Outcomes of Infants Starting Antiretroviral Therapy in Southern Africa, 2004–2012

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Background: There are limited published data on the outcomes of infants starting antiretroviral therapy (ART) in routine care in Southern Africa. This study aimed to examine the baseline characteristics and outcomes of infants initiating ART.

Methods: We analyzed prospectively collected cohort data from routine ART initiation in infants from 11 cohorts contributing to the International Epidemiologic Database to Evaluate AIDS in Southern Africa. We included ART-naive HIV-infected infants aged <12 months initiating ≥3 antiretroviral drugs between 2004 and 2012. Kaplan–Meier estimates were calculated for mortality, loss to follow-up (LTFU), transfer out, and virological suppression. We used Cox proportional hazard models stratified by cohort to determine baseline characteristics associated with outcomes mortality and virological suppression.

Results: The median (interquartile range) age at ART initiation of 4945 infants was 5.9 months (3.7–8.7) with follow-up of 11.2 months (2.8–20.0). At ART initiation, 77% had WHO clinical stage 3 or 4 disease and 87% were severely immunosuppressed. Three-year mortality probability was 16% and LTFU 29%. Severe immunosuppression, WHO stage 3 or 4, anemia, being severely underweight, and initiation of treatment before 2010 were associated with higher mortality. At 12 months after ART initiation, 17% of infants were severely immunosuppressed and the probability of attaining virological suppression was 56%.

Conclusions: Most infants initiating ART in Southern Africa had severe disease with high probability of LTFU and mortality on ART. Although the majority of infants remaining in care showed immune recovery and virological suppression, these responses were suboptimal.

Key Words: infants, antiretroviral therapy, outcomes, Southern Africa

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INTRODUCTION

Despite advances in Prevention of Mother-to-Child Transmission (PMTCT) programs, including possible reduction of vertical transmission to as low as 1%,[1] 900 HIV-infected infants were born daily in 2011, the vast majority in sub-Saharan Africa.[2] Infants differ from older children and adults with respect to rapid physical growth (especially of their developing brain), establishment of a functioning immune

system and rapidly changing physiology.[3–5] Furthermore, infants infected with HIV experience increased vulnerability to the multiple insults of the virus and its complications including accelerated disease progression and increased risk of morbidity and mortality.[6–12] These worsened outcomes, together with age-specific diagnostic treatment and monitoring challenges related to pediatric HIV policy, drugs, and testing, make infants a high-risk population.[5,8,13–15]

There has been much progress in infant HIV care in recent years: 2008 international guidelines recommended initiation of ART in all infants younger than 12 months, regardless of immunological and clinical status.[16] Subsequently, the 2010 and 2013 guidelines were amended to provide ART for all children younger than 2 years and younger than 5 years, respectively.[17,18] These changes were largely informed by studies such as the Children with Human Immune Deficiency Virus Early Antiretroviral Therapy Trial (CHER). This trial, conducted in South Africa (SA), quantified the benefits of early ART initiation before 12 weeks of age, demonstrating a 76% reduction in mortality and 75% reduction in HIV progression compared with deferring ART until World Health Organization (WHO) 2006 treatment initiation criteria were met.[19,20]

However, the features of this trial and its participants differ considerably from the context of the resource-scarce routine care setting of Southern Africa.[5,14,15,20–23] For example, the average age at commencement of ART was 7 weeks, there was availability of appropriate laboratory testing, and drug regimens including protease inhibitors, minimal loss to follow-up (LTFU), and those with comorbid conditions or severe immunosuppression were specifically excluded.

There are few studies on the outcomes of infants starting ART in routine care in resource-scarce settings including mostly only small numbers of infants starting therapy since the implementation of the WHO 2008 recommendation for immediate ART initiation in infants. Using data merged from cohorts in the International Epidemiologic Database to Evaluate AIDS in Southern Africa (IeDEA-SA), our study aimed to describe baseline characteristics of infants starting first-line ART in routine care within Southern Africa, their treatment outcomes, including clinical, immunological, and virological responses, and to identify determinants for these outcomes.

METHODS

We conducted an analysis of prospectively collected cohort data of infants initiating ART in routine care between January 2004 and December 2012 at sites contributing to the IeDEA-SA collaboration.[24] Infants were defined as less than 12 months of age at ART initiation. IeDEA-SA data are collated on site by cohort investigators through routine clinical follow-up of infants as part of the standard treatment and monitoring of HIV.[19,25–27] Anonymized data are then transferred to the central IeDEA-SA Data Centre using a Data Transfer Protocol.

We included 11 cohorts from SA, Zimbabwe, Malawi, and Zambia. Cohort inclusion required initiation of infants on ART both before and after January 1, 2010, so as to ensure that each cohort included a portion of infants initiated after the release of the WHO 2010 guidelines for early initiation.[27] HIV-infected (recorded PCR diagnosis or presumptive diagnosis), ART-naive (except for PMTCT exposure) infants with a recorded date of initiation of at least 3 antiretroviral drugs before the age of 12 months were eligible for inclusion. Participants with missing data for date of ART initiation, age, and gender were excluded as were infants identified as being virologically suppressed (HIV-RNA <400 copies/mL) at ART initiation due to possible non-naivety to ART. Eligibility for ART initiation was cohort specific and reflected the country guidelines at the time.

