# Cost effectiveness analysis of 4 first-line Highly Active Antiretroviral Therapy (HAART) for the treatment of HIV/AIDS in Colombia

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**Abstract**

*Background:* In Colombia HIV/AIDS cases have increased over time exerting a greater financial burden on the government and healthcare providers for its management. For this reason, resources to treat HIV/AIDS population must be efficiently allocated to obtain the most benefits possible.
*Objective:* This study compares the cost-effectiveness of 4 first-line HAART regimes for the treatment of HIV/AIDS over a 5-year time horizon, from a particular Colombian healthcare provider's perspective.
*Methods:* A Markov model was developed to simulate disease evolution through four health states based on CD4+ cell count. The initial distribution of the simulated population and new cases entering the system where based on information gathered from a reference cohort. For each health state, the model had input parameters of local direct medical costs and utility measures (QALYs). Sensitivity analysis for time horizon, probability of infection, and utility levels after treatment failures was performed.
*Results:* Cost-effectiveness rankings show that 3TC/ZID+NEV has the lowest cost-effectiveness ratio (thousand USD$3.81 per QALY) and 3TC/ABC+EFV the greatest (thousand USD$4.77 per QALY). According to the ICER, only 3TC/ABC+EFV provides 2696 more QALYs at a cost of thousand USD$26.31 per QALY. Cost-effectiveness and incremental cost-effectiveness ratios were most sensitive to changes in the time horizon of the simulation. Yet, in all scenarios, the ranking by cost-effectiveness ratio remained constant. For longer simulation periods, the ICER is reduced below both thresholds of 3xGDP per capita and WHO-CHOICE for the region.
*Conclusion:* All HAART therapies used are cost-effective based on the cost-effectiveness ratio, according to the ranking in the healthcare provider's setting. 3TC/ABC+EFV can provide additional benefits for an additional cost. Thus, if the healthcare provider has enough resources, the differences in costs, should be assumed to guarantee the most benefits from HIV/AIDS treatment.

**Key Points for Decision Makers**

- The 4 HAART regimes are cost effective for the treatment of HIV/AIDS from the healthcare provider's perspective.
- The 4 HAART regimes are under the cost-effectiveness threshold of 3xGDP per capita and the WHO-CHOICE threshold for the region.
- 3TC/ZID+NEV is the most cost effective regime, but 3TC/ABC+EFV can provide greater benefits at an increased cost with an ICER deemed as cost effective.
- The healthcare provider should use 3TC/ABC+EFV regime if it can pay for it, given the nature and background of the patients.

## 1. Introduction

Worldwide the number of people living with HIV/AIDS increases every year with new infections, longer lives of those infected and general population growth. In 2013 there were 35 million people living with HIV/AIDS, and 2.1 million new cases according to UNAIDS. Of these, 1.6 million lived in Latin America with 103.000 newly infected that year [1]. Since the first reported case in 1983 the HIV/AIDS epidemic in Colombia has followed this incremental pattern with a greater number of officially reported cases every year. Administrative data shows that between 1985 and 2007 there were around 57.500 reported HIV/AIDS cases, increasing to 71.509 in 2009 and 92.379 in 2013. Until 2013 over 40.000 HIV/AIDS related deaths have been registered in the country [2-4]. Yet, non-administrative estimations for the epidemic calculate over 150.000 living with HIV/AIDS, which implies an important underreport in the number of cases [2-3,5-6].

Colombia's epidemic is classified as concentrated: HIV has spread fast within one or more particular subpopulations but has not extended to the general population. Usually prevalence for these subpopulations is over 5%, while for the whole population prevalence remains under 1% [4]. Since the beginning of the epidemic, there has also been migratory phenomenon: differences in prevalence have diminished between greater cities and rural areas [7]. In addition, an increase in the number of infected females has been documented. Between 1985 and 2013, the ratio of infected men per infected woman decreased from 11.2 to 2.6 [2-4,8]. In terms of HIV/AIDS treatment with antiretroviral therapy (ART), around 23.000 patients were undergoing ART in 2010, while in 2013 this number increased to over 40.000 [2,6,8].

Colombia's healthcare system is composed of four mechanisms through which the population can access health services. The first one is the contributive regime, where all those who are currently working are affiliated, and are considered able to pay for the services. This regime includes the employed, self-employed and their families. The second one is the subsidized regime, where the poorest population without the ability to pay is affiliated, and accesses the services through subsidies paid by both the government and the payments made by those in the contributive regime. The third corresponds to the exceptional regime where those working in the magisterium, Colombia's petroleum company, the police and the army are affiliated and has special characteristics in terms of available services. The final regime is a government attention system that through public assistance offers coverage for the population that is not insured and not in one of the other regimes. In 2013 there were 43.207.473 affiliates in the healthcare system, corresponding to coverage of 91.7% of the total population, with 20.120.266 (42.8%) in the contributive regime, 22.669.543 (48.1%) in the subsidized regime and 387.664 (0.8%) in the exceptional regime. This implies the non-insured population was 3.913.297 (8.3%), although access to healthcare is guaranteed for these through government public assistance [4].

