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THE PERSISTENCE OF HIV-1 SPREADING IN MSM POPULATION IN CHINA*

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Abstract In this work, we develop and analyze mathematical models for the dynamics about the evolution of HIV/AIDS in men who have sex with men in China. We focus on the analyses of the basic reproduction number R_0 and the persistence of infection. Through simulations we also find that the interventions including antiviral therapy, condom using and potential vaccinations play very important roles in the HIV/AIDS spreading in MSM population in China.

Keywords Dynamic models, persistence, HIV/AIDS.

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1. Introduction

Men who have sex with men (MSM) is a description of a behavioral phenomenon, not an identity. Gay and bisexual men are only a part of the total MSM population. Many MSM, whether occasionally or frequently, do not regard themselves as ¡®homosexual¡¯ or ¡®bisexual¡¯. In recent years, they are at increased risk of human immunode- ficiency virus (HIV-1) infection. MSM are 19 times more likely to be infected with HIV-1 than the general population [19]. In China, the HIV-1 infection rate among MSM is climbing at an alarming rate, largely due to the neglect to this special sexual orientation subpopulation. In past decade, MSM have emerged as a high-risk group for HIV-1 in China. The proportion of nationally reported new case of HIV-1/AIDS among MSM increased from 0.7% in 2005 [4] to 21.4% in 2013 [5] in Beijing. But we estimate that the HIV-1 infection rate in MSM population in the whole China will not be so high as that in Beijing.

China's first official figure on male homosexuality was released in 2004, putting the total of gay men in the country at between five and ten million [12]. But the number keeps increasing in recent years. In Beijing except the gay and bisexual men, there are thousands of male sex workers serving men clients, who are called "money boys". Money boys are not necessarily gay themselves, and some also serve women clients.

In literature [24], Nick Yee made a survey in a 396 MSM population and finally gave a summary about the correlations between sex-role preference for partners among MSM through internet in 2002. In general, the categorization tested in this research includes 3 categories: Only Bottom (11.6%), Versatile (69.3%) and Only Top (10.9%) for these who has anal sex (AI) behaviour. Considering that the sex-

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role preference can reach different HIV-1 virus transmission rate, we would like to consider this character in our model: the sex-role preference of all MSM in our study will be divided into three subgroups: Only Bottom; Versatile; and Only Top.

In China, HIV-1 infected patients are receiving free treatments ("Four-Free-One-Care Policy") on combined antiretroviral therapy which are provided by the government. An effective ART predictably decreases plasma HIV-1 RNA levels to below the level of detection of currently available assays [13]. That gives people that is HIV-1 positive a chance to live longer. But there is one possibility: the reduction of plasma HIV-1 may lead to an increase in adverse behaviour (disinhibition), such as reducing condom. We will discuss these possibilities in this manuscript.

Recently, a research team of HongKong University has developed a new antibody drug that protects cells from HIV-1 infection and AIDS, and successfully tests them in mice [23]. The team points out that this medicine (BiIA-SG) can strategically ambush HIV-1 and protect cells from infection through combining CD4 proteins on the surface of host cells. In addition, the gene-led BiIA-SG can continue to function in mice and remove cells that have been infected by HIV-1. The new drug is expected to be introduced as soon as possible to other large mammals, including human clinical studies. Their results warrant the clinical development of BiIA-SG as a promising bs-bnAb-based biomedical intervention for the prevention and treatment of HIV-1 infection [23]. In this manuscript, we will discuss the possible effect of the possible vaccination in MSM population in China.

The rest of this paper is organised as follows. The next section presents the mathematical model. The mathematical analysis are established in Sections 3. Designed numerical simulations based on calculated effects of different interventions are illustrated in Section 4. A discussion section on the implications of the results are put in Section 5 and finally some appendix materials complete the paper.

2. The model formulation

Recently, the importance of linking mathematical immunology and mathematical epidemiology was recognized [1, 6, 9, 15–18]. In the following, we use S, I and A to represent the susceptive MSM, the HIV-1 positive MSM and the HIV-1 positive MSM who receive ART respectively. Subscript T, B and V respectively denote the sexual orientation of these groups to be the Only Top, the Only Bottom and the Versatile categories. Then the differential equations for the MSM groups are:

$$\begin{cases} \frac{dS_T}{dt} = r_T - S_T\left(\frac{\beta_{BT}I_B+\beta_{VT}I_V}{\tilde{N}_B+\tilde{N}_V}\right) - d_M S_T \\ \frac{dI_T}{dt} = S_T\left(\frac{\beta_{BT}I_B+\beta_{VT}I_V}{\tilde{N}_B+\tilde{N}_V}\right) - d_I I_T - aI_T \\ \frac{dA_T}{dt} = aI_T - d_A A_T \\ \frac{dS_V}{dt} = r_V - S_V\left(\frac{\beta_{TV}I_T+\beta_{BV}I_B+\beta_{VV}I_V}{\tilde{N}_T+\tilde{N}_B+\tilde{N}_V}\right) - d_M S_V \\ \frac{dI_V}{dt} = S_V\left(\frac{\beta_{TV}I_T+\beta_{BV}I_B+\beta_{VV}I_V}{\tilde{N}_T+\tilde{N}_B+\tilde{N}_V}\right) - d_I I_V - aI_V \\ \frac{dA_V}{dt} = aI_V - d_A A_V \\ \frac{dS_B}{dt} = r_B - S_B\left(\frac{\beta_{TB}I_T+\beta_{VB}I_V}{\tilde{N}_T+\tilde{N}_V}\right) - d_M S_B \\ \frac{dI_B}{dt} = S_B\left(\frac{\beta_{TB}I_T+\beta_{VB}I_V}{\tilde{N}_T+\tilde{N}_V}\right) - d_I I_B - aI_B \\ \frac{dA_B}{dt} = aI_B - d_A A_B \end{cases} \tag{2.1}$$

where $\check{N}_i = N_i + A_i$ and $N_i = S_i + I_i$, $i = T, V, B$.

