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Clinical impact and cost-effectiveness of making third-line antiretroviral therapy available in sub-Saharan Africa: A model-based analysis in Côte d'Ivoire

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Abstract

Objective—In sub-Saharan Africa, HIV-infected adults who fail 2nd-line antiretroviral therapy (ART) often do not have access to 3rd-line ART. We examined the clinical impact and cost-effectiveness of making 3rd-line ART available in Côte d'Ivoire.

Methods—We used a simulation model to compare four strategies following 2nd-line ART failure: continue 2nd-line ART [C-ART2]; continue 2nd-line ART with an adherence reinforcement intervention [AR-ART2]; immediate switch to 3rd-line ART [IS-ART3]; and continue 2nd-line ART with adherence reinforcement, switching patients with persistent failure to

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Conflicts of Interest Statement:

All authors declare no conflicts of interest.

CONTRIBUTORS

XA, EO, ER, YY and KAF designed the study. EO, ER, MR and AYW performed the analysis. XA, EO and KAF interpreted the results, and drafted the first report. EO, ER, MR, YY, EL, RPW, CD, ADP, SPE, KAF, and XA assisted with interpretation and revision of the report.

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3rd-line ART [AR-ART3]. Third-line ART consisted of a boosted-darunavir plus raltegravir-based regimen. Primary outcomes were 10-year survival and lifetime incremental cost effectiveness ratios (ICERs), in \$/year of life saved (YLS). ICERs below \$3,585 (3 times the country *per capita* GDP) were considered cost-effective.

Results—Ten-year survival was 6.0% with C-ART2, 17.0% with AR-ART2, 35.4% with IS-ART3, and 37.2% with AR-ART3. AR-ART2 was cost-effective (\$1,100/YLS). AR-ART3 had an ICER of \$3,600/YLS and became cost-effective if the cost of 3rd-line ART decreased by <1%. IS-ART3 was less effective and more costly than AR-ART3. Results were robust to wide variations in the efficacy of 3rd-line ART and of the adherence reinforcement, as well as in the cost 2nd-line ART.

Conclusion—Access to 3rd-line ART combined with an intense adherence reinforcement phase, used as a tool to distinguish between patients who can still benefit from their current 2nd-line regimen and those who truly need 3rd-line ART would provide substantial survival benefits. With minor decreases in drug costs, this strategy would be cost-effective.

INTRODUCTION

In sub-Saharan Africa, issues of laboratory monitoring for patients on antiretroviral therapy (ART), adherence reinforcement, and access to 2nd-line and 3rd-line ART, are closely related. Three factors complicate the decision to switch from one line of ART to another in patients who have failed therapy. First, the limited availability of viral load tests for routine monitoring makes it difficult to document true virologic failure, as immunologic criteria have poor sensitivity and specificity for the diagnosis of virologic failure.¹ Second, even when virologic failure is documented, the lack of access to resistance tests makes it difficult to distinguish between patients with poor adherence and no resistance and patients with treatment-compromising resistance. This unknown factor complicates the question of when and how to switch to subsequent lines of drugs.^{2,3} Third, the prices of 2nd- and of 3rd-line regimens are 3x and 10x higher, respectively, than that of 1st-line. Therefore, programs and health authorities prioritize access to 1st-line ART, which in turn may discourage physicians from documenting failure appropriately in the absence of further lines of drugs.^{4–6}

As a result, most virologic failures of ART are diagnosed late.⁶ A delayed regimen switch or continuing the same regimen with no virologic efficacy in patients with virologic failure leads to accrued resistance.^{7–10} This in turn leads to increased mortality in HIV-infected patients and to the spread of resistant viruses in the population.¹¹ There is an urgent need to evaluate the effectiveness and cost-effectiveness of different treatment strategies after ART failure in settings with no resistance tests, in order to help countries appropriately utilize 2nd- and 3rd-line regimens.^{12–14}

In this study, we used a validated model of HIV disease and treatment to examine the clinical impact and cost-effectiveness of making 3rd-line ART available to HIV-infected adults who have documented 2nd-line failure in Côte d'Ivoire, West Africa.

METHODS

Analytic overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model^{15,16} to answer the following questions:

- i. What are the likely long-term, patient- and population-level benefits associated with reinforcing 2nd-line adherence and/or making 3rd-line ART available in HIV-infected patients with observed 2nd-line failure in Côte d'Ivoire?
- ii. Under what conditions would it be cost-effective, according to international standards, to provide these patients with 3rd-line ART?

