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Economics of Switching to Second-Line Antiretroviral Therapy with Lopinavir/Ritonavir in Africa: Estimates Based on DART Trial Results and Costs for Uganda and Kenya

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A B S T R A C T

Background: Substantial immunological improvement has been reported for HIV-infected patients who switch from a failing regimen to a protease inhibitor regimen with Lopinavir/ritonavir (LPV/r). We use decision analysis modeling to estimate health and economic consequences expected from this switch. **Methods:** A Markov model combined best evidence for CD4$^+$ T-cell response, infectious disease events, death rates, and quality of life for African populations with Kenyan and Ugandan data on drug and medical care costs. We estimate the incremental cost-effectiveness ratio of switching to an LPV/r-based regimen versus remaining on a failed first antiretroviral (ARV) regimen or discontinuing all ARV drugs. The model assumes concurrent use of cotrimoxazole, and 4% annual loss to follow-up. Local effects due to prevalence of malaria and tuberculosis are included in the model. Sensitivity analysis examines the effects of varying disease, ARV therapy and CD4$^+$ T-cell cost, and ART discontinuation assumptions. **Results:** The base model estimates an improvement of 20 months in average survival for the LPV/r group. The respective LPV/r ICER for Kenya is $1483 per quality-adjusted life year (QALY) compared to $1673/QALY for Uganda. The ICERs increase to $1517 and $1707, respectively, if CD4$^+$ T-cell tests cost $25. The model comparing switching to LPV/r to discontinuing all ARV drugs decreases both costs and benefits proportionally for the treatment groups. **Conclusion:** The estimates are clearly below the most stringent World Health Organization benchmark for cost-effectiveness for Kenya and within the acceptable range of cost-effectiveness for Uganda. Thus, the switch to second-line therapy with LPV/r in these countries appears to be a cost-effective use of resources.

Keywords: Africa, AIDS, cost-utility analysis, decision analysis model, modeling.

Background

A large amount of resources, both economic and human, have been focused on the HIV/AIDS pandemic in sub-Saharan Africa, and especially on enabling universal access to antiretroviral (ARV) therapy (ART) for people living with HIV/AIDS [1,2]. Much of the focus has rightfully been on scaling up to provide first-line ART [3]. However, as the scale up is implemented, increasingly complex issues, beyond those of simply rolling out the least expensive ARV regimen to as many individuals as possible, must be considered. One issue is related to focusing on providing a primary low-cost ARV regimen to as many individuals as possible versus providing a second, often more costly, regimen to those in whom their first ARV regimen failed.

In high-income countries, discussions of resource decisions are increasingly informed by economic studies. However, in resource-limited countries, the insights of economic analyses have not been frequently used to inform discussions of the use of expensive drugs that have emerged over the past 20 years [4]. A number of recent studies [2,5–9] have provided valuable information on some of the cost or cost-effectiveness issues related to interventions associated with the HIV/AIDS epidemic in Africa, but additional work will be needed as our understanding of clinical and epidemiological complexities in the HIV/AIDS epidemic in low-income countries increases [10–12]. Recent clinical and epidemiological study findings indicate that the consideration of improvements affected by ART in patients with HIV/AIDS in African populations are inadequate without also considering issues related to tuberculosis (TB) and malaria [13–15]. Budgets and macroeconomic factors vary greatly across countries in Africa [16–21]. Thus, a cost-effectiveness ratio for one country or setting may be misleading if used to inform discussions in other settings [22].

