Survival of children on Antiretroviral Therapy in Swaziland:

A retrospective cohort study

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Abbreviations and Acronyms

AIDS	Acquired Immune Deficiency Syndrome
APMS	ART Patient Management System
ART	Anti-Retroviral Therapy
CSO	Central Statistics Office
DB	Database
DQ	Data Quality
EMR	Electronic Medical Records
HIV	Human Immunodeficiency Virus
HTC	HIV Testing and Counselling
HR	Hazard ratio
ICAP	International Centre for AIDS Care and Treatment Programs
KM	Kaplan Meier
MDGs	Millennium Development Goals
M&E	Monitoring and Evaluation
MOH	Ministry of Health
PH	Proportional Hazard
PLWHA	People living with HIV and AIDS
PMTCT	Prevention of Mother-To-Child Transmission
WHO	World Health Organisation

STATEMENT OF DECLARATION:

I, **Patrick L Shabangu, student number: 11261995** declare that the mini- dissertation, which I hereby submit for the degree Master of Public Health at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at another university.

Reference number:

University of Pretoria: 45/2014

Student's signature:…………………………date:……………………………………

Supervisor's signature:………………………date:……………………………………

Name of Journal for proposed submission

The Journal of Pediatrics

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Abstract

Survival of children on Antiretroviral Therapy in Swaziland: A retrospective study

Objectives: To evaluate effectiveness of Anti-Retroviral Therapy (ART) services on clinical outcomes and survival of HIV infected children [0-15 years) in Swaziland.

Study design: A retrospective cohort analysis of medical records for 4170 HIV-infected children who were initiated on ART between 2004 and 2008 was conducted. The Signed-ranks test, Kaplan Meier Estimator, and Cox-P H regression model were used to compare clinical outcomes between relevant predictors.

Results: The results reveal that clinical outcomes for HIV-infected children on ART were desirable as indicated by significant CD4 gain (from 17 CD4% to 35 CD4%, 14 CD4% to 34 CD4%, and from 194 to 592 CD4 count in mm^3 for children aged [0-2) years, [2-5) years and [5-15) years, respectively, $p<=0.001$). Early initiated children were dying at a rate estimated to be 67% times lower than children who were delayed ART ($p\text{-value}<=0.001$). Children within the age group of [2-5) years had higher hazard (HR=1.59, 95% CI: 1.33-1.89) of death than children within the age group of [5-15) years.

Conclusions: The ART paediatric programme in Swaziland proved to be effective as demonstrated by positive clinical outcomes. Early initiation proved to be effective in increasing survival time for children.

Key words: ART services, HIV infected children, Clinical outcomes, Survival, Swaziland

Introduction

Approximately, 91% of the estimated 3.4 million HIV infected children live in in Sub-Saharan Africa.[1, 2] and these children have exceptionally high risk of mortality in absence of any intervention. In fact, up to 52% of HIV infected children die before the age of two years in the absence of any intervention. [3] Countries are, therefore, encouraged to scale up early diagnosis to ensure early identification of HIV infected children. However, with accelerated early diagnosis of HIV, early initiation on ART of HIV infected children remains a global challenge. [4]

Swaziland being a country in Sub Saharan Africa where paediatric HIV infection was estimated at 12% in 2014 continues to accelerate efforts aimed at scaling up early infant diagnosis programme and early initiation of HIV infected children on ART. [5] It is thus imperative from a public health perspective, to evaluate if the paediatric HIV and AIDS care, treatment and support services influence survival of children living with HIV. Although several studies have been conducted in Sub-Saharan Africa, Africa, Asia and Europe, publications on the long term effect of paediatric HIV and AIDS care, treatment and support programs on survival of children living with HIV are limited.[13-36] The study results could inform policy development and improvement of paediatric HIV and AIDS care and treatment interventions in Swaziland.

The aim of this study was to evaluate effectiveness of ART services in Swaziland on clinical outcomes and survival of HIV-infected children within the age of [0- 15) years. The specific objectives of the study were (i) to determine clinical outcomes of children on ART using immunological response; (ii) to determine the survival of children who are on ART; (iii) to determine the effect of early ART initiation on survival of children who are within the age group of [0-15) years; and (iv) to determine association between relevant predictors and survival rate of children on ART.

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Methods

Study design and settings

A retrospective cohort analysis of medical records for 4170 children (<15 years) who were initiated on ART between 2004 and 2008 was conducted. The de-identified medical records were extracted from the National ART database deployed in clinical setting in 36 health care facilities that are implementing the national paediatric HIV and AIDS care and treatment programme. The health facilities contained clinics, Public Health Units, Health Centres, Regional Hospitals and Referral hospitals. These facilities were further stratified into public, private, NGOs and mission health institutions.

