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RESEARCH ARTICLE

Cost-effectiveness of early versus delayed antiretroviral therapy in tuberculosis patients infected with HIV in sub-Saharan Africa [version 1; peer review: 2 not approved]

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Abstract

Background: The most challenging issue physicians are facing is the appropriate timing of introducing antiretroviral therapy (ART) along with ongoing tuberculosis (TB) therapy in HIV and TB co-infected patients. This study examined the cost-effectiveness of early versus delayed ART initiation in TB patients, infected with HIV (co-infected patients) in a sub-Saharan Africa setting. **Methods:** A decision analytic model based on previously published and real-world evidence was applied to evaluate clinical and economic outcomes associated with early versus delayed ART in TB and HIV co-infection. Incremental cost-effectiveness ratio (ICER) was calculated with both costs and quality-adjusted life years (QALYs). Different assumptions of treatment benefits and costs were taken to address uncertainties and were tested with sensitivity analyses. **Results:** In base case analysis, the expected cost of giving early ART to TB patients infected with HIV was \$1372, with a QALY gain of 0.68, while the cost of delayed ART was \$955, with a QALY gain of 0.62. The ICER shows \$6775 per QALYs, which suggests that it is not as cost-effective, since it is greater than 3 x GDP per capita (\$5,086) for sub-Saharan Africa willingness to pay (WTP) threshold. At \$10,000 WTP, the probability that early ART is cost effective compared to delayed ART is 0.9933. At cost-effectiveness threshold of \$5086, the population expected value of perfect information becomes substantial ($\approx$ US\$5 million), and is likely to exceed the cost of additional investigation. This suggests that further research will be potentially cost-effective. **Conclusions:** From the perspective of the health-care payer in sub-Saharan Africa, early initiation of ART in HIV and TB co-infection cannot be regarded as cost-effective based on current information. The analysis shows that further research will be worthwhile and potentially cost-effective in resolving uncertainty about whether or not to start ART early in HIV and TB co-infection.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

HIV, tuberculosis, early intervention, sub-Saharan Africa

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Introduction

Co-infected patients with HIV and tuberculosis (TB) has been a serious concern to healthcare sectors in many countries, commonly countries with resource constrained settings (Blanc *et al.*, 2011; Manosuthi *et al.*, 2012; Sinha *et al.*, 2012). The incidence population of TB globally in 2012 was reported by the World Health Organisation (WHO) to be 8.6 million, and 1.1 million of this population were HIV-infected individuals (Mfinanga *et al.*, 2014; WHO, 2013). The most challenging issue physicians are facing is the appropriate timing of introducing antiretroviral therapy (ART) along with ongoing TB therapy in HIV and TB co-infected patients (Mfinanga *et al.*, 2014; Sinha *et al.*, 2012). Delaying the introduction of ART for co-infected patients, and prescribing antibiotics only to these patients, has been proven to increase the risk of reactivation and reinfection of TB among patients, as a result of the HIV infection (Daley *et al.*, 1992; De Cock *et al.*, 1992; Sinha *et al.*, 2012; Wilkinson & Moore, 1996). Hence it increases the death rate among co-infected patients, compared to individuals infected only with TB (Sinha *et al.*, 2012; Wilkinson & Moore, 1996). The combination of the two therapies (ART and antibiotics) has been reported to have a significant outcome in reducing the mortality among co-infected patients, leading to a 90% reduction of TB reinfection (Manosuthi *et al.*, 2006; Sanguanwongse *et al.*, 2008). However, combining the two therapies is complicated, and

can lead to drug-drug interactions, severe toxicities, poor medication adherence, increase pill burden, and risk of developing immune reconstitution inflammatory syndrome (IRIS) associated with TB (Mfinanga *et al.*, 2014). To date, the cost effectiveness of early versus delayed ART initiation in co-infected patients has not been reported. The aim of this study is to examine the cost effectiveness of early versus delayed ART initiation in TB patients infected with HIV (co-infected patients).

