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

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Abstract

Early initiation of antiretroviral therapy (ART) reduces the risk of drug-sensitive HIV transmission but may increase the transmission of drug-resistant HIV. We used a mathematical model to estimate the long-term population-level benefits of ART and determine the scenarios under which earlier ART (treatment at 1 year post-infection, on average) could decrease simultaneously both total and drug-resistant HIV incidence (new infections). We constructed an infection-age-structured mathematical model that tracked the transmission rates over the course of infection and modeled the patients' life expectancy as a function of ART initiation timing. We fitted this model to the annual AIDS incidence and death data directly, and to resistance data and demographic data indirectly among men who have sex with men (MSM) in San Francisco. Using counterfactual scenarios, we assessed the impact on total and drug-resistant HIV incidence of ART initiation timing, frequency of acquired drug resistance, and second-line drug effectiveness (defined as the combination of resistance monitoring, biomedical drug efficacy, and adherence). Earlier ART initiation could decrease the number of both total and drug-resistant HIV incidence when the second-line drug effectiveness is sufficiently high (>80%), but increase the proportion of new infections that are drug resistant. Thus, resistance may paradoxically appear to be increasing while actually decreasing.

Keywords. Early ART initiation; transmission of drug-resistant HIV; acquired drug resistance; second-line drug effectiveness; mathematical model.

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1. Introduction

Since 1995, antiretroviral therapy (ART) has substantially decreased HIV-related morbidity and mortality, and dramatically increased both the quality of life and life expectancy of persons living with HIV/AIDS [1–10]. However, the optimal timing of initiation has long been debated [11–14]. The World Health Organization (WHO) recommended CD4+ count threshold for starting ART has increased from ≤ 200 cells/mm^3 in 2006 [11], to ≤ 350 cells/mm^3 in 2010 [12], to ≤ 500 cells/mm^3 in 2013 [13], and to initiate ART among all adults living with HIV at any CD4 cell count in 2016 [14] based on latest randomized controlled trials [15,16]. San Francisco has been an early adopter of higher CD4 thresholds for ART initiation, consistently using more aggressive thresholds than those from contemporaneous WHO guidelines. In particular, in 2010 San Fransisco was one of the first areas that implemented immediate ART initiation upon HIV diagnosis regardless of CD4 cell count [17, 18]. Early initiation has been effective as demonstrated by the swift increase in observed CD4 count at ART initiation [19], with the proportion of patients on treatment increasing from 77% in 2010 [17] to 92% in 2015 [19] among persons exhibiting CD4 count between 351-500 cells/mm^3, and from 57% in 2010 [17] to 80% in 2015 [19] among persons with CD4 count above 500 cells/mm^3. Here, we aim to explore the effect of ramping up the 'test and treat' strategy to achieve even earlier ART initiation in San Francisco, focusing in particular on identifying the intensity of second-line drug effectiveness (defined as the combination of resistance monitoring, biomedical drug efficacy, and adherence) needed to prevent increasing the incidence (new infections) of drug-resistant HIV.

Despite mounting evidence for the clinical benefits of early ART initiation for both individual and public health [15,16,20–22], there exists the concern that early ART initiation may lead to the accumulated exposure to toxic drugs and early emergence of drug resistance which not only limits treatment options for a particular patient especially in resource-limited countries [23,24] but also can be transmitted to newly infected individuals causing early therapy failure in treatment-naive patients [25]. For resource-rich settings like San Francisco, second and third line regimens are available and the threat of drug resistance to patients' prognoses may be not as great as in low-income settings. However, data from San Francisco [26–32] suggests that the prevalence of transmitted drug resistance among newly infected individuals continues to remain relatively high (10-24%) [32] after a long history of ART implementation. Therefore, it is very important to consider the dynamics of acquired and transmitted resistance when examining the effectiveness of intensifying the 'test and treat' strategy by considering more frequent testing and, consequently, earlier ART initiation timing.

Mathematical models have been used to investigate the effect of expanding ART on HIV epidemic among men who have sex with men (MSM) in San Francisco [18,33–38]. Charlebois et al. [18] found that the 'test-and-treat'

strategy could decrease overall new infections by 81% without considering drug resistance. Blower et al. [33–38] studied the impact of expanding ART coverage in the presence of transmitted and acquired drug resistance and showed that expanding ART coverage can substantially reduce the overall HIV incidence whilst simultaneously increase the incidence of drug-resistant strains. Nichols et al. had similar findings in a modeling study [39] but demonstrated that early ART initiation (CD4 count <500 cells/mm^3) still averted more total new HIV infections than drug-resistant cases gained in East Africa. However, very few studies considered what scenarios can allow earlier ART initiation to decrease both total and drug-resistant HIV incidence. Indeed, this has already been observed in British Columbia, Canada, where ART scale-up has been implemented aggressively [40, 41].

