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Predictors of survival among HIV-positive children on ART in Swaziland

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The objective of the study was to determine predictors of survival among HIV-positive children (<15 years) in Swaziland. A retrospective cohort analysis of medical records for 4 167 children living with HIV who were initiated on antiretroviral therapy (ART) between 2004 and 2008, and followed up until 2014 was conducted in clinical settings at 36 health facilities. The Kaplan Meier Estimator, signed-ranks test, and the Cox proportional hazards regression model were applied to determine survival probabilities, significant difference among stratified survival functions and adjusted hazard ratios respectively. The results reveal that the median survival time for children was 78 months (95% CI: 77–79). Children who were initiated early on ART had higher survival probability over time (HR: 0.35 [95% CI: 0.21–0.57], $p < 0.001$) compared to those whose ART initiation was delayed. Children within the age group of <1 years had higher hazard (HR = 1.55 [95% CI: 1.16–2.08], $p < 0.001$) of death than children within the age group of 1–14 years. Children who were nourished had 88% lower hazard of death (HR: 0.12 [95% CI: 0.07–0.19], $p < 0.001$) than severely malnourished children. The study demonstrates that ART paediatric services are effective in increasing survival among HIV infected children and early initiated children have high survival probability. Active tuberculosis (TB), malnutrition, and delayed ART initiation remain predictors of poor survival among children living with HIV.

Keywords: ART services, clinical outcomes, HIV infected children, immunological gain, initiated early on ART

Introduction

Approximately 91% of the estimated 3.4 million HIV infected children in the world live in in sub-Saharan Africa, and these children have exceptionally high risk of mortality in absence of any intervention, according to the World Health Organization (WHO, 2013a) and the United Nations Programme on HIV/AIDS (UNAIDS, 2013). In fact, up to 52% of HIV infected children born to HIV infected mothers die before the age of 2 years in the absence of prevention of mother-to-child treatment (PMTCT) (Newell et al., 2004). In response to this problem of high mortality among HIV infected children, countries in sub-Saharan Africa have made paediatric HIV care an essential component of HIV, and maternal child and health (MCH) programmes, including early diagnosis of exposed infants to ensure early identification of children living with HIV. Despite improvements generally in PMTCT programmes and early diagnosis of HIV, early initiation on antiretroviral therapy (ART) of HIV infected children remains a global challenge leading to high mortality rates among HIV infected children (UNAIDS, 2012). In Swaziland, the paediatric HIV infection was estimated at 12% in 2014 (UNAIDS, 2010).

Countries in sub-Saharan Africa, including Swaziland, continue to accelerate efforts aimed at scaling up early infant diagnosis programmes and early initiation of HIV infected children on ART, regardless of WHO clinical stage or at any CD4 cell count (WHO, 2015). Despite the impressive strides made by the countries in scaling up paediatric HIV care and treatment, existence of a global body of research literature on the long-term effect of paediatric HIV and AIDS care and treatment programmes on survival of children living with HIV remain limited in sub-Saharan Africa (Callens et al., 2009; Cotton et al., 2013; Green et al., 2007; Janssens et al., 2007; Moore et al., 2007; Nachega et al., 2006). This article is a contribution to expanding the literature in sub-Saharan Africa, particularly information that will improve HIV programming among children living with HIV. It presents the findings of a retrospective cohort study of 4 167 children in Swaziland who were initiated on ART between 2004 and 2008, and were followed up until 2014.

The aim of the study was to evaluate effectiveness of ART services in Swaziland on clinical outcomes and survival of children living with HIV within the age of 0–14 years. The specific objectives of the study were to: (i) determine clinical outcomes of children on ART using immunological response (increased CD4), which was measured as CD4% for children <5 years old and CD4 count for children 5–14 years old; (ii) determine the survival of children who are on ART; (iii) determine the effect of early ART initiation on survival of children who are within the age group of 0–14 years; and (iv) determine association between relevant predictors and survival rate of children on ART (WHO, 2013b).

Estimating survival rate and understanding explanatory variables for survival among HIV-positive children would provide vital information for policy makers and to revise guidelines of paediatric care and treatment. The study results will also have implications for HIV care and treatment programming, and will inform decision making at various level of HIV and AIDS care and treatment and support programmes in Swaziland.

Methods

Study design and settings

The study design was retrospective cohort analysis of 4 167 children living with HIV (0–14 years at initiation) who were initiated on ART between 2004 and 2008, and were followed up until the end of 2014. De-identified medical records for children living with HIV were extracted from the national ART database deployed in clinical setting in 36 healthcare facilities that are implementing the national paediatric HIV and AIDS care and treatment programme. The health facilities included clinics, public health units, health centres, regional hospitals and referral hospitals. These facilities were further stratified into public, private, non-governmental organisations (NGOs) and mission health institutions.

