Supplementary Material for

Forecasting prevalence of HIV-1 integrase strand transfer inhibitor (INSTI) drug resistance: a modeling study

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Text S1. Full description of the model of HIV-1 transmission, ART adherence, and drug resistance

We designed an eight-state model – based on the classical susceptible (S), infectious (I), removed (R) – that expanded the infectious state into 6 categories to accommodate the complexities of HIV-1 dynamics. The eight states present in the model are:

1. Susceptible (S) individuals: never infected with HIV-1 and are ART naïve
2. Acutely infected individuals with wildtype HIV-1 (A_1)
3. Acutely infected individuals with HIV-1 with INSTI drug resistance (A_2)
4. Individuals living with wildtype HIV-1 that adhere with ART (C_1)
5. Individuals living with HIV-1 carrying INSTI drug resistance who adhere to ART (C_2)
6. Individuals living with wildtype HIV-1 that do not adhere to ART (Y_1)
7. Individuals living with HIV-1 with INSTI drug resistance that do not adhere to ART (Y_2)
8. Removed (R) individuals die from complications of HIV-1 infection (Figure 1).

Let i represent a specific HIV-1 strain, such that $i = 1$ represents wildtype HIV-1 and $i = 2$ represents INSTI resistant HIV-1. We calculate the force of infection for wildtype HIV-1 (λ_1) and the force of infection for HIV-1 with INSTI drug resistance (λ_2). Note that λ_2 represents transmitted drug resistance (TDR). For more details, see eqns. 1 and 2 in the main document.

Counts of susceptible individuals increase because individuals age into the adult category at rate b. Let N represent the number of 17 year olds, such that bN represents the number of new susceptible adults. Counts of susceptible individuals decease due to new HIV-1 infections ($\lambda_i S$) and death by causes unrelated to HIV-1 ($\mu_1 S_t$), such that

$$\frac{dS}{dt} = bN - \lambda_1 S - \lambda_2 S - \mu_1 S. \quad \text{(S1)}$$

Upon contracting HIV-1 infection, individuals enter the acutely infected state at rate λ_i. Individuals exit the acutely infected class at rate ω, which is equal to the inverse of the average duration of acute HIV-1 infection. A proportion of the acutely infected individuals, p, begin ART. The other proportion of acutely infected individuals, $1 - p$, never begin ART or do not adhere. Let μ_2 represent the per capita death rate of individuals with acute HIV-1 infection due causes unrelated to HIV-1. Then, the number of individuals acutely infected with strain i is

$$\frac{dA_i}{dt} = \lambda_i S - p\omega A_i - (1-p)\omega A_i - \mu_2 A_i. \quad \text{(S2)}$$

When individuals infected with wildtype HIV-1 begin ART, drug resistant mutants are selected[1]. Therefore, adherent individuals living with wildtype HIV-1 might acquire an INSTI drug resistance mutation and convert from the C_1 state to the C_2, state at rate τ_1. Let γ_1 represent the death rate due to HIV-related causes for individuals who had adhered to ART. Then, the number of individuals living with HIV-1 infection that adhered to ART can be calculated as

$$\frac{dC_1}{dt} = p\omega A_1 - \tau_1 C_1 - \gamma_1 C_1 \quad \text{(S3)}$$
$$\frac{dC_2}{dt} = p\omega A_2 + \tau_1 C_1 - \gamma_1 C_2. \quad \text{(S4)}$$

Alternatively, reduced ART could decrease selection for drug resistant mutants[2]. Therefore, non-adherent individuals living with HIV-1 carrying INSTI resistance mutations might convert

from the Y_2 state to the Y_1 state at rate τ_2. Let γ_2 represent the rate of death due to HIV-1/AIDS-related illness for individuals who had not adhered to ART. Then, we can represent the number of individuals living with HIV-1 infection that did not adhered to drug treatment as

$$\frac{dY_1}{dt} = (1-p)\omega A_1 + \tau_2 Y_2 - \gamma_2 Y_1 \quad \text{(S5)}$$

$$\frac{dY_2}{dt} = (1-p)\omega A_2 - \tau_2 Y_2 - \gamma_2 Y_2 \quad \text{(S6)}$$

