

**OUTCOMES OF CHILDREN TRANSFERRING OUT OF RED CROSS WAR  
MEMORIAL CHILDREN'S HOSPITAL HIV COHORT USING LINKAGE  
TO THE NATIONAL HEALTH LABORATORY SERVICE DATA**

by

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# PREAMBLE

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## **Declaration**

I, Oluwaseyi Arowosegbe with student number; ARWOLU002 declare that this dissertation is my own work and neither the whole work nor any part of it has been or being submitted for any award of any degree in this University or elsewhere.

Date: 18/03/2017

Place: University of Cape Town

Signed: O.A

## **Abstract**

**Title:** Outcomes of Children Transferring Out of Red Cross War Memorial Children's Hospital HIV Cohort using Linkage to the National Health Laboratory Service Data.

## **Background and Rationale**

Paediatric antiretroviral (ART) care in the Western Cape Province (WCP) has evolved following South Africa's (SA) massive roll-out of antiretroviral therapy in 2004 in response to the country's human immunodeficiency virus (HIV) epidemic. Decentralization of paediatric ART services was adopted in scaling up access to ART services for children living with HIV.

Although children now mainly initiate ART at lower level facilities, sick or very young infants continue to initiate ART at tertiary health facilities and become eligible for transfer to lower level facilities after stabilization at tertiary health facilities. There has been limited assessment of the effectiveness of this model of ART care since its implementation.

## **Aims and Objectives**

The primary objective of this study is to determine the proportion of children that successfully transferred from Red Cross War Memorial Children's Hospital (RCWMCH) to referral facilities for continued ART within 18 or 48 months of their last appointment at RCWMCH. Successful transfer was defined in two ways: a laboratory test performed by a lower level facility (i)  $\leq 18$  months or (ii)  $\leq 48$  months after transfer date. The first interval corresponds to guideline recommendations for annual CD4/viral load monitoring; the second captures all children retained in care.

Our secondary objectives are as follows:

1. To identify the determinants of successful transfer from RCWMCH.

2. To describe the CD4 and viral load outcomes of children that successfully transferred to referral lower health facilities within WCP.
3. To determine the feasibility of using the SA National Health Laboratory Service (NHLS) data for routine monitoring of children transferring between paediatric ART sites.

## **Methods**

A retrospective analysis was performed. The study population was children below the age of 16 years who were initiated onto ART at RCWMCH and transferred out to lower level facilities within the WCP from December 31, 2007 - January 1, 2012. We described children's characteristics before transfer out and post-transfer date. In those who successfully transferred, we compared their immunological and virological status at transfer out and at the first visit within 48 months after the transfer out date, using median change for continuous variables and difference in proportions for categorical variables.

## **Results**

Data from 1127 children with median age of 5.6 months (interquartile range [IQR] 3.1-19.9) was included; at ART initiation 85% had WHO stage III/IV disease and 57% were severely immunosuppressed. A total of 725 (64%) children were transferred; 69% (496) and 76% (541) successfully transferred within 18 and 48 months respectively. Since there is about 90% compliance with annual CD4/viral load monitoring guidelines, we estimate that up to 85% of children may have actually successfully transferred. Median time to successful transfer was 5.4 months (IQR 3.7-7.8). Among the 184 children (25%) who did not transfer successfully, 11% returned to RCWMCH. In patients who successfully transferred, median (IQR) CD4% increased between transfer out and first visit post-transfer [25.1% (17.3-33.8%) vs 30.2% (22.9-36.6%), p-value = 0.0000]. Children who had their transfer sites recorded in the database

and those transferred before 2010 were identified to be associated with successful transfer (adjusted odds ratio (aOR) 7.99, 95% Confidence Interval (CI) (2.3-28.5 and aOR 5.21, 95% CI 1.5-18.4 respectively).

## **Conclusion**

The proportion of children remaining in HIV care by 48 months after transfer out was at least 76% and 92% of those that transferred successfully reached the referral facility and undergoing a laboratory test within 18 months of transfer out. In children who successfully transferred, CD4% and viral load suppression improved after transfer. This suggests that paediatric ART decentralization is feasible with good outcomes. However, outcomes in those who were lost after transfer out need further investigation.

**Part A:** Is the study protocol as submitted for Departmental and Ethical Approval is presented here.

**Part B:** A structured literature review of observational studies conducted in low and middle income countries on the outcomes of patients in decentralized models of ART care is presented.

**Part C:** A journal-ready manuscript according to the requirements of the South African Medical Journal (author's information included as **Appendix E**) is presented.

**Appendices:** Includes all additional documents necessary as addendums in the presentation of this dissertation.

The Vancouver referencing style has been used for Part A and B of this mini-dissertation however, in keeping with the instructions for authors as specified by the South African Medical Journal Part C: The Journal Ready Manuscript includes references in the style recommended by the South African Medical Journal.

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## **List of Abbreviations**

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BAZ	Body Mass Index for Age Z -score
PMTCT	Prevention of mother to child transmission
CDC	Centers for Disease Control and Prevention
CD4	T cell cluster of differentiation 4
CI	Confidence Interval
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
HAART	Highly Active Antiretroviral Treatment
HAZ	Height-for-age Z score
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
RCWMCH	Red Cross War Memorial Children's Hospital
UNAIDS	Joint United Nations Programme on HIV/AIDS
WCP	Western Cape Province
WAZ	Weight-for-age Z-score
SA	South Africa
SAMJ	South African Medical Journal
UCT	University of Cape Town
NHLS	National Health Laboratory Service
LMICs	Low and middle-income countries
LTFU	Loss to follow-up
TBH	Tygerberg Children's Hospital
PHC	Primary Health Care
PEPFAR	Presidents Emergency Plan for AIDS Relief

## PART A: PROTOCOL

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# **1 Introduction**

## **1.1 Burden of Pediatric HIV and Poor Access to Treatment**

Sub-Saharan Africa remains the epicentre of the epidemic of human immunodeficiency syndrome (HIV), accounting for approximately 91% of the world's total number of children <16 years living with HIV (1). Between the year 2011 and 2012, globally 11% of children eligible for antiretroviral therapy (ART) were receiving it compared to 21% in adults (2). During this period, 360,000 South Africa (SA) children were living with HIV and about 16,000 children were newly infected with HIV (1). In the absence of treatment, about half of the children living with HIV will die before their second birthday (3, 4). Despite rapid expansion of ART access in resource-limited settings, infants and children continue to start ART late when their prognosis is sub-optimal (5, 6). In 2010, >60% of children initiated ART with severe immune suppression or with World Health Organization (WHO) Stage 3 or 4 disease across Southern African countries, both factors are associated with a poor prognosis (7).

The access of children to ART early in their disease has been described as important for an effective paediatric HIV/AIDS programme in resource-limited settings (8). The gap between adult's and children's access to ART services in resource-limited settings is partly due to rapid progression of HIV disease in children and poor access to early infant diagnosis testing. Other barriers include complex guidelines and treatment schedules for children and lack of staff who are skilled and confident in paediatric HIV care (9). In addition, there may be fewer facilities offering paediatric ART with long distances between the health facility and the patient's home (9-11). These barriers mean that children with HIV frequently present for care when their disease is advanced. Therefore, expansion of ART programmes to increase children's access to treatment in resource – limited settings is important.

## **1.2 Decentralization as a Solution**

Decentralization of paediatric ART care is a way of addressing the challenges of paediatric HIV care and treatment in resource-limited settings. This model of care had been previously adopted for scaling up access to ART services in adults (12). Decentralization of ART services aims to improve the outcomes of patients in resource-limited settings where there are frequently limited human resources and weak health systems (13).

Recently, this model has demonstrated promising results for scaling up ART services in resource-limited settings (14, 15). Even though models of decentralization differ across different settings, the shift of services from a centralized site to lower level health facilities forms the basic component of all models of decentralization (16). The lower level health facilities are not only closer to patient's home, but also help in decongesting the number of patients receiving ART at specialized central hospitals (16). This model of care may also include task shifting or the devolution of specific tasks from highly qualified health workers to less qualified health workers paving the way for better utilization of highly skilled health workers at centralized hospitals to manage the sickest children with poor clinical and immunological status, including children with comorbidities (10, 17). Although, task shifting and decentralization are different approaches to improving patients access to care, in some settings such as SA they are synonymous since services at lower level health care facilities are often delivered by lower cadres of staff. Furthermore, changes have been made to ART service delivery in SA to accommodate the decentralization and task-shifting model of care for people living with HIV (18).

In 2010, the government of SA revised its HIV treatment guidelines following the positive results of a pilot task-shifting intervention in routine care settings (19). These results, coupled

with the results of a SA randomized control trial, which reported similar treatment outcomes of patients who were initiated on ART by doctors but monitored by nurses at primary health care clinics thereafter compared to those managed by doctors alone, supported programme changes in the SA 2010 treatment guidelines (18, 19). Consequently, the SA 2010 treatment guidelines allow nurses to initiate antiretroviral drugs for the treatment and prevention of HIV and also enable primary health care facilities to initiate, manage, monitor and refer patients (20).

A recent systematic review on different models of decentralization in resource-limited settings suggests comparable outcomes in both adult and paediatric patients with HIV receiving ART services at decentralized health facilities compared to those receiving ART services at centralized health facilities. In addition, no significant differences in clinical and immunological outcomes were found irrespective of whether a less qualified health worker or a highly qualified health worker delivered the ART service (16). Consequently, decentralization of ART services through the primary health care system has been considered to be paramount for increasing patients access to HIV care and their retention in care as the HIV programme continue to expand in resource-limited settings (16, 17).

### **1.3 Western Cape Pediatric ART Decentralization Model**

South Africa, with the largest paediatric ART programme in the world (21) commenced rapid scale-up of ART services in 2004 following the launch of the SA national ART programme in April 2004. The majority of children were treated at secondary level facilities and were initiated on ART based on SA immunological and clinical eligibility criteria for ART initiation. The SA ART eligibility criteria for children from 2004 - 2010 are summarized in table 1 below, since the children's data that will be included in this study would have received ART services during this period.

**Table 1: SA ART Guidelines for Paediatric ART Management from 2004 – 2010 (7)**

Year	2004 – 2009	2010 onwards
ART initiation criteria	WHO disease stage III/IV	
	Recurrent (>2/years) or prolonged (>4weeks) hospitalizations for HIV-related illness.	≤ 11 months: all
	< 18 months: CD4% <20	12 – 59 months: CD4 <750 or 25%
	≥ 18 months: CD4% < 15	≥ 5 years: CD4 < 350

By the end of March 2006, thirty-seven public health facilities were accredited to manage children eligible for ART in the Western Cape Province (22). The accreditation of these public health facilities heralded the implementation of the decentralized delivery of paediatric ART services in Western Cape Province (22).

The decentralization of paediatric HIV care in the Western Cape Province was introduced systematically. Patients stable on pills were the first group transferred out from the tertiary health facilities, followed by stable children on syrups. However, as capacities improved at the lower level facilities, these facilities began to initiate and monitor children on site. Very sick unstable infants and children continued to be initiated and stabilized on ART at the tertiary health facilities and were then transferred out after stabilization for continued ART care at lower level health facilities within the Western Cape Province (22, 23).

In addition to transferring clinically stable children out of tertiary health care for the continuation of care at the lower level health facilities, tertiary health facilities have also

supported decentralization by contributing to building capacities of workers at lower level health facilities. Staff from tertiary facilities have provided mentoring and maintained regular communication with lower level health facilities. In addition, there were regular visits by the tertiary health care paediatricians to lower level health facilities as the number of children at the lower level health facilities increased.

Early outcomes of the Western Cape Province paediatric decentralized ART model of HIV care suggested that this approach facilitated remarkable progress in delivering ART services to HIV-infected children. Between March 2004 - September 2006, the proportion of children receiving ART at the three tertiary hospitals in the province decreased from 78.4% - 38% (9).

#### **1.4 Red Cross War Memorial Children's Hospital Paediatric ART Decentralization**

Red Cross Memorial Children's Hospital (RCWMCH) is a leading institution in advancing the care of HIV-infected children in the Western Cape Province and SA. The RCWMCH ART programme for children started at the beginning of 2002 prior to the national ART programme of 2004 by providing ART services for children and their HIV-infected parents. This programme was subsequently incorporated into the provincial decentralized network for the delivery HIV care, by the HIV/AIDS directorate of the Western Cape Department of Health in March 2004 (24, 25). The majority of children at RCWMCH requiring ART are children with advanced HIV infection (WHO stage 3 and 4). About 85% of these children start ART during a hospital admission, including 15-20% who start ART in the intensive care unit of the hospital (26).

The RCWMCH 2011 operational guidelines for ART include ART initiation within two weeks of admission for all HIV-infected ART-naïve children <12 months of age and children with advanced disease. Stable HIV-infected children > 12 months of age who are eligible for ART can be referred to commence ART at the local community ART clinic unless the child requires

specialist services at RCWMCH. RCWMCH children are referred to community clinics for the continuation of ART and routine follow up where possible (26). Children who are referred to lower level facilities are provided with a referral sheet containing the name of the referral site, next appointment date at referral site, medical summary, most recent laboratory test results, and, if already on ART, the current drug regimen. This referral sheet should be given to the referral facility upon arrival for the continuation of HIV care (26). The routine laboratory monitoring of RCWMCH children includes CD4 absolute and percent as well as viral load. Although the recommended frequency of monitoring has changed over time, current National Department of Health guidelines are that these should be measured at initiation, after 6 months, after 1 year and annually thereafter (26).

An early study on the provision of ART for children at RCWMCH reported that 409 children had enrolled on the ART programme at RCWMCH with a median age of 23 months (interquartile range (IQR): 8.9 - 54.6 months) by the end of December 2004. After a year on ART 46/409 (11.2%) had been transferred out to another ART treatment site (lower level of health facilities) for the continuation of ART care (25).

## **2 Support from Literature**

In the context of massive scale-up of HIV services in resource-limited settings, retention in care of patients infected with HIV is salient for optimal clinical outcomes in patients on ART (27). Although it is expected that a decentralized model of HIV care will help remove some barriers to HIV care in resource-limited settings, it is important to improve on the tracking system of patients transferring between HIV care sites to accurately assess retention at the level of the ART programme, and not just at a particular facility (28). The gaps in the methodological approach used to quantify retention of patients on ART in resource-limited settings have been well discussed (27). A 2014 systematic review of paediatric patients on HIV treatment in low

and middle-income countries between the year 2008 and 2013 reported that 85% of patients were retained in care at 12 months and 81% at both 24 and 36 months after ART initiation. However, when examining ART outcomes, this review excludes patients who were reported to have been transferred from treatment sites from both the numerator and the denominator since their outcomes are unknown after transfer out (29). Similarly, a study where patients were censored at the time of transfer reported an 86.9% and 82.4% retention in ART sites at 12 and 36 months after ART initiation respectively. In addition, this study also reported that most transfers of patients occurred between 6 and 12 months after initiation onto ART (83.4%) (30).

The interpretation of the above estimates of retention of patients on ART has been greeted with caution because these studies did not capture information either about patient`s referred by clinicians to lower level health facilities for continuation of HIV care or of silent transfers that occur between treatment sites. “Silent” transfers occur when patients themselves start to receive HIV care at a new treatment site without informing the previous treatment site that they will be transferring to a new facility for HIV care. Retention in care within a decentralized network of ART services could be underestimated if these retention estimates of patients on ART do not take into account patients that transfer care (27). Indeed, this gap in patients tracking systems hinders capacity to assess the retention outcome of patients in a decentralized model of ART services.

As transfer patterns and outcomes may be dependent on the context, it is important to conduct local research to evaluate interventions such as the decentralized delivery of ART services. In particular, new methodological approaches are needed to strengthen evaluation of the decentralized model of HIV care (27). To this end, a SA adult study shed light on the importance of evaluating the outcomes of patients transferred out in a decentralized ART care model. This study reported higher mortality in patients transferred out from ART sites compared to patients retained at ART initiation sites at three months after transfer date (31).

However, it is noteworthy that most studies assessing outcomes of patients on ART programmes censor transferred out patients. This explains the paucity of information on outcomes of patients moving from centralized ART sites (mostly higher level health facilities) to lower level health facilities and its impact on estimates of retention in care (14, 32, 33).

### **3 Problem Identification**

The ongoing scale-up of paediatric ART services in SA and Western Cape Province is through a decentralized service with different levels of health care. Knowledge of a patient's movement between facilities is, therefore, necessary for the evaluation of a patient's outcomes in the context of this decentralized model of HIV care (34, 35). This knowledge is important since effective HIV treatment requires uninterrupted treatment and retention of patients on ART programmes (27). However, there is sparse information on children's outcomes after transfer out from the treatment initiation site in resource-limited settings (10, 14, 27, 31).

This problem leads to the question: "What are the outcomes of children transferring out of RCWMCH?" and "What are the determinants of successful transfer in children transferred out from RCWMCH?".

### **4 The Rationale for the Proposed Study**

The ongoing scale-up of ART services in SA has achieved tremendous results with more than 2.7 million people taking antiretroviral drugs and improved access to services throughout the country (36). Yet, there are still challenges of patient adherence to treatment, long-term retention of children in a treatment programme and the continued engagement of HIV-infected children in care. These are all important in ensuring uninterrupted treatment of children on the treatment programme (32). Interruption of ART can reverse the health benefits of starting ART and also cause drug resistance mutations in patients, limiting future treatment options (37).

Therefore, successful retention of children in treatment programmes such as the decentralized paediatric ART programme of Western Cape Province is essential to achieve the National Strategic Plan 2012-2016 goal 2, to keep 70% of patients alive and on treatment five years after ART initiation. This is also in line with the global goal to retain 90% of all people with diagnosed HIV infection on ART by 2020 (38, 39).

Furthermore, a recent study on characteristics of patients transferring out of the ART service in SA has emphasized the importance of information tracking systems for patients transferring between ART sites, as the proportion of transferring patients are increasing due to the ongoing scale-up of ART services in SA (35). To the best of our knowledge, there are only two studies that published a sub-group analysis of outcomes of children transferred out from Tygerberg hospital and RCWMCH respectively. Both are Western Cape Province tertiary health facilities but neither of the two studies aimed to describe the overall proportion of patients successfully transferred from the tertiary facility or the predictors of successful transfer (40, 41).