There are two approaches to reduce the morbidity and mortality associated with HIV based on the implementation of non-pharmacological measures (prevention) and ART (treatment) [5]. Treatment objectives are: reduction in viral load to an undetectable level, and improvement in the immunity by increasing the amount of CD4+ lymphocytes (to improve the patients' life expectancy and quality) [9].

Since the development and FDA authorization of zidovudine (AZT) as the first ART, advances in HIV treatment have allowed the development of new drugs that offer alternatives to improve life quality and expectancy [10]. Currently, Highly active antiretroviral therapy (HAART), consisting of at least 3 drugs of 2 or more classes, represents the main type of treatment for HIV infected patients. These therapies reduce viral load, improve the immune system and delay the disease's development, resulting in a better life quality and expectancy [11-12]. The treatment's effectiveness is obtained using a tolerable regime that promotes adherence. Effectiveness is compromised when factors such as a defect in the patient's immune system, drug resistance development by the virus, poor adherence to the treatment regime and adverse effects (which vary depending on the drugs) are present during the treatment process [13-16].

HIV/AIDS treatment imposes a significant financial burden upon governments and healthcare providers. UNAIDS estimates that in 2013 global HIV funding totaled US$19.1 billion with US$8.5 billion being disbursed from donor countries to address HIV in low and middle income countries [1]. The report for 20 Latin American and Caribbean countries indicates a total international and domestic spending in HIV for 2009 was around US$1.6 billion, with US$108 million being spent in Colombia [17]. Resources must be well allocated to achieve an adequate balance between prevention, treatment and care, all relevant factors to treat the epidemic. Thus, the effectiveness of investments in HAART treatments should be a key object in public policy analyses [18-19].

Studies for HIV/AIDS treatment in Colombia have been descriptive and cost-based, or without looking at individual HAART regimes and comparing them. First line treatment regimes are usually composed of the first generation of ART drugs, which are usually the least costly. In Colombia, around 66% of the patients treated are in first line regimes [8], hence evaluating the economic impact of the most used regimes becomes relevant to assess which of these therapies gives the best value for money and their impact on the healthcare budget. In Colombia the most used regime has been lamiduvine/zidovudine + efavirenz, however not all patients can intake efavirenz so nevirapine is formulated instead. Other frequent regimes are lamiduvine/zidovudine with lopinavir/ritonavi, and lamiduvine/abacavir with efavirenz. These four HAART regimes were considered in this study:

1) Lamiduvine/zidovudine + lopinavir/ritonavir
2) Lamiduvine/zidovudine + nevirapine
3) Lamiduvine/zidovudine + efavirenz
4) Lamiduvine/abacavir + efavirenz.

The objective of this study is to evaluate the cost-effectiveness of these regimes for the population treated by a particular healthcare provider. To do this we use different databases containing information on drug costs, treatment of opportunistic infections and hospitalization costs associated with HIV/AIDS, regular follow up clinical exams costs and results for CD4+ cell count and viral load. These databases contained information for a patient cohort treated by one Colombian healthcare provider specialized in HIV/AIDS treatment. This provider treated around 2940 patients in 2013 and reported a total service satisfaction of 96% and timely appointment scheduling well under a week [20]. These patients belong to either the contributive or subsidized regimes in the Colombian healthcare system and represent one of the best-treated HIV/AIDS group of patients in the country. For this reason, this can be considered as a case study and its results represent one of the best possible outcomes for a HIV/AIDS population treatment in Colombia.

In particular, this information was used to develop the parameters for the Markov-like model simulation. The cost effectiveness ratios where calculated from the perspective of the healthcare provider for a 5 year time horizon. This healthcare provider receives a fixed payment for a pool of patients in the subsidized regime population and a variable payment for the package of services given to patients in the contributive regime. With these resources, it must comply with specific clinical guides. It is considered that the selected healthcare provider is the best at complying with the treatment guides, so the results are expected to reflect the best possible results in an empirical scenario. The clinical guide based on evidence for HIV/AIDS treatment was designed by the Colombian infectology association (ACIN) based upon WHO guides recommendations, to help health professionals to make adequate decisions under specific circumstances in the Colombian setting. This guide has a series of recommendations regarding prevention, diagnosis and detection, attention, initial assessment, HAART regime, patient follow-up, HIV and AIDS, opportunistic infections prophylaxis and exposure to risk [21-22].

The study relevance for the healthcare provider is found in cost reduction and better allocation of resources. In the case of a fixed payment for a pool of patients, the real number of treated patients can be over the size of the pool paid for. In the case of the variable payment, the healthcare provider is interested in having lower and competitive costs to provide the best possible service and treatment to the HIV/AIDS population.

## 1. Methods

### 1.1. *Data Collection*

In Colombia, every semester, all healthcare providers treating HIV/AIDS patients are required to generate a report to the Government that contains data regarding: all active patients treated by the healthcare provider, including information about date of diagnosis, ART initiation dates, initial and current ART regime, last ART switch date, initial and current clinical state, initial and last CD4+ and viral load count, previous diseases, opportunistic infections, and chronic diseases, amongst other information.