Inclusion/exclusion criteria for study participants

All HIV infected children who were initiated on ART between 2004 and 2008, were retained, or died or lost to follow up or discontinued from treatment by the end of 2013 were included in the study.

Sample size

All HIV infected children (< 15 years), 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, dropped out, and end of study) were part of the sampling frame. Included in the study were children with complete medical records in the National Database as of December 31, 2013. Children were stratified into two strata (Early initiated on ARV therapy or were delayed ART). Within the two arms further stratification was done to derive age categories including [0- 2) years, [2-5) years and [5-15) years. ART initiation (Early and Delayed initiation) and age categorization were defined based on WHO categorization as stipulated in the 2010 ART for HIV infected infants and children guidelines. [6]

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Measurement

The primary outcome measures were CD4 evolution (absolute CD4 count in mm^3 for children who are ≥5 years and CD4% for children who are < 5 years); the overall survival rates for children on ART stratified by early initiation on ART (>25% or >750 cd4 count for 2-4 years & >350 for 5-14 years) and delayed initiation (<=25% or <=750 cd4 count for 2-4 years & <=350 for 5-14 years) on ART; and association between the selected baseline predictors and survival of HIV infected children.

Data Management procedure

Electronic medical records were extracted from the national ART Patient Management Information System (APMIS) using Microsoft SQL stored procedures. Data quality profiling was done to pin-point data defects using Talend Data Quality tool. The identified data defects (incomplete, inaccurate and invalid data values) were cleaned up. The clean data set was exported into an Excel data file that was in turn imported into STATA. In STATA, further mapping and identification of invalid data types was done using the codebook command. Identified data errors, outliers and leverage data values were removed from the data set. Variables were recoded and encoded to generate categorical variables. Some string variables were also encoded to generate new numeric data values. The outcome variable of interest (death) was generated and 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

Normality of data distribution for continuous variables was checked using a histogram and Shapiro-Francia test. Data was found to be not normally distributed (p<0.001). The plot-box was used to identify outliers. The Wilcoxon matched –pairs signed-ranks test was applied to test for median difference between baseline

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CD4 and CD4 follow up. The Binomial probability test was run to test the significance of treatment efficacy rate. The Kaplan Meier and Nelson-Aalen methods were used to estimate survivorship functions stratified by selected independent variables. The log-rank test was used to test the significance of the difference in survival for selected categorical variables. Cox Proportional Hazards regression model was applied to examine association between survival and relevant predictors.

Ethical considerations

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and Good Clinical Practice (GCP). [7] The study was conducted in compliance with the protocol (number 45/2014) that was granted ethical clearance by the Faculty of Health Science Research Ethics Committee in the University of Pretoria, and the Scientific and Ethics Committee (SEC) for Ministry of Health in Swaziland. The rights, safety and well-being of participants were highly considered and prevailed over the interests of science and society during the study. The study was conducted by a researcher who is qualified by education, training, and experience to perform the research.

Characteristics of participants

A total of 4170 HIV infected children within the age group of [0-15) years were included in this study, of which 50.3% were females and 49.7% were males, respectively. The mean age (5.43 years, SD: 3.98) for female and (5.26 years, SD: 3.66) for male children were not different (p-value=0.867). Of the 4170 children, 20%, 27% and 53% were within the age groups of [0-2) years, [2-5) years, and [5-15) years, respectively. Majority (52%) of the children were initiated on AZT+3TC+NVP regimen.

Clinical treatment outcomes:

One of the objectives of the study was to determine clinical outcomes of children receiving ART services using immunological response (CD4 count for children≥5 years and CD4% for children<5 years) as a primary outcome measure. In an intent to treat analysis of the overall effect of ART on immunological gain, the median length of follow-up was 6 years (IQR: 1-7 years), 7 years ((IQR: 6-8 years), and 6 years ((IQR: 6-8 years) for children within the age of [0-2) years, [2-5) years and [5-15) years, respectively.

