OUTCOMES OF PAEDIATRIC ART PATIENTS DOWN-REFERRED FROM A TERTIARY AND A REGIONAL HOSPITAL TO PRIMARY CARE FACILITIES IN BUFFALO CITY MUNICIPALITY, EASTERN CAPE

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DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Any sources that I have used or quoted have been cited and referenced.

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ABSTRACT

Background: According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 340 000 children between 0-14years of age are living with HIV in South Africa as of 2019. Decentralization of HIV services was included in South Africa's paediatric guidelines since 2010 in a bid to improve access to care. The current study sought to address the paucity of Eastern Cape (EC) data on the outcomes of down-referred paediatric antiretroviral therapy (ART) patients. These outcomes included retention in care (RIC) and virological suppression after 12 months.

Methodology: This retrospective analysis was conducted in the Buffalo City Municipality (BCM) district of the EC. The study population included HIV positive males and females, 0-14 years of age at transfer, who were initiated on ART at a tertiary or a regional hospital and subsequently down-referred, between June 2013 and June 2017. Data were collected from electronic databases at the facilities (Tier.net), patient files and patient registers. A descriptive analysis was performed using SPSS Statistics software version 26.

Results: In total, 80.1% of patients successfully down-referred to a primary healthcare (PHC) facility, in a median of 42 days. Of those, 95.4% of patients were retained in care at 6 months and 93.1% at 12 months after arrival, with a median of 4 scheduled monthly visits missed. For those with results, virological suppression was maintained in 96.7% of patients at 6 months, 92.2% at 12 months and 96.2% for the entire post-transfer period of 2-14 months. In the 2-14 months post down-referral only 76.9% of patients had at least one viral load (VL) result and 50.3% had one CD4 result. For those with results, immune response (IR) to ART was maintained in 100% of patients at 6 months, 94.3% at 12 months and 97.7% in the 2-14 month period post successful down-referral.

Conclusions: This study confirmed that loss to follow-up (LTFU) and treatment interruption at the point of transfer are significant risk factors for paediatric ART patients. This study also demonstrated high levels of RIC once patients had successfully down-referred. However, missed clinic visits suggest possible treatment interruptions for many patients post down-referral. While good virological and immunological responses to ART were maintained at the PHC facilities, suboptimal VL and CD4 monitoring was highlighted by the low proportion of available results. Therefore, while there are a number of issues to address, this study confirms that down-referral is a feasible option for up-scaling paediatric HIV care in the EC.

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KEYWORDS

Antiretroviral therapy (ART)

Down-referral

Eastern Cape

HIV

Loss to follow-up

Outcomes

Paediatric

Primary healthcare facilities

Retention in care

Virological suppression

LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
CH	Community Hospital
CHC	Community Health Centre
CI	Confidence Interval
CRH	Chiangrai Prachanukroh Hospital
DNA	Did not arrive
DNH	Dora Nginza Hospital
DOH	Department of Health
EDH	Edendale Hospital
EC	Eastern Cape
HIV	Human Immunodeficiency Virus
IeDEA-SA	International epidemiology Databases to Evaluate AIDS in Southern Africa
IQR	Inter-quartile Range
IR	Immune Response (not used for "immune responder")
KZN	KwaZulu Natal
LDL	Lower than detectable limit
LTFU	Lost to follow-up/Loss to follow-up
NHLS	National Health Laboratory Service
PEPFAR	The President's Emergency Plan for AIDS Relief
PHDC	Provincial Health Data Centre
PHC	Primary Healthcare
PIR	Poor Immune Response
RCWMCH	Red Cross War Memorial Children's Hospital
RIC	Retention in care (not used for "retained in care")
TAH	Tygerberg Academic Hospital

TB	Tuberculosis
TBH	Tygerberg Children's Hospital
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VL	Viral load
WC	Western Cape
WCP	Western Cape Province
WHO	World Health Organization

DEFINITIONS FOR THIS STUDY

This section contains the definitions that were used for this study and in particular for assessment of the study outcomes.

i. *Age*: age in years of the patient at their last birthday.

ii. *Age categories*: age was categorized into 4 groups based on the different risk profile for each group: <1 year of age (infant); 1-4 years of age (young child); 5-9 years of age; 10-14 years of age (early adolescent). Infants are known to be a particularly vulnerable group with high mortality rates in the initial period following ART initiation (Morsheimer *et al.*, 2014; Copelyn *et al.*, 2018). Children <5 years of age are also a high risk group in terms of mortality (Morsheimer *et al.*, 2014), hence driving the 2013 change in South African treatment guidelines to include treatment of this group upon diagnosis of Human Immunodeficiency Virus (HIV), regardless of CD4 measurement (Copelyn *et al.*, 2018). In one study children aged 5-10 years of age were found to be more likely to have a poor immune response (PIR) to ART than those younger than 5 (The European Pregnancy and Paediatric HIV Cohort Collaboration [EPPICC] Study Group in EuroCoord, 2020). Adolescence has been reported in some studies as an age group with poor RIC and virological response to ART (Davies *et al.*, 2017).

iii. *Age at time of transfer*: age in years at the date of down-referral. Also called age at down-referral.

iv. *Date of down-referral*: the date of down-referral of the children on ART from the tertiary or regional hospital.

v. *Date of presentation*: the date on which the down-referred children on ART presented for treatment at the PHC facility. Also called the transfer-in date.

vi. *Successful down-referral*: presentation at a PHC facility in the BCM district after the date of down-referral from the tertiary or regional hospitals, as determined by a transfer-in date on Tier.net, or the first recorded clinic visit after the date of down-referral, at the PHC facility.

vii. *Unsuccessful down-referral*: also called LTFU at the point of down-referral. This was defined as no record of presenting to any facility other than the referring hospital after the date of down-referral.

viii. *Silent transfer*: an undocumented transfer to a different facility either at down-referral or after successful down-referral. In these instances the patient would be retained in care

however their transfer to this different facility was without the knowledge of the staff at the referral hospital or the PHC at which they were intended to present/continue care.

ix. *Retention in care*: patients were determined to be retained in care if they were alive and receiving ART at the down-referral PHC facility to which they presented at each of the study intervals. This was determined for each interval by at least one recorded visit in the 6 month window (4-8 months) and one recorded visit in the 12 month window (10-14 months) post successful down-referral.

x. *Lost to follow-up*: LTFU also refers to loss to follow-up. In this study a patient was considered lost to follow-up if they were recorded as such on Tier.net (the electronic database at the facilities) or if they had no recorded visits in the defined intervals with no record or re-engaging in care at a later date.

xi. *Defaulter*: for the purposes of this study defaulting was defined as the patient having no recorded clinic visit in the designated windows for the study intervals, but the patient does re-engage in care at a later date. Thus a patient would be considered a defaulter for the 12 month interval if there was no recorded visit in any of the months in the 10-14 month window post successful down-referral, but that patient has a recorded visit thereafter at a later time point.

xii. *Transfer out*: when a patient has presented to the PHC facility and thereafter has a documented transfer to another facility. To be considered a transfer out, the facility staff must have been informed of the transfer by the patient/caregiver or have knowledge of the transfer.

xiii. *Did not arrive (DNA)*: this is used to indicate when a patient missed, or did not arrive, for their monthly visit at the PHC facility.

xiv. *Viral load (VL)*: the VL value in copies/ml as per NHLS results where available in patient file or as per Tier.net record for the patients. Where VL was recorded as lower than detectable limit (LDL), the definition below was utilized for the purposes of this study.

xv. *Lower than detectable limit*: for the purposes of this study this was defined as <400 copies/ml, which is in keeping with the comparative literature (van Dijk *et al.*, 2014; Teasdale *et al.*, 2017). The lower limit for detectable viral load has changed over time and by 2015 was taken as <50 copies/ml, but prior to 2015 was <400 copies/ml (Teasdale *et al.*, 2017:2). As this study contains both time frames, <400copies/ml was used as the lower limit of detectable viral load.

xvi. *Virological suppression*: VL of <1000 copies/ml for the purposes of this study. This limit was used as according to the South African HIV treatment guidelines of 2015 a VL of

>1000 copies/ml initiates a cascade of step-up adherence and more frequent VL monitoring in order to ascertain whether there is a need to change to second-line treatment (Department of Health, 2015). Thus any VL of ≥1000 copies/ml was considered to be unsuppressed in this study.

xvii. *Viral load levels*: using definitions for LDL and virological suppression, VL results were categorized in levels of <400 copies/ml, 400-1000 copies/ml and ≥1000 copies/ml for the purposes of analysis.

xviii. *Immune response to ART*: this was defined in two ways. Firstly according to a study conducted on the prevalence and outcomes of children and adolescents with a PIR to ART despite being virologically suppressed. They based their definition on the WHO classification for immunological stages (World Health Organization [WHO], 2007) and defined an immune responder as follows: CD4 >30% for age <12 months; CD4 >25% for 12-35 months; CD4 >20% for 35-59 months; or CD4 >15% or <350 cells/mm^3 for ≥5 years of age (EPPICC Study Group in EuroCoord, 2020). The second definition was to account for those instances in which no CD4 percentage was available, and so IR needed to be determined by CD4 count. This definition was taken from the South Africa national HIV treatment guidelines of 2015 which defines immune reconstitution in order to gauge when to stop cotrimoxazole prophylaxis. Here immune reconstitution is defined as CD4 count ≥500 cells/µl for children 1-5 years of age; and CD4 count ≥350 cells/µl for those ≥5 years of age (Department of Health, 2015). For the purposes of this study if both CD4 percentage and CD4 count were available, and there was a discrepancy regarding immune response between the two: the CD4 percentage was used to gauge immune response for those <5 years of age; and CD4 count was used for those ≥5 years of age. Any patient in this study with values below these defined threshholds was considered to be a poor immune responder or have a PIR to ART.

CHAPTER 1: INTRODUCTION

1.1. Background

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS, 2019) 340 000 children between 0-14years of age are living with HIV in South Africa as of 2019. In this age group there were 10 000 new infections and 4100 deaths in the same year (UNAIDS, 2019). While the number of deaths has decreased from 9300 in 2016 (UNAIDS, 2018), so has the ART coverage from 55% in 2016 to 47% in 2019 (UNAIDS, 2018 & 2019). The UNAIDS 2016 data also showed that only 63% of children known to be receiving ART, remain on the treatment after 12 months (UNAIDS, 2018). UNAIDS did not display any paediatric specific data regarding VL suppression on ART.

With the aim to end the global AIDS epidemic by 2030, UNAIDS, along with global stakeholders proposed the 90-90-90 strategy. This strategy aimed to ensure that 90% of people living with HIV know their status, 90% of people diagnosed with HIV are receiving sustainable ART, and that 90% of those on ART are virally suppressed, by the year 2020 (UNAIDS, 2014). Calculations showed that should this be achieved then a new goal of 95-95-95 could feasibly be reached by 2030 (UNAIDS, 2015). This Fast-Track approach would mean rapidly up-scaling HIV services in the 5 years leading up to 2020 (UNAIDS, 2015). The South African statistics clearly demonstrate that paediatric ART programmes still have much work to do to achieve these goals. This can be seen by the 2019 ART coverage of 47%, which falls abysmally short of the 81% target for all children living with HIV.

With 859 329 people living with HIV, the EC ranks as the province with the 3rd highest HIV prevalence in South Africa, following after KwaZulu Natal (KZN) and Gauteng (MacDonell & Low, 2019). In terms of the 90-90-90 targets in the EC: 90.14% of people with HIV have been diagnosed; 61.60% of HIV-diagnosed people are receiving ART; and 48.41% of HIV-diagnosed people on ART have achieved virological suppression (VL <1000 copies/ml) (MacDonell & Low, 2019). When reviewing provincial statistics, it becomes clear that the greatest barrier to achieving the 90-90-90 target is "ensuring that people with diagnosed HIV are taking antiretroviral treatment" (MacDonell & Low, 2019).

Task shifting from doctor to nurse-initiated ART and decentralization of HIV services to PHC facilities was already included in South Africa's 2010 paediatric guidelines in a bid to

improve access to HIV care (Department of Health, 2010). Some of the factors found to adversely affect RIC of ART patients included the distance to healthcare facilities and the cost of transportation to get there (Mukumbang *et al.*, 2017). Therefore, it makes sense that decentralization of ART to primary care facilities was often associated with improved RIC (Suthar *et al.*, 2014). Another study from rural Zambia found that children who had longer travel times to health facilities were also less likely to achieve virological suppression after 6 months on ART (van Dijk *et al.*, 2011). As one of the likely benefits of decentralization is that it should bring HIV services closer to people's homes (World Health Organization [WHO], 2013), it thus has the potential to both reduce LTFU and improve the response to ART.

A study comparing outcomes of paediatric HIV patients at PHC facilities with those at urban secondary and tertiary health facilities in five Sub-Saharan African countries found, not only increased ART coverage in paediatric patients, but also suggested lower rates of LTFU and mortality in the PHC facilities (Fayorsey *et al.*, 2013). However, during the study period, the secondary and tertiary health facilities still accounted for over two thirds of the children on ART (Fayorsey *et al.*, 2013). According to the WHO (2013) decentralization of HIV care to PHC facilities would reduce the burden of routine care on other aspects of the health system; improve equity in access to ART; reduce transport costs; and decrease waiting times for patients in hospitals.

Despite findings in favour of decentralization, a systematic review on the effectiveness of service integration and decentralization in ART scale-up found that there was limited data available regarding the acceptability and quality of the services in this context (Suthar *et al.*, 2014). For example, high patient numbers in decentralized care may in fact result in staff shortages, long waiting times, medication stock-outs and lack of adequate space to provide confidential consultations in the clinics. All of which can adversely affect RIC of ART patients (Mukumbang *et al.*, 2017).

Furthermore, a qualitative study conducted in the EC province of South Africa found that health care professionals experienced a number of challenges in the treatment of paediatric ART patients at PHC facilities (Williams *et al.*, 2018). These included: shortages of staff, particularly staff trained in paediatric care; inadequate available space and equipment (e.g. scales); lack of confidence in treating HIV positive children due to the complexities of drug regimens, potential drug interactions and the skills required (e.g. drawing blood from babies

and children); and apprehension treating babies < 6 months of age (Williams *et al.*, 2018). This may be part of the reason why "Progress with paediatric down-referral has been slow" (Copelyn *et al.*, 2018:432).

The WHO (2013:190) has outlined three options for decentralization of ART initiation and maintenance:

1. "Initiation of ART in hospitals with maintenance of ART in peripheral health facilities."
2. "Initiation and maintenance of ART in peripheral health facilities."
3. "Initiation of ART at peripheral health facilities with maintenance at the community level (that is outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits."

The body of evidence has begun to grow for paediatric ART patients who are down-referred from hospitals to PHC facilities for ongoing treatment and care, as described in the first option for decentralization outlined by the WHO (2013). To our knowledge, a total of 6 studies have been conducted in South Africa: four of these are in the Western Cape (WC) (Morsheimer *et al.*, 2014; Arowosegbe, 2016; Davies *et al.*, 2017; Copelyn *et al.*, 2018); one in the EC (Teasdale *et al.*, 2017); and one in KZN (Spicer & Krishna, 2016). A further two studies were conducted in the international context: one in Zambia (van Dijk *et al.*, 2014) and one in Thailand (Hansudewechakul *et al.*, 2012). These studies outlined findings unique to the down-referral process, as well as the outcomes of the paediatric ART patients once they have successfully transferred from higher to lower level facilities. As these represent the existing knowledge for this study, they will be discussed in detail in the Literature Review in Chapter 2.

1.2. Problem Statement

Despite the findings in favour of decentralization of HIV care as a means to up-scale ART programs, improve access to ART and improve patient outcomes (van Dijk *et al.*, 2014); there may be ongoing concerns that down-referring paediatric ART patients to PHC facilities could negatively affect their outcomes. A number of factors may contribute to this, for instance the challenges to providing paediatric HIV care as described by healthcare professionals in PHC facilities in the EC, as outlined above (Williams *et al.*, 2018).

Furthermore, the fact that increased patient loads at PHC facilities may result in relative staff shortages and longer waiting times, which in turn affect RIC (Mukumbang *et al.*, 2017). Finally a paucity of data for the EC on the failure or success of down-referral of paediatric ART patients may contribute to this in the EC setting.

This study sought to address the latter by ascertaining whether children that have been initiated on ART in a hospital setting, stabilized on ART and then down referred to a designated PHC facility were: a) retained in care and b) remained virally suppressed after 12 months. These data could not only inform current medical practice, but could also provide a foundation for future research.

1.3. Purpose

This study sought to analyze the outcomes of paediatric ART patients, in terms of RIC and VL suppression, once they were down-referred from a tertiary and a regional hospital to primary care facilities in the BCM district of the EC. The data arising from this study will be useful to the paediatric departments at both hospitals, by informing their down referral policies. It will also support the paediatric District Clinical Specialist Teams (DCST), by informing their training and support of PHC staff regarding paediatric HIV care. Finally, the data will be useful for Non-governmental Organizations (NGO) supporting HIV care in the EC province; and to researchers, by informing future research needs.

1.4. Aim

The aim of this study was to determine the outcomes of paediatric HIV patients on ART that had been down-referred from a tertiary and a regional hospital to PHC facilities in the BCM district of the EC. The outcomes were measured by the proportion of patients retained in care, and VL suppression rates at 6 and 12 months post transfer.

1.5. Objectives

1. To ascertain the numbers of paediatric ART patients who fit the inclusion criteria that had been down-referred from a tertiary and a regional hospital in BCM to primary care facilities in the BCM district from June 2013 to June 2017.
2. To ascertain which primary care facilities these patients had been down referred to, and organize the patients into groupings as per facility.
3. To ascertain if patients referred to the primary care facilities: a) arrived for treatment; and b) were retained in care at 6 and 12 months post transfer.

4. To ascertain the patients' VLs at 6 (where applicable) and 12 months post transfer

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

With the view to improve access to ART and thus reduce HIV-related mortality, South Africa implemented decentralization of paediatric HIV treatment and care in 2010 (Department of Health, 2010). Having subsequently adopted strategies such as 90-90-90 in 2014 (UNAIDS, 2014) and Universal Test and Treat (UTT) as of the 1 September 2016 (Department of Health, 2016), it follows the numbers of patients accessing care would increase. Thus decentralization may have become even more critical in providing access to ART and reducing the burden of routine care on other aspects of the health system (WHO, 2013). Of the three decentralization options outlined by the WHO, this literature review seeks to explore the current available evidence for the success of the first option in paediatric HIV patients: "Initiation of ART in hospitals with maintenance of ART in peripheral health facilities" (WHO, 2013:190).

2.2. Review Process

2.2.1. Search Strategy

In order to find existing evidence on the outcomes of paediatric ART patients who are down-referred from higher levels of healthcare to primary care facilities, multiple literature searches were performed using Google, Google Scholar, PubMed and PubMed Central platforms. The initial search was conducted around the 13-16 June 2018 and the final search was on the 29 September 2020.

