Growth and Mortality Outcomes for Different Antiretroviral Therapy Initiation Criteria in Children Ages 1–5 Years

A Causal Modeling Analysis

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Background: There is limited evidence regarding the optimal timing of initiating antiretroviral therapy (ART) in children. We conducted a causal modeling analysis in children ages 1–5 years from the International Epidemiologic Databases to Evaluate AIDS West/Southern-Africa collaboration to determine growth and mortality differences related to different CD4-based treatment initiation criteria, age groups, and regions.

Methods: ART-naïve children of ages 12–59 months at enrollment with at least one visit before ART initiation and one follow-up visit were included. We estimated 3-year growth and cumulative mortality from the start of follow-up for different CD4 criteria using g-computation.

Results: About one quarter of the 5,826 included children was from West Africa (24.6%).The median (first; third quartile) CD4% at the first visit was 16% (11%; 23%), the median weight-for-age z-scores and height-for-age z-scores were −1.5 (−2.7; −0.6) and −2.5 (−3.5; −1.5), respectively. Estimated cumulative mortality was higher overall, and growth was slower, when initiating ART at lower CD4 thresholds. After 3 years of follow-up, the estimated mortality difference between starting ART routinely irrespective of CD4 count and starting ART if either CD4 count <750 cells/mm^3 or CD4% <25% was 0.2% (95% CI = −0.2%; 0.3%), and the difference in the mean height-for-age z-scores of those who survived was −0.02 (95% CI = −0.04; 0.01). Younger children ages 1–2 and children in West Africa had worse outcomes.

Conclusions: Our results demonstrate that earlier treatment initiation yields overall better growth and mortality outcomes, although we could not show any differences in outcomes between immediate ART and delaying until CD4 count/% falls below 750/25%.

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Despite a reduced number of newly infected children in 2012, the burden of HIV remains high with 260,000 new annual pediatric infections in low- and middle-income countries.[1] The optimal timing of antiretroviral treatment (ART) initiation in

children beyond 12 months of age remains controversial: early ART initiation may reduce morbidity and mortality but could increase the risk of toxicity, complications due to nonadherence, and early development of drug resistance.[2–6]

The World Health Organization (WHO) 2006 guidelines recommended treatment initiation for all children with WHO clinical stage III/IV (with exceptions for children ≥12 months, stage III, and particular clinical events) or based on age-dependent CD4 criteria for children with clinical stage I/II (starting ART if [1] CD4 count <350 cells/mm^3 or CD4% <15% for children ages 36–59 months, [2] CD4 count <750 cells/mm^3 or CD4% <20% for children ages 12–35 months). The CHER trial showed a 76% (95% CI = 49%, 89%) reduction in mortality in infants, enrolled at ages 6–12 weeks, for immediate ART initiation versus deferring ART until CD4% was lower than 25%.[7] These results caused WHO to update their guidelines in 2008 to recommend ART initiation in all HIV-infected children less than 12 months old, regardless of their clinical and immunological status. These recommendations were expanded to all HIV-infected children less than 24 months old in 2010 while for children between 24 and 59 months, with an asymptomatic or mild clinical disease, ART was recommended if either CD4 count <750 cells/mm^3 or CD4% <25%. Both the 2006 and the 2010 recommendations relied, however, solely on the evaluation of disease progression in analyses that were neither randomized experiments nor causally interpretable. In addition, many of these analyses were based on data from high-income countries.[8–11]

The question of when to start was also investigated in the PREDICT trial in which Asian children of ages 1–12 were included at a median age of 6.4 years, with only 6% in their second year of life.[3,12,13] This trial did not show any difference between immediate ART initiation and deferring ART until either the CD4% was below 15% or any CDC category C event occurred—with respect to mortality and morbidity outcomes. The trial did, however, show better height gain for children who start ART immediately. However, the authors suggested that the study was underpowered to detect differences due to the lower than expected event rate. In Southern African children, a causal modeling study showed no mortality difference (MD) in 2- to 5-year-old children for starting ART immediately versus starting ART when either the CD4 count falls below 750 cells/mm^3 or the CD4% drops below 25%.[14] In 2013, WHO guidelines were further updated to recommend ART initiation in all children less than 5 years. This change was mainly motivated by potential programmatic advantages, i.e., to provide simplified criteria for initiating ART and to bring young children into the health care system.

Thus, there still remain considerable evidence gaps: a comparison of different CD4 initiation criteria has never been explored for children ages 1–2 years. These children are known to have slower disease progression than infants, but also progress faster than older children and thus findings both from the CHER and PREDICT trial, as well from other recent analyses, may not apply to them.[3,5] Moreover, it is of interest whether the evidence for children ages 2–5 years can be generalized to West African populations and whether the different growth response suggested by the PREDICT trial applies to these populations.

We thus used g-computation[14–16] to determine mortality and growth differences for different ART initiation strategies in young children from West and Southern Africa. We chose g-computation because it allows adjustment for time-varying confounders affected by prior treatment; in our data, these are CD4 count, CD4%, and WHO stage (approximated by weight-for-age z-scores [WAZ]), which influence both ART initiation and our outcome measures. Traditional multivariate regression techniques may yield biased treatment effect estimates. An advantage of g-computation over competing methods is its suitability to compare dynamic intervention rules, its efficiency, and that it provides natural estimation of marginal effects.[17]

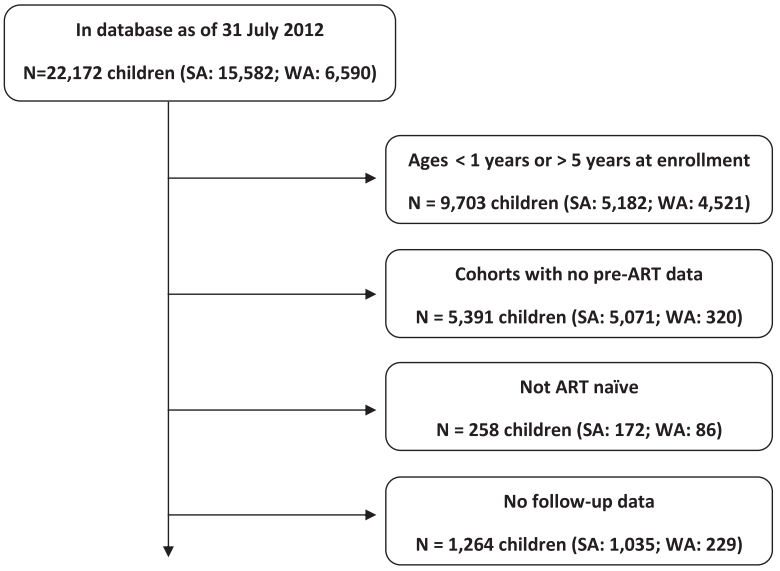
Our primary study aims were to (1) compare mortality and height outcomes for different CD4-based treatment initiation criteria (derived from selected CD4 criteria from WHO guidelines since 2006), (2) contrast mortality and growth of 1- to 2-year-old children with older children, and (3) investigate the heterogeneity of results from Southern Africa and West Africa. All our estimates are based on the idealized conditions of regular visits (every 3 months) at which CD4 measurements are taken, and instantaneous treatment initiation if a treatment threshold has been reached.

METHODS

This study includes data of 16 cohorts from Côte d'Ivoire, Burkina Faso, Ghana, Senegal, Togo, South Africa, Malawi, and Zimbabwe. All cohorts are part of either the IeDEA West Africa or IeDEA Southern Africa cohort collaboration. Both collaborations have been described elsewhere.[18–21] In brief, data were collected at each facility as part of routine monitoring and were transferred to the coordinating data centers at Bordeaux University, France, University of Cape Town, South Africa, and University of Bern, Switzerland. All contributing sites obtained ethical approval from the relevant local institutions before submitting anonymized patient data to the collaboration. The data centers in Bordeaux, Bern, and Cape Town got ethical approval from the respective universities' review boards to analyze these data.

This study is limited to cohorts which routinely capture both pre-ART and post-ART data of HIV-infected children. All ART naïve children of ages 12–59 months at enrollment with at least one visit before ART initiation and one follow-up visit were included (Figure 1).

The analysis made use of children's age at enrollment, their sex, treatment facility, date of ART initiation as well as CD4 count, CD4%, WAZ, and height-for-age z-scores, both at time of enrollment and during follow-up. All z-scores



Included in the study by cohort:

Lighthouse Trust Clinic	Malawi	428
Newlands Clinic	Zimbabwe	195
McCord Hospital	South Africa	382
Harriet Shezi Clinic	South Africa	1,626
Desmond Tutu HIV Centre Gugulethu	South Africa	88
Khayelitsha ART Programme	South Africa	509
Hlabisa HIV Treatment and Care Programme	South Africa	442
Rahima Moosa Mother and Child Hospital	South Africa	722
Hôpital Charles De Gaulle, Ouagadougou	Burkina Faso	142
Centre de Prise en Charge Enfant	Côte d'Ivoire	271
Centre Hospitalier Universitaire de Yopougon	Côte d'Ivoire	233
Centre Hospitalier Universitaire de Cocody	Côte d'Ivoire	155
Centre MTCT-Plus	Côte d'Ivoire	39
Korle Bu Teaching Hospital	Ghana	317
Hôpital Albert Royer, Dakar	Sénégal	182
Centre Hospitalier Universitaire de Tokoin	Togo	95

FIGURE 1. Flowchart: selection of patients.

were calculated using WHO standards.[22] We defined young children to be those who present at ages 12–24 months (1- to 2-year age group), and old children to be those who present at ages >24 months and ≤59 months (2- to 5-year age group). Follow-up data was evaluated 1 month after enrollment, 3 months after enrollment and then subsequently in 3-month intervals for a period of up to 3 years. If no data were available for a particular interval, the data were defined to be missing. Children were defined as being lost to follow-up (LTFU), and censored, if at the time of database closure they had no contact with their health care facility for at least 9 months since their last recorded visit. In a sensitivity analysis, we censored children 9 months after having no contact with their health care facility, even if they re-entered care after 10 months or more.

We carried forward missing CD4 count, CD4%, weight- and height-for-age z-score follow-up data and used multiple imputation by means of the expectation-maximization-bootstrap algorithm[23] to deal with missing baseline data. The imputation model included all baseline variables, follow-up variables (including lagged and lead versions of them), death, a carry-forward indicator variable, and region, and also accounted for the longitudinal, possibly nonlinear, structure of the data.

We summarized the data at time of enrollment, stratified by age and region, and during follow-up. Continuous data were described with medians (reported with first; third quartiles) and categorical data were summarized by proportions.

The primary analysis used g-computation to estimate cumulative mortality and growth (mean HAZ of children

who are alive) during 3 years of follow-up for different interventions strategies: (1) immediate ART, (2) delaying ART until CD4 fell below750 cells/mm^3 or 25%, (3) delaying ART until CD4 fell below 350 cells/mm^3 or 15%, or (4) no ART given. This analysis emulates the following clinical trial: HIV positive and ART-naïve children, ages 1–5 years, presenting at a health care facility for the first time, are randomly assigned one of the four treatment strategies (1)–(4). Each of the four arms is, therefore, differing by the CD4 thresholds used to determine the timing of ART initiation. Under full adherence to the regime, no administrative censoring, and no loss to follow-up, we can estimate the cumulative mortality at time t for each of the four regimes as well as the growth (mean height-for-age z-score) of those children who survived until time t. We assume that CD4 count/% is measured and evaluated regularly because we are interested in the outcomes that would be observed if treatment strategies were followed; we, therefore, evaluate the outcomes under an ideal monitoring situation. We report cumulative mortality and growth for different follow-up times t, together with 95% bootstrap confidence intervals. We also report differences between the different interventions, regions, and age groups.

The mean height-for-age z-score was chosen as the primary growth outcome to allow comparison with the PREDICT trial.[13] Secondary growth outcomes are median height-for-age z-score, proportion with height-for-age z-score greater than −2, and cumulative incidence of attaining height-for-age z-score greater than −2 before the competing event of death occurs. We estimate all growth outcomes under no administrative censoring, and no loss to follow-up, but allow for death of children, which means growth is estimated for children who survived until time t.

G-computation has been used before to determine the optimal timing of treatment initiation in adults.[24,25] Our implementation of the g-computation algorithm is similar to the one described by Westreich et al.[24] but differs slightly from this algorithm in that we use multiple imputation for baseline data and other variables, relevant to pediatric analyses, are included. To implement g-computation, we had to model (at each time point t) the associations of CD4 count, CD4%, weight- and height-for-age z-scores, and death with disease progression history (CD4 count, CD4%, weight- and height-for-age z-scores at time t-1), baseline characteristics (CD4 count, CD4%, weight- and height-for-age z-scores), demographics (age, sex, region), and the intervention (ART at times t-1 and t-2) using additive linear and logistic regression models. More details about our implementation are listed in eTextbox 2 (http://links.lww.com/EDE/A987).

We conducted several sensitivity analyses: cumulative mortality was estimated (1) if only children with complete baseline data are included, and (2) if missing follow-up data, as well as outcome data of lost children, are imputed (eTextbox 1; http://links.lww.com/EDE/A987). Growth was estimated (3) if only children with complete baseline data are included, and (4) under the assumption of no mortality in our population. We also estimated the outcomes and the confounders under the natural course, i.e., under no treatment intervention, and compared it to the observed data.[16,25]

In a secondary descriptive analysis, we estimated disease progression as the probability of falling below a CD4 value of 750 cells/mm^3 or 25% for those children who were above this threshold at enrollment. Children LTFU, dead, or initiating ART were censored (first analysis) and treated as a competing risk (second analysis). Results were summarized using the Kaplan–Meier estimator and cumulative incidence curves,[26] respectively.

RESULTS

Descriptive Results

Among 22,172 children in the database, 7,078 children were in the eligible age range from cohorts that capture pre-ART data. After excluding 258 non-ART naïve children and 1,264 children with no follow-up, 5,826 were included in the analysis, of which 1,434 (24.6%) were from West Africa (Figure 1). Median (first; third quartile) follow-up was 27.4 (8.6; 35.0) months. Of 267 deaths, 158 (59.2%) occurred in Southern Africa and 58.8% within the first 6 months. Out of 1,195 (20.5%) children LTFU, 869 (72.3%) were from Southern Africa.

