

A mathematical model for HIV prevention and control among men who have sex with men in China

Original Paper

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Abstract

In recent years, men who have sex with men (MSM) constitute a major group of HIV transmission in China. High primary drug-resistance (PDR) rate in MSM also represents a serious challenge for the Chinese antiretroviral therapy (ART) program. To assess the efficiency of ART in controlling HIV/AIDS infection among MSM, we developed a compartmental model for the annually reported HIV/AIDS MSM from 2007 to 2019 in the Zhejiang Province of China. R_0 was 2.3946 (95% CI (2.2961–2.4881)). We predict that 90% of diagnosed HIV/AIDS individuals will have received treatment till 2020, while the proportion of the diagnosed remains as low as 40%. Even when the proportion of the diagnosed reaches 90%, R_0 is still larger than the level of AIDS epidemic elimination. ART can effectively control the spread of HIV, even in the presence of drug resistance. The 90-90-90 strategy alone may not eliminate the HIV epidemic in Chinese MSM. Behavioural and biologic interventions are the most effective interventions to control the HIV/AIDS epidemic among MSM.

Introduction

Men who have sex with men (MSM) constitute a major fraction of the HIV population in China. By the end of 2017, 758610 HIV/AIDS patients had been reported in China, more than 28% of whom were MSM [1]. In Zhejiang Province, a southeastern coastal province of China, reported cases resulting from homosexual contact, which make up about 38%. A meta-analysis has shown that MSM are at a greater risk of being infected with HIV compared with general population [2]. Meanwhile, most MSM in China develop AIDS within 4–5 years after HIV infection [3]. Therefore, scaling up HIV testing is important for controlling the HIV epidemic among MSM. The stigmatisation of same-sex behaviours in China presents challenges for the discovery of HIV infected individuals.

Chinese antiretroviral therapy (ART) program, as a national policy, has seen an increasing coverage [4]. However, China has not reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets by 2020 [5]. A survey shows the treatment rate among the diagnosed HIV/AIDS MSM is only 56% in China [6]. The reason may be that MSM are relatively private in China [7]. HIV prevention among MSM largely depends on interventions that can reduce unprotected sexes and strengthen HIV testing [8]. Meanwhile, the high rate of MSM with HIV primary drug-resistance (PDR) also challenges the effectiveness of Chinese ART program [9].

In order to effectively predict and control the spread of AIDS, scholars at home and abroad have proposed a series of deterministic and stochastic models incorporating mathematics, clinical medicine and epidemiology [10–13]. Blower *et al.* [14, 15] studied the impact of expanding ART coverage in the presence of transmitted and acquired drug resistance.

Using variables about ART and PDR, we developed a compartmental model to evaluate the HIV/AIDS epidemic among MSM and the effect of related controlling efforts.

Materials and methods

Database used in the study

We obtained the annually reported drug-sensitive HIV cases and drug-resistant HIV cases on annually reported HIV/AIDS MSM between 2007 and 2019 in Zhejiang Province from Chinese Centre for Disease Control and Prevention (China CDC).

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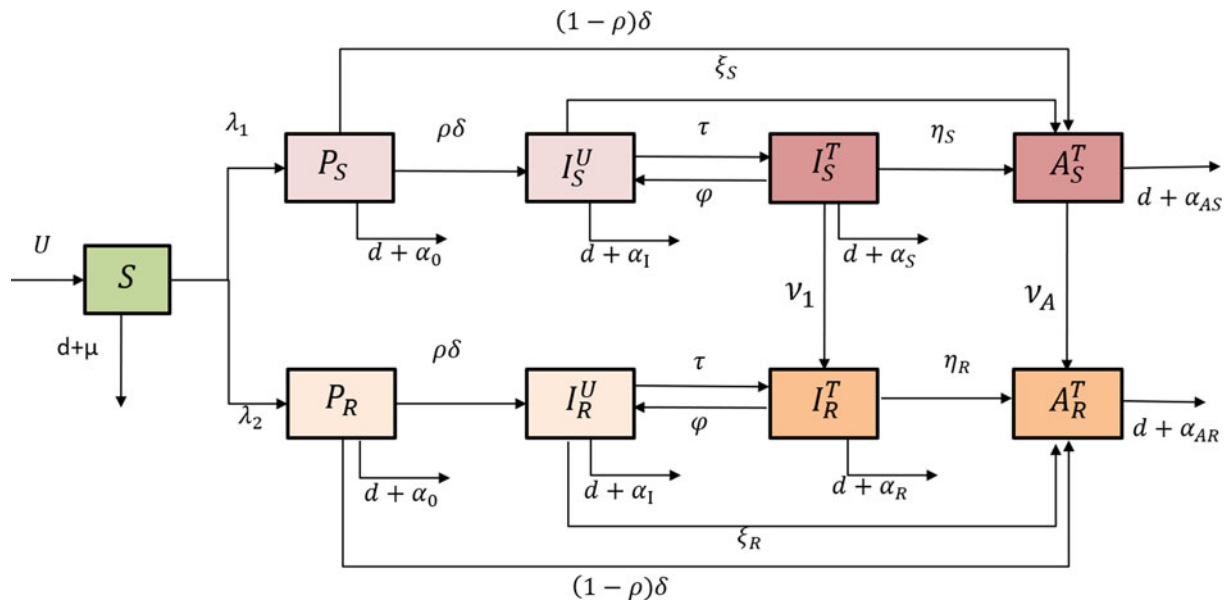


Fig. 1. Schematic flow diagram of model.

