The impact of attrition on the transmission of HIV and drug resistance

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Background: Attrition due to loss to follow-up or termination of antiretroviral therapy (ART) among HIV-infected patients in care may increase the risk of emergence and transmission of drug resistance (TDR), diminish benefit of treatment, and increase morbidity and mortality. Understanding the impact of attrition on the epidemic is essential to provide interventions for improving retention in care.

Methods: We developed a comprehensive HIV transmission dynamics model by considering $CD4^+$ cell count dependent diagnosis, treatment, and attrition involving TDR and acquired drug resistance. The model was calibrated by 11 groups HIV/AIDS surveillance data during 2008–2018 from Guangxi, China, and validated by the prevalence of TDR among diagnosed treatment-naive individuals. We aimed to investigate how attrition would affect the transmission of HIV and drug-resistance when expanding ART.

Results: In the base case with $CD4^+$ cell count dependent per capita attrition rates 0.025∼0.15 and treatment rates 0.23∼0.42, we projected cumulative total new infections, new drug-resistant infections, and HIV-related deaths over 2022–2030 would be 145 391, 7637, and 51 965, respectively. Increasing treatment rates by 0.1∼0.2 can decrease the above total new infections (deaths) by 1.63∼2.93% (3.52∼6.16%). However, even 0.0114∼0.0220 (0.0352∼0.0695) increase in attrition rates would offset this benefit of decreasing infections (deaths). Increasing treatment rates (attrition rates) by 0.05∼0.1 would increase the above drug-resistant infections by 0.16∼0.30% (22.18∼41.15%).

Conclusion: A minor increase in attrition can offset the benefit of treatment expansion and increase the transmission of HIV drug resistance. Reducing attrition rates for patients already in treatment may be as important as expanding treatment for untreated patients.

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Introduction

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) [1], 38.4 million people were living with HIV globally, and an estimated 1.5 million new infections and 650 000 AIDS-related deaths occurred worldwide in 2021. Among these people living with HIV, 85% were diagnosed, 88% of diagnosed people were accessing antiretroviral therapy (ART), and 92% of people on ART were virally suppressed [1]. However, these three proportions are only 71% [2], 80% [3], and 65% [4] in China, respectively, far less than the UNAIDS 95-95-95 targets [1]. One of the key challenges that hamper the progress toward achieving the above second and third targets is the high rate of attrition due to loss to follow-up (LTFU) or ART termination, with 9.42–17.52 attritions per 100 person-years within the first year of ART initiation and 24% of the cumulative probability of attrition after 5 years of ART [5–8]. A high attrition rate increases morbidity and mortality, diminishes the benefit of treatment, and increases the risk of emergence and transmission of the drug-resistant virus [5,9–13], which further limits the choice of drugs on the resumption of ART. Understanding the impact of attrition on the transmission of HIV and drug-resistant viruses at the population level is essential to provide interventions for improving retention in care.

Mathematical modeling has played an important role in evaluating how attrition affects HIV transmission dynamics. Blower *et al.* [14] proposed a two-strain model with the transmission of drug resistance (TDR) and acquired drug resistance (ADR) to study the effect of ART on the incidence rate and death rate in San Francisco with the assumption that drug-resistant patients would be twice as likely to give up ART as drug-sensitive patients. Smith *et al.* [15] extended the model by Blower *et al.* [14] by including seven drug-resistant strains to identify the key factors that led to a high level of TDR and assumed that the attrition rates were different for varied viral strains. Lu *et al.* [16] extended the model by Blower *et al.* [14] by including the primary and AIDS stage to access the effectiveness of ART on HIV infection in China and assumed the attrition did not occur for patients at the AIDS stage. However, these studies neither considered the possible increase in drug resistance due to attrition [5,9–13] nor validated the model by dynamic TDR data [17]. Moreover, the difference in attrition rates for treated individuals at different $CD4^+$ cell count levels is not involved and how the increase in attrition will balance the benefit of expanding treatment quantitatively remains unknown.

In this study, we proposed a dynamic compartmental model including TDR and ADR to explore the impact of attrition on new infections and TDR using the Guangxi Zhuang Autonomous Region (hereafter referred to as Guangxi), China as a case study. Guangxi has the second highest number of newly reported HIV/AIDS cases in China (14.3% of the total national during 2006–2015) [18], and more than 90% of cases are infected through heterosexual transmission since 2010 [19]. The mortality rate in Guangxi is 1.45 times the average national level due to late diagnosis [20]. We calibrated this dynamic model by multisource data during 2008–2018 exacted from Guangxi Center for Disease Control and Prevention (Guangxi CDC): the numbers of annual newly diagnosed people living with HIV and newly treated individuals at four levels of $CD4^+$ cell counts ($CD4^+$ $\geq$500 cells/μl, $CD4^+$ 350–499 cells/μl, $CD4^+$ 200–349 cells/μl, and $CD4^+$ <200 cells/μl), the number of deaths and drug-resistant individuals among the treated individuals, and the number of drug-resistant individuals among people with attrition. The model was validated by the dynamic prevalence of TDR among diagnosed treatment-naive individuals [21–28]. We evaluated how attrition would affect the HIV epidemic under different ART expansion scenarios. This will guide how to balance ART expansion and decreasing attrition in the presence of TDR and ADR.

Materials and methods

Data sources

We obtained the annual HIV/AIDS surveillance data (11 groups) between 2008 and 2018 from the Guangxi CDC (Appendix Table S1, http://links.lww.com/QAD/C829). We extracted the reported HIV cases and treatment data (eight groups): the numbers of annual newly diagnosed people living with HIV and newly treated individuals at four levels of $CD4^+$ cell counts ($CD4^+$ $\geq$500 cells/μl, $CD4^+$ 350∼499 cells/μl, $CD4^+$ 200∼349 cells/μl, and $CD4^+$ <200 cells/μl). We assumed that the observed $CD4^+$ cell counts at diagnosis and treatment are representative of all new diagnoses and all newly treated individuals, respectively [29,30]. This means the distribution of people with missing $CD4^+$ data is assumed to be the same as people with $CD4^+$ data, and adding people with missing $CD4^+$ data to those with $CD4^+$ data gives the total number of newly diagnosed and treated individuals at different levels of $CD4^+$ cell count. The treated individuals in each year and deaths among them (ninth group data) are extracted. Multiplying the number of treated individuals by the proportion (10% from Guangxi CDC) of people with viral load more than 1000 copies/ml among treated individuals and the proportion (40% from Guangxi CDC) of drug-resistant individuals among those with viral load more than 1000 copies/ml gives the number of drug-resistant individuals among treated each year (tenth group data). Similarly, multiplying the number of people with attrition by the proportion (86% from Guangxi CDC) of people with viral load more than 1000 copies/ml and the proportion (18.9% from Guangxi CDC) of drug-resistant