## **5 Study Objectives**

1. To estimate the proportion of children that successfully transferred to referral facilities providing continued ART services for children transferred out from RCWMCH within 18 months of their last appointment at RCWMCH using linkage to the Provincial National Health Laboratory Service (NHLS) data.
2. To describe CD4 and viral load outcomes of RCWMCH stabilized HIV-infected children that successfully transferred into referral sites.
3. To identify and examine predictors of successful transfer.
4. To determine the feasibility of using the SA NHLS data for routine monitoring children transferring within paediatric ART sites.

## **6 Methodology**

### **6.1 Study Design**

This will be a retrospective analysis of children initiated on ART at RCWMCH and transferred to lower level health facilities for continuation of HIV care from between December 31, 2007 and January 1, 2012. Routine clinical follow-up data was collected for this cohort of children as part of standard treatment and monitoring of HIV and ART.

### **6.2 Characteristics of Study Population and Red Cross War Memorial Children**

#### **Hospital**

This study will include all HIV-infected children who were below the age of 16 years at ART initiation at RCWMCH and were transferred to another facility in the Western Cape Province to continue ART. RCWMCH is a SA tertiary health facility affiliated with the University of Cape Town (UCT). Children are referred to RCWMCH from all the nine Provinces of SA and all over Africa. The range of paediatric services offered at RCWMCH includes quaternary, tertiary, and secondary services. RCWMCH is also actively involved in paediatric outreach and support programmes across SA (42). About 260 000 patients visit RCWMCH every year, the majority of these patients are from marginalized communities and are extremely poor. One-third of children managed at RCWMCH are younger than a year (43).

### **6.3 Data Collection and Variables**

Study data will come from patients who initiated ART at RCWMCH for the period from between December 31, 2007 and January 1, 2012 and transferred out during this period. All children's data were collected using a standard datasheet form according to the 2011 RCWMCH operational guideline for the management of HIV (26) and stored in a password protected access database kept on a password protected personal computer in a locked office. These patients' information were extracted from the RCWMCH database and linked to

Western Cape Province laboratory data by Western Cape Department of Health staff. Patients' follow-up outcomes can, therefore, be assessed using the linked data. The start of the study period in 2007 was chosen as the Western Cape implemented the use of a unique patient number in 2007, facilitating linkage of patient data across facilities. The end of the study period is at the end of 2011, as the linkage was conducted using data up to the end of 2012, and we wanted to ensure that there was at least a year of laboratory data available after the last patient was transferred out.

We will include children's laboratory information variables of CD4 counts/percentage and viral load from either the Western Cape NHLS Database or the RCWMCH database, in addition to demographic data, date of ART start and referral site of children who were transferred out extracted from the RCWMCH database.

#### **6.4 Sample size and Power Consideration**

The proportion of ART naïve children who remained in treatment clinics at 12 months on ART in the Western Cape Province, SA is estimated to be 0.87 (30, 44). We assume that transferring stabilized children to lower levels health facilities would neither increase nor decrease the rate of retention in their new health facilities. Thus, we hypothesized a difference of < 8% in retention rate. The table below provides a list of sample sizes that will be needed to detect a range of differences in retention at 0.05 alpha and 80% power.

**Table 2: List of Sample Sizes Needed to Detect a Range of Difference in Children's Retention in Care.**

	The Null Proportion of retention	The alternative proportion of retention	Difference	Sample size required
--	-------------------------------------	--	------------	-------------------------

1	0.87	0.92	0.05	316
2	0.87	0.93	0.06	213
3	0.87	0.94	0.07	151
4	0.87	0.95	0.08	111

We would like to be certain that the difference is not more than 5%, which requires a sample size of at least 316. However, based on preliminary analysis of RCWMCH data, 725 children transferred out to a Western Cape lower level health facility during the study period. We therefore expect to have >80% power to detect difference in retention of at least 5% from our null hypothesis of 87% retention.

## 7 Measurement

Analysis will be done on the following existing measurements that were taken during the routine ART programme:

### 7.1 Children`s Characteristics at Transfer out Date

This shall include markers of disease severity of viral load (copies/mL) and CD4 count or percentage at transfer out date to a lower level health facility for the continuation of ART. (i.e laboratory test performed closest to the transfer out date within a window of 12 months before date of transfer out from RCWMCH). Likewise, their characteristics at ART initiation and duration on ART before transfer out will be included. Date at which each test was conducted will be recorded. **Table 3 below.**

### 7.2 Children`s Characteristics at Referral Facilities.

This shall include patient`s markers of disease severity of viral load (copies/mL) and CD4 count or percentage performed at patient`s first appointment/contact with referred lower level

health facilities. The median time from transfer date to first laboratory information at referral facilities will also be recorded **Table 4 below**.

*Dummy Tables*

**Table 3: Children Characteristics at Transfer out.**

<b>Characteristic</b>	<b>Data</b>
Age in months at ART start	Median (Interquartile range)
Gender	Male – n, %, Female – n, %
The proportion of children immune suppressed at ART start.	Yes - n, %, No – n, %
The proportion of children with advanced WHO disease at ART start (WHO clinical stage 3 or 4)	Yes - n, %, No – n, %
Growth measurement of Weight for age z-score at ART start.	<-3 SD n, % < -3 to -2 SD n, % >-2 SD n, %
The proportion of children virologically suppressed at transfer (copies/mL).	Yes – n, %, No – n, %
The median CD4 count (cells/ $\mu$ l) or percentage status at transfer.	Median (Interquartile range)

Duration of time (months) on ART before transfer.	Median (Interquartile range)
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**Table 4: Children Characteristics at Referral Facilities.**

Characteristic	Data
Median time (months) from transfer date to first laboratory data at a referral facility.	Median (Interquartile range)
First CD4 count (cells/ $\mu$ l) data at referral site after transfer out date.	Median (Interquartile range)
The proportion virological suppressed at first visit at referral site after transfer out date (copies/mL).	Yes – n, %, No – n, %
The proportion of children immune suppressed at referral site after transfer out date	Yes – n, %, No – n, %

### 7.3 Validity and Reliability of Measuring Instruments

The validity of the data in the RCWMCH database is dependent on the recording of information at the site, and the validity of the laboratory data from other sites is dependent on data quality in the NHLS Provincial Database. The NHLS data will be used to measure successful transfer of children at referral sites after they were transferred out from RCWMCH. This laboratory

data has been reported to be effective in monitoring trends in early infant diagnosis of women on the prevention of mother to child transmission programme of SA (45). It is also noteworthy that a recent report on the short-term outcomes of children < 13 years that were initiated onto ART at RCWMCH intensive care unit assessed the outcomes of transferred children using NHLS data (41). Similarly, the outcomes of children < 15 years transferred out from Tygerberg Hospital (one of the three tertiary health facilities in Western Cape Province) were assessed using data on the NHLS server (40). Data cleaning and quality control routines will be implemented to enhance data validity.

## **8 Statistical Methods**

### **8.1 Data Access**

The NHLS performs all HIV-related laboratory tests for SA public health facilities. Its national network of > 260 laboratories provides services for those without medical insurance (about 85% of the SA population) (45). The RCWMCH linkage to Western Cape Provincial laboratory database will be used to monitor the transition and clinical outcomes of children transferred out from RCWMCH from between December 31, 2007 and January 1, 2012.

### **8.2 Data Linkage**

The RCWMCH children records were deterministically linked to Western Cape Provincial laboratory database using patient's folder number, date of birth and name by provincial staff. The integration of RCWMCH programme with the Western Cape programme has been described in previous publications (24, 25).

### **8.3 Data Cleaning**

Data cleaning will be undertaken by the researcher. The anonymized linked dataset will be transferred to the researcher in STATA for cleaning and analysis. First, patients' records will

be assessed to determine whether transfer was successful or not. A successful transfer will be defined as a RCWMCH transferred out child with a linked laboratory result record within 18 or 48 months after the transfer date from RCWMCH.

In contrast, RCWMCH transferred out children without laboratory information within 18 or 48 months of transfer out date from RCWMCH will be considered not to have successfully transferred.

The primary outcome of successful transfer was defined in two ways: a laboratory test performed by a lower level facility (i)  $\leq 18$  months or (ii)  $\leq 48$  months after the transfer date. The first interval corresponds to guideline recommendations for annual CD4/viral load monitoring; the second captures all children retained in care.

In addition, in children with laboratory results available from a transfer site within 18 months of transfer (i.e. successful transfers) we will assess whether the site from which the post-transfer sample was collected is in fact the site to which the child was transferred or a site that is in close proximity to the child's home address.

#### **8.4 Descriptive Analysis**

The analysis will be done using both univariate and multivariate methods. The characteristics of children at ART start and before transfer out as well as within 18 months of transfer out will be described using means and standard deviation for normally distributed continuous variables and medians and interquartile range for non-normally distributed continuous variables. Categorical variables will be summarized using proportions and differences between patient subgroups and will be compared using chi-squared tests or Fisher's exact tests if one or more cells have an expected frequency less than five.

Continuous variables will be assessed for normality using histograms and the Shapiro-Wilk test. Paired Wilcoxon signed rank test will be used to assess if there is any significant difference

between individual repeated measures of CD4 percentage/count and viral load if any of these variables is not normally distributed. A paired t-test for the difference between paired samples will be used if they are normally distributed.

### **8.5 Sensitivity Analysis**

A sensitivity analysis will be carried out to determine the potential impact of uncertainty around the pre-specified window of 18 months allowed for successful transfer. We will examine the impact on the proportion of children deemed to have successfully transferred using longer and shorter thresholds (e.g 15 months, 18 months, and 48 months). These intervals were selected to examine if the proportion of successful transfer differs substantially when reducing or increasing the successful transfer window after transfer out date.

### **8.6 Logistic Regression Model**

Multivariate logistic regression will be used to identify patient characteristics that are associated with successful transfer. A multivariate logistic regression will be built by sequentially adding variables considered *a priori* to be potentially associated with successful transfer based on evidence from the literature. For example, age has been described as a strong prognostic factor for children's outcomes (44). Therefore, age will be firstly introduced into the model, followed by other potential prognostic variables such as duration on ART, gender and most recent laboratory information (CD4 counts/percentage) of children (25). Any variable with a p-value  $< 0.1$  after adjustment for the variables already in the model or that changes the odds ratio of variables already in the model by  $\geq 10\%$  will be retained. No cut-off for p-value will be used to define statistical significance as all p-values for all the analysis will be reported exactly (46).

The log-likelihood ratio test will be used to compare nested models and Akaike's information criterion (AIC) to compare non-nested models. Best model fitness will be assessed using

Hosmer and Lemeshow goodness of fit test. All analyses will be two sided at an alpha of 0.05. Stata statistical software, version 14.1 will be used for analysis (47).

## **9 Ethics Considerations**

This study aims to abide by the ethical principles of health research that include justice, beneficence, and autonomy. This study will seek ethical approval from University of Cape Town Human Research Ethics Committee (HREC) before proceeding.

### **9.1 Autonomy**

This study will not require patient informed consent as the data collected for analysis was from routine operational monitoring data. Even though this study dataset will be extracted from the RCWMCH, utmost confidentiality of patient information is guaranteed because the extraction was done by the staff that provided patient clinical care and are responsible for data capture at the sites.

The dataset for analysis in this study has existing UCT HREC approval (REC REF: 261/2002) (Appendix B and C). In addition, provincial approval was obtained to link RCWMCH data to the Western Cape Provincial data warehouse in order to evaluate outcomes in their own patients (Appendix A). This was a deterministic linkage using identifiers such as folder number, name, and date of birth and was performed by provincial staff with permission to access identified data. The researcher will not have access to patient information details as all patients' identifying details have been removed and replaced with anonymized identifiers.

The analysis dataset will be securely stored on the student's computer in a password-protected folder. On completion of analysis, after manuscripts have been accepted for publication, the analysis dataset will be returned to UCT for secure archiving by the School of Public Health and Family Medicine and the copy on the student's computer will be permanently deleted.

Since this study is a secondary analysis of previously collected data, no additional laboratory tests will be conducted.

In all cases, individual level information will not be reported but aggregate level results will be reported in any paper that may arise from this work.

## **9.2 Beneficence and Justice**

The results of this study would be useful for designing interventions aimed at reducing attrition during transfers in the ART continuum of care for HIV-infected children of Western Cape, SA. Participants will not benefit directly from the outcomes of this study; however, the results can be used to improve care for the population of children represented in this study. Therefore, justice is achieved.

This study will be done in accordance with the 64<sup>th</sup> assembly of World Medication Association Declaration of Helsinki (48) and ethical regulations of SA.

## **10 Stakeholders**

Stakeholders will include staff at RCWMCH and other treatment sites providing ART care to children transferred out from RCWMCH within the Western Cape Province, SA. Stakeholders also include children and caregivers attending those sites, the academic community, and policy makers in the field of paediatric ART.

## **11 Dissemination of Study Results**

Results of this study will be made available and accessible to researchers in the field of infectious disease by publishing results in the form of a manuscript in a peer-reviewed journal that will be identified. The results of the study will also be made available to the staff at RCWMCH. The results of this study have a good prospect to influence Western Cape Province paediatric ART policy.

**Table 5: Timetable for Completion of Mini-dissertation.**

<b>Task</b>	<b>Duration</b>
Protocol Development	December 2014 – March 2016
Literature Review	May 2014 – July 2016
Data management	August 2016
Analysis	August – September 2016
Write-up	September – January 2017
Dissemination to stakeholders	February 2017
Submission	March 2017

## **12 Budget**

Since this will be a secondary analysis of routinely collected data, no anticipated costs are expected during the course of this study. The student researcher will conduct the analysis free of charge.

## **13 Study Limitations**

1. Due to the design of this study as a retrospective observational study and because routine programme data will be utilized, any existing deficiencies in the accuracy and consistency of routine data will be a limitation.
2. Survivor bias will also be of concern since patients are expected to be clinically stable before transfer out from RCWMCH. Consequently, the study results will apply to a cohort of children with severe disease who were initiated onto ART at a tertiary hospital and who survived and became stable on treatment prior to transfer. Therefore, the generalizability of the study results will be limited to children with similar

characteristics. Similarly, the study sites that were included in this study are Western Cape Province lower level health care facilities providing ART services for children transferred out from RCWMCH. Thus, the generalizability of this study results to children transferring in other provinces may be limited.

3. The estimated proportion of children successfully transferring in our study might be an artefact of our measuring tool of successful transfer i.e. NHLS data. The information provided by this data is consequent on patient's presentation at the transferred out lower level health facilities within Western Cape, SA *and* a laboratory test being performed according to national guidelines. If tests were not performed according to the national guidelines (i.e viral load done less frequently than recommended), we may underestimate transfer in children who actually transferred in successfully at referral sites but have not had laboratory monitoring performed as per guidelines. The use of a window of up to 18 months after transfer for a laboratory test in order for a child to be considered "successfully transferred" reduces this limitation, as does our sensitivity analysis which will examine how the duration of the allowable window after transfer affects the proportion of children deemed to have successfully transferred. Our study does not address passive or silent transfers of patients within or outside Western Cape lower health care facilities and hence cannot comment on overall retention in care at the level of the programme. However, the focus of our study is on successful transfer to the facility that a patient was referred to, rather than overall retention. In addition, we will not be able to ascertain the reasons for patients not transferring successfully, which may include death. There are many factors associated with the successful transfer of patients and we will only be able to examine factors that have been recorded in the RCWMCH electronic database. For example, we will be unable to explore whether socio-economic status, disclosure to the child or to other caregivers, caregiver education

or having a caregiver on treatment at the referral facility influences successful transfer or not.

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## PART B: LITERATURE REVIEW

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## 2 Introduction

In a move to remove the barriers of patients' access to Human Immunodeficiency Virus (HIV) care in low and middle-income countries (LMICs), the World Health Organization (WHO) recommended a public health approach for expanding antiretroviral therapy (ART) care in resource-limited settings. The multi-pronged approach includes - decentralization of ART services and task shifting which is a triage model for ART management of people living with HIV. Due to the urgency of scaling up ART in LMICs, both approaches are implemented in parallel to scale up HIV care in most LMICs (1-3).

The effectiveness of decentralized ART care in adults has been reported in the literature. These models of ART delivery have consistently been demonstrated to be effective for removing the barriers of patients' access to care in LMICs, and at improving the outcomes of patients (4-7). To address similar challenges in children, decentralization of ART care for children has been implemented in LMICs. Limited evidence in the literature suggests the use of decentralization models for scaling up paediatric ART care in LMICs improves the clinical, immunological and virological outcomes of children in ART programmes (8-10).

Due to the increasing use of decentralized models for ART care, Kredo et al (2013) (4) have categorized the different decentralization models used to scale up ART services in LMICs based on the evidence from the literature. Models of ART care adopted in different settings might be indicative of their human resource capacity (2, 11), and have been grouped into three broad categories;

1. A full decentralization model of ART care: Comprehensive ART services are provided for patients at any level of health facilities. The services provided range from ART initiation and patients' continued ART management at the same health facility.
2. A partial decentralization model of ART care: Patients are initiated on ART at higher level health care facilities before being transferred to lower level facilities for the continuation of ART care.

3. Community decentralization model of ART care: This model of ART care involves initiating patients on ART at either lower or higher level facilities before being transferred out to the community for continuation of care.

For the purpose of literature comparability, this review will focus on literature reporting on the outcomes of patients transferring care in order to be relevant with the aims and objectives of our study which focuses on the outcomes of children transferring out of Red Cross War Memorial Children's Hospital (RCWMCH). Based on the different decentralization ART models described above, the studies reviewed therefore include partial and community decentralization models of HIV care since these models include the transfer of patients between ART treatment sites.

A review of the literature reporting on the outcomes of transferring patients will provide insight on existing knowledge about the outcomes of these models of ART care and evidence gaps with respect to outcomes of patients transferring care between facilities.

## **2.1 Aims and Objectives**

This review aims to appraise the current literature on patients transferring between facilities for HIV care, with the aim to place our/my study within the context of other studies in this research area and identifying gaps for future research.

The specific review objectives are as follows:

1. To identify all published literature reporting on the outcomes of transferring HIV-infected patients on ART in LMICs.

2. To describe the evidence in the above published literature by synthesizing and critically examining the quality of evidence regarding the outcomes of patients transferring between ART sites in LMICs.
3. To identify questions that emerge on patient transfer that could form the basis for further research.

### **3 Review Process**

This review will make the process of literature search, quality and comparability assessment of all the studies identified explicit. The presentation of the findings of these studies will follow an organized and logical format. Therefore, the presentation layout for this review will include the characteristics of patients at ART initiation, outcomes of transferring patients in the HIV continuum of care, predictors of successful transfer, methodological approaches used for the assessment of successful transfer and loss to care. Results validity and study quality will also be discussed.