Figure 1 presents data on baseline and follow up CD4 (percent and count) stratified by age.
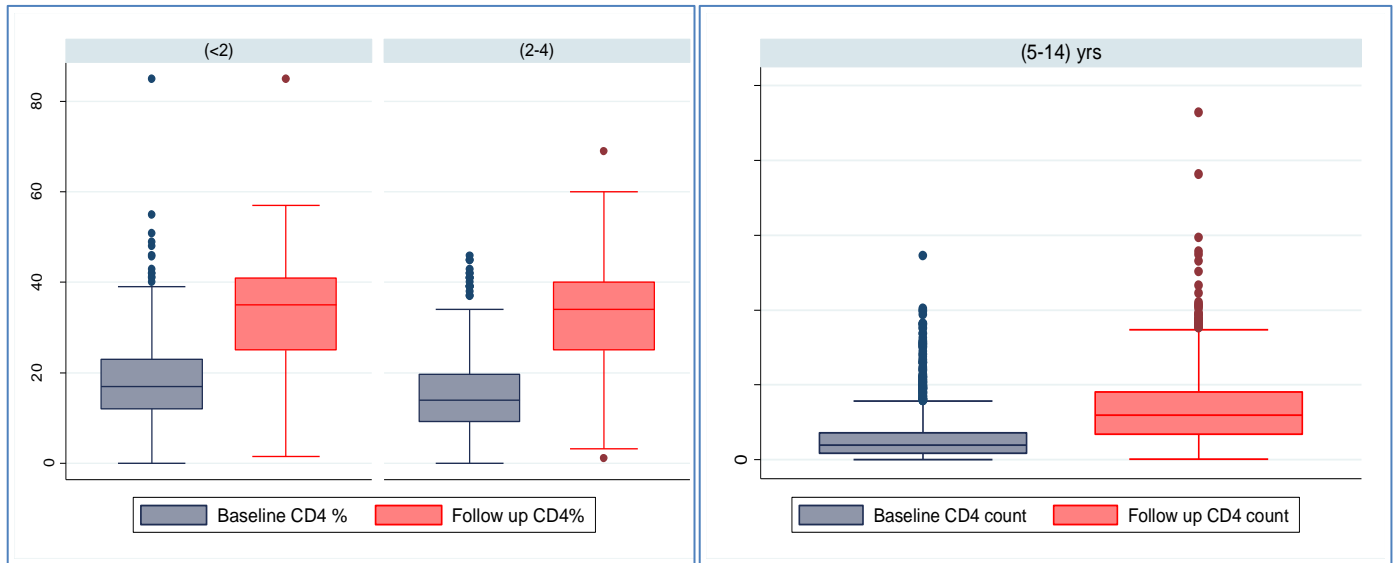

Figure 1: Box plot on baseline CD4 and follow up CD4 for children initiated on ART by age

The results presented in the box plot above (Figure 1) show that there was immunological gain among children within the different age groups. The Wilcoxon signed-rank test was performed to test difference between baselines and follow up CD4 among children within all different age groups ([5-15), [2-5) and [5-15)) years and the results were statistically different, as indicated by p-values of 0.001, 0.001, and 0.001, respectively.

Survival time descriptive analysis

The study also set out to determine survival of children receiving ART who are aged <15 years. The results show that the median survival time for children was 78 months (95% CI: 77-79). Survival time among children [5-15 years) was higher (79 months, 95% CI: 77-79) compared to other age groups. The Kaplan

Meier Estimator and curves were used to estimate survivorship function for children.
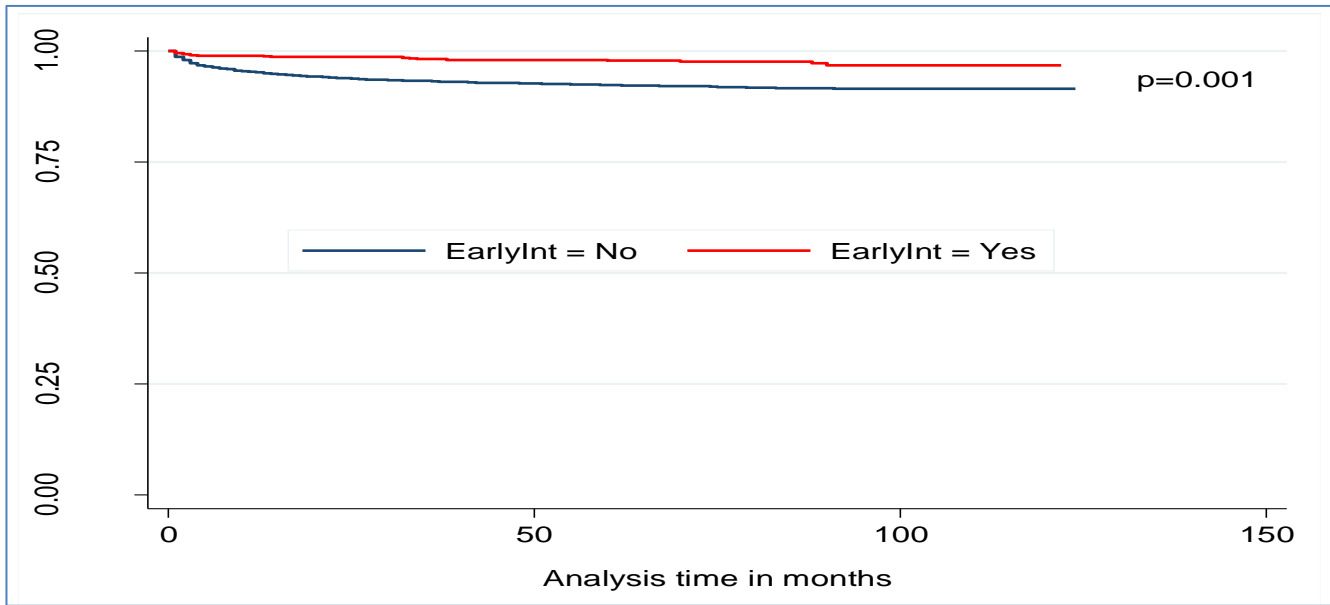
Figure 2: Kaplan-Meier plot on survival probability for children by early and delayed initiation