Each cohort has institutional ethical approval for contribution of data to IeDEA-SA. Ethical approval for the database and this analysis was obtained from the Human Research Ethics Committee of the University of Cape Town, SA.

Characteristics of infants at ART initiation included demographic details, anthropometric measures, hemoglobin (Hb), clinical (WHO clinical staging),[28] immunological, and virological markers of disease severity, and information about medicines administered including PMTCT drugs. These characteristics are presented overall and according to time period of initiation using medians and proportions and compared using Wilcoxon rank-sum and χ^2 tests, respectively.

Measurements from the closest date to ART initiation within an interval of 6 months before and 1 week after initiation were used for laboratory baseline characteristics and 3 months before, up to the day of initiation for anthropometric characteristics. Age at ART initiation was categorized as <3 months, 3 to <6, and 6 to <12 months. Severe anemia was defined using the Division of AIDS (DAIDS) guidelines[29]: Hb <10 g/dL (age: ≤ 21 days); <8 g/dL (age: 22–35 days); <7 g/dL (age: 36–56 days); and <7.5 g/dL (age: ≥ 57 days). Weight and height measures were converted to age- and gender-specific z-scores [weight-for-age z-score (WAZ), height-for-age z-score (HAZ), and weight-for-height (WFHZ) using the 2007 WHO growth reference standards].[30] WAZ and HAZ were further categorized as <-3, -3 to -2, and >-2. Severe immunosuppression was defined where the lowest of the CD4 absolute cell count or percentage met classification as per WHO criteria.[28] Virological suppression was defined as the first recorded viral load <400 copies per milliliter. Year of initiation was dichotomized as before or after first of January 2010 to reflect the 2010 WHO changes to guidelines for ART initiation.[27]

Outcomes were death, transfer out (TFO), LTFU, and virological suppression. LTFU was defined as the last recorded visit >9 months before cohort database closure with the date of LTFU being the date of the last visit. Response variables included CD4 absolute cell count and percentage, viral load, and anthropometric measures (WAZ and HAZ).

Statistical Methods

Anthropometric, immunological, and hemoglobin responses over time on ART were examined in infants who remained in care for at least 12 months. This was to

approximate a true change in averages by minimizing the effect of loss (through death, LTFU) of the sicker infants on these averages. We used the Kaplan–Meier method to estimate the probability of death, TFO, LTFU, and virological suppression. Because of the interdependence of death, TFO, and LTFU, we also conducted Competing Risk analysis to determine the Cumulative Incidence Functions for these outcomes. We used Cox proportional hazard models stratified by cohort to determine baseline characteristics associated with mortality. Because of the high levels of missing virological data from cohorts outside SA, a separate model including estimates for baseline virological characteristics within SA cohorts was analyzed. We used Cox proportional hazard models stratified by cohort to determine baseline characteristics associated with time to virological suppression in infants from SA cohorts who had a baseline viral load and at least 1 follow-up viral load measurement recorded.

Missing baseline data for CD4 count and percent, Hb, WAZ, HAZ, and WHO stage were modeled using multiple imputation. The imputation model, with the assumption of data missing at random, included all baseline characteristics, including cohort, age and year of initiation, outcomes of mortality, LTFU and TFO, and follow-up time. Five imputation sets were generated and reported estimates representing pooled imputed data estimates were calculated using Rubin Rules.[31] Independent variables for inclusion in the models were selected a priori and are complemented by a postimputation model selection method using model averaging based variable importance (VI) and an estimate weight according to both frequency and strength of association in the augmented data sets.[32,33] All statistical analysis was done using STATA 12.0 with multiple imputation done using ICE.[34]

RESULTS

The median [interquartile range (IQR)] age at ART initiation of 4945 infants was 5.9 months (3.7–8.7) with median follow-up of 11.2 months (IQR, 2.8–20.0). Among the 11 cohorts included representing all levels of care, 8 SA sites contributed 3473 (70%) of infants. About a quarter (26%) of infants initiated ART from 2010 onward.

Baseline Characteristics

At ART initiation, 77% of infants were classified as WHO clinical stage 3 or 4 and 87% were severely immunosuppressed (Table 1). The distribution of these characteristics by age group is summarized in Table S1 (see Supplemental Digital Content, http://links.lww.com/QAI/A689). Approximately 60% of infants were either moderately or severely underweight and approximately 60% were either moderately or severely stunted at initiation. The median viral load was 5.99 $\log_{10}$ copies per milliliter (IQR, 5.41–6.45). Infants initiating ART from the start of 2010 were generally younger with less severe illness than those initiating before 2010 (Table 1). Missing baseline data were seen in all anthropometric and laboratory measures, especially virological data (Tables 1 and 2).