Methods

Study design

Analytical decision model, comparing the early versus delayed ART initiation in co-infected patients, using cost utility analysis and cost effectiveness analysis.

Decision model

A decision tree model was developed to compare the impact of early introduction of ART to delayed ART in the management of tuberculosis patients infected with HIV, and their mortality rate using Microsoft Excel 2013 (Figure 1). Though both conditions are chronic and as such a Markov model would also have been an appropriate tool to use (Soto, 2002). However, since the interested outcome can be assessed within a short time period (12 weeks), the decision tree model was used (Halpern *et al.*, 1998).

Figure 1. Decision tree for early versus delayed ART treatment in tuberculosis patients infected with HIV. ART – Antiretroviral Therapy; OBS – Observational Studies; RCT- Randomised Controlled Trial.

Model perspective

The cost-effectiveness model was performed from the health-care's payer perspective, where only the direct programs and medical costs were included. Indirect costs incurred by patients were not considered.

Model time horizon

The study time horizon, used for the model is 12 weeks, and this was chosen based on the treatment period of latent TB, which can be 12 weeks (Manosuthi *et al.*, 2012; Sinha *et al.*, 2012).

Setting and population

The patients with TB, commencing on anti-TB treatment for 12 weeks, infected with HIV, are the population of interest. The setting was in sub-Saharan Africa. The data used in the model for both costs and consequences was extracted from previous published literature (summarised in Table 1; Abimbola *et al.*, 2012; Cleary *et al.*, 2006; Esfahani *et al.*, 2011; Holland *et al.*, 2009; Uthman *et al.*, 2015). We conducted focused searches for the studies in Medline (from inception to December 2016) using the following keywords: tuberculosis, HIV, cost, and quality of life. Probabilities derived from published literatures were used for each arm on the tree to determine the number of patients that will either have adverse events or no adverse events, and those that will either survive or die.

Model input parameters

Probabilities: Probabilities derived from published literatures were used for each arm on the tree to determine the number of patients that will either have adverse events or with no adverse events, and those that will either survive or die.

Utilities: The utility values, Quality adjusted life year (QALY) for each arm of the tree were also derived from published literatures.

Costs: Direct costs were the only cost considered in the model, as the perspective was based on health care only. The costs include costs of a complete treatment of TB with adverse or no adverse events (Esfahani *et al.*, 2011) and costs of ART and costs of additional treatments for dying patients (Table 1). All costs were converted to US dollars (\$), and inflated to 2014 price, using a USA inflation calculator (<http://www.usinflationcalculator.com/>).

Model output

Reduced death/mortality benefit was the primary outcome measured, and the incremental cost effectiveness ratio (ICER) was used, measured in QALY. The result will be presented on cost effectiveness plane (CE-plane), cost-effectiveness acceptability curves (CEACs), along with probabilistic sensitivity analysis (PSA) to represent the uncertainty in model output.

Assumptions

The following assumptions were made:

TB treatment - all patients were assumed to be undergoing anti-TB treatment that takes 3 months for completion (Holland *et al.*, 2009).

Total ART treatment - it was assumed that the total ART treatment for 12 weeks is half the cost of healthcare utilization of patients that died within the first 6 months of ART. Also the same assumption was used for the patients that survive the first 6 months of ART. The cost excluded the expected expenditure per ART of included patients.

Table 1. Model parameters. ART, antiretroviral therapy; QALY, quality-adjusted life year.