The terms used in these searches included various combinations of the following key terms to identify literature on:

- Paediatric age groups: "paediatric" OR "pediatric" OR "paediatrics" OR "pediatrics".
- HIV infected participants: "HIV".
- Decentralization of HIV care and treatment: "decentralized" OR "down-referral" OR "down referral" OR "down-referred" OR "transfer out" OR "transferred out".
- Patients' receiving ART: "ART" OR "antiretroviral" OR "antiretroviral therapy".
- General outcomes of patients on ART: "outcomes".
- Virological outcomes: "viral load" OR "virological suppression" OR "suppression".

- Retention in care: “retention in care”.

The AND operator was used to combine the different categories of search terms. No filters were used, except in part of the final search were articles were filtered by publication dates in the 2015 to 2020 time period.

2.2.2. Articles Included

Only studies reporting on the outcomes of HIV positive children and adolescents that were down-referred from a higher level of healthcare provision to a lower level of healthcare were included in this literature review. These studies are thus comparable with the current study since the same WHO model of decentralization is used (WHO, 2013). One article reported outcomes of adolescents who were transferred from both tertiary and primary care facilities to other sites, but did not specify the level of care of the transfer site. This study was included in the review as it provides insight into transfer success in the adolescent age group and the majority of transfers were from the tertiary institutions.

In the searches around the 13-16 June 2018, 6 articles were identified as having possible relevance to the study after reading the abstracts. Three of these were included in the literature review. On the 12 June 2019, another 2 articles were identified as relevant and both were included in the review. A further 4 potential articles were identified in the search on 21 May 2020, one of which was included in the review. Finally, on the 29 September 2020, of the 2 potential articles and 1 poster abstract identified, only the poster abstract was included. The full text article for this study could not be found.

One additional relevant article was identified from the bibliography of the other eligible literature and included in this literature review. The literature search is presented in Figure 2.1 below.

All the included studies were published in the last 10 years by virtue of the recent nature of this area of inquiry. A total of 6 of these studies were conducted in South Africa: four in the WC (Morsheimer *et al.*, 2014; Arowosegbe, 2016; Davies *et al.*, 2017; Copelyn *et al.*, 2018); one in the EC (Teasdale *et al.*, 2017); and one in KZN (Spicer & Krishna, 2016). A further two studies were conducted in the international context: one in Zambia (van Dijk *et al.*, 2014) and one in Thailand (Hansudewechakul *et al.*, 2012). These studies outline findings unique to the down-referral process, as well as the outcomes of paediatric ART patients once they have successfully transferred from higher to lower level facilities.

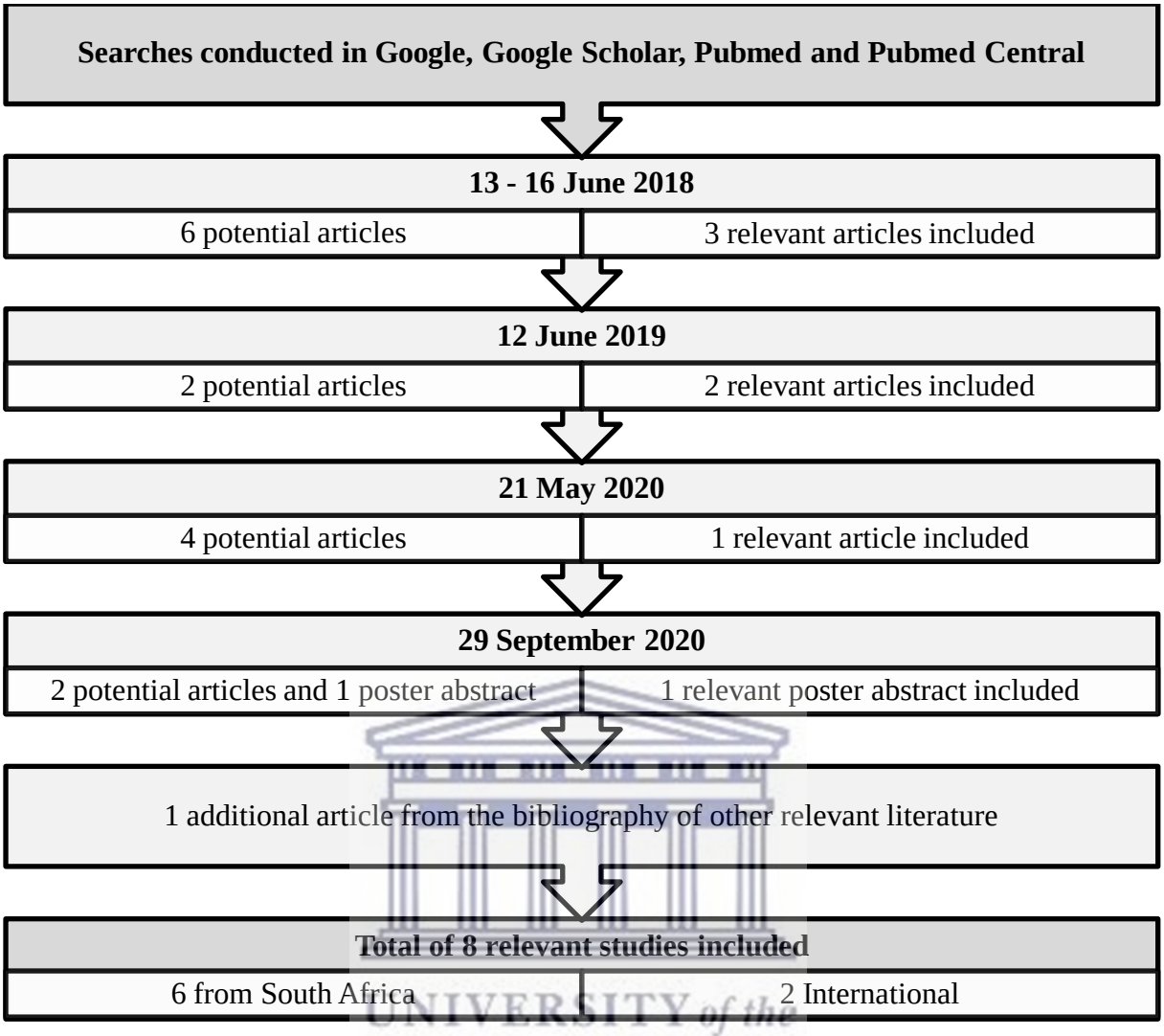


Figure 2.1: Schematic presentation of literature search

2.3. Article Characteristics

2.3.1. Aims and Focus of the Studies

Seven of the studies included in this review focus on children (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Morsheimer *et al.*, 2014; Arowosegbe, 2016; Spicer & Krishna, 2016; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018). Five of the seven define specific age ranges and two only specify that those included were HIV positive "children". However the WHO states that "For the purposes of HIV case definitions for reporting and surveillance, children are defined as younger than 15 years of age" (WHO, 2007:7), and it is assumed that they used this case definition. One study focuses on adolescents from 10 to <20 years of age (Davies *et al.*, 2017). However, the majority (72%) of those included in the study fell in the age group of 10-14 years of age (Davies *et al.*, 2017) and are thus comparable to the current study group.

All, but one, of the studies are from sub-Saharan Africa. This study reports on the outcomes of down-referred paediatric HIV patients in Chiangrai, Thailand (Hansudewechakul *et al.*, 2012).

Six of the seven paediatric studies reported on the outcomes of HIV-positive children that were initiated on ART in tertiary or secondary hospitals and down-referred to lower level facilities. One of the seven studies reported on the outcomes of children who were initiated on ART in a rural hospital in Zambia and subsequently down-referred to outreach clinics at rural health centres (van Dijk *et al.*, 2014). Four of the seven studies have two cohorts as comparison groups. Three of these compare the outcomes of the children who continued treatment at the referral hospital with those who were down-referred (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Teasdale *et al.*, 2017). One of the four compares the outcomes of those who were initiated on ART at PHC facilities with those who were initiated at higher levels of care and down-referred for ongoing treatment at PHC level (Morsheimer *et al.*, 2014). The remaining three paediatric studies had only a single cohort of patients.

The Davies *et al.* (2017) study reported on the outcomes of HIV-positive adolescents who were transferred out of two groups of facilities to other facilities in the Western Cape Province (WCP). The first group of referring facilities included two tertiary hospitals and the second group included two Community Health Centres (CHCs), however, 79% of transfers were from the tertiary facilities (Davies *et al.*, 2017). The outcomes for the patients in each of the groups were compared after transfer (Davies *et al.*, 2017).

Two of the studies had additional aims. One aimed to assess the adherence to guidelines for laboratory monitoring of paediatric HIV patients in KZN (Spicer & Krishna, 2016). The second aimed to assess whether transfer in adolescents could be feasibly examined using International epidemiology Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) cohorts linked to the WCP Department of Health data from the Provincial Health Data Centre (PHDC) (Davies *et al.*, 2017).

The outcomes assessed were similar across all the studies. Virological suppression was evaluated in all the studies. Undetectable VL was defined as <400 copies/ml in seven of these studies. The lower limit for detectable VL has changed over time and by 2015 was taken as <50 copies/ml, but prior to 2015 was <400 copies/ml (Teasdale *et al.*, 2017:2) and this is likely the reason for the use of the latter value in all the included studies. Immunological response was used in all but one study (Teasdale *et al.*, 2017), although it was not the main

outcome assessed. This was measured using CD4 absolute count and CD4 percentage in four of the studies (Morsheimer *et al.*, 2014; Arowosegbe, 2016; Spicer & Krishna, 2016; Copelyn *et al.*, 2018); only CD4 percentage in two of the studies (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014); and only CD4 absolute count in one study (Davies *et al.*, 2017). Successful transfer was specifically assessed in four of the studies (Arowosegbe, 2016; Davies *et al.*, 2017; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018) and the definitions of this varied according to the study in question. Retention in care was specifically assessed in five of the studies (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Davies *et al.*, 2017; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018); and adherence to ART medication was assessed in two of the studies (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014). Both defined optimal adherence as >95% and used pill counts or syrup volume measurements to assess adherence.

2.3.2. Study Design and Methodology

All of the studies reviewed had observational study designs. Seven of the eight were retrospective cohort studies, while one was a prospective cohort study (van Dijk *et al.*, 2014). All but one of the studies used analytical methods to assess the outcomes of their patients. The one which was purely descriptive formed the first arm of a larger case-control study, and only the abstract was available (Spicer & Krishna, 2016).

Only one of the studies provided a minimum required sample size of 316, based on sample size calculation, however the actual sample of 725 far exceeded this (Arowosegbe, 2016). The other studies included all eligible patients, and sample sizes ranged from: 77 – 725 patients.

Data was collected from various sources in the different studies. Paper-based records such as facility registers, patient files and other clinical records were used as one of the primary data sources in four studies (Hansudewechakul *et al.*, 2012; Morsheimer *et al.*, 2014; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018). Facility based electronic databases were used as one of the primary sources of data in four of the studies (Morsheimer *et al.*, 2014; Arowosegbe, 2016; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018). Two of the studies used the National Health Laboratory Services (NHLS) database as one of the primary data sources (Arowosegbe, 2016; Spicer & Krishna, 2016) and one study used it as a means to trace LTFU and transferred-out patients. This same study also made use of community tracing (Teasdale *et al.*, 2017). One study used linked data from the IeDEA-SA cohorts and the WCP PHDC as its primary data source (Davies *et al.*, 2017). The WCP PHDC is unique to the WC and is a data

system that uses a unique patient identifier (folder number) in all services to track outcomes across programmes and facilities. It captures data on visits to most health facilities in the province, as well as clinical, laboratory and pharmacy data (Davies *et al.*, 2017). The PHDC was used as secondary source of data in one study (Copelyn *et al.*, 2018), and to link facility based data to NHLS data in another study (Arowosegbe, 2016). The prospective cohort study used questionnaires administered to the caregivers pre- and post-transfer, and collected clinical and laboratory data at routine care visits (van Dijk *et al.*, 2014).

Inclusion of the lower level facilities to which patients were down-referred, was based on various factors. Copelyn *et al.* (2018) included 2 PHC clinics in the immediate drainage area of Red Cross War Memorial Children's Hospital (RCWMCH) that were <10km apart. Teasdale *et al.* (2017) selected 16 PHC facilities based on them having ≥10 children transferred to them and being situated in the area surrounding the city of Port Elizabeth. In the Thailand study, the 16 community hospitals (CHs) that referred to Chiangrai Prachanukroh Hospital (CRH) were included (Hansudewechakul *et al.*, 2012). The two studies using the data linked by PHDC were limited to facilities in the WCP, one looked at lower level facilities (Arowosegbe, 2016) and the other at all facilities in the province to which patients were transferred (Davies *et al.*, 2017). Morsheimer *et al.* (2014) included 7 PHC facilities that, through funding from the government and the President's Emergency Plan for AIDS Relief (PEPFAR), had received support from paediatric clinicians at Tygerberg Children's Hospital (TBH) Infectious Disease Clinic. The study from rural Zambia included 3 of the 13 rural health centres that refer to Macha Hospital, based on size of catchment populations and distance from the hospital (van Dijk *et al.*, 2014).

The follow up time periods were reported in a variety of ways depending on the study aims. These are outlined in Table 2.1 in Appendix C.

2.4. Themes arising

2.4.1. Down-referral guidelines and practices

In South Africa there are no national or provincial guidelines that outline the criteria for down-referral of paediatric HIV patients (Teasdale *et al.*, 2017). The criteria most often used by the health care providers in these studies are that the patients are stable on ART (5 of 8 studies) (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Arowosegbe, 2016; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018). This is further defined in two of the studies as the absence of opportunistic infections, recovering CD4 measurements (Hansudewechakul *et al.*, 2012;

Copelyn *et al.*, 2018) and virological suppression (Copelyn et al., 2018). One study listed virological suppression on ART as the only down-referral criteria (Spicer & Krishna, 2016). Other criteria used included: good adherence (2 of 8 studies) (van Dijk *et al.*, 2014; Copelyn *et al.*, 2018); that transfer is agreeable to the caregiver (Arowosegbe, 2016) or requested by the caregiver due to proximity of referral facility to their home (van Dijk *et al.*, 2014); and the feasibility of the transfer (Arowosegbe, 2016).

Due to the way these studies were designed, two did not require criteria for down-referral (Morsheimer *et al.*, 2014; Davies *et al.*, 2017).

Copelyn *et al.* (2018) described how as the WC ART programme matured, down-referral also occurred at the time of discharge from in-patient care, for those children initiated on ART while admitted to hospital. Interestingly, in the same study, documented viral suppression was not found to be associated with improved RIC and in the context of other research findings, this may place in doubt the "validity of 'clinical stability' as a down-referral criterion" (Copelyn *et al.*, 2018:437).

Only two of the eight studies described a protocol for the actual down-referral process (Arowosegbe, 2016; Copelyn *et al.*, 2018). Both of these studies reported on patients who were down-referred from RCWMCH. This protocol requires that the referring clinicians make telephonic contact with the receiving PHC facility and arrange the first appointment on behalf of the patients (Copelyn *et al.*, 2018). It also requires that the caregiver is provided with a written summary for the clinic staff (Copelyn *et al.*, 2018) that includes the name of the receiving facility, the date of the next appointment at the new facility, a medical summary, the most recent laboratory results for the patient and the current ART regimen (Arowosegbe, 2016:4). This could be an important step, as having a "recorded transfer out site in the RCWMCH database was found to be a strong predictor of successful transfer" (Arowosegbe, 2016:16).

2.4.2. Support for lower levels of healthcare & facility characteristics

Four of the eight studies mentioned the support offered to the lower level facilities by the referring hospitals (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Morsheimer *et al.*, 2014; Copelyn *et al.*, 2018). This support fell roughly into two categories: preparation of primary care facilities to treat paediatric HIV patients, and follow-up support after transfer. Hansudewechakul *et al.* (2012) described the training and mentoring of the community

hospitals by the tertiary hospital, CRH, between 2004 and 2006. This training covered all aspects of paediatric HIV care including clinical and adherence monitoring. After referral, the CRH team held regular teleconferences, individual case consultations, medical record reviews, home visit reviews and on-site visits (Hansudewechakul *et al.*, 2012). This intensive support is attributed as the reason for their excellent RIC (Copelyn *et al.*, 2018), with no LTFU during the study period (Hansudewechakul *et al.*, 2012). The support described in the Copelyn *et al.* (2018) study was in the post-transfer period, and consisted of telephonic support for the PHC clinicians and monthly visits by an infectious diseases specialist from RCWMCH. In Zambia, the district hospitals had mobile ART teams that supported the rural health centres designated as outreach sites. These teams visited the outreach sites every two weeks to increase the capacity of their staff to provide ART services (van Dijk *et al.*, 2014). They also provided medications, medical consumables and a means to access laboratory services from the hospital (van Dijk *et al.*, 2014). The outreach teams consisted of a clinical officer, a nurse, a pharmacy dispenser, a laboratory assistant, a counsellor and a data clerk (van Dijk *et al.*, 2014). Morsheimer *et al.* (2014) mentioned only that the seven PHC outreach sites included in the study received support from the Infectious Diseases Clinic at TBH, but did not go into detail as to what that support included.

In terms of the down-referral or receiving facilities in these studies: those in the Copelyn *et al.* (2018) study were doctor run. In the Hansudewechakul *et al.* (2012) study, the CHs in Chiangrai Thailand had at least two healthcare professionals including nurses, pharmacists and physicians. However, most of the care in these hospitals was done by nurses under the supervision of the physicians (Hansudewechakul *et al.*, 2012). In the Morsheimer *et al.* (2014) study on the other hand; it was shown that care for the paediatric ART patients was provided by physicians. Finally, in the Zambian study by van Dijk *et al.* (2014), the outreach clinics were staffed with an average of one clinical officer and a minimum of two nurses. One study included all lower level facilities in the WCP (Arowosegbe, 2016); and another all facilities to which the patients were transferred in the WCP (Davies *et al.*, 2017). These were likely to contain a mixture of health professional cadres. Two of the studies did not specify whether the down-referral facilities were doctor or nurse run (Spicer & Krishna, 2016; Teasdale *et al.*, 2017).

The level of support offered to the receiving facilities, as well as the cadres and training of health professionals at these facilities, would in all likelihood have an impact on the outcomes of the down-referred patients (Williams *et al.*, 2018; Copelyn *et al.*, 2018).

2.4.3. Successful Transfer

Of the four studies that specifically assessed success of down-referral, three had definitions for what would constitute a successful transfer. The first defined it as at least one recorded visit or medication pick up at the designated transfer facility (Teasdale *et al.*, 2017). The second defined it as a laboratory test, recorded with the NHLS from the lower level facility within two time frames: ≤18 months and ≤48 months after the date of transfer (Arowosegbe, 2016). The last one defined it as a record (visit, laboratory test or pharmacy) at a facility other than the referring facility after the date of transfer (Davies *et al.*, 2017). In addition, this latter study also determined the proportion of patients who successfully transferred within 18 months (Davies *et al.*, 2017).

