

Cost-effectiveness analysis of pre-ART HIV drug resistance testing in Kenya

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Abstract

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Aim: The prevalence of HIV pre-treatment drug resistance (**PDR**) is increasing in East Africa, which may decrease the effectiveness of antiretroviral therapy (**ART**) programs. Our objective was to evaluate whether testing for PDR with an oligonucleotide ligation assay (**OLA**), a low-cost point mutation assay, is a cost-effective strategy to address the challenges posed by PDR in resource-poor settings.

Methods: We developed an HIV drug resistance model that simulates the emergence and transmission of resistance mutations, calibrated to the Kenyan epidemic. We implemented 3 care strategies for PDR testing: current policy (no PDR testing), PDR testing with OLA, and PDR testing with consensus sequencing (**CS**), each with initial viral load (**VL**) testing performed at 6 months after ART initiation and every 12 months thereafter. This model was used to evaluate the health outcomes, lifetime costs, and cost-effectiveness of the strategies over a 15-year time horizon starting in 2018.

Results: OLA PDR testing had an incremental cost-effectiveness ratio (**ICER**) of \$1,790/QALY gained, which is cost-effective by national income standards. PDR testing with CS was not cost-effective. OLA PDR testing resulted in more patients maintaining viral suppression at 12 months after ART initiation compared to the current policy (82% vs. 77%, respectively). PDR testing with OLA was also associated with 3% fewer new HIV infections than the current policy. Initial PDR prevalence was 9.2% in 2018. By 2033, this prevalence increased to 20.3% when continuing the current policy, but only to 18.6% with OLA PDR testing.

Conclusions: Low-cost PDR testing is cost-effective compared to no PDR testing in settings where dolutegravir is not available. Over time, testing for PDR has the potential to reduce the growth of PDR prevalence in resource-poor settings.

Introduction

The expansion of antiretroviral therapy (**ART**) delivery programs across sub-Saharan Africa has resulted in significant reductions in HIV-related adult mortality.^{1,2} While ART delivery has expanded, the prevalence of pre-treatment drug resistance (**PDR**) to non-nucleoside reverse transcriptase inhibitors (**NNRTI**)-based ART regimens has increased,³ which may decrease the effectiveness of ART programs, as patients with PDR to their ART regimen have an increased risk of virologic failure.⁴⁻⁶ Routine PDR testing has been the standard of care in the U.S. for over ten years and is considered cost-effective in high-income settings.⁷⁻⁹ Meanwhile, the clinical use of drug resistance testing in resource-limited settings (**RLS**) has been extremely limited due to the costs of reagents and the infrastructure needed to perform conventional consensus sequencing (**CS**).¹⁰ Thus, there has been interest among experts to develop a simple, low-cost HIV drug resistance (**HIVDR**) assay to conduct cost-effective PDR testing to guide selection of initial ART regimens.¹¹

Alternatively, a second major strategy to improve health outcomes in settings with high prevalence of PDR to NNRTI agents is the implementation of empiric dolutegravir-based first-line ART. Generic dolutegravir recently became available in RLS, and it may obviate the need for PDR testing, as it has a high genetic barrier to resistance and currently costs less than NNRTI's.^{12,13} Indeed, a recent modeling study found that empiric dolutegravir-based first-line ART is likely to improve health outcomes and be cost-saving compared to empiric NNRTI-based first-line ART in sub-Saharan Africa.¹³ While use of dolutegravir is likely to contribute to improved health outcomes in RLS, there are still several uncertainties regarding its use, including its safety during pregnancy and breastfeeding and its potential interactions with tuberculosis drugs.¹⁴ In addition, it

will likely take several years to make dolutegravir available to all patients initiating ART in RLS.¹⁵ Thus, it is important to evaluate the cost-effectiveness of alternative strategies to address PDR in settings in which dolutegravir is not available. While prior cost-effectiveness analyses have included PDR testing as a potential strategy to address the high prevalence of PDR in RLS,^{13,16,17} none have evaluated simple, low-cost HIVDR assays separately from conventional CS. Moreover, given that multiple point-of-care HIVDR assays are currently in development,¹⁸ cost-effectiveness analyses are needed to guide their potential use in RLS.

The oligonucleotide ligation assay (**OLA**) is an HIVDR point-mutation assay that requires relatively simple and inexpensive equipment and is designed to detect “major mutations” commonly selected by NNRTI-based, first-line ART regimens.^{5,19,20} In a recent randomized clinical trial (**RCT**), Kenyan technicians were trained and successfully implemented a laboratory-based version of the OLA to guide choice of initial ART regimen.^{21,22} Within this RCT, OLA was performed at an average cost of \$42 per test,²² and a simpler kit is currently being developed, which is likely to have an even lower cost.²³ In this study, we present a cost-effectiveness analysis comparing three strategies to address the high prevalence of PDR in Kenya: status quo (no PDR testing), PDR testing with OLA, and PDR testing with CS, within the context of NNRTI-based ART as the standard first-line regimen.