To address the first question, we simulated a cohort of HIV-infected adults failing 2nd-line ART in Côte d'Ivoire. ART failure was diagnosed immunologically (CD4 counts) and then confirmed virologically. We compared projected outcomes under alternative assumptions regarding both the availability of 3rd-line drugs and the implementation of a systematic “adherence intervention” phase before switching to 3rd-line ART. Outcomes were 10-year cumulative survival, life expectancy (LE), costs, and incremental cost-effectiveness ratios (ICERs) measured in US dollars per years of life saved (\$/YLS).

To address the second question, we conducted extensive sensitivity analyses, varying model input parameters widely and noting their effect on the resultant ICER estimates. We applied international standards to denote a strategy as “cost-effective” if its ICER was less than three times the 2011 annual *per capita* Gross Domestic Product (GDP) of Côte d'Ivoire (\$3,585/YLS) and “very cost effective” if its ICER was less than the annual *per capita* GDP (\$1,195/YLS).^{17,18}

Model description

The CEPAC-International model is a microsimulation model of HIV infection incorporating natural history and treatment.^{15,16} Simulated patients are randomly generated from an initial distribution of age, sex, CD4 count, and plasma HIV RNA level (viral load), and are followed on a monthly basis from the time of entry into the model until death. In the absence of successful ART, patients' CD4 counts decline at a rate determined by their viral load level.¹⁹ Current CD4 count determines the risk of developing an HIV-related disease or dying from HIV infection.²⁰ ART decreases morbidity and mortality indirectly by means of viral load suppression and CD4 count increase, and directly by reducing the incidence of HIV-related morbidity.^{21,22} The clinical decision to switch from one line to further lines of ART can only be made if there is evidence of failure. That is, the model tracks the “true” updated CD4 count and viral load for each patient, but clinical decisions are based on CD4 and viral load values observed via periodic laboratory testing.²³ Patients in the model may be lost to follow-up at any time and return to care upon the occurrence of a severe HIV-related opportunistic disease. Additional details of model structure have been previously published and are available online (<http://web2.research.partners.org/cepac>).^{15,16}

Strategies

In patients diagnosed as failing 2nd-line ART (i.e. WHO criteria for clinical and/or immunological failure, and then confirmation of a viral load >1000 copies/ml), we compared four strategies (Figure 1): 1) continue 2nd-line ART [C-ART2]; 2) continue 2nd-line ART with a 6-month adherence reinforcement phase [AR-ART2]; 3) immediate switch to 3rd-line ART [IS-ART3]; and 4) continue 2nd-line ART with a 6-month adherence reinforcement phase, and then continue 2nd-line ART in patients successfully resuppressed, or switch to 3rd-line ART in patients with persistent failure [AR-ART3]. The adherence reinforcement phase was modeled as a 6-month period during which patients were seen every month for counseling and educational training on adherence, and had weekly phone and/or SMS contacts with social workers for the entire 6-month duration. At the end of the 6-month period, a repeat viral load test was done. In the AR-ART3 strategy, patients with a >2 log₁₀ copies/ml decrease in plasma viral load and/or an observed viral load <1000 copies/ml at the end of the adherence test phase were maintained on 2nd-line, while the others were switched to 3rd-line ART.

Input parameters

Age and gender were from the VOLTART cohort, a large HIV cohort that includes all adults who started ART at the CePreF clinic in Abidjan.² Input parameters on natural history of HIV disease were derived from published Côte d'Ivoire studies (Table 1 and appendix Table A1-1).^{2,20,24–26} Drug costs were from the Médecins Sans Frontières and the Clinton Health Access Initiative databases.^{4,5} Inputs on 2nd-line and 3rd-line ART efficacy were derived from the literature (Table 1 and appendix Table A1-1).^{4,5,7,27–30} Direct non-medical costs and indirect costs were not included. All costs were expressed in 2011 US dollars. Additional details are available in previous publications.^{15,16}

