Author's response to reviews

Title: When to start antiretroviral therapy in resource-limited settings: a human rights analysis

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Version: 2 Date: 20 January 2010

Author's response to reviews: see over
Dear editors

Thank you for sending the review comments to our submission “When to start antiretroviral therapy in resource-limited settings: a human rights analysis.” These comments were very useful and have certainly strengthened our paper.

We provide below a point-by-point response to the individual reviews, and a corresponding revision of the original submission.

We have also amended the abstract, as requested.

Yours sincerely,

Nathan Ford

Reviewer's report
Title: When to start antiretroviral therapy in resource-limited settings: a human rights analysis
Version: 1 Date: 27 December 2009
Reviewer: John A Bartlett
Reviewer's report:
Major Compulsory Revisions
The authors have written a provocative piece arguing for a human rights approach to when to start antiretroviral treatment (ART). Compelling evidence is available supporting the early initiation of ART, but implementing this plan is challenging given limited resources. Their arguments are sound with a few minor exceptions outlined in the comments to the authors. However, the authors have failed to consider one major conundrum; pursuing a human rights approach to health should suggest that all forms of treatment for all diseases should be made available to the entire global population. There are certainly profound disparities in access to care and prevention for cardiovascular disease, cancer and many
other treatable conditions- why should HIV infection and ART be any different? The authors need to present a logical rationale for this exception.

- Thank you for this thoughtful review. We fully agree that the arguments presented in this paper could be applied to any number of important health issues. As noted by one of the other reviewers, the purpose of a human rights analysis (in contrast to a systematic review) is to examine a policy issue from a number of different perspectives that are important for health policy (in our example health economics, social science, clinical medicine and public health). Such a framework could, as the reviewer suggests, be used to examine competing claims within health care, but that was not our aim.
- We hope that this concern has been addressed by expanding on the methodology used and including reference to previous studies using such an approach (this was also requested by reviewer 3).

Minor Essential Revisions

1) On page 2, in the section "When to start antiretroviral treatment", a principal benefit of earlier initiation is improved immune reconstitution and this should be mentioned.

- Thank you. We have included this important point

2) On pages 8-10, no mention is made of the potential for HIV/AIDS treatment as a decreasing priority for international funding. Certain programmes such as PEPFAR may be limiting the numbers of persons who may initiate ART. The possibility of declining resources may represent the greatest threat to expanding the pool of treated persons through earlier initiation.

- We completely agree that this is a critical issue
- However, we have deliberately chosen to not address this issue we do not wish to make our analysis conditional on how much funding may or may not be available in the near future. We acknowledge that this is a deliberate and perhaps subjective choice.

3) In the Conclusions on page 10, there are data regarding cost-effectiveness; the authors should review the CEPAC work by Kenneth Freedberg and others.

- Thank you for underlining this important work. We have included reference to one study by this group (reference 27) and would welcome suggestions for other important studies for inclusion if the reviewer feels these have been omitted.
Discretionary Revisions

1) On page 4, the most concerning toxicities are long-term and it may be useful to divide them into short-term and long-term categories.
   - We have clarified accordingly

2) On page 7, the generic production of tenofovir has scaled up and competition is resulting in lowered prices.
   - We have included this important point

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

Reviewer's report
Title: When to start antiretroviral therapy in resource-limited settings: a human rights analysis
Version: 1 Date: 23 December 2009
Reviewer: Herman Meulemans
Reviewer's report:
The article has exceptional merits. The approach is a multidisciplinary one and combines in a very readable way bioethical, medical and human rights insights into the early initiation of ART. In some sense the authors apply economic science too, since the scarcity of drugs and human resources is a focal point of interest. There are more qualities in this exquisite piece of research and discussion. I'm sure that the audience will have the feeling that not only the wisdom, collected from the long list of relevant references, is important, but also the field experience of the authors. This is illustrated by the many small interludia (f.i. pre-ART defaulting, human rights principles, the issue of stigma, task-shifting).
Super!
   - Thank you very much for this positive and encouraging review

Level of interest: An exceptional article
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

Reviewer's report
Title: When to start antiretroviral therapy in resource-limited settings: a human rights analysis
Version: 1 Date: 25 December 2009
Reviewer: Mark A Boyd