Inclusion/exclusion criteria for study participants

All HIV infected children who were initiated on ART between 2004 and 2008, and had complete medical records with complete data values were included in the study.

Sample size

All children (0–14 years) living with HIV, who were started on ART between 2004 and 2008, and were followed up until failure or until they were right censored (lost to follow-up, stopped treatment or dropped out) by the end of study in 2014 were part of the sampling frame. Included in the study were children with complete medical records in the national database as of 31 December 2014. The 4 167 children were stratified into 2 strata (early initiated on ART or delayed ART initiation). ART initiation (early and delayed initiation) and age categorisation were defined based on WHO categorisation as stipulated in the 2010 ART for HIV infected infants and children guidelines (WHO, 2010). Within the two arms, there was further stratification by age: <1 year, 1<2 years, 2–4 years, 5–9 years and 10–14 years (WHO, 2010). Risk of morbidity and death as well as probability of survival are associated with particular age ranges amongst children (WHO, 2010). Accordingly, in view of our focus on the long-term efficacy of paediatric ART in Swaziland, it was necessary to compare survival rates for different cohorts of children who had been on treatment for different time periods (12, 24, 36, 48, 60, 72, 84, 96, 108, and 120 months).

Measurement

Since we analysed data for children living with HIV who were initiated on ART between 2004 and 2008, these children were clinically managed and followed up until 2014 using WHO guidelines adopted by the country at the time. The WHO (2010) guidelines on ART for HIV infection in infants and children and WHO (2013b) consolidated guidelines for ART provide for absolute CD4 count in mm^3 and CD4% as biomarkers that should be used as eligibility criteria and monitored over time to measure for clinical outcomes. At the time of the study, the 2015 WHO Consolidated Guidelines on use of ART for Treating and Preventing HIV infection were not rectified and adopted by the country. Therefore the primary outcome measures used in this study were:

1. CD4 increase (absolute CD4 count in mm^3 for children who are ≥5 years and CD4% for children 0–4 years);
2. The overall survival function for children on ART stratified by:
   - Early initiation on ART (>25 CD4% for 0–4 years and >350 for 5–14 years)
   - Delayed initiation ≤25 CD4% for 0–4 years and ≤350 CD4 count for 5–14 years) on ART
   - Age group
   - Baseline CD4 categories
3. The association between the selected demographic and baseline predictors, and survival of HIV infected children was also tested. The demographic and baseline predictors that were regressed against survival were:
   - Age at initiation of highly active antiretroviral therapy (HAART)
   - Sex
   - Baseline nutritional status (normal, mild, moderate or severe malnutrition)
   - Baseline WHO stage
   - CD4 count/CD4% at baseline
   - Early initiation/delayed initiation
   - Tuberculosis (TB) positive at initiation of ART
   - Treatment supporter/caregiver
   - Baseline ART regimen
   - Type of facility
   - Facility authority/ownership

Data management procedure

Electronic medical records were extracted from the national ART Patient Management Information System (APMIS) using Microsoft SQL stored procedures in Microsoft SQL Server version 2012. Data quality profiling and cleaning were done using Talent Data Quality tool version 4.0. Data for participants with incomplete and inaccurate data records were excluded for analysis.

The final sample size after cleaning the data was 4 167 participants. The medical records for these HIV infected children were exported into an Excel data file that was, in turn, imported into STATA version 12. In STATA, mapping and identification of invalid data types was done using the codebook command. Identified data outliers (data points that diverged from the pattern of the sample) and leverage data values (influential data points that would have a large unrealistic effect on the regression model) were removed from the data set. Variables were recoded and encoded to generate categorical variables. String variables were also encoded to generate numeric data values, which were, in turn, recoded to dummy variables to facilitate multivariate regression analysis. The outcome variable of interest (death) was encoded into a binary (1/0) variable based on the deceased date variable. All the other censoring variables (lost to follow-up, dropped out, active) were also encoded to 0, indicating censoring.

Data analysis and modelling approach

Various statistical tests were performed to assess distribution of data before analysis. The histogram and Shapiro-Francia test were performed to test normality of data distribution for continuous variables. The plot-box was used to identify outliers. The Wilcoxon matched pairs signed-ranks test was applied to test for median difference between baseline CD4 and CD4 follow up. The Kaplan Meier and Nelson-Aalen methods were used to model survivorship function curves, stratified by selected independent variables. The log-rank test was performed to test the significance of the difference in survival for selected categorical variables. The Cox proportional hazards regression model was applied to examine association between survival and the selected explanatory variates and factors.