The proportion of patients that successfully down-referred ranged from 67.2% in the EC (Teasdale *et al.*, 2017) to 90.6% in the WC (Copelyn *et al.*, 2018). All three of the WC studies had higher proportions of successful transfer than the EC study, which required one recorded visit or medication pick up to confer a successful transfer (Teasdale *et al.*, 2017). The higher proportion of successful transfer in the WC could be due to better documentation with the PHDC, more resources and better health infrastructure (Teasdale *et al.*, 2017). Copelyn *et al.* (2018) who reported the 90.6% successful down-referral included those who arrived at the selected PHC clinics (81.9%) and those who arrived at another PHC clinic or hospital (8.6%) in the WC. The adolescent study by Davies *et al.* (2017) reported the proportion of successful transfer as 81% including all those who arrived at any facility other than the original facility, and 95% of these arrived within 18 months. This equates to 77% of patients successfully transferring within 18 months. Arowosegbe (2016) reported that 76% of patients transferred successfully within 48 months, and 68% within 18 months of the transfer date. However, NHLS results were used to assess this, and it was estimated that laboratory tests were likely to only be 90% complete (Arowosegbe, 2016). As such, the actual proportion of successful transfer is probably closer to 80-85% (Arowosegbe, 2016). This outcome is supported by the findings in the Davies *et al.* (2017), where it was shown that laboratory data taken in isolation only accounted for 73% of the successful transfers, with 63% within 18 months (versus the 81% and 77% respectively when all data sources were included). These findings indicate that LTFU is a considerable risk at the point of down-referral (Teasdale *et al.*, 2017).

The median time from down-referral to arrival at the transfer facility ranged from 27 days (IQR: 19-33) (Copelyn *et al.*, 2018) to 5.4 months (IQR: 3.7-7.8) (Arowosegbe, 2016). While Copelyn *et al.* (2018:435) had the shortest median transfer time, they found that 11.4% of the patients took >8 weeks to present to the PHC facilities, with a median of 77 days (IQR: 66-129) or approximately 11 weeks. Thus, these patients experienced possible treatment interruption (Copelyn *et al.*, 2018). The longer median time of 5.4 months in the Arowosegbe (2016) study could be accounted for by the use of laboratory data rather than actual clinic visits. Again, this is supported by the Davies *et al.* (2017) study who showed that the median time to successful transfer, or transfer delay, was overestimated by laboratory data when compared to clinic visit data with a median of 241days (IQR: 142-388) or approximately 7.9 months versus 73 days (IQR: 28-197) respectively. Using all data sources, the median transfer time was 56 days (IQR: 27-134) or approximately 8 weeks (Davies *et al.*, 2017). This would indicate that, in addition to LTFU, possible treatment interruption is a considerable risk at the point of down-referral (Copelyn *et al.*, 2018).

Teasdale *et al.* (2017) used the NHLS database to trace patients who were LTFU at three different points in time: 1) from Dora Nginza Hospital (DNH), 2) at the point of transfer, and 3) after successful transfer. According to Teasdale *et al.* (2017), of the 399 patients LTFU, 52.6% had laboratory results after their last known visit. However, only 16.3% (65/399) were within 18 months of their last known visit (Teasdale *et al.*, 2017). This suggests that 16.3% were "silent transfers" or undocumented transfers to another site (Teasdale *et al.*, 2017). Of the 210 LTFU patients that had results after their last known visit, 62.1% (131) were unsuccessful transfers (Teasdale *et al.*, 2017). Their results were at a median time of 31.8 months (IQR: 27.2-42.0) after their last known visit; and only 7.6% (10/131) of them were within 18 months, thus indicating possible silent transfer (Teasdale *et al.*, 2017). As silent transfers may account for a proportion of those patients designated as "unsuccessful transfer", the rates of successful transfer may be higher than these studies report. This underpins the importance of tracing children who don't present at their transfer facility (Teasdale *et al.*, 2017). It also highlights the usefulness of a province- or nation-wide database with a single patient identifier, like the PHDC in the WCP.

Only two studies found potential predictors of successful transfer. Arowosegbe (2016) found that having a recorded transfer out site in the tertiary hospital database was a strongly predicted of success of the transfer. Davies *et al.* (2017) found that transferring out of a tertiary institution as compared to a PHC facility; being 15 years of age or older; and

virological suppression at transfer, were predictors of successful down-referral. This latter finding may suggest that while virological suppression does not improve RIC (Copelyn *et al.*, 2018), it may still be a useful down-referral criterion to improve success of the down-referral itself. Further research is needed in this area.

While four of the studies did not look specifically at success of transfer, there are inferences made regarding this outcome in three of them. The Thailand study had no LTFU's recorded during the study period (Hansudewechakul *et al.*, 2012) and thus it can be assumed that all patients transferred successfully. Spicer and Krishna (2016) reported only the VL results obtained (73% of those down-referred), and assigned this to poor adherence to monitoring guidelines by the transfer facility. However, it is possible that a proportion of these missing results were in fact unsuccessful transfers or LTFUs. As the full text article is not available for the Spicer and Krishna (2016) study, there may be elements in the study design and methodology to explain this that are not accounted for here. The prospective cohort study by van Dijk *et al.* (2014) did define successful transfer as at least one study visit after transfer. However, researchers in this study did so as an inclusion criterion for the children in the outreach clinic group (van Dijk *et al.*, 2014), thus by selection all transfers were successful.

2.4.4. Retention in Care

Retention in care was defined by only one of the studies in which patients were considered to be retained if they had at least one visit within the 6 month period on either side of the designated time interval being assessed (Davies *et al.*, 2017). Two other studies defined what they considered to be LTFU. For one, they defined three categories of LTFU, but for the purposes of this review, we will focus on the group that was LTFU after successful transfer. In this group, LTFU was defined as no recorded visit for more than 6 months according to the record at the transfer facility (Teasdale *et al.*, 2017). The second study defined LTFU as a failure to attend a visit for at least 6 months prior to the end of the assessment period (van Dijk *et al.*, 2014).

The five studies that specifically assessed RIC had varying results. Hansudewechakul *et al.* (2012) reported perfect RIC, as there were no documented LTFUs in the study period. However, in the entire study cohort (those followed-up at CRH and those down-referred) 10% (42) of children died. In addition, one child refused ongoing treatment with ART, despite remaining in care and eight of the children were transferred out to other provincial clinics in that time period (Hansudewechakul *et al.*, 2012). The worst reported retention was

in the EC, where 62.6% of those who successfully transferred remained in care (Teasdale *et al.*, 2017). However, this study period of 11 years was the longest and the definition of LTFU related to the end of the study period (Teasdale *et al.*, 2017). For those who weren't retained in active care, 19.2% were LTFU at a median time of 31 months (IQR: 8-45) post down-referral; 0.5% died; and 17.8% transferred to another facility (Teasdale *et al.*, 2017). Davies *et al.* (2017) had the second longest study period of 10 years, but assessed RIC at 1, 2 and 3 years post transfer. They reported a decrease in retention from 90% at 1 year to 84% at 3 years post down-referral. However, their study design meant that they only included those with sufficient time before study closure to be assessed for that outcome at each specific time period (Davies *et al.*, 2017). Thus, the numbers assessed at 2 and 3 years post transfer were lower than at 1 year (Davies *et al.*, 2017). Taking into account that 85% of patients successfully transferred and that approximately 84% of those transferred, remained in care at 3 years, they calculated the overall RIC to be closer to 72% (Davies *et al.*, 2017). Furthermore, RIC was higher in the 10-14 year age group as compared to the 15-19 year age group at 1 and 2 years, but similar at 3 years of follow-up (Davies *et al.*, 2017:21). Van Dijk *et al.* (2014) compared RIC in the group attending the hospital-affiliated clinic with those down-referred to outreach sites, and found 95% and 75% RIC respectively after a median of 34 months of treatment. There were no LTFUs in either group; no deaths in the hospital clinic group, and only 1 death due to drowning in the outreach site group (van Dijk *et al.*, 2014). A total of 4.9% of the hospital group transferred out to other clinics; while 5.9% of the outreach site group transferred to other clinics; and 17.6% of the outreach site group transferred to one of the clinics included in the study when it became an independent ART site (van Dijk *et al.*, 2014). Copelyn *et al.* (2018) reported that at 12 months post down-referral 81% (94/116) of the children in the study cohort remained in care, with 64.7% (75/116) at the selected PHC clinics and 16.4% (19/116) at other sites. This would equate to around 89.5% (94/105) of those who successfully transferred, remaining in care at 12 months. It is also worth noting that 95 children presented to the selected PHC facilities, and 75 were retained in care at 12 months. Similarly 10 children presented to other sites, and that number had increased to 19 children at other sites at 12 months post down-referral (Copelyn *et al.*, 2018). This indicates that around 8.6% of those who successfully down-referred may have transferred between sites in the WCP during the follow–up period. This movement between facilities within the WCP could have been detected using the PHDC. In addition, the researchers in this study reported that 1.7% of children had a documented transfer to a facility out of the WC in the 12

month follow-up period (Copelyn *et al.*, 2018). Of those who successfully down-referred, 9.5% (10/105) were subsequently LTFU and one died (Copelyn *et al.*, 2018).

These findings in the Copelyn *et al.* (2018) study suggest that the proportions of those retained in care may possibly have been higher in the Teasdale *et al.* (2017) study if the EC had a database similar to the PHDC or if more facilities were included in the analysis. This is further confirmed by the NHLS tracing done in the EC study, indicating that 31.3% of children LTFU after successful down-referral, had laboratory results within 18 months of their last recorded visit, suggesting that they were in fact silent transfers (Teasdale *et al.*, 2017).

While Arowosegbe (2016) did not specifically assess RIC, the fact that 76% of children had blood results recorded in the NHLS database at 48 months post down-referral, suggests that they were likely retained in care at that point. However, for those patients treatment interruption cannot be excluded (Arowosegbe, 2016). Morsheimer *et al.* (2014) also didn't specifically assess RIC, but they did report a documented mortality of 2.2% and LTFU of 4% in the PHC cohort. In this study it was also found that a disproportionate number of children in the group who initiated ART at the PHC were LTFU as compared to those initiated in the hospital with subsequent down-referral (Morsheimer *et al.*, 2014).

2.4.5. Virological Suppression

Virological suppression was defined as <400 copies/ml by 5 of the studies (Hansudewechakul *et al.*, 2012; Morsheimer *et al.*, 2014; Arowosegbe, 2016; Davies *et al.*, 2017; Copelyn *et al.*, 2018). In 2 of the studies <400 copies/ml was used as the lower limit of detectable VL (van Dijk *et al.*, 2014; Teasdale *et al.*, 2017). More specifically, Teasdale *et al.* (2017) used <400 copies/ml as the lower limit of detectable for pre-transfer VL's and <50 copies/ml when checking for current engagement in care with NHLS results from the 2015/2016 period. In one study virological failure was defined as two sequential VL's of >1000 copies/ml (Morsheimer *et al.*, 2014). Detectable VL was defined in three ways in another study: >400 copies/ml; >1000 copies/ml and >10,000 copies/ml (van Dijk *et al.*, 2014).

All of the studies included in this literature review evaluated the virological suppression of patients after transfer. Three of them reported positive virological outcomes post down-referral. Arowosegbe (2016) found that the proportion of children who successfully down-

referred with a VL of <400 copies/ml increased from 55.9% at transfer to 81.4% at the first visit post transfer. The VL at transfer was defined as the result closest to the date of down-referral within a 12 month period of transfer; and the post-transfer VL as the results of the first test found after the date of down-referral (Arowosegbe, 2016:5). This improvement was ascribed to the patients being on a trajectory to improved health at the time of transfer rather than the transfer itself being responsible for the improvement in outcomes (Arowosegbe, 2016). Morsheimer *et al*. (2014) compared two groups: one group initiated at PHC facilities and the second initiated at higher levels of care and down-referred. The outcomes of this study showed that the down-referral group had higher baseline VLs at ART initiation (Morsheimer *et al.*, 2014). Furthermore it showed that those initiated at PHC level were 66% less likely to develop virological failure than the down-referred group (Morsheimer *et al.*, 2014). The median time to suppression was 29 weeks in the PHC initiated group, when compared to 44 weeks in the down-referred group (Morsheimer *et al.*, 2014). Of the 153 children down-referred from tertiary care, 80% were suppressed at the time of transfer, and 96% of these remained so at the last study evaluation (Morsheimer *et al.*, 2014). Three quarters of the 26 children with unsuppressed VL at transfer, met the criteria for virological failure (Morsheimer *et al.*, 2014). However, 77% of the 26 children achieved virological suppression after 6 months of treatment at the PHC facilities, with only one third requiring a regimen change (Morsheimer *et al.*, 2014). This shows that adherence improved at the PHC level of care most likely as a result of removing barriers to accessing care (Morsheimer *et al.*, 2014). Hansudewechakul *et al.* (2012) also compared the group that was down-referred to CHs, with those who continued care at the tertiary hospital (CRH). They assessed the virological response in the 29% (38) and 14% (22) of children at CRH and the CH's respectively, with a VL at baseline and at least one follow-up VL (Hansudewechakul *et al.*, 2012). It was also shown that one out of 37, 35 and 35 children at CRH, and none of the 20, 16 and 18 CH children had a VL> 400 copies/ml at 12, 24 and 36 months respectively (Hansudewechakul et al., 2012). Furthermore, at 48 months "none of the 27 CRH and 1 of the 18 CH children had a VL >400 copies/ml" (Hansudewechakul *et al.*, 2012:6). The researchers in this study attributed these positive outcomes to the high level of adherence to medication. They found that 95-100% and 93-100% of the children at the CH's and CRH respectively had a ≥95% adherence over the 48 month follow-up period (Hansudewechakul et al., 2012). This high level of adherence is likely to be a consequence of the intensive support offered to the community hospitals by the CRH program. However, the researchers concede that this level of support may not be feasible in less developed countries (Hansudewechakul *et al.*, 2012).

Two of the studies reported poorer virological outcomes in those children down-referred. Van Dijk *et al.* (2014) reported on adherence in an outreach site group and a hospital-affiliated group. They found that the proportion of children with optimal adherence (>95%) was lower for the outreach clinic group, with a median percentage of visits with optimal adherence of 69.2% versus 79.3% in the hospital-affiliated group (van Dijk *et al.*, 2014). The poorer adherence in the outreach clinic group is thought to be the reason for the lower proportion of children in this group with suppressed VL at each time point, up to 3 years after ART initiation (van Dijk *et al.*, 2014). Furthermore, VL in this group was significantly more likely to be unsuppressed for each defined threshold. Seventeen percent had VLs that were >400 copies/ml (versus 8% in the hospital affiliated group); 16% with VLs >1000 copies/ml (versus 7% in the hospital-affiliated group) and 10% with VL >10,000 copies/ml (versus 3% in the hospital affiliated group) (van Dijk *et al.*, 2014). Spicer and Krishna (2016) on the other hand, specifically assessed whether VL monitoring guidelines were adhered to in paediatric ART patients who were down-referred from Edendale Hospital in KZN to a local clinic. They did this by using the NHLS database to look for laboratory results at approximately 12 months post down-referral (Spicer & Krishna, 2016). They found that only 73% of those down-referred had a VL result at around 12 months post down-referral (Spicer & Krishna, 2016). In addition, 19% of those with VL results were found to be unsuppressed or have reversion to detectable VL at approximately 12 months, despite having achieved virological suppression pre-transfer (Spicer & Krishna, 2016).

One study had relatively good virological outcomes, but the proportion of children that actually had results was small, and so it may not be an accurate reflection of virological status in the entire cohort (Teasdale *et al.*, 2017). Teasdale *et al.* (2017) reported that 81% (188/232) of those down-referred from DNH for whom results were obtained had a pre-transfer VL <400 copies/ml. However 46.4% (201/433) of all those down-referred had no pre-transfer VL result (Teasdale *et al.*, 2017). Post-transfer, the VL results for all children that were transferred as well as all those LTFU (including those LTFU from DNH, at the point of down-referral and after successful transfer) were reported on. It was found that 19.6% had VL results for the 2015/2016 period, indicating current engagement in care, and 49.7% of these were <50 copies/ml (Teasdale *et al.*, 2017). For reference purposes, the 2015/2016 data was also searched for the 271 children who had successfully down-referred, and were known to be active in care. Only 40.2% of these (109/271) had recent laboratory monitoring (Teasdale et al., 2017). This percentage from the EC study is nowhere near

Arowosegbe's estimate that laboratory testing is 90% complete in the WCP (Arowosegbe, 2016). However, other WC studies also had lower proportions of VL results obtained, as seen for one of the RCWMCH studies (Copelyn *et al.*, 2018).

Copelyn *et al.* (2018) reported very similar proportions of virological suppression pre- and post-transfer. At the time of down-referral 47.4% were virologically suppressed within the preceding 6 months; 12.1% had no VL results; and 40.6% had an unsuppressed VL (Copelyn *et al.*, 2018). Of the 75 patients that remained in care at the selected PHC facilities 12 months post down-referral, 50.7% (38) were suppressed at the time of transfer, and 54.7% (41) were still suppressed approximately 12 months later (Copelyn *et al.*, 2018). However, at 6 months post down-referral (within a window of 4-8 months) 20% (15/75) had no VL results and at 12 months (within a window of 9-15 months) 28% (21/75) had no VL results. Thus, if only those with documented VL results are taken into account the suppression would be 86.4% (38/44) at down-referral and 75.9% (41/54) at 12 months (Copelyn *et al.*, 2018). Davies *et al.* (2017) assessed the VL measures taken on the date closest to the date of transfer plus 1, 2 or 3years, and within a 6 month window period either side of each of those time points. At transfer 78% of patients were virologically suppressed (Davies *et al.*, 2017). At 1 and 2 years post transfer, 80% and 75% remained so, respectively; and by 3 years VL suppression had decreased to 71% (Davies *et al.*, 2017). Viral load suppression post transfer was also found to be consistently lower in the adolescents who were older at the time transfer (Davies *et al.*, 2017). In terms of availability of VL results, Davies *et al.* (2017) report that at 1 year 11% of patients had missing VL results, and that this had increased to 20% by 3 years post-transfer.

These findings suggest that guideline-directed VL monitoring needs to be vastly improved if we are to accurately measure our progress towards 90-90-90 (followed by 95-95-95) (UNAIDS, 2014) and ultimately reach these goals. These results are also vital to ascertain the performance of the decentralization model for HIV care.

2.4.6. Immunological Response

Of the seven studies that included immunological response as an outcome, three used a definition of severe immunosuppression as a way to assess response to ART. Hansudewechakul *et al.* (2012) defined severe immune suppression at ART initiation as a CD4 percentage <5%, and at assessment of treatment outcomes as <15%. Both the Arowosegbe (2016) and van Dijk *et al.* (2014) studies used WHO definitions but from different WHO sources. The former considered the children to have severe immune

suppression if the lowest CD4 count and percentage met the WHO classification from its 2007 case definitions (WHO, 2007). This definition is per age category. Thus severe immunosuppression would be a CD4 percentage of <25% for a child <11months of age; <20% for a child aged 12-35 months; <15% for a child aged 36-59 months; and CD4 cell count <200 cell/mm^3 or CD4 percentage <15% for a child >5 years of age (WHO, 2007). The van Dijk *et al.* (2014) study used the WHO 2006 treatment guidelines. Thus they defined severe immune suppression as CD4 cell count or percentage <1500 cells/mm^3 or <25% respectively for a child <11 months of age; <750 cells/mm^3 or <20% respectively for a child 12-35 months of age; <350 cells/mm^3 or <15% respectively for a child 36-59 months of age; and <200 cells/mm^3 or <15% respectively for a child >5 years of age (WHO, 2006). Davies *et al.* (2017) on the other hand reported on the proportion that had a CD4 cell count of >500 cells/µl, using this value as an indication of immune response (IR) to ART.

