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COST-EFFECTIVENESS OF TENOFOVIR / EMTRICITABINE / EFAVIRENZ VERSUS ZIDOVUDINE/ LAMIVUDINE/ EFAVIRENZ AS FIRST-LINE REGIMENS FOR THE TREATMENT OF HIV-INFECTED PATIENTS IN LOW-INCOME SETTINGS

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"Every penny counts" English proverb

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ACRONYMS AND ABBREVIATIONS

3 TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
EFV	Efavirenz
FTC	Emtricitabine
GDP	Gross Domestic Product
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
ICER	Incremental Cost-Effectiveness Ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
LY	Life Year
MSF	Médecins Sans Frontières
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NtRTI	Nucleotide Reverse Transcriptase Inhibitors
QALY	Quality Adjusted Life Year
S1	WHO clinical Stage 1
S2	WHO clinical Stage 2
S3	WHO clinical Stage 3
S4	WHO clinical Stage 4
TDF	Tenofovir
VL	Viral Load
WHO	World Health Organization
ZDV	Zidovudine

1. INTRODUCTION

1.1 BURDEN OF HIV/AIDS IN LOW-INCOME SETTINGS

In the last 25 years, more than 25 million people have died of Acquired Immunodeficiency Syndrome (AIDS). Nowadays, about 95% of people with Human Immunodeficiency Virus (HIV) or AIDS live in developing countries. By 2006, it was estimated that 63% of all persons infected with HIV are living in Sub-Saharan Africa and 72% of all adults and child deaths due to AIDS occurred in Sub-Saharan Africa. Moreover, in this same region and for the year 2006 alone, it is estimated that 2.8 million people were newly infected and 2.1 million died of AIDS. [1] [2]

It is worth to add that the estimated average prevalence rate in this region, in the adult population aged between 15 to 49 year old, is 5.9% but this prevalence can exceed 20% in the worst-affected countries like Swaziland. The epidemic in this region is especially affecting young women. [1]

1.2 ANTIRETROVIRAL TREATMENT IN LOW-INCOME SETTINGS

1.2.1 The scaling-up of antiretroviral treatment in low-income countries

The Highly Active Antiretroviral Therapy (HAART) is the combination of at least three antiretroviral compounds. The combination purpose is to reduce the likelihood of drug resistance. However in the long-term the resistance to the first-line combination occurs and leads to treatment failure. Thus, a second-line and even a third-line regimen are recommended in the long run.

The prices decrease of antiretroviral compounds allowed the World Health Organization (WHO) to launch the "3 by 5 initiative" in order to promote the scale-up of antiretroviral treatments in low-income settings. [3] In low and middle income countries, it was estimated that by December 2006 some 2 million people living with HIV/AIDS were receiving treatment representing 28% of the estimated population in need.

In Sub-Saharan Africa, the WHO Progress Report shows that by December 2006, 1.3 million people were on antiretroviral treatment, with a coverage of 28%, while three years earlier there were only 100 000 patients on antiretroviral therapy and the coverage reached only 2%. [4]

1.2.2 Standardized and simplified approaches in low-income countries

On the basis of the available Evidence Based Medicine, standardized first-line and second-line regimens and simplified formularies have been established by 2003 WHO guidelines, which were reviewed in 2006.

The consensus for the first-line HAART is as follow: one compound from the Non Nucleoside Reverse Transcriptase Inhibitors class (NNRTI), generally Efavirenz or Nevirapine, supported by two compounds in the Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTI and NtRTI) classes like Zidovudine, Lamivudine, Emtricitabine, Tenofovir, etc. The choice of first-line regimens was broadened in 2006 WHO guidelines. Three new antiretroviral have been added as first-line compounds options: Tenofovir (TDF), Emtricitabine (FTC) and Abacavir. Tenofovir was previously recommended for second-line regimen. Emtricitabine is regarded as an equivalent to Lamivudine. [5]

In the management of HIV/AIDS disease, monitoring is necessary in order to determine the appropriate time to start the first-line antiretroviral therapy and also the right moment to stop the therapy and to switch to second-line therapy if available. Three main tools are available to allow a close monitoring of the disease progression. First, the clinical conditions determine roughly the disease progression. Secondly, the immunological laboratory monitoring follows the plasma CD4+ cells counts over time. Knowing that the CD4+ immune cells are the main target of HIV, a decrease in the CD4+ cells counts is correlated with the progression to AIDS or death. Thirdly, the virological laboratory monitoring measures the virus load (commonly referred as HIV-RNA levels or VL). A high VL level is correlated with the progression of the disease.

In high-income countries, all these tools are available and an individual approach allows for close monitoring of disease progression and the antiretroviral therapy efficacy. In resource-limited settings, advanced laboratory monitoring (CD4+ counts and VL) are rarely available due to high costs and inadequate infrastructure. Hence, many low-income countries rely only on the clinical axis of the WHO clinical staging system to monitor the HAART therapy and the progression of the HIV/AIDS disease. It is worth to outline that this population based approach of monitoring disease allowed the scaling-up of antiretroviral therapies in low-income countries.

The WHO clinical staging system is based on clinical parameters and it includes a clinical axis made of 32 clinical conditions divided into 4 Stages. **Stage 1** includes patients who are asymptomatic. **Stage 2** and **Stage 3** are intermediate stages related to mild and advanced symptoms respectively. Finally, Stage 4 is associated to severe infections and symptoms. **Stage 4** is equivalent to clinical Acquired Immunodeficiency Syndrome (AIDS). The WHO clinical stages classification is detailed in the Annex 1. [6] [7] [8]

1.2.3 The current distribution of HAART use in resource-limited countries

According to a 2006 survey conducted in 24 resource-constrained countries by Renaud Thery and al., the distribution of the first-line and second-line regimens use among adults was 96% and 4% respectively. These percentages outline the low accessibility to second-line regimen in low-income settings. [9]

In addition, the survey showed that 95% of the adults receiving the first-line treatments were on regimens consistent with those preferred by the WHO. The most common combinations used on the basis of the survey are as follow:

- Stavudine/ Lamivudine/ Nevirapine (61%)
- Zidovudine / Lamivudine / Nevirapine (16%)
- Zidovudine / Lamivudine / Efavirenz (9%)

The survey confirmed that the uptake of Tenofovir and Emtricitabine, less available and more expensive drugs, remains low. The situation will certainly change as manufacturers and stakeholders work to expand access. [6] [9]

1.3 AIMS OF THE STUDY

1.3.1 The two treatment alternatives under comparison

Tenofovir (300 mg) co-formulated with Emtricitabine (200mg) and Efavirenz (600 mg) currently known under the brand name Atripla® was introduced in July 2006 in the United States market. The excellent safety profile and ease of use make this combination a perfect first-line regimen in low-income settings. Therefore, this treatment option was recommended in WHO 2006 reviewed guidelines. [5] Unfortunately, Tenofovir and Emtricitabine compounds are still costly and not yet widely available. [6] For a matter of simplification this regimen is referred in this report as "the

recent" therapy.

Initially, we had in mind to consider the most frequently used first-line regimen in low-income countries (Stavudine/ Lamivudine/ Nevirapine) as a comparator for this economic evaluation. [9] Unfortunately, according to the literature review results (see Annex 3); there was no data available comparing head to head the effectiveness of this regimen with the recent one. Instead, we selected a less frequently but commonly used first-line regimen in low-income countries as a comparator: Zidovudine, Lamivudine, Efavirenz. [9] This combination has extensive experience in durability, safety and toxicity and seems to be an optimal choice for a first-line regimen according to the clinical trial group 384 team. [10] Furthermore, Zidovudine, one of the compounds of this combination is now recommended as one of the preferred NNRTI options to be considered by countries instead of Stavudine (the most used NNRTI in limited-income countries). [5] [9] [11] [12] As this combination has been included in the WHO guidelines as a first-line therapy since 2003 when WHO launched the "3 by 5" scaling-up initiative, this combination of drugs is referred in this report as the "old" therapy. [13] [14]

1.3.2 Objectives

The primary objective of this economic evaluation is to compare the two first-line HAARTs introduced above, in a low-income setting context. Both of these combinations are recommended by the 2006 WHO guidelines as potential first-line regimens. [5]

The secondary objective is to provide a simplified and comprehensible cost-effectiveness modeling tool in order to help policy makers, in resource-limited settings, make decisions about which first-line HAART to fund using the scarce resources available.

