Draft: When to Start ART

Optimal time of initiation for asymptomatic, HIV-infected, treatment naive adults

BACKGROUND
Provision of combination antiretroviral treatment (ART) to people infected with human immunodeficiency virus (HIV) reduces both progression to the acquired immunodeficiency syndrome (AIDS) and the morbidity and mortality associated with advanced HIV infection. According to consensus, initiation of therapy is best based on the CD4 count, a marker of immune status, rather than viral load, a marker of virologic replication (Sterling 2001). For patients with advanced symptoms, treatment should be started regardless of CD4 count. However, the point during the course of HIV infection at which ART is initiated in asymptomatic patients remains unclear and in a 2006 BMJ review, Deeks clearly articulated optimal timing of ART initiation as a key unanswered question for people infected with HIV, clinicians and policy-makers (Deeks 2006). Guidelines issued by various agencies provide different initiation recommendations according to resource availability. This can be confusing for clinicians and policy-makers when determining the best point to initiate therapy. In 2008, the United States Panel of the International AIDS Society recommended that antiretroviral treatment of adult HIV infection not be initiated before CD4 cell count declines to less than 350/µL (Hammer 2008). In patients with 350 CD4 cells/µL or more, the decision to begin therapy should be individualized based on the presence of comorbidities, risk factors for progression to AIDS and non-AIDS defining diseases (Hammer 2008). In comparison, in resource-constrained settings, the World Health Organization recommends that ART should not be initiated at concentrations of CD4 counts above 200 cells/µL in asymptomatic patients (WHO 2006) and does not address initiation at higher concentration of CD4 cells. Optimizing the initiation of ART is clearly complex and must, therefore, be balanced between individual and broader public health needs.

Initiating early treatment has the benefit of reducing or avoiding the irreversible damage done by HIV and opportunistic infections (OIs) (Day 2002). Additionally treating patients at higher CD4 counts may reduce infectivity and so play an important role in community prevention, although this has not been proved conclusively (Granich 2009). Starting ART too early has the disadvantage of exhausting drug options (as viral resistance is more likely to occur the longer treatment progresses) and the patient’s ability to tolerate drugs (Day 2002). However, delaying ART until later risks a deteriorating immune function, development of OIs, declining quality of life and progression to AIDS and death. A recent study using validated computer simulation to weigh important harms from earlier initiation of ART (toxicity, side effects, and resistance accumulation) against important benefits (decreased HIV-related mortality) found that earlier initiation of ART is often favoured compared with current recommendations but cautioned that the findings may not be generalisable to women (Braithwaite 2008). Two recent cohort studies from the USA and Canada recommended that initiation of ART begins at levels at least over 350 cells/µL and possibly over 500 cells/µL (Kitahata 2009) after analyses found improved survival in those patients begun on ART at higher levels. To our knowledge no similar studies have been conducted in resource-poor settings.

Ideally randomised controlled trials that compare clinical, virological and immunologic outcomes in asymptomatic patients initiating ART at different CD4 levels provide the best evidence to determine at what levels initiation of treatment is optimised. This systematic review of such trials will provide a much-needed evidence base to assist clinicians, policy-makers and consumers in their decision-making.

OBJECTIVES
To assess the evidence for the optimal time to initiate ART in adults.
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METHODS

Types of studies
Randomised controlled trials.
In order to address the question of whether to revise WHO guidelines for starting ART at CD4 count < 200 cells, we also included those cohort studies which stratified according to CD4 count conducted in resource-poor settings.

Types of participants
Asymptomatic, HIV-infected, treatment-naive adults (15 years and older).
Trials of participants co-infected with hepatitis B or C will not be excluded from this review. Trials of participants who are symptomatic regardless of CD4 counts are excluded from this review.

Trials of initiation of ART in TB co-infected participants will be excluded from this review as a concurrent Cochrane review is being conducted on this topic; the one identified trial (Karim 2009) from the concurrent review and related study information is included as an Appendix in this review.

Types of interventions
Highly active ART initiated early in the disease at high CD4 counts as defined by the trial. In adults, this may be at levels of 201-350, 351-500 and >500 cells/µL. The comparison group will be when ART is initiated at CD4 counts below 200 x 10^6 cells/µL.

Types of outcome measures
Primary outcomes
1. Death (all cause)
2. Responses to ART as measured by:
   a. Clinical occurrence of new HIV-related events (death or AIDS-defining illness)
   b. Proportion of patients achieving and maintaining an undetectable viral load, as defined by the trial
   c. Time to event of new HIV-related events (death or AIDS-defining illness)
   d. Immunologic (change in mean CD4+ cell count (mean relative change (percent) or mean absolute change, compared with baseline, and standard deviation)
   e. Virologic response (proportion of patients maintaining an undetectable viral load and/or change in HIV-RNA levels (mean relative change (percent) or mean absolute change, compared with baseline, and standard deviation))
3. Proportion of patients discontinuing or switching ART due to virologic failure, as defined by the trial
4. Adherence, tolerability and retention

Secondary outcomes
1. Development of ART resistance
2. Sexual transmission of HIV in discordant couples
3. Quality of life indicators as reported in the studies

ADVERSE EVENTS
Severe adverse events are reported. If classified according to grade 1 to 4 of the Adverse Event Toxicity Scale, we report grade 3 and 4 events. Using this scale, grade 1 and 2 denote mild to moderate symptoms, grade 3 denote serious symptoms and grade 4 denote life-threatening events requiring significant clinical intervention.
SEARCH METHODS FOR IDENTIFICATION OF STUDIES

A. Electronic searches for RCTs
We developed the search strategy with the assistance of the HIV/AIDS Review Group Trials Search Co-ordinator. We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in the section on Collaborative Review Groups in The Cochrane Library. We combined the RCT strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewers’ Handbook (Higgins 08) in combination with terms specific to initiation of antiretroviral therapy. We limited the date of publication year to 1996 onwards given that ART was not used prior to this year. The search was iterative and a number of trial searches were run first as there are no database-specific terms for ‘initiation’ of treatment and so we used many free text terms. This increased the yield and hence the search sensitivity but reduced the precision. We searched the following electronic databases:

1. Journal and trial databases
MEDLINE
This search was conducted on the 4 August 2009 using the strategy outlined in Table 1. This yielded 1389 records of which we identified 42 records for full article retrieval.

EMBASE
This search was conducted on the 4 August 2009 using the strategy outlined in Table 2. This yielded 547 records of which we identified 12 records for full article retrieval.

Cochrane Central Register of Controlled Trials (CENTRAL)
This search of CENTRAL, published in Issue 3 of The Cochrane Library (2009), was conducted on 4 August 2009 using the strategy outlined in Table 3. The search yielded 424 records of which we identified 11 records for full article retrieval.

2. Conference databases
We searched NLM Gateway on 4 August using the strategy outlined in Table 4. NLM Gateway covers abstracts from a number of relevant international conferences including the International AIDS Conference, Conference on Retroviruses and Opportunistic Infections, The British HIV Association Conference and the International Congress on Drug Therapy in HIV infection. The search yielded 2666 records of which 94 records were categorised as Meeting Abstracts and eight of these were identified for full article retrieval.

