Reviewer's report

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.

Version: 2  Date: 8 May 2013

Reviewer: Nandi Siegfried

Reviewer's report:

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 design will address the objective of whether treating individuals immediately with ART compared with 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.

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?
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.

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.

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.
Page 3: First para, 6th line: Should read: ‘and substantially decreases’ not ‘decreases substantially’
Second para, 2nd line: State where Hlabisa is
Third para, 1st line: delete ‘first’
Third para, 9th line: Suggest remove phrase: ‘Furthermore, not only may…’ This is subjective. I suggest state: ‘Earlier treatment may reduce HIV….’
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’
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?
Page 6: Setting, 2nd para, 1st line: Start with ‘In 2004…’ Was the African Centre devolved to 17 clinics?
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.
Randomisation: How was this done? Please check CONSORT
Allocation concealment is not addressed and must be.
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.
Patient follow-up, 7th line: Again, the CRF will be done on patients already on ART. For which outcomes?
Page 14: 9th line: delete ‘mainly’
Page 15: There is a need to identify adverse events to conform with CONSORT.