In the base case analysis, we considered ART regimens that conform with current national guidelines in Côte d'Ivoire: 2NRTIs (zidovudine or tenofovir + lamivudine or emtricitabine) + efavirenz for 1st-line; 2NRTIs + lopinavir/ritonavir for 2nd-line; and a combination of two recycled NRTIs + raltegravir + darunavir/ritonavir for 3rd-line.^{23,30} Patients on ART were routinely monitored with biannual CD4 counts. Viral load testing was available, but was only used to confirm virologic failure (viral load >1000 copies/ml) in patients with immunologic failure (a 50% decrease from peak CD4 count, a return to CD4 count nadir, a CD4 count <100/μL)²³ or clinical failure (the occurrence of a WHO stage III or IV disease after at least 12 months on ART).²³

In addition, we assumed that 60% of patients with viral load >1000 copies/ml on 2nd-line ART had no resistance to lopinavir/ritonavir, and that 50% of these patients would reach a viral load <1000 copies/ml at the end of the adherence reinforcement procedures (6 months).⁸ Therefore, the efficacy of the six-month “adherence reinforcement” phase was estimated as $60\% \times 50\% = 30\%$.⁸

Main outcomes

The simulation began at the time of first observed failure of 2nd-line ART. There were two types of main outcomes: clinical and economic. Clinical outcomes included life expectancy

and 10-year cumulative survival; both outcomes were assessed starting at the time of 2nd-line ART failure. Economic outcomes were total costs and ICER. The ICER was computed by ordering the strategies by increasing cost, and comparing each strategy to the next, less costly, non-dominated strategy.³¹ Dominated strategies were those that were less effective and more costly than another strategy or less costly but incrementally less cost-effective than a more effective strategy.³² All measures of resource use and outcomes used to compute ICERs were discounted at an annual rate of 3%.³¹

Secondary outcome

As a secondary analysis, we assessed the impact that 3rd-line strategies would have on secondary HIV transmission. We projected 2-year and 10-year cumulative HIV transmissions under each strategy, and report the relative reduction in new transmissions for each strategy relative to C-ART2. This cumulative number of secondary HIV cases was calculated based on a direct model output (updated level of plasma viral load) and from the literature (viral load strata-specific risk of HIV transmission) (Appendix A2).³³ Secondary HIV cases were not included in the cost-effectiveness analysis.

Analytic steps

The analysis consisted of four stages:

1. **Initialization phase.** In this stage, we used inputs and the assumptions defined above to simulate a cohort of 1,000,000 adults who started 1st-line ART and were monitored with biannual CD4 counts and targeted viral load for failure. Using these inputs, we determined the characteristics of patients who accessed 2nd-line ART and then failed, at the time when 2nd-line ART virological failure was actually diagnosed ('observed 2nd-line failure').
2. **Base case analysis.** In this stage, we simulated four cohorts of 1,000,000 patients with observed 2nd-line failure. For this analysis, the "baseline" was the time at which 2nd-line ART virologic failure was diagnosed. Patients' baseline characteristics were obtained at the end of the initialization phase and were the same for all four cohorts. Using these characteristics and inputs regarding the efficacy, toxicity and cost of 2nd-line and 3rd-line ART, we assessed model outputs for each of the four strategies.
3. **Scenario analysis.** In this stage, we examined whether the results of the base case analysis were robust to two different alternative monitoring contexts: 1) settings where viral load testing was not available, but in which CD4 count could be routinely measured, and 2) settings in which viral load testing was routinely measured biannually. For these analyses, initialization runs were done to determine the characteristics of patients with observed 2nd-line ART failure in different monitoring contexts.
4. **Sensitivity analyses.** In one-way sensitivity analyses, we varied all major parameters in the model to examine at which point the strategy considered the most cost-effective in the base case analysis would become cost-effective or very cost-effective, according to international standards. These parameters included patient

and drug regimen characteristics as well as program characteristics. The ranges examined in one-way sensitivity analyses were either based on the 95% confidence intervals around a reported parameter or were examined at the extreme values found in the literature. Finally, we included all highly-sensitive variables identified in one-way analyses in multi-way sensitivity analyses.

RESULTS

Initialization phase: pre-ART characteristics and characteristics at observed 2nd-line failure

We simulated a cohort of HIV-infected adults, 75% women, who started ART with a mean CD4 count of 154/ μ l (SD 102), and who were monitored with CD4 counts every 6 months and with viral load tests for confirmation of failure. For this cohort, the mean time from ART initiation to observed 2nd-line failure was 10.6 years (SD 6.3) and the mean CD4 count at observed 2nd-line failure was 240/ μ l (SD 195/ μ l). Because viral load testing was used for failure confirmation, all patients diagnosed as failing 2nd-line had a viral load of more than 1,000 copies/ml ('true virologic failure') (Table 1).

