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Prognosis of Children with HIV-1 Infection Starting Antiretroviral Therapy in Southern Africa: A Collaborative Analysis of Treatment Programs

Mary-Ann Davies, MD, PhD[1], **Margaret May, PhD**[2], **Carolyn Bolton-Moore, MD**[3], **Cleophas Chimbetete, MD**[4], **Brian Eley, MD**[5], **Daniela Garone, MD**[6], **Janet Giddy, MD**[7], **Harry Moultrie, MD, MSc**[8], **James Ndirangu, MSc**[9], **Sam Phiri, PhD**[10], **Helena Rabie, MD, MSc**[11], **Karl Technau, MD, MSc**[12], **Robin Wood, DSc**[13], **Andrew Boulle, MD, PhD**[1], **Matthias Egger, MD, MSc**[1,14], and **Olivia Keiser, PhD**[14] **for the IeDEA Southern Africa (IeDEA-SA) Collaboration**

[1]School of Public Health and Family Medicine, University of Cape Town, South Africa [2]School of Social and Community Medicine, University of Bristol, UK [3]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia and University of North Caroline at Chapel Hill, USA [4]Newlands clinic, Harare, Zimbabwe [5]Red Cross Children's Hospital and School of Child and Adolescent Health, University of Cape Town, South Africa [6]Médecins Sans Frontières (MSF) South Africa and Khayelitsha ART Programme, Cape Town, South Africa [7]Sinikithemba Clinic, McCord Hospital, Durban, South Africa [8]Wits Reproductive Health and HIV Institute, University of Witwatersrand, Johannesburg and Harriet Shezi Children's Clinic, Chris Hani Baragwanath Hospital, Soweto, South Africa [9]Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa [10]Lighthouse Trust Clinic, Kamuzu Central Hospital, Lilongwe, Malawi and Liverpool School of Tropical Medicine Liverpool, UK [11]Tygerberg Academic Hospital, University of Stellenbosch, Stellenbosch, South Africa [12]Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, and University of Witwatersrand, Johannesburg, South Africa [13]Gugulethu ART Programme and Desmond Tutu HIV Centre, University of Cape Town, South Africa [14]Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

Abstract

Background—Prognostic models for children starting antiretroviral therapy (ART) in Africa are lacking. We developed models to estimate the probability of death during the first year receiving ART in Southern Africa.

Methods—We analyzed data from children ≤10 years old who started ART in Malawi, South Africa, Zambia or Zimbabwe from 2004–2010. Children lost to follow-up or transferred were excluded. The primary outcome was all-cause mortality in the first year of ART. We used Weibull survival models to construct two prognostic models: one with CD4%, age, WHO clinical stage,

Corresponding author: Mary-Ann Davies, School of Public Health and Family Medicine, University of Cape Town Faculty of Health Sciences, Anzio Road, Observatory, 7925, SOUTH AFRICA, mary-ann.davies@uct.ac.za, Telephone: +27 21 4066051; Fax: +27 21 4066764.

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weight-for-age z-score (WAZ) and anemia and one without CD4%, because it is not routinely measured in many programs. We used multiple imputation to account for missing data.

Results—Among 12655 children, 877 (6.9%) died in the first year of ART. 1780 children were lost to follow-up/transferred and excluded from main analyses; 10875 children were included. With the CD4% model probability of death at 1 year ranged from 1.8% (95% CI: 1.5–2.3) in children 5–10 years with CD4% ≥10%, WHO stage I/II, WAZ ≥−2 and without severe anemia to 46.3% (95% CI: 38.2–55.2) in children <1 year with CD4% <5%, stage III/IV, WAZ< −3 and severe anemia. The corresponding range for the model without CD4% was 2.2% (95% CI: 1.8–2.7) to 33.4% (95% CI: 28.2–39.3). Agreement between predicted and observed mortality was good (C-statistics=0.753 and 0.745 for models with and without CD4% respectively).

Conclusion—These models may be useful to counsel children/caregivers, for program planning and to assess program outcomes after allowing for differences in patient disease severity characteristics.

Keywords

Mortality; HIV-1; children; sub-Saharan Africa; antiretroviral

Despite increased access to antiretroviral therapy (ART) for HIV-infected children in low-income settings, mortality remains high. In 2010, an estimated 230000 children died of AIDS in sub-Saharan Africa.[1] While many deaths occur in untreated patients,[2] mortality remains high during the first year of ART, especially for children starting therapy with advanced disease.[3–5] Knowing the short term prognosis associated with particular disease severity characteristics is important for individual children initiating ART and their caregivers, as well as for clinicians and for program planning. Further, comparison of actual mortality outcomes with predictions from a prognostic model that is generalizable across settings may be useful for benchmarking the quality of health care provision. While models of pediatric pre-ART mortality have been developed for high and low-income settings and used to inform decisions regarding treatment initiation,[6–9] prognostic models of mortality on ART have to date only been developed for adults.[10–12]

The characteristics associated with mortality in children starting ART have been well described.[3–5,13–20] However, the combined power of different disease severity markers to predict mortality and the absolute mortality risk associated with these markers remains unknown. Young children and those with low CD4% or advanced clinical disease are at high risk of morbidity and mortality.[3,4,13,18,20] HIV-1 RNA level and anemia are also independent mortality risk factors, although HIV-RNA is less predictive than CD4.[13,15,21] However, in low income settings, measurement of many of these prognostic factors, including CD4, is often unavailable.[22] The International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration includes data from children starting ART at 11 treatment programs in a range of settings in four countries.[3,20] We aimed to use these data to develop a prognostic model that estimates the cumulative probability of death at 3, 6 and 12 months after starting ART according to age, and prognostic factors commonly measured in resource-limited settings. Separate models were developed for settings with and without access to CD4% at ART initiation.

