

**Short-term treatment outcomes of children started on ART in the ICU,  
general medical wards and outpatient HIV clinics at Red Cross War  
Memorial Children's Hospital (RCWMCH): A Retrospective Cohort Study**

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## SYNOPSIS

### **Short-term treatment outcomes of children starting ART in the ICU, general medical wards and outpatient HIV clinics at Red Cross War Memorial Children's Hospital (RCWMCH): A Retrospective Cohort Study**

**Background:** Antiretroviral therapy (ART) has proven to decrease morbidity and mortality in HIV-infected children and improve immunologic, virologic and clinical outcomes. As clinical management policies evolved, an emphasis on early infant testing was adopted resulting in an increasing number of children being diagnosed and commenced on therapy before the onset of severe disease progression. However, a fair proportion still remain untested and subsequently present to hospital with advanced immunosuppression and severe disease. Since the advent of the 2013 national Standard Treatment Guidelines which encourage expedited initiation of ART within 7 days of HIV diagnosis in all children under the age of 12 months and in those with advanced immunosuppression, it is likely that many HIV-infected children are being initiated on ART during hospitalisation in South Africa. No local published data on these outcomes exist. We assessed the short-term outcomes of children initiated on ART in the intensive care unit (ICU), general medical wards (GMWs) and outpatient HIV clinics (OHCs) at RCWMCH.

#### **Methods:**

##### **Structured Literature Review**

A Pubmed search looking at outcomes of treatment naïve HIV-infected children and adolescents up to 19 years of age living in South Africa commenced on 1<sup>st</sup> line ART regimens in accordance to the national guidelines presiding at the time, over a 10 year period was performed. This served to identify gaps in knowledge around paediatric ART in a South African context warranting further research.

##### **Retrospective Cohort Study**

We conducted a retrospective cohort study of HIV-infected children <13 years of age, commenced on first line ART between January 2008 and December 2011 at RCWMCH. Outcome measures included death, virologic suppression and changes in CD4 count and percentage. Kaplan-Meier estimates, multivariate Cox proportional hazard ratios and logistic regression were used to estimate outcomes 6 months after ART initiation.

## **Results:**

### **Structured Literature Review**

This review identified several knowledge gaps. One of these gaps, the treatment outcomes of children started on ART at different service levels within tertiary health care settings was addressed in our retrospective cohort study and described in section C of this dissertation

### **Retrospective Cohort Study**

Seven hundred and forty-nine children were included: 106 were commenced on ART in the ICU, 509 in the GMWs and 127 in the OHCs. Four hundred and ninety-two (65.7%) children were <12 months old. Children in the ICU and GMW cohorts were significantly younger than the OHC cohort (median ages: 3 and 5 months respectively vs. 22 months) and had lower WAZ scores (-2.48 and -2.33 respectively vs -1.14). Three hundred and eighty-five (51.4%) children qualified for rapid ART initiation within 7 days of HIV diagnosis or hospitalisation, based on CD4 criteria in the 2013 national Standard Treatment Guidelines. Overall mortality was 6.4% (CI: 4.9 - 8.4). Mortality was significantly higher in the ICU cohort i.e. 14 (13.2%) deaths compared to 28 (5.5%) and 5 (3.9%) deaths in the GMWs and OHCs cohorts, logrank  $p=0.004$ . Predictors of mortality included being moderately underweight HR 2.4 (CI: 1.1 – 5.2;  $p=0.02$ ), severely underweight HR 3.2 (CI: 1.6 – 6.5;  $p=0.001$ ), absence of caregiver counselling sessions HR 2.9 (CI: 1.4 – 6.0;  $p=0.005$ ) and ART initiation in ICU HR 2.6 (CI: 1.4 – 4.9;  $p=0.003$ ).

**Conclusion:** The findings of our retrospective cohort study serve as a basis for understanding the implications of ART initiation in children during hospitalisation.

## **ACKNOWLEDGEMENTS**

I would like to thank my supervisor Brian Eley and co-supervisor Mary-Ann Davies for their time and guidance during the preparation of this dissertation. Their insight and expertise have been invaluable.

Many thanks to thank Spasina King for her assistance and contribution in the retrieval of patient records and subsequent data collection. Her contribution has been much appreciated.

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## **PART A: PROTOCOL**

### **Comparing short-term treatment outcomes of children started on ART in ICU versus general medical wards and outpatient department at the Red Cross War Memorial Children's Hospital (RCWMCH): A Retrospective Cohort Study**

#### **Background**

Paediatric populations are considered the most vulnerable of population groups globally, even more so since the emergence of HIV (Human Immunodeficiency Virus) and AIDS (Acquired Immunodeficiency Syndrome). Global summaries from 2009 estimate that 2.5 million children under the age of 15 years were infected with HIV and a further 260 000 paediatric deaths were due to AIDS-related illnesses.<sup>1</sup> In South Africa, by mid-2009 approximately 340 000 children under the age of fifteen were living with HIV. Of these 70 000 were on antiretroviral therapy (ART).<sup>2</sup> A study performed at Chris Hani Baragwanath Hospital in 2007 not only described the disease profile of HIV infection in children but also highlighted missed opportunities for early initiation of ART. Of the 94% of children diagnosed with HIV infection before admission to hospital only 46% were accessing ART even though 94.5% met the ART eligibility criteria.<sup>3</sup> Of the ART-naïve eligible children, only 4.1% were commenced on ART during the course of their admission.<sup>3</sup>

Many studies have highlighted the increased mortality associated with HIV-infected children in the absence of ART and the importance of commencing therapy early.<sup>4</sup> The World Health Organisation's (WHO) 2006 paediatric ART guidelines stipulated that HIV-infected children should only be started on ART after specific clinical or immunologic criteria had been met.<sup>5</sup> However, the Children with HIV Early Antiretroviral Therapy (CHER) trial illustrated that mortality was in fact lower in children who commenced ART at a baseline age of 7 weeks regardless of clinical and immunologic criteria, compared to those in the deferred arm who commenced ART only once CD4 decline or disease progression occurred.<sup>6</sup>

At the RCWMCH in Cape Town, of all the new ART enrolments between 2007 and 2011, 79.45% were enrolments during admission and 49.6% were children under 6 months of age.<sup>7</sup>

Treatment of children is often difficult to maintain for a number of reasons. Their vulnerability as a whole makes them dependent on others for day-to-day care and nurturing. The responsibility of providing care lies predominantly on the caregiver rather than on the child, thereby emphasising the importance of adequate education and counselling of respective carers around issues essential for optimal treatment.<sup>8</sup> Paediatric formulations are more complex and require regular dose adjustments due to the natural process of childhood growth and subsequent weight changes. Formulations also require a certain degree of preparation (crushing of tablets, suspending and mixing exact ratios of water to powder) prior to being dispensed thereby further adding to the complexity of administering medication.<sup>8</sup> Drugs such as Kaletra are particularly unpalatable making it difficult for children, especially

those of a younger age group, to tolerate. These, along with a host of other factors are thought to contribute greatly to treatment failure, morbidity and mortality.

Virologic failure is defined as 2 consecutive unsuppressed viral loads, with the second being >1000 copies/ml, after 24 weeks of therapy. Virologic failure has significant consequences for both the individual and the population at large. For the individual, failure of suppression leads to an increased risk of morbidity and mortality. The development of resistant strains places the remaining population at greater risk of contracting a more virulent organism; one which could potentially become resistant to multiple drug classes and subsequently become more difficult to treat. In data analysed from children on ART in 7 Southern African treatment programmes in 2011, it was found that the 3 year probability of virologic failure among 5485 children was 19.3% (CI: 17.6 to 21.1).<sup>9</sup> This suggests that even though the majority of children respond to treatment programmes, a large proportion remain unsuppressed and are failing treatment regimens.

Clinical, virologic and immunological outcomes of HIV infected children started on ART have been previously assessed in various countries, including South Africa. Formal research into factors that positively or negatively affecting these outcomes in a tertiary setting such as Red Cross War Memorial Children's hospital has yet to be performed. This study aims to assess these factors and their influence on clinical, virologic and immunologic outcomes in order to indicate where efforts should be enhanced to optimise treatment.

### **Aim**

The overall aim of this study is to compare the short term clinical, virologic and immunological outcomes of children started on ART in ICU versus those started on ART in the general medical wards and the outpatient HIV clinics at the Red Cross War Memorial Children's Hospital and to assess the factors affecting these outcomes.

### **Objectives**

The following research objectives were identified:

- To determine factors predicting a good outcome (ie: suppressed viral load)
- To assess survival and predictors of mortality and loss to follow-up within a 6 month period
- To assess changes in viral load results, and CD4 counts and percentages after 6 months on ART

## **Methods**

### **Study Design, setting, participants and data collection**

This study design was a retrospective cohort study looking at the Paediatric ART programme at Red Cross War Memorial Children's Hospital (RCWMCH). Data from the Paediatric ART Programme from January 2008 up to and including December 2011 were extracted. All ART-naïve children under the age of thirteen years, commenced on standardised 1<sup>st</sup> line ART therapy (according to the Department of Health National Guidelines), were included in this analysis. Nine hundred and fifteen patient Folders and patient Clinical Record Forms (CRF's) were reviewed for study eligibility by myself and Spasina King. Thirty-seven records were excluded from the analysis due to duplicate or triplicate data records. A further 129 patients did not meet inclusion criteria. Of these, 101 children were ART experienced and 28 had been initiated on ART at other health care facilities.

Pre-treatment characteristics included *patient age, gender, CD4 percentage and absolute count, viral load (VL), weight-for-age z-scores (WAZ), height-for-age (HAZ) and weight-for-height (WHZ), World Health Organization (WHO) clinical staging, presence or absence of TB disease, ART initiation relative to TB treatment initiation, ART initiation relative to HIV diagnosis, ART initiation relative to hospital admission.* Pre-treatment WAZ scores, HAZ scores, CD4 and VL values included measurements within one month of ART initiation. Where multiple measurements were recorded values closest to ART initiation were used. Baseline primary and secondary co-morbidities as well as the degree of medical intervention needed were used to describe the severity of illness prior to ART initiation. Patients were stratified into one of three groups based on the site of ART initiation. These included the ICU, General Medical Wards (GMWs) and outpatient HIV clinics (OHCs) at RCWMCH.

Due to the complexity of the variable age in paediatric patients, *patient age* was grouped into one of 4 categories: <3 months, 3-12 months, 13-60 months and >60 months. *CD4 counts and percentages, WAZ scores, HAZ scores, WHZ scores and VL* were classified into groups according to the WHO criteria.

A further sub-analysis was performed on patients transferred out to primary health care facilities within six months of starting ART.

### **Outcomes and case definitions**

Outcome measures included: death, loss to follow-up (LTFU), virologic suppression and changes in CD4 count and percentage. Outcomes were evaluated at 6 months using the measure taken closest to 6 months after initiation within a window of three to nine months after ART initiation. LTFU was defined as failure to attend a follow-up visit for three months after the last scheduled appointment was missed. Viral load suppression was defined as a viral load of <400 copies/ml and <50 copies/ml. CD4 counts and percentages as well as viral loads were measured by the Western Cape Provincial laboratory services.

## **Statistical analysis**

Pre-treatment continuous variables were compared using ANOVA or Kruskal-Wallis, as was appropriate. Frequencies and proportions were used to describe pre-treatment categorical variables. Kaplan-Meier curves were fitted to estimate mortality, LTFU and attrition rates of patients between ART initiation sites. Multivariable Cox proportional hazards regression was used to assess factors associated with mortality, LTFU and attrition after six months of ART, adjusting for pre-treatment clinical and demographic variables.

Logistic Regression was used to assess factors associated with VL suppression of <400 copies/ml and <50 copies/ml, again adjusting for pre-treatment clinical and demographic variables.

