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Supplementary Appendix: Early antiretroviral therapy and potent second-line drugs could decrease HIV incidence of drug resistance

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This is a supplementary document describing mathematical details and analytical derivations used for our results presented in the main text and parameters estimation. In section 1, we present our mathematical model which describes the dynamics of the emergence and transmission of drug resistance in MSM population. It is followed by a section of how the parameters are chosen or estimated. In section 3, we provide supplementary figures and table to support the methods section in the main text.

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1 Model formulation

We extend the model in [1] by considering a group of male homosexual population in San Francisco which is decomposed into eleven categories (see figures S1-S2): susceptible individuals (S), untreated individuals infected with drug-sensitive strains at the primary stage (I^U_{s1}), chronic stage (I^U_{s2}) and AIDS stage (I^U_{s3}), untreated drug-resistant cases at the primary stage (I^U_{r1}), chronic stage (I^U_{r2}) and AIDS stage (I^U_{r3}), individuals treated with combination antiretroviral therapy (ART) but did not develop drug resistance (I^T_{s1}) and those who have entered the AIDS stage (I^T_{s2}), and ART-treated individuals with drug resistance before the AIDS stage (I^T_{r1}) and at the AIDS stage (I^T_{r2}). The variable's subscript identifies whether the infection is drug-sensitive (s) or drug-resistant (r); the superscript specifies whether the individuals are treated with ART (T) or untreated (U).

Denote the duration of the primary, chronic, AIDS stage for untreated drug-sensitive individuals as a_p, d_c, d_A, and assume untreated drug-resistant individuals have a longer chronic stage $d_r(\geq d_c)$ due to weaker viral replication capacity (lower viral load in the absence of drug pressure) and thus longer life expectancy [2, 3]. We assume that the duration of the primary and AIDS stages did not differ with or without treatment and resistance, as in [1,4]. Let $A^U_s(= a_p + d_c), A^U_r(= a_p + d_r), A^T_s, A^T_r$ and $D^U_s(= A^U_s + d_A), D^U_r(= A^U_r + d_A), D^T_s, D^T_r$ be the time when the AIDS stage starts and the infected individual dies because of AIDS for untreated drug-sensitive, untreated drug-resistant, treated drug-sensitive and treated drug-resistant individuals, respectively. Assume that treatment starts at time a_{ART} after infection irrespective of being infected with sensitive or resistant strains. Uninfected individuals are recruited into the susceptible population at a positive constant rate b. People exit the sexually-active population at a positive constant rate m due to behavior changes. The infected individuals at the chronic stage are assumed to receive antiviral treatment with a rate $\eta = 1/(a_{ART} - a_p)$ (For example, if all infected individuals are treated at an annual rate of 50%, then the average interval between infection and ART initiation is 2 years [5]). The parameter f_r is the fraction of treated individuals who develop drug resistance. Let t denote time and a denote the infection age. We assume that all of the infected individuals with the same infection age are homogeneous and have the same rates.

Let $i^U_{qj}(a,t)$, $i^T_{q1}(a,t)$ and $i^T_{q2}(a,t)$ (where $j = 1,2,3$ and $q \in \{s,r\}$) be the respective density of infected individuals in I^U_{qj}, I^T_{q1} and I^T_{q2} classes at time t and infection age a. It follows that

$$\begin{aligned} I^U_{q1}(t) &= \int_0^{a_p} i^U_{q1}(a,t)da, I^U_{q2}(t) = \int_{a_p}^{A^U_q} i^U_{q2}(a,t)da, I^U_{q3}(t) = \int_{A^U_q}^{D^U_q} i^U_{q3}(a,t)da, \\ I^T_{q1}(t) &= \int_{a_{ART}}^{A^T_q} i^T_{q1}(a,t)da, I^T_{q2}(t) = \int_{A^T_q}^{D^T_q} i^T_{q2}(a,t)da,\ q \in \{s,r\}, \end{aligned} \tag{1}$$

are the number of infected individuals in I^U_{qj}, I^T_{q1} and I^T_{q2} classes ($j = 1,2,3$ and $q \in \{s,r\}$), respectively, at time $t \geq 0$. We denote the disease-induced mortality rates in the classes $I^U_{s2}, I^U_{r2}, I^T_{s1}, I^T_{r1}$ and AIDS classes (including $I^U_{s3}, I^U_{r3}, I^T_{s2}, I^T_{r2}$) as $\mu^U_s, \mu^U_r, \mu^T_s, \mu^T_r$ and μ_A, respectively.

The probability that an infected individual in the I^U_{qj}, I^T_{q1} and I^T_{q2} class (where $j = 1,2,3$ and $q \in \{s,r\}$) still

stays in the original class at infection age a [1] is given by

$$\begin{aligned}
\sigma_{q1}^U(a) &= e^{-\int_0^a (m+\delta_1)ds},\ a \in [0, a_p],\ q \in \{s, r\},\\
\sigma_{q2}^U(a) &= e^{-\int_{a_p}^a (m+\mu_q^U+\delta_q^U+\eta)ds},\ a \in [a_p, A_q^U],\ q \in \{s, r\},\\
\sigma_{q3}^U(a) &= e^{-\int_{A_q^U}^a (m+\mu_A)ds},\ a \in [A_q^U, D_q^U],\ q \in \{s, r\},\\
\sigma_{q1}^T(a) &= e^{-\int_{a_{ART}}^a (m+\mu_q^T+\delta_q^T)ds},\ a \in [a_{ART}, A_q^T],\ q \in \{s, r\},\\
\sigma_{q2}^T(a) &= e^{-\int_{A_q^T}^a (m+\mu_A)ds},\ a \in [A_q^T, D_q^T],\ q \in \{s, r\},
\end{aligned} \tag{2}$$

where δ_1 is the progression rate to the chronic stage and δ_q^U, δ_q^T ($q \in \{s, r\}$) are the progression rates to the AIDS stage for untreated and treated individuals.

