Supplementary Appendix

This Supplementary Appendix includes a detailed discussion of our HIV microsimulation model, calibration techniques, and additional methods and results not presented in main manuscript.

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Section 1: HIV Model

A. Overview

We developed a microsimulation model of the HIV epidemic in Kenya, where the mode of transmission is predominantly heterosexual. We first run the model starting in 2003 with 100,000 individual adults over age 15 years, representative of Kenya's population, in order to reproduce historical epidemiologic trends through 2018. Starting in 2018, we use the model to simulate and compare individual and population level health outcomes and costs associated with different HIV pre-treatment drug resistance (PDR) testing strategies over a 15-year time horizon. The model includes detailed HIV transmission, disease progression, and care parameters, which we describe below.

Each adult has several individual-level characteristics, including age, gender, HIV status, circumcision status, and number of sexual partnerships. In addition, individuals who are HIV-positive are further described by their CD4 cell count, viral load, treatment regimen, treatment history, opportunistic diseases, and drug resistance status. Each of these individual characteristics is evaluated on a monthly basis. The population size changes based on maturation into the population (people who age into the population at age 15 years) and deaths.

A similar model was previously applied to the South African context.[1-3]We have re-parameterized and calibrated this model using demographic, health, and epidemiologic data from Kenya. In addition, the model has also been further developed to simulate the emergence and transmission of drug resistance to first-line ART, described in detail in **Section 2**. We chose to use a model that includes transmission in order to capture both the treatment and prevention benefits of PDR testing. We follow a large number of individual-based characteristics, which led us to use an individual-based model instead of a deterministic compartmental model.

B. Demographic Population Structure

We used age- and gender-stratified population data from Kenyan population pyramids to construct the basic population.[4] The initial HIV prevalence of 8·4% in 2003 was based on age- and gender-stratified Kenyan HIV prevalence data from both the Kenyan Demographic and Health Survey and UNAIDS HIV prevalence estimates[5,6]. We obtained the prevalence of male circumcision from published estimates.[5,7,8]

Each individual is modeled as having either 0, 1, 2, or 3 sexual partners based on primary data from the Demographic and Household Survey (DHS) in Kenya (DHS asks the number of people with whom an individual has had sexual relationships in the past 12 months).[5,7,8] We fixed the distribution of sexual partnerships, but people were allowed to dissolve partnerships and select new partners every 12 months on average. We assumed that all partnerships last 12 months regardless of the number of partners one has. We assumed that the HIV status of partners remains unchanged throughout the period of partnership. This approach may underestimate the risk of transmission. For example, an individual with only one HIV-negative spousal partnership had no risk of infection throughout the time horizon, while in reality there is some chance that the partner may get infected by another concurrent partner.

C. HIV Disease Model – Natural History, Treatment, and Monitoring

Natural History

We have previously published a description of our HIV disease model.[1] We followed the disease progression of all infected individuals using the following attributes: age, CD4 cell count, viral load, ART regimen, ART duration, history of opportunistic diseases, virologic failure, and resistance status. The values of all attributes were re-evaluated during each monthly cycle. HIV disease progression was characterized by two primary biological parameters: CD4 cell count and viral load. CD4 cell count was used to determine the monthly probability of opportunistic infection and HIV-related mortality, and the rate of decrease or increase CD4 cell count depending upon ART and virologic failure status, age, and viral load.

Initial assignment of CD4 cell count

Since it was unknown how long they had been infected with HIV, patients who already had chronic HIV at the start of the model in 2003 randomly assigned a CD4 cell count value from a uniform distribution ranging from 0-750. The same approach was used to assign CD4 cell count values to adolescents already infected with HIV when they entered the model population at age 15 years. Individuals who became newly infected with HIV after they entered the model

population were assigned a CD4 cell count value of 750. For individuals who became newly infected with HIV after the start of the microsimulation, they were assigned an initial CD4 cell count of 750.

Initial assignment of viral load

Among patients who were already infected with HIV at the start of the model in 2003, initial viral load was assigned differently depending on whether was already on treatment and whether the patient had chronic HIV. Patients already on treatment were assigned an initial viral load of 2·6 logs (398 copies/mL). Patients with chronic HIV who were not yet on treatment were assigned an initial viral load drawn from a normal distribution with a mean viral load of 4·5 logs, a standard deviation of 0·8 logs, and with lower and upper bounds of 2·6 logs and 6·0 logs, respectively. Patients with acute HIV at the start of the model in 2003 were assigned a viral load of 6·0 logs. For new infections, we assign a viral load drawn from a normal distribution with a mean viral load of 4·5 logs, a standard deviation of 0·8 logs, and with lower bound of 2·6 logs.

CD4 cell count dynamics

The CD4 cell count was modeled as a continuous variable that varied based on the viral load, ART, and virologic failure status. CD4 cell count decreases each month that a patient is either: a) not on ART, b) not adherent to ART, or c) is experiencing virologic failure while on ART. CD4 cell count decreases at a rate that depends on viral load.[9] Given the controversial relationship between HIV viral load and CD4 change, we allowed two non-linear determinants of CD4 decline, both guided by published data[9,10]: random variability around the regression line, and a slower rate of decline with lower CD4. Each month there is a drop in CD4 cell count, the new value is calculated by the following equation:

"this month" CD4 cell count = "last month" CD4 cell count – monthly CD4 decrease,

where the "monthly CD4 decrease" value is drawn at random from a distribution centered around the "monthly decrease in CD4 cell count" according to viral load level (Table S1). However, if a patient has an opportunistic infection, the CD4 cell count decrease that month is equal to 58·5, independent of viral load level, with the caveat that, in our model, CD4 cell count is never allowed to drop below 1.0.

Log viral load	Monthly Decrease in CD4 Cell Count
0 – 2·6	0
2·601-3·7	4·4
3·701- 4·5	5·5
>4·5	6·6

Table S1. Monthly Decrease in CD4 Cell Count by Viral Load

After starting an ART regimen that begins to effectively decrease the patient's viral load, the CD4 cell count rises each month that the ART regimen remained effective. The monthly rate of increase in CD4 cell count gradually decreases with each additional month that a patient has been on ART, and the strongest reproducible predictor of the maximum level the CD4 cell count will achieve while on effective ART is the CD4 cell count at the time of treatment initiation.[11-14] We assume that after 48 months of effective ART there is no further increase in CD4 cell count. Published data on CD4 rise were extracted using the graph digitizing program DigitizeIt v.1.5 (Braunschweig, Germany), and the following model was fit to the data to describe the monthly rate of CD4 cell count increase:

*Monthly increase in CD4 cell count = 75*log((ART duration + 2) / (ART duration + 1))*,
where ART duration is the number of months since ART initiation. The *monthly increase in CD4 cell count* is multiplied by 0·8 for patients older than 40 years, based on data suggesting that older individuals have an incomplete CD4 cell count response to ART.[13]

Viral load dynamics

Effective ART suppresses viral replication. Each month that a patient receives an effective ART regimen, the viral load decreases by 0·7 logs, for a maximum of 6 months. Thus, if patient began with a viral load of 6 logs (1 million copies/mL), which is the maximum possible viral load in the model, then after 6 months of effective ART the patient would have a viral load of 1·7 logs (50 copies/mL). Also, the lowest possible viral load allowed in the model is 1·7 logs. After a patient experiences virologic failure on ART or stops taking ART, the viral load immediately increases to the highest prior viral load level for the patient.

Risk of opportunistic infections and mortality

The risk of opportunistic diseases and mortality were dependent on the current CD4 cell count level (Table S2).[15-17] We calculated the risk of a severe opportunistic disease based on the risk of developing a World Health Organization (WHO) Stage 4 disease plus the risk of developing opportunistic pulmonary tuberculosis (TB). We aggregated data on the risk of chronic diarrhea, esophageal candidiasis, wasting syndrome, severe bacterial infection, pulmonary TB, extrapulmonary TB, PCP, CMV, cryptococcal meningitis, and toxoplasmosis when calculating the risk of severe opportunistic diseases. [15,17]

HIV disease parameter	Parameter Value	Source
Monthly probability of developing opportunistic diseases by CD4 lymphocyte count, %		Holmes et al,[16] Badri et al[15]
0-49 cells/μL	10·0	
50-99 cells/μL	5·0	
100-199 cells/μL	3·7	
200-299 cells/μL	2·4	
300-399 cells/μL	1·0	
400-499 cells/μL	0·3	
≥500 cells/μL	0	
Monthly probability of HIV mortality without ART, by CD4 lymphocyte count, %		Badri et al.[15]
0-49 cells/μL	4·8	
50-99 cells/μL	2·0	
100-199 cells/μL	1·6	
200-299 cells/μL	1·2	
300-399 cells/μL	1·0	
400-499 cells/μL	0·8	
≥500 cells/μL	0·5	
Monthly HIV mortality with ART, by CD4 lymphocyte count, %		Lawn et al.[17]
0-49 cells/μL	3·2	
50-99 cells/μL	1·1	
100-199 cells/μL	0·5	
200-299 cells/μL	0·2	
300-399 cells/μL	0·2	
400-499 cells/μL	0·2	
≥500 cells/μL	0·1	

Table S2. Probability of opportunistic infections and HIV-related mortality by CD4 cell count