Variables were assessed for inclusion in the regression analyses, based on results of the univariate analysis. These included patient baseline factors (patient age, gender, WAZ, HAZ, WHZ, CD4 count and percent, VL, WHO clinical staging, presence or absence of TB disease, ART initiation site), maternal/primary caregiver factors (reported maternal HIV status at ART initiation, MTCT (mother to child transmission) prophylaxis, maternal ART use at ART initiation, primary caregiver relationship to the child, caregiver support).

Quantitative and qualitative data was analysed using the STATA Release 12.0 statistical software package (STATA Corp, College Station, USA).

## **Ethical consideration**

Ethical approval was obtained from the University of Cape Town's Ethics Committee in 2003 (HREC REF: 261/2002).

As this was a retrospective review of patient information, no risks were incurred to the patients.

There are no direct benefits to the participants however the following will contribute to an anticipated gain in scientific knowledge:

- The recognition of factors inhibiting virologic suppression of patients on ART therefore highlighting areas where efforts need to be targeted in order to improve overall outcomes in HIV infected children.
- The results would be generalizable to other institutions across the country as well as to areas sharing a similar demographic and socio-economic profile as South Africa.

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## **PART B: STRUCTURED LITERATURE REVIEW**

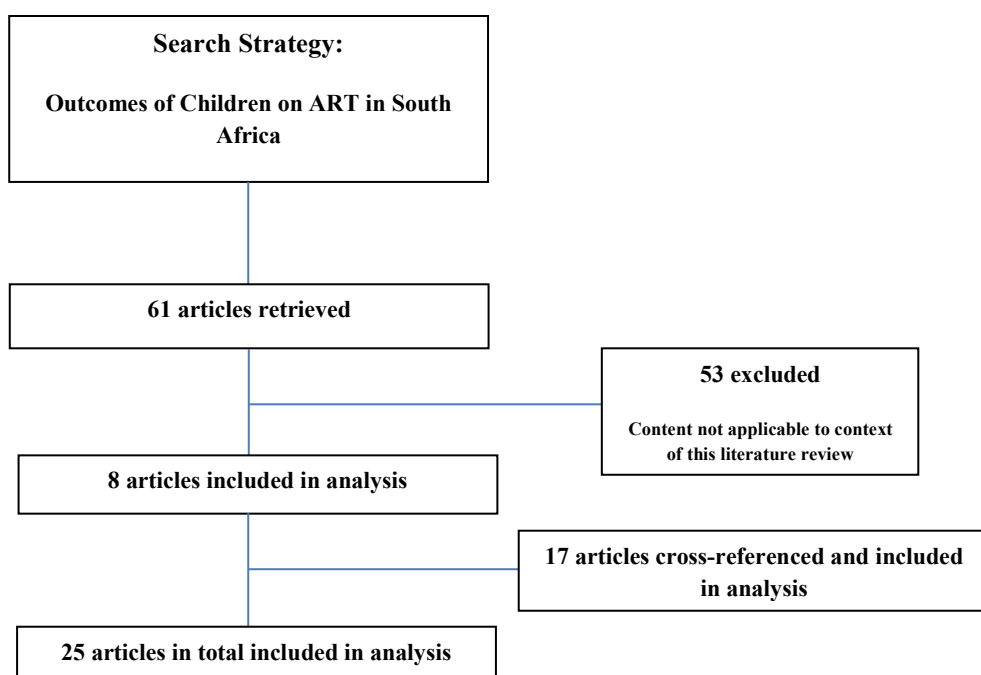
In 2012, 410 000 (370 000 – 450 000) children infected with HIV, were estimated to be living in South Africa. At the end of 2012, an estimated 63% of 220,000 children <15 years of age qualifying for antiretroviral therapy (ART) in South Africa, were receiving therapy.<sup>1</sup> ART has been proven to decrease morbidity and mortality in HIV-infected children and improve immunologic, virologic and clinical outcomes. The increasing number of children commenced on therapy in South Africa has encouraged outcomes research. Consequently, an emerging body of literature has begun to describe the impact of ART in HIV-infected children in South Africa.

The purpose of this literature review is:

1. To provide an overview of the immunologic, virologic and clinical outcomes of children and adolescents in South Africa started on antiretroviral therapy (ART) over the past 10 years.
2. To summarize the impact of paediatric ART initiation at level 1, 2 and 3 health care facilities on these outcomes.
3. To understand the impact of urban and rural settings on these outcomes.
4. To identify gaps in knowledge around paediatric ART in a South African context requiring further research.

### **Search Strategy**

A Pubmed search was used to extract literature relating to the above mentioned objectives. Inclusion criteria included citations related to outcomes of treatment naïve HIV-infected children and adolescents up to 19 years of age living in Southern Africa commenced on 1<sup>st</sup> line ART regimens in accordance to the national guidelines presiding at the time, over a 10 year period extending from 01 July 2004 until 01 July 2014.



## **Quality of Evidence**

Twenty-five articles were critically examined for the purpose of this literature review. The remaining thirteen were policies, reports and publications used to enhance the context of this review. Of the articles that were analysed, the majority were observational studies conducted retrospectively by accessing patient clinical records with only a few reporting results of randomised control studies. Eleven were retrospective cohort studies, six prospective cohort studies, two retrospective cross-sectional studies and the remainder, randomised control studies. Observational studies are typically low quality studies but are the most practical and feasible to conduct in over-burdened, understaffed public health care settings with high-patient turnovers. Randomised control trials provide a much higher quality of evidence, with increased validity and reliability of estimates. Although the majority of published data extracted for this review is of an observational nature, the consistency of results in addressing the objectives outlined above increase the reliability of the findings.

<b>PUBLISHED DATA ON CHILDREN AND ADOLESCENTS RECEIVING ART</b>							
<b>First Author</b>	<b>Year of Publication</b>	<b>Study Period</b>	<b>Geographic Location</b>	<b>Setting</b>	<b>Study Design</b>	<b>Age Spectrum</b>	<b>Sample Size</b>
<b>Temporal Trends in Baseline Characteristics at ART Initiation</b>							
Fatti, G [5]	2011	01 January 2004 – 30 September 2009	South Africa	Primary, Secondary	Retrospective Cohort Study	< 16 years	3007
Davies, MA [2]	2013	01 January 2005 – 31 December 2010	Malawi, South Africa, Zambia, Zimbabwe	Primary, Secondary, Tertiary	Retrospective Cohort Study	< 16 years	30 300 (*15872)
<b>Immunologic, Virologic and Clinical Outcomes</b>							
Reddi, A [6]	2007	31 August 2003 – 31 October 2005	South Africa	Secondary	Retrospective Cohort Study	< 16 years	151
Davies, MA [7]	2009	01 June 1999 – 29 February 2008	South Africa	Primary, Secondary, Tertiary	Prospective Cohort Study	< 16 years	6078
Davies, MA [8]	2011	01 June 1999 – 29 February 2008	South Africa	Primary, Secondary, Tertiary	Prospective Cohort Study	< 16 years	5485
Meyers, T [9]	2011	01 April 2004 – 31 March 2008	South Africa	Tertiary	Retrospective Cohort Study	< 15 years	2102
Violari [11]	2008	August 2005 – February 2007	South Africa	Tertiary	Randomised Control Trial	6 – 12 weeks	377
Prendergast [12]	2008	August 2005 – February 2007	South Africa	Tertiary	Randomised Control Trial	4 - 5 weeks	60
Fenner, L [13]	2010	January 1999 – December 2008	South Africa, Malawi, Mozambique, Zimbabwe	Tertiary, Primary	Retrospective Cohort Study	< 16 years	8225 (*6072)
<b>Anthropometric Changes</b>							

Chhagan, M [19]	2012	September 2006 – July 2009	South Africa	Tertiary	Prospective Cohort Study	< 12 years	151
Gsponer [20]	2012	January 1997 – December 2010	Malawi, Zambia, Zimbabwe, Mozambique, South Africa	Primary, Secondary, Tertiary	Retrospective Cohort Study	< 10 years	17 990 ( <sup>§</sup> 6749)
Feinstein, L [21]	2012	01 April 2004 – 31 March 2008	South Africa	Tertiary	Retrospective Cohort Study	< 15 years	2399
Shiau, S [22]	2013	08 April 2005 – 10 July 2007	South Africa	Secondary	Randomised Control Trial	< 2 years	195
<b>Neurodevelopmental Outcomes with Early ART</b>							
Laughton, B [23]	2012	August 2005 – February 2007	South Africa	Tertiary	Randomised Control Trial	6 – 12 weeks	90
Smith, L [24]	2008	February 2002 – December 2003	South Africa	Tertiary	Prospective Cohort Study	< 13 years	39
<b>Incidence of Otorrhoea with Early ART</b>							
Hainline, C [25]	2011	August 2005 – February 2007	South Africa	Tertiary	Randomised Control Trial	6 – 12 weeks	113
<b>Effect of ART on the Risk of Incident Tuberculosis</b>							
Martinson, NA [27]	2009	September 1994 – June 2006	South Africa	Tertiary	Retrospective Cohort Study	< 15 years	1132
<b>Immune Reconstitution Inflammatory Syndrome</b>							
Smith, K [28]	2009	April 2005 – November 2006	South Africa	Secondary	Prospective Cohort Study	< 2 years	169
Rabie, H [29]	2011	August 2005 – February 2007	South Africa	Tertiary	Randomised Control Trial	6 – 12 weeks	369
<b>Treatment Outcomes of Adolescents</b>							
Nglazi, MD [33]	2012	September 2002 – June 2009	South Africa	Primary	Prospective Cohort Study	9 – 28 years	883 (*65)
Nachega, JB [34]	2009	January 1999 – August 2006	Southern Africa	Private - sector	Retrospective Cohort Study	11 - >30 years	7776 ( <sup>†</sup> 154)
<b>Impact of ART Initiation at Primary, Secondary and Tertiary Health Care Facilities on Clinical Outcomes</b>							
Bock, P [10]	2008	April 2004 – April 2006	South Africa	Primary, Secondary, Tertiary	Retrospective Cohort Study	< 15 years	1741
Dramowski, A [36]	2011	01 October 2007 – 31 December 2007	South Africa	Tertiary	Retrospective Cross-sectional Study	< 14 years	1510
Meyers, T [37]	2012	01 July 1996 – 31 January 2011	South Africa	Tertiary	Retrospective Cross-sectional Study	< 15 years	3063

Outcomes in Rural versus Urban Settings							
Fatti, G [38]	2010	01 November 2003 – 31 March 2008	South Africa	Secondary, Primary	Retrospective Cohort Study	< 16 years	2332

<sup>#</sup> 15 872 of children included in analysis were receiving ART at South African health care facilities.

<sup>§</sup> 6749 of children included in analysis were receiving ART at South African health care facilities.

<sup>+</sup> 6072 of children included in analysis were receiving ART at South African health care facilities.

<sup>\*</sup> 65 of cohort were adolescents (9-19 years).

<sup>‡</sup> 154 of cohort were adolescents (11-19 years).

## **Interpretation of Literature**

### **Temporal Trends in Baseline Characteristics at ART Initiation**

Two studies have examined temporal changes in the characteristics of children starting ART in South Africa. In December 2013, the IeDEA-SA Collaboration published data from 4 countries examining temporal changes in characteristics of children at the time of ART initiation across Southern Africa between 2005 and 2010.<sup>2</sup> The principal findings of this study revealed that the median age of ART initiation declined from 63 months in 2006 to 56 months in 2010. The proportions of children <1 year increased from 12% to 19% and children  $\geq 10$  years, from 18% to 22% (probably reflecting the change in WHO policy at the time<sup>3</sup>). As policies evolved, an emphasis on early infant testing was adopted.<sup>4</sup> Younger children were being diagnosed and initiated on ART before the onset of severe disease progression. This is reflected in this analysis in which children, including infants, showed significant declines in the percentage with severe immunosuppression, WHO stage 3 and 4 disease and weight-for-age z-scores (WAZ) <-3 at ART initiation. Another study looking at temporal trends in characteristics of children at the time of ART initiation from 2004 to 2009, but focusing on those in a South African context, yielded similar findings.<sup>5</sup> The proportions of children <18 months initiating ART increased from 6.8% to 10.8% and from 15.3% to 24.8% in children  $\geq 10$  years. The median age however, comparatively increased from 5.8 years in 2004 to 6.7 years in 2009. Significant declines over time were again noted in the percentage with severe immunosuppression and in those with WHO stage 3 and 4 disease. Median CD4 percentage increased from 10.8% to 13.0% between 2004 and 2009, while the proportion of children with severe immunodeficiency decreased from 85.5% to 64.5% during this period. The proportion of children with WHO stage 3 and 4 disease decreased from 72.9% to 49.0%. These changes in temporal trends once again reflect changes in policy at a global and national level, focusing on early infant testing, initiation of ART in children at younger ages irrespective of degree of immunodeficiency and WHO clinical staging as well as expanding CD4 threshold values for starting ART in older children.