Mathematical model

A compartmental model was established with variables about antiretroviral therapy (ART) and transmitted HIV-1 drug resistance (TDR) among the MSM population of Zhejiang Province. We divided the population into nine categories (Fig. 1): susceptible individuals (S), undiagnosed individuals infected with drug-sensitive or drug-resistant strains (P_S and P_R), diagnosed individuals infected with drug-sensitive or drug-resistant strains but have not progressed to AIDS stage (I_S^U and I_R^U), treated individuals infected with drug-sensitive or drug-resistant strains and have not progressed to AIDS stage (I_S^T and I_R^T) and those diagnosed with AIDS stage (A_S^T and A_R^T). The variable's subscript described whether the infection was drug-sensitive (S) or drug-resistant (R); the superscript described whether the individuals were treated with ART (T) or untreated (U). The high-risk population size was represented by N : $N = S + P_S + I_S^U + I_S^T + A_S^T + P_R + I_R^U + I_R^T + A_R^T$. The parameters definition and formula are shown in Supplementary Material A.

Threshold dynamics

The basic reproduction number R_0 represented the average number of secondary cases generated by one primary case in a fully susceptible population during its average infectious period (the average time between the initiation and the elimination of infection) [16]. R_0 is a threshold parameter for the infectious disease and can help determine whether an infectious disease can spread out of a population. $R_0 > 1$ indicates that the disease will continue to prevail and $R_0 < 1$ indicates the disease will be eliminated. In the present model, R_0 represented the number of cases infected by a HIV-positive individual per year. We can get R_0 following the next-generation matrix (Supplementary Material B).

Parameter values estimated

We set 2007 as the starting year for the dynamical model, i.e., $t = 0$. According to the 2013 Statistical Yearbook of China [17], the life expectancy of men in Zhejiang Province (L) in 2007 was 75.58

years and the natural death rate ($d = 1/L$) was 0.0132 per year. We assumed the duration in which males can have sex (L_S) was 49 years (age 15–64 years) and the exit rate (the rate at which the susceptible cases are excluded) of the susceptible ($\mu = 1/L_S$) was 0.0204 per year. We set the duration of the chronic stage without treatment (T_C) as 4.5 years, then the rate of progression from HIV infection stage to AIDS stage (untreated, drug-sensitive) ($\zeta_S = 1/T_C$) as 0.2222 per year and the rate of progression from HIV infection to AIDS stage (untreated drug-resistant) ($\zeta_R = 1/(1.25 \times T_C)$) as 0.1778 per year [13]. The duration of AIDS stage was 1.2 years [18] and the disease-related death rate at AIDS stage ($\alpha_A = 1/T_A$) was 0.8333 per year. The rate of progression from HIV infection stage to AIDS stage (treated, drug-sensitive) (η_S) was 0.020 per year and rate of progression from the HIV infection stage to AIDS stage (treated, drug-resistance) (η_R) was 0.026 per year [12]. The disease-related death rate for HIV-positive individuals undiagnosed (α_0) and at HIV infection stage untreated (α_U) was both chosen 0.28 per year [12]. The disease-related death rate at HIV infection stage (treated, drug-sensitive) (α_S) was 0.05 per year [12] and 1.75×0.05 per year for treated drug-resistant individuals (α_R). In the database, the proportion of diagnosed individuals at HIV infection stage (ρ) was set as 0.7400 and the treatment rate (τ) as 1.6949 per year. We assumed the withdrawal rate as 0.1 per year. Reference was the results of a 6-year cohort study on HIV-1 resistance in AIDS patients receiving antiviral treatment in Henan Province [19]. Among half of the individuals in the cohort, the time point that resistance emerged was 25.1 months (95% CI 19.0–33.3) in those whose VL was $<4.0 \text{ lgU/ml}$ and 4.8 months (95% CI 4.1–5.6) in those whose VL was $>4.0 \text{ lgU/ml}$ during the first investigation. We chose $1/25.1 \times 12$ per year as the rate of acquired drug resistance after treatment began at HIV infection stage (ν_1) and $1/4.8 \times 12$ per year as the rate at AIDS stage (ν_A). Table 1 shows the settings for parameters and initial values.

Data fitting and verification

We utilised the Markov-Chain Monte Carlo (MCMC) method to estimate the main parameters of the formula (1). Starting value

Table 1. Setting values for parameters and initial values

Parameter	Description	Value
L	Life expectancy for men in Zhejiang province	75.58
L_S	Duration of male sexual activity stage	49
T_C	Duration of chronic stage without treatment	4.5
T_A	Duration of AIDS stage	1.2
d	Natural death rate ($=1/L$)	0.0132
μ	Exit rate of susceptible ($=1/L_S$)	0.0204
α_0	Disease-related death rate (undiagnosed)	0.28
α_I	Disease-related death rate (diagnosed, untreated)	0.28
α_S	Disease-related death rate at the HIV infection stage (treated, drug-sensitive)	0.05
α_R	Disease-related death rate at the HIV infection stage (treated, drug-resistance)	1.75×0.05
α_A	Disease-related death rate at the AIDS stage ($=1/T_A$)	0.8333
P	Proportion of diagnosed individuals at the HIV infection stage	0.7400
τ	The treatment rate	1.6949
φ	Withdrawal rate	0.1
ζ_S	Rate of progression from the HIV infection stage to the AIDS stage (untreated, drug-sensitive) ($=1/T_C$)	0.2222
ζ_R	Rate of progression from the HIV infection stage to the AIDS stage (untreated, drug-resistance) ($=1/(1.25 \times T_C)$)	0.1778
η_S	Rate of progression from the HIV infection stage to the AIDS stage (treated, drug-sensitive)	0.02
η_R	Rate of progression from the HIV infection stage to the AIDS stage (treated, drug-resistance)	0.026
ν_I	The rate of acquired drug resistance after treatment begins at the HIV infection stage	0.4781
ν_A	The rate of acquired drug resistance after treatment begins at the AIDS stage	2.5000
Initial values	Description	Value
$I_S^U(0)$	HIV infection stage (diagnosed, drug-sensitive, untreated)	123
$I_R^U(0)$	HIV infection stage (diagnosed, drug-resistance, untreated)	3
$I_S^T(0)$	HIV infection stage (diagnosed, drug-sensitive, treated)	65
$I_R^T(0)$	HIV infection stage (diagnosed, drug-resistance, treated)	4
$A_S^T(0)$	AIDS stage (diagnosed, drug-sensitive, treated)	16
$A_R^T(0)$	AIDS stage (diagnosed, drug-resistance, treated)	0