2. MATERIALS AND METHODS

2.1 MODEL OVERVIEW: KEY FEATURES OF THE MODEL

Economic evaluation is the comparative analysis of alternative interventions in terms of both their costs and consequences. Three main types of economic evaluation are commonly used: cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. The fundamental differences between these approaches remains in the methodology to measure the benefits or consequences of alternative health interventions (see Figure 1). [15]

The monetary valuation of the outcomes of health-care in cost-benefit analysis, in particular the value of life, doesn't reach consensus. Cost-effectiveness and cost-utility analysis are the most suitable approaches to compare health interventions that produce similar units of outcomes. Cost-utility analysis is seen as a useful technique because it allows incorporating quality of life adjustments to treatment outcomes. Since we compare two interventions in the same therapeutic category, cost-effectiveness analysis and cost-utility analysis will be considered. [16]

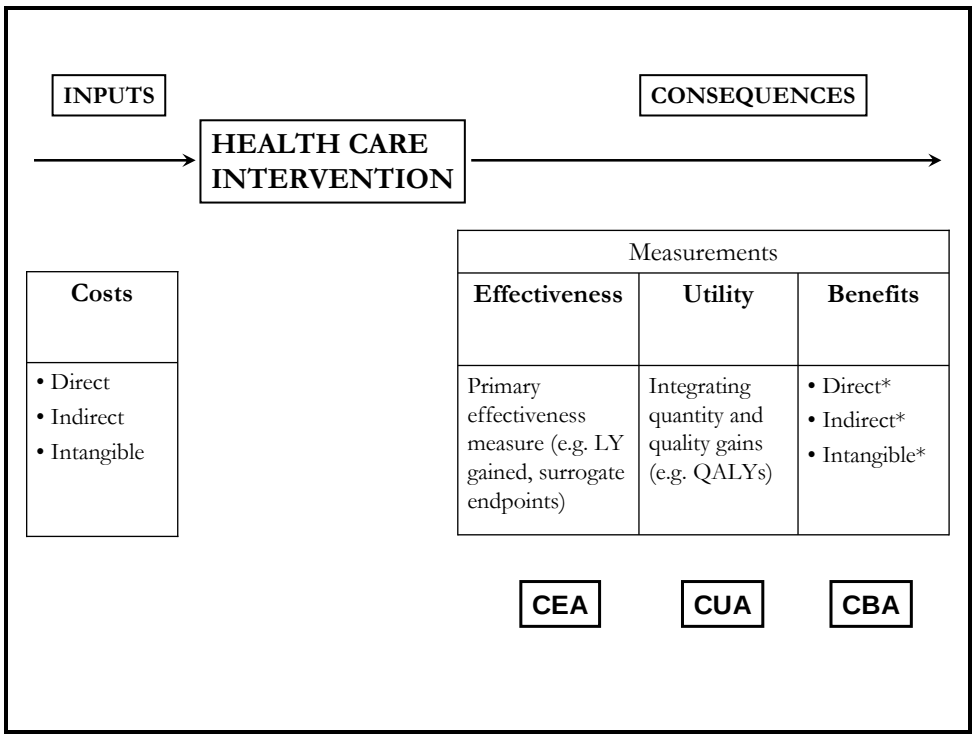


Figure 1 - Potential components of economic evaluation in health care (*valued in monetary terms/ CEA, CUA and CBA stands for cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis respectively)[15] [16]

Economic evaluation will usually need to consider multiple factors and data from multiple sources. Thus, it often requires the systematic integration of data through modeling. In this study, modeling will be used to synthesize the available data and to relate this available evidence to the specific decision issue studied. [16] [17] [18]

Within this study, we constructed an overall model in two subsequent parts - the short and the long-term. First, the short-term part evaluates the costs and effects of the two alternatives over two years. Then the long-term element extrapolates the patient costs and outcomes beyond the first two years. Data for the whole model were mainly derived from a literature search of published clinical trials on the common medical databases (Embase, Cochrane and Medline), HIV/AIDS reports and health economics' articles. It is worth to outline that the model was constructed from the healthcare system perspective.

In order to reflect the low-income countries practice and to simplify the reality, the following assumptions had to be incorporated in the modelling:

- It was assumed that all healthcare professionals would be fully compliant to the WHO guidelines and to our assumptions.
- All patients were assumed naïve to previous antiretroviral compounds at the initiation of the therapy.
- As laboratory monitoring is often unavailable in low-income setting, we assumed that the management of the disease and the antiretroviral treatment is based on WHO clinical staging system (accounting for the symptomatic criteria alone). [5] The whole model is founded on the basis of the four WHO clinical stages (see Annex 1).
- According to WHO guidelines, failure (and interruption) of the therapy is defined as progressing to Stage 3 or Stage 4 after at least 6 months of receiving therapy. In fact, the severe clinical events occurring during the first 6 months are mostly due to Immune Reconstitution Inflammatory Syndrome (IRIS) related to pre-existing conditions. During these first 6 months following the initiation of the HAART, it is difficult to differentiate between failure and IRIS events on the basis of the WHO clinical axis. [5]
- Due to the low accessibility to substitute first-line or second-line therapy in the low-income settings, the model does not consider any salvage therapy in case of failure or major toxicity after starting one of the alternative combinations. [9]

Costs were expressed in US dollars at 2006 price base. The study included the annual acquisition costs of the drugs based on Médecins sans Frontières 2007 pricing guide. We assumed in the model that the alternatives compared have different acquisition costs (US$ 385 per patient per year for the recent therapy vs. US$ 347 per patient per year for the old one). [19] We also incorporate estimations of the average healthcare costs associated with each year spent in a specific WHO clinical stage on the basis of literature findings. [20] [21] The average cost related to the transition to the death state was also accounted for. [22] On the contrary to the acquisition costs of HAART, healthcare costs related to WHO-clinical stages and the costs relative to the transition to the death state are assumed identical for both options.

On the benefits side, both Life Years (LYs) and Quality-Adjusted Life-Years (QALYs) gained were considered. LYs gained are calculated by summing up the years spent in all the stages excluding the patients that reached the death state. The advantage of the QALY as a measure of health output is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure. In order to derive the generic QALY outcome, the length of life gained is adjusted to the quality of life thanks to utility ratios attributed to each WHO clinical stage (the utility ratios vary from 0 to 1 where 0 is death and 1 is perfect health). [16] [17] Hence, QALYs are calculated by applying these quality of life ratios to each year spent in a specific WHO clinical stage. These ratios are drawn from an empirical Ugandan study on the quality of life of HIV-infected patients. [23] [24]

Other categories of costs and benefits such as indirect costs, intangible costs, indirect benefits and intangible benefits to patients are excluded from the analysis because it has not been performed from a societal perspective (see Figure 1).

The whole costs and benefits where assumed to occur totally at the beginning of each year. An annual discount rate of 3% is adopted for both costs and outcomes values according to WHO-

2003 recommendations. [25]

The inputs described in the paragraphs above (costs, quality of life ratios and discount rates) are average estimates predicated on the basis of data found in the literature for low-income countries. These data inputs are used for both the short and long-term parts. Details of these data inputs, together with their sources, are outlined in the table of the Annex 2. With the general framework of the overall model established, the following sections detail the descriptions of both the short-term and the long-term parts of the model.