Figure 2 presents a comparison of the survivor function curves for children who were early initiated against those who were delayed ART. The curves presented in figure 2 illustrate that survival probability for children who were early initiated on ART was higher over time compared to those who were delayed initiation of ART (p=0.001).

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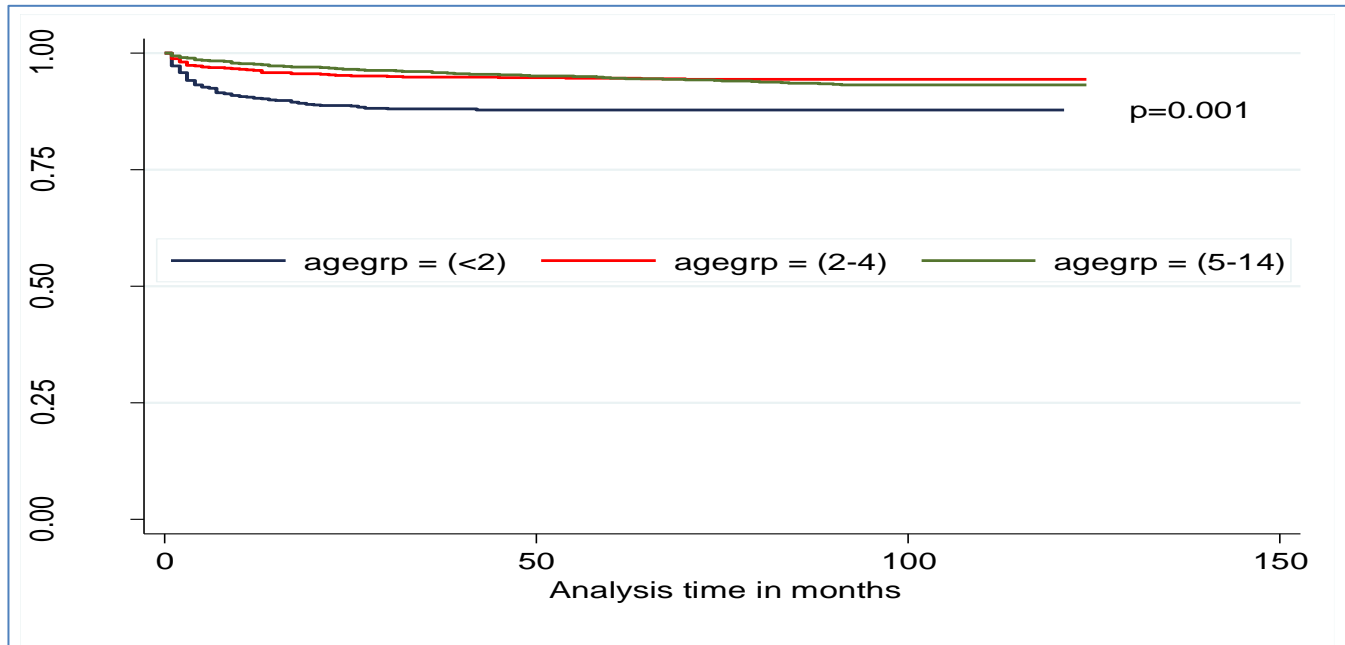
Figure 3: Kaplan-Meier plot on survival probability for children by age group