Let F_q be the fraction of the untreated drug-sensitive population that receives treatment [2]. It is given by

$$F_q = \frac{\eta}{m + \mu_q^U + \delta_q^U + \eta}, q \in \{s, r\}. \tag{3}$$

Denote the transmission rate at the primary stage, chronic stage and AIDS stage for untreated drug-sensitive and drug-resistant individuals as $\beta_s^p, \beta_s^U, \beta_s^A$, and $\beta_r^p, \beta_r^U, \beta_r^A$, respectively. The transmission rate of a treated drug-sensitive (β_s^T) or drug-resistant (β_r^T) case is the infectivity of an untreated individual (β) multiplied by a constant, i.e., $\beta_s^T = \alpha_s \beta_s^U$ and $\beta_r^T = \alpha_r \beta_s^U$ where $\alpha_s \leq \alpha_r$, i.e., the first-line drug effectiveness $1 - \alpha_s$ is greater than the second-line drug effectiveness $1 - \alpha_r$.

Patients starting ART with higher baseline CD4 counts had longer life expectancies [4,6–13]. The relationship between prior-treatment CD4+ count and infection age shown in Fig. 1(B) in [14] also suggested that a higher CD4+ count corresponded to an earlier infection stage. Thus, the earlier ART starts, the longer the patient is expected to live and vice versa. Similar to the assumption in [4], we assume that the duration from treatment initiation to death for treated individuals is a linear decreasing function of ART initiation timing a_{ART} as follows (see figure S3):

$$L_q^T = L_q^0 - \xi_q^T a_{ART},\ q \in \{s, r\}, \tag{4}$$

where L_q^0 is the average maximum expectancies for those who are treated immediately after infection (i.e.,$a_{ART} = 0$) and ξ_q^T is the slope. Therefore, we have

$$D_q^T = a_{ART} + L_q^T, A_q^T = D_q^T - d_A,\ q \in \{s, r\}. \tag{5}$$

We develop the complete dynamical model as follows

$$
\begin{cases}
\dfrac{dS(t)}{dt} = b - mS(t) - \dfrac{S(t)}{N(t)} \displaystyle\sum_{q\in\{s,r\}} \left(\int_0^{a_p} \beta_q^p i_{q1}^U(a,t)da + \int_{a_p}^{A_q^U} \beta_q^U i_{q2}^U(a,t)da + \int_{A_q^U}^{D_q^U} \beta_q^A i_{q3}^U(a,t)da \right. \\
\qquad \left. + \displaystyle\int_{a_{ART}}^{A_q^T} \beta_q^T i_{q1}^T(a,t)da + \int_{A_q^T}^{D_q^T} \beta_q^A i_{q2}^T(a,t)da \right), \\
\dfrac{\partial i_{q1}^U(a,t)}{\partial t} + \dfrac{\partial i_{q1}^U(a,t)}{\partial a} = -(m+\delta_1) i_{q1}^U(a,t), \quad 0 < a \le a_p, \ q \in \{s,r\}, \\
\dfrac{\partial i_{q2}^U(a,t)}{\partial t} + \dfrac{\partial i_{q2}^U(a,t)}{\partial a} = -(m+\mu_q^U+\delta_q^U+\eta) i_{q2}^U(a,t), \quad a_p < a \le A_q^U, \ q \in \{s,r\}, \\
\dfrac{\partial i_{q3}^U(a,t)}{\partial t} + \dfrac{\partial i_{q3}^U(a,t)}{\partial a} = -(m+\mu_A) i_{q3}^U(a,t), \quad A_q^U < a \le D_q^U, \ q \in \{s,r\}, \\
\dfrac{\partial i_{q1}^T(a,t)}{\partial t} + \dfrac{\partial i_{q1}^T(a,t)}{\partial a} = -(m+\mu_q^T+\delta_q^T) i_{q1}^T(a,t), \ a_{ART} < a \le A_q^T, \ q \in \{s,r\}, \\
\dfrac{\partial i_{q2}^T(a,t)}{\partial t} + \dfrac{\partial i_{q2}^T(a,t)}{\partial a} = -(m+\mu_A) i_{q2}^T(a,t), \ A_q^T < a \le D_q^T, \ q \in \{s,r\}, \\
i_{q1}^U(0,t) = \dfrac{S(t)}{N(t)} \left(\displaystyle\int_0^{a_p} \beta_q^p i_{q1}^U(a,t)da + \int_{a_p}^{A_q^U} \beta_q^U i_{q2}^U(a,t)da + \int_{A_q^U}^{D_q^U} \beta_q^A i_{q3}^U(a,t)da \right. \\
\qquad \left. + \displaystyle\int_{a_{ART}}^{A_q^T} \beta_q^T i_{q1}^T(a,t)da + \int_{A_q^T}^{D_q^T} \beta_q^A i_{q2}^T(a,t)da \right), \ q \in \{s,r\}, \\
i_{q2}^U(a_p,t) = \displaystyle\int_0^{a_p} \delta_1 i_{q1}^U(a,t)da, \ q \in \{s,r\}, \\
i_{q3}^U(A_q^U,t) = \displaystyle\int_{a_p}^{A_q^U} \delta_q^U i_{q2}^U(a,t)da, \ q \in \{s,r\}, \\
i_{s1}^T(a_{ART},t) = (1-f_r) \displaystyle\int_{a_p}^{A_s^U} \eta i_{s2}^U(a,t)da, \\
i_{r1}^T(a_{ART},t) = f_r \displaystyle\int_{a_p}^{A_s^U} \eta i_{s2}^U(a,t)da + \int_{a_p}^{A_r^U} \eta i_{r2}^U(a,t)da, \\
i_{q2}^T(A_q^T,t) = \displaystyle\int_{a_{ART}}^{A_q^T} \delta_q^T i_{q1}^T(a,t)da, \ q \in \{s,r\}, \\
S(0) = S_0 \ge 0, i_{qj}^U(a,0) = i_{qj0}^U(a), j = 1,2,3, q \in \{s,r\}; i_{q1}^T(a,0) = i_{q10}^T(a), i_{q2}^T(a,0) = i_{q20}^T(a), q \in \{s,r\}.
\end{cases} \tag{6}
$$