individuals gives the number of drug-resistant individuals among people with attrition each year (11th group data). Here, attrition was due to loss to follow-up (LTFU, defined as missing more than 90 days after the last date seen in the clinic, or the date of withdrawal) or stopping ART [8]. The dynamic prevalence data of TDR among treatment-naive individuals during 2008–2015 in Guangxi were obtained from the published literature [21–28]. The demographic data about population size and age distribution were obtained from Guangxi Population and Employment Statistical Yearbook [31].

Model formulation

We developed a dynamic HIV transmission model involving the ADR and TDR among the general population aged above 15 years in Guangxi, based on the natural history of progression, diagnosis, and treatment by extending our previous studies [33–37]. The population was divided into 25 compartments (Fig. 1): susceptible population (S), undiagnosed infections (I_{qj}^{U}), diagnosed but untreated infections (I_{qj}^{D}), and treated infections (I_{qj}^{T}), where $q \in \{s, r\}$ denoted drug-sensitive and drug-resistant strains, $j = 1,2,3,4$ denoted the four stages of $CD4^+$ at least 500 cells/μl, $CD4^+$ 350∼499 cells/μl, $CD4^+$ 200∼349 cells/μl, and $CD4^+$ less than 200 cells/μl. We modelled treatment effects of ART by assuming that ART reduced infectivity, progression and mortality rate, and improved the reversion from a lower $CD4^+$ level to a higher $CD4^+$ level [14,15,17,32]. We assumed that drug-resistant infections had lower infectivity (in the absence of ART), faster progression, higher mortality, and would be less responsive to therapy than drug-sensitive infections [14,17]. Drug resistance can be acquired for those treated drug-sensitive infections with treatment failure and transmitted by infections with drug-resistant strains at different $CD4^+$ levels.

Denote b as the per capita recruitment rate of individuals engaging in sexual behavior, and m as the per capita natural death rate. λ_s and λ_r are the forces of HIV infections, that is, the per capita rates for the susceptible to acquire the infection with the HIV drug-sensitive and drug-resistant strains, respectively (see Appendix for details, http://links.lww.com/QAD/C829). The time-dependent per capita diagnosis and treatment rates are denoted as $\delta_j(t)$ and $\tau_j(t)$, $j = 1,2,3,4$, respectively. It is worth noting that the per capita treatment rate used here is different from the annual treatment rate, that is, the proportion of diagnosed individuals who initiate

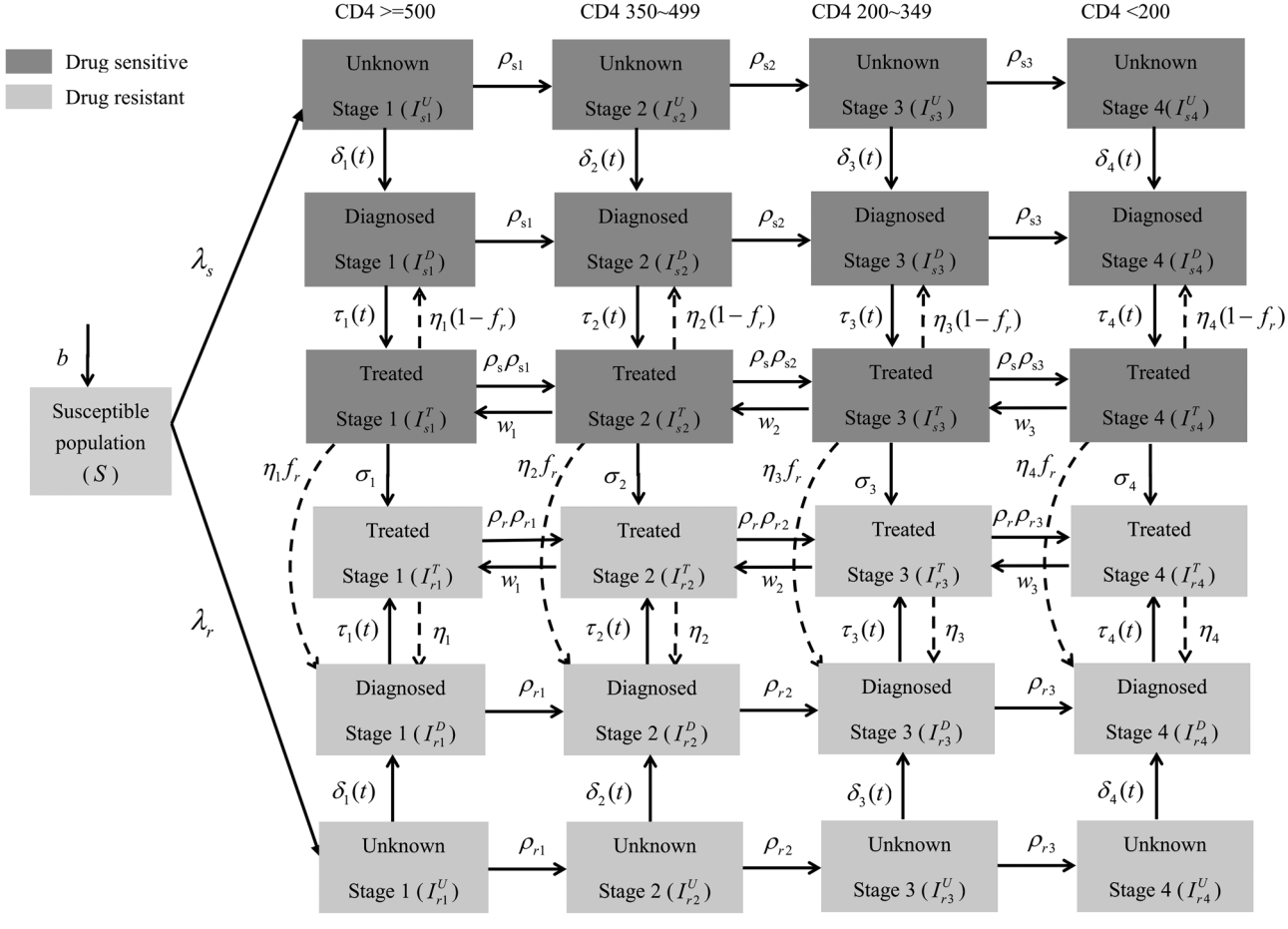

Fig. 1. A compartmental model of HIV transmission in the presence of TDR and ADR.