The Cochrane HIV/AIDS Assistant Managing Editor also searched all the abstract records from the following major related conferences: 1st-5th IAS Pathogenesis (2001-2009); 10th-17th IAC (1994-2008); 1st-16th CROI (1994-2009); US National HIV Prevention Conference (*99, ’03, ’05); 7th-14th BHIVA (2001-2008); and 8th-9th European AIDS Society Conference (2001, 2003), using the search terms "when to start" OR ("early" AND "initia*") in any field. This retrieved 89 records from which we identified no RCTs (we attempted to retrieve full reports for 9 abstract records but only for the purposes of background literature).

We also attended the International AIDS Society conference held in Cape Town, South Africa in July 2009 and identified one relevant study presented as a late-breaker study (CIPRAHT001 2009).

3. Ongoing trials
We searched ClinicalTrials.gov (http://clinicaltrials.gov/) (70 records identified and five for download) and the Pan-African Clinical Trials Registry (www.pactr.org) for HIV-related records (7 in total) but found no relevant records for download.
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4. Researchers and relevant organizations
We were in close contact with individual researchers working in the field, and policymakers based in inter-governmental organizations including the World Health Organization (WHO).

5. Reference lists
We also checked the reference lists of all studies identified by the above methods and examined any systematic reviews, meta-analyses, or prevention guidelines we identified during the search process for references.

There was some overlap between the search yields above.

B. Electronic searches for cohort studies in resource-poor settings
Two additional cohort studies conducted in resource-poor settings were identified from the above RCT searches.

In addition to the search for the RCTs, we also conducted an additional search in PUBMED and EMBASE in which we did not limit the search strategy and excluded the RCT search string. The search of PUBMED and EMBASE databases provided a total of 3997 citations. After adjusting for duplicates 3637 records remained. OU and NS read each record and discarded 3587 studies as from the abstracts it appeared that these papers clearly did not meet the criteria. The full text of the remaining 50 citations were examined in more detail. Forty-three studies did not meet the inclusion criteria. Three met the inclusion criteria. One additional study had been identified from the RCT searches. Overall, four cohort studies were included in the systematic review.

Flow diagram of eligibility process for identification of relevant cohort studies

![Flow diagram of eligibility process for identification of relevant cohort studies]
DATA COLLECTION AND ANALYSIS

Selection of studies
NS and OU read the titles, abstracts and descriptor terms of all downloaded material from the electronic searches to identify potentially eligible reports. Full text articles were obtained for all citations identified as potentially eligible and NS and OU independently inspected these to establish the relevance of the article according to the pre-specified criteria. Where there was any uncertainty as to the eligibility of the record, we obtained the full article.

NS and UO independently applied the inclusion criteria, and any differences arising were resolved by discussions with the third reviewer, GR. Studies were reviewed for relevance based on study design, types of participants, exposures and outcome measures.

Data extraction and management
NS and UO independently extracted data into a standardised data extraction form - see The following characteristics were extracted from each included study.
- Administrative details: Trial identification number; author(s); published or unpublished; year of publication; number of studies included in paper; year in which study was conducted; details of other relevant papers cited;
- Details of the study: study design; type, duration and completeness of follow-up; country and location of study (e.g. higher-income vs. lower-income country); informed consent and ethics approval;
- Details of participants: setting, numbers, relevant baseline characteristics including CD4 count and viral load;
- Details of intervention: CD4 count at which treatment was initiated; drug combinations; additional co-interventions; and
- Details of outcomes: mortality; HIV-related morbidity; HIV-RNA viral load measurements and proposed levels for suppression, as defined by the authors; CD4+ cell counts; adverse events and toxicity.

Assessment of risk of bias in included studies
NS and OU independently examined the components of each included trial for risk of bias using a standard form. This included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the trials were assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 08). Where differences arose, these were resolved by discussions with the third reviewer, GR.

Sequence generation
- Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelopes shuffling etc
- Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number
- Unclear: insufficient information to permit judgment of the sequence generation process

Allocation concealment
- Adequate: participants and the investigators enrolling participants cannot foresee assignment, e.g. central allocation; or sequentially numbered, opaque, sealed envelopes.
- Inadequate: participants and investigators enrolling participants can foresee upcoming assignment, e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered
- Unclear: insufficient information to permit judgment of the allocation concealment or the method not described
**Blinding**
- Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.
- Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding
- Unclear: insufficient information to permit judgment of adequacy or otherwise of the blinding

**Incomplete outcome data**
- Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups
- Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data
- Unclear: insufficient reporting of attrition or exclusions

**Selective Reporting**
- Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report
- Inadequate: the primary outcome differs between the protocol and final trial report
- Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present

**Other forms of bias**
- Adequate: there is no evidence of bias from other sources
- Inadequate: there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design)
- Unclear: insufficient information to permit judgment of adequacy or otherwise of other forms of bias

**Measures of treatment effect**
Data analysis was conducted using Review Manager (RevMan) version 5.0.15 (2008). Outcome measures for dichotomous data (e.g. death, virological suppression) were calculated as a relative risk with 95% confidence intervals. We had planned to calculate continuous data (e.g. CD4+ cell counts, HIV-RNA viral loads) using the weighted mean difference and standard deviations but at time of writing we did not have access to any of this data.

**Assessment of heterogeneity**
Where trials were found to be methodologically or clinically comparable, we pooled trial results in a meta-analysis. As we anticipated the presence of statistical heterogeneity we combined data using the random effects model. We formally tested for statistical heterogeneity using the Chi-square test for statistical homogeneity with a 10% level of significance as the cut-off. The impact of any statistical heterogeneity was quantified using the I² statistic (Higgins 02). Where studies do not have combinable outcomes, we provide the data in a narrative form.

**Subgroup analysis and investigation of heterogeneity**
We anticipated statistical heterogeneity due to differences between trials conducted in resource-constrained compared with resource-rich settings, and planned to present the results according to this sub-group. However, as only two trials were identified we did not undertake this analysis. We also planned to present trials of participants co-infected with Hepatitis B or C viruses as a sub-group, but no such trials were identified.

**Sensitivity analysis**
We planned to explore the effect of trial quality on the results by excluding those trials where allocation concealment was unclear or inadequate from the meta-analysis and assessing the effect of this on the overall results.
RESULTS

RCT DATA

Description of studies
Two completed trials and two ongoing trials were identified. Full details for each are provided in the Tables of Included Studies and of Ongoing Studies.

Included studies
The CIPRAHT001 2009 trial was conducted in Haiti and aimed to directly answer the question of whether starting ART at CD4 counts between 200 and 350 cells/µL improved mortality and morbidity significantly more than commencing ART at CD4 count of 200 cells/µL or below. The trial was conducted in one centre in a resource-poor country and provides the best evidence to date to determine the optimal time of initiation of ART determined by CD4 count levels. The trial began enrollment in August 2005 and was stopped early in May 2009.