This study provides an example of how we may approach the task of providing needed economic information for informing discussions related to the use of scarce resources for managing HIV/AIDS in Africa. It integrates data from an unpublished presentation [23] reporting important outcomes for 477 patients in the DART (Development of AntiRetroviral Therapy in Africa) study who switched to second-line ARV treatment with cost data from Uganda and Kenya. It uses transition matrices that capture disease progression reported for the DART study [23] at 1 year and uses a second matrix in subsequent years to reflect the expected progression for a population managed by CD4$^+$ T-cell monitoring [24]. The objectives of the study were to use the DART study CD4$^+$ T-cell count

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increases reported for the 477 patients who switched from the initial non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen to a boosted protease inhibitor (PI) regimen to:

1. Compare the estimated survival benefits and costs for populations in Uganda and Kenya who are switched to a PI-based regimen of lopinavir + ritonavir (LPV/r) + zidovudine (ZDV) and lamivudine (3TC) to remaining on a failing first-line regimen
2. Examine the effects of prophylaxis with cotrimoxazole for infectious events, effect of cost of CD4$^+$ T-cell testing, and effects of variations in rates of malaria on model estimates of incremental cost-effectiveness, survival, and expected expenditure for persons treated in Uganda and Kenya

Methods

Recent reports from the DART trial indicate a median increase of 204 CD4$^+$ T cells at 48 weeks after switching from the failing first-line ART (nevirapine) to a PI-based regimen with LPV/r [23]. The effectiveness of switching is dependent on the application of stringently defined and operational switching criteria. DART switch criteria are any one of the following: 1) new or recurrent World Health Organization (WHO) stage 4 event, 2) multiple new or recurrent WHO stage 3 events, 3) CD4$^+$ T-cell count less than 100 cells/mm^3 after 48 weeks.

The objective of this study was to estimate the long-term health and economic consequences expected as a result of the CD4$^+$ T-cell increase observed after the switch from a failing first-line regimen to a PI-based regimen for patients in Uganda and Kenya. A Markov model was used to capture cost and benefits over the lifetime of a patient cohort and also to project 5-year cost estimates.

Population

The model's population assumptions are based on the characteristics of the patients enrolled in the DART trial [25]. The most important of these assumptions are related to the baseline immune status as measured by the distribution of CD4$^+$ T-cell counts and a history of two WHO stage 3 events or a current WHO stage 4 event.

The DART trial [26] is a multicenter, open-label study that randomized 3316 ARV-naïve patients in Uganda and Zimbabwe to clinical monitoring only or clinical plus laboratory monitoring while on a regimen of ZDV/3TC + tenofovir, abacavir, or nevirapine (NVP). The 477 patients in whom this first-line regimen failed by the criteria mentioned previously were switched to a second-line regimen composed of LPV/r + NNRTI ± nucleoside reverse transcriptase inhibitor (NRTI) or LPV/r + NRTIs [23,26]. The median and interquartile range (IQR) of CD4$^+$ T-cells/mm^3 at baseline (at failure of first-line and switch to second-line) were 46 CD4$^+$ T-cells/mm^3 and an IQR of 23 to 84 CD4$^+$ T-cells/mm^3, respectively; this increased to 250 CD4$^+$ T-cells/ mm^3 at 48 weeks, with an IQR of 165 to 340 CD4$^+$ T-cells/mm^3 for patients who were switched to an LPV/r regimen [23]. Because the DART switching trial had no comparison arm, the base-case model assumes that patients who were not switched would remain on their initial ART and would have the same baseline CD4$^+$ T-cell count, which would decrease by 20 CD4$^+$ T-cells/mm^3 per quarter based on estimates for patients in whom treatment failed or untreated patients reported in the literature [5,27]. An alternative scenario explores the result of no ART after the initial ARV regimen fails in patients. The difference illustrated under this assumption captures the avoided costs after a discontinuation of the failed regimen and the more rapid CD4$^+$ T-cell decrease expected for patients who are not on any ART.

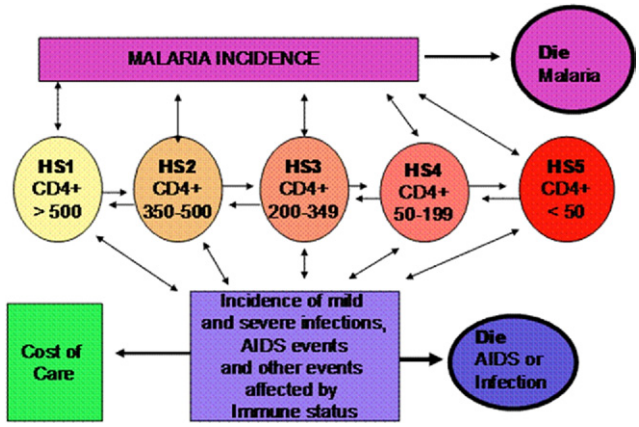

Fig. 1 – Model structure.