where $i_{q10}^U(a) \in L_+^1(0,a_p), i_{q20}^U(a) \in L_+^1(a_p,A_q^U), i_{q30}^U(a) \in L_+^1(A_q^U,D_q^U), i_{q10}^T(a) \in L_+^1(a_{ART},A_q^T), i_{q20}^T(a) \in L_+^1(A_q^T,D_q^T), q \in \{s,r\}$. Here L_+^1 is the space of functions that are nonnegative and Lebesgue integrable over the specified interval.

The number of persons living with HIV/AIDS at any time t is given by

$$
I_{total}(t) = \sum_{q\in\{s,r\}} \left(\sum_{j=1}^{3} I_{qj}^U(t) + I_{q1}^T(t) + I_{q2}^T(t) \right). \tag{7}
$$

The total population size at any time t is given by

$$
N(t) = S(t) + I_{total}(t). \tag{8}
$$

The HIV prevalence at any time t is given by

$$
Prevalence(t) = \frac{I_{total}(t)}{N(t)}. \tag{9}
$$

Notice that we keep track of the numbers of newly diagnosed AIDS cases and AIDS deaths at time t using the following equations:

$$\begin{aligned} Cases(t) &= \sum_{q\in\{s,r\}} \left(\int_{a_p}^{A_q^U} \delta_q^U i_{q2}^U(a,t)da + \int_{a_{ART}}^{A_q^T} \delta_q^T i_{q1}^T(a,t)da \right), \\ Deaths(t) &= \sum_{q\in\{s,r\}} \left(\int_{A_q^U}^{D_q^U} \mu_A i_{q3}^U(a,t)da + \int_{A_q^T}^{D_q^T} \mu_A i_{q2}^T(a,t)da \right). \end{aligned} \tag{10}$$

The prevalence of transmitted drug resistance (TDR) among newly infected individuals (the fraction of new infections that are drug resistant) at any time t is given by

$$TDR(t) = \frac{i_{r1}^U(0,t)}{i_{s1}^U(0,t) + i_{r1}^U(0,t)}. \tag{11}$$

The number of total new HIV infections that occur in the entire population over the time horizon T ($T = 20$ years in this paper, i.e., from 2018 to 2038) is calculated by

$$\text{Total new infecions over } T \text{ years} = \int_0^T (i_{s1}^U(0,t) + i_{r1}^U(0,t))dt, \tag{12}$$

and the number of new drug-resistant infections over T years is calculated by

$$\text{New drug-resistant infecions over } T \text{ years} = \int_0^T i_{r1}^U(0,t)dt. \tag{13}$$

2 Parameter estimation

We obtained data of the annual newly diagnosed AIDS cases and AIDS deaths from 1980 to 2014 in MSM population in San Francisco from the Department of Public Health HIV Epidemiology Section. Using the maximum likelihood estimation, we fit the model to the data between 1980 and 1995 to estimate the prior-treatment parameters (figure 1a in the main text): the recruitment rate of susceptible MSM is $b = 4000$ (95%CI:2295-5705) per year, the disease-induced death rate at the chronic stage for untreated drug-sensitive individuals is $\mu_s^U = 0.28$ (95%CI:0.18-0.39) per year, and the transmission rate in this stage is $\beta_s^U = 0.62$ (95%CI:0.57-0.68) per year. The estimation of the transmission rate is the same as the value of 0.62 shown in [15] for MSM in San Francisco.

The values of other parameters are given as follows. The initial MSM population size is chosen as 69122 [16,17]. The expected duration of a sexual career in San Francisco is assumed to be about 47 years (age 18-65) as in [18]. Thus, we have the removal rate $m = 1/47 = 0.021$ per year. For untreated drug-sensitive individuals, we choose the duration of the primary stage as $a_p = 1.7$ months [19], the duration of the chronic stage as $d_c = 7.5$ years [20], and the duration of the AIDS stage as $d_A = 1.2$ years (12 months to 20 months in [21]). Thus, we obtain the rate of progression to the asymptomatic stage is $\delta_1 = 1/a_p = 1/(1.7/12) = 7.06$ per year. Similarly, we have the rate of progression to the AIDS stage is $\delta_s^U = 1/d_c = 1/7.5 = 0.13$ per year and the disease-induced death rate in the AIDS stage is $\mu_A = 1/d_A = 1/1.2 = 0.83$ per year. We assume the chronic stage d_r for untreated drug-resistant cases is 25% longer than untreated drug-sensitive cases, i.e., $d_r = 1.25d_c = 9.38$ years, then the progression rate to the AIDS stage is $\delta_r^U = 1/d_r = 1/9.38 = 0.11$ per year. The transmission rates in the primary stage and AIDS stage are assumed to be 5.3 and 7 times more infectious than during chronic infection, respectively, i.e., $\beta_s^p = 5.3\beta_s^U, \beta_r^p = 5.3\beta_r^U$ [19] and $\beta_s^A = 7\beta_s^U, \beta_r^A = 7\beta_r^U$ [22] (see figures S4-S5). Here we assume all infected

