, 100000, 50000, 1000, 10000, 50000, 1000)$ or $y_0^2 = (763240, 50000, 30000, 1000, 10000, 1000, 10000)$ converge to the coexistent equilibrium E_{sr}, while solutions initiating from the initial values $y_0^3 = (763240, 10000, 5000, 1000, 1000, 100, 500)$ or $y_0^4 = (763240, 1000, 500, 100, 100, 100, 500)$ tend to disease-free equilibrium E_0.

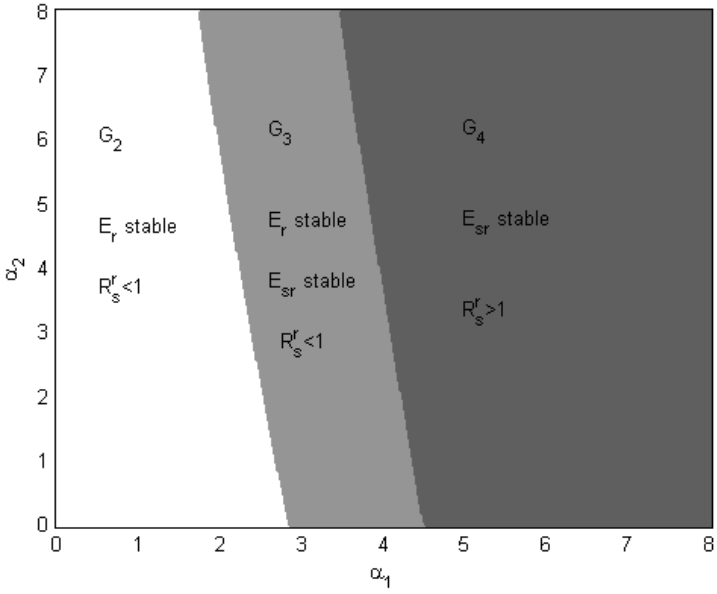

FIGURE 5. Plot of stability of E_r and E_{sr} in the plane $\alpha_1 - \alpha_2$ when $R_s < 1 < R_r$. $\beta_s = 0.14, \beta_r = 0.2, \beta_{sr} = 0.85, p = 0.85, \varepsilon_{T_s} = 0.3507, \varepsilon_{T_r} = 0.4, \varepsilon_{T_{sr}} = 0.37$.

When $R_s < 1 < R_r$, by using similar method we can get three different regions for plane $\alpha_1 - \alpha_2$, shown in figure 5. It follows from Theorem 3.1 and 3.3 that both disease-free equilibrium E_0 and drug resistant strain-only boundary equilibrium E_r exist when (α_1, α_2) lies in any of these three regions. In such case the disease-free equilibrium is unstable. Figure 5 shows that coexistence equilibrium E_{sr} exists when $(\alpha_1, \alpha_2) \in G_3 \cup G_4$. Meanwhile, we can get when $(\alpha_1, \alpha_2) \in G_2$, only E_r is locally stable, when $(\alpha_1, \alpha_2) \in G_3$, both E_r and E_{sr} are locally bistable, and when $(\alpha_1, \alpha_2) \in G_4$ only E_{sr} is stable. For a given value of α_2, increasing α_1 induces system changes from the stable resistant strain-only equilibrium E_r to the bistable states of E_r and E_{sr} and to the stable coexistent state E_{sr}. This implies that superinfection of the sensitive strain makes the sensitive strain invade successfully and hence is also beneficial for two strains to coexist. Choosing $\alpha_1 = 4, \alpha_2 = 0.3$, which lies in G_3, we can get that solutions initiating from different values stabilize at different equilibria. Figure 6 shows that solutions starting from initial values $y_0^1 = (763240, 100000, 50000, 1000, 10000, 50000, 1000)$ or $y_0^2 = (763240, 50000, 30000, 1000, 10000, 1000, 10000)$ converge to the coexistent state E_{sr}, while solutions from initial values $y_0^3 = (763240, 10000, 5000, 1000, 1000, 100, 500)$ or $y_0^4 = (763240, 1000, 500, 100, 100, 100, 500)$ tend to the drug resistant strain-only boundary equilibrium E_r.