Note that the Only Top category can have sex with the Only Bottom and the Versatile population. The Only Bottom category can have sex with the Only Top and the Versatile population. The Versatile category can have sex with all categories. We assume that susceptible and infected MSM can *die* at rates d_M and d_I and the new MSM are recruited into the appropriate susceptible compartment at rates r_T, r_B and r_V respectively. Also, we suppose the subgroups A_i can not spread HIV-1 virus since they carry quite low HIV-1 virus load because of the effect of ART.

The key to quantify the transmission of HIV-1 is the parameter β_{yx}, the transmission rate that an individual from compartment y infects his partners from compartment x. Using the detail of an epidemiological survey that was held in 2008 [11], the HIV-1 transmission rate through anal sex in MSM can be described on six quantities:

$$\beta_{yx} = n_x c_x h_{yx}(1 - \eta^c \rho^c)(1 - \alpha_y(1 - \rho^c)\nu_y \eta^c)(1 + \mu^s \psi^s).$$

1. the number of different AI sex partners per year, n_x, for individuals from compartment x;
2. the number of AI with each sex partner per year, c_x, for individuals from compartment x;
3. the viral transmission probability per anal sex act, h_{yx};
4. the level of protection against HIV-1 infection due to condom usage (if condoms are used, HIV-1 transmission is decreased by a factor of $(1-\eta^c\rho^c)$, where η^c is the condom efficacy and ρ^c is the proportion of condom use);
5. the proportion of infected MSM who know that they are infected, α_y. This term denotes the effect of HIV-1 census in MSM population; ν_y denotes the proportion of these infected MSM who begin to control their behaviour (such as condom use) to avoid the spreading of HIV-1, if they did not use condom before they know that they have been infected by HIV-1.
6. other STIs increase both the rate of transmission and acquisition of HIV-1 (the proportion with other STIs is assumed to be ψ^s, with μ^s being the multiplication factor for HIV-1);

Note that $\check{N}(t) = \check{N}_T + \check{N}_V + \check{N}_B$. So we have

$$\begin{aligned}\frac{d\check{N}(t)}{dt} &= r_T + r_V + r_B - d_M(S_T + S_V + S_B) - d_I(I_T + I_V + I_B) - d_A(A_T + A_V + A_B) \\ &\le r_T + r_V + r_B - d_M \check{N}(t), \end{aligned} \tag{2.2}$$

which implies

$$\lim_{t\to\infty} \check{N}(t) \le \frac{r_T + r_V + r_B}{d_M} \triangleq K. \tag{2.3}$$

Similarly we have $\check{N}_i \le \dfrac{r_i}{d_M} \triangleq K_i$, $i = T, V, B$. Thus we can get the positive invariant domain of system (2.1):

$$D = \left\{(\check{N}_i, \check{N}) : 0 \le \check{N}_i \le K_i, i = T, B, V, 0 \le \check{N} \le K\right\}.$$

3. Dynamics of the model

In this manuscript, we will discuss totally three dynamic models, including system (2.1) which includes the intervention "ART" (we call it the "with ART" model); the "naive" model of system (2.1), i.e., neglect the intervention ART (we call it also the "No ART" model); and a model with intervention "vaccination" (we call it "with vaccination"). For simplify and also considering the significance, we only discuss the dynamics of the "naive" model (i.e., the "No ART" model) in this section. But in the following sections, we will give simulations for all the three models.

The naive model always has a disease-free equilibrium $E^0=\left(\frac{r_T}{d_M}, 0, \frac{r_V}{d_M}, 0, \frac{r_B}{d_M}, 0\right)$. As mentioned in reference [8] the reproductive number (R_0) is the effected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a demographically steady susceptible population. Therefore, in order to study whether HIV-1 will invade a population or stabilize over a given region we must investigate R_0. Following the "next-generation operator" method of literatures [8,10], we can get the explicit solution of R_0 (in the Appendix 2) and also the stability of E_0: when $R_0 < 1$, E_0 is stable; Otherwise, it is unstable.

The naive system (2.1) may also exist an internal equilibrium E_*. But it is difficult to give the simple conditions that guarantee the existence of an internal equilibrium. But we will prove the existence of E_* using the result that the system is persistence of infection which will be proved in the following.

To study the persistence of HIV-1 infection, we discuss the equivalent system of the naive system as the following:

$$\begin{cases} \dfrac{dI_T}{dt} = (N_T - I_T)\left(\dfrac{\beta_{BT}I_B + \beta_{VT}I_V}{N_B + N_V}\right) - d_I I_T \\ \dfrac{dN_T}{dt} = r_T - d_M N_T - (d_I - d_M)I_T \\ \dfrac{dI_V}{dt} = (N_V - I_V)\left(\dfrac{\beta_{TV}I_T + \beta_{BV}I_B + \beta_{VV}I_V}{N_T + N_V + N_B}\right) - d_I I_V \\ \dfrac{dN_V}{dt} = r_V - d_M N_V - (d_I - d_M)I_V \\ \dfrac{dI_B}{dt} = (N_B - I_B)\left(\dfrac{\beta_{TB}I_T + \beta_{VB}I_V}{N_T + N_V}\right) - d_I I_B \\ \dfrac{dN_B}{dt} = r_B - d_M N_B - (d_I - d_M)I_B \end{cases} \tag{3.1}$$

The positive invariant domain of system (3.1) is

$$D = \{(I_i, N_i) : 0 \le I_i \le N_i, 0 \le N_i \le K_i\}, \quad i = T, V, B,$$

and the equivalent disease-free equilibrium of E^0 is

$$E_0 = (I_T^0, N_T^0, I_V^0, N_V^0, I_B^0, N_B^0) = \left(0, \ \frac{r_T}{d_M}, \ 0, \ \frac{r_V}{d_M}, \ 0, \ \frac{r_B}{d_M}\right).$$

First we introduce some basic definition and a Lemma that will be useful for our discussion. For more definitions and results about persistence, please refer literature [22] by Thieme.