#### **3.1 Search Strategy**

Multifaceted Boolean searches of the Medline bibliographic database using the PubMed interface (National Library of Medicine, Bethesda, MD) and the Scopus (Embase bibliography database) electronic database were performed simultaneously.

The search strategy started by combining all sets of key terms under the following Medical Subject Headings (MeSH) to identify literature on HIV infected participants: "HIV" OR "AIDS" OR "human immunodeficiency syndrome" OR "acquired immune deficiency syndrome".

To identify literature on decentralization models of ART care for HIV infected patients the following key terms were combined: “Down referral” OR “HIV continuum of care” OR “decentralization” OR “retention in care” OR “transfer out” OR “task shifting” OR “connection to care”.

Then, to identify literature on HIV infected participants receiving ART the following MeSH key terms were combined: “Antiretroviral” OR “antiretroviral therapy” OR “ART” OR “HAART” OR “ARV” OR “cART”.

Also, to identify literature on the outcomes of HIV-infected participants on ART the following key terms were combined “outcome” OR “suppression” OR “mortality” OR “survival” OR “effect” OR “health” OR “effectiveness” NOT “maternal” NOT “PMTCT” NOT “MTCT” NOT “maternity” NOT “cure” NOT “pregnancy” NOT “pregnant”.

Furthermore, to identify studies from LMICs the following key terms were combined based on World Bank classification of LMICs and MeSH key terms (12): “Africa” OR “Asia” OR “Caribbean region” OR “Central region” OR “Central America” OR “Latin America” OR “South America” OR “Southern Africa” OR “Sub Saharan” OR “middle income countries” OR “low and middle income countries” OR “resource limited” OR “resource constrained” OR “developing countries”.

Lastly, the five sets of specific terms searched were combined together using the AND operator in PubMed and Scopus concurrently.

### **3.2 Inclusion Criteria**

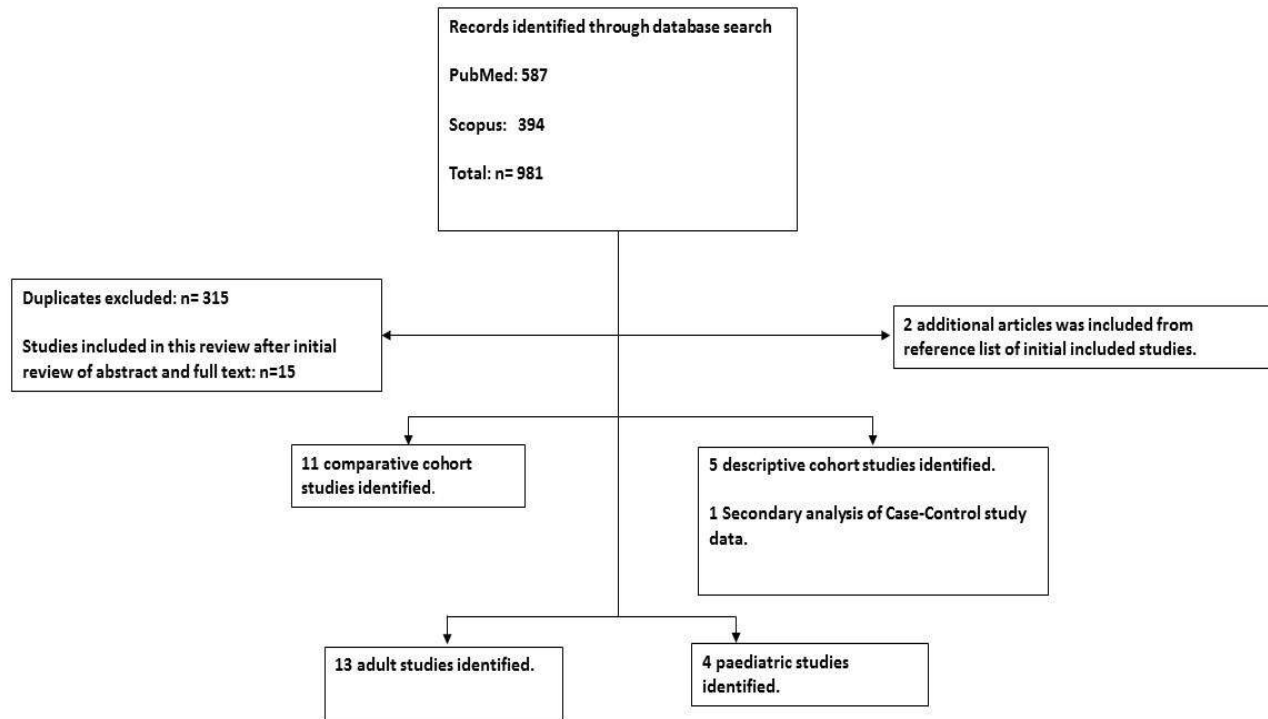
- All published articles written in English from LMICs reporting on outcomes of transferring patients in the HIV continuum of care were included. This review was not limited to paediatric studies; adult studies were included because the literature reporting on outcomes of children transferring between higher level facilities and lower level facilities in LMICs is extremely limited.
- The outcomes included were mortality, immunological and virological outcome, loss to care, successful transfer, loss to follow-up (LTFU), adherence.
- Studies reporting on outcomes of transferring patients that were ART-naïve at ART initiation were included.
- Observational studies were included in this review, which comprised of both descriptive and analytic studies. More recent studies (published in the past 10 years [January 2006 to July 2016]) were given priority.

### **3.3 Exclusion Criteria**

- Studies reporting only on patients' outcomes in a full decentralization model of ART care.
- Studies reporting on outcomes of transferring patients in highly specified patient groups e.g. commercial sex workers or senior citizens.
- Studies reporting pre-ART outcomes of patients regardless of the model of ART care.
- Randomized control trials, qualitative studies and studies from high-income countries.

The bibliographies of all the literature that met the inclusion criteria were further examined based on the inclusion criteria used for the initial literature search from in PubMed and Scopus database. This led to the inclusion of two additional studies, which met the inclusion criteria.

**Figure 1: Flow diagram of the studies included in this review.**



### 3.4 Articles published

The search strategy presented above yielded 981 published articles in PubMed and Scopus. However, only fifteen studies met the pre-specified inclusion criteria after removing studies that overlapped between the two databases. Two additional studies from the bibliography search of the initial studies selected were subsequently included after meeting the pre-specified eligibility criteria. One study by Bock et al (2008) was included in this review although it primarily aimed to compare outcomes of patients at different levels of care in a full decentralization model of ART care (13). However, this study also captured the information of children transferred out to lower

level facilities for continuation of ART care and these children were subsequently included in the study analysis. This study was included because of the sparse literature reporting on the outcomes of children transferring in the HIV continuum of care. In addition, two studies that reported the outcomes of patients in a community decentralization model of ART care were included in this review because both met the inclusion criteria (14, 15).

#### **4 Quality and Comparability of study**

Patient characteristics relevant to the study research questions were extracted and presented in tables. The quality of the studies included was assessed in terms of the aim and scope of the study. The quality criteria included were: study design, sample size and treatment initiation guidelines followed (Tables 1–2c).

Different studies were described and compared in terms of the model of ART care, year of study, follow-up time, patients' immunovirological characteristics at ART initiation or at transfer, patient's eligibility criteria before transfer out as well as how missing and incomplete outcomes were managed.

##### **4.1 Primary aims and focus of the study**

Of the seventeen studies that were identified and included in this review, only four studies comprised entirely child participants (10, 13, 16, 17). Eleven studies only included adults (14, 15, 18-26), while children accounted for a proportion of patients' in two studies, 11.5% (Yu et al 2008) and 9.61% (Chan et al 2010) respectively (27, 28).

All but two studies included in this review are from sub-Saharan Africa. Hansudeweschakul et al (2012) reported on the outcomes of children in Thailand while Ghate et al (2014) reported on the outcomes of adult patients' transferring between ART treatment sites in India (10, 21). The

majority of the studies reported both on transfers and task-shifting for the provision of HIV treatment and care.

Characteristics of patients transferred out are reported at the time of transfer or at ART initiation where possible. Ten of the seventeen studies were comparative in design, comparing the outcomes of patients who started ART at the higher level facilities and continued to be managed there with the outcomes of patients who transferred out to lower level facilities for continuation of ART care.

## **4.2 Study design**

All the studies reviewed were observational studies in line with the inclusion criteria. The majority of the studies used data collected retrospectively. However, Colasanti et al (2016) used prospectively collected data for their analysis.

Five studies were descriptive in design and reported on the outcomes of transferring patients in the HIV continuum of care (14, 20, 21, 24, 26). Colasanti et al (2016) conducted a secondary analysis of a case (virologic failure)-control (no virologic failure) study using individual-level factors collected from patients prospectively to assess the predictors of not being in care (25). Most studies used analytical methods to assess the outcomes of their patients.

## **4.3 Sample size**

No study provided sample size calculations for the number of participants included, but rather included all eligible participants based on their pre-specified eligibility criteria. The sample size of adult studies ranges from 158 – 8,093, while that of paediatric studies is generally lower (range 109 – 1741).

#### **4.4 Follow-up duration**

Because of the scope of the studies included in this review, follow-up time was reported in a variety of ways. While some studies reported follow-up time of patients before transfer out to lower level facilities, others reported patient follow-up time only at transferred out sites before the assessment of outcomes.

Brennan et al (2013) specifically ensured that both transferred out patients and patients managed at the initial treatment site had comparable follow-up time before the assessment of their study outcomes. To achieve this, time zero for participants was defined as the time at which patients became eligible for transfer out based on improvement in their immunovirological outcomes regardless of whether they were actually transferred out. Thereafter, person-time accrued from time zero to the earliest outcome of interest (18).

The follow-up duration of patients was relatively long in both paediatric and adult studies (ranges 18-40 months and 12-60 months respectively). However, the Indian study did not report patient duration of follow-up (21).

#### **4.5 Study Population and Initiation Guideline**

Patients were all ART-naïve at ART initiation except for the study from Thailand that reported about 90% of study participants were ART-naïve at initiation (10). Nevertheless, ART-experienced patients were excluded from their sub-analysis to prevent potential bias in patient outcomes. The age threshold used to define children differs across the studies ranging from less than 14 to less than 16 years (10, 13, 17, 29). Two adult studies reported a threshold defining adults, namely those  $\geq 18$  years of age in these studies (18, 19).

The studies included in this review utilized routine data sources, i.e. data were collected prior to the development of research questions. The inclusion criterion used in these studies was essentially ART-naïve patients who are eligible for ART at the time of initiation. Importantly, all patients' were initiated on ART using their setting's HIV/AIDS management guidelines adopted from WHO HIV/AIDS management guidelines (30).

All but two studies participants were managed at public health facilities operated by the government. In the studies by Cloete et al (2014) and Colasanti et al (2016) participants were initiated on ART at a semi-private, government-subsidized clinic with partial Presidents Emergency Plan for AIDS Relief (PEPFAR) funding. Patients paid a monthly fee of \$18 (25, 26). Thus, the results from these studies might not be completely generalizable to public health facility settings.

#### **4.6 Model of ART care**

The decentralization of HIV-infected patients on ART to lower level facilities for continuation of care is an intervention geared towards expanding HIV care coverage in LMICs and is an alternative to the continued management of patients at already overstretched higher level facilities in LMICs.

In most studies, stable patients were transferred to lower level facilities for continuation of care and patients could be transferred back to higher level facilities if the need arose due to failure in health status, poor adherence and for the management of adverse events as per partial decentralization (10, 18, 29). However, in two studies transfer of patients to public health facilities was mandatory irrespective of their clinical status due to shortage of funding at the initiation facility (25, 26). The community decentralization studies allowed for the transfer out of stable patients to the community in form of self-forming ART adherence club (14, 15).

In both decentralization models described, higher level facility staffs in some settings provided continued support, monitoring and mentoring to lower level facility staffs (13, 15, 17, 18, 27, 29).

#### **4.7 Transfer out eligibility**

Patients' were generally defined as being eligible for transfer when stable on ART at treatment initiation sites (mostly higher level facilities) in terms of their clinical status improvement. In addition, the absence of opportunistic infections and, in some cases, demonstrated high level of adherence to treatment were used to identify patients for transfer out to lower level facilities. These eligibility criteria may give rise to survival bias with better outcomes in those transferring out.

In some studies, patients were required to have been on ART for a specified period before becoming eligible for transfer. This period varied across studies from 3 months (27, 29, 31) to 6 months (14, 20) and up to 18 months (15, 18, 19). Some paediatric studies also required parents to consent to the transfer option (10, 17, 29).

#### **4.8 Confounders**

Unmeasured confounding is of concern for almost all the studies included in this review. In particular, patient socio-economic information may impact outcomes after transfer out and was not measured in most of the studies included. However, most studies did attempt to adjust for possible confounding variables at the analysis stage using multivariate regression analyses. It is worth noting that, confounding was addressed at the design stage of two studies by including transferred out and non-transferred patients in a 1:3 ratio matched on probable confounding variables of age, gender, time on ART, ARV regimen at study eligibility and CD4 count at study eligibility. Propensity scores were used to achieve comparable baseline characteristics in patients transferred out compared to patients remaining at the treatment initiation site (18, 19).

Nevertheless, Brennan et al (2011) also conducted a sensitivity analysis to assess the potential impact of unmeasured confounders on the outcomes of patients transferred out to lower level facilities compared to those managed at the treatment initiation site. This analysis showed that patients' managed at the treatment initiation site are more likely to have their estimates biased towards the null by unmeasured confounders compared to those transferred out (45% versus 1%) respectively. This underscores the vulnerability of the results of observational studies to be biased by confounding variables. This study also assessed the possibility of effect modification of their results by stratifying the effect measures by plausible confounding variables of gender and CD4 count ( $\geq 350$  cells/mm<sup>3</sup> versus 200-349 cells/mm<sup>3</sup>) (18).

#### **4.9 Missing data**

Due to the retrospective design of all the studies included in this review and the utilization of routine data, some level of data missingness is expected. However, the extent and potential impact of missingness on effect estimates reported in these studies are paramount to addressing internal validity of the results reported since this can be a source of bias. Most studies included only patients with complete data on the outcome and exposure variables of interest. Of note, one of the studies included which reported substantial level of missing data on patient viral load data used multiple imputation under the assumption that the data are missing at random (10, 32-34). In contrast, another study presented the number of missing data in their study and highlighted the fact that patients with missing data that were excluded from their analysis had similar characteristics to patients included in their analysis (18)

**Table 1: Quality and Comparability paediatric studies.**

Author	Observation Period	City/Country	Study design	Sample size	Median (IQR) age in years at study enrolment	Median(IQR) Immunological and virological characteristics at transfer out or at ART initiation	Patients eligibility criteria for transfer out	Median (IQR) time in months on ART before transfer out	Follow-up time after transfer out	ART Initiation guidelines followed
<b>Bock et al (2008)</b>	2004 (April) - 2006 (April)	Western Cape Province, South Africa	Retrospective Comparative Cohort	1741 children < 15 years	NR	NR	Children who are stable on ART	NR	18 months	SA national guidelines for management of HIV-infected children, 2005
<b>Hansudewchakul et al (2012)</b>	2002 (Feb) – 2008 (April)	Chiangrai Province, Thailand	Retrospective Comparative Cohort	410 children (287 children include in analysis)	CRH: 8.0 years (6.7- 11.3)  Vs CH: 8.0 (6.8-10.3)	CRH: CD4 % 20% (14%-24%) <sup>b</sup>  Vs CH: CD4 % 5% (16%-26%) <sup>b</sup>	Clinically stable children plus caregiver willingness to have child receive ART at a community hospital.	At least 6 months	CRH: 35 months (IQR 16-48) Vs CH: 29 months (IQR 20-40)	Thailand national ART guideline.
<b>Van Dijk et al (2014)</b>	2007 (Sep) – 2012 (March)	Macha, Zambia	Retrospective Comparative Cohort	109 children: HC: 41 and OC: 68	OC: 2.9 years (1.6- 7.5 years) Vs HC: 4.9 years (2.2-9.4 years)	OC: CD4% 14.2 % (10.5-18.9) Vs HC:14.4 % (11.0-19.5) <sup>a</sup>	Stable on ART for at least three months & demonstrated good adherence.	9.1 months (3.9-14.4 months)	OC: 32.3 months (IQR 22.3- 38.8) Vs 33.5 months HC:(IQR 23.1- 42.6)	Zambian ART guidelines for HIV-infected children and infants, 2010.
<b>Morsheimer et al (2014)</b>	2004 (Jan)-2009 (Jan)	Cape Town, South Africa	Retrospective Comparative Cohort	613 children < 14 (7 PHC clinic (n=343) & DR from TBH (n=270).	DR: 25.1 months (10.5- 59.3) Vs PHC: 29.6 months (10.0-68.4)	DR: CD4% 16% (10- 21.8) Vs PHC: 17.8% (11.0-24.2) <sup>a</sup>	Stable children on ART who caregivers consented to down referral	2 years (IQR 13.6-34 months)	6 months	SA national guidelines for management of HIV-infected children.