When $R_r < 1 < R_s$, numerical studies indicate that the coexistence equilibrium E_{sr} always exists and is locally stable for any values of α_1 and α_2 (i.e., no matter when $R_s^r < 1$ or $R_s^r > 1$), as shown in figure 7. When $1 < R_s < R_r$ and $1 < R_r < R_s$, the results are described in figure 8 and figure 9, respectively. Both figure 8 and figure 9 show that the drug resistant strain-only boundary equilibrium E_r is stable for $R_s^r < 1$ and the coexistence equilibrium E_{sr} is stable for $R_s^r > 1$. It is interesting

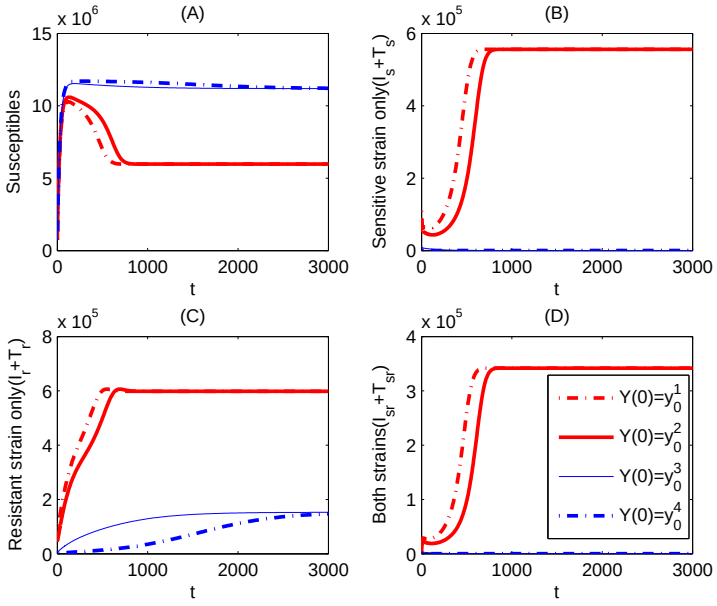

FIGURE 6. Plot of stability of E_0 and E_{sr} for different initial values when $R_s < 1, R_r > 1$. $\beta_s = 0.14, \beta_r = 0.2, \beta_{sr} = 0.85, p = 0.85$, $\varepsilon_{T_s} = 0.3507, \varepsilon_{T_r} = 0.4, \varepsilon_{T_{sr}} = 0.37, \alpha_1 = 3.2, \alpha_2 = 4.8$, $y_0^1 = (763240, 100000, 50000, 1000, 10000, 50000, 1000)$, $y_0^2 = (763240, 50000, 30000, 1000, 10000, 1000, 10000)$, $y_0^3 = (763240, 10000, 5000, 1000, 1000, 100, 500)$, $y_0^4 = (763240, 1000, 500, 100, 100, 100, 500)$.