Our dataset includes the results for all of the diagnostic exams for every patient serviced by the healthcare provider. The exams are conducted every 6 months. In particular, this database contains the results for CD4+ cell count, which allows for the computation of transition probabilities for every period. Additionally, we have precise estimates of provision costs for each HAART regime by combining administrative data on (i) prices of exams, HAART drugs and relevant hospitalization services (related only to treatment HIV opportunistic diseases) and (ii) the observed frequency of service orders at different health states.

### *1.2. Model Overview*

A Markov structure with a 6-month cycle was chosen to model the disease progression and assess the cost-effectiveness of the HAART regimes. The progression for the simulated HIV infected population consists on the transition across three different health states defined by CD4+ cell count ranges. These

ranges were chosen based upon the CDC health state definitions and the clinical relevance in terms of differentiated probabilities of contracting opportunistic infections, required treatment for these infections, the costs associated with treatment and the size of the study's reference cohort [23-27]. The chosen states correspond to the following ranges of CD4+ cells/$mm^3$: >200, 101-200 and 0-100, The 0-100 range is a transitory state, meaning that population starting in this health state can transition to other health states but there are no transitions from other health states into this one. There is an additional absorbent "failure" state that includes all cases where patients require a change of therapy due to clinical, virologic or immunologic failures. Reasons for failure include the regime's inability to suppress the viral load below detectable levels, increase the CD4+ cell count to normal levels, and appearance of adverse effects including damage to kidneys and liver. Although death could be considered as additional absorbent state, in the data we observe zero deceases, making the transition probability zero for all HAART regimes evaluated.

We simulate a population of 10,000 initial patients that enter the model with different cell count ranges (i.e. health states) in the same proportion as the observed distribution in the reference cohort. In every 6-months cycle, the patients could either move to another health state or stay in their current state. Whenever a patient makes a transition to the 0-100 range the model automatically moves this person to the absorbing failure state since it is considered as a treatment failure.

Cost-effectiveness studies elsewhere represent the disease progression in a closed system in which initial patients transition between defined health states and there is no input of new patients throughout the simulation process [11-12]. Since the patients treated by the healthcare provider increase in number every year, it is assumed that these patients can infect others, thus bringing new infected patients into the system. The number of new patients at each cycle is calculated based on infection probabilities, which depend on the viral load distribution found in the reference cohort, and the number of patients in each health state [28]. The new patients enter the system in the same proportion as in the observed distribution of CD4+ cell count ranges. The possible movements across the different states and new patient entrance are displayed in figure 1.

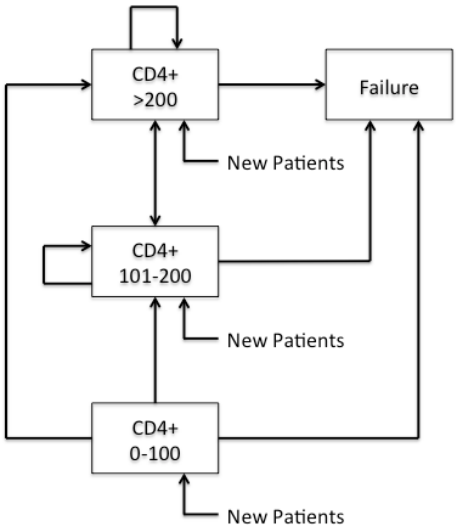


**Fig. 1** Possible transitions across states in the model in each cycle

The perspective of the model corresponds to the healthcare provider, which is the treatment payer. The cost-effectiveness ratio for the evaluated HAART regimes uses the direct costs from treating the patients in the numerator and quality adjusted life years (QALYs) in the denominator. For each health state, the patients incurred in a series of direct costs derived from the treatment of HIV/AIDS, which were calculated from the healthcare provider databases. Each CD4+ range also had a utility value associated which quantified the average wellbeing an individual has for being in a particular health state [29]. This value ranges between zero and one. A utility value of zero represents death and one perfect health. QALYs calculation results from taking the time spent in each health state for every patient and multiplying by these utility values. According to the data, there are no significant differences in the adverse effects and opportunistic infections across populations receiving different HAART regimes. The costs, QALYs and cost-effectiveness ratios obtained after the 10 cycles simulated are the result of the transition probabilities

inherent to each HAART regime evaluated. When patients are kept in the best possible state, the costs are reduced and the QALYs increased, resulting in a better cost-effectiveness ratio.

The disease evolution in terms of CD4+ cell counts for the modeled population in each HAART regime is completely dependent on the treatment ability to increase the cell count. The model structure and simulations where developed in a stock and flows manner using iSeeSystems STELLA 10.0.6 [30] and was divided into a series of modules corresponding to: 1) Health States, 2) Transition Probabilities, 3) New Cases and 4) Costs and Benefits. The main model structure is shown in figure 2.

