Cost-effectiveness of once-daily versus twice-daily regimens in the treatment of HIV infection in sub-Saharan Africa: a probabilistic decision model [version 1; referees: 1 approved with reservations, 1 not approved]

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Abstract

BACKGROUND: Regimen simplification of ART, by administering them less frequently, has been suggested as a practical approach to improve adherence. The aim of this study was to assess the cost-utility of once-daily (QD) versus twice-daily (BID) antiretroviral (ART) regimens in the treatment of HIV.

METHODS: A Model-based Markov modelling of cost-effectiveness using secondary data sources was developed to determine the incremental cost per quality-adjusted life year (QALY) gained of QD versus BID ART regimen for a hypothetical cohort treatment-naïve adults with HIV, from the Sub-Saharan African healthcare payer’s perspective.

RESULTS: At base-case values for all parameters, the total number of QALY gained by QD regimen was 0.27 and the incremental cost difference of $2147.04. The incremental cost-effectiveness ratio (ICER) of QD versus BID regimen was $8087/QALY gained. The ICER was most sensitive to the variations in the total medical cost of state A (asymptomatic, non-AIDS, CD4> 350 cells/μL), total medical Cost State D (symptomatic AIDS or severe symptoms), and utility of State A. In our bootstrap analysis, 60% of bootstrap replicates for the ICER shows that QD is more costly and more effective than BID regimen, while the remaining 40% replicates shows that QD is less costly and less effective than BID. If decision-makers were willing to pay $1000 per QALY gained, the probability of QD being cost-effective was 44%. The probability of QD regimen being cost-effective was 48% when the willing to pay was $5000.

CONCLUSIONS: From a sub-Saharan Africa societal perspective QD regimen cannot be regarded as cost-effective, although there is substantial decision uncertainty. Findings from the economic evaluation are important for low- and middle-income countries (LMIC) to consider as they decide whether to adopt the new branded single tablet regimen. Generic-based ART could yield substantial budgetary saving to HIV programmes in LMIC.
Background
Sub-Saharan Africa (SSA) is the region most heavily affected by human immunodeficiency virus (HIV)\(^1\). It is estimated that in 2012, as much as 68% of all people infected with HIV were living in SSA, and about 20% of all deaths and disability adjusted life years (DALYs) lost in Africa are due to HIV or acquired immunodeficiency syndrome (AIDS)\(^1\). The overarching aim of the antiretroviral therapy is to achieve optimal suppression of viral load, preserve immune functions and ultimately improve quality of life and reduce overall mortality\(^2\). The use of ART among people living with HIV has led to significant reduction in morbidity and mortality associated with HIV by slowing down the disease progression\(^3\). However, it is important to note that for the ART to effective, its clinical success depends on optimal adherence to the regimens\(^4\). It has been documented that optimal adherence to ART is associated with good viral suppression, slowing of disease progression and reduced all-cause mortality in people living with HIV\(^5,6\). Regimen simplification of ART, by administering them less frequently, has been suggested as a practical approach to improve adherence and patient convenience\(^7\). Recently, major advances have been made towards simplifying ART regimens. One of the most important advances is decreasing the dosing frequency and pill burden from more than 10 tablets to a one table once a day (QD) fixed dose combination\(^7\).

While the literature has focused on the effectiveness of QD versus twice a day (BID) regimens\(^7-20\), little interest has been paid to the economic evaluations\(^21-25\). Economic evaluation provides a useful framework to assist policy makers in allocating resources across competing needs. To the best of our knowledge, there have been no recent attempts to assess the likely cost-effectiveness of QD versus BID regimen from sub-Saharan’s perspective. Therefore, the objective of this study was to determine the cost-effectiveness of QD versus BID antiretroviral regimen in the HIV treatment.