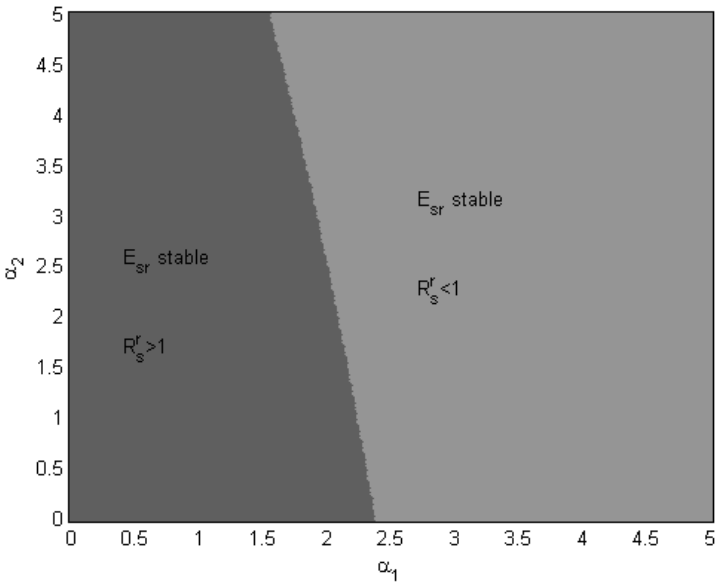

FIGURE 7. Plot of stability of E_r and E_{sr} in the plane $\alpha_1 - \alpha_2$ when $R_r < 1 < R_s$. $\beta_s = 0.18, \beta_r = 0.175, \beta_{sr} = 0.85, p = 0.85$.

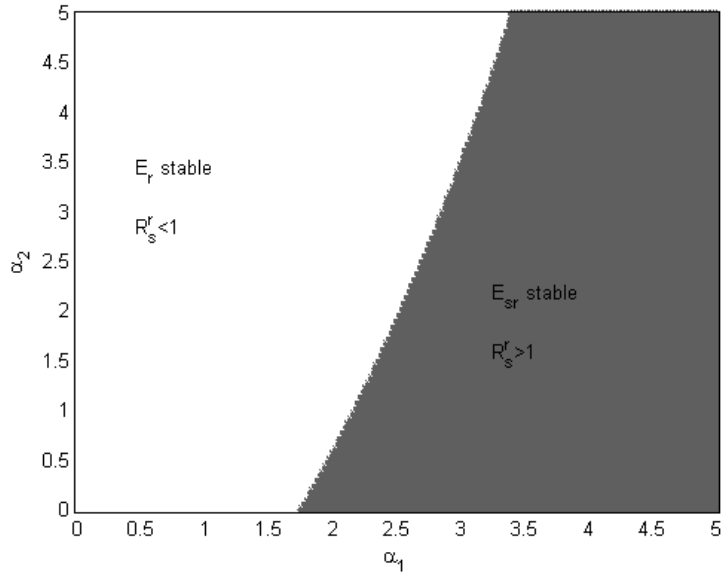

FIGURE 8. Plot of stability of E_r and E_{sr} in the plane $\alpha_1 - \alpha_2$ when $1 < R_s < R_r$. $\beta_s = 0.3, \beta_r = 0.21, \beta_{sr} = 0.55, p = 0.25$.

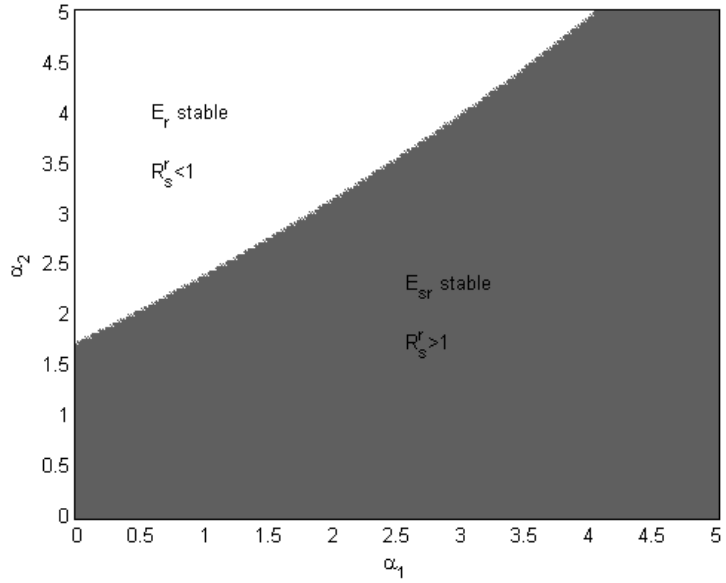

FIGURE 9. Plot of stability of E_r and E_{sr} in the plane $\alpha_1 - \alpha_2$ when $1 < R_r < R_s$. $\beta_s = 0.36, \beta_r = 0.23, \beta_{sr} = 0.25, p = 0.19, \varepsilon_{T_s} = 0.3507, \varepsilon_{T_r} = 0.4, \varepsilon_{T_{sr}} = 0.37$.

to note that for a given value of α_1, increasing α_2 may induce system changes to stabilize at the equilibrium E_r from the stable coexistent state E_{sr}. This implies that superinfection of the resistant strain is beneficial for the resistant strain to dominate and sustain in a population.