Let X be a locally compact matric space with metric d. Let X be the disjoint union of two sets X_1 and X_2 such that X_2 is compact. Let Φ be a continuous semi-flow on X_1. An invariant subset M of X is said to be isolated if M is the maximal invariant set in some neighborhood of itself. Let A and B be two isolated invariant sets, A is chained to B ($A \to B$) if there is a full orbit through x which is not either in A or in B, such that $\omega(x) \subset B, \alpha(x) \subset A$. Moreover, a finite sequence $\{M_1, M_2, ..., M_k\}$ of a invariant sets is also called a chain if $M_1 \to M_2 \to ... \to M_k$. The chain is called cyclic if $M_k = M_1$. Otherwise, it is called acyclic.

Lemma 3.1. *Let X be locally compact, and let X_2 be compact in X and X_1 be forward invariant under the continuous semiflow Φ on X. Let x_n be a sequence of elements in X_1 satisfying*

$$\lim_{t\to\infty} \sup d(\Phi_t(x_n), X_2) \to 0, \qquad n \to \infty.$$

Let $M = \cup_{k=1}^{m} M_k$ be an isolated covering of Ω_2 such that $\omega(x_n) \nsubseteq M_k$ for all n, k. Then M is cyclic.

For more details of Lemma 3.1, please refer to the Proposition 4.3 of reference [22]. For the persistence of infection of out model, we have the following Theorem 3.1.

Theorem 3.1. *When $R_0 > 1$, system (3.1) is uniformly persistent of infection, i.e., there exists a $\varepsilon > 0$ for system (3.1), such that*

$$\lim_{t\to\infty} \inf \min\{I_T(t), I_V(t), I_B(t)\} > \varepsilon,$$

for any solution $x(t)$ with $N_T(0) > 0, N_V(0) > 0, N_B(0) > 0$ and any one of the three initial conditions holds: $I_T(0) > 0, I_V(0) > 0$ or $I_B(0) > 0$.

Proof. First we calculate the Jacobin matrix of system (3.1) at E_0. It is more convenient to change the order of coordinates to $I_T, I_V, I_B, N_T, N_V, N_B$ to study the Jacobian matrix.

The Jacobian matrix can be wrote as follows

$$J|_{E_0} = \begin{bmatrix} J_{LT} & 0 \\ J_{LB} & J_{RB} \end{bmatrix},$$

where

$$J_{LT} = \begin{bmatrix} -d_I & \frac{r_T\beta_{VT}}{r_B + r_V} & \frac{r_T\beta_{BT}}{r_B + r_V} \\ \frac{r_V\beta_{TV}}{r_T + r_V + r_B} & \frac{r_V\beta_{VV}}{r_T + r_V + r_B} - d_I & \frac{r_V\beta_{BV}}{r_T + r_V + r_B} \\ \frac{r_B\beta_{TB}}{r_T + r_V} & \frac{r_B\beta_{VB}}{r_T + r_V} & -d_I \end{bmatrix},$$

$$J_{LB} = \begin{bmatrix} -(d_I - d_M) & 0 & 0 \\ 0 & -(d_I - d_M) & 0 \\ 0 & 0 & -(d_I - d_M) \end{bmatrix}$$

and

$$J_{RB} = \begin{bmatrix} -d_M & 0 & 0 \\ 0 & -d_M & 0 \\ 0 & 0 & -d_M \end{bmatrix}.$$

Define

$$D_2 = \{(I_T, N_T, I_V, N_V, I_B, N_B) | I_T = 0, \text{ or } I_V = 0, \text{ or } I_B = 0, 0 \le N_i \le K_i\},$$

$$D_1 = D \backslash D_2,$$

$$\tilde{D}_1 = \{(I_T, N_T, I_V, N_V, I_B, N_B) | 0 < I_i < N_i, 0 < N_i \le K_i\},$$

where $i = T, V, B$ respectively and D_1 and $\tilde{D}_1$ are forward invariant.

Let $x^0 = (I_T(0), N_T(0), I_V(0), N_V(0), I_B(0), N_B(0))$. From system (3.1) and the assumptions ($N_i(0) > 0$ and at least any one of $I_i(0) > 0$, $i = T, V, B$ holds), it is easy to get that $\Phi_t(x^0) \in \tilde{D}_1$ for all $t > 0$. So we can then assume $x_0 \in \tilde{D}_1$.

Define $\Omega_2 = \cup_{x \in D_2} \omega(x)$. It is easy to see that $\Omega_2 = \{E_0\}$. Then in the following we will prove three content step by step:

1. $\{E_0\}$ is a weak repeller for $\tilde{D}_1$;
2. D_2 is a uniform weak repeller for $\tilde{D}_1$;
3. D_2 is a uniform strong repeller for $\tilde{D}_1$.

First, let's prove that $\{E_0\}$ is a weak repeller for $\tilde{D}_1$. Suppose $x(t)(= \Phi_t(x^0))$ stays in a small neighbor of E_0, then we have two cases:

1. if $I_T(0) = I_V(0) = I_B(0) = 0$, then $I_T(t) = I_V(t) = I_B(t) \equiv 0$. System (3.1) shows that $(N_T(t), N_V(t), N_B(t))$ goes far away from E_0 as $t \to -\infty$.
2. if $I_T(0) > 0$, or $I_V(0) > 0$, or $I_B(0) > 0$ holds, then $I_T(t) > 0, I_V(t) > 0$ and $I_B(t) > 0$ for all $t > 0$. When $x(t)$ stays very close to E_0, by system (3.1) we know that there exists some $\delta > 0$ which is related to the size of the neighborhood of E_0, such that

$$\frac{dX}{dt} > J_\delta X, \tag{3.2}$$

where matrix

$$J_\delta = \begin{bmatrix} J_{LT}^{11} - \delta & J_{LT}^{12} - \delta & J_{LT}^{13} - \delta \\ J_{LT}^{21} - \delta & J_{LT}^{22} - \delta & J_{LT}^{23} - \delta \\ J_{LT}^{31} - \delta & J_{LT}^{32} - \delta & J_{LT}^{33} - \delta \end{bmatrix}.$$

$J_{LT}^{ij} (i, j = 1, 2, 3)$ are the entries of the top-left matrix J_{LT} of the matrix $J|_{E_0}$. Since $R_0 > 1$, then by choosing δ small enough, J_δ has positive non-diagonal elements and its largest eigenvalue is positive.