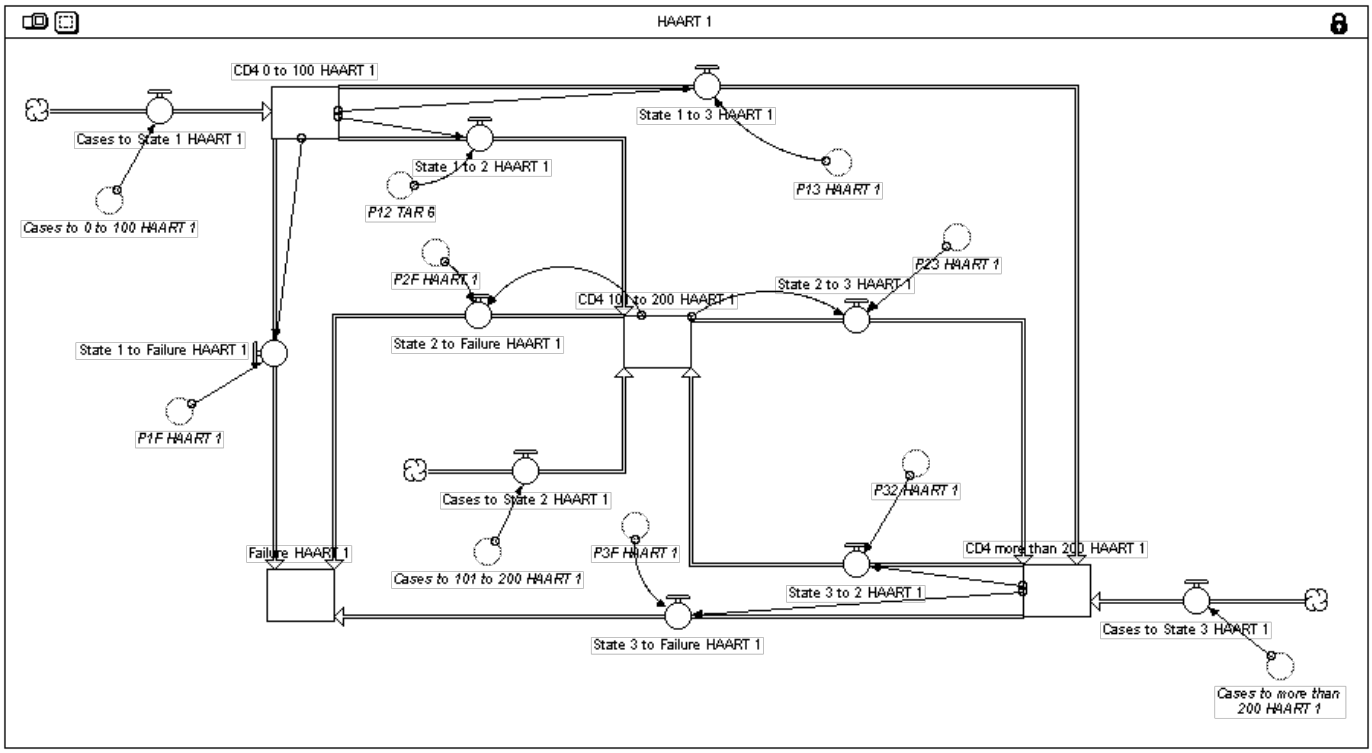


**Fig. 2** Model structure including possible health state transitions and new cases entrance. Failure includes clinical, virologic and immunological failures. Probabilities to stay in the current state are implicit in the structure

### *1.3. Input parameter values*

#### 1.3.1. Baseline Population Distribution

The initial population in the model and the new cases entering at each cycle correspond to the observed CD4+ cell count distribution in the reference cohort. The input values used in the model are shown in table 1.

**Table 1.** Cohort characteristics for modeled population

| Input Parameter | Reference Cohort |
|---|---|
| CD4+ cell count range | Patients |
| 0-100 | 3,411 |
| 101-200 | 2,022 |
| >200 | 4,567 |
| New Cases | Proportion |
| 0-100 | 0.3411 |
| 101-200 | 0.2022 |
| >200 | 0.4567 |

Source: Own estimations using healthcare provider's data

### 1.3.2. Transition Probabilities

The transition probabilities for the movement between health states at each cycle were estimated for each HAART regime using the CD4+ count results in clinical exams for the reference cohort. This was done by looking at the health state transition in every cycle for each individual patient in the cohort, and calculating the overall probabilities to transition to from a particular health state to all others.

### 1.3.3. Failure Rates

Failure rates where estimated for each HAART regime using the healthcare provider's databases for regime switch and cell count at the switch dates. It is assumed that failure rates incorporate all types of failure that require a switch in the patient's HAART regime. This includes clinical (adverse effects), virologic (inability to cause viral load suppression) or immunologic (inability to increase CD4+ cell count) failures. The pooling of observed movements between defined health states, including failure, was used to estimate the probabilities shown in table 2.

