Comparison of different strategies for controlling HIV/AIDS spreading in MSM

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ABSTRACT

As proposed in the UNAIDSs 2014 report, to end global AIDS epidemic by 2030, 90% of people living with HIV need to be diagnosed, 90% of the diagnosed need to receive antiretroviral therapy (ART), and 90% of those on treatment need to achieve viral suppression (90-90-90 strategy). The strategies focus on the reservoir. It controls HIV spreading by reducing infectiousness of HIV infected individuals via diagnosis and treatment. In this manuscript, we compared the effects of HIV/AIDS interventions that focus on different individuals in MSM population through a dynamics model. Our results showed that, the success or not of the "90-90-90" strategies depends on a very important factor: the infectious strength among individuals taking ART. Without highly effective HIV treatment, the "90-90-90" strategies are likely to fail. Therefore, we call for the combination of both primary prevention among the susceptible with the 90-90-90 strategy among the infected to curb the HIV epidemic in Chinese MSM.

1. Introduction

According to the report by the United Nations Programme on HIV/AIDS (UNAIDS) in 2014, there were more than 35 million people living with HIV/AIDS (PLWHA) worldwide by the end of 2013 (UNAIDS, 2016). In 2014, UNAIDS proposed an HIV/AIDS "90-90-90" strategy: having 90% of PLWHA diagnosed, 90% of the diagnosed receiving antiretroviral therapy, and 90% of those on treatment achieving viral suppression. The final target is "ending global AIDS epidemic in 2030". The hypothesis of this strategy is that HIV spreading can be controlled by reducing infectiousness of infected individuals via treatment (UNAIDS, 2016). By the end of 2015, China reached the targets of 68%, 67% and 91% respectively (Wu, 2016). In 2016, the updated treatment criteria including all HIV infected individuals made the 90% of treatment goal promising in

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Among the “90-90-90” strategy, diagnosing 90% of people living with HIV is the most critical and challenging step. Therefore, the main target individuals under the “90-90-90” strategy are the HIV positive population, but not the susceptible.

Despite increasing efforts to control transmission of HIV/AIDS, men who have sex with men (MSM) are the risk group with the highest HIV incidence both domestically and internationally (Estimated HIV Incidence in the United States, 2010; Hall et al., 2008; Jaffe, Valdiserri, & De Cock, 2007; Prejean et al., 2011). The epidemic of HIV in China is driven by the high prevalence among MSM, despite the ongoing efforts of the government of China (Lou et al., 2014). The unrelenting HIV epidemic among Chinese MSM urgently calls for innovative, practical, and effective HIV prevention interventions.

China has made a lot of efforts to curb the epidemic. One promising intervention combined the expanding HIV testing with timely linkage of newly diagnosed individuals to HIV care (e.g., risk reduction and antiretroviral therapy (ART)) has been carried out in MSM population (Velasco-Hernandez, Gershengorn, & Blower, 2002). Some studies also evaluated individual or joint impacts on HIV incidence of the intervention components among MSM (Ahlgren, Gorny, & Stein, 1990; Huang, Zhang, Wu, & Lou, 2017; Jacquez, Koopman, Simon, & Longini, 1994; Phillips et al., 2013; Tan & Xiang, 1999; Van Sighem et al., 2012; Wilson, Hoare, Regan, & Law, 2009; Wirtz et al., 2013). However, none of any existing strategies can curb the epidemic effectively in China (Chinese Center for Disease).

In the current study, we explored additional components beyond the 90-90-90 strategy. Instead of focusing on HIV infected individuals, we examined the effect of behavioral interventions among susceptible individuals using a dynamic mathematical model.

