HIV Treatment

Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe

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Abstract

Background: There is limited knowledge about the optimal timing of antiretroviral treatment initiation in older children and adolescents.

Methods: A total of 20,576 antiretroviral treatment (ART)-naive patients, aged 1-16 years at enrolment, from 19 cohorts in Europe, Southern Africa and West Africa, were included. We compared mortality and growth outcomes for different ART initiation criteria, aligned with previous and recent World Health Organization criteria, for 5 years of follow-up, adjusting for all measured baseline and time-dependent confounders using the g-formula.

Results: Median (1st;3rd percentile) CD4 count at baseline was 676 cells/mm\(^3\) (394; 1037) (children aged \(\geq 1\) and \(< 5\) years), 373 (172; 630) (\(\geq 5\) and \(< 10\) years) and 238 (88; 425) (\(\geq 10\) and \(< 16\) years). There was a general trend towards lower mortality and better growth with earlier treatment initiation. In children \(< 10\) years old at enrolment, by 5 years of follow-up there was lower mortality and a higher mean height-for-age z-score with immediate ART initiation versus delaying until CD4 count \(< 350\) cells/mm\(^3\) (or CD4\% \(< 15\)\% or weight-for-age z-score \(< -2\)) with absolute differences in mortality and height-for-age z-score of 0.3\% (95\% confidence interval: 0.1\%; 0.6\%) and -0.08 (-0.09; -0.06) (\(\geq 1\) and \(< 5\) years), and 0.3\% (0.04\%; 0.5\%) and -0.07 (-0.08; -0.05) (\(\geq 5\) and \(< 10\) years). In those aged \(\geq 10\) years at enrolment we did not find any difference in mortality or growth with immediate ART initiation, with estimated differences of -0.1\% (-0.2\%; 0.6\%) and -0.03 (-0.05; 0.00), respectively. Growth differences in children aged \(< 10\) years persisted for treatment thresholds using higher CD4 values. Regular follow-up led to better height and mortality outcomes.

Conclusions: Immediate ART is associated with lower mortality and better growth for up to 5 years in children \(< 10\) years old. Our results on adolescents were inconclusive.

Key words: Antiretroviral treatment, paediatrics, g-formula, causal inference

Key Messages

- We found lower mortality and better growth with immediate versus delayed antiretroviral treatment initiation in children \(< 10\) years of age after 5 years of follow-up.
- We showed neither benefits nor harms with immediate treatment initiation in adolescents aged 10-16.
- The best outcomes were observed in European children who attained growth outcomes comparable to HIV-negative children. The effects for the different ART initiation criteria were similar in Southern Africa, West Africa and Europe.
- Irregular clinic visits led to worse outcomes than with regular follow-up, but the comparative effectiveness of different ART initiation criteria were not affected.
Introduction

The World Health Organization (WHO) recommendations on when to start treatment in children and adolescents have changed substantially in recent years. In 2006, antiretroviral treatment (ART) was only recommended for children and adolescents with advanced or severe HIV-associated clinical disease or if CD4 count (or CD4%) fell below an age-dependent critical value.1,2 Reasons for delaying therapy initiation were due to concerns about toxicities, non-adherence, drug resistance, logistical challenges, cost considerations and limited future options for patients failing therapy.3–8

An increasing body of evidence from recent years suggests that delaying ART initiation for too long may be harmful: the results of the CHER trial, which showed a striking mortality benefit for immediate ART initiation in children less than 3 months of age, prompted WHO to recommend ART in all HIV-positive children presenting under the age of 1 year.9 CD4 treatment-initiation thresholds for older children and adolescents persist, but were gradually increased in 2010 and 2013.10–12 From 2013, WHO recommended ART for children older than 5 years and for non-pregnant adolescents with asymptomatic or mild clinical disease when CD4 count is below 500 cells/mm3. Children younger than 5 years were to be started immediately irrespective of CD4 count. These changes were motivated by programmatic and operational considerations favouring simplified treatment guidelines, the rapid decline in CD4 among children presenting with CD4 above the threshold for treatment initiation and no demonstrated harm of immediate initiation in the PREDICT trial or causal modelling studies.13–17 The newly released WHO 2015 guidelines recommend universal ART for all.18