Figure 3 illustrates a graphical presentation of survival curves stratified by age groups. As presented on the graph all three curves assume a similar exponential decline. Nonetheless, the results show that children within age group [0-2) years had their survival probability declining 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 the age group of [0-2) years was lower than the survival rate for the other age groups, and the difference was statistically significant (p-value=0.001).
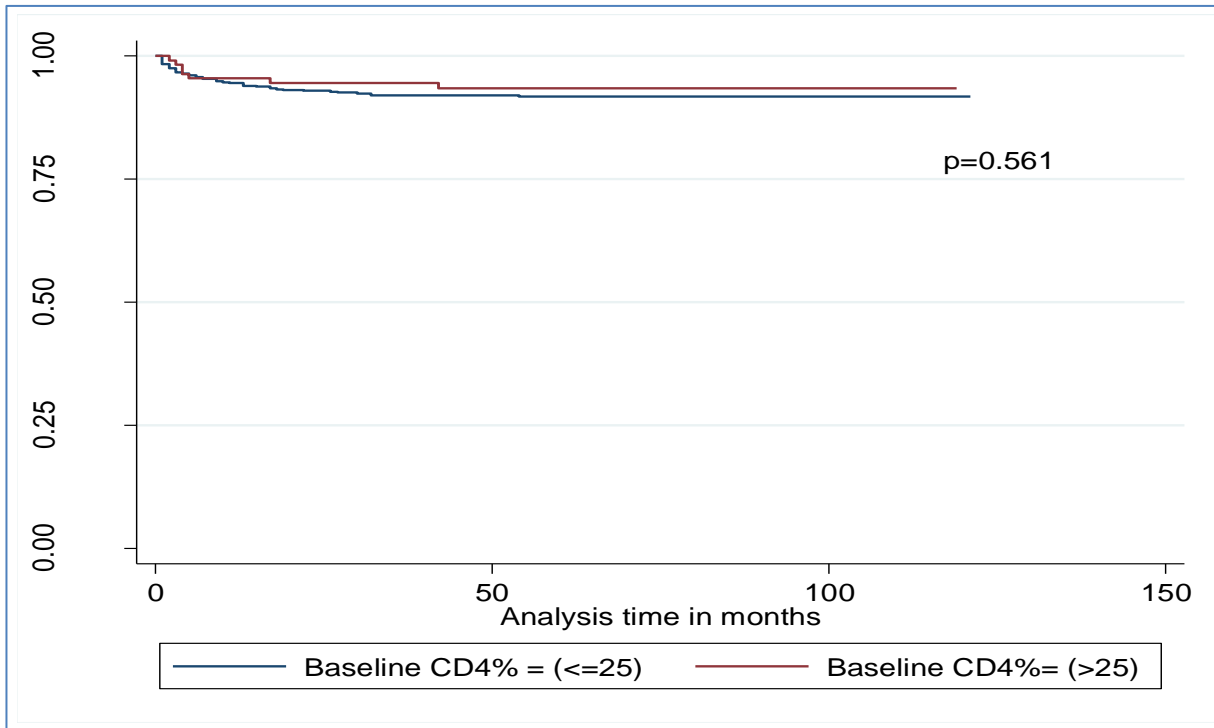
Figure 4: Kaplan-Meier plot on survival probability for children [0-5) years by baseline CD4 %

Figure 4 is a Kaplan-Meier plot of survivor functions by baseline CD4% (CD4 %< =25 versus CD4 % > 25%) for children within the age of [0-5) years. As present in figure 4, the survival plot 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 was used to test the significance of the difference, and the test results suggest that the difference was not statistically significant (p=0.561).