## Immunologic, Virologic and Clinical Outcomes

A number of cohort studies have demonstrated good clinical, immunologic and virologic outcomes among children initiating ART.

In March 2007, a retrospective cohort study was performed in Kwazulu-Natal looking at preliminary outcomes of children initiated on ART at Sinikithemba HIV/AIDS clinic.<sup>6</sup> The median increase in CD4% from baseline was 10.2 percentage points at 6 months and 16.2 percentage points at 12 months post-ART initiation. At 6 and 12 months, 84% and 80.3% had undetectable viral loads respectively. Kaplan Meier estimates predicted a 90.9% survival rate 12 months after initiation of treatment. Another multi-cohort study looking at seven ART programmes in Gauteng, Western Cape and KwaZulu-Natal estimated the median change in CD4%, from baseline to be approximately 23%, 3 years post-ART initiation. Mortality and viral load suppression rates at 3 years were 7.7% and 80% respectively.<sup>7</sup> In contrast to virologic suppression, subsequent analysis on a largely similar cohort including the same seven South African ART programs estimated a 19.3% probability of virologic failure by 3 years of treatment amongst over five thousand children commenced on first line ART.<sup>8</sup> The cumulative probability of immunologic failure at 3 years, defined according to South African guidelines was 12.6%. Another treatment centre situated at a level 3 facility in Soweto, South Africa looked at ART responses amongst children attending the outpatient clinic.<sup>9</sup> ART was initiated in slightly older children with a median age of 4.3 years compared to those in hospital settings, which tend to provide treatment to much younger children who already have severe disease progression. The mean CD4% increased from 12.7% at baseline to 25.1% within 12 months of initiating treatment and subsequently continued to increase to reach 30.6% by 36 months. This change in CD4% occurred at a faster rate in children less than 18 months of age. 84% of children initiated on ART achieved virologic suppression by 12 months and 96% by 24 months. The rate of mortality was only 4.2 deaths per 100 child-years which is again less pronounced than in-hospital mortality rates<sup>10</sup> reflecting the more stable and less immunocompromised nature of children attending outpatient clinics. The proportion of children experiencing virologic rebound after initial suppression increased progressively over time from 1.3% at 6 months, to 11.6% and 16.3% at 24 and 36 months respectively. Concomitant TB treatment, especially among children < 3 years receiving a Lopinavir/Ritonavir-based regimen was associated with an increased hazard of viral rebound. This could be explained by the drug interaction between rifampicin-containing TB treatment and the protease inhibitors. Children  $\geq$  3 years receiving an Efavirenz-based regimen were less likely to experience virologic rebound.

There have been two clinical trials focusing mainly on outcomes of ART during infancy rather than older children, published in short succession of each other, with contrasting results. The first, more commonly known as the CHER study reported findings of mean changes in CD4% post-ART initiation, in early and deferred-therapy groups of +5.9% and -5.6% at 6 months and 4.5% and -4.8% at 8 months respectively. The results of this study further suggest that early HIV diagnosis and early initiation of ART in infancy significantly reduces mortality by 76% and HIV disease progression by 75%.<sup>11</sup> In contrast to the CHER study, the Prendergast trial showed the difference in mortality between early and deferred

treatment to be negligible and not statistically significant.<sup>12</sup> This contrast is most probably due to differences in trial designs and sample sizes used across the two studies. The CHER study was a fully-powered randomized controlled trial whereas the Prendergast trial was a pilot randomized controlled trial designed as a feasibility study evaluating three different approaches to ART in HIV-infected children, rather than a study primarily assessing virological responses. Fewer differences were noted across the groups due to low patient numbers. More intensive follow-up and easier access to medical care within the dedicated study setting, could have also accounted for the favourable outcomes obtained across the treatment groups.

LTFU is a common phenomenon found in many paediatric ART programs, especially those in resource-limited settings. LTFU in children proves more challenging compared to adults as children form a more vulnerable group of the population and are largely dependent on caregivers for support and continued care. Caregivers affected by ill health or death often directly influence the outcomes of children on ART. In addition, a substantial proportion of paediatric ART services are located at larger health care facilities situated in urban areas resulting in limited access to care due to increased travelling distances and increased transport costs. The inconvenience of having to attend different clinics compared to respective adult caregivers may also contribute to barriers in care.<sup>13</sup> Data from studies mentioned above have reported rates of LTFU ranging of 8.2%<sup>7</sup> and 7.0%<sup>13</sup> at 1 year and 4.4% at 3 years post-ART initiation.<sup>9</sup> LTFU has also been shown to contribute substantially to an underestimation of mortality rates. Data extracted from the IeDEA-SA collaboration estimated mortality for children remaining in care, to be below 5% but 8.7% in children at a program level across both tertiary and community-based sites, when taking the likely mortality amongst those LTFU into account.<sup>13</sup> This highlights the potential bias of LTFU in mortality estimates.

### **Anthropometric Changes**

Growth failure has been well documented among HIV-infected children not receiving ART.<sup>14,15,16</sup> Poor nutritional status is also highly correlated with a poor prognosis in untreated HIV-infected children.<sup>17</sup> Anthropometric improvement has previously been documented in other African cohorts in response to ART.<sup>18</sup> A prospective study of a cohort of HIV-infected children commencing ART at the King Edward VIII Hospital in Durban, South Africa revealed a significant improvement of mean WAZ and HAZ by 0.86 and 1.37 respectively, over a 2 year period.<sup>19</sup> The steepest increase in WAZ was observed within the initial 6 months of ART. On average, almost normal rates of weight gain were achieved by 2 years of treatment. Mean HAZ showed a more gradual increase with the greatest increase being observed in the second year of treatment. Although improvements in HAZ were noted, children who manifested stunting at baseline continued to have significantly lower HAZ 2 years after ART initiation possibly reflecting the role of altered hormone milieu early on, attributed to chronic malnutrition and co-infections associated with untreated HIV infection. Similarly, findings published in an analysis looking at growth responses to ART over a 3 year period, reported a rapid increase in WAZ and WHZ scores within the first year with significant tapering or reversal thereafter. HAZ scores comparatively, showed a more

gradual increase which persisted over time.<sup>20</sup> Another study conducted at a clinic in Soweto, South Africa showed that 81% of underweight HIV-infected children achieved normal weight recovery within 2 years of initiating ART.<sup>21</sup> Kaplan-Meier estimates suggested that younger children who were severely underweight at the start of ART were more likely to achieve recovery to normal weight bands compared to older children. Only 64% of stunted children achieved height recovery within the first 2 years of ART once again suggesting that a sizeable proportion of children do not achieve adequate stature improvement during the early stages of ART. The more severe the degree of stunting at ART initiation, the less likely was recovery to a normal height. Older children (older than 35 months) were less likely to achieve recovery to a normal height than younger children. A severe degree of immunosuppression at ART initiation did appear to influence growth recovery. Data collected and analysed from the Rahima Moosa Mother and Child Hospital in Johannesburg reported similar findings with regards to younger children experiencing more rapid increases in WAZ and HAZ as compared to older children, especially if ART was initiated during the first 6 months of life.<sup>22</sup>

### **Neurodevelopmental Outcomes with Early ART**

Neurodevelopmental delay is a well-documented phenomenon occurring commonly in HIV-infected children not receiving ART. Early ART initiation has been shown to significantly improve neurodevelopmental outcomes in HIV-infected children.<sup>23</sup> In a sub-analysis of the CHER study, better short-term outcomes were experienced by children who start ART at an early stage compared to those in whom treatment was deferred. A comparison of mean scores on the Griffiths Mental Development Scales shows that all scores were lower in the deferred group compared to the early ART group. General and locomotor scores were significantly lower. Most scores in the early ART group were comparable to those in the HIV-uninfected (HIV-exposed and HIV-unexposed) groups. The only exception was the locomotor scores wherein the HIV-exposed uninfected group performed better than the early ART group.

In another study conducted at a tertiary centre in Cape Town no improvement was found in the neurodevelopmental outcomes of children commenced on ART.<sup>24</sup> This study however, looked at children over a shorter follow-up period of 6 months in comparison to the CHER study, which followed up children over a longer time period. Children were also older and had more advanced immunosuppression compared to those in the CHER study. Forty-four percent and 56% had Centre for Disease Control (CDC) clinical category B and C disease respectively and 92%, severe immunosuppression. As a result, neurological and cognitive deficits were already present prior to the onset of ART. Non-reversal of deficits subsequent to initiation of ART, were thought to be due to arrested encephalopathy and persistent poor socio-demographic factors.

### **Incidence of Otorrhoea with Early ART**

Otorrhoea, commonly associated with chronic suppurative otitis media, is classified as a WHO stage 2 event for HIV-infected children. It's particularly associated with impaired hearing and ultimately affects comprehension, language skills and development especially in

those of a school-going age. Another sub-analysis of the CHER study looked at the role of early ART in reducing the incidence of otorrhoea.<sup>25</sup> Early ART was associated with significantly less otorrhoea compared to deferred treatment initiation. Those in the deferred group had 3 times the risk of developing otorrhoea compared to those receiving early treatment.

### **Effect of ART on the Risk of Incident Tuberculosis**

Tuberculosis (TB) is a condition commonly associated with HIV infection. Although difficult to definitively diagnose, especially in HIV-infected children, it has been estimated that children aged 0-14 years constitute between 16% and 21% of all TB notifications in settings carrying a high burden of disease.<sup>26</sup> In a multi-centre retrospective cohort study of HIV-infected children in South Africa, the incidence of any TB episode per 100 person-years before ART initiation was 16.4 compared to 6.3 in children on ART.<sup>27</sup> ART was associated with a 70% reduction in risk of all-case incident childhood TB and a strongly protective effect in incident, culture confirmed TB. Increasing age and increasing CD4% were also protective against TB. For each year of age increase, an 11% and 17% reduction in risk for all cases of TB and culture confirmed cases of TB respectively was noted. For every percentage increase in CD4%, a 0.04% reduction in risk was observed. Due to the low yield of smear positive and culture confirmed TB and the inability to definitively diagnose TB in children these results may in fact underestimate the burden of disease in HIV-infected children. Disease prevalence and incidence may be higher than what was observed in the context of this study.

### **Immune Reconstitution Inflammatory Syndrome**

Immune reconstitution inflammatory syndrome (IRIS) is a condition associated with those initiating ART on a background of advanced HIV disease and low pre-treatment CD4 cell percentages / counts. In 2009, results of a prospective cohort of HIV-infected children under 2 years initiating ART were analysed.<sup>28</sup> Twenty-one percent of children developed some degree of IRIS. Seventy-three and a half percent manifested symptoms within 30 days of initiating ART. Fourteen point eight percent of the total treatment cohort and 70.6% of those who developed IRIS, experienced BCG-related (bacille Calmette-Guerin) complications which is higher than reported in other studies.<sup>11</sup> Risk factors included younger children, lower pre-treatment CD4 cell percentages, higher pre-treatment viral loads and lower WAZ scores. Children with IRIS were less likely to achieve viral suppression after 24 weeks of treatment compared to those who did not manifest symptoms. Eight point eight percent of those who developed IRIS died. The CHER study more recently looked at the effect of early ART initiation on reducing the risk of BCG immune reconstitution adenitis.<sup>29</sup> The rate of BCG-IRIS reported was far lower than reported in the above findings, with only 8.7% of children developing symptoms within 6 months after ART initiation. Early initiation of ART, prior to immune suppression and HIV disease progression was again associated with a reduction in risk of BCG-IRIS.