2. Methods

We used a compartmental ordinary differential equations model for simulating and projecting the HIV epidemic among MSM population under different strategies. Fig. 1 shows our intention. We would like to use the MSM population in Beijing as our target population. Using existing databases in Beijing, we formulated a baseline model that reflects some key epidemiological properties of the HIV/AIDS epidemic. In addition, we modeled several scenarios of public-health interventions (e.g., condom use, partner reduction). The left row of compartments show uninfected MSM who are Susceptible to HIV infection. They are divided into Non-interventions (S), and effective-interventions (Se). The dotted line means the line may exist (if the “primary prevention” holds) or not (only the “90-90-90” strategies). The next two rows representing two stages of HIV infection: I1 is the acute infection stage while I2 is the chronic infection stage. Correspondingly, we have (Ie1) and (Ie2) for the infections who accept effective behavior interventions. The compartments in the middle of the two infection stages show HIV-infected individuals who have initiated antiretroviral therapy (T1) and (T2). Finally, the last column represents the HIV infected who enter into AIDS stage (A). M is the recruitment rate per year into the MSM population. They are local HIV-MSM who turn 18 years old, or those from other areas who immigrate into Beijing. China has adopted the World Health Organizations “Treat All” approach. So the diagnosis rates of HIV infected individuals are also their treatment rates (g1, g2, ge1 and ge2). The rates of ART failure or dropout are denoted by a1, a2, a1e and a2e. Movement from Susceptible to Infected (W(t)) is the HIV transmission rate. It is estimated from multiple parameters. The natural removal rate (d) represents death, being older than 60 years, or migration out of Beijing. The rate of disease progression is different for HIV-infected individuals on ART (k and s) or not on ART (n and u). Finally, the effective behavior interventions rate on the susceptibles and the infected are parameterized by rates b1 and b2 respectively.

Fig. 1. Schematic diagram of HIV combination prevention intervention model in the presence of ART.
### 3. Results

We used data from local HIV surveillance systems and published studies (Fan et al., 2012; Liu, Liu, & Xiao, 2001; Lou et al., 2014; Ruan et al., 2009a, 2009b; Xu et al., 2010; Zhou et al., 2010) to simulate the HIV prevalence rates during 2000–2010 among MSM in Beijing. The observed HIV prevalence rates among MSM in Beijing during 2000C2010 were: 1.2% in 2000, 3.2% in 2005, 4.8% in 2006, 5.1% in 2007, 6.5% in 2008, 6.8% in 2009, and 7.8% in 2010. As available data include no identifiers that could link the data to individual subjects in the local HIV surveillance systems or participants from the published studies, consent was waived and the mathematical modeling protocol was approved by the institutional review boards of the National Center for AIDS/STD Control and Prevention of Chinese Center for Disease Control and Prevention.

The earliest HIV prevalence data among MSM in Beijing were available from 2000. The observed HIV prevalence rates among MSM in Beijing during 2000–2010 were: 1.2% in 2000 (Liu et al., 2001), 3.2% in 2005 (Ruan et al., 2009a, 2009b), 4.8% in 2006 (Ruan et al., 2009a, 2009b), 5.1% in 2007 (Ruan et al., 2009a, 2009b), 6.5% in 2008 (Xu et al., 2010; Zhou et al., 2010), 6.8% in 2009 (Fan et al., 2012), and 7.8% in 2010 (Li et al., 2012). We employed a Metropolis-Hastings algorithm to carry out extensive Markov-chain Monte-Carlo simulations for estimating the mean values of some unknown parameters, including yearly recruitment rates (e.g., number of new members into the pool of the study population each year), rates of receiving treatments at acute and chronic infection stages (during 2000–2010), infectious transmission coefficients at the acute infection stage, the relative infectiousness of the chronic infection subgroup to the acute subgroup, the relative infectiousness of the acute infection subgroup who received interventions to the acute subgroup who did not receive any interventions, the relative infectiousness of chronic infection subgroup who received intervention to acute subgroups, the relative infectiousness of acute or chronic infection subgroup who received ART to acute subgroup who did not receive ART, and the initial value of each subgroup in 2000. The algorithm ran for 1,000,000 iterations, and we adapted the proposal distribution after 500,000 fitted by MCMC can be found in Table 1 and Table 2 respectively.