individuals are initially infected with drug-sensitive strains, so there are only susceptible compartment and untreated drug-sensitive individuals at different infection stages at the beginning of the epidemic (1980-1995).

We used the data from 1996 to 2006 (because ART was widely available after 1995 [23]) to estimate treatment-related parameters. The treatment rate is estimated as $\eta = 0.38$ (95%CI:0.08-0.81) per year, i.e., the average time from infection to ART initiation is $a_{ART} = 2.8$ years according to the relationship $\eta = 1/(a_{ART} - a_p)$. The fraction of treated gay men in San Francisco is calculated as $F_s = 46.4\%$ (95%CI:15.3%-64.9%) based on Eq. (3), which is close to the fraction in [2] where about 50% of HIV-infected MSM take ART. The disease-induced death rate in the post-treatment chronic stage is estimated as $\mu_s^T = 0.05$ per year (95%CI:0.01-0.27) for drug-sensitive individuals and $\mu_r^T = 1.75\mu_s^T = 0.088$ per year for drug-resistant individuals [24]. In this fitting process, we chose a bigger recruitment rate $b = 5600$ per year to yield simulated prevalence, total infected individuals and population size simultaneously consistent with the prevalence data [25–35] (figure 1b in the main text), persons living with HIV/AIDS data [18, 30, 33, 36–38] and total MSM population size data [16, 17, 29, 30, 39–41] respectively as closely as possible, which we did not fit directly (see figure 1b in the main text and figure S6). We also chose the relative transmissibility for treated drug-resistant individuals ($\beta_r^T = 0.2\beta_s^U$, i.e, the baseline second-line drug effectiveness was estimated as 80%) to match the prevalence data of transmitted drug resistance [42–48] (figure 1c in the main text) under the assumption that the transmission rate for untreated drug-resistant individuals β_r^U was the average of that for treated drug-resistant β_r^T and untreated drug-sensitive individuals β_s^U based on their relationship $\beta_s^U > \beta_r^U > \beta_r^T$ [2], i.e., $\beta_r^U = (\beta_r^T + \beta_s^U)/2 = 0.6\beta_s^U$. The fraction of treated cases that are drug resistant is chosen as $f_r = 25\%$ (33% of MSM are virally unsuppressed [18] and of which 76% have drug resistance [49]). The result of the HPTN 052 clinical trial [50, 51] showed that treatment led to 96% reduction in infectivity. Thus, the transmission rate in treated individuals without drug resistance is only 4% as transmissible as HIV positives not receiving ART ($\beta_s^T = 0.04\beta_s^U$).

After 2006, San Francisco had name-based HIV reporting and incorporated monitoring initial primary care visit into standard HIV public health investigation for newly diagnosed cases which improved the treatment rate and shortened the time to entry into HIV medical care [52]. So we used the data from 2006 to 2014 to estimate the growing treatment rate $\eta = 0.7$ per year and earlier ART initiating timing $a_{ART} = 1.6$ years. All the other parameters are fixed in Table S1.

Next, we derive the relationship between extended life expectancies and infection age shown in figure S3a. It can be seen from [11, 13] that suppressed patients (HIV-1 RNA $\leq$ 400 copies/ml) who had CD4+ count < 200 or ≥ 350 cells/mm^3 at ART start can live mean 30 or 45 years after treatment, respectively. In addition, Fig. 1(B) in [14] shows that CD4+ count decreases with time since infection (infection age). Specifically, CD4+ count < 200 and ≥ 350 cells/mm^3 correspond to the infection age of 7-9 years and 0-6 years, respectively. We chose the average infection age 8 years and 3 years for CD4+ count < 200 and ≥ 350 cells/mm^3, respectively. Therefore, if an infected individual is treated at 8 years post-infection with viral suppression, then he would live 30 years. However, if the treatment begins at 3 years, he would live 45 years. According to the assumed linear decreasing relationship Eq. (4) between the average duration L_s^T from ART initiation to death for suppressed individuals and ART initiation timing a_{ART} (blue line in figure S3a), we obtain

$$L_s^T - 45 = \frac{30-45}{3-8}(a_{ART} - 3), \text{ i.e., } L_s^T = 54 - 3a_{ART}.$$

This implies that there would be 3 years longer to live if ART had started one year earlier. The unsuppressed

individuals (HIV-1 RNA $>$ 400 copies/ml) will take 11 years off life expectancy than treated suppressed individuals [11, 13]. Thus, if an infected individual is treated at 8 and 3 years post-infection without viral suppression, then he can live 19 and 34 years, respectively. Similarly, we have the relationship between the average duration L_r^T from ART initiation to death for unsuppressed individuals and ART initiation timing a_{ART} (red line in figure S3a) as follows

$$L_r^T - 34 = \frac{19-34}{3-8}(a_{ART} - 3), \text{ i.e., } L_r^T = 43 - 3a_{ART}.$$

When $a_{ART} = 2.8$ before 2006, we have $L_s^T = 45.6$ and $L_r^T = 34.6$. When $a_{ART} = 1.6$ after 2006, we have $L_s^T = 49.2$ and $L_r^T = 38.2$. Notice that 76% of treatment-failed patients have resistance to one or more antiretroviral drugs [49]. Therefore, we assume that the above relationships between the extended life expectancy and ART initiating timing for unsuppressed and suppressed patients still hold for treated individuals who do or do not develop drug resistance.

