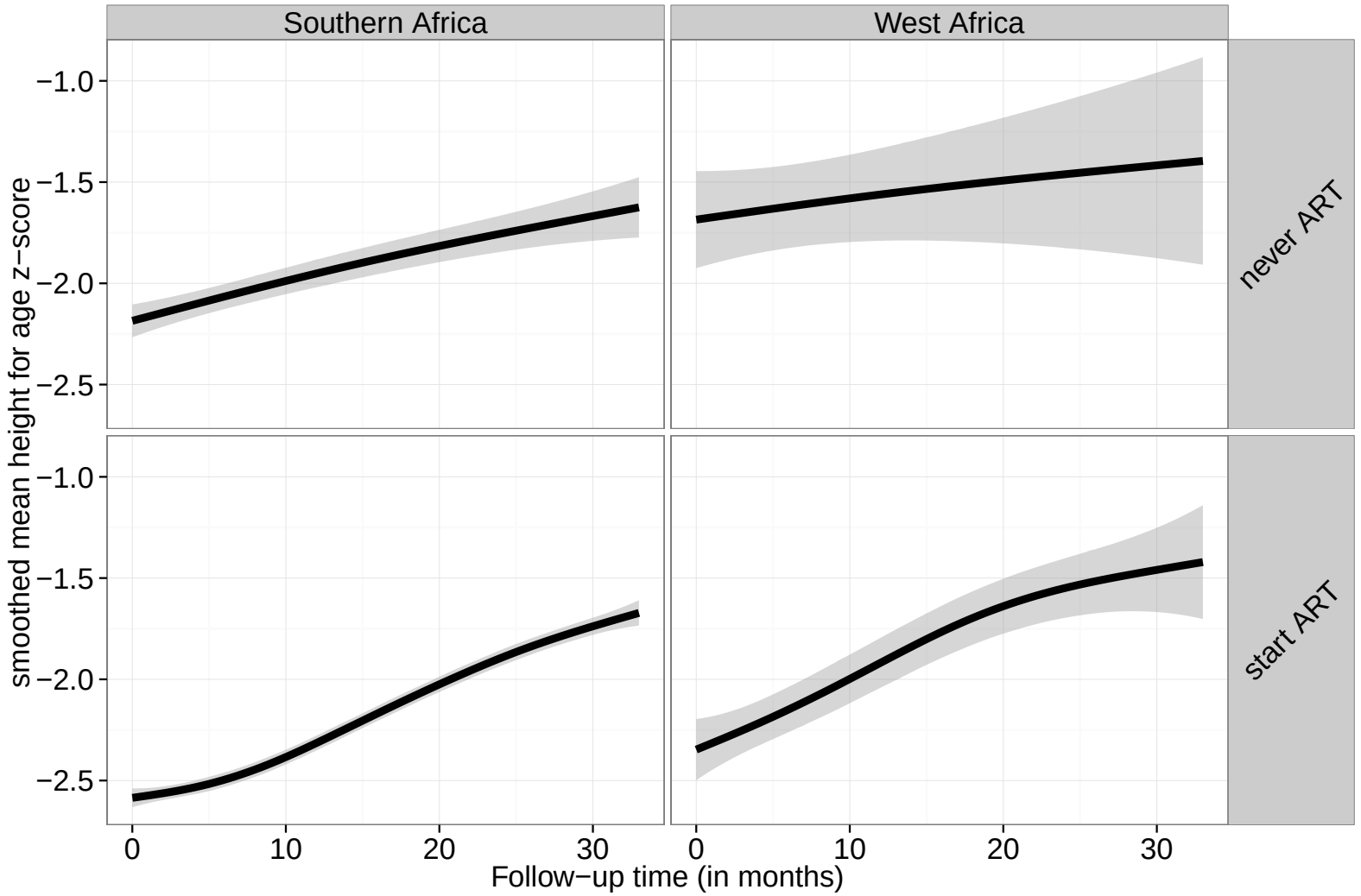
eTable 1. Evolution of CD4 count, CD4 percentage, WAZ and HAZ over time from enrolment by region, reported as median (first; third quartile). Results are reported for available data[1].

	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.