The backward elimination approach was adopted to build the final Cox proportional hazard regression model (Pagano & Gauvreau, 2000). All predictor variables were fitted in the initial model. Variables were dropped one at a time, beginning with variables that were not statistically significant using the significance level of 0.10 (Collect, 2003; Williams, 2014). The model was diagnosed for multi-collinearity of independent variables using the variance inflation factor test in STATA 12. The diagnosis results indicate that some IVs were highly correlated with high variance inflation factors (variance inflation factor ≥10.00). All IVs with high variance inflation factors were omitted from the initial model as they had inadequate data and/or were of different operationalisations of the same identical concept and had high multicollinearity that could affect the model (Rovny, 2014). The likelihood ratio test was performed to inform the variable exclusion decision. All non-significant variables ($p > 0.10$) were eliminated from the initial full model (model A). The likelihood ratio test was performed to compare the initial full model and all the nested models (nested in model A to model F). The likelihood ratio test *p*-values were non-significant ($p = 0.688$ for model nested in A, $p = 0.851$ for model nested in B, $p = 0.543$ for model nested in C, $p = 0.506$ for model nested in D, $p = 0.165$ for model nested in E, $p = 0.524$ for model nested in F, and $p = 0.120$ for model nested in G), suggesting that the eliminated variables were not significantly explaining the variability.

Results

Characteristics of study population

A total of 4 167 HIV-positive children who initiated ART between 2004 and 2008 were included for analysis. Table 1 presents the background and demographic characteristics of the study participants.

As presented in Table 1, 50.37% of the children were female and 49.63% were male. The mean age for female (5.43 years, SD: 3.98) and for male (5.26 years, SD: 3.66) children at ART initiation was not significantly different ($p = 0.867$). Of the 4 167 children, 12.67%, 13.15%, 23.28%, 37.08% and 13.28% were within the age groups of <1 year, 1<2 years, 2–4 years, 5–9 years, and 10–14 years respectively. At the time of the analysis, 93.35 % of the HIV infected children were still alive.

Table 2 presents characteristics of participants at baseline. About half (50.88%) the children ($n = 4\ 167$) were classified to be in WHO stage III at baseline. Approximately 10% of the children were in WHO stage IV at baseline. Forty-nine per cent of the children had a baseline CD4 count of ≤350 at baseline. Approximately 8% of the children were co-infected with HIV/TB when starting ART. Approximately half (52%) of the children were initiated on an a zidovudine+Lamivudine+Nevirapine (AZT+3TC+NVP) regimen. Of the 4 167 for analysis, 25.53%, 9.65%, 5.02% and 2.83% were initiated on stavudine (D4T)+3TC+NVP, AZT+3TC+efavirenz (EFV), D4T+3TC+EFV, and AZT+3TC+lopinavir/ritonavir (LPV/r) respectively.

Table 1: Background and demographic characteristics of HIV-positive children

Variables	Frequency	Per cent	**Cumulative %**
Sex			
Female	2 099	50.37	50.37
Male	2 068	49.63	100
Total	4 167	100	
Age group			
(<1)	528	12.67	12.67
(1<2)	548	13.15	25.82
(2–4)	970	23.28	49.1
(5–9)	1 545	37.08	86.18
(10–14)	576	13.82	100
Total	4 167	100	
Region			
**	33	0.79	0.79
Hhohho	1 790	42.96	43.75
Lubombo	825	19.8	63.55
Manzini	921	22.1	85.65
Shiselweni	598	14.35	100
Total	4 167	100	
Facility type			
**	33	0.79	0.79
Clinic	1 050	25.2	25.99
Health centre	683	16.39	42.38
Hospital	2 347	56.32	98.7
Public health unit	54	1.3	100
Total	4 167	100	

** Indicates missing data values for a specific variable

Clinical treatment outcomes

Clinical outcomes for children receiving ART services were measured using immunological response (CD4 count for children ≥5 years and CD4% for children <5 years). In an intent to treat analysis of the overall effect of ART on immunological gain, the median length of follow-up was 78 (IQR, 66 to 91) months. Figure 1 presents CD4% at baseline and follow-up CD4% stratified by age and sex among children living with HIV.

The results presented in Figure 1 show that there was immunological (CD4%) gain among children by the end of follow-up period. As presented Figure 1, inasmuch as infants <1 year living with HIV were initiated with baseline median CD4% of 18%, they had marginal immunological gain compared to other age groups (1–14 years) for both sexes. Nonetheless, there was generally an increase of CD4 among all age group at the end of follow-up. The Wilcoxon signed-rank test was performed to test the significance of difference between baselines and follow up CD4% among children within all the different age groups, <1, 1<2 and 2–4