METHODS

Treatment programs

IeDEA-SA is a regional collaboration of ART programs, which is part of a larger international network.[23] Data are collected at ART initiation and follow-up visits and regularly transferred to data centers at the Universities of Cape Town, South Africa, and Bern, Switzerland. All sites have ethical approval to collect data and participate in IeDEA-SA. This analysis was based on data from 11 programs in four countries, including eight clinics in three provinces in South Africa (Red Cross Children's Hospital, Khayelitsha and Gugulethu ART Programs and Tygerberg Academic Hospital, Western Cape; McCord Hospital and Hlabisa HIV Treatment and Care Program, Kwazulu-Natal; Harriet Shezi Children's Clinic and Rahima Moosa Mother and Child Hospital, Gauteng) and one program each in Zambia (Ministry of Health and Centre for Infectious Disease Research in Zambia program [MoH-CIDRZ]; Lusaka), Malawi (Lighthouse Trust Clinic at Kamuzu Central Hospital; Lilongwe) and Zimbabwe (Newlands Clinic; Harare).

Inclusion criteria

All HIV-infected, ART-naïve (except for antiretrovirals to prevent vertical transmission) children who initiated treatment with ≥3 antiretrovirals at age ≤10 years between 1 January 2004 and 31 January 2010 were eligible. Children with <1 year of potential follow-up (ART initiation <1 year prior to site database closure) were excluded. Children were excluded from the main analysis if, within 6 months of starting ART, they were lost to follow-up (LTFU) or transferred out (TFO) to a different treatment site. As clinic visits may be up to 6 months apart, LTFU was defined as the last visit being ≥270 days before database closure.

Outcomes and prognostic models

We used an intention-to-continue-treatment analysis, ignoring treatment changes and interruptions. The outcome was all-cause mortality during the first year on ART. Follow-up was censored on the earliest of: date of death, last visit date +90 days in children LTFU/TFO, or 1 year after ART initiation (Supplementary Figure S1). The 11 cohorts were grouped into five geographic regions as some cohorts had small patient numbers. Three regions were provinces within South Africa where ART programs at different sites are coordinated by provincial Departments of Health (Western Cape, Kwazulu-Natal and Gauteng). The fourth region comprised two cohorts with similar patient characteristics in Malawi and Zimbabwe, while the MoH-CIDRZ cohort (Zambia) comprised the fifth region. Treatment initiation criteria at these sites were based on WHO and national guidelines at the time. In South Africa, the recommended first-line regimen was 2 nucleoside reverse transcriptase inhibitors (NRTI) plus either lopinavir/ritonavir (children <3 years or <10kg) or efavirenz (children > 3 years and >10kg). In Malawi, Zimbabwe and Zambia 2 NRTIs plus nevirapine was the recommended first-line for all children.

The following prognostic variables measured at ART initiation were considered for inclusion in a prognostic model and associations with mortality were explored using Kaplan-Meier survival curves in the pre-specified categories of age (<1 year, 1 year, 2–4 years, 5–10 years); WHO Clinical Stage (I/II compared to III/IV); CD4% (<5, 5–9.9, 10–14.9; ≥15);

weight-for-age z-score (WAZ) calculated using WHO 2006 standards (<−3.00; −3.00 to −2.01, −2.00 to −1.01 and ≥ −1.00 standard deviations below mean)[24] and anemia defined using CDC classification that incorporates both hemoglobin and age.[25] Apart from age and gender, data on prognostic variables were not recorded for all patients. Missing data were modeled using multiple imputation by chained equations, with 25 imputed datasets.[26–29] The following variables were used in imputation equations: cohort, sex, age, WHO Stage, CD4%, WAZ, hemoglobin, interactions between age, CD4% and WAZ, survival time and mortality indicator. Log or square root transformations were used for non-normally distributed variables. Weibull proportional hazards models were used to explore crude and adjusted associations between prognostic variables and mortality.

A set of candidate models (with and without CD4%) were selected using the Akaike Information Criterion (AIC). These were flexible parametric survival models[30] with spline smoothing of the baseline hazard to model the steep mortality during the first 3 months of treatment. We used a system of leave-one-out cross-validation to select the most generalizable models with and without CD4%.[31,32] This method fits the model using data from four regions and tests discrimination of predictions of the model when applied to the omitted fifth region. This was repeated sequentially rotating the omitted region. Discrimination was assessed using the D-statistic (averaged across the imputed datasets) which measures the prognostic separation between the survival distributions for two independent prognostic groups.[32] We calculated the D-statistic for the model fitted on the four regions and applied to the omitted region (D_{test}) and compared this to the D-statistic for the model when coefficients were re-estimated using data only from the omitted region (D_r). The difference ($D_r - D_{test}$) is a measure of the degradation in model fit and discrimination when applied to independent data compared with when applied to the data used to estimate the model coefficients. Models with a low AIC score, high D_{test} and low $D_r - D_{test}$ were favored.

Concordance between predicted mortality and observed mortality for the final selected models was assessed using Harrell's C-statistic (0.5 = agreement expected by chance; 1 = perfect agreement). The explained variation (R^2) of the final selected models was calculated.[33,34] Model calibration was assessed by comparing Kaplan-Meier curves of observed mortality with curves predicted from the model for groups with poor to good prognosis, and for each region. All analyses were conducted in STATA version 12.0 (STATA Corporation, College Station, Texas).

Sensitivity analyses

In sensitivity analyses we included children LTFU/TFO within six months of starting treatment. We examined Kaplan-Meier estimates of one-year mortality first censoring their follow-up at the last visit date +90 days, and then assuming 30% and 50% mortality in those LTFU/TFO with time to death randomly assigned based on the distribution in those not LTFU/TFO. Finally, we developed models including children LTFU/TFO, censoring follow-up time at the last visit date +90 days.

RESULTS

In the 11 treatment programs, 12655 children started ART. 1780 children (14%) were LTFU or TFO within 6 months of ART start and excluded from the main analyses. The main analysis included 10875 children (70% ≥2 years old) with 10204 child-years of follow-up (Table 1). Most children had advanced disease at ART initiation (72% WHO Clinical Stage III/IV; median [IQR] CD4%: 13% [8–19]). There was considerable between-region heterogeneity in age and disease severity; the percentage of children <1 year ranged from 3% to nearly 30%; the percentage with WHO Stage III/IV disease ranged from approximately 60% to >90%. There was substantial missing data on many covariates; anemia and CD4% were not reported for 37% (range across regions: 18–88%) and 32% (16–56%) of children respectively. The estimated cumulative mortality by 1 year after ART start was 8.6% (95% CI: 8.0–9.2) (range across regions: 5.8%–10.5%).