Treatment and Monitoring

We assume that, as of 2016, all individuals diagnosed with HIV qualify to receive ART, regardless of CD4 cell count, as currently recommended by the Kenyan Ministry of Health guidelines.[18] Use of dolutegravir in Kenya began in 2018 for 10,000 patients initiating ART across 24 different health facilities as a pilot project.[19] According to UNAIDS estimates, there 62,000 new HIV infections in Kenya in 2016, with estimates ranging from 45,000 to 81,000.[6] Based on this, we roughly estimated that in 2018 there would be ~50,000 new HIV infections. Thus, for our model, since there were 10,000 patients who received dolutegravir-based ART in 2018, we assume that for any given patient initiating ART in 2018 there is a 20% chance they will receive dolutegravir-based ART (as 10,000 / 50,000 = 20%). Patients who do not receive dolutegravir-based ART receive non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART. We assume protease inhibitor (PI)-based ART is the second-line ART regimen for patients in whom virologic failure is detected on either dolutegravir-based or NNRTI-based ART. This dolutegravir pilot phase began prior to May 2018 when evidence from Botswana revealed a potential early signal for about a potential increased risk of neural tube defects in association with use of dolutegravir-based ART from the time of conception.[20]

In July 2018, WHO recommended use dolutegravir-based ART as the preferred empiric first-line regimen for women only if they are receiving an effective form of contraception.[21] More recent evidence from Botswana suggests that while the potential increased risk of neural-tube defects is still significant it may not be as large as what the 2018 analysis found.[22] In response, WHO has updated its guidelines to provide reassurance and strongly recommend dolutegravir-based ART as the preferred empiric first-line ART regimen for HIV-infected women.[23] However, it

remains to be seen what proportion of HIV-infected women will use dolutegravir-based ART moving forward. Thus, for women, in our base-case scenario, we assume that for any given woman initiating ART there is a 40% chance she will receive dolutegravir-based ART. This assumption was made in anticipation of potential concerns about dolutegravir from either from health facilities delivering ART or from the patient herself and takes into account estimates that about 40% of women in Kenya use some form of contraception.[8] For men, we assume scale-up of dolutegravir use occurs relatively quickly with 75% of HIV-infected men initiating ART in 2019 receiving dolutegravir-based ART and 100% of men initiating ART in 2020 or later receiving dolutegravir-based ART (Table S3).

Year	Men	Women
2018	20%	20%
2019	75%	40%
2020 & onwards	100%	40%

Table S3. Proportion Who Receive DTG-based ART Among HIV-Infected Men & Women Initiating ART

We modeled and compared three different testing strategies for women who do not initiate dolutegravir-based ART in Kenya over a 15-year time horizon starting in 2019 (t0): 1) empiric NNRTI-based ART with no PDR testing, 2) PDR testing with OLA, and 3) PDR testing with CS (diagnostic performance of OLA and CS are discussed in detail in Section 2). For PDR testing strategies using either OLA or CS, PI-based ART is initiated when PDR is detected, and NNRTI-based ART is used for all other patients. The probability of virologic failure on one's initial ART regimen is determined by PDR status and the ART regimen where individuals who have PDR to their initial ART regimen have a higher probability of virologic failure compared to those who do not have PDR to their initial ART regimen (discussed in detail in Appendix Section 2).

During the period from 2003 to 2017, which was used for calibration, initial viral load testing switches from occurring at 12 months after ART initiation to 6 months after ART initiation in the year 2014. From that point on, we assume viral load testing occurs at 6 months after ART initiation and every 12 months thereafter. To estimate the cost of CD4 cell count testing, we assume that CD4 cell count is checked at baseline and when virologic failure is detected to assess for risk of opportunistic infections.[24] Switching from first-line to second-line therapy is indicated when virologic failure was identified through viral load testing (the probability of switching to 2nd-line ART when indicated is described in more detail below in the Cascade of Care Section). Patients who experience treatment failure on PI-based second-line ART continue this therapy because of survival advantages associated with a non-suppressive regimen compared with discontinuation of ART.[25] Patients with virologic failure who were continued on ART had a lower viral "set point" and their rate of CD4 decline was slower.[25]

D. Cascade of Care and ART Coverage

Overview

The cascade of care model input parameters are designed to be consistent with Kenyan Ministry of Health guidelines and calibrated to achieve ART coverage rates that have been observed in Kenya over time. ART coverage is an important population level outcome that strongly influences the prevalence of PDR. As ART coverage increases, the number of HIV-infected individuals who can develop acquired drug resistance (ADR) increases, and patients with ADR have the potential to transmit drug resistance mutations to others they infect. Therefore, the prevalence of PDR tends to increase as ART coverage increases. Thus, it was important to model ART coverage accurately from 2003-2017, in order to ensure we made accurate assumptions about other key parameters involved in the emergence and transmission of drug resistance, including the probability of virologic failure, of developing ADR among those who experience virologic failure, and of switching to second-line ART when virologic failure is identified by a viral load test. A detailed explanation of how drug resistance is modeled is provided in Appendix Section 2, and our model calibration is explained in Appendix Section 3.

ART initiation thresholds over time were based on published guidelines.[18,26,27] Other cascade of care parameters were based on a range of values published in the literature and adjusted such that the ART coverage rates generated by the model matched observed ART coverage rates in Kenya.

Cascade of Care Parameters

Our model includes the following cascade of care parameters:

- Annual probability of being tested/screened for HIV
- Linkage to care parameters
  - Probability of being linked to care when a patient becomes aware of her HIV-infected status
  - Probability of being lost-to-follow-up (LTFU) after being diagnosed with HIV but before ART initiation
  - Probability of having access to ART when ART is indicated
  - Probability of LTFU after ART initiation
  - Probability of a LTFU individual returning to care when she has an acute OI
- ART initiation threshold
- Probability of switching to second-line ART when virologic failure is identified by a viral load test

Annual Test Probability

According to the 2012 Kenya AIDS indicator survey report, in 2007 and 2012, 34·3% and 71·3% of individuals 15-64 years old in Kenya had ever been tested for HIV, respectively.[28,29] To reproduce a similar data trend, we assumed that in 2003 the annual probability of receiving an HIV test among uninfected individuals was low at 10% and that this probability increased by approximately 10% each year (Table S4).

Year	Annual Test Probability
2003	0·1
2005	0·2
2006	0·3
2007	0·34
2008	0·4
2009	0·5
2010	0·6
2011	0·7
2012 and onward	0·8

Table S4. Annual Probability of an Adult Being Screened for HIV

Linkage to Care Parameters

We obtained baseline estimates for LTFU parameters from a systematic review that examined attrition rates determined by death after starting ART, treatment discontinuation, and LTFU (Table S5).[30] We assume that when a patient who has initiated ART is LTFU they stop taking ART, and CD4 cell count and viral load dynamics are modeled accordingly. Among those who are lost to follow-up, there is a probability assigned to them of returning to care and resuming ART. We focused primarily on the issue of loss to follow-up as a separate event from early mortality after ART initiation.

Parameter	Monthly Probability
Probability of being LTFU after being diagnosed with HIV but before ART initiation	0·005
Probability of having access to ART when ART is indicated	0·8
Probability of LTFU after ART initiation	0·000875
Probability of returning to care after being LTFU with an acute OI	0·5

Table S5. Linkage to care parameters

ART Initiation Threshold

Although new recommendations regarding when to initiate ART are likely adopted gradually over time, we assumed that they were fully implemented the year they were recommended (Table S6).[18,26,27]

Year	CD4 Cell Count
2003-2009	< 200
2010-2013	< 350
2014-2015	< 500
2016 and onward	Treat all regardless of CD4 cell count

Table S6. ART Initiation Thresholds in Kenya

Probability of Switching to Second-line ART

Viral load testing for individuals on NNRTI-based first-line ART is used to inform the decision of whether to continue first-line ART or to switch to second-line ART. Ideally, individuals with unsuppressed viral load, despite optimal adherence, should be switched to PI-based second-line ART. However, prior studies suggest that rates of switching to 2nd-line ART when clinically indicated have been inappropriately low in sub-Saharan Africa.[31,32] Data on the probability of switching to second-line ART when virologic failure on first-line ART is not readily available for Kenya. We assume that the probability of switching to second-line ART has gradually increased since ART roll-out began as the price of PI-based ART has decreased and access has presumably improved.