Table 2: Clinical characteristics of HIV-positive children at baseline

Variables	Frequency	Per cent	Cumulative %
Baseline WHO stage			
**	297	7.13	7.13
Deferred	83	1.99	9.12
I	454	10.9	20.01
II	810	19.44	39.45
III	2 120	50.88	90.33
IV	403	9.67	100
Total	4 167	100	
Baseline CD4 count			
≤50)	531	12.74	12.74
(51–200)	903	21.67	34.41
(201–350)	608	14.59	49.00
(351–500)	368	8.83	57.84
(>500)	840	20.16	77.99
**	917	22.01	100
Total	4 167	100	
Baseline CD4%			
(≤25)	1 324	31.77	31.77
(26–50)	172	4.13	35.9
(51–75)	1	0.02	35.93
**	2 670	64.07	100
Total	4 167	100	
Baseline viral load			
(<1 000)	171	58.76	58.76
(≥1 000)	120	41.24	100
Total	291	100	
TB-positive			
No	4 010	96.23	96.23
Yes	157	3.77	100
Total	4 167	100	

** Indicates missing data values for a specific variable

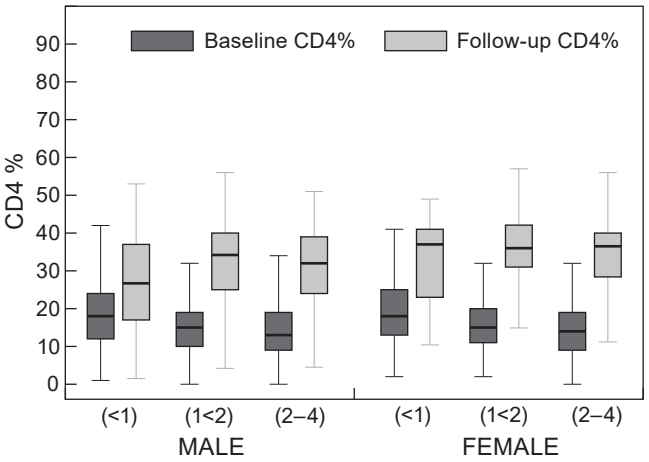

Figure 1: Box plot on baseline and follow-up CD4% by age and sex

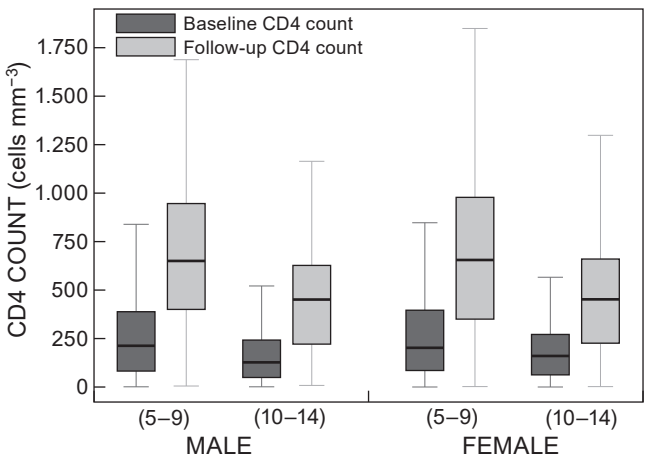

Figure 2: Box plot on baseline and follow-up CD4 count by age and sex

years. The test results suggest that the difference between baseline and follow up CD4 was statistically different, as indicated by $p < 0.001$, $p < 0.001$, and $p < 0.001$ for children within the age groups of <1, 1<2 and 2–4 years respectively.

Figure 2 is a graphical presentation of baseline and follow-up CD4 count among children living with HIV within the 5–14 years age group stratified by sex. The results show that there was immunological gain among the children within the age group by the end of the follow-up period (Figure 2). The Wilcoxon signed-rank test results showed that the difference between the baseline and follow-up CD4 count was statistically significant for the children within the age group of 5–9 years ($p < 0.001$) and 10–15 years ($p < 0.001$).

Survival time descriptive analysis

The results showed that the median survival time for children was 78 months (95% CI: 77–79). Survival time among children 5–9 years was higher (79 months, 95% CI: 78–80) than for other age groups.

The person-time for all the 4 167 children was 281 053 months with 277 failures by the end of the follow-up. The incidence rate was higher (1.03, 95% CI: 0.76–1.39) among children <1 years than in the other age groups.

We also analysed survival for children on ART stratified by early initiation (17.53%) on ART (>25 CD4%/>750 CD4 count for 0–4 years and >350 for 5–14 years) and delayed initiation (82.47%) on ART ≤25 CD4%/≤750 CD4 count for 0–4 years and ≤350 CD4 count for 5–14 years). The Kaplan Meier Estimator and curves were used to estimate survivorship function for children.

Figure 3 presents a comparison of the survivor function curves for children who were early initiated against those whose initiation on ART was delayed. Figure 3 illustrates that survival probability for children who were early initiated on ART was higher over time than for those whose initiation of ART was delayed ($p < 0.001$).

Figure 4 is a graphical presentation of survival curves stratified by age groups. All three curves show a similar exponential decline. The survival probability of children within age group <1 years declined as soon as they were initiated on ART, and they had low probability of surviving over time compared to other age groups. The log-rank test results confirmed that the survival rate for children within this age group years was lower than the survival rate for the other age groups, and the difference was statistically significant ($p < 0.001$).