Patient characteristics are summarized in the Table. At presentation, the median age was 2.6 (1.8; 3.8) years. The median CD4 count was 662 cells/mm^3 (389; 1,011), the median CD4 percent 16% (11%; 23%), and median height- and weight-for-age z-scores were −2.5 (−3.5; −1.5) and −1.5 (−2.7; −0.6), respectively. Almost 75% of children started ART. Characteristics at enrollment were similar when comparing 1- to 2-year-old with 2- to 5-year-old children, although the latter had a slightly better weight- and height-for-age z-scores profile. In both regions, there was an improvement in median CD4 count/CD4%/weight- and height-for-age z-scores over time, all outcomes being slightly better in Southern Africa than West Africa except for height-for-age z-scores (eTable 1, eFigure 1; http://links.lww.com/EDE/A987). The increase of the mean height-for-age z-score applied to children both on ART and not on ART (eFigure 1; http://links.lww.com/EDE/A987). The proportion of missing data at baseline varied from 18.4% for CD4 count to 40.3% for HAZ (Table). CD4 count/% was available every 3 months for 18%/15% of children; the median availability was every 6 months for CD4 count and every 8 months for CD4%. 19% (14%) of the 921 patients who had both a 3 monthly CD4 count and CD4% measurement started ART instantaneously given a 750/25% (350/15%) threshold.

Progression to CD4 Threshold

The estimated proportion of children who progressed to below the threshold of 750 cells/mm^3 or 25% was similar

TABLE. Patient Characteristics at First Clinic Visit, Overall (Total), and Stratified According to Age and Region

	1–2 Years	2–5 Years	Southern Africa	West Africa	Total
Sex	1,910 (100%)	3,916 (100%)	4,392 (100%)	1,434 (100%)	5,826 (100%)
Male	954 (50.0%)	2,026 (51.7%)	2,222 (50.6%)	758 (52.9%)	2,980 (51.2%)
Age (in years)			4,392 (100%)	1,434 (100%)	5,826 (100%)
Median (1st; 3rd quartile)			2.6 (1.7; 3.7)	2.7 (1.8; 3.8)	2.6 (1.8; 3.8)
CD4 count	1,545 (80.9%)	3,208 (81.9%)	3,692 (84.1%)	1,061 (74.0%)	4,753 (81.6%)
Median (1st; 3rd quartile)	790 (475; 1,196)	607 (365; 912)	646 (380; 984)	719 (433; 1,081)	662 (389; 1,011)
>750	818 (52.9%)	1,165 (36.3%)	1,486 (40.3%)	497 (46.8%)	1,983 (41.7%)
CD4%	1,384 (72.5%)	2,775 (70.9%)	3,409 (77.6%)	750 (52.3%)	4,159 (71.4%)
Median (1st; 3rd quartile)	16% (11%; 22%)	16% (10%; 23%)	16% (11%; 23%)	16% (10%; 22%)	16% (11%; 23%)
>25%	242 (17.5%)	507 (18.3%)	633 (18.6%)	116 (15.5%)	749 (18.0%)
WAZ	1,446 (75.7%)	2,914 (74.4%)	3,766 (85.8%)	594 (41.4%)	4,360 (74.8%)
Median (1st; 3rd quartile)	−1.9 (−3.2; −0.8)	−1.4 (−2.4; −0.6)	−1.5 (−2.6; −0.6)	−1.9 (−3.2; −0.9)	−1.5 (−2.7; −0.6)
<−2	700 (48.4%)	981 (33.7%)	1,397 (37.1%)	284 (47.8%)	1,681 (38.6%)
HAZ	1,092 (57.2%)	2,387 (61.0%)	2,972 (67.7%)	507 (35.4%)	3,479 (59.7%)
Median (1st; 3rd quartile)	−2.6 (−3.8; −1.5)	−2.5 (−3.4; −1.5)	−2.6 (−3.6; −1.6)	−2.1 (−3.1; −1.0)	−2.5 (−3.5; −1.5)
<−2	703 (64.4%)	1,504 (63.0%)	1,929 (64.9%)	278 (54.8%)	2,207 (63.4%)
Region	1,910 (100%)	3,916 (100%)			5,826 (100%)
West Africa	452 (23.7%)	982 (25.1%)			1,434 (24.6%)
Ever started ART	1,910 (100%)	3,916 (100%)	4,392 (100%)	1,434 (100%)	5,826 (100%)
Yes	1,421 (74.4%)	2,936 (75.0%)	3,318 (75.6%)	1,039 (72.5%)	4,357 (74.8%)

Available data are given in absolute numbers (percentages in brackets).

in Southern and West Africa throughout follow-up, irrespective of whether a competing risk approach was used or not (Figure 2). After 3 years, 71.6% (95% CI = 64.8%; 78.1%) of Southern African children and 74.9% (95% CI = 59.5%; 87.9%) of West African children were estimated to have progressed below the threshold (Kaplan–Meier estimator). The estimates obtained from the cumulative incidence curves were slightly higher (75.7% [69.7%; 81.9%] and 83.6% [68.1%; 94.4%], respectively).

Mortality Analysis

The estimated cumulative mortality for different treatment strategies is summarized in Figure 3 (top left) and eTable2 (http://links.lww.com/EDE/A987). There is a trend toward higher mortality associated with starting ART at lower CD4 thresholds during the whole follow-up period. After 3 years of follow-up, mortality for the different strategies was estimated to be 8.8% (7.7%; 11.1%; no ART), 5.7% (5.0%; 6.6%; ART if CD4 <350/15%), 5.0% (4.3%; 5.9%; ART if CD4 <750/25%), and 4.8% (4.3%; 5.9%; immediate ART). The estimated MD between the latter two strategies was 0.2% (−0.2%; 0.3%) after 3 years and 0.9% (0.3%; 1.2%) between immediate ART and giving ART if CD4 <350/15% (Figure 3, top right and eTable 2a; http://links.lww.com/EDE/A987). The trends can be seen in all age groups and regions (eTable2; http://links.lww.com/EDE/A987). Mortality after 3 years was estimated to be higher among 1- to 2-year-olds compared with older children (MD for immediate ART 1.3% [0.5%; 2.8%], Figure 3, bottom left, eTable 2b; http://links.lww.com/EDE/A987) and in West Africa compared with Southern Africa (MD for immediate ART: 4.6% [2.9%; 5.9%], Figure 3, bottom right and eTable2; http://links.lww.com/EDE/A987). The MDs between age groups and regions are mostly driven by the first 3 months after the first visit and remain reasonably stable thereafter (Figure 3, bottom panel). The sensitivity analyses led to similar conclusions when comparing interventions, age groups, and regions (eFigures 2 and 3; http://links.lww.com/EDE/A987). Mortality was somewhat greater when using the extended imputation approach, and slightly smaller when restricting the analysis to children with complete baseline data.

Growth Analysis

Figure 4 (top left) demonstrates that the mean HAZ of surviving patients after 3 years of follow-up ranges between −1.92 (−2.09; −1.72; no ART) and −1.73 (−1.88; −1.50; immediate ART). In comparison to immediate ART, the differences in mean HAZ after 3 years were estimated as −0.02 (−0.04; 0.01; CD4 count/% threshold of 750/25%), −0.08 (−0.10; −0.05; threshold: 350/15%), and −0.19 (−0.25; −0.16; no ART; Figure 4, top right). Using the median HAZ, the probability of HAZ greater than −2 and the cumulative incidence of HAZ greater than −2 as outcome yield the same conclusions (eFigure 4, eTable 3; http://links.lww.com/EDE/A987). The mean HAZ is generally lower in younger children and in South Africa; the differences between the age groups are, however, reasonably stable over time (Figure 4, bottom panel, eFigure 5; http://links.lww.com/EDE/A987). The sensitivity

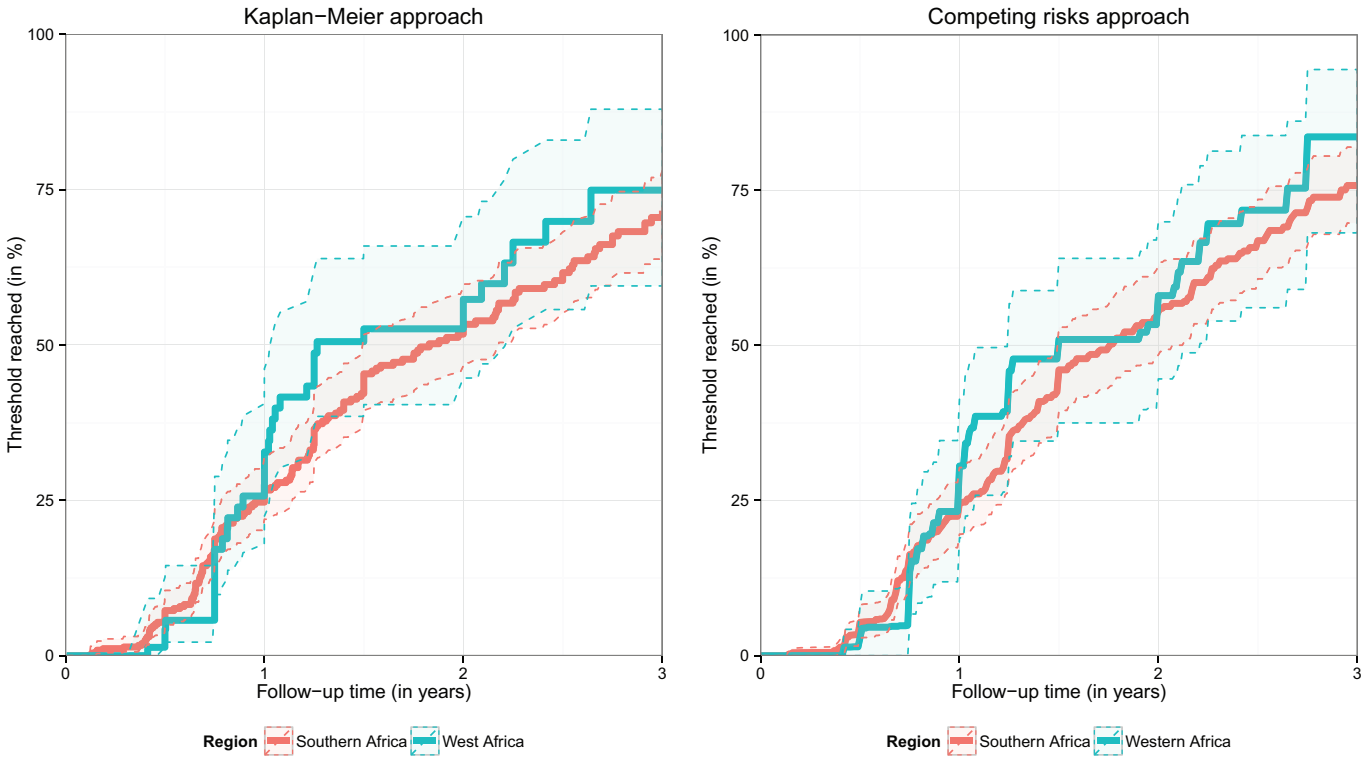


FIGURE 2. Estimated probability of falling below a CD4 count of 750 cells/mm^3 or a CD4 percentage of 25%. A, via the Kaplan–Meier estimator: this figure is based on 613 children (514 from Southern Africa, 99 from West Africa) presenting with a CD4 count of 750 cells/mm^3 or above and a CD4% of 25% or above. Only pre-ART follow-up is considered and lost or dead children were censored at the time of the respective event. B, ART initiation, death, and LTFU were treated as competing risks. The probability of falling below the threshold was estimated via the cumulative incidence of falling below the threshold before any other event occurred divided by one minus the probability that any other event occurred before the threshold was reached. 95% confidence intervals were obtained via bootstrapping and are visualized via the *shaded area*. ART indicates antiretroviral treatment; LTFU, loss to follow-up.

analyses confirm the above findings (eFigures 6 and 7; http://links.lww.com/EDE/A987).

The data characteristics are overall similar when comparing the observed data with the data simulated with g-computation under the natural course scenario, i.e., under no intervention, although for the CD4 measurements there are some deviations after 1 year of follow-up (eFigure 8; http://links.lww.com/EDE/A987). A different definition of LTFU led to overall similar results (eFigure9; http://links.lww.com/EDE/A987).

DISCUSSION

Statement of Principal Findings

We found overall lower mortality and better growth when starting ART earlier in children ages 1–5. These differences were very small when comparing immediate ART initiation with deferring ART until the CD4 threshold of 750/25% is reached, but clearer when comparing it with the CD4 threshold of 350/15%. Our findings were consistent over age groups and regions, but mortality was estimated to be lower, and growth to be faster, in children ages 2–5 and in Southern Africa.