The crude and adjusted associations between prognostic variables and mortality are shown in Table 2 (a). In adjusted analyses there was a significant interaction between age and both CD4% (p=0.028) and WAZ (p=0.002). The effect of an increase in either of these variables had a greater impact on reducing mortality risk in older children compared to younger children (Table 2 [b]), although mortality overall was lower for older children.

The two final models selected by internal-external cross-validation included age (in four categories), clinical stage (two), WAZ (three) and anemia (two), with one model additionally including CD4% (in three categories, Table 3). There were thus 144 risk groups (model with CD4%) or 48 risk groups (model without CD4%). The C-statistics over the entire first year on ART were 0.753 and 0.745 for the models with and without CD4% respectively. Concordance was lower when restricting to the second six months on ART (C-statistics of 0.708 and 0.705 for models with and without CD4% respectively). The R^2 values were 32.1% and 31.1% for the whole first year and 23.6% and 23.9% for the second six months for the models with and without CD4% respectively. As hemoglobin was imputed for a large proportion of children, model diagnostics were recalculated restricted to children in whom hemoglobin was recorded. This resulted in slightly higher C-statistics (0.762 [with CD4%] and 0.754 [no CD4%]) and R^2 (33.8% [with CD4%] and 32.9% [no CD4%]) for both models with very little difference between the two models.

For both models, predicted mortality closely followed observed mortality for five prognostic groups of children with approximately 20% of deaths in each group (Figure 1[a]). Within each region predicted and observed mortality for groups of children with different prognosis were also similar (Figure 1[b]), indicating generalizability of the models. The majority of children (57% [model with CD4%] and 58% [model without CD4%] were in the group with a good prognosis and one-year mortality <5%. Predicted mortality from the model with CD4% closely approximated observed mortality for all regions except Kwazulu-Natal (observed>predicted) and Malawi & Zimbabwe (observed<predicted) (Figure 1[c]). Predicted mortality from the model without CD4% only approximated observed mortality closely for CIDRZ (figure 1[b]). This was the only region where <20% of hemoglobin values were missing. In other regions, hemoglobin may not have been well imputed, particularly in Gauteng and Malawi & Zimbabwe where >60% of values were missing.

Children age <1 year in clinical stage III/IV with WAZ <−3, severe anemia and CD4% <5 had the highest predicted cumulative mortality at one year (46.3%) and children age 5–10 years in stage I/II with WAZ ≥ −2, no severe anemia and CD4% ≥10 the lowest mortality (1.8%). Predictions for all combinations of prognostic variables are shown in appendix Table S1. The 1780 children LTFU/TFO within the first six months of treatment were younger and had more advanced disease compared to those included (appendix Table S2). In sensitivity analyses that included these children, Kaplan-Meier one-year mortality estimates ranged from 7.2% (censoring children LTFU/TFO at last visit date +90 days) to 11.6% and 14.4% (assuming 30% and 50% mortality in those LTFU/TFO respectively). When developing the prognostic models including all children (censoring children LTFU/TFO at last visit date +90 days) the predicted cumulative one-year mortality for the best and worst prognostic groups ranged from 1.72% to 39.0% (CD4% model) and from 2.1% to 27.7% (model without CD4%). The corresponding C-statistics were 0.741 and 0.733 and R^2 values were 29.5% and 28.3% respectively, which were very similar to the main analysis.

DISCUSSION

Main findings

These prognostic models for one year mortality in children commencing ART are generalizable with good discrimination and prognostic separation. The majority of children (>55%) starting ART and remaining in care have a one year mortality risk of ≤5%, with 6% of children having >20% predicted risk of dying. For predicting mortality on ART, low cost prognostic markers such as WAZ and anemia may be almost as good as CD4%.

Overall mortality, loss to follow-up and transfer out

There was substantial heterogeneity between regions in overall mortality rate, disease characteristics and age. Crude mortality was highest in the Western Cape which includes the only exclusively tertiary care treatment sites and has the highest proportion of children <2 years initiating treatment. These sites rapidly transfer children to primary care once they are getting better (12.7% TFO from Western Cape tertiary care sites between six and twelve months on ART)[35] which may result in over-estimating mortality. We excluded children LTFU/TFO within six months of starting ART to reduce bias by underascertainment of deaths if these patients had been included and censored. This does not completely remove bias as children classified as LTFU may have died before meeting the LTFU definition and mortality might be higher in children LTFU compared to children remaining in care.[1136,37] Our sensitivity analysis including children LTFU/TFO within six months of ART start showed that assumptions about their mortality impact on estimated overall mortality, and their exclusion may result in underestimated predicted mortality at the program level. Indeed, excluded children were more likely to have characteristics associated with mortality compared to those included in the main analysis.

Comparison to pre-ART prognostic model

While predictors of mortality pre-ART and on ART have been examined in developing and wealthy countries, this is the first prognostic model for children on ART.[6,7,9,13,18,38] A similar model for pre-ART mortality has been developed in children from high income

settings.[8] A weighted score incorporating weight percentile, WHO stage, symptoms, general health rating, total lymphocyte count, packed cell volume and albumin predicted mortality well with a C-statistic of 0.852 (higher than the values of 0.753 and 0.745 for our models with and without CD4% respectively). The study also showed that CD4% can be replaced by simpler measures to predict pre-ART mortality and so could be applied to resource-limited settings where CD4% is not routinely available. However, as expected from high income settings, children had less advanced disease. Furthermore, the mothers of all children participated in a randomized trial and the model may not be applicable to routine care in resource-limited settings.