However, large evidence gaps remain: the PREDICT trial enrolled children aged 1-12 years but was underpowered (due to the lower than expected event rate) and did not include older adolescents.15 Causal modelling studies only included children younger than 5 years.16,17 The optimal timing of treatment initiation in adolescents, a key population in the HIV epidemic, is unknown. This is concerning, as findings from adult studies, including the morbidity benefit associated with immediate ART found in the START and TEMPRANO trials,19,20 may not apply to adolescents – due to different lifestyle factors, adherence, modes of infection and the effects of puberty, including rapid physical and neurological change. Moreover, all the above studies implicitly assume that children come for regular visits, typically 3-monthly. It is possible that in real-world settings (with less frequent or missed visits and lag in ART initiation after meeting the treatment initiation criteria) the effects of different treatment initiation criteria differs from idealized study conditions. Also, there are no data after 3 years of follow-up although possible disadvantages of immediate treatment initiation may only be visible in the long term, for example for children failing multiple treatments or with drug complications. In addition, all mentioned studies evaluate criteria which are not exactly identical and comparable to WHO criteria.

In order to inform the WHO 2015 guidelines on the timing of treatment initiation, we attempted to address the above evidence gaps by analysing observational data from West Africa, Southern Africa and Europe, adjusting for time-dependent confounders affected by previous treatment by using the g-formula.21–24 We chose the g-formula since traditional multivariate regression techniques may yield biased treatment effect estimates in our context. We compared mortality and growth outcomes for different treatment initiation rules, aligned with previous and recent WHO criteria, for patients 1-16 years of age and with up to 5 years of follow-up. We consider both a best-case scenario, which uses similar assumptions to other studies regarding visit frequency and prompt ART initiation once treatment thresholds are met, and an alternative scenario which uses assumptions that aim to resemble the real-world situation in some of our cohorts.

Methods

Study population

We used data from 19 cohorts of the IeDEA Southern Africa, IeDEA West Africa and COHERE in EuroCoord collaborations, representing 11 countries (Supplementary Table 1, available as Supplementary data at IJE online).25–29 All contributing cohorts obtained ethical approval from the relevant institutions before submitting anonymized patient data to the networks. Patients aged ≥1 year of age and presenting before their 16th birthday were included if their first clinic visit was no earlier than 1 January 1996 to ensure that every patient received combination antiretroviral therapy, and those that received antiretrovirals had at least one pre-ART visit recorded. Database closure was 31 December 2014.

Variables and definitions

For our analysis we used children’s age at enrolment, health care facility, sex, date of ART initiation and year of enrolment as well as CD4 count, CD4%, weight-for-age z-scores (WAZ, if ≤ 10 years), and body mass index (BMI)-for-age z-scores (BMIAZ, if ≥ 5 years)–both at time of enrolment and during follow-up. The outcomes variables were height-for-age z-score (HAZ) and death. Most sites measured supine length until a child was comfortable to stand, though
some sites worked with supine length until the age of 2 years. All z-scores were based on WHO definitions, i.e., standards developed by the WHO Multicenter Growth Reference Study conducted between 1997 and 2003 in multifaceted settings. Motivated by historical initiation criteria, we defined the following three age groups: 1-5 years (AG1, ≥ 1 and < 5 years), 5-10 years (AG2, ≥ 5 and < 10 years), and 10-16 years (AG3, ≥ 10 and < 16 years).

Follow-up data were evaluated at 3-monthly intervals for a period of up to 5 years. Data were defined to be missing if no data were available for a particular interval. Children were defined as lost to follow-up (LTFU), and censored, if LTFU was confirmed or if at the time of database closure they had had no contact with their health care facility for at least 12 months since their last recorded visit.