## **Treatment Outcomes of Adolescents**

Little is known about treatment outcomes of HIV-infected adolescents, particularly those between 15 and 19 years of age. Adolescence in itself is a challenging time where risk-taking behaviour, experimentation and peer-influenced behaviour predominates. Management of infected adolescents becomes complex and challenging as many psychosocial factors come into play. Data from well-resourced countries, have found low rates of ART adherence and increased risk of virological failure, LTFU and death in HIV-infected adolescents on ART.<sup>30, 31, 32</sup> One of the few studies performed in South Africa, looked at data extracted from a well established peri-urban clinic in Cape Town comparing treatment outcomes of adolescents aged 9 and 19 years, to those of young adults aged 20 and 28 years.<sup>33</sup> Adolescents had lower rates of virologic suppression at 48 weeks than young adults (27.3% and 63.1% respectively) as well as increased rates of treatment failure (8.2 and 5.0 per 100 person-years respectively), in keeping with results of previous studies. In a sub-analysis of perinatally infected adolescents and all infected young adults, similar rates of virologic suppression were obtained. Rates of failure however, though higher in the perinatally infected adolescent group, were less marked compared the adolescent group as a whole. The route of infection in young adults was not documented so direct comparisons of perinatally infected adolescents and young adults could not be made. Median changes in CD4 count at 48 weeks however, were significantly greater for adolescents than for young adults (373 versus 187 cells/L). Surprisingly, there were no significant differences in LTFU or mortality between the two groups even though adolescence is associated with adverse behavior patterns. Another study looked at records from HIV-1 infected adults and non-perinatally infected adolescents across 9 countries in Southern Africa.<sup>34</sup> Significantly fewer adolescents achieved 100% adherence at 6, 12 and 24 month follow-up periods compared to the adult group. Adolescents who achieved viral load suppression, had a significantly shorter time interval to viral rebound. Adolescents were also less likely to experience long-term immunologic recovery, regardless of initial CD4 counts.

## **Impact of ART Initiation at Primary, Secondary and Tertiary Health Care Facilities on Clinical Outcomes**

Primary/district, secondary and tertiary level health care institutions each have different experiences with regards to management and outcomes of HIV infection in paediatric populations. Little data exists comparing clinical outcomes of HIV-infected children on ART, across these different levels of care. In 2008 a retrospective review of all children started on ART in the Western Cape Province, South Africa looked at outcomes between 2004 and 2006.<sup>10</sup> Increased mortality was found at level 2 and 3 hospital facilities with estimated cumulative death rates being higher at 6, 12 and 18 months, post-ART initiation. This phenomenon was most probably reflective of the natural recruitment of sicker patients requiring more specialised and intensive care at a regional and tertiary level. Rates of LTFU were similar across all levels of care. No significant differences between viral load suppression rates and CD4% increases of >20%, across different levels of care were found suggesting that HIV-infected children receiving ART with uncomplicated disease, can be effectively managed at a basic level of care. In 2000, a study conducted at a major tertiary

hospital in Johannesburg, South Africa looked at the contribution of paediatric HIV infection to in-hospital mortality rates over a 4 year period.<sup>35</sup> These results reflect the state of paediatric HIV infection before the introduction of ART. In those above 15 months of age, who were tested for HIV, 4.9% tested positive in 1992 and 35% in 1996, suggesting an increasing trend in the number of incident paediatric HIV infected cases detected. In children under 15 months of age, 9% tested positive in 1992 and 46% in 1996. A larger proportion of infected children (16.9%) died within the first year of life in comparison to uninfected and untested children (6.4 and 3.7% respectively). The proportion of hospital deaths occurring in children diagnosed with HIV infection significantly increased from 6.7% in 1992 to 46.1% in 1996 thereby emphasizing the rapid degree of disease progression and associated comorbidity in the absence of ART. Comparatively, a study performed at the same tertiary institute approximately 10 years later surprisingly revealed very similar findings, even after the onset of the national PMTCT (Post Mother to Child Transmission) programmes and ART roll-out in South Africa in 2004.<sup>36</sup> Missed opportunities for prevention of mother-to-child transmission (PMTCT), delayed HIV diagnosis and delayed ART initiation reflecting programmatic failures, were all thought to contribute to these persistently high rates of infection in children. Delayed HIV PCR (Polymerase Chain Reaction) testing occurred in 87.5% of infants between the ages of 6 weeks and 6 months. Of this group, 45.6% received no PMTCT intervention at all, prior to diagnosis. As was reported in previous studies, the highest case fatality rate was seen in infants less than 12 months. More recently however, the same tertiary institute revealed more promising results with HIV prevalence among inpatients dropping from 26.2% in 1996 to 19.3% in 2010/2011.<sup>37</sup> Rates of mortality also appeared to drop from 46.1% in 1996 to 12.3% in 2010/2011. The drop in prevalence and mortality probably reflects improved PMTCT coverage, early HIV testing and wider ART coverage in HIV exposed and HIV infected children.

### **Outcomes in Rural versus Urban Settings**

A large proportion of HIV-infected children in South Africa live in rural settings characterised by inadequate housing, poor sanitation low rates of literacy, inadequate vaccinations and limited access to health care services. Little data exists describing the outcomes of these children after ART initiation. A retrospective cohort study was published in 2010 looking at the comparison of outcomes of HIV-infected children after initiation of ART, in rural and urban health care settings in four provinces across South Africa.<sup>38</sup> At baseline, children starting ART in rural settings were older, had the lowest median baseline CD4 percentage reflecting a more advanced state of immunosuppression and the lowest mean baseline WAZ score suggesting a greater degree of wasting. This most probably reflects a delayed access to ART in this group of children. Mortality after 24 months of starting ART was significantly higher in the rural group and showed the greatest peak between all groups, during the first 6 months of treatment. Kaplan-Meier estimates showed a 2.41 increased probability of mortality in rural versus urban children, after adjusting for baseline demographic and clinical variables. Rates of loss to follow up (LTFU) were highest in rural children travelling to urban settings which was probably a reflection of increased travelling

distances to urban health care facilities, lack of transportation and financial constraints. These results highlight the relative vulnerability of children treated in rural settings

### **Research Gaps Still to be Addressed**

Although advances have been made in understanding the natural progression of HIV-infection in children as well as the effect of ART on their immunologic, virologic and clinical outcomes at both a national and global level, many aspects of treatment are still incompletely understood. The following are a gaps in knowledge identified within a South African context, whilst performing this literature review:

1. The immunologic, virologic and clinical outcomes of children transferred out to health care facilities other than the site of ART initiation and the effect it has on rates of mortality and loss to follow up.
2. The long-term (> 4 years) effect of ART on anthropometric measures in HIV-infected children including the effect hormonal changes during puberty and adolescence with respect to growth trends and catch-up growth.
3. Long-term neurodevelopmental outcomes and cognitive function of peri-natally infected children started on ART early on in life.
4. The long-term effect of chronic otorrhoea on hearing / speech / comprehension and development in HIV-infected children.
5. Treatment outcomes of adolescents, particularly those between 15 and 19 years of age.
6. Treatment outcomes of children started on ART at different levels of care within a tertiary health care setting.
7. The effect of ART on incidence and spectrum of opportunistic infection.

The following analysis, attempts to bridge the gap in knowledge on treatment outcomes of children initiated on ART at different levels of care within a tertiary level hospital and to assess the impact of these different levels of care on short term clinical outcomes.

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## PART C: DISSERTATION

### ABSTRACT

#### **Short term treatment outcomes of children starting ART in the ICU, general medical wards and outpatient HIV department at Red Cross War Memorial Children's Hospital (RCWMCH): A Retrospective Cohort Study**

Vashini Pillay, Mary-Ann Davies, Spasina King, Brian Eley

**Background:** Many HIV-infected children are initiated on ART during hospitalisation in South Africa. No published data on these outcomes exist.

**Objectives:** We assessed the short-term outcomes of children initiated on ART in the intensive care unit (ICU), general medical wards (GMWs) and outpatient HIV clinics (OHCs) at RCWMCH.

**Methods:** We conducted a retrospective cohort study of HIV-infected children <13 years of age, commenced on first line ART between January 2008 and December 2011 at Red Cross War Memorial Children's Hospital. Outcome measures included death, virologic suppression and changes in CD4 count and percentage. Kaplan-Meier estimates, multivariate Cox proportional hazard ratios and logistic regression were used to estimate outcomes 6 months after ART initiation.

**Results:** Seven hundred and forty-nine children were included: 106 were commenced on ART in the ICU, 509 in the GMWs and 127 in the OHCs. Sixty-five point seven percent of all children were <12 months. Children in the ICU and GMW cohorts were significantly younger than the OHC cohort (median ages: 3 and 5 months respectively vs. 22 months) and had lower WAZ scores (-2.48 and -2.33 respectively vs -1.14). One hundred and eighty two (24.9%) children qualifying for rapid ART initiation according to the 2013 national Standard Treatment Guidelines were commenced on therapy. Overall mortality was 6.4% (CI: 4.9 - 8.4). Mortality was significantly higher in the ICU cohort i.e. 14 (13.2%) compared to 28 (5.5%) and 5 (3.9%) deaths in the GMWs and OHCs cohorts, logrank  $p=0.004$ . Predictors of mortality included being moderately underweight HR 2.4 (CI: 1.1 – 5.2), severely underweight HR 3.2 (CI: 1.6 – 6.5), absence of caregiver counselling sessions HR 2.9 (CI: 1.4 – 6.0) and ART initiation in ICU HR 2.6 (CI: 1.4 – 4.9).

**Conclusion:** These findings serve as a basis for understanding the implications of ART initiation in children during hospitalisation.

## DISSERTATION

### **Background**

Without antiretroviral therapy (ART) HIV infection progresses rapidly in children in low and middle income countries (LMICs). The majority of infected children have manifested with clinical features of HIV infection by 12 months of age.<sup>[1-4]</sup> A pooled analysis looking at mortality in HIV-infected children living in Africa showed that without optimal therapy 35.2% and 52.5% died by 12 and 24 months of age, respectively.<sup>[5]</sup> Infants who are perinatally infected are particularly vulnerable. Mortality at 12 months post-infection was shown to be almost twice as high in perinatally infected children compared to postnatally infected children (52% versus 26%) in the absence of ART.<sup>[6]</sup> Reliable CD4 count and percentage predictors of disease progression have not been identified among HIV-infected infants.<sup>[4,7]</sup>

The CHER Study showed that if ART was commenced during the first 3 months of life in predominantly asymptomatic HIV-infected infants with limited immunological suppression, mortality risk was reduced by 76% and disease progression by 75%.<sup>[8]</sup> Consequently treatment programs in LMICs have progressively increased access to universal ART for infected children. In April 2008 the World Health Organization (WHO) recommended ART for all HIV-infected children under 12 months of age irrespective of CD4 thresholds and WHO clinical stage.<sup>[9]</sup> In July 2010 this directive was extended to all HIV-infected children under the age of 24 months and in July 2013 universal ART was recommended for all HIV-infected children under 5 years of age.<sup>[10,11]</sup> In South Africa, ART for all HIV-infected children under the age of 12 months was implemented in December 2009.<sup>[12]</sup> In March 2013, this policy was extended to all HIV-infected children under 5 years of age, and in addition, expedited initiation of ART within 7 days of HIV diagnosis was recommended for all children under the age of 12 months as well as for children more than 12 months of age with WHO stage 4 disease and / or a CD4 count  $< 200 \text{ cells/mm}^3$  or  $< 15\%$ .<sup>[13]</sup>