The SMART 2008 trial included 318 sites in 33 countries and enrollment commenced in January 2002 and was stopped early on 10 January 2006 by the Board. The trial compared a Viral Suppression strategy, with an experimental Drug Conservation strategy. The results for a sub-set of those participants within the larger trial who were ARV treatment-naive are included in this review. This analysis was reported as post-hoc and included a group of participants who were either ART-naive or who had received ART and ceased to take it 6 months prior to enrollment. For this review we report the results only for those ART-naive participants. The analysis of the sub-set differs slightly from that of the CIPRAHT001 2009 trial in that it compared starting ART at 350 cells/µL with starting ART at 250 cells/µL.

Excluded studies

Risk of bias in included studies
See Figure 1 and Figure 2 for a graphical representation of the risk of bias in both trials.

Allocation
Generation of the random sequence was by computer and allocation concealment was done centrally so we judged both random generation and allocation concealment to be adequate for the CIPRAHT001 2009 and not likely to introduce bias. Neither the method of generation nor the method of allocation concealment was clearly reported for the SMART 2008 trial, although blocked stratification was used and was likely to be done by computer. As the analysis reported here is for a sub-group within randomized groups, there is a possible potential for bias but this is unlikely to be due to the method of randomization.

Blinding
In both trials the deferred groups were not provided with placebo and the participants and providers were therefore not blinded. Although in the CIPRAHT001 2009 trial, the investigators and members of the protocol team were blinded to the randomisation groups, we assessed the risk for bias from blinding to be moderate due to the lack of placebo. Similarly in the SMART 2008 trial the assessors in the endpoint committee were blinded to the randomized groups and so we assessed the risk to be moderate.

Incomplete outcome data
Attrition was low and less than 10% in both trials at the time the trials were stopped. However, we rated the risk of bias due to incomplete outcome reporting as moderate in both trials as acceptable statistical survival analysis techniques were used to estimate HIV event distribution over time by accumulating for staggered enrolment and incomplete discrete follow-up.

Selective reporting
Both trial reports compare favourably with the protocols published on www.clinicaltrials.gov and so the risk of bias is likely to be low from selective reporting.
Other potential sources of bias

The CIPRAHT001 2009 trial was stopped early due to significant benefits in the early ART group. Although the reported results make use of survival analyses in an attempt to reduce the risk from bias due to early stopping, we assessed the bias to be moderate because of the early stopping. The results reported here for the SMART 2008 trial could be susceptible to publication bias as the analysis of the ART-naive was post-hoc and it is possible that investigators of other trials may not have conducted post-hoc analyses of similar nested sub-groups within their trials. We assessed the risk of bias from this as high.

Effects of Interventions

Results were not available for all the outcomes we wished to include and we only report those outcomes which were available in the trials below.

Primary outcome

We combined the mortality data for both trials comparing initiating ART at CD4 levels at 350 cells/µL (SMART 2008) or between 200 and 350 cells/µL (CIPRAHT001 2009) with deferring initiation of ART to CD4 levels of 250 cells/µL (SMART 2008) or 200 cells/µL (CIPRAHT001 2009). We found a statistically significant reduction in death when starting ART at higher CD4 counts. Risk of death was reduced by 75% and could be reduced by between 38 to 89% (RR = 0.26; 95% CI: 0.11, 0.62; p = 0.002). There was little statistical heterogeneity between the trial results (Chi² = 0.01, df = 1; p = 0.93) with the degree of heterogeneity quantified by the I² at 0%. See Analysis 1.1.

Analysis 1.1  Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early ART</th>
<th>Statdeferred ART</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRAHT001 2009</td>
<td>5 408</td>
<td>23 408</td>
<td>0.26 (0.11, 0.63)</td>
<td></td>
</tr>
<tr>
<td>SMART 2008</td>
<td>0 131</td>
<td>1 118</td>
<td>0.30 (0.01, 3.31)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>539</td>
<td>526</td>
<td>0.26 (0.11, 0.62)</td>
<td></td>
</tr>
</tbody>
</table>

Total events 6 24
Heterogeneity Tau² = 0.00, Chi² = 0.01, df = 1 (P = 0.93), I² = 0%
Test for overall effect Z = 3.06 (P = 0.002)

Secondary outcomes

Tuberculosis (TB):

We combined the data for TB for both trials although the SMART 2008 trial only contributed one incident case to the meta-analysis. Risk of TB was reduced by 50% in the groups starting ART early; this was not statistically significant with the reduction as much as 74% or an increased risk of up to 12% (RR = 0.54; 95% CI: 0.26, 1.12; p = 0.01). There was little statistical heterogeneity between the trial results (Chi² = 1.05, df = 1; p = 0.31) with the degree of heterogeneity quantified by the I² at 4%. See Analysis 1.2.

Analysis 1.2  Tuberculosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early ART</th>
<th>Statdeferred ART</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRAHT001 2009</td>
<td>18 408</td>
<td>36 408</td>
<td>0.50 (0.25, 0.97)</td>
<td></td>
</tr>
<tr>
<td>SMART 2008</td>
<td>1 131</td>
<td>0 118</td>
<td>2.70 (0.11, 65.76)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>539</td>
<td>526</td>
<td>0.54 (0.26, 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

Total events 19 36
Heterogeneity Tau² = 0.06, Chi² = 1.05, df = 1 (P = 0.31), I² = 4%
Test for overall effect Z = 1.66 (P = 0.10)

Favours experimental  Favours control
Disease progression measured by opportunistic infections:
This outcome was only reported for the SMART 2008 and only four events in total were recorded. Starting ART at enrollment (when participants had CD4 counts of 350 cells/µL) rather than deferring to starting at a CD4 count of 250 cells/µL reduced the risk of disease progression by 70%; this was not statistically significant with the reduction in risk as much as 97% or an increased risk of up to 185% (RR = 0.30; 95% CI: 0.03, 2.85; p = 0.29). See Analysis 1.3

Analysis 1.3 Disease progression measured by opportunistic disease

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early ART Events</th>
<th>Stated deferred ART Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART 2008</td>
<td>1</td>
<td>3</td>
<td>118</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>131</td>
<td>118</td>
<td>100.0%</td>
<td>0.30 [0.03, 2.85]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (p = 0.29)

Adverse effects

Results were only available for CIPRAHT001 2009. For the SMART 2008 trial, the adverse events were not categorized according to the ART-naive participants and so it was not possible to extract data specific to the sub-group included in this review.

In the CIPRAHT001 2009 there was no statistically significant difference in the number of independent Grade 3 or 4 adverse events occurring in the early and standard ART groups when we conducted an intention-to-treat analysis (i.e. we used the total number of participants randomised into each group as the denominators in both groups with both = 408) (RR = 1.72; 95% CI: 0.98, 3.03; p = 0.06). See Analysis 1.4. When analysing only those participants who actually commenced ART in the deferred group (n = 160), the authors report a statistically significant increase in the incidence of zidovudine-related anaemia in the 160 participants who started ART in the deferred group (8.1%) compared with those in the early initiation group (3.4%) (RR = 0.42; 95% CI: 0.20; 0.88; p = 0.02). See Analysis 1.5.