Parameters	Early ART	Delayed ART	Distribution	Reference
Probabilities				
Adverse event	0.18 (18%)	0.1 (10%)	Beta	(Uthman <i>et al.</i> , 2015)
Death from adverse event	0.24 (24%)	0.27 (27%)	Beta	(Uthman <i>et al.</i> , 2015)
Death from no adverse event	0.08 (8%)	0.09 (9%)	Beta	(Uthman <i>et al.</i> , 2015)
Cost, \$				
ART treatment cost (patients that died within 3 months)	320	-		(Abimbola <i>et al.</i> , 2012)
ART treatment cost (patients that survive)	350	-		(Abimbola <i>et al.</i> , 2012)
Tuberculosis treatment with adverse event	908	908		(Esfahani <i>et al.</i> , 2011)
Tuberculosis treatment without adverse event	868	868		(Esfahani <i>et al.</i> , 2011)
Additional cost for dying patients	832	832		(Cleary <i>et al.</i> , 2006)
Utilities				
QALY of adverse event	0.5	0.5		(Holland <i>et al.</i> , 2009)
QALY of no adverse event	0.81	0.71		(Holland <i>et al.</i> , 2009)

Mortality rate - it was assumed that the relative risk is three times more in patients with an adverse event group, than in a non-adverse group (Hoyo-Ulloa *et al.*, 2011).

Additional costs of dying patients - it was assumed that the additional cost of treating dying patients was a result of the adverse event developed by the patients, which can result in death.

Sensitivity analyses

To handle uncertainty surrounding the model parameters, and the robustness of the model outcome, probabilistic sensitivity analysis was carried out to justify the decision on whether starting ART early or delaying treatment in TB patients infected with HIV is cost effective. About 10,000 random variables were generated, using the Microsoft Excel 2013 random generator. Cost effectiveness acceptability curves (CEAC) can also be used to summarize the uncertainty around cost effectiveness analysis (Fenwick *et al.*, 2006). CEAC shows the probability of how cost effective an intervention is, compared with the alternative intervention, based on the range of threshold values accepted by decision makers per QALY (Fenwick *et al.*, 2006).

Expected value of perfect information (EVPI)

Uncertainties around the cost effectiveness estimates can also be assessed using EVPI (Eckermann *et al.*, 2010). Errors in cost effectiveness estimates can lead to wrong decisions, in which health benefit and resources can be forgone to an alternative choice (Briggs *et al.*, 2006). The value cost of the forgone health benefit and resources as a result of uncertainty in the estimate, can be expressed as the EVPI (Briggs *et al.*, 2006). EVPI can be expressed as the different association between the expected net benefit with no uncertainty and the expected net benefit with uncertainties. The value of EVPI rises as the threshold increases, as a result of the increment in decision uncertainty (Briggs *et al.*, 2006). EVPI reaches the maximum when the value of threshold and expected ICER are equal, and this is the highest level of decision uncertainty (Briggs *et al.*, 2006). The population EVPI was estimated by multiplying per patient EVPI by the effective population, i.e. the estimated number of people with TB and HIV co-infection. According to the WHO report in 2012, there were 1.1 million cases of co-infected patients, and 320,000 deaths were recorded among this population globally (WHO, 2013: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf).

Results

Table 1 summarizes the model input parameters. The results of the analysis are shown in Table 2. From the tabulated results, the expected cost of providing early ART to TB patients infected with HIV was \$1372, with a QALY gain of 0.68, while the cost of delayed ART was \$955, with a QALY gain of 0.62. The results demonstrate that early ART provides a higher QALY value than delayed ART, but with a higher cost. The ICER shows \$6775 per QALYs, which suggests that it is not cost-effective, since it is greater than $3 \times$ GDP per capita (\$5086) for the sub-Saharan Africa willingness to pay threshold (Evans *et al.*, 2005; Murray *et al.*, 2000).

Probability sensitivity analysis

The output for the probabilistic sensitivity analysis for 10,000 simulations is shown in Figure 2. All of the model outputs were in the northeast quadrant of the cost-effectiveness plane, suggesting that early ART is more costly and more effective than delayed ART; it is never cost saving and never has a negative impact on patient outcomes. At a threshold of \$9,000, directly administered ART was found to be 50% more likely to be cost-effective, and if the willingness to pay for a QALY was \$18,000 then directly administered ART is likely to be at least 95% cost-effective. The probability that early ART was cost-effective at the WHO-CHOICE threshold (Evans *et al.*, 2005; Murray *et al.*, 2000) of \$5086 was just 1% (Figure 3). However, if the policy makers are willing to pay for a QALY (\$10,000), then early ART is likely to be at least 95% cost-effective.