Methodology
Model structure
We developed a computer-based mathematical model of HIV infection to simulate the effect of QD versus BID regimen (Figure 1). The model is a traditional Markov stage-transition model\(^26\), which was used to extrapolate the costs and health outcomes over the lifetime of patients. The analysis was performed from a societal perspective, where both all direct and indirect cost was considered. Health outcomes and cost accrued beyond 1 year was discounted at 3.5%, to adjust for future costs and health benefits and expresses them in terms of their present values\(^27\). Based on recent clinical guidelines for the use of ART in HIV-infected individuals, the Markov model has five health states to represent the progression through HIV disease states to death\(^28,29\):

1) State A: HIV positive, asymptomatic, non-AIDS, CD4 >350 cells/μL;
2) State B: HIV positive, asymptomatic, non-AIDS, CD4 >200 cells/μL, but \(\leq\) 350 cells/μL;
3) State C: HIV positive, asymptomatic, AIDS, CD4 <200 cells/μL;
4) State D: HIV positive, symptomatic AIDS or severe symptoms;
5) State E: Death (age- and disease-related). People living with HIV may either die from HIV-related causes or from any other causes.

Figure 1. Markov model. State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 >200 cells/μL, but ≤350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 <200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.
Patients can remain in the same state, progress or retreat from an AIDS state to a non-AIDS state. The final state is E, death. The Markov model was based on a cohort of 1,000 hypothetical individuals, and a cycle length of one year was applied and simulated over 20 years.

Model input
Parameter estimates were extracted from published data\(^{33-34}\) (http://www.msfaccess.org/content/untangling-web-antiretroviral-price-reductions-17th-edition-%E2%80%93-july-2014). We conducted a series of focused literature searches in PubMed and Google Scholar to identify appropriate model input parameters to populate the model. The search terms included the following: “once-daily”, “fixed-dose combination”, “twice-daily”, “adherence”, “transition probabilities”, “HIV treatment costs”. Table 1 presents the model input parameters and their sources. Costs of treatment were incurred in US dollars and were adjusted for inflation; these were inflated to 2015 prices using a price inflation index (http://www.bls.gov/data/inflation_calculator.htm).

The values of HIV-related utility scores and quality-adjusted life years (QALYs) stratified by CD4 are also shown in Table 1. The antiretroviral naïve HIV patient is assumed to have a better initial response to medication therapy than individuals who have received previous antiretroviral treatment. Transition probabilities of naïve HIV patient between the five states for twice-daily regimen were extracted from the literature. The transition probabilities for the QD regimen were based on an adjustment to the baseline values, according to the treatment effect of BID regimen relative to QD regimen. This transition effect took the form of a relative risk, which was derived from a meta-analysis of treatment naïve patients\(^{35}\).

Sensitivity analysis
In order to examine the uncertainty around the robustness of the input parameters, a sensitivity analysis was performed on the parameters. One-way sensitivity analysis was performed on a deterministic parameter by varying all the input parameters at lower and higher values at 25%. In the best and worst case scenarios, the parameters were set to values more favourable and less favourable to QD regimen respectively. We also performed a probabilistic sensitivity analysis to assess parameters uncertainty in the model using the using the Monte Carlo technique\(^{35}\), were model parameters were varied according to their intrinsic distributions. Beta distribution was used for all probabilities. All costs were assumed to follow a normal distribution. Uniform distribution was used for utilities, discount, and time horizon. Results were based on 10,000 Monte Carlo simulations\(^{35}\).

Model output
Results were presented as mean incremental costs and effects, incremental cost-effectiveness ratio (ICER), cost-effectiveness planes (CE-plane) and cost-effectiveness acceptability curves (CEACs). CEACs provides a measure of the likelihood that a decision to apply a given intervention is correct across a range of ‘willingness-to-pay’ thresholds\(^{36}\). ‘Willingness-to-pay’ in this context represents the maximum amount a decision maker is prepared to pay for a gain of one QALY. The WHO-CHOosing Interventions that are Cost Effective (CHOICE) Working Group threshold for Africa region was adopted\(^{37,38}\). An intervention was defined as follows: very cost-effective, ICER < GDP per capita ($1,695); cost-effective, ICER = 1–3 × GDP per capita ($1,695 to $5,086); and not cost-effective, ICER is > 3 × GDP per capita ($5,086)\(^{37,38}\).