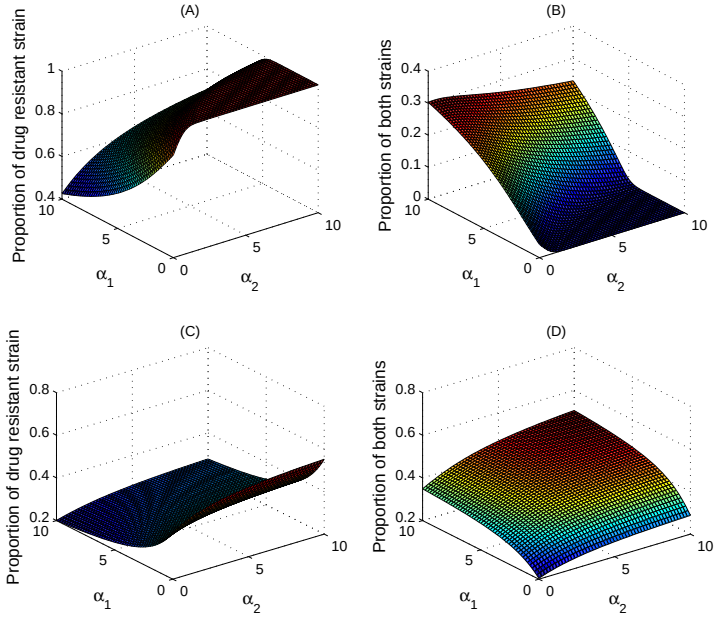

FIGURE 10. Effect of superinfection. (A) (C), proportions of individuals infected with drug resistant strains. (B) (D), proportions of individuals infected with both strains. Parameter values for (A) and (B) are $\beta_s = 0.5, \beta_r = 0.3, \beta_{sr} = 0.45, \varepsilon_{T_{sr}} = 0.4, p = 0.4, \sigma = 0.5$. Parameter values for (C) and (D) are $\beta_s = 0.5, \beta_r = 0.3, \beta_{sr} = 0.6, \varepsilon_{T_{sr}} = 0.7, p = 0.8, \sigma = 0.5$.

By comparing the main results with and without superinfection we summarize the results in table 2. It's worth pointing out that the coexistence equilibrium E_{sr} may exist and be stable even when $R_0 < 1$, as figure 3 and figure 4 show. This implies that superinfection is beneficial for two strains to coexist. Further, for $R_s < 1 < R_r$ the coexistent state E_{sr} can be bistable with the equilibrium E_r, and then becomes to be a solely stable state as the parameter value α_1 increases, as figure 5 shows. This illustrates that superinfection of the sensitive strain makes the sensitive strain invade successfully and hence is helpful for two strains to coexist. Meanwhile, E_r can be stable when $R_s > R_r > 1$ for great values of α_2, as figure 9 shows. This indicates that superinfection of the resistant strain helps to make the resistant strain dominate in the system and increases the chances of extinction of drug sensitive strain.