**Table 2**. Transition Probabilities for 4 evaluated HAART regimes

| Health States | | Transition Probabilities % (SE in parenthesis) | | | |
|---|---|---|---|---|---|
| Initial | Final | 3TC/ZID + LPVr | 3TC/ZID + NEV | 3TC/ZID + EFV | 3TC/ABC + EFV |
| 0-100 | 0-100 | 25 (5.25) | 31.82 (5.73) | 28.33 (5.82) | 62.5 (12.1) |
| 0-100 | 101-200 | 51.47 (6.06) | 39.39 (6.01) | 46.67 (6.44) | 18.75 (9.76) |
| 0-100 | >200 | 8.83 (3,44) | 10.61 (3.79) | 5 (2.81) | 5.25 (6.05) |
| 0-100 | Failure | 14.71 (4.29) | 18.18 (4.75) | 20 (5.16) | 12.5 (8.27) |
| 101-200 | 101-200 | 50 (4.9) | 53.44 (4.36) | 49.17 (4.56) | 52.94 (6.99) |
| 101-200 | >200 | 39.42 (4.79) | 36.64 (4.21) | 37.5 (4.42) | 35.29 (6.69) |
| 101-200 | Failure | 10.58 (3.02) | 9.92 (2.61) | 6.67 (3.1) | 11.76 (4.51) |
| >200 | 101-200 | 2.41 (0.79) | 1.75 (0.46) | 0.9 (0.3) | 1.77 (0.72) |
| >200 | >200 | 94.91 (1.14) | 96.37 (0.66) | 97.89 (0.46) | 96.46 (1.00) |
| >200 | Failure | 2.68 (0.84) | 1.88 (0.48) | 1.21 (0.35) | 1.77 (0.72) |

Source: Own estimations using healthcare provider's data

In Colombia, there are no studies that estimate the utility weights associated with different HIV/AIDS health states. Therefore, the utility weight estimates were taken from Schakman et al. [29], who derive utility values from community and patient preferences. The weights are shown in table 3.

**Table 3**. Utility weights by CD4+ cell count range

| CD4+ cell count range | Utility Value |
|---|---|
| 0-100 | 0.841 |
| 101-200 | 0.850 |
| >200 | 0.865 |

Source: Own estimations using healthcare provider's data

### 1.3.4. Resources and costs

All costs used in the model are presented in 2013 thousand US dollars (thousand USD$). We estimate the costs associated with each health state including three types of direct medical costs where taken into account in the model. First, the cost of antiretroviral drugs was taken from the healthcare provider's prices database, which indicates the price paid to drug providers. The average cost per patient was calculated according to the recommended doses in the AIDS Study Group (GeSIDA) [31]. The costs for each HAART regime are shown in table 4.

**Table 4**. Six-months drug cost per patient (2013 USD$)

| HAART regime | Drug Costs |
|---|---|
| 3TC/ZID + LPVr | 457.632 |
| 3TC/ZID + NEV | 191.065 |
| 3TC/ZID + EFV | 259.537 |
| 3TC/ABC + EFV | 507.517 |

Source: Own estimations using healthcare provider's data

Second, the cost of clinical exams was calculated using several healthcare provider's databases that include: exam orders, results, and procedure prices. The CD4+ count results allowed us to establish the health state at the time the exams were taken. The exam orders represented the invoices for exams performed by the clinical laboratory and CD4+ count results allowed us to establish the health state at the time the exams were taken. Third, the hospitalization and treatment costs related to opportunistic infections was calculated with: (i) administrative records of the total cost and reason/cause of hospitalizations, and (ii) observed opportunistic infection incidence taken from the report made to the High Cost Account. With this information we estimate the hospitalization and treatment costs at each health state. Total costs at each health state (including exams, hospitalization and opportunistic infections treatment) are shown in table 5.

**Table 5**. Six-months exams and opportunistic infection treatment costs per patient (2013 USD$)

| CD4+ cell count range | Exams | Hospitalizations |
|---|---|---|
| 0-100 | 111.169 | 1485.457 |
| 101-200 | 107.687 | 1382.204 |
| >200 | 108.562 | 808.135 |

Source: Own estimations using healthcare provider's data

#### 1.3.5. Discount Rate

The discount rate used in the model is 3%, following the recommendation of the Pan-American Health Organization (PAHO) and the Ministry of Health and Social Protection recommendation for cost-effectiveness analysis [32-33].

### *1.4. Sensitivity Analysis*

We conduct one-way sensitivity analysis in order to test the impact of parameter variation on the costs-effectiveness ratios for the HAART regimes evaluated. Parameters included in the analysis are: time horizon, infection/contagion probability, discount rates, and the inclusion of benefits at the failure state. For each individual parameter, the value is varied across a range of plausible and realistic values, with individual simulation results recorded. The list of scenarios used to evaluate the economic outcomes across different parameter values are shown in table 6.