Methods

HIV Model

We developed an individual-based stochastic model that simulates HIV disease, treatment, and transmission,²⁴⁻²⁶ as well as the selection and transmission of mutations conferring drug resistance

to NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) drugs and their effect on treatment.²⁷ The model was parameterized and calibrated to simulate a population similar to the adult population in Kenya. We designed the model to follow a group of 100,000 adults over age 15-years, representative of the population in Kenya, where the mode of transmission is predominantly heterosexual. We run the model starting in 2003 with parameters that reproduce the HIV epidemic in Kenya through the end of 2017. In 2018, we begin simulating different PDR testing strategies to compare their associated costs and health outcomes over a 15-year time horizon.

Individual-level characteristics include 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. To construct the initial population in 2003, we used age- and gender-stratified population data from Kenyan population pyramids,²⁸ as well as Kenyan age- and gender-stratified HIV prevalence data.²⁹ We obtained the prevalence of male circumcision from published estimates.²⁹ The population size changes based on maturation into the population (people who age into the population at age 15 years) and deaths.²⁸ Mortality attributable to HIV was subtracted from the model's age- and gender-stratified background mortality rates,³⁰ and the probability of HIV-related death was predicted by CD4 cell count.³¹

The risk of infection for those who are HIV-negative was evaluated monthly in several stages, based on number of sexual partners,²⁹ the likelihood that an individual has a partner who is HIV-

infected (based on the dynamic HIV prevalence), and the likelihood of transmission of HIV as a function of number of sex acts per month, partner's HIV status (acute HIV vs. chronic HIV with consideration of viral load),^{32,33} and risk modifications such as male circumcision.³⁴ Key model parameter values are shown in **Table 1**.

Testing Strategies Modeled

We modeled comparative clinical and cost-effectiveness outcomes of the status quo, PDR testing with OLA, and PDR testing with CS, over a 15-year time horizon starting in 2018 (t0). In the status quo, NNRTI-based ART is empirically given as the first-line regimen to all individuals diagnosed with HIV, regardless of CD4 cell count, as currently recommended by the Kenyan Ministry of Health guidelines.³⁵ 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. We assume an OLA that tests for mutations K103N, M184V, Y181C, and G190A will detect 80% 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,¹¹ 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.²¹ Thus, our assumption that OLA detects 80% of PDR cases is intended to synthesize data from these two studies. We assume CS will detect 100% of PDR cases, which is likely a generous estimate given that CS can typically detect mutants comprising at least 15-25% of an individual's virus population,³⁶ compared to OLA which can detect mutants present with at least 2% frequency. We assume OLA and CS testing cost \$30 and \$300 per test, respectively.^{22,37} For all strategies, initial viral load (VL) testing is performed 6 months after ART initiation and is subsequently performed at 12-month intervals.

ART

We assume 2 lines of ART (NNRTI-based and PI-based) are available at a cost of \$125 and \$316 per person per year, respectively.³⁸ Individuals with PDR initially treated with NNRTI-based ART have a higher probability of virologic failure compared to those who do not have PDR and initially receive NNRTI-based ART or those with PDR given PI-based ART (47% vs. 20% during first 12 months on ART).^{6,21,39} When viral load testing detects virologic failure (unsuppressed viral load) in a patient receiving NNRTI-based ART, we assume the regimen is immediately changed to PI-based 100% of the time. If a patient experiences virologic failure with a PI-based regimen, we assume no third-line ART is available; however, the patient continues to receive PI-based ART.

Health and Economic Outcomes

For each strategy modeled, we measured two primary outcomes: total costs incurred (\$US) and total QALYs gained by each strategy, which were then used to calculate incremental cost-effectiveness ratios (ICERs) in terms of \$US/QALY gained. We also measured other important epidemiologic and health outcomes, including: rates of viral suppression, rates of PI use, number of new HIV infections, adult HIV prevalence, and adult PDR prevalence. We adopted a health sector perspective, discounted future costs and benefits 3% annually, and adhered to the recent recommendations of the Panel on Cost-Effectiveness in Health and Medicine.⁴⁰ An intervention is considered “very cost-effective” if its ICER is less than the country’s per capita gross domestic product (**GDP**) (\$1,455 for Kenya in 2016), and is considered “cost-effective” if the ICER is less than the three times the country’s per capita gross domestic product (\$4,365).^{41,42}

Sensitivity Analyses

We performed sensitivity analyses to test the robustness of our results. We conducted one-way sensitivity analyses for multiple parameters including: probability of virologic failure on first-line ART with PDR, probability of virologic failure on PI-based second-line ART, diagnostic sensitivity of OLA, as well as cost of first-line ART, second-line ART, OLA testing, CS testing, and viral load testing.

Results

Our model was calibrated to HIV and PDR prevalence in Kenya (**Figure 1**). **Table 2** presents characteristics of the population at t0 (2018).

Health Outcomes

PDR testing strategies (OLA & CS) were associated with higher rates of viral suppression and fewer new infections than the currently recommended Kenyan practice (**Figure 2; Table 3**). For example, OLA PDR testing had a higher viral suppression rate at month-12 of ART use among all HIV-infected individuals on ART (82.1% for OLA+VL12 vs. 77.0% for NT+VL6) and among those with PDR (77.5% for OLA+VL12 vs. 59.5% for NT+VL6) and had 3.4% fewer new infections than the current policy. Among HIV-infected patients, PDR testing strategies did not lead to higher mean CD4 cell count (NT+VL6 = 600 vs. OLA_VL12 = 598) but were associated with slightly lower mortality rates among HIV-infected patients (NT+VL6 = 3.63 vs. OLA_VL12 = 3.60 deaths per 100 person-years).