Reviewer's report:
SUMMARY
This manuscript argues for an earlier start for antiretroviral therapy (ART) in resource-limited settings. It attempts to do so using an argument elaborated from a human rights framework rather than from a clinical standpoint. The authors make a reasonable and cohesive case and their argument is logical. There is a major problem however in that the strength of the evidence on which the recommendation for earlier therapy is based is hotly contested. Unfortunately while the authors believe the evidence for earlier initiation of ART is ‘overwhelming’, many others (including this reviewer) are sceptical. In my opinion in the absence of more robust data coming in the near future we must await the results of a recently initiated multi-centre, international prospective randomized clinical trial (The ‘START ‘ study) to finally adjudicate this debate. This study is taking patients with CD4+ >500 and randomizing to early (after CD4 crosses 500) or late (after CD4+ crosses 350) ART. The primary endpoint is clinical (e.g. death, AIDS, non-AIDS serious events etc.)

- Thank you for this comment. We acknowledge that the strength of the evidence is contested and have moderated the claim in several places to reflect this concern

MAJOR COMMENTS
As stated in the summary, the major problem in this paper is that the authors are at pains to make the case that the evidence for early initiation of ART is ‘overwhelming’ when in fact many would argue (including this reviewer) that this evidence is not as robust as required to confidently make sweeping changes to treatment recommendations in either resource-rich or –limited settings.

The authors are a little unfortunate that only in the last few weeks (on World AIDS Day 2009) two sets of major guidelines panels which are highly influential in the use of ART in both the developed (the USSA DHHS Adult
and Adolescent Treatment Guidelines) and the developing (the WHO Treatment Adult and Adolescent Treatment Guidelines) world released new iterations that both altered the CD4+ thresholds for initiation of ART (although WHO have issued to date only a summary of changes rather than the complete update guideline document to date).

- We have made reference to the latest WHO Guidelines. While this policy change is welcome, it has yet to be adopted as policy at the national level in all but a minority of developing countries. We therefore believe our article still has value, as implementers are now at a stage where countries have to debate how to implement these recommendations and consider the different issues at stake.

What is perhaps most interesting in the DHHS Guidelines is that the panel publicly reported the division between the panel members on the strength of the evidence for increasing the initiating CD4+ threshold value, in the first instance from ‘between 350 to 500’ and then for initiating above 500. In both cases the panel was almost 50/50 split between members who thought the evidence was ‘strong’ and those who thought the evidence was ‘moderate’. I think this split perfectly encapsulates the difference captured in this review process between the authors (‘strong’) and this reviewer (‘moderate’). I think most ‘moderates’ would feel far more confident if and when the START study reports its expected outcomes (see above). Unfortunately it is possible that this study may not reach its planned conclusion for a whole host of reasons, now including the issue of ‘equipoise’ given that the DHHS guidelines have shifted to a treatment threshold > 350 already. Only time will tell.

- We recognize there is disagreement about the optimum threshold for initiation. Our article aims to focus on the shift from 200 vs 350.
- We recognize that this specific focus was not always clear, and have revised our article in ensure that this focus is clearly stated.

With reference to the WHO guidelines these have now shifted the threshold for initiation of ART to a CD4+ of 350. In the manuscript it seems that at least one point the authors are arguing that in fact 350 should be the new threshold level for commencement of ART in RLS. However they go on to quote the ART-CC (Lancet 09) and NA-ACCORD (NEJM 2009) cohort reports (both using data gathered exclusively resource-rich, fully developed settings) making one wonder if in fact they are arguing for commencement f ART in RLS at CD4+ thresholds of 350-500 or perhaps even >500. This confusion should be addressed in any revision.

The authors are quiet about the possible drawbacks and negative consequences of initiating ART at CD4+ thresholds greater than 350 or 500. What will be the long term consequences of treating people who generally feel well? How certain can we be that these apparently more potent, less toxic drugs still seem that way after 20 years of exposure? How long can current sequential ART regimens last, particularly in treating young people infected in their teens or twenties? How does the human-rights based argument for ART
balance with the current situation in RLS where even second-line regimens can be difficult to access (despite them being recommended in WHO guidelines for >5 years now) and publicly funded third-line regimens, particularly in the contemporary economic climate, seem many years from reach?