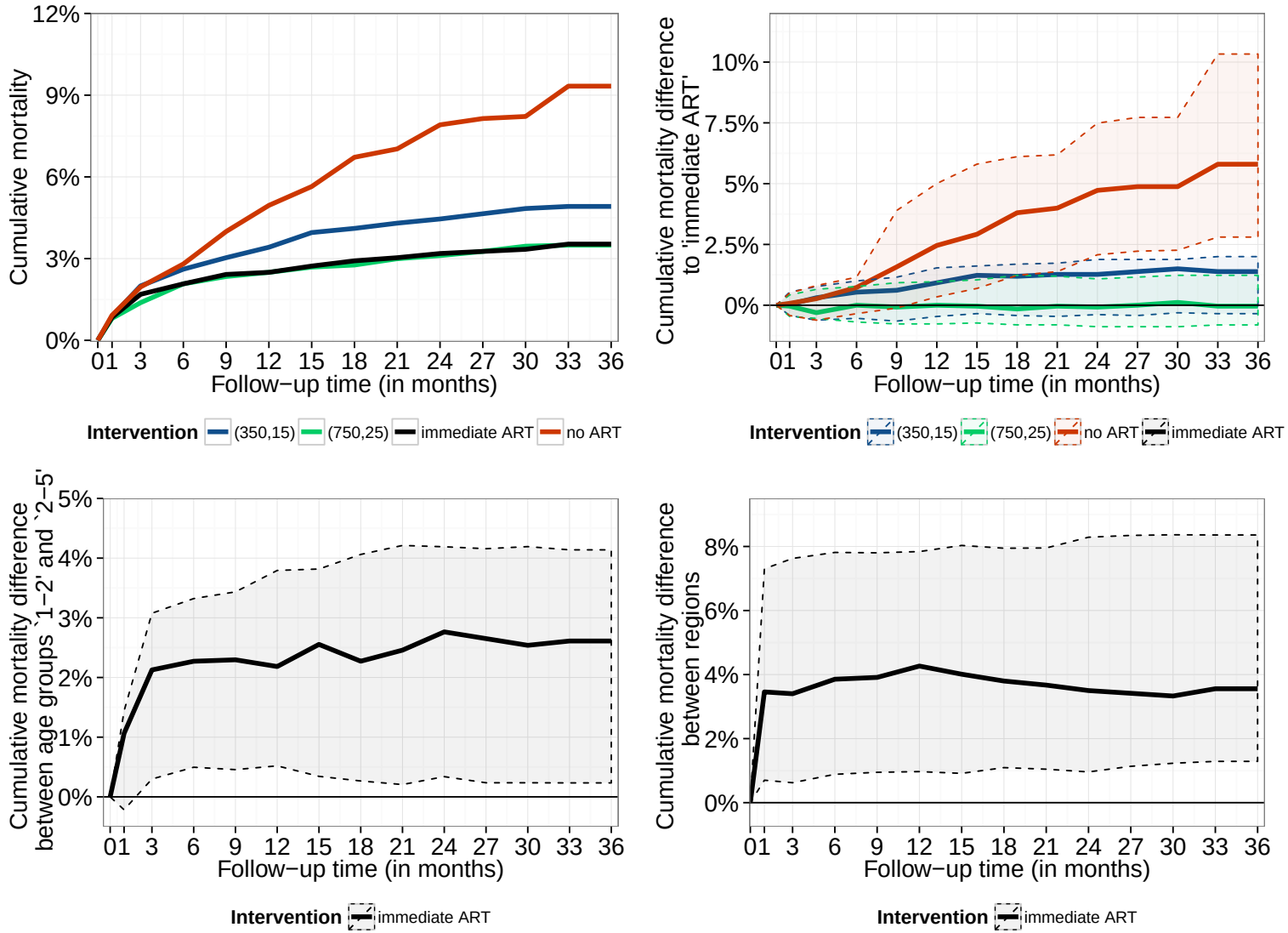
eTable 2. Estimated mortality and mortality difference [MD] to 'immediate ART initiation', (a) overall, (b) stratified according to age at 3 years of follow-up, (c) stratified according to region at 3 years of follow-up, and for differences between age groups and regions at 3 years of follow-up. 95%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