Mortality and Programmatic Outcomes

Mortality was highest in the few months after ART initiation with 6- and 12-month cumulative probabilities of 10.1% [95% confidence interval (CI): 9.3 to 11.1] and 13.2% (95% CI: 12.1 to 14.3), respectively (Fig. 1A). LTFU was considerable in the first year with 6 and 12 months probabilities of 13.7% (95% CI: 12.7 to 14.7) and 18.8%

TABLE 1. Baseline Characteristics of Infants Initiating ART, 2004–2012: Demographic, Clinical, and Laboratory Characteristics at Initiation

Characteristics	N = 4945, N (%)	Overall*	2004–2009	2010–2012	*P*
Age, mo, median (IQR)	4945 (100)	5.9 (3.7 to 8.7)	6.1 (3.8 to 8.9)	5.4 (3.4 to 8.4)	0.0000
Female, n (%)	4945 (100)	2546 (51.5)	1845 (50.7)	701 (53.7)	0.0603
WHO stage 3 or 4, n (%)	4347 (87.9)	3327 (76.5)	2605 (81.2)	722 (63.4)	0.0000
Absolute CD4, median (IQR)	3417 (69.1)	765 (347 to 1334)	724 (324 to 1274)	887 (440 to 1535)	0.0000
CD4 percentage, median (IQR)	3244 (65.6)	18.5 (12 to 26)	18 (11.5 to 24.9)	20.7 (13.6 to 28.4)	0.0000
Severe immunosuppression (WHO 2006), n (%)	3514 (71.1)	3063 (87.2)	2336 (89.2)	727 (81.3)	0.0000
Viral load ≥1,000,000, n (%)	2042 (41.3)	1012 (49.6)	815 (49.5)	197 (49.6)	0.9777
Severe anemia (DAIDS 2009), n (%)	2813 (56.7)	248 (8.8)	176 (8.7)	72 (9.0)	0.8182
WAZ, median (IQR)	3795 (76.7)	−2.5 (−3.9 to −1.2)	−2.7 (−4.1 to −1.3)	−2.1 (−3.5 to −0.8)	0.0000
WAZ category, n (%)					
>−2		1523 (40.1)	1.037 (37.1)	486 (48.3)	0.0000
≤−2 to >−3		686 (18.1)	510 (18.3)	176 (17.5)	0.5762
≤−3		1586 (41.8)	1242 (44.5)	344 (34.2)	0.0000
HAZ, median (IQR)	2919 (59.0)	−2.5 (−3.9 to −1.1)	−2.6 (−4.0 to −1.3)	−2.2 (−3.5 to −0.8)	0.0000
HAZ category, n (%)					
−2		1177 (40.3)	844 (38.6)	333 (45.5)	0.0010
≤−2 to >−3		538 (18.4)	392 (17.9)	146 (19.9)	0.2222
≤−3		1204 (41.3)	951 (43.5)	253 (34.6)	0.0000

*Proportions represent proportion of nonmissing (N) observations.
N, number of nonmissing observations.

TABLE 2. Baseline Characteristics of Infants Initiating ART, 2004–2012: Drug Regimens and PMTCT Exposure

		N (%)	Overall,* N (%)
First-line regimen, n (%)	D4T + 3TC + lopinavir/ritonavir	4653 (94.1)	2068 (44.4)
	D4T + 3TC + nevirapine		971 (20.9)
	ABC + 3TC + lopinavir/ritonavir		598 (12.9)
	AZT + 3TC + nevirapine		343 (7.4)
	AZT + 3TC + lopinavir/ritonavir		286 (6.2)
	Other		387 (8.3)
Third ART drug, n (%)	lopinavir/ritonavir	4659 (94.2)	2957 (63.5)
	ritonavir		214 (4.6)
	nevirapine		1399 (30.0)
	efavirenz		89 (1.9)
PMTCT exposed, n (%)		1637 (33.1)	948 (57.9)

*Proportions represent proportion of nonmissing (N) observations.
3TC, lamivudine; ABC, abacavir; AZT, zidovudine; D4T, stavudine; N, number of nonmissing observations.

(95% CI: 17.6 to 20.1), respectively (Fig. 1A). TFO from a higher level of care to another facility occurred throughout follow-up with the 36-month probability being 34.2% (95% CI: 32.3 to 36.1) (Fig. 1A). The cumulative incidence functions from a competing risk analysis provided a 12-month probability of mortality (competing with LTFU and TFO) of 11.3% (95% CI: 10.4 to 12.2) (Fig. 1B). The corresponding probabilities of being alive and in care at 6 and 12 months were 71.5% (95% CI: 70.2 to 72.7) and 59.6% (95% CI: 58.2 to 61.0), respectively. Unadjusted comparison of outcomes according to time period of initiation suggested decreased mortality and a trend to lower LTFU in those initiating ART from the start of 2010 (Log-rank test $P = 0.0005$ and 0.0576, respectively) (Figs. 1C, D).

Severe immunosuppression [adjusted hazard ratio (aHR), 2.19; 95% CI: 1.44 to 3.33], WHO stage 3 or 4 (aHR, 1.36; 95% CI: 1.04 to 1.78), lower WAZ, and initiation of ART from the start of 2010 were found to be independently associated with mortality (Table 3). Compared with having a WAZ of >-2 those infants with WAZ <-3 at baseline had a 2.34-fold (aHR, 2.34; 95% CI: 1.78 to 2.80) increased risk of death. After adjusting for disease severity at baseline, infants initiating ART from the start of 2010 had a reduced risk of death compared with those initiated before 2010 (aHR, 0.75; 95% CI: 0.59 to 0.94). There was no evidence of an effect of infant age group on mortality. Overall estimates from the imputed data sets provided similar estimates to complete case analysis (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/A689 demonstrating imputed and complete case survival analyses). In an analysis restricted to infants from SA cohorts, there was no association between baseline viral load category and death after adjustment for other disease severity characteristics at baseline (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/A689 demonstrating an analysis of the association of baseline viral load category and the outcome mortality in a subset of SA infants).