Model description

The Markov model used to capture the treatment-modified disease progression of HIV/AIDS patients on the new ARV regimens has five transitional health states defined by CD4$^+$ T-cell ranges and two absorbing health states that capture death related to HIV disease and death related to malaria or other causes. The structure of the model is depicted in Figure 1. This structure is a simplification of a previously developed model used in resource-rich countries that included viral load levels in the model health state definition [28]. The health states are defined as 1) more than 500 CD4$^+$ T cells; 2) 350 to 500 CD4$^+$ T cells; 3) 200 to 349 CD4$^+$ T cells; 4) 50 to 199 CD4$^+$ T cells; 5) fewer than 50 CD4$^+$ T cells; 6) death from AIDS or infection; 7) death from malaria. Transitions between the health states in the model are assumed to cycle every 3 months. The model counts the number of individuals in each of the health states once in each 3-month cycle; estimates the number of disease events for the population occupying each live health state for that model cycle; assigns a cost per event, the cost of a visit, and the cost of ARV drugs for each health state; and totals these costs and months of survival for that cycle. The rate of progression between the health states in the model is determined by two transition matrices. The first transition matrix is calculated from the results at 48 weeks from the DART trial. This rate of response reflects patients who are switched to a regimen containing at least two active drugs. A second transition matrix is used after the first year in the model. This transition matrix is based on archival data from patients on ART who were monitored only by CD4$^+$ T-cell count changes after the first year of treatment. These data were collected during 1994 to 1996 for AIDS patients on PI-based regimens that were monitored only with CD4$^+$ T-cell counts. These transitions capture the assumption that the major improvement in patients' immune status takes place during the first 48 weeks after the initiation of a new ARV regimen and that the type of monitoring test used could affect patients' rates of progression. The transition matrix for the comparison group who are not switched to a PI regimen are derived from the literature [5,29]. The transition matrices used in the model are provided in the Appendix found at doi:10.1016/j.val.2011.06.011. The model assumes that the first ARV regimen consists of an NNRTI + two NRTI drugs because the majority of first regimens in Uganda and Kenya today contain an NNRTI and two NRTI drugs. This assumption allows us to use the most appropriate costs to inform current decisions. The base model assumes that the PI regimen consists of LPV/r + two NRTI drugs. The model reflects the ARV regimen failure rate in the DART trial, and failure is thus defined as a new WHO stage 4 event or two or more new WHO stage 3 events [30] or a decrease to or less

Table 1 – Quarterly risk of clinical event by health state without cotrimoxazole prophylaxis and the relative risk applied to model cotrimoxazole prophylaxis.

Event type	Health state					RR with cotrimoxazole
	1	2	3	4	5	
Mild infections	0.01358	0.01358	0.02237	0.03568	0.05991	0.484
Severe infections	0.00680	0.00680	0.01512	0.02192	0.02344	0.498
Isosporiasis	0.00010	0.00010	0.00020	0.00050	0.00159	0.818
Toxoplasmic encephalitis	0.00000	0.00000	0.00008	0.00034	0.00042	0.832
Mycobacterium avium	0.00000	0.00000	0.00000	0.00123	0.03108	0.591
Tuberculosis	0.00614	0.00614	0.00982	0.01104	0.01350	0.591
Mild other	0.01521	0.01521	0.01926	0.02423	0.04319	0.591
Severe other	0.01521	0.01521	0.04025	0.07816	0.086750	0.591
Malaria	0.00020	0.00020	0.00020	0.00020	0.00020	0.884
Death: severe infection*	0.2499	0.2499	0.2499	0.2499	0.2499	0.51
Death: other cause*	0.0049	0.0049	0.0049	0.01338	0.13226	0.51
Death: malaria†	0.120	0.120	0.120	0.120	0.120	0.51

* Sources: Mermin et al., 2004 [39]; Goldie et al., 2006 [5].
† Source: Reyburn et al., 2004 [32].

than 100 $CD4^+$ T cells at week 48 after initiation of the NNRTI regimen. The structure of the model is depicted in Figure 1.

