Early Versus Delayed Initiation of Antiretroviral Therapy (ART) in Patients with HIV Infection and Concurrent Cryptococcal Meningitis: A Systematic Review of Randomized Controlled Trials

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BACKGROUND

- Currently, initiation of HIV therapy is based on CD4 cell count.
- However, the point during the course of HIV infection at which ART is best initiated in patients with concomitant Cryptococcal meningitis (CM) remains unclear.
- Guidelines issued by various agencies provide different initiation recommendations according to resource availability.

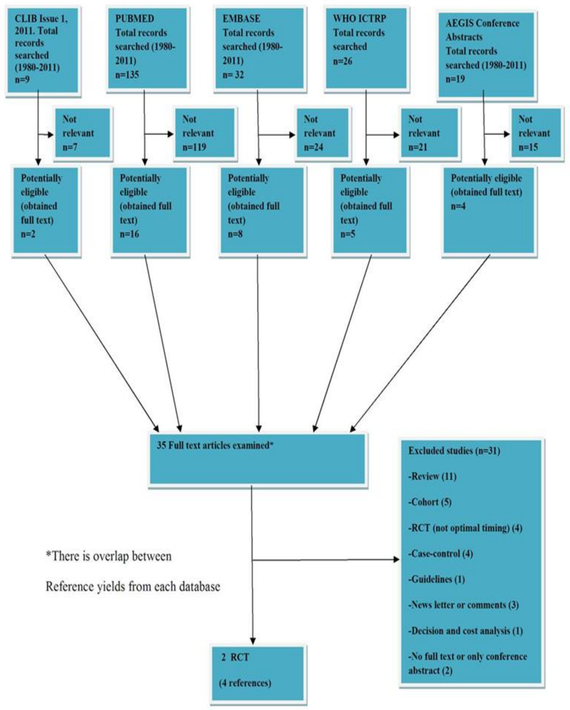
PURPOSE OF STUDY

- To compare the efficacy and benefits of early versus delayed initiation of ART in HIV patients with concurrent cryptococcal meningitis.

METHODS

- Search of peer-reviewed literature from 1980 to 2011 on PUBMED, EMBASE, and WHO International Clinical Trials Registry Platform, AEGIS database for conference abstracts, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews.
- Reference list of identified studies were manually reviewed for additional studies.
- Studies considered were peer-reviewed RCTs or observational studies that evaluated initiation of ART in HIV patients with concurrent cryptococcal meningitis.
- Our primary outcomes were: Mortality and AIDS progression
- Two review authors independently assessed study eligibility, extracted data, and graded methodological quality and bias.
- Data abstracted included: study design; RRs with 95% CIs, year of publication and first author's last name .
- Fixed-effects or Random-effects(if heterogeneity+) meta-analysis
- Publication bias evaluated before analysis
- Analysis done using REVMAN version 5.1

PRISMA FLOW DIAGRAM FOR RCTs



RESULTS

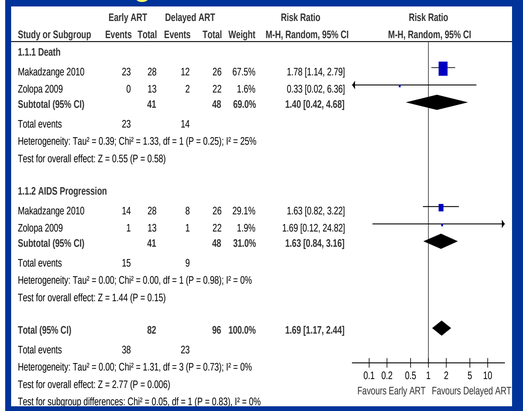
Search Results

- A total of 35 full text articles were identified and supplemented by a bibliographic search.
- Two eligible randomized controlled trials were included (N = 691).
- Clinical data for both trials comparing early initiation ART (less than four weeks after starting antifungal treatment) versus delayed initiation of ART (four weeks or more after starting antifungal treatment).

Meta-analysis of All Studies (n=2)

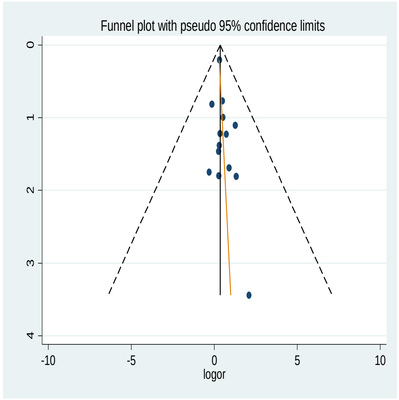
- 40% increase in death (RR=1.40, 95% CI [0.42, 4.68]) in the group with early initiation of ART.
- 63% increased risk of non-fatal AIDS progression (RR=1.63, 95% CI [0.84-3.16]) for early initiation of ART.
- There was no evidence of publication bias.

Figure 1: Forrest Plot



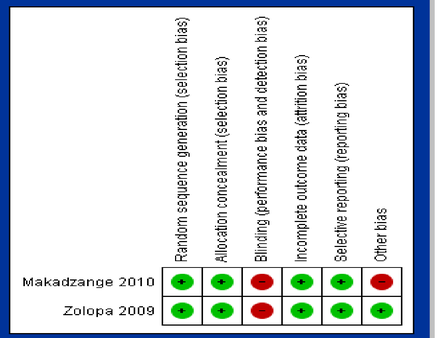
This output is from a Random effects model

Egger's funnel plot with pseudo 95% CIs for all studies combined

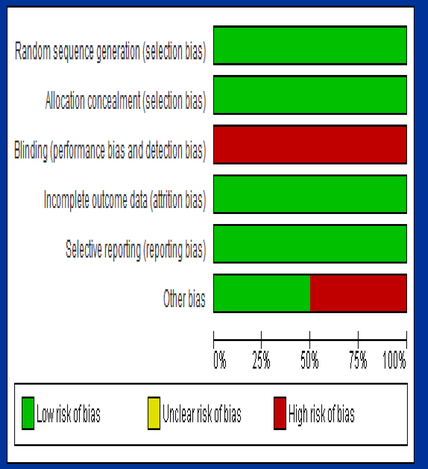


Plot suggests that there was very little relationship between study size and results being published.

Risk of bias summary



Risk of bias graph



CONCLUSIONS

- This systematic review shows that there is insufficient evidence in support of either early or late initiation of ART.
- As such large studies with appropriate comparison groups, and adequate follow-up are warranted to provide the evidence base for effective decision making
- Practitioners and policy-makers may consider delaying the initiating ART for HIV patients who present to health services and are diagnosed with cryptococcal meningitis.
- However, evidence for initiating ART in this group of patients remains unclear.
- For the moment we will recommend that the decision on what time to initiate treatment be based on informed patient preference.