In this study, we assessed the requirements for earlier ART initiation to simultaneously reduce overall and drug-resistant HIV incidence. We fitted an infection-age-structured transmission model (using partial differential equations) to epidemiological data among MSM in San Francisco. We first fitted the model directly to annual AIDS cases and AIDS deaths data that are routinely recorded by the San Francisco Department of Public Health HIV Epidemiology Section, using maximum likelihood estimation to estimate the recruitment rate for 1980-1995, the treatment rate, the transmission rate and disease-induced death rate. We then chose a second recruitment rate (i.e. post-1995) and the second-line drug effectiveness parameters by visually matching (indirect fit) this fitted model to a variety of published data after 1995 on the HIV prevalence [42–52], the fraction of drug-resistant cases among newly infected individuals [26–32], the number of persons living with HIV/AIDS [19, 47, 50, 53–55], and total MSM population size [46, 47, 56–60]. A novelty of our model over previous work [18, 33–39] is that it tracks life expectancy for different ART initiation times for both drug-sensitive and drug-resistant cases based on updated survival data [9, 61] (a similar assumption was used in [62] but only for treated drug-sensitive individuals). With this model, we used counterfactual simulations to identify drug resistant scenarios (i.e., the second-line drug effectiveness and the frequency of acquired drug resistance) that might render earlier ART initiation beneficial to decrease both overall and drug-resistant incidence.

2. Methods

(a) Model outline

To investigate the impact of ART initiation timing on HIV-1 spread among an MSM population (aged 18 to 65 years [19]) in the presence of both transmitted (primary) drug resistance and acquired (secondary) drug resistance [33–35, 37, 38] , we developed a novel HIV transmission model that tracked the infection age (time

since infection) [62–64] of each infected individual (described in detail in the electronic supplementary material). We divided the population into eleven classes (see electronic supplementary material, figure S1-S2): susceptible individuals, untreated individuals infected with drug-sensitive or drug-resistant strains at the primary stage, chronic stage and AIDS stage, treated individuals infected with either drug-sensitive or drug-resistant strains at the chronic and AIDS stages. In our modeling framework, the treated drug-resistant individuals who experience first-line treatment failure are assumed to be maintained on second-line (or subsequent lines) therapy through life with successful viral suppression and still stay in the same class (treated resistant class). The second-line drug effectiveness depends on a variety of factors such as resistance monitoring, biomedical drug efficacy, adherence. For simplicity, we model all these factors by a single measure–drug effectiveness.

We assumed that earlier ART initiation post-infection conferred longer life expectancy [3–6, 8–10, 62] (shown in electronic supplementary material, figure S3). We parameterized this relationship based on CD4+ cell count trajectories after infection as shown in Fig. 1(B) in [65] and on the positive correlation between life expectancy at age 35 and CD4+ count at ART initiation [9, 61]. We derived this relationship (see the electronic supplementary material for more detail, the similar relationship between survival and ART initiation timing has been used in [62] but it didn't consider drug resistance) for treated drug-sensitive and drug-resistant individuals by using life expectancy data stratified by the absence or presence of viral suppression (i.e. treatment failure or success) [9,61], respectively, based on the assumption that treatment failure could serve as a proxy for resistance. For instance, Richman et al. [66] found that 76% of patients with treatment failures in US were due to resistance to one or more antiretroviral drugs. The finding in [9, 61] that unsuppressed patients have life expectancies 11 years shorter than suppressed patients underlies our assumed differences in life expectancies between treated patients with and without drug resistance. It is assumed that 25% of treated MSM in San Francisco (33% of MSM are virally unsuppressed [19] and of which 76% have drug resistance [66]) have acquired drug resistance in the base case, lying in the range of 20% in San Diego [67] and 48% in US [66], and that all of these drug-resistant cases use second-line drugs. We varied this fraction of acquired drug resistance in San Francisco from 0 to 100% and the shortened lifespan for treated drug-resistant cases relative to treated drug-sensitive cases from 0 to 20 years in the sensitivity analyses.

We assumed a 7.5-year chronic stage [68] in the absence of treatment for drug-sensitive individuals, with a constant transmission rate β_s^U (the 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)), and a 1.7-month primary and 1.2-year AIDS stage with transmission rates 5.3- and 7-fold greater than the chronic

stage, respectively [69–71] (see electronic supplementary material, figure S4-S5). Untreated drug-resistant cases were assumed to have a 25% longer chronic stage than untreated drug-sensitive cases due to weaker viral replication capacity (lower viral load in the absence of drug pressure) and thus longer life expectancy [33, 72]. We assumed that the duration of the primary and AIDS stages did not differ with or without treatment and resistance, as in [62, 64], but instead let treatment and resistance affect the duration of the chronic stage. We assumed that treatment, in the absence of acquired drug resistance, led to a 96% (first-line drug effectiveness) reduction in infectivity from the chronic phase, based on the results of the HPTN 052 clinical trial [20, 73].

(b) Model calibration

Before analyzing the consequences of transmitted and acquired drug resistance, we fitted our model to a well-characterized epidemic to ensure a realistic baseline scenario. Specifically, we obtained data on the annual incidence of newly diagnosed AIDS cases and AIDS deaths from 1980 to 2014 among MSM in San Francisco from the San Francisco Department of Public Health HIV Epidemiology Section. We assumed a Poisson observation model for the data around our deterministic transmission model (figure 1a). We fitted the model to data from the pre-ART period (1980-1995) to estimate the recruitment rate b, the transmission rate β_s^U and the disease-related death rate μ_s^U at the chronic stage before widespread ART using maximum likelihood estimation. Here we assumed 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).