Suppose that the dot lines in Fig. 1 do not exist at this stage during 2000–2014. Table 2 got under the assumption that maintaining the coverage of interventions as the average coverage during 2000–2010. The comparison between the reported HIV prevalence and history data of Beijing MSM population from 2000 to 2010 with maximum 95% confidence interval that is fitted by 500,000 MCMC simulations is shown in Fig. 2 (the left one). The red line is the mean of the 500,000 MCMC simulations. Since the data during 2011–2017 were critically missing except that of 2013, and also considering that some changes in HIV intervention strategies, we adjusted the model using parameters in Tables 1 and 2 but with the modified ART rates $\gamma_1 = \gamma_2 = \gamma_1^u = \gamma_2^u = 0.5$. This means, half of HIV patients in Beijing can be treated. Then the dynamics of the model under the new assumptions go as the yellow box-plot in the right figure of Fig. 2. Through Matlab code we can get some statistical data as follows. The 10,000 sets of simulations showed that the mean by 2015 is 15.66% and interquartile ranges (IQR: 25%–75%) of HIV prevalence rate by 2015 were from 14.12% to 17.38%, and the $\alpha$ value by 2015 is 15.66% and interquartile ranges (IQR: 25%–75%) of HIV prevalence rate by 2015 were from 14.12% to 17.38%, and the $\alpha$ value by 2015 is 15.66%

### Table 1

| Parameter | Value | Unit | Description | Source |
|-----------|-------|------|-------------|--------|
| $d$       | 1/42  | /year| Rate of removal from the sexually-active population unrelated to HIV | Lima et al. (2008) |
| $\delta$  | 1     | /year| Rate of death from AIDS | Lima et al. (2008) |
| $\nu$     | 4     | /year| Rate of transitioning from acute to chronic infection | Chow et al., 2012; Granich, Gillks, Dye, De Cock, & Williams, 2009; Ruan et al., 2009a, 2009b |
| $\omega$  | 1/10  | /year| Rate of transitioning from chronic infection to AIDS | Chow et al., 2012; Granich et al., 2009; Ruan et al., 2009a, 2009b |
| $k$       | 4     | /year| Rate of transitioning from acute to chronic infection under ART | Chow et al. (2012) |
| $\sigma$  | 1/20  | /year| Rate of transitioning from chronic infection to AIDS under ART | Chow et al. (2012) |
| $\gamma_1$| 0.017 | /year| ART rate for acute infection stage MSM, received intervention | Annual Report onV/ (2010) |
| $\gamma_2$| 0.53  | /year| ART rate for chronic infection stage MSM, received intervention | Annual Report onV/ (2010) |
| $\gamma_1^u$| 0.017 | /year| ART rate for acute infection stage MSM, received intervention | Annual Report onV/ (2010) |
| $\gamma_2^u$| 0.53  | /year| ART rate for chronic infection stage MSM, received intervention | Annual Report onV/ (2010) |
| $\alpha$  | 1/42  | /year| Quit rate from ART | Annual Report onV/ (2010) |
In the following, we use the final population that were predicted in 2015 as our new initial values to predict HIV prevalence from 2015 to 2025 and the distribution of basic reproduction number ($R_0$) under six different scenarios (here we suppose the dot-lines in Fig. 1 can exist under certain scenarios):

1. $S_1$: It maintains the coverage of interventions as that during 2010–2015 and has not considered the "primary prevention" among the susceptible population ($b_3 = 0$).
2. $S_2$: Similar to the "90-90-90" strategy: the positive diagnosis rate (and also the ART rate because of the policy "treatment once diagnosis") of HIV infected individuals increase to 90% for all kinds of HIV positive individuals (i.e., $\gamma = 0.9$). It assumes 90% HIV positive individuals receive enhanced behavioral interventions ($b_1 = b_2 = 0.9$), but has not considered the "primary prevention" among susceptible individuals ($b_3 = 0$).
3. $S_2^*$: It is the same as the $S_2$ except that it assumes the ART sub-populations lost their infectivity ($\varepsilon_4 = \varepsilon_5 = 0$).
4. $S_3$: It considers effective "primary prevention" among susceptible individuals (the dot-lines exist in Fig. 1). It assumes that half of the susceptible population receives effective behavioral interventions each year ($b_3 = 0.5$). These people can reduce their risk behaviors by half ($\eta = 0.5$) (e.g., by using condoms or reducing their sexual partners). We still maintain the coverage rate of interventions to another subpopulation as that during 2010–2015.
5. $S_3^*$: The same as $S_3$ except suppose the ART sub-populations lost their infectivity ($\varepsilon_4 = \varepsilon_5 = 0$).
6. $S_4$: The joint use of $S_2$ and $S_3$.