2.2 SHORT-TERM MODEL

2.2.1 Model structure

The short-term model is structured as a decision tree model as illustrated in Figure 2. The decision tree represents possible prognoses under one of the drug alternatives compared. It considers costs and effects over a 2-years period mirroring the follow-up period of the clinical trial considered (see paragraph below - data inputs). [26] [27]

The analysis was conducted on a hypothetical cohort of 10 000 HIV-infected patients. We assumed the following average baseline characteristics for this cohort based on data found in the literature for low-income countries:

- The patients are antiretroviral-naïve adults with the same baseline characteristics defined in the clinical trial except for the CD4+ count and the clinical stage at entry. [26]
- In settings where a CD4+ cell monitoring is unavailable, WHO advises to start the antiretroviral drugs at an advanced stage: Stage 3 or 4. In practice, the majority of the patients in low-income settings start the therapy at Stage 3. [28] [29] In order to simplify the model, we supposed that HAART therapy was initiated at Stage 3 for all the patients.
- In view of the fact that the median CD4+ count at start is lower in low-income settings compared to high-income countries, we assumed that the average CD4+ counts at start for both the alternatives hypothetical cohorts is around 108 cells /µl (instead of the 233 and 241 cells /µl reported by the clinical trial considered, which are in the range of high-income countries' levels). [30]

2.2.2 Data source

Efficacy data for the purpose of the short-term model comparing the two alternatives were identified by searches of clinical data in the following electronic databases: Medline, Embase and Cochrane. The research methodology details and the investigations results are outlined in the Annex 3 of this report.

Two records, associated to the same initial cohort (study 934), were eligible for inclusion in the context of our study. [26] [27] These records compare head to head the efficacy (in term of surrogate endpoints) of the two alternatives after one year and two years of follow-up. It is worth to add that the design of this study is a prospective, randomized, open-label, non-inferiority trial. We mainly consider for the short-term model the results of two years of follow-up. [26] A summary of the main results of this clinical trial is presented in the Annex 4.

Succinctly, the study reported these two main conclusions:

- "Over 96 weeks, the combination of TDF/FTC/EFV was superior to fixed dose of ZDV/3TC/EFV for achieving and maintaining an HIV RNA level < 400 copies/mL and an increase in CD4 cells." [26]

- "Through 96 weeks, significantly more patients in the ZDV/3TC/EFV group experienced adverse events that resulted in discontinuation of study medications (11% in the ZDV/3TC group vs. 5% in the TDF + FTC + EFV group)." [26]

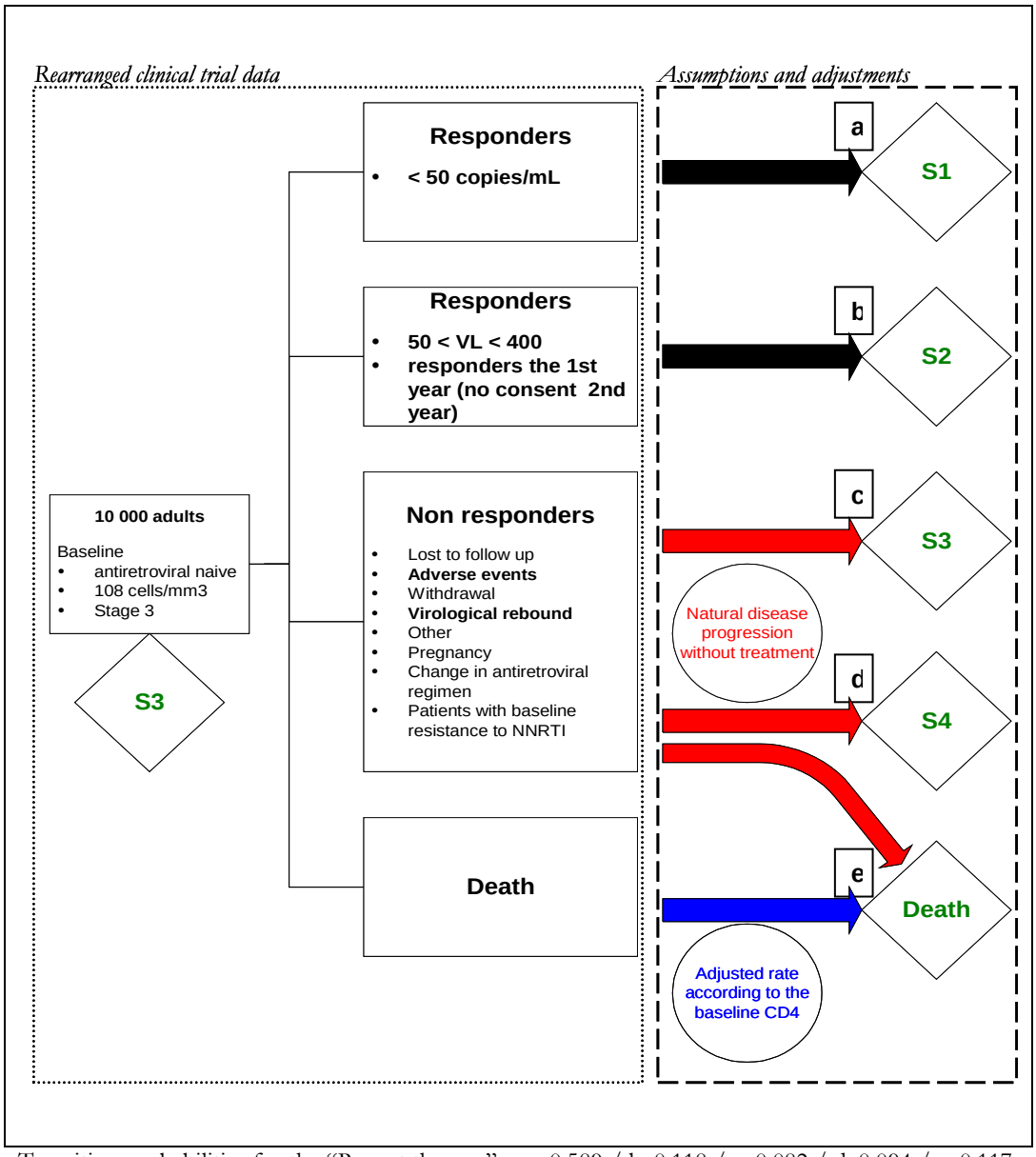
The clinical study reports the efficacy of the two regimens as the percent of patient with a VL below 400 copies/mL. In fact, VL is a good predictor of progression of the disease to AIDS or death. [31] Unfortunately, there is no global clear equation translating VL measurements into the probable clinical progression of the disease, according to medical experts consulted (Mme Valérie Journot – Institut de Santé publique, d'épidémiologie et de développement – Bordeaux – France).

2.2.3 Data adjustments and assumptions

The clinical trial selected mirrors the presumable health efficacy in high-income countries and are unlikely to provide reliable estimates for low-income countries where the management of the disease is different. [27] Moreover, the results reported are in terms of viral load measurements (which are not available in our study setting), instead of WHO-clinical stages reached. Therefore, clinical trial results were processed and rearranged to reflect the differences of practice and effectiveness in low-income settings given the following assumptions:

- We assume that patients, who reached a viral load below 50 copies per mL (meaning that the therapy for the set of patients is very efficient,) are attributed to Stage 1.
- Patients achieving a viral load lower than 400 copies/mL but above 50 copies/mL or patients that achieved a viral load below 50 copies/mL during the first year but did not consent to continue the therapy the 2nd year, are attributed to Stage 2.
- We conservatively judged that all non responders to the therapy and missing data to represent treatment failure. We also included in this node of the tree, patients that were tested to be initially resistant to NNRTI (Efavirenz) who were not accounted in the clinical trial results. In fact, we assume that no laboratory monitoring is available to detect initial resistance in our study setting. Then, for this entire portion of non-responders the treatment is maintained for 6 months as mentioned in the WHO-guidelines. [5] We suppose that no benefit is accounted from these 6 months of antiretroviral treatment. As we assume that no replacement treatment is available, these patients will then progress according to the natural history of the disease without antiretroviral treatment. Hence, these patients will remain in Stage 3 or progress to Stage 4 or death according to probabilities drawn from the literature. [32]
- Patients starting HAART in resource-limited settings have increased morality rates in the first months on therapy, compared with those in developed countries. [30] It is partly explained by the lower baseline CD4+ counts at start of the treatment. In order to include this difference in mortality rate, we consider that in our model patients are 3,41 times more likely to die than reported in the clinical trial. [33] The deaths estimated from this adjustment are extracted from the responders in Stage 1 (patients reaching a VL below 50 copies /mL).