Hence the solution of the linear quasi-monotonic system

$$\frac{dY}{dt} = J_\delta Y,$$

where

$$Y = \Big[y_1,\ y_2,\ y_3 \Big]^T,$$

with $y_1(0) > 0, y_2(0) > 0, y_3(0) > 0$ are exponentially increasing as $t \to \infty$. By the comparison principle, $(I_T(t), I_V(t), I_B(t))$ goes far away from $(0, 0, 0)$.

Conclude the above two cases, $\{E_0\}$ is isolated in D and it can not be chained to itself in D_2, i.e., $\{E_0\}$ is an acyclic covering for Ω_2. From the proof of case 2 we know that $\{E_0\}$ is a weak repeller for $\tilde{D}_1$.

Second, let's prove that D_2 is a uniform weak repeller for $\tilde{D}_1$. If D_2 is not a uniform weak repeller for $\tilde{D}_1$, then we can find a sequence

$$x_n = (I_{Tn}, N_{Tn}, I_{Vn}, N_{Vn}, I_{Bn}, N_{Bn}) \in \tilde{D}_1 \subset D_1,$$

satisfying

$$\lim_{t\to\infty} \sup d(\Phi_t(x_n), D_2) \to 0, \quad n \to \infty.$$

As $\{E_0\}$ is a weak repeller for $\tilde{D}_1$, we have $\omega(x_n) \not\subseteq \{E_0\}$ for all n. Using Lemma 3.1 we get that $\{E_0\}$ should be cyclic, which is contrary to our discussion above. So D_2 is a uniform weak repeller for $\tilde{D}_1$, i.e. there exists a $\tilde{\varepsilon} > 0$ such that

$$\lim_{t\to\infty} \sup \min\{I_T(t), I_V(t), I_B(t)\} > \tilde{\varepsilon} \tag{3.3}$$

for any solution $x(t)$ with $I_i(0) > 0, i = T, V, B$ holds.

Finally, let's prove that D_2 is a uniform strong repeller for $\tilde{D}_1$. Suppose that D_2 is not a uniform strong repeller for $\tilde{D}_1$. Then there exist sequences

$$x_j^0 = (I_T^j(0), N_T^j(0), I_V^j(0), N_V^j(0), I_B^j(0), N_B^j(0)) \in \tilde{D}_1$$

and $0 < \varepsilon_j < \tilde{\varepsilon}$, such that

$$\lim_{t\to\infty} \inf \min\{I_T^j(t), I_V^j(t), I_B^j(t)\} < \varepsilon_j \quad \text{for} \quad j = 1, 2, \cdots. \tag{3.4}$$

Here $\lim_{t\to\infty} \varepsilon_j = 0$ and $(I_T^j(t), N_T^j(t), I_V^j(t), N_V^j(t), I_B^j(t), N_B^j(t))$ are the solutions of system (3.1) with initial values $x_j^0 \in \tilde{D}_1$.

From (3.3) and (3.4) we can find sequences $0 < r_j < s_j < t_j$ with $\lim_{j\to\infty} r_j = \infty$ such that

$$\lim_{j\to\infty} \min\{I_T^j(s_j), I_V^j(s_j), I_B^j(s_j)\} = 0, \tag{3.5}$$

$$\min\{I_T^j(r_j), I_V^j(r_j), I_B^j(r_j)\} = \min\{I_T^j(t_j), I_V^j(t_j), I_B^j(t_j)\} = \tilde{\varepsilon}, \tag{3.6}$$

$$\min\{I_T^j(r_j), I_V^j(r_j), I_B^j(r_j)\} \le \tilde{\varepsilon} \quad \text{for} \ \ r_j \le t \le t_j. \tag{3.7}$$

Now for sequence $(I_T^j(r_j), N_T^j(r_j), I_V^j(r_j), N_V^j(r_j), I_B^j(r_j), N_B^j(r_j))$ which is convergent, from (3.6) we say it converges to

$$(I_T^*(0), N_T^*(0), I_V^*(0), N_V^*(0), I_B^*(0), N_B^*(0)) = x^*(0) \in \tilde{D}_1$$

when $j \to \infty$.

Now we prove that $t_j - r_j$ is unbounded when $j \to \infty$. Suppose it is not the truth, then after taking a subsequence, $s_j - r_j$ converge to s^* when $j \to \infty$.

Let $x^*(t)$ denote the solution of system (3.1) with initial value $x^*(0) \in \tilde{D}_1$, then according to the basic properties of flow and $\tilde{D}_1$ is invariant we can get that

$$\lim_{j\to\infty}(I_i^j(r_j+s^*), N_i^j(r_j+s^*)) = x^*(s^*) \in \tilde{D}_1, \quad i = T, V, B. \tag{3.8}$$

Also from (3.5) we can get that

$$\lim_{j\to\infty}(I_T^j(s_j), N_T^j(s_j), I_V^j(s_j), N_V^j(s_j), I_B^j(s_j), N_B^j(s_j)) = x^*(s^*) \in D_2, \tag{3.9}$$

which causes contradiction. So we say $t_j - r_j$ is unbounded when $j \to \infty$.

Now let $x^*(0) \in \tilde{D}_1$, then from (3.3) we can get that

$$\lim_{t\to\infty} \sup \min\{I_T^*(t), I_V^*(t), I_B^*(t)\} > \tilde{\varepsilon}. \tag{3.10}$$

In fact from the above discussion case 2 we know that the inequality (3.10) always holds when $x^*(0) \in D_1$.