A Kaplan-Meier plot of survivor functions by baseline CD4 per cent (CD4% ≤25 versus CD4% > 25%) for children within the age of (0-4) years was also conducted (Figure 5). The results show that children who had CD4% ≤25 at baseline had lower probability of surviving over time compared to children who had CD4% ≤25 at baseline. The log-rank test results suggest that the observed difference was not statistically significant ($p = 0.561$).

Figure 6 is a graphical illustration for survivor functions for children aged 5–15 years by baseline CD4 count. The survival curves presented in Figure 5 demonstrate that children who had a CD4 count within the range of 351 to 500 or more than 500 absolute CD4 count at baseline had higher survival probability than children who had ≤350 CD4 count at baseline. The log-rank test was performed to test the significance of survival difference. Children who had a low CD4 count at baseline had their survival rate compromised compared to children with high CD4 count at baseline. The difference in survival was statistically significant ($p < 0.001$).

The final Cox proportional hazards regression model

The application of the backward elimination approach produced the following final Cox proportional hazards regression model. Influential explanatory variables were retained in the final model (Table 3).

The partial log likelihood ratio test suggests that at least one of the covariates fitted in the final model (Table 3) was significantly (likelihood ratio chi^2 (10) = 204.49, $p < 0.001$) related to survival time for children on ART. The estimated hazard ratio of death for children who were early initiated on ART relative to those who were delayed ART is 0.35(95% CI: 0.21–0.57). This hazard ratio (0.35) suggests that children who were early initiated on ART, while holding all other predictors constant, were dying at a rate that was estimated to be 65% lower than children who were delayed ART ($p < 0.001$). Children who were diagnosed with TB at baseline were estimated to have 2.24 (95% CI: 1.37–3.67) times higher hazard of death than those who were TB negative, all other variables held constant. Children < 1 year had a 55% higher hazard of death (HR: 1.55 [95% CI:

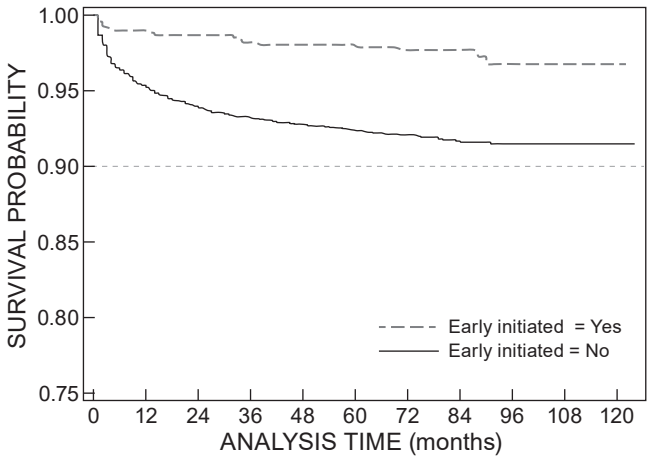

Figure 3: Kaplan-Meier plot on survival probability for children by early and delayed initiation

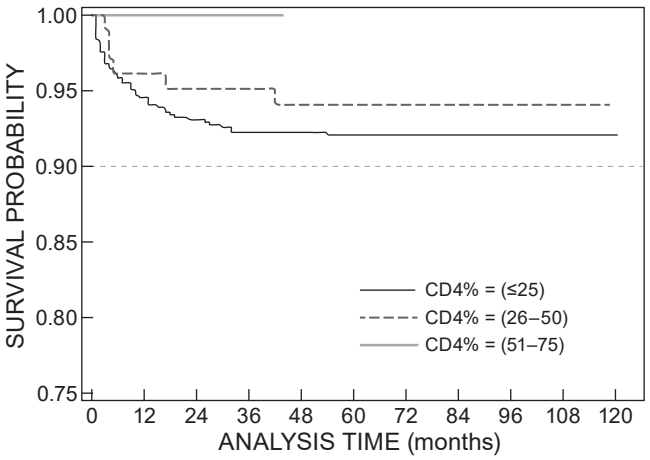

Figure 5: Kaplan–Meier plot on survival probability for children (0–4) years by baseline CD4 percentage