Analysis 1.4 Any Grade 3 or 4 adverse events ITT analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early ART Events</th>
<th>Stated deferred ART Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRAHT001 2009</td>
<td>31</td>
<td>18</td>
<td>408</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>408</td>
<td>408</td>
<td>100.0%</td>
<td>1.72 [0.98, 3.03]</td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (p = 0.06)

Analysis 1.5 Grade 3 or 4 anaemia Per Protocol analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early ART Events</th>
<th>Stated deferred ART Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRAHT001 2009</td>
<td>14</td>
<td>13</td>
<td>408</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>408</td>
<td>160</td>
<td>100.0%</td>
<td>0.42 [0.20, 0.88]</td>
</tr>
<tr>
<td>Total events</td>
<td>14</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (p = 0.02)
GRADE Assessment

Using the GRADE tool, we evaluated the evidence provided by the RCTs and rated this for each outcome identified as critical or important to determining whether or not to change the current WHO guidelines for timing of initiation of ART.

For the critical outcomes of death and TB, we rated the quality of the evidence as moderate. Although the data comes from two RCTs, the data was down-graded to moderate due to the possibility of publication bias and the fact that the data was obtained from only one high-quality RCT directly aimed at answering the question combined with data from a sub-group nested within a larger trial not directly aimed at answering the question. For the critical outcome of disease progression we rated the evidence as low given that the data was only available from the sub-group nested within the larger trial.

For the critical adverse events we rated the evidence as moderate. In this case, despite the data coming from a high-quality trial, we downgraded the quality of the evidence as it was only obtained from one RCT and could therefore be imprecise. Ideally additional trials would be needed to improve precision. The important outcomes of sexual transmission, immunological and virologic response, adherence, tolerance and retention, and HIV drug resistance were not measured in either of the trials.

See GRADE table that follows.
### Summary of findings

<table>
<thead>
<tr>
<th>Death</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early ART versus standard or deferred ART (CD4 ≤ 200 or CD4 ≤ 250 cells/µl)</td>
<td>control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>(95% CI)</td>
<td>number fewer per 1000</td>
<td>(from x fewer to y fewer)</td>
</tr>
<tr>
<td>Death</td>
<td>2 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Disease progression measured by opportunistic disease (follow-up mean 18 months; Opportunistic disease events)</td>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Any Grade 3 or 4 adverse event</td>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Sexual transmission - not measured</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunologic response - not measured</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence/tolerance/retention - not measured</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV drug resistance - not measured</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic response - not measured</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The SMART study is a post hoc analysis of a subset of a larger trial
2. As the SMART sub-set is a post hoc analysis there may be other trials which did not conduct or publish similar analyses of potential sub-sets within the original trials. This is a form of publication bias and we have therefore downgraded the results accordingly
3. This result is a post hoc subset analysis from only one trial and the evidence is therefore not directly able to answer the outcome of disease progression
4. The results are from one trial only and therefore were downgraded for imprecision.
COHORT DATA

We found four cohort studies conducted in resource-limited settings that examined the optimal threshold of CD4 cell count for starting ART (Moh 2007; Badri 2004; Wong 2007; Erhabor 2006).

These are summarized in the Table below.

Table of Included Cohorts

<table>
<thead>
<tr>
<th>Author (year) Country</th>
<th>Sample size</th>
<th>Age</th>
<th>Dates</th>
<th>ART naive</th>
<th>Intervention and CD4 monitoring</th>
<th>Comparison group</th>
<th>Analysis</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moh (2007) Cote d'Ivoire</td>
<td>792</td>
<td>Median (IQR) =34 (29-40)</td>
<td>77</td>
<td>Enrollm ent from Decemb er 2002. patients followed for 18 months after date of ART initiation</td>
<td>Yes</td>
<td>Zidovuine, lamivudine, and efavirenz OR Zidovudine, lam+indinavir/ritonavir. CD4 monitored every 3 months</td>
<td>CD4 &lt; 200cells/µL; CD4 201-350; and CD4 &gt; 350</td>
<td>Multivariable Cox proportional hazard regression</td>
</tr>
<tr>
<td>Badri (2004) South Africa</td>
<td>HAART (n=292, No-HAART (n=974)</td>
<td>Median =33</td>
<td>1992-2000</td>
<td>Yes</td>
<td>A non-nucleoside reverse transcriptase inhibitor or protease inhibitor together with 2 nucleoside analogues or 3 nucleoside analogues. CD4 monitoring every 2 to 3 months or more frequently if clinically indicated</td>
<td>HAART vs non-HAART</td>
<td>Multivariable Cox proportional hazard regression</td>
<td>In those patients on HAART, the incidence of AIDS was higher among patients with CD4 &lt;200 cells/µL (6.9 incidence per 100 person-year; 95% CI 3.1 to 13.3) than those with baseline of CD4 &gt;350 cells/µL (1.4 incidence per 100 person-year; 95% CI 0.2 to 4.9). The incidence of death was higher among patients with CD4 &lt;200 cells/µL (8.9 incidence per 100 person-year; 95% CI 4.96 to 14.5) than those with baseline of CD4 200-350 cells/µL, (0.9 incidence per 100 person-year; 95% CI 0.02 to 5.1).</td>
</tr>
<tr>
<td>Erhabor (2006) Nigeria</td>
<td>100</td>
<td>Range =18-56</td>
<td>47.0</td>
<td>Enrollme nt from February 2004 to March 2005. Assume completi on 48 weeks later in March 2005.</td>
<td>Yes</td>
<td>Stavudine, lamivudine, and nevirapine. CD4 counts monitored every 8 weeks</td>
<td>CD4 &lt; 200cells/µL; CD4 201-350; and CD4 &gt; 350</td>
<td>chi-squared analysis</td>
</tr>
<tr>
<td>Wong 2007) Chinese in Hong</td>
<td>223</td>
<td>Range =30-49</td>
<td>11.7</td>
<td>Enrollm ent from January 1997 to yes</td>
<td>Two nucleoside analogue reverse</td>
<td>CD4 cell subgrou</td>
<td>Multivariable Cox proportional hazard</td>
<td>With other factors controlled, pre-treatment CD count &lt;100 cells/µL was associated with an increased risk of progression to</td>
</tr>
</tbody>
</table>
### Kong

| Decemb er 2002. Median follow-up of 38.6 months and study ended Decemb er 2003 | Transcriptase inhibitors plus one protease inhibitor or non-nucleoside analogue. CD4 monitoring every 3 to 4 months | ps (100, 101–149, 150–199, 200–249, 250–299, 300–349, and _350_ cells/µl | Regression | New AIDS-defining illness (ADI) or death (HR=14.44; 95% CI 1.95 – 106.98) and for death alone (HR=4.90; 95% CI 1.08 – 22.22). |