**Table 6.** Scenarios for one-way sensitivity analysis

| Scenarios |
|---|
| Time Horizon |
| 2.5 years |
| 5 years (Baseline) |
| 10 years |
| Discount Rates |
| 0% |
| 3% (Baseline) |
| 5% |
| Contagion Probability |
| No contagion |
| Low |
| Medium (Baseline) |
| High |
| Failure Cost and Benefits |
| Cost of failures only (Baseline) |
| Cost and benefits of failures |

## 2. Results

### *2.1. Baseline Results*

The results for the 5-year baseline analysis comparing the cost-effectiveness for 4 HAART regimes ranked by cost-effectiveness ratio (Cost per QALY gained) are shown in table 7. In this scenario we use a 3%

discount rate and we present the QALYs and cost estimates for each HAART regime. The effectiveness for the HAART regimes in this study is lower than those reported in clinical trials for each regime. This is due to therapy adherence, adverse effects, and other reasons for therapy failure being implicitly included in the transition probabilities used, which are not taken into account during clinical trials. The cost for exams and hospitalizations for the four regimes are similar, while the cost for drugs show important differences between regimes.

These results show that 3TC/ZID+NEV regime had the lowest total cost (230,027 thousand USD$) whilst 3TC/ABC+EFV had the greatest total cost (300,959 thousand USD$). In terms of benefits, 3TC/ZID+EFV had the lowest benefits (59,153 QALYs) and 3TC/ABC+EFV the greatest (63,142 QALYs). Ranking results show that 3TC/ZID+NEV is the most cost-effective regime (3.81 thousand USD$/QALY), which implies that the cost per QALY gained is greater for the other regimes, being the greatest for 3TC/ABC+EFV (4.77 thousand USD$/QALY).

After ranking the HAART regimes by their respective cost-effectiveness ratios, we estimate the incremental cost effectiveness ratios (ICER) to determine how much additional benefit is achieved for the additional cost incurred. In this analysis 3TC/ZID+NEV was used as reference point to calculate the ICER (shown in table 7).

**Table 7.** Base case (5 year horizon) cost-effectiveness analysis for 5 HAART regimes

| Outcome Measure | 3TC/ZID+NEV | 3TC/ZID+EFV | 3TC/ZID+LPVr | 3TC/ABC+EFV |
|---|---|---|---|---|
| QALYs | 60,446 | 59,153 | 59,866 | 63,142 |
| Costs thousand USD$ | | | | |
| Drugs | 32,650 | 43,670 | 78,313 | 90,569 |
| Hospitalizations | 178,733 | 175,160 | 180,179 | 190,898 |
| Exams | 18,644 | 18,360 | 18,670 | 19,492 |
| Total Cost | 230,027 | 237,190 | 277,162 | 300,959 |
| Cost per QALY gained thousand USD$ | 3.81 | 4.01 | 4.63 | 4.77 |
| ICER | - | -5.54 | -81.27 | 26.31 |

Note: Negative ICER indicate that 3TC/ZID+NEV dominates the compared therapy

Compared to 3TC/ZID+NEV, 3TC/ZID+EFV and 3TC/ZID+LPVr had a negative ICER, indicating that they are dominated by the reference regime since they provide lower benefits at a greater cost. On the contrary, regime 3TC/ABC+EFV had a positive ICER of thousand USD$26,31 per QALY and had the greatest number of QALYs gained after the 5-year simulation. The ICER was above the 3xGDP per capita threshold and below the World Health Organization's Choosing Interventions that are Cost-Effective (WHO-CHOICE threshold for the respective region. The incremental cost evaluation results are shown in figure 3.