Strengths of the Study

This is the first implementation of g-computation to estimate growth differences associated with different treatment initiation rules. Consistent findings from the Southern and West Africa regions with differences in background morbidity, access and standard of HIV care, patient populations, and training possibilities are reassuring in terms of generalizability of our results. Our findings complement other studies which either focused on other age groups[7,14] or were underpowered.[13]

Limitations

The outcomes of children LTFU were not known. While censoring by drop out can be handled using g-computation, and we conducted sensitivity analyses using multiple imputation, it may be possible that those defined to be lost have a particular high risk of being dead. In some settings, this is known to be true for adults.[27–29] However, in children less is known about

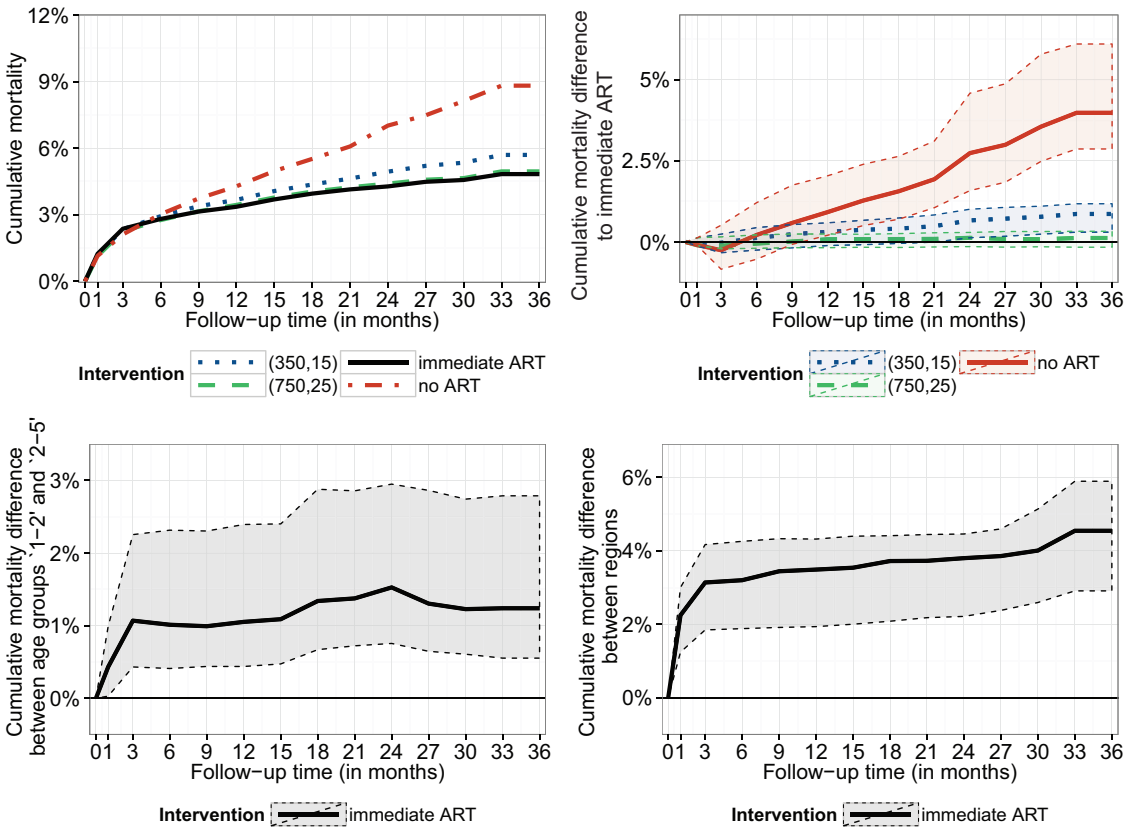


FIGURE 3. Estimated cumulative mortality by intervention strategy (*top left*) and differences between these intervention strategies (*top right*). For the intervention "immediate ART" cumulative mortality differences are displayed for both comparing the two different age groups and regions (*bottom panel*). Results are based on g-computation, and 95% bootstrap confidence intervals are represented by the *shaded area*. ART indicates antiretroviral treatment.

those LTFU because reasons for missing an appointment may relate to the caregiver's work responsibilities, family situations, economic opportunities, and own health status.[30] Studies that trace lost children or link them to vital registries are needed to gain more knowledge about this group. While it is possible that the deviations between observed CD4 data and the data generated under the natural course scenario (eFigure 8; http://links.lww.com/EDE/A987) are due to informative censoring, unmeasured confounding related to clinical events not captured by WAZ data (i.e., encephalopathy or HIV-associated nephropathy), or model misspecification, offer alternative explanations.

Our study requires children to have at least one follow-up visit. Children who were excluded because of no follow-up data had higher CD4 counts (median [first; third quartile]: 742 [422; 1,220]) and higher CD4% (20 [13; 28]) but lower weight- and height-for-age z-score values (−2.3 [−3.7; −0.9] and −2.8 [−3.8; −1.5], respectively). This means that mortality at the population level could potentially differ from our estimates.

We assume CD4 count/% to be measured 3 monthly and ART to be started instantaneously after patients become eligible under the respective treatment strategy. Our estimates are, therefore, obtained under idealized conditions and may not be directly applicable to existing conditions in sub-Saharan Africa, i.e., if CD4 is performed less frequently or initiation of ART is not instantaneous after dropping below the threshold, it is possible that mortality and growth differences between immediate and deferred ART would be different from our estimates. However, it is noteworthy that both the PREDICT and the CHER trial scheduled visits no more than 3 months apart.

Other limitations relate to the lack of long-term outcome data and therefore the possibility of examining effects of toxicities and drug resistance. Also, missing data on first-line regimens and differences in drug use between countries make it difficult to evaluate growth and mortality outcomes stratified by ART regimen. It may be possible that children on nevirapine show better growth outcomes compared with children using lopinavir, but also higher virological failure which could result in higher mortality.[31]

Results in Context

While we found a trend toward higher mortality being associated with starting ART at lower CD4 thresholds, differences between the criteria of starting ART immediately and delaying until CD4 < 750/25% were negligible, for all follow-up times and across regions and age groups. In line

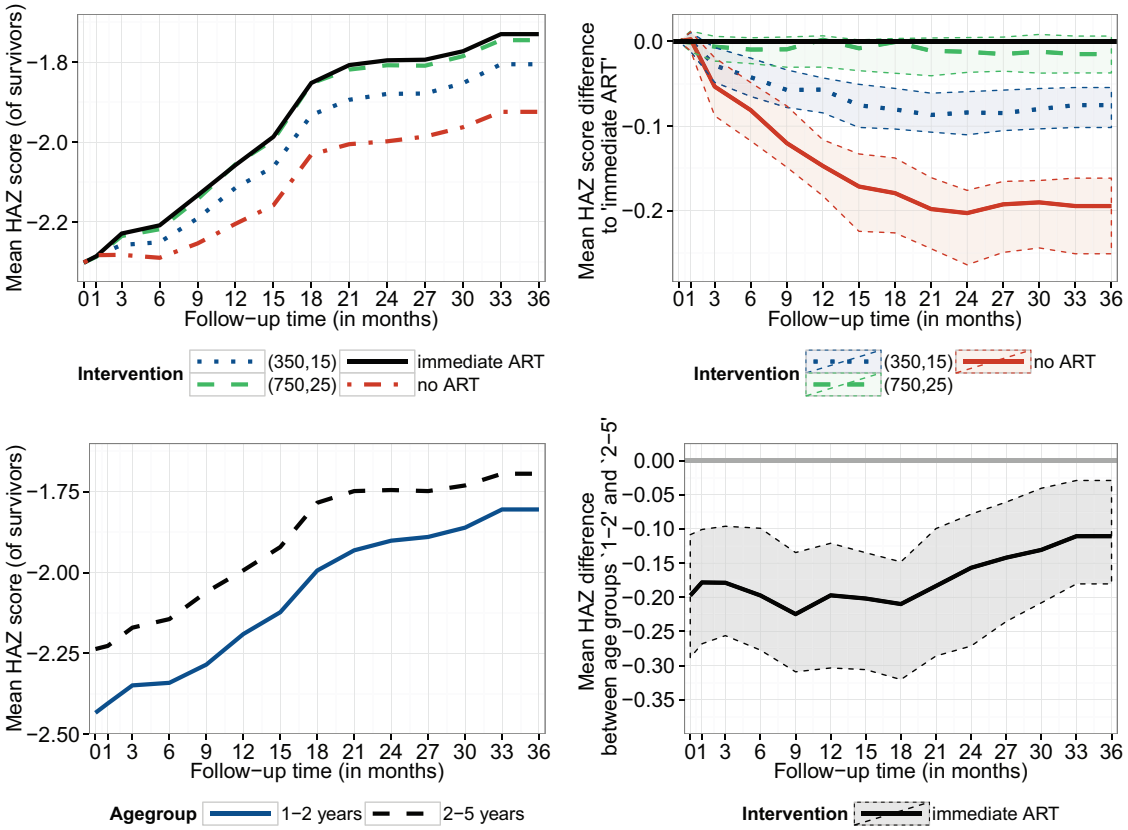


FIGURE 4. Estimated mean height-for-age z-score by intervention strategy (for survivors at the respective time point, [The number of survivors is different for each time point and strategy. Consult the discussion for more insight] *top left*) and differences between these intervention strategies (*top right*). For the intervention "immediate ART" the mean height-for-age z-score for both age groups as well as the difference between them are displayed (*bottom panel*). Results are based on g-computation and 95% bootstrap confidence intervals are represented by the *shaded area*. ART indicates antiretroviral treatment.

with previous reports,[13,14] this suggests that the change in WHO guidelines in 2013 may neither result in increased nor decreased mortality in young children. However, estimated mortality was higher, and growth slower, when starting ART at the 350/15% threshold, confirming that later ART initiation, as recommended in 2006, may have consequences in terms of both mortality and growth.

In line with the results of the PREDICT trial, where children were enrolled with higher HAZ than in our study (mean HAZ −1.7 vs. −2.5), we found a better growth response related to early ART initiation. We could, however, show no difference related to the criteria of starting ART immediately versus delaying until the threshold of 750/25% is reached. An important consideration regarding interpretation and understanding of our growth results relates to the fact that at different time points and for different interventions a different number of survivors remain, and thus comparisons are difficult. However, our results from the competing risk and sensitivity analyses (eTable 3, eFigure 7; http://links.lww.com/EDE/A987) address this concern and confirm the overall findings of the mean height-for-age z-score results. Moreover, our results can be considered as conservative estimates of the effect of earlier ART initiation: the number of survivors at lower ART initiation thresholds is overall lower with some of the sicker patients, with lowest height-for-age z score, thus excluded from the mean score when compared with higher thresholds; therefore, true differences between initiation criteria for any particular group of survivors might be larger than reported by us.

In our data, mortality was estimated to be higher in West Africa when compared with Southern Africa. This may relate to higher malnutrition in West Africa, a different background of coinfections, such as malaria, difficult access to care, different ART monitoring, and the role of stigma.[32,33] However, these differences were largely driven by differences during the first 3 months after enrollment. As indicated earlier, it might be possible that the high proportion of lost children in the first 3 months in Southern Africa includes a substantial proportion of children who died. It is still possible that some of the differences between regions can be attributed to under-ascertained mortality in Southern Africa.

Mortality was estimated to be higher, and growth slower, in children ages 1–2 compared with older children. This mainly reflects the differences at presentation: the group of children ages 1–2 contains many children who have

probably been infected in utero or at birth. These children tend to have more severe disease, with a worse survival prognosis: if a child is not diagnosed with HIV in early infancy, it may only be identified too late (i.e., when caregivers arrive at a health care facility with a very sick child). These children have a high risk of death before or shortly after presentation. The age group of children ages 2–5 contains fewer of these children because these children are more long-term survivors when they are 2 or older than earlier. In addition, even in the absence of HIV, mortality is highest in infants and declines with increasing age during childhood.

Further Considerations and Future Directions

Our results suggest no negative consequences regarding mortality and growth response when starting ART at the earliest presentation to health care services in young children ages 1–5. There are, however, other relevant considerations for determining the optimal time of treatment initiation: in settings with limited resources and few trained health care workers the allocation of resources needs to be considered carefully. Rapid ART initiation should not happen at the expense of neglecting early infant diagnosis and withholding care from the most vulnerable children. However, only about 11% of the children in our data presented with a CD4 count >750 cells/mm^3 and CD4% >25% and about 75% of those progressed to below this threshold within 3 years. This suggests that the additional burden of early treatment initiation may be moderate, although probably underestimated by us because our cohorts may not be representative of all HIV infected children between 1 and 5 years old. ART also implies lifelong therapy and therefore early treatment goes along with longer exposure to the risks of nonadherence, toxicity, and resistance. It remains important to identify a caregiver who understands the implications and responsibilities of starting ART. Moreover, there may be non-identified long-term risks and changing WHO guidelines back to delayed treatment may not be feasible anymore.

Nevertheless, recommending treatment initiation in all young children regardless of their immunological and clinical stage, may improve access to care, simplify pediatric treatment and facilitate expansion of ART coverage. Given the rapid disease progression in young children, using CD4 criteria may not delay the onset of therapy very much and risk children of dropping out of health care. Moreover, regular CD4 measurements are not available in all resource-limited settings. Early treatment initiation may also be beneficial for immune recovery and neurodevelopment.

CONCLUSIONS

Early treatment initiation yields better growth and mortality outcomes in children ages 1 to 5 from West and Southern Africa, although differences between immediate ART initiation and delaying until CD4 <750/25% are negligible. Younger children had worse outcomes in our study, but future studies need to confirm this and address programmatic and long-term implications and challenges of early treatment initiation to improve their survival.

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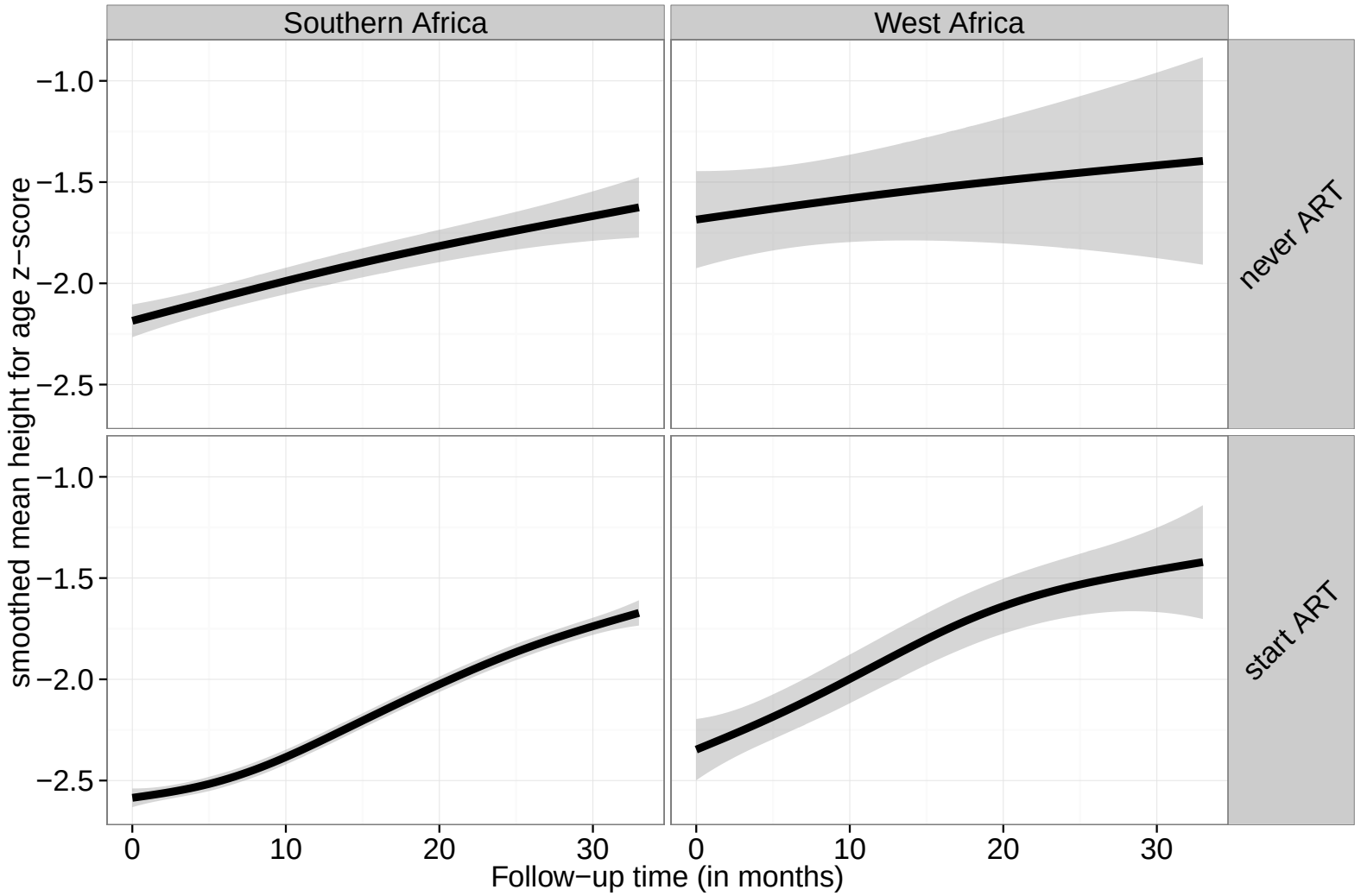
eTable 1. Evolution of CD4 count, CD4 percentage, WAZ and HAZ over time from enrolment by region, reported as median (first; third quartile). Results are reported for available data[1].