Expected value of perfect information (EVPI)

The population EVPI is illustrated in Figure 4. At a cost-effectiveness threshold of \$5086, the population EVPI becomes substantial ($\approx$ \$5 million), and is likely to exceed the cost of additional investigation. This suggests that further research will be potentially cost-effective. Co-infected early versus delayed antiretroviral therapy is unlikely to be cost-effective.

Dataset 1. Raw data for Figure 2, Figure 3 and Figure 4 (in zipped file)

<http://dx.doi.org/10.5256/f1000research.10620.d151708>

Table 2. Incremental cost-effectiveness results for early ART versus delayed ART in tuberculosis patients infected with HIV. ART, antiretroviral therapy; QALY, quality-adjusted life year.

Strategy	Cost (\$)	Incremental cost (\$)	QALY	Incremental QALY	ICER (\$/QALY)
Early ART	1372		0.68		
Delayed ART	955	417	0.62	0.06	6775/QALY

Figure 2. Probabilistic sensitivity analysis presented on a cost effectiveness plane. QALY- Quality Adjusted Life Years.

Figure 3. Cost effectiveness acceptability curves. QALY- Quality Adjusted Life Years.

Figure 4. Expected value of perfect information. EVPI – Expected value of perfect information; QALY- Quality Adjusted Life Years.

Discussion and conclusions

The decision analysis model was used to assess the cost effectiveness of early ART in TB patients infected with HIV. According to the ICER estimates, early ART is not cost effective from a sub-Saharan Africa health-care payer perspective, i.e. the ICER is $>3 \times$ GDP per capita (\$5086) (Evans *et al.*, 2005; Murray *et al.*, 2000).

To the best of our knowledge, this is the first cost-effectiveness model on optimal timing of ART in people with HIV and TB co-infection from sub-Saharan Africa's perspective. Our cost-effectiveness model incorporated probabilistic sensitivity analysis to simultaneously and comprehensively estimate uncertainty around model input parameters. This approach follows WHO health economists' recommendations for economic evaluation and priority setting (Baltussen *et al.*, 2002). In addition, the decision analytical approach we used have several advantages compared with economic evaluations alongside clinical trials (Ehlers *et al.*, 2009). Evidence from multiple sources were combined, reflective of real-world evidence rather than evidence from just one trial conducted in a restricted setting. This can be combined and systematic sensitivity analyses performed (Ehlers *et al.*, 2009).

The specific appropriate time to initiate ART within an early period could not be stated in the model, but it may be assumed that it should be within 8 weeks, as this is the recommended time by the WHO (Mfinanga *et al.*, 2014). Only direct costs were considered in the model, based on the health care perspective. The costs, probabilities and utilities used in the model were estimated from published literature, and probabilistic sensitivity analysis was conducted to assess the uncertainties around parameter's value. The costs used seem to be general costs, which might not be the appropriate cost setting in sub-Saharan Africa.

In conclusion, from the perspective of the health-care payer in sub-Saharan Africa, early initiation of ART in HIV and TB co-infection cannot be regarded as cost-effective based on current information. The value of information analysis shows that further research will be worthwhile and potentially cost-effective in resolving the uncertainty about whether or not to start ART early in HIV and TB co-infection.

Data availability

Dataset 1: Raw data for Figure 2, Figure 3 and Figure 4 (in zipped file). doi, [10.5256/f1000research.10620.d151708](https://doi.org/10.5256/f1000research.10620.d151708) (Uthman & Uthman, 2017).

Author contributions

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

Competing interests

No competing interests were disclosed.