Three of the four studies provide evidence in clear support of early initiation of ART (Moh 2007; Badri 2004; Wong 2007). Moh 2007 found that incidence of mortality decreased with increasing pre-ART CD4 cell count. Badri 2004 also provided evidence that a pre-ART initiation baseline CD4 cell count < 200 cells/µL was associated with increased mortality and risk of developing AIDS compared with patients with baseline CD4 cell count > 350 cells/µL. Wong 2007 examined Chinese patients in Hong Kong, and found that a baseline CD4 cell count <100 cells/µL prior to ART was associated with increased risk of progression to new AIDS-defining illness or death; and new AIDS-defining illness or non-accidental death. Contrary to other studies, Erhabor 2006 found that there is no long-term advantage in CD4+ response in initiating HAART at a pre-therapeutic CD4 count of >350 cells/µL rather than at 200 – 350 cells/µL or <200 cells/µL among 100 HIV-infected previously ART-naïve individuals in Nigeria. However, a mortality rate of 3% was observed in the study, all of the deaths occurring in those who initiated treatment at CD4 levels < 200 cells/µL.
DISCUSSION

Pooled data from one trial of 816 participants and one sub-group analysis of 248 participants provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/µL reduces mortality rates in asymptomatic, ART-naive, HIV-infected people. Evidence regarding a reduction in morbidity is less strong with incidence of severe adverse events appearing low but this data is available from only one trial and so must be viewed with caution.

Overall completeness and applicability of evidence
Only the CIPRAHT001 2009 trial directly answered the question of whether starting ART at CD4 levels above 200 cells/µL improves mortality and morbidity compared with the current WHO guideline recommendations (WHO 2006). The results from the SMART 2008 were from a post-hoc analysis of ART-naive participants nested within a larger trial which aimed to provide evidence regarding treatment interruptions rather than optimal timing of ART. For this reason the evidence from the SMART 2008 trial must be interpreted with caution. The data from the CIPRAHT001 2009 trial is compelling and as it is from a trial located in a resource-poor setting, the applicability of these results to determining a change in WHO guidelines is high. However, full results from this trial have yet to be published and must therefore be viewed as incomplete. There is no available data on follow-up beyond the median of 21 months and no available data on development of possible resistance in those initiating ART.

Ideally additional trials would strengthen the nature and quality of the above evidence. We identified two ongoing trials (START 2009; NCT00491556). Both of these trials are being conducted in high-income settings and the comparison is between initiation of ART at CD4 levels above either 350 cells/µL (NCT00491556) or 500cells/µL (START 2009) with standards of care which are above those recommended by the WHO. Although these trials will provide useful data to inform initiating ART at CD4 levels above current guidelines operational in many high-income countries, the data will not add to the evidence base for determining whether initiating ART at levels above current WHO guidelines is optimal compared with initiating at CD4 counts < 200 cells/µL. We did not identify and are not aware of any ongoing trials aiming to answer this question apart from the CIPRAHT001 2009 trial, although a number of trials aimed at timing of ART in patients co-infected with TB are underway.

We did not identify any trials which evaluated the effects of optimal initiation of ART in people co-infected with either hepatitis B or C, or both, and evidence for these populations remains limited.

Quality of the evidence
The quality of the methodological conduct for both trials was moderate to high and the risk of bias was likely to be low to moderate for both trials. However, caution must be exercised when interpreting the results from the SMART 2008 trial as this was a post-hoc analysis and as such, may be prone to the effects of publication bias. This would occur if other trials did not conduct or publish similar analyses of potential sub-sets within the original trials. For this reason, the evidence rating using the GRADE tool was rated as moderate or low throughout.

Both trials employed early stopping rules considered acceptable statistical practice (Kim 1987). Use of survival analysis which incorporates the results from all those who completed the trial and who are censored due to loss-to-follow-up or early stopping of the trial, will have reduced the potential for attrition bias in each trial. This was done in both trials, but survival data was not available for the sub-set in the SMART 2008 trial. For this reason, in our meta-analysis we present the proportions at the time of stopping the trial. It is important to note that in a systematic review of RCTs stopped early for benefit, such RCTs were found to overestimate treatment effects (Montori 2005). When trials with events fewer than the median number (n=66) were compared with those with event numbers above the median, the odds ratio for a magnitude of effect greater than the median was 28 (95% CI 11–73) (Montori 2005). Both trials included in our review yielded fewer than 66 events, and may thus overestimate the treatment effect. However, the magnitude of effect was consistent across both trials which strengthens the evidence in favour of starting ART earlier than standard WHO guidelines recommend.
Potential biases in the review process
We conducted comprehensive searches of both journal and conference databases to ensure all relevant published and unpublished trials were identified. We did not limit the searches to a specific language. Our ongoing interaction with the investigator of the CIPRAHT001 2009 trial allowed us access to preliminary and unpublished data. Given the high profile nature of the intervention and the complexity of conducting ART initiation trials, it is unlikely that our search strategy failed to detect existing current trial evidence. Potential bias in the conduct of our review was also minimised by having two independent researchers extracting data and assessing the methodological quality of each study. This detailed process allows for a thorough assessment of trial conduct and an exploration of the possible biases that may be present in each trial.

When we pooled data in the meta-analysis we combined the arms from both trials although these were slightly different as the analysis of the SMART 2008 sub-set compared starting ART at CD4 levels of 350 cells/µL with starting ART at 250 cells/µL, whereas the CIPRAHT001 2009 trial compared starting at CD4 levels of between 200 and 350 cells/µL with starting ART at 200 cells/µL. Given that both trials compared initiating ART at higher levels with deferring the start of ART we did not consider this difference to be a source of bias, but the evidence must be viewed as less direct.

Lastly, it must be noted that the identification and methodological evaluation of cohort studies remains controversial at the current time. It is not clear what the key methodological factors associated with cohort quality are and the additional data provided by the cohort studies should not be viewed as being of the same rigour as that provided by the RCTs in this review.

Agreements and disagreements with other studies or reviews
The RCT results are consistent with previous cohort studies both from high-income and low-income studies, which showed that early initiation of ART may reduce morbidity and mortality associated with HIV/AIDS (Sterne 2009; Moh 2007; Badri 2004; Wong 2007). Most recently, the When To Start Consortium (Sterne 2009) analysed data from 18 cohort studies from Europe and North America and provided evidence that deferring combination therapy to a CD4 cell count of 251-350 cells/µL was associated with higher rates of AIDS and death than starting therapy in the range 351-450 cells/µL. Sterne 2009 suggested that a CD4 cell count of 350 cells/µL should be the minimum threshold for initiation of ART, and should help to guide physicians and patients in deciding when to start treatment.