treatment per year. There is a nonlinear relationship between them (see the Section of Model Formulation in Appendix for details, http://links.lww.com/QAD/C829). σ_j is the per capita rate of acquired drug resistance after first-line treatment. The per capita disease progression rates for drug-sensitive (drug-resistant) individuals from the stage of $CD4^+$ at least 500 cells/μl to $CD4^+$ 350∼499 cells/μl are ρ_{s1} (ρ_{r1}), from $CD4^+$ 350∼499 cells/μl to $CD4^+$ 200∼349 cells/μl ρ_{s2} (ρ_{r2}), and from $CD4^+$ 200∼349 cells/μl to $CD4^+$ less than 200 cells/μl are ρ_{s3} (ρ_{r3}). The per capita HIV-related death rates for drug-sensitive (drug-resistant) individuals in these four stages are $\mu_{sj}(\mu_{rj})$, $j=1,2,3,4$, respectively. After treatment, these progression rates decreased with a modification factor ρ_s (ρ_r) and HIV-related death rates decreased with a modification factor μ_s (μ_r) for drug-sensitive (drug-resistant) individuals, respectively, compared with untreated individuals. This means that the treatment reduced the above progression rates by $1-\rho_s$ ($1-\rho_r$) and HIV-related death rates by $1-\mu_s$ ($1-\mu_r$) for drug-sensitive (drug-resistant) individuals, respectively. The per capita reversion rates of the above stages from lower $CD4^+$ level to higher $CD4^+$ level after effective treatment are w_1, w_2, w_3, respectively, and we assumed that these reversion rates were the same among drug-sensitive and drug-resistant individuals [32,33]. The per capita attrition rates in the four stages are $\eta_j(j=1,2,3,4)$ and f_r is the fraction of drug-resistant individuals among those with attrition. We also note that the per capita attrition rate used here is different from the annual attrition rate (i.e., the proportion of treated individuals who give up treatment per year). There is a nonlinear relationship between them (see Appendix, http://links.lww.com/QAD/C829). The per capita death rates (natural death and HIV-related death) were not shown in Fig. 1 for simplification.

Model calibration

We obtained the recruitment rate and natural death rate from Guangxi Population and Employment Statistical Yearbook [31]. We chose disease-related progression rates and reversion rates from the published literature [32,33,35,38,39], which were assumed the same in different settings. However, for some setting-specific parameters (including per capita time-dependent diagnose rates and treatment rates, transmission rates, acquired drug-resistance rates, and HIV-related death rates) and the initial population size of each compartment, we estimated them using the nonlinear least-squares method (NLS) as listed in Appendix Tables S2-S3, http://links.lww.com/QAD/C829. These parameters were estimated by calibrating the model to the following Guangxi data during 2008−2018: the numbers of annual newly diagnosed individuals and newly treated individuals at four $CD4^+$ cell count groups ($CD4^+ \geq 500$ cells/μl, $CD4^+$ 350∼499 cells/μl, $CD4^+$ 200∼349 cells/μl, and $CD4^+$ <200 cells/μl), the number of deaths and drug-resistant individuals among the treated individuals, and the number of drug-resistant individuals among people with attrition (Fig. 2a−k). We used the dynamic prevalence of TDR among diagnosed treatment-naive individuals for model validation (Fig. 2l). The epidemic trend of these 12 indicators was projected until 2030 (Fig. 2). We obtained the point estimate of the unknown parameters based on the NLS method and sampled these parameters within their ranges by the Latin hypercube sampling method and repeated 1000 times. In each simulation, we calculated the sum of square errors between the model output and data and selected the top 10% with the least square errors to generate 95% confidence intervals (95% CIs) [33]. Other model parameters were obtained from the published literature or the database from Guangxi CDC. All analyses and simulations were performed in MATLAB R2019b.

Simulated impact of increasing attrition and expanding treatment

To explore how attrition may undermine the effect of expanding treatment, we simulated six different scenarios with the combination of the per capita attrition rate $\eta_j(j=1,2,3,4)$ increases by 0, 0.05 (i.e. $\eta_j+0.05$), 0.1 (i.e., $\eta_j+0.1$), or the per capita treatment rate $\tau_j(t)(j=1,2,3,4)$ increases by 0, 0.5 [i.e. $\tau_j(t)+0.5$] from 2022 based on the above-estimated parameters (Fig. 3). The scenario in which the per capita attrition rate and the per capita treatment rate increase by 0 [η_j+0 and $\tau_j(t)+0$] is the baseline scenario 1 (status quo or base case). The rest five scenarios are scenario 2 [$\eta_j+0.05$ and $\tau_j(t)+0$], scenario 3 [$\eta_j+0.1$ and $\tau_j(t)+0$], scenario 4 [η_j+0 and $\tau_j(t)+0.5$], scenario 5 [$\eta_j+0.05$ and $\tau_j(t)+0.5$], scenario 6 [$\eta_j+0.1$ and $\tau_j(t)+0.5$]. For the varied per capita attrition rate and treatment rate in these six scenarios, the overall annual treatment rate changed from 73.73% in 2022 to 78.81, 69.73, 62.42, 90.59, 85.54, 81.03% in 2030 (Figure S1 in Appendix, http://links.lww.com/QAD/C829**)**, while the overall annual attrition rate changed from 3.21% in 2022 to 3.07, 8.13, 13.20, 3.03, 8.06, 13.09% in 2030, respectively (Figure S2 in Appendix, http://links.lww.com/QAD/C829). In this study, we define that the increase in these rates with decimals (e.g. 0.1) means they plus decimals (0.1 here), while an increase with percentage (e.g. 10%) means they multiply 1+percent (110% here). We predicted the trend of the total new infections (both drug-sensitive and drug-resistant infections), new drug-resistant infections, the prevalence of TDR among new infections, and HIV-related deaths among diagnosed and treated individuals during 2022−2030.