3 Supplementary figures and table

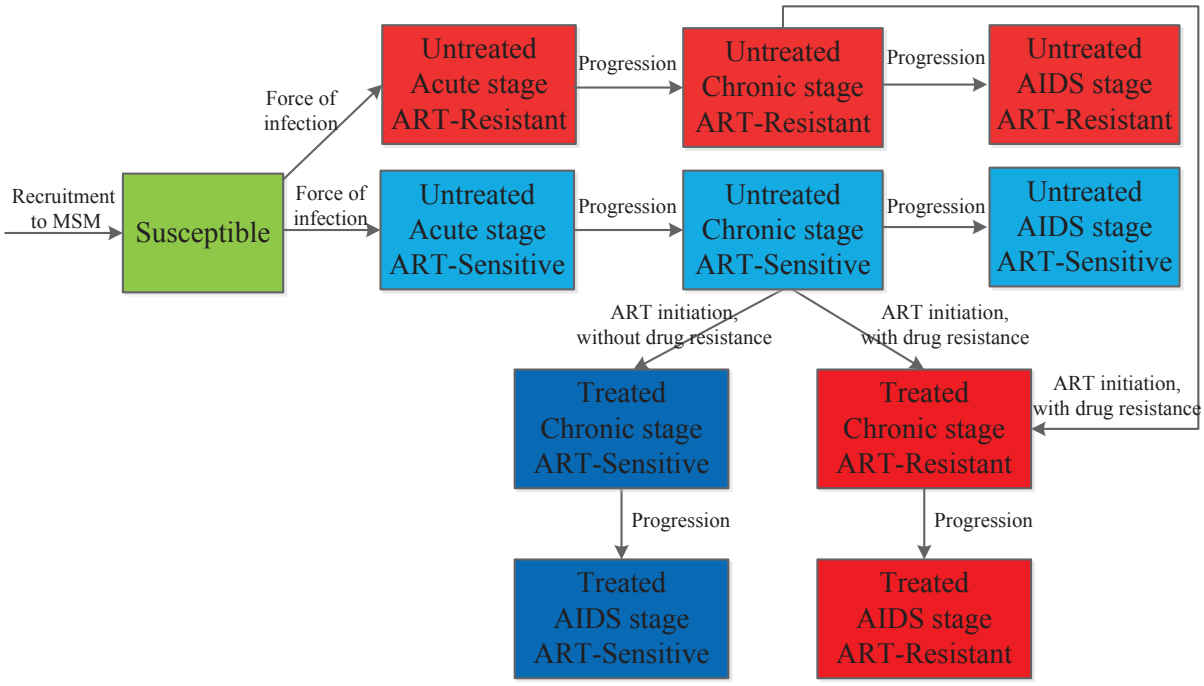

Figure S1: A schematic flow diagram illustrating the transmission dynamics of an HIV epidemic with transmitted and acquired drug resistance. For clarity, removal rates (including disease-induced death rate and the rate of changing behavior) are not shown. See figure S2 for mathematical descriptions about the model flow diagram. ART, antiretroviral therapy; MSM, men who have sex with men.

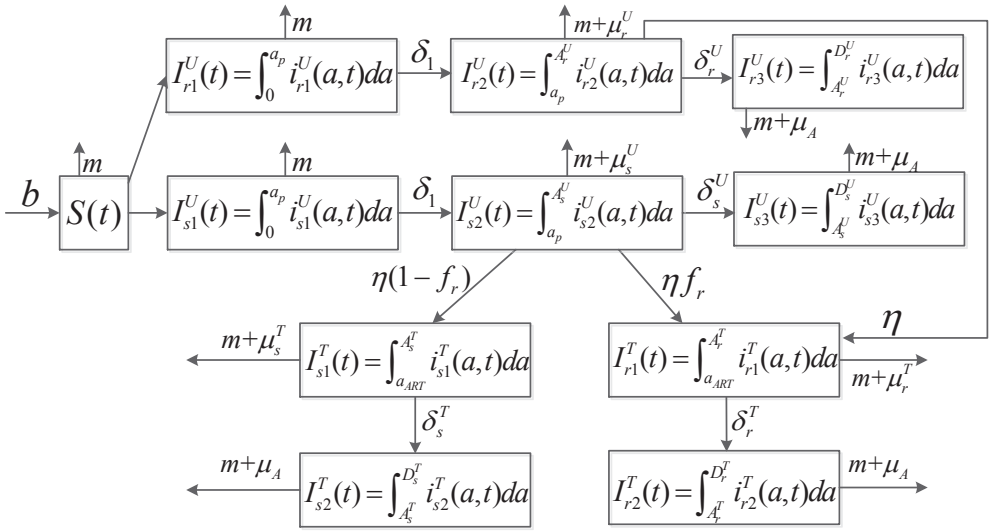

Figure S2: A full flow diagram illustrating the between-host transmission dynamics of an HIV epidemic in the presence of acquired and transmitted drug resistance for model (6). See figure S1 for detailed description of the corresponding classes.