Responses to ART

Anthropometric, immunological, and hemoglobin responses to ART were examined for infants remaining in care for at least 12 months. Weight-for-age showed rapid improvement in the first 6 months of therapy with an increase from a median WAZ of -2.40 to -0.97 (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A689 demonstrating growth response on ART over time for infants remaining in care for at least 1 year). Height-for-age showed a slower increase reaching a median HAZ of -1.97 from a baseline of -2.34 after 1 year on ART.

Absolute CD4 count showed a rapid increase in the first year after initiation with a 12-month median CD4 cell count of 1573 cells per milliliter almost double that at baseline (Fig. 2A). As expected, CD4 percentages, adjusting more appropriately for age-related immunological changes, showed a similar initial trend of improvement that was sustained, only plateauing at 36 months (Fig. 2B). These combined effects can be seen in the change in the proportion of infants meeting the WHO criteria for severe immunosuppression with a reduction from 87% (95% CI: 86 to 89) at baseline to 17% (95% CI: 15 to 18) at 12 months and 3% (95% CI: 2 to 4) at 36 months. Median (IQR) hemoglobin increased from a baseline of 9.7 to 11 g/dL (10.2–12.0) at 6 months (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/A689 demonstrating the change in median hemoglobin over time for infants remaining in care for over 12 months).

Among a subset of SA infants with at least baseline and one other viral load measurement (n = 1364), the probabilities of virological suppression at 6 and 12 months were 28.1% (95% CI: 25.6 to 30.7) and 56.1% (95% CI: 53.2 to 59.1), respectively (Fig. 2C). A viral load of $\geq$1 million copies per milliliter at ART start was the only independent predictor of failure to suppress (aHR, 0.78; 95% CI: 0.68 to 0.89) (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/A689 demonstrating imputed and complete case analyses of virological suppression in this subset of infants).

DISCUSSION

In this study, we found that infants initiating ART in Southern Africa between 2004 and 2012 were older with a high prevalence of severe baseline disease. The improvement in these characteristics from the start of 2010 onward reflects WHO guideline changes: a proportion of infants initiating ART in the latter period had no severe disease characteristics. Despite considerable early responses to ART and a reduction in the prevalence of severe disease characteristics, infants remaining in care experienced suboptimal immunological, anthropometric, and virological responses. Furthermore, mortality, particularly in the initial stage after ART initiation, was high and LTFU was substantial throughout the observation period. Initiation of ART before 2010 was an independent predictor of mortality. Similar LTFU before 2010 and from the start of 2010 suggests that the apparent