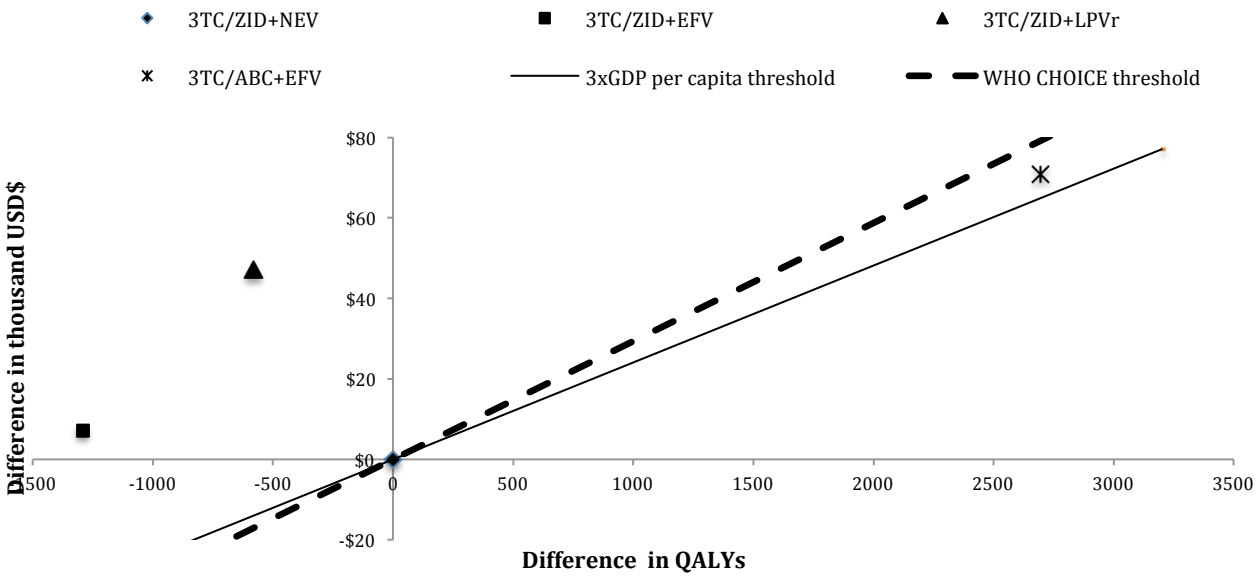

**Fig. 3** Base case Cost-effectiveness plane for HAART regimes comparison, using 3TC/ZID+NEV is as reference (0,0). Source: Own estimations using healthcare provider's data.

### *2.2. Sensitivity Analysis Results*

In all scenarios, 3TC/ZID+NEV had the lowest cost per QALY gained. For this reason, it was used as reference regime. The cost-effectiveness ratios were most sensitive to the varied parameters (in descending order of sensitivity): including benefits of failures, time horizon, contagion probability and discount rates. Incremental cost-effectiveness ratios were most sensitive to the varied parameters (in descending order of sensitivity): contagion probability, time horizon, cost and benefits of failures and discount rates. In all tested scenarios the HAART regime ranking by cost-effectiveness ratios remained the same. The CER and ICER for simulated scenarios are shown in table 8.

**Table 8.** CER and ICER for simulated scenarios (thousand USD$)

| | 3TC/ZID+NEV | | 3TC/ZID+EFV | | 3TC/ZID+LPVr | | 3TC/ABC+EFV | |
|---|---|---|---|---|---|---|---|---|
| Scenarios | CER | ICER | CER | ICER | CER | ICER | CER | ICER |
| Time Horizon | | | | | | | | |
| 2.5 years | 3.62 | - | 3.84 | -10.61 | 4.33 | 497.69 | 4.50 | 41.35 |
| 10 years | 4.13 | - | 4.26 | -0.98 | 5.16 | -22.44 | 5.18 | 17.73 |
| Discount Rates | | | | | | | | |
| 0% | 3.81 | - | 4.02 | -5.39 | 4.64 | -77.90 | 4.78 | 25.99 |
| 5% | 3.80 | - | 4.01 | -5.64 | 4.62 | -83.59 | 4.76 | 26.52 |
| Contagion Probability | | | | | | | | |
| No contagion | 3.88 | - | 4.08 | -58.38 | 4.76 | -52.22 | 4.89 | -203.69 |
| Low | 3.83 | - | 4.03 | -13.49 | 4.67 | -58.98 | 4.81 | 76.58 |
| High | 3.71 | - | 3.92 | -1.43 | 4.47 | 1462.70 | 4.61 | 14.13 |
| Failure Cost and Benefits | | | | | | | | |
| Cost and Benefits of Failures | 3.14 | - | 3.29 | -6.42 | 3.78 | 551.28 | 3.94 | 22.42 |

Source: Own estimations using healthcare provider's data

## 3. Discussion

The results of the cost-effectiveness analysis show that for the 4 first-line HAART regimes evaluated, the cost-effectiveness ratios are below the GDP per capita in Colombia. They are also below both thresholds of 3xGDP per capita and the one established by WHO-CHOICE for the Americas region. Thus, they are deemed as cost-effective under the range of assumptions used in this study. Even under diverse scenarios (varying input parameters), all the cost-effectiveness ratios remained under the aforementioned thresholds, which indicates these analysis results are robust.

For the evaluated HAART regimes, the cost-effectiveness ratio ranking corresponded to the drug pricing where the cost per QALY gain was the lowest for 3TC/ZID+NEV and the greatest for 3TC/ABC+EFV. The effect of drug pricing in HAART therapies cost-effectiveness has been reported before, indicating how reduced/lower prices directly affects the cost per QALY ratios [34-35]. Results show that the costs for hospitalization are not very different across therapies, since they are mostly dependent on the CD4+ cell count range, which determines the chances for opportunistic infections. The same is true in the case of exams cost because there is a mandatory exam battery that must be performed on all patients and other extra exams are required mainly for those in the lowest CD4+ cell count range.

HAART regime 3TC/ZID+NEV had greater total benefits than 3TC/ZID+EFV and 3TC/ZID+LPVr at a lower cost (resulting in a negative ICER). Hence, 3TC/ZID+EFV and 3TC/ZID+LPVr are dominated by 3TC/ZID+NEV. Only 3TC/ABC+EFV had greater benefits at a greater cost, resulting in an ICER of thousand USD$26.31. In order to determine if the extra cost to be paid for the extra benefits can be deemed as cost effective, a comparison against an adequate threshold is required.