The number of individuals removed (R) from the population due to death from HIV/AIDS-related causes can be represented as

$$R_{t+1} = \gamma_1 C_1 + \gamma_1 C_2 + \gamma_2 Y_1 + \gamma_2 Y_2. \quad \text{(S7)}$$

Text S2. Parameters

We found parameter values in the peer-reviewed literature. For four parameters ($\alpha, \delta, p, \omega$), the literature provided a common value and a range of values that were biologically plausible (Table S1). Following Medlock *et al*.[3], we represented these parameter ranges as triangle distributions and we used the *triangle* package in R[4]. For two parameters (τ_2 and γ_1), the literature provided a range of values that were biologically and equally plausible (Table S1). We represented these parameter ranges with a uniform distribution. Finally, for four parameters (τ_1, b, μ_1, and μ_2), the literature provided a single parameter value (Table S1). We represented these values with a uniform distribution where the minimum value was 90% of the reported value and the maximum value was 110% of the reported value (Table S1).

Table S1. Parameter values

Parameter	Definition	Value (min, max)	Reference
$\boldsymbol{\alpha}$	Reduction in transmission from chronically infected cases without ART compared to transmission from acutely infected cases	5.3 (0.79,57)	Bellen *et al*.[5]
$\boldsymbol{\delta}$	Discounts transmission of this less fit strain, which is the INSTI resistant strain	0.2 (0,1)	Leigh Brown *et al*.[6]
$\boldsymbol{p}$	Proportion of those living with HIV-1 in Washington, DC on ART	0.627 (0.477,0.787)	DC DoH[7]
$\boldsymbol{\omega}$	Inverse of the duration of acute HIV-1 infection	1/51 days^{-1} (1/14, 1/204)	Bellen *et al*.[5] Pilcher *et al*[8]
$\boldsymbol{\tau_1}$	Rate of converting from a wildtype strain to an INSTI resistant for chronically infected ART experienced cases	*RAL:* 1.85 x 10^{-4} *EVG:* 2.36 x 10^{-4} *DTG:* 2.11 x 10^{-4}	Lepik *et al*.[1] *See note #1 below*
$\boldsymbol{\tau_2}$	Rate of converting from an INSTI resistant strain to a wildtype stain for chronically infected cases not using ART	(2.44 x 10^{-3}, 2.20 x 10^{-2})	Canducci *et al.*[9]
$\boldsymbol{\gamma_1}$	Rate of death from HIV-related causes for chronically infected ART experienced cases	(1.18 x10^{-5}, 1.88 x10^{-5})	DC DoH[7] *See note #2 below*
$\boldsymbol{\gamma_2}$	Rate of death from HIV-related causes for chronically infected cases not using ART	(1.18 x10^{-5}, 3.16 x 10^{-5})	DC DoH[7] *See note #2 below*
b	Rate that 17-year-old children become 18-year-old adults in Washington, DC	0.00274 days^{-1}	n/a
$\boldsymbol{N}$	Number of 17 year olds in Washington, DC	5881*	US Census[10]

μ_1	Death rate of susceptible individuals due to all causes	1.98 x 10^{-5}	**
μ_2	Death rate of acutely infected individuals due to all causes unrelated to HIV-1	5.01 x 10^{-5}	DC DoH[7] *See note #2 below*

** considering 1% of DC population size to be 17 years old* [10]
*** via https://www.kff.org/other/state-indicator/death-rate-per-100000/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D*

Note #1: To calculate τ_1, we considered the number of cases with emergent drug resistance mutations from Lepik *et al*., Table 2[1]. Only 2% of individuals in this cohort exhibited emergent raltegravir resistance mutations. We used proportion to motivate the probability of any individual acquiring a raltegravir mutation such that $p = 0.07$. We converted this probability to a per capita rate using $p = 1 - e^{-rate}$. The study was conducted over a 12-month period, which implies that we calculated a yearly rate. The per capita rate we calculated was 0.0676 per year. When we divided this value by 365 days, we calculated a per capita daily rate of 1.85 x10^{-4} per day.