Sensitivity analysis

We considered more combination of the increase in the per capita attrition rate (0−0.1, with step 0.01) and the per capita treatment rate (0−0.5, with step 0.05) to perform sensitivity analysis (Fig. 4). We plotted the ratio of cumulative total new infections (Fig. 4a), cumulative new drug-resistant infections (Fig. 4b), cumulative HIV-

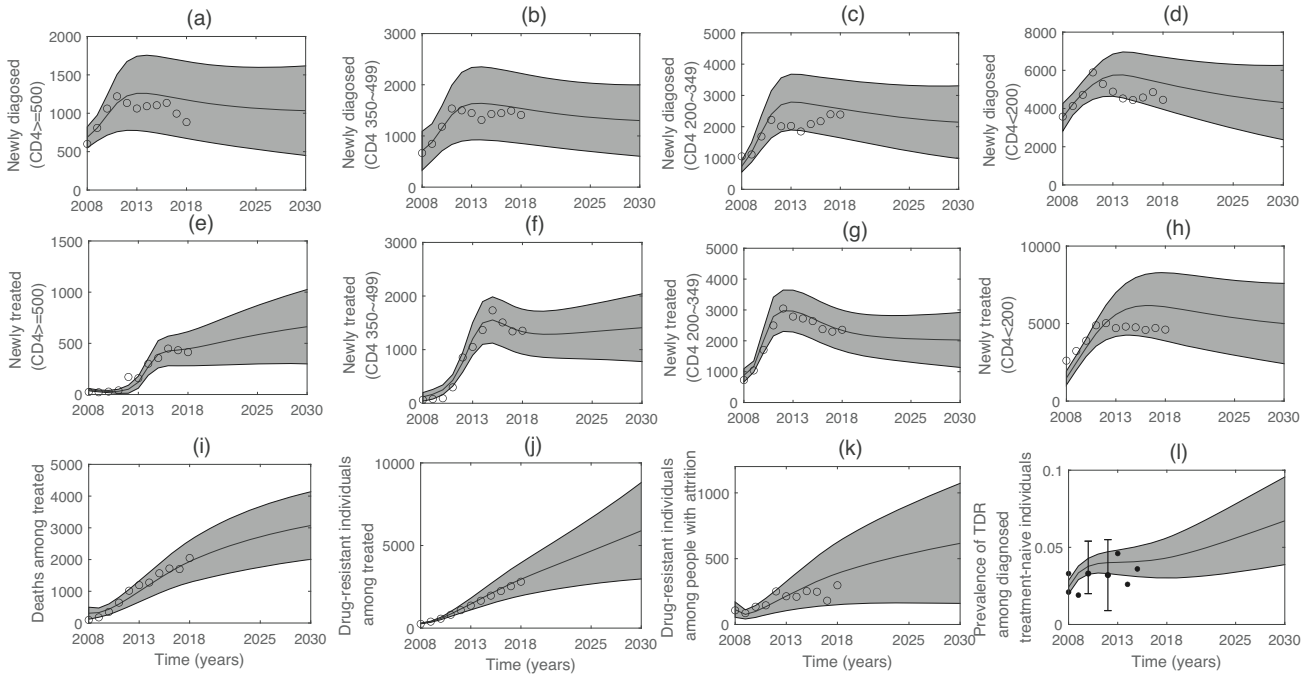

Fig. 2. Model fit (blue lines) to the annual reported data (black circles) of newly diagnosed individuals with $CD4^+$ ≥500 cells/μl, $CD4^+$ 350–499 cells/μl, $CD4^+$ 200–349 cells/μl, and $CD4^+$ <200 cells/μl (a–d), newly treated individuals at these four stages (e–h), the number of deaths and drug-resistant individuals among the treated individuals (i–j), and the number of drug-resistant individuals among people with attrition (k). The observed prevalence of TDR among diagnosed treatment-naive individuals was used for validation (l). Grey areas show a 95% confidence interval (CI).