NR: Not reported, DR: Down referred, CRH: Changari prachanukroh hospital, CH: Community hospital, HC: Hospital affiliated clinics, OC: Outreach clinics, PHC: Primary health care, ART: Antiretroviral therapy, TBH: Tygerberg children's hospital, IQR: Interquartile range, Vs: versus, a: at ART initiation, b: at transfer out

**Table 2a: Quality and Comparability adult studies.**

Author	Observation Period	City/Country	Study design	Sample size	Median (IQR) age in years at study enrolment	Median(IQR) Immunological and virological characteristics at transfer out or at ART initiation	Patients eligibility criteria for transfer out	Median (IQR) time in months on ART before transfer out	Follow-up time	ART Initiation guidelines followed
Yu et al (2008)	2004(June) - 2006(Dec)	Mzuzu, North Region, Malawi	Retrospective Comparative Cohort	4175 patients (805 patients DR and 11.5% were children)	DR:36 years Vs NDR: 37 years	NR	NR	NR	NR	NR
Chan et al (2010)	2004(Oct) - 2008(Dec)	Rural Zomba district of Malawi	Retrospective Comparative Cohort	8093 patients (778 were children (9.6%))	HP: Mean age 33.2 years; sd ( $\pm$ 13.6) Vs DC: 35 years; sd ( $\pm$ 16.7)	HP: 1183 of 4653 (25.4%) Vs DC: 962 of 3440 (28.0%) patients had CD4 < 250 cells/mm <sup>3</sup> <sup>a</sup>	(i)Stable patients (> 3 months on ART) with no evidence of active OIs or drug intolerance. (ii) ART provider confidence in patient adherence. (iii) Patient lives in a location closer to DC than HS.	HP: 6 months (IQR 3-16 months) Vs DC: 11 months (IQR 5 – 20 months)	HP: 6 months (IQR: 3-16 months) Vs DC: 6 months (IQR 2 – 13 months)	Malawi ART guidelines 2004
Brennan et al (2011)	2004(April) - 2009 (Jan)	Johannesburg South Africa	Retrospective Comparative Cohort	693 DR patients were matched to 2079 TI patients 1:3	35.3 years (30.8 – 41.6)	389 cells/mm <sup>3</sup> (IQR 311- 507 cells/mm <sup>3</sup> ) <sup>b</sup>	Undetectable VL <10 months, on ART > 11 months, CD4 $\geq$ 200 cells/mm <sup>3</sup> , stable weight and no OIs and consented to DR	At least 11 months on ART	12 months	SA national ART guidelines, 2004 & 2010.
Long et al (2011)	2008(Feb)- 2009 (Jan)	Johannesburg South Africa	Retrospective Comparative Cohort	712 (PHC) & 2,136 TI matched by gender & age	38.5 years	TI: 397 cells/mm <sup>3</sup> (309- 521) Vs DR:404 cells/mm <sup>3</sup> (318- 526) <sup>b</sup>	Undetectable VL <10 months, on ART > 11 months, CD4 $\geq$ 200 cells/mm <sup>3</sup> , stable weight and no OIs and consented to DR	At least 11 months on ART	12 months	SA national ART guidelines, 2004 & 2010.

NR: Not reported, DR: Down referred, NDR: Not down-referred, DC: down-referred sites, HP: Hospital, sd: standard deviation, OIs: Opportunistic infections, TI: Treatment initiation site, ART: Antiretroviral therapy, PHC: Primary health care, Vs: versus, VL: Viral load, a: at ART initiation, b: at transfer out

**Table 2b: Quality and Comparability adult studies continued.**

Author	Observation Period	City/Country	Study design	Sample size	Median (IQR) age in years at study enrolment.	Median(IQR) Immunological and virological characteristics at transfer out or at ART initiation.	Patients eligibility criteria for transfer out.	Median (IQR) time in months on ART before transfer out.	Follow-up time	ART Initiation guidelines followed
Searle et al (2010)	2006-2008	eThekweni district, KwaZulu-Natal, South Africa	Retrospective descriptive cohort study	2071 patients	37 years	264 cells/mm <sup>3</sup> . % Virologic suppression: 1298 (99.6%) <sup>b</sup>	Stable patients on ART for at least 6 months.	NR	1154 (56%) followed for 0-5 months.	SA ART guidelines 2004 & 2010.
Connor et al (2011)	2007(Sep) 2009(Sep)	Johannesburg (inner city). South Africa	Retrospective descriptive Cohort	3361 patients	38 years (33 – 42 years)	CD4 count: 117.72 cells/mm <sup>3</sup> (IQR 50-179 cells/mm <sup>3</sup> ) <sup>a</sup>	Clinically stable with improved CD4 count, undetectable VL, absence of OIs and good adherence to treatment.	1.56 years (0.64-2.24 years)	0.57 years (0.15-0.92 years)	SA ART guidelines 2010.
Decroo et al (2011)	2008 (Feb) - 2010 (May)	Tete Province central Mozambique	Retrospective descriptive Cohort	1384 patients	36 years (30 – 43 years)	CD4 count: 176 cells/mm <sup>3</sup> (IQR 105 – 247) cells/mm <sup>3</sup> ) <sup>a</sup>	Clinically stable patient on ART for a minimum of 6 months and have CD4 ≥ 200 cells/mm <sup>3</sup> and who are interested in joining the CART.	22.3 months (9.7-34.2 months)	12.9 months (IQR 8.5-14.1 months)	Mozambique ART guidelines
Luque-Fernandez et al (2013)	2004(April) -2009 (Jan)	Khayelitsha, Cape Town, South Africa	Retrospective Comparative Cohort	2829 patients: 502 in adherence club	32.9 years (28.5 – 39.0 years)	Virologic suppression at study entry was reported in 2501 patients (88.4%) <sup>a</sup>	Clinically stable patients with CD4 count was above 200 cells/μl in the previous 6 months and have had sustained VL suppression.	At least 18 months on ART	8 months (IQR 7 - 10 months)	SA ART guidelines 2010
Ghate et al (2014)	2006 (January) – 2013 (July)	India	Retrospective descriptive Cohort	158 patients	TS: < 40 years-86(57.0%) Vs NTS: <40 years-10(66.7%)	TS: 69(57.0%) ≤ 200 cells/mm <sup>3</sup> NTS: 11(78.6%) ≤ 200 cells/mm <sup>3</sup> <sup>a</sup>	Patients were transferred out on their request.	NR	NR	India national ART guidelines, 2012

NR: Not reported, OIs: Opportunistic infections, ART: Antiretroviral therapy, CART: Community antiretroviral therapy group, TS: Transferred successfully, NTS: Not transfer successfully, VL: Viral load, a: at ART initiation, b: at transfer out

**Table 2c: Quality and Comparability adult studies continued.**

Author	Observation Period	City/Country	Study design	Sample size	Median (IQR) age in years at study enrolment	Median(IQR) Immunological and virological characteristics at transfer out or at ART initiation	Patients eligibility criteria for transfer out	Median (IQR) time in months on ART before transfer out.	Follow-up time	ART Initiation guidelines followed
Grimsrud et al (2014)	2002-2011	Cape Town, South Africa	Retrospective Comparative Cohort	2341 patients	33.8 (28.9-40.2 years)	NR	Patient who had most recent viral load was < 50 copies/ml and had no OIs or poorly controlled chronic conditions and they were on first-line ART regimen, had demonstrated good adherence by pill count.	1.6 years (0.9-2.6 years)	Patients were followed up through 60 months until analysis closure or censoring. Total person-time accrued was 4662.1 years	SA ART guidelines 2010.
Cloete et al (2014)	2012(March)-2012(June)	Durban, South Africa	Retrospective descriptive cohort study	3913 patients	Mean age 40 years; sd; ( $\pm 9.5$ )	CD4 count: 375 cells/ $\mu$ l (250-530 cells/ $\mu$ l) <sup>b</sup>	Mandatory transfer regardless of patients' clinical status in preparation for facility closure.	NR	5-10 months' post-transfer.	SA ART guidelines 2010.
Colasanti et al (2016)	2010(Oct)-2012(June)	Durban, South Africa	Secondary analysis of Case-Control study data	158 cases and 300 controls	38.4 years	CD4 count: 300.5 cells/ $\mu$ l (183.5-448.0) <sup>c</sup>	Mandatory transfer regardless of patients' clinical status in preparation for facility closure.	Mean time: 30.2 months sd; ( $\pm 24.3$ ) <sup>c</sup>	30.7 months sd; ( $\pm 24.5$ )	SA ART guidelines 2010
Hickey et al (2016)	2011(Nov)-2013(Nov)	Mfangano Island, Kenya	Retrospective descriptive cohort study	369 patients	Mean age: 40 years; sd; ( $\pm 12$ )	CD4 count: Mean 387 cells/ $mm^3$ , sd; ( $\pm 217$ ).	Request for official transfer.	Mean time: 2.5 years sd; ( $\pm 1.9$ ) <sup>a</sup>	6 months	NR

NR: Not reported, OIs: Opportunistic infections, ART: Antiretroviral therapy, a: at ART initiation, b: at transfer out, sd: standard deviation, c: study start

**Table 3: Characteristics of children at ART initiation.**

Author	Age	Disease severity	CD4	Viral load	WAZ	Tuberculosis
Bock et al (2008)	NR	NR	<u>% with CD4 percentage &lt;15% (CI)</u> <u>Higher level facilities</u> 48.1 (CI 36-52) <u>Intermediate level facilities</u> 52.1 (CI 36-52) <u>Lower level facilities</u> 35.5 (CI 31-41)	NR	NR	NR
Hansudewechakul et al (2012)	See table 1	<u>Higher level facility</u> 85.7% overall CDC HIV clinical stage Stage N or A 51(38%) Stage B 30(23%) Stage C 33(25%) <u>Lower level facilities</u> 90.26% overall CDC HIV clinical stage Stage N or A 50(32%) Stage B 28(18%) Stage C 61(40%)	<u>Higher level facility</u> Median CD4% 6 (IQR 2-12) <u>Lower level facilities</u> Median CD4% 5 (IQR 2-11)	<u>Higher level facility</u> (copies/ml) (available in 38 patients) 133,570 (IQR 49380-230700)  <u>Lower level facilities</u> (copies/mL) (available in 22 patients) 80400(IQR 17622-153032)	<u>Higher level facility</u> Median WAZ score (%) -1.6 (IQR -2.6 to -0.8) <u>Lower level facilities</u> Median WAZ score (%) -2.1 (IQR -2.8 to -1.5)	NR
Van Dijk et al (2014)	See table 1	<u>Severe immunosuppression (%)</u> <u>Higher level facility</u> 23(62.2%) <u>Lower level facilities</u> 36(65.5%)	See table 1	NR	<u>Higher level facility</u> Median WAZ score (%) -1.7 (IQR -2.5 to -0.7) <u>Lower level facilities</u> Median WAZ score (%) -2.3 (IQR -3.6 to -1.3)	NR
Morsheimer et al (2014)	See table 1	<u>Down referred on ART to lower level facilities</u> WHO clinical stage (%) 89.8 stage III/IV	See table 1	<u>Down referred on ART to lower level facilities</u> Median VL log <sub>10</sub> 5.5 (IQR 4.8 -6.0)	NR	<u>Down referred on ART to lower level facilities</u> TB (%) 25.3

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, TB: Tuberculosis, WHO: World Health Organization, ART: Antiretroviral therapy, VS: versus, VL: viral load, sd: standard deviation, WAZ: Weight for age z score, HAZ: height for age z-score.

**Table 4: Characteristics of adults at ART initiation continued.**

Author	Age	Disease severity	CD4	Tuberculosis
Chan et al (2010)	See table 2a	<p><b>Higher level facility</b> WHO clinical stage (%) Stage 3 2394 (51.5) Stage 4 1076 (23.1)</p> <p><b>Lower level facilities</b> Stage 3 1906 (55.4) Stage 4 572 (16.6)</p>	See table 2a	NR
Brennan et al (2011)	See table 2a	<p><b>Higher level facility</b> WHO clinical stage (%) Stage 3 792 (38.1) Stage 4 120 (5.8)</p> <p><b>Lower level facilities</b> Stage 3 254 (36.7) Stage 4 43 (6.2)</p>	<p><b>Higher level facility</b> Median CD4 count Median CD4 count cells/mm<sup>3</sup> 101 (IQR 40-168)</p> <p><b>Lower level facilities</b> Median CD4 count cells/mm<sup>3</sup> 108 (IQR 43-168)</p>	<p><b>Higher level facility</b> 362 (17.4%)</p> <p><b>Lower level facilities</b> 104 (15.0%)</p>
Long et al (2011)	See table 2a	NR	<p><b>Higher level facility</b> Median CD4 count cells/mm<sup>3</sup> 94 (IQR 36-163)</p> <p><b>Lower level facilities</b> Median CD4 count cells/mm<sup>3</sup> 103 (IQR 41-168)</p>	NR

CI: Confidence interval, IQR: Interquartile range, WHO: World Health Organization, ART: Antiretroviral therapy, WAZ: Weight for age z score, HAZ: height for age z-score.

## **5 Patient characteristics at ART initiation/transfer out**

The tables (1-4) above summarize the characteristics of patients included in this review at ART initiation or at transfer out. Patient-level variables of age, HIV/AIDS WHO/Center for Disease Control and Prevention (CDC) clinical stage, and immunovirological status were commonly reported in both adult and paediatric studies. These characteristics were mostly comparable between patients managed at higher level facilities compared to those transferred out to lower level facilities for continuation of HIV care. In general, nine studies reported the regimen used by their patients (10, 18-20, 22, 23, 29). In addition, two paediatric studies reported weight-for-age z-score (WAZ) in their patients (10, 29).

The quasi-experimental design method adopted by South Africa (SA) studies (18) and (19) ensured comparable characteristics in patients at transfer out eligibility. Other patients characteristics reported at ART initiation was the prevalence of HIV co-morbidity with tuberculosis and this was reported in two studies: one paediatric and one adult study (17, 18).

### **5.1 Age**

All but one paediatric study included in this review reported the median/mean age of their participants (35). In the *Zambian study*, the median age of children transferred out to lower level facilities was younger 2.9 years (IQR 1.7-7.3 years) compared to those managed at a higher level facility 5.9 years (IQR 2.4-10.4 years), suggesting that younger children were more likely to be transferred out (29). While age was comparable between those transferring out and those remaining at the initiation site in other studies, the age of children included in each study was very different. In a *Thailand study*, the median age was 8.6 years raising the question of generalizability to younger children. In contrast, a study conducted in the *Western Cape Province of SA* utilizing

routine data from one of the three tertiary hospitals in Cape Town (Tygerberg Children's Hospital) had the youngest participants with cohort median age of 25.1 months (IQR: 10.5 – 59.3 years) (17). Age at transfer out is a key consideration in children because of rapid early disease progression in younger children (36).

In the adult studies included in this review age was comparable irrespective of where patients received HIV care. The median age of the adult participants at ART initiation across the studies included in this review ranged from 32.9 years to 38.5 years (15, 19).

## **5.2 Virological status**

Only a handful of studies reported viral load measurements due to the lack of capacity for viral load monitoring in most LMICs. Among paediatric studies, the Thailand study reported a lower median viral load (copies/mL) of 80 400 copies/mL (IQR 17 622 – 153 022 copies/mL) in 22 patients' transferred out to lower level facilities compared to 133 570 copies/mL (IQR 49 380 – 230 700 copies/mL) in 38 patients' managed at higher level facilities at ART initiation (10). This difference is probably because sicker patients tend to be managed at higher level facilities before being transferred out to lower level facilities for continued HIV care. However, the number of patients with viral load measurements was quite small at both levels of health care. In the same vein, in the Tygerberg children's hospital study, the median viral load at ART initiation was 326 969 copies/mL (IQR 87 841 – 1 554 457 copies/mL) in children transferred out to lower level facilities compared to 230 000 copies/mL (IQR 32 000 – 830 000 copies/mL) in patients initiated on ART and managed at primary health care (PHC) facilities (17).

No adult study reported viral load measurements at ART initiation. However, Luque-Fernandez et al (2013) reported that 2501 (88.4%) of their patients were virologically suppressed before adherence club participation. The high proportion of virologically suppressed patients might be due to the fact only stable patients were presented with the option of adherence club (15).

### **5.3 Immunological status**

CD4 count, percentage or both measures were reported in most studies included in this review. Paediatric studies mostly reported CD4 percentage:

The Thailand paediatric study, reported comparable but very low median (IQR) CD4% among children managed at higher level facility and those transferred out to lower level facilities (6% (IQR 2-12%) vs 5% (IQR 2-11%)) respectively (10). A Zambian paediatric study reported comparable but higher median CD4% among patients' managed at higher and lower levels facilities (14.4% (IQR 11.0–19.5%) and 14.2% (IQR 10.5 – 18.9%)) respectively at ART initiation (29). However, children transferred out from Tygerberg children's hospital had a slightly higher overall CD4% of 16% (IQR 10.0 – 21.8) at ART initiation (17).

In adult studies, the median CD4 counts of patients' at ART initiation were generally low. The vast majority of patients had CD4 count cells of  $< 350 \text{ cells/mm}^3$  at initiation in line with the 2010 WHO ART guidelines recommendation that adults living with HIV with CD4 count cells of  $< 350 \text{ cells/mm}^3$  should be started on ART (37). Median CD4 count in the different studies ranged from  $94 \text{ cells/mm}^3$  (19) –  $202 \text{ cells/mm}^3$  (15). CD4 count characteristics were similar for patients' managed at either level of health care.

#### **5.4 Clinical disease classification**

The WHO classification of disease status was used in all but one study included in this review (38). The latter study used the 1993 CDC classification to assess the severity of HIV disease (10, 39). The Tygerberg children's hospital study found that nearly 90% of children transferred out to lower level facilities had advanced/severe clinical status of HIV disease at ART initiation (17). In addition, 40% (61/154) of children transferred out to lower level facilities were classified to have severe HIV disease at ART initiation based on CDC clinical staging compared to 25% (33/133) of children managed at a higher level facility in Thailand (10).

Among adult patients, those managed at higher level facilities had relatively better clinical status at ART initiation compared to patients' transferred out to lower level facilities. For example, the Indian study reported that 84% of patients managed at higher level facilities had WHO clinical stage 3 or 4 disease compared to about 93% of patients transferred out to lower level facilities at ART initiation (28).

#### **5.5 Presence of tuberculosis.**

Only one paediatric study and one adult study reported the proportion of their patients' with tuberculosis co-infection (17, 19). Among children who initiated ART at Tygerberg children's hospital, 25.3% of them had tuberculosis co-infection at ART initiation (17) and Brennan et al (2011) reported 17.4% prevalence of tuberculosis co-infection in patients' managed at higher level facility compared to 15.0% in those transferred out to lower level facilities (18).

## **5.6 Growth**

Child growth was assessed using weight-for-age Z-score (WAZ) in two paediatric studies. The Thailand paediatric study, calculated WAZ using the Thailand national standards for height and weight adapted from WHO guidelines and reported a median WAZ of -1.6 (IQR -2.6 to -0.8 ) in children managed at a higher level facility compared to -2.1 (IQR -2.8 to -1.5) for those transferred out to lower level facilities at ART initiation (10, 40). In Zambia, using WHO growth reference standards the median WAZ was -1.7 (IQR -2.5 to -0.7 ) in children managed at higher level facility compared to -2.3 (IQR -3.6 to -1.3 ) for those transferred out to lower level facilities at ART initiation (29). These results suggest that children managed at higher level facilities had better nutritional status at ART initiation compared to those transferred out to lower level facilities.

## **5.7 Anemia**

Anemia is a risk factor for death in HIV-infected patients and this can occur at any clinical stage of the disease (41, 42). Only Brennan et al (2011) reported the haemoglobin of their patients at ART initiation. Patients managed at higher level facility median haemoglobin was 13.8 ug/dL (IQR 12.9 – 14.9 ug/dL) compared to 14.1 ug/dL (IQR 13.1–15.2 ug/dL) in patients transferred out to lower level facilities (18).

