When to start ART in children aged 2-5 years?

A collaborative causal analysis of cohort studies from Southern Africa

The iDeA Southern Africa Paediatric Collaboration

Background

There is limited evidence from randomized controlled trials and causal modeling studies regarding the optimal timing of antiretroviral therapy (ART) initiation in children aged two to five years [1,2]. While earlier ART initiation may reduce mortality and morbidity, it could also increase the risk of toxicity and earlier development of drug resistance.

Objectives

To use causal modeling to determine the difference in mortality when starting ART in children aged 2-5 years

• immediately (irrespective of CD4 criteria) compared to

• deferring to lower CD4 thresholds (for example, the WHO recommended threshold of 750 cells/mm$^3$ or 25%).

Methods

Cohort description: This study is based on observational data from HIV treatment cohorts in Southern Africa that take part in the iDeA-SA collaboration. Eight cohorts from South Africa, Malawi, and Zimbabwe were included.

Selection of children: All children who were at least 24 months of age at their first clinic visit and not older than 60 months were included. Children who were not ART-naive at their time of entry into HIV care programs or had no follow-up data were excluded from the analysis.

Variables included: The outcome was mortality, the intervention variable was ART. Baseline characteristics included CD4 count, CD4%, weight-for-age z-score (WAZ) and height-for-age z-score (HAZ) as well as the child’s sex and age at first visit. Follow-up data consisted of CD4 count, CD4%, WAZ scores.

Missing data: Missing follow-up data of CD4 count, CD4% and WAZ was carried forward for a maximum of 9 months. For the remaining missing follow-up data, as well as the missing baseline data of CD4 count, CD4%, WAZ, and HAZ, longitudinal multiple imputation was used.

Causal analysis: Since a child’s CD4 and WHO stage information influence both mortality and ART initiation, they are time-dependent confounders. Mortality for different CD4 thresholds was thus estimated using causal modeling, i.e. g-computation [3] – adjusting for measured time-dependent confounding of CD4 count, CD4%, and WAZ (as a proxy for WHO stage).

Results

The results of the g-computation analysis indicated that there was a trend to higher mortality associated with initiating ART at lower CD4 values or not initiating ART at all (Figure 1). This trend becomes clearer at longer durations, especially from 2 years after the first visit onwards.

There was no mortality difference between initiating ART irrespective of CD4 values (2.1%, 95% CI 1.3%-3.5%) after 3 years of follow-up) and ART initiation according to the WHO 2010 guidelines threshold of 750 cells/mm$^3$ or 25% (2.2%, 95% CI 1.4%-3.5%). Figure 2 illustrates this in detail, highlighting the almost identical estimated cumulative mortality (and 95% confidence intervals) for both thresholds during the entire follow-up period.

Discussion Points & Implications

• Loss to follow-up: A sensitivity analysis confirmed that mortality might indeed be 2-3% higher and LIFTFU appreciable.

• Unmeasured confounding: For example, WHO stage data was not routinely available but was approximated by WAZ.

• Our data comprises a cohort of survivors who haven’t died and reached health care only at the age of 2.

• Long-term outcomes and morbidity were not explored; thus resistance and toxicity issues as well as immunological recovery were not addressed.

• Programmatically it may be simpler to have a single treatment initiation approach for all children >5 years of age that does not require regular pre-ART follow-up and CD4 measurement.

Conclusions

Our results indicate higher mortality associated with initiating ART at lower CD4 values (or not at all), but no mortality difference for up to 3 years between ART initiation irrespective of CD4 value and ART initiation at a threshold of 750 cells/mm$^3$ or 25%. Overall clinical and programmatic implications of earlier ART initiation remain to be explored.

References


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