We used estimates of the proportion of patients on ART in Kenya using PI-based ART at two time points (2006 and 2018) to inform the model inputs for the probability of switching to PI-based second-line ART when virologic failure is detected (Table S6). First, a multi-country survey conducted in resource-limited settings by WHO found that in 2006, among adults on ART, 4% were on second-line ART (PI-based) and 96% were on first-line ART.[33] Second, based on data published online by the Kenyan National AIDS/STD Control Programme (NASCOP), we estimate that in 7.4% of patients on ART in Kenya in 2018 were using PI-based ART.[34]

In the model, when testing reveals an unsuppressed viral load in a patient, a random number is generated for this patient, and if the random number is less than the assigned probability of switching to second-line ART, then the patient will switch to second-line ART. Otherwise, the patient will remain on first-line ART. If a patient is detected with virologic failure but is not switched to second-line ART at that time, they will be eligible for switching regimens the next time viral load testing is performed (using the same algorithm), which we assume occurs 12 months later, although there is little data to guide this assumption. We implement the following probabilities of switching to 2nd-line ART, given unsuppressed viral load at testing, over time (Table S7):

Year	Probability
2003-2007	0·1
2008-2012	0·2
2013	0·25
2018 and onwards	0·6

Table S7. Probability of Switching to PI-based Second-Line ART When Virologic Failure is Diagnosed

E. HIV Transmission

Our model was set in a region where HIV disease transmission is predominantly through heterosexual contact. The risk of infection for those who are HIV-negative was evaluated monthly in multiple stages. First, the model determined whether any of an individual's partners were infected with HIV, based on the number of partners that individual had and the prevalence of HIV during that month. For each infected partner, the model determined what HIV state he/she was in, either acutely infected (for no more than three months), on effective ART, or chronically infected with any one of four classes of elevated viral load.[9,35,36] The probability of being in each any one of those states was proportional to the proportion of HIV-infected persons in that state in the population. If an HIV-negative person had an HIV-infected partner, the monthly probability of acquiring HIV that month was a function of the number of sex acts per month, his/her partner's HIV state, and risk modifications such as male circumcision. We assumed the probability of transmission per sexual act was higher with acute HIV and with higher viral load levels of the infected partner,[35-37] and we assumed that men who were circumcised had a 55% reduction in risk of acquiring HIV.[38-40]

For the purpose of modeling transmission, from 2003-2017, HIV prevalence and the probability of an HIV-infected partner being in a given viral load category were dynamically calculated each month among men and women as a a whole. Starting in 2018, these calculations became sex-specific because rates of virologic failure were no longer uniform for men and women with the introduction of dolutegravir. Further, using sex-specific calculations allowed us to project sex-specific PDR prevalence trends.

F. Population Growth and Size

We modeled population growth, which provides a measure of the secondary benefits of each improved care strategy. That is, because we modeled "entries" into the population as a function of the size of population in childbearing age, reducing deaths may be expected to lead to an increase in population growth. We made simplifying assumptions in modeling population size, such as the assumption that fertility rates will remain unchanged over the next 15 years and with different courses of the HIV epidemic. As a result, our estimates of population growth provide a comparison among the strategies about the potential demographic benefits of HIV care rather than real predictions about population size change.

Each time we simulated a scenario with a unique set of parameter values (such as the base-case scenario or various sensitivity analysis scenarios), the simulation began running in 2003 with an initial population size of 3 million people, and it was run 3,000 times. Model outcomes from these simulations that are count data (such as costs, QALYs gained, number of new infections, etc.; as opposed to proportions, such as percentage of HIV-infected adults with viral suppression) were scaled-up to a population size equivalent to the population size of Kenya.

Section 2: Modeling Drug Resistance

A. Overview of Drug Resistance Model

Our model simulates the emergence of ADR in patients receiving ART and the transmission of drug resistance mutations from HIV-infected individuals to previously uninfected individuals. We model drug resistance status in each patient as the presence or absence of a mutation that confers resistance to the NNRTI class of antiretroviral drugs, and each mutation is modeled as being in either the majority or minority state over time. Each patient can have a maximum of one mutation. We define the development of ADR as the emergence of a drug resistance mutation while a patient is on ART. We define a transmitted drug resistance (TDR) mutation as a mutation in a patient that was transmitted to her by her source partner. Of note, we assume mutations can only be transmitted to others when they are in the majority state. When describing our model, we primarily use the term PDR, but PDR and TDR are essentially interchangeable terms, with respect to the model. The is different from the more common use of the term PDR, which includes both resistance among ART-naïve individuals (namely TDR) and resistance among individuals who are about to initiate first-line ART but have a prior history of ART exposure.[41] PDR, ADR, and majority/minority states are described in more detail below.

Although, in reality, HIV-infected individuals can have more than one mutation and can have mutations that confer resistance to multiple drugs or classes of drugs, we chose to only model mutations that confer resistance to the NNRTI class of drugs and allow a maximum of one mutation per individual for a few important reasons. First, this approach makes it feasible to conduct a one-way sensitivity analysis on the diagnostic sensitivity of OLA, which is important because we hypothesized that the diagnostic sensitivity of OLA would be correlated with whether or not OLA was cost-effective. If we had modeled more than one type of mutation and allowed individuals to have more than one mutation, the proportion of individuals with mutations detectable by OLA would likely change of time, preventing us from being able to directly control the diagnostic sensitivity of OLA through input parameters. Second, there is very little data describing the proportion of PDR at the population level that is made up by NNRTI vs. NRTI mutations over time, making it difficult to know if we are modeling these trends correctly. Third, when an HIV-infected individual has multiple mutations and transmits HIV to a sexual partner, there is limited data describing what proportion of the time more than one of these mutations is transmitted. We chose to focus on modeling NNRTI mutations because they are the most common PDR mutations, and in the absence of selective pressure, they tend to stay in the majority state for a longer period of time relative to other types of mutations.[42] For example, if a patient had PDR with a K103N and an M184V mutation, in the absence of selective pressure, the M184V mutation would likely convert to minority state prior to the K103N mutation would.

One of the limitations of modeling a maximum of one mutation per person is that when making assumptions about the probability of virologic failure in a patient with PDR, one cannot assign different probabilities associated with different types of mutations or with having multiple mutations. In general, there is limited published data describing increased risk of virologic failure associated with specific types of mutations or multiple mutations. However, we address this limitation through a one-way sensitivity analysis of the probability of virologic failure associated with

having PDR. Also, by modeling only one type of mutation, this may underestimate the prevalence of PDR, which we address through a one-way sensitivity analysis of PDR prevalence, described in detail in Section 5.

B. Transmission of Drug Resistance

Overview of transmission of drug resistance

We assume that when a source partner with a drug resistance mutation transmits HIV to another individual through sexual contact, the source partner's mutation will be also be transmitted if this mutation is in the majority state. We apply this assumption to all mutations, regardless of whether they originated from PDR or ADR. We also assume the presence of drug resistance does not affect the probability of HIV transmission occurring.

Because our model does not explicitly represent sexual partnerships between individuals in the model, it cannot determine who the source partners are for newly infected individuals. Thus, we do not know whether or not those source partners had drug resistance. As described in Section 1, at the start of each monthly cycle, the model probabilistically determines which individuals become infected with HIV, as a function of multiple factors, including number of sexual partners and viral load distribution in the population. Each monthly cycle, after the model determines which individuals are newly infected, we use a similar probabilistic approach to determine who among them received PDR. Individuals who have a mutation transmitted to them receive a maximum of one PDR mutation, as our model allows for a maximum of one mutation per individual. Although prior studies show that some patients may have multiple PDR mutations, the majority of patients with PDR have only one mutation.[43]

Algorithm for determining who receives PDR:

Step 1: For each newly infected individual, we assume the *probability of receiving PDR* is equal to the *prevalence of drug resistance in the majority state among patients of the opposite sex with unsuppressed viral load (>500 copies/mL)*, which is calculated by the following equation:

(number of individuals with unsuppressed viral load with a mutation in majority state) / (number of individuals with unsuppressed viral load)

This prevalence is calculated among patients with unsuppressed viral load because the probability of a patient with viral suppression transmitting HIV is close to zero.

Step 2: For each newly infected individual, a random number between 0 and 1 is generated and compared to the *probability of receiving PDR* (as defined in Step 1). For each newly infected individual, if this random number is less than or equal to the *probability of receiving PDR*, then the individual receives PDR.

C. Emergence of Acquired Drug Resistance

Overview

Our model simulates the emergence of ADR among patients who experience virologic failure on NNRTI-based first-line ART. A systematic review found that 53% to 90% of individuals with unsuppressed viral load at 48 weeks after ART initiation had drug resistance.[44] We assume the probability of developing ADR among patients with virologic failure on NNRTI-based first-line ART is 80%, based on published data and model calibration. Importantly, because our model allows for a maximum of one general mutation per individual, patients who already have a TDR mutation cannot develop a second mutation through ADR, and a patient can only develop one mutation through ADR while on ART.

Algorithm to determine who develops ADR

Step 1: During each monthly cycle, the model identifies patients who are eligible for developing ADR, based on meeting all of the following criteria:

1) No current drug resistance
2) On first-line ART
3) Experiencing virologic failure

Step 2: For each individual who is eligible for developing ADR, a random number between 0 and 1 is generated during the monthly cycle in which virologic failure occurs.

Step 3: This random number generated for each eligible individual is compared to the probability of developing ADR among patients who experience virologic failure on first-line ART, which is 80%.

Importantly, the presence of an ADR mutation does not increase the probability of failure in this model, as emergence of an ADR mutation is conditional upon a patient already experiencing virologic failure on first-line ART. The main purpose of simulating the emergence of ADR is to model the transmission of ADR and its contribution to the increasing prevalence of PDR. Also, we do not account for the emergence of ADR among patients who do not fail ART. We do not model the development of ADR among individuals on PI-based ART, including those who initiated treatment with PI-based ART in response to drug resistance testing results. Finally, we do not model the development of ADR among individuals on dolutegravir (**DTG**)-based ART.