Base case analysis: outcomes after observed 2nd-line failure

Compared to C-ART2, AR-ART2 increased 10-year survival from 6.0% to 17.0%, increased discounted LE from 49.6 to 64.2 months, and had an ICER of \$1,100/YLS (Table 2). Compared to AR-ART2, AR-ART3 further increased 10-year survival to 37.2%, increased discounted LE from 64.2 to 90.4 months, and had an ICER of \$3,600/YLS. Compared to AR-ART3, IS-ART3 increased lifetime costs and decreased both 10-year survival and LE, and was thus considered a "dominated" strategy. Initially, survival for the IS-ART3 exceeded that of AR-ART3, but by 7 years the survival of AR-ART3 exceeded that of IS-ART3 (Appendix, Figure A5). Undiscounted results can be found in the Appendix, Table A3. With C-ART2, the estimated number of secondary HIV cases 10 years after observed 2nd-line failure was 347/1,000 persons. Compared to C-ART2, the percentage of secondary HIV cases averted at 10 years with AR-ART2, AR-ART3, and IS-ART3 was 5.8%, 16.8% and 15.1% (Table 2).

Scenario analysis: outcomes in settings with different contexts of monitoring

In settings where viral load monitoring was completely unavailable and patients were monitored only with biannual CD4 counts, mean time from ART initiation to observed 2nd-line failure was 10.5 years (SD 6.1) and mean CD4 count at observed 2nd-line failure 240/ mm^3 (SD 210). Because viral load was not available for failure confirmation, 6.2% of patients diagnosed as failing 2nd-line ART had a viral load <1,000 copies/ml (that is, they did not have 'true virologic failure') even though they met criteria for immunological failure (Appendix Table A1–2).

In a context where viral load was used for routine monitoring, mean time from ART initiation to observed 2nd-line failure was 7.7 years (SD 5.3) and mean CD4 count at observed 2nd-line failure 495/ μ l (SD 255). Because viral load was available for failure

confirmation, all patients diagnosed as failing 2nd-line had true virologic failure (Appendix Table A1–2).

In both contexts, IS-ART3 was dominated by AR-ART3, and AR-ART2 was cost-effective. When viral load testing was not available, AR-ART3 had approximately the same ICER (\$3,700/YLS) as in the base case analysis (with targeted viral load available). When viral load was routinely available, the ICER of AR-ART3 (\$4,800/YLS) was above the 3 x GDP *per capita* cost-effectiveness threshold (Table 2).

Sensitivity analyses

Figure 2 shows the effects of one-way sensitivity analyses on the cost-effectiveness of AR-ART3, in a context of CD4 count monitoring every 6 months with viral load confirmation of failure. Compared to AR-ART2, the ICER of AR-ART3 was most sensitive to the cost of 3rd-line ART drugs. AR-ART3 became cost-effective (ICER < 3x the Côte d'Ivoire GDP) if the monthly cost of 3rd-line ART drugs decreased by <1%, to \$163. The ICER of AR-ART3 was also sensitive to the efficacy of 3rd-line ART and to 2nd-line ART cost. Additional results from one-way sensitivity analyses can be found in table A4 in the Appendix.

Figure 3 shows multi-way sensitivity analyses simultaneously varying 3rd-line ART cost and 3rd-line ART efficacy, 2nd-line ART cost, or adherence reinforcement efficacy. Here, we define the “recommended strategy” as the strategy that conferred the greatest survival benefit, while maintaining an ICER below the cost-effectiveness threshold (ICER < 3x GDP).

A modest decrease in the price of 3rd-line ART consistently led AR-ART3 to become the recommended strategy, even with wide variation in 3rd-line ART efficacy and 2nd-line regimen cost. **With decreases in the cost of 3rd-line, while keeping the adherence reinforcement efficacy constant, AR-ART3 became the recommended strategy. If the efficacy of the adherence intervention were to increase, then the cost of 3rd-line would have to decrease for AR-ART3 to remain cost-effective. Otherwise, AR-ART2 became the best strategy.**

DISCUSSION

We examined alternative approaches to the care of patients with observed 2nd-line ART failure in settings with limited access to ART and laboratory monitoring tests. In particular, we considered combining access to 3rd-line ART with an adherence reinforcement, which could help distinguish between patients who could still benefit from their current 2nd-line regimen and those who truly need to switch to 3rd-line ART.