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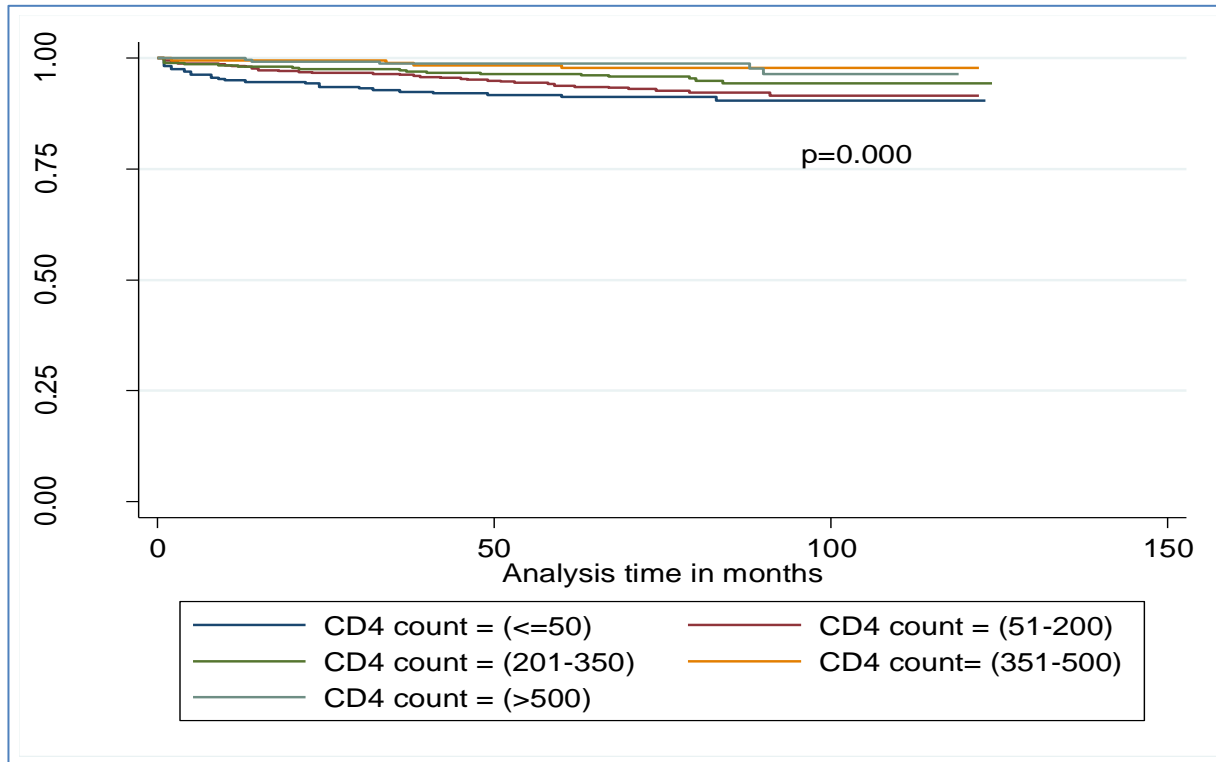
Figure 5: Kaplan-Meier plot on survival probability for children [5-15) years by baseline CD4 count

Figure 5 presents graphical illustration for survivor functions for children within [5-15) years by baseline CD4 count. The survival curves presented in figure 5 demonstrate that children who had CD4 count within the range of 351 to 500 or more than 500 absolute CD4 count at baseline had higher survival probability compared to children who had <350 CD4 count at baseline. The log-rank test for equality was applied to test the significance of survival difference. The log-rank test results confirm that the survival rate for children who had low CD4 count at baseline had their survival rate compromised compared to children with high CD4 count at baseline, and the difference in survival was statistically significant (p=0.000).

The Cox Proportional Hazard Regression model

The Backward elimination approach was adopted to build the final Cox Proportional hazard regression model. [8]. 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.[9, 10] The model was diagnosed for multi-collinearity of independent variables (IVs) using the **corr, collin & vif** commands in STATA 12. The diagnosis results indicate that some IVs were highly correlated with high Variance Inflation Factor (VIFs >=10.00). All IVs with high VIFs were omitted from the initial model as they were discovered to be having inadequate data and/ or were of different operationalizations of the same identical concept and effect to the model.[11, 12]

The likelihood-ratio (LR) test was performed to inform variables 'exclusion decision. Based on the significance level of 0.10, all non-significant variables were eliminated from the initial full model (model A). The LR test was performed to compare the initial full model and all the nested models (nested in model A to model F). The LR test the 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..

The final Cox –Proportional Hazard Regression model

The application of the backward elimination approach produced the following final Cox -Proportional Hazards regression model, and influential explanatory variables were retained in the final model.

Table 1: Cox regression -Breslow method for ties presenting HRs by predictors for children initiated on ART between 2004 and 2008 in Swaziland

Prognostic factors	Haz. Ratio	P>|z|	[95% Conf.	Interval]
TB status				
TB positive	3.808	0.000	2.365	6.129
ART Initiation				
Early initiation	0.388	0.000	0.235	0.639
Age group				
[0-2) years	1.657	0.000	1.283	2.139
Facility ownership				
Mission	1.348	0.022	1.045	1.739
Nutritional status				
Normal limits	0.162	0.000	0.103	0.255
Mild malnutrition	0.406	0.002	0.231	0.714
Moderate malnutrition	0.353	0.000	0.233	0.533
WHO Clinical stage				
WHO II	0.613	0.018	0.409	0.919
WHO IV	1.732	0.001	1.255	2.389
Caregiver relationship				
Grand mother	0.599	0.037	0.369	0.971

The partial log likelihood ratio test, as presented in the output of the model, suggests that at least one of the covariates fitted in the final model (Table 1) was significantly (LR chi2 (10) = 228.94, p =0.000) 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 0.39 (95% CI: 0.23-0.64). This hazard ratio (0.39) 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 61% lower than children who were delayed ART (p=0.001). Children who were diagnosed with TB at baseline, all other variables hold constant, were estimated to have 3.81 (95% CI: 2.36-6.13) times higher hazard of death than those who were TB negative. Children [0-2 years) had 66% higher hazard of death (HR: 1.66 [95% CI: 1.28- 2.14], p<0.001) than children within the age group of [5-15) years. Children who were nourished had 84% lower hazard of death than severe malnourished children (HR: 0.16[95% CI: 0.10-0.26], p<0.001).

