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Implications of causal modelling studies on the question of when to start antiretroviral treatment in young children

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Recent changes in the World Health Organization (WHO) guidelines on the use of antiretroviral drugs for treating and preventing HIV infection have revived discussions on the optimal timing of treatment initiation in young children (1-4). While in the past antiretroviral treatment (ART) for children aged 2-5 years was started only when the CD4 count or CD4% fell below a critical threshold, or a clinically severe event occurred, the new 2013 guidelines recommend immediate treatment initiation regardless of the child's immune status.

Immediate ART of all HIV positive children is expected to reduce mortality and morbidity, simplify paediatric treatment, and improve access to care. However, there may be long term risks related to the development of drug resistance and toxicity. Therefore, delaying treatment for healthy children, who face lifelong ART, could help to preserve multiple treatment options for the future and reduce the burden of possible side effects.

Scientific evidence which can guide policies is sparse, but exists. In 2008, the CHER trial showed a 76% (95% CI: 49%-89%) reduction in mortality in infants, enrolled at age 6-12 weeks, for immediate ART initiation versus deferring ART when the CD4 percentage was lower than 25% (5). However, from a treatment guidelines point of view, new-born infants are considerably different from older children: children who present at health care facilities only at ages 2 or older comprise a group of survivors who lived despite lack of ART and likely have a relatively good immune system. How can this group be handled best by the health care system? The PREDICT trial, conducted on Asian children of age 1-12 years, could not show any difference in mortality and other outcomes between immediate ART initiation and deferring ART until either the CD4% was below 15% or any CDC category C event occurred (6, 7). This study included, however, only 96 children in the 2-5 year old age group for which WHO changed their guidelines; moreover, according to the authors, their study was "underpowered".

Conducting trials on the optimal timing of ART initiation is lengthy, costly, and ethically difficult. Instead, routinely captured observational data can be used to answer this question if the statistical analysis makes use of methods which allow a causal interpretation. When speaking of a "causal" interpretation, this means that, for example, differences in outcomes related to different treatment strategies represent the (hypothetical) difference that would have been observed if all children had received treatment strategy A compared to if all children had received treatment strategy B (though this is of course practically never possible). One of these methods which allows causal interpretations is called "g-computation". G-computation first estimates the associations in the data by means of regression models, at different follow-up times: after first presenting at health care facilities how does mortality relate to immune status, demographics and ART? What are these associations after one year? How does immune status relate to past immune status and demographics? Given these models (which are many!), and the raw baseline data, g-computation predicts/simulates how the data would develop over time if we were to apply a certain treatment rule to all children, i.e. what would the regression models predict if no one receives ART and therefore in the regression models ART is always set to equal zero. Based on the simulated data, which is different for different treatment strategies, the success of each strategy can be evaluated (see Box 1 in (8) for a detailed summary on how to use g-computation in this setting). One assumption that needs to be fulfilled to make the method work is that we have sufficient data on the variables which determine treatment assignment, that is CD4 count, CD4 percent, and WHO stage (which summarizes clinically severe events).

Causal modelling research on optimal timing of ART initiation in young children

Using g-computation, a recent causal modelling study (8), including data from nearly 3000 2-5 year old children from South Africa, Zimbabwe, and Malawi, could not show any difference in 3 year mortality when comparing the two strategies of (i) giving ART immediately, irrespective of CD4 criteria (WHO 2013 CD4 criterion), and (ii) giving ART as soon as either the CD4 count fell below 750 cells/mm^3 or the CD4% fell below 25% (WHO 2010 CD4 criterion). This is visualized in Figure 1 which shows the estimated cumulative mortality for both strategies (for all children) from time of presenting at the health care facility (follow-up time is zero) until three years of *follow-up.*