Fixing the above two parameters β_s^U and μ_s^U and assuming the untreated drug-resistant individuals have the same disease-related death rate $\mu_r^U = \mu_s^U$ as untreated drug-sensitive individuals at the chronic stage, we used maximum likelihood estimation to fit the post-1995 (1995-2006) data by estimating two parameters. The first estimated parameter is the treatment rate η. The estimated η during this time window corresponds to an average ART initiation timing $a_{ART} = 2.8$ years (the average time to initiation is equal to the inverse of the treatment rate; electronic supplementary material, figure S4-S5) for patients at the chronic stage. For example, if all infected individuals are assumed to be treated at an annual rate of 50%, then the average interval between infection and receipt of ART is two years [74]. The second parameter estimated in this time window is the disease-related death rate during the chronic stage μ_s^T for treated drug-sensitive individuals. The HIV-related death rate for treated drug-resistant individuals μ_r^T is assumed to be 1.75 times than that for treated drug-sensitive individuals [75], i.e., $\mu_r^T = 1.75\mu_s^T$. In this fitting process using maximum likelihood

estimation, we chose a bigger recruitment rate to yield simulated prevalence, total infected individuals and population size simultaneously consistent with the prevalence data [42–52] (figure 1b), persons living with HIV/AIDS data [19, 47, 50, 53–55] and total MSM population size data [46, 47, 56–60] respectively as closely as possible (electronic supplementary material, figure S6), which we did not fit directly. 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 among newly infected individuals [26–32] (figure 1c) 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 $\beta_s^U > \beta_r^U > \beta_r^T$ [33].

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 [76]. So we used the cases and deaths data from 2006 to 2014 to estimate the growing treatment rate and earlier ART initiating timing $a_{ART} = 1.6$ years using maximum likelihood estimation. The electronic supplementary material provides details of the model equations and calibration. Estimated parameter values and 95% confidence intervals (obtained by the Fisher information matrix) are listed in Table S1 in the electronic supplementary material. All analyses were carried out in the Matlab software.

(c) Sensitivity analysis

We used our validated epidemic model to predict the impact of a more aggressive 'test and treat' strategy (such as an intense program which leads to the average time from infection to ART initiation 1 year, called 'early ART'), compared with the current 1.6 years (late ART), on the cumulative number of total new infections and new drug-resistant infections over time (2018-2038) as shown in figure 2a-b. We examined the impact of varying resistance parameters across a wide range of values, including the second-line drug effectiveness, the fraction of acquired drug resistance and the shortened lifespan for treated drug-resistant individuals relative to the treated drug-sensitive individuals, on the ratios of cumulative number of total new infections (the sum of new infections with drug-sensitive and drug-resistant strains) after 20 years (early versus late ART, C^e_{Total}/C^l_{Total}) and new drug-resistant infections (early versus late ART, C^e_r/C^l_r) by one-way sensitivity analyses (figure 2c-d) while holding all the other parameters fixed (Table S1 in the electronic supplementary material). We also used two-way sensitivity analyses (figure 2e) to visualize the effect of the most two important resistance parameters

(based on the results of one-way sensitivity analyses) on the above two ratios (C^e_{Total}/C^l_{Total} and C^e_r/C^l_r).

(d) Latin Hypercube Uncertainty Analysis

We used our fitted model to explore the potential effects of early treatment on HIV transmission. Specifically, we performed an uncertainty analysis using Latin hypercube sampling (LHS) methods [77,78], in which we sampled multiple uncertain parameters (the second-line drug effectiveness, the fraction of acquired drug resistance and the shortened lifespan for treated drug-resistant individuals relative to the treated drug-sensitive individuals) from a wide range of plausible values while fixing all the other parameters at their baseline fixed or fitted values shown in Table S1 in the electronic supplementary material. For each of 1000 sampled parameter sets, we simulated an epidemic based on these parameter values (figure 3). This allowed us to assess the sensitivity of ratios (C^e_{Total}/C^l_{Total} and C^e_r/C^l_r) to key parameters across a wide range of values.

We assumed treatment had a multiplicative effect on infectivity, which differs between drug-sensitive (β^T_s) and drug-resistant (β^T_r) cases i.e., $\beta^T_s = \alpha_s\beta^U_s, \beta^T_r = \alpha_r\beta^U_s$. We fixed the baseline value of $\alpha_s = 4\%$ [20,73], and sampled α_r from a uniform distribution ranging from α_s to 100% (baseline value of 20%), under the assumption that treated cases with drug resistant strains are always more infectious than treated cases with drug susceptible strains ($\beta^T_r \geq \beta^T_s$) [33]. The second-line drug effectiveness ($1-\alpha_r$) was less than the first-line drug effectiveness ($1-\alpha_s = 96\%$). We also sampled the fraction of acquired drug resistance (f_r) uniformly in the range from 1% to 100% (baseline value of 25%), and the shortened lifespan for treated drug-resistant individuals relative to the treated drug-sensitive individuals from 0 to 20 years (baseline value of 11 years).