Results
The expected costs and QALY gained generated from the model are shown in Table 2. At base-case values for all parameters, when all parameters assumed best values from the published literature, the total number of QALY gained by regimen simplification was 0.27. The base case was associated with an incremental cost of $2,147. The incremental cost-effectiveness ratio of QD versus BID regimen was $8,102/QALY gained. Figure 2 shows the result of one-way sensitivity analysis when one parameter value was varied at a time, while holding other parameters at their base-case values. However, incremental cost was most sensitive to the variations in the total medical cost of state A, total medical cost state D, utility of state A and total medical cost of state C. The incremental cost ranged from $2,352 to $13,822 when total medical cost of state A varied from $13,736 to $22,893 and ICER could increase to as much as $38,314/QALY gained.

Incremental cost and QALYs are plotted on a scatter plot, as shown in the CE plane in Figure 3. About 60% of incremental cost-effect pairs fall in the northeast quadrant, indicating that the QD regimen is more costly and more effective than the BID regimen. The remaining 40% of the points lie in the southwest quadrant, indicating that QD regimen saves money, although is still less effective compared to the BID regimen. Figure 4 presents the cost-effectiveness acceptability curves (CEACs) for the incremental cost per QALY gained. As shown in Figure 4, if decision-makers were willing to pay $1,000 per QALY gained, the probability of QD being cost-effective was 44%. The probability of QD regimen being cost-effective was 48% when the willingness to pay was $5,000.

Dataset 1. Raw data for Table 1, Model parameters
http://dx.doi.org/10.5256/f1000research.9954.d142423

Dataset 2: Raw data for Figure 2, Tornado plot for incremental plot
http://dx.doi.org/10.5256/f1000research.9954.d142424

Dataset 3: Raw data for Figure 3, Incremental cost-effectiveness plane for once daily (QD) versus twice-daily regimen (BID)
http://dx.doi.org/10.5256/f1000research.9954.d142425