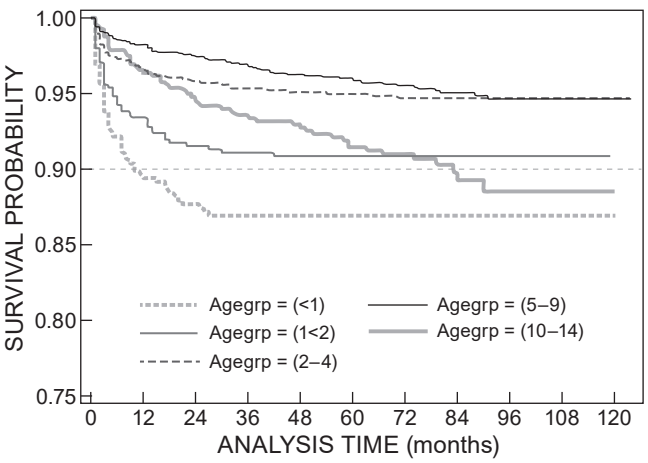

Figure 4: Kaplan-Meier plot on survival probability for children by age group

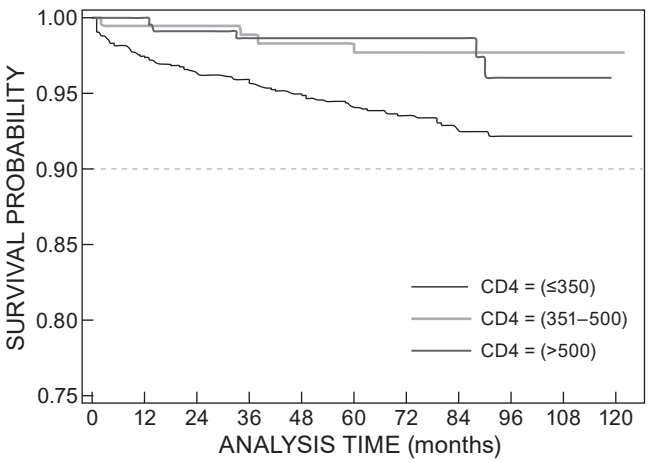

Figure 6: Kaplan-Meier plot on survival probability for children (5–15) years by baseline CD4 count

Table 3: Cox regression — Breslow method for ties presenting hazard ratios (HRs) by predictors of survival for children initiated on ART between 2004 and 2008 in Swaziland

Prognostic factors	Multivariate regression			
	Adjusted HR	*P*-value	95% CI	
TB status				
TB-positive	2.24	0.00	1.37	3.67
ART Initiation				
Early initiation	0.35	0.00	0.21	0.57
Age group				
(<1) years	1.55	0.00	1.16	2.08
Facility ownership				
Mission	2.17	0.00	1.53	3.06
Nutritional status				
Normal limits	0.12	0.00	0.07	0.19
Mild malnutrition	0.27	0.00	0.15	0.48
Moderate malnutrition	0.29	0.00	0.19	0.44
WHO clinical stage				
Bwho2	0.60	0.01	0.40	0.90
Bwho4	1.42	0.04	1.02	1.99
Caregiver				
Grandmother	0.56	0.02	0.35	0.92

1.16–2.08], $p < 0.001$) than children within the age group of 1–14 years. Children who were nourished had 88% lower hazard of death than severely malnourished children (HR: 0.12 [95% CI: 0.07–0.19], $p < 0.001$). The WHO stage IV remained associated with increased risk of mortality (HR: 1.42 [95% CI: 1.02–1.99], $p < 0.05$) than WHO stage I and WHO stage II (Table 3).

Children's survival functions were also adjusted by their specific ART regimen. The results show that children who were on D4T+3TC+EFV (HR: 1.14[95% CI: 0.76–1.67], $p = 0.528$) and AZT+3TC+EFV (HR: 1.21 [95% CI: 0.77–1.88], $p = 0.416$) had survival probability that was constantly lower over time than those who were on ABC+3TC+EFV. The results were not statistically significant using the significance level of 0.10. ART regimen, as a predictor, was therefore omitted from the final model (Table 3).

Post estimation for the Cox proportional hazards model

We examined whether the proportional-hazards assumption holds for the model with the included covariates. We performed the proportional-hazards test for covariates included in the model, testing the proportional-hazards assumption on the basis of both scaled and non-scaled Schoenfeld residuals after fitting the model.

Table 4 presents results of the proportional-hazards test. The correlates TB status (1 = Yes, 0 = No), early initiation, facility ownership (mission), nutritional status (normal limits, mild malnutrition, moderate malnutrition) and WHO clinical stage IV did not violate the proportional-hazard assumption. These covariates fitted appropriately in the model. Hence, the hazard ratios describing the effect of these independent variables are valid and correctly inform the adequacy of the model. However, the hazard ratios describing the effect of age group <1 year, caregiver relationship and WHO clinical stage two, were inappropriate.