These adjustments and assumptions are also illustrated in Figure 2. After their incorporation to the clinical trial data mentioned above, we obtain the transition probabilities for the decision tree (depicted in Annex 5).



Transition probabilities for the "Recent therapy" = a: 0,589 / b: 0,118 / c: 0,082 / d: 0,094 / e: 0,117;
Transition probabilities for the "Old therapy" = a: 0,536 / b: 0,055 / c: 0,118 / d: 0,134 / e: 0,157

Figure 2 - Structure of the short-term part of the model including the assumptions and clinical trial data adjustments incorporated

2.3 LONG-TERM MODEL

The purpose of the long-term part of the model is to extrapolate the costs and the effects beyond the two years follow-up period of the clinical trial.

2.3.1 Model structure

In this part of the model, we use a Markov model approach in order to handle the complexity of modeling options with the multiplicity of possible consequences for patients on HAART therapy in the long-term. This Markov model characterizes a patient's prognosis in terms of five states. Thus, the long-term model is based on a five-compartment Markov model as depicted in Figure 3. Four of these are based on the four WHO-clinical stages. The last state is the death absorbing state. Portions of the initial cohort distribution of patients (obtained after running the short-term part of the model) run through the model according to transition probabilities that govern how likely it is to transit from one state to another.

2.3.2 Data source

Probability data, determining how proportion of patients move between states, was derived from an observational study in Uganda reporting the natural disease progression. [32] A summary of the main results of this study is shown in the Annex 6.

2.3.3 Data adjustments and assumptions

In this part of the model, we conservatively assumed that both the alternatives ceased to confer major health improvements after the two years under treatment of the short-term part. We supposed, in the long-term part, that patients can only remain in the same state or progress to a more severe state. However, we assumed that the HAART therapy confers a minor benefit by delaying the progression of the disease.

Moreover, we run this part of the model with the following hypothesis:

- We use the same transition probabilities for the two alternatives, as we assumed that the major health benefits already occurred during the short-term part of the model.
- Each Markov cycle is taken as 1year.
- All transition probabilities are assumed to take place at the start of the cycle.
- No discontinuation due to acute toxicity is considered. In fact, discontinuation of the therapy due to major adverse events occurs mainly in the first-year under HAART and very few patients interrupted the therapy in the second year of follow-up. [26] [27]
- No discontinuation due to chronic toxicity is accounted even if these kinds of adverse events may appear in the long-run and may lead to the interruption of the therapy (e.g. lipodystrophy).
- As in the short-term model, we consider that the therapy is interrupted when patients have entered Stage 3 or 4, and that no salvage therapy is initiated.

The transition probabilities governing the direction and speed of transitions between disease states in the Markov model are shown in Annex 7. [32] In view of the lack of data, especially concerning Stage 1 and Stage 2, some probabilities were roughly estimated and will be tested in the sensitivity analysis. (See Annex 7)

The transition probabilities are assumed fixed with respect to time and the Markov model is run until almost 90% of the initial hypothetical cohort of 10 000 patients has entered the death absorbing state.

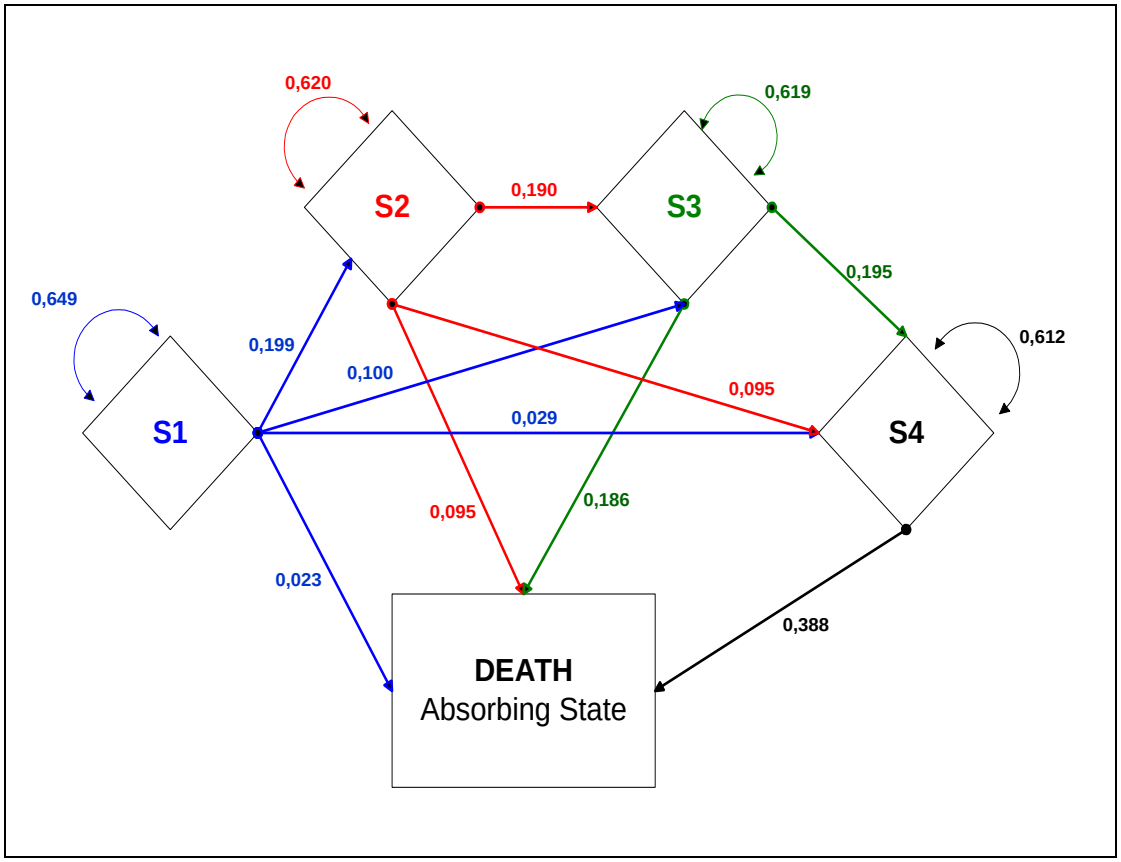


Figure 3 - Structure of the long-term part of the model (the decimal numbers are the base-case transition probabilities)

2.4 ANALYTICAL METHODS

2.4.1 Computation

The model was developed in Excel - Microsoft Office 2003. The results of the model are presented in term of costs (US$), Life Years gained (LY) and Quality-Adjusted Life-Years (QALYs) gained. The two therapies are then compared, calculating the Incremental Cost-effectiveness Ratios (ICERs) in terms of cost per life year gained (US$/LY) and in terms of cost per quality-adjusted life-year gained as well (US$/QALY). The results of both the short-term model alone and the overall model (combining the results of the short-term part and the long-term part) are presented.

2.4.2 Sensitivity analysis

A number of one-way sensitivity analyses were undertaken to assess the robustness of the results of the base-case analysis to variations in the data inputs and assumptions. The sensitivity analyses were divided into three main sections:

First, we varied some cost inputs:

- The acquisition costs of the combinations according to different manufacturers prices published in the MSF report. [19]
- The average healthcare costs associated with Stage 2 and Stage 3.

Secondly, as recommended by the WHO-CHOICE guidelines, we altered the discount rates. Thus, discount rates of 6% for costs and 0% for benefits were applied instead of the 3 % discount rates in the base-case. [25]

Finally, we modified some transition probabilities and assumptions:

- In the short-term, we assumed that all responders were attributed to Stage 2, even patients that achieved a viral load below 50 copies/mL. Thereby, we supposed that no patient progressed to Stage 1.
- In the long-term part, we varied some transition probabilities associated with Stage 1 and Stage 2 that were roughly estimated in the base-case.

