Prognosis of Children With HIV-1 Infection Starting Antiretroviral Therapy in Southern Africa

A Collaborative Analysis of Treatment Programs

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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 of age who started ART in Malawi, South Africa, Zambia or Zimbabwe from 2004 to 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 2 prognostic models: 1 with CD4%, age, World Health Organization clinical stage, weight-for-age z-score (WAZ) and anemia and the other without CD4%, because it is not routinely measured in many programs. We used multiple imputation to account for missing data.

Results: Among 12,655 children, 877 (6.9%) died in the first year of ART. We excluded 1780 children who were lost to follow up/transferred from main analyses; 10,875 children were therefore included. With the CD4% model probability of death at 1 year ranged from 1.8% [95% confidence interval (CI): 1.5–2.3] in children 5–10 years with CD4% ≥10%, World Health Organization 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).

Conclusions: 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.

Key Words: mortality, HIV-1, children, sub-Saharan Africa, antiretroviral

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Despite increased access to antiretroviral therapy (ART) for HIV-infected children in low-income settings, mortality remains high. In 2010, an estimated 230,000 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 4 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.

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Separate models were developed for settings with and without access to CD4% at ART initiation.

MATERIALS 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 4 countries, including 8 clinics in 3 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 1 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 January 1, 2004, and January 31, 2010, were eligible. Children with <1 year of potential follow up (ART initiation <1 year before 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 (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/B781). The 11 cohorts were grouped into 5 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 2 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 World Health Organization (WHO) and national guidelines at the time. In South Africa, the recommended first-line regimen was 2 nucleoside reverse transcriptase inhibitors plus either lopinavir/ritonavir (children <3 years or <10 kg) or efavirenz (children >3 years and >10 kg). In Malawi, Zimbabwe and Zambia 2 nucleoside reverse transcriptase inhibitors 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 prespecified categories of age (<1 year, 1 year, 2–4 years and 5–10 years); WHO Clinical Stage (I/II compared with 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 nonnormally 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. 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 4 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 2 independent prognostic groups.[32] We calculated the D-statistic for the model fitted on the 4 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 the data used to estimate the model coefficients. Models with a low Akaike Information Criterion 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, TX).

Sensitivity Analyses

In sensitivity analyses, we included children LTFU/TFO within 6 months of starting treatment. We examined Kaplan-Meier estimates of 1-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, 12,655 children started ART. We excluded 1780 children (14%) from the main analysis as they were LTFU or TFO within 6 months of ART start. The main analysis included 10,875 children (70% ≥2 years old) with 10,204 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 percent of children <1 year ranged from 3% to nearly 30%; the percentage with WHO

TABLE 1. Pediatric 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 and Zimbabwe	Zambia	Total
Number of children	1505 (14%)	2015 (19%)	791 (7%)	706 (6%)	5858 (54%)	10,875
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 (yr)						
<1	441 (29%)	306 (15%)	74 (9%)	23 (3%)	583 (10%)	1427 (13%)
1	290 (19%)	282 (14%)	128 (16%)	71 (10%)	1008 (17%)	1779 (16%)
2–4	412 (27%)	629 (31%)	224 (28%)	219 (31%)	1809 (30%)	3293 (30%)
5–10	362 (24%)	798 (40%)	365 (46%)	393 (56%)	2458 (40%)	4376 (40%)
WHO stage*						
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*						
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 (9–19)%	11 (7–15)%	13 (8–17)%	14 (9–20)%	14 (9–20)%	13 (8–19)%
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 (4.97–6.09)	5.23 (4.69–5.79)	4.52 (3.81–5.26)	5.09 (4.62–5.45)		5.27 (4.69–5.84)
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
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	10,204.3
At 1 year†						
% 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 (8.9–12.4)	6.0 (5.0–7.2)	6.8 (5.1–8.9)	5.8 (4.2–7.9)	9.6 (8.8–10.5)	8.6 (8.0–9.2)

IQR, interquartile range; K-M, Kaplan-Meier.