Since $t_j - r_j$ is unbounded, we also can assume that it is increasing monotonically (we can realize this by choosing a subsequence) and $\lim_{j\to\infty} t_j - r_j = \infty$. So when $k > j$ and $0 \le r \le t_j - r_j$, we have

$$\min\{I_i^k(r_k + r)\} \le \tilde{\varepsilon}, \quad i = T, V, B.$$

Now fix r and j and let $j \to \infty$, we get that

$$\min\{I_i^*(r)\} = \lim_{k\to\infty} \min\{I_i^k(r_k + r)\} \le \tilde{\varepsilon}, \quad i = T, V, B. \tag{3.11}$$

In fact (3.11) holds for all $r \ge 0$ since $t_j - r_j$ is unbounded when j tends to infinity. This is contrary to (3.10). So D_2 is a uniform strong repeller for $\tilde{D}_1$. This finishes the proof. □

Since $N_i \ge I_i, i = T, V, B$, then from the strong uniform persistence of infection we can get the strong uniform persistence of populations. Finally, we can obtain the strong uniform persistence of (3.1) relatively to all components.

Theorem 3.2. *When $R_0 > 1$, then there exists a $\varepsilon > 0$ for system (3.1), such that, for any solutions $x(t)$ with initial values $N_T(0) > 0, N_V(0) > 0, N_B(0) > 0$ and any of the following three conditions holds: $I_T(0) > 0, I_V(0) > 0, I_B(0) > 0$, we have*

$$\lim_{t\to\infty} \inf \min\{I_T(t), N_T(t), I_V(t), N_V(t), I_B(t), N_B(t)\} > \varepsilon.$$

According to a general result from persistence theory we can get the existence of disease equilibrium for system (3.1).

Theorem 3.3. *When $R_0 > 1$, there exists at least one disease equilibrium of system (3.1).*

From the theory results we get that HIV-1 will be spread in the MSM population so long as one infected gay is introduced in this population, no matter he is an Only Top or a Versatile or an Only Bottom one, when $R_0 > 1$.

4. Simulations

In this section, we will totally discuss the three dynamic models (including the "naive" (or "No ART") model, the "with ART" model (2.1) and the "with vaccination" model (5.1)) that mentioned above. Some parameter values are calculated from the cohort study in 2008, which is on "high-risk behaviours and HIV-1/syphilis prevalence among men who have sex with men in Beijing" [11]. The reason to use this survey is that its data are relatively comprehensive, which can reflect complex sexual relationships among the MSM population in China. From these data, we can estimate the range of parameters in our model. Normally to say, the values of these parameters are uncertainty, even if it has a mean. For each uncertainty analysis we used Latin hypercube sampling [2], a type of stratified Monte Carlo sampling. To make predictions, we assigned each uncertain parameter a probability density function (pdf). The ranges of all biological and behavioural parameters used in this model are shown in Table 1.

Table 1. Parameters (V-Versatile; T-Top; B-Bottom)

Para	Description	Range	Distribution	Source
r_T	source rate of Only-T MSM	$[72500, 96667, 120834]$	Triangular	estimate
r_V	source rate of MSM-V	$[452962, 603950, 754937]$	Triangular	estimate
r_B	source rate of Only-B MSM	$[53113, 70817, 88521]$	Triangular	estimate
d_M	death rate of susceptible MSM	0.022	Constant	[21]
d_I	death rate of infected MSM	[0.067, 0.091, 0.2]	Triangular	[21]
d_A	death rate of MSM in AIDS stage	1		[21]
n_T	no. of anal-intercourse sex parter per year of MSM-only-T	[8.63, 11.5, 14.38]	Triangular	[11]
n_V	no. of anal-intercourse sex parter per year of MSM-V	[9.3, 12.4, 15.5]	Triangular	[11]
n_B	no. of anal-intercourse sex parter per year of MSM-only-B	[10.2, 13.6, 17]	Triangular	[11]
c_T	no. of anal intercourse with each sex parter per year of Only-T	[3.3, 4.4, 5.5]	Triangular	[11]
c_V	no. of anal intercourse with each sex parter per year of V	[3.38, 4.5, 5.63]	Triangular	[11]
c_B	no. of anal intercourse with each sex parter per year of Only-B	[3.15, 4.2, 5.25]	Triangular	[11]
h_{TB}	transmissibility of HIV-1 from T to B	[0.0075, 0.01, 0.0125]	Triangular	[3, 20]
h_{VB}	transmissibility of HIV-1 from V to B	[0.0075, 0.01, 0.0125]	Triangular	[3, 20]
h_{TV}	transmissibility of HIV-1 from T to V	[0.0075, 0.01, 0.0125]	Triangular	[3, 20]
h_{BT}	transmissibility of HIV-1 from B to T	[0.00375, 0.005, 0.00625]	Triangular	[3, 20]
h_{VT}	transmissibility of HIV-1 from V to T	[0.00375, 0.005, 0.00625]	Triangular	[3, 20]
h_{BV}	transmissibility of HIV-1 from B to V	[0.00375, 0.005, 0.00625]	Triangular	[3, 20]
h_{VV}	transmissibility of HIV-1 from V to V	[0.00563, 0.0075, 0.00938]	Triangular	estimate
α_y	proportion of the infected MSM who know they are infected	[0.225, 0.375]	Uniform	[11]
η^c	condom efficacy	[0.75, 0.9]	Uniform	[11]
ρ^c	rate of condom use	[0.1, 0.8]	Uniform	[11]
ρ_d^c	rate of condom use with disinhibition	[0.1, 0.4]	Uniform	[11]
ψ^s	proportion with STI	[0.1, 0.3]	Uniform	[11]
μ^s	multiplication factor of STI for HIV-1	$[1, 2.89, 3.5]$	Triangular	[7]
ν_y	proportion of these infected MSM who's in the know that begin to control their behavior	[0.3, 0.7]	Uniform	[11]
a	rate of ART	$[0.2, 0.6]$	Uniform	Estimated
υ	rate of vaccine	$[0.2, 0.6]$	Uniform	Estimated
e	effectiveness of vaccine	$[0.5, 0.8]$	Uniform	Estimated

Using the data from the cohort [11], we have the following estimations for the ranges of initial values. The cohort study estimated that the prevalence of HIV-1

in MSM in China was about 1.5% by the end of 2008 [11]. The total population of China is about 1.3029×10^9, and 50% of them are male. We suppose 3% of men in China have sex with men, 91.5% of whom experience AI, distributed as in reference [24] : 10.9% are Only-Top, 69.3% are Versatile and 11.6% are Only-Bottom. Then we have 1.8214×10^7 MSM experiencing AI, which is in the range estimated by [14]: the total number of gays in China is between 1.8×10^7 and 2.4×10^7. Also considering professional money boys that have homosexual sex behaviours, we estimate that the estimated ranges of initial values for each compartment which are shown in Table 2.