Annex 8 summarizes the parameters used in the base-case analysis and how these were varied in the sensitivity analyses.

Using the results of the overall model sensitivity analyses, ICER elasticities, associated with the variation of some input variables, were calculated. The elasticity of the ICER was defined as the percentage variation of the ICER (in terms of US$/QALY) over the percent change in the input parameter varied. The calculation of the ICER elasticity is detailed in the following equation:

$$e = \frac{(ICER_{SA} - ICER_{BC}) \Big/ ICER_{BC}}{(Parameter_{SA} - Parameter_{BC}) \Big/ Parameter_{BC}}$$

Where:

e is the ICER elasticity associated with the variation of an input variable

ICER $_{SA}$ is the overall model ICER (in terms of US$/QALY) of the sensitivity analysis considered

ICER $_{BC}$ is the overall model ICER (in terms of US$/QALY) of the base-case

Parameter $_{SA}$ is the value of the parameter varied in the sensitivity analysis

Parameter $_{BC}$ is the base-case value of the parameter varied in the sensitivity analysis

It is worth to note that the larger the elasticity, the greater the impact of the variable on the ICER.

3. RESULTS

3.1 BASE-CASE RESULTS

3.1.1 Short-term part results

Table 1 and table 2 present the base-case results for the short-term part of the model. After two years under HAART, patients under the recent antiretroviral treatment have higher overall costs and higher overall benefits (both in terms of QALYs and LYs) compared to patients under the old treatment. The ICERs of the recent regimen compared to the old regimen are 1289 $US/LY and 898 $US/QALY. It is worth to outline that the use of QALY instead of LY as an outcome measure results in a decrease in the ICER. This difference arises from the fact that the new therapy confers higher benefits in term of QALYs than in term of LYs: 0,1132 QALY gained vs. 0,0788 LY gained for one patient.

Table 1 - Results of the short-term part (base-case) for the 10 000 patients cohort

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	16614	10159	5460633	**1289 $US/LY** **898 $US/QALY**
Recent therapy	17403	11291	6477185	
Difference	***788***	***1132***	***1016552***	

Table 2 - Results of the short-term part (base-case) for 1 patient

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	1,6614	1,0159	546,0633	**1289 $US/LY** **898 $US/QALY**
Recent therapy	1,7403	1,1291	647,7185	
Difference	***0,0788***	***0,1132***	***101,6552***	

3.1.2 Long-term part results

Table 3 and table 4 detail the results of the long-term part of the model. As noticed for the short-term part, the recent regimen confers higher benefits and costs compared to the old regimen. On the opposite of the short-term part, the outcomes difference between the two alternatives in term of QALYs is lower than the outcome difference in terms of LYs. It results in an ICER in terms of LYs (503 $/LY) lower than the ICER in terms QALYs (721$/QALY). Besides, it is worth to add that in terms of cost per QALY gained no significant variation is observed compared to the short-term part.

Table 3 - Results of the long-term part of the model (base-case) for the 10 000 patients cohort

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	32891	18942	8138684	**503 $US/LY** **721 $US/QALY**
Recent therapy	36243	21279	9824252	
Difference	***3352***	***2337***	***1685567***	

Table 4 - Results of the long-term part of the model (base-case) for 1 patient

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	3,2891	1,8942	813,8684	**503 $US/LY** **721 $US/QALY**
Recent therapy	3,6243	2,1279	982,4252	
Difference	***0,3352***	***0,2337***	***168,5567***	

3.1.3 Overall model results

Table 5 and table 6 summarize the results of the overall model (short-term combined to the long-term). Once again, the recent combination confers higher costs and benefits compared to the old regimen. The difference in benefits between the two alternatives is lower if considering QALY instead of LYs as outcome measure. It results in an ICER in terms of US$ per QALYs gained greater than the ICER in terms of US$ per LYs gained.

In summary, the results from base-case analysis demonstrate that if the health system is prepared to pay $653 per additional LY and $779 per additional QALY, then the choice of the recent combination as the first-line regimen instead of the old combination would be optimal (this conclusion is from a pure economic perspective and on the basis of purely competitive market hypothesis).

Table 5 - Results of the overall model (base-case) for the 10 000 patients cohort

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	49505	29101	13599317	**653 $US/LY** **779 $US/QALY**
Recent therapy	53646	32570	16301437	
Difference	***4140***	***3469***	***2702120***	

Table 6 - Results of the overall model (base-case) for 1 patient

Strategies	LY gained	QALYs	Costs ($US)	ICER
Old therapy	4,9505	2,9101	1359,9317	**653 $US/LY** **779 $US/QALY**
Recent therapy	5,3646	3,2570	1630,1437	
Difference	***0,4140***	***0,3469***	***270,2120***	

3.2 SENSITIVITY ANALYSIS RESULTS

Table 7 presents the main results of the sensitivity analyses undertaken for the short- term part and the overall model. More detailed results of the sensitivity analyses are reported in Annex 9 and Annex 10. In the purpose of quantifying the impact of some variables on the model results, elasticities were computed. The details of these calculations are outlined in table 8. For instance the elasticity of 4.84 (depicted for the recent therapy acquisition cost) translates that a 1% increase of recent therapy acquisition cost will affect the overall ICER by a 4.84% increase. This high elasticity value reveals that the model is highly sensitive to this specific input variable. We have to keep in mind that the larger the elasticity in term of absolute value, the greater the impact of the variable on the ICER.

The results show that the ICERs were slightly sensitive to variations in Stage 2 and Stage 3 healthcare costs (with elasticities of 0.03 and 0 for the selected examples - see table 8). Moreover, the sensitivity analyses on the discount rates have a small impact on ICERs for both the short-term part and the overall model (with elasticities of -0.08 and 0.09 for the selected parameters varied - see table 8).

However, ICERs were mildly sensitive to assumptions regarding the transition probabilities associated to the short-term and the long-term part of the model. But, the most influential of the base-case parameters were the acquisition costs of the two HAART combinations. In fact, the ICERs (in term of QALYs or LYs as outcome measure) were extremely sensitive to variations in therapies acquisition costs. For instance, the increase of the new therapy acquisition cost (from $385 to $487 per year per patient) resulted in more than a two fold increase of the ICERs. This result is also outlined by the large ICER elasticities obtained when varying the acquisition costs of the therapies compared (elasticities of 4.84 and -3.83 for the selected values - see table 8).

Overall, few of the sensitivity analyses undertaken resulted in significant variation in the ICERs. These results outline the robustness of our model to some of the parameters investigated, but also emphasize the importance of accurately reporting the acquisition costs of the therapies in order to fully strengthen the uncertainty about our model results.

Table 7 - Results of the sensitivity analyses using data summarized in Annex 8

RESULTS / PARAMETERS VARIED (see Annex 8)	Short-term Part		Overall model (Short-term + Long-term)	
	ICER $/LY	**ICER $/QALY**	**ICER $/LY**	**ICER $/QALY**
No parameters varied - Base Case	**1289**	**898**	**653**	**779**
COSTS VALUES				
Recent combination acquisition costs				
487 vs. 385 $	3283	2286	1490	1778
613 vs. 385 $	5743	4001	2524	3013
Old combination acquisition costs				
410 vs. 347 $	195	136	199	237
434 vs. 347 $	- 222	- 154	26	31
Stages healthcare costs				
Stage 2 healthcare costs 0 vs. 30 $	1242	865	632	755
Stage 3 healthcare costs 100 vs. 70 $	1262	879	653	779
DISCOUNT RATES VALUES				
Cost discount rate (6% vs. 3%)	1268	884	602	718
Benefit discount rate (0% vs. 3%)	1271	881	577	710
TRANSITION PROBABILITIES				
Short-term part assumption (no S1 progression)	1329	1167	634	889
Long-term part - a lower S1 to S1 and S2 to S2 transition probabilities : 0.50 vs. 0.6	-	-	574	733
Long-term part - a lower S1 to S1 and S2 to S2 transition probabilities : 0.20 vs. 0.6	-	-	493	681