Discussion

The results show clinical outcomes for children living with HIV ($n = 4\,167$) who were enrolled in the national ART programme were desirable. Substantial immunological gains among the children initiated on ART were evident. Findings of the study confirm existing evidence that suggests that initiating HIV infected children on effective ART and management of HIV-related opportunistic infections drastically reduces disease regression, in turn enhancing immunological response and survival of children living with HIV. Similar clinical outcomes were reported in a retrospective cohort study conducted in South Africa, where HIV-infected children were initiated on ART and followed up for only 12 months (Reddi et al., 2007). Nacro et al. (2011) conducted a similar study in Burkina Faso and found that children had desirable clinical outcomes (mean CD4% gain of 24%) at 12 months follow up. Resino et al. (2002) also reported similar findings in a study where they used both CD4 and viral load to measure clinical outcomes for 253 vertically infected children. The researchers found that desirable clinical outcomes were associated with increased survival of HIV infected children. One study analysed surveillance data for 3 936 children <5 years of age initiated on ART in 48 HIV and AIDS programmes in Africa and Asia (Sauvageot, Schaefer, Olson, Pujades-Rodriguez, & O'Brien, 2010). The researchers observed similar encouraging clinical outcomes. The randomised control trial (Children with HIV Early antiRetroviral [CHER]) conducted by Cotton et al. (2013) found that infants (median age = 7.4 months) with early-time limited ART had better clinical and immunological outcomes than infants whose ART was deferred.

Ferris et al. (2007) conducted a retrospective study in Romania to investigate effect of institutionalisation on clinical outcome (CD4 decline) and death in a cohort of HIV infected children on ART. The researchers found a significant difference in CD4 improvement between the two groups. They observed a trend toward CD4 decline among children who were staying with their biological families. Children who

Table 4: Test of proportional-hazards assumption as post estimation for Cox probability hazards model

	rho	chi^2	df	Prob>chi^2
TB status				
TB-positive	0.009	0.020	1	0.883
ART Initiation				
Early initiation	0.009	0.020	1	0.879
Age group				
(<1) years	−0.188	9.740	1	0.002
Facility ownership				
Mission	0.032	0.270	1	0.605
Nutritional status				
Normal limits	0.052	0.730	1	0.394
Mild malnutrition	−0.040	0.450	1	0.502
Moderate malnutrition	0.077	1.540	1	0.214
WHO clinical stage				
WHO II	0.219	12.980	1	0.000
WHO IV	0.058	0.940	1	0.332
Caregiver				
Grandmother	0.201	11.360	1	0.001
Global test		41.670	10	0.000

were living with their biological families were more likely to die than were children in institutional care.

Unlike in previous studies, our study analysed data from an adequate sample size of 4 167 HIV infected children (<15 years) who were initiated on ART and followed up for a maximum of 10 years (2004–2014). We used the immunological response (CD4% for 0–4 years and CD4 count for 5–14 years) as a primary clinical outcome measure. Nonetheless, the results of our study and those of others are in agreement that if HIV infected children are administered with ART and managed appropriately by trained healthcare workers they will have desirable clinical outcomes.

Data were further analysed to determine the effect of early ART initiation on survival of children living with HIV <15 years of age. Survival rate for children who were early initiated on ART was higher than that of children who were delayed ART. Our findings are consistent with those from previous studies that suggest that early initiation of ART shortly after HIV infection limits both the reservoir of persistent HIV and viral diversity, in turn enhancing immunological response (Persaud, Gay, & Ziemniak, 2013; Sáez-Cirión et al., 2013). A meta-analysis of 18 cohort studies conducted by Sterne et al. (2009) under the "When to Start Consortium" also confirmed that early initiation of ART is associated with increased survival rates. The findings of this study are, however, inconsistent with those of the Ugandan Cluster Randomised Trial of 300 HIV infected children (1–12 years], which revealed that survival and growth of children who were early initiated (CD4% $>$ 15) on ART compared to those who were delayed (CD4% $\leq$ 15) ART was not different (Jaffar et al., 2009). Similarly, a prospective study conducted by Kipp et al. (2010) revealed that early initiation on ART had poor survival benefits among children 2–5 years old. The indifference in survival rate for children who were early initiated on ART compared to those who were delayed ART in the Ugandan cluster randomised trial could be explained by the use of a lower CD4 threshold (CD4% $>$ 15) instead of CD4% $\geq$ 25, as suggested by the revised 2010 WHO guidelines for ART for HIV infected children. The 2015 WHO Consolidated Guidelines recommend early initiation of HIV infected children on ART, regardless of WHO clinical stage or at any CD4 cell count (WHO, 2015).

As indicated in the results, further adjustment of survival by age group revealed that children within the age group of <1 year had higher hazard of death than children within the age group of 5–14 years and the findings were statistically significant. These findings may be explained by impaired or depleted immune systems among the younger age group <1 year hence failure to suppress disease progression. The findings could also suggest poor adherence among the younger age group due to unavailability of formulations that are of good taste, palatable and liquid. The difficulty of administration of therapy among this age group could also be an explanation of the foregoing findings.

The findings also suggest that the ABC+3TC+EFV regimen was an effective combination of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI) for HIV infected infants and children as it yielded better outcomes compared to the other ART regimens. Abacavir (ABC) and Lamivudine (3TC), in particular, are known to be effective NRTIs with an excellent record of efficacy, safety and tolerability in HIV infected children, and are highly recommended by WHO (2010) and Green et al. (2007). The findings of this study are consistent with WHO provisions and results from the study conducted by Green et al. (2007).