## **5.8 Regimen**

First-line ART regimens were reported by a number of the studies reviewed. The most commonly used first-line regimen was two nucleoside reverse transcriptase inhibitors (NRTI) with a non-nucleoside reverse transcriptase inhibitors (NNRTI) regimen (10, 18-20, 22, 23, 29). Two studies excluded patients' on second line regimens (18, 22), and a paediatric study excluded patients

initiated on protease inhibitor-based regimens to account for potential bias in patients' immunological and virological status (10).

In general, patients had improved immunovirological and clinical characteristics at transfer out compared to ART initiation characteristics in both paediatric and adult studies (10, 18, 19, 23, 26).

**Table 5: Outcomes of paediatric studies.**

Author	Follow-up	Mortality rate	Mortality (cumulative probabilities)	Loss to follow-up	Virological	Immunological (CD4)	Adherence
Bock et al (2008)	18 months	<b>Incidence rate ratio of PHC Vs level 2 &amp; 3 children</b> 6m: aIRR 0.33 p< 0.001) 12m: aIRR 0.39 p< 0.003) 18m: aIRR 0.38 p< 0.018)	<b>Survival (Death &amp; LTFU)</b> <b>Higher level facilities</b> 6m: 0.91(CI 0.89-0.93) 12m:0.88(CI 0.86-0.91) 18m: 0.85(CI 0.81-0.88) <b>District level facilities</b> 6m: 0.96(CI 0.91-0.98) 12m: 0.94(CI 0.89-0.97) 18m: 0.94(CI 0.88-0.97) <b>Lower level facilities</b> 6m: 0.94(CI 0.89-0.96) 12m: 0.94(CI 0.89-0.96) 18m:0.92(CI 0.87-0.95)	See mortality cumulative probability	<b>Viral load suppression (%)</b> <b>Higher level facilities</b> 6m: 70.4(CI 66.4-74.2) 12m:70.5(CI 64.9-75.8) 18m:71.6(CI 60.5-81.1) <b>District level facilities</b> 6m: 61.2(CI 51.1-70.6) 12m:90.9(CI 80.0-96.9) 18m:90.3(CI 74.2-97.9) <b>Lower level facilities</b> 6m: 87.6(CI 81.1-92.5) 12m:81.4(CI 72.4-88.4) 18m:76.9(CI 63.2-87.5)	<b>CD4 &gt;20%</b> <b>Higher level facilities</b> 6m: 59.1(CI 54.9-63.1) 12m:73.3(CI 67.9-78.3) 18m: 100 <b>District level facilities</b> 6m: 65.5(CI 55.8-74.3) 12m:74.2(CI 60.9-84.7) 18m:90.3(CI 74.2-97.9) <b>Lower level facilities</b> 6m: 63.6(CI 54.6-71.9) 12m:83.9(CI 74.8-90.7) 18m:90.9(CI 78.3-97.5)	NR
Hansudewchakul et al (2012)	48 months	<b>Higher level facility</b> Total: 42 over 1,016CY Crude mortality rate: 4.1/100CY (CI 3.0-5.6). <b>Lower level facilities</b> No mortality was reported among 158 children followed up at lower health facilities through the median months of 29 (IQR 20-40)	NR	<b>Lower level facility Vs higher level facilities.</b> none of the patients was loss to follow-up regardless of the level of health care.	<b>Viral load suppression (%)Higher level facility</b> 12m: 1/37(2.7%) 24m: 1/35 (2.85%) 36m: 1/35 (2.85%) 48m: 0/27 (0%) <b>Lower level facilities</b> 12m: 0/20(0%) 24m: 0/16 (0%) 36m: 0/18 (0%) 48m: 1/18 (5.6%)	<b>Median CD4% change</b> <b>Higher level facility</b> CD4% at time of transfer: 6% (IQR2-13) <b>Lower level facilities</b> CD4% at time of transfer: 5% (IQR 2-11)  Median difference between HP Vs OC children was 19% and 21% respectively p=0.207)	<b>Higher level facility in 73-93% of patients</b> 93 - 100%  <b>Lower level facilities in 83-95% of patients</b> 95 - 100%
Van Dijk et al (2014)	36 months	NR	NR	NR	<b>All measures during follow-up (473)</b> VL > 400 copies/mL was likely detectable in children in lower health facilities compared to children in higher level facility (17% Vs 8%, p=0.002).	Mean difference between last visit and 6 months after transfer (mean difference was -1.4, (-4.5, 1.7 <sup>CI</sup> p = 0.37) among HP Vs OC children	<b>Higher level facility <sup>a</sup></b> 79.3% <b>Lower level facilities</b> 69.2%
Morsheimer et al (2014)	25.1 months (IQR 10.5-59.3)	<b>3months of transfer from higher health facility: 1/153 (0.65%)</b>	NR	NR	96% of children down referred with VL suppressed remained suppressed at the last study evaluation. 77% of children down referred with subtherapeutic response to ART achieved VL suppression.	NR	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, VL: viral load, CY: child year, aIRR: adjusted incidence rate ratio, HR: hazard ratio, a: median % of visits with optimal adherence, HP: Hospital affiliated, OC: Outreach clinic.

**Table 6a: Outcomes adult studies.**

Author	Follow-up	Mortality rate	Mortality (cumulative probabilities)	Loss to follow-up	Virological	Immunological (CD4)	Adherence
Yu et al (2008)	24 months	NR	<u>Odds of mortality between patients successfully transferred in Vs not down-referred</u> OR:0.4(CI 0.3-0.06)	<u>Traced transferred out patients</u> 22 of 634 alive and on ART (4%) <u>Not transferred out</u> 120 of 3370 ART (3.5%)	NR	NR	NR
Chan et al (2010)	50 months	NR	<u>Odds of mortality between patients follow up at lower health facilities Vs higher facility</u> aOR 0.19(CI 0.15-0.25)	<u>Cumulative probability of LTFU between patients follow up at lower level facilities Vs higher level facility</u> aOR 0.48(CI 0.40-0.58)	NR	NR	NR
Brennan et al (2011)	12 months	NR	<u>Mortality Lower health facilities Vs higher health facility</u> aHR 0.2(CI 0.04-0.8)	<u>Lower health facilities Vs higher health facility.</u> aHR 0.3(CI 0.2-0.6)	<u>Viral rebound (cumulative probability) Lower health facilities Vs higher health facility.</u> aHR 0.6(CI 0.4-0.9)	<u>Change in CD4 count Higher level facility</u> Median increase in CD4 count: 59 cells/mm <sup>3</sup> (IQR -12 - 146) <u>Lower level facilities</u> Median increase in CD4 count: 55 cells/mm <sup>3</sup> (IQR -24 - 127)	NR
Long et al (2011)	12 months	<u>Mortality (%) Higher level facility</u> 25/2136 (1.2%) <u>Lower health facilities</u> 0/712 (0%)	<u>Relative risk (Death &amp; LTFU) of patients in lower facilities Vs higher health facility.</u> RR 0.27(CI 0.15-0.49)	<u>LTFU (%) Higher level facility</u> 108/2136 (5.1%) <u>Lower level facilities</u> 12/712 (1.7%)	NR	NR	NR
Connor et al (2011)	Mean follow-up time of 0.57 years	NR	NR	<u>LTFU (%)</u> 4.11% of 3361 patients	NR	NR	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, VL: viral load, Viral Rebound: > 1000 copies/ml after suppression, OR: Odd ratio, aOR: adjusted odd ratio, HR: hazard ratio, aHR: adjusted hazard ratio, LTFU: Loss to follow-up

**Table 6b: Outcomes of adult studies continued.**

Author	Follow-up	Mortality rate	Mortality (cumulative probabilities)	Loss to follow-up	Virological	Immunological (CD4)	Adherence
Decroo et al (2011)	Median follow-up time within a group was 12.9 months (IQR 8.5-14.1)	<u>Mortality (%)</u> 12.9m: 30/1301 (2.3%)	NR	<u>LTFU</u> 12.9m: (0.2%) 2/1301	NR	NR	<u>Adherence (%) n= 1269</u> (92%) 1173/1269
Luque-Fernandez et al (2013)	8821 patient years	<u>Mortality and LTFU</u> <u>Higher level facility</u> 116.8 per 1000py <u>Lower level facility</u> 29.8 per 1000py	<u>Overall cumulative probability of mortality and LTFU between lower and higher level facilities.</u> aHR 0.43(CI 0.21-0.91)	NR	<u>Overall cumulative probability of virologic rebound between lower and higher level facilities.</u> aHR 0.33(CI 0.16-0.67)	NR	<u>Adherence (%) n= 502</u> <b>97%</b>
Grimsrud et al (2014)	60 months	See mortality cumulative probability	<u>Overall cumulative probability of mortality and LTFU between lower and higher level facilities.</u> aHR 1.51(CI 0.90-2.55)	<u>Cumulative probability of LTFU between patients follow up at lower health facilities Vs higher facility</u> aHR 1.36(CI 1.09-1.69)	<u>Cumulative probability of Viral load failure between lower level facilities and higher level facility.</u> aHR 0.94(CI 0.78-1.13)	NR	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, VL: viral load, Viral load failure: > 1000 copies/ml after suppression, aHR: adjusted hazard ratio, LTFU: Loss to follow-up.  
Py: person year

## **6 Outcomes**

Clinical outcomes (successful transfer, mortality, loss to care and loss to follow-up (LTFU)), as well as immunological and virological, outcomes, were reviewed (Tables 5-7).

### **6.1 Successful transfer**

In keeping with the focus of this study “successfully transferred” are patients’ that successfully re-engaged with HIV care at transferred out lower level facilities during a specified time interval. The transfer from one facility to another is potentially a period of high risk of LTFU when patients may be unable to re-engage in care at a facility that is not familiar to them. Successful transfer in this context is methodologically the opposite of loss to programme at the time of transfer. In evaluating the effectiveness of the decentralization model of HIV care in LMICs, a better understanding of patients transfer pattern is critical as the effective transfer of patients through the HIV continuum of care is central to the success of decentralized care models.

While some studies report on LTFU overall and outcomes after transfer out, only seven adult studies and no paediatric studies reported on successful transfer itself, due to the challenges in tracking transferring patient outcomes in LMICs (43). The proportion of patients that successfully transferred to a referral site ranged from 78% to 96% (21, 24). A median time to successful transfer of 1.3 months was reported in a Malawian study. Since medication is dispensed monthly, this means that a substantial number of patients may have interrupted treatment for more than 2 weeks before presenting at the transfer out site.

Furthermore, a Kenyan study found that patients formally transferred to lower level facilities are more likely to re-engage with HIV care at lower level facilities than those not formally transferred. However, even among patients successfully transferring, about 40% could have experienced a treatment interruption defined as a treatment gap of greater than 14 days (24). The tracking methods adopted by these studies were mostly resource intensive and might be expensive to replicate routinely in a large decentralization programmes. None of the seven studies used an electronic record system to track the movement of transferring patients (Table 7).

**Table 7: Successful transfer outcome**

Author	Proportion of successful transfer.	Median time to successful transfer	Tracking Method
Hickey et al (2016)	96% of 23	Cumulative incidence of successful transfer at 3 months after last appointment at higher level facility 91% (95% CI 69-98%).	Chart abstraction.
Colasanti et al (2016)	$\left(\frac{436}{458}\right) = 95\%$	NR	Self-reported questionnaire.
Ghate et al (2014)	$\left(\frac{123}{158}\right) = 78\%$	NR	Telephonic calls to transferred out patients or sites.
Yu et al (2008)	$\left(\frac{737}{805}\right) = 92\%$	1.3 months	Telephonic calls to transferred-out sites + Active follow up
Connor et al (2011)	$\left(\frac{3208}{3361}\right) = 96\%$	NR	Active patients recording tracing + Active follow up + Telephonic calls to patients.
Searle et al (2010)	$\left(\frac{1624}{2071}\right) = 78\%$	NR	File Audit.
Cloete et al (2014)	82% of 3913	NR	Self-reported + validation through survey.

NR: Not reported

## 6.2 Mortality/survival

Ten studies reported mortality or survival outcomes, most commonly as cumulative probabilities using a product limit estimator.

Nonetheless, the Thailand paediatric study presented a crude death rate of 4.1 per 100 child years in children managed at higher level facility compared to no mortality reported in those transferred out to lower level facilities. The authors explained the 100% survival of children transferred out to lower level facilities by the fact that these children were stabilized on ART with at least 6 months follow-up time at higher level facility before transfer out occurred (10). Furthermore, the Tygerberg children's hospital study reported 1 death among 153 children transferred out to lower level facilities within 3 months of transfer out (17). This result could also be due to the fact that children transferred out were stable on ART because 80% had a suppressed viral load at the time of transfer out for continuation of HIV care (17).

A number of studies compared mortality in those treated at different level of health care or in those transferred out to lower level facilities compared to those remaining at higher level facilities. In children, Bock et al (2008) reported a reduced mortality risk in children managed at level 1 health care facilities (PHC) compared to level 2 and 3 health care facilities at 6 months (IRR=0.33  $p<0.001$ ), at 12 months (IRR=0.39  $p<0.003$ ) and at 18 months (IRR=0.38  $p<0.018$ ). This study did not present the confidence intervals for effect size estimates (13).

Almost all adult studies showed lower mortality among patients transferred out to lower level facilities compared to those remaining at high level facilities with estimates of the effect ranging from aHR 0.2; (CI 0.04-0.80) at 12 months on ART (18) to aHR 1.51; (CI 0.90-2.55) at 60 months

on ART (22). The latter study is the only one to show evidence of an increased risk of mortality in patients transferred out to lower level facilities compared to those managed at higher level facility, however this was not significant.

While it is possible that even in adjusted analyses there is residual confounding with patients that are clinically well-being preferentially transferred to lower level facilities, these results suggest at a minimum that mortality in stable patients on ART is no worse when transferred to lower level facilities versus remaining at higher level facilities.

### **6.3 Loss to follow-up**

Despite the WHO definition of LTFU or drop as > 90 days from missed clinical or drug pickup appointment without any follow-up contact (44), disparate definitions of LTFU were used by researchers to assess this outcome. Benjamin et al (2011) suggested a universal definition of LTFU as no clinic visit 180 days after the last visit to clinic and before database closure (45). However, this is a “retrospective” definition of LTFU mainly used to assess the likely completeness of mortality outcomes. In contrast, the WHO definition is prospective and allows focuses on all gaps in care (46).

Bock et al (2008) reported less attrition (describe as patients who died plus those LTFU) in children managed at lower levels facilities of Western Cape Province, SA through 18 months of follow-up (13). Remarkably, the Thailand paediatric study showed that no child was loss to care at both lower and higher level facilities through 24 months of follow-up (10). All adult studies that reported

LTFU showed less LTFU in patients managed at lower level facilities compared to those managed at higher level facilities (18, 19, 22, 27).

In summary, these results suggest that the decentralization of patients to lower level facilities reduces loss to follow-up, possibly because patients are being seen at facilities that are closer to their homes with fewer barriers to access the facility.

#### **6.4 Adherence Outcomes**

Patients' adherence to treatment was described in two adults and two paediatric studies. Optimal adherence was consistently defined as at least 95% pills or liquid medications taken based on pill counts or volume measurement. In Thailand, children had similar and high adherence of 100% irrespective of the level of facilities at which they were managed through 48 months of follow-up (10). In contrast, the Zambian paediatric study reported better adherence in children managed at higher level facilities compared to those managed at lower level facilities. However, the median percentage of optimal adherence before and after transfer was not different for children transferred out, 75% (IQR:50-100) and 75% (IQR:44-100) respectively. Nevertheless, this study also reported that 99% of 77 caregivers agreed that lower level facilities were closer to their homes compared to ART initiation sites (29). Both adult studies of community decentralized models of ART care reported similar and good adherence measured by self-report (14, 15).

#### **6.5 Virological Outcomes.**

Virological outcomes were measured in seven studies including all studies in children (10, 13, 17, 29) which is encouraging considering that viral load monitoring is not always routinely available

in LMICs. This is also important because this outcome could serve as a proxy measurement for patients' adherence to treatment.

Bock et al (2008), found that viral load suppression was highest at level 1 (lower level) facilities compared to level 3 facilities at 12 and 18 months on ART (13). Transfer out to lower level facilities of stable children might partly explain the better viral load outcome of patients in lower level facilities.

In contrast, there was a higher proportion of viral load suppression in Thailand's children managed at higher level facilities compared to those transferred out to lower level facilities at 12, 24 and 36 months respectively. However, the number of children with viral load results at each interval was low and children transferred out to lower level facilities had a relatively smaller proportion with viral load data (10). Similarly, the Zambian paediatric study also reported that viral load (> 400 copies/mL) was more likely in children managed at lower level facilities compared to those managed at a higher level facility (29). It is possible that at lower level facilities children who were less well were more likely to undergo viral load testing, accounting for lower viral suppression.

In contrast, among children transferred out of Tygerberg children's hospital, who had suppressed viral load at the time of transfer out (80% of 153), virologic suppression was maintained in 96% after a median follow-up of 2 years. In addition, 77% of the 26 children not virologically suppressed at transfer achieved virologic suppression after 6 months of support and treatment at lower level facilities.

In adult studies, Brennan et al (2011) reported an increased probability of viral rebound (> 400 copies/mL) in patients managed at a higher level facility compared to those managed at lower level facilities at 12 months follow-up (18). Similarly, a community decentralized ART study reported a decreased cumulative probability of viral rebound in patients managed in the community compared to those managed at the ART initiation facility (15). Furthermore, Grimsrud et al (2014) found that patients managed at lower level facilities are less likely to experience virologic failure compared to higher level facilities at 60 months of follow-up (22). Nonetheless, in the SA adherence club study patients in a community adherence club are less likely to experience virologic rebound compared to those not in adherence club (15).

These results put together suggests that patients' virologic trajectories continued to improve at lower level facilities or at the community. This also underscores the fact transferring patients to lower level facilities closer to their home can also help improve their adherence to treatment.

## **6.6 Immunological outcome**

Only three paediatric studies and one adult study reported on CD4 outcomes. Bock et al (2008) reported a comparable increase in the proportion of children with CD4% > 20% in children managed at the level 1, 2 and 3 facilities through 18 months on ART, using programme-level data (13). Similarly, the Thailand and Zambian paediatric studies showed that changes in CD4% in children transferring to lower level facilities were comparable to children remaining at higher level facilities through 36 and 48 months respectively (10, 29).