PDR testing strategies were also associated with a slightly greater average number of QALYs gained per person, both among the entire population and among the HIV-infected population. Among the entire population, on average each individual gained 11.2528 QALYs and 11.2542 QALYs with NT+VL6 and OLA+VL12, respectively. Among HIV-infected individuals, on average each patient gained 7.558 QALYs and 7.637 QALYs with NT+VL6 and OLA+VL12, respectively.

Finally, over time, PDR testing strategies were also associated with a lower PDR prevalence (**Figure 3**).

Costs and Cost-Effectiveness

Total program costs over a 15-year time horizon were higher for PDR testing strategies compared to the status quo (**Table 4; Figure 4**). The two largest contributors to additional costs relative to the status quo were PDR testing itself and greater overall ART costs. Although OLA PDR testing was associated with fewer new HIV infections and incurred fewer total person-months of ART use than the current policy (266.4 vs. 267.8 million person-months), OLA PDR testing also had a higher proportion of patients on ART using a PI-based regimen (18.0% vs. 14.4%), which contributed to higher ART costs. OLA PDR testing also incurred lower costs of viral load and CD4 testing, inpatient care, and HIV screening compared to the current policy. However, these differences in cost were relatively small and ranged from 0.4% (inpatient care) to 9.4% (HIV screening) difference in total cost between OLA PDR testing and the current policy. Compared to the current policy, OLA PDR testing provided 70,671 additional QALYs at an additional cost of

\$127 million (over 15 years for the entire adult Kenyan population) resulting in an ICER of US\$1790/QALY gained (**Figure 5**).

Sensitivity analyses

The two parameters whose range of values affected the cost-effectiveness of OLA PDR testing most in one-way sensitivity analyses were cost of PI-based ART and probability of virologic failure on first-line ART with PDR (**Figure 6**).

Discussion

Our simulation found that, compared to empiric NNRTI-based first-line ART, HIV PDR testing leads to improved rates of viral suppression, fewer new HIV infections, and a lower prevalence of PDR over time. By conventional standards, OLA PDR testing is cost-effective (ICER of US\$1790/QALY) in Kenyan settings where dolutegravir is not yet widely available. This is 23% above the per capita GDP threshold for being very cost-effective.

The reduction in the number of new HIV infections associated with PDR testing strategies is consistent with achieving higher rates of viral suppression than the standard of care, as lower viral load levels are known to be associated with lower risk of transmission of HIV per sexual act.^{32,33} Similarly, we attribute the lower prevalence of PDR associated with PDR testing to improved viral suppression among individuals with PDR, who thereby have a lower probability of transmitting drug resistant HIV to others. The overall health benefit of PDR testing relative to the standard of care, measured in QALYs gained, was the result of both HIV prevention at the population level as well as an increase in QALYs gained per HIV-infected person.

In general, the health benefits associated with PDR testing, including improved viral suppression, percentage of new infections averted, and QALYs gained, were greater for CS than for OLA PDR testing. This outcome resulted from our assumption that CS has a higher diagnostic sensitivity than OLA (100% vs. 80%), which leads to more patients with PDR receiving PI-based ART as their initial regimen with CS strategies than with OLA strategies. However, the ICER of \$58,879 per QALY gained for CS relative to OLA is far from being cost-effective.

Given the high prevalence of PDR to NNRTI-based ART regimens in many parts of sub-Saharan Africa,⁴³ new ART strategies are needed to ensure we achieve UNAIDS 90-90-90 goals.⁴⁴ In addition to PDR testing, one such strategy is empiric dolutegravir-based first-line ART, which has a high genetic barrier to resistance and in clinical trials achieves higher rates of virologic suppression than NNRTI-based ART, even in patients without PDR.^{12,45} Although not included in this analysis, Phillips et al. found that empiric dolutegravir-based first-line ART will improve health outcomes while requiring lower overall costs compared to the status quo.¹³ This is not surprising as this strategy does not require additional spending on PDR testing and dolutegravir-based ART is available at a lower cost than NNRTI-based regimens.¹³ Strategies that save costs while improving health outcomes are ideal, given the potential for decreased global health funding.⁴⁶ Thus, in settings where dolutegravir is available, this is likely the optimal empiric first-line ART regimen. However, full scale-up of dolutegravir implementation will likely take several years,¹⁵ so it is important to evaluate potential cost-effective strategies to manage PDR in the absence of this new drug.

By conventional standards, OLA PDR testing is a cost-effective strategy to address the high prevalence of PDR and improve health outcomes. In addition to considering this strategy's ICER, it is essential to carefully consider the total financial investment required to implement this strategy, as not all interventions that are considered cost-effective by conventional standards are actually affordable.⁴⁷ Over a 15-year time horizon, we estimated that it would cost an additional US\$127 million to scale-up PDR testing with OLA for all adults initiating ART in Kenya, compared to continued use of empiric NNRTI-based first-line ART. Similarly, Phillips et al. found that while PDR testing improves health outcomes, it is associated with additional spending.¹³ Thus, our study confirms that, even with a low-cost test, PDR testing is not a cost-saving strategy.