- As above, we note the potential for confusion and have attempted to clarify that our main focus is towards 350.
- Accordingly, we have deleted reference to the NA-ACCORD study (Kitahata et al, 2009).

The authors refer to the tension between increased access to HIV care including ART and the needs of other aspects of the health-care systems in RLS. On page 3 for instance the authors discuss ‘…significant health systems costs associated with ART provision to large numbers of people when there are already too few doctors and hospitals are saturated’. This note potentially moves the argument on to an exploration of the tension between human-rights based access to HIV care including ART, the extra burden on the HIV service (including not only hospitals but clinics, provincial services, administrative support and so on) and therefore the health system in general. Inevitably in this situation there will be competition for resources that in most if not all of these settings are simply insufficient to meet all identified needs. While the authors’ argument contains an internal consistency, there does not seem to be much appetite to grapple with the larger questions that their argument must surely raise questions about the proper and adequate distribution of resources in any society, initially from the narrow perspective of the health sector (e.g. what about TB, malaria, maternal and infant health, neglected tropical diseases, chronic health conditions, provision of potable water, occupational health and safety, etc.) and then moving on to the issue of other worthy and urgent problems that require funding (e.g. as expressed in the Millennium Development Goals). I think to strengthen the argument for a human rights based access to ART the authors must address the sad realities of the still gross inequities that exist in RLS compared with resource-rich settings and even within resource-rich examples (e.g. the USA), and how a human-rights based access to ART may mean some other worthy health cause suffers as a result of a diversion of (scarce) funds.

- The reviewer is right to mention these competing claims as in the main barrier to embracing WHO’s new guidelines and moving towards 350 will be the financial cost involved.
- These broader issues are however for the most part beyond the scope of our analysis. The point of the paper is not to defend ART as a human right, but to use a human rights analytical framework to analyse a particular issue relating to ART (in this case earlier initiation)
- We hope that this has been clarified by two other helpful suggestions made by the reviewer: elaborating on the methodology deleting Table 1 (which emphasizes general human rights principles relating to ART).
- Thus while such a human rights analytical framework could be employed to assess such issues as HIV vs other diseases or health vs
other MDGs, that would be a separate analysis.

The authors favour a wider introduction of monitoring mechanisms routinely used in the rich-resource world – throughout the paper there are references to the need for wider access to immunological monitoring and also in a couple of instances to plasma HIV load monitoring. Again the authors are a little unlucky in some ways as this argument has been thrown an interesting and timely challenge as a result of the publication of the DART study (see Lancet December 2009 on-line publication). A revision of the paper would need to take this interesting and important study’s results into account.

- We acknowledge that the issue of monitoring is an important policy issue. However, we do not see this as being within the scope of our paper to address these issues directly. While viral load and infectivity is mentioned briefly, we have been careful not to discuss the utility of viral load monitoring as this is beyond the scope of the paper
- CD4 monitoring is implicit as it is inherent to the discussion of 200 vs 350. However, the point of our analysis is not to advocate for or against a particular form of monitoring, and therefore we would prefer not to go into this issue in any detail.

On a couple of occasions the authors quote what they term ‘evidence’ from mathematical modeling exercises (e.g. on page 4 in relation to wider use of ART and reduction in HIV transmission). I don’t believe that mathematical modeling results can be counted as ‘evidence’. They are important and useful exercises that are ‘hypothesis generating exercises’ that require clinical study in order to gather the evidence that may or may not support the modeling findings.

- We have altered the wording accordingly to allow for this point

In this instance the ‘confirmatory’ study offered (ref 28) is simply not relevant to the topic.

- Apologies; the reviewer has rightfully noted a mis-numbering of the references which have now been amended.

On page 5 the authors make passing reference to the fact that despite the push for universal access to ART for those deemed to require it, in reality probably <50% of those eligible today are actually receiving the therapy. The majority of those eligible simply do not know and importantly some do not want to know their HIV status. How does one balance the human right to ART with the human right not to be tested for HIV (and the human right to not even want to be tested)?

