Author's response to reviews

Title: A cluster randomised trial to evaluate the impact of immediate versus WHO recommendations-guided ART initiation on HIV incidence. The ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, Kwazulu-Natal, South Africa.

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Version: 3 Date: 28 May 2013

Author's response to reviews: see over
Cover letter

Dear Editor

Title: A cluster randomised trial to evaluate the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence. The ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa

Reviewer 1: Nandi Siegfried

General:

This is a well-written article describing an innovative trial protocol which is attempting to answer a key question in the treatment of individuals with HIV/AIDS. As the trial protocol has already received ethics approval and is funded by the French Agency for AIDS and Viral Hepatitis Research (ANRS), it is highly likely that the protocol has already been extensively peer reviewed. As such, most of my comments are minor. There are some key omissions from the CONSORT Statement which need to be addressed and I have identified these clearly in my comments below.

1. Will the study design adequately test the hypothesis?

Yes, the trial has been designed specifically to address the objective of whether treating individuals immediately with ART rather than delaying treatment until specified WHO guidelines are reached, will result in a decrease in the incidence of HIV in the general population over 24 months. By treating HIV infected people at any stage of their infection, their viral load will be reduced in all body compartments to low levels earlier than would otherwise be the case, and with the low viral load the risk of transmission would be minimised at individual as well as population levels (Miller WC et al. Lancet 2013).

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing? The key areas which need to be addressed are omissions from the CONSORT Statement, viz.:

a. How will the random sequence generated?

b. How will allocation concealment be achieved?

c. What adverse events will be collected?

Authors: The management of adverse drug events is covered under toxicity and treatment failure on page 14 of the manuscript. To add clarity, the words ‘adverse events’ have been added in brackets next to the word toxicity. We also realise that it was not clear what information would be collected about adverse events in terms of the secondary outcomes. This has now been clarified in the ‘Outcomes’ section, explaining that grade 3 and 4 clinical and laboratory events will be documented
The detail regarding inclusion criteria will need to describe how patients already on ART will be included in the trial as they will not be eligible for allocation to treatment or control.

Authors: The above statement is relevant to an “individual” randomized trial. The ANRS 12249 study is a cluster-randomised trial in which communities are the units of randomization. The individuals within these communities who meet the inclusion criteria are included in the study by default irrespective of whether they are on ART or not, as long as they give informed consent.

3. Is the planned statistical analysis appropriate?

The CONSORT Statement checklist states:

“Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results” (www.icmje.org). It is also important to describe details of the statistical analysis such as intention-to-treat analysis.’

Currently the statistical analysis section on page 16 is very brief. The authors report that they ‘may’ use Logistic regression to analyse other outcomes. The method is not sufficiently comprehensive to allow others to verify the reported results once they are available. Although the explanation of the correlation coefficient on page 7 and 8 is extensive, the overall analysis requires more information. The authors should also commit to a specific mode of analysis.

Authors: This section was deliberately kept brief as a detailed description is present in the main study protocol. We have now expanded the analysis description on page 17 to address the reviewer’s comment.

4. Is the writing acceptable?

Yes. I have made some suggestions in the detailed comments below.

Detailed comments:

Page 1: The title meets CONSORT requirements. Please write ART in full in the title.

Author: This has been addressed

Page 3: First para, 6th line: Should read: ‘and substantially decreases’ not ‘decreases substantially’

Authors: Thank you for the suggestion. This has been addressed

Second para, 2nd line: State where Hlabisa is

Authors: Addressed

Third para, 1st line: delete ‘first’

Authors: Addressed

Third para, 9th line: Suggest remove phrase: ‘Furthermore, not only may…’ This is subjective. I suggest state: ‘Earlier treatment may reduce HIV….’

Authors: Thank you. Addressed
Page 4: Main Trial Objective: Remove ‘reduction’. The objective here is to evaluate the impact of ART on the incidence of HIV, not the ‘reduction in incidence’

Authors: Done

Page 5: Study Design: 7th line: the bracketed months of (six, four and four months) is confusing. Do you mean at six, ten and 14 months?