Although these policy changes have encouraged increased access to ART, treatment coverage among HIV-infected children has remained relatively low in South Africa resulting in high hospitalisation rates among HIV-infected children due to severe co-morbidity. At the end of 2012, an estimated 63% of 220,000 children  $< 15$  years of age who required therapy were actually receiving ART in South Africa.<sup>[14]</sup> At Chris Hani Baragwanath Hospital despite significant decline in HIV prevalence and inpatient mortality among all children hospitalised from 1996 onwards, 18.4% of all children admitted to that hospital in 2010 – 2011 were HIV-infected, many of whom were ART-naïve.<sup>[15]</sup> Similarly, at Red Cross War Memorial Children's Hospital (RCWMCH) HIV prevalence among children admitted to the general paediatric wards declined from 27.6% in 2007 to 17.9% in 2010.<sup>[16,17]</sup> The majority of HIV-infected children requiring hospitalisation at RCWMCH are ART-naïve infants, including many young infants. The median age of 1360 children initiated on ART at the hospital over a 6-year period was 8 months and 25% were  $\leq 3$  months of age.<sup>[18]</sup> Because the majority of HIV-infected children hospitalized at RCWMCH are infants with severe co-morbidity, initiating ART during hospitalisation is a common clinical practice at RCWMCH.<sup>[19]</sup> In

contrast, in 2011 Chris Hani Baragwanath Hospital reported that only 4.1% of ART-naïve children, eligible for treatment over a 2 month period in 2007 were actually initiated on ART during hospitalisation.<sup>[20]</sup> ART coverage during hospital admission was therefore low despite it being an established paediatric ART service. Most publications of paediatric ART outcomes focus on children started on ART in outpatient clinics. With the advent of the 2013 national guidelines, especially the recommendation to expedite ART initiation for all infants as well as children with severe clinical or immunological disease, it is likely that larger numbers of young, HIV-infected infants and children at other health care facilities across South Africa are being initiated on ART during hospitalisation. No published local studies have however, reported the outcomes of children initiated on ART during hospitalisation. To address this question, we undertook the present study in which the short term outcomes of children initiated on ART in the intensive care unit (ICU), general medical wards (GMWs) and outpatient HIV clinics (OHCs) at RCWMCH were described.

## **Methods**

### **Study location**

This study was undertaken at RCWMCH, a tertiary referral hospital in Cape Town, South Africa, dedicated to the care of children up to 13 years of age. The hospital provides inpatient care, intensive care and outpatient follow-up for HIV-infected children.

### **Study design, inclusion criteria & baseline data collection**

A retrospective cohort study was conducted. Children qualified for inclusion if they were less than 13 years of age and commenced on first-line ART between January 2008 and December 2011 at RCWMCH. A list of all children receiving ART during the study period was extracted from a Microsoft Access Database containing information on children treated with ART at RCWMCH. Children meeting the inclusion criteria were identified and data relating to their ART history was retrieved. Additional baseline patient clinical information and maternal information including counselling practices were, extracted retrospectively from patient hospital records. Data collected prior to starting ART included age, gender, CD4 percentage and absolute count, plasma HIV RNA concentration (viral load), body mass and length / height, WHO clinical stage, the presence or absence of active tuberculosis and the time interval between HIV diagnosis and ART initiation. Age was grouped into one of 4 categories: <3 months, 3 - 12 months, 13 - 60 months and >60 months. Mass and length/height measurements were transformed into weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ) and weight-for-height z-scores (WHZ) using WHO 2006 Child Growth Standards.<sup>[21]</sup> Moderate underweight, stunting and wasting were defined as WAZ, HAZ and WHZ between -2 and -3, respectively. Severe underweight, stunting and wasting were defined as WAZ, HAZ and WHZ below -3, respectively. Baseline primary and secondary co-morbidities as well as the degree of medical intervention required were used to describe the severity of illness prior to ART initiation. Patients were stratified into one of three groups based on the site of ART initiation i.e. during ICU admission, GMW admission

or an OHC visit. Primary baseline clinical conditions were defined as the disease process that most likely contributed to the respective hospital admission and was determined by the attending clinician on duty. Extrapulmonary tuberculosis (EPTB) for the purpose of this analysis has been defined as a patient with tuberculosis involving organs other than the lungs such as pleura, pericardium, lymph nodes, abdomen, joints and bones and meninges.

Counselling of caregivers by trained paediatric ART counsellors prior to ART initiation is usually practiced at RCWMCH. The primary aim is to equip caregivers with the knowledge and skills needed to provide treatment to their children. Three counselling sessions, each covering different aspects of the disease process, practical issues around treatment as well as a formal demonstration in administering ART to respective patients, are performed prior to and during the course of ART initiation. These sessions are formally documented on a prescribed checklist.

### **Study outcomes**

Outcome measures included death, loss to follow-up (LTFU), attrition, virological suppression and changes in CD4 count and percentage. Outcomes were evaluated at 6 months using the measure taken closest to 6 months after initiation within a window of three to nine months after ART initiation. Loss to follow-up was defined as failure to attend a follow-up visit within three months after the last scheduled appointment was missed. Attrition was defined as a combination of patients who had died and those who were LTFU during the study period. Two cut-off values were used to define virological suppression (i.e. a plasma HIV RNA concentration (viral load) <400 copies/mL or <50 copies/mL) in order to reflect the sensitivities of different viral load assays used in low resource countries. HIV RNA measurements were performed using Abbott Realtime HIV-1 assay.<sup>[22]</sup> CD4 measurements were performed by the PanLeucogated method.<sup>[23]</sup>

### **Statistical Analysis**

Pre-ART continuous variables were non-normally distributed and therefore compared using the Kruskal-Wallis test. Frequencies and proportions were used to describe pre-treatment categorical variables. Chi-squared test of association or Fisher's Exact tests were used to assess associations between these variables. CD4 percentage and viral load (VL) results at 6 months were compared to the respective baseline results using the Wilcoxon signed-rank test for paired samples. Kaplan-Meier curves were fitted to estimate mortality, LTFU and attrition probabilities during the first 6 months of ART.

Multivariable Cox proportional hazards regression was used to assess factors associated with mortality, LTFU and attrition during the first six months of ART, adjusting for pre-treatment clinical and demographic variables. Logistic Regression was used to assess factors associated with an unsuppressed VL during the first 6 months of ART i.e. plasma HIV RNA concentration > 400 copies/mL or > 50 copies/mL, adjusting for pre-treatment clinical and demographic variables. Variables with p-values <0.1 on univariate analysis were included in the regression models.

The data was analysed using the STATA Release 12.0 statistical software package (STATA Corp, College Station, USA).

### **Ethical consideration**

The study was conducted in accordance with the Declaration of Helsinki, and was approved by Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town, reference number: HREC REF: 261/2002

### **Results**

In total, 878 children were treated with ART at RCWMCH during the study period. Of these, 129 were excluded from the analysis for the following reasons: 101 children were ART experienced and 28 had been initiated on ART other health care facilities. Data from the remaining 749 children who fulfilled the inclusion criteria were analysed.

### **Baseline Characteristics**

Tables 1 and 2 describe patient and caregiver characteristics prior to ART initiation. Of the 749 included children, 106 (14.5%) were commenced on ART in the ICU, 509 (68.0%) in the GMWs and 127 (17.0%) in OHCs. Seven hundred and thirty-two (97.7%) children would have qualified for expedited initiation of ART according to the 2013 South African national treatment guidelines. Of these, 492 were children < 12 months, 129 were children >12 months with CD4 < 15% and 111 were children >12 months with WHO stage 4 disease. One hundred and eighty-two of the 732 (24.9%) children who would have qualified for expedited initiation were commenced on ART within 7 days of diagnosis. However, 367 (50.1%) were initiated within 7 days of hospital admission and a further 198 (27.0%) within 14 days. Children commenced on ART in the OHCs were significantly older than those in the ICU and GMWs. Overall, 65.7% of all children initiated on ART were <12 months old. The median age at ART initiation was lowest in the ICU cohort. Those in the ICU and GMW cohorts had significantly lower median WAZ scores of -2.48 and -2.33 respectively when compared to those in the OHCs cohort, median WAZ of -1.14 (p=0.0001). Wasting was more frequent in the ICU and GMW cohorts compared to the OHC cohort, although there was no significant difference in the frequency of wasting between these inpatient cohorts. More than 75% of children had sub-normal CD4 percentages of less than 25%, and 385 (51.4%) children had CD4 < 15% and/or CD4 < 200 cells/mm<sup>3</sup>. More children who were initiated on ART in the ICU and GMWs had a baseline VL > 100,000 copies/ml. Younger children, particularly infants, presented with higher viral loads compared to older children. The median VL log<sub>10</sub> value of children < 12 months was 6.0, while the median value of those > 60 months was 4.8 (p=0.001). Overall 24.7% of children had current tuberculosis. Of those, 6.5% had culture confirmed disease and 19.2% probable tuberculosis. Seventy-one point nine percent were treated for pulmonary tuberculosis (PTB) only, 20% for both PTB and EPTB and 8.1% for EPTB only. The time from HIV diagnosis to ART initiation as well as the time from hospital admission to ART initiation was significantly shorter in the ICU cohort. No obvious

differences were noted in caregiver characteristics between the different cohorts prior to ART initiation. Ninety-two point nine percent of caregivers underwent at least 1 counselling session at RCWMCH, while 53 (7.1%) caregivers received none. Of caregivers not receiving counselling sessions, 61.4% were due to lack of caregiver availability during ART initiation, 10.3% were due to patients being transferred out to other health care facilities before counselling sessions could be initiated, 17.2% were counselled during follow-up visits after discharge from hospital and 11.1% had no documentation of reasons counselling sessions were not performed. Table 3 describes the primary diagnoses of children admitted to the GMWs and ICU prior to ART initiation. Pneumonia was the predominant condition, present in 90.6% and 45.0% of children initiated on ART in the ICU and GMWs respectively.

### **Outcomes at 6 months**

The Kaplan-Meier probability of overall mortality after 6 months of ART was 6.4% (95% CI: 4.9, 8.4). The mortality estimate at 6 months was significantly higher in the ICU cohort i.e. 13.2% (14 deaths) compared to 5.5% (28 deaths) and 3.9% (5 deaths) in the GMW and OHC cohorts, log-rank  $p=0.004$ , Figure 1(a). Of those who died, median time to death after ART initiation was 25 days. Of the deaths in the GMW and ICU cohorts, 38 (90.5%) occurred during the primary hospital admission. 6 (3.1%) children from the GMW cohort, 4 (3.2%) from the OHCs and 4 (2.4%) from the ICU were LTFU by 6 months after starting ART. No statistical differences were found in the probabilities of LTFU (log-rank  $p=0.78$ ) or attrition between the three groups, log-rank  $p=0.12$ , Figure 1(b).

After 6 months of ART, 51.0% of children remaining in care at RCWMCH had achieved a  $CD4\% \geq 25\%$  and 62.3% a viral load  $\leq 50$  copies/mL. Paired analyses documented a significantly greater increase in median  $CD4\%$  over the first 6 months of ART among children initiated on ART in the ICU, but similar, substantial declines in the median  $\log_{10}$  VL values among the three treatment cohorts. The proportion of children achieving virologic suppression was significantly lower in the ICU cohort (Table 4).

Of the 749 patients analysed, 257 were transferred out to primary health care facilities for continuation of care, within 6 months of ART initiation. Where possible,  $CD4$  and viral load results after transfer-out were obtained from the Western Cape Provincial laboratory database. Of those transferred out, 142 (55.3%) had  $CD4$  count results and 109 (42.4%) had VL results available 6 months after ART initiation. Paired analyses showed no significant differences in  $CD4$  and VL log values at 6 months in those who were transferred out compared to those who remained in care at RCWMCH. Median increases in  $CD4\%$  at 6 months in those transferred out and in those who remained in care were 4.0 and 5.8 respectively ( $p=0.165$ ). Median decreases in VL log values at 6 months in those transferred out and in those who remained in care were 4.4 and 4.6 respectively ( $p=0.33$ ) with no significant differences being found in proportions of children achieving virologic suppression. Of patients who were transferred out, 10 (3.9%) were LTFU and 9 (3.5%) died. Outcomes of those transferred out were determined using linkage with the Western Cape Provincial laboratory database and folder reviews. Mortality ascertainment was based on documented death in the RCWMCH folder, usually after representing and being admitted to

RCWMCH. Children who had specimen results of any nature recorded on the National Health Laboratory Service (NHLS) database at 6 months post-ART initiation were considered alive. Children with no record of specimen results post-transfer out and who were not documented to have died by 31<sup>st</sup> March 2013 were assumed LTFU.