Table 8 - ICER elasticities associated with the variation of some input parameters

	Parameters values		ICER ($/QALY) for the overall model		Elasticities
Parameters varied	**Base-case**	**Sensitivity analysis**	**Base-case**	**Sensitivity analysis**	**-**
Recent combination acquisition costs	385 $	487 $	779	1778	**4.84**
Old combination acquisition costs	347 $	434 $	779	31	**- 3.83**
Stage 2 healthcare costs	30 $	0 $	779	755	**0.03**
Stage 3 healthcare costs	70 $	100 $	779	779	**0**
Cost discount rate	3%	6%	779	718	**- 0.08**
Benefit discount rate	3%	0%	779	710	**0.09**

4. DISCUSSION AND LIMITATIONS

4.1 COST-EFFECTIVENESS ANALYSIS IN DECISION MAKING

From the healthcare system perspective, the model clearly predicts that the implementation of the "recent" Tenofovir/Emtricitabine/Efavirenz combination as a first-line regimen to treat HIV in scarce-resource countries will be both more effective and more expensive than the "old" Zidovudine/Lamivudine/Efavirenz combination. The base-case analysis predicts an incremental cost-effectiveness ratio of $653 per LY gained and $779 per additional QALY gained in the long-term.

The cost-effectiveness ratio is a measure of value for money. Hence, the question to be considered would be if the healthcare systems are disposed to afford this amount of money for this gain in effectiveness (cost per additional LY or cost per additional QALY). Nowadays, there is no evidence that any health system, in low-income countries, has implemented explicit cost-effectiveness ratio thresholds. [35] However, the 2002 World Health Report proposed a quite universal definition of threshold ratios below which an intervention would be considered cost-effective. It suggests that intervention with a "cost effectiveness ratio less than the per capita GDP for a given country would be considered as "highly cost-effective" and less than three times the per capita GDP would be considered as "cost-effective" ". [36] In light of this cost-effectiveness threshold definition, we report on table 9 the GDP and 3 times GDP per capita of a random subset of low-income countries with a high prevalence of HIV. [37] Based on the base-case overall model results ($779/QALY) and according to this threshold definition, the "recent" combination (long-term use) as compared to the "old" combination is expected to be highly cost-effective for some low-income countries such as Kenya, Mozambique and Zambia. On the contrary, it is not expected to be highly cost-effective in Malawi (see table 9).

We have to be aware to the fact that these thresholds are not well defined. In fact, this thresholds' definition do not specify the types of costs to include in calculating the cost-effectiveness ratio (which depend on the perspective adopted). [35] [36] Furthermore, it is worth to outline that the cost-effectiveness ratio is not the only criteria to be considered in decision making. Many other factors influence priority setting such as equity (especially in low-income countries), opportunity costs within or outside the healthcare sector (e.g. prevention of transmission), the acceptance of the treatment and the affordability. [17]

Table 9 - Theoretical thresholds values according to the WHO Report 2002

Country	1 * GDP (PPP) per capita	3 * GDP (PPP) per capita
Kenya	1357	4071
Malawi	706	2118
Mozambique	1494	4482
Tanzania	806	2418
Zambia	1087	3261

GDP (PPP) per capita: Gross domestic product based on purchasing power-parity per capita (2006 – current international dollar) – Source: International Monetary Fund. [37]

4.2 LIMITATIONS: A NEED TO STRENGTHEN HEALTH DATA MANAGEMENT

The model developed is kept as simple as possible in order to make it understandable to decision makers. However, this simplification is associated with several limitations.

The model greatly simplifies reality and is based on two highly conservative assumptions. First, for the short-term part, we conservatively assumed that patients reaching low viral load ranges will automatically progress to better WHO clinical stages. Secondly, we also postulated the hypothesis of "one time benefit" of the HAART therapy. In fact, we assumed that the therapy confers major health improvements only within the two first years under treatment (possible transition to better health states in the short-term part) and only minor benefits within the long-term part (slow-down of disease progression). These two assumptions may be regarded as too conservative and should be revisited as new information emerges especially additional findings concerning the viral load as surrogate endpoint and the long-term benefits of HAART therapy in low-income settings.

Another important restriction in the long-term part model relates to what is known as the memoryless feature of the Markov model. In fact, the transition probabilities depend only upon the health state patients are in and not on how long they had been in this health state or on the pathway followed to reach a specific health state. Incorporating time dependency into transition probabilities should be considered in further development of the model (in light of data on the long-term benefits of HAART). [16] [17]

In addition, in view of the scarcity of published data available many other limitations arise from our model:

- Data is combined from various sources and roughly estimated. We have to be careful to the fact that effectiveness and cost data may vary substantially across and within low-income countries.
- Effectiveness data incorporated was based on controlled clinical trials data that may not, even with the adjustments incorporated, mimic reliably the real-life clinical outcomes.
- There is a paucity of data concerning the healthcare costs especially in low-income countries. One should be particularly careful in accurately reflecting the price paid for the drugs as our model is extremely sensitive to this parameter. This finding is correlated with the fact that HAART drugs amount for more than half of the cost of treatment of HIV-patients. [38]

Finally, some major HIV/AIDS issues were not captured in the perspective of this analysis as a matter of simplification and could be included in future improvements of this model, including:

- Productivity costs: In fact, antiretroviral therapy results in a gain of years of productivity and this is of major importance in countries with high prevalence of HIV within the working population. [39]
- We did not consider the disease transmission factor (external benefit): HAART lower the VL in HIV+ individuals, thereby reducing the probability of HIV transmission to others. However, at the same time it prolongs the survival of potential infective hosts. [40] We lack data about the exact impact of this external benefit.
- The impact of adherence to HAART therapy on its effectiveness. The new combination is the first once daily pill for the treatment of HIV and this is certainly of importance in promoting adherence and thus effectiveness especially in scarce-resource settings.

Overall, it seems that the most important limitation that arises from our study is the limited availability of reliable data related to low-income countries. These limitations mean that interpretation and generalizations of the results should be viewed with caution. Because of the

scarcity of relevant data, approximations for many variables and assumptions were used in our model. These findings emphasize the need to develop health data management in low-income countries. More robust country estimates and additional research on the assumptions incorporated can result in more accurate and reliable estimates of the cost-effectiveness results obtained.

5. CONCLUSION

In conclusion, the results of this model suggest that the Tenofovir/Emtricitabine/Efavirenz combination, newly introduced as first-line regimen, is expected to be cost-effective relatively to the Zidovudine/Lamivudine/Efavirenz combination in some low-income countries.

However, additional data about viral load as surrogate endpoints, lifetime benefits of HAART, and more precise country-specific data on effectiveness and costs, are needed to fully strengthen the uncertainty about this economic model of antiretroviral therapies in low-income countries.

Hence, this study provides a simplified and understandable "framework" model that may be used, incorporating more accurate country-data, to assess the cost-effectiveness of new antiretroviral drugs in low-income countries.