Table 2. Initial Conditions.

Compartment	Description	Min value	Max value
S_T	susceptible MSM-Only-Top	2×10^6	3×10^6
S_V	susceptible MSM-Versatile	1×10^7	2×10^7
S_B	susceptible MSM-Only-Bottom	2×10^6	3×10^6
I_T	infected MSM-Only-Top	3×10^4	4×10^4
I_V	infected MSM-Versatile	2×10^5	3×10^5
I_B	infected MSM-Only-Bottom	3.5×10^4	4.5×10^4

Our uncertainty estimations for the HIV-1 spreading for the naive (No ART) system are shown in Figure 1. We totally give 2000 realizations in this simulations. Parameter values are randomly chosen from Table 1, in which some are estimated from the situation of 2008 in China [11]. We obtained that the mean of $R_0 = 3.0839$. In other words, one HIV-1-infected MSM can infect 3 other HIV-susceptible individuals in the same population before he dies, if without ART or other intervention. Since $R_0 = 3.0839 > 1$, epidemic will be firmly established in MSM population of China. Our simulation predicts that, the mean of HIV-1 prevalence rate in MSM population in the whole China will be close to 15.81% (Figure 1.D) by the year 2020, which is about 10 times higher than that in 2008 (1.5% [11]). The HIV-1 prevalence rates in Only-Top, Versatile and Only-Bottom populations will be 10.88% (Figure 1.A), 15.84% (Figure 1.B), and 20.69% (Figure 1.C), respectively. Note that the infected Only-Bottom MSM increases much faster than the other two sub-populations. It shows that a quite high risk exists in this subpopulation if no intervention measure is implemented since they are possible "bridge population" lead to the general population.

Fortunately, HIV-1 infected patients in China can receive HIV free treatments that are provided by the government now. Considering some HIV-1 infected MSM do not make a definite diagnosis, here we assume that about 20% to 60% HIV-1 positive MSM are taking ART each year in China. Since ART can decrease plasma HIV-1 RNA levels to quite low level (which is difficult to be detected by currently available assays [13]), we suppose that patients receiving ART are no longer infectious. But every coin has two sides: good effect of ART may cause a "disinhibition" phenomenon, i.e., MSM will reduce condom use among MSM since they think they are quite safe now. Without doubt, the "disinhibition" will destroy the efficiency of ART. We want to know how powerful it is.

Considering that HongKong University has developed a new antibody drug that protects cells from HIV-1 infection and AIDS, and successfully tests them in mice [23], here we want to discuss the effect of a potential vaccination in the not long future. It is easy to realize by adding one compartment for each of the unin-

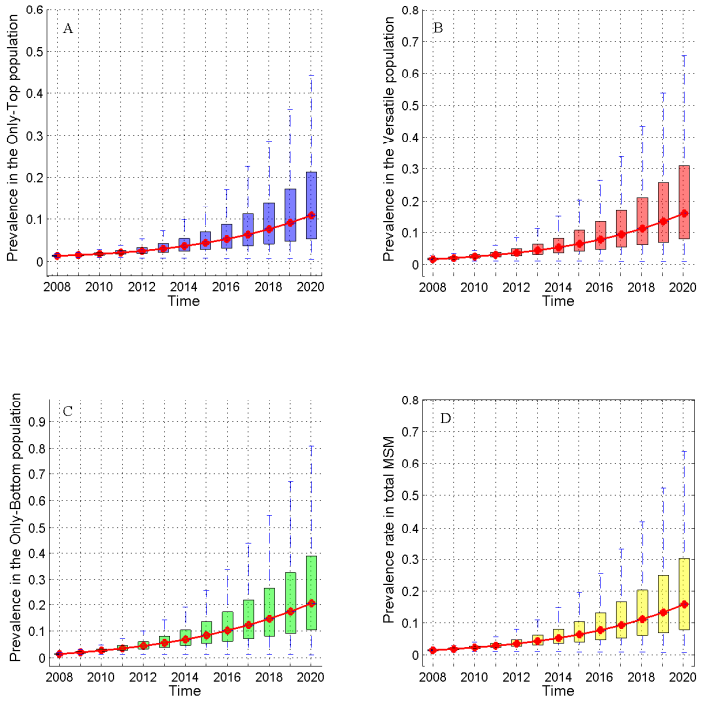

Figure 1. Time-dependent uncertainty analyses of HIV-1 epidemic among different MSM subpopulations in China without intervention. Each box-plot represents the results of 2000 simulations. These plots show median values (horizontal red line), upper and lower quartiles, and outlier cutoffs.

fected groups (see system 5.1). This vaccination has the property that vaccinated individuals may become infected, if the efficacy of the vaccine is less than 100%. In our simulations, we assume that uninfected individuals are vaccinated at the same rate of ART, and we explore the vaccine efficacy ranges from 50% to 80% (see Table 1). Equations of the vaccination model can be found in the Appendix 1.

Summarize the above points, we will totally discuss three scenarios in the following simulations. S1: the "with ART" model (2.1); S2: the "with vaccination" model (5.1)); and S3: the "with ART but disinhibition" model. Instead of plotting the dynamics curves as that in Figure 1, we prefer to plot the distribution of the reproductive number R_0 for each scenario. The explicit solution of R_0 for each of the three models can get using the method in [8]. The final results can be found in Appendix 2.

Under the uncertainty ranges of all universal parameters that shown in Table 1, the distributions of the basic reproduction numbers R_0 under four different scenarios are shown in Table 3 (Here we also consider the "naive" situation for comparison). For the special possibility: the disinhibition phenomenon under "with ART" scenario, we suppose that the condom use rate under disinhibition ranges in [0.1, 0.4], different from the range of [0.1, 0.8] under the "with ART" scenarios (see Table 1). We totally give 2000 realizations in this simulations. We show the means and

Table 3. Summary statistics of R_0 under four different scenarios.