Dataset 4: Raw data for Figure 4, Cost-effectiveness acceptability curve for once daily (QD) versus twice-daily regimen (BID)
http://dx.doi.org/10.5256/f1000research.9954.d142426
Table 1. Model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case scenario</th>
<th>Range (Best-case – Worst case scenarios)</th>
<th>Probability distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State A</td>
<td>0.38</td>
<td>0.35–0.41</td>
<td>Beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State B</td>
<td>0.28</td>
<td>0.26–0.31</td>
<td>Beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State C</td>
<td>0.23</td>
<td>0.21–0.26</td>
<td>Beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State D</td>
<td>0.11</td>
<td>0.09–0.13</td>
<td>Beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State E</td>
<td>0.00</td>
<td>0.00–0.00</td>
<td>Beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>Annual total medical cost (US$)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State A</td>
<td>18,314</td>
<td>13,736–22,893</td>
<td>Gamma</td>
<td>Alistar, Athan &amp; MSF31,33</td>
</tr>
<tr>
<td>State C</td>
<td>39,862</td>
<td>29.897–49,828</td>
<td>Gamma</td>
<td>Alistar, Athan &amp; MSF31,33</td>
</tr>
<tr>
<td>State D</td>
<td>48,215</td>
<td>36.161–60,269</td>
<td>Gamma</td>
<td>Alistar, Athan &amp; MSF31,33</td>
</tr>
<tr>
<td>State E</td>
<td>0.00</td>
<td>0.00–0.00</td>
<td>Gamma</td>
<td>Alistar, Athan &amp; MSF31,33</td>
</tr>
<tr>
<td>Mean drug cost**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BID regimen</td>
<td>638</td>
<td>478–798</td>
<td>Gamma</td>
<td>CHAI</td>
</tr>
<tr>
<td>QD regimen</td>
<td>610</td>
<td>458–763</td>
<td>Gamma</td>
<td>CHAI</td>
</tr>
<tr>
<td>QALY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State A</td>
<td>0.90</td>
<td>0.66–1.00</td>
<td>Uniform</td>
<td>Tengs30</td>
</tr>
<tr>
<td>State B</td>
<td>0.90</td>
<td>0.66–1.00</td>
<td>Uniform</td>
<td>Tengs30</td>
</tr>
<tr>
<td>State C</td>
<td>0.75</td>
<td>0.63–0.87</td>
<td>Uniform</td>
<td>Tengs30</td>
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<tr>
<td>State D</td>
<td>0.56</td>
<td>0.55–0.80</td>
<td>Uniform</td>
<td>Tengs30</td>
</tr>
<tr>
<td>State E</td>
<td>0.00</td>
<td>0.00–0.00</td>
<td>Uniform</td>
<td>Tengs30</td>
</tr>
<tr>
<td>Probabilities***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State A to B</td>
<td>0.132</td>
<td>0.120–0.144</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State A to C</td>
<td>0.013</td>
<td>0.009–0.018</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State A to D</td>
<td>0.002</td>
<td>0.000–0.004</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State A to E</td>
<td>0.002</td>
<td>0.000–0.004</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State B to A</td>
<td>0.251</td>
<td>0.229–0.272</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State B to C</td>
<td>0.153</td>
<td>0.134–0.172</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State B to D</td>
<td>0.006</td>
<td>0.003–0.010</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State B to E</td>
<td>0.003</td>
<td>0.001–0.006</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State C to A</td>
<td>0.030</td>
<td>0.022–0.040</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State C to B</td>
<td>0.223</td>
<td>0.200–0.247</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State C to D</td>
<td>0.085</td>
<td>0.070–0.101</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State C to E</td>
<td>0.005</td>
<td>0.002–0.009</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State D to A</td>
<td>0.005</td>
<td>0.001–0.010</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State D to B</td>
<td>0.012</td>
<td>0.006–0.019</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State D to C</td>
<td>0.164</td>
<td>0.142–0.188</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>State D to E</td>
<td>0.022</td>
<td>0.019–0.033</td>
<td>beta</td>
<td>Goshu32</td>
</tr>
<tr>
<td>Relative risk QD vs BID****</td>
<td>0.95</td>
<td>0.91 to 1.00</td>
<td>logNormal</td>
<td>Nachega34</td>
</tr>
<tr>
<td>Discount rate (%)</td>
<td>3.5</td>
<td>2.0–5.0</td>
<td>uniform</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

*both direct and indirect cost; **per patient-year of treatment; ***annual transitional probabilities for BID regimen; ****relative risk of QD versus BID for virologic suppression

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 >200 cells/μL, but ≤350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

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In the base-case scenario, all model parameters assumed best values from the published literature. In the best and worst case scenarios, the parameters were set to values more favourable and less favourable to QD regimen respectively.
Table 2. Base case results.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost</th>
<th>Incremental cost (ΔC)</th>
<th>QALY</th>
<th>Incremental QALY (ΔQ)</th>
<th>ICER (ΔC/ΔQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID</td>
<td>$275,017.02</td>
<td>-</td>
<td>8.630</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>QD</td>
<td>$277,164.06</td>
<td>$2,147.04</td>
<td>8.896</td>
<td>0.265</td>
<td>8102.04</td>
</tr>
</tbody>
</table>

BID – twice daily regimen, QD – once daily regimen, QALY – Quality Adjusted Life Years, ICER – Incremental Cost-Effectiveness Ratio, ΔC – incremental costs; ΔQ -incremental QALY

Figure 2. Tornado plot for incremental cost. State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 >200 cells/μL, but ≤350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 <200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms. The y-axis shows the model parameter that was varied. The bars indicate the change in the incremental cost caused by changes in the value of the indicated variable holding all other parameters similar. All costs are in 2015 US dollars.