For the studies that had comparison groups, the immunological outcomes were mostly similar between the down-referral group and the comparison group assessed. These studies were also done earlier (all before 2015) and reported immunological outcomes in greater detail than the majority of the later studies. In the entire Thailand cohort, the CD4 percentage increased from a median of 6% (IQR: 2-13) at baseline to 24% (IQR: 20-29) at 24 months and 26% (IQR: 22-31) at 48 months (Hansudewechakul *et al.*, 2012). Those with severe immune suppression decreased from 80% at ART initiation to 7.1% at 24 months and 4.8% at 48 months (Hansudewechakul *et al.*, 2012). The median CD4 percentage at down-referral was 20% (IQR: 14-24) and 20% (IQR: 16-26) for the CRH group and the CH group respectively (Hansudewechakul *et al.*, 2012). In the sub-group analysis, there was no significant difference in CD4 percentage gain between those who continued treatment at the tertiary hospital (CRH) and those who were down-referred to community hospitals (CH's) (Hansudewechakul *et al.*, 2012). In the Zambian study the mean CD4 percentage at transfer did not differ between the hospital-affiliated and outreach site groups (van Dijk *et al.*, 2014). Post-transfer the outreach site group's mean CD4 percentage was lower than that for the hospital-affiliated group, but the difference was not statistically significant (van Dijk *et al.*, 2014). At 6 months post-transfer the changes in CD4 percentage from the pre-transfer to 6 month measurement did not differ between the two groups (van Dijk *et al.*, 2014). Morsheimer *et al.* (2014) did not report on the CD4 outcomes for each of the comparison groups separately, but rather for the entire longitudinal cohort. They reported that 80% of the cohort maintained a CD4 percentage above baseline. However, as the median baseline CD4

percentage was 17.8% (IQR: 11.0-24.2) in the PHC initiated group and 16% (IQR: 10.0-21.8) in the down-referred group (Morsheimer *et al.*, 2014), this does not infer much about the children's IR to ART. Having said that, these researchers further documented that the average percentage improvement over the baseline CD4 percentage, increased from a median of 8.7% (IQR: 2.3-13.8) at 6 months, to a mean of 17.4% (95% CI: 15.5-19.2) at 36 months (Morsheimer *et al.*, 2014). This improvement would in essence indicate good immune recovery. While these researchers did not define immunological failure, they reported that 2% (13) of children in the cohort had evidence of this after 24 weeks of adherent ART (Morsheimer *et al.*, 2014). Five of these recovered by 18 months, and were thus merely exhibiting delayed reconstitution. A further five had only transient immunological failure despite virological suppression and had recovered by the next measurement. Finally, three had persistent failure despite ongoing virological suppression (Morsheimer *et al.*, 2014).

For those studies with single cohort designs: one of the four reported improvement in immune status post down-referral (Arowosegbe, 2016). Two of the four studies reported maintenance of pre-transfer immunological gains after down-referral (Spicer & Krishna, 2016; Copelyn *et al.*, 2018). The last study showed a decline in immune status post-transfer (Davies *et al.*, 2017). In the one Cape Town based study (Arowosegbe, 2016), 55.45% of the down-referred group were immunosuppressed at ART initiation. Of those with results at transfer: 32.35% had a CD4 percentage of <20%; 17.38% had a CD4 percentage between 20-24%; and 50.28% had a CD4 percentage of >25% (Arowosegbe, 2016). Nonetheless, this researcher reported good immunological outcomes post transfer, demonstrating an increase in both median CD4 count and percentage between transfer and the first visit post-transfer (Arowosegbe, 2016). Median CD4 count improved from 1026 cells/mm^3 (IQR: 563-1577) at transfer to 1260 cells/mm^3 (IQR: 788-1802) post-transfer; and CD4 percentage improved from 25.1% (IQR: 17.25-33.75) to 30.15% (IQR: 22.88-36.62) at the same time points (Arowosegbe, 2016). In another Cape Town based study, Copelyn *et al.* (2018) compared median CD4 percentage at ART initiation, the time of down-referral, and at 6 and 12 months post down-referral. They demonstrated that the median CD4 percentage increased from 17% (IQR: 11-23) at ART initiation, to 31% (IQR: 23-37) at down-referral. The latter was maintained at 6 and 12months post down-referral with results of 33% (IQR: 26-39) and 32% (IQR: 27-35) respectively (Copelyn *et al.*, 2018). Though these authors did not define what would constitute severe immunodeficiency, they nonetheless reported that the proportion of children with severe immunodeficiency reduced from 69.3% at ART initiation to 1.3% at 12

months post down-referral (Copelyn *et al.*, 2018). Spicer and Krishna (2016) found that those with CD4 results showed maintained or improved immune status post-down-referral (Spicer & Krishna, 2016). However, similar to their VL results findings, only 71% of patients had a CD4 result at 12 months post down-referral (Spicer & Krishna, 2016).

Davies *et al.* (2017) found that 64% of the children had a CD4 count of >500 cells/µl at transfer. The median CD4 count showed a significant decline from 654 cells/µl (IQR: 444-926) at transfer to 639 cells/µl (IQR: 461-903) at 2 years and 580 cells/µl (IQR: 429-793) at 3 years (Davies *et al.*, 2017). Even taking into account that these means are >500 cells/µl and thus still constitute an IR to ART, the proportion of patients with CD4 count >500cells/µl decreased from 71% at 1-2 years to 59% at 3 years post down-referral (Davies *et al.*, 2017). This indicates ongoing or reversion to poor immune response in 41% of patients after down-referral. The proportion with CD4 count >500 cells/µl was consistently lower in the older adolescents (15-19 years of age) at all time points (Davies *et al.*, 2017). Similar to what they found with VL results, those with missing CD4 measurements increased from 13% at 1 year to 28% at 3 years (Davies *et al.*, 2017). In contrast to VL missing results, this finding may be attributed to a change in the 2013 South African treatment guidelines which recommended that in clinically stable, virologically suppressed patients, CD4 monitoring is in fact not indicated (Davies *et al.*, 2017). However, taken in conjunction with the missing VL results it may indicate poor laboratory monitoring of HIV in general.

2.5. Conclusion

The existing evidence for the outcomes of paediatric HIV patients, that have been down-referred from higher to lower levels of healthcare, shows promising results. However, it also highlights certain key concepts that require further consideration. Firstly, a number of the studies presented in this chapter confirm that the point of transfer is a high risk for LTFU of these patients and is also a high risk for treatment interruption. This underscores the need for improved down-referral procedures and ongoing communication between referral and transfer sites. Furthermore, it demonstrates the need for further research into factors affecting the success of transfer.

Secondly, those studies that had access to an electronic database (whether this was the NHLS, the WCP PHDC or the IeDEA-SA) were better able to trace patients who had "silently transferred", and obtain more complete information on patient outcomes post-transfer. This was particularly true where these databases were linked and where a unique patient identifier

was used. This could have massive implications for continuity of care in patients if implemented on a national scale. It may also improve accuracy of monitoring and evaluation in HIV programs.

Thirdly, suboptimal adherence to laboratory monitoring guidelines for HIV could give a false impression of the success of ART programs, as reporting on virological suppression and immunological recovery can only be done in those with results. Research into the causes for this may be another area for future inquiry, as they are likely to be multifactorial. A review of guidelines and current practice may be necessary depending on what said research discovers in this regard. One potential contributing factor identified thus far is a lack of confidence in drawing blood from paediatric patients at PHC level as touched on in the Williams *et al.* (2018) study in the EC.

Finally, the research in South Africa has mostly been conducted in the WCP, which has better health infrastructure and resources than many of the other provinces (Teasdale *et al.*, 2017). Hence, the outcomes of patients may seem better than what could be expected in the other South African provinces. Aside from scaling-up services in the less resourced provinces, more research also needs to be done in these settings if we are to improve the HIV outcomes in all South African populations.

CHAPTER 3: METHODOLOGY

3.1. Introduction

In this chapter the details pertaining to how the study was conducted are discussed. This includes the study design used, the setting for this research, population and sampling, data collection, data analysis, validity and reliability of the study, and ethical considerations.

3.2. Study Design

An observational design was used for this study, as it was for all 8 of the comparative studies outlined in the literature review in Chapter 2 (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Morsheimer *et al.*, 2014; Arowosegbe, 2016; Spicer & Krishna, 2016; Davies *et al.*, 2017; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018). In order to ascertain whether being down-referred to a PHC facility from a tertiary or regional hospital, had any effect on RIC or the virological outcomes of paediatric ART patients, this study was conducted as a retrospective cohort analysis, with a single cohort of patients. All of the comparative studies used a retrospective design, except for van Dijk *et al.* (2014), which was a prospective cohort analysis. Four of the studies outlined in Chapter 2 also had only a single cohort of patients. Two of these were similar to the current study, and looked at the outcomes of paediatric ART patients that were transferred out of RCWMCH to primary care facilities in Cape Town (Arowosegbe, 2016; Copelyn *et al.*, 2018). The third was also in the WC and assessed the outcomes of adolescents who were transferred to other facilities (Davies *et al.*, 2017). The fourth was another similar study but conducted in KZN (Spicer & Krishna, 2016). When a single cohort is used, the patients who do not develop the outcome of interest act as internal controls (Mann, 2003). The data used had already been collected and captured in both patient records and on Tier.net (the electronic database at the facilities) as part of routine care of these patients, thus making a retrospective analysis cost effective and time efficient (Mann, 2003).

3.3. Study setting

This study was conducted in the BCM district of the EC. Buffalo City Municipality is divided into three sub-districts called “management areas” by the Buffalo City Metro Health Department (BCMHD), namely: the East London, Mdantsane and Bisho sub-districts (Information Systems:

BCMHD, personal communication, 2020 September 14). A tertiary and a regional hospital were included in this study as the referral hospitals from which the study population was derived. There was no pre-selection of the PHC facilities, the only criteria being that they were situated within the BCM district. Those included in this study were the facilities at which the down-referred patients presented for ongoing HIV care. Forty-six PHC facilities were included in this way. These facilities were for the most part urban (82.6%; 38/46), but also included rural (13%; 6/46) and peri-urban facilities (4.4%; 2/46) (Information Systems: BCMHD, personal communication, 2020 September 14). While the majority were PHC clinics (93.5%; 43/46), there were also three CHCs (6.5%; 3/46) (Information Systems: BCMHD, personal communication, 2020 September 14). According to information obtained from the BCMHD, all clinics in this district are nurse run, with doctor's visits up to once a week or twice a month, although often less frequent (Information Systems: BCMHD, personal communication, 2020 October 5). At the CHCs, doctors are appointed full-time, in addition to the nurses (Information Systems: BCMHD, personal communication, 2020 October 5).

3.4. Population and sampling

3.4.1. Inclusion and exclusion criteria

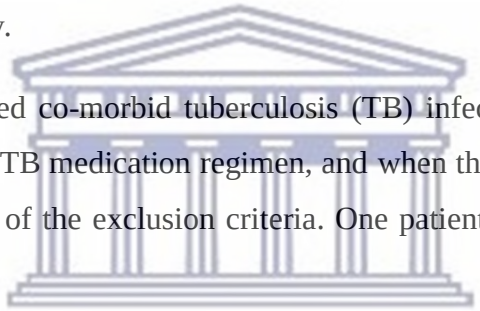
The study population included male and female HIV positive children between the ages of 0-14 years. These children had been initiated on their current ART regimen (i.e. either initiated on the first line regimen or changed to the second line regimen) at a tertiary or a regional hospital in the BCM district. They were then subsequently down-referred to primary care facilities between June 2013 and June 2017. Furthermore, the reason for them to be down-referred had to be stability on ART, as defined by virological suppression, immune reconstitution and, where possible to ascertain, clinical improvement (as per the treating doctor). This ensured that all study units had the potential to develop the outcome of interest (Mann, 2003), which in this case was virological suppression on ART.

Aside from not fulfilling the inclusion criteria listed above, children were excluded if they had been down-referred for reasons other than stability on ART (e.g. convenience down-referral). Also if they were re-initiated on ART after defaulting treatment on 2 or more occasions. They were excluded if they were down-referred to primary care facilities outside of the BCM district, as well as when they were referred to levels of care other than PHC. Finally they were excluded

if they were on a third-line ART regimen. The reasons for these exclusion criteria are described in the paragraph below.

Firstly, a history of defaulting may have increased the chances of LTFU in the study, thus introducing bias. Secondly, defaulting treatment may have resulted in resistance to ART and thus may have caused poorer patient outcomes unrelated to the fact that treatment was received at a primary care facility. It was not logistically feasible to collect data from facilities outside the BCM district for this study. As the aim was to evaluate the outcomes of children on ART that were down-referred from a tertiary and a regional hospital to primary care facilities, transfers to other levels of care was beyond the scope of this study. Finally, the complexity of the third line regimens, and the fact that the patient would have already failed on first and second line treatment, may have caused poorer patient outcomes that were unrelated to the fact that the care was received at a PHC facility.

Those children with confirmed co-morbid tuberculosis (TB) infection were included provided that they were stable on their TB medication regimen, and when they fulfilled all other inclusion criteria and did not have any of the exclusion criteria. One patient with suspected TB was also included.



No sampling was done, as it was anticipated that the numbers of children down-referred would be close to the calculated required sample size of 285 patients and hence that all study units would be included. However, after identifying all the eligible study units, the total number was less than the calculated sample size. The details will be explained in the next chapter.

3.4.2. Sample size calculation

This was a retrospective cohort study (Hansudewechakul *et al.*, 2012; Morsheimer *et al.*, 2014; Arowosegbe, 2016; Spicer & Krishna, 2016; Davies *et al.*, 2017; Teasdale *et al.*, 2017; Copelyn *et al.*, 2018) with a single cohort (Arowosegbe, 2016; Copelyn *et al.*, 2018). The main outcome of interest was VL suppression at 12months post down-referral. A similar study conducted in the WC showed that of the paediatric ART patients down-referred from a tertiary hospital to a decentralized site: 80% were virally suppressed at the time of transfer, and 96% of those remained virally suppressed at the last measurement of viral load (Morsheimer *et al.*, 2014). Thus 76.8% of patients remained virally suppressed. With a margin of error of 5%, the desired

95% confidence interval would be 71.8- 81.8%. Thus, the standard error was estimated to be 2.5%.

Parameters for sample size calculation measuring one variable (single proportion):

n – sample size

e – required size of standard of error.

p– percentage (preliminary idea of what we are trying to estimate)

Calculation of sample size:

$n = p\,(100-p) / e^2$

$= 76.8\,(100-76.8) / 2.5^2$

$= 1781.76 / 6.25$

$= 285.1$

Therefore, the required sample size was 285 patients.

3.5. Data Collection

Data collected at the tertiary and the regional hospital for the patients that were included in the current study cohort included: the i) age and gender of the patients; ii) the date of ART initiation; iii) the date of initiation of current ART regimen; iv) the current ART regimen (with medication names); v) the date and value of the last VL and CD4 measurement prior to down-referral; vi) the presence of TB co-infection, as well as vii) the date of down-referral and viii) the duration of treatment issued to the patient at the point of down-referral. For those who had been transferred out of the tertiary hospital HIV clinic these data were obtained from the individual patient files, as using Tier.net was not logistically feasible for the department there. In total, 523 patient files were assessed for eligibility. Of these 428 were excluded based on the above mentioned criteria. Thus, initially 95 patients were included in the study from the tertiary hospital. It was noted that the doctors would down-refer some patients to a PHC facility, and then would bring them back for 6 monthly follow-up visits at the tertiary care facility. Where this was done, patients were only included in the study if they had eventually been completely transferred out of the hospital.

In these instances, the date the patient was completely transferred out was taken as the date of down-referral and the date of presentation at the PHC facility was taken as the next recorded consultation following the date of down-referral. This was done because the study aimed to assess the outcomes of the patient once they were completely in the care of the PHC facility.

At the Regional Hospital these data were extracted from Tier.net. The patient database was exported from Tier.net to an excel file on the computer in the paediatric out-patients department (POPD). Of the 12 650 HIV patients on the Tier.net database for the hospital, 251 were identified as potentially eligible after filtering for the following: outcome listed as "Transferred out"; down referral to a primary care facility in the BCM district; the date of birth to ensure the patient was between 0-14years of age when reaching our selected down-referral period (June 2013 – June 2017); ART started in the hospital; and the most recent viral load result being <1000 copies/ml prior to down referral. These 251 patient profiles were then assessed in Tier.net individually to ensure they met the remaining criteria. A further 123 patients were excluded, and 128 were included in the study from the Regional Hospital.

After this process the CD4 measurements for the eligible patients were examined to assess for IR to ART as per the above definition, and a further 7 patients were excluded due to having a poor immune response (PIR) to ART.

A list of the included down-referred patients was compiled and categorized by the primary care facilities to which they were down-referred. Some facilities had similar names and so the names of the patients referred to these facilities were included on the list of all the facilities with similar names, so as to ensure a rigorous search for the patients. In addition, some down-referral facilities were named, on the transfer letter, for the geographical area when there was no clinic by that name in BCM. In that case, the patient's name was added to the list of nearby clinics. Fifty PHC facilities were visited, and Tier.net was used at each facility to obtain the follow-up data for these patients. Only 46 of the 50 PHC facilities were ultimately included in the study due to the fact that the down-referred patients had presented to these.

The patient data collected from the primary care facilities included: the date of presentation to the clinic; VL and CD4 at 6 months (within the range of 4-8 months) post successful down-referral and at 12 months (within the range of 10-14 months) post successful down-referral.

During data collection at the PHC facilities, it was noted that there appeared to be no standardized protocol for timing of the VL monitoring post down-referral. The national HIV treatment guidelines of 2015 require an annual VL measurement after suppression on ART is attained (Department of Health, 2015), however, how this is timed is left to the discretion of the healthcare providers. Some PHC facilities timed the VL measurement according to cohorts determined by the date of ART initiation. Others timed it according to transfer dates; and still others according to last VL taken, and so on. For this reason, VL and CD4 results often fell outside of the designated time intervals for this study. However, they had still been recorded for the patients within the first year (up to 14 months) post successful down-referral. In order to reduce potential bias in the results obtained (e.g. finding that VL monitoring was done for a smaller percentage of patients than in reality), VL and CD4 results for the entire post down-referral period, defined as 2-14 months post successful down-referral, were collected for analysis. The lower bound of 2 months was used, as prior to that the results would still likely reflect pre-transfer care received at the hospitals, for those patients who transferred within the duration of their script.

Where there were gaps in data, patient files and clinic registers were used to try and address these gaps. A number of patients had different dates of birth or surnames recorded on Tier.net at the clinic as compared to those recorded at the referral hospital. Where this was the case, the patient file was drawn at the clinic to verify the patients' identities. If these could still not be verified at the clinic, the patient file was drawn and checked at the hospital in question and, where necessary, so was the electronic patient register at the hospital. Using these additional information sources it was possible in most cases to verify patients' identities. However, 5 patients could not be verified as the same patient that was down-referred, and hence were excluded from the study.

All data were recorded in the data collection tool created for this study (see Appendix A).