D. Majority and Minority States

We model mutations as being in either the majority or minority state, and mutations can transition from the majority state to the minority state over time in the absence of selective pressure. The main purpose of modeling mutations as being in either the majority or minority state over time is to accurately model the prevalence of PDR over time, as we assume that only mutations in the majority state can be transmitted. Conceptually, we define a mutation as being in the majority state if it can be detected by consensus sequencing, which typically detects mutations present in at least 20% of the viral population. Individuals with a mutation present in less than ~ 20% of the viral population are referred to as being in the minority state. We assume mutations that develop through ADR transition from the majority to minority state within 3 months without selective pressure.[45,46] In contrast, PDR mutations (those transmitted from one partner to another) persist in the majority state for a significantly longer period of time.[42]

When an individual is first infected with HIV and receives PDR, the drug resistance mutation begins in the majority state. Because we model drug resistance status in each patient as the presence or absence of a mutation that confers resistance to the NNRTI class of antiretroviral drugs, selective pressure is applied to the mutation only when the patient is taking NNRTI-based ART. In the absence of selective pressure, each month we assume there is some probability the mutation will convert from the majority to the minority state. We will henceforth refer to this probability as the *minority conversion probability*. Our estimate of the *minority conversion probability* is based on a study that followed ART-naïve, HIV-infected individuals with PDR longitudinally to estimate what proportion of patients continue to have mutations detectable by consensus sequencing over time.[42] They used a parametric proportional hazard model to predict the percentage of transmitted mutations that would be expected to be in the minority state by 6 months, 1 year, 2 years, 3 years, and 4 years after HIV infection. Using data from Table 2 from *Jain et al.*, we calculated the monthly rate of conversion for NNRTI mutations, based on model projections for 6 months, 1 year, 2 years, 3 years, and 4 years after HIV infection. Next, we take the average of each of these monthly rates and convert to a monthly probability, which was equal to 0·0037 (95% CI 0·0009 – 0·0143). Based on our calibration (described in detail in Section 3), we used a value of 0·001, in order for our model PDR prevalence trends to be consistent with empirically observed trends.

Finally, if a mutation converts to the minority state, we assume that the mutation converts back to the majority state within one month of initiating first-line ART.[47]

E. Performance of Drug Resistance Tests

We define the **diagnostic sensitivity** of a PDR test as the proportion of individuals who truly have PDR who are diagnosed as having PDR.[48] First, in order for a PDR test to detect a PDR mutation in a patient, the PDR testing method must be capable of detecting the specific type of mutation this patient has. We assume consensus sequencing can detect all types of mutations that can confer resistance to ART. In contrast, OLA is designed to detect a pre-specified set of common and clinically significant mutations. For example, in a recent randomized trial in Kenya, the version of OLA used was designed to detect K103N, Y181C, G190A, and M184V.[49] Second, in order for a PDR test to detect a PDR mutation in a patient, the mutation must be present at a frequency above the PDR testing method's **analytical sensitivity**, which we define as the lowest frequency (or concentration) of a specific mutation in a sample detectable by a drug resistance test.[48] While OLA can detect mutants present with at least 2% frequency, consensus sequencing can typically detect mutants comprising at least 15-25% of an individual's virus population.[50]

We assume that OLA will detect 80% of PDR cases and CS will detect 100% of PDR cases. Although a meta-analysis found that only 59% of PDR cases in low- and middle-income countries had at least one mutation detectable by OLA,[51] a recent trial found that among subjects with virologic failure at 12 months, 100% of subjects with PDR detected by CS were also detected by OLA.[49] Thus, our assumption that OLA detects 80% of PDR cases is intended to synthesize data from these two studies. Our assumption that CS will detect 100% of PDR cases is likely an overestimation, given that OLA can detect mutations present at a lower frequency than CS.[50] We assume both tests have a specificity of 100%.

In the model, the ability of OLA or CS to detect PDR in an individual with a drug resistance mutation is independent of whether or not the mutation is in majority or minority state. In essence, this is assigning OLA and CS the same analytical sensitivity, which is not accurate. However, the reason we do this is it allows us to directly control the diagnostic sensitivity of OLA through the use of a "diagnostic sensitivity" input parameter. Finally, we conduct a one-way sensitivity analysis on the diagnostic sensitivity of OLA to address the simplifying assumptions we make regarding this parameter and also to understand how uncertainty associated with this parameter affects the cost-effectiveness of PDR testing with OLA.

F. Probability of Virologic Failure

Overview

The rationale behind each of the assumptions in Table S8 is described in detail below and are based on three major sources of data:

1. Studies describing viral suppression rates on first-line and second-line ART in sub-Saharan Africa, including Kenyan data[52-55]
2. Studies describing the increased risk of virologic failure associated with PDR compared to no PDR[49,56]
3. Model calibration to ensure that virologic failure parameters are consistent with observed PDR prevalence in East Africa (Appendix Section 3)

2003-2017		Source
Initial ART (over 12 months)		McMahon et al[52]; Hamers et al[56]; Chung et al[49]; Calibration
No PDR on NNRTI-based	20%	
PDR on PI-based	20%	
PDR on NNRTI-based[%]	47%	
Second-line, PI-based ART (over 24 months)	15·2%	Stockdale et al[55]
2018 to future		**Source**
Initial dolutegravir-based ART (over 12 months)	6·2%	Literature review in appendix of Dugdale et al[57] (see "Dolutegravir-based First-line ART" section below)
Initial non-dolutegravir-based ART (over 12 months)		Kenya Ministry of Health[53]; Hamers et al[56]; Chung et al[49]
No PDR on NNRTI-based	13·6%	
PDR on PI-based	13·6%	
PDR on NNRTI-based[%]	32·0%	
Second-line, PI-based ART (over 24 months)	15·2%	Stockdale et al[55]

Table S8. Probability of virologic failure by PDR and ART status

We assume a lower probability of virologic failure on first-line ART from 2018 and onwards compared to 2003-2017 compared to 2018 and onwards to reflect recent trends of lower rates of virologic failure, which are likely due in large part to improved adherence in an effort to achieve UNAIDS 90-90-90 goals. Our assumptions about the probability of virologic failure from 2003-2017 are consistent with systematic reviews and allow the model to generate a PDR prevalence consistent with observed trends (see Section 3),[52] and our assumptions from 2018 onwards are consistent with recent estimates of viral suppression in Kenya.[53] The probability of virologic failure on an initial ART regimen is assigned based on a patient's PDR status and ART regimen. During the time periods "2003-2017" and "2018-future", we assume that the odds of virologic failure are 3·5 times and 3.0 times higher, respectively, for patients with PDR to one's ART regimen compared to those with no PDR.[49,56] The lower odds ratio for the "2018-future" time period is meant to reflect more recent evidence suggesting that the risk of virologic failure associated with PDR is lower with NNRTI-based regimens including efavirenz/tenofovir compared to those containing nevirapine and/or zidovudine.[58] For patients who fail NNRTI-based first-line ART and switch to PI-based second-line ART, we assume the same probability of virologic failure before and after 2018.

Of note, to operationalize a 12-month probability of failure in the model, it is converted into a monthly probability through the following steps, where p = probability, t = time, and r = rate:

1) Convert the 12-month probability to a 1-month rate: $\boldsymbol{p = 1 - \exp^{(-rt)}}$**, where** $\boldsymbol{t = 12}$
2) Convert the 1-month rate to a 1-month probability: $\boldsymbol{r = (-\ln(1 - p)) / t}$**, where** $\boldsymbol{t = 1}$

2003-2017 First-Line NNRTI-based ART without PDR and with PDR

First-line NNRTI-based ART Without PDR

Prior to 2018, estimates of the probability of virologic failure after 12 months on first-line (NNRTI-based) ART in sub-Saharan Africa vary widely, with reported values ranging between 8 to 30% at 12 months after ART initiation.[52] In the 2012 Kenya AIDS Indicator survey, 26·1% of those surveyed who were on ART did not have viral suppression.[59] It is important to note that most of these studies do not make a distinction between individuals with and without PDR, so there may be some individuals included in these analyses who had PDR to NNRTI-based ART.

We assumed the "true" mean probability of virologic failure on NNRTI-based first-line ART in Kenyan adults was within the range of values reported in the literature. In order to select a point estimate for use as a model input parameter, we calibrated the model to multiple targets, including PDR prevalence. As described in Section 2B, both PDR mutations and ADR mutations can be transmitted to newly infected individuals. Thus, as the prevalence of ADR increases, the prevalence of PDR also increases because there is a larger pool of individuals with resistance that can transmit mutations to others. The majority of ADR occurs in patients with treatment failure, and our model only allows for ADR to develop in patients on ART experiencing treatment failure. The prevalence of ADR increases as the absolute number of people experiencing virologic failure increases, which increases with a higher probability of virologic failure. We found that, when using a 20% probability of virologic failure on first-line ART over 12 months, our model generated PDR prevalence levels consistent with observed levels. This probability was also applied to those with PDR on PI-based ART because prior studies have found rates of failure similar to those without PDR on NNRTI-based ART.[56]

First-line NNRTI-based ART with PDR

Once we established the probability of virologic failure on initial ART for patients without PDR, we used data from two studies to estimate the odds ratio of virologic failure for patients with PDR to initial ART compared to patients without PDR to initial ART. First, a multi-center cohort study conducted in six sub-Saharan African countries (including Kenya) found that compared to participants without PDR, the odds ratio for virologic failure was increased (OR = 2·13) in participants with PDR to at least one prescribed drug, but not in individuals with PDR and fully active ART.[49,56] Second, in a randomized clinical trial in Kenya, among subjects with PDR to first-line ART, those who underwent drug resistance testing and started PI-based ART had a 14·3% probability of failure at 12 months compared to 50·0% probability of failure at 12 months in those who were not tested for drug resistance and started NNRTI-based ART.[49] Expressed a different way, compared with subjects with PDR on PI-based ART, the odds ratio for virologic failure was 5·99 in subjects with PDR to at least one prescribed drug. Because failure rates were similar in those without PDR on NNRTI-based ART and those with PDR on PI-based ART, we assumed the odds ratio is also applicable to comparing those with PDR to at least one prescribed drug to those without PDR on NNRTI-based ART.