*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.

†Note that LTFU and transferred outcomes refer to children LTFU or transferred between 6 and 12 months after ART start as children LTFU/TFO within 6 months of ART start were excluded from the main analysis.

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% confidence interval (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. 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 with younger children (Table 3), although mortality overall was lower for older children.

The 2 final models selected by internal-external cross validation included age (in 4 categories), clinical stage (2), WAZ (3) and anemia (2), with 1 model additionally including CD4% (in 3 categories, Table 4). 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 6 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 6 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 2 models.

For both models, predicted mortality closely followed observed mortality for 5 prognostic groups of children with approximately 20% of deaths in each group (Fig. 1A). Within each region predicted and observed, mortality for groups of children with different prognosis were also similar (Fig. 1B), indicating generalizability of the models. Many children [57% (model with CD4%) and 58% (model without CD4%)] were in the group with a good prognosis and 1-year mortality <5%. Predicted mortality from the

TABLE 2. 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

					Analysis Based on Imputed Data (25 Multiple Imputation Datasets)			
					Crude Mortality HR (n = 10,875)		Adjusted Mortality HR (n = 10,875)	
Variable	Available data	N(%) missing	Person-years	N Deaths	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (yr)				877				
<1	1427		1221	260	1		1	
1	1779		1588	261	0.74 (0.62–0.88)	0.001	0.72 (0.39–1.33)*	0.291
2–4	3293		3152	187	0.27 (0.23–0.33)	<0.001	0.31 (0.17–0.57)*	<0.001
5–10	4376		4243	169	0.18 (0.15–0.22)	<0.001	0.28 (0.17–0.46)*	<0.001
Sex								
Male	5515		5178	438	1		1	
Female	5360		5026	439	1.04 (0.91–1.18)	0.598	1.06 (0.93–1.21)	0.372
Stage		1615 (15)						
Less advanced	2583		2503	111	1		1	
Advanced	6677		6179	650	2.21 (1.80–2.71)	<0.001	1.93 (1.58–2.37)	<0.001
CD4%		3480 (32)						
<5	854		766	114	1		1	
5–9	1588		1479	143	0.72 (0.57–0.91)	0.006	0.84 (0.51–1.38)†	0.490
10–14	2036		1936	141	0.59 (0.47–0.75)	<0.001	0.57 (0.34–0.96)†	0.035
≥ 15	2917		2733	238	0.64 (0.52–0.79)	<0.001	0.59 (0.38–0.92)†	0.021
Anemia		3985 (36)						
Severe	588		509	104	1		1	
Moderate	794		710	113	0.80 (0.62–1.03)	0.080	0.83 (0.64–1.08)	0.165
Mild/none	5508		5206	401	0.43 (0.35–0.53)	<0.001	0.61 (0.49–0.75)	<0.001
WAZ		1622 (15)						
≤–3	2715		2373	451	1		1	
–3 to –2	1975		1852	163	0.51 (0.43–0.61)	<0.001	0.90 (0.62–1.29)‡	0.560
–2 to 1	2258		2191	87	0.27 (0.21–0.33)	<0.001	0.83 (0.57–1.21)‡	0.332
≥–1	2305		2251	70	0.21 (0.17–0.27)	<0.001	0.52 (0.35–0.80)‡	0.003

Results shown only for imputed data; results for complete cases were similar.
*HRs are shown for a child with CD4% <5%.
†HRs are shown for a child <1 year of age.
‡HRs are shown for a child <1 year of age with CD4% <5%.
HR, hazard ratio.

model with CD4% closely approximated observed mortality for all regions except Kwazulu-Natal (observed > predicted) and Malawi and Zimbabwe (observed < predicted; Fig. 1C). Predicted mortality from the model without CD4% only approximated observed mortality closely for CIDRZ (Fig. 1B). 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, Malawi and Zimbabwe where >60% of values were missing.