3.6. Analysis

Once data had been collected it was processed by: categorizing; coding; and summarizing the data (Varkevisser *et al.*, 2003). Data were categorized for various parameters in order to complete analysis. For example: age was categorized into groups as per the definition above.

Presentation to the PHC facility was categorized according to success of the down-referral. The raw VL data was categorized into suppressed or unsuppressed, as well as into the levels outlined above. Finally, the CD4 data was categorized into IR and PIR to ART. Coding involved assigning codes to variables and categories of variables to give them a numeric value that could be used in subsequent processing and analysis (Varkevisser *et al.*, 2003; Bhattacherjee, 2012a) in the SPSS Statistics software. A codebook was used to ensure that all the information for each variable was described, and the code assigned to that variable was listed (Bhattacherjee, 2012a).

Summarizing of data for this study involved organizing the raw data and categories of data in a data extraction tool in Microsoft Excel (Bhattacherjee, 2012a) that was developed by the primary investigator, and received both face and content relevance validity (Sproule, 2009; Boateng *et al.*, 2018) by 2 independent research expert judges. These judges rated the relevance and representativeness of the items included in the Excel spreadsheet, to ascertain whether they adequately measured the domains of interest i.e. patient characteristics, RIC and VL suppression (see Appendix A). Excel formulas assisted with sorting the data; tally counting of data; as well as calculating variables (e.g. number of days from down-referral to presentation at the PHC facility). Frequent data verification was done by the primary investigator to check for errors (Varkevisser *et al.*, 2003). From Microsoft Excel database, the data were imported into the statistical software (Bhattacherjee, 2012a). In this case, the analysis software used to analyze the data was SPSS Statistics version 26.

Descriptive analysis of the data involved univariate analysis including the frequency, central tendency and dispersion (Bhattacherjee, 2012a). The proportion of patients that successfully down-referred and the proportion of patients that were RIC at the PHC facilities at 6 and 12 months post successful down-referral were also calculated. The rate of virological suppression was also calculated for these patients at 6 and 12 months, as well as for the 2-14 month period post successful down-referral. The Sign Test was used to calculate the difference between the VL levels for the pre-transfer VL and those at 6 and 12 months, as well as for the entire post down-referral period of 2-14 months. Other tests performed in the analysis included: Chi-square test of independence and Fisher's Exact test for associations for categorical data (Grande, 2015); Point-Biserial correlation testing for continuous and dichotomous variable correlations (Lund Research Ltd, 2018b); Spearman's correlation for non-normally distributed continuous variable

correlations; t-test for differences in CD4 pre- and post-transfer (Lund Research Ltd, 2018a); and Sign Test as a non-parametric alternative (Lund Research Ltd, 2018c). Data are presented in percentages, counts/total numbers, means and medians, based on normality in distribution. Significance is shown using confidence intervals (CIs) that do not overlap and p-values < 0.05 (Bhattacherjee, 2012b). The details of the statistical analysis performed for each objective are listed in Table 3.6.1.

Table 3.6.1: Data Analysis Plan

	Objective	Analysis
1	To ascertain the numbers of paediatric ART patients who have been down referred from a tertiary and a regional hospital in BCM to primary care facilities in the BCM district from June 2013 to June 2017.	**Descriptive Statistics** Mean/Median values for: • age at ART initiation • age at time of down-referral • duration on ART prior to down-referral • number of months prior to down-referral of pre-transfer VL and CD4 • CD4 count and percentage Proportion of: • male to female • patients in each age category: <1year (infants); 1-4years (young child); 5-9 years; 10-14years (adolescents) at ART initiation and time of down-referral. • patients on 1st or 2nd line ART regimen at time of down-referral • patients with TB co-infection at the time of down-referral • patients in each category for VL level
2	To ascertain which primary care facilities these patients have been down referred to, and organize the patients into groupings as per facility.	**Descriptive Statistics** Number of: • PHC facilities included in the study • CHCs vs. PHC clinics • PHC facilities that are urban, rural or peri-urban • PHC facilities in each sub-districts of BCM Proportion of: • patients down-referred from the Tertiary vs. the Regional Hospital • patients that arrived at PHC facility as per each classification of facility

3	To ascertain if patients referred to the primary care facilities: a) arrived for treatment	**Descriptive Statistics** Mean/Median values for: • number of days from down-referral to presentation at PHC facilities • duration of script Proportion of: • patients that presented to a PHC facility in the BCM district • patients LTFU at point of down-referral • patients that arrived within the duration of the script issued • patients in each age category that successfully down-referred **Tests of Association** **Chi-square test of Independence/Fisher's Exact:** • age categories, gender and referring facility cross-tabulated with success of down-referral **Point-Biserial correlation:** • between duration on ART pre-transfer and success of down-referral
3	To ascertain if patients referred to the primary care facilities: b) were retained in care at 6 and 12 months post transfer.	**Descriptive Statistics** Mean/Median values for: • number of monthly clinic visits missed for those with DNA's Proportion of: • patients with no recorded missed clinic visits/DNA's • patients with recorded DNA's • patients retained in care at 6 and 12 months post successful down-referral • patients LTFU, defaulting or transferred out for the same intervals • latter two proportions as per age category **Tests of Association** **Chi-square test of Independence/Fisher's Exact:** • age categories and facility type cross-tabulated with success of down-referral **Point-Biserial correlation:** • between duration on ART pre-transfer and RIC at 6 and 12 months post successful down-referral
4	To ascertain the patients' viral loads at 6 (where applicable) and 12 months	**Descriptive Statistics** Proportion of: • patients with VL results for 6 and 12 months post

	post transfer	successful down-referral • with at least one VL result in 2-14months post successful down-referral • patients that are virologically suppressed each time interval: i) of those with results; ii) of the total • patients with VL's that are: i) <400 copies/ml; ii) 400-1000 copies/ml; or iii) ≥1000 copies/ml • the above parameters as per age category • Kruskal-Wallis test for significance of differences between age groups for levels of VL at each study time interval. **Tests of Association** **Chi-square test of Independence/Fisher's Exact:** • age categories, gender, regimen type and facility type cross-tabulated with VL suppression at the different time intervals **Point-Biserial correlation:** • between duration on ART pre-transfer and VL suppression at the different time intervals **Tests for difference (before and after)** **Sign test** • test for difference in VL levels for pre-transfer VL vs. VL at 6, 12 and 2-14 month intervals
	To assess immune response to ART at 6 and 12 months post successful down-referral.	**Descriptive Statistics** Mean/Median values for: • CD4 count and percentage at 6 and 12 months post successful down-referral • CD4 count and percentage in 2-14 month period post successful down-referral • the above parameters as per age category Proportion of: • patients with a CD4 result at the 6 and 12 months post successful down-referral • with at least one CD4 result in 2-14 months post successful down-referral • patients that with ongoing IR to ART at 6, 12 and 2-14 month intervals • the above parameters as per age category • Kruskal-Wallis test for significance of differences between age groups for CD4 results at each study time interval. **Normality of CD4 data** • as per Shapiro Wilks test

		• as per skewness and kurtosis • histograms **Tests of association** **Chi-square test of Independence/Fisher's Exact:** • age categories and gender cross-tabulated with IR at the different time intervals **Point-Biserial correlation:** • between gender and CD4 count/percentage for each time interval **Spearman's correlation:** • between age at time of down-referral and CD4 count/percentage for each of time intervals **Tests for difference (before and after)** **Paired samples t-test** • to assess difference in mean CD4 count/percentage between CD4 results pre-transfer and at each of the post-transfer time intervals **Sign test** • to assess difference in median CD4 count/percentage between CD4 result pre-transfer and at each of the post-transfer time intervals

3.7. Validity & Reliability

The actual sample size was smaller than the required sample size, a condition that may affect the statistical power of the study. All eligible patients were included according to inclusion and exclusion criteria, and the study only consisted of a single cohort, therefore selection bias should be minimal. A retrospective cohort uses already existing data that was collected for another purpose, prior to the beginning of the study, thus there is an inherent lack of bias in this regard (Mann, 2003). Clear definitions of the variables measured means that there was consistency in the data collection and thus the findings could be reproduced. Finally, since the current study sought to determine the outcomes of down-referred paediatric ART patients; the outcomes measured were RIC and VL suppression rates. Both are valid measures of the patient outcomes in terms of the 90-90-90 strategy, as a patient must be retained in care in order to be virally suppressed, and must be virally suppressed on ART in order to be considered to have successful treatment outcomes. Hence, it can be said that the face validity of the measurement of the patient outcomes is good.

3.8. Ethics Considerations

Before the study was commenced, the proposal was submitted to the University of the Western Cape (UWC)'s higher degrees office for project registration and for approval to conduct the study. Ethics approval was obtained from the Biomedical Research Ethics Committee of UWC, the Eastern Cape Health Research Committee and the relevant Hospitals' Research Ethics Committee. Permission to conduct the research at the facilities in BCM was obtained from the Buffalo City Metro Health District Manager. Permission to access the information from the Tier.net, patient files and facility registers was obtained from the Acting Head of Clinical Governance at the tertiary hospital and from the Senior Manager of Medical Services at the regional hospital. Letters of approval can be found in Appendix B. The study was completed in accordance with the Declaration of Helsinki guidelines. Moreover, the current research followed the ethics principles outlined in the Department of Health Ethics in Health Research Principles (2015) policy document. Following these principles ensured that the research prevented and minimized harm to the owners of the data that was used, also balancing this against the health benefit of the research to the broader group of children in the EC.

No consent was obtained from participants, given that this is a retrospective study. In fact, there was no direct contact with patients. However, all data were treated with total confidentiality. Records were accessed only at the proposed health facilities onsite and at times convenient for the facility. All data were de-identified and anonymised by the researcher at the facility using study codes in data tools. A separate Excel spreadsheet that links the study codes to patients' identifiers was stored separately to the data collection tool. Access to the patient identifying data, apart from the facility data managers and custodians (the healthcare providers who manage the onsite patient files), was restricted to the researcher. Data were electronic in nature and will be stored (for no more than five years) in a password protected electronic file on the primary researcher's computer. The results of the study will be communicated to the participating health facilities and the Department of Health. No patient or facility details were used during outcome reporting (i.e. thesis document writing and technical report writing) and thus the identities of the patients have been protected.

CHAPTER 4: RESULTS

4.1. Introduction

This chapter presents the descriptive and analytical results of this study, which were conducted according to the methodology outlined in the previous chapter. These results include patient and facility characteristics, as well as the findings for the main study outcomes, namely: success of down-referral, RIC, virological suppression and immunological response.

4.2. Patient Characteristics

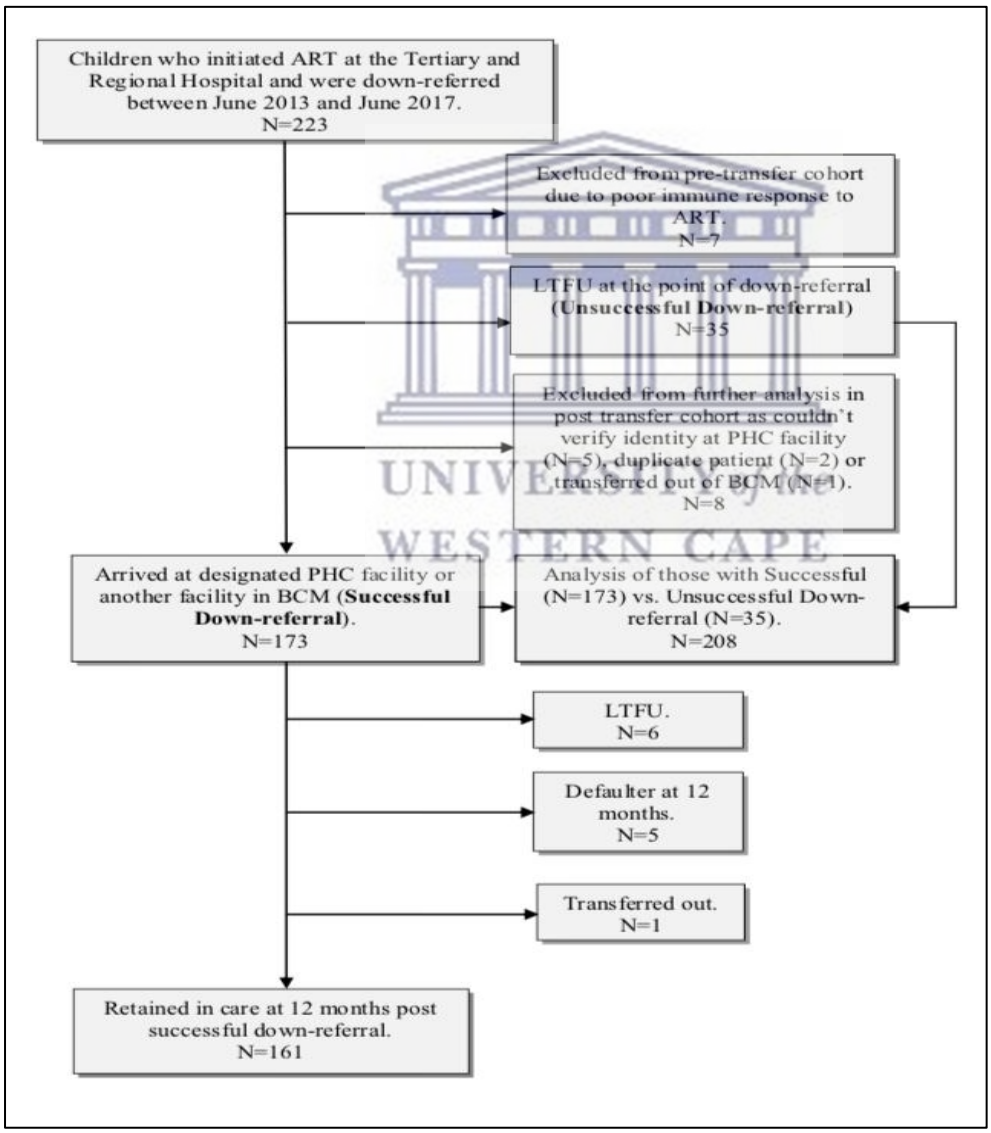


Figure 4.2.1: Flow diagram illustrating selection of study sample and their progression
Abbreviations: ART – Antiretroviral therapy; LTFU – Lost to follow-up; PHC – Primary Healthcare; BCM – Buffalo City Municipality.

All the patient files for those transferred out of the HIV clinic at the tertiary hospital, and the electronic database from the HIV clinic at the regional hospital were reviewed. From these it was found that there were only 223 patients who were HIV positive, stable on ART, between the ages of 0-14 years and transferred out between June 2013 and June 2017. Upon examination of the CD4 results, a further 7 of the patients were excluded due to PIR to ART, leaving a total of 216 patients in the current study cohort. Hence those who fit the inclusion criteria for this study fell short of the calculated sample size of 285, by 24.2% (69). This information as well as the patients progression in the current study is presented in Figure 4.2.1.

Patient characteristics are presented in Table 4.2.1. Of the 216 patients included in the study, 53.2% were female. The median age at ART initiation was 3 years (IQR: 1-5), with 13.4% (29/216) <1 year of age (infants), 55.6% (120/216) between 1-4 years of age (young child), 26.9% (58/216) between 5-9 years of age and 4.2% (9/216) between 10-14 years of age (early adolescence) at ART initiation. The median age at the time of down-referral was 9 years (IQR: 7-12), with 4.2% (9/216) in the 1-4 years age group, 47.7% (103/216) in the 5-9 years age group and 48.1% (104/216) in the 10-14 years age group at the time of down-referral. The patients had been on ART for a mean duration of 5.38 years (95% CI: 5.03-5.73) at the point of down-referral; one patient was down-referred within 8 months (minimum duration) of initiating ART and 2 patients were on ART for 12 years (maximum duration) prior to transfer.

Table 4.2.1 also presents the ART regimens the patients were on at the time of down-referral. Ninety four point nine percent (205/216) of the patients were down-referred on a first-line ART regimen. The majority of patients were taking an Abacavir containing regimen at the time of down-referral, with 57.4% (124/216) on Abacavir, Lamivudine, and Efavirenz; and 29.2% (63/216) on Abacavir, Lamivudine and Lopinavir/Ritonavir. The proportion of patients on a PI based regimen was 38% (82/216). Only one patient had confirmed TB co-infection and was down-referred on TB treatment. One other patient had symptoms of suspected TB and sputum was sent for testing prior to down-referral.

In terms of VL measurement (also presented in Table 4.2.1), the pre-transfer VL measurements were taken a median of 3 months (IQR: 1-6) prior to down-referral, with a maximum number of 29 months noted in one patient. All patients had to be virologically suppressed at their pre-transfer VL, for inclusion in the current study. Of these 99.5%

(215/216) had VLs of <400 copies/ml. The remaining patient fell into the category of between 400 and 1000 copies/ml which, by the definition for this study, is suppressed.

The pre-transfer CD4 measurement was taken a median of 5 months (IQR: 2-7) prior to down-referral, with a maximum of 32 months noted in one patient. For the 97 patients with recorded CD4 count results, the mean and median count were 1035.61 (95% CI: 935.52-1135.70) and 920 (IQR: 695.5-1243), respectively. For the 209 patients with recorded CD4 percentage results, the mean and median percentage were 32.30% (95% CI: 31.44-33.25) and 32.20% (IQR: 27.65-37.75), respectively. The pre-transfer CD4 count, the CD4 count at 6 months post successful down-referral and the CD4 count in the 2-14 month period post successful down-referral were not normally distributed. The other CD4 data (pre-transfer CD4 percentage, CD4 percentage at 6 months, CD4 count and percentage at 12 months, and CD4 percentage in the 2-14 month period post successful down-referral) were normally distributed. For this reason, both the means and medians are reported for the purposes of comparison between the time intervals. All this is presented in more detail under the "Normality of CD4" section further on in the current chapter.

All patients that were included were classified as IRs according to the study definition. The pre-transfer CD4 findings are presented in Table 4.2.1.

Table 4.2.1: Patient Characteristics prior to and at down-referral

	N	Percent (%)	95% CI or IQR	
			Lower	Upper
Sample Size	216	100.0	.	.
Female	115	53.2	46.4	60.0
Male	101	46.8	40.0	53.6
Age at ART initiation, median	3.00	.	1.0	5.0
<1 year	29	13.4	9.2	18.7
1-4 years	120	55.6	48.7	62.3
5-9 years	58	26.9	21.1	33.3
10-14 years	9	4.2	1.9	7.8
Age at time of down-referral, median	9.00	.	7.0	12.0
1-4 years	9	4.2	1.9	7.8
5-9 years	103	47.7	40.9	54.6
10-14 years	104	48.1	41.3	55.0

Duration on ART pre-transfer (years), mean	5.38	.	5.03	5.73
Duration on ART pre-transfer (months), mean	69.61	.	65.42	73.81
Months prior to down-referral of VL, median	3.00	.	1.00	6.00
Pre-transfer VL				
<400 copies/ml	215	99.5	97.4	100.0
400-1000 copies/ml	1	0.5	0.0	2.6
Months prior to down-referral of CD4, median	5.00	.	2.00	7.00
Pre-transfer CD4				
Mean CD4 count	1035.61	.	935.52	1135.70
Median CD4 count	920.00	.	695.50	1243.00
Mean CD4 percentage	32.30	.	31.34	33.25
Median CD4 percentage	32.20	.	27.65	37.75
Regimen at time of down-referral				
First-line Regimen	205	94.9	91.1	97.4
Second-line Regimen	11	5.1	2.6	8.9
ABC+3TC+EFV	124	57.4	50.5	64.1
ABC+3TC+LPV/r	63	29.2	23.2	35.7
D4T+3TC+EFV	6	2.8	1.0	5.9
D4T+3TC+LPV/r	8	3.7	1.6	7.2
TDF+FTC+EFV	1	0.5	0.0	2.6
TDF+3TC+EFV	1	0.5	0.0	2.6
AZT+3TC+EFV	2	0.9	0.1	3.3
AZT+ABC+LPV/r	7	3.2	1.3	6.6
AZT+3TC+LPV/r	4	1.9	0.5	4.7
TB co-infection				
None	214	99.1	96.7	99.9
Confirmed, on treatment	1	0.5	0.0	2.6
Suspected	1	0.5	0.0	2.6

Abbreviations: N – count/number; CI – Confidence Interval; IQR – Inter-quartile range; ART – antiretroviral therapy; VL – viral load; ABC – Abacavir; 3TC – Lamivudine; EFV – Efavirenz; LPV/r – Lopinavir/Ritonvir; D4T – Stavudine; TDF – Tenofovir; FTC – Emtricitabine; AZT – Zidovudine.