Two cost-effectiveness studies on when to start ART in resource-limited settings have been published. However, there is conflicting evidence from these two studies (Walensky 2009; Loubiere 2008). Walensky 2009 conducted a cost-effectiveness analysis using a computer simulated model of HIV disease. Published data from randomised trials and observational studies in South Africa were used to populate the model. Walensky 2009 provided evidence that if HIV-infected patients are identified and linked to care, a CD4 cell count threshold for ART initiation of CD4 350 cells/µL would reduce severe diseases substantially during the next five years compared with ART initiation at CD4 250 cells/µL. Walensky 2009 concluded that earlier initiation of ART in South Africa would likely reduce morbidity and mortality, improve long-term survival, and would be cost-effective. Another study (Loubiere 2008) from Morocco assessed the cost-effectiveness of HIV treatment alternatives based on the CD4 T-cell count at the initiation of treatment using data from 286 HIV-positive individuals. Loubiere 2008 demonstrated a statistical significant difference in mean survival time between patients with baseline CD4 cell counts < 200 cells/µL compared with those with baseline CD4 <100 cells/µL (58.8 versus 16.75 months; p<.0001). However, the incremental cost-effectiveness ratio was 100 times higher for patients who started HAART with CD4 cell count >200 cells/mm3 compared with patients who started HAART with CD4+ T- cell count <100 cells/mm3. Loubiere 2008 concluded that in the Moroccan context, HAART is more cost-effective when the CD4 cell count drops to <200 cells/mm3.

Implications for practice
Implications for research

Acknowledgements
We thank the GHESKIO-Cornell team for providing us with details of their trial and are grateful for their willingness to share these with us.

We thank the World Health Organization and CDC Global Fund of HIV/AIDS for funding.

We are grateful to Elizabeth Pienaar for conducting the searches, assisting with procurement of articles and her support. We are also thank Joy Oliver and Vicki Badenhorst for article procurement, prompt administration support and their encouragement.

NS wishes to acknowledge the assistance and patience of Eliza Humphreys in co-ordinating the review process.
## CHARACTERISTICS OF STUDIES

### Characteristics of included studies

<table>
<thead>
<tr>
<th>CIPRAHT001 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
</tbody>
</table>
| **Outcomes**    | PRIMARY OUTCOME Death - documented by one of the following: obituary, autopsy report, hospital death certificate, or contact report documenting verbal communication with the participant's healthcare provider, family member, or significant other. SECONDARY OUTCOME incidence of TB - HIV infected patients with a cough or other symptoms suggestive of tuberculosis are routinely screened at the clinic with a chest radiograph and three sputum smears for acid fast bacilli (AFB) by Ziehl-Neelsen staining and Mycobacterium tuberculosis culture on Lowenstein Jensen media. TB case definition was based upon American Thoracic Society with diagnosis requiring symptoms consistent with tuberculosis and microbiologic confirmation of disease, or symptoms, a chest }
radiograph consistent with tuberculosis, and a positive response to anti-
tuberculosis therapy.

ADVERSE EVENTS
Information not presented and outstanding at current time.

Notes
The National Institute of Allergy and Infectious Diseases (NIAID), part of
the National Institutes of Health, is the study sponsor. NIAID funded the
study through the Comprehensive International Program of Research on
AIDS (CIPRA). Other support came from The Global Fund Against AIDS,
Tuberculosis, and Malaria, Glaxo Smith Kline, Abbott and Fondation
Merieux. The trial was carried out by the Haitian Group for the Study of
Kaposi's Sarcoma and Immune Deficiency Disorders (GHESKIO) Centers
in Port-au-Prince, Haiti. The principal investigator is Jean William Pape,
M.D., the director of the GHESKIO Centers and a professor of medicine
at Weill Medical College of Cornell University in New York.

The trial was approved by the Institutional Review Board at the GHESKIO
Centres in Haiti and at Cornell University (information provided Prof Dan
Fitzgerald).

Risk of bias table

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Randomization was by a computer-generated random numbers list in blocks of eight in a 1:1 ratio (information provided by Prof Dan Fitzgerald)</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Randomization was performed by Frontier Science and Technology Research Foundation in New York (central randomization) and transmitted to the clinical site electronically (information provided by Prof Dan Fitzgerald)</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Open-label and the standard (deferred) group did not receive a placebo so primary care clinicians and participants were aware of their treatment status. Investigators and members of the protocol team were blinded to the data stratified by randomization group.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Attrition was less than 5% in both intervention and comparison groups so risk of bias due to high loss to-follow-up judged as being low.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Compares favourably with protocol on <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Stopped early but used survival analysis to overcome effects of attrition.</td>
</tr>
</tbody>
</table>

SMART 2008

Methods
The trial included 318 sites in 33 countries and enrollment commenced in
January 2002 and was stopped early on 10 January 2006 by the Board.
The trial compared a Viral Suppression (VS) strategy, with an
experimental Drug Conservation (DC) strategy. The results for a sub-set
of those participants within the larger VS-DC trial who were ARV
treatment-naive are included in this review. This analysis was reported as
post-hoc and included a group of participants who were either ART-naive
or who had received ART and ceased to take it 6 months prior to
enrollment. For this review we report the results only for those ART-naive
participants.
Routine visits occurred at 1 and 2 months, every 2 months thereafter for the first year, and every 4 months in subsequent years. Visits included clinical assessments, and samples were obtained for measurement of CD4 cell count and plasma HIV RNA level. At baseline and annually, a 12-lead electrocardiogram was obtained, and data were electronically transmitted to a central reading facility for assessment of silent myocardial infarction.

Median period of follow-up was 18 months for entire RCT and for the subset (including those participants who had received ART 6 months earlier). Follow-up is not reported specifically for the ART-naive participants only. Median follow-up for the subset is reported as 15 months.

Participants

5,472 HIV-infected participants with CD4 cell count > 350 cells/µL were randomly assigned to VS or DC.

Of these, 477 participants were either treatment-naive (n = 249) or had not received ART in the preceding 6 months (n = 228).

Inclusion criteria: HIV-infected, age ≥13 years of age, CD4 T cell count > 350 cells/µL, willing to initiate, modify, or stop antiretroviral therapy according to study guidelines.

Exclusion criteria: pregnant or breast-feeding. Additional criteria for post-hoc sub-set analysis were that participants were antiretroviral-naive or not on treatment for greater than 6 months. We report the results for only those participants who were ART-naive. Median age was 39 in the ART-naive Viral Suppression group and 40 years in the ART-naive Drug Conservation group. There were 27.5% females in the ART-naive VS group and 20.3% in the ART-naive DC group. Median log viral load at baseline was 4.3 copies/ml in the ART-naive VS group and 4.6 in the ART-naive DC group. Median CD4 count at baseline was 432 cells/ul in the ART-naive VS group and 441 cells/ul ART-naive DC group.

Interventions

Intervention: EARLY: In the Viral Suppression strategy available antiretroviral regimens were to be used in an uninterrupted manner with the goal of maximal and continuous suppression of HIV replication.

Comparison: DEFERRED: The Drug Conservation strategy entailed the episodic use of antiretroviral therapy according to CD4+ count thresholds: the use of antiretroviral therapy was deferred until the CD4+ count decreased to less than 250 cells per cubic millimeter, at which time antiretroviral therapy was to be initiated (or reinitiated) and continued until the CD4+ count increased to more than 350 cells per cubic millimeter.