TABLE 3. Hazard Ratios for the Associations Between Age, CD4% and 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. Data With Missing Covariate Values Modeled Using Multiple Imputation (N = 10,875)

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

TABLE 4. Adjusted Mortality HR in the Selected Best Models With and Without CD4%

	Model With CD4%		Model Without CD4%	
Variable	Adjusted Mortality HR (95% CI)	*P*-value	Adjusted Mortality HR (95% CI)	*P*-value
Age (yr)				
<1	1		1	
1	0.78 (0.66–0.93)	0.006	0.78 (0.66–0.93)	0.005
2–4	0.34 (0.28–0.41)	<0.001	0.35 (0.29–0.43)	<0.001
5–10	0.22 (0.18–0.27)	<0.001	0.25 (0.2–0.3)	<0.001
WHO clinical stage				
I or II	1		1	
III or IV	1.39 (1.13–1.71)	0.002	1.39 (1.13–1.72)	0.002
CD4%				
<5%	1		Not in model	
5–9.9%	0.69 (0.54–0.87)	0.002	Not in model	
≥10%	0.56 (0.45–0.68)	<0.001	Not in model	
WAZ				
<−3	1		1	
−3 to −2	0.66 (0.55–0.79)	<0.001	0.63 (0.53–0.76)	<0.001
≥−2	0.35 (0.29–0.42)	<0.001	0.33 (0.27–0.4)	<0.001
Anemia				
Severe	1		1	
Mild/moderate/none	0.71 (0.57–0.88)	0.002	0.7 (0.57–0.87)	0.001

HR, hazard ratio.

Children aged <1 year in clinical stage III/IV with WAZ <−3, severe anemia and CD4% <5 had the highest predicted cumulative mortality at 1 year (46.3%) and children aged 5–10 years in stage I/II with WAZ ≥−2, no severe anemia and CD4% ≥10 had the lowest mortality (1.8%). Predictions for all combinations of prognostic variables are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/B782.

The 1780 children LTFU/TFO within the first 6 months of treatment were younger and had more advanced disease compared with those included (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B782). In sensitivity analyses that included these children, Kaplan-Meier 1-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 1-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 1-year mortality in children commencing ART are generalizable with good discrimination and prognostic separation. Many children (>55%) starting ART and remaining in care have a 1-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, LTFU and TFO

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 of age 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 6 and 12 months on ART),[35] which may result in overestimating mortality. We excluded children LTFU/TFO within 6 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 with children remaining in care.[11,36,37] Our sensitivity analysis including children LTFU/TFO within 6 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 with 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 because of the powerful prognostic value of age in