Comparison with adult model

Our pediatric model compares favorably with the adult model for resource-limited settings (higher R^2 and C-statistic).[11] This is probably due to the powerful prognostic value of age in children. Mortality declines rapidly with increasing age in all children, irrespective of HIV-infection. In the context of ART eligibility in a perinatally HIV-infected child only after "waiting" for disease severity criteria to be met, the age at therapy start is a proxy for rate of disease progression since birth and thus a strong prognostic factor.[3] The model predictions may therefore not be applicable to children <5 years who start ART without clinical/immunological progression as recommended in the WHO guidelines.[39,40] The Children with HIV Early Antiretroviral Therapy (CHER) trial demonstrated a better prognosis in infants starting ART before disease progression.[41]

Utility of the models

The likely mortality of a patient with a particular set of characteristics can be determined using the supplementary tables in this paper. This may be useful for guiding clinicians and patients regarding prognosis, and for risk stratification. In a similar way the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) online calculator for pre-ART mortality has been used to guide decisions on when to start ART in Europe.[6] Our models are useful for program planning, and their generalizability makes them useful for comparing outcomes across different programs after adjusting appropriately for different patient disease severity.

Strengths and limitations

To our knowledge this is the first pediatric prognostic model of mortality on ART and is based on a very large cohort across a range of settings. The large number of missing values for some variables (e.g. hemoglobin) is a limitation. In particular, this limited our ability to determine whether a model based on hemoglobin alone was as good as including CD4% and hemoglobin for prognostic purposes. Due to imputation of a large proportion of hemoglobin values for all regions except Zambia, there was misfit of predicted mortality at the level of the region for the model without CD4% (Figure 1[c]]). However, there was little difference in measures of fit when restricting to patients in whom hemoglobin was measured, and the fit of the models with and without CD4% were comparable in Zambia for which <20% of hemoglobin values were imputed. In addition, associations with mortality were similar if missing values were imputed or a complete case analysis was performed. This, together with the cross validation, underlines the robustness of our findings. The majority of children in this analysis started ART with advanced disease, hence we were unable to examine

mortality for higher values of CD4% and WAZ. Nevertheless, the model predictions are applicable to most children starting ART as the majority of children in this region still commence ART with advanced disease.[42,43]

Despite the fact that many sites from different settings are represented, the good fit between predicted and observed mortality for different prognostic groups (figure 1[a]) may be driven by the large MoH-CIDRZ region where concordance at a regional level was also good. Discrepancies between predicted and observed mortality for other regions may be due to differences in LTFU and mortality ascertainment, proportion of imputed data, differences in prognostic variables not measured or included in the models or differences in background mortality, access to health services and models of care. Other factors such as nutrition supplements, co-trimoxazole prophylaxis, co-infections including malaria, first-line regimen, adherence, HIV-1 RNA and exposure to vertical transmission prevention regimens may be associated with outcomes in children.[15,44–47] However, these factors are often not easily available. There is a trade-off between models which would be more accurate but less applicable and useful in general health care settings in low-income countries. Poor availability of any of the variables in our models would limit their utility, hence developing models both with and without CD4 percent. This may be increasingly important if programs phase out CD4 monitoring with increasing emphasis on universal ART for children irrespective of CD4 values and on routine HIV-RNA monitoring. In this respect, the poor availability of hemoglobin values is a concern, however likely reflects failure to record rather than measure these values. Many of the sites that had low proportions of hemoglobin recorded have reasonable access to laboratory testing or point of care hemoglobinometers and it is likely that hemoglobin values would be available for a clinician wanting to use them for prognostication. In addition all children came from largely urban regions and all sites had medical record systems available, limiting generalizability to less well-resourced cohorts and primary care facilities where pediatric ART increasingly occurs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. WHO. GLOBAL HIV/AIDS RESPONSE. [Accessed July 20, 2012] Epidemic update and health sector progress towards Universal Access. Progress Report 2011. 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf
2. Anglaret X, Minga A, Gabillard D, et al. AIDS and non-AIDS morbidity and mortality across the spectrum of CD4 cell counts in HIV-infected adults before starting antiretroviral therapy in Cote d'Ivoire. Clin Infect Dis. 2012; 54:714–723. [PubMed: 22173233]
3. Davies M, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment (ART) programme for children - The IeDEA Southern Africa Collaboration. S Afr Med J. 2009; 99:730–737. [PubMed: 20128272]
4. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. JAMA. 2007; 298:1888–1899. [PubMed: 17954540]
5. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. Lancet Infect Dis. 2008; 8:477–489. [PubMed: 18652994]
6. Dunn D. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet. 2003; 362:1605–1611. [PubMed: 14630440]
7. Dunn D, Woodburn P, Duong T, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. J Infect Dis. 2008; 197(3):398–404. [PubMed: 18248303]
8. Patel K, Weinberg GA, Buchacz K, et al. Simple Pediatric AIDS Severity Score (PASS): a pediatric severity score for resource-limited settings. J Acquir Immune Defic Syndr. 2006; 43(5):611–617. [PubMed: 17003691]
9. Cross Continents Collaboration for Kids (3Cs4kids) Analysis and Writing Committee. . Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. AIDS. 2008; 22:97–105. [PubMed: 18090397]
10. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002; 360:119–129. [PubMed: 12126821]
11. May M, Boulle A, Phiri S, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet. 2010; 376:449–457. [PubMed: 20638120]
12. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. AIDS. 2007; 21:1185–1197. [PubMed: 17502729]
13. The KIDS-ART-LINC Collaboration. Low risk of death, but substantial program attrition, in pediatric treatment cohorts in sub-Saharan Africa. J Acquir Immune Defic Syndr. 2008; 15:523–531.
14. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire. AIDS. 2004; 18:1905–1913. [PubMed: 15353976]
15. Eley B, Davies MA, Apolles P, et al. Antiretroviral treatment for children. S Afr Med J. 2006; 96:988–993. [PubMed: 17077930]
16. Davies M, Egger M, Keiser O, Boulle A. Paediatric antiretroviral treatment programmes in sub-Saharan Africa: a review of published clinical studies. Afr J AIDS Res. 2009; 8:329–338. [PubMed: 21124759]
17. Peacock-Villada E, Richardson BA, John-Stewart GC. Post-HAART outcomes in pediatric populations: comparison of resource-limited and developed countries. Pediatrics. 2011; 127:e423–441. [PubMed: 21262891]
18. Walker AS, Prendergast AJ, Mugyenyi P, et al. Mortality in the year following antiretroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. Clin Infect Dis. 2012; 55:1707–1718. [PubMed: 22972859]

19. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. J Acquir Immune Defic Syndr. 2010; 53:86–94. [PubMed: 20035164]
20. Fenner L, Brinkhof M, Keiser O, et al. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. J Acquir Immune Defic Syndr. 2010; 54:524–532. [PubMed: 20588185]
21. [Accessed September 1, 2012] Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2011. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf
22. Musoke PM, Young AM, Owor MA, et al. Total lymphocyte count: not a surrogate marker for risk of death in HIV-infected Ugandan children. J Acquir Immune Defic Syndr. 2008; 49:171–178. [PubMed: 18769352]
23. Egger M, Ekouevi DK, Williams C, et al. Cohort Profile: The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol. 2012; 41:1256–64. [PubMed: 21593078]
24. WHO. [Accessed November 23, 2008] The WHO Child Growth Standards. 2006. Available at: http://www.who.int/childgrowth/en/
25. Division of AIDS. [Accessed January 2, 2012] Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December 2004. Clarification August 2009. 2009. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf
26. Royston P. Multiple imputation of missing values. Stata J. 2004; 4:227–241.
27. Royston P. Multiple imputation of missing values: further update of ice, with am emphasis on interval censoring. Stata J. 2009; 7:445–464.
28. Sterne J, White I, Carlin J, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 29:b2393. [PubMed: 19564179]
29. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011; 30:377–399. [PubMed: 21225900]
30. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002; 21:2175–2197. [PubMed: 12210632]
31. May M, Royston P, Egger M, Justice AC, Sterne JA. Development and validation of a prognostic model for survival time data: application to prognosis of HIV positive patients treated with antiretroviral therapy. Stat Med. 2004; 23:2375–2398. [PubMed: 15273954]
32. Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. Stat Med. 2004; 23:907–926. [PubMed: 15027080]
33. Royston P, Sauerbrei W. A new measure of prognostic separation in survival data. Stat Med. 2004; 23:723–748. [PubMed: 14981672]
34. Royston P. Explained variation for survival models. Stata J. 2006; 6:83–96.
35. Eley B, Nuttall J. Antiretroviral therapy for children: challenges and opportunities. Ann Trop Paediatr. 2007; 27:1–10. [PubMed: 17469726]
36. Braitstein P, Songok J, Vreeman RC, et al. “Wamepotea” (they have become lost): outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. J Acquir Immune Defic Syndr. 2011; 57:e40–46. [PubMed: 21407085]
37. Weigel R, Hochgesang M, Brinkhof MW, et al. Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi. BMC Infect Dis. 2011; 11:31. [PubMed: 21272350]
38. Leroy V, Malateste K, Rabie H, et al. Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration. J Acquir Immune Defic Syndr. 2013; 62:208–219. [PubMed: 23187940]
39. WHO. [Accessed October 19, 2010] Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Recommendations for a public health approach: 2010 revision. 2010. Available at: http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html

40. WHO. [Accessed September 12, 2013] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. http://www.who.int/hiv/topics/treatment/technical/en/index.html
41. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008; 359:2233–2244. [PubMed: 19020325]
42. Fatti G, Bock P, Eley B, Mothibi E, Grimwood A. Temporal trends in baseline characteristics and treatment outcomes of children starting antiretroviral treatment: an analysis in four provinces in South Africa, 2004–2009. J Acquir Immune Defic Syndr. 2011; 58:e60–67. [PubMed: 21857355]
43. Davies M, Phiri S, Wood R, et al. Temporal trends in the characteristics of children at antiretroviral therapy initiation in Southern Africa: The International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. PLoS ONE. 2013 In Press.
44. Davies M, Moultrie H, Eley B, et al. Virologic failure and second-line antiretroviral therapy in children in South Africa: The IeDEA Southern Africa collaboration. J Acquir Immune Defic Syndr. 2011; 56:270–278. [PubMed: 21107266]
45. Duggan C, Fawzi W. Micronutrients and child health: studies in international nutrition and HIV infection. Nutr Rev. 59(11):358–369. [PubMed: 11720341]
46. Walker AS, Mulenga V, Ford D, et al. The impact of daily cotrimoxazole prophylaxis and antiretroviral therapy on mortality and hospital admissions in HIV-infected Zambian children. Clin Infect Dis. 2007; 44(10):1361–1367. [PubMed: 17443476]
47. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012; 366:2380–2389. [PubMed: 22716976]

IeDEA Southern Africa Steering Group

Maureen Wellington, Newlands Clinic, Harare, Zimbabwe; Brian Eley, Red Cross Children's Hospital, Cape Town, South Africa; Christiane Fritz, SolidarMed Zimbabwe, Zimbabwe; Kathryn Stinson, Khayelitsha ART Programme and Médecins Sans Frontières, Cape Town, South Africa; Janet Giddy, McCord Hospital, Durban, South Africa; Matthew Fox, Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg, South Africa; Sabine Heinrich, SolidarMed Lesotho; Christopher Hoffmann, Aurum Institute for Health Research, South Africa; Harry Moultrie, Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg and Harriet Shezi Children's Clinic, Chris Hani Baragwanath Hospital, Soweto, South Africa; James Ndirangu, Hlabisa HIV Treatment and Care Programme, South Africa; Sabrina Pestilli, SolidarMed Mozambique, Mozambique; Sam Phiri, Lighthouse Clinic, Lilongwe, Malawi; Hans Prozesky, Tygerberg Academic Hospital, Stellenbosch, South Africa; Benjamin Chi, Center for Infectious Disease Research in Zambia, Zambia; Karl Technau, Empilweni Service and Research Unit, Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, Johannesburg, South Africa; Robin Wood, Gugulethu and Masiphumelele ART Programmes and Desmond Tutu HIV Centre, Cape Town, South Africa.