The protocol also permitted as initiated (or reinitiated) if symptoms of disease from HIV infection (e.g., oral thrush) developed or the percentage of CD4+ lymphocytes (CD4+ percentage) was less than 15%. On confirmation that the CD4+ count was more than 350 cells per cubic millimeter, antiretroviral therapy was to be stopped and then resumed when the CD4+ count was less than 250 cells per cubic millimeter.

The sub-set of 477 participants were those participants who were treatment-naive or not on ART for greater than 6 months. Of these 131 were ART-naive in the Viral Suppression Group and 118 in the Drug Conservation Group. We report the results for this group.
Draft: When to Start ART

**Outcomes**

1. **Primary outcome:**
   a. Death or Opportunistic Disease

2. **Secondary outcomes:**
   a. Death from any cause
   b. Opportunistic Disease (fatal or non-fatal)
   c. Serious non-AIDS events (major cardiovascular, renal, or hepatic disease, and non-AIDS cancers, and deaths from non-OD causes)
   d. Composite outcome of b. and c.

3. **Adverse effects:**
   a. Grade 4 adverse events (not including opportunistic disease) or death from any cause. Grade 4 adverse events were defined as potentially life-threatening symptomatic events requiring medical intervention, according to the toxicity table of the Division of AIDS of the NIAID. Data on lower-grade toxic effects were not collected.

**Notes**

The study was approved by the institutional review board at each site, and written informed consent was obtained from all participants.

**Risk of bias table**

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Stratified according to clinical site with the use of permeated blocks of random sizes. Assume computer-generated</td>
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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>As for above</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Investigators and participants were aware of treatment assignments. For primary outcome, death or Opportunistic Disease, an end-point review committee reviewed the events classification unaware of treatment assignments.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Eleven were lost to follow-up of subset of 477 and median follow-up was 15 months.</td>
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<tr>
<td>Free of selective reporting?</td>
<td>Unclear</td>
<td>Compares favourably with protocol on <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> but outcomes not clearly reported in the online protocol (possibly due to trial registration on the registry prior to World Health Organization mandatory 20 item minimum dataset criteria for prospective trial registration). We will need to contact investigators to confirm reported outcomes conform to those in protocol.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Stopped early but acceptable statistical stopping rules applied to reduce effects of attrition bias. An O’Brien-Fleming boundary and the Lan-DeMets alpha spending function was used to determine whether to terminate the trial early. The results reported here are not free of bias as the analysis of the ART-naive was post-hoc and it is possible that other studies may not have conducted similar post-hoc analysis so there is a threat of publication bias.</td>
</tr>
</tbody>
</table>

**Characteristics of excluded studies**

**Erhabor 2006**

**Reason for exclusion**

Although the text of the article refers to randomizing patients, email communication with the first author confirmed that this is a stratified
**Characteristics of ongoing studies**

<table>
<thead>
<tr>
<th>NCT00491556</th>
</tr>
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<tbody>
<tr>
<td><strong>Study name</strong></td>
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</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
</tbody>
</table>
- Impact of early HAART initiation on thymic output
- Determine the emergence of drug resistance in subjects who fail therapy de-intensification
- Evaluate the safety of initiating ART prior to significant CD4+ T cell loss with respect to emergence of drug associated toxicity and drug resistance
- Monitor prevalence of genotypic drug resistance within an ARV naïve or minimally exposed adolescent and young adult population; evaluate the associations of subject demographic and clinical variables with presence of genotypic mutation

**Starting date**
October 2007

**Contact information**
University of Minnesota (James D. Neaton, Ph.D/Principal Investigator)

**Notes**
NCT00867048
### Table 1: Search strategy for PUBMED

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<th>Search</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>#3</td>
<td>Search Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw])) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw]))</td>
<td>99790</td>
</tr>
<tr>
<td>#4</td>
<td>Search &quot;THERAPY INITIATION&quot; OR &quot;TREATMENT INITIATION&quot; OR &quot;DRUG THERAPY INITIATION&quot; OR &quot;WHEN TO START&quot; OR &quot;EARLY INITIATION&quot; OR DRUG ADMINISTRATION SCHEDULE[MeSH Terms] OR &quot;DRUG ADMINISTRATION SCHEDULE&quot;</td>
<td>71826</td>
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<tr>
<td>#5</td>
<td>Search #1 AND #2 AND #3 AND #4 Limits: Publication Date from 1996 to 2009</td>
<td>1389</td>
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</table>
Draft: When to Start ART

### Table 2: Search strategy for EMBASE

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<tbody>
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<td>random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross*:ti AND cross*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'single-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/exp OR allocat*:ti OR allocat*:ab AND [1990-2009]/py</td>
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<td>#3</td>
<td>'drug administration schedule'/exp OR 'when to start' OR 'drug therapy initiation' OR 'treatment initiation' OR 'therapy initiation' AND [1990-2009]/py</td>
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<td>'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus'/exp OR 'b cell lymphoma'/exp OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab AND [1990-2009]/py</td>
<td>275,043</td>
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### Table 3: Search strategy for CENTRAL

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<thead>
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<th>ID</th>
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<tbody>
<tr>
<td>#1</td>
<td>(HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (VIRAL SEXUALLY TRANSMITTED DISEASES), from 1996 to 2009</td>
<td>6956</td>
</tr>
<tr>
<td>#2</td>
<td>&quot;THERAPY INITIATION&quot; OR &quot;TREATMENT INITIATION&quot; OR &quot;DRUG THERAPY INITIATION&quot; OR &quot;WHEN TO START&quot; OR &quot;EARLY INITIATION&quot; OR DRUG ADMINISTRATION SCHEDULE&quot;, from 1996 to 2009</td>
<td>14455</td>
</tr>
<tr>
<td>#3</td>
<td>&quot;Highly Active Antiretroviral Therapy&quot; OR &quot;Anti-Retroviral Agents&quot; OR ((anti) AND (hiv)) OR antiretroviral* OR ((anti) AND (retroviral*)) OR HAART OR ((anti) AND (acquired immunodeficiency)) OR (anti AND (acquired immunodeficiency)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immune-deficiency)) OR ((anti) AND (acquired immun*) AND (deficiency)), from 1996 to 2009</td>
<td>3092</td>
</tr>
<tr>
<td>#4</td>
<td>(#1 AND #2 AND #3)</td>
<td>424</td>
</tr>
</tbody>
</table>