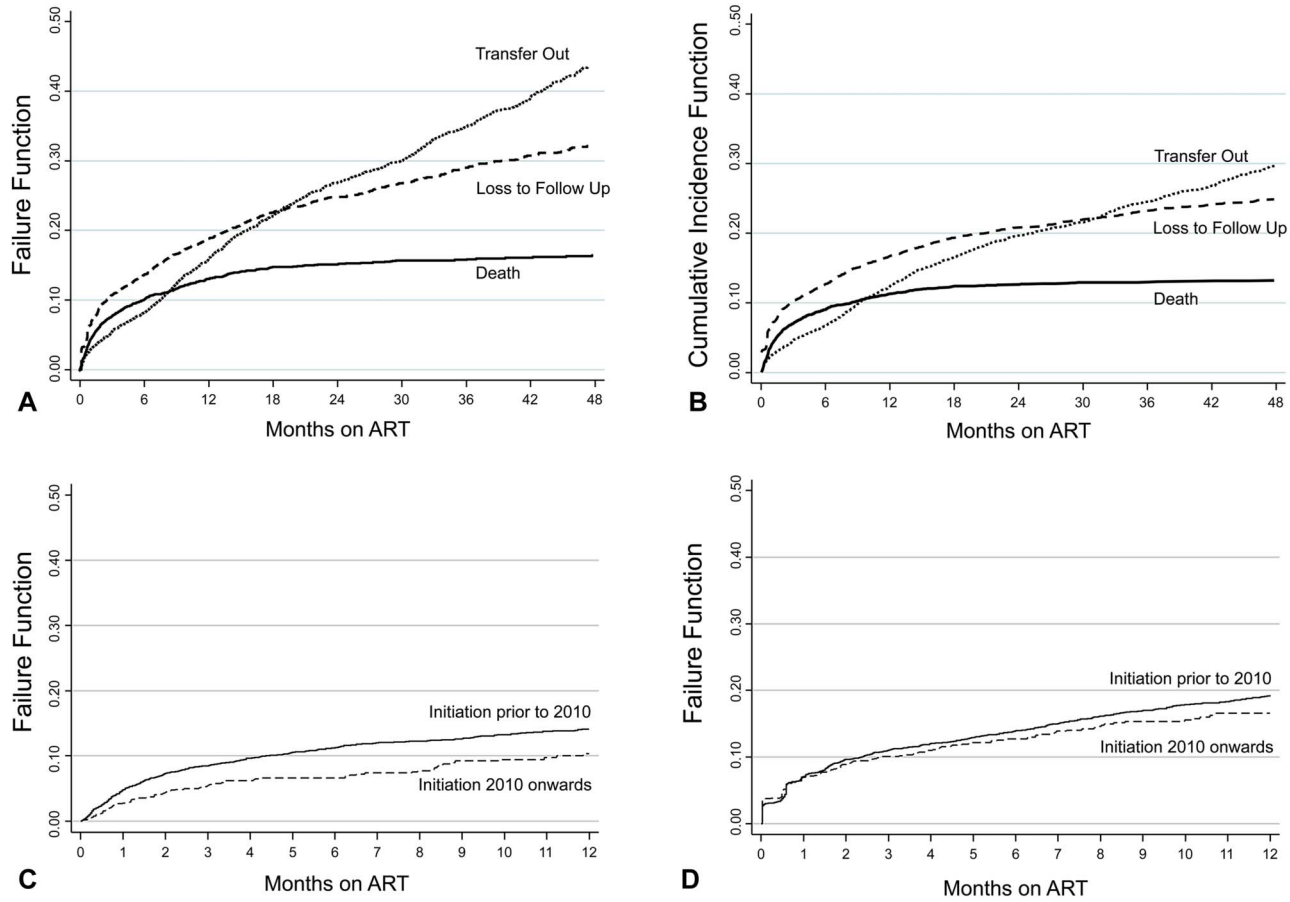

FIGURE 1. Survival analysis for outcomes mortality, loss to follow-up, and transfer out in infants initiating ART in Southern Africa 2004–2012. A, Kaplan–Meier estimates for outcomes of infants initiating ART in Southern Africa. B, Competing risk analysis for outcomes of infants initiating ART in Southern Africa. C, Kaplan–Meier estimates for mortality by time period of initiation. D, Kaplan–Meier estimates for loss to follow-up by time period of initiation.

decreased mortality was unlikely to be due to under-ascertainment of mortality in the later period.

The CHER trial showed the benefits of early ART in a cohort of very young infants with complete absence of severe immunosuppression at baseline.[20] The low likelihood of fully achieving these benefits in the SA routine care setting due to suboptimal coverage of early infant HIV diagnosis was highlighted by Johnson et al[35] in a model-based analysis examining the effect of early ART. Our study has confirmed through observation what this analysis suggested—within the context of delayed initiation infant ART outcomes are suboptimal. The predominance of severe baseline disease and failure to attain normal immunological, anthropometric, and virological measures, as well as high mortality and LTFU are cause for considerable concern. Furthermore, with an estimated 45% of in utero-infected and 22% of intrapartum-infected infants dying or lost to follow-up by 14 weeks of age,[36] our concern is exacerbated by the uncaptured pre-ART losses seen with delayed initiation.

This study has described improvements in delay in ART initiation over time, a trend seen when comparing earlier observational studies from sub-Saharan Africa to more recent studies. These improvements include reductions in age at initiation,[21,37] baseline disease severity, and mortality.[9,21] Our results are also comparable with more recent studies of immunological[38,39] and anthropometric responses[21,40] as well as mortality[41] in infants on ART within sub-Saharan Africa. However, our findings regarding virological suppression differ considerably from previous studies such as Kay et al[42] who described a 45% 12 month probability of virological suppression (defined as 2 consecutive viral load $<$400 copies/mL) and Tukei et al[21] who described a 72% 12 month probability of virological suppression in a cohort of infants with at least 6 months of ART. These differences are largely due to population and treatment program differences in these studies. The low probability of virological suppression seen in our study may be due specifically to the use of suboptimal regimens such as regimens using nevirapine or ritonavir alone as "third drugs" with known poorer virological efficacy.[43,44] Another possible cause is cotreatment for tuberculosis, complicating ART regimen choice and, in some cases, reducing virological efficacy.[45]

We found improved mortality from the start of 2010 (when early initiation was implemented on a national scale)

TABLE 3. Survival Analysis of Imputed Data: Cox Regression for Predictors of Mortality Stratified by Cohort

	Univariate			Multivariate*			Model Selection †		
Variable	**HR**	***P***	**95% CI**	**HR**	***P***	**95% CI**	**HR**	**95% CI**	**VI**
Female gender	0.97	0.716	0.83 to 1.14	—	—	—	—	—	0.31
Age at initiation, mo									
0–2	Reference			Reference			Reference		
3–5	0.90	0.417	0.71 to 1.15	0.87	0.268	0.68 to 1.11	—	—	0.22
6–11	0.98	0.898	0.78 to 1.25	0.84	0.161	0.66 to 1.07	—	—	—
Nonsevere immune suppression (WHO 2006)	Reference			Reference			Reference		
Severe immune suppression (WHO 2006)	2.51	0.000	1.66 to 3.79	2.19	0.000	1.44 to 3.33	2.15	1.42 to 3.27	1
WHO stage 1 or 2	Reference			Reference			Reference		
WHO stage 3 or 4	1.89	0.000	1.47 to 2.45	1.36	0.023	1.04 to 1.78	1.35	1.04 to 1.77	0.87
Mild or moderate anemia (DAIDS 2009)	Reference			Reference			Reference		
Severe anemia (DAIDS 2009)	1.57	0.003	1.18 to 2.10	1.34	0.062	0.98 to 1.82	1.29	0.82 to 2.05	0.79
WAZ category									
Greater than −2	Reference			Reference			Reference		
−2 to −3	1.40	0.015	1.07 to 1.84	1.29	0.063	0.99 to 1.71	1.29	0.99 to 1.71	1
Lesser than −3	2.55	0.000	2.04 to 3.19	2.23	0.000	1.78 to 2.80	2.22	1.78 to 2.79	—
ART initiation before 2010	Reference			Reference			Reference		
ART initiated from the start of 2010	0.65	0.000	0.52 to 0.83	0.75	0.015	0.59 to 0.94	0.75	0.59 to 0.95	0.88
‡Viral load ≤1 million copies/mL	Reference			Reference			Reference		
‡Viral load >1 million copies/mL	1.30	0.045	1.01 to 1.68	1.17	0.267	0.88 to 1.56	1.14	0.79 to 1.62	0.56