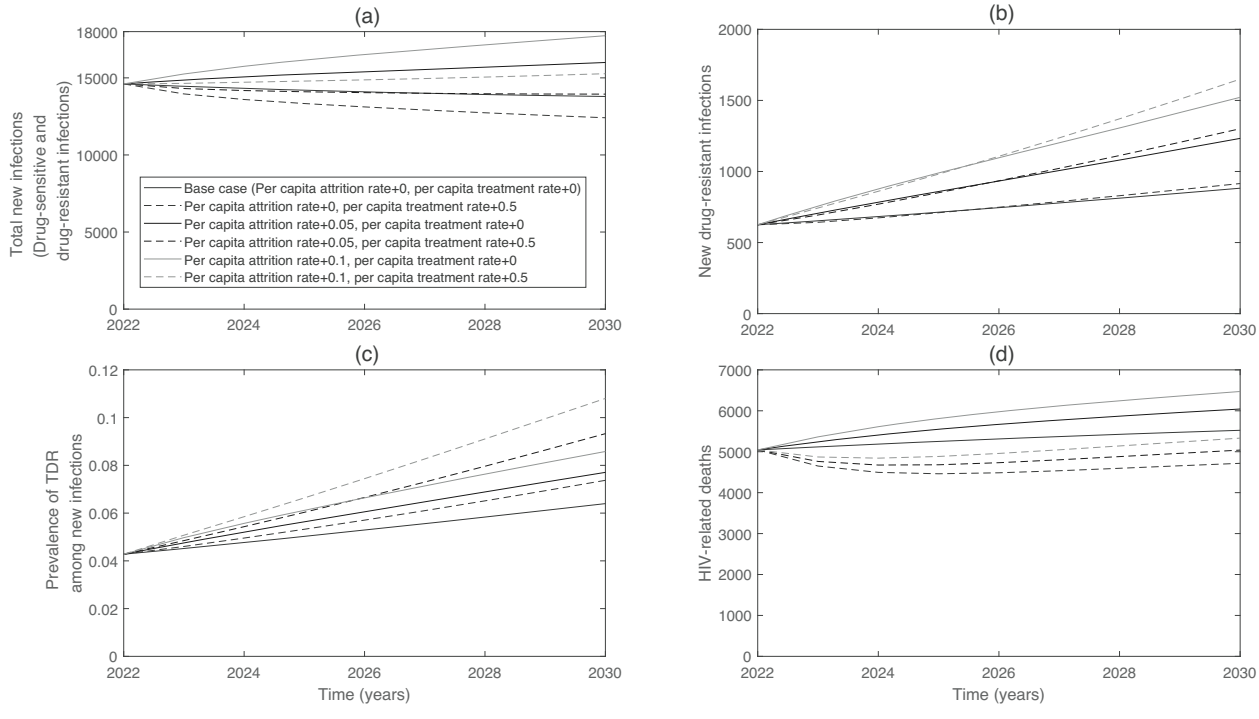

Fig. 3. Projections of total new infections (a), new drug-resistant infections (b), the prevalence of TDR among new infections (c), and HIV-related deaths (d) in six scenarios with a combination of increasing the per capita attrition rate η_j(j = 1,2,3,4) by 0, 0.05 (i.e. $\eta_j + 0.05$), 0.1 (i.e. $\eta_j + 0.1$) and increasing the per capita treatment rate $\tau(t)$(j = 1,2,3,4) by 0, 0.5 [i.e. $\tau_j(t) + 0.5$] from 2022.

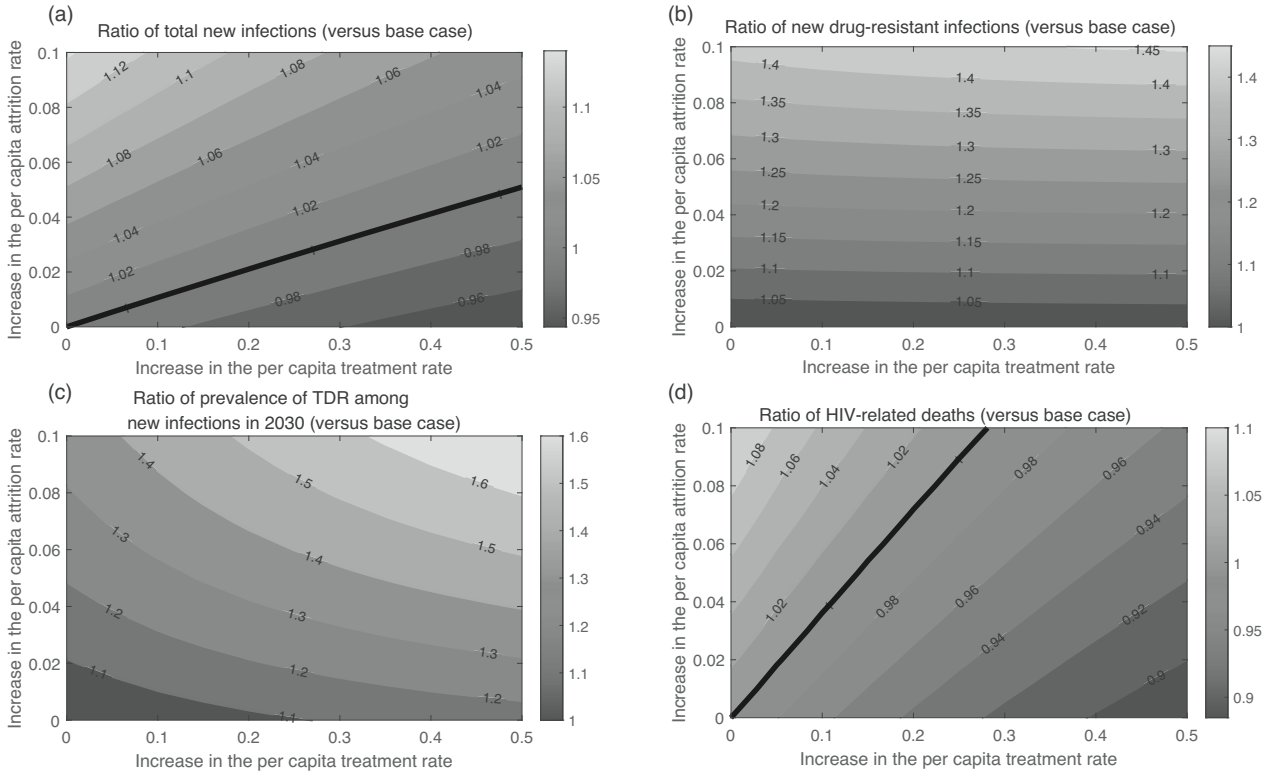

Fig. 4. Contour plots of the ratios of cumulative total new infections (a), new drug-resistant infections (b), HIV-related deaths (d) over 9 years (during 2022–2030), and prevalence of TDR among new infections in 2030 (c) as a function of increase in the per capita treatment rate and per capita attrition rate versus the base case (no increase for per capita attrition and treatment rate). The black solid isoclines in (a) and (d) indicate the threshold that the ratio is one.

related deaths (Fig. 4d) over 9 years (during 2022–2030), and the prevalence of TDR among new infections in 2030 (Fig. 4c) for various increase in the per capita attrition rate and the per capita treatment rate versus the baseline scenario. The threshold in Figs. 4a and 4d was defined as the combination of attrition and treatment such that the above ratio was equal to one.

Results

HIV transmission dynamics

Figure 2 shows the model fitting to the reported data of HIV cases with diagnosis, treatment, and drug resistance, and most of the observed data fall within the estimated 95% CI. On the basis of our parameter estimates (Appendix Table S2-S3, http://links.lww.com/QAD/C829), we projected the number of diagnosed cases at four $CD4^+$ cells count groups ($CD4^+$ $\geq$500 cells/μl, $CD4^+$ 350∼499 cells/μl, $CD4^+$ 200∼349 cells/μl, and $CD4^+$ <200 cells/μl) in 2030 would decrease to 1034 (95% CI: 450∼1617), 1301 (603∼1998), 2145 (983∼3307), and 4314 (2366∼6261), respectively. With the expanded treatment coverage, the number of newly treated cases with $CD4^+$ cell count at least 500 cells/μl in 2030 would increase to 1325 (598∼2051), and the other three $CD4^+$ cells count groups would reach 1409 (777∼2041), 2028 (1137∼2918), and 5001 (2408∼7593), respectively. The number of deaths and drug-resistant individuals among the treated individuals in 2030 would reach 3072 (2007∼4137) and 5893 (2974∼8813), respectively, and the number of drug-resistant individuals among people with attrition would reach 616 (160∼1073). The prevalence of TDR among diagnosed treatment-naive individuals would reach 6.72% (3.88∼9.56%).