In extensive uncertainty analyses, 10,000 parameter sets were randomly sampled from corresponding uncertainty ranges (Table 2 and other parameters that we specified for the ranges). Fig. 3 shows the results of the basic reproduction number ($R_0$) under six different scenarios: $S_1 – S_4$. In Fig. 3, the red histogram is of $S_1$, the blue histogram and the brown histogram are of

| Parameter   | mean     | std      | geweke  | Description                              |
|-------------|----------|----------|---------|------------------------------------------|
| $M$         | 6556.5   | 866.96   | 0.99508 | No. of recruitment nodes                 |
| $b_1$       | 0.3014   | 0.057691 | 0.97031 | Rate of receiving intervention of acute infection stage |
| $b_2$       | 0.3011   | 0.05774  | 0.99174 | Rate of receiving intervention of chronic infection stage |
| $\beta$     | 0.77691  | 0.050956 | 0.99617 | Infectious transmission coefficient of acute infection stage |
| $\varepsilon_1$ | 0.49245 | 0.057145 | 0.99532 | Modification factor in transmission coefficient of $I_2$ to $I_1$ |
| $\varepsilon_2$ | 0.59644 | 0.057538 | 0.99867 | Modification factor in transmission coefficient of $I_1^f$ to $I_1$ |
| $\varepsilon_3$ | 0.29563 | 0.057564 | 0.97477 | Modification factor in transmission coefficient of $T_2$ to $I_1$ |
| $\varepsilon_4$ | 0.14919 | 0.028809 | 0.99328 | Modification factor in transmission coefficient of $T_1$ to $I_1$ |
| $S_0$       | 1.0071e+05 | 14367   | 0.99069 | Initial value of susceptible MSM          |
| $I_1$       | 252.98   | 36.892   | 0.98941 | Initial value of acute infection stage MSM |
| $I_2$       | 381.86   | 55.662   | 0.99203 | Initial value of chronic infection stage MSM |
| $I_1^f$     | 50.789   | 7.328    | 0.9974  | Initial value of acute infection stage MSM, received treatment |
| $I_e^1$     | 77.12    | 11.087   | 0.98251 | Initial value of chronic infection stage MSM, received treatment |
| $T_1$       | 5.9998   | 2.3281   | 0.94814 | Initial value of acute infection stage MSM, received ART |
| $T_2$       | 254.76   | 37.044   | 0.9939  | Initial value of chronic infection stage MSM, received ART |
| $A$         | 255.89   | 36.947   | 0.99677 | Initial value of AIDS stage MSM           |

Fig. 2. Left: The comparison between the reported HIV prevalence and history data of Beijing MSM population from 2000 to 2010 with maximum 95% confidence interval that is fitted by 1000000 MCMC simulations. Right: The predicted curve of HIV prevalence in Beijing MSM population from 2010 to 2015. The red dot is the history data.
S2 and S2*, respectively. The distribution of the $R_0$ of $S1$ is with a mean of 1.3067 (standard deviation: 0.0613), and with an interquartile range of 1.263–1.351. No possibility of estimates falls below the epidemic threshold ($R_0 < 1$). The distribution of $R_0$ of $S2$ is with a mean of 1.2135 (standard deviation: 0.0569), and with an interquartile range of 1.1698–1.2560. Again, no possibility of the estimates falls below the epidemic threshold ($R_0 < 1$).