6. ANNEXES

6.1 ANNEX 1: WHO CLINICAL STAGING FOR ADULTS AND ADOLESCENTS

Table A1 – WHO clinical staging for adults and adolescents for HIV infection [8]

WHO clinical Stages	Symptoms classification	Examples of clinical events associated
Stage 1	Asymptomatic	• Painless lymph nodes
Stage 2	Mild	• Recurrent bacterial upper respiratory tract infection • Herpes zoster • Fungal nail infection • Seborrhoeic dermatitis
Stage 3	Advanced	• Oral candidiasis • Pulmonary tuberculosis • Severe bacterial infection
Stage 4	Severe	• Recurrent bacterial pneumonia • Chronic herpes simplex virus • Oesophageal candidiasis • Extrapulmonary Tuberculosis • Meningitis

6.2 ANNEX 2: PARAMETERS USED IN THE WHOLE MODEL AND SOURCES

Table A2 – Overall model base-case parameters

Items	Values (Base case)	Source of Data	Notes
Antiretroviral drugs acquisition costs of treatment per patient per year (US$)	-	MSF	Prices listed are quoted as sale prices by the manufacturers. These prices does not include add-ons as import taxes or distribution mark-ups
ZDV-3TC-EFV (old regimen)	385	[19]	For the base-case, we consider the lowest prices provided by the cheapest producer for low-income countries.
TDF-FTC-EFV (new regimen)	347	[19]	
Healthcare costs associated with WHO clinical Stages per patient per year US$			Due to the paucity of data in the published literature, we estimate roughly these costs - expecting increased healthcare costs for later stages of the disease. Some of these data inputs and their impact on results of the model will be investigated in the sensitivity analysis.
Healthcare costs - Stage 1	0	-	Estimate
Healthcare costs - Stage 2	30	-	Estimate
Healthcare costs- Stage 3	70	-	Estimate
Healthcare costs - Stage 4	150	[20] [21]	Data are from Kenya
Costs related to the transition to the death state (palliative care)	75	[22]	Costs derived from estimates, using data from Sub-Saharan African countries. It was assumed that it was completely incurred in the last year of life.
Quality adjustment of life years per year spent in a specific WHO clinical Stage			Parameters drawn from an empirical study of the quality of life from Uganda.
For one year spent in Stage 1	1	[23] [24]	1 year spent in Stage 1 is taken to be 1
For one year spent in Stage 2	0,7	[23] [24]	1 year spent in Stage 2 is taken to be 0,7
For one year spent in Stage 3	0,45	[23] [24]	1 year spent in Stage 3 is taken to be 0,45
For one year spent in Stage 4	0,15	[23] [24]	1 year spent in Stage 4 is taken to be 0,15
Discount rates per year		WHO	-
Effects discount rate (LYs and QALYs)	3%	[25]	-
Costs discount rate	3%	[25]	-

6.3 ANNEX 3: LITERRATURE REVIEW

6.3.1 Objective

The systematic research subsequently described aims at identifying the major relevant outcome research publications that compares head to head the two alternatives of interest in this study. Adjusted results of these publications are to be used in the cost-effectiveness analysis comparing these two regimens.

As mentioned in the introduction of this report, the two combinations compared are:

- Zidovudine, Lamivudine, Efavirenz
- Tenofovir, Emtricitabine and Efavirenz. The commonly used medical abbreviations used for these compounds are respectively as follow: TDF, FTC and EFV.

6.3.2 Criteria for considering studies

We only selected studies that included the following criteria:

- Type of intervention: Studies comparing Tenofovir, Emtricitabine and Efavirenz combination to the Zidovudine, Lamivudine and Efavirenz combination.
- Type of studies: Randomized studies.
- Type of participants: Adults and/or adolescents aged 15 years old or more without prior exposure to antiretroviral therapy.
- The study also has to report at least one of the following primary or secondary outcome measures
    - Primary outcomes measures: death or AIDS defining illness, proportion of patients that discontinued the 1st line combination therapy, time to withdrawal of the 1st line therapy, survival (time to death), virologic failure rates.
    - Secondary outcomes: CD4+ cells counts changes compared with a baseline mean, proportion of patients reaching defined viral load levels, quality of life indicators, any major or minor adverse events.

6.3.3 Search methodology

As the recent combination is the limiting search criteria, we based the quest on the recent 1st line combination drugs names. We searched the following major electronic database:

- Medline via PubMed using the following search terms (drug commonly used names and abbreviations) joined with the "AND" and "OR" Boolean operators. The search was performed on the 7th of September 2007 using the following research string:

  (Tenofovir OR TDF) AND (Emtricitabine OR FTC) AND (Efavirenz OR EFV)

- A similar search strategy was performed on the Cochrane Library (2007/Issue3) on the 7th of September 2007. The search was separately applied on titles, abstracts and key words.
- Using the same search strategy, a research was performed on EMBASE Database (records from 1989 to 08/2007) through ERLWebSPIRS research interface on the 10th of September 2007. The research was applied separately on titles and keywords.

  In order to limit the results obtained from the EMBASE database search on keywords,

we applied an advanced search strategy on keywords as well. For this purpose, we combined the search terms used previously with terms specific to the type of the study (terms related to randomized clinical trials) and to the health condition of interest (terms related to HIV). Thus, we investigated the keywords of the EMBASE database with the following advanced research string:

> "(Tenofovir OR TDF) AND (Emtricitabine OR FTC) AND (Efavirenz OR EFV) AND (clinical trial OR randomized trials) AND (AIDS OR HIV OR Immune deficiency)"

6.3.4 Results of the databases searches

The searches in the three databases yielded to the following results:

In the Medline database, 46 records were found. On the basis of the titles and/or the abstracts (if available), five publications were considered potentially relevant and selected for full article retrieval. The two following publications were found to be the most relevant for the purpose of our study:

1. Pozniak AL, Gallant JE, DeJesus E, Arribas JR, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, Emtricitabine, and Efavirenz versus fixed-dose Zidovudine/Lamivudine and Efavirenz in antiretroviral-Naïve Patients: virologic, Immunologic, and morphologic changes – a 96-week analysis. J. Acquir. Immune Defic. Syndr. 2006; 43 (5):535-40.
2. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, et al. Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV. N. Engl. J. Med. 2006; 354 (3) :251-60.

The Cochrane Library search yielded to two records in total. The two publications found were already identified through the previous Medline database search.

Finally, the Embase research applied on titles identified six records from which two were relevant. The two publications were the ones identified through the Medline Database search. The Embase search applied on the keywords yielded 606 records in total. Instead of reviewing all these records, we applied the advanced search strategy described above, which identified 71 records. On the basis of the titles and/or abstract review none of these publications were relevant to the purpose of our study.

In summary, two records were eligible for inclusion in the context of our study. These two publications quoted above are related to the same cohort (study 934 Group) respectively after one year and 2 years of follow-up. The design of this clinical trial is a prospective randomized, open-label, non-inferiority trial.

6.4 ANNEX 4: MAIN RESULTS OF THE CLINICAL TRIAL CONSIDERED

Table A4 – Main results of the clinical trial considered in the short-term part of the model [26]

	TDF/FTC/EFV "recent"	**ZDV/3TC/EFV "old"**
Responders: Portion of patients achieving and maintaining virologic suppression below:		
< 50 copies/mL HIV RNA	67% (ns)	61% (ns)
< 400 copies/mL HIV RNA	75%	62%
Proportion of patients who discontinued the study medications due to :		
Adverse events	5%	12%

ns: not statistically significant difference

6.5 ANNEX 5: BASELINE PROBABILITIES IN THE SHORT-TERM PART

Table A5 – Baseline probabilities used in the short-term part of the model

Transition probabilities From S3 (initial state) to:	**"Recent therapy" TDF/FTC/EFV**	**"Old therapy" ZDV/3TC/EFV**
to S1	0,589	0,536
to S2	0,118	0,055
to S3	0,082	0,118
to S4	0,094	0,134
to death	0,117	0,157

6.6 ANNEX 6: RESULTS CONSIDERED IN THE LONG-TERM PART

Table A6 – Main results of the publication considered in the long-term part of the model [32]

Prevalent and incident cases	Four years Cumulative probability of entering Stage 4 (95% CI)	Four years cumulative probability of death (95% CI)
Entered Stage 1	0.11	0.09
Entered Stage 2	0.33	0.33
Entered Stage 3	0.58	0.56
Entered Stage 4	-	0.86

6.7 ANNEX 7: ANNUAL TRANSITION PROBABILITIES USED IN THE LONG-TERM MODEL

Table A7 – Markov annual transition probabilities derived from observational data in Uganda [32]

Description		Transition probabilities for the base-case	Source and Notes
From Stage 1	to Stage 1	0.649	Assumption* Ω
	to Stage 2	0.199	Assumption* Ω
	to Stage 3	0.100	Assumption*
	to Stage 4	0.029	[32]**
	to death	0.023	[32]**
From Stage 2	to Stage 2	0.620	Assumption* Ω
	to Stage 3	0.190	Assumption* Ω
	to Stage 4	0.095	[32]**
	to death	0.095	[32]**
From Stage 3	to Stage 3	0.619	Calculation : 1-(0.195+0.186)
	to Stage 4	0.195	[32]**
	to death	0.186	[32]**
From Stage 4	to Stage 4	0.612	Calculation : 1- 0.388
	to death	0.388	[32]**

* These estimates will be tested in the sensitivity analysis

** [34] Assuming a fixed rate with respect to time, the one year probabilities were derived from the four year probability shown on Annex 6 using the following formula: One year probability = 1-exp [1 year*(ln(1-"Four year probability"))/4 year]

Ω These transition probabilities were estimated on the basis of the transition probabilities of remaining in Stage 3 and the transition probability of moving from Stage 3 to Stage 4.