Interestingly, we found that a large portion of these additional costs arise from increased use of PI-based ART rather than OLA PDR testing itself, as the additional cost of ART was 3.6 times larger than the additional cost of PDR testing. In a sensitivity analysis assuming that PI-based ART cost the same as NNRTI-based ART (\$125/person/year), OLA PDR testing was very cost-effective with an ICER of \$72/QALY gained and cost only an additional US\$5 million over 15 years. However, unless there is a significant decrease in the cost of PI-based ART, our findings suggest that large-scale OLA PDR testing may not be an affordable strategy to optimize initial ART selection when dolutegravir is not available. This highlights the importance of steadfast efforts to scale-up use of dolutegravir and maintain its current low cost.

Despite the eventual widespread use of dolutegravir, there may be an important role for simple, low-cost DR assays in resource-limited settings. For example, OLA PDR testing may be a valuable strategy for women of child-bearing age and patients co-infected with HIV and tuberculosis, as

there is currently not sufficient evidence to guide use of dolutegravir in these populations,⁴⁸ and in young children, as a pediatric formulation of dolutegravir is not yet available,⁴⁹ and there is a high prevalence of PDR in children.⁵⁰ OLA testing may play an important role in guiding the selection of second-line agents for those who have failed dolutegravir-based first-line ART.^{14,48} Future economic modeling studies are needed to evaluate the potential cost-effectiveness of these alternative applications of simple HIVDR assays.

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Tables

Table 1. Model Parameters for Base-Case Analysis		
Parameter	Base-Estimate	Source
Probability of Virologic Failure		
Initial ART (over 12 months)		McMahon et al, ³⁹ Hamers et al, ⁶ Chung et al ²¹ , and 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)	25%	Boender et al, ⁵¹ Ajose et al, ⁵² and De Beudrap ⁵³
Drug Resistance Test Performance		
Sensitivity of OLA	80%	Rhee et al ¹¹ , Chung et al ²¹
Sensitivity of CS	100%	Assumption
Specificity of OLA & CS	100%	Beck et al ²⁰
Utilization and Costs		
Unit Costs		
ART Annual Cost		WHO ³⁸
First-line ART (NNRTI-based)	\$125	
Second-line ART (PI-based)	\$316	
Inpatient Day	\$41	IHME ⁵⁴
Outpatient Visit	\$10	IHME ⁵⁴
HIV Test	\$10	Eaton et al ⁵⁵
CD4 Test	\$10	Keebler et al ⁵⁶
Viral Load Test	\$43	MSF ⁵⁷
OLA Test	\$30	Duarte et al ²²
Consensus Sequencing Test	\$300	Levison et al ³⁷
Utility Weights by Health State*		
HIV-negative	1	Salomon et al ⁵⁸
HIV-positive, CD4 > 350	0.947	
HIV-positive, CD4 = 200-350	0.779	
HIV-positive, CD4 < 200	0.453	
*Utility weights are equal to 1 – disability weight from Salomon et al ⁵⁸		

Table 2. Characteristics of simulated population at t0	
HIV prevalence	5.9%
PDR Prevalence	9.2%
Proportion of HIV-infected people on ART	79.8%
Of people remaining on ART 1 year after starting ART, proportion with viral suppression	78.8%
Proportion of all HIV-infected people with viral suppression	66.5%
Of people on ART, proportion now on second-line (bPI) regimen	12.6%

Table 3. Health and ART Outcomes Over 15 years from t0			
	Current Policy	OLA PDR Testing	CS PDR Testing
Health Outcomes			
Proportion with suppressed VL at month-12 on ART [#]	76.9%	82.0%	83.1%
Proportion with suppressed VL at month-12 on ART among patients with PDR [∞]	59.5%	77.9%	82.2%
New Infections Averted	reference group	3.4%	4.2%
HIV Mortality Rate*	0.359	0.355	0.355
Average QALY's gained per HIV-infected person	5.94	6.02	6.03
Average QALY's gained per person	8.599	8.600	8.600
ART Outcomes			
Proportion on PI-based regimen [#]	14.4%	18.0%	18.6%
Person-months of ART use (million)	267.8	266.4	265.9
Person-months of PI-based ART use (million)	41.0	51.1	52.9
[∞] Average over 15-year time period; *per 100 person-years over 15-year period			

Table 4. Costs, QALYs, and Incremental Cost-Effectiveness of PDR Testing Strategies			
	Discounted Costs (US\$)	Discounted QALYs	ICER (US\$ per QALY gained)
Current Policy	45,421,142,363	438,476,473	NA
OLA PDR Testing	45,547,885,903	438,547,292	1,790
CS PDR Testing	45,833,054,410	438,552,135	58,879
Note- NA = not applicable. QALYs = quality-adjusted life years. ICER = incremental cost-effectiveness ratio.			