Events

The distribution of the total population among the five health states in the model captures the immune status of the population and thus determines the rate at which patients experience AIDS and other infectious disease events and die as a result of these conditions. The types of events associated with immune status include isosporiasis, toxoplasmic meningitis, *Mycobacterium avium* complex, TB, other severe infections, and other mild infections [5,31]. The infectious event rates used in the model are specific for each model $CD4^+$ T-cell stage, as those reported by Goldie et al. [5] and described in Table 1. Because the clinical event rates are specified as quarterly risks of an event happening for each $CD4^+$ T-cell count category, they are applied to the number of individual who occupy the $CD4^+$ T-cell category during each model cycle iteration and summed at the end of the model. Thus, if health state 1 is occupied by 50 patients during time 1 and by 80 patients during time 2 and the event risk is 2%, then the number of events at the end of time 2 will be $(50 \times 0.02) + (80 \times 0.02) = 2.6$ expected events. This approach avoids having to use specific health states for each type of event and allows us to still include valid infection event estimates for each time period.

Malaria events and death from malaria or other causes that are not associated with AIDS, however, can also occur in the model. The rates of malaria and the cost of malaria episodes were based on data reported by Reyburn et al. [32]. These rates are applied to all persons still alive in the model for each time period. This allows the model to capture both the costs and competing causes of death due to TB and malaria. This is important for a model that is used to predict events and costs in environments where the average life expectancy is low and competing mortality may have a large effect on both the benefits and costs related to a disease-specific intervention. The benefit of treatment is estimated in years of survival. The incremental cost-effectiveness ratios (ICERs) are calculated based on taking the discounted difference in the total health-care cost for the LPV/r and NNRTI cohorts and dividing this difference by the differences in discounted quality-adjusted life years (QALYs) for the two cohorts expressed for the model year 2007. The discount rate used is the standard prescribed for US economic analyses. This was used because no specific rates for Kenya or Uganda were published in the literature. This rate converts the value of future costs and benefits to the model base year, which is 2007, and is not related to the potential inflation rates in a country.

Quality-adjusted survival

At present, only summary utility weights assigned to WHO health states by a subgroup of individuals enrolled in the DART cohort are available [33]. The specific health states used to solicit these values are based on the WHO classification for HIV/AIDS. In contrast, the model health states are defined by $CD4^+$ T-cell count ranges. One may expect, however, relatively high congruence between the WHO stages and our $CD4^+$ T-cell count–defined model health states. Thus, we used the mean utility values reported by Medina et al. [33], which appear to adjust for differences in quality of life for the health states. The values used are listed in Table 2. Published values for QALY weights by $CD4^+$ T-cell groups are available for patients in high-income countries. However, we were reluctant to use these values for several reasons. The values from the African cohort are from the DART trial and may therefore better reflect the health-related quality of life experienced for patients living in an environment with little technology available to assist with daily activities and with greater difficulties in getting medical care. Indeed, as would be expected, the values reported by Medina et al. [33] for African populations are lower across all health states than values published for patients in high-income countries [34–36]. The African values also exhibit a substantially higher differential between high and low health state parameters than the published values that are derived from populations in high-income countries. QALYs are discounted at 3% per year for the base model when they are used to estimate an ICER.

Table 2 – Utility weights used in the model.

Model health state	$CD4^+$ T-cell range	WHO stage match	Utility weight
1	>500 cells/ml	Symptomatic HIV	.75
2	350–500 cells/ml	Symptomatic HIV	.75
3	200–349 cells/ml	Minor AIDS-defining illness	.49
4	50–199 cells/ml	Mean of minor and major AIDS-defining illness	.35
5	<50 cells/ml	Major AIDS-defining illness	.20

WHO, World Health Organization.