3. Results

(a) HIV transmission dynamics

Figure 1a shows the estimated epidemic curve along with observed incidence of diagnosed AIDS cases and deaths. Based on our parameter estimates (Table S1 in the electronic supplementary material), we estimate the cumulative number of averted AIDS cases, AIDS deaths, and new infections from 1995 to 2014 are 5788 (95%CI:5507-6069), 3543 (95%CI:3370-3716), and 18594 (95%CI:17513-19676), respectively.

We compared the projections of our model to a counterfactual scenario without ART (figure 1b) and found that our fitted model captured the decreasing and stable trend of the HIV epidemic after the introduction of ART. It is shown that ART could decrease the prevalence at the steady state by 63% (46% versus 17% for no

treatment versus treatment). The model did not provide a good fit to the prevalence data before 1995, perhaps because the prevalence data were obtained among sampling MSM population aged 25 to 55 years [42] while the AIDS diagnosis and death data were collected from a specific MSM cohort and the model-generated prevalence was for entire MSM population aged 18 to 65 years. Since the model fits much better during the post-1995 ART era, it is sufficiently robust for analyzing potential trade-offs of early ART.

Figure 1c shows that the proportion of new infections that are drug resistant among MSM in San Francisco has increased quickly since ART was widely used after 1995 and continued to increase after expanding ART use in 2006. This proportion is reaching 29% in 2017 and we predict it will increase gradually to 35% in 2030 (figure 1c). Our prediction is in accordance with the predicted value 35% (median value: interquartile range (IQR) 26-43%) in [79] although our model assumptions and interventions are different from [79], where Supervie et al. predicted the proportion of new infections due to resistant strains would reach the above value after a decade preexposure prophylaxis (PrEP) intervention among MSM in San Francisco in the absence of risk compensation.

(b) Effect of ART initiation timing on HIV transmission

Figures 2a and 2b show that early treatment (dashed lines) always reduces the expected cumulative number of both total new infections and new drug-resistant infections relative to late treatment (solid lines) in the base case (all other parameters are fixed in Table S1 in the electronic supplementary material), which is in accordance with the observed results in Canada [40, 41].

In one-way sensitivity analyses (figure 2c-d), we find that the second-line drug effectiveness is the most sensitive parameter to both the ratio of cumulative number of total new infections after 20 years (early versus late ART, $C^e_{Total}/C^l_{Total} = 0.74$ for the base case) and the ratio of cumulative number of new infections that are drug resistant (early versus late ART, $C^e_r/C^l_r = 0.94$ for the base case). Particularly, if the second-line drug effectiveness increases by 20% from the base value 80% to 96%, then the ratio C^e_{Total}/C^l_{Total} decreases by 13.51% from 0.74 to 0.64, and the ratio C^e_r/C^l_r decreases by 7.45% from 0.94 to 0.87. The ratio C^e_r/C^l_r is more likely to exceed one (figure 2d) than C^e_{Total}/C^l_{Total} (figure 2c) for low effectiveness of second-line drugs. Early ART always leads to lower level of both total incidence and drug-resistant incidence than late ART when the fraction of acquired drug resistance and the shortened lifespan for treated drug-resistant individuals relative to the treated drug-sensitive individuals vary across their respective possible ranges because the ratios C^e_{Total}/C^l_{Total} and C^e_r/C^l_r are always less than one when these two parameters vary.

Since the second-line drug effectiveness and the fraction of acquired drug resistance are the two most sensitive

parameters based on one-way sensitivity analyses results (figure 2c-d), we plotted two-way sensitivity analyses in figure 2e and found that early ART decreases both total incidence and drug-resistant incidence in the green region when the second-line drug effectiveness is higher than about 80%, decreases total incidence but increases drug-resistant incidence in the blue region when the second-line drug effectiveness lies between about 30% and 70%, increases both total incidence and drug-resistant incidence in the red region when the second-line drug effectiveness is lower than about 20%.

One interesting phenomenon is that although early ART decreases both total incidence and drug-resistant incidence as shown in the green region in figure 2e, it increases the proportion of new infections that are drug resistant (drug-resistant incidence/total incidence, i.e., C_r^e/C_{Total}^e for early ART and C_r^l/C_{Total}^l for late ART). For example, in the base case (black star in figure 2e), early ART decreases total incidence by 26% ($C_{Total}^e/C_{Total}^l = 0.74$ in figure 2c) and decreases drug-resistant incidence by 6% ($C_r^e/C_r^l = 0.94$ in figure 2d), but increases the proportion of new drug-resistant infections by 27% ($(C_r^e/C_{Total}^e)/(C_r^l/C_{Total}^l) = (C_r^e/C_r^l)/(C_{Total}^e/C_{Total}^l) = 1.27$). We call this phenomenon (the number of new infections with transmitted drug resistance decreases but the proportion of new infections caused by resistant strains increases) as the paradox of early ART. A similar paradox of preexposure prophylaxis (PrEP) on transmitted drug resistance (PrEP interventions increase the proportion of new infections with drug-resistant strains but actually decrease the number of new infections caused by resistant strains compared to without a PrEP intervention) was found in [79]. The mechanism for this paradox is that early ART leads to a reduction in new drug-resistant infections and a greater reduction in drug-sensitive new infections. Thus, there is a greater reduction in total new infections, resulting in an increase in the proportion of resistant infection.