*Adjusted for age, weight-for-age category, severe immunosuppression, WHO stage 3 or 4, severe anemia, and initiation from the start of 2010.
†Using AIC and model averaging.
‡Modeled on a subset of infants from South African cohorts, adjusted for variables as above.
CI, confidence interval; DAIDS, Division of AIDS; HR, hazard ratio; VI, variable importance; WAZ, weight-for-age z-score; WHO, World Health Organization.

over and above that expected from the improvements in age and baseline characteristics. This indicates a possible role of subtle changes in baseline disease severity and programmatic improvements on the outcomes observed, suggesting that the implementation of guidelines for early infant initiation may have resulted in an improvement in mortality through a greater urgency and attention toward infant HIV diagnosis and ART initiation.

To our knowledge, this is the largest study of infant ART outcomes in sub-Saharan Africa to date. The study includes HIV-infected infants initiating ART from several Southern African routine care cohorts representing all levels of health care. In addition, the data cover a period of considerable guideline changes, strengthening the study. The use of multiple imputation to account for missing baseline data has prevented the bias associated with complete case analysis.[46,47] The high proportion of missing virological data, due to unavailability of virological measures outside SA, meant virological predictors and outcomes could only be assessed for South African cohorts.

The observed median age at ART initiation was considerably beyond 3 months of age. While this is the reality of routine care, it is likely to have resulted in some survival bias. This survival effect, greater in older infants having survived longer, would reduce any potential benefit of starting ART at a younger age and may explain the lack of age effect on outcomes. In addition, lack of data on comorbidities, infant feeding practices, PMTCT, cotrimoxazole prophylaxis, and socioeconomic factors may have resulted in residual confounding. Furthermore, associations between regimen and outcomes were not examined due to a near perfect correlation with cohort/country of origin. There may also be under-ascertainment of mortality in view of the high proportion of infants LTFU. The IeDEA-SA database requires electronic data capturing by cohorts; hence, the results may not be representative of all cohorts providing routine care in Southern Africa.

Recommendations

Ongoing attention to the initiation and continued management of ART in infants is required to optimize infant HIV care and outcomes. This needs to include considerable effort toward early diagnosis, successful referral, and retention in care. The continued vulnerability of infants on ART could be reduced through efforts to achieve the standards set by the trials on whose evidence guidelines for early initiation were based. Research is therefore necessary to identify how to overcome barriers to early initiation and optimal care of HIV-infected infants, including issues of PMTCT linkage, birth testing, infant ART initiation, optimization and maintenance, and a reduction of LTFU.

CONCLUSIONS

In a large cohort of HIV-infected infants in routine care in Southern Africa, we observed improvements in both disease severity characteristics at ART initiation and subsequent outcomes on ART. However, even after 2010, ART initiation was delayed with severe baseline illness and persistent vulnerability of infants despite receiving ART.