Figures

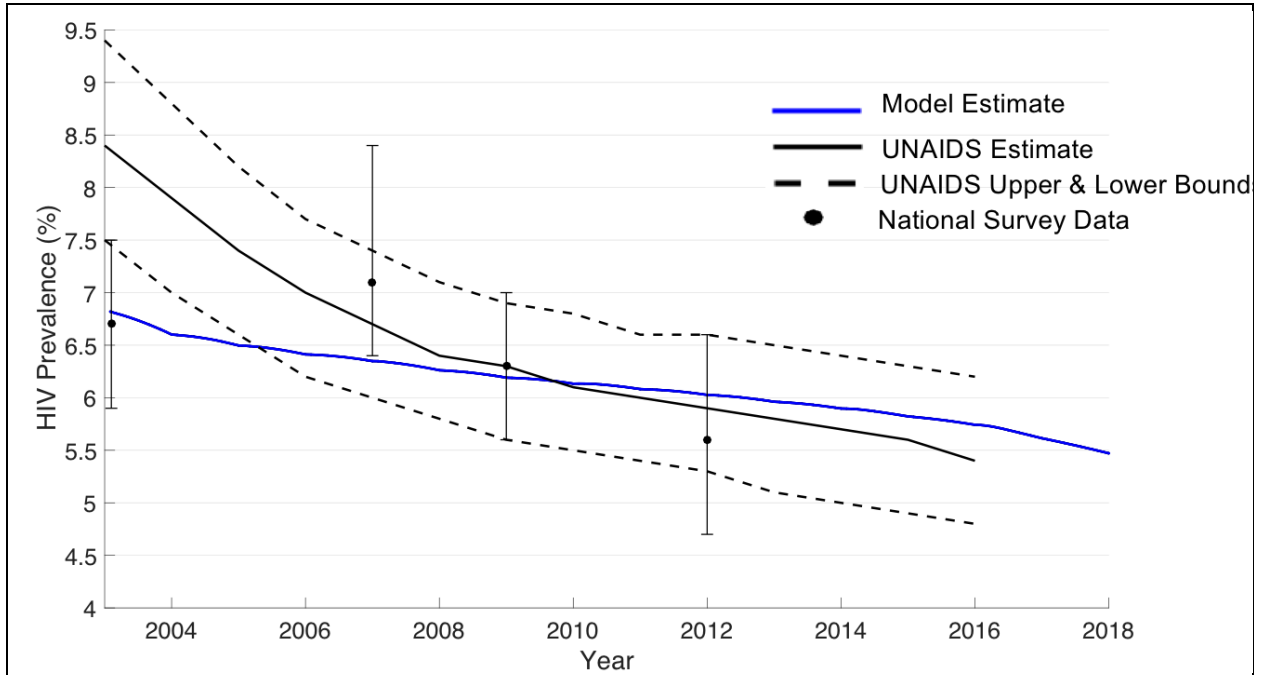


Figure 1A. Calibration to Kenyan HIV prevalence trends

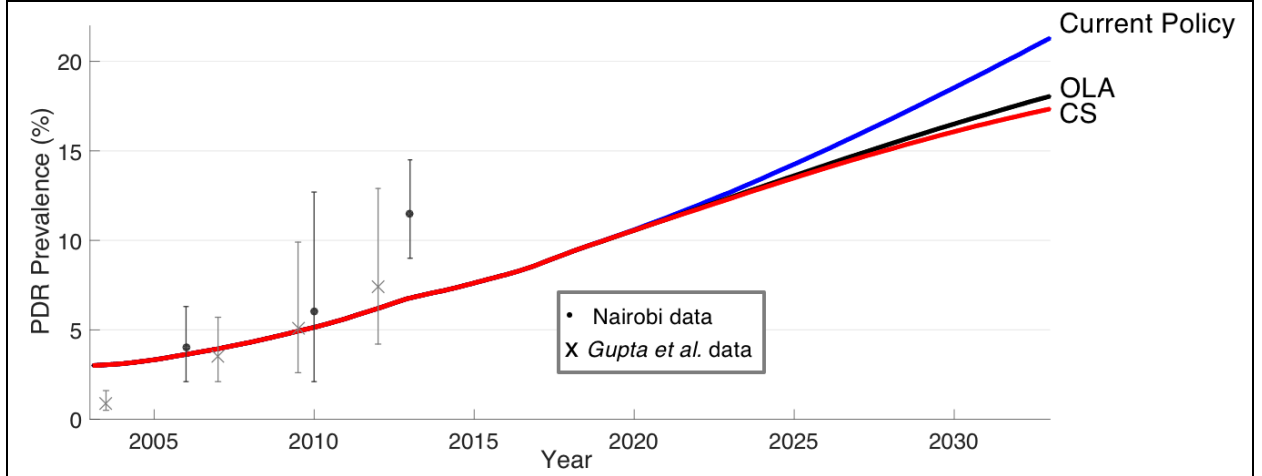


Figure 1B. Calibration to Kenyan HIV PDR prevalence trends

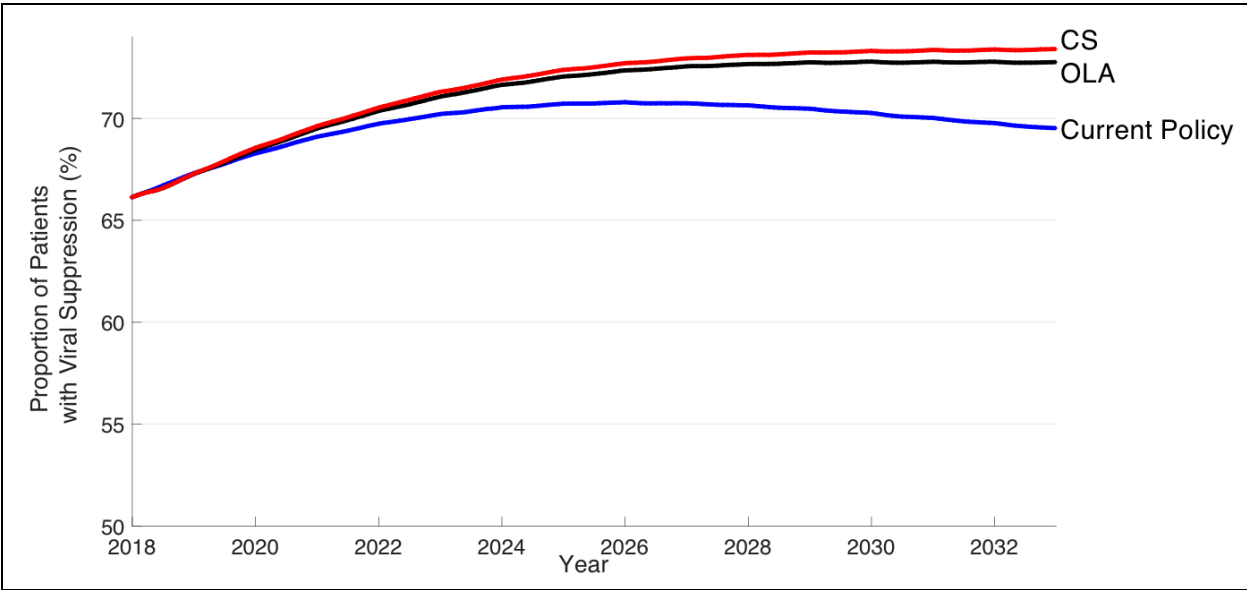