and range setting for unknown parameters is shown in Table 2. Metropolis-Hastings (M-H) algorithm was employed for MCMC simulation [20]. The algorithm ran 250 000 iterations with a burn-in of 50 000 iterations. We obtained our estimates using the rest 200 000 samples. Using the simulation results of these parameters, we got the Markov Chain of basic reproduction number R_0 and its variations. Mean Absolute Percentage Error (MAPE) and Root Mean Square Percentage Error (RMSPE) were used to evaluate the effectiveness of the model [21]. The formula is as follows:

$$MAPE = \frac{1}{n} \sum_{t=1}^n \left| \frac{actual(t) - forecast(t)}{actual(t)} \right| \times 100\%$$

$$RMSPE = \sqrt{\frac{\sum_{t=1}^n [(actual(t) - forecast(t))/actual(t)]^2}{n - 1}} \times 100\%$$

Generally, if MAPE and RMSPE are less than 10%, the simulation of the model is accurate. If 10% to 20%, the simulation is good. If 20% to 50%, the simulation is reasonable. If more than 50%, the simulation is inaccurate.

Sensitivity analysis

We used Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) [22] to examine the dependence of the reproduction number R_0^S and R_0^R to parameter variations. We respectively choose the sample size ($n = 6000$), parameters of interest as the input variables and R_0^S and R_0^R values as the output variable.

Software

Maple Software 2018 was used to compute the basic reproduction number. Berkeley Madonna Version 9.1.19 (Berkeley Madonna Inc., University of California, Berkeley, CA, USA) was used to fit and explore the appropriate range of parameters. All other

Table 2. Starting value and range setting for unknown parameters

Parameter	Description	Starting value	Range
β_S	Transmission probability of HIV per high-risk behaviour (drug-sensitive)	–	
β_R	Transmission probability of HIV per high-risk behaviour (drug-resistance)	–	
c	High-risk behaviour contact rate per year	–	
π	Protection rate by intervention measures	–	
β_{S0}	Transmission coefficient (drug-sensitive), $\beta_{S0} = \beta_S c (1-\pi)$	1.07	0.5–2
β_{R0}	Transmission coefficient (drug-resistance), $\beta_{R0} = \beta_R c (1-\pi)$	0.89	0.5–2
$\varepsilon_{I_S}^{\mu}$	Modification factor for untreated drug-sensitive individuals at the HIV infection stage	0.47	0–0.5
$\varepsilon_{I_R}^{\mu}$	Modification factor for untreated drug-resistant individuals at the HIV infection stage	0.16	0–0.5
$\varepsilon_{I_S}^I$	Modification factor for treated drug-sensitive individuals at the HIV infection stage	$0.04 \times \varepsilon_{I_S}^{\mu}$	
$\varepsilon_{I_R}^I$	Modification factor for treated drug-resistance individuals at the HIV infection stage	$0.04 \times \varepsilon_{I_R}^{\mu}$	
$\varepsilon_{A_S}^I$	Modification factor for treated drug-sensitive individuals at the AIDS stage	$7 \times \varepsilon_{I_S}^{\mu}$	
$\varepsilon_{A_R}^I$	Modification factor for untreated drug-sensitive individuals at the AIDS stage	$7 \times \varepsilon_{I_R}^{\mu}$	
U	Recruitment rate of susceptible	108	100–10 000
δ	Diagnose rate	0.12	0.1–10
$S(0)$	Initial value of S (high-risk susceptible)	24 000	10 000–50 000
$P_S(0)$	Initial value of P_S (infected with sensitive strains)	1000	10–10 000
$P_R(0)$	Initial value of P_R (infected with resistance strains)	10	1–100