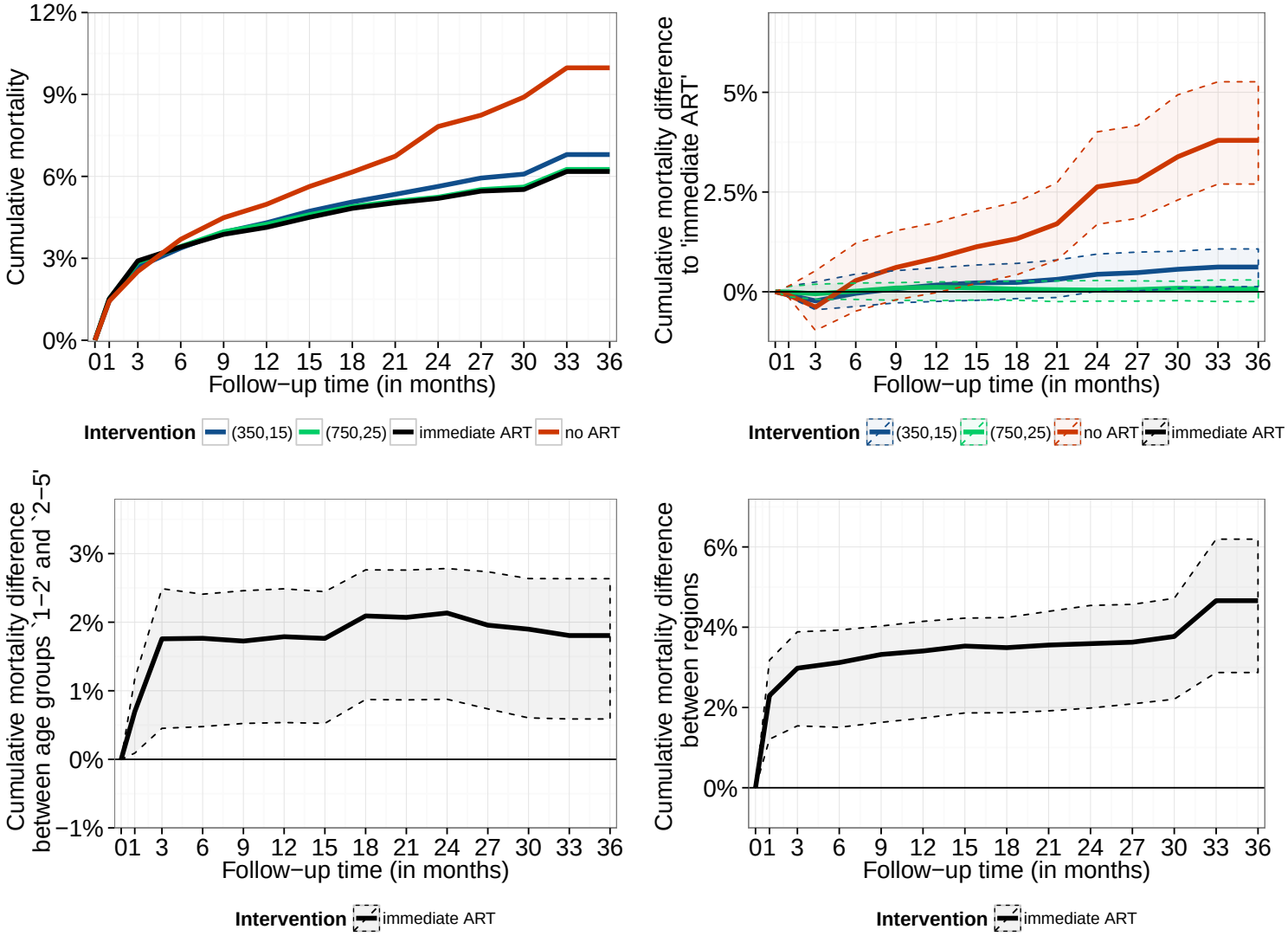
(b)	**Children age 1-2, after 3 years**						**Children age 2-5, after 3 years**						**MD between**		
	Mortality			**MD**			**Mortality**			**MD**			**age groups**		
no ART	9.9%	8.0%	12.7%	4.2%	2.4%	6.4%	8.3%	7.1%	11.4%	3.9%	2.8%	6.6%	1.6%	-1.1%	3.5%