This result shows that, without other interventions assist, the present "90-90-90" cannot control the HIV/AIDS spreading in MSM in Chinese settings. As a contrast, the distribution of $R_0$ of $S2^*$ is with a mean of 0.86443, and with an interquartile range of 0.8446–0.8840). Percentage of the estimates falls above the epidemic threshold is 0. The results show that, the success of the "90-90-90" strategy depends on a very important factor: the infectious strength of the ART sub-population. Even if a quite "low infectiousness" assumption in our model, the infectious ability is only as low as 15% of what it was before treatment (see $e_4$ and $e_5$ in Table 2). Even with the lower infectiousness, the HIV spreading in this population cannot be curbed yet, as the green histogram (Fig. 3) shows, although we assumed the sub-population using ART can completely lose their infectivity prior to this analysis. Literature (Lou, Wu, Chen, Ruan, & Shao, 2009) states that the relation between $R_0$ and the lifespan of HIV patients follows the power law distribution, $P(k) \sim k^{-\gamma}$, with $0 < \gamma \leq 1$. $R_0$ is a decreasing function of the disease mortality. This means that longer life of HIV patients, the more likely they bring new infections, even if the infectivity of patients is quite low.

Similarly we explored the possibility of the "primary prevention" intervention S3. It’s distribution of $R_0$ (the blue histogram in Fig. 3) is with a mean of 1.0087 (standard deviation: 0.0471 and interquartile range: 0.9737–1.0437). Percentage of the $R_0$s that falls above the epidemic threshold is 57%. If we assumed that all ART sub-populations completely lost their infectivity ($S3^*$), the mean of the $R_0$ s is only 0.7659 with an interquartile range of 0.7480–0.7831 (the yellow histogram in Fig. 3). The percentage of the $R_0$ s that falls above the epidemic threshold is 0 again, similar to that of the S2*. This result states the significance of treatment effectiveness in China. We may control HIV spreading in MSM easily with efficient treatments, even if we only implement behavioral interventions in susceptible populations.

Suppose we cannot get more efficient HIV medicines at this moment. S4 (the magenta histogram in Fig. 3) tell us that we have possibility to control HIV spreading in MSM in Beijing under this strategy since its distribution of $R_0$ is with mean 0.9907 (standard deviation: 0.0468 and interquartile range: 0.9538–1.0272). A quite big percentage (56.38%) of estimates falls below the epidemic threshold ($R_0 < 1$).

This results indicated, neither the "90-90-90" strategy that focuses on HIV infected individuals works effectively, nor the "primary prevention" that focuses on the susceptible individuals does. Even if we suppose that half of the susceptible population receives effective behavioral interventions each year and these people can reduce their risk behaviors by half), if we can not get more efficient treatment. Therefore, the optimal strategy is to combine the "90-90-90" and the "primary prevention" strategies among this high-risk population.

The dynamics of the HIV prevalence under different situations are shown in Fig. 4. Assuming that the baseline levels of HIV prevalent in 2015 are sustained (i.e., under $S_1$). HIV prevalence among MSM in Beijing will increase as high as 35.1% by 2025 (the median value of 10,000 simulations, the blue line of the $S_1$ in Fig. 4). Under the $S_2$ (the "90-90-90" intervention), HIV prevalence among MSM in Beijing keeps increasing to 27.43% by 2025 (the red line of $S_2$ in Fig. 4). However, under the "primary prevention" $S_3$, the median value of 10,000 simulations of HIV prevalence has a slow increasing at the beginning and then followed by a decrease, and finally arrives at 16.84% by 2025 (the black line of $S_3$ in Fig. 4). The prevalence is lower than both the base line situation $S_1$ as well as the "90-90-90" situation $S_2$. Therefore, the HIV/AIDS epidemic still keeps skyrocketing in this population. Combinations of the two strategies together may curb the HIV transmission among this at-risk population. The mean of the 10,000 sets of prevalence under $S_4$ is 15.27% by 2025, which is lower than that in 2015 (the brown line of $S_4$ in Fig. 4).
4. Discussion

In this manuscript, we explored the effect of HIV/AIDS intervention among Chinese MSM through a dynamics model. We found that compared to the effect of the “90-90-90” strategy proposed by the UNAIDS that targets HIV patients, HIV/AIDS can be better controlled if we can target both susceptible and infected individuals using the primary prevention and the 90-90-90 strategy, respectively. The “primary prevention” may include sexual health education, behavioral interventions (e.g., sexual partners reduction, condom use promotion). In the current study, however, we did not compare costs of these two types of interventions.