In contrast, the only adult study that reported the immunological outcome of patients reported a better median increase in CD4 count in patients managed at a higher level facility compared to those managed at lower level facilities at 12 months of follow-up (18).

## **7 Determinants of patients' outcome**

The predictors of primary outcomes that were assessed were at ART initiation/ at time of transfer out characteristics of clinical, immunological, virological, disease severity, treatment regimen and follow-up time, as well as socio-demographic variables of age, sex, gender, education level, employment status, levels of health care, orphan status, transfer pattern, attributable stigma, distance from health facility and marital status (Tables 8-9c).

### **7.1 Determinants of successful transfer outcome**

Of note, four adult studies assessed the predictors of successful transfer/relinkage to care (21, 24-26). These studies assessed both patient-level characteristics and structural-level characteristics which include HIV care programme characteristics.

In India, patients' that were either single, divorced or widowed were more likely to re-engage with care at transfer out facilities in univariate regression analysis. However, the reported odds ratio was imprecise with large confidence intervals due to the small sample size of the study and an adjusted analysis was not presented (21).

An SA study found that patients who were not pleased with the transfer out facilities were less likely to re-engage with care (25). Similarly, attributable stigma was identified as a predictor of

patients' failure to re-engage with care in Kenya (24). Other patient-level characteristics identified to be associated with patients' reengagement with HIV care in SA were better adherence score and shorter duration of ART before transfer (25).

At the programme level, "official transfer" was identified as a significant predictor of patients' reengagement with care in Kenya (24). Cloete et al (2014) described the structural factors associated with not being found at transfer out facilities. For every 1 kilometre that the transfer out facility was from the higher level facility there was an increased risk of patients not being found in care. This highlights the fact that transferring patients to a site closer to their home might be effective in keeping patients' in care (26). In addition, patients' on second-line ART transferred out to lower level facilities were less likely to transfer successfully (26).

## **7.2 Determinants of mortality outcome.**

Predictors of mortality were presented in two paediatric studies. Lower level facilities were associated with reduced mortality through 18 months follow-up in an SA paediatric study (13). Furthermore, In Thailand, children severely underweight and those with severe immune suppression ( $CD4 < 5\%$ ) were found to be associated with increased mortality in multivariate analysis (10).

Of the seven studies that described the predictors of their outcomes in adult studies, five of these studies reported the predictors of mortality (18, 19, 22, 27, 28). All of the five studies reported lower level facilities as an independent predictor of reduced risk of mortality in univariate regression analyses. Lower level facilities and community adherence clubs remained associated with reduced risk of mortality in multivariate regression analyses presented by four studies (15,

18, 27, 28). In addition, the predictors of LTFU were assessed in five adult studies (15, 18, 19, 22, 27). Three of these studies reported lower level facilities and community adherence clubs as associated with reduced risk of LTFU (15, 18, 27).

### **7.3 Determinants of viral load and adherence outcome.**

The Zambian paediatric study, assessed the predictors of viral load suppression using a generalized estimating equation model with levels of health care facility as a time dependent covariate (29). Patients managed at lower level facilities had increased risk of detectable viral load defined as >400 copies/mL, >1000 copies/mL and >10000 copies/mL through 3 years of follow-up (29).

Furthermore, patients' characteristics associated with viral load rebound were assessed in five studies, which included one paediatric study (17-19, 22). The results of these analyses suggest that lower level facilities or community ART club are associated with reduced risk of viral load rebound in all but one study. The Tygerberg children's hospital study reported that children initiated on ART at PHC are less likely to experience viral rebound compare to patients transferred out from higher level health care facility (17). This result raised the question about the level of adherence of patients transferred out from higher level facilities and suggests that patients transferred out may experience an interruption in treatment during the transition period.

The predictors of adherence were assessed by the Zambian paediatric study. The result suggests that children transferred out to lower level facilities are less likely to achieve optimal adherence defined as the > 95% clinic visits. However, this result was not significantly different from children managed at higher level facility (29).

**Table 8: Predictor of outcomes in paediatric studies.**

Author	Primary Outcome identified	Successful transfer outcome	Mortality outcome	Loss to follow-up	Virological outcome	Adherence
Bock et al (2008)	Mortality	NR	<p><b>Reference:</b> Level 2 and 3 hospitals PHC: <u>6m:</u> aIRR = 0.33 (p&lt;0.001) <u>12m:</u> aIRR = 0.39 (p=0.003) <u>18m:</u> aIRR = 0.38 (p=0.018)</p>	NR	NR	NR
Hansudewechakul et al (2012)	Mortality	NR	<p><b>Reference:</b> &gt;5% &lt; 5% at ART initiation: aHR:3.1(CI 1.2 -7.7)</p>	NR.	NR	NR
Van Dijk et al (2014)	Viral load suppression	NR	NR	NR	<p><b>&gt;10000copies/mL</b> <b>Reference:</b> Higher level facility Lower level facilities: aOR:5.14(CI 1.50 -17.61)</p>	<p><b>Reference:</b> Higher level facility Lower level facilities: aOR:0.69(CI 0.41-1.15)</p>
Morsheimer et al (2014)	Virologic failure	NR	NR	NR	<p><b>Reference:</b> Down referred patients PHC initiated patients: aOR:0.34(CI 0.31-0.84)</p> <p>Also every 1 log increase in baseline VL, the odds of developing VF doubled. CI (1.3-3.2)</p>	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, VL: viral load, PHC: Primary Health Care, ART: Antiretroviral therapy, aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted Odds ratio.

**Table 9a: Predictor of outcomes in adult studies.**

Author	Primary Outcome identified	Successful transfer outcome	Mortality outcome	Loss to follow-up	Virological	Adherence
Yu et al (2008)	Death	NR	<b>Reference:</b> Not down-referred Down-referred: aOR:0.4(CI 0.3-0.06)	NR	NR	NR
Chan et al (2010)	Mortality, LTFU	NR	<b>Reference:</b> Higher level facility Lower level facilities: aOR:0.19(CI 0.15-0.25)	<b>Reference:</b> Higher level facility Lower level facilities: aOR:0.48CI (0.40-0.58)	NR	NR
Brennan et al (2011)	Down-referral, mortality, LTFU, viral load rebound	NR	<b>Reference:</b> Not down-referred Down-referred: aHR:0.2(CI 0.04-0.8)	<b>Reference:</b> Not down-referred Down-referred: aHR:0.3(CI 0.2-0.6) <b>Reference:</b> ≥ 50 years 18-24.9 years: aHR:3.1(CI 1.1-8.6)	<b>viral load rebound</b> <b>Reference:</b> Not down-referred Down-referred: aRR:0.6(CI 0.4-0.9) <b>Reference:</b> ≥ 50 years 25-29.9 years: aRR:3.1(CI 1.2-8.0)	NR
Long et al (2011)	Virologic failure, death and LTFU	NR	<b>No longer in care (death &amp; LTFU)</b> <b>Reference:</b> Treatment initiated site Down-referred sites: RR:0.27(CI 0.15-0.49)	See mortality.	<b>in care and responding to treatment (undetectable viral load/sufficient change in CD4)</b> <b>Reference:</b> Treatment initiated site Down-referred sites: RR:1.07(CI 1.04-1.09)	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, ART: Antiretroviral therapy, aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted Odds ratio, RR: risk ratio.

**Table 9b: Predictor of outcomes in adult studies continued**

Author	Primary Outcome identified	Successful transfer outcome	Mortality outcome	Loss to follow-up	Virological	Adherence
Luque-Fernandez et al (2013)	Death/LTFU, adherence and virologic rebound	NR	<u>loss to care (death/LTFU)</u> <u>Reference:</u> Not in adherence club Adherence club: aHR:0.43(CI 0.21-0.91)	See mortality	<u>Virologic rebound</u> <u>Reference:</u> Not in adherence club Adherence club: aHR:0.33(CI 0.16-0.67)	<u>Adherence club enrolment</u> <u>Reference:</u> Females males: HR:0.75(CI 0.60-0.93)
Ghate et al (2014)	Transferred in	<u>Transferred in</u> <u>Reference:</u> Living with partner Not living with a partner: OR:4.53(CI 1.24-16.51)	NR	NR	NR	NR
Grimsrud et al (2014)	LTFU	NR	NR	<u>Reference:</u> Higher level facility Lower level facilities: aHR:1.36(CI 1.09-1.69)	NR	NR
Cloete et al (2014)	Not successfully transfer	Every 1KM from clinic: aRR:1.07(CI 1.02-1.13) Patients on 2 <sup>nd</sup> line regimen assigned to community health clinic: aRR:1.70(CI 1.20-2.42)	NR	NR	NR	NR

NR: Not reported, CI: Confidence interval, IQR: Interquartile range, ART: Antiretroviral therapy, aHR: adjusted hazard ratio, OR: Odds ratio, HR: hazard ratio, aRR: adjusted risk ratio, KM: Kilometres

**Table 9c: Predictor of outcomes in adult studies continued**

Author	Primary Outcome identified	Successful transfer outcome	Mortality outcome	Loss to follow-up	Virological	Adherence
Colasanti et al (2016)	Retention in care	<p><b><u>Patient sentiment towards attending the clinic</u></b>  <b>Reference:</b> Not pleased with the clinic  Pleased with the clinic:  aOR:3.07(CI 1.13-8.34)</p> <p><b><u>Adherence score</u></b>  <b>Reference:</b> &lt; median score  ≥ median score:  aOR 3.89(CI 1.21-12.48)</p> <p><b><u>Duration of ART</u></b>  <b>Reference:</b> Short duration  Longer duration:  aOR 0.96(CI 0.93-0.99)</p>	NR	NR	NR	NR
Hickey et al (2014)	Relinking to care	<p><b><u>Transfer status</u></b>  <b>Reference:</b> Without official transfer  Official transfer: aHR 6.15(CI 3.44-11.0)</p> <p><b><u>Attributable stigma</u></b>  1-point increase in perceived stigma in the community:  aHR: 0.90(CI 0.84-0.96)</p>	NR	NR	NR	NR

NR: Not reported, CI: Confidence interval, IQR: ART: Antiretroviral therapy, aHR: adjusted hazard ratio, aOR: adjusted Odds ratio

## 8 Summary, interpretation and needs for further research

Despite an extensive search, there were only fifteen studies that met the pre-specified inclusion and exclusion criteria for this review with two additional studies (21, 28) identified from the bibliography search of these studies. Only four of the studies were done specifically in children. The primary focus of our study, namely successful transfer, was sparsely reported in the studies included. Indeed, no paediatric study aimed to assess this outcome, which is not surprising because conventional survival analyses censor patients at transfer out date (47). Seven adult studies reported on this outcome, but the review highlights the resource intensive methods required to be able to do this. Most studies showed a high proportion of patients successfully transferring and an encouragingly short median time to successful transfer of 1.3 months in Malawi underscoring the effectiveness and feasibility of decentralizing HIV care to lower level facilities in LMICs (28). Nevertheless, some studies reported delays in time to successful transfer which could result in treatment interruptions.

None of the seven studies that reported on the transfer status of patients' used a laboratory or an electronic monitoring system to monitor the movements of their patients' transferring between ART sites. These studies tracked their transferring patient's through resource-intensive methods, which might be logistically challenging for a large decentralization programme and cannot be implemented as part of routine programme evaluation. Nonetheless, an SA paediatric study extracted missing laboratory tests of children transferred out from Tygerberg children's hospital using SA NHLS data (17), suggesting that the approach of our study is feasible and that the SA NHLS could potentially provide a reliable and real-time efficient method for tracking the outcomes of transferring patients.

All four paediatric studies included in this review suggest that children transferred out to lower level facilities had comparable viral load and CD4 outcomes with those managed at higher level facilities, and highlights that lower level facilities have sufficient capacity to manage HIV-infected children.

Results about the predictors of patients' reengagement with HIV care after transfer highlight the importance of conducting context-specific research to improve decentralized models of HIV care. Evidence from the literature reviewed indicates that programmes characteristics, patients' characteristics and structural factors are major determinants of patients' reengagement with HIV care. Therefore, the predictors of successful transfer are most likely a function of an interplay between these factors which are important for informing programmatic decision.

### **8.1 Summary of study quality and validity**

As the studies included in this review differed by age group, decentralization model for ART services (partial and community decentralization model), follow-up time, immunological and virological thresholds, sample size and setting, comparability of results between studies is challenging. The ideal good quality study would be done prospectively, have adequate sample size backed up by sample size calculation to assess patients' transfer, immunological, virological outcomes and ensure comparable characteristics between patients transferred out or remaining in care at the higher level facility.

None of the studies reviewed fulfilled these criteria. The retrospective design of the studies reviewed is of major concern with regards to the quality of data and the inherent flaws of retrospective studies. Of note, survival bias is a major threat to internal validity in the studies reviewed because most of the studies included in this review transfer out patients based on the improvement in the clinical status thereby leaving sicker patients to be managed at higher level

health care facilities. This ultimately favours the intervention group (transferred out patients) and might explain the better outcomes reported in patients' transferred out to lower level facilities for continuation of HIV care. Furthermore, since the studies reviewed are all observational studies the non-randomization of patients' to transfer out/not transfer out group is also a concern with regards to selection bias. Another source of threats to internal validity in the studies reviewed were how missing data were treated and unmeasured confounders, which were sparsely handled in most of the studies included in this review.

In addition, the retention estimates among those who successfully transfer are important to report, but they are biased. Patients that successfully transfer have already demonstrated retention by successfully transferring, and so are likely to have better long term retention. Thus the outcomes of these patients do not represent overall retention of all patients transferring out and are not directly comparable with patients not transferred from their primary care site.

Nevertheless, Brennan et al (2011), Long et al (2011) and Hansudewechakul et al (2012) studies used advanced methodological approaches to improve the internal validity of their studies (10, 18, 19).

## **8.2 Questions that emerge and could form the basis for further research**

The findings from the studies reviewed shows that decentralized models of ART care have been used effectively for optimizing the delivery of ART care for patients in LMICs with weak health systems and a high burden of HIV/AIDS, with satisfactory clinical and laboratory outcomes. Nevertheless, results in children remain very limited with no studies reporting on the outcome of successful transfer in children. This review highlights the importance of understanding patient-level, program-level and structural factors impacting transfer outcomes in different contexts in order to optimize transfer success and the outcomes of decentralized care.

Decentralization is likely to become widespread as the promising results from existing studies have spurred the International AIDS Society to commit to a two year differentiated models of ART delivery project aimed at supporting LMICs to adopt decentralization of HIV care and task-shifting among other strategies. While this project aims to expand coverage of ART services in LMICs, it will also come with challenges of finding an efficient way for tracking the movement of patients' between treatment sites considering the poor record systems and constrained health systems in LMICs. This review highlights the challenges of tracking patients and methods used by studies that reported on the successful transfer outcome in their patients, and there is a clear need to explore the feasibility of using electronic systems and laboratory data to track patient outcomes at scale.

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PART C: JOURNAL READY  
MANUSCRIPT

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## **Outcomes of HIV-infected Children Transferring Out of a Specialist Paediatric Clinic using Linkage to Laboratory Data.**

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Part of these data was presented as a poster at the 8<sup>th</sup> International Workshop on HIV Paediatrics in Durban, South Africa March 2012, 15-16 July 2016 (abstract number 66).

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Word count: 3524 words

Abstract: 279 words

Tables: 3

Figures: 2

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The following journal manuscript is in keeping with requirements as stated in the instructions for authors of South African Medical Journal (Appendix E).

The following deviations from journal requirements have been made in keeping with instructions for the mini-dissertation.

1. Co-authors have not been listed however their contributions, including that of Supervisors, have been noted in the acknowledgements section of the mini-dissertation.
2. Figures and tables have been inserted in the text of the dissertation rather than attached individually as a supplementary file.

## **Abstract**

**Background.** Decentralisation of paediatric HIV care in resource-limited settings has expanded ART access. However, there is limited data on outcomes of children transferred from higher to lower level health facilities.

**Objectives.** To describe the outcomes of children who initiated ART at Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary paediatric facility in the Western Cape Province (WCP) of South Africa, and were transferred to lower level facilities within the WCP.

**Method.** This was a retrospective study of ART-naïve HIV-infected children <16 years old who started ART at RCWMCH from December 31, 2007 to January 1, 2012. We linked RCWMCH cohort data to National Health Laboratory service data (NHLS) data using the unique identifier. Successful transfer was defined in two ways: a laboratory test performed by a lower level health facility (i)  $\leq 18$  months or (ii)  $\leq 48$  months after transfer date.

**Results.** The median age at ART initiation of 1127 children included was 5.6 months (interquartile range [IQR] 3.1-19.9); at ART initiation 85% had WHO stage III/IV disease and 57% were immunosuppressed. Of 725 (64%) children who were transferred, 69% (496) and 76% (541) successfully transferred within 18 and 48 months respectively. Median time to successful transfer was 5.6 months (IQR 3.8-9.1). In patients who successfully transferred, median (IQR) CD4% increased between transfer and first visit post-transfer (25.1% (17.3-33.8%) vs 30.2% (22.9-36.6%), p-value <0.001) and the proportion of children with HIV RNA <400 copies/mL increased from 55.9% to 81.4% (p-value <0.001). Children with the transfer site recorded in the RCWMCH database and those transferred out before 2010 were more likely to successfully transfer (adjusted odds ratio (aOR):7.99; 95% CI:2.3-28.5 and aOR:5.21; 95% CI:1.5-18.4 respectively).

**Conclusion.** The results suggest that paediatric ART decentralisation is feasible with good outcomes.

## **Introduction**

The burden of paediatric human immunodeficiency virus (HIV) is disproportionately distributed with sub-Saharan Africa accounting for more than 80% of the global burden of paediatric HIV. Despite the progress seen with HIV-infected patients' access to antiretroviral therapy (ART), only 49% of about 1.8 million children living HIV have access to ART.<sup>[1]</sup>

To guide global action on paediatric HIV care, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has called for 90-90-90 targets – to identify 90% of HIV-infected children, maintain 90% of those identified on treatment and achieve 90% viral load suppression among those on treatment.<sup>[2]</sup> Building on this, decentralisation of HIV care was recommended by the World Health Organisation (WHO) to address the human resources shortage and long-term retention challenges of patients in HIV care. These treatment models involve shifting HIV care services to lower level facilities, thereby encouraging patients' retention in care and improving access of patients to care.<sup>[3, 4]</sup> In the same vein, decentralisation of paediatric HIV care aims to strengthen the paediatric HIV continuum of care.<sup>[4, 5]</sup>

Across LMICs, decentralised HIV care models are increasingly being used to remove children's barriers to accessing paediatric HIV services.<sup>[4, 6]</sup> The Western Cape Province (WCP) of South Africa (SA) adopted a decentralised model of paediatric HIV care soon after the start of ART roll-out in 2004, and the proportion of children receiving ART at the 3 tertiary health care facilities in WCP declined from 78.4% to 38% between March 2004 and September 2006.<sup>[7]</sup>

Red Cross War Memorial Children's Hospital (RCWMCH), a WCP tertiary level health facility initiates infants or sick children on ART. These children are transferred to lower level facilities within the WCP for continuation of HIV care within the decentralised model once they are stable on ART. However, there is no published information on whether these children reached transfer out sites and how they fare if they successfully transfer. This study, therefore, aims to investigate the outcomes of children transferred out from RCWMCH using RCWMCH data linkage to the South African National Health Laboratory Service data (NHLS).