Post estimation for the Cox PH Model

We examined whether the proportional-hazards assumption holds for the model with covariates. We performed **estat phtest** for both individual covariates and globally. The **estat phtest** tested the proportional-hazards assumption on the basis of both scaled and non-scaled Schoenfeld residuals after fitting the model.

Table 2: Test of proportional-hazards assumption as post estimation for Cox PH Model

	rho	chi2	df	Prob>chi2
TB	0.00126	0.00	1	0.9833
EarlyInt	-0.01474	0.06	1	0.8064
agegrp1	-0.26500	19.00	1	0.0000
FOwner3	0.04771	0.61	1	0.4332
Bnutri1	0.05434	0.79	1	0.3755
Bnutri2	-0.03660	0.37	1	0.5404
Bnutri3	0.07677	1.54	1	0.2146
Bwho2	0.21550	12.51	1	0.0004
Bwho4	0.06487	1.18	1	0.2770
Caregiver_~3	0.19899	11.05	1	0.0009
global test		50.91	10	0.0000

Table 2 presents results of the estat phtest. As presented in the table the covariates TB positive (1= Yes, 0=No), Early initiation, Facility ownership (mission), Nutritional status (Normal limits, Mild malnutrition, Moderate malnutrition) and WHO clinical stage 4 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 were appropriate. The model fitted well and adequately for the aforementioned covariates. However, the hazard ratios describing the effect of age group [0-2) years, caregiver relationship and WHO clinical stage two, were inappropriate.

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Discussion

In this study, the clinical outcomes for HIV-infected children (n=4170) who were enrolled in the National ART program were found to be desirable. The Wilcoxon signed-rank test was performed to test the significance of immunological gain and it was found to be statistically significant. This may be explained by that initiating HIV infected children on effective ART and management of HIV related opportunistic infections drastically reduces disease progression, in turn enhancing immunological response. 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.[13] Nacro et al 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. [14] Resino et al 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. [15] In addition, Sauvageot et al analysed surveillance data for 3936 children < 5 years of age initiated on ART in 48 HIV and AIDS programs in Africa and Asia. The researchers observed similar encouraging clinical outcomes in such resource-limited settings. [16]The RCT (CHER) conducted by Cotton at al found that infants (median age=7.4 months) with early-time limited ART had better clinical and immunological outcomes compared to infants whose ART was deferred. [17]

Unlike in our study where clinical outcomes were measured in health facility settings, Ferris et al conducted a retrospective study in Romania to investigate effect of institutionalization on clinical outcome (CD4 decline) and death in a cohort of HIV infected children on antiretroviral therapy (ART). The researchers found significant difference in CD4 improvement between the two groups. They observed a trend toward

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CD4 decline among children who were staying with their biological families. Children who were living with their biological families were more likely to die than were children in institutional care. [18] Unlike the aforementioned studies, we analysed data for 4170 HIV infected children (<15 years) who were initiated on ART and followed up for at least 5 years. We used the immunological response (CD4 % for 0-4 years and CD4 count for 5-14 years) as a primary clinical outcome measure (figure 1).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 health care workers will have desirable clinical outcomes.

Data was further analysed to determine the effect of early ART initiation on survival of HIV-infected children < 15 years of age. Survival rate for children who were early initiated on ART was higher compared to those who were delayed ART. The hazard of dying among children who were early initiated on ART was 61% lower than the hazard of death for children who were delayed ART, and the difference was statistically significant. The findings may be explained by that early initiation of ART shortly after HIV infection limits both the reservoir of persistent HIV and viral diversity, in turn enhancing immunological response.[19, 20] Our findings are consistent with a meta-analysis of 18 cohort studies conducted by the When to Start Consortium. The Consortium found that early initiation of ART was associated with increased survival rates. [21] Our findings are, however, inconsistent with the Ugandan Cluster Randomized 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%≤15) ART was not different. [22] Similarly, a prospective study conducted by the IeDEA Southern African Network in Uganda revealed that early initiation on ART had poor survival benefits among children [2-5 years]. [23] The indifference in survival for children who were early initiated on ART compared to those who were delayed ART in the Ugandan CRT could be explained by the

use of lower CD4 threshold (CD4% >15) instead of CD4 % ≥25%, as suggested by the revised 2010 WHO guidelines for ART for HIV infected children.[6]

A further adjustment of survival by age group revealed that children within the age group of [0-2) years had 66% higher hazard of death than children within the age group of [5-15) years and the findings were statistically significant (p<0.001). These findings may be explained by impaired or depleted immune system among the younger age group, 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 liquids. The difficulty of administration of therapy among this age group could also be an explanation of the foregoing findings.