In the following, we choose parameter values associated with the HIV epidemic among MSMs [35, 20, 48] to investigate effects of superinfection on HIV infection. Because of the fitness cost, infectiousness for people infected with drug resistant strains is smaller than that for people infected with drug sensitive strains[5, 21]. We simply take $\beta_s = 0.5, \beta_{sr} = 0.45, \beta_r = 0.3, \varepsilon_{T_{sr}} = 0.4, p = 0.4$. Let superinfection coefficients α_1 and α_2 vary while keeping other parameters unchanged to examine the variation in fractions of individuals infected with drug resistant strain-only or with both strains. The proportions of individuals infected with drug resistant strains and both strains are described in figure 10 (A) and (B), respectively. A repeat of plotting is given in figure 10 (C) and (D) if we take parameter values

TABLE 1. Parameter values

Para	Definition	Value/Range	Source
U	Recruitment rate of susceptible	402450 capita/year	[35]
μ	Exit rate	0.0343 year^{-1}	[35]
β_s	Transmission coefficient for individual infected with drug sensitive strains	0.5 (capita year)$^{-1}$	variable
β_r	Transmission coefficient for individual infected with drug resistant strains	0.4 (capita year)$^{-1}$	variable
β_{sr}	Transmission coefficient for individual infected with both strains	0.45 (capita year)$^{-1}$	variable
β_s'	Superinfection coefficient for individual infected with drug sensitive strains without treatment	$\alpha_1\beta_s$	variable
β_r'	Superinfection coefficient for individual infected with drug resistant strains with treatment	$\alpha_2\beta_r$	variable
β_{sr}'	Superinfection coefficient for individual infected with both strains without treatment	$\alpha_1\beta_{sr}$	variable
β_{sr}''	Superinfection coefficient for individual infected with both strains with treatment	$\alpha_2\beta_{sr}$	variable
p	Probability for individuals infected with both strains to transmit sensitive strains	0-1	variable
ε_{T_s}	Modification factor for individuals infected with drug sensitive strains	0.3507	[35]
ε_{T_r}	Modification factor for individuals infected with drug resistant strains	0.4500	assumed
$\varepsilon_{T_{sr}}$	Modification factor for individuals infected with drug resistant strains	0.4000	assumed
σ	Treatment rate	0.2 year^{-1}	[20, 48]
r_1	Progression rate of drug resistance from T_s to T_{sr}	0.12 year^{-1}	[43]
r_2	Progression rate of drug resistance from T_{sr} to T_r	0.05 year^{-1}	assumed
v_i^j	Disease related death rate for each infected group	0-0.2 year^{-1}	[5]

as $\beta_s = 0.5, \beta_{sr} = 0.6, \beta_r = 0.3, \varepsilon_{T_{sr}} = 0.7, p = 0.8$. It follows from figure 10 that increasing superinfection coefficient of the sensitive strain (i.e. increasing α_1) leads to an increase in the fraction of individuals infected with both strains, but a decrease in the fraction of individuals infected with resistant strain. Whereas, increasing the superinfection coefficient of the resistant strain (i.e. increasing α_2) leads to an increase in the fraction of individuals infected with drug resistant strains, and may lead to an increase or decrease in the fraction of cases infected with both strains, depending on the level of infectious individuals with sensitive strain infected by individuals with both stains.

TABLE 2. Stability Results

Conditions	With superinfection	Without superinfection
$R_r < 1, R_s < 1$	E_0 stable for $(\alpha_1, \alpha_2) \in G_0$, E_{sr} stable for $(\alpha_1, \alpha_2) \in G_1$	E_0 stable
$R_s < 1 < R_r$	E_r stable for $(\alpha_1, \alpha_2) \in G_2$, E_r, E_{sr} bistable for $(\alpha_1, \alpha_2) \in G_3$ E_{sr} stable for$(\alpha_1, \alpha_2) \in G_4$	E_r stable
$R_r < 1 < R_s$	E_{sr} stable	E_{sr} stable
$1 < R_s < R_r$	E_r stable for $R_s^r < 1$, E_{sr} stable for $R_s^r > 1$	E_r stable
$1 < R_r < R_s$	E_r stable for $R_s^r < 1$, E_{sr} stable for $R_s^r > 1$	E_{sr} stable

5. **Conclusions.** A number of recent reports indicate that HIV-1 superinfection can occur in infected individuals[17, 23, 34, 13]. However, few mathematical models have been formulated to model superinfection so far. The existing mathematical models are associated with the transmission dynamics of drug sensitive and resistant strains under an assumption of no superinfection [5, 38, 3, 32, 19, 28, 44]. In this article, we proposed a mathematical model of HIV infection with superinfection, and investigated the transmission dynamics of drug resistant strain and provided insight into the potential for HIV superinfection to affect the epidemic. Since superinfection makes the dynamics more complicated we initially examine the transmission dynamics without superinfection and then numerically focus on influence of superinfection.