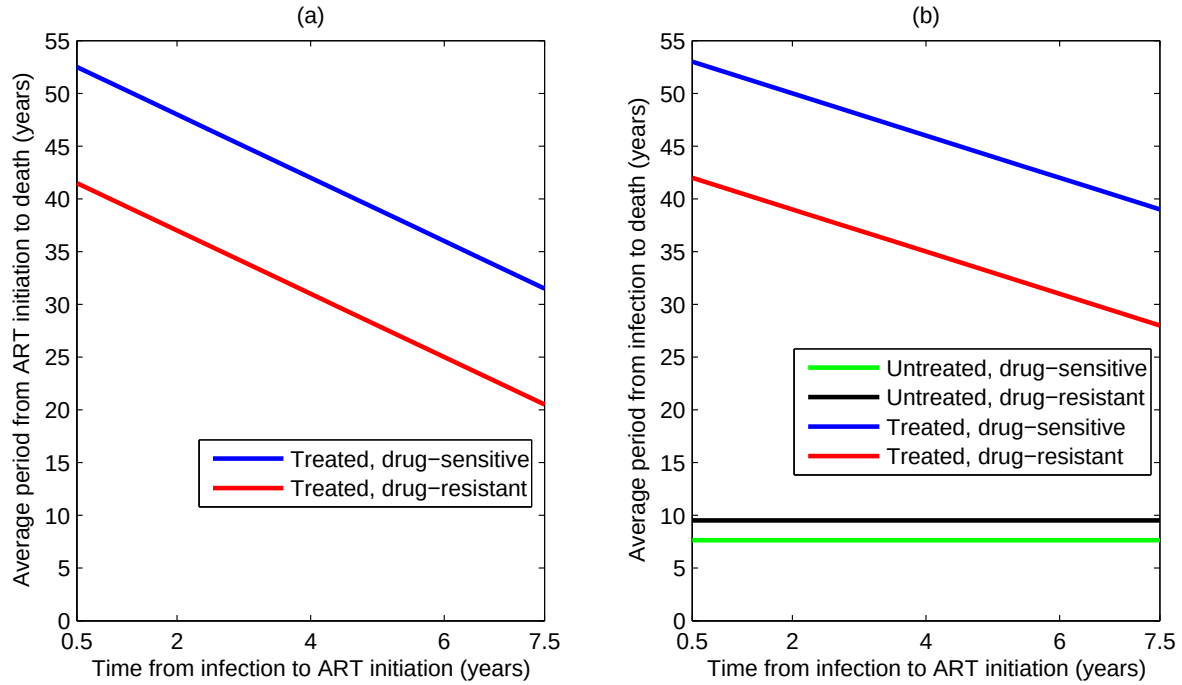

Figure S3: Average durations from ART initiation to death (a) and from infection to death (b) are assumed to be a linear decreasing function of time from infection to ART initiation for treated drug-sensitive cases (blue lines) and for treated drug-resistant cases (red lines). This assumption is based on the relationship that CD4+ count decreases with time since infection (infection age) as shown in Fig. 1(B) in [14] and the relationship that longer extended life expectancies correspond to higher CD4+ count at start of ART with or without drug resistance [11,13]. Therefore, we derive the relationship between extended life expectancies and ART initiation timing as shown in sub-figure (a). This similar relationship between survival and timing of ART initiation was used in [4] in the absence of drug resistance. We assume the treated drug-resistant individuals will take 11 years off life expectancy than treated drug-sensitive individuals [11,13]. Green and black lines in sub-figure (b) denote the lifespans of untreated individuals with drug-sensitive and drug-resistant strains respectively, which do not change with the ART initiation timing. Here, untreated drug-resistant cases are assumed to survive longer than untreated drug-sensitive cases due to weaker replication capacity (lower viral load in the absence of drug pressure) and thus longer life expectancy [2,3] (see figure S4a and figure S5a). ART, antiretroviral therapy.