	CD4 count	N(%)	CD4%	N(%)	WAZ	N(%)	HAZ	N(%)
Overall								
first visit	662 (389; 1011)	4753 (81.6 %)	16 (11; 23)	4159 (71.4 %)	-1.5 (-2.7; -0.6)	4360 (74.8 %)	-2.5 (-3.5; -1.5)	3479 (59.7 %)
12 months	953 (652; 1351)	1521 (36.2 %)	24 (19; 30)	1381 (32.9 %)	-1.0 (-1.8; -0.2)	2630 (62.6 %)	-2.2 (-3.1; -1.3)	2136 (50.8 %)
24 months	1034 (711; 1405)	1175 (35.7 %)	28 (22; 34)	1079 (32.8 %)	-0.8 (-1.5; -0.2)	2050 (62.2 %)	-1.9 (-2.7; -1.1)	1715 (52.1 %)
West Africa								
first visit	719 (433; 1081)	1061 (74.0 %)	16 (10; 22)	750 (52.3 %)	-1.9 (-3.2; -0.9)	594 (41.4 %)	-2.1 (-3.1; -1.0)	507 (35.4 %)
12 months	1004 (664; 1360)	394 (37.7 %)	24 (20; 29)	301 (28.8 %)	-1.2 (-2.1; -0.4)	270 (25.8 %)	-1.9 (-2.9; -1.0)	206 (19.7 %)
24 months	1030 (685; 1388)	315 (37.6 %)	27 (21; 34)	254 (30.3 %)	-1.0 (-1.6; -0.3)	150 (17.9 %)	-1.4 (-2.3; -0.7)	114 (13.6 %)
South Africa								
first visit	645 (380; 985)	3692 (84.1 %)	16 (11; 23)	3409 (77.6 %)	-1.5 (-2.6; -0.6)	3766 (85.8 %)	-2.6 (-3.6; -1.6)	2972 (67.7 %)
12 months	939 (644; 1345)	1127 (35.7 %)	24 (18; 30)	1080 (34.2 %)	-1.0 (-1.7; -0.2)	2360 (74.8 %)	-2.3 (-3.1 ; -1.4)	1930 (61.2 %)
24 months	1040 (733; 1421)	860 (35.0 %)	28 (22; 34)	825 (33.6 %)	-0.8 (-1.5; -0.1)	1900 (77.3 %)	-1.9 (-2.6; -1.1)	1601 (65.2 %)

[1]Available data at 12 months comprises any data measured between 10.5 and 13.5 months after enrolment; available data at 24 months comprises any data measured between 22.5 and 25.5 months after enrolment.

eFigure 1. Smoothed mean height for age z-score stratified by children who never receive ART during follow-up and children who do receive ART some time during follow-up. Results are reported separately for each region. Only available baseline and follow-up data is included. 95% confidence intervals are represented by the grey shaded area.



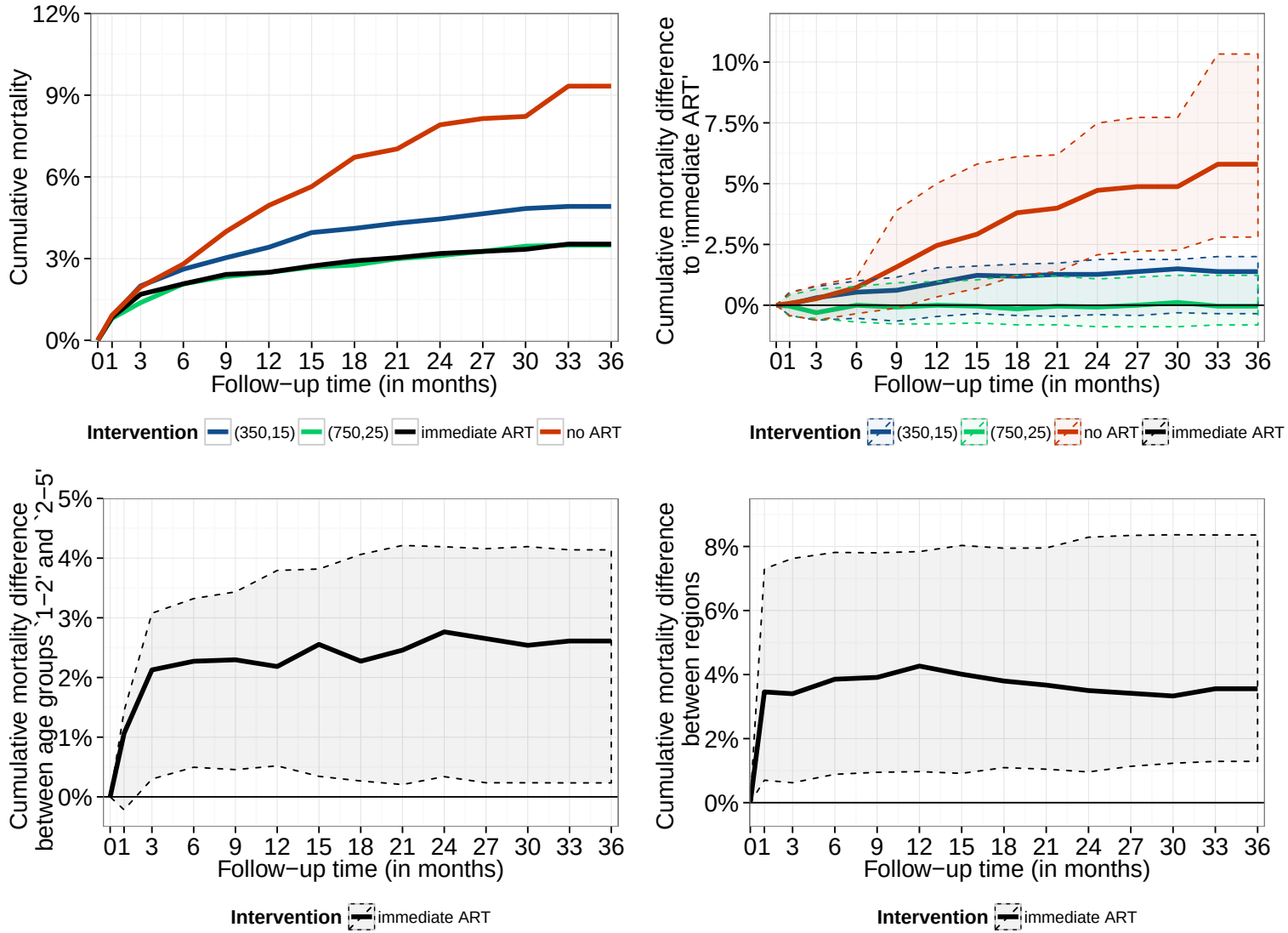
eTable 2. Estimated mortality and mortality difference [MD] to 'immediate ART initiation', (a) overall, (b) stratified according to age at 3 years of follow-up, (c) stratified according to region at 3 years of follow-up, and for differences between age groups and regions at 3 years of follow-up. 95% confidence intervals are obtained from bootstrapping and are shown in grey color.

(a)	**Mortality estimates (95% CI in grey)**									**Mortality difference (95% CI in grey)**								
	after 1 year			**after 2 years**			**after 3 years**			**after 1 year**			**after 2 years**			**after 3 years**		
no ART	4.3%	3.7%	5.5%	7.0%	6.0%	9.0%	8.8%	7.7%	11.1%	0.9%	0.2%	2.0%	2.7%	1.6%	4.6%	4.0%	2.9%	6.1%
350/15	3.7%	3.2%	4.4%	4.9%	4.3%	5.7%	5.7%	5.0%	6.6%	0.3%	-0.1%	0.6%	0.6%	0.1%	1.0%	0.9%	0.3%	1.2%
750/25	3.4%	2.9%	4.3%	4.4%	3.8%	5.3%	5.0%	4.3%	5.9%	0.0%	-0.2%	0.2%	0.1%	-0.1%	0.3%	0.2%	-0.2%	0.3%
immediate	3.4%	2.8%	4.3%	4.3%	3.7%	5.3%	4.8%	4.3%	5.9%									

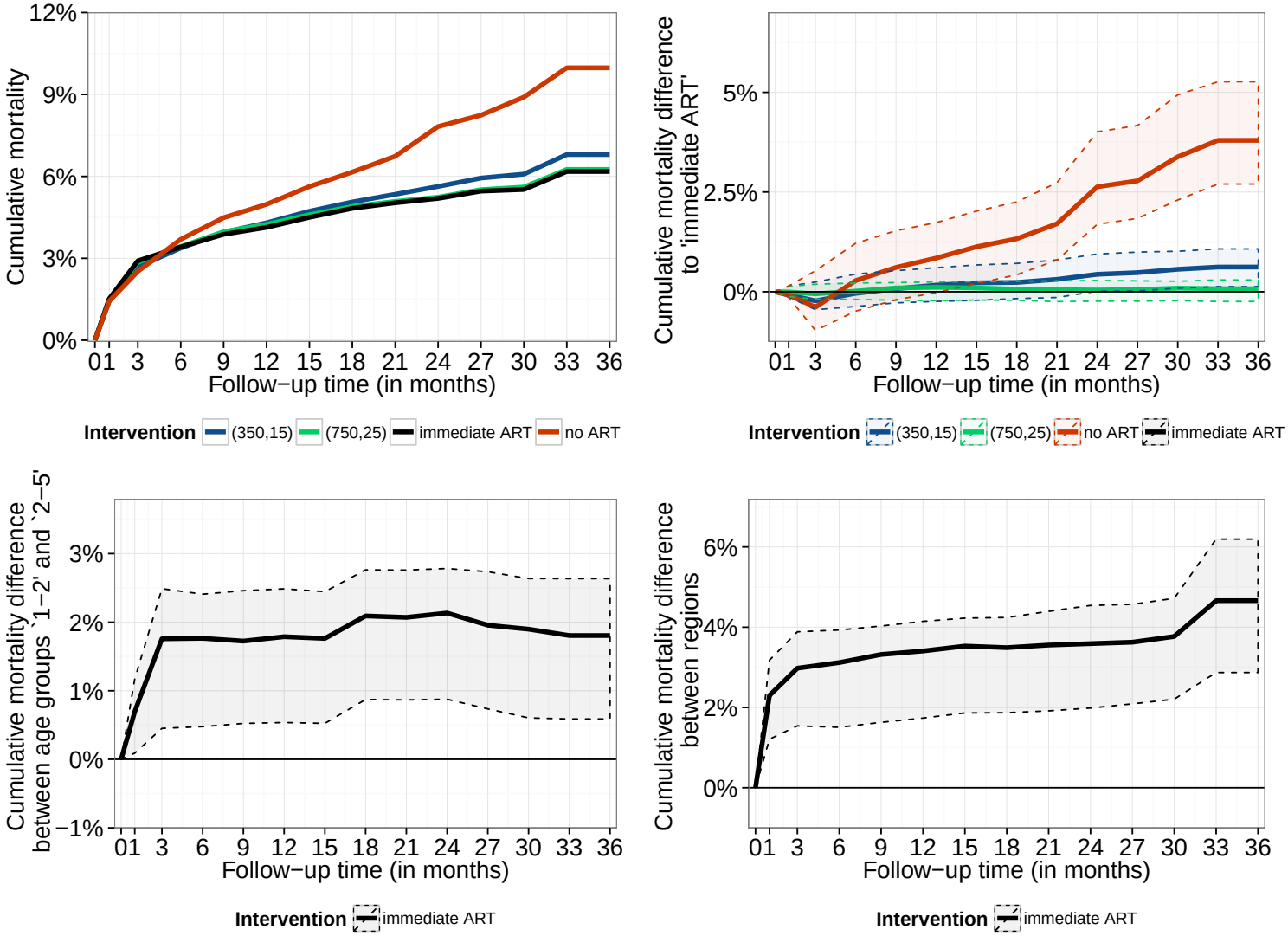
(b)	**Children age 1-2, after 3 years**						**Children age 2-5, after 3 years**						**MD between**		
	Mortality			**MD**			**Mortality**			**MD**			**age groups**		
no ART	9.9%	8.0%	12.7%	4.2%	2.4%	6.4%	8.3%	7.1%	11.4%	3.9%	2.8%	6.6%	1.6%	-1.1%	3.5%
350/15	6.8%	5.8%	8.2%	1.1%	0.2%	1.5%	5.1%	4.5%	6.0%	0.7%	0.3%	1.1%	1.7%	0.5%	2.9%
750/25	6.2%	5.1%	7.5%	0.5%	-0.3%	0.5%	4.4%	3.8%	5.3%	0.0%	-0.2%	0.4%	1.8%	0.6%	2.8%
immediate	5.7%	5.0%	7.4%				4.4%	3.8%	5.3%				1.3%	0.5%	2.8%

(c)	**Children from WA, after 3 years**						**Children from SA, after 3 years**						**MD between**		
	Mortality			**MD**			**Mortality**			**MD**			**regions**		
no ART	14.4%	12.1%	18.9%	6.1%	3.6%	10.7%	7.0%	5.9%	9.2%	3.3%	2.3%	5.2%	7.4%	4.9%	11.4%
350/15	9.3%	8.0%	11.4%	1.0%	0.3%	2.1%	4.5%	3.9%	5.3%	0.8%	0.2%	1.0%	4.8%	3.7%	6.5%
750/25	8.1%	6.9%	10.2%	-0.2%	-0.4%	0.8%	3.9%	3.4%	4.8%	0.2%	-0.2%	0.3%	4.2%	3.1%	6.0%
immediate	8.3%	6.8%	10.1%				3.7%	3.3%	4.8%				4.6%	2.9%	5.9%

eFigure 2. Sensitivity analysis I, mortality analysis: only children with complete baseline data (CD4 count, CD4%, WAZ, HAZ) are included (N=2604). Cumulative mortality as well as mortality differences between interventions, age groups and regions are reported. 95% confidence intervals are represented by shaded areas.



eFigure 3. Sensitivity analysis II, mortality analysis: Both outcome data (time to death/censoring) and follow-up data (CD4 count, CD4%, WAZ, HAZ) are imputed in addition to imputation of missing baseline data, see eTextbox 1 for more details. Follow-up data is imputed only from nine months without any visit data, as from there on it may be assumed that follow-up measurements that determine ART assignment (e.g. CD4 count) were taken (and are thus needed to adjust for time-dependent confounding) but not electronically recorded, probably because of administrative errors. Cumulative mortality as well as mortality differences between interventions, age groups and regions are reported. 95% confidence intervals are represented by shaded areas.



eTextbox 1. Details of the imputation procedure used for sensitivity analysis II.