We carried forward previous values for missing CD4 count, CD4%, WAZ and HAZ follow-up data until a patient was censored or died. To deal with missing baseline data we used the expectation-maximization-bootstrap algorithm for multiple imputation. The imputation model included all baseline and follow-up variables (including lagged and lead versions of them), death, LTFU, both a carry-forward and an attended visit indicator variable and region. The algorithm accounted for the non-linear and longitudinal structure of the data.

Statistical analyses

Both baseline and follow-up data were summarized with medians (first;third quartile) and by proportions (categorical data). HAZ trajectories, stratified by age and region, were displayed smoothly using additive models. We used the g-formula to estimate cumulative mortality and growth (mean HAZ) for up to 5 years of follow-up for different treatment initiation criteria. The criteria differ by age group and are based on recent and old guidelines, see Table 1 for a comprehensive overview.

With the g-formula we took into account time-dependent confounding affected by previous treatment. Time-dependent variables which affected both treatment assignment and the outcome were clinical stage, CD4 count and CD4% (for children ≤ 10). We followed the approach of previous work and approximated stage with WAZ (BMIAZ for AG3) since many stage-defining events in our context, such as persistent diarrhoea or tuberculosis, are likely to affect a child’s weight. Our algorithm implementing the g-formula required comprehensive model fitting for the time-varying variables and the outcome, which we utilized using additive models, non-linear interactions and model selection (Supplementary Textbox 1, available as Supplementary data at IJE online).

Table 1. Intervention rules used in all g-formula analyses

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 &amp; &lt; 5 years</td>
<td>i) Start ART immediately, irrespective of CD4 count</td>
</tr>
<tr>
<td></td>
<td>ii) Start ART if CD4 count &lt; 750 cells/mm³ or CD4% &lt; 25% or WAZ &lt; -2 (as a proxy for a severe event)</td>
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<tr>
<td></td>
<td>iii) Start ART if CD4 count &lt; 350 cells/mm³ or CD4% &lt; 15% or WAZ &lt; -2 (as a proxy for a severe event)</td>
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<td></td>
<td>iv) Do not start ART</td>
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<tr>
<td></td>
<td>v) Reference criterion</td>
</tr>
<tr>
<td>≥ 5 &amp; &lt; 10 years</td>
<td>i) Start ART immediately, irrespective of CD4 count</td>
</tr>
<tr>
<td></td>
<td>ii) Start ART if CD4 count &lt; 500 cells/mm³ or WAZ &lt; -2 (as a proxy for a severe event)</td>
</tr>
<tr>
<td></td>
<td>iii) Start ART if CD4 count &lt; 350 cells/mm³ or WAZ &lt; -2 (as a proxy for a severe event)</td>
</tr>
<tr>
<td></td>
<td>iv) Start ART if CD4 count &lt; 200 cells/mm³ or WAZ &lt; -2 (as a proxy for a severe event)</td>
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<tr>
<td></td>
<td>v) Do not start ART</td>
</tr>
<tr>
<td></td>
<td>Reference criterion</td>
</tr>
<tr>
<td>≥ 10 &amp; &lt; 16 years</td>
<td>i) Start ART immediately, irrespective of CD4 count</td>
</tr>
<tr>
<td></td>
<td>ii) Start ART if CD4 count &lt; 500 cells/mm³</td>
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<td></td>
<td>iii) Start ART if CD4 count &lt; 350 cells/mm³</td>
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<tr>
<td></td>
<td>iv) Start ART if CD4 count &lt; 200 cells/mm³</td>
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<tr>
<td></td>
<td>v) Do not start ART</td>
</tr>
<tr>
<td></td>
<td>Reference criterion</td>
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</table>

See [http://www.who.int/hiv/pub/guidelines/en] for WHO guideline documents

For children aged 36-59 months.

WHO 2006 criteria for children aged ≥ 5 years also supported ART initiation if CD4% < 15%.