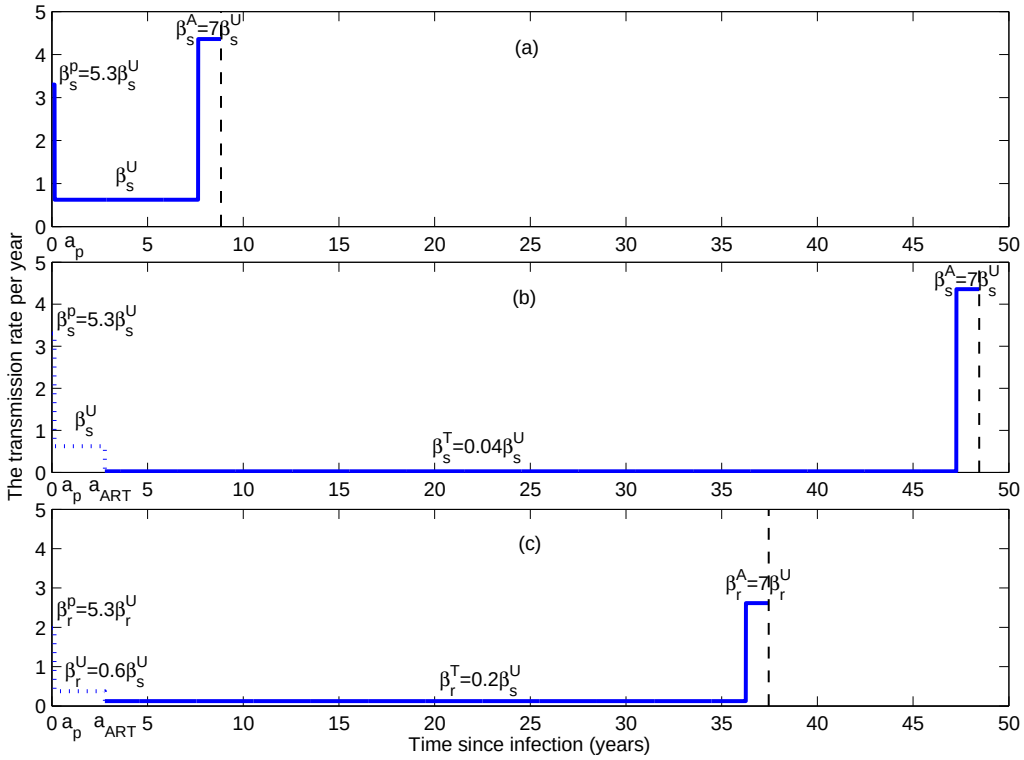

Figure S4: Assumed relationships between the annual HIV transmission rate and time since infection for untreated drug-sensitive cases (a), treated drug-sensitive cases (b) and treated drug-resistant cases (c). Here, a_p and a_{ART} denote the duration of primary stage and the ART initiating timing respectively. Vertical dashed line represents the time of death for each scenario. Primary infection (lasting for 1.7 months [19]) and AIDS infection (lasting for 1.2 years [21]) are assumed to be 5.3 and 7 times [19, 22] more infectious than chronic infection (without treatment) respectively for both drug-sensitive and drug-resistant individuals. In our baseline scenarios, we assumed that the transmission rate in treated drug-sensitive individuals (β_s^T) is only 4% as transmissible as HIV positives not receiving ART (first-line drug effectiveness is 96% [50, 51]) and that treated drug-resistant individuals are 80% less infectious than untreated drug-sensitive individuals based on the data of fraction of new drug-resistant infections (second-line drug effectiveness is 80%, estimated from figure 1c in the main text). The transmission rate for untreated drug-resistant individuals (β_r^U) is greater than that for treated drug-resistant individuals (β_r^T) but smaller than that for untreated drug-sensitive individuals (β_s^U), i.e., $\beta_s^U > \beta_r^U > \beta_r^T$ [2]. We assume β_r^U is the average of β_r^T and β_s^U ($\beta_r^U = (\beta_r^T + \beta_s^U)/2$) as the base case. We vary these transmission rates in sensitivity and uncertainty analyses. The treatment initiating time before 2006 is estimated as $a_{ART} = 2.8$ years on average, and the extended life expectancies after treatment are calculated as 45.6 years and 34.6 years for those treated drug-sensitive and drug-resistant cases respectively according to the relationship shown in figure S3a. For the case that ART averagely starts at 1.6 years post-infection after 2006, the similar plots can be obtained (not shown). ART, antiretroviral therapy.

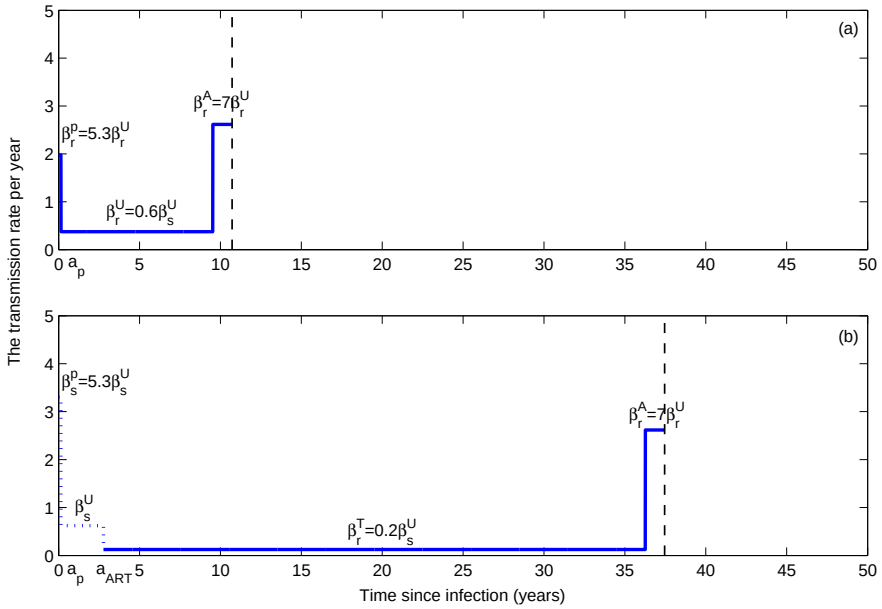

Figure S5: Assumed relationships between the annual HIV transmission rate and time since infection for untreated drug-resistant cases (a), and treated drug-resistant cases (b) which is different with figure S4c in that the individuals are first infected with drug-sensitive strain before ART initiation (dashed lines) and then become drug-resistant in the pressure of drug. All the other parameters and caption are the same as figure S4.