350/15	6.8%	5.8%	8.2%	1.1%	0.2%	1.5%	5.1%	4.5%	6.0%	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

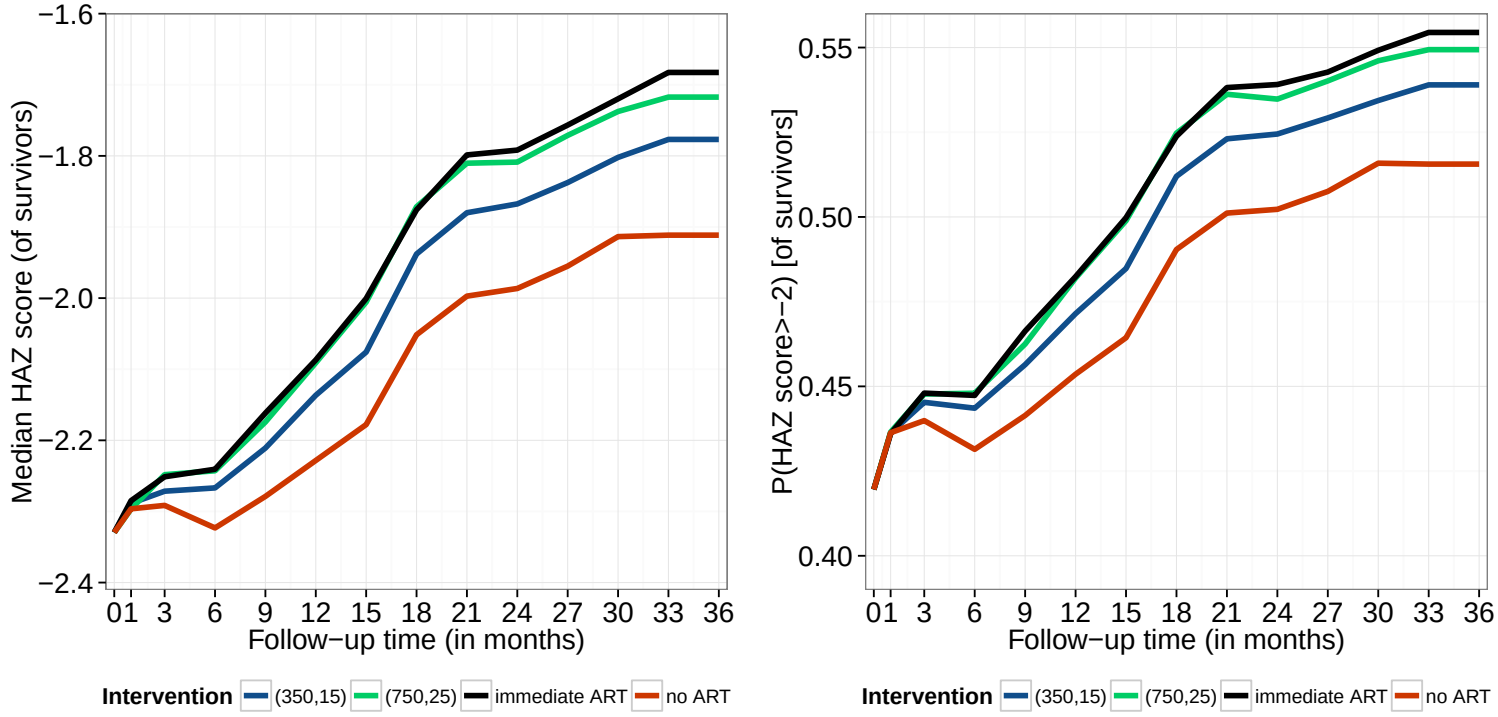
Outcome/Month	1	3	6	9	12	15	18	21	24	27	30	33	Total
Death	30	33	22	16	9	12	9	7	9	6	1	4	158
LTFU	278	165	102	77	41	42	30	34	29	29	17	25	869
Ratio LTFU/Death	9.27	5.00	4.64	4.81	4.56	3.50	3.33	4.86	3.22	4.83	17.00	6.25	5.50