Grant information

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General Comments:

This study attempts to undo the WHO recommendation, and the huge body of evidence that supports early ART initiation in all HIV infected patients irrespective of CD4 count or co-infection status. The analysis presents data from a variety of sources in a conceptual framework of a decision analysis model. Whether the model incorporated the best available evidence is extremely doubtful, as the variety of sources collated is limited and the information drawn was not described in enough detail. The cost-effectiveness analysis itself is over simplified and may not be of particular use to policy- or decision-makers. The scientific merits are lacking in this particular piece of work and a lack of transparency in reporting has been noted. The extent of this study's ability to add value to existing scientific literature is debatable. Moreover, substantial language editing is required to enable an ease of understanding by readers. There is direct repetition of information provided by the authors across multiple adjacent sections. For example, the use of "probabilities derived from published literature". Numerous grammatical errors were observed, largely involving the confusion of single and plural terms – "literatures" instead of "literature".

Critique of Scientific Merit

Introduction

While the research question and the economic importance thereof is clearly stated, the relevance of the research question is ambiguous, given that recommendations of early ART administration regardless of co-infection status, or CD4 cell count, were issued by the WHO in September 2015, (WHO, 2015). Furthermore, the question of risk vs benefit of ART timing in TB therapy has also previously been addressed. These recommendations have been ignored, hence this study should therefore have not been conducted on those grounds.

It should be mentioned in the introduction and abstract that the cost-effectiveness analysis is based on the synthesis and meta-analysis of other studies. This information only arises on page 4

of the article.

The alternative interventions were not described in sufficient detail to enable the reader to assess the relevance of all setting specific interventions. More specifically, early and late ART initiation strategies were not described in time units. The authors failed to define early ART initiation and delayed ART initiation.

Study design

The use of economic evaluation, namely cost-utility analysis and cost-effectiveness analysis have not been substantiated. The authors need to provide a clear justification of why they have chosen both economic evaluation methods, in the context of the research question stated.

Decision model

The use of a decision analytic model is clearly articulated but perhaps incorrectly substantiated: The authors have justified the use of decision tree model instead of a Markov model on the rationale that the outcome of interest can be assessed within a 12-week period – this is questionable.

The actual decision tree (Figure 1) is too cluttered, cannot be interpreted on face value and there is no referring explanation within the text.

Model perspective

The viewpoint of the analysis is not entirely clear – the authors refer to a “health-care’s payer perspective” (page 4) this could be interpreted as either the health care provider or the health care user. Their use of this perspective also needs to be substantiated within the context of the analysis.

Model time horizon

The choice of time horizon is dubious –as the treatment of latent TB may vary, HIV-TB coinfectd patients may be infected with either latent or active TB, and patients with resistant or extrapulmonary manifestations of TB may require lengthier treatment. Time horizon should account for the minimum and the lengthiest duration of treatment.

Setting and population

The method of synthesis or meta-analysis of evidence is not described in enough detail. For example, only a brief description of the search strategy was mentioned while the criteria for inclusion of studies in the overview was omitted (page 4).

Model input parameters

The authors did not provide sufficient detail regarding the model used within the study. The actual resources costed and quantities thereof are not mentioned.

Key parameters of the model are mentioned but not discussed at length or justified. For example, why were those parameters included in the model? What does ART treatment cost comprise – are overheads and personnel costs included or are these estimations limited to the cost of drugs? Did all authors included in the cost estimation (Table 1) use similar methodology to calculate these costs? If not, this would impact on the usefulness of the analysis. The country settings of these

published studies used to collect evidence is not mentioned, yet should be. Even though there was no need for discounting due to the time horizon being less than a year, this should have been made explicit within the text.

Model output

The time horizon of the model was too short to accurately observe the primary outcome measure of reduced mortality, and thus both time horizon and primary outcome measure are inappropriate.

Assumptions

Once again, the assumption that TB treatment is completed within a three-month period is incomplete and inaccurate (refer to comments above).