Table 3 – Cost parameters used in the base model and sensitivity analyses (2007 US$)*.

Variable	Cost per event: Uganda, $	Cost per event: Kenya, $	Range tested for sensitivity analysis, $
Mild infectious event	30	30	24–36
Severe infectious event	90	90	78–108
Isosporiasis event	60	61	48–72
Mycobacterium avium event	60	61	48–72
Toxoplasmic encephalitis	60	61	48–72
Tuberculosis event	60	61	48–72
Mild other event	30	30	24–36
Severe other event	60	61	48–72
Malaria	41	41	33–49
Routine visit	5	5	4–6
$CD4^+$ T-cell count†	3	3	12 and 25
LPV/r, AZT, 3TC per quarter †	155.50	158	124.40–186.60
NVP, ATZ, 3TC per quarter†	44	50	35.20–52.80
Cotrimoxazole per quarter†	54.75	2.43	43.80–65.70

AZT, azidothymidine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; 3TC, lamivudine.
* Source: Diagbouga et al., 2003 [40].
† Source: .Médecins Sans Frontières. Untangling the web of price reductions, July 2007 [41].

Costs

The annual cost of the second-line therapy LPV/r component in the model is assumed to be $500. The cost of the NNRTI components is assumed to be a weighted average of NVP and efavirenz, which cost $71 per year. The costs used in the model are provided as quarterly costs (Table 3, 2007 US currency) for the ARV regimens, cost of cotrimoxazole used for prophylaxis against *Pneumocystis* pneumonia and other AIDS-related illnesses, the cost of $CD4^+$ T-cell monitoring and monitoring visits every 6 months, as well as the cost of treatments for episodes of infectious events and malaria. The cost perspective used in the model is that of the health system for 2007. Because no indirect cost weights are assigned, the model will tend to underestimate the cost-effectiveness that would be expected if a societal costing perspective were used. The cost weights and the data sources for the weights used in the model are provided in Table 1. Costs are discounted at 3% per year for the base model when it is used to estimate an ICER.

Results

The base model estimates an improvement of 20 months in average survival for the LPV/r group at an ICER of $1673/QALY for Uganda and $1483/QALY for Kenya (Table 4). The ICER increases to $1687 (Uganda) and $1487 (Kenya) if $CD4^+$ T-cell tests cost $25 instead of $3 and improves to $1328/QALY (Uganda) and $1329/QALY (Kenya) when we assume no use of cotrimoxazole (Table 5). The survival benefit due to the LPV/r regimen, however, decreases from 20 months for the base model to 13 months when cotrimoxazole prophylaxis is excluded from the model. When we compare switching patients to the LPV/r regimen to the discontinuation of all ARV drugs for the comparison group (assuming no use of cotrimoxazole in either group), the ICER is $1570 (Kenya). In this same scenario, when the use of cotrimoxazole is retained in the LPV/r regimen group only, survival improves by 55.7 months (4.6 years) and the ICER is $1266/QALY (Kenya). Doubling the malaria incidence has no effect on the ICER when we assume that cotrimoxazole is used, but increases the ICER from $1329/QALY to $1346/QALY (Kenya) when we assume no use of cotrimoxazole.

The DART trial results were based on data from 477 patients. The model included all those data, but for ease of interpretation to cohorts of different sizes, we report the model costs and outcomes for a cohort of 100 people over the first 5 years after the time of ART switch. We used these estimates to calculate the average yearly cost per additional patient switched to an LPV/r regimen compared to the cost of remaining on an NNRTI regimen (Table 4). These costs are not simply the added drug costs per patient because patients on the two regimens die at different rates. Thus, using the mean incremental added cost per year for ART, cotrimoxazole and $CD4^+$ T-cell testing are the most appropriate measures for predicting the true budget impact of switching ARV regimens. The budget estimates at 5 years for a representative cohort of 100 patients started on an LPV/r regimen are always higher than the estimates for a cohort that remains on a failing NNRTI regimen. This is both because of the higher ARV costs and because fewer patients die; thus, more patients will still need care over the 5 years on the ARV regimen that has not failed. For each patient switched to the LPV/r regimen, a clinic should expect to increase the $CD4^+$ T-cell testing budget by $0.70 per year, the cotrimoxazole budget by $25.42 per year, and the ARV budget by $361 per year.