Early ART also increases in the proportion of drug resistance amongst new infections in the following two cases: (1) early ART increases the incidence of drug-resistant infections while decreases the total incidence (blue region in figure 2e), and (2) early ART increases total incidence but disproportionately increases the incidence of infections that are drug-resistant (red region in figure 2e). In these two cases, it is a valid concern that early ART could increase the number of drug-resistant incidence and this concern should be particularly heightened in resource-constrained countries with limited second-line drug options. However, this concern is unfounded for the case when the above paradox occurs because early ART actually decreases the number of drug-resistant incidence. This suggests that we should be cautioned to differentiate these three different cases when all of them lead to an increase in the proportion of new drug-resistant infections but the number of drug-resistant incidence may increase or decrease.

(c) Uncertainty analysis

Figure 3 graphs the ratios of cumulative total new infections after 20 years (early versus late ART, C^e_{Total}/C^l_{Total}) and new drug-resistant infections (early versus late ART, C^e_r/C^l_r), as a function of the second-line drug effectiveness, the fraction of acquired drug resistance and the shortened lifespan for treated drug-resistant individuals relative to the treated drug-sensitive individuals. For example, if $C^e_{Total}/C^l_{Total} < 1$, then early ART results in less total new infections than late ART. If $C^e_r/C^l_r > 1$, then early ART causes more drug-resistant incidence than late ART, which occurs for low and moderate second-line drug effectiveness (<80%, red points in figure 3a). The ratio C^e_r/C^l_r (red points in figure 3a) is always greater than C^e_{Total}/C^l_{Total} (blue points in figure 3a), which means that early ART always increases the proportion of new infections that are drug resistant (the ratio of this proportion $(C^e_r/C^e_{Total})/(C^l_r/C^l_{Total})$ is always greater than 1) in the three regions in figure 2e (see the last subsection).

4. Discussion

In this study, we assessed the epidemiological consequences of ART timing on the transmission of HIV involving the acquired and transmitted drug resistance which may limit treatment options and cause early therapy failure in treatment-naive patients [23–25]. We found that early ART initiation can reduce both total and drug-resistant HIV incidence when the second-line drug effectiveness (combination of resistance monitoring, biomedical drug efficacy, and adherence) is sufficiently high (>80%) although it increases the proportion of new drug-resistant infections (green region in figure 2e). PrEP interventions have previously been shown, in an apparent paradox, to be able to increase the proportion of new infections with drug-resistant strains while actually decreasing the incidence of drug-resistant infections [79]. In a similar apparent paradox, we show here that early ART can appear to be increasing the amount of resistance (as measured by the proportion of new infections that are drug resistant), whilst actually decreasing resistance (as measured by the incidence of resistant infections), compared with late ART. Therefore, we strongly emphasize that caution must be paid to the empirical metrics being used to monitor drug resistance in a population, lest concerns centering around transmitted drug-resistance be misplaced. We recommend employing the *number* of incident drug-resistant infections [40, 41] to monitor drug resistance in the entire population versus in less smaller, representative cohort studies [26–32] when possible, rather than the *proportion* of new infections that are drug-resistant.

The primary innovation of our analysis compared with prior studies [18, 33–39] is the assumption that the life expectancies of treated drug-sensitive and drug-resistant individuals are dependent on ART initiating timing

(electronic supplementary material, figure S3) based on clinical results that patients would live longer if treatment is started earlier [3–6, 8–10]. This assumption has been used in [62] in the absence of drug resistance, and we extended it according to the latest published data [9, 61] on life expectancy (conditional upon treatment and resistance). We assumed the relationship between life expectancy and different CD4+ count at ART initiation for individuals with and without viral suppression in [9, 61] also held for drug-sensitive and drug-resistant individuals even not all unsuppressed patients have drug resistance [66]. Based on this assumption, we obtained that treated drug-sensitive individuals lived 11 years longer on average than treated drug-resistant individuals, following the studies by May et al. [9, 61]. This is consistent with the inverse relationship between viral load and lifespan in [72] in that drug-resistant individuals maintain higher viral loads in the presence of drugs than drug-sensitive individuals. The survival data we used is from individuals at age 35 [9, 61], which may not hold for younger or older individuals (the extended life expectancy decreases with age, see Fig. 2 in [4]). However, the majority of newly diagnosed MSM in San Francisco were aged 30-49 years [19]. Thus, our assumption is still reasonable and will not affect the main results.