Note #2: For γ_1, we divided the 55 deaths due to HIV-1-related causes in 2015 (Table 17 from DC DoH[7] by 7,987 (those suppressed at last known viral status; Table 10 from DC DoH[7]) and 12,732 (all HIV-1; Table 10 from DC DoH[7]) and converted that probability to a per capita yearly rate. For γ_2, we performed similar calculations, but for the denominator, we used those not using care (12,732-7,987) or all those with HIV-1 (12,732). For μ_2, we performed similar calculations but used the 235 deaths not due to HIV-1 causes divided by the total number of individuals with HIV-1 (12,732), which assumes equal mortality for all those living with HIV-1.

Text S3. Calculating values for λ and β

We estimated the force of infection before INSTI drug resistance was widely observed, λ_1, from data describing yearly HIV incidence in Washington, DC from 2013 to 2017[11]. We report the median, minimum, and maximum (Table S2). From these, we calculated values for the transmission coefficient (β) following equation 2 and assuming that all infections are INSTI responsive, such that

$$\beta = \frac{\lambda_1}{A_1 + \alpha Y_1}. \quad \text{(S7)}$$

To find the number of acutely infected individuals, A_1, we assumed that cases were equally dispersed throughout the year. There were 359 individuals infected with HIV-1 in 2017[7], which we round up to 365 for ease of calculation. Because the duration of the acute phase is approximately 51 days (minimum: 14 days; maximum 204 days; Table S1)[5,8], we can assume that there were 51 individuals (minimum: 14 individuals; maximum 204 individuals) in the infectious period at any given time. Using these estimates for A_1, our estimated value for λ_1, and the value for α listed in Table S1, we calculated the value of β (Table S2).

Table S2. Values for the force of infection (λ) and transmission coefficient (β)

Parameter	Definition	Value (min, max)
λ_1	Force of infection, or the per capita rate at which susceptible individuals acquire infection	1.976 x 10^{-6} person^{-1} (1.813 x 10^{-6} person^{-1}, 2.636 x 10^{-6} person^{-1})
β	Transmission coefficient, or contact rate multiplied by the probability that a susceptible individual will acquire infection given contact with an infectious individual	2.537 x 10^{-10} person^{-2} (7.858 x 10^{-12} person^{-2}, 8.214 x 10^{-10} person^{-2})

Table S3. Values for initial conditions set to mimic disease and demographic processes in Washington, DC

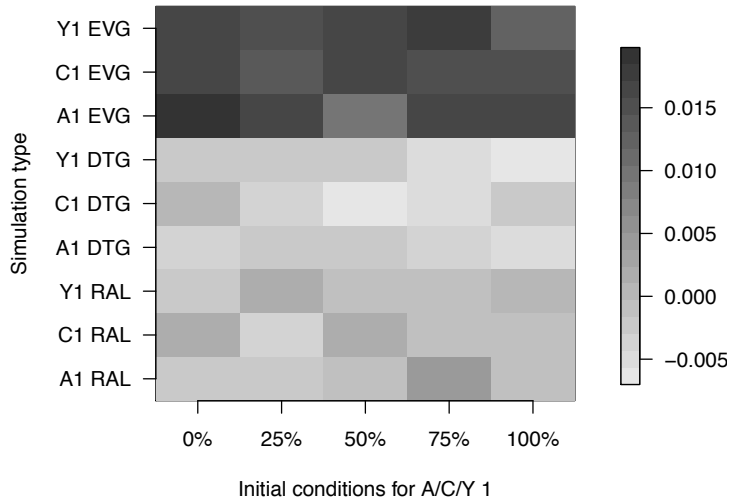
Variable	Definition	Value (in # of individuals)	Reference
S	Susceptible individuals (no HIV-1; no ART)	556,093	*
A_1	Acutely infected individuals with wildtype HIV-1 (no ART)	50	DC DoH[7] *See Text S3*
A_2	Acutely infected individuals with INSTI-resistant HIV-1 (no ART)	1	Aldous et al.[12] DC DoH[7] **
C_1	Chronically infected individuals with wildtype HIV-1 and ART adherence	9748	Aldous et al.[12] DC DoH[7] **
C_2	Chronically infected individuals with INSTI-resistant HIV-1 and ART adherence	98	Aldous et al.[12] DC DoH[7] **
Y_1	Chronically infected individuals with wildtype HIV-1 (no ART)	3036	Aldous et al.[12] DC DoH[7] **
Y_2	Chronically infected individuals with INSTI-resistant HIV-1 (no ART)	31	Aldous et al.[12] DC DoH[7] **
N	Total population size	569,057	US Census[10]