Thus, these two studies provide odds ratios ranging from 2·13 to 5·99 estimating the increased risk of failure in those with PDR to at least one prescribed drug to those on fully active ART. For the 2003-2017 time period, we chose to use an odds ratio of 3·5 to calculate the probability of failure among those with PDR to at least one prescribed drug. This OR of 3·5 is skewed slightly towards the cohort study because it had a larger sample size of subjects with PDR. Using a 20% probability of failure over 12 months among individuals without PDR on NNRTI-based first-line ART (during 2003-2017) and an OR of 3·5, this produces a 12-month probability of failure of 47% among those with PDR to NNRTI-based first-line ART.

2018 to Future Efavirenz-based First-Line ART with and without PDR

In response to UNAIDS 90-90-90 goals, rates of viral suppression have increased over time, likely due in large part to improved adherence. According to 2018 estimates, approximately 84% of HIV-infected adults on ART in Kenya are virally suppressed (16% had virologic failure).[53] This data does not provide estimates of virologic failure rates among those without PDR and among those with PDR, which is what we need to parameterize our model. We used an algebraic approach to estimating these parameters, where:

- X = probability of virologic failure on efavirenz-based ART without PDR (over initial 12 months on ART)
- Y = probability of virologic failure on efavirenz-based ART with PDR (over initial 12 months on ART)

Our algebraic approach included the following assumptions:

- Proportion of HIV-infected patients on ART with virologic failure in 2018 = 16%
- We assumed proportion of patients with virologic suppression among patients on ART stays relatively stable after the first 12 months on ART[54] (see section on "Long-term Probability of Failure on First-line ART" below)
- PDR prevalence in 2018 = 12·6%. This was the average PDR prevalence in 2018 based on estimates from our model, which is calibrated to observed trends.
- Odds ratio of the probability of virologic failure for patients with PDR to initial ART compared to patients without PDR to initial ART is 3·0.

We solved for X and Y using the following 2 equations:

- $0.874X + 0.126Y = 0{\cdot}16$
- $(Y/(1-Y)) / (X/(1-X)) = 3{\cdot}0$

We found X = 13.6% and Y = 32%.

We used an odds ratio of 3.0 for "2018 to future", as opposed to the odds ratio of 3·5 we used for 2003-2017, to reflect evidence suggesting that suggest the risk of virologic failure with PDR may be lower with the tenofovir/emtricitabine/efavirenz combination compared to other NNRTI-based regimens.[58] In a one-way sensitivity analysis, we varied the probability of virologic failure on efavirenz-based ART with PDR from 23·9-48·6%, such that the odds of virologic failure for those with PDR on efavirenz-based ART compared to those with either no PDR on efavirenz-based ART or those with PDR on PI-based ART varied from 2·0 to 6·0.

Dolutegravir-based First-line ART

There are currently no population-level estimates of rates of virologic suppression with dolutegravir-based ART in Kenya. Thus, we used a recent literature review to inform our assumptions about the relative risk of virologic failure with dolutegravir-based ART compared to efavirenz-based ART.[57] To parameterize their model-based analysis, Dugdale et al performed a literature review of randomized clinical trials reporting virologic suppression with dolutegravir or efavirenz in combination with two nucleoside reverse transcriptase inhibitors and then pooled these estimates (and weighted by study size). They estimated that the probabilities of viral suppression after 48-weeks on efavirenz-based (only subjects without PDR were eligible) and dolutegravir-based ART were 91% and 96%, respectively. Based on these estimates, for patients without efavirenz-associated PDR, the odds of virologic failure with efavirenz-based ART are 2·37 times higher (odds ratio = 2·37) than the odds of virologic failure with dolutegravir-based ART. Based on this odds ratio of 2·37 and our prior assumption that the probability of virologic failure with efavirenz-based ART without PDR (during the first 12 months of ART) is 12%, we estimate that the probability of virologic failure with dolutegravir-based ART in Kenyan adults (during the first 12 months of ART) is 5·5%. We assume efavirenz-associated PDR does not influence the probability of virologic failure on dolutegravir-based ART. To our knowledge, data from Botswana is the only published programmatic data (non-clinical trial) evaluating viral suppression rates on dolutegravir-based ART sub-Saharan Africa, which found an overall viral suppression rate of 97·4% at 12 months after initiating dolutegravir-based ART.[60]

Long-term Probability of Failure on First-line ART

Data from the clinical studies described above are limited to the first 12 months after ART initiation. Our assumptions about the long-term probability of virologic failure are based on a systematic review/meta-analysis.[54] Table 2 from Boender *et al*. provides estimates of the probability of virologic suppression over 6 to 60 months after initiation of first-line ART, using both on-treatment and intention-to-treat analyses.[54]

Months on ART	Random Effects Meta-Analysis		
	Summary Estimate	Low 95% Confidence Interval	High 95% Confidence Interval
6	84·9	83·5	86·3
12	85·6	84·4	86·9
24	84·4	82·0	86·9
36	88·5	85·5	91·4
48	88·6	84·2	93·0
60	85·2	76·6	93·9

Table S9. Virologic Suppression after 6 to 60 Months of First-Line ART On-Treatment Analysis. Adapted from Boender *et al*.[54]

Because our model already accounts for individuals dropping out of ART use, from either being lost to follow-up and mortality, we focused on the on-treatment analysis results, which suggests that the proportion of patients who experience virologic failure while on first-line ART does not grow substantially after the first 12 months.[54] Our interpretation of these results is that, after the first 12 months on ART, some patients who previously had virologic failure eventually achieve viral suppression and some patients who previously had virologic suppression experience virologic failure. Amongst patients on ART, the rate of switching between these two states occurs at such as rate that the overall proportion of patients with virologic suppression remains relatively stable over the long-term.

We wanted our model assumptions to produce results consistent with the meta-analysis' finding that the overall proportion of patients with virologic suppression remains relatively stable over the long-term. One option would have been to actually model some long-term probability of virologic failure beyond the first 12 months of ART, as well as some long-term probability of re-achieving virologic suppression after experiencing virologic failure. However, we identified two disadvantages to using this approach. First, we do not know what these long-term probabilities of virologic suppression and failure are. Second, we thought this would make our model unnecessarily more complex and prone to potential errors in the code.

Instead, we assume that if an individual on first-line ART has not experienced virologic failure during the first 12 months of first-line ART that they will continue to maintain viral suppression on this regimen in the future. To be consistent, we apply this assumption to all individuals on NNRTI-based first-line ART, regardless of PDR status, and individuals on DTG-based first-line ART. However, if an individual discontinues ART due to being lost to follow up after 12 months, then this individual will not maintain viral suppression.

PI-based Second-line ART

Our estimate of the probability of virologic failure on PI-based second-line ART is based on a meta-analysis of sub-Saharan African studies by Stockdale et al.[55] Based on their on-treatment analysis at 96 weeks, we assume that once an individual has switched from first-line ART to second-line PI-based ART, the probability of virologic failure is 15·2% over 24 months in our base-case analysis (range for one-way sensitivity analysis is 10·1-21·2% over 24 months). We assume that if a patient has not experienced virologic failure on second-line ART after 24 months, she will maintain viral suppression while on second-line ART. Because we do not model resistance to PI-based ART, this probability of virologic failure is applied uniformly to all individuals on second-line ART.

Section 3: Model Calibration

A. Overview of Calibration

In order to determine what combination of input parameter values to use in the model, we calibrated our simulation model to observed trends in Kenya and sub-Saharan Africa for multiple target outcomes: HIV and PDR prevalence, proportion of HIV-infected individuals on any ART, proportion of HIV-infected individuals on PI-based ART, and population growth. Some aspects of the calibration have been described above in Sections 1 and 2. Here, we provide an overview of our model calibration and additional details that have not been described thus far.

At the beginning of the calibration process, we started with parameter values based on best available reported estimates. These estimates were subsequently adjusted manually to match relevant calibration targets, while using estimates that are within reported 95% confidence intervals for these parameters. Only parameters that strongly influence the value of our calibration targets over time were adjusted through calibration and are described below.

First, we adjusted parameters related to the cascade of care in order to reproduce ART coverage trends similar to those observed in Kenya over time, as described in Section 1. Next, multiple parameters were adjusted to match PDR prevalence and HIV prevalence, simultaneously. This included: 1) probabilities of virologic failure (during 2003-2017), based on PDR status and ART regimen; 2) probability of developing ADR among individuals with virologic failure on NNRTI-based first-line ART); 3) probability of switching to second-line ART when virologic failure is identified (during 2003-2017); and 4) probability of mutation to converting from majority to minority state over time.