For many years the USA has used a US$50,000 per QALY as its threshold for benchmarking the value of care in healthcare interventions [36]. However, in Colombia as in many other countries, there is no threshold that represents the willingness to pay per unit of effectiveness [37]. For this reason, The World Health Organization developed the WHO-CHOICE project to allow decision makers decide upon

interventions to maximize health results with available resources. Regarding the willingness to pay for a QALY, the WHO established a guideline for a threshold corresponding to a value equivalent to 3xGDP per capita [37-39]. Additionally, WHO-CHOICE has also established threshold values for interventions cost-effectiveness by regions [39-41]. For Colombia this values in 2013 were of thousand USD$24.08 and thousand USD$29.37 respectively [41-43].

The results show that 3TC/ABC+EFV has an ICER that is above the 3xGDP per capita, and should be deemed not cost effective by this threshold. However, according to the sensitivity analysis, over a longer simulation period, the ICER values are reduced below this threshold. Additionally, the ICER value for 3TC/ABC+EFV is under the threshold established by WHO-CHOICE for the region, which classifies it as cost effective.
The uncertainty of the threshold in Colombia creates controversy since 3xGDP per capita per QALY gained might be different from the willingness to pay by decision makers in Colombia [37]. Other factors beyond cost-effectiveness, including budgetary impact are important for decision making, especially in countries in the low to medium income range (LMICs) [38-39]. Healthcare providers in Colombia must provide the service for all the patients it treats, given a predetermined fixed payment per patient. This implies that there are other factors beyond cost-effectiveness that are taken into account by the healthcare provider, and resource allocation based upon budget might allow the payment of HAART therapies with ICER above the suggested thresholds. For this reason, the healthcare provider's willingness to pay for the treatment of its patients can be above the suggested thresholds and switching to 3TC/ABC+EFV regime to obtain greater benefits can be considered as cost-effective.

Another important result emerging from our economic evaluation is that both CER and ICER are sensitive to time horizon, a result reported previously by Mauskopf et al. [12] while evaluating the cost-effectiveness of Darunavir/Ritonavir and comparing differences of other studies with Enfuvirtide. As the time horizon increases, the cost per QALY gains increase, while the ICER is reduced. The reason behind these results is that, given the modeling assumptions, at every additional cycle a larger mass of patients enters the system compared to de mass leaving it due to failure. This patient inflow over time implies increasing costs at a higher rate than the QALYs gained, resulting in a greater cost per QALY gained. Regarding the ICER reduction, for dominated therapies, these results are explained by the fact that for longer simulation periods, they result with both costs and QALYs below those of the therapy established as reference (3TC/ZID+NEV). In the case of 3TC/ABC+EFV, over longer simulation periods the difference in QALYs gained compared to the reference expands faster than the difference in costs, resulting in the observed reduced ICER.

CER sensitivity to the inclusion of benefits at failure state shows a lower cost per QALY gained. This is explained since this scenario acts as a removal of failure from the model. With a greater number of QALYs and constant costs, the CER is necessarily reduced. However, the cost-effectiveness ratio ranking and the ICER are not significantly affected. The ICER sensitivity to the contagion probability is due to the effect of an increased patient inflow. When the patient inflow increases, the difference in costs and QALYs gained in each HAART regimes varies amongst them. The result in these varying differences is a reduced ICER. It is important to note that for the scenario with no contagion 3TC/ABC+EFV was dominated by the reference. In all other scenarios 3TC/ABC+EFV offered greater benefits at a greater cost, compared to the reference HAART regime.

The model used in this study uses input parameters specific to the Colombian context and takes the healthcare provider's perspective. Transition probabilities and costs are estimated from data gathered for a reference cohort of patients treated by one healthcare provider. Nevertheless, the model parameters can be modified in order to estimate the cost-effectiveness of HAART treatment programs used by other healthcare providers in Colombia. The flexibility in the model parameterization allows for testing multiple scenarios based on sensitivity analysis requirements. Factors such as therapy adherence, adverse effects, other reasons for therapy failure are implicitly included in the transition probabilities used for all HAART regimes evaluated. This is an advantage resulting from the data source used to feed the model since such factors are hard to evaluate. Additionally, the dynamic feature resulting from including contagion in the model, is an element that can be expected in a healthcare provider setting where the number of patients it treats tis not constant over time.

The recommendation for the healthcare provider is that, given the nature and background of the patients they serve and if permitted by current budget constraints, they should when possible use the 3TC/ABC+EFV regime. Even though the 4 first-line regimes are deemed cost-effective, this regime offers the most benefits at a reasonable cost under the willingness to pay threshold for the healthcare provider. If a budget impact analysis indicates that the therapy is not within the financial constraints, then 3TC/ZID+NEV should be the second treatment of choice.

## 4. Conclusions

All HAART therapies used by the healthcare provider are cost-effective based on the cost-effectiveness ratio. 3TC/ZID+NEV is the most cost-effective therapy. However, 3TC/ABC+EFV can provide additional benefits for a cost of thousand USD$26.31 per QALY, a cost that (when financially feasible) the healthcare provider should assume in order for its treated patient population to experience the most benefits from the HIV/AIDS treatment.

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