## **Methods**

### **Study design and population**

We conducted a retrospective analysis of children initiated on ART at RCWMCH and transferred to lower level health facilities for continuation of HIV care from between December

31, 2007 and January 1, 2012. (Figure 1). Routine clinical follow-up data were collected for this cohort of children as part of standard treatment and monitoring of HIV care and stored in an electronic database. Since 2007, a single unique patient identifier is used across all health services in WCP. The NHLS conducts all WCP public sector laboratory tests. Provincial approval was obtained to link RCWMCH data to WCP data and this linkage was performed by province staff with permission to access identified data.

The analysis included NHLS data on CD4 and viral load results from all WCP facilities providing HIV care for children during the study period. Children were managed using the South Africa (SA) paediatric ART guidelines during the study period which are adapted from the WHO paediatric ART guidelines<sup>[8]</sup> According to the RCWMCH ART guidelines, children should be transferred out to lower level health facilities once they are stable on ART if feasible (i.e. there is a suitable clinic close to patient's home and caregiver is agreeable to transfer). and provided with a referral sheet containing the name of the referral site, next appointment date at referral site, medical summary, most recent laboratory test results, and, if already on ART, the current drug regimen. This referral sheet was presented at the referral facility upon arrival for the continuation of HIV care.<sup>[9]</sup> Routine laboratory monitoring in the WCP included CD4 absolute and percent as well as viral load at initiation, after 6 months, after 1 year and annually.<sup>[9]</sup> A laboratory test performed closest to the transfer out date defined as at least 12 months of ART care at RCWMCH was used to identify patients' characteristics at transfer. Children transferred out to a site outside the WCP were excluded from the analysis (Figure 1). Ethical approval for this analysis was obtained from the University of Cape Town Human Research Ethics Committee, Faculty of Health Sciences (Appendix D).

### **Key cohort characteristics and outcomes**

Clinical and laboratory characteristics of children at ART start were summarised using medians and interquartile ranges (IQR) for continuous variables and proportions for categorical variables. Age at ART initiation was categorised as < 1 year, 1-1.9 years, 2-4.9 years, 5-9.9 years and  $\geq$  10 years due to faster disease progression in infants and young children, and different adherence and retention expected in those >10 years. Weight for age z-score (WAZ), height for age z-score (HAZ) and body mass index for age z-score (BAZ) were categorised using WHO 2006 standards as <-3, -3 to -2 and >-2. Children were considered severely immunosuppressed if the lowest of the CD4 absolute cell count or percentage met the WHO

immunosuppression classification criteria for their age.<sup>[10]</sup> Viral load suppression was defined as HIV-RNA < 400 copies/ml.

The primary outcome of successful transfer was defined in two ways: a laboratory test performed by a lower level facility (i)  $\leq 18$  months or (ii)  $\leq 48$  months after the transfer date. The first interval corresponds to South African national guideline recommendations for annual CD4/viral load monitoring; the second aimed to capture all children retained in care even if monitoring was not carried out as frequently as required by guidelines.

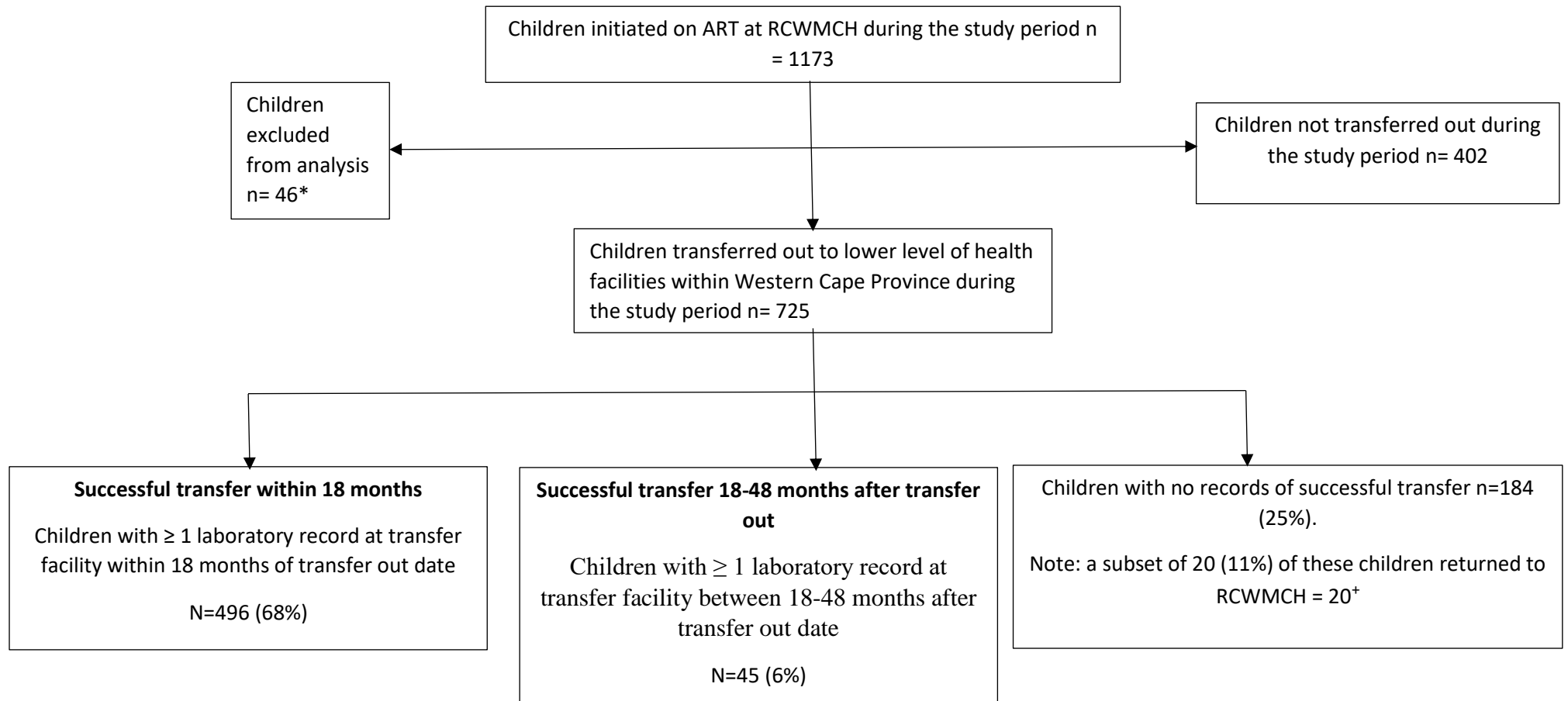
In children that transferred successfully, their change in immunological and virological outcomes at transfer out and post-transfer was described. CD4 and viral load at transfer were the values closest to the transfer out date within a window of 12 months prior to transfer out from RCWMCH, while post-transfer values were the results of the first CD4/viral load test after transfer. Also, the predictors of successful transfer were assessed, while the feasibility of using NHLS for tracking the movement of children between HIV treatment sites was demonstrated.

### **Statistical methods**

We compared successful transfer of children from three broad categories; (i) Children whose transfer out site was recorded in the RCWMCH database (ii) Children with no recorded transfer out site but recorded residential information (iii) Children with neither recorded transfer out site nor residential information. Logistic regression was used to assess the effect of these categories on transfer outcomes after adjusting for other predictors of successful transfer. No cut-off for p-value was used to define statistical significance to include the variables into the logistic multivariate analysis as all p-values for all the analysis was reported exactly.<sup>[11]</sup> The median time to successful transfer was also reported.

In patients who successfully transferred, we compared characteristics of patients at transfer out and first visit post-transfer, using Wilcoxon Signed Rank Test for paired samples and chi-squared test/Fishers-exact test for continuous and categorical variables respectively. This analysis was restricted to patients with measurements recorded both at transfer out and at first visit post-transfer date. All statistical analysis was done using STATA 14.1 version.<sup>[12]</sup>

**Figure 1: Flow Chart of RCWMCH HIV-Infected Children in the HIV Care Network, 2007-2012**



**\*: Children were excluded from analysis because they were transferred to sites outside Western Cape Province.**

**+: A sub-analysis including these children was conducted.**

## Results

### Cohort and patient characteristics at ART start

The median age at ART initiation of 1127 children included was 5.6 months (IQR 3.1-19.9 months) with median follow-up at RCWMCH of 8.5 months (IQR 1.3-22.9). During this period, 725 (64%) children who initiated ART at RCWMCH were transferred out to lower level facilities within the WCP for continuation of HIV care (Figure 1). The characteristics at ART start of children transferred out to lower level facilities and those managed only at RCWMCH were similar, except that children transferred out had higher median CD4 count of 471 (IQR 195-1044) vs 385 (IQR 131-960) (p-value=0.045) (Table 1). At ART initiation, most of the children had advanced disease; approximately 85% of children were classified as WHO clinical stage III/IV, 57% were immunosuppressed and median log<sub>10</sub> viral load (copies/ml) was 5.9 log<sub>10</sub> copies/ml (IQR 5.1-6.5). Approximately 71% of children were either moderately or severely underweight (Table 1).

**Table 1. Characteristics of RCWMCH patients transferred from 31<sup>st</sup> December 2007 – 1<sup>st</sup> January 2012 at ART start**

Characteristics at ART initiation	Entire cohort that initiated ART (n= 1,127)	Patients transferred to lower level health care facilities (n= 725)	Patients not transferred (n= 402).	p – value *
<b>Gender, n (%)</b>				
Male	548 (48.62)	345 (47.59)	203 (50.50)	0.35
Female	579 (51.28)	380 (52.41)	199 (49.50)	
<b>Age, months</b>				
Median (IQR)	5.6 (3.1 to 19.9)	5.1 (3.0 to 19.8)	6.2 (3.2 to 19.9)	0.44
<b>WHO HIV staging 3 and 4, n (%)</b>				
• Yes	960 (85.18)	623 (85.93)	337 (83.83)	0.48
• No	147 (13.04)	91 (12.55)	56 (13.93)	
• Missing	20 (1.77)	11 (1.52)	9 (2.24)	
<b>CD4 count</b>				
Median (IQR)	436.5 (175 to 999)	471 (195 to 1044)	385 (131 to 960)	0.05

<b>Missing, n (%)</b>	325 (28.84)	218(30.07)	107(26.49)	
<b>CD4 %</b>				
<b>Median (IQR)</b>	17 (9.8 to 25.1)	17.2 (10 to 25)	16.6 (9.45 to 25.6)	
<b>Missing, n (%)</b>	333(29.55)	223(30.76)	110(27.23)	0.38
<b>Log viral load (copies/ml)</b>				
<b>Median (IQR)</b>	5.88 (5.14 to 6.48)	5.88 (5.15 to 6.46)	5.88 (4.98 to 6.48)	
<b>Missing, n (%)</b>	398(35.31)	260(35.86)	8(34.16)	0.73
<b>WAZ score</b>				
<b>Median (IQR)</b>	-2.44 (-3.57 to -1.37)	-2.37 (-3.43 to -1.39)	-2.57 (-3.87 to -1.29)	0.16
<b>WAZ score category, n (%)</b>				
<b>&lt;-3 SD</b>	302(26.80)	181 (24.97)	121 (30.10)	
<b>&lt; -3 to -2 SD</b>	496 (44.01)	337 (46.48)	159 (39.56)	
<b>&gt;-2 SD</b>	43 (3.81)	29 (4.00)	14 (3.48)	0.14
<b>Missing, n</b>	286 (25.38)	178(24.55)	108 (26.87)	
<b>HAZ score</b>				
<b>Median (IQR)</b>	-2.29 (-3.47 to -1.28)	-2.28 ( -3.41 to -1.26)	-2.41 (-3.64 to -1.49)	0.17
<b>HAZ score category, n (%)</b>				
<b>&lt;-3 SD</b>	216 (19.17)	135 (18.62)	81 (20.15)	
<b>&lt; -3 to -2 SD</b>	364 (32.3)	250 (34.48)	114 (28.36)	
<b>&gt;-2 SD</b>	41 (3.64)	31 (4.28)	10 (2.49)	0.27
<b>Missing, n</b>	506(44.90)	309 (42.62)	197 (49.00)	
<b>BAZ score</b>				
<b>Median (IQR)</b>	-1.65(-3.2 to -0.58)	-1.64( -3.15 to -0.59)	-1.65 (-3.43 to -0.43)	0.79
<b>BAZ score category, n (%)</b>				
<b>&lt;-3 SD</b>	179 (15.88)	115 (15.86)	64 (15.92)	
<b>&lt; -3 to -2 SD</b>	349 (30.96)	241 (33.25)	108 (26.86)	
<b>&gt;-2 SD</b>	98(8.70)	63 (8.69)	35 (8.71)	0.27
<b>Missing, n</b>	501(44.45)	306(42.21)	195(48.51)	

<b>Immunosuppression, n (%)</b>				
<b>Yes</b>	641 (56.88)	402 (55.45)	239(59.45)	0.46
<b>No</b>	164 (14.55)	108 (14.90)	56 (13.93)	
<b>Missing</b>	322 (28.57)	215 (29.66)	107(26.62)	

NB: The p.value compares the characteristics of patients that transferred to lower level facilities compared those to those not transferred during the study period.

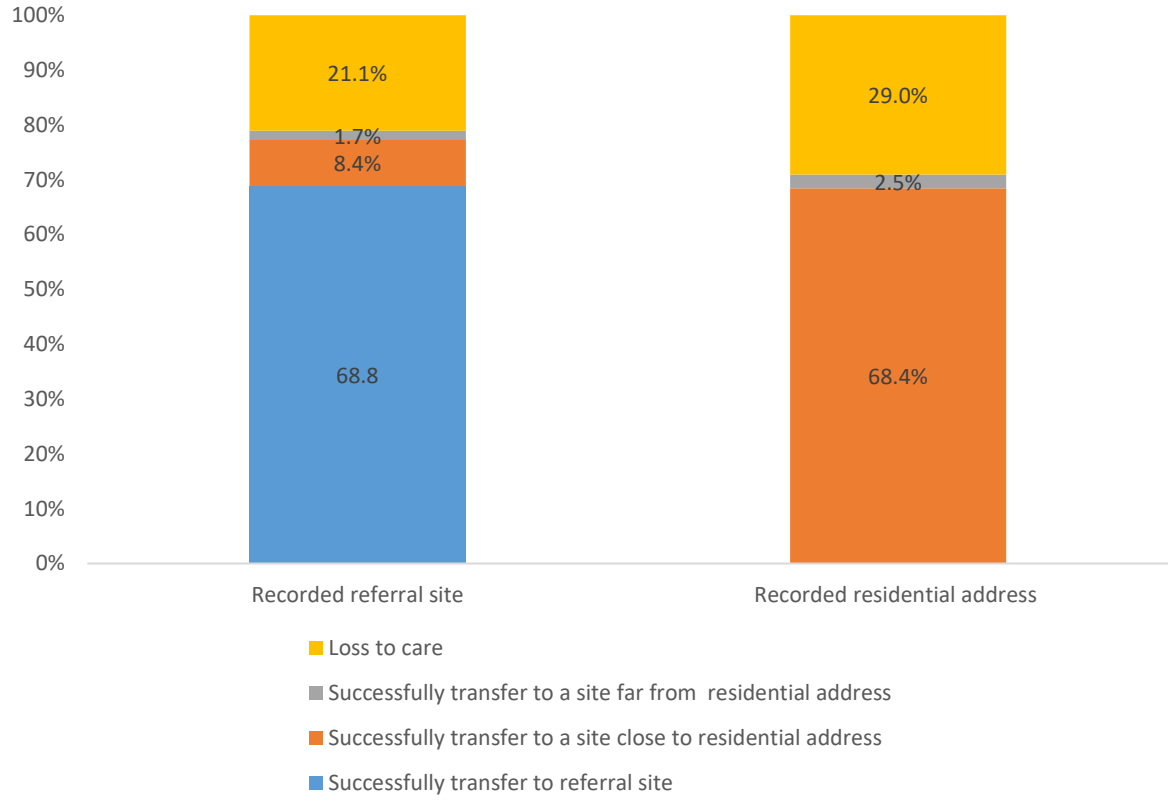
### **Successful transfer outcome**

The proportion of patients who successfully transferred was 76% (541/725 children) within 48 months of the transfer out date, with 92% of these (496/541) successfully transferring within 18 months of the transfer out date. A total of 68% of all children, therefore, achieved successful transfer within a window of 18 months from transfer-date and this proportion did not differ substantially in a sensitivity analysis when reducing the successful transfer window to 15 months after transfer out date. The median time to transfer successfully was 5.4 (IQR 3.7-7.8) months (Table 3). Among 184 children who did not transfer successfully, 20 (11%) returned to RCWMCH for HIV care. Among children with recorded referral sites, 21% did not transfer successfully, compared to 29% among those with no referral site recorded (Figure 2).

### **Predictors of successful transfer**

In multivariable analysis, children transferred out before 2010 are 5 times more likely to successfully transfer to lower level facilities compared to children transferred out after 2010 (adjusted odd ratio (aOR)): 5.16, 95% CI 1.5-18.4) (Table 2). Similarly, children with recorded transfer out sites in the RCWMCH database were 8 times more likely to transfer successfully to lower level facilities compared to those with recorded residential address (aOR: 7.99; 95% CI:2.3-28.4) (Table 2). There were no child clinical or laboratory characteristics that predicted successful transfer in multivariable analysis.

**Figure 2: Transfer patterns of children transferred out of RCWMCH**



N.B: 356 (49.1%) children had recorded referral sites in the database while 358 (49.4%) had their residential address recorded in the database. Only 11 (1.5%) children had neither recorded referral site or residential address recorded in the database and 6(54.5%)of these children transferred successfully to a site during the study period.