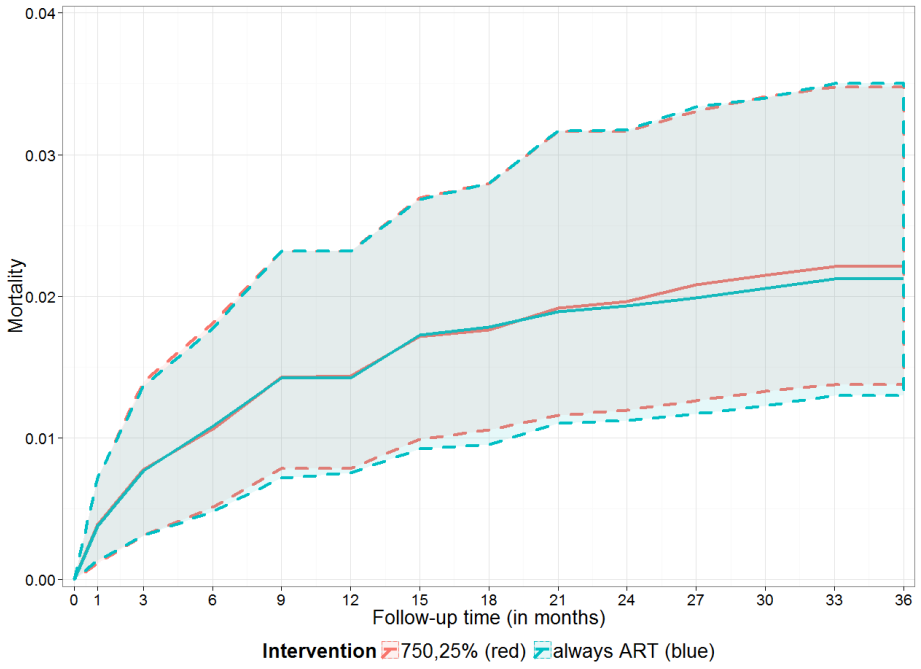

Figure 1: Estimated cumulative mortality for immediate versus deferred ART. Estimated cumulative mortality (including 95% bootstrap CI, dashed lines) over 3 years if ART was given irrespective of CD4 count and CD4% (blue line, ''always ART'') and if ART was given if the CD4 count was below 750 cells/mm3 or the CD4% was below 25% (red line, ''750,25%''). Source: (8)

After 3 years the estimated mortality is very similar when comparing immediate versus deferred ART initiation. Of note, the estimated difference between the strategies after 3 years is only 0.085% (95% CI: -0.72%; 0.78%).

While the above results showed no difference between always giving ART and deferring until CD4 dropped below 750/25%, the study also compared several other initiation criteria. It showed that the later in the course of disease ART is initiated (with the extreme being never given at all), the higher the estimated mortality: for example, after 3 years of follow-up estimated mortality was 3.4% if no ART was given at all compared to 2.1% if ART was given immediately. Using additional data from national vital registration systems to take into account that some of the children lost to follow-up in the study may have died, this difference becomes even larger with mortality being estimated to be 7.8% and 6% respectively.

Preliminary unpublished results further suggest that the above findings may be generalized to populations other than those from Southern Africa and to outcomes other than mortality.

How can these results of causal modelling be interpreted?

What is important to realize is that in reality children received ART at very different stages for different reasons: some immediately simply because they presented in a very sick condition, some late because they presented in a healthy condition, some late

because they were lost to care for a while, some just a bit late because their immune system got worse between two consecutive clinic visits, etc. With causal modelling we do not compare the group of children who start immediately with those who start only below a certain CD4 threshold; instead we estimate what would have happened hypothetically to all children if they all had received treatment based on the same treatment strategy; we give in our simulation all children all possible interventions (which we cannot do in real life!) and compare the outcome of these interventions for all children.

It follows therefore that we can interpret the quantities as counterfactuals: The estimated 6% mortality is the mortality one would observe if all children, presenting at a health care facility for the first time between 2 and 5 years of age, did actually receive immediate ART. The 1.8% difference in mortality therefore refers to a population difference that can never be directly observed; but is interesting from a policy perspective. If the government had never provided ART to its population the mortality would be 1.8% higher after 3 years compared to when the government had given immediate ART to all children aged 2-5.