Discussion
Main findings
Poor adherence to ART can lead to virological failure, poor clinical outcome, and diminish future treatment options. Ensuring adherence to prescribed ART continues to be a major public health concern. To the best of our knowledge, this is the first economic evaluation that evaluates the cost effectiveness of QD HAART regimen versus BID regimen from a sub-Saharan societal perspective. Compared with the BID regimen, the increase cost-effectiveness ratio of the QD regimen ($8,102/QALY gained) exceeds the WHO-CHOICE willingness to pay threshold (three times the country’s per capita GDP: $5,086)\textsuperscript{37,38}. The incremental cost-effectiveness ratio was most sensitive to variations in the total medical cost of state A, total medical cost state D, utility of state A and total medical cost of state C.

The results of cost-effectiveness of QD versus BID literature have been mixed, while some studies demonstrated that regimen simplification to be cost-effective\textsuperscript{21–23}, other found it not be cost-effective\textsuperscript{24,25}. Fogolia and colleagues estimated the lifetime cost utility of QD regimens versus BID regimens in Italian human immunodeficiency virus (HIV)-infected patients naïve to treatment using a Markov microsimulation model\textsuperscript{24}. Fogolia showed a cost-utility value advantage for twice-daily over QD regimen. Walensky conducted an economic evaluation of a three pill generic antiretroviral therapy and demonstrated cost-saving of
Figure 3. Incremental cost-effectiveness plane for once daily (QD) versus twice-daily regimen (BID). QALY – Quality Adjusted Life Years.

Figure 4. Cost-effectiveness acceptability curve for once daily (QD) versus twice-daily regimen (BID). QALY – Quality Adjusted Life Years.
such a regimen. Similarly, Walensky and co-researchers found that generic antiretroviral therapy will be cost-saving in the USA. Brogan and colleagues found that the QD regimen was more effective and cost-saving compared with the BID regimen in people living with HIV that are treatment naïve.

Strengths and limitations of the study
Our Markov model incorporated a probabilistic sensitivity analysis to give a comprehensive estimate of uncertainty associated with model parameters. Compared with a cost-effectiveness study conducted alongside a trial, this model-based approach has several advantages; we combined evidence from several sources and also conducted different sensitivity analyses. However, our analysis also has some limitations. There were a few parameters for which data from low-middle income countries (LMIC) were not available, and we had to rely on data from the high-income countries or make simplifying assumptions. Another limitation includes uncertainty in parameter values and the demonstrated sensitivity of the results to changes in some parameter values. All model input parameters used in the model were extracted from the published literature, and although there are intrinsic uncertainties associated with these parameters, there were, however, modelled appropriately. We conducted a probabilistic sensitivity analysis to concurrently assess the impact of these model input parameters. Our model was also limited by the assumptions about the mechanism of HIV disease progression.

Conclusion
From a sub-Saharan Africa country societal perspective, the QD HAART regimen cannot be regarded as cost-effective. However, there is considerable decision uncertainty, driven particularly by the variations in the total medical cost of state A (asymptomatic, non-AIDS, CD4 >350 cells/μL), total medical cost state D (symptomatic AIDS or severe symptoms), and utility of State A; future research should focus on reducing uncertainty in these parameters. Findings from the economic evaluation are important for LMIC as they consider whether to adopt the new branded single tablet regimen. Generic-based ART could yield substantial budgetary saving to HIV programmes in LMIC.

Data availability
Dataset 1: Raw data for Table 1, Model parameters, doi:10.5256/f1000research.9954.d14242
Dataset 2: Raw data for Figure 2, Tornado plot for incremental plot, doi:10.5256/f1000research.9954.d14242
Dataset 3: Raw data for Figure 3, Incremental cost-effectiveness plane for once daily (QD) versus twice-daily regimen (BID), doi:10.5256/f1000research.9954.d14242
Dataset 4: Raw data for Figure 4, Cost-effectiveness acceptability curve for once daily (QD) versus twice-daily regimen (BID), doi:10.5256/f1000research.9954.d14242

Author contributions
MBS and OAU were responsible for conception and design of the research. Acquisition of data was carried out MBS and OAU. Economic modelling and statistical analysis were carried out by MBS and OAU. MBS, OAU and JBN were responsible for review, analysis and interpretation of the outcomes. MBS, OAU and JBN were responsible for development of the manuscript. MBS, OAU and JBN were responsible for critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Competing interests
No competing interest were disclosed.