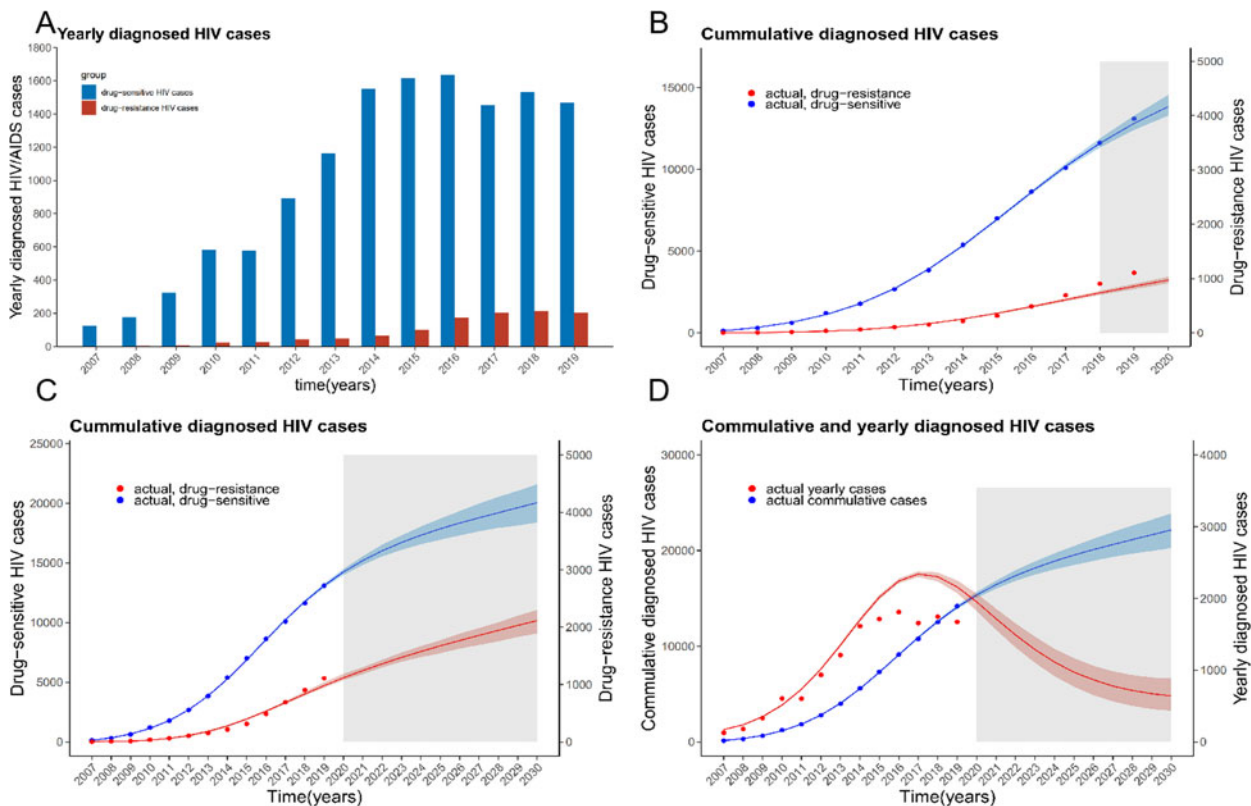
**Fig. 2.** A: Number of confirmed cases HIV sensitive and HIV resistant strains reported 2007–2019; B: Data fitting diagram; C, D: Predictive trends (The shaded area is the predicted area).

Table 3. Fitting results of unknown parameters and initial values

Parameter	Description	Estimated mean value
β_{S0}	Transmission coefficient (drug-sensitive), $\beta_{S0} = \beta_{SC} (1-\pi)$	1.2140 (95% CI (1.1443–1.2700))
β_{R0}	Transmission coefficient (drug-resistance), $\beta_{R0} = \beta_{RC} (1-\pi)$	1.0851 (95% CI (0.7089–1.4856))
ϵ_{S0}^U	Modification factor for untreated drug-sensitive individuals at the HIV infection stage	0.3750 (95% CI (0.3136–0.4402))
ϵ_{R0}^U	Modification factor for untreated drug-resistant individuals at the HIV infection stage	0.0428 (95% CI (0.0084–0.0912))
U	Recruitment rate of susceptible	1207 (95% CI (767–1654))
δ	Diagnose rate	0.8786 (95% CI (0.6588–1.1268))
$S(0)$	Initial value of S (high-risk susceptible)	36 414 (95% CI (31101–41985))
$P_S(0)$	Initial value of P_S (infected with sensitive strains)	271 (95% CI (200–359))
$P_R(0)$	Initial value of P_R (infected with resistance strains)	2 (95% CI (1–5))

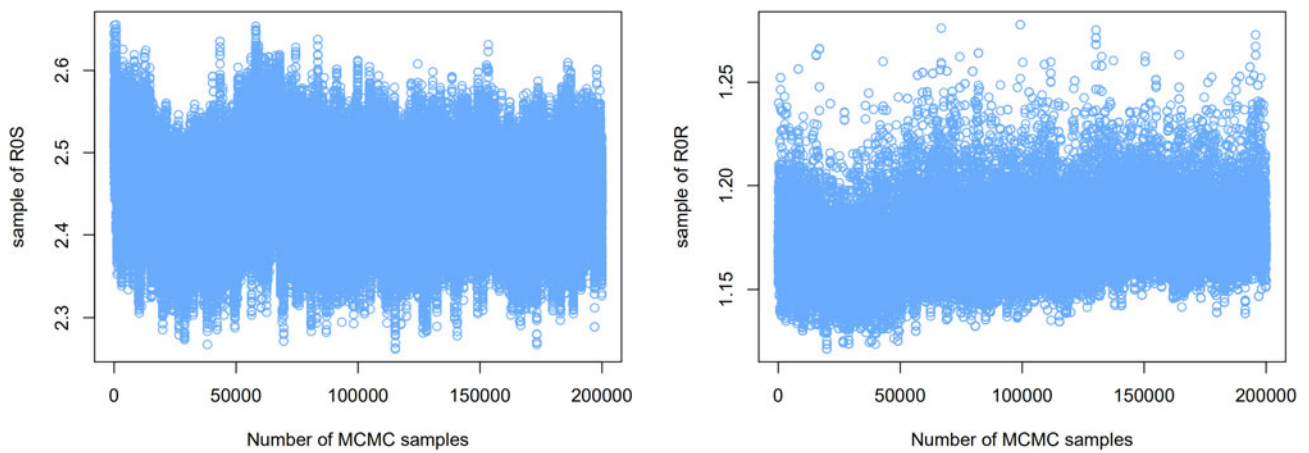


Fig. 3. The partial rank correlation coefficient (PRCC) between the basic reproduction number and model parameters.