Table 4 – Results of base model estimates for Uganda and Kenya.

	LPV/r regimen	NNRTI regimen	Difference
Uganda			
Mean life expectancy per patient in years	6.1	4.4	1.7
Total QALYs per 100 patients*	314	142	172
Total lifetime cost per 100 patients, $*	473,542	185,656	287,886
ICER, $			1673
Kenya			
Mean life expectancy per patient in years	6.1	4.4	1.7
Total QALYs per 100 patients*	314	142	172
Total lifetime cost per 100 patients, $*	366,422	111,202	255,219
ICER, $			1483

ICER, incremental cost-effectiveness ratio; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; QALYs, quality-adjusted life-years.
* Discounted by 3% per year.

Table 5 – Results of sensitivity analyses for Uganda*.

Model assumptions	Added months of survival	Increase in ARV cost per patient per year, $	Increase in cotrimoxazole cost per patient per year, $	ICER, $	Percentage of change in ICER from baseline
Baseline estimates	20.0			1649	
Change ARV regimens to reflect drug use in DART trial	20.0	363	25	1729	5
Increase all costs by 20% (excluding ARV and cotrimoxazole)	20.0	351	28	1641	−0.5
Decrease all costs by 20% (excluding ARV and cotrimoxazole)	20.0	351	28	1657	0.5
No discounting of cost and benefits	20.0	351	28	1631	−1
Increase $CD4^+$ T-cell test cost to $25	20.0	351	28	1687	2
Discontinue ART at time of switch for comparison group (retain cotrimoxazole in LPV/r group)	55.8 (4.6years)	457	161	1652	0
No cotrimoxazole	13.3	195	0	1328	−19
No cotrimoxazole for either arm and no ART for comparison group	13.3	229	0	1538	−7
Rate of malaria from Kasirye et al., 2009 [15], no cotrimoxazole for either arm and no ART for comparison group	13.3	225	0	1528	−7

ART, antiretroviral therapy; ARV, antiretroviral; ICER, incremental cost-effectiveness ratio; LPV/r, lopinavir/ritonavir.
* The results for Kenya were of similar magnitude and are therefore not reported.

These budget increases are mean numbers derived from the model estimates for 100 patients and can be used for planning purposed for programs in which their budget projections reflect the fact that more individuals will be alive and in care each year for a patient cohort who is switched to the PI-based regimen than those in a cohort who remain on the failing regimen and that not all the patients who switched will remain on the PI-based regimen for a full 5 years. The base results for Uganda and Kenya are presented in Table 4. Thus, although not classic budget-impact figures that capture all expected changes in drug uptake and populations covered, these marginal cost-impact measures may be used to assist programs in constructing local budget-impact models that reflect changes in both drug uptake and population size.

Sensitivity Analysis

The model's estimated ICERs for Kenya and Uganda were robust to changes in most of the variables used in the analysis, and the two country models behaved similarly in the sensitivity analysis. For that reason, only the results for Uganda are reported in the scenario sensitivity analysis (Table 5) and in the probabilistic sensitivity analysis (Fig. 2). When we tested the model's sensitivity to change for Uganda, assuming that there was no use of cotrimoxazole for either group, the ICER was $1579/QALY, and when all ART also was discontinued at the time of switching for the NNRTI regimen comparison group, the ICER was $1538/QALY (Table 5). The model estimate changed minimally from an ICER of $1649/QALY for the base model to $1729/QALY when the actual ART mix from the DART switch trial was used. For Uganda, the effect of doubling