We found that combining access to 3rd-line ART with an intense adherence reinforcement phase would provide the greatest long-term survival benefits to patients with observed 2nd-line ART failure. This phased intervention reached the cost-effectiveness threshold with a minimal decrease in the price of the 3rd-line drugs. If 3rd-line drugs were not available in the country, reinforcing adherence to 2nd-line ART in patients with observed 2nd-line failure would be a cost-effective intervention. In addition, our study also suggests that reinforcing

adherence in patients with observed 2nd-line failure and making 3rd-line ART available to patients who need it could substantially decrease the number of secondary HIV cases and therefore provide population-level benefits.³⁴

Our results suggest that an adherence reinforcement program could be an important tool to decide whether to switch regimens in case of 2nd-line failure. Adherence interventions can improve long-term survival by delaying the switch to 3rd-line ART in patients without resistance to 2nd-line and who therefore do not yet need it. However, unlike genotype testing, an adherence intervention cannot be used to adapt ART regimens according to resistance profiles and therefore cannot spare specific drugs for further lines of treatment.³⁵

Because this analysis started at the time of 2nd-line failure documentation, patients with observed 2nd-line failure had different baseline characteristics depending on the context of monitoring. Thus, our sensitivity analysis simulating different cohorts in different monitoring contexts did not aim to compare the efficacy of different types of monitoring, but rather to examine the robustness of our findings in different contexts of monitoring. We found that our conclusions would likely be the same if viral load testing was either completely unavailable or routinely available. We also found that our main results were robust to wide variations in 3rd-line ART efficacy, adherence reinforcement efficacy, and 2nd-line drugs costs.

Our study has several limitations. First, the efficacy of the adherence intervention phase **was difficult to estimate for two reasons.** 1) Previous studies reported wide variation in the resistance rate to protease inhibitors in patients failing 2nd-line ART.^{8,11,36} Estimating the proportion of patients failing 2nd-line ART with no resistance to protease inhibitors who could respond to an adherence reinforcement intervention was equally challenging.^{37,38} 2) **The large scale applicability of such interventions still remains to be documented.** Therefore, we **adopted a conservative approach, assuming a low efficacy for the intervention, and conducted a wide range of sensitivity analyses on this parameter.** Second, we did not consider all possible combinations of parameter variation in multi-way sensitivity analyses. Instead, we focused our two-way sensitivity analyses on the treatment parameters that we found to be most critical to driving the variation in main outcomes. However, parameters that did not have an impact in one-way sensitivity analyses are unlikely to have much influence on the results in multi-way analyses. **Third, the CEPAC-International model does not explicitly control for important socioeconomic parameters such as level of education and access to care for individuals, though it implicitly accounts for access through clinical factors such as CD4 count at presentation to care. This may limit how representative our simulated cohort is of the general population in Côte d'Ivoire. Interested readers may also wish to refer to several publicly available sources for additional detail on the CEPAC-International Model, its assumptions, and their limitations.**^{15,16,22,39}

In conclusion, combining access to 3rd-line ART with a strategy including an intense adherence reinforcement phase would provide substantial long-term survival benefits. **Minimal reductions in the cost of 3rd-line ART agents would render such an approach cost-effective in Côte d'Ivoire. In resource-limited settings with poor access to**

resistance tests, additional research to evaluate the cost-effectiveness of alternative treatment strategies following ART failure could inform more appropriate use of 2nd- and 3rd-line regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Simulation profile

C-ART2: Continue 2nd-line ART. AR-ART2: Adherence reinforcement, continue 2nd-line ART, IS-ART3: Immediate switch to 3rd-line ART, AR-ART3: Adherence reinforcement, 3rd-line ART if failure persists.

Figure 2. One-way sensitivity analyses of cost-effectiveness in the strategy consisting of adherence reinforcement and switch to 3rd-line ART in patients in whom failure persists (AR-ART3)

This figure shows the variation of the incremental cost effectiveness ratio of the AR-ART3 strategy compared to AR-ART2, when varying the input parameters. In this figure we included the input variation which led to a variation in the ICER higher than \$100/YLS. AR-ART3: Adherence reinforcement, 3rd-line ART if failure persists, GDP: Gross domestic product, ICER: Incremental cost-effectiveness ratio, PY: person-years.