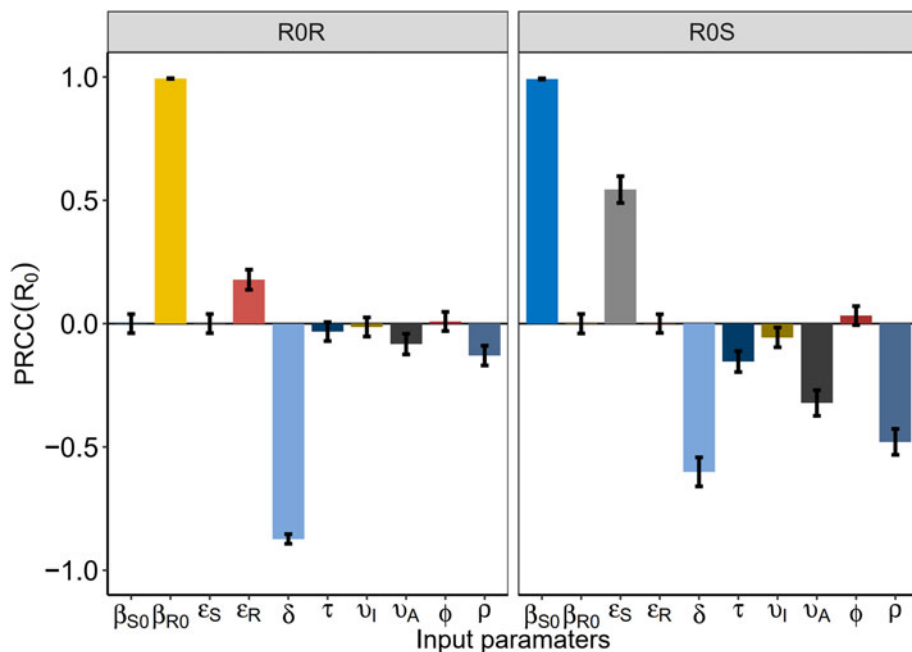


Fig. 4. Plots of estimated number of drug-resistant HIV/AIDS and the PDR rate after interventions.

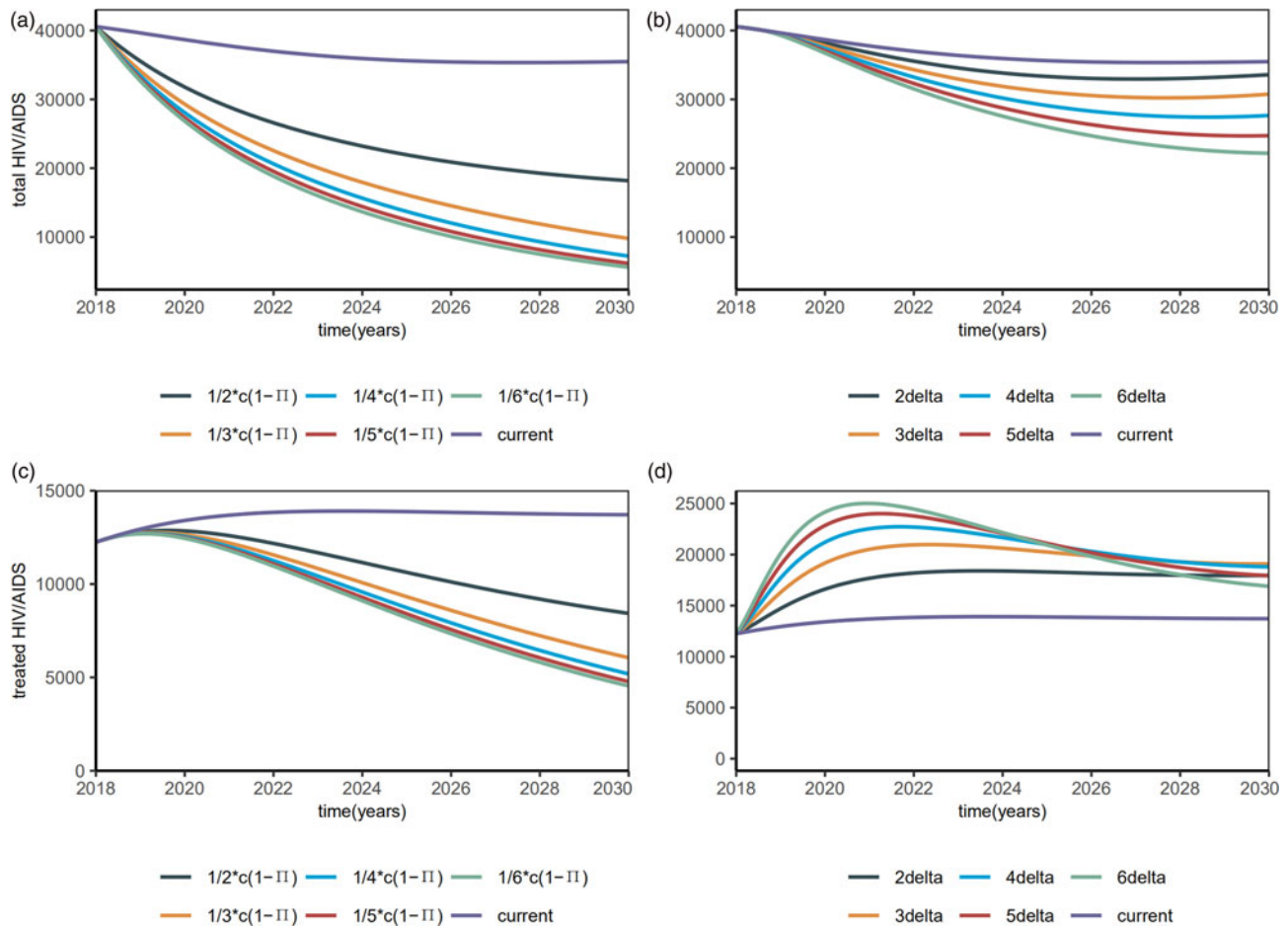


Fig. 5. Plots of estimated number of the total HIV/AIDS (including undiagnosed HIV/AIDS) and the total HIV/AIDS treated with interventions.

analyses, data visualisations and modelling were programmed in R Software Version 3.6.3 (The R Foundation for Statistical Computing).