Prior	0.93	0.39	0.36	0.38	0.35	0.24	0.22	0.38	0.21	0.38	0.95	0.54	

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.

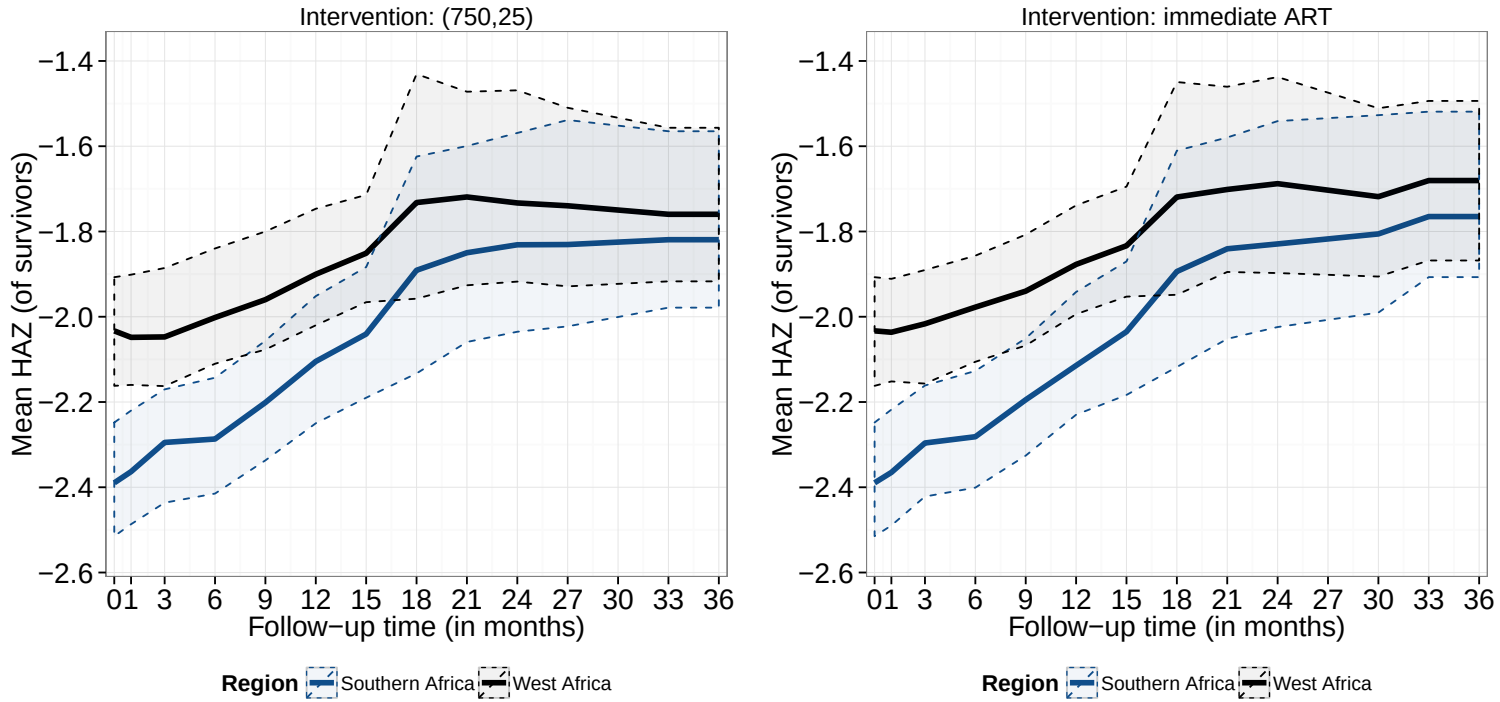
eFigure 4. Main analysis, growth: estimated median HAZ of survivors and probability of HAZ> −2 of survivors.



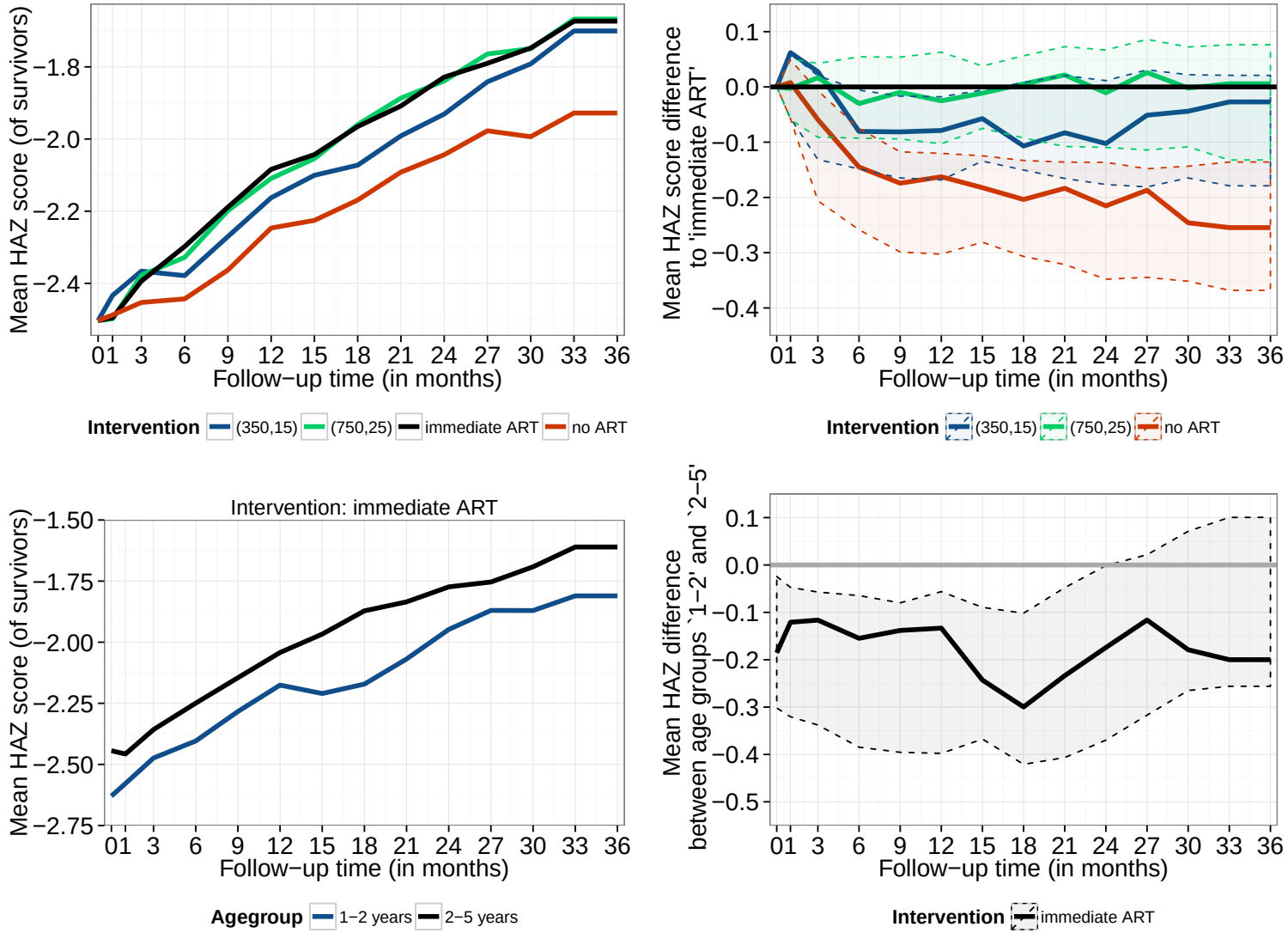
