Reviewer's report

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

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Reviewer: Mark A Boyd

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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.)

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). 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.

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 of 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?

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 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.

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

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 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.

MINOR COMMENTS

HIV causes immunodeficiency not immunosuppression.

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.

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.

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.

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

Page 9 – typo: ‘pre-requist’.

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.

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?

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.

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:

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