Figure 2. Proportion of HIV-infected patients with viral suppression over time

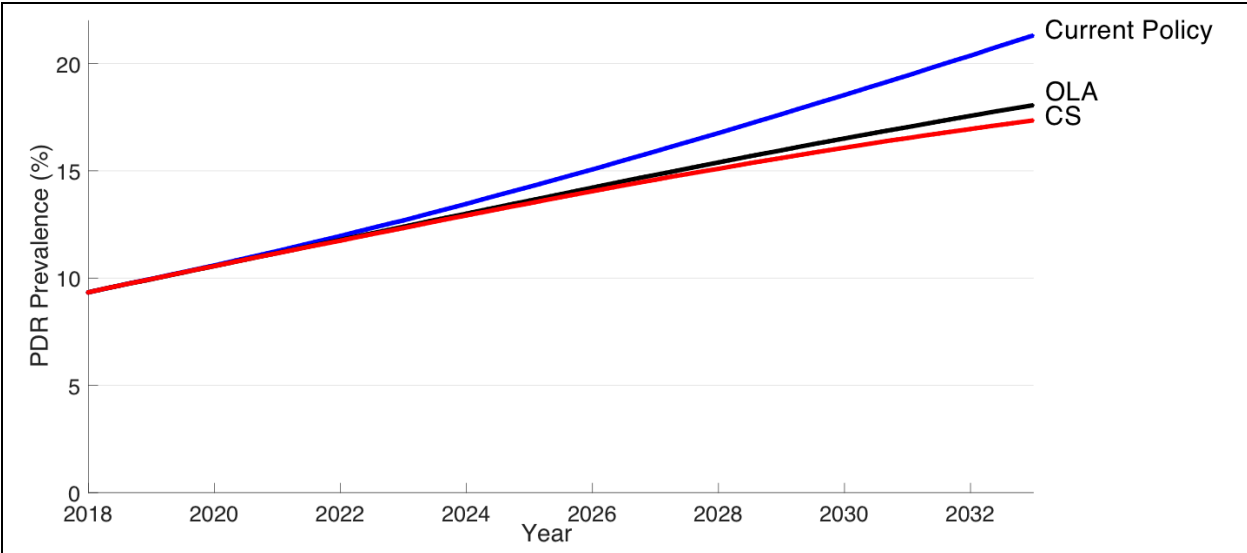


Figure 3. Prevalence of PDR among HIV-infected patients over time

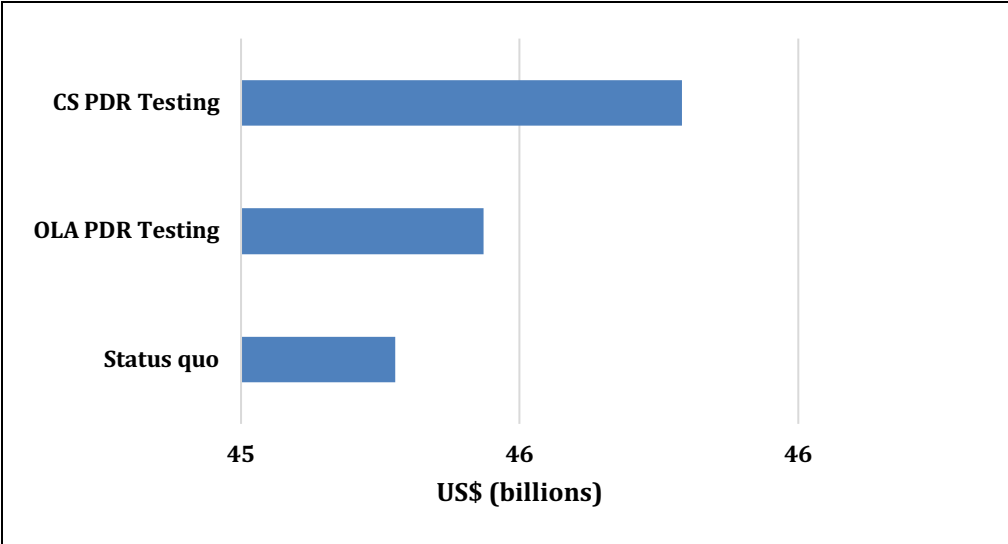