One plausible explanation of the under-effective 90-90-90 strategy is that HIV treatment cannot cover across the long life span among HIV patients. Therefore, ART in China does not mean zero infectivity. Literature (Lou et al., 2009) also states that the relation between $R_0$ and the lifespan of HIV patients follows a power law: $R_0$ is a decreasing function of the disease mortality. As a consequence, the longer life expectancy of the HIV infected individuals, the higher probability that they may spread more infections.

Based upon our findings from the current study, we strongly call for interventions targeting susceptible and infected individuals using both “primary prevention” and the “90-90-90” strategy. Only targeting both susceptible and infected individuals, can the HIV epidemic be curbed in China.

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Supporting information: the model and the basic reproductive number $R_0$

The model equations of Fig. 1 are as the follows:

\[
\begin{align*}
\frac{dS}{dt} &= M - W(t) - dS - b_S S \\
\frac{dI_1}{dt} &= W(t) + \alpha_1 T_1 - dI_1 - b_{I_1} I_1 - \nu I_1 - \gamma_1 I_1 \\
\frac{dI_2}{dt} &= \nu I_1 + \alpha_2 T_2 - dI_2 - b_{I_2} I_2 - \omega I_2 - \gamma_2 I_2 \\
\frac{dS_e}{dt} &= b_S S - dS_e - W_e(t) \\
\frac{dI_e}{dt} &= W(t) + b_1 I_1 + \alpha_1^e T_1 - \nu I_1 - \gamma_1^e I_1 \\
\frac{dI_e^e}{dt} &= \nu I_e + b_2 I_2 + \alpha_2^e T_2 - dI_e^e - \omega I_e^e - \gamma_2^e I_e^e \\
\frac{dI_1}{dt} &= \gamma_1 I_1 + \gamma_1^e I_e^e - dT_1 - k T_1 - \alpha_1 T_1 - \alpha_1^e T_1 \\
\frac{dI_2}{dt} &= k T_1 + \gamma_2 I_2 + \gamma_2^e I_e^e - dT_2 - \sigma T_2 - \alpha_2 T_2 - \alpha_2^e T_2 \\
\frac{dA}{dt} &= \omega I_2 + \omega I_e^e + \sigma T_2 - dA - \delta A
\end{align*}
\]

where

\[
\begin{align*}
W(t) &= \frac{S}{N} (\beta I_1 + \beta I_2 + \beta I_e T_1 + \beta I_e^e T_1 + \beta I_2 + \beta I_2) \\
W_e(t) &= \frac{S_e}{N} (1 - \eta) (\beta I_1 + \beta I_2 + \beta I_e T_1 + \beta I_e^e T_1 + \beta I_e T_2 + \beta I_e^e T_2) \\
N &= S + I_1 + I_2 + S_e + I_e^e + I_e^e + T_1 + T_2 + A.
\end{align*}
\]

The definitions for parameters in the equation (1) are described in Tables 1 and 2 above.

From this model, we can calculate the basic reproduction number in terms of model parameters using the “next-generation operator” method (Van den Driessche & Watmough, 2002). $R_0$ is the number of secondary cases produced by a typical HIV-infected MSM during his entire period of infectiousness in a demographically steady susceptible population. Calculating $R_0$ is critical to determine whether HIV will increase, stabilize, or decline among the MSM population. But considering the calculation of $R_0$ is traditional and tedious, we omit the calculation here.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2018.10.002.

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