R_0	**Naive**	**With ART**	**With Vaccination**	**With ART but disinhibition**
Mean	3.0839	0.7120	1.1901	1.0974
Media	2.8830	0.6622	1.0757	1.0416
SD	1.1614	0.2817	0.5404	0.3351
95% CI	3.0329-3.1347	0.6997-0.7243	1.1664-1.2138	1.0827-1.1121
IQR	2.2535-3.7219	0.505 1-0.8660	0.7949-1.4818	0.8463-1.2941

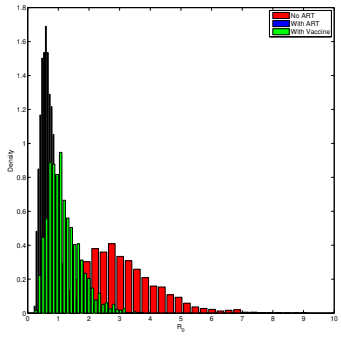

Figure 2. The basic reproduction number R_0 under three different scenarios respectively.

the medias of R_0; the standard deviation [SD]; 95% confidence interval [CI] (represents the upper and lower bound medias estimated from 2000 realizations); and interquartile range [IQR], respectively in Table 3. Obviously, the mean of R_0 for the "naive" scenario is the biggest one in the total four scenarios, which arrives 3.0839, with 95% CI: [3.0329, 3.1347]. As a strong contrast, the mean of R_0 under "with ART" scenario as low as 0.7120, with 95% CI: [0.6997, 0.7243]. The results mean that HIV-1 can be completely controlled in MSM population in China under this scenario. But if MSM population think that the ART can protect them from being infected by HIV-1 and begin to relax their vigilance, such as reduce highest condom use rate from 0.8 to 0.4 (see parameters ρ^c and ρ_d^c in Table 1) , then the dynamics will be reversed from being controlled to out of control. This is because the mean of R_0 of the "with ART but disinhibition" scenario can reach 1.1901, which is greater than 1. As a comparison, the mean of R_0 for the "with vaccination" reaches 1.0974, with 95% CI: [1.0827, 1.1121] (3). The most reason for this $R_0 > 1$ should be the effectiveness of the vaccine or antibody. This alerts us to improve the actual effect of our HIV-1 interventions to MSM population.

In order to describe our results more visually, we plot the histogram of these different basic reproduction numbers. Figure 2 give a visual graphic about the distributions of R_0 under the "no ART" system, the "with ART" system and the "with vaccination" system. We did not show the histogram of the "with ART but disinhibition" inside the figure to avoid too much clutter in the diagram. Anyway, both ART (even if with the disinhibition situation) and a potential vaccine are powerful interventions to control HIV-1 spreading in MSM population. But if we hope to get an ideal result for the interventions, such as the vaccination, we should pay more attention to the effectiveness of the vaccie and get repeat vaccinations year by year if possible.

5. Discussion

We developed a mathematical model using a sex-role-preference framework to predict HIV-1 infection in the MSM population in China considering different interventions. An analytic expression of the basic reproduction ratio R_0 was obtained using model parameters, and we estimated the R_0 as 3.0839 without any interventions. Our theory results (Theorem 3.2 and Theorem 3.3) also show that: HIV/AIDS will inevitable persistence in MSM population if we do not carry on any interventions in this population. It's worth mentioning that the infected Only-Bottom MSM increases much faster than the other two sub-populations. Since some of them are "money boy", it is quite possible that they will become a "bridging population" and lead the epidemic spreading to the general population.

Our simulations suggest that both antiretroviral therapy and the potential vaccine are powerful interventions, even if disinhibition may exist during these interventions. First of all, considering the diversity of the number of different sexual partners for each MSM (which is possible to obey a "power-law distribution"), we guess that a complex network model should be a more suitable method to model the spreading of HIV-1 in MSM. This is also what we want to try in our next work. Second, many MSM in China, whether occasionally or frequently having sex with men, do not necessarily regard themselves as homosexual or bisexual. They are very often married. Even if they are not, they may have sex with women as well. This applies particularly to those societies wherein marriage is strongly promoted by the society and the family. This is especially largely true for rural workers, most of whom are married. Thus, infected MSM can transmit HIV/AIDS to their heterosexual partners and thereafter to the general community as a "bridging population".

Appendix 1: Equations of vaccination strategy

Let V_T, V_V and V_B denote the Only-Top, Versatile and Only-Bottom MSM population respectively that were vaccinate. Then we have the following equations for the vaccination strategy.

$$\begin{aligned}
\frac{dS_T}{dt} &= r_T - S_T\left(\frac{\beta_{I_B S_T} I_B + \beta_{I_V S_T} I_V}{\tilde{N}_B + \tilde{N}_V}\right) - d_M S_T - vS_T \\
\frac{dI_T}{dt} &= S_T\left(\frac{\beta_{I_B S_T} I_B + \beta_{I_V S_T} I_V}{\tilde{N}_B + \tilde{N}_V}\right) + V_T\left(\frac{\beta_{I_B S_T} I_B + \beta_{I_V S_T} I_V}{\tilde{N}_B + \tilde{N}_V}\right)(1-e) - d_I I_T \\
\frac{dV_T}{dt} &= vS_T - V_T\left(\frac{\beta_{I_B S_T} I_B + \beta_{I_V S_T} I_V}{\tilde{N}_B + \tilde{N}_V}\right)(1-e) - d_M V_T \\
\frac{dS_V}{dt} &= r_V - S_V\left(\frac{\beta_{I_T S_V} I_T + \beta_{I_B S_V} I_B + \beta_{I_V S_V} I_V}{\tilde{N}_T + \tilde{N}_V + \tilde{N}_B}\right) - d_M S_V - vS_V \\
\frac{dI_V}{dt} &= S_V\left(\frac{\beta_{I_T S_V} I_T + \beta_{I_B S_V} I_B + \beta_{I_V S_V} I_V}{\tilde{N}_T + \tilde{N}_V + \tilde{N}_B}\right) \\
&\quad + V_V\left(\frac{\beta_{I_T S_V} I_T + \beta_{I_B S_V} I_B + \beta_{I_V S_V} I_V}{\tilde{N}_T + \tilde{N}_V + \tilde{N}_B}\right)(1-e) - d_I I_V \qquad (5.1) \\
\frac{dV_V}{dt} &= vS_V - V_V\left(\frac{\beta_{I_T S_V} I_T + \beta_{I_B S_V} I_B + \beta_{I_V S_V} I_V}{\tilde{N}_T + \tilde{N}_V + \tilde{N}_B}\right)(1-e) - d_M V_V
\end{aligned}$$