* We calculated the number of susceptible adults using census data[10] and subtracting individuals under the age of 18[10] and subtracting individuals infected with HIV-1[7]. ** Aldous *et al.*[12] reports that 75.65% of those living with HIV-1 in Washington DC had low viral loads – which we categorized as chronically infected individuals with ART adherence – and an average 1% of those living with HIV-1 in Washington DC had HIV-1 resistant to an ART in the INSTI class, which we distributed evenly among all disease categories. DC DoH report[7] provided counts of those living with HIV-1.

Text S4. Simulation procedure

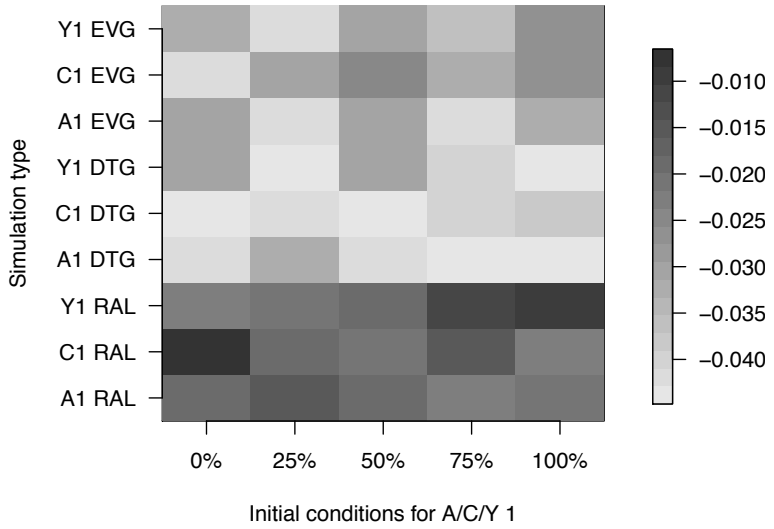
We performed 100 stochastic simulations of the model using different parameter values randomly selected from identified ranges (Table S1, Table S2) using *rtriangle* or *runif* in R.

Figure S1. Difference in mean proportion of HIV-1 cases with INSTI resistance due to varying initial conditions.



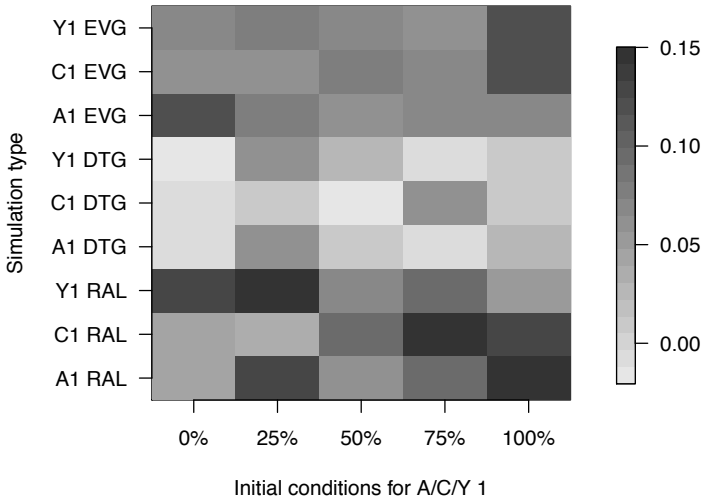
The mean proportion of HIV-1 cases with INSTI resistance was similar for baseline simulations and simulations using varying initial conditions. Means differed by 1.9% or less. The greatest difference in means between baseline simulations and simulations using varying initial conditions was observed in simulations representing EVG.

Figure S2. Difference in minimum proportion of HIV-1 cases with INSTI resistance due to varying initial conditions.