The epidemic among MSM in San Francisco has been well-studied [18, 33–38] and it is useful to compare our results to previous work. Charlebois et al. [18] found that an aggressive 'test and treat' strategy could decrease total new infections by 81% after 20 years, which is 3 times more than our estimate of 26%. The discrepancy arises for several reasons. First, they did not consider transmitted drug resistance that can undermine the benefit of ART. Second, they compared the full 'test and treat' strategy (annual HIV testing combined with immediate treatment) with initiating ART at CD4 count <350 cells/mm^3 (base case), while we compared a similar full test-and-treat strategy (ART initiating at 1 year post-infection on average) with the status quo test-and-treat strategy (ART initiating at 1.6 years post-infection on average); where ART initiation timing difference is smaller than that in [18] so that the averted total new infections is smaller. Third, they did not consider the impact of acute transmission, which may partially undermine the transmission reductions of early treatment. Fourth, they assumed the efficacy of ART was 99%, which was larger than our assumed efficacy of 96%. Compared with previous studies [33–38], in addition to distinctly different model structure, our study also leverage the latest data on the drug resistance [26–32] to estimate the current effectiveness of second-line drugs. Finally, in contrast to previous work, we explicitly identify the level of second-line drug effectiveness that is necessary to reduce the incidence of drug resistance.

Another modeling study in East Africa [39] found that the number of new infections averted by earlier ART initiation far exceed gained drug-resistant cases, i.e., earlier ART could prevent total incidence despite increasing

the incidence of drug resistant HIV. This is a particular case of our results represented by the blue region in figure 2e. Our results, by highlighting the importance of second-line drug effectiveness, thus clarify the discrepancy between the observed data on decreasing drug-resistant incidence [40, 41] and previous mathematical modeling results [33–39] suggesting that early treatment initiation should increase the incidence of drug resistance.

Our model fit to the San Francisco MSM population was imperfect for a variety of reasons. First, we simultaneously fitted to AIDS diagnoses and deaths data from a cohort study directly and population-level prevalence data [42–52], the number of persons living with HIV/AIDS data [19, 47, 50, 53–55], total MSM population size data [46, 47, 56–60] and the fraction of drug-resistant cases among newly infected individuals data [26–32] indirectly. While fitting to different data sets allows us to formulate a well-informed model, a perfect fit to all data sets simultaneously (each with their own distinct reporting biases) is challenging. A key part of this challenge is that rarely are long-term data sets available on different variables (incidence, drug resistant incidence, mortality, prevalence, etc) for the same population, necessitating ad hoc decisions for how to weight each data set based on its perceived relevance to the modeled population. The collection of systematic longitudinal data multiple variables from a single population would facilitate greater rigor in joint fitting. Second, we assumed that ART scale-up was the only factor impacting transmission throughout the 1995-2014 time period, and that sexual risk behavior was constant. We did not consider other new interventions, such as implemented PrEP since 2012 [80]. These factors may explain why our model is unable to capture the continuing decline in AIDS cases in recent years (figure 1a). While the fit is imperfect, our original objective is to assess the impact of early ART initiation on transmission in a realistic setting. It is not to fully characterize the San Francisco MSM epidemic. The primary conclusion that a high second-line drug effectiveness can allow early ART to decrease both total and drug-resistant HIV incidence is robust to modeling assumptions. While our model is specifically constructed and calibrated to reflect the unique epidemiology of HIV transmission among MSM in San Francisco and the results may not be generalizable to other cities in US or other countries, our approach can be applied to other settings to evaluate whether earlier ART initiation and potent second-line drug effectiveness could decrease the incidence of drug resistance.

In summary, we identify the level of second-line drug effectiveness (e.g. efficacious drugs along with good adherence and drug resistance monitoring) that is necessary for early ART initiation can reduce the overall and drug-resistant incidence. This provides further support for as early treatment initiation as possible for all persons living with HIV regardless of CD4+ T cell count even amidst the presence of acquired and transmitted

drug resistance.

Data accessibility. All of the epidemic incidence data employed in this paper are being made publicly available in the electronic supplementary material.

Authors' contributions. M.S., Y.X., L.R., L.A.M. and S.E.B. conceived and designed the study. 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., L.A.M. and S.E.B. contributed to writing the paper and agreed with manuscript results and conclusions.

Competing interests. The authors declare that they have no competing interests.