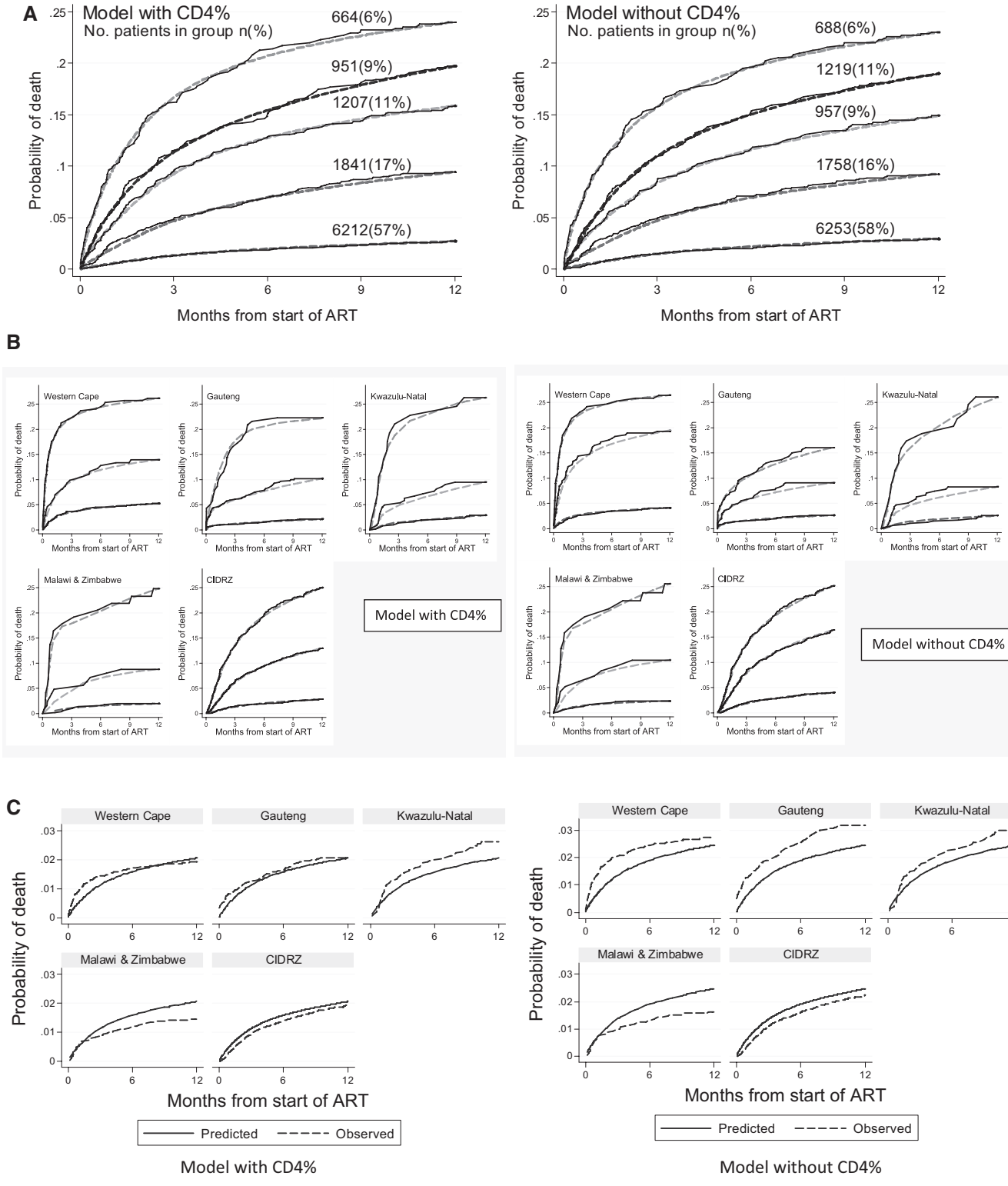

FIGURE 1. A) Cumulative mortality predicted from prognostic models (dashed lines) compared with Kaplan-Meier observed mortality (solid lines) for 5 prognostic groups of children commencing ART, ranging from worst to best prognosis. Prognostic groups were defined by ranking the children in order of mortality 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

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/immunologic 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 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 (eg, 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% (Fig. 1C). 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. Many 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 many 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 (Fig. 1A) 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, trimethoprim-sulfamethoxazole 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%. 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.

In conclusion, the majority of children starting ART in Southern Africa have a low risk of one-year mortality, despite many having characteristics of severe disease. As more children are diagnosed and initiate ART early, and the duration of follow-up increases, it is important to monitor ART outcomes and develop prognostic models for long-term prognosis in children starting ART without severe disease.

FIGURE 1. (*Continued*) that each group contained approximately 20% of deaths and were ordered from low to high risk. Number of patients in each group (%) is shown. B) Cumulative mortality predicted from prognostic models (dashed lines) compared with Kaplan-Meier observed mortality (solid lines) for each region for 3 prognostic groups of children commencing ART, ranging from worst to best prognosis. Prognostic groups were defined as for (A) but only 3 prognostic groups were used due to the smaller number of children for individual regions. Each group contains approximately one-third of deaths. 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 WAZ −3 to −2.

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