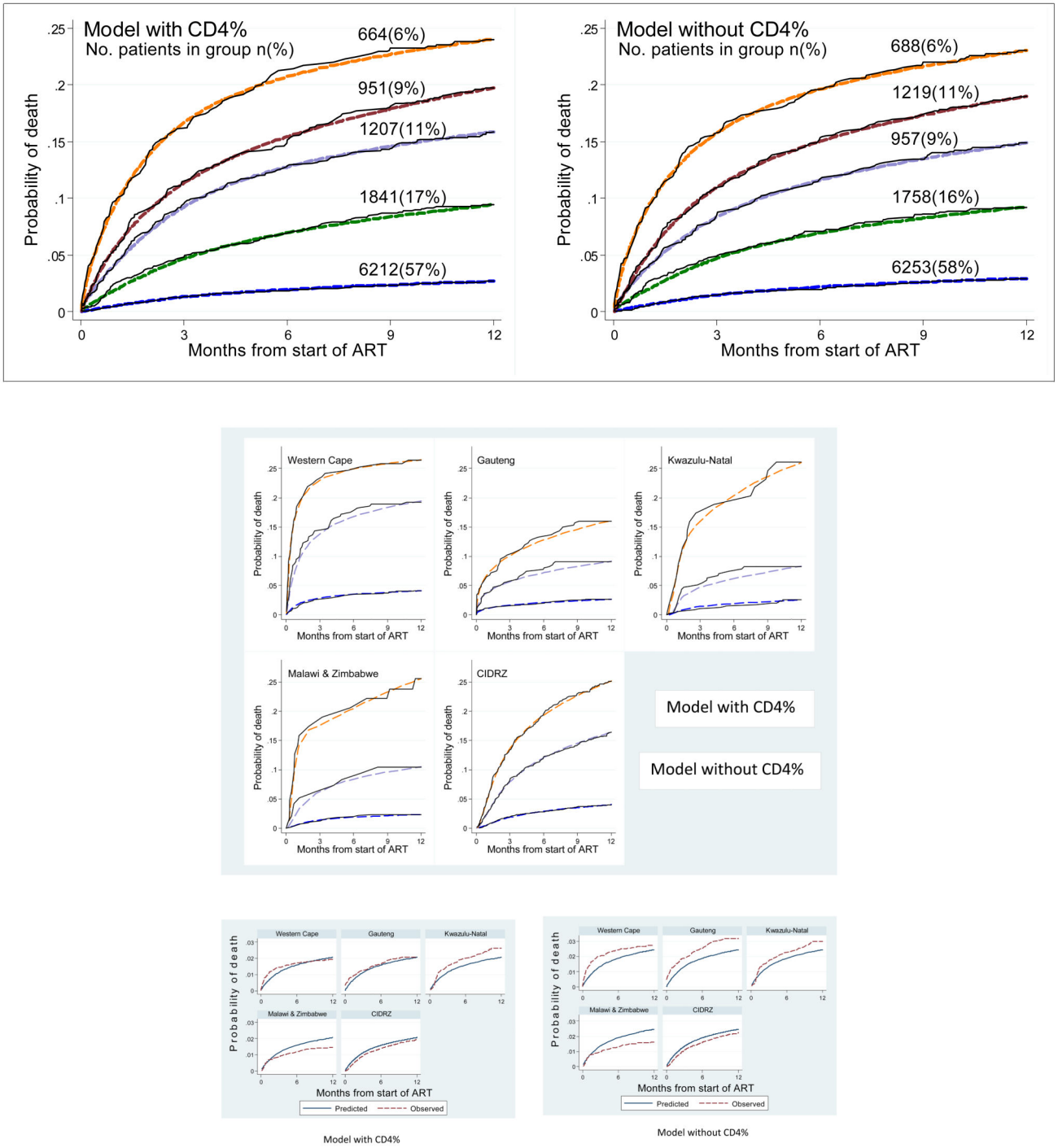

Figure 1.

Figure 1 (a): Cumulative mortality predicted from prognostic models (dashed lines) compared with Kaplan-Meier observed mortality (solid lines) for five prognostic groups of children commencing antiretroviral therapy, ranging from worst to best prognosis. Prognostic groups were defined by ranking the children in order of mortality risk according to their risk factors. Mortality risk was estimated by the linear predictor of the prognostic

model. The cut-points for each prognostic group were determined so that each group contained approximately 20% of deaths and were ordered from low to high risk. Number of patients in each group (%) is shown.

Figure 1 (b): Cumulative mortality predicted from prognostic models (dashed lines) compared with Kaplan-Meier observed mortality (solid lines) for each region for three prognostic groups of children commencing antiretroviral therapy, ranging from worst to best prognosis. Prognostic groups were defined as for figure 1 (a) but only three prognostic groups were used due to the smaller number of children for individual regions. Each group contains approximately one third of deaths.

Figure 1 (c): Cumulative mortality predicted from prognostic models (solid lines) compared with Kaplan-Meier observed mortality for each region (dashed lines) for patients with the most commonly occurring values of prognostic variables. Patients were age 5–10 years with WHO Stage III/IV disease, CD4≥10% and weight-for-age z-score −3 to −2.

Table 1

Pediatric antiretroviral therapy (ART) programs with number of patients, characteristics at ART initiation, follow-up duration, status by 1 year after ART initiation and Kaplan-Meier estimates of mortality by 1 year after ART initiation.