- The issue of testing and human rights is beyond the scope of our paper
We do acknowledge however that this again suggests a potential for confusion in the purpose of the paper between discussing human rights issues around treatment in general, and using a human rights analysis frameworks to interrogate a particular policy. We have reviewed the paper thoroughly to minimize the potential for such confusion among readers.

The authors forward an argument that raising the CD4+ threshold for initiation of ART would help retain registered patients in programs (page 6). This is an untested assumption and should be acknowledged as such.

- We fully concede that this point is experience- rather than evidence-based
- We note however that this was seen as a strength by another reviewer and would therefore prefer to keep it in.
- In deference to the reviewers concerns, we changed ‘should’ to ‘could’

MINOR COMMENTS
HIV causes immunodeficiency not immunosuppression.

- Thank you; we have amended accordingly

Reference 6 is missing. Reference 17 is inappropriate. Reference 23 should be to the quoted study itself (not its reporting in a news section of a medical journal).

- We have reviewed the bibliography thoroughly
- With specific reference to reference 23 [now 21], we included this because the article has yet to be published and the abstracts are not database listed. If this changes we will amend

The authors also make a case that ‘newer medicines are more potent’ but it is not clear which medicines they refer to and what the evidence is that they exhibit greater potency (and less toxicity). It would be helpful and add scientific rigour if references were given to substantiate these arguments.

- We have added three references accordingly

The authors argue that ‘there is no clear evidence that the rapid scale up achieved to date...has had negative health system consequences’ (page 4). This is a ‘big’ and controversial statement and requires a more robust reference (and preferably references (plural) – one assumes that there is a substantial amount of data accessible in the grey literature of WHO, the World Bank, UNAIDS and the myriad institutes and NGOs with an interest in this area) than the single conference paper proffered.

- The reviewer is quite right to point out that this is a highly contested
area, and that such a basic statement risks drawing attention away from the main point of the paper. We have therefore deleted this point.

Tables 1 and 2 are dull and don’t really help strengthen the argument elaborated in the text.

- We have deleted Table 2 but prefer to keep Table 1

Page 9 – typo: ‘pre-requist’.

- Thank you. We have done a thorough copy-edit

DISCRETIONARY COMMENTS

The introduction would benefit from a slightly lengthier explanation of the process of a human rights analysis, and how it differs from (or perhaps even enhances) a more traditional clinical argument. While 2 references are given in the text I suspect most readers would prefer to see something more in the Introduction.

- Thank you for this suggestion. We have briefly expanded on the methodology and added references to provide further examples of other analyses that have been done

The authors do make passing reference to cost-effectiveness and argue that earlier initiation of ART may be cost-effective. While it may not be an attractive argument for those pursuing the right to ART on the basis of human rights, it is surely useful to know that certain interventions look to be cost effective, particularly when policy makers (even those sympathetic to human rights arguments) are usually forced to temper their enthusiasm with a close watch over their (often limited) budgets. Isn’t a range of weapons (clinical, cost-effectiveness, human rights, public health prevention) ultimately more important than pursuing a single argument to achieve a universal goal?

- We completely agree and this is why we felt a human rights framework analysis was an interesting methodology to apply, as it allows for consideration of evidence/concerns from diverse fields
- This has been briefly indicated in the justification of the methodology added in response to the previous comment

In order to start earlier and treat more and perhaps reach a level of treatment that may make some difference to HIV transmission rates, how would the authors seek to practically achieve these ends? Do they support opt-out rather than opt-in testing in Africa? I think this issue is a direct consequence of trying to offer more ART on the basis of human rights and so ultimately should be addressed.
This point again reflects a potential for confusion between undertaking a human rights analysis (the purpose of the paper) and arguing for human rights.

We hope our purpose has been clarified in responding to previous points.

A human rights analysis of test-and-treat is surely warranted, but well beyond the scope of our paper.

Level of interest: An article whose findings are important to those with closely related research interests.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
Mark Boyd has received honoraria or research grants, or been a consultant or investigator in clinical trials sponsored by Abbott, Janssen-Cilag, Merck and Roche.