We do not use WAZ for treatment assignment because there are no WAZ standards for children aged ≥ 10 years. We also do not use BMIAZ for treatment assignment since there is no clear threshold to approximate severe clinical events.
In our main analysis, we used similar assumptions as Schomaker et al.: we estimated all counterfactual outcomes under no administrative censoring, no loss to follow-up, full adherence to the regimen, immediate ART initiation after reaching eligibility and regular (3-monthly) follow-up. We further assumed no unmeasured confounding and no model mis-specification. We present results separately for each age group and for all patients presenting with a CD4 count > 500 cells/mm³. In an alternative secondary analysis, we changed our assumptions: we do not assume regular follow-up, but rather infrequent follow-up which we modelled based on the visit frequency in our data. In addition, we assumed that treatment is started at one visit after reaching eligibility; see Supplementary Textbox 1 and other work for implementation details. To explore whether our implicit assumptions of correct model specification and non-informative censoring were likely met or not, we compared the estimates of the g-formula under no treatment strategy (‘natural course scenario’) with the observed data. All results are presented with 95% nonparametric bootstrap confidence intervals (CI). Our analyses were implemented in R.

Results

Descriptive results

Of the 20,576 patients included in our study, most came from the youngest age group (42.1%) and from Southern Africa (78.9%). The median follow-up time was 900 (366;1827) days and 37.2% of our patients did not start ART during follow-up (Table 2). About 29%, 35% and 7% of patients met our LTFU definition in Southern Africa, West Africa and Europe, respectively. Most deaths (53.7%) occurred during the first 6 months after the first visit (Supplementary Table 2, available as Supplementary data at IJE online).

Both baseline and follow-up characteristics differed markedly between regions and age groups (Table 2; Supplementary Table 3, available as Supplementary data at IJE online): European children presented with substantially higher CD4 count, CD4%, WAZ, HAZ and BMIAZ than African children. Children from both African regions had similar baseline characteristics, though West African children had higher HAZ but lower WAZ at baseline. Older children had lower CD4 counts and lower CD4% than younger children. All characteristics improved gradually during follow-up (Supplementary Table 3). Of note, the shapes of growth trajectories were very similar for all three regions but differed by age group: children aged 1-5 showed clear improvement during the whole follow-up period, whereas growth in children aged 5-10 plateaued after 2-3 years. On average, adolescents showed a slow but steady increase in mean HAZ (Figure 1).

About 79.1% of the European adolescents were confirmed perinatally infected, and for 13.2% the mode of infection was unknown. We had no data on mode of infection for African adolescents.

Analyses using g-formula

Our implementations of the g-formula were in general able to reproduce the relevant data characteristics in the natural course scenario (Supplementary Figures 8-9, available as Supplementary data at IJE online). Some deviations for the mean HAZ measurements in the 5th year of follow-up for AG2 indicate caution with respect to these results. We therefore report only results up to 4 years for the growth analysis of this age group.

There was a trend towards lower mortality and better growth for earlier treatment initiation (Figures 2-4; Supplementary Figure 7, available as Supplementary data at IJE online). The mortality differences between immediate ART initiation and thresholds using CD4 count ≤ 350 cells/mm³ were clear in children ≤ 10 years, but not very clear for higher thresholds or for adolescents (95% CIs in Table 3a). Growth differences with respect to different treatment interventions were more pronounced than the mortality differences, suggesting clear benefits of immediate ART initiation in all age groups.

Patients presenting with CD4 count > 500 cells/mm³ had lower mortality and higher mean HAZ values than other patients (Figures 2-4). The mortality and growth differences at 5 years for immediate ART initiation versus delaying ART until CD4 count < 750 cells/mm³ (or CD4% < 25% or WAZ < -2), as shown in Figure 2, were 0% (-0.1%;0.3%) and 0.03 (0.01;0.04) for AG1. Comparing immediate ART initiation with deferring ART until CD4 count < 500 cells/mm³ (or WAZ < -2), as shown in Figures 3 and 4, yielded differences of 0.4% (0.1%;0.6%) and 0.10 (0.07;0.12) for AG2 and 0.1% (-0.1%;0.9%) and 0.06 (-0.01;0.09) for AG3.