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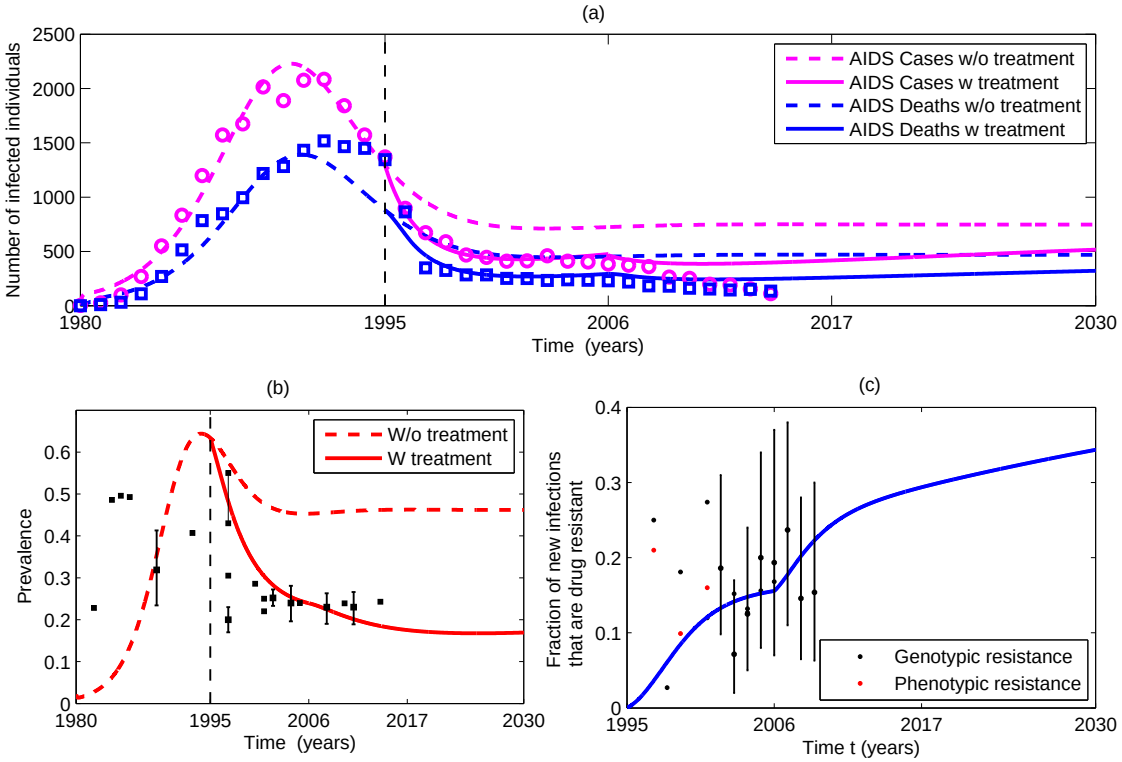

Figure 1: (a) Model fit (lines) to the incidence of AIDS diagnoses (magenta circles) and AIDS deaths (blue squares) from 1980 to 2014 among MSM population in San Francisco. Dashed vertical black line denotes the divide between the pre-treatment and post-treatment phases of our model, roughly approximating the increase in ART availability post-1995 in San Francisco. (b) Observed HIV prevalence data among the sampling MSM populations (black square and 95% confidence interval if available) from previous different studies [42–52] and model fit with and without (w/o) considering the effect of treatment post-1995. (c) Observed proportion of new infections that are drug resistant (black dots, with 95% confidence interval if available, denote genotypic resistance and red dots denote phenotypic resistance) among previous cohorts [26–32] and model fit (blue line). Previous comparison between model and empirical data for trends of percentage of new drug-resistant infections in San Francisco (1996-2005) can be found in [37]. ART, antiretroviral therapy; MSM, men who have sex with men.