B. Relationship Between PDR Prevalence and Key Parameters

There are several key parameters that strongly influence the prevalence of PDR over time. Both PDR mutations and ADR mutations can be transmitted to newly infected individuals (described in Section 2). As the prevalence of ADR increases, the pool of individuals with resistance that can be transmitted to others increases, and prevalence of PDR increases as a result of this. Because we assume ADR develops among a portion of patients on ART who experience virologic failure, the prevalence of ADR increases as the absolute number of people experiencing virologic failure increases, which increases with higher ART coverage rates and a higher probability of virologic failure. Therefore, PDR prevalence will increase with *increasing* values of: 1) ART coverage, 2) probability of virologic failure on initial ART, and 3) probability of developing ADR among individuals with virologic failure on 1st-line ART. PDR prevalence will also increase as the probability of switching to second-line ART when virologic failure is detected *decreases* because this prolongs the time during which patients with drug resistance mutations are virally unsuppressed and able to transmit their resistance to others.

Estimates of the probability of virologic failure at one year on first-line, NNRTI-based ART in sub-Saharan Africa vary widely, with reported values ranging between 8 to 30% at one year (see Section 2F).[52] We found that a 12-month probability of virologic failure of 20% on 1st-line ART among HIV-infected adults without PDR, along with an 80% probability of developing ADR among patients with virologic failure would generate sufficient ADR to allow for the PDR prevalence trend observed empirically in Kenya/East Africa (while using values for the probability of switching to PI-based second-line ART after virologic failure was detected, described in Section 1).

C. Comparing Model Outputs to Calibration Targets

Overview

HIV and PDR prevalence trends and model outputs are illustrated in Figure 1 of the manuscript. In this section, Figures S1 and S2 illustrate model outputs for ART coverage and the proportion of patients on ART on PI-based second-line ART alongside historical trends in Kenya.

PDR Prevalence

Our model was calibrated to two sources of data on the prevalence of PDR in East Africa. First, Gupta *et al*. 2012 provided estimates of PDR prevalence (including both NNRTI and NRTI mutations) in East Africa among ART-naïve individuals from 0-9 years after the initiation of ART roll-out (with the assumption that ART became available in 2001 in Kenya).[61] Second, Gupta *et al*. 2017 provided an estimate of NNRTI-associated PDR prevalence in East Africa

in 2016, which includes both treatment-naïve individuals and those reporting prior exposure to ART who are initiating first-line ART.[41] The PDR prevalence predicted by our model was within the 95% confidence intervals for three out of the four empirical estimates that served as calibration targets. The PDR prevalence projected by our model in 2016 is below the range estimated by Gupta *et al*, 2017.[41] The numerator and denominator for PDR prevalence are "number of pre-ART patients with PDR" and "number of pre-ART patients", respectively.

In Figure 1B, there are three relatively small discontinuities in our model PDR prevalence estimates at the start of the years 2010, 2014, and 2016, which are caused by a combination of ART coverage expansion and the stochastic nature of our model. At the beginning of each of these three years, we assume ART coverage expands, based on evolving ART initiation criteria in treatment guidelines (see Section 1D). When ART coverage expands from one month to the next, both the numerator for PDR prevalence (number of pre-ART patients with PDR) and the denominator (number of pre-ART patients) should decrease. Whether PDR prevalence itself increases or decreases depends on the percent reduction in the size of the numerator and denominator.

After accounting for ART initiation criteria (either based on CD4 cell count threshold pre-2016 or treating all HIV-infected patients after 2016), our model selects patients for ART initiation at random and without considering PDR. Thus, in theory, when ART coverage suddenly expands, the percent reduction in the PDR prevalence numerator and denominator should be the same, which would keep PDR prevalence constant. For example, let us consider a case in which PDR prevalence is currently 10%, with 10 pre-ART patients with PDR (PDR prevalence numerator) and 100 pre-ART patients (PDR prevalence denominator). The following month ART coverage expands such that an additional 10 patients are started on ART. The model would choose 10 out of the 90 pre-ART patients, at random, to initiate ART. If the sampling is done at random an infinite number of times, on average, the model would select 1 patient with PDR and 9 patients without PDR, since the prevalence of PDR is 10%. Now, we have 9 pre-ART patients with PDR (10% reduction in numerator), 90 pre-ART patients (10% reduction in denominator), and PDR prevalence remains constant at 10%. This also assumes that PDR prevalence is not changing for reasons other than changes in ART coverage. Because of the small number of pre-ART patients with PDR relative to the size of the population and the stochastic nature of the model, the proportion of patients with PDR among new patients initiating ART is not always equal to the PDR prevalence at that time. Thus, the percent reduction in the numerator and the denominator each time ART coverage expansion happens is not exactly the same, which results in the visible model estimate discontinuities.

In Table S10, we show the number of pre-ART patients and the number of pre-ART patients with PDR in the month preceding and first month of 2010, 2014, and 2016, and we show the percent reduction in each of these numbers from one month to the next. In 2010 and 2014, the percent reduction in the denominator is larger than that for the numerator, which results in a sudden increase in PDR prevalence. In contrast, in 2016, the percent reduction in the numerator is larger than that for the denominator, which results in a sudden decrease in PDR prevalence.

	Number pre-ART with PDR (numerator)	% change in number pre-ART with PDR (numerator)	Number pre-ART (denominator)	% change in number pre-ART (denominator)
Final month 2009	2,678		47,990	
First month 2010	2,547	-5%	43,412	-10%
Final month 2013	3,363		36,764	
First month 2014	2,860	-15%	30,442	-17%
Final month 2015	3,091		27,249	
First month 2016	1,510	-51%	15,428	-43%

Table S10. Values for Numerator and Denominator of PDR Prevalence at Discontinuous Data Points

HIV Prevalence

Population-level survey estimates of HIV prevalence (15-49 years) in Kenya are from the Kenya Demographic and Health Survey (2003 & 2009) and the Kenya AIDS Indicator Survey (2007 & 2012).[5,7,28,62]

ART Coverage

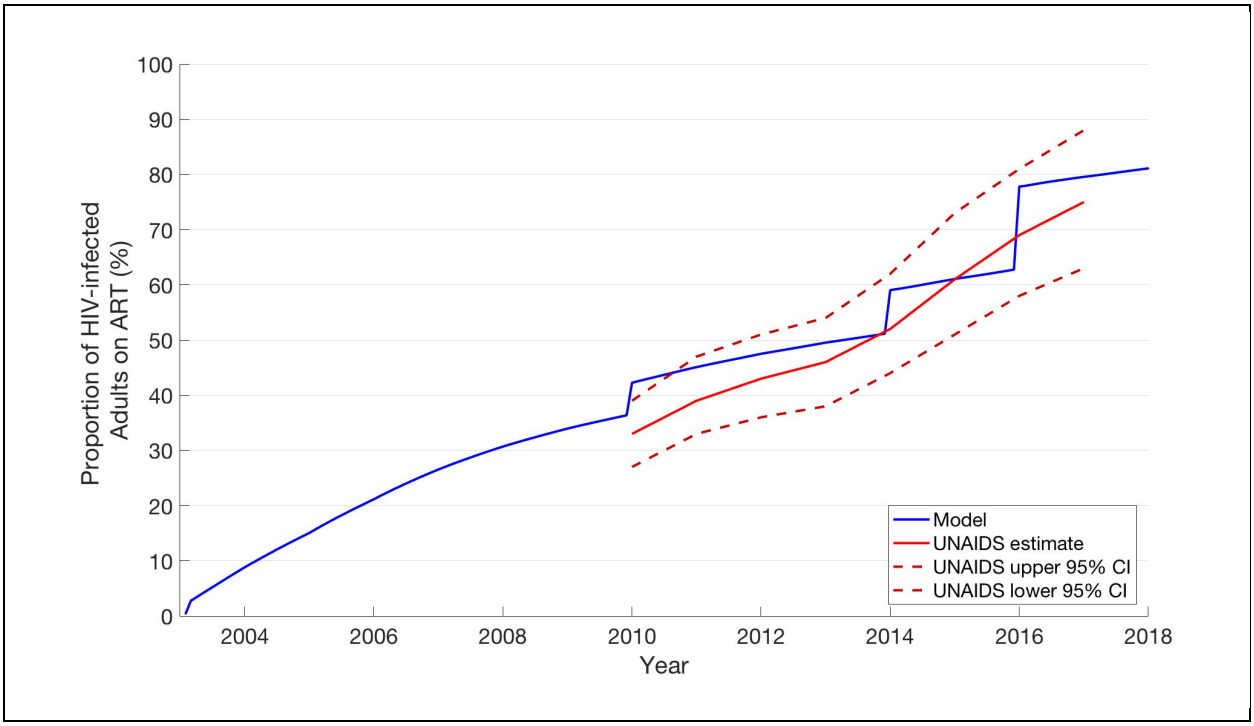

Figure S1. Proportion of adults 15 year and older living with HIV on ART.
UNAIDS Kenya data from 2010-2017 was used for calibration, as ART coverage data prior to 2010 was not readily available.

Proportion of Patients on ART on PI-based Second-line ART

We calibrated our model to estimates of the proportion of patients on ART in Kenya using PI-based ART at two time points (2006 and 2018), which was used to inform the model inputs for the probability of switching to PI-based second-line ART when virologic failure is detected.