### **Predictors of mortality, attrition and an unsuppressed viral load**

The multivariate analysis examining factors that influenced mortality (Table 5) within 6 months of ART initiation revealed the following: children under 3 months of age had a 1.8 fold (CI: 0.97 – 3.4 ; p= 0.07) increase in mortality compared to older children. Severely malnourished and moderately malnourished children had an increased hazard ratio of 3.2 (CI: 1.6 – 6.5; p=0.001) and 2.4 (CI: 1.1 – 5.2; p=0.02) respectively compared to those who had mild-normal nutrition. Children of caregivers who had received no counselling sessions prior to and during initiation of ART also had a significantly higher risk of experiencing death compared to those children who's caregivers had received counselling (2.9 HR ; CI: 1.4 – 6.0 ; p=0.005). Children initiated on ART in the ICU had a 2.6 increased hazard of death (CI: 1.4 – 4.9; p=0.003) compared to those in the GMW and OHC groups. Children with caregivers who were not on ART at baseline, had a decreased hazard of death (0.5 HR; CI: 0.3 – 0.9; p=0.02).

Regression modelling of those children who were LTFU within 6 months of ART initiation revealed that age was the only variable associated with LTFU; children between the ages of 3 and 12 months had a 3.16 increased risk of LTFU (CI: 1.2 – 8.1 ; p=0.02) compared to older children.

Factors influencing attrition (Table 6) within 6 months of ART initiation included patient age, WAZ scores, number of caregiver counselling sessions and caregivers who were on ART at baseline. Older children between the ages of 13 and 60 months had a decreased hazard of attrition (0.5 HR; CI: 0.2 – 1.1; 0.08). Children who were severely malnourished and children who had caregivers who did not receive any counselling sessions were at increased risk of attrition (1.8 HR; CI: 1.1 – 2.8; p=0.02 and 2.6 HR; CI: 1.4 – 5.0; p=0.003 respectively).

Logistic Regression looking at factors predicting failure to suppress after 6 months of ART (Table 7) revealed the following: For both VL outcomes (VL > 50 copies/ml and VL > 400 copies/ml), age was the major determinant in predicting failure to suppress. Younger children were significantly less likely to suppress after 6 months of ART in both groups - 35.8% of children under 12 months and 15.9% of children over 12 months did not achieve a viral load <400 copies/mL within 6 months of ART start. In comparison to children >12 months old at ART start, children under 3 months of age had a 3.1 fold increased risk of a VL > 50 copies/ml (CI: 1.8 – 5.3; p=0.001), while children between 3 and 12 months of age had a 2.6 fold increased risk of a VL > 50 copies/ml (CI: 1.3 – 4.9; p=0.005) after adjusting for other predictors of virologic response. Similarly, children under 3 months of age had a 3.0 fold increased risk of a VL > 400 copies/ml (CI: 1.5 – 5.9; p=0.002) while children between 3

and 12 months of age had a 2.6 increased risk of a VL > 400 copies/ml (CI: 1.4 – 4.6; p=0.002).

## **Discussion**

Our study shows that young ART naïve HIV-infected children are still very much at risk for HIV-related morbidity and mortality, particularly those under the age of 3 months. The majority of children initiating ART at RCWMCH were <12 months old; 85.4% had WHO Stage 3 or 4 disease and 75.7% were immunocompromised (CD4 < 25%) at presentation to hospital. Nevertheless, our study demonstrates that it was feasible to initiate ART rapidly after admission even in sick children in our setting, with mortality of 6.4% overall and <15% even in the sickest children where ART was started in ICU. In addition, LTFU was <5% among all groups of children. While most children experienced immune recovery, the low proportion with virologic suppression by 6 months after ART start, especially among infants is a concern.

The severity of illness at ART start is consistent with an analysis of infants <3 months of age initiating ART across twenty public clinics in Cape Town and the ART service at the Chris Hani Baragwanath Hospital in Soweto between June 2007 and September 2010. Although the median age of children starting ART was 8.4 weeks; 62% of infants already had advanced HIV disease (CD4% < 25% or absolute CD4 < 1500 cells/mm<sup>3</sup> or WHO clinical Stage 3 or 4, suggesting that ART initiation even as early as 3 months of age may not be sufficient to prevent morbidity and mortality in young children.<sup>[24]</sup> Previous studies have demonstrated that ART initiation in children at more advanced stages of disease, yields poorer clinical and immune recovery and outcomes.<sup>[25,26]</sup> This highlights the need for even earlier HIV testing and diagnosis in infants as well as rapid initiation of ART in those who are infected.

Our finding that 35.8% of children under 12 months and 15.9% of children over 12 months did not achieve a viral load <400 copies/mL within 6 months of ART start is consistent with previous studies. Poor responses in viral load suppression in young children especially those younger than 24 months were described in a Soweto clinic where the cumulative probability of achieving viral load suppression (< 400 copies/mL) by six months after ART initiation, was 59.4%. Children older than 36 months were more likely to achieve virologic suppression at an earlier stage compared to those younger than 36 months.<sup>[27]</sup> Failure to achieve virologic suppression in young children could be attributed to a combination of factors including palatability of drug formulations in young children resulting in poor adherence, high baseline viral loads in vertically HIV-infected infants possibly requiring longer time periods to suppress and choice of first-line ART drug regimens. In 2011, the European Pregnancy and Paediatric HIV Cohort Collaboration analysed data across 13 European countries and found virologic and immunologic responses twelve months after ART initiation, to be superior using a 4-drug NNRTI-based regimen compared to a boosted PI-based or 3-drug NNRTI regimen.<sup>[28,29]</sup>

Growth failure has been previously documented among HIV-infected children not receiving ART.<sup>[30,31,32]</sup> Poor nutritional status has also been highly correlated with a poor prognosis in untreated HIV-infected children.<sup>[33]</sup> Our results show that moderately and severely underweight children have a significantly increased risk of mortality during the first six months of ART compared to children who are only mildly underweight. More children in the ICU and GMW settings were moderately to severely underweight compared to those children seen in the OHC. This reflects the contribution a poor nutritional status prior to ART initiation has, on the clinical condition of children requiring admission to a tertiary level health care facility.

Before the advent of ART, the majority of HIV-infected children in our setting required hospital admission to ICU facilities before reaching 6 months of age.<sup>[34]</sup> Mortality was high in the absence of ART, with rates of 27% and 44% being documented at the RCWMCH and Tygerberg Hospital in Cape Town, respectively. Since the introduction of ART in children, mortality has decreased substantially. Our study reports a mortality probability of 13.2% in children infected with HIV, admitted to the ICU and subsequently commenced on ART, which although is significantly higher than those in the GMW and OHC's, is approximately half of previously reported hospital mortality in children not receiving ART. This could be due to a combination of factors including increased early HIV diagnosis and ART initiation resulting in children admitted to ICU being relatively less ill than those admitted in the pre-ART era. That being said, children requiring ICU care at admission, even during the era of ART are more ill on presentation to hospital which probably influences the clinical, immunologic and virologic outcomes and possibly explains the increased mortality rate compared to the GMW's and OHC's. Our study reports that 90.6% of children admitted to ICU had an associated severe pneumonia requiring some level of assisted ventilation highlighting the severity of disease on presentation to hospital. Severity of baseline clinical conditions have previously been of concern in relation to potential drug toxicity in the setting of multi-organ failure.<sup>[34]</sup> Our results do therefore suggest that ART may have played a role in lowering ICU mortality. Other factors possibly leading to improved outcomes include increased awareness and experience in managing ill HIV-infected children as well as improved treatment practices. The exact nature and impact of these factors have, however, yet to be assessed.

A quarter of children presenting to RCWMCH were diagnosed with tuberculosis either before or during presentation to hospital. The majority were commenced on anti-tuberculous treatment prior to ART initiation in keeping with WHO and national guidelines. The median time between initiating tuberculosis treatment and ART overall was 12 days. In those admitted to ICU however, the median time to initiating tuberculosis treatment was 6.5 days after ART initiation. Tuberculosis diagnosis was confirmed in only 6.5% of patients started on anti-tuberculous treatment reflecting the lack of accurate diagnostic tests available in diagnosing tuberculosis in HIV-infected children.

Only 24.9% of children qualifying for expedited ART initiation according to WHO 2013 criteria were commenced within 7 days of diagnosis. This number is low probably due to the fact that we analysed data from Jan 2008 to Dec 2011 and guidelines for expedited initiation

were only implemented after 2013. Also, 152 children were diagnosed outside of RCWMCH, mainly at primary health care facilities. The proportion of children initiated on ART within 7 and 14 days of admission to RCWMCH was 49.0% and 75.4% respectively. South African national guidelines recommend ART initiation within 7 days of diagnosis in young children or in those with advanced disease though this may not prove practical at a program level.

Psychosocial factors contribute substantially to successful outcomes of ART in children, in particular, counselling of caregivers prior to and during the course of ART initiation. Our study demonstrates a greater than two-fold increased risk of mortality and attrition respectively, in the absence of caregiver counselling sessions. As most deaths occurred early and during the current hospital admission in hospitalized patients, lack of counselling is unlikely to have a causal effect on mortality. Indeed, the major reason for caregivers not receiving counselling was lack of caregiver availability during ART initiation, reflecting the likely rapidity of ART initiation in these patients and the challenge of providing counselling when expediting ART.

### **Strengths and Limitations**

The strength of this study lies in its' novel contribution to existing literature in relation to examining the impact of ART initiation at different levels of health care within a tertiary hospital setting. It also provides an accurate reflection of health care function at an operational level in an over-burdened health care system with a high turnover of patients.

Due to this being a retrospective analysis, limitations in availability of routine data such as feeding practices, were found. Due to a high TFO rate of children to other health care facilities after ART initiation, access to follow-up clinical and laboratory data proved challenging. In particular, six month follow-up anthropometric data, viral load and CD4 results were lacking, impeding our ability to accurately reflect on growth patterns, immunologic reconstitution and virologic suppression amongst the original cohort of children initiated on ART at RCWMCH. In general, children transferred out are less ill than those remaining in care. Virologic and immunologic outcomes of the entire cohort initially started on ART could in fact be better than reported, had we complete follow-up data on those transferred out. The results of this study are not generalizable to the general HIV-infected paediatric population as the cohort of children included in this analysis were, by virtue of being admitted to a tertiary health care centre, more ill and displayed more severe forms of disease. The catchment of patients itself, adds a degree of selection bias to this analysis. The study was also restricted to those initiating ART as this was the primary focus. However this limits our ability to assess the feasibility of commencing ART in all severely ill children, some of whom may have died before treatment could be initiated.

Similar studies at tertiary level health care facilities should be performed in order to corroborate our findings and provide a basis for developing and optimising consensus guidelines for managing severely ill HIV-infected infants and children.

### **Conclusion**

These results highlight the importance of understanding the context in which children initiate ART when comparing outcomes in different settings. This study highlights that even with early diagnosis, many infants will already have advanced disease, and ART initiation in these

children may be challenging. While our study demonstrates the feasibility and good mortality outcomes of starting ART in very ill young children, there is a need to develop and optimize consensus guidelines for managing severely ill HIV-infected young infants and children in order to ensure optimal long term outcomes.