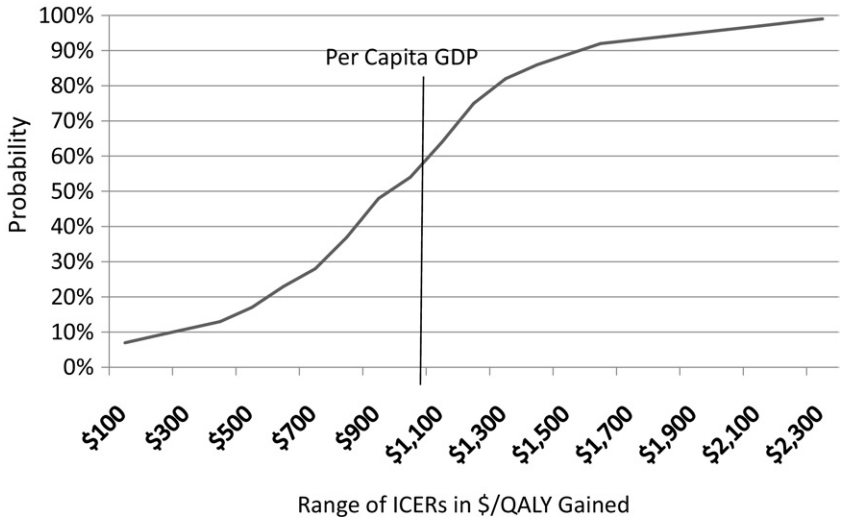

Fig. 2 – Cost-effectiveness acceptability curve for Uganda showing the probability that switching to LPV/r is cost-effective compared to not switching for different ICERs.

the malaria incidence has no effect on the ICER when we assume that cotrimoxazole is used and improves the ICER from $1649/QALY to $1159/QALY when we assume no use of cotrimoxazole.

The combined effects of all changes in the model parameters and the assumption of a 10% variation in the model transition rates were tested in a probabilistic sensitivity analysis using Crystal Ball software to perform 30,000 probabilistic estimates using the model for Uganda. Costs of events were assumed to have a log-normal distribution, whereas cost of medications, medical visits, and tests were assumed to have a triangular distribution. Risks of events and transitions to new health states had a beta distribution, and utility weights were normally distributed. Correlations between model parameters were not defined. Thus, the estimates may have a larger spread than would be expected if correlations were known. The results of the probabilistic sensitivity analysis were used to estimate a cost-effectiveness acceptability curve in Figure 2.

The budget estimates were quite sensitive to some of the changes made. The expected ART cost increase per patient who was switched to the LPV/r regimen was $361 per year in the base estimate. This number changes to $229 per patient per year when we assumed that no cotrimoxazole was given and decreased further to $193 if malaria rates were assumed to be 12% per year and no cotrimoxazole was provided. It is important, however, to realize that these savings are due strictly to the increased deaths that remove patients from the care system. These ARV budget-impact figures demonstrate clearly why it is unwise to rely exclusively on cost estimates or a budget-impact model to inform treatment policy. The results of the sensitivity analysis for Uganda are depicted in Table 5.

Discussion

We used decision analysis modeling to estimate health and economic consequences expected for HIV-infected patients who switch from a failing ARV first-line regimen to a PI regimen with LPV/r based on data reported in the DART trial poster presented by Chimbetete et al. [23]. The model was structured as a Markov transition model in Microsoft Excel and combined the best evidence for $CD4^+$ T-cell response, infectious disease events, death rates, and health-related quality of life for African populations with Kenyan and Ugandan data on drug and medical care costs. We estimated the ICER of switching to an LPV/r-based regimen versus remaining on a failed first ARV regimen or to discontinuing all ARV drugs. The model assumed concurrent use of cotrimoxazole, and 4% annual loss to follow-up. Local effects due to prevalence of malaria and TB were included in the model. Sensitivity analysis examined the effects of varying disease, ARV, and $CD4^+$ T cell cost, and ARV discontinuation assumptions. The base model estimates an improvement of 20 months in average survival for the LPV/r group. The respective LPV/r ICER for Kenya is $1483/QALY compared to $1673/QALY for Uganda.