Impact of increasing attrition and expanding treatment

The benefit of expanding treatment may be undermined by increasing attrition (Fig. 3). In the base case with $CD4^+$ cell count dependent per capita attrition rates 0.025∼0.15 and per capita treatment rates 0.23∼0.42 as shown in Table S3, http://links.lww.com/QAD/C829 (these rates increase by 0, blue solid lines), the cumulative total new infections and cumulative new drug-resistant infections over the next 9 years (during 2022–2030) would be 145 391 (90 957∼199 826) and 7637 (3970∼11 305), respectively. The prevalence of TDR among new infections in 2030 would reach 6.56% (3.76∼9.36%) and the cumulative HIV-related deaths over 9 years would be 51 965 (42 929∼61 001). Increasing the per capita

treatment rate by 0.5 while maintaining the baseline per capita attrition rate (blue dashed lines) would decrease the cumulative total new infections and HIV-related deaths by 5.60% (4.22∼6.99%) and 11.16% (3.41∼18.90%), respectively. Meanwhile, this would increase the cumulative new drug-resistant infections and the prevalence of TDR among new infections in 2030 by 0.97% (−0.33∼2.27%) and 15.26% (12.32∼18.20%), respectively. However, increasing the per capita treatment rate by 0.5 while increasing the per capita attrition rate by 0.05 (black dashed lines) would only slightly decrease the cumulative total new infections by 0.04% (−1.63∼1.71%), and increasing the per capita attrition rate by 0.1 (red dashed lines) can inversely increase these infections by 4.89% (2.49∼7.29%). This implied that even a little increase in attrition would counteract the benefit of treatment expansion. Moreover, increasing the per capita attrition rate by 0.1 while maintaining the baseline per capita treatment rate (red solid lines) would increase the cumulative total new infections and HIV-related deaths by 14.32% (11.12∼17.52%) and 10.20% (6.18∼14.21%), respectively.

Sensitivity analysis

There exist critical thresholds of per capita attrition rate which offset the benefit of expanding treatment on the cumulative total new infections and HIV-related deaths over 9 years (Fig. 4). If the per capita treatment rate increased by 0.1 (or 0.2) while maintaining the baseline attrition, the cumulative total new infections would decrease by 1.63% (1.21∼2.04%) [or 2.93% (2.19∼3.67%)], but even a 0.0114 (0.0079∼0.0149) [or 0.0220 (0.0153∼0.0286)] increase in the per capita attrition rate would offset the benefit of expanding treatment on these new infections (Fig. 4a). Moreover, increasing the per capita attrition rate by more than 0.0513 (0.0353∼0.0672) would always increase these new infections once the per capita treatment rate increased by less than 0.5. Similarly, for the same increase in per capita treatment rate without increasing attrition, the cumulative HIV-related deaths would decrease by 3.52% (1.07∼5.96%) [or 6.16% (1.88∼10.45%)], but even a 0.0352 (0.0129∼0.0575) [or 0.0695 (0.0225∼0.1165)] increase in the per capita attrition rate would offset the benefit of expanding treatment on the cumulative HIV-related deaths (Fig. 4d).

Increasing the per capita attrition rate and per capita treatment rate can both increase the number of cumulative new drug-resistant infections (Fig. 4b) and the prevalence of TDR among new infections in 2030 (Fig. 4c), and the former is more sensitive to these drug-resistance results than the latter. For example, a 0.05 and 0.1 increase in the per capita treatment rate would increase the number of cumulative new drug-resistant infections by 0.16% (0.01∼0.38%) and 0.30% (0.01∼0.70%), respectively, while a 0.05 and 0.1 increase in the per capita attrition rate would increase this number by 22.18% (14.55∼29.80%) and 41.15% (27.07∼55.23%), respectively. Similarly, a 0.05 and 0.1 increase in the per capita treatment rate would increase the prevalence of TDR among new infections in 2030 by 2.32% (1.87∼2.77%) and 4.39% (3.54∼5.25%), respectively, while a 0.05 and 0.1 increase in the per capita attrition rate would increase this prevalence by 20.08% (8.70∼31.46%) and 33.48% (14.85∼52.12%), respectively.

Discussion

In this study, we have developed a comprehensive HIV transmission dynamic model to investigate the impact of attrition on the HIV epidemic with expanding ART coverage in the presence of TDR and ADR in China. We found that increasing the per capita attrition rate by 0∼0.1 would cause the cumulative total new infections from decreasing by 5.60% (4.22∼6.99%) to increasing by 14.32% (11.12∼17.52%) when the per capita treatment rate increases by 0∼0.5. This means that there exists a critical threshold of attrition that can offset the benefit of treatment expansion. There also exists a critical threshold for cumulative HIV-related deaths, which changes from decreasing by 11.16% (3.41∼18.90%) to increasing by 10.20% (6.18∼14.21%). Increasing the per capita attrition rate by 0.05∼0.1 would cause more increase (22.18∼41.15% versus 0.16%∼0.30%) in the number of cumulative new drug-resistant infections than increasing the per capita treatment rate by 0.05∼0.1.

Our study shows that expanding treatment can decrease the cumulative total new infections and HIV-related deaths, but this benefit would be offset by even a little increase in the attrition rate. Increasing the per capita treatment rate by 0.1∼0.2 can decrease the cumulative total new infections by 1.63∼2.93%. However, even a 0.0114∼0.0220 increase in the per capita attrition rate would offset this benefit. Similarly, a 0.0352∼0.0695 increase in the per capita attrition rate would offset the benefit of decreasing the cumulative HIV-related deaths by 3.52∼6.16%. This is because the number of treated individuals far exceeds untreated individuals and even little increase in the per capita attrition rate among treated individuals may cause a huge negative effect on controlling the epidemic. Therefore, improving the quality of HIV treatment and care and thus reducing the per capita attrition rate may be as important as treatment expansion, especially in low-resource areas. It is worth noting that the quantitative results on the effect of increasing attrition and treatment have not been investigated in previous modelling studies [14–17].