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## TABLES, FIGURES & LEGENDS

**Table 1:** Characteristics of HIV-infected children prior to ART initiation

	Overall Patient Baseline Characteristics	Patient Characteristics Stratified According to ART Initiation Location			
		Outpatient HIV clinics	General Medical Wards	ICU	P-value
<b>Age in months</b> (median,IQR)	N=749 5 (3 ; 23)	N=127 22 (5 ; 71)	N=509 5 (3 ; 21)	N=106 3 (3 ; 4)	0.0001
<b>Age categories (%)</b>	N=749	N=127	N=509	N=106	0.0001
<3 months	130 (17.4)	14 (11.0)	90 (17.7)	25 (23.6)	
3-12 months	362 (48.3)	37 (29.1)	247 (48.5)	72 (67.9)	
13-60 months	147 (19.6)	39 (30.7)	102 (20.047)	6 (5.7)	
>60 months	110 (14.7)	37 (29.1)	70 (13.8)	3 (2.8)	
<b>Gender (%)</b>	N=749	N=127	N=510	N=106	0.61
Female	379 (50.6)	60 (47.2)	258 (50.6)	57 (53.8)	
Male	370 (49.4)	67 (52.8)	252 (49.4)	49 (46.2)	
<b>WAZ</b> (median, IQR)	N=700 -2.14 (-3.42 ; -0.95)	N=115 -1.14 (-2.47 ; -0.23)	N=477 -2.33 (-3.56 ; -1.17)	N=102 -2.48 (-3.91 ; -1.37)	0.0001
<b>WAZ categories (%)</b>	N=700	N=115	N=477	N=102	0.0001
Mild-normal	331 (47.3)	82 (71.3)	210 (44.0)	47 (46.1)	
Moderate underweight	141 (20.1)	14 (12.2)	109 (22.9)	17 (16.7)	
Severe underweight	228 (32.6)	19 (16.5)	167 (35.0)	38 (37.3)	
<b>HAZ</b> (median, IQR)	N=525 -2.14 (-3.55 ; -0.95)	N=121 -1.92 (-2.84 ; -0.91)	N=338 -2.16 (-3.7 ; -1.1)	N=61 -2.00 (-3.72 ; -0.2)	0.20
<b>HAZ categories (%)</b>	N=525	N=121	N=338	N=61	0.02
Mild-normal	248 (47.2)	63 (52.1)	153 (45.8)	30 (49.2)	
Moderate stunting	110 (20.1)	34 (28.1)	64 (18.9)	10 (16.4)	
Severe stunting	167 (31.8)	24 (19.8)	120 (35.5)	21 (34.4)	
<b>WHZ</b> (median, IQR)	N=446 -1.2 (-2.61 ; -0.04)	N=83 -0.04 (-1.29 ; 0.8)	N=297 -1.53 (-2.8 ; -0.3)	N=61 -1.37 (-2.82 ; -0.31)	0.0001
<b>WHZ categories (%)</b>	N=446	N=81	N=297	N=61	0.0001
Mild-normal	293 (65.7)	72 (88.9)	180 (60.6)	37 (60.7)	
Moderate wasting	70 (15.7)	7 (8.6)	50 (16.8)	12 (19.7)	
Severe wasting	83 (18.6)	2 (2.5)	67 (22.6)	12 (19.7)	
<b>CD4 percent</b> (median, IQR)	N=742 17.00 (10.0 ; 24.6)	N=127 17.6 (10.4 ; 24.4)	N=509 17.12 (10 ; 25.3)	N=106 14.35 (8.9 ; 22.5)	0.12
<b>CD4 percent (%)</b>	N=742	N=127	N=509	N=106	0.27
1 (>=25%)	180 (24.3)	29 (22.8)	132 (25.9)	19 (17.9)	
2 (<25%)	562 (75.7)	98 (77.2)	377 (74.1)	87 (82.1)	
<b>Viral Load (%)</b>	N=691	N=123	N=465	N=96	0.0001
1 (<100 000)	183 (26.5)	58 (47.2)	109 (23.4)	15 (15.6)	
2 (>100 000)	508 (73.5)	65 (52.9)	356 (76.6)	81 (84.4)	
<b>Staging (%)</b>	N=741	N=127	N=502	N=106	0.0001
Stage 1	39 (5.3)	9 (7.1)	29 (5.8)	1 (1.0)	
Stage 2	62 (8.4)	19 (15.0)	40 (8.0)	3 (2.8)	
Stage 3	258 (34.8)	68 (53.5)	182 (36.3)	6 (5.7)	
Stage 4	382 (51.6)	31 (24.4)	251 (50.0)	96 (90.6)	
<b>TB Disease (%)</b>	N=743	N=127	N=504	N=105	0.0001
None	558 (75.1)	82 (64.6)	380 (75.4)	89 (84.8)	
PTB	133 (17.9)	33 (26.0)	87 (17.3)	6 (5.7)	
EPTB	15 (2.0)	8 (6.3)	10 (1.98)	4 (3.8)	
PTB + EPTB	37 (5.0)	4 (3.1)	27 (5.4)	6 (5.7)	
<b>Time to ART initiation relative to TB rx initiation (days)</b> (median, IQR)	N=173 12 (24 ; 1)	N=43 29 (92 ; 16)	N=114 9 (16 ; 2)	N=16 -6.5 (3 ; -16)	0.0001
<b>Time to ART initiation relative to HIV dx (days)</b> (median, IQR)	N=648 13 (7 ; 38.5)	N=100 48 (26 ; 250.5)	N=445 12 (7 ; 28)	N=97 5 (3 ; 9)	0.0001
<b>Time to ART initiation relative to hospital admission (days)</b> (median, IQR)	N=749 7 (3 ; 11)	N=127 NA	N=510 8 (6 ; 13)	N=106 5 (3 ; 7)	0.0001

\*In table 1 non-normally distributed continuous variables were analysed using the Kruskal- Wallis non-parametric test. The Chi-squared test of association and Fisher's Exact test were used to test associations between categorical variables.

**Table 2:** Characteristics of caregivers of HIV-infected children prior to ART initiation

	Overall Baseline Caregiver Characteristics	Caregiver Characteristics Stratified According to ARV Initiation Location			P-value
		Outpatient HIV clinics	General Medical Wards	ICU	
<b>Reported Maternal HIV Status at ART initiation (%)</b>	N=749	N=127	N=509	N=106	0.1
Positive	540 (72.1)	103 (81.1)	358 (70.3)	72 (67.9)	
Negative	46 (6.1)	4 (3.2)	32 (6.3)	10 (9.4)	
Unknown	163 (21.8)	20 (15.8)	119 (23.4)	24 (22.6)	
<b>Maternal MTCT Prophylaxis (%)</b>	N=749	N=127	N=509	N=106	0.05
Yes	258 (34.5)	43 (33.9)	164 (32.2)	46 (43.4)	
No	353 (47.1)	68 (53.5)	243 (47.7)	40 (37.7)	
Unknown	138 (18.4)	16 (12.6)	102 (20.0)	20 (18.9)	
<b>Maternal ART at ART initiation (%)</b>	N=749	N=127	N=509	N=106	0.33
Yes	98 (13.1)	21 (16.5)	67 (13.2)	9 (8.5)	
No	487 (65.0)	85 (66.9)	325 (63.9)	70 (66.0)	
Unknown	118 (15.7)	10 (7.9)	94 (18.5)	15 (14.2)	
NA	46 (6.1)	11 (8.7)	23 (4.5)	12 (11.1)	
<b>Primary Caregiver Status (%)</b>	N=749	N=127	N=509	N=106	0.004
Mother	647 (86.4)	104 (81.9)	435 (85.8)	101 (95.3)	
Other	69 (9.2)	18 (14.2)	50 (9.9)	1 (0.9)	
None	33 (4.4)	5 (3.9)	24 (3.9)	4 (3.8)	

\*The Chi-squared test of association and Fisher's Exact test were used to test associations between categorical variables.

**Table 3:** Primary diagnosis of children on presentation to hospital

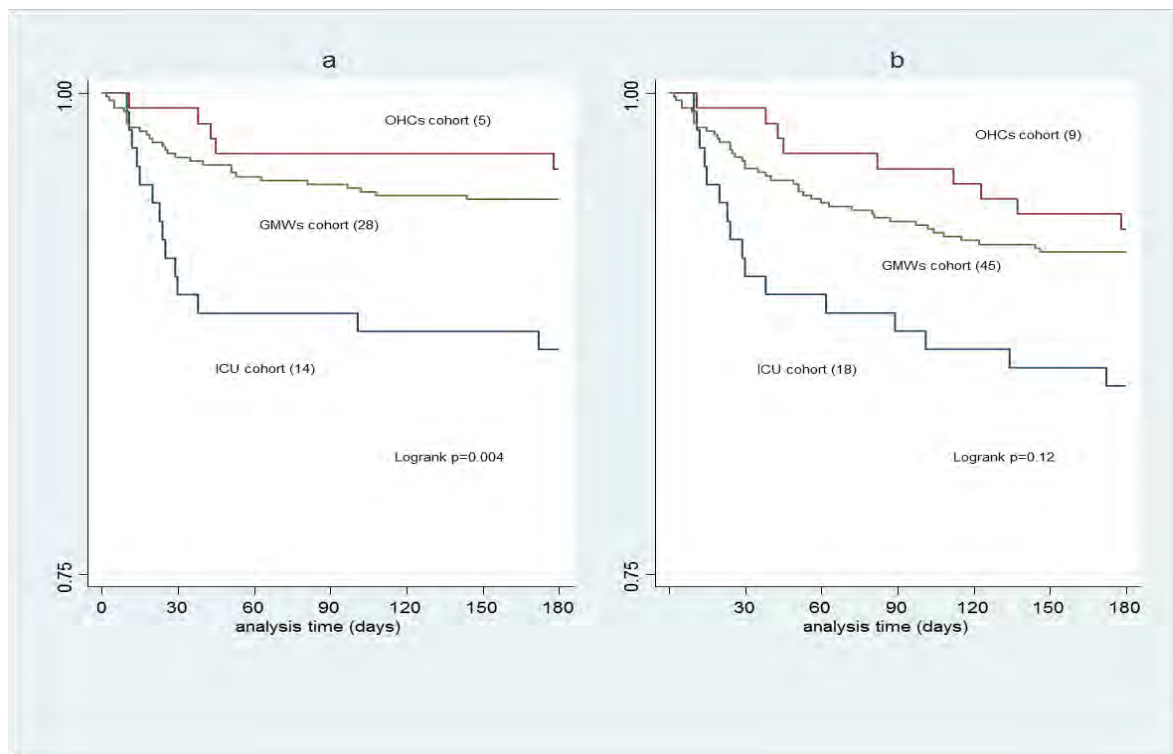
	ICU (N=106)	GMWs (N=509)
<b>Pneumonia</b>	96	229
<b>Gastroenteritis</b>	5	137
<b>Malnutrition</b>	1	33
<b>Septicaemia</b>	1	14
<b>PTB</b>	-	13
<b>EPTB</b>	1	19
<b>Upper Airway Obstruction</b>	-	17
<b>Meningitis</b>	1	11
<b>Non-accidental Injury</b>	-	4
<b>Surgical conditions</b>	1	9
<b>Other Medical Conditions</b>	-	23

**Table 4:** CD4 percentage and viral load responses after 6 months of ART

	GMWs	OHCs	ICU	p-value
<b>CD4 percent at 6 months</b>	N=330	N=99	N=59	0.1
Number (%) with CD4 $\geq$ 25%	158 (47.9%)	55 (55.6%)	36 (61.0%)	
Number (%) with CD4 <25%	172 (52.1%)	44 (44.4%)	23 (39.0%)	
<b>*CD4% change at 6 months</b>	N=320	N=91	N=54	0.001
Median percentage difference (IQR)	4.7 (0.7 ; 11.3)	3.2 (0.1 ; 9.2)	9.1 (4.9 ; 14.7)	
<b>Viral Load at 6 months</b>	N=280	N=93	N=51	0.004
Number (%) $\leq$ 50 copies/mL	171 (61.1%)	69 (74.2%)	24 (47.1%)	0.004
Number (%) $\leq$ 400 copies/mL	198 (70.7%)	75 (80.7%)	32 (62.8%)	0.05
<b>*Log<sub>10</sub> viral load change at 6 months</b>	N=216	N=90	N=39	0.35
Median percentage difference (IQR)	-4.7 (2.9 ; 5.9)	-4.7 (3.8 ; 5.4)	-4.1 (1.5 ; 5.3)	

\*Analyses of the differences between 6 month and baseline CD4% or Log10 viral load values in children with paired specimen results.