eTable 3. Main analysis, growth: cumulative incidence of HAZ> −2. All results are obtained from g-computation and 95% confidence intervals are obtained from bootstrapping.

	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

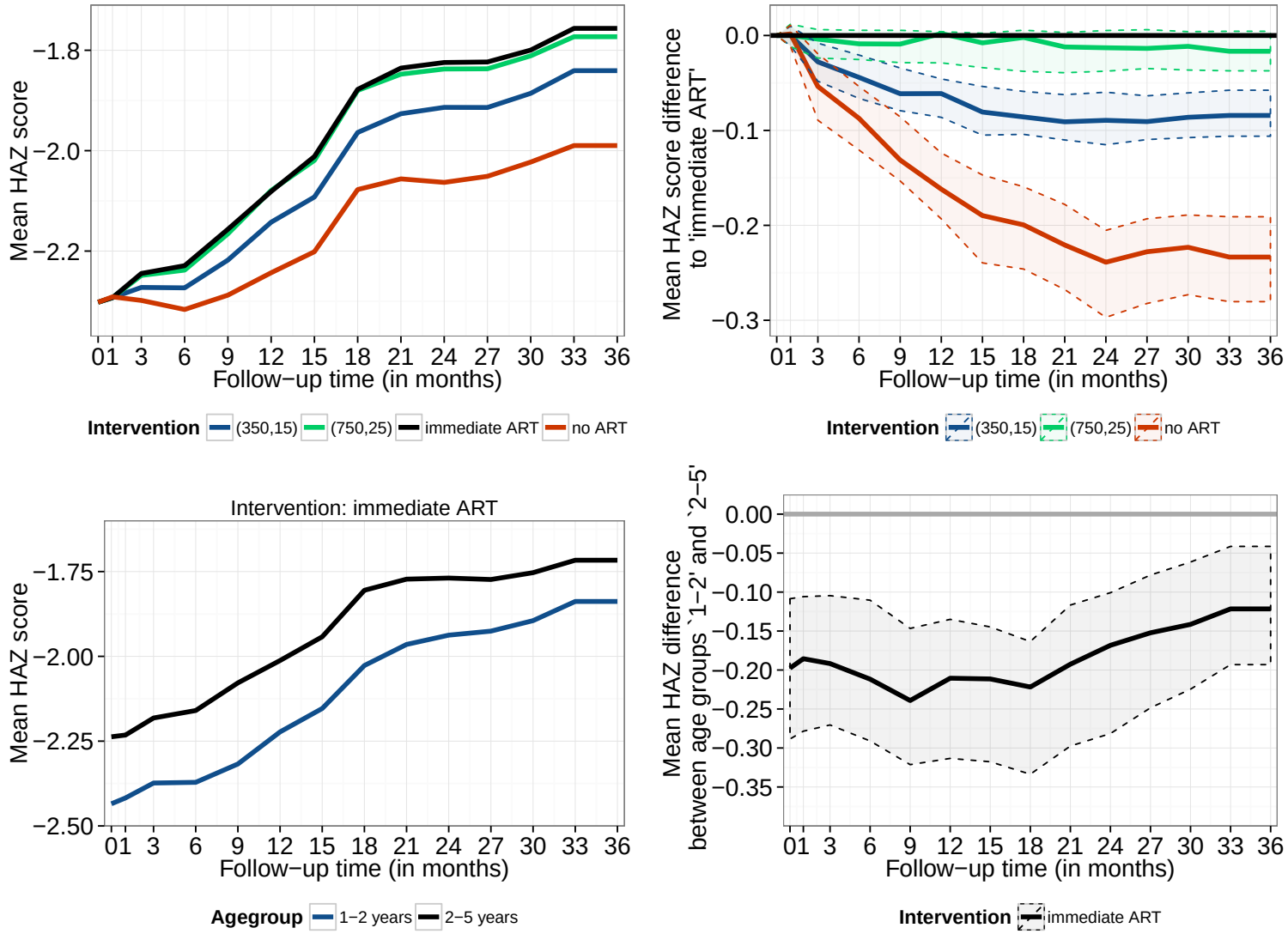
eFigure 5. Main analysis, growth: estimated mean HAZ of survivors for different regions and interventions.