$$\frac{dS_B}{dt} = r_B - S_B\left(\frac{\beta_{I_T S_B} I_T + \beta_{I_V S_B} I_V}{\tilde{N}_T + \tilde{N}_V}\right) - d_M S_B - vS_B$$
$$\frac{dI_B}{dt} = S_B\left(\frac{\beta_{I_T S_B} I_T + \beta_{I_V S_B} I_V}{\tilde{N}_T + \tilde{N}_V}\right) + V_B\left(\frac{\beta_{I_T S_B} I_T + \beta_{I_V S_B} I_V}{\tilde{N}_T + \tilde{N}_V}\right)(1-e) - d_I I_B$$
$$\frac{dV_B}{dt} = vS_B - V_B\left(\frac{\beta_{I_T S_B} I_T + \beta_{I_V S_B} I_V}{\tilde{N}_T + \tilde{N}_V}\right)(1-e) - d_M V_B$$

where $\tilde{N}_i = S_i + I_i + V_i$, $i = T, V, B$.

Appendix 2: The basic reproductive number R_0

1. **R_0 of the "no ART" (or the "naive") model**
   The reproductive number (R_0) is the effected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a demographically steady susceptible population. Therefore, in order to study whether HIV-1 will invade a population or stabilize over a given region we must investigate R_0. Following the "next-generation operator" method of [8, 10], we can finally get the R_0 of the "No ART" system as follows:
   Define

$$\tilde{a} = \frac{r_T \beta_{VT}}{d_I(r_B + r_V))}, \quad \tilde{b} = \frac{r_T \beta_{BT}}{d_I(r_V + r_B)}, \quad \tilde{c} = \frac{r_V \beta_{TV}}{d_I r_a}, \quad \tilde{d} = \frac{r_V \beta_{VV}}{d_I r_a},$$
$$\tilde{e} = \frac{r_V \beta_{BV}}{d_I r_a}, \quad \tilde{f} = \frac{r_B \beta_{TB}}{d_I(r_T + r_V)}, \quad \tilde{g} = \frac{r_B \beta_{VB}}{d_I(r_T + r_V)}, \quad r_a = r_T + r_V + r_B.$$

   Let

$$\begin{aligned}
\tilde{A} &= \tilde{f}\tilde{b} + \tilde{g}\tilde{e} + \tilde{c}\tilde{a};\\
\tilde{B} &= -\tilde{f}\tilde{a}\tilde{e} - \tilde{g}\tilde{c}\tilde{b} + \tilde{d}\tilde{f}\tilde{b};\\
\tilde{E} &= 81\tilde{B}^2 - 12\tilde{A}^3 - 3\tilde{A}^2\tilde{d}^2 - 54\tilde{A}\tilde{B}\tilde{d} - 12\tilde{B}\tilde{d}^3;\\
\tilde{C} &= \sqrt{\tilde{E}};\\
\tilde{F} &= 36\tilde{A}\tilde{d} + 8\tilde{d}^3 + 12\tilde{C} - 108\tilde{B};\\
\tilde{D} &= \sqrt[3]{\tilde{F}}
\end{aligned} \tag{5.2}$$

   and

$$\tilde{G} = \frac{\tilde{d}}{3}; \tilde{H} = \frac{\tilde{D}}{6}; \tilde{I} = \frac{2\tilde{A}}{\tilde{D}}; \tilde{J} = \frac{2\tilde{d}^2}{3\tilde{D}}.$$

   Then we get the reproductive number (R_0) for the "naive" system as:

$$R_0 = \tilde{G} + \tilde{H} + \tilde{I} + \tilde{J}.$$

2. **R_0 of the "with ART" model**
   For this situation, we just have to replace d_I in the R_0 for the "no ART" model with $d_I + a$, and everything else is exactly the same.

3. **R_0 of the "with Vaccination" model**

For this situation, we just have to replace $\tilde{a}, \tilde{b}, \tilde{c}, \tilde{d}, \tilde{f}$ and $\tilde{g}$ in the R_0 for the "no ART" model with the following expressions respectively, and everything else is exactly the same.

$$\begin{aligned}
\tilde{a} &= \frac{r_T\beta_{VT}[d_M+(1-e)\upsilon]}{d_I(r_V+r_B)(d_M+\upsilon)},\\
\tilde{b} &= \frac{r_T\beta_{BT}[d_M+(1-e)\upsilon]}{d_I(r_V+r_B)(d_M+\upsilon)},\\
\tilde{c} &= \frac{r_V\beta_{TV}[d_M+(1-e)\upsilon]}{d_I(r_V+r_B+r_T)(d_M+\upsilon)},\\
\tilde{d} &= \frac{r_V\beta_{VV}[d_M+(1-e)\upsilon]}{d_I(r_V+r_B+r_T)(d_M+\upsilon)},\\
\tilde{e} &= \frac{r_V\beta_{BV}[d_M+(1-e)\upsilon]}{d_I(r_V+r_B+r_T)(d_M+\upsilon)},\\
\tilde{f} &= \frac{r_B\beta_{TB}[d_M+(1-e)\upsilon]}{d_I(r_V+r_T)(d_M+\upsilon)},\\
\tilde{g} &= \frac{r_B\beta_{VB}[d_M+(1-e)\upsilon]}{d_I(r_V+r_T)(d_M+\upsilon)}.
\end{aligned} \tag{5.3}$$

Following the "next-generation operator" method of [8], we can get the result as follows:

Lemma 5.1. *The disease-free equilibrium E_0 for corresponding model is always exists and locally stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

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