**Figure 1:** Kaplan-Meier estimates for outcomes of (a) mortality, n=742 and (b) attrition, n=742 at 6 months, according to ART initiation location



**Table 5:** Predictors of mortality during the first 6 months of ART

	<b>Univariate HR (95% CI) of Mortality</b>	<b>P-value</b>	<b>Adjusted HR (95% CI) of Mortality (N=700)</b>	<b>P-value</b>
<b>Age at ART initiation</b>	(N=749)			
<3 months	1.8 (0.95 – 3.4)	0.07	1.8 (0.9 – 3.4)	0.07
3 – 12 months	1.2 (0.7 – 2.1)	0.59	1	
13 – 60 months	0.5 (0.2 – 1.2)	0.12	1	
>60 months	1		1	
<b>WAZ categories</b>	(N=700)			
Mild-normal	1		1	
Moderate malnutrition	2.3 (1.1 – 4.8)	0.02	2.4 (1.1 – 5.2)	0.02
Severe malnutrition	2.5 (1.3 – 4.9)	0.008	3.2 (1.6 – 6.5)	0.001
<b>Number of Caregiver Counselling Sessions*</b>	(N=749)			
0	3.8 (1.9 – 7.6)	0.0001	2.9 (1.4 – 6.0)	0.005
1	2.7 (0.7 – 11.1)	0.17	1	
2	0.6 (0.1 – 4.1)	0.58	1	
3	1		1	
<b>ART initiation location</b>	(N=742)			
GMW	0.7 (0.4 – 1.2)	0.144	1	
OHC	1		1	
ICU	2.6 (1.4 – 4.9)	0.002	2.6 (1.4 – 4.9)	0.003
<b>Caregiver Support†</b>	(N=749)			
Yes	1		1	
No	1.0 (0.6 – 1.8)	0.95	1	
Not Available	2.5 (1.2 – 5.2)	0.013	2.4 (1.1 – 5.0)	0.02
<b>Maternal ART at ART initiation</b>	(N=749)			
Yes	1.1 (0.5 – 2.5)	0.762	1	
No	0.5 (0.3 – 0.8)	0.011	0.5 (0.3 – 0.9)	0.02
Not Available	2.3 (1.3 – 4.3)	0.005	1	
NA	1		1	

\* Number of counselling sessions received by caregiver prior to or during ART initiation.

† Is there a second caregiver who is able to administer ART to the child in the event of the primary caregiver not being present.

**Table 6:** Predictors of attrition during the first 6 months of ART

Patient Factor	Univariate HR (95% CI) of Attrition	P-value	Adjusted HR (95% CI) of Attrition (N=700)	P-value
<b>Age at ART initiation</b>	(N=749)			
<3 months	1.3 (0.7 – 2.3)	0.4	1	
3 – 12 months	1.6 (0.97 – 2.5)	0.1	1	
13 – 60 months	0.5 (0.2 – 1.0)	0.1	0.5 (0.2 – 1.1)	0.08
>60 months	1		1	
<b>WAZ categories</b>	(N=700)			
Mild-normal	1		1	
Moderate malnutrition	1.2 (0.7 – 2.1)	0.53	1	
Severe malnutrition	1.8 (1.1 – 2.9)	0.014	1.8 (1.1 – 2.8)	0.02
<b>Number of Caregiver Counselling Sessions*</b>	(N=749)			
0	3.1 (1.7 – 5.7)	0.0001	2.6 (1.4 – 5.0)	0.003
1	2.9 (0.9 – 9.3)	0.07	1	
2	1.2 (0.4 – 3.9)	0.72	1	
3	1		1	
<b>Maternal ART at ART initiation</b>	(N=749)			
Yes	1		1	
No	0.7 (0.4 – 1.0)	0.07	1	0.08
Not Available	1.9 (1.1 – 3.1)	0.018	1.6 (0.9 – 2.7)	
NA	1		1	

\* Number of counselling sessions received by caregiver prior to or during ART initiation.

**Table 7:** Predictors of an unsuppressed viral load after 6 months of ART: (a) predictors of viral load > 50 copies/mL and (b) predictors of viral load >400 copies/mL

<b>(a)</b>				
	<b>Univariate OR (95% CI)</b>	<b>P-value</b>	<b>Adjusted OR (95% CI) (N=338)</b>	<b>P-value</b>
<b>Age at ART initiation</b>	(N=429)			
<3 months	1.6 (0.95 – 2.7)	0.078	3.1 (1.8 – 5.3)	0.001
3 – 12 months	2.4 (1.6 – 3.5)	0.001	2.6 (1.3 – 4.9)	0.005
13 – 60 months	0.6 (0.4 – 0.9)	0.029	1	
>60 months	1		1	
<b>Caregiver Support*</b>	(N=429)			
Yes	1		1	
No	0.6 (0.4 – 0.97)	0.039	0.5 (0.3 – 0.9)	0.013
Not Available	0.7 (0.3 – 1.4)	0.298	1	
<b>Maternal ART at ART initiation</b>	(N=429)			
Yes	0.8 (0.5 – 1.4)	0.433	1	
No	1.7 (1.1 – 2.7)	0.012	1	
Not Available	0.4 (0.2 – 0.8)	0.009	0.4 (0.2 – 0.8)	0.011
NA	1		1	
<b>(b)</b>				
	<b>Univariate OR (95% CI)</b>	<b>P-value</b>	<b>Adjusted OR (95% CI) (N=338)</b>	<b>P-value</b>
<b>Age at ART initiation</b>	(N=429)			
<3 months	1.9 (1.1 – 3.3)	0.018	2.95 (1.5 – 5.9)	0.002
3 – 12 months	1.7 (1.1 – 2.7)	0.01	2.6 (1.4 – 4.6)	0.002
13 – 60 months	0.6 (0.4 – 1.1)	0.12	1	
>60 months	1		1	
<b>Caregiver Support*</b>	(N=429)			
Yes	1		1	
No	0.6 (0.4 – 0.97)	0.039	0.5 (0.3 – 0.9)	0.017
Not Available	1.0 (0.5 – 2.3)	0.871	1	
<b>Reported Maternal HIV Status at ART initiation</b>	(N=429)			
Negative	1		1	
Positive	1.8 (1.1 – 3.1)	0.024	1	
Not Available	0.4 (0.2 – 0.7)	0.005	0.3 (0.1 – 0.6)	0.002

\* Is there a second caregiver who is able to administer ART to the child in the event of the primary caregiver not being present.

## PART D: APPENDICES

### 1) DATA CAPTURE FORM

<b>DATA CAPTURE SHEET</b>				
<b>Patient Folder Number</b> <b>Date of Birth</b> <b>Gender</b>				
<b>ADMISSION DETAILS</b>				
<b>Date of admission</b>				
<b>Date of discharge</b>				
<b>Ward</b>	ICU	General Wards	OPD	
<b>Length of stay in general ward (days)</b>				
<i>If admitted to ICU:</i>				
<b>Date of ICU admission</b>				
<b>Indication for ICU admission</b>				
<b>Length of stay in ICU (days)</b>				
<b>Ventilation</b>		Yes		No
<i>If yes, mode of ventilation</i>		CPAP	IPPV	HFOV
<b>Mortality (in hospital)</b>		Yes		No
<i>If yes, date of death</i>				
<i>Cause of death</i>				
<b>PATIENT BASELINE FACTORS</b>				
<b>HIV diagnosis</b>	Date			Site
<b>ARV initiation site</b>	ICU	General Wards	OPD	
<b>ARV start date:</b>				
<b>Age (years):</b>				
<b>CD4 count:</b>		<b>CD4 %:</b>		
<b>Viral Load:</b>				
<b>Stage</b>	1	2	3	4

<b>Weight (kg):</b>		<b>Height (cm):</b>		
<b>Baseline co-morbidity</b>	Primary diagnosis			
	Secondary diagnosis			
<b>TB co-morbidity</b>	Yes		No	
	Definite		Probable	
	Site of disease			
	Complicated	Uncomplicated	TB Meningitis	
Date of treatment initiation				
<b>MATERNAL/CAREGIVER FACTORS (at ARV initiation)</b>				
<b>Age (years):</b>				
<b>Relationship to child</b>				
<b>Literate</b>	Yes		No	
<i>Maternal history</i>				
<b>HIV status</b>	Positive		Negative	Unknown
<b>ARV treatment</b>		Yes		No
<b>MTCT drugs</b>	None	NVP	AZT/NVP	HAART
<b>SOCIAL FACTORS</b>				
<b>Household Disclosure</b>	Yes		No	
<b>Housing</b>	Formal		Informal	
<b>Support</b>	Yes		No	
<b>Income</b>	Yes	R	No	
<b>ARV DRUG REGIMEN</b>				
Stavudine		Abacavir		Lamivudine
Lopinavir/Ritonavir		Efavirenz		Ritonavir
Other:				

<b>CAREGIVER COUSSELLING SESSIONS</b>		
<b>1.</b>	<b>2.</b>	<b>3.</b>
<b>6 MONTH OUTCOMES</b>		
<b>CD4 count:</b>		<b>CD4 %:</b>
<b>Viral Load:</b>		
<b>Weight (kg):</b>		<b>Height (cm):</b>
<b>Loss to Follow-Up</b>	Yes	No
<i>If yes, date of last visit</i>		
<b>Discontinued Treatment</b>	Yes	No
<i>If yes, date treatment stopped</i>		
<b>Mortality</b>	Yes	No
<i>If yes, date of death</i>		
<b>Transferred Out</b>	Yes	No
<i>If yes, date of transfer</i>		
<i>If yes, health care facility transferred out to</i>		

## 2) ETHICAL APPROVAL FROM THE UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

UNIVERSITY OF CAPE TOWN



Research Ethics Committee  
E52 Room 24, Old Main Building Groote  
Schoor Hospital, Observatory, 7925  
Queries : Lamees Emjedi  
Tel : (021) 406-6338 Fax: 406-6411  
E-mail : lemjedi@curie.uct.ac.za

18 July 2003

REC REF: 261/2002

Dr B Eley  
Paediatrics  
Red Cross

Dear Dr Eley

ANTIRETROVIRAL THERAPY-GUIDELINES FOR THE TREATMENT OF A COHORT OF HIV-INFECTED CHILDREN AND THEIR INFECTED PARENTS AT RED CROSS CHILDREN'S HOSPITAL

*Thank you for your letter to the Research Ethics Committee dated 13 July 2003.*

*It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study on the 16 July 2003.*

*Please quote the REC. REF in all your correspondence.*

Yours sincerely

PROF T. ZABOW  
CHAIRPERSON

Signature removed

### 3) SAMJ AUTHOR GUIDELINES



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**Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.**

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Provide evidence of Research Ethics Committee approval of the research where relevant.

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#### **ETHNIC CLASSIFICATION**

References to ethnic classification must indicate the rationale for this.

#### **MANUSCRIPTS**

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

**Research articles** (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

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**Editorials**, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the **SAMJ** peer review process.

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**Obituaries** should be about 400 words and may be accompanied by a photograph.

**Guidelines** must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

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Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - [www.icmje.org](http://www.icmje.org). Manuscripts must be provided in **UK English**.

**Qualification, affiliation and contact details** of ALL authors must be provided in the manuscript and in the online submission process.

**Abbreviations** should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

**Scientific measurements** must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to  $\pm$  and  $^{\circ}$ , i.e. '35 $\pm$ 6' and '19 $^{\circ}$ C'.

**Numbers** should be written as grouped per thousand-units, i.e. 4 000, 22 160...

**Quotes** should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

**General formatting** The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

## ILLUSTRATIONS AND TABLES

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**Book references:** Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975: 96-101. **Chapter/section in a book:** Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974: 457-472.

**Internet references:** World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

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