The minimum proportion of HIV-1 cases with INSTI resistance between baseline simulations and simulations using varying initial conditions varied more than the means. Minimums differed by 4.4% or less. The greatest difference in means between baseline simulations and simulations using varying initial conditions was observed in simulations representing EVG.

Figure S3. Difference in maximum proportion of HIV-1 cases with INSTI resistance due to varying initial conditions.



The maximum proportion of HIV-1 cases with INSTI resistance between baseline simulations and simulations using varying initial conditions varied more than the means and the minimums. Maximums differed by 14.6% or less. The greatest difference in maximums between baseline simulations and simulations using varying initial conditions was observed in simulations representing RAL.

Table S4. Sensitivity of all parameters

Parameter	Change in parameter value	Mean change in proportion of HIV-1 cases with RAL resistance	Mean change in proportion of HIV-1 cases with EVG resistance	Mean change in proportion of HIV-1 cases with DTG resistance
α	+ 10%	1.76%	1.06%	1.61%
α	+ 20%	3.40%	2.01%	3.17%
α	- 10%	-1.85 %	-1.21%	-1.62%
α	- 20%	-3.74%	-2.58%	-3.21%
δ	+ 10%	0.00%	0.00%	0.00%
δ	+ 20%	0.00%	0.00%	0.00%
δ	- 10%	0.00%	0.00%	0.00%
δ	- 20%	0.00%	0.00%	0.00%
p	+ 10%	6.58%	6.96%	7.14%
p	+ 20%	12.85%	13.03%	14.29%
p	- 10%	-7.28%	-7.83%	-7.47%
p	- 20%	-15.23%	-16.36%	-15.41%
ω	+ 10%	0.10%	0.07%	0.08%
ω	+ 20%	0.18%	0.14%	0.15%
ω	- 10%	-0.12%	-0.09%	-0.10%
ω	- 20%	-0.27%	-0.20%	-0.22%
τ_1	+ 10%	4.72%	3.66%	4.22%
τ_1	+ 20%	8.93%	6.83%	7.94%
τ_1	- 10%	-5.30%	-4.25%	-4.81%
τ_1	- 20%	-11.26%	-9.20%	-10.30%
τ_2	+ 10%	0.00%	0.00%	0.00%
τ_2	+ 20%	0.00%	0.00%	0.00%
τ_2	- 10%	0.00%	0.00%	0.00%
τ_2	- 20%	0.00%	0.00%	0.00%
γ_1	+ 10%	-0.48%	-0.49%	-0.47%
γ_1	+ 20%	-0.96%	-0.98%	-0.94%
γ_1	- 10%	0.48%	0.49%	0.47%
γ_1	- 20%	0.96%	0.98%	0.94%
γ_2	+ 10%	0.45%	0.54%	0.48%
γ_2	+ 20%	0.90%	1.08%	0.96%
γ_2	- 10%	-0.45%	-0.54%	-0.48%
γ_2	- 20%	-0.91%	-1.09%	-0.97%
b	+ 10%	-0.59%	-0.57%	-0.58%
b	+ 20%	-1.14%	-1.12%	-1.13%
b	- 10%	0.61%	0.60%	0.61%
b	- 20%	1.26%	1.22%	1.24%
n	+ 10%	-0.59%	-0.57%	-0.58%
n	+ 20%	-1.14%	-1.12%	-1.13%
n	- 10%	0.61%	0.60%	0.61%
n	- 20%	1.26%	1.22%	1.24%
μ_1	+ 10%	0.08%	0.07%	0.08%
μ_1	+ 20%	0.17%	0.14%	0.16%
μ_1	- 10%	-0.08%	-0.07%	-0.07%
μ_1	- 20%	-0.16%	-0.14%	-0.15%
μ_2	+ 10%	0.00%	0.00%	0.00%
μ_2	+ 20%	0.00%	0.00%	0.00%
μ_2	- 10%	0.00%	0.00%	0.00%
μ_2	- 20%	0.00%	0.00%	0.00%
β	+ 10%	1.77%	1.07%	1.62%
β	+ 20%	3.43%	2.02%	3.19%
β	- 10%	-1.86%	-1.21%	-1.63%
β	- 20%	-3.76%	-2.59%	-3.22%

Text S5. References

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