Their assumption of the cost of ART treatment is not well articulated, neither is it justified or at least referenced within the text. The same can be said for the assumption of additional costs of dying patients.

It is completely unclear from the text how these assumptions (page 4) were derived or the basis of their foundation. What evidence supports these assumptions or derivations?

Sensitivity analyses/Probability sensitivity analysis

No mention was made of the actual variables chosen for the sensitivity analysis, the justification of the choice, and the ranges over which they were varied. There is no conclusion to the sensitivity analysis regarding the robustness of their results.

Results

It is not clear how the estimates displayed by Table 1 generate the results in Table 2 – again touching on the notion of an incomplete description of the model used. The results section fails to clearly differentiate between the results of the cost utility analysis and those of the cost-effectiveness analysis.

Discussion and conclusions

While the answer to the original research question has been answered, the presentation of results is too simplistic and has not been accompanied by appropriate qualifications and reservations.

The authors' acknowledgement of study limitations has not been clearly set out.

The authors discuss items that should have been addressed in previous sections first, and therefore only seen by the reader at the end of the text: the recommended time of ART initiation by WHO; the presumption of the use of general costs by the literature base which provided inputs for the model.

Based on the methodological and structural issues raised above, the discussion and conclusions drawn may not carry much weight.

Conclusion

This study simply brought together data from a variety of sources into the conceptual framework of a decision analysis model. Whether the model incorporated the best available evidence is unsure, as the variety of sources collated was quite limited and the information drawn was not described in enough detail. The cost-effectiveness analysis itself is over simplified and may not be of particular use to policy- or decision-makers. The scientific merits are lacking in this particular

piece of work and a lack of transparency in reporting has been noted. The extent of this study's ability to add value to the surrounding literature base is debatable. Moreover, substantial language editing is required to enable an ease of understanding by readers.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB-HIV Treatment

I confirm that I have read this submission and 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.

Reviewer Report 03 April 2017

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It is unclear if the authors realize that cost-effectiveness is a tool employed by decision makers to arrive at a decision regarding resource allocation. Given that early versus delayed ART is not debatable any more, the researchers need to motivate their study in this context i.e. decision makers already agreed to initiate ART early in TB/HIV patients from a clinical point-of-view and public health perspective to avert new TB cases.

The study is not well motivated for economic evaluation. Issues surrounding why cost-effectiveness of the study is useful are not explained

The decision analysis tree needs to be simplified. As it is now, it is a busy figure. Secondly, the argument that the outcome of interest is short term is not true i.e. is death from TB a short outcome event?

Which outcome are the researchers referring to for the 12 weeks period? I think, if they intend to pursue this question further, they need to employ Markov modelling as well.

Under model time horizon, the authors infer that latent TB is treated for 12 weeks. This appears to be in contradiction to WHO guidelines for 6-9 months of treatment for latent TB. It is also not clear from the outset that the authors are treating for latent TB. In the beginning, I thought the study referred to TB/HIV co-infection from the disease point of view i.e. HIV patient with signs & symptoms of TB.

Literature for model parameters appears to be so limited. Authors need to utilize assumptions based on standard practice guidelines issued by for example the WHO. Authors need to be clear which costs were considered.

The general approach to the study is appropriate. However, the authors need to refer to this work to improve the quality of reporting of their report: [JAMA](#). 1996 Oct 23-30;276(16):1339-41.

Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine.

It is likely that the authors conclude that early versus delayed ART in TB/HIV patients is not cost-effective because of the limited time horizon, assumptions on duration of treatment, unclear disease being treated i.e. latent TB infection or TB disease in HIV patients and limited literature search. Moreover, these are not well discussed.

The argument that an intervention is not cost-effective based on threshold of $3 \times \text{GDP per capita}$ is debatable nowadays. Authors need to consult more about this.

Finally, the discussion section is so limited and it does not adequately discuss the results of the study. Including the implications of the findings considering the current treatment guidelines for TB/HIV patients. This needs to be improved.

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and 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.

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