We carried forward missing CD4 count, CD4%, WAZ, and HAZ data for up to nine months and then used longitudinal multiple imputation by means of the Expectation-Maximization-Bootstrap (EMB) algorithm (Honaker et al., 2011) to deal with the remaining missing follow-up data as well as the missing baseline data. Imputations were utilised only after nine months without any visit data, as from there on it can be speculated that follow-up measurements that determine ART assignment (e.g. CD4 count) were taken (and are thus needed to adjust for time-dependent confounding) but not electronically recorded, probably because of administrative errors. The imputation model included all baseline variables, follow-up variables (including lagged and lead versions of them), death, a carry-forward indicator variable, region, and also accounted for the longitudinal, possibly non-linear, structure of the data.

If a child was defined as LTFU we also imputed the outcome data (i.e. time to death/censoring, death/alive). In the first three months there was substantial loss to follow-up in Southern Africa, which is high both compared to the reported number of deaths and compared to West Africa:

West Africa

Outcome/Month	1	3	6	9	12	15	18	21	24	27	30	33	Total
Death	41	20	11	5	4	5	3	3	3	3	4	7	109
LTFU	71	49	32	24	18	7	13	7	12	14	14	65	326
Ratio LTFU/Death	1.73	2.45	2.91	4.80	4.50	1.40	4.33	2.33	4.00	4.67	3.50	9.29	2.99
Prior	0.09	0.14	0.18	0.37	0.34	0.06	0.31	0.13	0.29	0.36	0.24	0.94	

Southern Africa

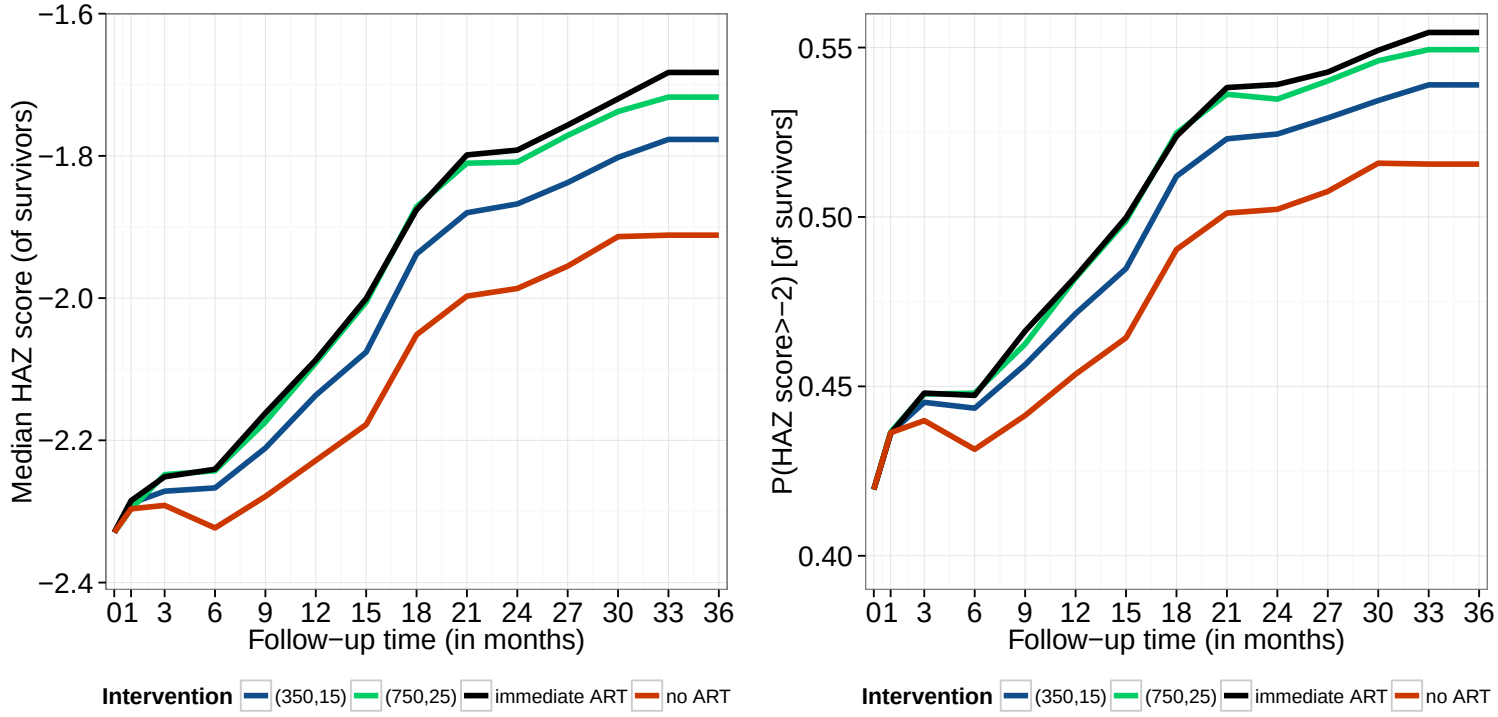
Outcome/Month	1	3	6	9	12	15	18	21	24	27	30	33	Total
Death	30	33	22	16	9	12	9	7	9	6	1	4	158
LTFU	278	165	102	77	41	42	30	34	29	29	17	25	869
Ratio LTFU/Death	9.27	5.00	4.64	4.81	4.56	3.50	3.33	4.86	3.22	4.83	17.00	6.25	5.50
Prior	0.93	0.39	0.36	0.38	0.35	0.24	0.22	0.38	0.21	0.38	0.95	0.54	

We therefore speculated that a large percentage of these children may have died and included this prior knowledge in the imputation model. For most months there is a similar ratio of LTFU/death, varying between 3 and 5. However, there is a high number of children being defined as lost shortly after their first visit in Southern Africa. In comparison to the number lost, the number of children who die is small as can be seen from the ratio of 9.27. It is likely that among these 278 lost children a substantial proportion died and that the percentage of those who died in the first month is higher when compared to the other months. This may be because children were brought only at a very advanced stage to the clinic, and were never able to come back (their baseline characteristics were worse than those of other children: median CD4 = 449, median CD4% = 14.6%, median WAZ = −4, median HAZ = −3.5). Thus, we now assume a higher probability of a lost child being dead if the ratio LTFU/dead is high. We define our prior knowledge via the function

$$f(\text{ratio}) \quad = \quad \min\left(\sqrt{\frac{\text{ratio}}{0.75}} \times \left\{1 - 1/\exp(\text{ratio}/3 - 0.3\,\text{ratio})\right\}, 0.95\right)$$

which yields prior probabilities for being dead among those lost between 0.2 and 0.3 for LTFU/Death ratios from 3 to 4, and this can be considered 'normal', see Table 1 in Schomaker et al. (2014). However, higher ratios, such as the one in Southern Africa in month 1 receive higher prior probabilities to be dead and these prior probabilities are added to the imputation model, see the appendix of Honaker and King (2010) and also Honaker et al. (2011) for details. Note, however, that the finally imputed value depends on both the imputation model that takes the whole covariate data and trajectories into account and the prior probability defined by us.

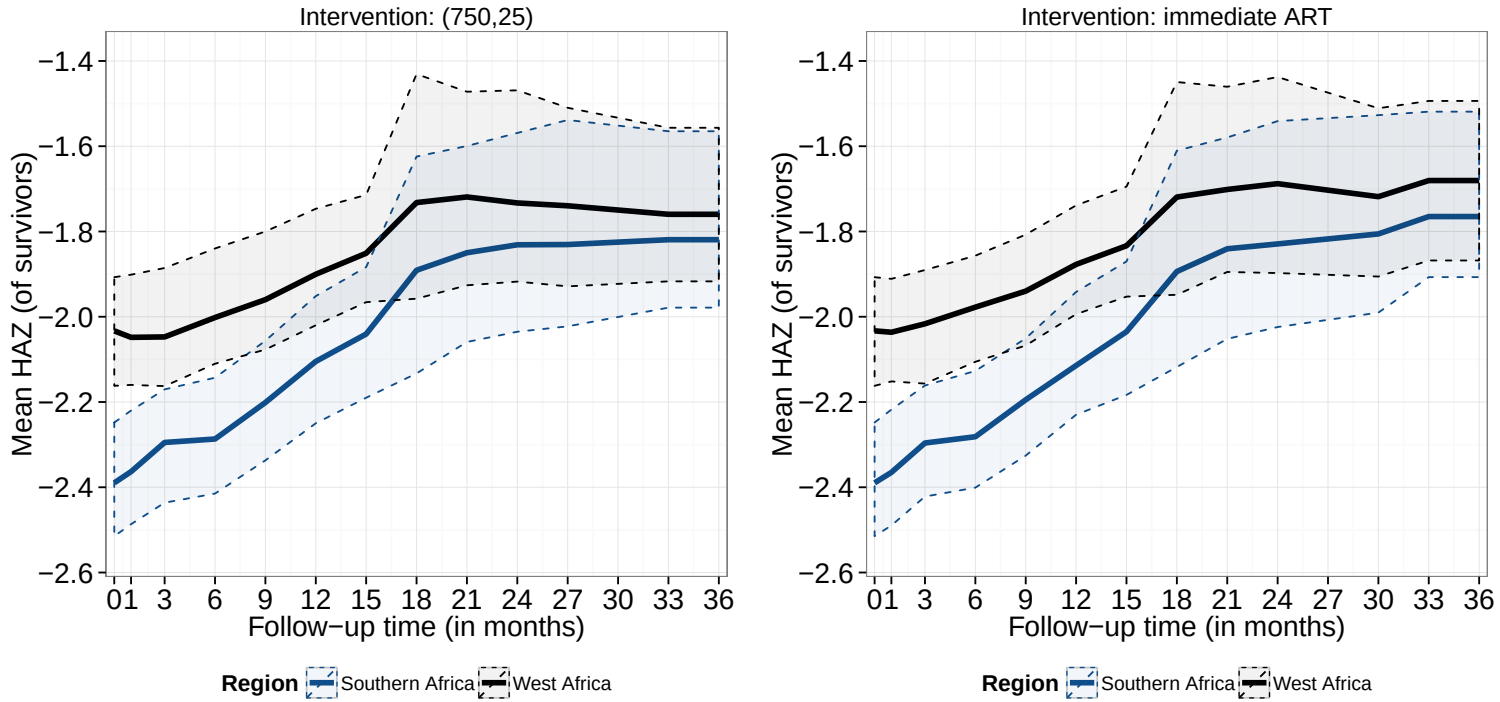
eFigure 4. Main analysis, growth: estimated median HAZ of survivors and probability of HAZ> −2 of survivors.



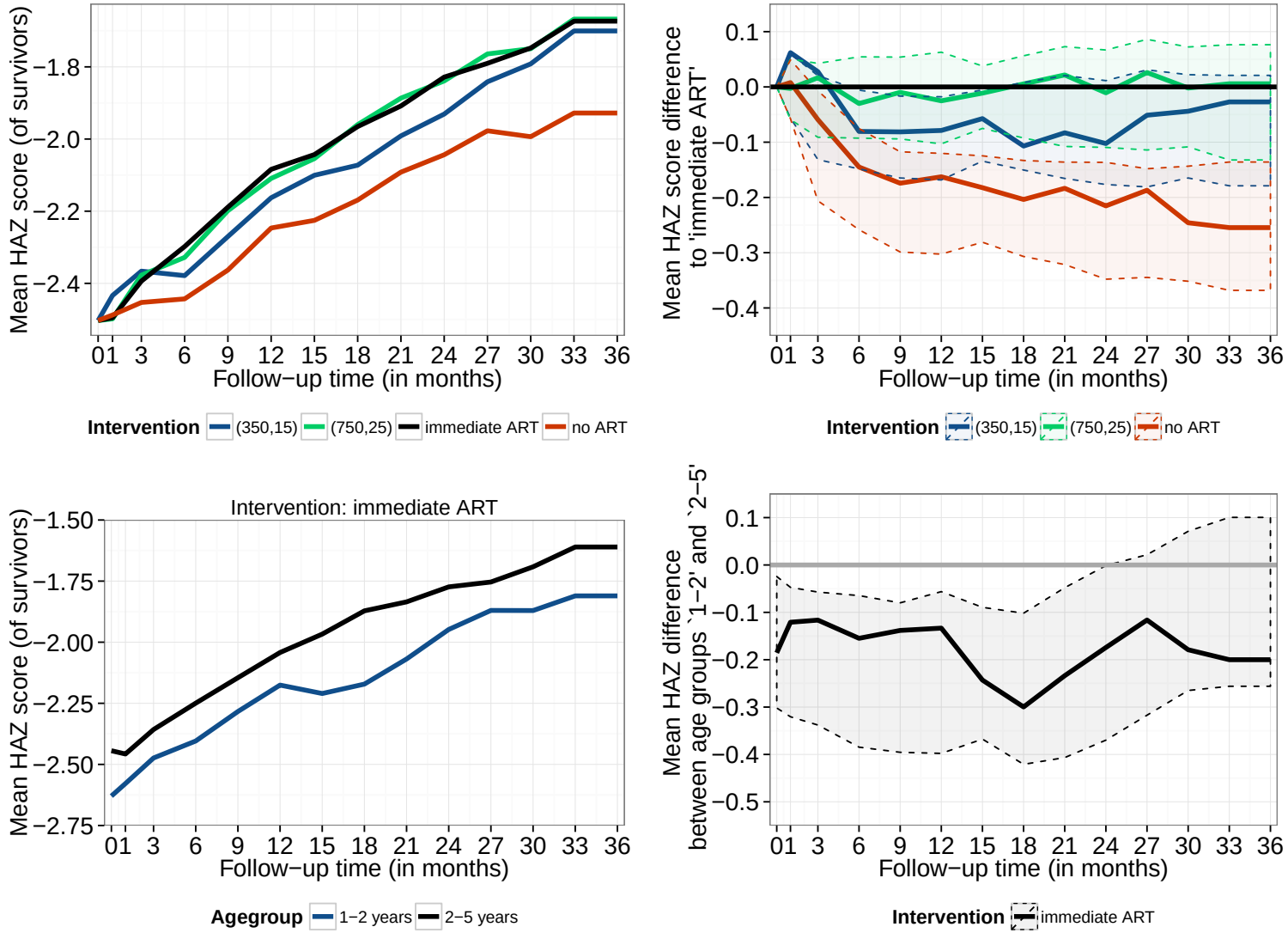
eTable 3. Main analysis, growth: cumulative incidence of HAZ> −2. All results are obtained from g-computation and 95% confidence intervals are obtained from bootstrapping.