Authors: We have expanded the statement in bracket to make it clearer (page 5)

Page 6: Setting, 2nd para, 1st line: Start with ‘In 2004...’ Was the African Centre devolved to 17 clinics?

Authors: The sentence has been restructured as advised

Page 8: 1st line: What was the assumption of 0.25 based on? If this was not based on anything specifically, this should be stated.

Authors: The source of the 0.25 has been clarified and referenced (page 7)

Randomisation: How was this done? Please check CONSORT

Authors: Random number generation and the randomisation procedure were performed in MapInfo version 11.0 (page 8)

Allocation concealment is not addressed and must be.

Authors: As above

Page 11: 2nd para, 2nd line: I don’t quite understand how the patients already on ART are included in the trial. They will be encouraged to transfer their care to the trial clinics, but will they be included in the trial for measurement of outcomes? This is not clear from this paragraph. The inclusion criteria may need to be developed more on page 6 as I am not able to follow how those already on ART are to be included. There is mention on page 15 that genotypic testing will be done on those already on ART and who are identified with virological failure at enrolment. It is very confusing whether these individuals are part of the trial or not.

Authors: All HIV-infected participants irrespective of ART status will be followed up and will contribute to the secondary outcomes where appropriate. Some outcomes are only relevant to HIV-infected participants who are naïve to ART at enrolment (e.g. uptake of ART) whereas others are applicable to all participants on ART. We have made this clearer in the ‘Outcomes’ section on page 16, detailing which secondary outcomes will be measured in all participants on ART and which will be measured in only those naïve to ART at enrolment. It should be borne in mind that the primary outcome of this trial (acquisition of HIV expressed as HIV incidence) is documented amongst HIV-negative participants. This is clearly stated in the manuscript to be the number of HIV-negative participants who seroconvert during the course of the trial as measured by HIV testing of longitudinal dried blood spots. As earlier indicated, this is a cluster randomised trial with communities being the unit of randomisation. By definition, the community in which a participant lives defines the arm of the trial in which they belong to. Individuals within those communities are
eligible for inclusion in the trial if they are 16 years and above as indicated under the section on trial participants. Inclusion and exclusion criteria are now added in brackets.

*Patient follow-up, 7th line:* Again, the CRF will be done on patients already on ART. For which outcomes?

**Authors:** The outcomes are addressed under “main secondary outcomes” sub-section “Amongst HIV-infected participants”. A sentence under “patient follow-up” has been rephrased for more clarity (page 13).

*Page 14: 9th line: delete ’mainly’*

**Authors:** Done

*Page 15: There is a need to identify adverse events to conform with CONSORT*

**Authors:** Already addressed but referred to as Toxicity in the manuscript. We have added adverse events in brackets on page 13 and indicated on page 17 that grade 3 and 4 adverse events will be documented.

**Reviewer 2:** Sarah Fidler

*Major comments:*

The article is well written and the trial describes a very important research question that needs to be addressed in a clear randomised trial that is adequately powered and appropriately designed to answer this question.

*Background:*

*Para 3 comment on "earlier treatment conferring likely individual benefit"—this should be referenced and expanded as this is a key element to the debate—there remains no RCT evidence for CD4 > 350 despite guidelines changing The question of when to start— is indeed controversial BUT only for people with CD4 >350—there is clear evidence that CD4 < 350 all people living with HIV will benefit from ART*

**Authors:** This sentence has been expanded on page 3 of the manuscript and the relevant references cited.

*Objectives:*

Secondary outcomes do not explore uptake of other prevention approaches which may impact on the overall HIV incidence—MMC, condom use, STI treatments,

**Authors:** Information on MMC and condom use is gathered from the questionnaire administered to all individuals in the homestead during each HIV testing round and this has been added to the section on data collection on page 14. Information on STI treatment is collected in the clinic questionnaire as indicated in Tables 1 and 2 for HIV-infected participants only.
Study design:

*On what basis were the number of pilot sites chosen and how were the pilot sites chosen? are they representative of all potential sites?*

**Authors:** The last paragraph in the section with subheading “contamination minimisation” has been expanded to address this concern on page 9.