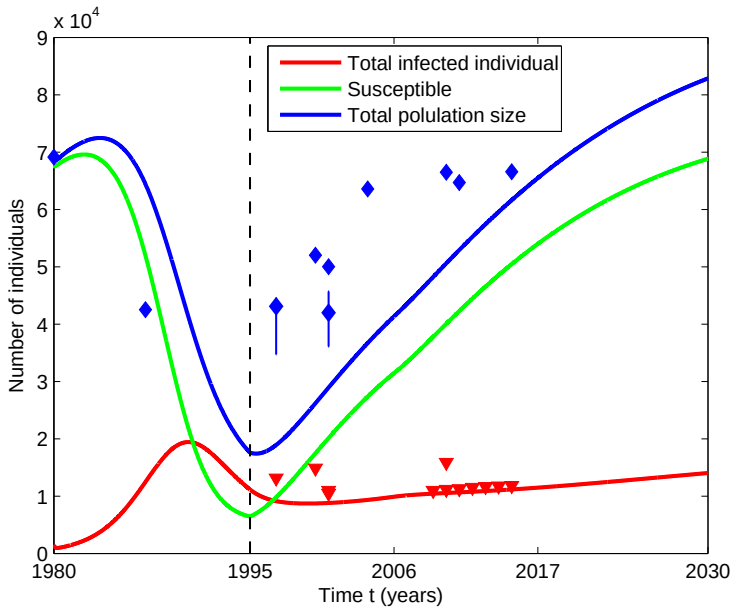

Figure S6: Comparing observed persons living with HIV/AIDS data (red triangles) [18, 30, 33, 36–38] and total MSM population size data (blue diamonds and 95% confidence interval if available) [16, 17, 29, 30, 39–41] with model simulation (lines).

Table S1: Parameters and values for simulation and data fitting

Parameter	Description	Baseline or estimated mean value	Source
a_p	The duration of the primary stage	1.7 months	[19]
d_c	The duration of the chronic stage (untreated, drug-sensitive)	7.5 years	[20]
d_r	The duration of the chronic stage (=1.25d_c, untreated, drug-resistant)	9.38 years	Assumed
d_A	The duration of the AIDS stage	1.2 years	[21]
b	Susceptible population admission rate	4000 per year before 1995 (95%CI:[2295,5705])	Fitted
		5600 per year after 1995	Chosen*
m	Removal rate due to changes in sexual behavior	0.021 per year	[18]
$N(0)$	Initial total MSM population size	69122	[16, 17]
μ_s^U	The disease-induced death rate at the chronic stage (untreated, drug-sensitive)	0.28 per year (95%CI:[0.18,0.39])	Fitted
μ_A	The disease-induced death rate at the AIDS stage (=1/d_A)	0.83 per year	Calculated
δ_1	Rate of progression to the chronic stage (=1/a_p)	7.06 per year	Calculated
δ_s^U	Rate of progression to the AIDS stage for untreated drug-sensitive individuals (=1/d_c)	0.13 per year	Calculated
δ_r^U	Rate of progression to the AIDS stage for untreated drug-resistant individuals (=1/d_r)	0.11 per year	Calculated
β_s^U	The transmission rate at the chronic stage (untreated, drug-sensitive)	0.62 per year (95%CI:[0.57,0.68])	Fitted
β_s^p	The transmission rate at the primary stage (untreated, drug-sensitive)	$5.3\beta_s^U$	[19]
β_s^A	The transmission rate at the AIDS stage (drug-sensitive)	$7\beta_s^U$	[22]
β_s^T	The transmission rate in the post-treatment chronic stage (drug-sensitive)	$0.04\beta_s^U$	[50, 51]
β_r^T	The transmission rate in the post-treatment chronic stage (drug-resistant)	$0.2\beta_s^U$	Chosen†
β_r^U	The transmission rate at the chronic stage (=$(\beta_s^U + \beta_r^T)/2$, untreated, drug-resistant)	$0.6\beta_s^U$	Assumed
β_r^p	The transmission rate at the primary stage (untreated, drug-resistant)	$5.3\beta_r^U$	[19]
β_r^A	The transmission rate at the AIDS stage (drug-resistant)	$7\beta_r^U$	[22]
η	The treatment rate	0.38 per year before 2006 (95%CI:[0.08,0.81])	Fitted
		0.7 per year after 2006 (95%CI:[0.68,0.71])	Fitted
a_{ART}	The average time from infection to ART initiation	2.8 years before 2006	Appendix
		1.6 years after 2006	
L_s^T	The post-treatment extended life expectancy for drug-sensitive cases	45.6 years before 2006	Appendix
		49.2 years after 2006	
L_r^T	The post-treatment extended life expectancy for drug-resistant cases	34.6 years before 2006	Appendix
		38.2 years after 2006	
δ_s^T	Rate of progression to the AIDS stage for treated drug-sensitive individuals (=1/($L_s^T - d_A$))	0.022 per year before 2006	Calculated
		0.020 per year after 2006	
δ_r^T	Rate of progression to the AIDS stage for treated drug-resistant individuals (=1/($L_r^T - d_A$))	0.029 per year before 2006	Calculated
		0.026 per year after 2006	
μ_s^T	The disease-induced death rate in the post-treatment chronic stage (drug-sensitive)	0.05 per year (95%CI:[0.01,0.27])	Fitted
μ_r^T	The disease-induced death rate in the post-treatment chronic stage (drug-resistant)	$1.75\mu_s^T$	[24]
f_r	The fraction of acquired drug resistance	0.25	[18, 49]

Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

* The recruitment rate after 1995 was chosen to match the data on prevalence, persons living with HIV/AIDS and total MSM population size.

† The transmission rate of treated drug-resistant individuals was chosen to match the data on proportion of new infections with drug-resistant strains.

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