A multi-country survey conducted in resource-limited settings by WHO found that in 2006, among adults on ART, 4% were on second-line ART (PI-based) and 96% were on first-line ART.[33] Based on data published online by the Kenyan National AIDS/STD Control Programme (NASCOP), we estimate that in 7·4% of patients on ART in Kenya in 2018 were using PI-based ART.[34] NASCOP reports the number of viral load tests that have been performed in Kenya, providing a breakdown of the number of patients on each specific combination of antiretroviral agents. We summed the total number of viral load tests performed for patients on PI-based ART and divided by the total number of viral load tests performed for all patients on ART. Assuming that the probability of a patient having a viral load test performed does not significantly differ between different ART regimens, this should provide a reasonable estimate for the proportion of patients on ART in Kenya using PI-based ART in 2018 year.

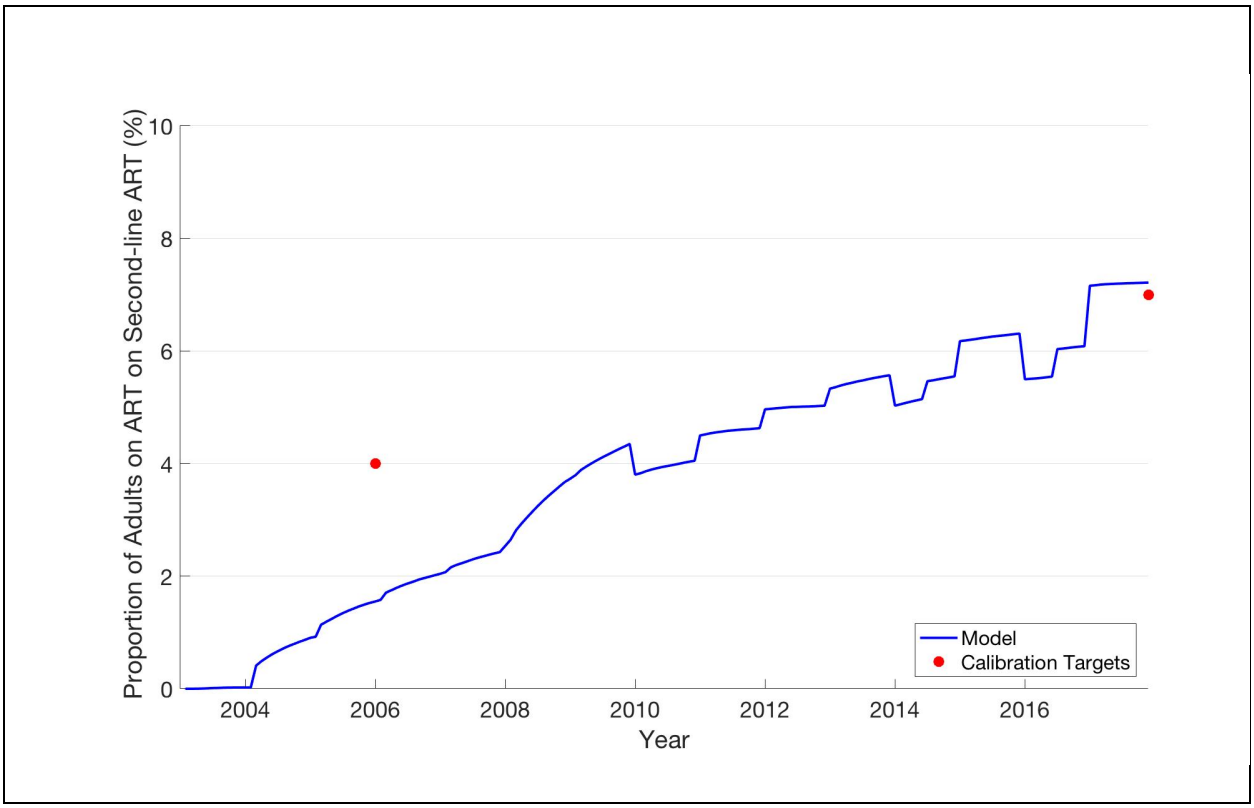

Figure S2. Proportion of adults on ART on PI-based second-line ART
Estimates for 2006 and 2018 calibration targets are from Renaud-Thery et al. and Kenyan National AIDS/STD Control Programme data.[33,34]

Section 4: Costs and Resource Utilization

A. Assumptions for Inpatient Costs

In the model, the probability of an HIV-infected individual developing an opportunistic infection depends on the patient's CD4 cell count. When someone does develop an opportunistic infection, we assume the patient is admitted to an inpatient health facility, and the number of inpatient days needed depends on the CD4 cell count and ART status (Table S11).[63] After adjusting for inflation, the unit cost of an inpatient day in Kenya is $60 (2019 US$).[64] To calculate the total cost of an opportunistic infection, the number of inpatient days is multiplied by the unit cost of an inpatient day in Kenya.

CD4 Cell Count	Mean Length of Stay (days)
Pre-ART	9·8
≤ 100 cells/mm^3	8·1
101-200 cells/mm^3	7·8
201-350 cells/mm^3	6·4
>350 cells/mm^3	7·8
On ART	
≤ 100 cells/mm^3	12·3
101-200 cells/mm^3	13·4
201-350 cells/mm^3	9·5
>350 cells/mm^3	7·0

Table S11. Average number of inpatient days per opportunistic infection by ART status and CD4 cell count. Adapation of Table 2 from Meyer-Rath et al.[63]

While the unit cost used per inpatient day is based on an estimate from Kenya, the number of inpatient days per opportunistic infection is based on a South African study.[63] To address uncertainty in the total inpatient costs, we conducted a one-way sensitivity analysis of the unit cost per inpatient day ranging from US$15 to US$240 (base-case unit = US$ $60). This range was meant to capture uncertainty in both unit cost per inpatient day and the number of inpatient days per opportunistic infection. For example, the $15-unit cost scenario was meant to represent a situation in which the unit cost was only $30 (50% of base-case unit cost) and each opportunistic infection resulted in only 50% the number of inpatient days relative to those found in the South African study. Similarly, the $240-unit cost scenario was meant to represent a scenario in which the unit cost was $120 (double the base-base unit cost) and each opportunistic infection resulted in double the number of inpatient days relative to those found in the South African study. This approach is based on the mathematical relationship that doubling, or halving, the number of inpatient days per opportunistic infection has the same effect on total inpatient costs as doubling, or halving, the cost per inpatient day, respectively.

B. Adjusting for inflation

Unit cost estimates for each inpatient day and each outpatient visit in Kenya were originally reported in 2011 US$.[64] For these estimates, we adjusted for inflation in Kenya from 2011 to 2019 by using inflation indices provided by the International Monetary Fund (IMF).[65]

We visited the IMF website on 5/16/19 and obtained the following inflation indices for the Kenyan health sector.

- Kenya Health Inflation Index 2011 M01 = 110.42
- Kenya Health Inflation Index 2019 M01 = 160.89

The unit cost estimates provided by IHME in 2011 US$ for inpatient day and outpatient visit were:[64]

- Inpatient day =US$41
- Outpatient visit = US$10

We used the following equation for adjusting for inflation and converting from 2011 cost to 2019 cost:

- Cost2019 = (Cost2011 * Index2019) / Index2011
- Cost2019 = (Cost2011 * 160.89) / 110.42

Using this equation, and after rounding to the nearest dollar, the unit cost estimates that adjust for inflation per inpatient day and outpatient visit were US$60 and US$15, respectively.

C. Currency conversion

While other unit cost estimates we obtained were already reported in US$, the unit cost estimate for CD4 cell count test we obtained in April 2019 was originally in Kenyan shillings (KES). On April 19, 2019 the conversion rate from Kenyan shillings (KES) to US$ was 0.009863 KES to US$1. Using this conversion rate, the cost per CD4 cell count test equaled US$11.83. We rounded up to $12 for the base-case, and in sensitivity analysis explored values ranging from US$6 to US$24