*What are the Stop/Go criteria for expanding the study to all sites: will results from the pilot inform the main trial design, power and intervention approach? site selection: although it is stated that an assumption of sexual mixing between communities is only 10% please expand on this data- as very important given the close proximity of the communities.*

**Authors:** It was stated on page 5 that the aim of the first phase will be to inform the decision making process in the second phase. This was further expanded on page 18 under criteria for continuation/discontinuation of the trial. The discussion on contamination (sexual mixing) has been further expanded in the section with subheading “contamination minimisation” on page 8 to address this concern. The figure of 10% was selected on the basis of earlier work in the Africa Centre (referenced in the manuscript) which showed there is a strong geographical dimension to sexual partnership.

*Are sites chosen excluding other research trials- vaccine microbicide, PrEP studies- are these excluded from the chosen communities Please state how available PEP is in this setting Please state the exact average distances between communities. Whilst it is important sexual mixing is taken into account, what proportion of individuals is assumed will travel to neighbouring health care facilities to access intervention if they wish to? how will this impact on power?*

**Authors:** There are no research trials of HIV vaccine, microbicides or PrEP taking place in the trial communities. There are South African Department of Health guidelines for the prescription of post-exposure prophylaxis (PEP) in specific cases, mostly related to occupational exposure and sexual assault, but the uptake is low. Health care practitioners will offer PEP in cases of sexual assault presenting to the clinic according to the standard treatment guidelines. In the author’s experience, no participant has presented to the trial clinic requesting PEP because they are negative and have had unprotected sexual intercourse with someone in the community whose status is unknown or HIV-positive. Generally speaking, the prevention, care and treatment interventions used in the study population are those recommended by the South African authorities (except the TasP intervention that is under investigation).

The section under cluster design describes in detail how the communities were constructed and it specifies that they are contiguous neighbourhoods and this is further buttressed by the map of the clusters-Figure 2.

*How are the community boundaries confirmed?*

**Authors:** The study procedures under “home-based procedures” on page 9 have been further expanded to address this comment.

*Study procedures:*
What is done for IHV+ individuals who do not attend a clinic visit? How will their attendance be monitored? Will the research teams link their ID with national database clinical records to determine who is on ART has supressed VL etc?

Authors: The sections under “HCT procedures and prevention services” and “Referral procedures to trial clinic” on page 11 have been expanded to address the above comments.

The 20% assumed lost to follow up- is this for research follow up or loss from clinical care?

Authors: The 20% assumed loss to follow-up refers to HIV-negative participants being followed up for HIV seroconversion with longitudinal dried blood spots. This is now clarified on page 7.

1. Will the study design adequately test the hypothesis?

Yes but only if all communities are enrolled- ie the expanded study is undertaken.

The lack of clear Stop/Go criteria is an essential component prior to publication

Authors: This is a study protocol which describes both the pilot phase and the full trial and as the reviewer pointed out, the design is adequate to test the hypothesis when fully implemented. This protocol has been extensively reviewed and has ethics clearance and the criteria for stopping or continuing will be informed by the results of the first phase as stipulated under the section for continuation/discontinuation.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The exact details of data collection- who is considered a study participant or expanded standard care is a little uncertain, -clarification of this is needed

Authors: The section on study procedures has been significantly expanded for clarity. This is a 2-arm trial and cluster of residence defines which arm a participant belongs to. The treatment procedures for both intervention and control arms are described on page 12

3. Is the planned statistical analysis appropriate?

As far as I am aware

4. Is the writing acceptable?

The quality of the writing is acceptable