Figure 3. Multi-way sensitivity analysis: variation of 3rd-line ART efficacy, 2nd-line ART cost, or adherence reinforcement phase efficacy

This figure displays the recommended ART strategy as a function of 3rd-line cost and either 3rd-line ART efficacy, 2nd-line ART cost, or the adherence reinforcement phase efficacy.

Values on the X-axis and Y-axis are multipliers with reference to the base case value (*e.g.*: 1.0 corresponds to the value used in the base case analysis). The colored areas denote the strategy that confers the greatest benefit, among those whose ICER is below the cost-effectiveness threshold (\$3,585/YLS).

AR-ART3: Adherence reinforcement, 3rd-line ART if failure persists

Table 1

Main model input parameters

	Base case value	Ref	Sensitivity analysis	
			Range	Type
Sex, female, %	75	2	--	
Pre-ART characteristics				
Age, mean (SD), years	37 (9)	2	[28 to 46]	CI
CD4, mean (SD), cells/ μ l	154 (102)	2	[52 to 256]	CI
Characteristics at 2nd-line ART failure				
Age, mean (SD), years	44 (10)	Modeled	NA	
CD4, mean (SD), cells/ μ l	240 (195)	Modeled	NA	
Interventions after 2nd-line ART failure⁽¹⁾				
2nd-line with 6-month adherence reinforcement⁽²⁾				
HIV-1 RNA suppression at 6 months, % ⁽³⁾	30	Assump	[15 to 45]	CI
Virologic failure after 6 months, per 100 PY	15	2	[7 to 22]	CI
Monthly CD4 increase, mean (SD), cell/ μ l ⁽⁴⁾				
Between 0 and 2 months	77 (19)	2	[58 to 97]	CI
2 months	4 (1)	2	--	
3rd-line ART⁽¹⁾				
HIV-1 RNA suppression at 6 months, %	80	2	[50 to 90]	ExtrV
Virologic failure after 6 months, per 100 PY	15	2	[7 to 22]	CI
Monthly CD4 increase, mean (SD), cell/ μ l ⁽⁴⁾				
Between 0 and 2 months	77 (19)	2	[58 to 97]	CI
3 months	4 (1)	2	--	
Monitoring and follow-up				
Interval between clinic visits, months	3	Assump	[1 to 6]	ExtrV
Interval between HIV RNA or CD4 tests, months	6	Assump	[3 to 12]	ExtrV
Loss to follow-up, per 100 PY	9	25	[4 to 15]	CI
Costs, USD				
Drugs, per month				
2 nd -line ART	42	4	[21 to 63]	ExtrV
3 rd -line ART	164	5	[82 to 246]	ExtrV
6-month adherence reinforcement ⁽²⁾	153	Assump	[77 to 230]	CI

ART: antiretroviral therapy; SD: standard deviation; USD: US dollars; Ref: references; Assump: assumption; NA: not applicable; CI: confidence interval; ExtrV: extreme values; PY: person-years.

Confidence intervals were derived from input data or estimated by multiplying the base case value by 0.5 for the lower bound and 1.5 for the upper bound.

⁽¹⁾ 2nd-line ART: tenofovir or zidovudine + emtricitabine or lamivudine + lopinavir/ritonavir; 3rd-line ART: 2 nucleoside reverse transcriptase inhibitors + raltegravir + darunavir/ritonavir.

(2) The adherence reinforcement involved 6 adherence training sessions (one/month) and weekly SMS reminders; patients continued to take tenofovir or zidovudine + emtricitabine or lamivudine + lopinavir/ritonavir. Following adherence reinforcement, a repeat viral load was done; only patients without substantial decrease in viral load were switched to 3rd-line ART.

(3) We assumed that 60% patients with documented 2nd-line failure harbored virus still sensitive to lopinavir/ritonavir,⁸ and that 50% of these patients would achieve virologic suppression after the adherence reinforcement phase.