In our alternative scenario, with infrequent visits and slightly delayed treatment assignment, mortality was typically higher and the mean HAZ lower than in our main scenario. However, the comparative effectiveness of the different interventions was in general similar, and was slightly attenuated only in a few comparisons (Table 3).

Our results for the effectiveness of the different treatment interventions were consistent in all three regions (Figure 5; Supplementary Figures 1-6, available as Supplementary data at IJE online). As in the raw data, results were best for European patients, followed by West
Table 2. Patient characteristics at the first visit, stratified by region and age group

<table>
<thead>
<tr>
<th></th>
<th>Europe (N = 991)</th>
<th>Southern Africa (N = 16230)</th>
<th>West Africa (N = 3355)</th>
<th>1-5 years (N = 8665)</th>
<th>5-10 years (N = 7358)</th>
<th>10-16 years (N = 4553)</th>
<th>Total (N = 20576)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>male</td>
<td>468 (47.2%)</td>
<td>7888 (48.7%)</td>
<td>1708 (50.9%)</td>
<td>4419 (51.1%)</td>
<td>3644 (49.6%)</td>
<td>2001 (44.4%)</td>
<td>10064 (49.0%)</td>
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<tr>
<td>Age</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>6.08 (3.18; 9.73)</td>
<td>5.99 (2.98; 9.64)</td>
<td>5.51 (2.9; 8.78)</td>
<td>2.56 (1.7; 3.74)</td>
<td>7.19 (6.06; 8.46)</td>
<td>12.42 (11.15; 14.04)</td>
<td>5.94 (2.98; 9.48)</td>
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<tr>
<td>CD4 count</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>835 (84.3%)</td>
<td>11077 (68.3%)</td>
<td>2651 (79.0%)</td>
<td>6019 (69.5%)</td>
<td>5272 (71.7%)</td>
<td>3272 (71.9%)</td>
<td>14563 (70.8%)</td>
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<td>WAZ</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>615 (62.1%)</td>
<td>8189 (50.5%)</td>
<td>2002 (59.7%)</td>
<td>5956 (68.7%)</td>
<td>4850 (65.9%)</td>
<td>10806 (52.5%)</td>
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<tr>
<td>HAZ</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>-0.07 (-0.87; 0.69)</td>
<td>-1.46 (-2.49; -0.6)</td>
<td>-1.94 (-3.34; -0.98)</td>
<td>-1.46 (-2.66; -0.5)</td>
<td>-1.47 (-2.48; -0.62)</td>
<td>-1.46 (-2.57; -0.56)</td>
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<td>BMIAZ</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>0.24 (-0.46; 0.94)</td>
<td>-0.56 (-1.45; 0.21)</td>
<td>-1.4 (-2.72; -0.43)</td>
<td>-0.42 (-1.3; 0.32)</td>
<td>-1.02 (-2.08; -0.15)</td>
<td>-0.62 (-1.61; 0.19)</td>
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<tr>
<td>Treatment start</td>
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<tr>
<td>(1995, 1999)</td>
<td>142 (14.3%)</td>
<td>16206 (99.9%)</td>
<td>3355 (100%)</td>
<td>8656 (99.9%)</td>
<td>7352 (99.9%)</td>
<td>4544 (99.8%)</td>
<td>20552 (99.0%)</td>
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<tr>
<td>ART started</td>
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<tr>
<td>(1999, 2004)</td>
<td>433 (43.7%)</td>
<td>1663 (10.3%)</td>
<td>679 (20.2%)</td>
<td>1432 (16.5%)</td>
<td>983 (13.4%)</td>
<td>360 (7.9%)</td>
<td>2775 (13.5%)</td>
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<td>Treatment start</td>
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<tr>
<td>(2004, 2007)</td>
<td>235 (23.7%)</td>
<td>5571 (34.3%)</td>
<td>1289 (38.4%)</td>
<td>3165 (36.5%)</td>
<td>2629 (35.7%)</td>
<td>7095 (34.5%)</td>
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<tr>
<td>Follow-up time (days)</td>
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<tr>
<td>Median (1st; 3rd quartile)</td>
<td>1827 (1612; 1827)</td>
<td>824 (285; 1785)</td>
<td>829 (366; 1813)</td>
<td>969 (366; 1827)</td>
<td>982 (366; 1827)</td>
<td>656 (217; 1538)</td>
<td>900 (366; 1827)</td>
</tr>
</tbody>
</table>

*Note that WAZ is not calculated for children > 10 years, and BMIAZ is not calculated for children < 5 years; thus, reported percentages seem small.
African patients when looking at growth and South African patients when evaluating mortality.