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This paper shows promise; however there are some critical aspects which mean that it cannot be approved. (The following review is based on the manuscript alone and not a review of the related literature or secondary sources.)

Major observations

**Efficacy data**

- There seem to be two key differences between QD and BID regimens: direct cost and relative risk (in the model this single efficacy measure seems to incorporate adherence and viral suppression). For direct cost, Table 1 shows that the mean drug cost for once daily regimen (610) is lower than twice daily regimen (638). For efficacy, based on the meta-analysis, there appears to be a benefit to using once daily regimens (QD). Based on that, it is unclear whether the cost utility analysis is warranted (i.e. the intervention (QD) appears to be less costly and have higher efficacy than BID).

**Country Focus**

- The authors state that the analysis is done “from the Sub-Saharan African healthcare payer’s perspective.” SSA is a large geographical region which includes different countries with diverse health care systems. Consider whether the work will have more impact if one country is chosen as a focus.
- The authors propose that “Findings from the economic evaluation are important for low- and middle-income countries (LMIC) to consider as they decide whether to adopt the new branded single tablet regimen.” However SSA does not only include LMIC. I do not find anything in the paper which makes it particularly relevant to SSA as opposed to other similar regions which include LMIC.

**Model structure and assumptions**

- Please explain the rationale behind the choice of model structure.
- The model structure schematic is inaccurate. Table 1 shows the transition probabilities from State A to B, A to C, A to D and A to E however this is not included in the schematic.
- The model seems to assume that in a patient’s lifetime they will never fail first line and /or switch to second line therapy. What is the rationale for this assumption in the model?
- What is the rationale and justification for using a yearly cycle for the markov states?
- Adherence is not an explicit parameter in the model (although it appears to be factored into the relative risk from the meta-analysis.) Please explain the rationale and justification for this.
Perspective and related cost data

- It is unclear what perspective has actually been used for the analysis. Although the authors state that they have performed the analysis “from the Sub-Saharan African healthcare payer’s perspective”, this appears to be contradicted by the statement “both all direct and indirect cost was considered”. Furthermore the authors conclude the study “From a sub-Saharan Africa societal perspective”. [A clear description of the cost data would clear this point, however the “annual total medical cost” is aggregated and without going into the secondary data sources it is not possible to see exactly what has been included.]
- It is unclear which specific drugs have been used for the QD and BID regimens, therefore it is difficult to evaluate the calculation of the mean drug cost in Table 1.

Time horizon

- It is unclear what time horizon has been used for the analysis. The authors state that the analysis was performed “over the lifetime of patients”, and later they state that the cohort was “simulated over 20 years”. It is not clear whether the time horizon was 20 years and (possibly) some patients did not reach State E, or the simulation was run for a lifetime until all patients reached State E.

Evidence

- Which search terms were used for which parameters?
- If the target countries are SSA then what was the rationale for using the US Public Health Service Guidelines?

Limitations

- More discussion is needed around the limitations, it is necessary to explain how they influence the results and how (if at all) they could be improved.

Uncertainty

- An explanation is required regarding the large uncertainty around the results.
- It is unclear whether the relative risk has been varied in the one way sensitivity analysis. If not, please explain why.