Our finding demonstrates that treatment expansion will increase the transmission of drug resistance and attrition will further increase the risk. The attrition rate is high among patients with high $CD4^+$ cell counts [7,8] because patients with higher $CD4^+$ cell counts are more likely to be asymptomatic and they may be less willing or motivated to

take ART drugs. Lower adherence to ART among these patients with higher $CD4^+$ cell counts may increase the risk of treatment failure and facilitate the emergence and transmission of drug-resistant viruses. Thus, enhancing adherence education is urgently needed, especially for patients with high $CD4^+$ cell counts, and training healthcare providers on ART adherence should also be taken seriously. As the treatment coverage is expanding and the $CD4^+$ level before ART is increasing constantly, it is necessary to focus on the management of people living with HIV to decrease or even avoid attrition.

Our study may have a few limitations due to model assumptions. First, some patients missed $CD4^+$ cell count data and we assumed that the distribution of people with missing $CD4^+$ data was the same as people with $CD4^+$ data [29,30]. Second, we considered attrition due to loss to follow-up or stopping ART as a whole, but the reasons for attrition of them may be different. Third, we did not consider geographical heterogeneities in the diagnosis, treatment, and drug-resistance levels at the city scale. Fourth, our model considered the sexual transmission among the general population without differentiating the heterosexual or homosexual transmission. Fifth, our model of drug resistance considered the nucleoside reverse transcriptase inhibitor (NRTI), non-NRTI (NNRTI), and protease inhibitor resistance as a whole, and did not discriminate the difference among them. This may overestimate the effect of drug resistance because protease inhibitor resistance is rare, and the protease inhibitor resistant strains are less transmissible than NRTI-resistant and NNRTI-resistant strains [15]. Sixth, because of the complexity of the model structure and a large number of parameters, the uncertainty of predictions would become large and the prediction of absolute values in the long term should be interpreted with caution. Finally, the results of the balance between increasing attrition and expanding treatment in Guangxi may not be simply generalized to China as a whole or other countries due to the great difference in HIV incidence, attrition, and treatment coverage. Setting-specific analysis was needed on the basis of the local epidemic level.

In conclusion, a minor increase in attrition can offset the benefit of expanding treatment and increase the transmission of HIV drug resistance. Reducing the attrition rate by enhancing adherence education of patients and improving the management quality of HIV treatment and care for patients already in treatment, may be as important as expanding treatment for untreated patients.

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M.S., Y.X., H.X., Y.R., and G.L. conceived and designed the study. J.H., Q.Z., S.L., H.C., and J.L. extracted the HIV data from Guangxi CDC. M.S. analyzed the data, carried out the analysis, and performed numerical simulations. M. S. wrote the first draft of the manuscript. M.S., Y.X., L.R., H.X., Y.R., and G.L. critically revised the manuscript. All the authors contributed to writing the paper and agreed with the manuscript results and conclusions.

Supplementary materials: The additional file includes the supplementary materials used to describe model details and parameter estimation. The data utilized in this study are referenced in the article and included in its supplementary information files.

Conflicts of interest

All authors declare that they have no competing interests.

References

1. UNAIDS. Global HIV & AIDS statistics–2021 fact sheet. https://www.unaids.org/en/resources/fact-sheet [Accessed 10 November 2022]
2. Wu Z, McGoogan JM, Detels R. **The enigma of the human immunodeficiency virus (HIV) epidemic in China.** *Clin Infect Dis* 2021; **72**:876–881.
3. Zhang F, Ma Y, Zhao Y, Dong W. **Strategy to achieve full coverage in the national free antiretroviral therapy program.** In: Wu Z, Wang Y, Detels R, Bulterys M, McGoogan JM,editors. *HIV/AIDS in China: epidemiology, prevention and treatment* Singapore: Springer; 2020. pp. 271–289.
4. Ma Y, Dou Z, Guo W, Mao Y, Zhang F, McGoogan JM, *et al*. **The human immunodeficiency virus care continuum in China: 1985–2015.** *Clin Infect Dis* 2018; **66**:833–839.
5. Zhu H, Napravnik S, Eron J, Cole S, Ma Y, Wohl D, *et al*. **Attrition among human immunodeficiency virus (HIV)- infected patients initiating antiretroviral therapy in China, 2003–2010.** *PLoS One* 2012; **7**:e39414.
6. Gu D, Mao Y, Tang Z, Montaner J, Shen Z, Zhu Q, *et al*. **Loss to follow-up from HIV screening to ART initiation in rural China.** *PLoS One* 2016; **11**:e0164346.