Figure 4A. Total program costs for 3 policy options

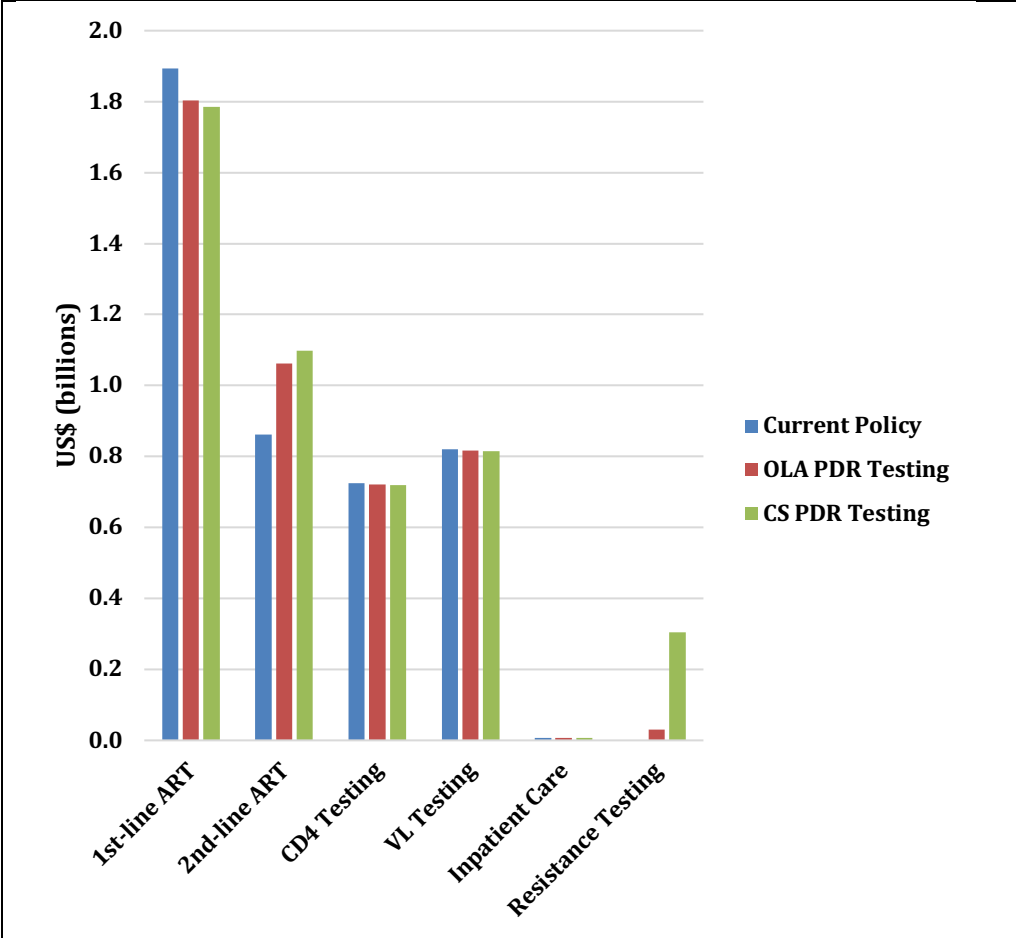


Figure 4B. Comparison of policy option costs by category
 Note: does not include HIV Screening and Background Health Spending categories.