**Table 2: Factors associated with successful transfer among children transferred out from RCWMCH from December 2007 – January 2012**

Characteristics	Number of successful transfer (%)	Unadjusted Analysis		Adjusted Analysis	
		OR(95%CI)	P-value	OR(95%CI)	P-value
<b>Gender (n=725)</b>					
Female	285(52.68)	1		1	
Male	256(47.32)	0.96(0.69-1.34)	0.81	0.97(0.67-1.39)	0.89
<b>Age in years at transfer (n=725)</b>					
< 1 years	148(27.36)	1		1	
1-1.9 years	127(23.48)	1.22(0.77-1.95)	0.40	0.89(0.51-1.56)	0.66
2-4.9 years	124(22.92)	1.19(0.75-1.91)	0.46	0.99(0.55-1.78)	0.97
5-9.5 years	103(19.04)	1.24(0.75-2.05)	0.40	1.35(0.70-2.61)	0.37
≥ 10 years	39(7.21)	1.00(0.51-1.95)	0.99	1.31(0.54-3.18)	0.56
<b>CD4% at transfer (n=722)</b>					
< 20%	175(32.35)	1		1	
≥ 20%	94(17.38)	1.01(0.62-1.65)	0.97	1.17(0.67-2.03)	0.58
> 25%	272(50.28)	1.12(0.77-1.63)	0.56	1.18(0.74-1.88)	0.49
<b>Immunosuppressed at transfer (n=720)</b>					
No	321(59.44)	1			
Yes	219(40.56)	0.85(0.61-1.19)	0.36		
<b>Viral load suppressed at transfer (n=688)</b>					
No	241(45.64)	1		1	
Yes	287(54.36)	1.69(1.19-2.43)	0.00	1.48(0.84-2.59)	0.18
<b>Follow-up time(n=725)</b>					
< 6 months	194(35.86)	1		1	
≥ 6-11.9 months	125(23.11)	1.78(1.11-2.86)	0.02	1.33(0.72-2.47)	0.36
≥ 12 months	222(41.04)	1.34(0.92-1.94)	0.12	1.04(0.53-2.05)	0.18
<b>Transfer site (n=714)</b>					
Recorded resident address	254(47.48)	1		1	
Recorded transfer site	281(52.52)	1.53(1.09-2.16)	0.01	7.99(2.25-28.47)	0.00
<b>Year of transfer (n=725)</b>					

From 2010	258(47.69)	1		1
Before 2010	283(52.31)	1.39(0.99-1.95)	0.05	5.16(1.45-18.38) 0.01

NB: Immunosuppressed at transfer variable was not included in the multivariate regression analysis because CD4% percentage variable was included in the analysis.

### **Change in Children’s Immunological and Virological Status for those who remained in care.**

#### **Immunological and Virological Response**

The patient-level analysis of children shows improvement in immunologic and virological markers among children who successfully transferred from RCWMCH (Table 3). The median CD4% increased between transfer out and first visit post-transfer in children that successfully transferred (25.1%; IQR (17.3 to 33.8) versus 30.2%; IQR (22.9 to 36.6) p-value <0.001). In the same vein, median CD4 count increased between transfer out and first visit post-transfer (1026 cells/mm<sup>3</sup>; (IQR 563 to 1577 cells/mm<sup>3</sup>) versus 1260.5 cells/mm<sup>3</sup>; (IQR 788 to 1802 cells/mm<sup>3</sup>) p-value<0.001) (Table 3). The proportion of children with HIV RNA < 400 copies/mL between transfer out date and first visit post-transfer increased from 265(55.9%) to 386(81.4%) (p-value<0.001) (Table 3).

#### **Children who did not successfully transfer and returned to RCWMCH**

In the sub-group analysis of 20 children transferred out who did not successfully transfer but returned to RCWMCH for HIV care, the median (IQR) CD4% and count were lower on return to RCWMCH compared to at transfer out (25.7%; (13.4 to 30.2) vs 27.8%; (19.3 to 33.2) p-value= 0.01 and 818 cells/mm<sup>3</sup> (598 to 1026 cells/mm<sup>3</sup>) vs 1057 cells/mm<sup>3</sup> (707 to 1420 cells/mm<sup>3</sup>) p-value<0.001. However, the proportion of children with viral load suppression was not significantly different at transfer out (11(73.3%) versus 9(60.0%) after returning to RCWMCH p-value = 0.24) (Table 3)

**Table 3. CD4 and Viral load in patients transferred out who successfully reached a site within 48 months of transfer out date**

Characteristics	Patients laboratory information at transfer	Patients first laboratory information at transfer out site	P-value
<b>CD4 count (n=512)</b>			
Median (IQR)	1026 (563 to 1577)	1260.5(788 to 1802)	0.0001
<b>CD4 % (n=516)</b>			
Median (IQR)	25.1 (17.25 to 33.75)	30.15 (22.88 to 36.62)	0.0001
<b>Viral load suppression (n=474),</b>			
n (%)	265 (55.91)	386 (81.43)	0.0001
<b>Time to successful transfer (Months)</b>			
Median (IQR)	5.41 (3.72-7.84)		
<b>Children who returned to RCWMCH without successfully transferring, n=20*</b>			
<b>CD4 count (n=19)</b>			
Median (IQR)	1057(707 to 1420)	818(598 to 1026)	0.0001
<b>CD4 % (n=19)</b>			
Median (IQR)	27.8(19.30 to 33.20)	25.71(13.40 to 30.15)	0.02
<b>Viral load suppression (n=15),</b>			
n (%)	11(73.33)	9(60.00)	0.25
<b>Time to return to RCWMCH (Months)</b>			
Median (IQR)	6.09(3.57 to 12.02)		

\*: The statistics presented in this section of the table are for the 20 children who failed to transfer successfully and returned to RCWMCH

## **Discussion**

### **Principle findings**

In this study, of the substantial number of children transferred out to lower level facilities from RCWMCH, more than three-quarters successfully transferred to a referral facility, with 90% of these children transferring within 18 months of their transfer out date from RCWMCH. The 69% of children who have a laboratory test at the transfer site within 18 months of transfer out constitutes about 80-90% of children who actually transfer successfully since annual laboratory testing is about 80- 90% complete. Therefore the proportion actually transferring within 18 months (in terms of clinic visits) is likely 75-80% estimate. Children's CD4 count and percent increased after transfer, as did the proportion with HIV-RNA<400 copies/ml.

### **Strengths and Limitations of Findings**

To our knowledge, this is one of the first paediatric studies assessing the post-transfer outcomes of children transferred out from higher level to lower level facilities for continuation of HIV care in sub-Saharan Africa. The use of NHLS linkage data to track transferred out children provided an easy and efficient mechanism for monitoring post-transfer outcomes, and the availability of a unique identifier across the health service platform in the WCP ensured the fidelity of linkage results. The use of NHLS data was particularly valuable for tracking patients where the transfer facility was not recorded or who engaged in care at a different facility from the one to which they were referred to. Our study demonstrates the feasibility of using patient laboratory data to assess outcomes at facilities other than the treatment initiation sites both for programme monitoring and to improve patient care by tracking in real-time that patients reach their transfer site. Nevertheless, a limitation of using NHLS data is that we could only identify successful transfer if patients had undergone laboratory testing and so may underestimate actual clinical visits at the transfer site, and so, it is hard to estimate the actual proportion successfully transferring based on assumed completeness of laboratory monitoring. The young age and relative diseases severity of children included in this study are also a notable strength as it demonstrates that decentralisation of paediatric HIV care is possible for infants and sick children once they are stable on ART.

Further limitations of the study relate to the use of routinely captured data only, so there was missing data on clinical and laboratory characteristics as well as incomplete documentation of transfer out sites. We could also not assess the effect of family socio-economic and

demographic characteristics as well as adherence on transfer outcomes as this data was not collected.

### **Interpretation**

An increasing number of adult studies are reporting on the outcomes of patients transferring between ART sites in LMICs, with 78-96% of patients successfully transferring.<sup>[13-19,21]</sup> Although 10% of patients in a Malawian study reporting transfer were children, transfer outcomes for paediatric patients were not specifically reported.<sup>[17]</sup> To our knowledge, no paediatric study to date has reported on this outcome despite evidence that children do transfer between treatment sites in LMICs.<sup>[20]</sup> Our study demonstrates that transfer outcomes in children are comparable with adult results; 76% of children transferred out reached lower level facilities according to laboratory testing, and 80-85% may have actually transferred successfully as laboratory testing is likely only 90% complete. Only 3 studies have reported on patient's time to re-engage with HIV care at lower level facilities, with a median of 1.3 months in Malawi and 91% of patients re-engaging in care within 3 months in Kenya. Similar result of 91% of patients re-engaging in care within a year of transfer out was reported in SA<sup>[14, 17, 21]</sup> Our study reported a longer median time to successful transfer of 5.4 months, which is likely due to using laboratory testing as an indicator of successful transfer rather than actual clinic visits. Although, >90% of children who transferred successfully did so within 18 months of the transfer date (recommended interval for annual CD4/viral load monitoring), a small proportion only underwent laboratory testing at the transfer site later. This delay in laboratory testing could indicate that patients transferred out experienced treatment or HIV care interruptions during the transition period, as noted in a Kenyan adult study.<sup>[14]</sup>

Similar to a SA study which reported that 20.8% of adults not transferring successfully had gone back to the treatment initiation site, we found that 11% (20) of patients who did not reach lower level facilities returned to RCWMCH for HIV care, and were generally less well when returning to RCWMCH compared to at the time of transfer. It is possible that these patients also experience a treatment interruption before returning to RCWMCH.<sup>[18]</sup>

We observed favourable immunological and virological outcomes in children who transferred out successfully despite a relatively low proportion being virologically suppressed at transfer. This is likely because patients were on a trajectory of improving health at the time of transfer, and that this trajectory continued at the transfer site, rather than transfer causing an improvement in their health status. This also suggests good adherence in this group of children.

Both individual-level and structural-level factors have been identified as predictors of successful transfer for adults. An SA adult study showed that successful transfer was associated with living close to the transfer out site,<sup>[13]</sup> while a Kenyan adult study found a strong association between programme factors such as having an official transfer letter and successful transfer.<sup>[14]</sup> In our study, having a recorded transfer out site in the RCWMCH database was a strong predictor of successful transfer. It is possible that the record of a clinic site in the database indicates overall better documentation and management of the transfer process, such as contacting the referral clinic to make a specific booking for the patient. In addition, children transferred out from RCWMCH before 2010 are more likely to successfully transfer overall (i.e. have a laboratory test within 48 months of the transfer out date) compared to those transferred out after 2010. This is expected because children transferred out before 2010 had more time to re-engage with lower level facilities.<sup>22</sup>

### **Recommendation and Conclusion**

A high proportion of children successfully transferred from RCWMCH with positive CD4 and viral load outcomes. These results indicate that decentralised paediatric HIV care is a feasible and promising strategy for improving both paediatric ART access and long-term retention in resource-limited settings, thus supporting the UNAIDS 90-90-90 goals for children.

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## PART D: APPENDICES

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# Appendix A: Provincial approval to link Red Cross War Memorial Children's Hospital data to the Western Cape Provincial data Warehouse



Directorate: Health Impact Assessment  
Contact: Dr T. Naledi  
Email: Tracey.Naledi@pgwc.gov.za tel: +27  
483 9366 fax: +27 21 483 6058

REFERENCE: Authority for Dr Andrew Boule to provide laboratory data on ART-treated children from Red Cross War Memorial Children's Hospital

To: Prof. Eley head of infectious disease and anti-retroviral therapy at Red Cross War Memorial Children's Hospital

ADDRESS: 12/02/2013  
School of Child and Adolescent Health  
Division: Paediatric Medicine  
Red Cross War Memorial Children's Hospital (RCWMCH)  
Klipfontein Road  
Rondebosch  
7700

Dear Prof. Eley

Re: Your request for Authority for Dr Boule to provide laboratory data on ART-treated children

This letter serve as a formal advise for Dr Boule to proceed and provide laboratory data on ART-treated children from Red Cross War Memorial Children's Hospital. It gives permission only to data for patients who have initiated ART at RCWMCH and subsequently been transferred to primary care facilities for continuation of treatment. This letter is granted under the following conditions and understanding:

- i. That children on whom data is required will be identified by existing infectious diseases staff at RCWMCH; ii. The data will be extracted from the Provincial Data Warehouse under Dr Boule's oversight on the basis of a CLINICOM number;
- iii. The data received will be securely stored in the Infectious Disease Department at RCWMCH;
- iv. Only existing RCWMCH clinical and data capture staff will have access to the new laboratory data provided;
- v. RCWMCH staff will have no direct access to the Provincial Data Warehouse, and will not have access to identified data on any patients other than those that have initiated ART at RCWMCH.

We wish you all the best with this important investigation. YOU are welcomed to contact us if you have any queries or need clarification regarding this communication.

5<sup>th</sup> Floor, 8 Riebeeck Street, Cape Town, 8001 PO Box 2060, Cape Town, 8000 tel: +27  
21 483 9366 fax: +27 21 483 9921

Sincerely

Tracey Naledi MBChB, FCPHM(SA)  
Director: Health Impact Assessment  
Western Cape Department of Health  
5th Floor 8 Riebeeck Str, Cape Town  
Tel: 021 483 9366  
Fax: 021 483 9921  
Email: tracey.naledi@westerncape.gov.za  
Website: www.westerncape.gov.za

12/2/2013

## Appendix B: Primary study research ethics approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty  
Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory  
7925 Telephone [021] 406 6338 Facsimile [021]  
406 6411 e-mail: nosi.tywabi@uct.ac.za

13 May 2008

REC REF: 261/2002

Prof B Eley  
Paediatric Medicine  
Infectious Diseases  
Red Cross Children's Hospital

Dear Prof Eley

PROJECT TITLE: 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 06<sup>th</sup> May 2008.

It is a pleasure to inform you that the Ethics Committee has granted approval, via expedited review, of the above mentioned study for further 12 months until 15 May 2009.

Approval is granted in terms of category 5 of the OHRP guidelines.

A progress report detailing paediatric cohort data from the Red Cross Children's Hospital is noted with thanks.


Please note that the ongoing ethical conduct of the study remains the responsibility of the principal Investigator.

Please quote the REC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN  
CHAIRPERSON HSF HUMAN ETHICS

# Appendix C: Annual progress report/renewal of primary study


**UNIVERSITY OF CAPE TOWN**  
 ETHICS  
**17 AUG 2015**  
**FACULTY OF HEALTH SCIENCES**  
 Human Research Ethics Commi

**FHS017: Annual Progress Report / Renewal**

**Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registri**

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
<b>This serves as notification of annual approval, including any documentation described below.</b>			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.6.20
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	15/8/2015

1 Renewal

Principal Investigator to complete the following:

**1. Protocol information**

Date form submitted	17 August 2015		
HREC REF Number	261/2002	Current Ethics Approval was granted until	30 June 2015
Protocol title	ANTIRETROVIRAL THERAPY: GUIDELINES FOR THE TREATMENT OF A COHORT OF HIV-INFECTED CHILDREN AND THEIR INFECTED PARENTS AT RED CROSS CHILDREN'S HOSPITAL		
Principal Investigator	Brian Eley		
Department / Office	Room 506, 5 <sup>th</sup> floor, ICH building, Red Cross War Memorial Children's Hospital		
Internal Mail Address			
1.1 Does this protocol receive US Federal funding?	a Yes	v' No	

**2. Protocol status tick**

	Research-related activities are ongoing
<b>a</b>	Data collection complete, data analysts only

**3. Protocol summary**

Total number of records or specimens collected, reviewed or stored since the original approval	1942
Total number of records or specimens collected, reviewed or stored since last progress report	69

Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach With this report.

	yes	
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**4. Signature**

Signature of PI	15/8	Date	17 August 2015
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Signature of Supervisor (if PI is a student)		Date	
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# Appendix D: Official letter of ethical approval from University of Cape Town Faculty of Health Sciences Research Ethics Committee



UNIVERSITY OF CAPE TOWN  
Faculty of Health Sciences  
Human Research Ethics Committee



Room E52-24 Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone [021] 406 6492  
Email: [sumayah.arietdien@uct.ac.za](mailto:sumayah.arietdien@uct.ac.za)  
Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

24 May 2016

**HREC REF: 324/2016**

**A/Prof M Davies**  
School of Public Health & Family Medicine  
Room 5.42  
Level 5, Entrance 5  
Falmouth Building-FHS

Dear A/Prof Davies

**PROJECT TITLE: OUTCOMES OF CHILDREN TRANSFERRING OUT OF RED CROSS MEMORIAL CHILDREN'S HOSPITAL HIV COHORT USING LINKAGE TO THE NATIONAL HEALTH LABORATORY SERVICE DATA (Dissertation-candidate-O Arowosegbe)** sub-study linked to 261/2002

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 May 2017.**

Please obtain permission from the UCT student and staff administration to conduct research at UCT.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

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

**We acknowledge that the following student, Oluwaseyi Arowosegbe will also be involved in this study.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938  
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.  
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## Appendix E: Instructions for Authors: South African Medical Journal (SAMJ)

### Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:

[www.editorialmanager.com/samj](http://www.editorialmanager.com/samj)

To access and submit an article already in production, please see the guidelines [here](#).

### Author Guidelines

Please view the [Author Tutorial](#) for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: [submissions@hmpg.co.za](mailto:submissions@hmpg.co.za)).

### Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to [www.icmje.org](http://www.icmje.org))

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

### Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

### Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the [National Health Research Database](#). Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on [Ethics in Health research: principles, processes and structures](#) to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's [General Ethical Guidelines for Health Researchers](#) have been adhered to.

### Protection of rights to privacy

#### Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent

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for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to [Protection of Research Participants](#). The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

#### Other individuals

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Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the

investigators. Please note that it is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

### Continuing Professional Development (CPD)

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### Manuscript preparation

#### Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

### General article format/layout

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

General:

- Manuscripts must be written in UK English.
- 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).
- Please make your article concise, even if it is below the word limit.

- Qualifications, *full* affiliation (department, school/faculty, institution, city, country) 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 an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.

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- Please be sure to insert proper symbols e.g.  $\mu$  not u for micro,  $\alpha$  not a for alpha,  $\beta$  not B for beta, etc.
- 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.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

## **Research**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.  
Do not replicate data in tables and in text.

#### *Structured abstract*

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

#### *Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

#### *Results*

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
  - E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the  $\pm$  symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

### *Discussion*

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

### *Conclusions*

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.