These observations point towards the usefulness of causal modelling when benefits of different policy interventions need to be compared: without expensive trials and major ethical problems (one cannot withhold treatment from sick children) one can evaluate the implications, and possibly even costs, of several competing interventions. However, there remain a couple of limitations with respect to the conclusions that can be drawn from such studies, some of which will be discussed below.

What do these results not imply and what other considerations are relevant?

Changing existing structures in a health care system is a difficult and complex task. The differences estimated by causal modelling do not necessarily reflect all factors which affect population outcomes; for example, treating more children implies the need for more resources such as trained health care workers and doctors. If they are not available it may be possible that expanding treatment eligibility to all children happens at the cost of early infant diagnosis or treatment of the sickest children. If this is the case, immediate ART could potentially lead to worse outcomes than those estimated by the causal modelling.

This leads to the general question what outcomes are of interest: while there may be no mortality differences when comparing immediate versus deferred ART initiation there could be differences with respect to immune recovery, growth or life quality. It is not entirely clear whether enough data exists to explore the latter outcome, but forthcoming causal modelling analyses are expected to target the implications of early treatment initiation on growth and immune recovery. Similar to the PREDICT trial, one could speculate that either small or no differences with respect to these outcomes may be found (when comparing the WHO 2010 and 2013 criteria). From a broader perspective one could nevertheless ask whether on the basis of various patient outcomes, health care facility resources, training, and possible future policy changes the current state of initiating ART is the best; it may turn out that these issues cannot be answered completely by modelling studies (and trials) and qualitative and programmatic research needs to be taken into account.

These considerations are not trivial. Balancing the potential programmatic benefits from early treatment initiation (bringing children into care and keeping them in care) with the possible disadvantages (resources which may be needed somewhere else) can only be partially targeted by quantitative analyses, e.g. such as evaluating an overall measure for the quality of care. The rest remains an informed trade-off between multiple sources of information – which should not be guided by speculation and misinterpretation. For example, it is often claimed that early treatment initiation keeps children in care; but children remaining in care are also those who are more likely to get started on therapy and it is possible that studies reporting these claims face selection bias due to the latter point. If children on ART are lost, the consequences can be severe too: poor adherence may lead to resistance which in turn may lead to less treatment options during adulthood.

This is exactly why long term outcomes play an important role in the evaluation of treatment options. However, in the above causal modelling study, we evaluated mortality only up to 3 years of follow-up. It is possible that effects derived from the data reverse in the long run exactly because of long term issues such as resistance due to non-adherence. Of course, it may also turn out that immediate ART is even more beneficial from a long term perspective (because, for instance, the immune function is restored sooner). It will be important to update causal modelling analyses on the optimal timing of treatment initiation once more long term data is available, with respect to both mortality and morbidity of children.

Another point to reflect on is that treatment initiation is guided not only by CD4 count and CD4%, but also by WHO stage. This has not been taken into account in detail by current causal modelling studies, mostly because of limited data availability. While weight for age z-scores have been successfully used to approximate WHO stage information, future studies could incorporate these z-scores for treatment allocation, not only CD4 count and CD4 percent. To better resemble the exact WHO guideline criteria for delaying ART, a z-score smaller -2 could imply treatment initiation, in addition to checking whether CD4 count <750 cells/mm^3 or CD4%<25%. This would also help to retrospectively evaluate historic WHO guidelines and the implications they had; this has indeed never been done and would help not only to guide the timing of treatment initiation of young children, but also older children and adolescents which are an increasing population living lifelong with HIV.

In conclusion, causal modelling studies suggest that for children presenting between age 2 and 5 there is no increased risk in mortality for up to three years of follow-up when deferring therapy until CD4 drops below 750 cells/mm^3 or 25% compared to when starting ART immediately as recommended by the WHO since 2013. However, given the currently unexplored long term consequences of ART on both mortality and morbidity, as well as the additional resources needed for consequent implementation of policy changes, the optimal timing of initiating ART remains an open question to be explored in more detail in future.

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