Region	Western Cape	Gauteng	Kwazulu-Natal	Malawi & Zimbabwe	Zambia	Total
Number of children	1505 (14%)	2015 (19%)	791 (7%)	706 (6%)	5858 (54%)	**10875**
Sex						
Female	720 (48%)	997 (49%)	396 (50%)	364 (52%)	2883 (49%)	**5360 (49%)**
Male	785 (52%)	1018 (51%)	395 (50%)	342 (48%)	2975 (51%)	**5515 (51%)**
Age group						
< 1 year	441 (29%)	306 (15%)	74 (9%)	23 (3%)	583 (10%)	**1427 (13%)**
1 year	290 (19%)	282 (14%)	128 (16%)	71 (10%)	1008 (17%)	**1779 (16%)**
2–4 years	412 (27%)	629 (31%)	224 (28%)	219 (31%)	1809 (30%)	**3293 (30%)**
5–10 years	362 (24%)	798 (40%)	365 (46%)	393 (56%)	2458 (40%)	**4376 (40%)**
WHO Stage[1]						
I/II	241 (18%)	461 (41%)	98 (19%)	37 (6%)	1746 (31%)	**2583 (28%)**
III/IV	1078 (82%)	669 (59%)	428 (81%)	538 (94%)	3964 (69%)	**6677 (72%)**
Not reported	*186 (12%)*	*885 (44%)*	*265 (34%)*	*131 (18%)*	*148 (3%)*	***1615 (15%)***
Anemia[1]						
Mild/none	903 (83%)	209 (87%)	464 (85%)	196 (87%)	3736 (78%)	**5508 (80%)**
Moderate	114 (10%)	18 (8%)	54 (10%)	18 (8%)	590 (12%)	**794 (12%)**
Severe	72 (7%)	13 (5%)	31 (6%)	11 (5%)	461 (10%)	**588 (9%)**
Not reported	*416 (28%)*	*1775 (88%)*	*242 (31%)*	*481 (68%)*	*1071 (18%)*	***3985 (37%)***
Median (IQR) CD4%	13 (9 to 19)%	11 (7 to 15)%	13 (8 to 17)%	14 (9 to 20)%	14 (9 to 20)%	**13 (8 to 19)%**
Not reported	*460 (31%)*	*313 (16%)*	*230 (29%)*	*397 (56%)*	*2080 (36%)*	***3480 (32%)***
Median (IQR) WAZ	−1.9 (−3.5 to −0.8)	−2.0 (−3.1 to −1.1)	−1.4 (−2.5 to −0.5)	−1.8 (−2.9 to −0.8)	−2.2 (−3.3 to −1.1)	−2.0 (−3.2 to −1.0)
Not reported	*537 (36%)*	*385 (19%)*	*168 (21%)*	*213 (30%)*	*319 (5%)*	***1622 (15%)***
Median (IQR) $\log_{10}$HIV-RNA (copies/ml)	5.56 (4.97 to 6.09)	5.23 (4.69 to 5.79)	4.52 (3.81 to 5.26)	5.09 (4.62 to 5.45)		**5.27 (4.69 to 5.84)**
Not reported	*430 (29%)*	*516 (26%)*	*459 (58%)*	*578 (82%)*	*5856 (>99%)*	***7839 (72%)***
Year of ART initiation						
2004	487	414	47	78	261	**1287**
2005	572	884	123	188	812	**2579**

Region	Western Cape	Gauteng	Kwazulu-Natal	Malawi & Zimbabwe	Zambia	Total
2006	433	706	144	101	994	**2378**
2007	13	11	158	80	1244	**1506**
>2008	0	0	319	259	2547	**3125**
Follow-up (child years)	1377.9	1920.5	754.0	671.7	5480.2	**10204.3**
AT 1 YEAR[2]						
% in follow-up	86.4	92.3	92.0	89.7	87.3	**88.6**
% transferred	3.3	0.8	0.3	2.5	0	**0.8**
% LTFU	0.7	1.1	1.3	2.3	3.7	**2.5**
% deceased	9.6	5.8	6.4	5.5	9.0	**8.1**
1-year mortality rate						
K-M estimate (95% CI)	10.5 (8.9 to 12.4)	6.0 (5.0 to 7.2)	6.8 (5.1 to 8.9)	5.8 (4.2 to 7.9)	9.6 (8.8 to 10.5)	8.6 (8.0 to 9.2)

IQR: interquartile range; LTFU: loss to follw-up; K-M: Kaplan-Meier

[1] Note that percentages for particular categories of this variable are calculated with the denominator being the number of children in whom this variable was reported.

[2] Note that LTFU and transferred outcomes refer to children LTFU or transferred between 6 and 12 months after anti retroviral therapy (ART) start as children LTFU/TFO within 6 months of ART start were excluded from the main analysis.

Table 2(a)

Prognostic variables and mortality for children starting ART and not LTFU or TFO during the first 6 months of treatment in 11 treatment programs in Southern Africa. Note: results shown only for imputed data; results for complete cases were similar.

					Analysis based on imputed data (25 multiple imputation datasets)			
Variable	**Available data**	**N(%) missing**	**Person years**	**N deaths**	**Crude mortality HR n=10875**		**Adjusted mortality HR n=10875**	
					HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)				877				
< 1	1427		1221	260	1		1	
1	1779		1588	261	0.74 (0.62 to 0.88)	0.001	0.72 (0.39 to 1.33)[1]	0.291
2–4	3293		3152	187	0.27 (0.23 to 0.33)	<0.001	0.31 (0.17 to 0.57)[1]	<0.001
5–10	4376		4243	169	0.18 (0.15 to 0.22)	<0.001	0.28 (0.17 to 0.46)[1]	<0.001
Sex								
Male	5515		5178	438	1		1	
Female	5360		5026	439	1.04 (0.91 to 1.18)	0.598	1.06 (0.93 to 1.21)	0.372
Stage		1615 (15)						
Less advanced	2583		2503	111	1		1	
Advanced	6677		6179	650	2.21 (1.80 to 2.71)	<0.001	1.93 (1.58 to 2.37)	<0.001
CD4 percent		3480 (32)						
less than 5	854		766	114	1		1	
5 to 9	1588		1479	143	0.72 (0.57 to 0.91)	0.006	0.84 (0.51 to 1.38)[2]	0.490
10 to 14	2036		1936	141	0.59 (0.47 to 0.75)	<0.001	0.57 (0.34 to 0.96)[2]	0.035
≥ 15	2917		2733	238	0.64 (0.52 to 0.79)	<0.001	0.59 (0.38 to 0.92)[2]	0.021
Anemia		3985 (36)						
Severe	588		509	104	1		1	