7. Tang Z, Pan SW, Ruan Y, Liu X, Su J, Zhu Q, *et al*. **Effects of high CD4 cell counts on death and attrition among HIV patients receiving antiretroviral treatment: an observational cohort study.** *Sci Rep* 2017; **7**:3129.
8. Zhu J, Yousuf MA, Yang W, Zhu Q, Shen Z, Lan G, *et al*. **Mortality and attrition rates within the first year of antiretroviral therapy initiation among people living with HIV in Guangxi, China: an observational cohort study.** *Biomed Res Int* 2021; **2021**:6657112.
9. Dybul M, Nies-Kraske E, Daucher M, Hertogs K, Hallahan CW, Csako G, *et al*. **Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters.** *J Infect Dis* 2003; **188**:388–396.
10. Li X, Margolick JB, Conover CS, Badri S, Riddler SA, Witt MD, Jacobson LP. **Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study.** *J Acquir Immune Defic Syndr* 2005; **38**:320–328.
11. Rosen S, Fox MP, Gill CJ. **Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.** *PLoS Med* 2007; **4**:e298.
12. Mugavero MJ, Lin H-Y, Willig JH, Westfall AO, Ulett KB, Routman JS, *et al*. **Missed visits and mortality among patients establishing initial outpatient HIV treatment.** *Clin Infect Dis* 2009; **48**:248–256.
13. Colasanti J, Kelly J, Pennisi E, Hu Y, Root C, Hughes D, *et al*. **Continuous retention and viral suppression provide further insights into the HIV care continuum compared to the cross-sectional HIV care cascade.** *Clin Infect Dis* 2016; **62**:648–654.
14. Blower SM, Gershengorn HB, Grant RM. **A tale of two futures: HIV and antiretroviral therapy in San Francisco.** *Science* 2000; **287**:650–654.
15. Smith RJ, Okano JT, Kahn JS, Bodine EN, Blower S. **Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco.** *Science* 2010; **327**:697–701.
16. Lu Z, Wang L, Wang LP, Xing H, Fu G, Yan H, *et al*. **A mathematical model for HIV prevention and control among men who have sex with men in China.** *Epidemiol Infect* 2020; **148**:e224.
17. Shen M, Xiao Y, Rong L, Meyers LA, Bellan SE. **Early antiretroviral therapy and potent second-line drugs could decrease HIV incidence of drug resistance.** *Proc Roy Soc B-Biol Sci* 2017; **284**:20170525.
18. Fu MH, Qiao Q, Yang HF. **Analysis on the epidemiological characteristics of HIV/AIDS in China from 2006 to 2015.** *Chin J Human Sexuality* 2019; **28**:125–127.
19. Ge XM, Yang WM, Zhu QY, *et al*. **Epidemiological characteristics of HIV/AIDS in Guangxi Zhuang Autonomous Region, 2010–2017.** *Chin J Epidemiol* 2019; **40**:315–321.
20. Hu X, Liang BY, Zhou CX, Jiang J, Huang J, Ning C, *et al*. **HIV late presentation and advanced HIV disease among patients with newly diagnosed HIV/AIDS in Southwestern China: a large-scale cross-sectional study.** *AIDS Res Ther* 2019; **16**:6.
21. Liang SJ, Xing H, Liu W, Liao L, Bi Z, Chen J, *et al*. **HIV-1 drug resistance in recently infected individuals in Guangxi.** *Chin J AIDS STD* 2011; **17**:503–505.
22. Zhou P, Su QJ, Cen P, Li M, Zang N, Xiao X, *et al*. **HIV subtype distribution based on the pol gene and prevalence of primary drug resistance in 60 HIV strains from Liuzhou.** *J Med Pest Control* 2010; **26**:785–787.
23. Li L, Chen L, Liang S, Liu W, Li T, Liu Y, *et al*. **Subtype CRF01_AE dominate the sexually transmitted human immunodeficiency virus type 1 epidemic in Guangxi, China.** *J Med Virol* 2013; **85**:388–395.
24. Li L, Sun G, Liang S, Li J, Li T, Wang Z, *et al*. **Different distribution of HIV-1 subtype and drug resistance were found among treatment naive individuals in Henan, Guangxi, and Yunnan Province of China.** *PLoS One* 2013; **8**: e75777.
25. Li GJ, Liang SJ, Harrison TJ, Tang Z, Shen Z, Wang X, *et al*. **Prevalence of transmitted HIV-1 drug resistance remains low in Guangxi, China, eight years after scale-up of highly-active antiretroviral therapy.** *Intervirology* 2014; **57**:270–276.
26. Zhang J, Shen ZY, Li Z, Liang S, He C, Liang F, *et al*. **Genetic characteristics of CRF01_AE among newly diagnosed HIV-1-infected 16- to 25-year olds in 3 geographic regions of Guangxi, China.** *Medicine* 2015; **94**:e894.
27. Shen P, Su QJ, Huang YY, Jiang L, Zhang D, Guo J, *et al*. **Study of primary drug resistance and its influencing factors in antiretroviral treatment-naive HIV-1 patients of South district of Qinzhou city.** *China Trop Med* 2015; **15**:1181–1185.
28. Zhao S, Feng Y, Hu J, Li Y, Zuo Z, Yan J, *et al*. **Prevalence of transmitted HIV drug resistance in antiretroviral treatment naïve newly diagnosed individuals in China.** *Sci Rep* 2018; **8**:12273.
29. Birrell PJ, Chadborn TR, Gill ON, Delpech VC, Angelis DD. **Estimating trends in incidence, time-to-diagnosis and undiagnosed prevalence using a CD4-based Bayesian back-calculation.** *Stat Commun Infect Dis* 2012; **4**:6.
30. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, *et al*. **HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study.** *Lancet Infect Dis* 2013; **13**:313–318.
31. Guangxi Zhuang Autonomous Region Bureau of Statistics. http://tjj.gxzf.gov.cn/tjsj/tjnj/ [Accessed 10 November 2022]
32. Zhang L, Peng P, Wu Y, Ma X, Soe NN, Huang X, *et al*. **Modelling the epidemiological impact and cost-effectiveness of PrEP for HIV Transmission in MSM in China.** *AIDS Behav* 2019; **23**:523–533.
33. Jin X, Shi L, Wang C, Qiu T, Yin Y, Shen M, *et al*. **Cost-effectiveness of oral preexposure prophylaxis and expanded antiretroviral therapy for preventing HIV infections in the presence of drug resistance among men who have sex with men in China: A mathematical modelling study.** *Lancet Regional Health-Western Pacific* 2022; **23**:100462.
34. Shen M, Xiao Y, Rong L. **Global stability of an infection-age structured HIV-1 model linking within-host and between-host dynamics.** *Math Biosci* 2015; **263**:37–50.
35. Shen M, Xiao Y, Rong L, Meyers LA, Bellan SE. **The cost-effectiveness of oral HIV preexposure prophylaxis and early antiretroviral treatment in the presence of drug resistance among men who have sex with men in San Francisco.** *BMC Med* 2018; **16**:58.
36. Shen M, Xiao Y, Rong L, Meyers LA, Bellan SE. **Conflict and accord of optimal treatment strategies for HIV infection within and between hosts.** *Math Biosci* 2019; **309**:107–117.
37. Shen M, Xiao Y, Rong L, Zhuang G. **Global dynamics and cost-effectiveness analysis of HIV preexposure prophylaxis and structured treatment interruptions based on a multiscale model.** *Appl Math Model* 2019; **75**:162–200.
38. Zhou Y, Shao Y, Ruan Y, Xu J, Ma Z, Mei C, Wu J. **Modeling and prediction of HIV in China: transmission rates structured by infection ages.** *Math Biosci Eng* 2008; **5**:403–418.
39. Sun X, Yang W, Tang S, Shen M, Wang T, Zhu Q, *et al*. **Declining trend in HIV new infections in Guangxi, China: insights from linking reported HIV/AIDS cases with CD4-at-diagnosis data.** *BMC Public Health* 2020; **20**:919.