In the absence of superinfection, the dynamics of the system can be determined by two reproduction numbers (R_s and R_r), as shown in table 2. However, these two reproduction numbers are not enough to describe the dynamics of the system when superinfection is present. Thus, an invasion reproduction number (R_s^r) is introduced to determine whether the sensitive strain can invade a population where the resistant strain is at equilibrium. The disease-free equilibrium unconditionally exists, which is similar to the models with two different strain types [32, 2, 47]. It is interesting to note that in the presence of superinfection if the basic reproduction number $R_0 < 1$, the disease-free equilibrium E_0 may be either solely stable or bistable with the coexistence E_{sr}, depending on the superinfection parameters α_1 and α_2. In particular, for a relatively large superinfection coefficient of the sensitive strain (large α_1) the stable coexistence equilibrium is feasible. This implies that superinfection of the sensitive strain makes the coexistence state more likely.

We proved that the drug resistant strain-only equilibrium exists when $R_r > 1$ without and with superinfection. In the absence of superinfection E_r is stable when $R_r > R_s$. While, when superinfection is present, E_r is stable when $R_s^r < 1$. However, it is possible that $R_s^r > 1$ when $R_s < R_r$, that means the drug resistant strain-only equilibrium could become unstable due to superinfection. In such case, the coexistence equilibrium E_{sr} may exist and be stable, shown in figure 5 and figure 8. Moreover, figure 5 illustrates that system experienced from the stable resistant-strain only equilibrium E_r to the bistable states of E_r and E_{sr} and then to the stable coexistent state E_{sr} with increasing superinfection coefficient α_1. This

implies that superinfection of the sensitive strain makes it invade more likely and hence is also beneficial for two strains to coexist.

It is worth noting that superinfection of the resistant strain may induce the stability of drug resistant strain-only equilibrium or the coexistence state, depending on the values of R_s, R_r and the level of superinfection coefficient α_1, α_2, as shown in figure 3, 5, 7-9. When the system stabilizes at the disease-free equilibrium in the absence of superinfection, increasing the superinfection coefficient α_2 may induce the stability of coexistence state, which is dependent on the value of α_1, as shown in figure 3. When the system stabilizes at the coexistence equilibrium in the absence of superinfection, increasing the superinfection coefficient α_2 may induce the stability of drug resistant strain-only equilibrium, as illustrated in figure 9. When the system stabilizes at the equilibrium E_r in the absence of superinfection, increasing the superinfection coefficient α_1 may induce the bistability E_r and E_{sr} or the stability of coexistence state E_{sr}, which is dependent on the value of α_1, as shown in figure 5 and 8. This indicates that superinfection of the drug resistant strain makes its persistence in a population more likely, and may increase chance of existence of the coexistence state, depending on the level of superinfection coefficient of sensitive strain (the value of α_1).

It should be noted that superinfection may result in an increase in the fractions of individuals infected with the drug resistant strain or with both strains. This will bring more difficulties to the treatment of the infected individuals, especially in mainland China where the second-line treatment options are very limited and are not available to all infected individuals needed [46]. From the point of HIV infection control, superinfection may cause more difficulties to eradicate the disease or reduce HIV infection. Thereby, it is essential to enhance education for high-risk population to reduce the infectivity per high-risk behaviour (say, using condom) or decrease the frequency of high risk behaviour.

Acknowledgments. The authors are supported by the national Megaproject of Science Research no. 2012ZX10001-001, by the National Natural Science Foundation of China(NSFC, 1171268(YX)), by the International Development Research Center, Ottawa, Canada(104519-010).

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Received October 18, 2014; Accepted July 14, 2015.

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