### Table 4: Search strategy for NLM Gateway

<table>
<thead>
<tr>
<th>Search Number</th>
<th>Search</th>
<th>Items Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>#10</td>
<td>Search: #8 AND #9</td>
<td>2666*</td>
</tr>
<tr>
<td></td>
<td>Search: Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw]) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR (anti AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immune-deficiency[tw])) OR ((anti) AND (acquired immun*) AND (deficiency[tw]))</td>
<td>123249</td>
</tr>
<tr>
<td>#9</td>
<td>Search: #1 AND #7</td>
<td>3599</td>
</tr>
<tr>
<td></td>
<td>Search: #2 OR #3 OR #4 OR #5 OR #6</td>
<td>86724</td>
</tr>
<tr>
<td>#8</td>
<td>Search: DRUG ADMINISTRATION SCHEDULE[MeSH] OR &quot;DRUG ADMINISTRATION SCHEDULE&quot;</td>
<td>70915</td>
</tr>
<tr>
<td>#7</td>
<td>Search: &quot;WHEN TO START&quot;</td>
<td>12948</td>
</tr>
<tr>
<td>#6</td>
<td>Search: &quot;THERAPY INITIATION&quot;</td>
<td>126</td>
</tr>
<tr>
<td>#5</td>
<td>Search: &quot;TREATMENT INITIATION&quot;</td>
<td>2581</td>
</tr>
<tr>
<td>#4</td>
<td>Search: &quot;DRUG THERAPY INITIATION&quot;</td>
<td>1710</td>
</tr>
<tr>
<td>#3</td>
<td>Search: &quot;THERAPY INITIATION&quot;</td>
<td>352167</td>
</tr>
</tbody>
</table>

* Of the 2666 records, 94 were identified as Meeting Abstracts and these were the records searched.
Draft: When to Start ART

REFERENCES TO STUDIES

Included studies
CIPRAHT001 2009
Unpublished data only

SMART 2008


* The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. The Journal of Infectious Diseases 2008;197(15 April):1133-44.

Excluded studies
Erhabor 2006

Studies awaiting classification

Ongoing studies
NCT00491556
START 2009

Other references

Additional references
Badri 2004

Braithwaite 2008

Day 2002

Deeks 2006
Draft: When to Start ART

Erhabor 2006

Granich 2009

Hammer 2008

Higgins 02

Higgins 08

Kim 1987
Kim K and DeMets DL. Design and analysis of group sequential tests based on the type 1 error spending rate function. Biometrika 1987;74:149-54.

Kitahata 2009

Loubiere 2008

Moh 2007

Montori 2005
Montori VM, Devereaux PJ and Adhikari NK et al.. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-09..

Sabin 2009

Sterling 2001
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**Sterne 2009**

**Walensky 2009**

**WHO 2006**

**Wong 2007**

**Classification pending references**

**Data and analyses**
1 Early ART versus standard or deferred ART (CD4 ≤ 200 or CD4 ≤ 250 cells/µl)

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Death</td>
<td>2</td>
<td>1065</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.26 [0.11, 0.62]</td>
</tr>
<tr>
<td>1.2 Tuberculosis</td>
<td>2</td>
<td>1065</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.54 [0.26, 1.12]</td>
</tr>
<tr>
<td>1.3 Disease progression measured by opportunistic disease</td>
<td>1</td>
<td>249</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.30 [0.03, 2.85]</td>
</tr>
<tr>
<td>1.4 Any Grade 3 or 4 adverse events ITT analysis</td>
<td>1</td>
<td>816</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.72 [0.98, 3.03]</td>
</tr>
<tr>
<td>1.5 Grade 3 or 4 anaemia Per Protocol analysis</td>
<td>1</td>
<td>568</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.42 [0.20, 0.88]</td>
</tr>
</tbody>
</table>
Methodological quality summary: review authors’ judgments about each methodological quality item for each included study.

Sources of support

Internal sources
- South African Cochrane Centre, South Africa
- Cochrane HIV/AIDS Review Group, USA

External sources
- World Health Organization, Switzerland
APPENDIX: TB AND HIV COINFECTED POPULATIONS

Included studies (one unpublished abstract retrieved manually)
SAPiT 2009
Unpublished data only

Figure. Search results, TB and HIV When to Start systematic review

Timing of ART in patients being treated for TB

| Comprehensive database search results | n = 1024 |
| Two authors screened all abstracts | |
| References excluded as irrelevant or not addressing the research question (e.g. animal studies, news reports etc.) | n = 1011 |
| Full text articles obtained for closer review | n = 13 |
| Studies selected for inclusion | n = 0 |

SAPiT 2009

Methods
A triple-arm, randomized trial conducted in Durban, South Africa. Enrollement began on 28 June 2005 and the last patient was enrolled on 11 July 2008. The trial was stopped early in September 2008 for safety issues.

Participants
645 patients were enrolled.
Inclusion criteria:
- Male or Female
- HIV positive
- 18 years or older
- Smear-positive pulmonary TB

Interventions
For each arm the ARV treatment comprised once-a-day didanosine, lamivudine and Efavirenz combination.
- Integrated Arm 1: ARV started within 4 weeks of TB treatment
- Integrated Arm 2: ARV started within 4 weeks after starting TB treatment
- Sequential Arm 3: ARV started in first 4 weeks after completion of TB treatment [6 to 8 months]

Outcomes
PRIMARY:
Draft: When to Start ART

All-cause mortality at 18 months after initiation of ART

SECONDARY:

ADVERSE EFFECTS:

Notes

The study is not complete but the Sequential arm was stopped in September 2008 when the mortality rate was noted to be two and a half that of the Integrated arm

Risk of bias table

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Computer-generated random blocks of 3 and 6; no stratification</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Consecutively numbered, opaque sealed envelopes with tear-off strips so once open, cannot be closed</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Participants and providers were not blinded. Assessors of death were made by independent verification by death certificate (1); hospital report (28); and carer or relative report (23)</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear</td>
<td>Approximately 25% loss to follow-up; survival data used to minimise effects of attrition. The interim data analysis reported here comprises about 60% of the follow-up time that would be expected to be accrued at the end of the trial.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Compares favourably with study protocol</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>The trial was stopped early. The protocol stated to to use O’ Brien Fleming Early Stopping Statistical Rule but the trial was stopped on the basis of safety by Safety Monitoring Board using a less conservative p value of 0.05 due death rate was two and a half times higher in the sequential arm.</td>
</tr>
</tbody>
</table>

Risk of Bias: SAPiT trial
## GRADE Table

### Question:
Integrated versus sequential initiation of ART for HIV in people co-infected with TB

### Settings:

### Bibliography:
Optimal initiation of ART for HIV in people co-infected with TB. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

### Summary of findings

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients Integrated versus sequential initiation of ART</th>
<th>Summary of findings</th>
<th>Effect Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (Hospital reports, death certificates, and verbal report from carers)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>25429 (5.8%)</td>
</tr>
<tr>
<td><strong>TB treatment successful</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>258631 (77.9%)</td>
</tr>
<tr>
<td><strong>Incidence of IRIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>52/429 (12.1%)</td>
</tr>
<tr>
<td><strong>ART adherence &gt; 95% pill count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>311/344 (90.4%)</td>
</tr>
<tr>
<td><strong>Viral load &lt; 1000 at 12 mths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>201/221 (91%)</td>
</tr>
</tbody>
</table>

The results are from one trial only which was stopped early. The results must be interpreted with caution.

The trial presentation has a hazard ratio = 0.44 (95% CI: 0.25; 0.79) p = 0.003 which is very similar to the RR obtained here.