Minor observations

- What software was used for the model?
- Reconsider the title probabilistic “decision” model - it is a probabilistic markov model (as opposed to decision tree model).
- “The antiretroviral naïve HIV patient is assumed to have a better initial response to medication therapy than individuals who have received previous antiretroviral treatment” please substantiate
- “An intervention was defined as follows: very cost-effective, ICER < GDP per capita ($1,695); cost-effective, ICER = 1–3 × GDP per capita ($1,695 to $5,086); and not cost-effective, ICER is > 3 × GDP per capita ($5,086)”. Which GDP was used from which SSA country?
- Small cohort noted.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Competing Interests: No competing interests were disclosed.
This manuscript discusses the cost-effectiveness of QD versus BID in resource-limited settings such as sub-Saharan Africa (SSA). Using computer simulation, authors found that QD could not be considered cost-effective in SSA.

**Major comments:**

- **Background:** Literature cited in this manuscript is quite old, and in general most of the literature cited in this study was published before 2013. This is a critical issue since HIV treatment is a very dynamic field that is constantly changing. In fact, in 2013 the World Health Organization published the guidelines for ART that were updated in 2016, in which they recommended ART coverage for every HIV-infected individual, but prioritizing individuals with a CD4 count < 500. Also, a **Once-daily** regimen comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) was found to be cost-effective and therefore recommended to be used as a first-line ART in HIV naïve patients. Based on the framework proposed by these guidelines, how relevant is this study and what would be the potential impact and application of the study results?

- **Model:** It is very hard to understand the model with the description that is currently being provided. If adherence is an important difference between QD and BID, is this factor included in the simulation? What about potential adverse events or treatment failure? Also, why is > 350 CD4 cell count used for early state (state A)? Latest ART guidelines advise priority for treatment initiation at < 500 CD4 cell count, so why did authors not consider using this value for this state? If this is a computer simulation, why did authors decide to include such a small number of individuals (only 1,000 simulated agents)? In most published studies these simulations usually include about 1,000,000 individuals. Did the simulation consist of 1,000 individuals for each ART regimen, or 500 in one and 500 in the other one? How many individuals survived? How many died in each ART regime? Also, why did they decided to use a 1-year time step?

- Model parameters in Table 1 indicate that individuals can move from states beyond the next state, and return. For example, an individual in state A could move to state D, and could also return from state D to state A. However, diagram in Figure 1 indicates that movement of individuals is from one state to only the immediate adjacent state, for example, individuals in state A only can progress to state B, and return from B to A. Please clarify.

- **Model parameters:** The main flaw of this manuscript is the data used for model parameterization. Authors claimed to have conducted an extensive review of the literature available on this topic. However, no more than three sources were used for data parameterization. Furthermore, after I searched through the original sources, I was not able to find the values that authors used in this model. For example, in Goshu & Dessie (2013), they used a model in which state A was > 500 CD4 cell count and not > 350 CD4 cell count, as used in this study. Also, the probabilities of the transition states reported in Table 1 in Goshu & Dessie do not correspond with the probabilities of the transition states that authors used in their model. Moreover, the model in Goshu & Dessie included a monthly time step, whereas the model developed in this manuscript uses yearly time steps. Taking these changes in consideration, I consider that authors should address how this could affect the parameter values used from Goshu & Dessie. Did authors transform these monthly probabilities to annual probabilities? Similarly I was not able to find the values that the authors used.
in this study for the baseline population from each state in Goshu & Dessie. Please clarify.

- Authors mentioned that there were few parameters for which data from low and middle-income countries were not available, what were those parameters?

- Also, why is beta distribution used as the probability distribution of state probabilities for uncertainty analyses?

- What is exactly included in total medical cost?

- Limitations of the study: In the last paragraph of the discussion, authors mentioned that the model was limited by the assumptions about the mechanism of HIV progression. What are these assumptions?

**Minor comments:**

- In general there are several grammar mistakes and typos that need to be addressed.

- ART acronym is used the first time in paragraph 1 of background but it was not defined before. Also authors use ART in some parts of the manuscript and HAART in others. Please specify.

- If authors examined the uncertainty around the robustness of imputed parameters, why did they call it sensitivity analysis and not uncertainty analysis?

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

**Competing Interests:** No competing interests were disclosed.