(4) The CD4 increase occurs only in patients with virologic suppression. In the base case analysis, we assumed no plateau effect and a continued increase CD4 count. In sensitivity analysis, we assumed that there was a plateau effect, with no CD4 count increase in patients on ART after 5 years of treatment.⁴⁰

Table 2

Outcomes of different treatment strategies in patients with observed 2nd-line antiretroviral therapy failure: base case analysis and analyses in different contexts of monitoring (discounted life expectancy and lifetime cost)

	Primary outcomes			Secondary outcomes		
	Clinical	Economic				
	% alive at 2 years	% alive at 10 years	LE (months) (4)	Lifetime cost (2011 USD)(4)	ICER (USD/YLS)	% cases averted at 2 years (5) 10 years (5)
Base case analysis: routine CD4, viral load testing to confirm failure⁽¹⁾						
Continue 2 nd -line ART (C-ART2)	75.8	6.0	49.6	4,700	--	- -
Adherence reinforcement, continue 2 nd -line ART (AR-ART2)	80.3	17.0	64.2	6,000	1,100	22.2 5.8
Adherence reinforcement, 3 rd -line ART if failure persists (AR-ART3)	85.5	37.2	90.4	13,800	3,600	37.7 16.8
Immediate switch to 3 rd -line ART (IS-ART3)	87.8	35.4	88.3	16,600	Dominated	59.2 15.1
Context analyses						
Routine CD4, viral load unavailable⁽²⁾						
Continue 2 nd -line ART (C-ART2)	75.4	8.0	51.3	4,600	--	- -
Adherence reinforcement, continue 2 nd -line ART (AR-ART2)	80.1	18.8	65.9	6,000	1,100	22.1 5.4
Adherence reinforcement, 3 rd -line ART if failure persists (AR-ART3)	85.3	38.0	91.2	13,800	3,700	37.5 16.1
Immediate switch to 3 rd -line ART (IS-ART3)	87.8	36.6	89.9	16,600	Dominated	59.0 14.6
Routine CD4 and routine viral load⁽³⁾						
Continue 2 nd -line ART (C-ART2)	90.8	28.2	80.8	8,000	--	- -
Adherence reinforcement, continue 2 nd -line ART (AR-ART2)	92.2	38.4	94.0	9,200	1,100	22.8 9.4
Adherence reinforcement, 3 rd -line ART if failure persists (AR-ART3)	94.1	57.5	120.0	19,600	4,800	52.8 31.4
Immediate switch to 3 rd -line ART (IS-ART3)	94.6	55.3	115.9	21,100	Dominated	60.9 25.4

ART: antiretroviral therapy; LE: life expectancy; USD: US dollars; YLS: years of life saved.

Cases averted: relative number of cases from secondary HIV transmission that were averted in strategies AR-ART2, AR-ART3, and IS-ART2, compared to C-ART2.

(1) **Routine CD4, viral load testing to confirm failure:** In the base case we assumed that viral load testing was available and used to confirm immunological failure. CD4 count was done every 6 months. ART failure was diagnosed according to WHO criteria for immunological failure.²³ All patients diagnosed with immunological failure were included in the analysis. All projections of outcomes started when immunological failure was diagnosed and then confirmed by viral load test (Table A1-2 in the Appendix).

(2) **Routine CD4, viral load unavailable:** In these settings we assumed that viral load testing was not available, that CD4 count was done every 6 months, and 2nd-line failure was diagnosed according to WHO criteria for immunological failure.²³ All patients diagnosed with immunological failure were included in the analysis. All projections of outcomes started when immunological failure was diagnosed. As immunological criteria are imperfectly predictive of virologic failure, 93.7% of the patients included in the analysis had true virologic failure (i.e. a plasma viral load >1000 copies/ml) and 6.3% had no virologic failure (i.e. a plasma viral load <1000 copies/ml) (Table A1-2 in the Appendix).

(3) **Routine CD4 and routine viral load:** In these settings we assumed that CD4 count and viral load testing were done routinely every 6 months. 2nd-line failure was diagnosed as a plasma viral load >1000 copies/ml. All patients diagnosed with virologic failure were included in the analysis. All projections of outcomes started after virologic failure was confirmed (See Table A1-2 in the Appendix).

(4) The life expectancy and the lifetime cost were discounted at an annual rate of 3%.

(5) In these cohorts with observed second-line failure, the estimated number of secondary HIV cases at 2 and 10 years with the C-ART2 strategy were 148/1,000 persons and 347/1,000 persons in the base case, 140/1,000 persons and 326/1,000 persons in the context of routine CD4, viral load unavailable and 133/1,000 persons and 435/1,000 persons in the context of routine CD4 and routine viral load.