Results

HIV transmission dynamics

The number of annual confirmed cases of HIV-sensitive and HIV-resistant strains reported in 2007–2019 is shown in Figure 2a. We fitted the model to the data of annually reported drug-sensitive HIV cases and drug-resistant HIV cases in 2007–2017 to estimate the unknown parameters (Fig. 2b). MAPE and RSMPE were used to evaluate the fitting and predictive effectiveness of the model. I_S^U fitting MAPE is 2.5% and RMSPE is 4.4%. I_R^U fitting MAPE is 8.6% and RMSPE is 11.6%. We used 2018 and 2019 data to evaluate the model prediction effect. I_S^U predictive MAPE is 1.2% and RMSPE is 2.1%. I_R^U predictive MAPE is 20.5% and RMSPE is 29.2%. The results show that the model has excellent fitting and prediction effect on infected HIV-sensitive strains, the MAPE and RMSPE were less than 5% and the fitting effect on HIV resistant strains was excellent and the prediction effect deviation was a little large but still within 30%.

Further, we use the data reported in 2007–2019 for final fitting to obtain unknown parameter values. Estimated parameters and initial conditions are given in Table 3. The estimated recruitment

rate of the susceptible was 1207 (95% CI (767–1654)), meaning that about 1207 individuals entered the high-risk AIDS group per year. The estimated drug-sensitive transmission coefficient (β_{S0}) was 1.2140 (95%CI (1.1443–1.2700)) and the drug-resistant transmission coefficient (β_{R0}) was 1.0851 (95%CI (0.7089–1.4856)). The estimated modification factor for untreated drug-sensitive individuals at HIV infection stage $\varepsilon_{I_S^U}$ was 0.3750 (95% CI (0.3136–0.4402)) and that for untreated drug-resistant individuals at HIV infection stage $\varepsilon_{I_R^U}$ was 0.0428 (95% CI (0.0084–0.0912)). The estimated diagnostic rate δ was 0.8786 (95% CI (0.6588–1.1268)). The estimated initial value of high-risk susceptible S was 36 414 (95% CI (31101–41985)). The estimated initial value of individuals infected with drug-sensitive strains P_S was 271 (95% CI (200–359)). The estimated initial value of individuals infected with drug-resistant strains P_R was 2 (95% CI (1–5)). The predictive curve is shown in Figures 2c and 2d. On the premise that the current prevention and control measures remain unchanged, the cumulative confirmed cases of HIV-sensitive and HIV-resistant strains in Zhejiang province by 2030 were 20 039 (95% CI 18382–21584) and 2114 (95% CI 1889–2298), respectively (Fig. 2c). The cumulative number HIV confirmed infections will reach 21 153 (95% CI 20271–23882) (Fig. 2d).

Using the 200 000 simulation samples of these parameters, we got the Markov Chain of basic reproduction number R_0^S and R_0^R . Figure 3 describes the Markov Chain for R_0^S and R_0^R with good convergences. We can use these 200 000 samples to get the point and interval estimates of R_0^S and R_0^R . Based on the estimated