6.8 ANNEX 8: PARAMETERS VARIED IN THE SENSITIVITY ANALYSES

Table A8 – Values of the parameters varied in the sensitivity analyses

Elements	Base-case inputs	Variations in sensitivity analysis	Sources
Costs			
Acquisition costs of the "recent" drug combination	385	487 or 527 or 613	MSF [19]
Acquisition costs of the "old" drug combination	347	410 or 420 or 434	MSF [19]
Healthcare costs associated with Stage 2	30	0	Assumption
Healthcare costs associated with Stage 3	70	100	Assumption
Annual Discount rates			
Costs discount rate	3%	6%	WHO [25]
Benefits discount rate	3%	0%	WHO [25]
Transition probabilities and assumptions			
Short-term part: All respondent achieving a viral load below 400 copies per mL are attributed to Stage 2 (none to Stage 1)	Old therapy: * S3 to S1 node: 0.536 * S3 to S1 node: 0.055 New therapy: * S3 to S1 node: 0.589 * S3 to S1 node: 0.118	Old therapy: * S3 to S1 node: 0 * S3 to S1 node: 0.591 New therapy: * S3 to S1 node: 0 * S3 to S1 node: 0.707	Assumption
Long-term part: Transition probabilities associated with Stage 1 and Stage 2	Stage 1 probabilities: *S1 to S1: 0.649 *S1 to S2: 0.199 *S1 to S3: 0.100 Stage 2 probabilities: *S2 to S2: 0.620 *S2 to S3: 0.190	Stage 1 probabilities: *S1 to S1: 0.50 *S1 to S2: 0.224 *S1 to S3: 0.224 Stage 2 probabilities: *S2 to S2: 0.50 *S2 to S3: 0.31	Assumption
Long-term part: Transition probabilities associated with Stage 1 and Stage 2	Stage 1 probabilities: *S1 to S1: 0.649 *S1 to S2: 0.199 *S1 to S3: 0.100 Stage 2 probabilities: *S2 to S2: 0.620 *S2 to S3: 0.190	Stage 1 probabilities: *S1 to S1: 0.20 *S1 to S2: 0.37 *S1 to S3: 0.37 Stage 2 probabilities: *S2 to S2: 0.20 *S2 to S3: 0.61	Assumption

6.9 ANNEX 9: RESULTS OF THE SENSITIVITY ANALYSES FOR THE SHORT-TERM PART

Table A9 – Results of the sensitivity analyses (short-term part) using data summarized in Annex 8

Element	Values varied	Base case inputs	Strategy	LYs gained	QALYs gained	Costs	ICER
Base case	**None**	**-**	Old	**16614**	**10159**	**5460633**	**1289 $/LY**
	None	**-**	Recent	**17403**	**11291**	**6477185**	**898 $/QALY**
Costs							
Recent therapy Drug costs	487	385	Old	16614	10159	5460633	3283 $ /LY
			Recent	17403	11291	8047891	2286 $/QALY
	527	385	Old	16614	10159	5460633	4063 $ /LY
			Recent	17403	11291	8663854	2830 $/QALY
	613	385	Old	16614	10159	5460633	5743 $ /LY
			Recent	17403	11291	9988175	4001 $/QALY
Old therapy Drug costs	410	347	Old	16614	10159	6323283	195 $ /LY
			Recent	17403	11291	6477185	136 $/QALY
	420	347	Old	16614	10159	6460212	22 $/ LY
			Recent	17403	11291	6477185	15 $/QALY
	434	347	Old	16614	10159	6651912	- 222 $ /LY
			Recent	17403	11291	6477185	- 154 $ /QALY
Stage 2 costs	0	30	Old	16614	10159	5428114	1242 $ /LY
			Recent	17403	11291	6407416	865 $/ QALY
Stage 3 costs	100	70	Old	16614	10159	5530402	1262 $ /LY
			Recent	17403	11291	6525669	879 $/ QALY
Discount rates (d.r.)							
Cost d.r.	6%	3%	Old	16614	10159	5396037	1268 $ /LY
			Recent	17403	11291	6395968	884 $/ QALY
Benefit d.r.	0%	3%	Old	16860	10348	5460633	1271 $ /LY
			Recent	17660	11501	6477185	881 $/ QALY
Transition probabilities (t.p.) and assumptions							
Short-term assumption	No S1	S1 and S2	Old	16614	7794	5777550	1329 $ /LY
			Recent	17403	8692	6825439	1167 $/ QALY
Long-term t.p.	See Annex 8		No effect in the short-term part of the model				

6.10 ANNEX 10: RESULTS OF THE SENSITIVITY ANALYSES FOR THE OVERALL MODEL

Table A10 – Sensitivity analyses results for the overall model (short-term + long-term) using data summarized in Annex 8

Element	Values varied	Base case inputs	Strategy	LYs gained	QALY gained	Costs	ICER
Base case	**None**	**-**	Old	49505	29101	13599317	**653 $/LY** **779 $/QALY**
	None	**-**	Recent	53646	32570	16301437	
Costs							
Recent therapy Drug costs	487	385	Old	49505	29101	13599317	1490 $ /LY 1778 $/QALY
			Recent	53646	32570	19767407	
	527	385	Old	49505	29101	13599317	1818 $ /LY 2170 $/QALY
			Recent	53646	32570	21126611	
	613	385	Old	49505	29101	13599317	2524 $ /LY 3013 $/QALY
			Recent	53646	32570	24048899	
Old therapy Drug costs	410	347	Old	49505	29101	15479090	199 $ /LY 237 $/QALY
			Recent	53646	32570	16301437	
	420	347	Old	49505	29101	15777467	127 $/ LY 151 $/QALY
			Recent	53646	32570	16301437	
	434	347	Old	49505	29101	16195194	26 $ /LY 31 $ /QALY
			Recent	53646	32570	16301437	
Stage 2 costs	0	30	Old	49505	29101	13345761	632 $ /LY 755 $/ QALY
			Recent	53646	32570	15963581	
Stage 3 costs	100	70	Old	49505	29101	13919231	653 $ /LY 779 $/ QALY
			Recent	53646	32570	16622888	
Discount rates (d.r.)							
Cost d.r.	6%	3%	Old	49505	29101	12564661	602 $ /LY 718 $/ QALY
			Recent	53646	32570	15056612	
Benefit d.r.	0%	3%	Old	54821	31945	13599317	577 $ /LY 710 $/ QALY
			Recent	59507	35753	16301437	
Transition probabilities (t.p.) and assumptions							
Short-term assumptions	No S1 improvement	S1 and S2 improvement	Old	42516	18872	11479499	634 $ /LY 889 $/ QALY
			Recent	45952	21323	13657901	

Annex 10 (continued)							
Element	**Values Varied**	**Base Case inputs**	**Strategy**	**LYs gained**	**QALY gained**	**Costs**	**ICER**
Long-term t.p.	S1 to S1:0.5 S2 to S2:0.50	S1 to S1:0.65 S2 to S2:0.62	Old	46192	24672	11565550	574 $ /LY 733 $/ QALY
			Recent	49878	27560	13682026	
	S1 to S1:0.20 S2 to S2:0.20	S1 to S1:0.65 S2 to S2:0.62	Old	42993	20686	9849923	493 $ /LY 681 $/ QALY
			Recent	46197	23004	11428233	

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