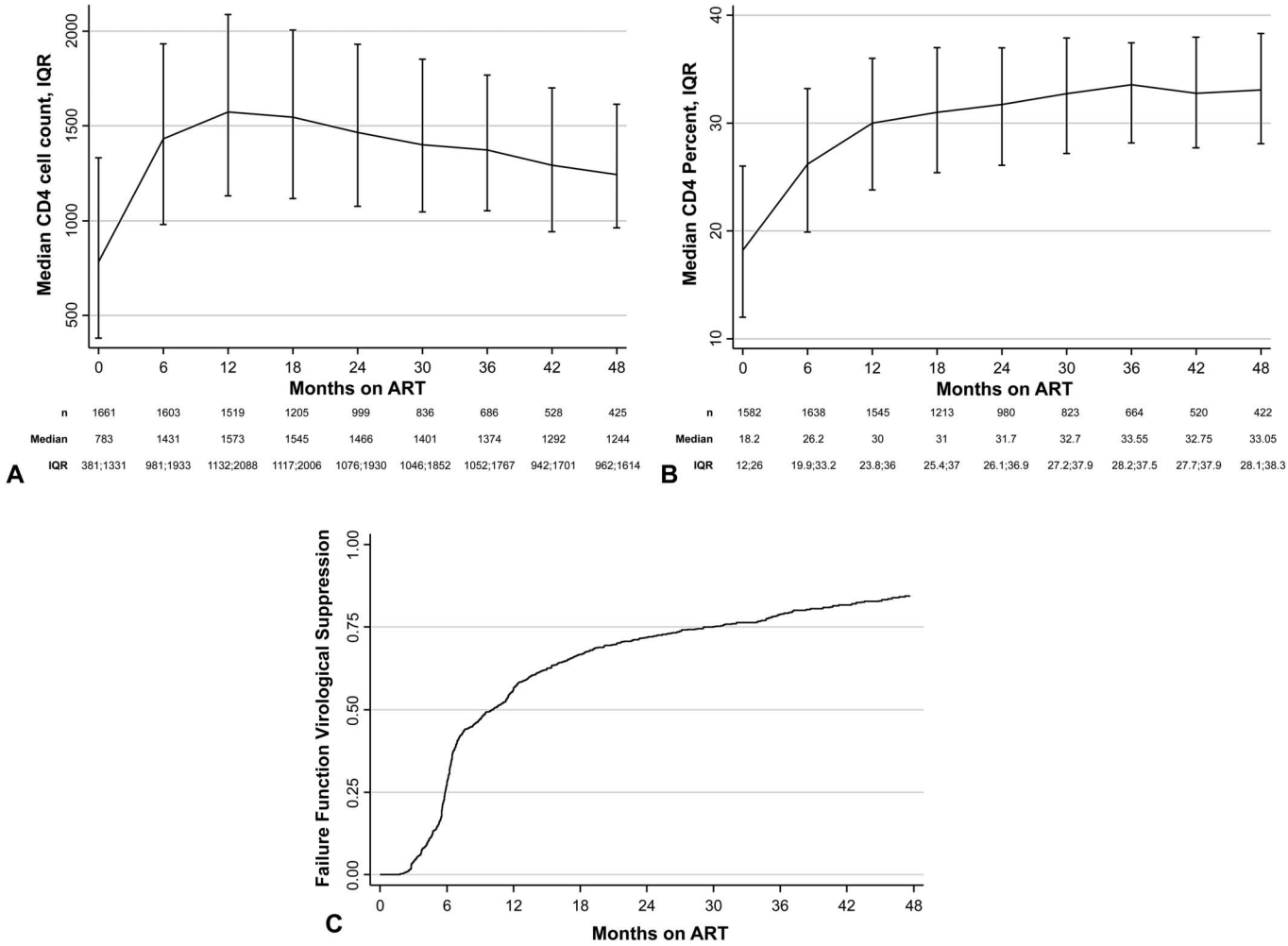

FIGURE 2. Responses in laboratory measures over time on ART. A, Median absolute CD4 cell count over time on ART for infants remaining in care for at least 12 months. B, Median CD4 percent over time on ART for infants remaining in care for at least 12 months. C, Kaplan–Meier estimates for virological suppression in a subset of South African infants.