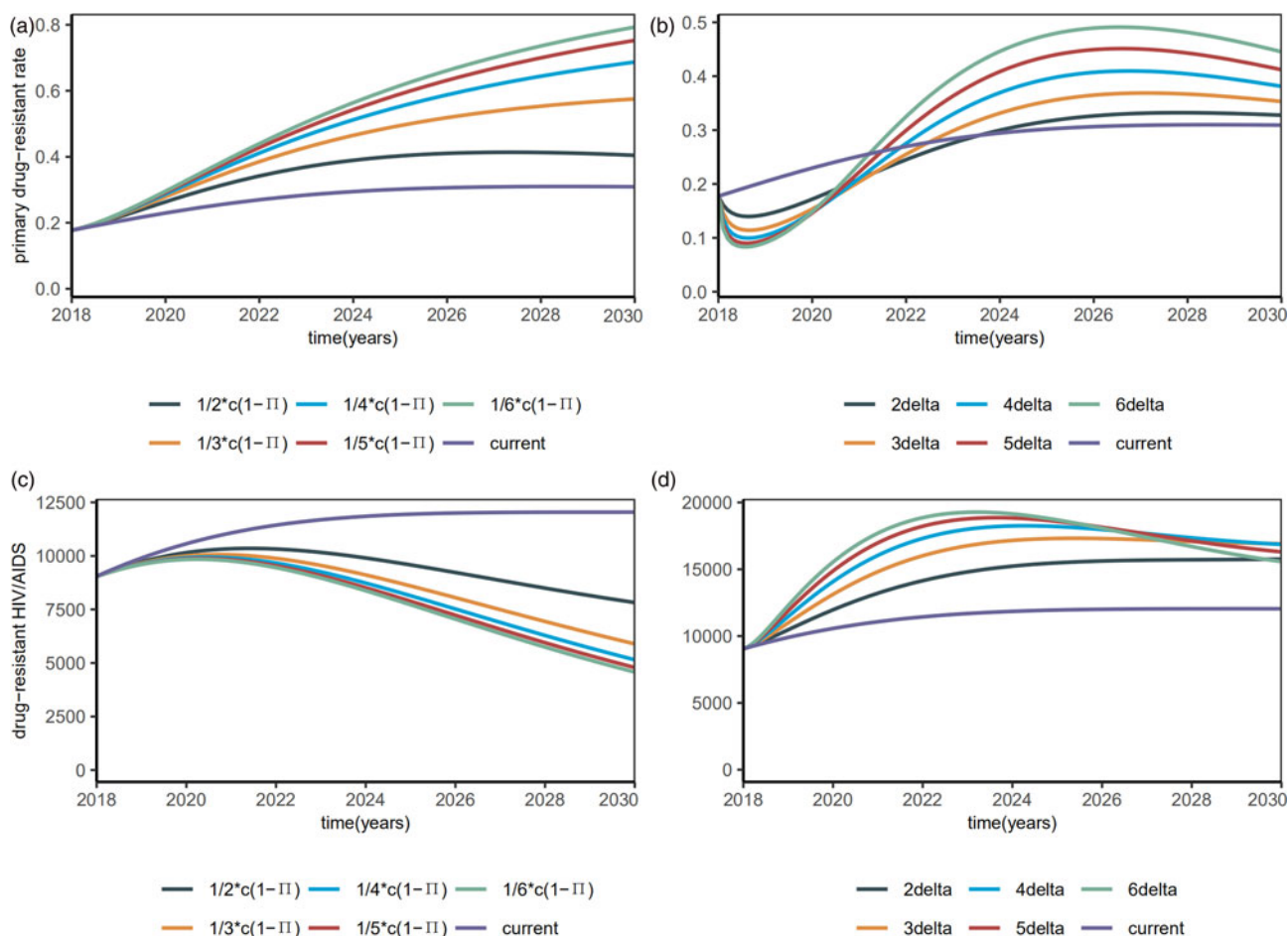


Fig. 6. Plots of estimated number of drug-resistant HIV/AIDS and the PDR rate after interventions.

parameters, we calculated the value of R_0 as R_0^S : 2.3946 (95% CI (2.2961–2.4881)) and R_0^R : 1.1739 (95% CI (1.1339–1.2281)).

Effect of interventions on HIV transmission

Figure 4 shows the PRCC variable of each parameter. β_{S0} and ϵ_{I^U} had positive impact upon R_0^S , whilst δ , τ , v_B , v_A and ρ had negative impact upon R_0^S . The most influential parameters were β_{S0} , β_{R0} and δ . β_{R0} and ϵ_{I^U} had positive impact upon R_0^R , whilst δ , v_A and ρ had negative impact upon R_0^R . The most influential parameters were β_{S0} , β_{R0} and δ . We concluded that reducing the contact rate c , strengthening the protected power π and increasing the diagnostic rate δ were the most effective intervening measures to control the HIV/AIDS epidemic among MSM.

To address the influence of each intervention on HIV infection, we investigated the number of HIV/AIDS infected, treated HIV/AIDS, drug-resistant HIV/AIDS, PDR rate, rate of the undiagnosed and the untreated. β_{S0} and β_{R0} were reduced by behavioural and biologic interventions, like decreasing the contact rate c or strengthening the protected power π (such as condom use) and increasing the diagnosed rate δ .

Reducing the contact rate c and increasing condom use were two major efforts to control the total HIV/AIDS (Fig. 5a). Both can be realised by strengthening the education for a high-risk population. In particular, when the contact rate c decreased by 50%, the total number of HIV/AIDS infected individuals among MSM also decreased by 20 000, at a rate six times of the increasing diagnostic

rate (Fig. 5b). Smaller β_{S0} and β_{R0} reduced the total HIV/AIDS and the total treated HIV/AIDS (Fig. 5c). Increasing the diagnostic rate increased the number of people treated in the near future, but this number could be reduced in the long run (Fig. 5d).

Figure 6 shows the estimated PDR rate and the number of total drug-resistant HIV/AIDS that change with interventions. Total number of drug-resistant HIV/AIDS dropped quickly with β_{S0} and β_{R0} (Fig. 6c), but PDR rate still increased (Fig. 6a). With the increasing diagnostic rate, the PDR rate tended to increase (Fig. 6b) while the number of drug-resistant HIV/AIDS increased slightly and then decreased (Fig. 6d).

Then, we investigated the proportions of the diagnosed and treated. When the diagnostic rate δ increased by 6 times, the diagnosed proportion will be reduced to about 90% and remain stable (Fig. 7a), with a R_0 of 1.4354 (95% CI 1.0626–1.6281). When β_{S0} and β_{R0} decreased by 6 times, the diagnosed proportion was reduced to about 90% and remained stable (Fig. 7b), with a R_0 of 1.9133 (95% CI 1.5354–2.1159). Till 2020, the treated proportion will have increased to about 90% and slightly abate by interventions (Figs 7c and 7d), which means 90% of the diagnosed HIV/AIDS individuals will have received treatment.

Discussion

In this study, according to the dynamics theory of SIR infectious diseases, we analysed the effect of ART on HI V/AIDS infection in the MSM population in Zhejiang Province with an improved