Our findings, however, are inconsistent with the multicentre (67 centres) randomised control trial conducted by Lennox et al. (2009) in 5 continents. The researchers for the multicentre randomised control trial found that patients who were initiated on efavirenz experienced more drug-related adverse events than those who were initiated on raltegravir. According to Lennox et al. (2009), raltegravir proved to be safer and quite efficacious when compared to efavirenz. Janssens et al. (2007), however, found undesirable clinical outcomes (detectable viral load) among children (<13 years) in a study done in Cambodia. Such poor clinical outcomes were associated with resistance to lamivudine. A prospective cohort study conducted in the USA between 1993 and 2007 found that ART regimens were associated with decrease in the incidence of HIV encephalopathy, and the risk of death was found to be lower among children who were taking central nervous system (CNS)-penetrating ART regimens than children who were not on CNS-penetrating ART regimens (Patel et al., 2009).

In this study, we also examined the possible association between baseline WHO clinical staging and survival of HIV infected children initiated on ART. Our findings show that children who were classified WHO clinical stage IV at baseline had low survival probability compared to children who were classified stage I at baseline. Our findings are consistent with a prospective cohort study conducted in Kenya by Wamalwa et al. (2010).

We also examined the hazard of death as adjusted by level of health system at which children were receiving ART services. We found that children who were receiving ART in mission health facilities had higher hazard of death than children who were receiving their ARV treatment and care in government facilities as evident in the results. Unlike our study, Moore et al. (2007) conducted a study in Zambia and found that clinical outcomes for children receiving ART in primary health care settings were found to be positive.

Nutritional status was also analysed as a predictor in this study. Children who were nourished had increased survival compared to children who were severely malnourished. The findings may be explained by the fact that children living with HIV who are significantly underweight are much more likely to die than children living with HIV who nourished, as observed by Callens et al. (2009). Our findings are also consistent with the Niekerk et al. (2006) findings where nourished children living with HIV were found to have significantly increased survival.

TB status (positive or negative) was also regressed against survival in this study, and the findings show that children whose immune systems were not compromised by TB were more likely to survive than those who were co-infected with TB and HIV. Our findings could be explained by the fact that HIV infected children who develop active TB have impaired cell-mediated immunity through depletion of CD4 and lymphocytes; hence their probability of survival would be lower than that of TB-negative children living with HIV (Delay et al., 2009; Selwyn et al., 1989).

Caregiver relationship was also included as a predictor variable for survival in the multivariate Cox proportional hazards regression analysis. Caregiver relationship was stratified into four categories (biological mother, father, aunt, and grandmother). Living with grandmother was found to be positively associated with increased survival. Children who were receiving maternal care and treatment support from grandmothers had lower hazard of death compared to children whose caregivers were biological mothers. This could be explained by the fact that the biological mothers were too sick and weak to take good care of their children living with HIV. This may also be because the young HIV infected mothers were inexperienced in taking care of their children. However, the foregoing findings warrant further investigation on possible reasons for grandmothers being good maternal caregivers.

Conclusion and recommendations

In conclusion, ART paediatric services demonstrate effectiveness in producing desired clinical outcomes for children living with HIV and increased survival probability for HIV infected children who are early initiated on ART. However, active TB, malnutrition, delayed ART initiation and being a child within the age group of <1 year remain predictors of poor survival among children living with HIV in resource limited settings. Our findings are consistent with previous studies and are reinforcing operationalisation of 2015 WHO treatment guidelines, which provides for early initiation for all children living with HIV, irrespective of their WHO clinical stage and CD4 count (WHO, 2015). It is therefore against the foregoing findings that we make the following relevant recommendations:

- Continue to conduct CD4 test, particularly viral load testing before initiation of ART, and conduct routine viral load monitoring to measure immunological again among children living with HIV in resource-limited settings like Swaziland.
- Accelerate efforts targeted at early infant diagnosis interventions, particularly targeting children younger than 1 year to ensure diagnosis of infants in their first year of life, and early initiation on ART regardless of their clinical classification and CD4 cell count.
- Adopt and operationalise the 2015 WHO guidelines on early initiation of children living with HIV (0–10 years).
- Procure and ensure availability of formulations that taste good taste, are palatable and are liquids to facilitate easier administration of therapy to children living with HIV;
- Ensure screening, early diagnosis and treatment of active TB among HIV infected children, and start ART as soon as possible afterwards to ensure quick recovery of depleted immunity to enhance immunological response and survival of HIV infected children.
- Intensify nutrition interventions and ensure proper integration and alignment with paediatric HIV and AIDS care, treatment and support services.
- Conduct further investigation on facility ownership and caregiver relationship as predictors for survival of children living with HIV.

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