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REFERENCES

1. UNAIDS. *Report on the Global AIDS Epidemic*. Geneva, Switzerland: UNAIDS; 2010. Available at: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf. Accessed April 10, 2014.
2. UNICEF. *Towards an AIDS-free Generation*. Geneva, Switzerland: UNICEF; 2012. Available at: http://www.unicef.org/aids/files/hiv_InfographicREV2.pdf. Accessed April 09, 2014.
3. UNICEF. *HIV and AIDS. Eastern and Southern Africa*. Geneva, Switzerland: UNICEF; 2013. Available at: http://www.unicef.org/esaro/5482_HIV_AIDS.html. Accessed October 14, 2013.
4. World Health Organisation. *Early Detection of HIV Infection in Infants and Children. Guidance Note on the Selection of Technology for the Early Diagnosis of HIV in Infants and Children. Summary of Recommendations*. Geneva, Switzerland: WHO; 2007. Available at: http://www.who.int/hiv/paediatric/EarlydiagnostictestingforHIVVer_Final_May07.pdf. Accessed October 14, 2013.
5. DNDi. Drugs for Neglected Diseases Initiative. *Paediatric HIV*. Geneva, Switzerland: DNDi; 2013. Available at: http://www.dndi.org/diseases-projects/diseases/paediatric-hiv.html. Accessed June 14, 2013.
6. World Health Organisation. *Children Are Not Little Adults, Children's Health and the Environment. WHO Training Package for the Health Sector*. Geneva, Switzerland: WHO; 2008. Available at: http://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf. Accessed June 14, 2013.
7. Puthanakit T, Bunupuradah T. Early versus deferred antiretroviral therapy in children in low-income and middle-income countries. *Curr Opin HIV AIDS*. 2010;5:12–17.
8. Chiappini E, Galli L, Tovo PA, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS*. 2006;20:207–215.
9. 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.
10. Fetzer BC, Hosseinipour MC, Kamthuzi P, et al. Predictors for mortality and loss to follow-up among children receiving anti-retroviral therapy in Lilongwe, Malawi. *Trop Med Int Health*. 2009;14:862–869.
11. Davies MA, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment Programme for Children: the IeDEA Southern Africa collaboration. *S Afr Med J*. 2009;99:730–737.
12. Dunn D, Gibb DM, Duong T. 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.
13. Prendergast AJ, Penazzato M, Cotton M, et al. Treatment of young children with HIV infection: using evidence to inform policymakers. *PLoS Med*. 2012;9:e1001273.
14. Prendergast A, Mphatswe W, Tudor-Williams G, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. *AIDS*. 2008;22:1333–1343.
15. Lallemant M, Chang S, Cohen R, et al. Pediatric HIV—a neglected disease? *N Engl J Med*. 2011;365:581–583.
16. World Health Organisation. *Report of the WHO Technical Reference Group: WHO Antiretroviral Therapy for Infants and Children 2008*. Geneva, Switzerland: WHO; 2008. Available at: http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf. Accessed April 23, 2014.
17. World Health Organisation. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. Geneva, Switzerland: WHO; 2013. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html. Accessed October 20, 2013.
18. World Health Organisation. *Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector. Progress Report*. Geneva, Switzerland: WHO; 2010. Available at: http://www.who.int/hiv/pub/2010progressreport/summary_en.pdf. Accessed June 19, 2014.
19. World Health Organisation. *Antiretroviral Therapy of HIV Infection in Infants and Children Recommendations for a Public Health Approach (2006 Revision)*. Geneva, Switzerland: WHO; 2006. Available at: http://www.who.int/hiv/pub/paediatric/infants/en/index.html. Accessed October 20, 2013.
20. 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.
21. Tukei VJ, Murungi M, Asiimwe AR, et al. Virologic, immunologic and clinical response of infants to antireteroviral therapy in Kampala, Uganda. *BMC Pediatr*. 2013;13:42.
22. Hsiao NY, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. *PLoS One*. 2013;8:e55308.
23. 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.
24. IeDEA-SA. *International Epidemiologic Databases to Evaluate AIDS Southern Africa*. Available at: http://www.iedea-sa.org/index.php?id=2732. Accessed June 14, 2013.
25. National Department of Health of South Africa. *Guidelines for the Management of HIV Infected Children*. Pretoria, South Africa: Jacana Media; 2005.
26. National Department of Health of South Africa. *Guidelines for the Management of HIV in Children*. 2010. Available at: http://www.sahivsoc.org/upload/documents/Guidelines_for_Management_of_HIV_in_Children_2010.pdf. Accessed July 14, 2014.
27. World Health Organisation. *Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach. 2010 Revision*. Geneva, Switzerland: WHO; 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf. Accessed October 20, 2013.
28. World Health Organisation. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. Geneva, Switzerland: WHO; 2007. Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf?ua=1. Accessed April 30, 2014.
29. Division of AIDS (DAIDS). *Table for Grading the Severity of Adult and Pediatric Adverse Events*. Bethesda, MD: DAIDS; 2009. Available at: http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf. Accessed April 30, 2014.
30. World Health Organisation. *WHO Child Growth Standards Based on Length/height, Weight and Age*. Geneva, Switzerland: WHO; 2006;450:76–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16817681. Accessed June 14, 2013.
31. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91:473–489.
32. Burnham K, Anderson D. *Model Selection and Multimodal Inference. A Practical Information-Theoretic Approach*. New York, NY: Springer; 2002.
33. Schomaker M, Heumann C. Model selection and model averaging after multiple imputation. *Comput Stat Data Anal*. 2014;71:758–770.
34. STATA [computer program]. Version 12. College Station, TX: StataCorp LP; 2011.
35. Johnson LF, Davies MA, Moultrie H, et al. The effect of early initiation of antiretroviral treatment in infants on pediatric AIDS mortality in South Africa: a model-based analysis. *Pediatr Infect Dis J*. 2012;31:474–480.
36. Lilian RR, Kalk E, Bhowan K, et al. Early diagnosis of in utero and intrapartum HIV infection in infants prior to 6 weeks of age. *J Clin Microbiol*. 2012;50:2373–2377.
37. KIDS ART LINC. Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. *J Acquir Immune Defic Syndr*. 2008;49:523–531.
38. Purchase SE, Van der Linden DJ, McKerrow NH. Feasibility and effectiveness of early initiation of combination antiretroviral therapy in HIV-infected infants in a government clinic of Kwazulu-Natal, South Africa. *J Trop Pediatr*. 2012;58:114–119.
39. Meyers TM, Yotebieng M, Kuhn L, et al. Antiretroviral therapy responses among children attending a large public clinic in Soweto, South Africa. *Pediatr Infect Dis J*. 2011;30:974–979.

40. Feinstein L, Yotebieng M, Moultrie H, et al. Effect of baseline immune suppression on growth recovery in HIV positive South African children receiving antiretroviral treatment. *J Acquir Immune Defic Syndr.* 2012; 61:235–242.
41. McNairy ML, Lamb MR, Carter RJ, et al. Retention of HIV-infected children on antiretroviral treatment in HIV care and treatment programs in Kenya, Mozambique, Rwanda, and Tanzania. *J Acquir Immune Defic Syndr.* 2013;62:e70–e81.
42. Kay J, Wanzira H, Sandison T, et al. Virologic suppression in nevirapine-exposed HIV-infected infants initiating antiretroviral therapy in rural Uganda. *J Trop Pediatr.* 2012;58:194–199.
43. 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.
44. Davies MA, 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.
45. Frohoff C, Moodley M, Fairlie L, et al. Antiretroviral therapy outcomes in HIV-infected children after adjusting protease inhibitor dosing during tuberculosis treatment. *PLoS One*. 2011;6: e17273.
46. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med.* 1999; 18:681–694.
47. Patrician PA. Multiple imputation for missing data. *Res Nurs Health.* 2002;25:76–84.