D. Results

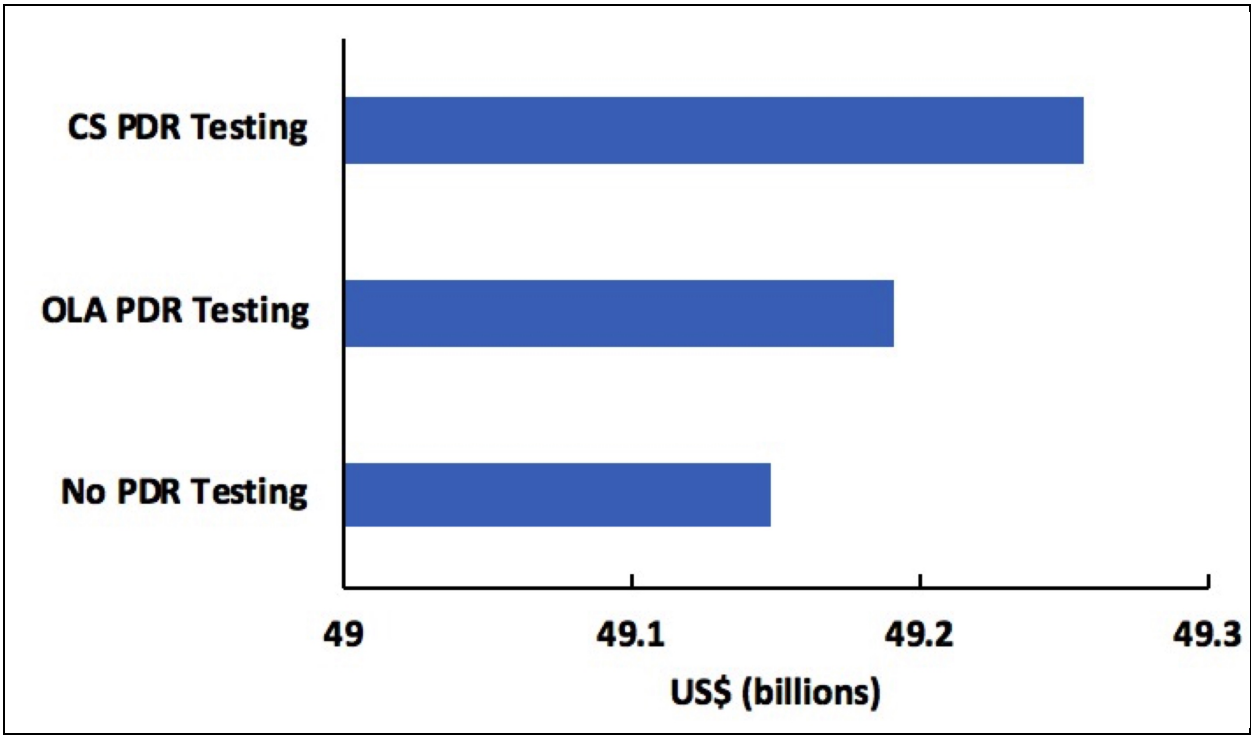

Figure S3. Total cost of each strategy over 15 years

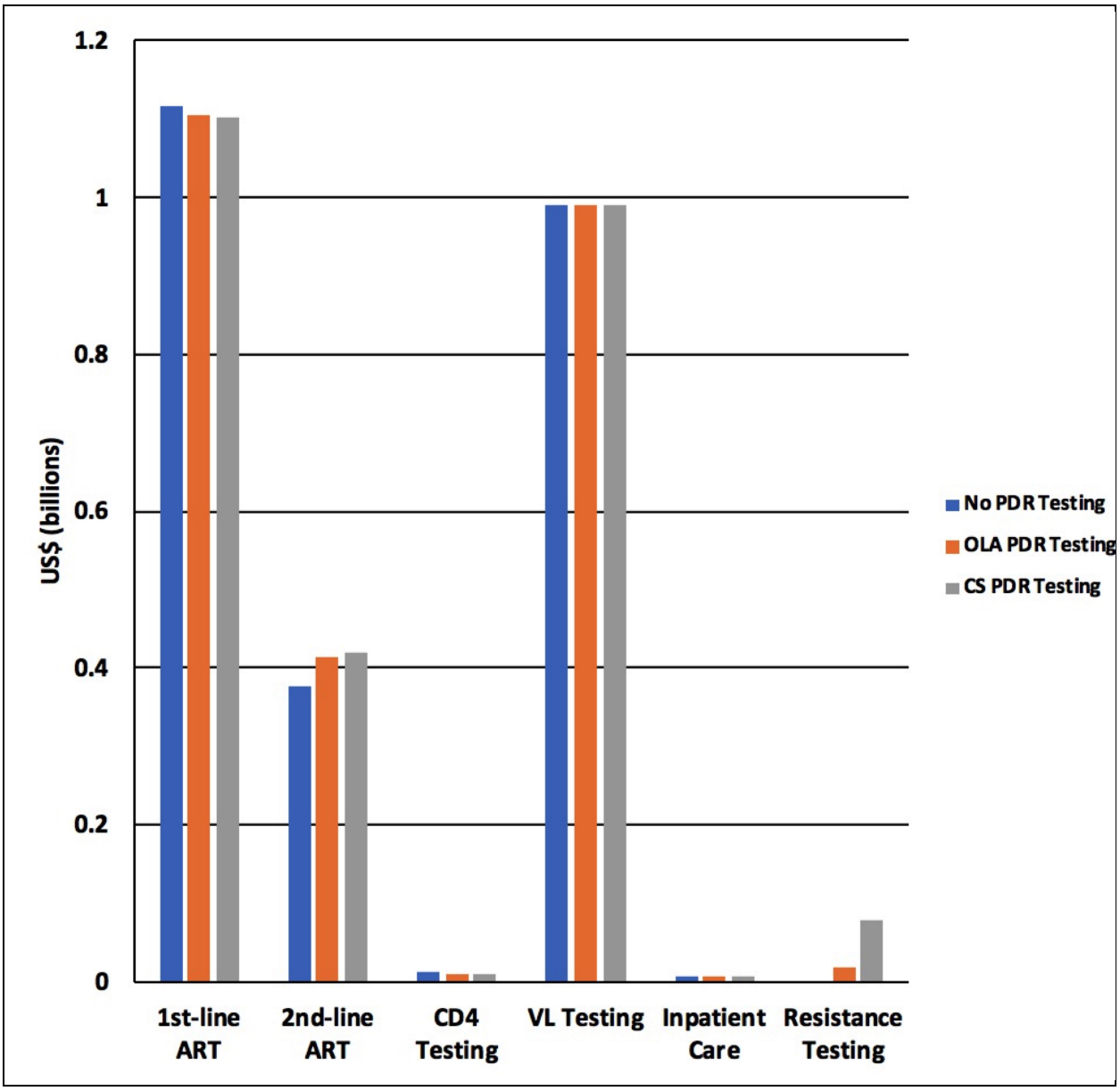

Figure S4. Cost for each strategy by spending category over 15 years
This figure does not include HIV screening and background health spending categories.

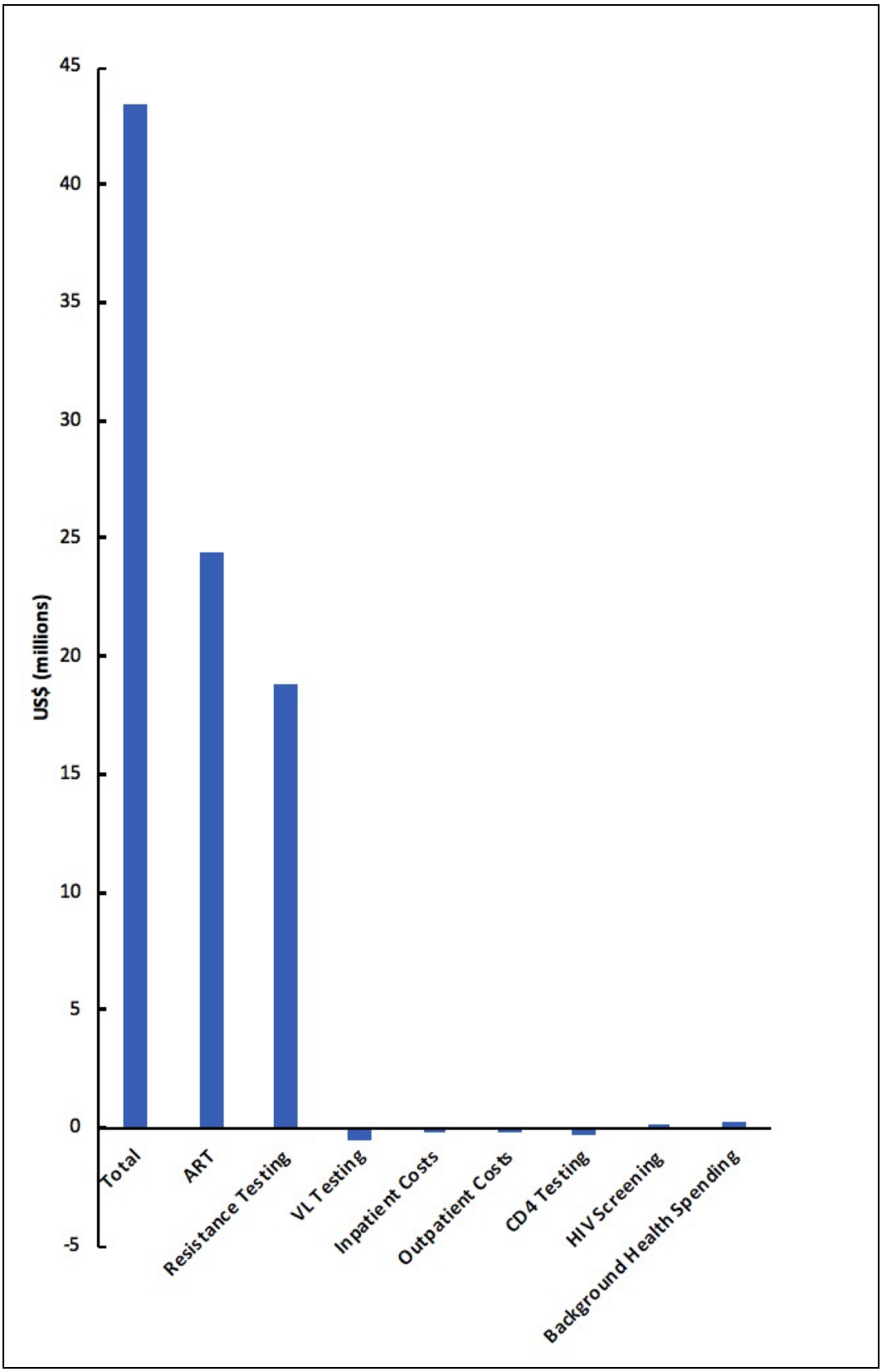

Figure S5. Difference in cost between OLA PDR testing and no testing over 15 years by category

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