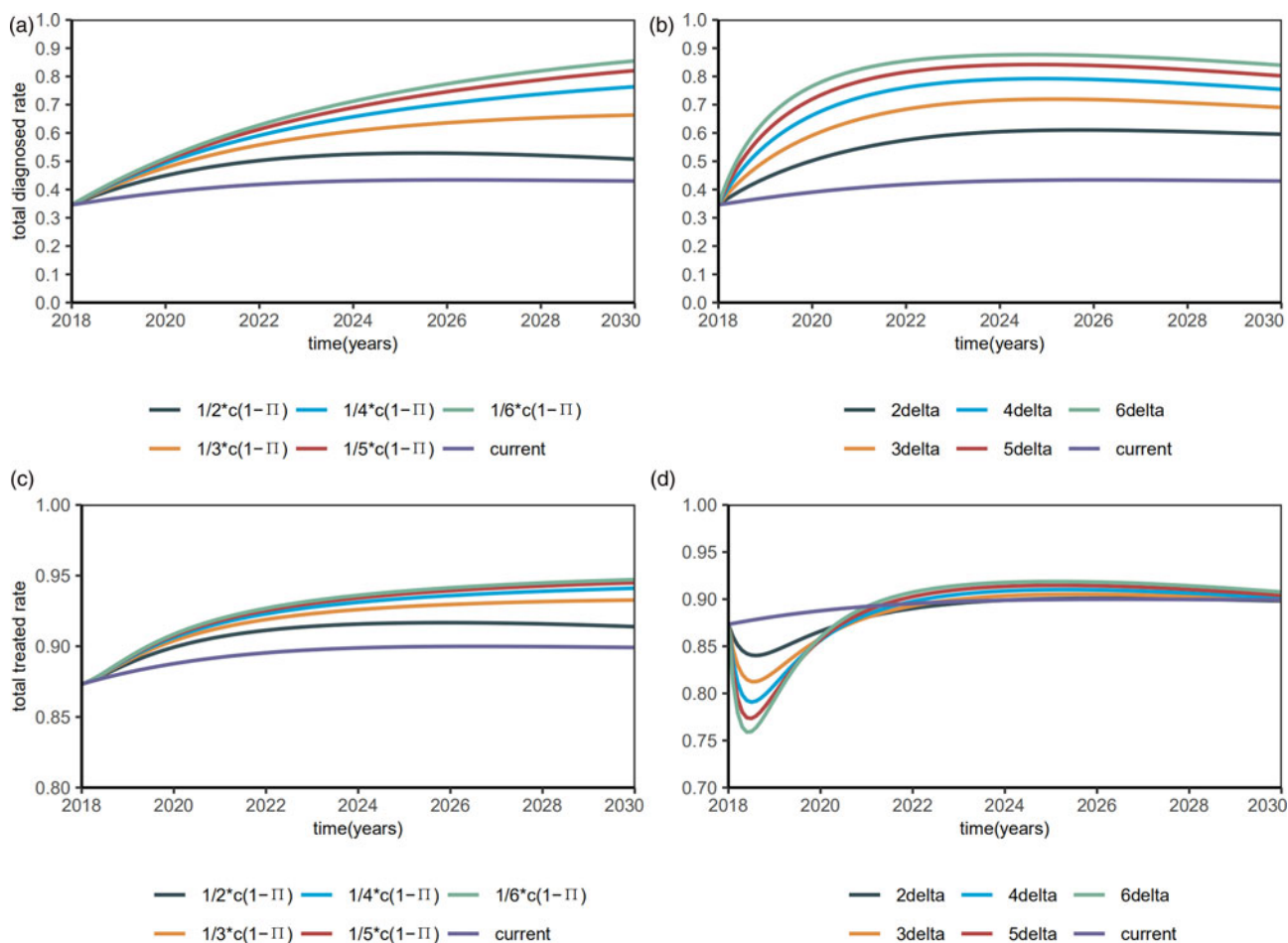


Fig. 7. Plots of estimated proportions of the diagnosed and the treated after interventions.

compartmental model. The estimated reproduction number we have calculated is 2.4507 (95% CI 2.3564–2.5441) in Zhejiang MSM population, smaller than the estimated 3.88 (95% CI 3.69–4.07) in national MSM population in 2013 [12]. This suggests that the interventions in recent years have exerted a positive effect on AIDS control.

Reducing the high-risk behaviours, mainly through education, is the top choice to control the total number of HIV/AIDS patients. The estimated drug-sensitive transmission coefficient β_{S0} (1.2140 (95% CI 1.1443–1.2700)) was larger than the estimated drug-resistant transmission coefficient β_{R0} (1.0851 (95% CI 0.7089–1.4856)). The reason may be that individuals can be infected with drug-resistant strains from the patients receiving treatment, which brings a smaller transmission probability of HIV per high-risk behaviour (β), lower high-risk behaviour contact rate per year (c), or larger protection rate by intervention measures (π). This also shows that ART can reduce the spread of HIV in the MSM population. Shen *et al.* [13] suggested that early treatment might increase the incidence of drug resistance. Under the current conditions, the PDR rate will reach 31% till 2030. This also reflects the need for additional second-line drugs.

Our estimated diagnostic rate was only 0.8786 (95% CI 0.6588–1.1268), that is, the average time from infection to diagnosis is 1.14 years (95% CI 0.89–1.52), which is consistent with the low rate of prior HIV testing among MSM [23]. Increasing HIV

tests is the first step toward the 90-90-90 targets for NDAIDS and China still faces many challenges in achieving this goal. Early detection enables timely antiretroviral treatment to reduce HIV viral load, thus reducing the spread of HIV. We propose that increasing the diagnostic rate may increase the total number of treated HIV/AIDS in a short time, but reduce this number in the long run. The World Health Organization recommends HIV self-testing, as a supportive approach [24], can increase the efficiency of HIV testing [25]. When β_{S0} and β_{R0} were decreased by 6 times, the diagnosed proportion was reduced to about 90% and remained stable, with a R_0 of 1.9133 (95% CI 1.5354–2.1159). Consistent with previous study [26, 27], R_0 is still larger than the level of epidemic elimination even if the 90-90-90 strategy is completed, which means the strategy alone may not be sufficient to eliminate HIV transmission among MSM in China.

The present study also demonstrated the effectiveness of these interventions for controlling HIV/AIDS epidemic. In particular, when the contact rate c decreased by 50%, the total number of c HIV/AIDS infected individuals among MSM also decreased by 20 000, at a rate six times of the increasing diagnostic rate. This also underscores that behavioural and biologic interventions are critical to control the spread of HIV among Chinese MSM [28].

Our model also shows deficiencies. First, the drug resistance data may be biased because not all treated patients are tested at an early stage. Second, heterosexual transmission among MSM was not discussed in our model, since some of them may also

marry a woman. Finally, some parameters were set based on assumptions and may not reflect the actual situation.

In summary, our findings suggest that behavioural and biologic interventions, in addition to HIV testing, are needed for HIV prevention among MSM. ART can effectively control the spread of HIV, even in the presence of drug resistance. The 90-90-90 strategy alone may not be enough to eliminate the HIV/AIDS epidemic in Chinese MSM.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0950268820000850>

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Conflict of interest. None.

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