4.2.1. Normality of CD4 data

As CD4 is one of the outcomes of this study and is the only outcome that is continuous in nature, choice of central tendency measure for CD4 results was based on the data distribution.

The Shapiro Wilks test is more appropriate for sample sizes <50 but can evaluate sample sizes up to 2000 (Lund Research Ltd, 2018d). If the Shapiro Wilks significance (sig.) value is >0.05 then the data is normally distributed (Lund Research Ltd, 2018d). From Table 4.2.2 it can be ascertained that according to the Shapiro Wilks test pre-transfer CD4 count (p=0.000), CD4 count at 6 month post successful down-referral (p=0.012) and CD4 count in the entire evaluated post-transfer period (2-14 months) (p=0.042) are non-normally distributed (see Figures 4.2.2; 4.2.3 and 4.2.4). The remaining data are normally distributed according to Shapiro Wilks.

Using skewness and kurtosis, the z-score for each was calculated by dividing the value for skewness or kurtosis by their respective standard errors (Kim, 2013). For a sample size <50 the null hypothesis of normal distribution can be rejected if the absolute z-score for either skewness or kurtosis is >1.96 (which corresponds with alpha level 0.05) (Kim, 2013), otherwise the data is normally distributed if between -1.96 and 1.96. Using this method it is confirmed that CD4 count at 6 months is non-normally distributed as per a skewness z-score of 2.804. All the other data with sample size <50, are normally distributed according to skewness and kurtosis. These findings are presented in Table 4.2.2.

For sample sizes 50-300, the null hypothesis of normal distribution can be rejected with an absolute z-score for either skewness or kurtosis of >3.29 (which corresponds with alpha level 0.05) (Kim, 2013). Thus between -3.29 and 3.29 the data are considered normally distributed. Pre-transfer CD4 count is non-normally distributed according to skewness and kurtosis as well as Shapiro Wilks. Pre-transfer CD4 percentage is normally distributed; and CD4 count in the entire post transfer period (2-14 months) is normally distributed according to skewness and kurtosis measures, although non-normal with the Shapiro Wilks test. These findings are also presented in Table 4.2.2.

Table 4.2.2: Normality testing for CD4 data using Shapiro Wilks Test, Skewness and Kurtosis

	Sample size (n)	Shapiro Wilks			Skewness	$SE_{skewness}$	$Z_{skewness}$	Kurtosis	$SE_{kurtosis}$	$Z_{kurtosis}$
		statistic	df	sig.						
Pre-transfer CD4 count	80	0.870	80	0.000	1.578	0.269	5.866	3.123	0.532	5.870
Pre-transfer CD4 percent	167	0.985	167	0.080	-0.426	0.188	-2.266	0.221	0.374	0.591
CD4 count 6 months	38	0.923	38	0.012	1.074	0.383	2.804	1.418	0.750	1.891
CD4 percent 6 months	4	0.902	4	0.442	-0.625	1.014	-0.616	-2.333	2.619	-0.891
CD4 count 12 months	33	0.972	33	0.538	0.373	0.409	0.912	0.529	0.798	0.663
CD4 percent 12 months	3	0.948	3	0.559	1.106	1.225	0.903	.	.	.
CD4 count 2-14 months	82	0.969	82	0.042	0.580	0.266	2.180	0.539	0.526	1.025
CD4 percent 2-14 months	8	0.908	8	0.339	0.082	0.752	0.109	-1.488	1.481	-1.005

Abbreviations: df – degrees of freedom; sig. – significance; SE – standard error.

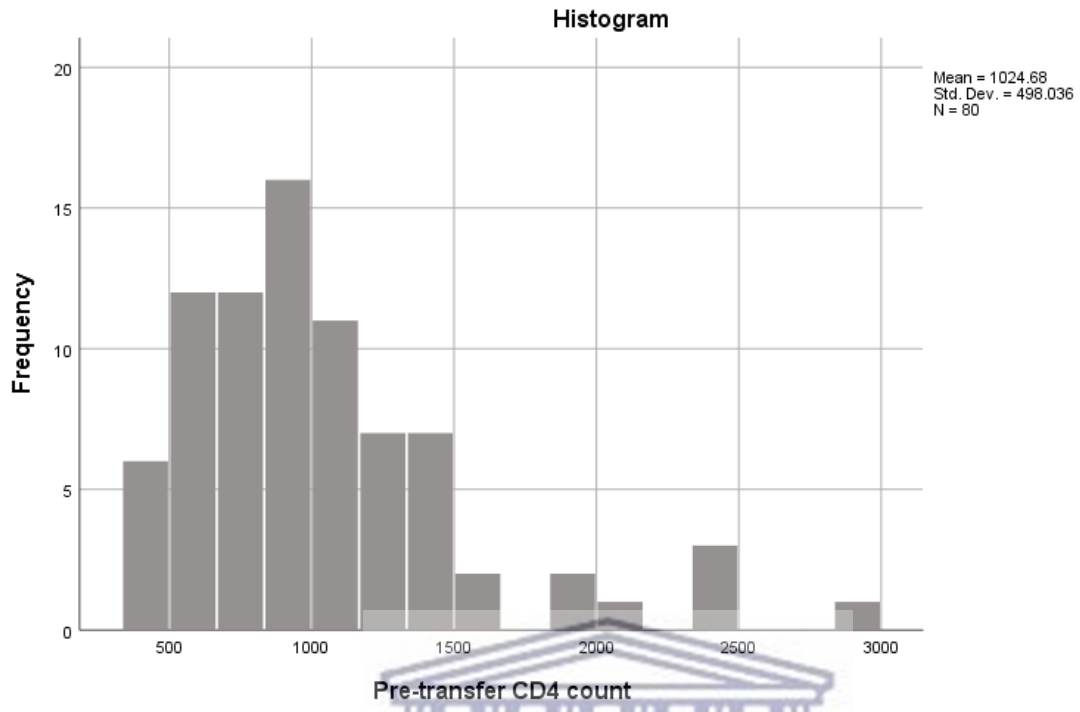


Figure 4.2.2: Histogram of Pre-transfer CD4 count showing distribution

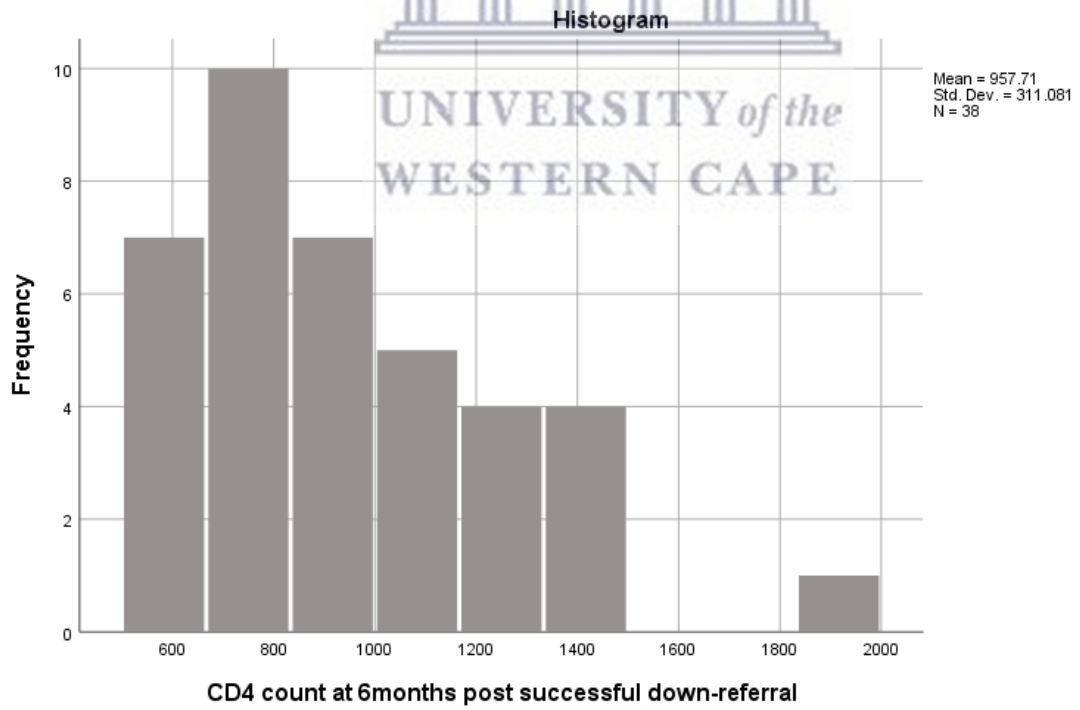


Figure 4.2.3: Histogram of CD4 count at 6 months post transfer showing distribution

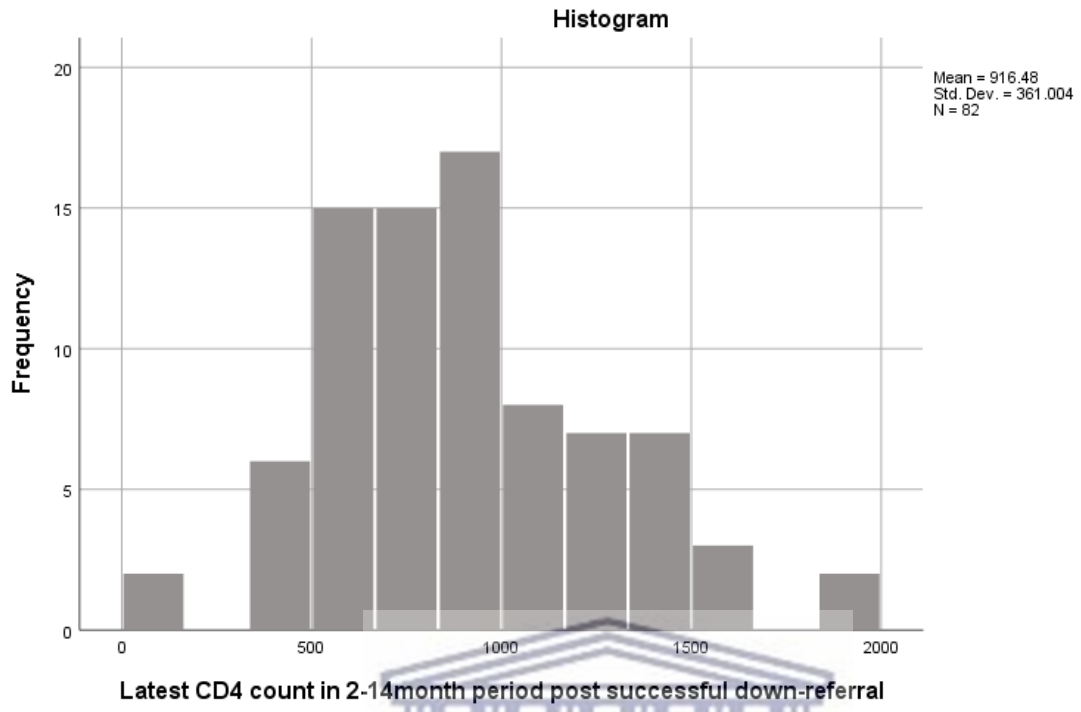


Figure 4.2.4: Histogram of latest CD4 count obtained in post transfer period of 2-14months showing distribution.

In summary some of the CD4 data is normally distributed and some non-normally distributed. Thus both mean and median are used as the measure of central tendency for this parameter in the results of this study to allow for comparison at the different time intervals.

4.3. Facility Characteristics

4.3.1 Pre-Transfer

The proportion of patients included in the study from the tertiary hospital was 43.5% (94/216) and from the Regional Hospital was 56.5% (122/216).

4.3.2 Post Transfer

The 173 patients that successfully down-referred, arrived at 46 different PHC facilities in the BCM district. Of the 46 facilities, 3 were CHC's and 43 were PHC clinics. All this data is presented in Table 4.3.1. The majority of patients, 85.5% (148/173), arrived at the clinics, and 14.5% (25/173) arrived at CHC's. The majority of the PHC facilities 52.2% (24/46) were situated in the East London sub-district; with 32.6% (15/46) in the Mdantsane and 15.2% (7/46)

in the Bisho sub-districts respectively. Despite this, the Mdantsane sub-district facilities received 52.6% (91/173) of the successfully down-referred patients; while East London received 41% (71/173) and Bisho 6.4% (11/173). The facilities were overwhelmingly urban, with 82.6% (38/46) of facilities in urban areas, and only 13% (6/46) rural and 4.4% (2/46) peri-urban facilities included. The urban facilities also received 90.8% (157/173) of the patients, with 7.5% (13/173) arriving at rural and 1.7% (3/173) at peri-urban facilities respectively.

Table 4.3.1: Facility Characteristics – Descriptive Statistics

	N	Percent (%)	95% CI	
			Lower	Upper
Referring Facilities - patients referred from				
Tertiary Hospital	94	43.5	36.8	50.4
Regional Hospital	122	56.5	49.6	63.2
Receiving Facilities - Type				
Clinic	43	93.5	.	.
CHC	3	6.5	.	.
Patients arrived at clinic	148	85.5	79.4	90.4
Patients arrived at CHC	25	14.5	9.6	20.6
Receiving Facilities - Classification				
Urban	38	82.6	.	.
Rural	6	13.0	.	.
Peri-urban	2	4.4	.	.
Patients arrived at urban	157	90.8	85.4	94.6
Patients arrived at rural	13	7.5	4.1	12.5
Patients arrived at peri-urban	3	1.7	0.4	5.0
Receiving Facilities - Sub-district Location				
East London (EL)	24	52.2	.	.
Mdanstane (M)	15	32.6	.	.
Bisho (B)	7	15.2	.	.
Patients arrived at facility in EL	71	41.0	33.6	48.8
Patients arrived at facility in M	91	52.6	44.9	60.2
Patients arrived at facility in B	11	6.4	3.2	11.1

Abbreviations: N – count/number; CI – Confidence Interval; CHC – Community Health Centre; EL – East London; M – Mdantsane; B - Bisho

4.4. Successful Down-referral

Figure 4.4.1 and Table 4.4.1 present the data on the successful down-referral outcomes. Of the 216 patient that were down-referred, 77.3% (167/216) arrived at the designated down-referral PHC facility. A further 2.8% (6/216) were found to have arrived at other PHC facilities within the BCM district. Thus a total of 173 patients were considered to have successfully down-referred to a PHC facility in the BCM district. In total 16.2% (35/216) of patients did not arrive at their designated PHC facility, nor were they found at one with a similar name or geographical area in BCM. Thus these were considered to be LTFU at the point of transfer or unsuccessful down-referrals. One patient opted to receive care at a facility in another district of the Eastern Cape after down-referral, according to their designated down-referral facility. They were thus excluded from further analysis. Two patients were found to be duplicates when followed up at the PHC level, and the identity of 5 patients could not be confirmed due to discrepancies between hospital identifying data and clinic identifying data. These 7 patients were thus excluded from further analysis.

Results for successful down-referral are summarized in Table 4.4.1. The 173 patients that were successfully down-referred took a median of 42 days (IQR: 21-59) to arrive at the PHC facility following transfer out of their respective hospitals. The maximum number of days from transfer out of the hospital to arrival at the PHC facility was 665 days (approximately 21 months), and one patient presented to the PHC facility on the same day as they were down-referred. The majority of patients (76.9%) had arrived within one calendar month of the down-referral date; 89.6% within 2 calendar months; 94.8% within 4 months and 97.7% within 6 months post down-referral. By 12 calendar months post down-referral, 99.4% (172/173) patients had arrived at the PHC facility.

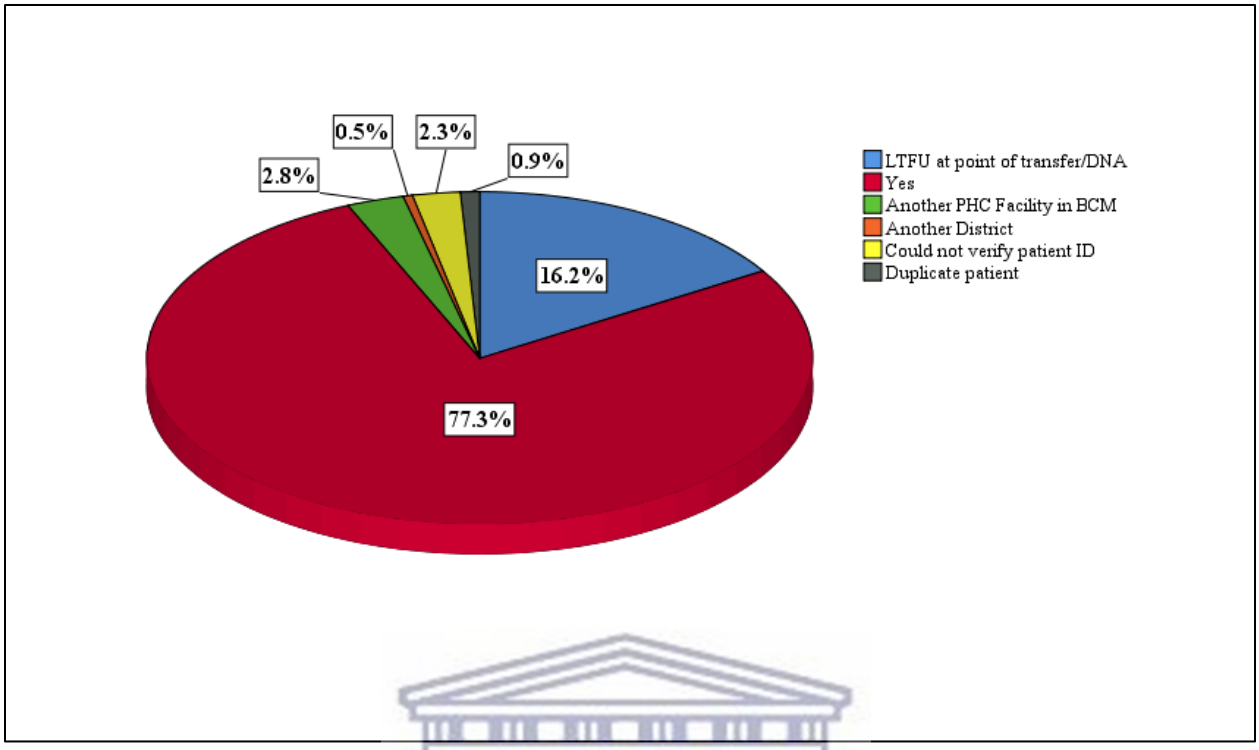


Figure 4.4.1: Arrival at Designated PHC Facility

Abbreviations: LTFU – Lost to follow-up; DNA – Did not arrive; PHC – Primary Healthcare; BCM – Buffalo City Municipality; ID – identity.