In the current study, we also adjusted survival functions by specific ART regimen. We found that children who were on D4T+3TC+EFV (HR: 1.14[95% CI: 0.74-1.78], p=0.685) and AZT+3TC+EFV (HR: 1.08 [95% CI: 0.74-1.59], p=0.540) had survival probability that was constantly lower overtime than those who were on ABC+3TC+EFV, although, 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. The findings may be explained by that the ABC+3TC+EFV regimen is a combination of effective NRTIs and NNRTI for HIV infected infants and children. Abacavir (ABC) and Lamivudine (3TC), in particular, are effective NRTIs with an excellent record of efficacy, safety and tolerability in HIV infected children, and are highly recommended by WHO. [6, 24] Our findings are, however, inconsistent with a multicentre (67 centres) Randomized Control Trial (RCT) conducted by Lennox at al in 5 continents. The researchers 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, raltegravir proved to be safer and quite efficacious when compared to efavirenz.

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25. Janssens et al, on the other hand, conducted a study in Cambodia where they analysed clinical outcomes for 212 children (<13 years) and found undesirable clinical outcomes (detectable viral load) among children. Such poor clinical outcomes were associated with resistance to lamivudine. [26] A prospective cohort study conducted in the United States of America (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 CNS-penetrating ART regimens than children who were not on CNS-penetrating ART regimens. [27]

In this study, we also examined possible association of baseline WHO clinical staging with survival of HIV infected children initiated on ART. Our findings demonstrate 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 (p<0.001). Our findings are consistent with a prospective cohort study conducted in Kenya, which also proved that WHO stage 4 was a predictor of mortality among HIV-infected 135 children. [28]

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 35% higher hazard of death than children who were receiving their ARV treatment and care in government facilities. The increase in hazard for children who were receiving their ART in missionary facilities could be as high as 74%% or as low as 5 % with 95% confidence. Unlike our study, Moore et al conducted a study in Zambia where they analysed clinical outcomes for children on ART and adjusted by health system level. The researchers found that clinical outcomes for children receiving ART in Primary Health Care settings were found to be desirable. [29]

Nutritional status was also analysed as a predictor in this study. Children who were nourished had increased survival and compared to children who were severely malnourished, and the results were statistically significant (p<0.001) in a multivariate analysis. The findings may be explained by that HIV-infected children who are significantly underweight are much more likely to die than HIV-infected children who nourished. [30] Our findings are consistent with Niekerk et al's findings where nourished HIV-infected children were found to have significantly increased survival. [31]

In a multivariate analysis, we further analyse the hazard of HIV-infected children adjusted by baseline TB status (positive or negative). The findings demonstrate that children who were co-infected with TB and HIV had lower survival rate compared to HIV-infected who were TB negative. Our findings could be explained by that HIV infected children who develop active TB have impaired cell-mediated immunity through depletion of CD4^{+} lymphocytes; hence their probability of survival will be lower compared to TB negative HIV-infected children. [32, 33]

Caregiver relationship was also included as a predictor variable for survival in the multivariate Cox PH regression analysis. We adjusted caregiver relationship by biological mother, father, aunt, and grandmother. Living with grandmother was found to be positively associated with increased survival, and the results were statistically significant (HR: 0.60 [95% CI: 0.37-. 0.97], p=0.04). In fact, children who were receiving maternal care and treatment support from grandmothers had 40% lower hazard of death compared to children whose caregivers were biological mothers. This could be explained by that the biological mothers were too sick and weak to take good care of their HIV-infected children. This may also be explained by that 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, while ART paediatric services demonstrate to be effective in producing desired clinical outcomes for HIV-infected children, in general and increased survival probability for HIV infected children who were early initiated on ART, active TB, malnutrition, and delayed ART initiation remain predictors of poor survival among HIV-infected children in resource limited settings. Our findings are consistent with previous studies and are reinforcing operationalization of 2013 WHO treatment guidelines, which provides for early initiation for all HIV-infected children (<5 years), irrespective of their WHO clinical stage and CD4 count. [34] It is, therefore, against the foregoing findings that the following relevant recommendations are deduced.

- Continue to measure DC4 prior to initiation of ART, and conduct CD4 monitoring to measure immunological again among HIV-infected children in resource-limited settings;

- Accelerate efforts targeted to early infant diagnosis interventions 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 2013 WHO guidelines on early initiation of HIV-infected children (5-14 years);

- 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 in order 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; and

- Conduct further investigation on facility ownership and caregiver relationship as predictors for survival of HIV-infected children.

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