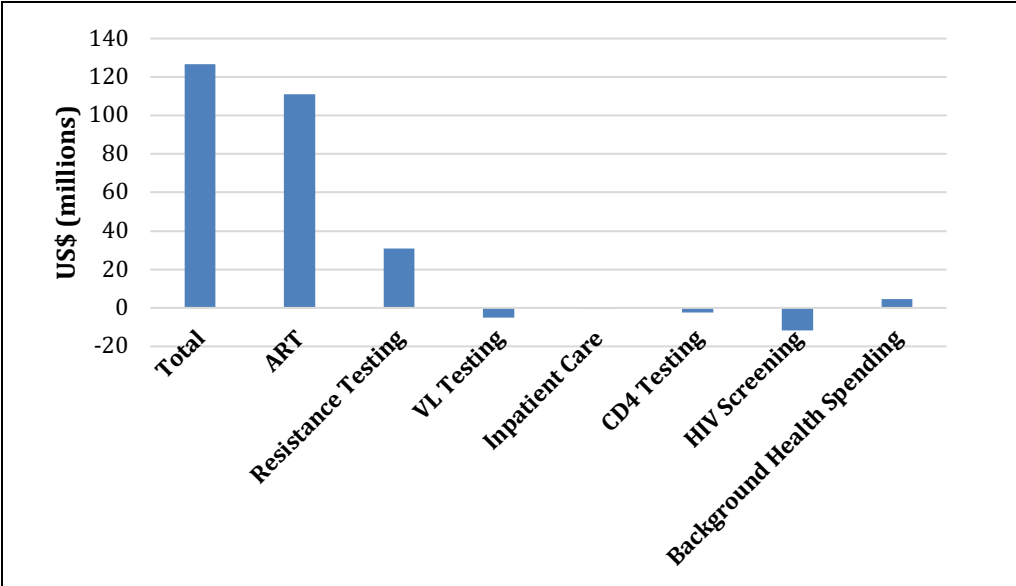


Figure 4C. Cost Difference Between OLA PDR Testing and Status Quo By Category

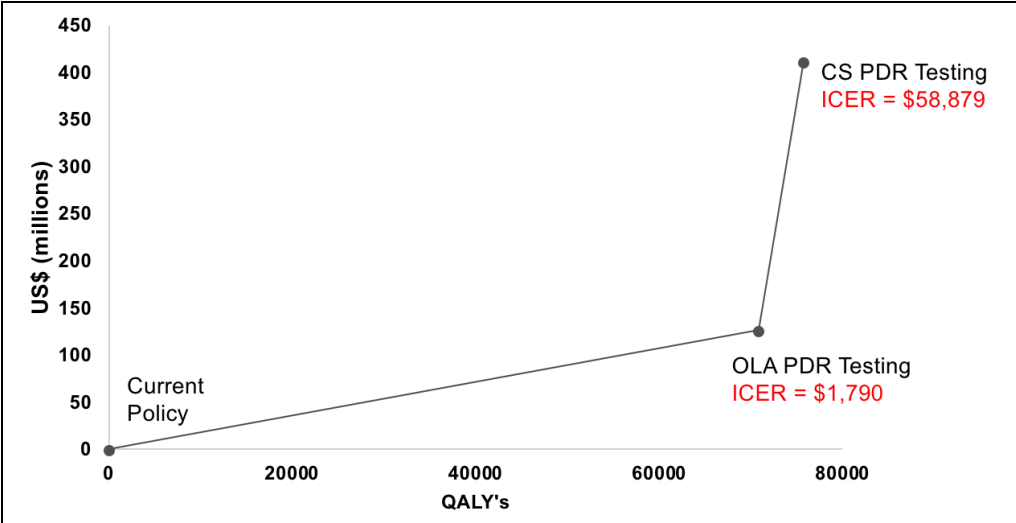


Figure 5. Incremental costs and health benefits of PDR testing strategies compared to current policy. Note, incremental costs and health benefits are scaled-up to the entire adult Kenyan population over a 15-year time horizon starting in 2018.

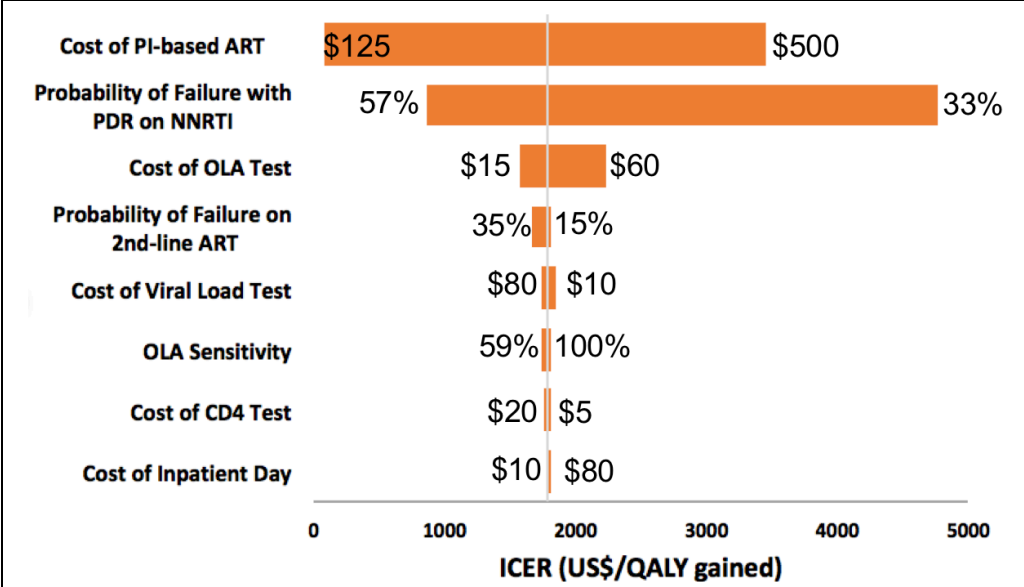


Figure 6. One-way sensitivity analyses ICER values are for OLA PDR testing compared to Current Policy. Each horizontal bar represents the range of ICER values for the specified range of values for the parameter. The vertical bar represents the \$1790/QALY gained ICER, based on base-case parameter assumptions.

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