	after 1 year			after 2 years			after 3 years		
	cumulative incidence	95% CI		cumulative incidence	95% CI		cumulative incidence	95% CI	
no ART	0.69	0.67	0.70	0.78	0.76	0.79	0.82	0.80	0.83
350/15	0.70	0.68	0.71	0.80	0.78	0.81	0.84	0.82	0.85
750/25	0.70	0.69	0.71	0.80	0.79	0.82	0.84	0.83	0.86
immediate	0.70	0.69	0.72	0.80	0.79	0.82	0.85	0.83	0.86

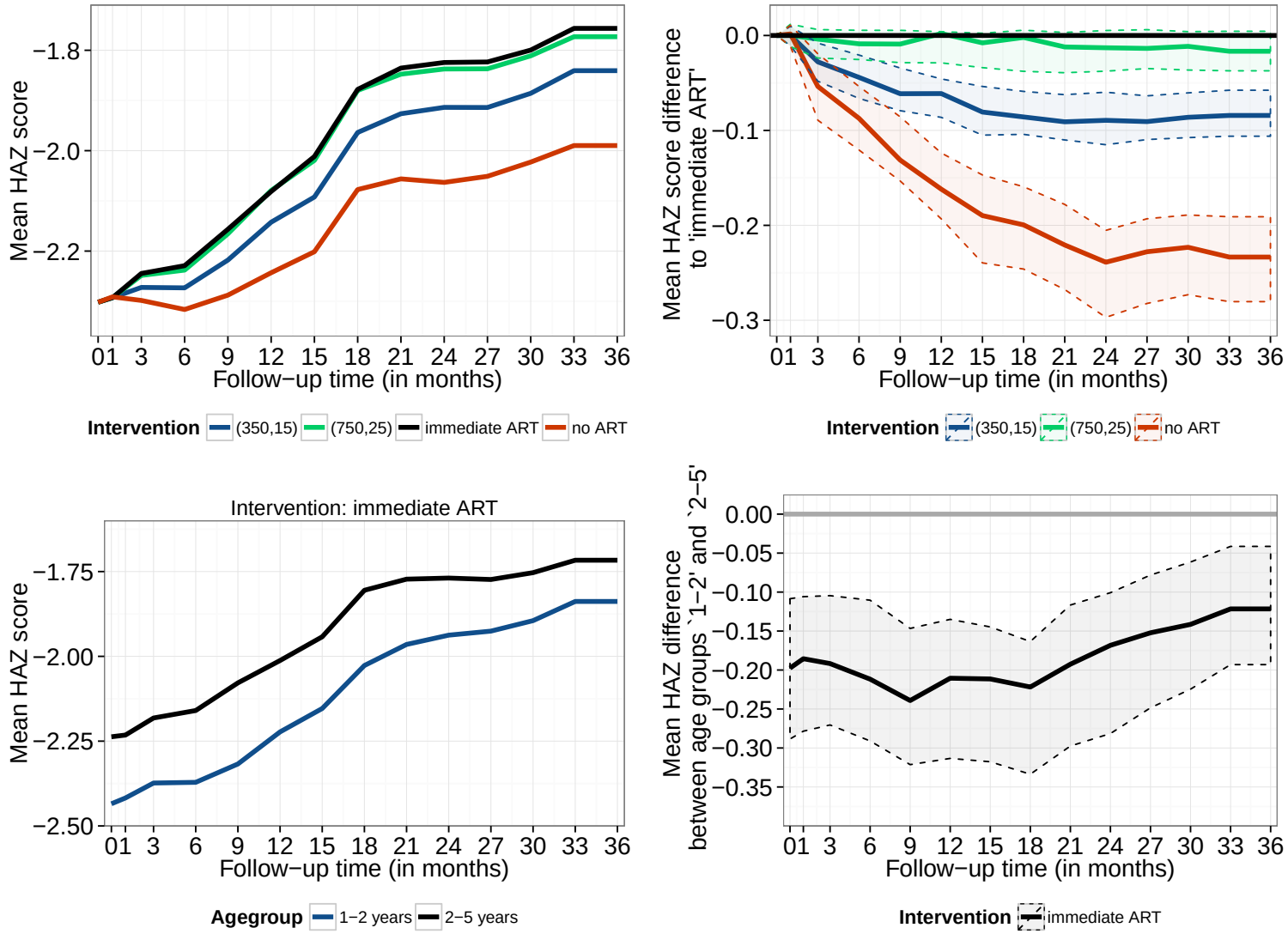
eFigure 5. Main analysis, growth: estimated mean HAZ of survivors for different regions and interventions.



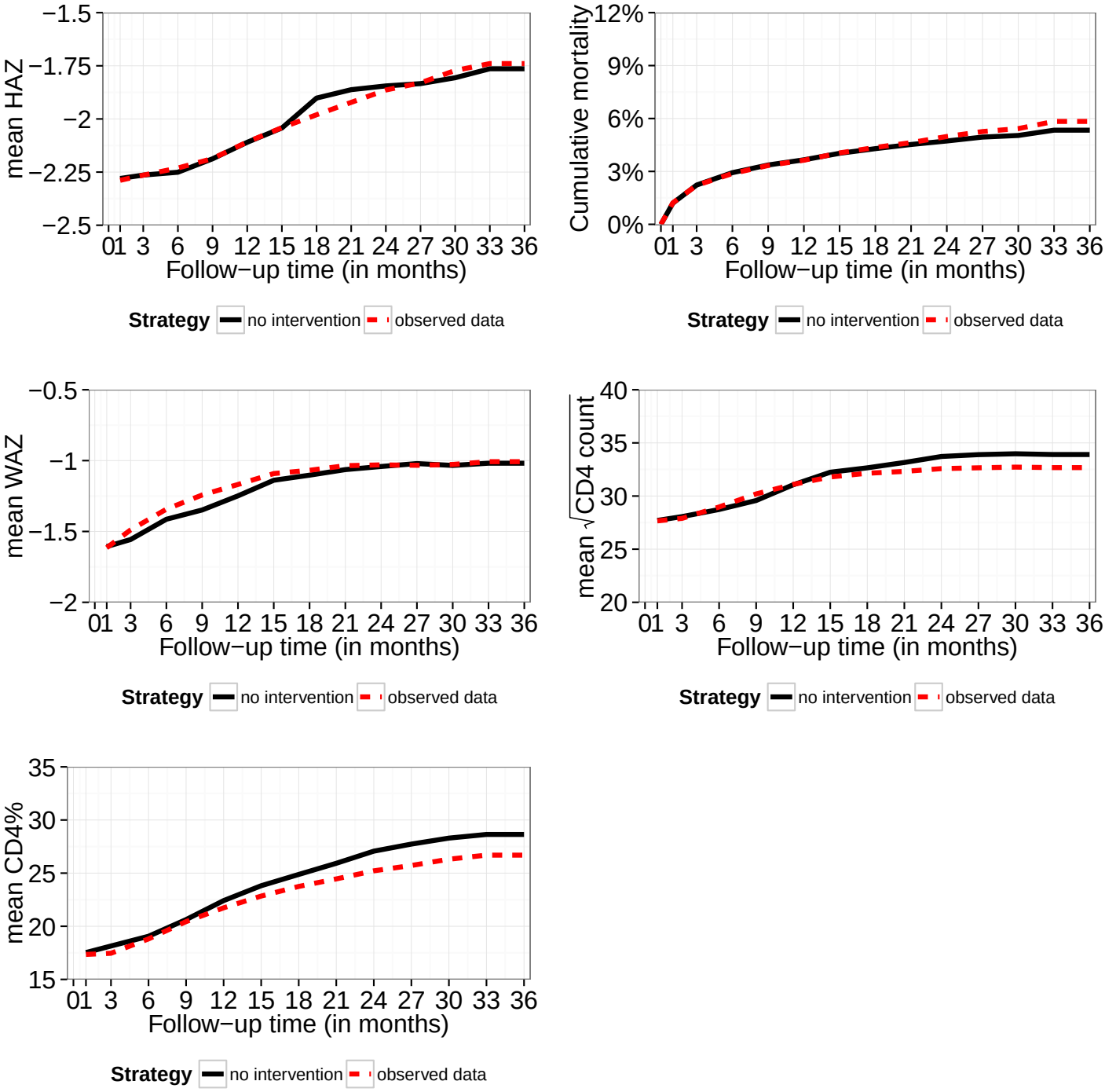
eFigure 6. Sensitivity analysis III, growth analysis: only children with complete baseline data (CD4 count, CD4%, WAZ, HAZ) are included (N=2604). Mean HAZ of survivors (top left), differences between interventions (top right), mean HAZ for different age groups (bottom left), and differences between age groups (bottom right) are reported. 95% confidence intervals are represented by shaded areas.



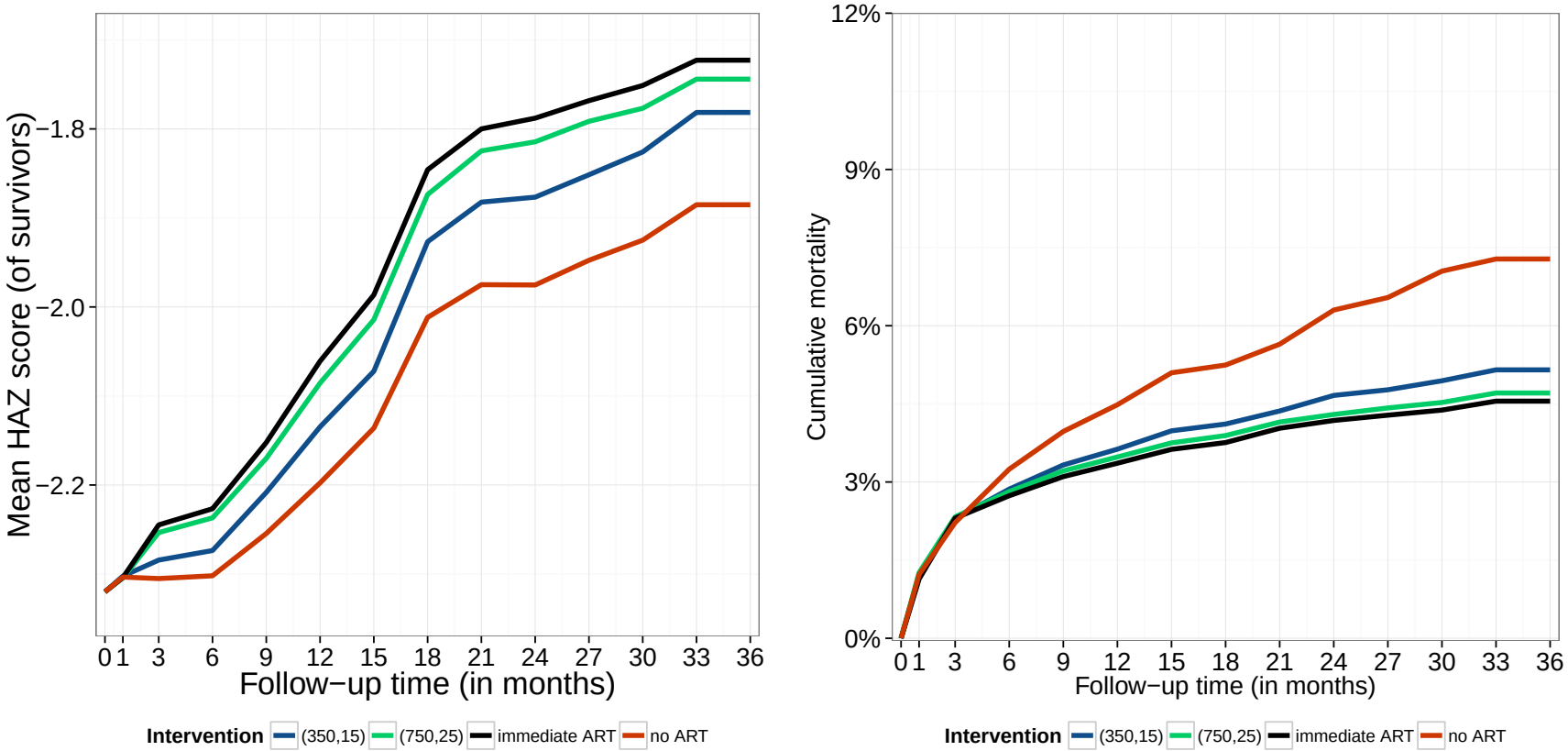
eFigure 7. Sensitivity analysis V, growth analysis: the mean HAZ is calculated under the assumption of no mortality. Mean HAZ (top left), differences between interventions (top right), mean HAZ for different age groups (bottom left), and differences between age groups (bottom right) are reported. 95% confidence intervals are represented by shaded areas.



eFigure 8. Mean HAZ, WAZ, $\sqrt{\text{CD4 count}}$, CD4%, and cumulative mortality estimated from both the observed data (red line, dashed) and using g-computation under the natural course ('no intervention', black line, solid).



eFigure 9. Sensitivity Analysis VI: mean HAZ and cumulative mortality for different intervention strategies under an alternative loss to follow-up definition: children were censored 9 months after having no contact with their health care facility, even if they re-entered care after 10 months or more.



eTextbox 2. Details on our specification of the g-computation algorithm.