These estimates have several limitations. First, the data on the effect of switching patients from a failed first ARV regimen are from an unpublished study describing the $CD4^+$ T-cell count increases observed in 477 patients in the DART trial. Although the poster that we used to model the $CD4^+$ T-cell increases were well described in the poster graphs, these data have not undergone peer review and may not reflect the final findings from the study. This must be considered in the interpretation of our results. Second, patients in the DART trial were monitored by nurses every 4 weeks and were highly adherent to both their visit schedule and taking their ARV drugs [26]. Patients in other settings may exhibit poorer patterns of adherence and/or they may be monitored less often, which may decrease switching effectiveness and lower cost-effectiveness. Additionally, the costs used for visits in this model and the practice patterns underlying these costs will vary by location and by health-care system infrastructure. Thus, cost-effectiveness may be negatively affected in locations with less efficient health-care systems.

The model was also limited in its ability to capture any decrease in patient adherence to an ARV regimen that may be expected to take place after the end of the DART trial data. Although the model captures complete discontinuation, its structure does not allow us to capture decreasing adherence, except as it is included in the progression between health states that is guided by the model transition matrices.

A Markov model is a structure that allows us to integrate data from different sources under clearly specified assumptions. Such models may contain two types of errors that could affect the model estimates. The first is an error in the structure of the model itself; the second is mis-estimation of the parameters used to populate the model. We feel quite confident that the present model with its five health states based on $CD4^+$ T-cell distribution is an appropriate structure for this model. $CD4^+$ T-cell counts have been used to differentiate the risk of AIDS events and death in HIV-infected populations for many years and are clearly used in practice to make ART switching decisions. They were collected carefully and under clinical trial quality control conditions in the DART trial; thus, they may be expected to do well at capturing the immune status of trial participants in the model, giving us high confidence in the validity of the model's structure.

We clearly cannot have a similar level of confidence in the parameters that we used to populate the model because they come from many sources and time periods. Thus, we examined the individual and joints effects of changing the model parameters in the sensitivity analyses. As may be seen in Table 5, few of the variations in the model parameters have a large individual effect on the estimated ICERs. The mean budget impact figures, however, may change substantially with changes in model input costs. The effect of the cost of $CD4^+$ T-cell monitoring is important to note. The model assumed that each test cost $3.00. If this assumption is changed to use a cost of $25.00 per test, then the ICER changes by about 3%. This is an important finding because the objective of the DART trial was to compare outcomes for patients managed with and without the use of this test. Thus, it is important to note that testing costs had a small but measurable effect on the cost-effectiveness of ART switching.

It is important to note the very large changes in the per-person budget impact that we show under the different assumptions used in the sensitivity analysis. It is common practice to estimate the budget impact based on mean per-person cost with the rate of new people added to each year's cohort. In the case of second-line ART, we would multiply the number of individuals switched each year by $361 (mean cost per person per year) and calculate a total for a specific time period. The estimated budget impact, however, would be 37% too high if patients received cotrimoxazole because our model shows that the annual per-person cost decreases from $361 to $229 when no cotrimoxazole use is assumed. The estimated budget impact would be even less for groups in areas with high rates of malaria, where the marginal annual cost is estimated to be $119. This is a very important finding from the modeling study, which indicates that budget impact estimates should take local epidemiology and practice patterns into account before decisions are made about affordability.

Conclusion

The estimates of the model indicate that under the WHO benchmark threshold for cost-effective ICERs [37], a strategy of switching to LPV/r appears to be acceptably cost-effective for this region. The WHO benchmark defines an acceptability threshold based on one to three times a country's per-capita gross domestic product (GDP). Uganda's 2007 GDP was $1100 [38] and Kenya's 2007 GDP

was $1700. Thus, an ICER of $1673/QALY (Uganda) is 1.5 times the Ugandan GDP and $1483/QALY (Kenya) is 87% of the GDP for Kenya for a switch to an LPV/r-based regimen using stringent clinical or immunological failure criteria, which appears to be quite cost-effective for Kenya and probably acceptable for Uganda.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version s as a hyperlink at doi:10.1016/j.val.2011.06.011, or if hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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