**Discussion**

**Statement of principal findings**

Our study suggests better growth and lower or equal mortality for early ART initiation in children < 10 years, but results were inconclusive for adolescents. Outcomes were better, with more pronounced benefits of immediate ART initiation, for children presenting with CD4 ≥ 500 cells/mm³ and under regular follow-up assumptions. The comparative effectiveness of the different initiation criteria was similar in all regions and for irregular follow-up and slightly delayed initiation.

**Strengths of the study**

We included a large study population from three different contexts of HIV care, which enabled us to investigate the generalizability of our results. Our choice of treatment initiation criteria and assumptions provide a good comparison to WHO criteria and former trials and modelling studies. Moreover, the present study is the first to include adolescents, to evaluate outcomes after 3 years and to contrast estimates from idealized STUDY SETTINGS with estimates from more realistic settings. We believe that our results therefore give a comprehensive and concise overview of the key implications of the timing of ART in children and adolescents.

**Limitations**

We were constrained with respect to the availability of some data: our African cohorts did not collect regular...
Figure 3. Cumulative mortality and mean HAZ for children aged ≥5 and < 10 years. Results are displayed for different intervention strategies and patient groups; 95% bootstrap confidence intervals for absolute estimates and estimated differences between strategies are listed in Table 3a. All results were obtained using the g-formula. Treatment thresholds refer to CD4 count (< 200/350/500) and WAZ (< -2). Panels B and D are restricted to patients presenting with CD4 count > 500 cells/mm³.

Figure 4. Cumulative mortality and mean HAZ for adolescents aged ≥10 and < 16 years. Results are displayed for different intervention strategies and patient groups; 95% bootstrap confidence intervals for absolute estimates and estimated differences between strategies are listed in Table 3a. All results were obtained using the g-formula. Treatment thresholds refer to CD4 count (< 200/350/500). Panels B and D are restricted to patients presenting with CD4 count > 500 cells/mm³.
Table 3. Estimates of g-formula: cumulative mortality at 5 years, cumulative mortality difference (MD) between interventions at 5 years, mean measured HAZ at 5 years, and mean measured HAZ difference (MHD) at 5 years. Results are shown (a) for the main scenario (3-month follow-up as in many trials) and for the alternative scenario (irregular follow-up with visit frequency modelled based on our data). All results are reported with 95% bootstrap confidence intervals. Treatment thresholds refer to CD4 count (< 200/350/500/750), CD4% (< 15%/25%), and WAZ (< -2).

(a) Regular follow-up (3-monthly, as in a trial)

<table>
<thead>
<tr>
<th>Age 1-5</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>8.4%</td>
<td>7.5%</td>
<td>10.4%</td>
<td>3.7%</td>
</tr>
<tr>
<td>&lt; 350/15%-2</td>
<td>5.0%</td>
<td>4.6%</td>
<td>5.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>&lt; 750/25%-2</td>
<td>4.7%</td>
<td>4.3%</td>
<td>5.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Immediate</td>
<td>4.7%</td>
<td>4.3%</td>
<td>5.5%</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 5-10</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>7.4%</td>
<td>6.5%</td>
<td>9.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>&lt; 200/-2</td>
<td>4.6%</td>
<td>4.1%</td>
<td>5.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>&lt; 350/-2</td>
<td>4.4%</td>
<td>3.9%</td>
<td>5.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>&lt; 500/-2</td>
<td>4.2%</td>
<td>3.8%</td>
<td>5.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Immediate</td>
<td>4.1%</td>
<td>3.7%</td>
<td>5.1%</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 10-16</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>12.5%</td>
<td>11.1%</td>
<td>15.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>10.0%</td>
<td>9.1%</td>
<td>12.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>&lt; 350</td>
<td>9.2%</td>
<td>8.7%</td>
<td>11.3%</td>
<td>-0.1%</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>9.4%</td>
<td>8.6%</td>
<td>11.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Immediate</td>
<td>9.3%</td>
<td>8.5%</td>
<td>11.1%</td>
<td>-</td>
</tr>
</tbody>
</table>