In total 54.9% (95/173) of patients had a recorded "duration" for their ART script issued at the time of down-referral. Of these 85.3% (81/95) were issued a script for 1 month (28 days), and only 33.7% (32/95) arrived at the PHC facility within the duration of their script. This could mean that up to 66.3% of patients experienced possible treatment interruption at the point of transfer. A second analysis was done, assuming that all those with no recorded script duration, 45.1% (78/173), were issued a script for 28 days (the most common duration issued). In this second analysis, still only 39.9% (69/173) of patients arrived within the duration of their script.

Table 4.4.1: Successful down-referral outcome – Descriptive Statistics

	N	Percent (%)	95% CI or IQR	
			Lower	Upper
Total successfully down referred	173			
Arrived at designated PHC facility	167	77.3	71.1	82.7
Another PHC facility in BCM	6	2.8	1.0	5.9
LTFU at point of transfer	35	16.2	11.6	21.8
Another District	1	0.5	0.0	2.6
Could not verify patient ID	5	2.3	0.8	5.3
Duplicate patient	2	0.9	0.1	3.3

Days from down-referral to arrival at PHC facility, median	42.00	.	21.00	59.00
Patients with script duration specified	95	54.9	.	.
Duration of script issued, median	28.00	.	28.00	28.00
28 days (% of those with script duration specified)	81	85.3	.	.
28 days (% of total)	81	46.8	39.2	54.5
Arrived with duration of script				
Yes (% of those with script duration specified)	32	33.7	.	.
Yes (% of total)	32	18.5	13.0	25.1
No (% of those with script duration specified)	63	66.3	.	.
No (% of total)	63	36.4	29.2	44.1
Unknown Script Duration (% of total)	78	45.1	37.5	52.8

Abbreviations: N – count/number; CI – Confidence Interval; IQR – Inter-quartile range; PHC – Primary Healthcare; BCM – Buffalo City Municipality; LTFU – Lost to follow-up; ID – Identity.

4.4.1 Successful Down-referral by Age Categories

Having removed the 2 duplicate patients, the 5 whose identities could not be verified at PHC level and the 1 patient who continued care outside of the BCM district (Table 4.4.2), the remaining 208 patients were reviewed by categories of age at the time of transfer in terms of success of down-referral.

Table 4.4.2: Arrived at designated facility

		N	Totals (n)	Percent (%)	Totals (%)
Successful down-referral	Yes	167	173	77.3	80.1
	Another PHC Facility in BCM	6		2.8	
Unsuccessful down-referral	LTFU at point of transfer/DNA	35	35	16.2	16.2
Removed from analysis	Another District	1	8	0.5	3.7
	Could not verify patient ID	5		2.3	
	Duplicate patient	2		0.9	
Total		216	216	100	100

Abbreviations: N – count/number; LTFU – Lost to follow-up; DNA – Did not arrive; PHC – Primary Healthcare; BCM – Buffalo City Municipality; ID – identity.

According to Table 4.4.3, the proportion of those who successfully transferred was similar between the age categories with 87.5% (7/8) (95% CI: 47.3-99.7%), 85.9% (85/99) (95% CI:

77.4-92.0%) and 80.2% (81/101) (95% CI: 71.1-87.5%) successfully transferring at 1-4 years of age, 5-9 years of age and 10-14 years of age respectively (Table 4.4.3). This means that 12.5% (1/8) (95% CI: 0.3-52.7%); 14.1% (14/99) (95% CI: 8.0-22.6%) and 19.8% (20/101) (95% CI: 12.5-28.9%) were LTFU at the point of down-referral in the 1-4 year old, 5-9 year old and 10-14 year old groups respectively.

Table 4.4.3: Probabilities of Successful Down-referral with 95% Confidence Intervals by Age Category

Age Categories	Outcome	Percent (%)	95% CI	
			Lower	Upper
1-4 years	Successful Down-referral	87.5	47.3	99.7
	Unsuccessful Down-referral	12.5	0.3	52.7
5-9 years	Successful Down-referral	85.9	77.4	92.0
	Unsuccessful Down-referral	14.1	8.0	22.6
10-14 years	Successful Down-referral	80.2	71.1	87.5
	Unsuccessful Down-referral.	19.8	12.5	28.9

Abbreviations: CI – Confidence Interval.

4.4.2 Successful Down-referral Associations

i. Effect of age at time of down-referral on success of down-referral

The data for age at the time of down-referral in the "Pre-Transfer" dataset (216 patients) was not normally distributed for each category of the dichotomous variable, according to the Shapiro Wilks test. However, the Z-score for skewness and kurtosis showed normal distribution (Kim, 2013). The Levene's test was significant and thus indicated inequality of variances. Thus, a Point-Biserial Correlation could not be done to assess the relationship of age at transfer with successful down-referral (Lund Research Ltd, 2018b). The effect of age categories on the success of down-referral could not be assessed due to the low numbers of patients in the 1-4 year age group, thus violating the assumptions for a Chi-square test of Independence (Grande, 2015).

Age was re-categorized into "child (0-9 years)" and "adolescent (10-14 years)" and a Chi-square test of Independence was done to check the association of these age categories with successful down-referral. According to Table 4.4.4, more children from the 0-9 year age group successfully down-referred than from the 10-14 year age group. However, there was no statistically

significant association between age at transfer (child vs. adolescent) and success of down-referral (Pearson Chi-square=1.242; p=0.265).

Table 4.4.4: Age at transfer by Success of Down-referral Cross-tabulation

		Success of Down-referral % (n)		Total % (n)
		Unsuccessful	Successful	
Age at transfer	0-9 years	7.2 (15)	44.2 (92)	51.4 (107)
	10-14 years	9.6 (20)	38.9 (81)	48.6 (101)
Total % (n)		16.8 (35)	83.2 (173)	100.0 (208)

ii. Effect of gender on success of down-referral

Furthermore, according to Table 4.4.5, more females successfully down-referred than males. However, gender also showed no significant association with success of transfer (Pearson chi-square=0.241; p=0.623) when using a Chi-square test of Independence.

Table 4.4.5: Gender by Success of Down-referral Cross-tabulation

		Success of Down-referral % (n)		Total % (n)
		Unsuccessful	Successful	
Gender	Female	9.6 (20)	43.8(91)	53.4 (111)
	Male	7.2 (15)	39.4(82)	46.6 (97)
Total % (n)		16.8 (35)	83.2 (173)	100.0 (208)

iii. Effect of duration on ART pre-transfer on success of down-referral

In the pre-transfer dataset containing all 216 patients, data for the duration on ART pre-transfer (in months) was normally distributed for each category of the dichotomous variable as per non-significant Shapiro Wilks test, and Levene's test was not statistically significant suggesting equality of variances (Lund Research Ltd, 2018b). Using Point-Biserial Correlation there was no statistically significant correlation between duration on ART pre-transfer (as measured in months) and successful down-referral (Pearson correlation -0.118; p=0.090). Data is not shown in a figure or table.

iv. Effect of referring hospital of success of down-referral

As seen in Table 4.4.6, more patients successfully down-referred from the regional hospital than from the tertiary hospital. However, referring hospital showed no association with success of transfer (Pearson chi-square=0.017; p=0.896) when using a Chi-square test of Independence.

Table 4.4.6: Referring Hospital by Success of Down-referral Cross-tabulation

		Success of Down-referral % (n)		Total % (n)
		Unsuccessful	Successful	
Referring Hospital	Tertiary	7.7 (16)	37.0 (77)	44.7 (93)
	Regional	9.1 (19)	46.2 (96)	55.3 (115)
Total % (n)		16.8 (35)	83.2 (173)	100.0 (208)

4.5. Retention in Care

As per the electronic database at the PHC facilities, 69.9% (121/173) of patients did not miss a monthly visit to their PHC facility in the 14 months of follow-up for this study. The remainder were recorded as "Did Not Arrive" (DNA) for a median of 4 months (IQR: 3-7), and notably 5.9% (10/173) were recorded as DNA for 10 or more monthly visits.

Ninety eight point eight percent (171/173) of patients were not transferred out of their arrival PHC facility. One patient transferred from their arrival facility to another facility in the BCM district and was thus followed up regarding all outcomes. One patient transferred out of their arrival facility with no record of where they had been transferred to and are described below relating to RIC.

The definition used in this study for RIC is that the patient must have attended at least one clinic visit in the 6 month window period (4-8 months) and one in 12 month window period (10-14 months) in order to be considered retained in care at each of those points. At 6 months post successful down-referral 95.4% (165/173) of patients were retained in care. Four patients were recorded as LTFU and three had defaulted but later re-engaged in care for this time interval. At 12 months, 93.1% (161/173) of patients were retained in care. An additional two patients were recorded as LTFU at this point, thus in total 3.5% (6/173) were LTFU. Furthermore, an additional two patients had defaulted but later re-engaged in care, thus in total 2.9% (5/173) were defaulters. The patient who transferred to an unspecified facility was not followed up for

subsequent outcomes and so is listed as “transfer out” in further analyses. These findings for RIC are summarized in Table 4.5.1.

Table 4.5.1: Retention in care outcome – Descriptive statistics

	N	Percent (%)	95% CI or IQR	
			Lower	Upper
Missed Appointments/Did Not Arrive, median	4.00	.	3.00	7.00
Patients with no DNA's	121	69.9	62.5	76.7
Retention in care at 6 months				
Yes	165	95.4	91.1	98.0
LTFU	4	2.3	0.6	5.8
Defaulter	3	1.7	0.4	5.0
Transfer out (facility unspecified)	1	0.6	0.0	3.2
Retention in care at 12 months				
Yes	161	93.1	88.2	96.4
LTFU	6	3.5	1.3	7.4
Defaulter	5	2.9	0.9	6.6
Transfer out (facility unspecified)	1	0.6	0.0	3.2

Abbreviations: N – count/number; CI – Confidence Interval; IQR – Inter-quartile range; DNA – Did Not Arrive; LTFU – Lost to follow-up.

4.5.1 Retention in Care by Age Categories

When comparing the differences in RIC between groups as categorized by age at the time of down-referral, it is noted that 100% (7/7) of those who fell into the 1-4 year old group remained in care at both the 6 and 12 month intervals. In the 5-9 year old group 96.5% (82/85) remained in care at 6 months, with 1 LTFU, 1 defaulter and 1 patient who transferred out. From the 10-14 year old group 93.8% (76/81) remained in care, with 3 LTFU and 2 defaulters (Table 4.5.2).

Table 4.5.2: Retention in Care at 6 months post successful down-referral by age category

Age Categories	RIC at 6 months	N	Percent (%)	95% CI	
				Lower	Upper
1-4 years	Yes	7	100	59.0	100.0
5-9 years	Yes	82	96.5	90.0	99.3
	LTFU	1	1.2	0.0	6.4
	Defaulter	1	1.2	0.0	6.4
	Transfer Out	1	1.2	0.0	6.4

	Total	85	100	.	.
10-14 years	Yes	76	93.8	86.2	98.0
	LTFU	3	3.7	0.8	10.4
	Defaulter	2	2.5	0.3	8.6
	Total	81	100	.	.

Abbreviations: N – count/number; CI – Confidence Interval; RIC – Retention in care; LTFU – Lost to follow-up.

At the 12 month interval the retention was similar to 6 months with 95.3% (81/85) in the 5-9 year age group retained, 2 LTFU, 1 defaulter and still only the 1 transfer out. Finally, in the 10-14 year age group 90.1% (73/81) were retained in care, with 4 LTFU and 4 defaulters. The numbers of patients LTFU or defaulting at these intervals were small (in total 6 patients LTFU and 5 defaulters at 12 months). Notably 66.7% (4/6) of the LTFU patients and 80% (4/5) of the defaulters were in the early adolescent age group (Table 4.5.3).

Table 4.5.3: Retention in care at 12 months post successful down-referral by age category

Age Categories	RIC at 12 months	N	Percent (%)	95% CI	
				Lower	Upper
1-4 years	Yes	7	100	59.0	100.0
5-9 years	Yes	81	95.3	88.4	98.7
	LTFU	2	2.4	0.3	8.2
	Defaulter	1	1.2	0.0	6.4
	Transfer Out	1	1.2	0.0	6.4
	Total	85	100	.	.
10-14 years	Yes	73	90.1	81.5	95.6
	LTFU	4	4.9	1.4	12.2
	Defaulter	4	4.9	1.4	12.2
	Total	81	100	.	.

Abbreviations: N – count/number; CI – Confidence Interval; RIC – Retention in care; LTFU – Lost to follow-up.

4.5.2 Retention in Care Associations

i. Effect of age at the time of down-referral on retention in care

Point-Biserial Correlation could not be done to assess the relationship between actual age at time of down-referral and RIC, as age was found to be non-normally distributed in all categories of the dichotomous variable (Lund Research Ltd, 2018b). The effect of age categories on RIC could

not be assessed due to the low numbers of patients in the 1-4 years age group, thus violating the assumptions for a Chi-square test of Independence (Grande, 2015).

Age was re-categorized into "child (0-9 years)" and "adolescent (10-14 years)" as adolescents had the greater proportion of those LTFU and of defaulters, and thus warranted further assessment. In addition, the 1-4 years category contained only 7 patients. A Chi-square test of independence was performed using this new age classification to check for association with RIC at 6 and 12 months. As two cells had an expected count of <5, Fisher's Exact test was reported on for RIC at 6 months post down-referral, as opposed to the Chi-square statistic. As seen in Table 4.5.4 more patients in the 0-9 year age group were retained in care at the receiving facility at 6 month than in the 10-14 year age group. However, there was no statistically significant association between age category and RIC at 6 months post successful down-referral (p=0.476) using Fisher's Exact test. Furthermore, according to Table 4.5.5, more patients in the 0-9 year age group than in the 10-14 year age group, were retained in care at the receiving facility at 12 months. However, there was also no significant association between age category and RIC at 12 months (Pearson Chi-square=2.040; p=0.153).

Table 4.5.4: Age at transfer by Retention in care at receiving facility at 6 months post successful down-referral Cross-tabulation

		Retained in care at receiving facility at 6 months % (n)		Total % (n)
		No	Yes	
Age at transfer	0-9 years	1.7 (3)	51.4 (89)	53.2 (92)
	10-14 years	2.9 (5)	43.9 (76)	46.8 (81)
Total % (n)		4.6 (8)	95.4 (165)	100.0 (173)

Table 4.5.5: Age at transfer by Retention in care at receiving facility at 12 months post successful down-referral Cross-tabulation

		Retained in care at receiving facility at 12 months % (n)		Total % (n)
		No	Yes	
Age at transfer	0-9 years	2.3 (4)	50.9 (88)	53.2 (92)
	10-14 years	4.6 (8)	42.2 (73)	46.8 (81)
Total % (n)		6.9 (12)	93.1 (161)	100.0 (173)

ii. Effect of duration on ART pre-transfer on retention in care

In the post-transfer dataset containing 173 patients, the duration on ART pre-transfer (in months) was shown to be approximately normally distributed for each category of the dichotomous variables as per Shapiro Wilks test. It was also found to have homogeneity of variance as per Levene's test. There were however one to two outliers in certain categories (Lund Research Ltd, 2018b). Using Point-Biserial Correlation, duration on ART pre-transfer did not have a statistically significant correlation with RIC at 6 months (Pearson correlation=0.117, p=0.125). It did, however, have a weak but statistically significant correlation with RIC at 12 months (Pearson correlation=0.185, p=0.015) with alpha level of 0.05 for this correlation (Figure 4.5.1). However, this needs to be interpreted with caution due to the presence of two outliers in the "Yes" category for RIC at 12 months.

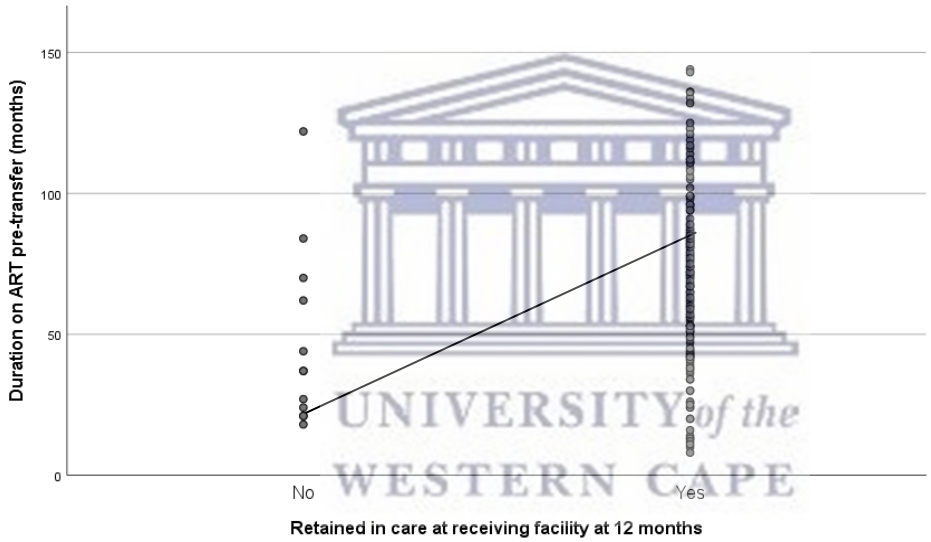


Figure 4.5.1: Point-Biserial Correlation between duration on ART pre-transfer in months with retention in care at 12 months post successful down-referral.

Abbreviations: ART – antiretroviral therapy

iii. Effect of facility characteristics on retention in care

While more patients were retained in care at the clinics than at the CHC's at both 6 and 12 months post successful down-referral (Table 4.5.6 and 4.5.7), facility type (CHC vs. clinic) had no significant association with RIC at these time intervals as per the Fisher's Exact test (p=1.00 for both time intervals).

Table 4.5.6: Facility Type by Retention in care at receiving facility at 6 months post successful down-referral Cross-tabulation

	Retained in care at receiving	Total % (n)

		facility at 6 months % (n)		
		No	Yes	
Facility Type	Clinic	4.0 (7)	81.5 (141)	85.5 (148)
	CHC	0.6 (1)	13.9 (24)	14.5 (25)
Total % (n)		4.6 (8)	95.4 (165)	100.0 (173)

Abbreviations: CHC – Community Health Centre.

Table 4.5.7: Facility Type by Retention in care at receiving facility at 12 months post successful down-referral Cross-tabulation

		Retained in care at receiving facility at 12 months % (n)		Total % (n)
		No	Yes	
Facility Type	Clinic	6.4 (11)	79.2 (137)	85.5 (148)
	CHC	0.6 (1)	13.9 (24)	14.5 (25)
Total % (n)		6.9 (12)	93.1 (161)	100.0 (173)

Abbreviations: CHC – Community Health Centre.