					Analysis based on imputed data (25 multiple imputation datasets)			
Variable	**Available data**	**N(%) missing**	**Person years**	**N deaths**	**Crude mortality HR n=10875**		**Adjusted mortality HR n=10875**	
					HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Moderate	794		710	113	0.80 (0.62 to 1.03)	0.080	0.83 (0.64 to 1.08)	0.165
Mild/none	5508		5206	401	0.43 (0.35 to 0.53)	<0.001	0.61 (0.49 to 0.75)	<0.001
Weight-for-age z-score		1622 (15)						
≤ − 3	2715		2373	451	1		1	
−3 to −2	1975		1852	163	0.51 (0.43 to 0.61)	<0.001	0.90 (0.62 to 1.29)[3]	0.560
−2 to −1	2258		2191	87	0.27 (0.21 to 0.33)	<0.001	0.83 (0.57 to 1.21)[3]	0.332
≥ −1	2305		2251	70	0.21 (0.17 to 0.27)	<0.001	0.52 (0.35 to 0.80)[3]	0.003

HR: hazard ratio; CI: confidence interval

[1] HRs are shown for a child with CD4 percent <5%;

[2] HRs are shown for a child < 1 year of age;

[3] HRs are shown for a child <1 year of age with CD4 percent <5%

Table 2(b)

Hazard ratios for the associations between age, CD4% and weight-for-age z-score (WAZ) adjusted for these variables as well as WHO Clinical Stage and sex, taking into account the interactions between age and CD4% and age and WAZ for data with missing covariate values modeled using multiple imputation (N=10875)

AGE	WAZ	CD4% <5	CD4% 5–9.9	CD4% 10–14.9	CD4% ≥ 15
< 1 year	**< −3**	1	0.87 (0.52 to 1.44)	0.60 (0.36 to 1.00)	0.62 (0.40 to 0.98)
	−3 to −2	0.90 (0.62 to 1.29)	0.78 (0.41 to 1.45)	0.54 (0.29 to 0.98)	0.56 (0.32 to 0.97)
	−2 to −1	0.83 (0.57 to 1.21)	0.72 (0.38 to 1.36)	0.50 (0.26 to 0.95)	0.52 (0.29 to 0.92)
	≥ −1	0.52 (0.35 to 0.80)	0.45 (0.24 to 0.87)	0.31 (0.16 to 0.60)	0.33 (0.18 to 0.59)
1 year	**< −3**	0.88 (0.47 to 1.65)	0.60 (0.35 to 1.02)	0.73 (0.43 to 1.22)	0.49 (0.30 to 0.80)
	−3 to −2	0.66 (0.34 to 1.31)	0.45 (0.26 to 0.81)	0.55 (0.31 to 0.98)	0.37 (0.22 to 0.63)
	−2 to −1	0.31 (0.15 to 0.67)	0.22 (0.11 to 0.43)	0.26 (0.12 to 0.51)	0.18 (0.09 to 0.33)
	≥ −1	0.26 (0.11 to 0.57)	0.17 (0.09 to 0.35)	0.21 (0.11 to 0.41)	0.14 (0.07 to 0.27)
2–4 years	**< −3**	0.50 (0.27 to 0.92)	0.43 (0.25 to 0.73)	0.26 (0.15 to 0.46)	0.32 (0.19 to 0.52)
	−3 to −2	0.21 (0.11 to 0.42)	0.18 (0.10 to 0.33)	0.11 (0.06 to 0.15)	0.13 (0.07 to 0.24)
	−2 to −1	0.09 (0.04 to 0.20)	0.08 (0.04 to 0.16)	0.05 (0.02 to 0.10)	0.06 (0.03 to 0.12)
	≥ −1	0.10 (0.05 to 0.22)	0.09 (0.04 to 0.17)	0.05 (0.03 to 0.11)	0.06 (0.03 to 0.12)
5–9 years	**< −3**	0.41 (0.25 to 0.68)	0.20 (0.11 to 0.35)	0.14 (0.08 to 0.27)	0.14 (0.08 to 0.26)
	−3 to −2	0.22 (0.12 to 0.40)	0.11 (0.06 to 0.20)	0.07 (0.04 to 0.15)	0.08 (0.04 to 0.15)
	−2 to −1	0.12 (0.06 to 0.23)	0.06 (0.03 to 0.11)	0.04 (0.02 to 0.08)	0.04 (0.02 to 0.08)
	≥ −1	0.08 (0.04 to 0.18)	0.04 (0.02 to 0.09)	0.03 (0.01 to 0.06)	0.03 (0.01 to 0.06)

Table 3

Adjusted mortality hazard ratios (HR) in the selected best models with CD4% and withoutCD4%

	Model with CD4%		Model without CD4%	
Variable	**Adjusted mortality HR (95% CI)**	**p-value**	**Adjusted mortality HR (95% CI)**	**p-value**
Age				
<1 year	1		1	
1 year	0.78 (0.66 to 0.93)	0.006	0.78 (0.66 to 0.93)	0.005
2 to 4 years	0.34 (0.28 to 0.41)	<0.001	0.35 (0.29 to 0.43)	<0.001
5 to 10 years	0.22 (0.18 to 0.27)	<0.001	0.25 (0.2 to 0.3)	<0.001
WHO Clinical Stage				
I or II	1		1	
III or IV	1.39 (1.13 to 1.71)	0.002	1.39 (1.13 to 1.72)	0.002
CD4%				
<5%	1		not in model	
5–9.9%	0.69 (0.54 to 0.87)	0.002	not in model	
≥10%	0.56 (0.45 to 0.68)	<0.001	not in model	
Weight-for-age z-score				
<−3	1		1	
−3 to −2	0.66 (0.55 to 0.79)	<0.001	0.63 (0.53 to 0.76)	<0.001
≥ −2	0.35 (0.29 to 0.42)	<0.001	0.33 (0.27 to 0.4)	<0.001
Anemia				
Severe	1		1	
Mild/moderate/none	0.71 (0.57 to 0.88)	0.002	0.7 (0.57 to 0.87)	0.001

HR: hazard ratio; CI: confidence interval