(b) Irregular follow-up (visit frequency modelled based on our data)

<table>
<thead>
<tr>
<th>Age 1-5</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>7.7%</td>
<td>6.8%</td>
<td>9.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>&lt; 350/15%-2</td>
<td>5.9%</td>
<td>5.4%</td>
<td>6.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>&lt; 750/25%-2</td>
<td>5.8%</td>
<td>5.3%</td>
<td>6.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Immediate</td>
<td>5.7%</td>
<td>5.2%</td>
<td>6.4%</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 5-10</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>7.1%</td>
<td>5.7%</td>
<td>8.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>&lt; 200/-2</td>
<td>5.5%</td>
<td>4.7%</td>
<td>6.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>&lt; 350/-2</td>
<td>5.5%</td>
<td>4.7%</td>
<td>6.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>&lt; 500/-2</td>
<td>5.4%</td>
<td>4.5%</td>
<td>6.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Immediate</td>
<td>5.2%</td>
<td>4.6%</td>
<td>6.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 10-16</th>
<th>Mortality</th>
<th>MD 95% CI</th>
<th>Mean HAZ 95% CI</th>
<th>MHD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ART</td>
<td>12.2%</td>
<td>10.8%</td>
<td>14.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>11.0%</td>
<td>9.6%</td>
<td>12.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>&lt; 350</td>
<td>10.6%</td>
<td>9.4%</td>
<td>12.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>10.4%</td>
<td>9.2%</td>
<td>11.9%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Immediate</td>
<td>10.3%</td>
<td>9.2%</td>
<td>12.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

Information on clinical stage, the outcomes of children LTFU were not known and we had missing baseline data. Moreover, we did not look at secondary outcomes such as immune recovery and other morbidity measures.

To deal with the unavailability of stage data, we used WAZ as a proxy measure. This may be appropriate, as argued in other studies, but for adolescents we had to use BMIAZ since there are no WHO-based z-scores for weight. BMIAZ may not respond as quickly to clinically severe events as WAZ, but the results from the natural course scenario (Supplementary data at IJE online) gives some reassurance of its use. In general, our sensitivity checks suggest that we may be able to estimate our outcomes reasonably well and that unmeasured confounding and model mis-specification may not be severe in our analysis, though these
assumptions can never be tested completely from the data. The g-formula can deal with LTFU as long as censoring is uninformative. However, we cannot exclude the possibility that particularly sick children get lost and die soon thereafter—possibly because some of them may stay with caregivers struggling to maintain adherence and clinic visits. Absolute mortality estimates and comparisons between regions should therefore be interpreted with caution. We have, however, successfully imputed missing baseline data. Patients with missing data may have different characteristics and therefore outcomes, but comparisons between interventions may not differ much as suggested in another study.16

Interpretation of the study
Our study highlights the heterogeneity and characteristics of the different age groups in our cohorts. The youngest age group consists of infants who were infected perinatally. This group is affected by high early mortality, but those who survive can expect steady improvement in height with immediate ART initiation, and in Europe even up to the level of HIV-uninfected children.