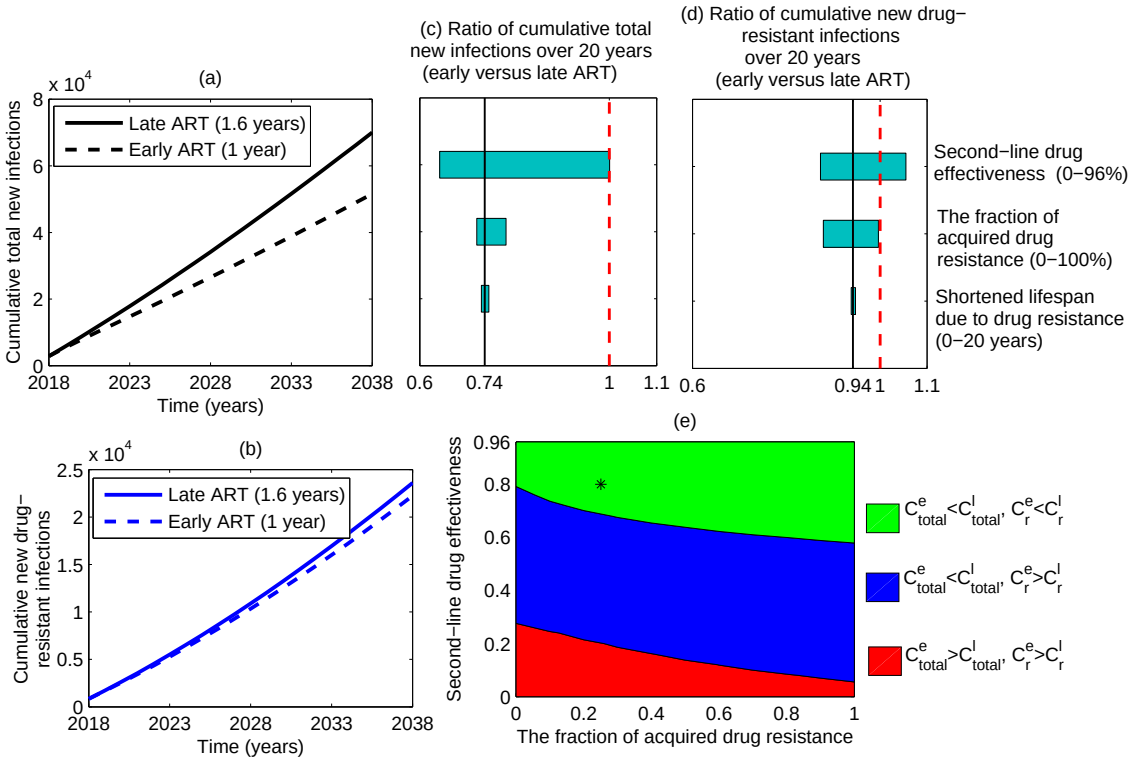

Figure 2: (a) and (b) show the cumulative total incidence (new infections) and drug-resistant incidence over time from 2018 to 2038 for early ART (assumed ART initiation timing of 1 year, solid lines) and late ART (estimated ART initiation timing of 1.6 years, dashed lines) respectively. (c) and (d) show one-way sensitivity analysis about the ratios of cumulative total incidence over 20 years (early versus late ART, denoted as C^e_{total} and C^l_{total}) and drug-resistant incidence (early versus late ART, denoted as C^e_r and C^l_r) respectively. The horizonal bars represent the range of the ratios (C^e_{total}/C^l_{total} and C^e_r/C^l_r) as each variable (second-line drug effectiveness, the fraction of acquired drug resistance, and the shortened lifespan for treated drug-resistant individuals compared with treated drug-sensitive individuals) is varied across its plausible range listed. The black solid vertical lines indicate the base case ratios ($C^e_{total}/C^l_{total} = 0.74$ and $C^e_r/C^l_r = 0.94$). The red dashed vertical line represents the threshold whether early ART would increase incidence. (e) Area plots of the ratios of cumulative incidence. In the red area, it shows that early ART can increase both total incidence and drug-resistant incidence. In the blue area, it shows that early ART can decrease total incidence, but increase drug-resistant incidence. In the green area, early ART can decrease both total incidence and drug-resistant incidence. The black star denotes the base case (second-line drug effectiveness is 80%, and 25% of treated cases have acquired drug resistance and all of them switch to second-line drugs timely). All the other parameters are fixed as shown in Table S1 in the electronic supplementary material. ART, antiretroviral therapy.

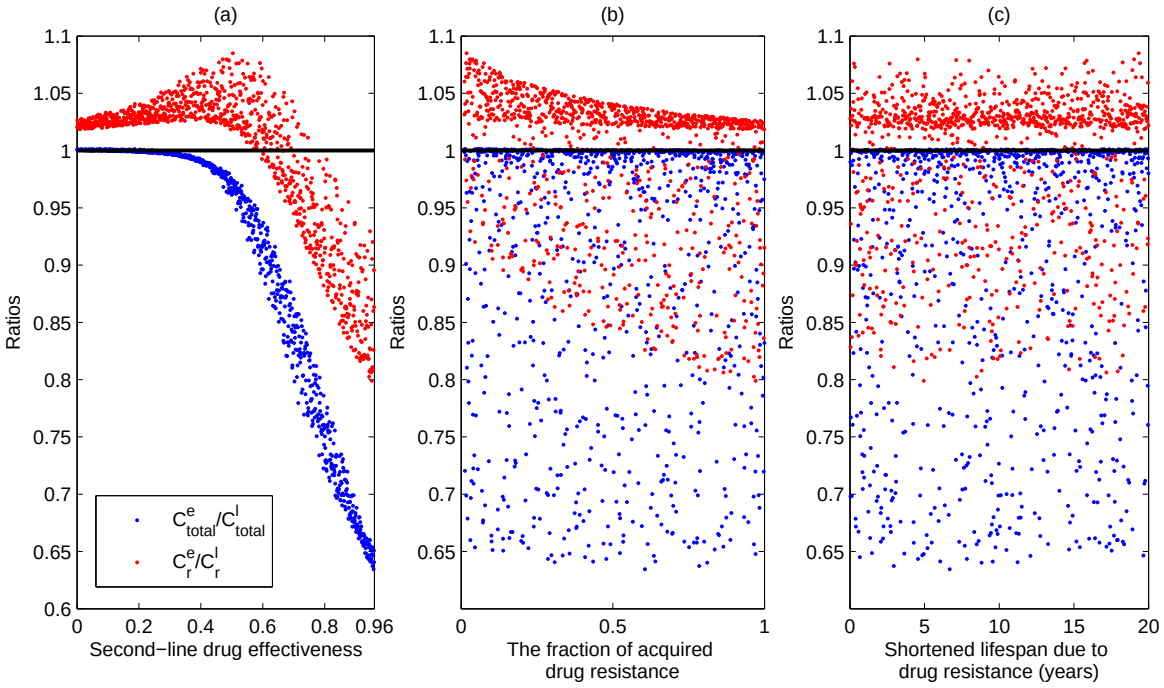

Figure 3: Results of Latin Hypercube uncertainty analysis, with scatterplots showing the effect of second-line drug effectiveness (a), the fraction of acquired drug resistance (b), and the shortened lifespan for treated drug-resistant individuals compared with treated drug-sensitive individuals (c) on the ratios of cumulative incidence between treatment scenarios (early versus late ART for total incidence, C^e_{total}/C^l_{total}, in blue; early versus late ART for drug-resistant incidence, denoted as C^e_r/C^l_r, in red), where C^e_{total}, C^l_{total}, and C^e_r, C^l_r are the same as shown in figure 2. Each point represents a single simulation from a sample 1000 Latin Hypercube parameter samples. All the other parameters are fixed as shown in Table S1 in the electronic supplementary material. ART, antiretroviral therapy.