Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2 to 5 years old

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ABSTRACT

Background

The use of combination antiretroviral therapy (cART) comprising three antiretroviral medications from at least two classes of drugs is the current standard treatment for HIV infection in adults and children. Current World Health Organization (WHO) guidelines for antiretroviral therapy recommend early treatment regardless of immunologic thresholds or the clinical condition for all infants (less than one year of age) and children under the age of two years. For children aged two to five years current WHO guidelines recommend (based on low quality evidence) that clinical and immunological thresholds be used to identify those who need to start cART (advanced clinical stage or CD4 counts ≤ 750 cells/mm3 or per cent CD4 ≤ 25%). This Cochrane review will inform the current available evidence regarding the optimal time for treatment initiation in children aged two to five years with the goal of informing the revision of WHO 2013 recommendations on when to initiate cART in children.

Objectives

To assess the evidence for the optimal time to initiate cART in treatment-naive, HIV-infected children aged 2 to 5 years.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the AEGIS conference database, specific relevant conferences, www.clinicaltrials.gov, the World Health Organization International Clinical Trials Registry platform and reference lists of articles. The date of the most recent search was 30 September 2012.
Selection criteria

Randomised controlled trials (RCTs) that compared immediate with deferred initiation of cART, and prospective cohort studies which followed children from enrolment to start of cART and on cART.

Data collection and analysis

Two review authors considered studies for inclusion in the review, assessed the risk of bias, and extracted data on the primary outcome of death from all causes and several secondary outcomes, including incidence of CDC category C and B clinical events and per cent CD4 cells (CD4%) at study end. For RCTs we calculated relative risks (RR) or mean differences with 95% confidence intervals (95% CI). For cohort data, we extracted relative risks with 95% CI from adjusted analyses. We combined results from RCTs using a random effects model and examined statistical heterogeneity.

Main results

Two RCTs in HIV-positive children aged 1 to 12 years were identified. One trial was the pilot study for the larger second trial and both compared initiation of cART regardless of clinical-immunological conditions with deferred initiation until per cent CD4 dropped to <15%. The two trials were conducted in Thailand, and Thailand and Cambodia, respectively. Unpublished analyses of the 122 children enrolled at ages 2 to 5 years were included in this review. There was one death in the immediate cART group and no deaths in the deferred group (RR 2.9; 95% CI 0.12 to 68.9). In the subgroup analysis of children aged 24 to 59 months, there was one CDC C event in each group (RR 0.96; 95% CI 0.06 to 14.87) and 8 and 11 CDC B events in the immediate and deferred groups respectively (RR 0.95; 95% CI 0.24 to 3.73). In this subgroup, the mean difference in CD4 per cent at study end was 5.9% (95% CI 2.7 to 9.1). One cohort study from South Africa, which compared the effect of delaying cART for up to 60 days in 573 HIV-positive children starting tuberculosis treatment (median age 3.5 years), was also included. The adjusted hazard ratios for the effect on mortality of delaying ART for more than 60 days was 1.32 (95% CI 0.55 to 3.16).

Authors' conclusions

This systematic review shows that there is insufficient evidence from clinical trials in support of either early or CD4-guided initiation of ART in HIV-infected children aged 2 to 5 years. Programmatic issues such as the retention in care of children in ART programmes in resource-limited settings will need to be considered when formulating WHO 2013 recommendations.