Older children, aged 5-10 years, are long-term survivors who tend to present at health care facilities much sicker than younger children. Since they are long-term survivors, their early mortality after presentation is not as high. However, likely because of the longer time period they

Figure 5. Mean HAZ and cumulative mortality overall and for different regions, stratified by age group. Treatment thresholds refer to CD4 count (<200/350/500/750), CD4% (15%/25%), and WAZ (<-2).


have been exposed to HIV, it may be more difficult to re-
store their immune system and other physiological func-
tions, which in turn results in slower growth. When the
children have reached an age of 8-13 years, 2-3 years after
presentation, their growth slows down as seen in both the
raw data and the counterfactual outcomes. This could be
explained by a delay in the start of puberty.\textsuperscript{37,38} It is not
surprising that immediate ART initiation proves to have
the most beneficial effect compared with the other criteria
in this age group.

Adolescents comprise a mixed population of long-term
perinatally infected survivors and some newly sexually in-
fected patients. Their growth trajectories look different
from those of younger patients, but potential changes in adoles-
cence, for example lifestyle and adherence, may complicate
comparisons. Moreover, the poor baseline characteristics
and overall high mortality highlight the vulnerability of this
Group. It remains unclear whether behavioural factors or
baseline characteristics drive the results of this age group, in
particular the identical results for immediate ART initiation
and delayed initiation until CD4 count < 350 cells/mm\textsuperscript{3}.

Another important finding is that, irrespective of the
treatment strategy, growth is better and mortality lower
when patients have frequent visits and start ART as
soon as they are eligible. It is not surprising that this is the
case, but the differences we found quantify this benefit
and highlight how results from trials need to be interpreted
carefully when translated into policy in real-world
settings. Moreover, it shows the importance of retaining
children in regular care to achieve optimal treatment
outcomes.

Results in context

The comparative effectiveness of the different treatment
strategies in the youngest age group is almost identical to a
recent causal modelling study which included a subset of
our data (compare Figure 2a and c with Figures 3 and 4 in
Schomaker et al.\textsuperscript{16}). Smaller differences, particularly with
respect to our higher and smoother growth curves, can be
explained by different sample sizes, the inclusion of
European data and small differences with respect to eligi-
bility criteria, LTFU definitions and imputation models.

The PREDICT trial, enrolling Asian children aged 1-12
years, showed no mortality benefit between immediate
ART initiation and deferring ART until either the CD4% was
below 15% or any CDC category C event occurred.
The trial did however show better height gain for children
who start ART immediately. Our results support the claim
that immediate ART initiation enhances growth in children.
However, our results also suggest mortality benefits of
immediate ART initiation in older children. The differences of
the two studies may be because of: (i) the small number of
children aged 5-10; and (ii) the lower than expected event
rate in the trial. The mortality benefit we have found is
small in absolute terms and it would be surprising to see
this effect in a trial with only few events which, in addition,
did not enrol many children aged 5-10. Moreover, the chil-
dren in the trial presented as healthier than ours and eligi-
bility criteria differed, i.e. only children with CD4% between
15% and 24% were considered in the trial.

We did not find major negative consequences of delaying
initiation of ART in adolescents until immunological
criteria are met, even when considering a threshold of 350
cells/mm\textsuperscript{3} or restricting to individuals with a high CD4
count at baseline. This yields similar interpretations to a re-
cent causal modelling study conducted in over 50 000
adults in North America and Europe.\textsuperscript{39} Preliminary find-
ings from the START and TEMPRANO trials point to-
wards a morbidity benefit of immediate ART initiation
but, as Lodi et al.\textsuperscript{39} have also highlighted, different popula-
tions with different co-infections, different follow-up times
and different assumptions complicate comparisons between
different settings. Furthermore, findings from adults can
likely not be transferred to adolescents due to different pa-
tient care systems, durations of infection, issues with non-
adherence, drug combinations and lifestyle factors. It
remains important to couple ART initiation strategies in
children and adolescents with appropriate patient adher-
ence and support strategies including better drug formul-
tions, to reduce the risk of treatment failure and to
monitor neurodevelopmental progress.

Conclusions

Immediate ART initiation is likely of benefit for all chil-
dren aged \( \leq 10 \) years. However, more research on adoles-
cents and long-term outcomes is required.

Supplementary Data

Supplementary data are available at IJE online.

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References