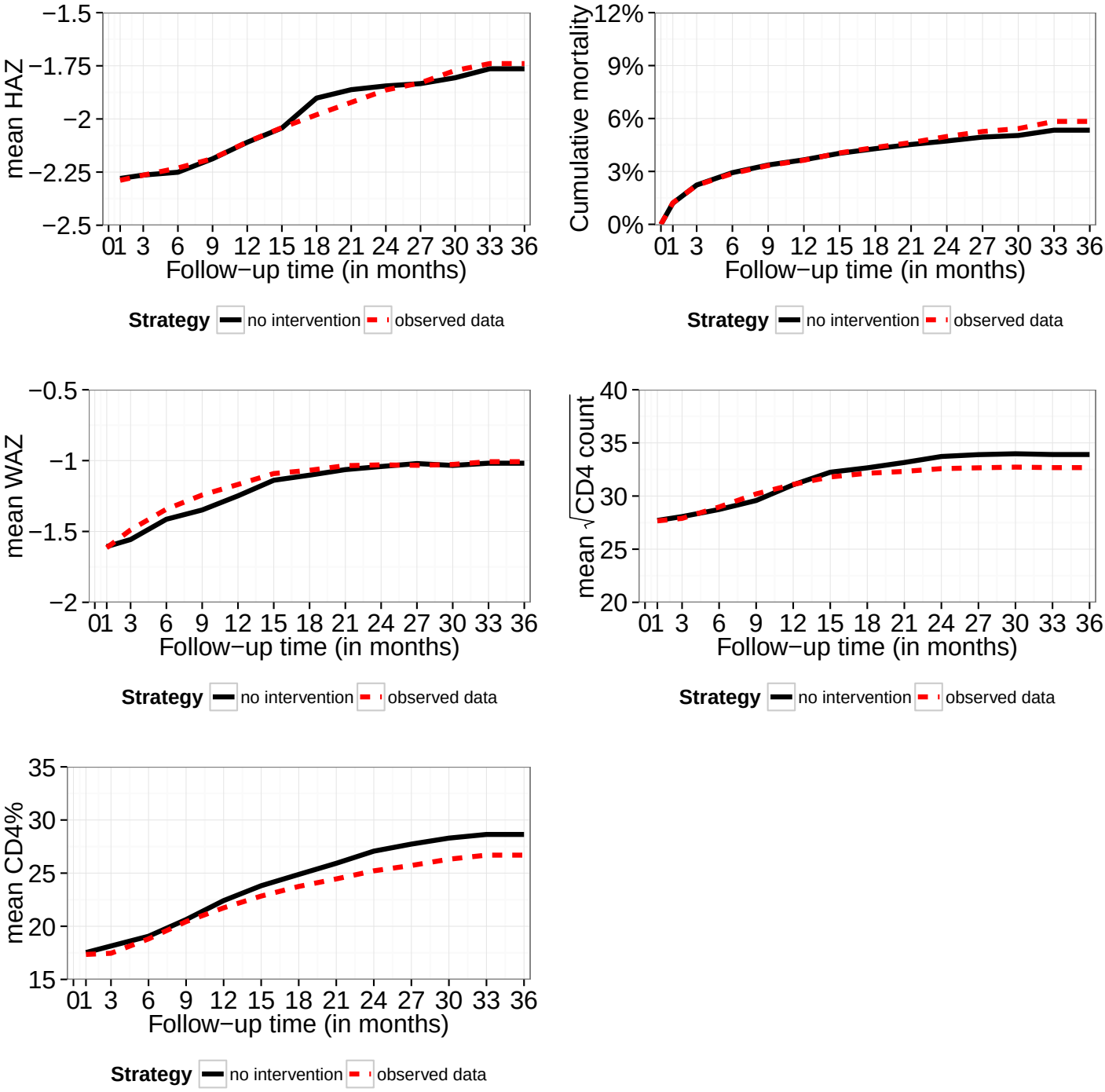
eFigure 6. Sensitivity analysis III, growth analysis: only children with complete baseline data (CD4 count, CD4%, WAZ, HAZ) are included (N=2604). Mean HAZ of survivors (top left), differences between interventions (top right), mean HAZ for different age groups (bottom left), and differences between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



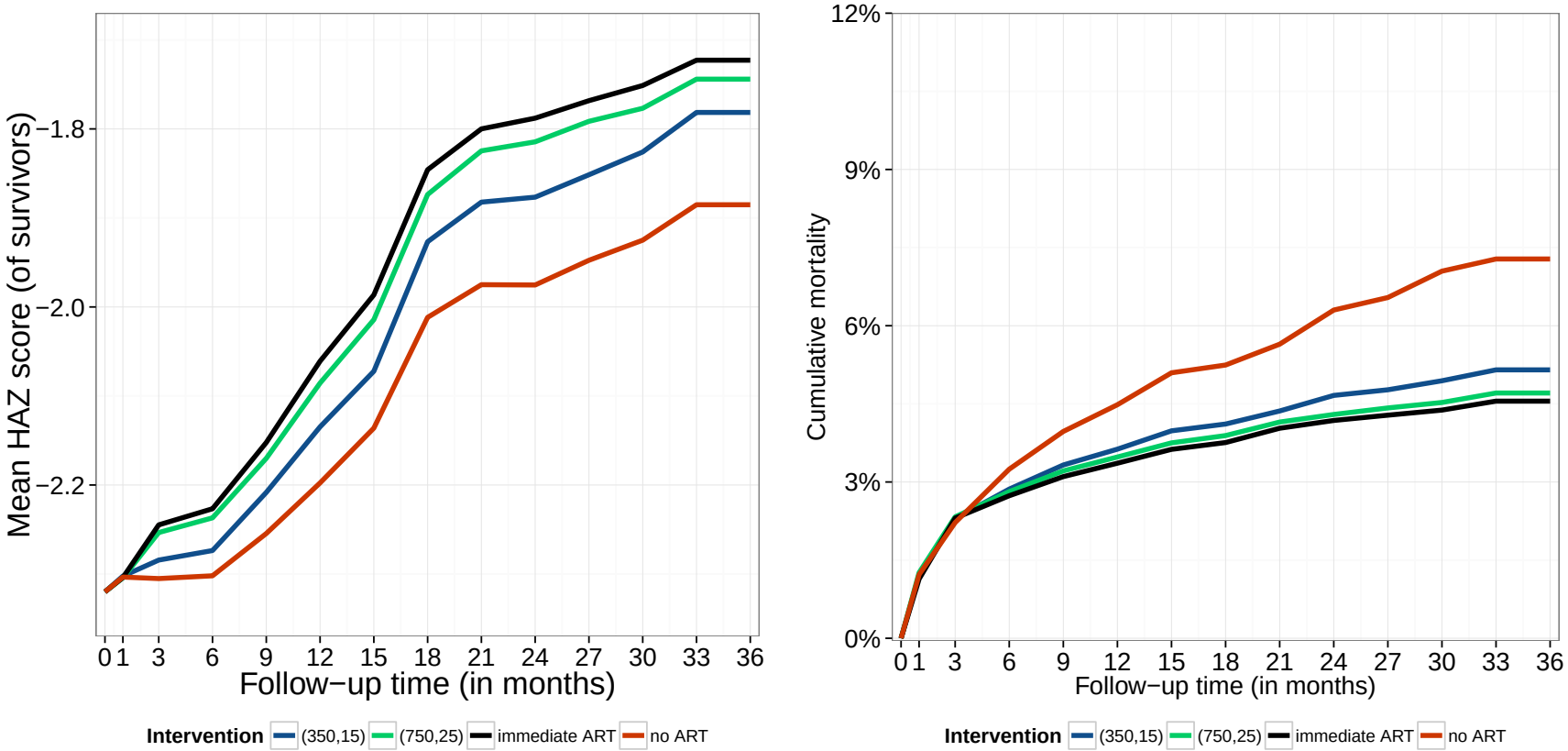
eFigure 7. Sensitivity analysis V, growth analysis: the mean HAZ is calculated under the assumption of no mortality. Mean HAZ (top left), differences between interventions (top right), mean HAZ for different age groups (bottom left), and differences between age groups (bottom right) are reported. 95%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

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