Background:

Notation: Consider n subjects studied at baseline ($t = 0$) and during discrete follow-up times ($t = 1, \ldots, T$). The data consists of the outcome Y_t, an intervention variable A_t, q time-dependent covariates $\mathbf{L}_t = \{L_t^1, \ldots, L_t^q\}$, an indicator for administrative censoring C_t, and a censoring due to loss to follow-up (drop-out) indicator M_t. The covariates may also include baseline variables $V = \{L_0^1, \ldots, L_0^{q_V}\}$. The treatment and covariate history of an individual i up to and including time t is represented as $\bar{A}_{t,i} = (A_{0,i}, \ldots, A_{t,i})$ and $\bar{L}_{t,i}^s = (L_{0,i}^s, \ldots, L_{t,i}^s)$, $s \in \{1, \ldots, q\}$, respectively. C_t equals 1 if a subject gets censored administratively in the interval $(t-1, t]$, and 0 otherwise. Therefore, $\bar{C}_t = 0$ is the event that an individual remains administratively uncensored until time t. The same notation is used for M_t and $\bar{M}_t$.

Let $\mathbf{L}_{t+1}^*$ be the covariates which had been observed under a deterministic dynamic intervention rule $d_t^* = d_t^*(\bar{\mathbf{L}}_t)$ which assigns treatment $A_{t,i} \in \{0, 1\}$ as a function of the covariates $\bar{L}_{t,i}^s$. The counterfactual outcome $Y_{(\bar{a}^*,t,i)}$ refers to the hypothetical outcome that would have been observed at time t if a subjects had received, likely contrary to the fact, the treatment history $\bar{A}_t = \bar{a}_t^*$ related to rule d_t^*.

The g-computation formula: If the outcome is binary, and we are interested in the cumulative probability of $Y = 1$ at time T (under no loss to follow-up and no administrative censoring), the g-computation formula can be written as

$$\sum_{t=1}^{T} \mathbb{P}(Y_{(\bar{a}^*,t)} = 1 | \bar{C}_t = 0, \bar{M}_t = 0) \quad =^1 \quad \sum_{t=1}^{T} \int_{\bar{\mathbf{l}} \in \bar{\mathbf{L}}_t} \mathbb{P}(Y_t = 1 | \bar{A}_t = \bar{a}_t^*, \bar{\mathbf{L}}_t = \bar{\mathbf{l}}_t, \bar{C}_t = 0, \bar{M}_t = 0) \times \prod_{t=1}^{T} f(\mathbf{L}_t | \bar{A}_{t-1} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{l}}_{t-1}, \bar{C}_t = 0, \bar{M}_t = 0) \, d\bar{\mathbf{l}}, \tag{1}$$

see Westreich et al. (2012). For ordered $\mathbf{L}_t = \{L_t^1, \ldots, L_t^q\}$ we can write the second part of (1) as

$$\prod_{t=1}^{T} \prod_{s=1}^{q} f(L_t^s | \bar{A}_{t-1} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{l}}_{t-1}, L_t^1 = l_t^1, \ldots, L_t^{s-1} = l_t^{s-1}, \bar{C}_t = 0, \bar{M}_t = 0) \,. \tag{2}$$

Our setting: In our setting we study $n = 5826$ children for $t = 0, 1, 3, 6, 9, \ldots$ where the follow-up time points refer to the intervals $(0, 1.5)$, $[1.5, 4.5)$, $[4.5, 7.5)$, $[7.5, 10.5)$, $[10.5, 13.5)$, $[13.5, 16.5)$, $[16.5, 19.5)$, $[19.5, 22.5)$, $[22.5, 25.5)$, $[25.5, 28.5)$, $[28.5, 31.5)$, $[31.5, 36)$ months respectively. The exact measurement date (days after first visit) is denoted as $\tilde{t}$. Follow-up measurements, if available, refer to measurements closest to the middle of the interval. In our data

- Y_t refers to death at time t (i.e. occurring during the interval $(t-1, t]$)
- A_t refers to antiretroviral treatment (ART) taken at time t
- $\mathbf{L}_t = (L_t^1, L_t^2, L_t^3)$ refer to CD4 count, CD4%, and weight for age z-score (WAZ)[2]
- $V = \mathbf{L}_0^V$ refers to baseline values of CD4 count, CD4%, WAZ, height for age z-score (HAZ) as well as sex, age, and region
- $d_{t,j}(\mathbf{L}_t)$ refer to dynamic treatment rules assigning treatment based on CD4 count and CD4%

We want to estimate cumulative mortality (under no administrative censoring and loss to follow-up) after T months, that is $\sum_{t=1}^{T} \mathbb{P}(Y_{(\bar{a}^*,t)} = 1 | \bar{C}_t = 0, \bar{M}_t = 0)$ for $T = 1, 3, 6, \ldots$.

[1] The equality holds under assumptions such as *consistency* (if $\bar{A}_{t,i} = \bar{a}_{t,i}$, then $Y_{(\bar{a},t)} = Y_t$ for $\forall t, \bar{a}$), *no unmeasured confounding* (conditional exchangeability, $Y_{(\bar{a}^*,t)} \perp A_t | \bar{\mathbf{L}}_t, \bar{A}_{t-1}$ for $\forall t, \bar{a}$), *positivity* ($\mathbb{P}(\bar{A}_t = \bar{a}_t | \bar{\mathbf{L}}_t = \mathbf{l}_t) > 0$ for $\forall t, \bar{a}, \mathbf{l}$), as well as correctly specified models etc. – see Robins and Hernan (2009), Daniel et al. (2013, 2011), Young et al. (2011) and Robins et al. (2004) for more details and interpretations.

[2] Note that weight for age-z-scores serve as a proxy for WHO stage because most stage-defining events relate to a child's WAZ, such as tuberculosis or persistent diarrhoea, see Schomaker et al. (2013) for more details

a) Detailed g-computation algorithm for outcome "death":

Step 1: Modelling.

a) Time dependent confounders: We used additive linear models to estimate the association of the time-dependent confounders (CD4 count, CD4 percentage, weight for age z-score at time t) with disease progression history (CD4 count, CD4 percentage, weight for age z-score at time $t-1$), demographics (age, sex, region), and the intervention (ART at times $t-1$ and $t-2$) for $\forall t$. This corresponds to fitting 3 models (relating to the 3 time-dependent confounders) for 12 points in time. In more detail, we initially fit the linear models:

$$\begin{aligned}\sqrt{\text{CD4 count}_t} &= f_1(\text{CD4 count}_{t-1}) + f_2(\text{CD4\%}_{t-1}) + f_3(\text{WAZ}_{t-1}) \\ &\quad + f_4(\text{CD4 count}_0) + f_5(\text{CD4\%}_0) + f_6(\text{WAZ}_0) + f_7(\text{HAZ}_0) + f_8(\tilde{t}) + f_9(\text{Age}) \\ &\quad + \beta_0 + \beta_1\text{Region} + \beta_2\text{Sex} + \beta_3\text{ART}_{t-1} + \beta_4\text{ART}_{t-2} + \epsilon\,, \quad \epsilon \sim N(0, \sigma^2 I) \end{aligned} \tag{3}$$

$$\begin{aligned}\text{CD4\%}_t &= f_1(\text{CD4 count}_t) + f_2(\text{CD4 count}_{t-1}) + f_3(\text{CD4\%}_{t-1}) + f_4(\text{WAZ}_{t-1}) \\ &\quad + f_5(\text{CD4 count}_0) + f_6(\text{CD4\%}_0) + f_7(\text{WAZ}_0) + f_8(\text{HAZ}_0) + f_9(\tilde{t}) + f_{10}(\text{Age}) \\ &\quad + \beta_0 + \beta_1\text{Region} + \beta_2\text{Sex} + \beta_3\text{ART}_{t-1} + \beta_4\text{ART}_{t-2} + \epsilon\,, \quad \epsilon \sim N(0, \sigma^2 I) \end{aligned} \tag{4}$$

$$\begin{aligned}\text{WAZ}_t &= f_1(\text{CD4\%}_t) + f_2(\text{CD4 count}_t) + f_3(\text{CD4 count}_{t-1}) + f_3(\text{CD4\%}_{t-1}) + f_5(\text{WAZ}_{t-1}) \\ &\quad + f_6(\text{CD4 count}_0) + f_7(\text{CD4\%}_0) + f_8(\text{WAZ}_0) + f_9(\text{HAZ}_0) + f_{10}(\tilde{t}) + f_{11}(\text{Age}) \\ &\quad + \beta_0 + \beta_1\text{Region} + \beta_2\text{Sex} + \beta_3\text{ART}_{t-1} + \beta_4\text{ART}_{t-2} + \epsilon\,, \quad \epsilon \sim N(0, \sigma^2 I) \end{aligned} \tag{5}$$

These models estimate the conditional densities from equation (2) for $\forall s, t$.

b) Outcome: We used a logistic additive model to estimate the association of the outcome (death) with the time dependent confounders at time t, disease progression history, baseline characteristics, demographics, and intervention for $t = 1, 3, 6, ..., 36$. This corresponds to fitting 1 (non-pooled) model for 12 points in time.

$$\begin{aligned}\log\left(\frac{\mathbb{P}(Y_t=1)}{1-\mathbb{P}(Y_t=1)}\right) &= f_1(\text{CD4 count}_t) + f_2(\text{CD4\%}_t) + f_3(\text{WAZ}_t) \\ &\quad + f_4(\text{CD4 count}_{t-1}) + f_5(\text{CD4\%}_{t-1}) + f_6(\text{WAZ}_{t-1}) \\ &\quad + f_7(\text{CD4 count}_0) + f_8(\text{CD4\%}_0) + f_9(\text{WAZ}_0) + f_{10}(\text{HAZ}_0) + f_{11}(\tilde{t}) + f_{12}(\text{Age}) \\ &\quad + \beta_0 + \beta_1\text{Region} + \beta_2\text{Sex} + \beta_3\text{ART}_{t-1} + \beta_4\text{ART}_{t-2} \end{aligned} \tag{6}$$

These models estimate the first part of equation (1) for $\forall t$.

Note: The models (3)-(6) are restricted to those subjects who survived until time t and were not censored (administratively or due to LTFU). The functions f_j are estimated via penalized regression splines (with smoothness determined by generalized cross validation [GCV, Golub et al., 1979]). All models implicitly assume that time-dependent risk factors measured before or on time $t-2$ do not predict the respective outcome. All models are updated based on model selection, see item c) below.

c) Model selection:

i) To allow for flexible disease progression depending on how sick children are when they present at their first visit, interactions of baseline characteristics (represented in categories)[3] with all other variables were added. Depending on the functional form of the covariates these interactions were either linear or non-linear. If an interaction improved the GCV score the interaction was kept in the model, otherwise it was removed again.

ii) After adding interactions to the respective models in a forward selection, variables and interactions were removed in a backward selection if this again improved the GCV score. If the plotted nonlinear interactions showed signs of volatility they were removed as well.

iii) The order in which variables and their interactions were first added and then removed corresponds to the order of the variables listed in equations (3)-(6).

[3] categories for first visit CD4 count are '$[0,50), [50,200), > 200$', for CD4% '$[0,20), [20,30), > 30$', and for WAZ '$< -3, [-3,-1.5), > 1.5$'

↓

Step 2: Intervention choice and repitition. We choose one of the following four interventions:

i) Give a child ART immediately, irrespective of his/her CD4 count:

$$d^*_{t,i,1}(\text{CD4 count}_{t,i}, \text{CD4\%}_{t,i}) = \begin{cases} a^*_{t,i} = 1 & \text{always} \\ a^*_{t,i} = 0 & \text{never} \end{cases}$$

ii) Give a child ART when his/her absolute CD4 count falls below 750 cells/mm^3 or his/her CD4 percentage falls below 25%:

$$d^*_{t,i,2}(\text{CD4 count}_{t,i}, \text{CD4\%}_{t,i}) = \begin{cases} a^*_{t,i} = 1 & \text{if} \quad \text{CD4 count}^*_{t,i} < 750 \quad \text{or} \quad \text{CD4\%}^*_{t,i} < 25 \\ a^*_{t,i} = 0 & \text{otherwise} \end{cases}$$

iii) Give a child ART when his/her absolute CD4 count falls below 350 cells/mm^3 or his/her CD4 percentage falls below 15%:

$$d^*_{t,i,3}(\text{CD4 count}_{t,i}, \text{CD4\%}_{t,i}) = \begin{cases} a^*_{t,i} = 1 & \text{if} \quad \text{CD4 count}^*_{t,i} < 350 \quad \text{or} \quad \text{CD4\%}^*_{t,i} < 15 \\ a^*_{t,i} = 0 & \text{otherwise} \end{cases}$$

iv) Never give a child ART:

$$d^*_{t,i,4}(\text{CD4 count}_{t,i}, \text{CD4\%}_{t,i}) = \begin{cases} a^*_{t,i} = 1 & \text{never} \\ a^*_{t,i} = 0 & \text{always} \end{cases}$$

↓

Step 3: Monte-Carlo Simulation. We simulate data for the children for each specific intervention rule *forward in time* based on the estimated conditional distributions from Step 1.

At the first visit, $t = 0$, the data corresponds to the observed data of *all* children.

a) Simulation of the covariates $\mathbf{L}^*_t = (\text{CD4 count}^*_t, \text{CD4\%}^*_t, \text{WAZ}^*_t)$ for $t = 1, 3, 6, 9, \ldots$:

- Applying the chosen treatment rule from step 2[4] (i.e. $d^*_{t,j}$) to the models (3)-(5) yields predicted square root CD4 counts ($\hat{L}^1_t$), CD4% ($\hat{L}^2_t$), and WAZ ($\hat{L}^3_t$).

[4] For example, setting $\text{ART}_t = 0$ in all models if $d_{t,4}$ [never give a child ART] is applied

- Drawing from the conditional distributions in (2) relates to drawing from normal distributions with mean $\hat{L}_t^1$ and variance $\hat{\sigma}^2_{\mathcal{M}}$ (which is the estimated residual variance from the respective model):

$$\tilde{L}_t^s \quad \text{drawn from} \quad N(\hat{L}_t^s, \hat{\sigma}^2_{\mathcal{M}})$$

- The simulated counterfactual covariates related to the chosen treatment rule are therefore $\mathbf{L}_t^* = \tilde{\mathbf{L}}_t^s$.
- The simulated values of CD4 count, CD4% and WAZ at time $t-1$ ($\tilde{\mathbf{L}}_{t-1}$) are used when predicting CD4 count, CD4% and WAZ at time t ($\hat{\mathbf{L}}_t$ and $\tilde{\mathbf{L}}_t$).

b) As in a), we apply the chosen treatment rule from step 2. The hypothetical outcome (death) is simulated based on a draw from a Bernoulli distribution with the probability obtained from the logistic additive model fitted in Step 1b), that is $\hat{p}_t$.

$$\tilde{Y}_t \quad \text{drawn from} \quad B(\hat{p}_t)$$

If the simulated outcome for an individual at time t is equal to 1 (death), then there will be no more follow-up at time t+1.

Note that we intervene on administrative censoring and loss to follow-up by setting $\bar{C}_t = 0$ and $\bar{M}_t = 0$ and therefore simulate a dataset with no administrative censoring and drop-out.

By applying a) and b) over time (from $t = 1$ onwards) a simulated dataset, consisting of ($\tilde{Y}$, $\tilde{\mathbf{L}}$), is generated for each particular treatment rule. Repeating this for all interventions yields $(\tilde{Y}, \tilde{\mathbf{L}})^d = \{(\tilde{Y}, \tilde{\mathbf{L}})^{d_1}, (\tilde{Y}, \tilde{\mathbf{L}})^{d_2}, (\tilde{Y}, \tilde{\mathbf{L}})^{d_3}, (\tilde{Y}, \tilde{\mathbf{L}})^{d_4}\}$

The simulation procedure approximates the integral in (1) for a specific treatment rule with the aim to estimate cumulative mortality as defined in (1).

↓

Step 4: Estimation of mortality. We estimate the cumulative relative mortality $\omega_T = \sum_{t=1}^{T} \mathbb{P}(Y_{(\bar{a}^*,t)} = 1 | \bar{C}_t = 0, \bar{M}_t = 0)$ for $T = 1, 3, 6, \ldots$ months: the proportion of children who died at the different time points in the simulated dataset $(\tilde{Y}, \tilde{\mathbf{L}})^{d_i}$ from Step 3 equates to the g-computation formula estimate of the cumulative mortality under intervention rule d_i.

↓

Step 5: Multiple Imputation. Steps 1 to 4 are implemented for 10 imputed sets of data. Multiple imputation was utilized with the `Amelia II` package in R (Honaker et al., 2011). The imputation model included all measured baseline and follow-up variables, mortality, follow-up time, a variable indicating which observations were carried forward, and the region (West Africa, Southern Africa). The longitudinal structure of the data was explicitly considered in the EMB algorithm, nonlinear time trends were allowed and lag- and lead-variables of CD4 count, CD4%, and HAZ were added to the imputation model. For the main analysis only missing baseline data was imputed. Imputation diagnostics (comparing imputed and observed densities, overimputation, convergence of EM chains, time-series plots; see also Honaker et al., 2011) were evaluated to ensure the convergence of the algorithm and the appropriateness of the imputations.

The procedure yields 10 different mortality estimates related to the 10 imputed sets of data ($\hat{\omega}_T^{(m)}; m = 1, \ldots, 10$). The final point estimate for the cumulative mortality is therefore

$$\hat{\omega}_T^{\text{MI}} = \frac{1}{10} \sum_{m=1}^{10} \hat{\omega}_T^{(m)} \quad \text{for} \quad T = 1, 3, 6, \ldots . \tag{7}$$

↓

Step 6: Bootstrap repetitions. We repeat steps 1 to 5 for 200 bootstrap samples to obtain 95% confidence intervals. Each bootstrap sample includes missing data and needs to be multiply imputed. Thus, for each bootstrap sample we estimate $\hat{\omega}_T^{MI}$ which yields 200 cumulative mortality estimates $\hat{\omega}_T^{b,d_i}, b = 1, \ldots, 200$ for each intervention. The bounds of the 95% confidence intervals are set at the 2.5^{th} and 97.5^{th} percentiles of the distribution of these 200 estimates.

b) G-computation algorithm for outcome "growth": The algorithm corresponds to the above algorithm for outcome "death", but with the following additions:

Background: The main quantity of interest for this analysis is the expected height-for-age z-score of all survivors under no loss to follow-up and no administrative censoring for different time points and interventions. Consider the notation from the analysis above, but let Y_t be the height-for-age z-score at time t and S_t an indicator variable which is 1 if a patient is still alive at time t and 0 otherwise. Then the g-computation formula from (1) can be re-written as

$$\begin{aligned}\mathbb{E}(Y_{(\bar{a}^*,t)}|\bar{C}_t = 0, \bar{M}_t = 0, S_t = 1) &= \int_{\bar{\mathbf{l}} \in \bar{\mathbf{L}}_t} \mathbb{E}(Y_t|\bar{A}_t = \bar{a}_t^*, \bar{\mathbf{L}}_t = \bar{\mathbf{l}}_t, \bar{C}_t = 0, \bar{M}_t = 0, S_t = 1) \\ &\quad \times \prod_{t=1}^{T} \big\{ f(\mathbf{L}_t|\bar{A}_{t-1} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{l}}_{t-1}, \bar{C}_t = 0, \bar{M}_t = 0, S_t = 1) \times \\ &\qquad \mathbb{P}(S_t = 1|\bar{A}_{t-1} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{l}}_{t-1}, \bar{C}_t = 0, \bar{M}_t = 0) \big\} \, d\bar{\mathbf{l}} \end{aligned} \tag{8}$$

Evaluating secondary outcomes (probability of having a WAZ> -2, 50% quantile of WAZ, cumulative incidence of HAZ> -2) also makes use of the above formula but replaces the expectation with the respective quantity of interest. To estimate (8) the algorithm for the outcome death can be used, with the following additions and changes:

Step 1: We used an additive linear model to also model the association of (the outcome) height for age z-score with disease progression history, baseline variables, demographics, and the intervention:

$$\begin{aligned}\text{HAZ}_t &= f_1(\text{CD4\%}_t) + f_2(\text{CD4 count}_t) + f_3(\text{WAZ}_t) \\ &\quad + f_4(\text{CD4 count}_{t-1}) + f_5(\text{CD4\%}_{t-1}) + f_6(\text{WAZ}_{t-1}) + f_7(\text{HAZ}_{t-1}) \\ &\quad + f_8(\text{CD4 count}_0) + f_9(\text{CD4\%}_0) + f_{10}(\text{WAZ}_0) + f_{11}(\text{HAZ}_0) + f_{12}(\tilde{t}) + f_{13}(\text{Age}) \\ &\quad + \beta_0 + \beta_1 \text{Region} + \beta_2 \text{Sex} + \beta_3 \text{ART}_{t-1} + \beta_4 \text{ART}_{t-2} + \epsilon\,, \quad \epsilon \sim N(0, \sigma^2 I) \end{aligned} \tag{9}$$

In addition, models (3)-(6) contain $f_i(\text{HAZ}_{t-1})$. Model (6) is used to model survival.

Step 2: as in a)

Step 3: We simulate height for age z-score data for all children for a specific intervention forward in time. The predictions are based on a random draw from a normal distribution where mean and standard error are obtained from the prediction of the additive linear model (9) fitted in Step 1, i.e. $\tilde{Y}_t$ drawn from $N(\hat{Y}_t, \hat{\sigma}^2_{\mathcal{M}})$. The probability of death is simulated as in a), i.e. as specified in (6), and $\tilde{S}_t$ is drawn from $B(\hat{p}_t)$. Note that we still intervene on administrative censoring and loss to follow-up by setting $\bar{C}_t = 0$ and $\bar{M}_t = 0$ and therefore simulate a dataset with no administrative censoring and no drop-out. However, in the main analysis, we do not intervene upon S_t which implies that if the simulated outcome for an individual at time t is equal to 1 (death), then there will be no more follow-up at time $t + 1$. Consequently, the number of individuals in the simulated datasets $(\tilde{Y}, \tilde{\mathbf{L}})^d$ varies with respect to time and intervention.

Step 4: We estimate the expected height-for-age z-score of all survivors under no loss to follow-up and no administrative censoring, $\mathbb{E}(Y_{(\bar{a}^*,t)}|\bar{C}_t = 0, \bar{M}_t = 0, S_t = 1)$, for $t = 1, 3, 6, ...$ months: the mean HAZ at time t in the simulated dataset $(\tilde{Y}, \tilde{\mathbf{L}})^{d_i}$ from Step 3 equates to the g-computation formula estimate of the expected HAZ under intervention rule d_i. Similarly, the secondary outcomes (median HAZ and proportion/cumulative incidence of HAZ> 2 at time t in the simulated data) estimate the 50% quantile, the probability of having a HAZ> -2 and the probability of having a HAZ> -2 before dying.

Step 5 and 6: as in a)

References

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eTextbox 3. Steering Groups of IeDEA-SA and IeDEA-WA.

IeDEA-SA Steering Group: Frank Tanser, Africa Centre for Health and Population Studies, University of Kwazulu-Natal, Somkhele, South Africa; Christopher Hoffmann, Aurum Institute for Health Research, Johannesburg, South Africa; Benjamin Chi, Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; Denise Naniche, Centro de Investigacao em Saude de Manhica, Manhica, Mozambique; Robin Wood, Desmond Tutu HIV Centre (Gugulethu and Masiphumelele clinics), Cape Town, South Africa; Kathryn Stinson, Khayelitsha ART Programme and Medecins Sans Frontieres, Cape Town, South Africa; Geoffrey Fatti, Khet'Impilo Programme, South Africa; Sam Phiri, Lighthouse Trust Clinic, Lilongwe, Malawi; Janet Giddy, McCord Hospital, Durban, South Africa; Maureen Wellington, Newlands Clinic, Harare, Zimbabwe; Kennedy Malisita, Queen Elizabeth Hospital, Blantyre, Malawi; Brian Eley, Red Cross War Memorial Childrens Hospital and School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa; Jara Llenas, SolidarMed SMART Programme, Pemba Region, Mozambique; Christiane Fritz, SolidarMed SMART Programme, Masvingo, Zimbabwe; Matthew Fox and Mhairi Maskew, Themba Lethu Clinic, Johannesburg, South Africa; Hans Prozesky, Tygerberg Academic Hospital, Stellenbosch, South Africa; Karl Technau, Empilweni Clinic, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa; Shobna Sawry, Harriet Shezi Childrens Clinic, Chris Hani Baragwanath Hospital, Soweto, South Africa.

IeDEA-WA Paediatric Group, steering and executive committee: Benin, Cotonou: Pediatrics: Sikiratou Koumakpai, Florence Alihonou, Marcelline d'Almeida, Irvine Hodonou, Ghislaine Hounhoui, Gracien Sagbo, Leila Tossa-Bagnan, Herman Adjide (CNHU Hubert Maga). Burkina Faso: Pediatrics: Diarra Ye, Fla Koueta, Sylvie Ouedraogo, Rasmata Ouedraogo, William Hiembo, Mady Gansonre (CH Charles de Gaulle, Ouagadougou). Cote d'Ivoire, Abidjan: Pediatrics: Koffi Ladji Issouf, Jean-Claude Kouakou, Marie-Sylvie N'Gbeche, (ACONDA-CePReF); Toure Pety, Divine Avit-Edi (ACONDA-MTCT-Plus); Kouadio Kouakou, Magloire Moh, Valerie Andoble Yao (CIRBA); Madeleine Amorissani Folquet, Marie-Evelyne Dainguy, Cyrille Kouakou, Veronique Tanoh Mea-Assande, Gladys Oka-Berete, Nathalie Zobo, Patrick Acquah, Marie-Berthe Kokora (CHU Cocody); Tanoh Francois Eboua, Marguerite Timite-Konan, Lucrece Diecket Ahoussou, Julie Kebe Assouan, Mabea Flora Sami, Clemence Kouadio (CHU Yopougon). Ghana, Accra: Pediatrics: Lorna Renner, Bamenla Goka, Jennifer Welbeck, Adziri Sackey, Seth Ntiri Owiafe (Korle Bu TH). Mali, Bamako: Pediatrics: Fatoumata Dicko, Mariam Sylla, Alima Berthe, Hadizatou Coulibaly Traore, Anta Koita, Niaboula Kone, Clementine N'Diaye, Safiatou Toure Coulibaly, Mamadou Traore, Naichata Traore (CH Gabriel Toure).Senegal, Dakar: Pediatrics: Haby Signate Sy, Abou Ba, Aida Diagne, Helene Dior, Malick Faye, Ramatoulaye Diagne Gueye, Aminata Diack Mbaye (CH Albert Royer).Togo, Lome: Pediatrics: Koko Lawson-Evi, Yawo Atakouma, Elom Takassi, Amyo Djeha, Ayoko Ephoevi-gah, Sherifa El-Hadj Djibril (CHU Tokoin/Sylvanus Olympio). Executive Committeee: Franois Dabis (Principal Investigator, Bordeaux, France), Emmanuel Bissagnene (Co-Principal Investigator, Abidjan, Cote d'Ivoire), Elise Arrive (Bordeaux, France), Patrick Coffie (Abidjan, Cote d'Ivoire), Didier Ekouevi (Abidjan, Cte dIvoire), Antoine Jaquet (Bordeaux, France), Valeriane Leroy (Bordeaux, France), Annie J Sasco (Bordeaux, France).Operational and Statistical Team: Jean-Claude Azani (Abidjan, Cote d'Ivoire), Eric Balestre (Bordeaux, France), Serge Bessekon (Abidjan, Cote d'Ivoire), Sophie Karcher (Bordeaux, France), Jules Mahan Gonsan (Abidjan, Cote d'Ivoire), Jerome Le Carrou (Bordeaux, France), Severin Lenaud (Abidjan, Cte dIvoire), Celestin Nchot (Abidjan, Cote d'Ivoire), Karen Malateste (Bordeaux, France), Amon Roseamonde Yao (Abidjan, Cote d'Ivoire). Administrative Team: Abdoulaye Cisse (Abidjan, Cote d'Ivoire), Alexandra Doring (Bordeaux, France), Adrienne Kouakou (Abidjan, Cote d'Ivoire), Guy Gneppa (Abidjan, Cote d'Ivoire), Elodie Rabourdin (Bordeaux, France), Jean Rivenc (Pessac, France).