The effect of facility classification and sub-district on RIC could not be assessed due to the low numbers of patients in non-urban facilities (rural and peri-urban) and in the Bisho sub-district which violated the assumptions for Chi-square test of Independence (Grande, 2015).

4.6. Virological Outcomes

For those who were retained in care, VL results were obtained for only 37% (61/165) of patients who had been successfully down-referred for the 6 month window period (4-8 months). Thus 63% (104/165) of the patients had no VL results recorded. For the 12 month window period (10-14 months post successful down-referral) 39.8% (64/161) of patients had viral load results obtained while 60.2% (97/161) had no viral load results recorded.

It was noted that there appeared to be no standardized protocol for when VL testing was done post down-referral. The National Consolidated Guidelines of 2015 recommend that VL be taken annually (Department of Health, 2015). However, in the PHC setting in BCM the timing of this annual VL differs between facilities, with some timing it according to the ART initiation month, others from the time of transfer and still others using a different framework. For this reason, it was decided to determine the proportion of patients with at least one VL result obtained in the period of 2-14 months post successful down-referral. In the instances were more than one result was found, the later result was used. The lower limit of 2 months post successful down-referral

was used as earlier results would still reflect pre-transfer care received at the hospital in those patients who transferred within the script duration.

Using this approach 76.9% (133/173) of the patients had a VL result in the 2-14 month period post successful down-referral. Only 17.3% (30/173) had no recorded VL result; 2.9% (5/173) had no result in that period due to being LTFU for the entire period; 2.3% (4/173) had no result due to having defaulted from care for that entire period; and 0.6% (1/173) were transferred out after their initial visit to the PHC facility as mentioned above in the RIC outcome section. The LTFU and defaulter numbers appear to be lower in this period than for the 12 month interval, because it includes both the 6 and 12 month interval. A patient may have had VL result in the first half of 2-14 month period, and thus in these calculations were not counted as a LTFU or defaulter. Of the 133 patients with VL results for this time period, 45.1% (60/133) had their latest results from the first half of that time period (2-8 months) and 54.9% (73/133) had their latest results from the second half of that time period (9-14 months).

Of the 61 patients with VL results in the 6 month window period, 96.7% (59/61) were virologically suppressed. In the 12 month window period 92.2% (59) of the 64 patients with VL results were virologically suppressed, and in the 2-14 month period 96.2% (128) of the 133 with results were suppressed. When assigning levels to these VL results, it was found that 93.4% (57/61) had a VL of <400 copies/ml in the 6 month window period, with 3.3% between 400-1000 copies/ml and 3.3% ≥1000 copies/ml. In the 12 month window period, 92.2% (59/64) had a VL <400 copies/ml and 7.8% had a VL ≥1000 copies/ml. When looking at the latest viral load from the 2-14 month period post successful down-referral, 94.7% (126/133) had a VL <400 copies/ml; 1.5% (2/133) were between 400-1000 copies/ml and 3.8% (5/133) had VLs of ≥1000 copies/ml. These Virological outcomes are summarized in Table 4.6.1.

Table 4.6.1: Virological outcomes including results obtained and levels of suppression – Descriptive Statistics

	N	Percent (%)	95% CI	
			Lower	Upper
Viral Load Results obtained = Yes				
6 month interval (% of those RIC)	61	37.0	.	.
6 month interval (% of total)	61	35.3	28.2	42.9

12 month interval (% of those RIC)	64	39.8	.	.
12 month interval (% of total)	64	37.0	29.8	44.7
2-14 month period (% of total)	133	76.9	69.9	82.9
Virological Suppression 6 months				
<400 copies/ml	57	93.4	84.1	98.2
400 - 1000 copies/ml	2	3.3	0.4	11.3
≥1000 copies/ml	2	3.3	0.4	11.3
Virological Suppression 12 months				
<400 copies/ml	59	92.2	82.7	97.4
400 - 1000 copies/ml	.	.	.	.
≥1000 copies/ml	5	7.8	2.6	17.3
Virological Suppression 2-14 months				
<400 copies/ml	126	94.7	89.5	97.9
400 - 1000 copies/ml	2	1.5	0.2	5.3
≥1000 copies/ml	5	3.8	1.2	8.6

Abbreviations: N – count/number; CI – Confidence Interval; RIC – Retention in care.

4.6.1 Virological Outcomes by Age Categories

For the purposes of this study virological suppression was defined as <1000 copies/ml (Department of Health, 2015) and undetectable VL as <400 copies/ml (Teasdale et al., 2017). Of those who had VL results at 6 months post successful down-referral: 57.1% (4/7) in the 1-4 years age group, 40% (34/85) in the 5-9 years age group and 28.4% (23/81) in 10-14 years age group; 100% of them in the 1-4 years, 88.2% in 5-9 years and 100% in 10-14 years of age group had a VL <400 copies/ml. A further 5.9% (2/34) had a VL between 400 and 1000 copies/ml in the 5-9 years age group and thus were still counted as suppressed. Only the 5-9 year age group had any unsuppressed patients at this time interval, with 5.9% (2/34) having a VL ≥1000 copies/ml. Despite the fact that the 5-9 year age group had a lower proportion of patients with VL <400 copies/ml, a Kruskal-Wallis test showed no significant difference in VL suppression levels across the age categories at down-referral (p=0.188) (Table 4.6.4). All the VL data for the 6 month interval are presented in Table 4.6.2 and 4.6.3.

At the 12 month interval, of the patients with VL results: 14.3% (1/7), 37.7% (32/85) and 38.3% (31/81) in the 1-4 year, 5-9 year and 10-14 year age groups respectively; 100% of them in the 1-

4 years, 90.6% in the 5-9 years and 93.5% in the 10-14 years age group had VLs <400 copies/ml. There were 9.4% (3/32) and 6.5% (2/31) with VLs ≥1000 copies/ml in the 5-9 year and 10-14 year age groups respectively. The 1-4 year age group had a higher proportion of patients with VL <400 copies/ml, however there was no significant difference in VL suppression levels at 12 months across categories of age at down-referral according to a Kruskal-Wallis test (p=0.874) (Table 4.6.4). All the VL data for the 12 month interval are presented in Table 4.6.2 and 4.6.3.

When looking at the whole 2-14 month period post successful down-referral, the proportion of patients with VL results was much higher than at the 6 and 12 month intervals. There were 85.7% (6/7), 80% (68/85) and 72.8% (59/81) with results in the 1-4 years, 5-9 years and 10-14 years age group respectively. Of these 100%, 92.6% and 96.6% had VLs of <400 copies/ml in the 1-4 year, 5-9 year and 10-14 year age groups respectively. Only 2.9% had VL between 400 and 1000 copies/ml in the 5-9 year age group. Finally, 4.4% and 3.4% had unsuppressed VLs in the 5-9 and 10-14 year age groups respectively. Again the 1-4 year group had a higher proportion of patients with VL <400 copies/ml, however using a Kruskal-Wallis test there was no significant difference in VL levels in the 2-14 month period across categories of age at down-referral (p= 0.526) (Table 4.6.4). All the VL data for the 2-14 month period post down-referral are presented in Table 4.6.2 and 4.6.3.

Table 4.6.2: Viral Load results obtained for each post down-referral time interval by age the at time of down-referral in categories

Age Categories	Results Available	VL at 6months		VL at 12months		VL in 2-14months	
		N	Percent (%)	N	Percent (%)	N	Percent (%)
1-4 years	With Results	4	57.1	1	14.3	6	85.7
	No Results	3	42.9	6	85.7	1	14.3
	Not Retained	.	.	.	.	.	.
	Total	7	100.0	7	100.0	7	100.0
5-9 years	With Results	34	40.0	32	37.7	68	80.0
	No Results	48	56.5	49	57.6	13	15.3
	Not Retained	3	3.5	4	4.7	4	4.7
	Total	85	100.0	85	100.0	85	100.0
10-14 years	With Results	23	28.4	31	38.3	59	72.8
	No Results	53	65.4	42	51.9	16	19.8
	Not Retained	5	6.2	8	9.8	6*	7.4
	Total	81	100.0	81	100.0	81	100.0

Abbreviations: N – count/number; VL – viral load.
*This number is lower than at 12 months as it reflects the entire period of 2-14 months post successful down-referral, and results may have been obtained from first half of that period i.e. when the patients were still retained in care.

Table 4.6.3: Virological Suppression categories by age category at the time of down-referral

			VL suppression at 6 months			VL suppression at 12 months			VL suppression in 2-14 months		
Age Categories		VL category in copies/ml	With Results (n)	With Results (%)	Percent of Total in age category (%)	With Results (n)	With Results (%)	Percent of Total in age category (%)	With Results (n)	With Results (%)	Percent of Total in age category (%)
1-4 years	Suppressed	<400	4	100.0	57.1	1	100.0	14.3	6	100.0	85.7
		400 - 1000	.	.	.	.	.	.	.	.	.
	Unsuppressed	≥1000	.	.	.	.	.	.	.	.	.
	Total with results		4	100.0	57.1	1	100.0	14.3	6	100.0	85.7
5-9 years	Suppressed	<400	30	88.2	35.3	29	90.6	34.1	63	92.6	74.1
		400 - 1000	2	5.9	2.4	.	.	.	2	2.9	2.4
	Unsuppressed	≥1000	2	5.9	2.4	3	9.4	3.5	3	4.4	3.5
	Total with results		34	100.0	40.0	32	100.0	37.6	68	100.0	80.0
10-14 years	Suppressed	<400	23	100.0	28.4	29	93.5	35.8	57	96.6	70.4
		400 - 1000	.	.	.	.	.	.	.	.	.
	Unsuppressed	≥1000	.	.	.	2	6.5	2.5	2	3.4	2.5
	Total with results		23	100.0	28.4	31	100.0	38.3	59	100.0	72.8

Abbreviations: VL – viral load

Table 4.6.4: Independent-samples Kruskal-Wallis Test Summary for post down-referral VL levels across age categories at the different study time intervals

Distribution of post down-referral VL levels across categories of age at down-referral	N	Test Statistic	df	Asymp. Sig. (2-sided test)
VL levels at 6 months	61	3.340	2	0.188
VL levels at 12 months	64	0.269	2	0.874
VL levels in 2-14 months	133	1.286	2	0.526

Abbreviations: VL – viral load; N – number; df – degrees of freedom; Asymp. Sig.- asymptotic significances.

4.6.2 Virological Outcomes Associations

i. Effect of age at the time of down-referral on virological suppression

Tables 4.6.5, 4.6.6 and 4.6.7 show that more 0-9 year old patients had virological outcomes that remained suppressed than the 10-14 year old patients at 6, 12 and 2-14 month intervals post successful down-referral. However, categories of age at the time of down-referral (child vs. adolescent) showed no statistically significant association with VL suppression at the 6 month interval (p=0.522), the 12 month interval (p=1.000) nor in the 2-14 month period (p=1.000) post successful down-referral using Fisher's Exact test.

Table 4.6.5: Age at transfer by Viral Load Suppression at 6 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 6 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Age at transfer	0-9 years	3.3 (2)	59.0 (36)	62.3 (38)
	10-14 years	0.0 (0)	37.7 (23)	37.7 (23)
Total % (n)		3.3 (2)	96.7 (59)	100.0 (61)

Table 4.6.6: Age at transfer by Viral Load Suppression at 12 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 12 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Age at transfer	0-9 years	4.7 (3)	46.9 (30)	51.6 (33)
	10-14 years	3.1 (2)	45.3 (29)	48.4 (31)
Total % (n)		7.8 (5)	92.2 (59)	100.0 (64)

Table 4.6.7: Age at transfer by Viral Load Suppression in the 2-14 month period post successful down-referral Cross-tabulation

		Viral Load Suppression in 2-14month period % (n)		Total % (n)
		Unsuppressed	Suppressed	
Age at transfer	0-9 years	2.3 (3)	53.4 (71)	55.6 (74)
	10-14 years	1.5 (2)	42.9 (57)	44.4 (59)
Total % (n)		3.8 (5)	96.2 (128)	100.0 (133)

ii. Effect of gender on virological suppression

Tables 4.6.8, 4.6.9 and 4.6.10 show that more female patients had virological outcomes that remained suppressed than males at 6, 12 and 2-14 month intervals post successful down-

referral. However, the Fisher's Exact test showed no statistically significant association between gender and VL suppression at the 6 month interval (p=1.000), 12 month interval (p=0.659) nor in the 2-14 month period (p=0.660) post successful down-referral.

Table 4.6.8: Gender by Viral Load Suppression at 6months post successful down-referral Cross-tabulation

		Viral Load Suppression at 6 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Gender	Female	1.6 (1)	50.8 (31)	52.5 (32)
	Male	1.6 (1)	45.9 (28)	47.5 (29)
Total % (n)		3.3 (2)	96.7 (59)	100.0 (61)

Table 4.6.9: Gender by Viral Load Suppression at 12months post successful down-referral Cross-tabulation

		Viral Load Suppression at 12 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Gender	Female	3.1 (2)	50.0 (32)	53.1 (34)
	Male	4.7 (3)	42.2 (27)	46.9 (30)
Total % (n)		7.8 (5)	92.2 (59)	100.0 (64)

Table 4.6.10: Gender by Viral Load Suppression in 2-14month period post successful down-referral Cross-tabulation

		Viral Load Suppression in 2-14month period % (n)		Total % (n)
		Unsuppressed	Suppressed	
Gender	Female	1.5 (2)	52.6 (70)	54.1 (72)
	Male	2.3 (3)	43.6 (58)	45.9 (61)
Total % (n)		3.8 (5)	96.2 (128)	100.0 (133)

iii. Effect of ART regimen type on virological suppression

Tables 4.6.11, 4.6.12 and 4.6.13 show that more patients on a first line regimen had virological outcomes that remained suppressed than those on second line regimen at 6, 12 and 2-14 month periods post successful down-referral. However, the regimen at time of transfer (1^{st} or 2^{nd} line) did not have a statistically significant effect on VL suppression at the 6 month interval (p=1.000), the 12 month interval (p=0.220) nor in the 2-14 month period (p=0.240) using Fisher's Exact test.

Table 4.6.11: Regimen at down-referral by Viral Load Suppression at 6 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 6 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Regimen at down-referral	First Line	3.3 (2)	91.8 (56)	95.1 (58)
	Second Line	0.0 (0)	4.9 (3)	4.9 (3)
Total % (n)		3.3 (2)	96.7 (59)	100.0 (61)

Table 4.6.12: Regimen at down-referral by Viral Load Suppression at 12 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 12 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Regimen at down-referral	First Line	6.3 (4)	89.1 (57)	95.3 (61)
	Second Line	1.6 (1)	3.1 (2)	4.7 (3)
Total % (n)		7.8 (5)	92.2 (59)	100.0 (64)

Table 4.6.13: Regimen at down-referral by Viral Load Suppression in 2-14 month period post successful down-referral Cross-tabulation

		Viral Load Suppression in 2-14 month period % (n)		Total % (n)
		Unsuppressed	Suppressed	
Regimen at down-referral	First Line	3.0 (4)	91.7 (122)	94.7 (126)
	Second Line	0.8 (1)	4.5 (6)	5.3 (7)
Total % (n)		3.8 (5)	96.2 (128)	100.0 (133)

iv. Effect of duration on ART pre-transfer on virological suppression

Duration on ART pre-transfer was shown to be approximately normally distributed per category of the dichotomous variables as per Shapiro Wilks test at 6, 12 and 2-14 months, and to have homogeneity of variance as per Levene's test. There was however one outlier (Lund Research Ltd, 2018b) in the "Suppressed" category at 6 months, one at 12 months and 3 outliers in this category in 2-14 months post successful down-referral. Using Point-Biserial Correlation the duration on ART pre-transfer showed no statistically significant correlation with VL suppression at the 6 month interval (Pearson correlation=0.100; p=0.445), the 12 month interval (Pearson correlation=0.125; p=0.324) nor during the 2-14 month period (Pearson correlation=0.038; p=0.666) post successful down-referral. These data are not presented in a figure or table format.

v. Effect of facility characteristics on virological suppression

Tables 4.6.14, 4.6.15 and 4.6.16 show that more patients at the clinics had virological outcomes that remained suppressed than those at the CHCs at 6, 12 and 2-14 month intervals post successful down-referral. However, there was no statistically significant association between facility type (CHC vs. clinic) and VL suppression at the 6 month interval (p=1.000), 12 month interval (p=0.578) nor in the 2-14 month period (p=1.000) post successful down-referral using Fisher's Exact test.

Table 4.6.14: Facility Type by Viral Load Suppression at 6 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 6 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Facility Type	Clinic	3.3 (2)	85.2 (52)	88.5 (54)
	CHC	0.0 (0)	11.5 (7)	11.5 (7)
Total % (n)		3.3 (2)	96.7 (59)	100.0 (61)

Abbreviations: CHC – Community Health Centre.

Table 4.6.15: Facility Type by Viral Load Suppression at 12 months post successful down-referral Cross-tabulation

		Viral Load Suppression at 12 months % (n)		Total % (n)
		Unsuppressed	Suppressed	
Facility Type	Clinic	7.8 (5)	75.0 (48)	82.8 (53)
	CHC	0.0 (0)	17.2 (11)	17.2 (11)
Total % (n)		7.8 (5)	92.2 (59)	100.0 (64)

Abbreviations: CHC – Community Health Centre.

Table 4.6.16: Facility Type by Viral Load Suppression in 2-14 month period successful down-referral Cross-tabulation

		Viral Load Suppression in 2-14 month period % (n)		Total % (n)
		Unsuppressed	Suppressed	
Facility Type	Clinic	3.8 (5)	82.7 (110)	86.5 (115)
	CHC	0.0 (0)	13.5 (18)	13.5 (18)
Total % (n)		3.8 (5)	96.2 (128)	100.0 (133)

Abbreviations: CHC – Community Health Centre.

vi. Differences between pre- and post-transfer viral load levels of suppression

Viral load results at pre-transfer, 6 and 12 months post successful down-referral were categorized into levels of <400 copies/ml, 400-1000 copies/ml and ≥1000 copies/ml which is

an ordinal variable. The same was done for VLs in the post down-referral period of 2-14 months. Pre-transfer VL organized in this way was then compared to each of the post-transfer time intervals (6 and 12 months), as well as the entire post-transfer period (2-14 months) to see if there was a significant difference in VL levels between these time points. As the variables are ordinal, and the differences between variables were neither normally distributed, nor symmetrical, neither a paired-sample t-test, nor a Wilcoxan signed rank test were appropriate (Lund Research Ltd, 2018c). Thus, a Sign Test was used to compare these data.

The comparison between pre-transfer VL level and 6 month VL level showed a non-significant difference in the VL level between these two time points (p=0.375). The comparison between the pre-transfer VL level and the 12 month VL level also showed a difference that was not statistically significant (p=0.063). When pre-transfer VL level was compared to VL level from the entire post-transfer follow-up period (2-14 months) it again showed a difference in VL level between the two time points that was not statistically significant (p=0.070). These results are outlined in Table 4.6.17. A summary comparison of those with suppressed VL at the different time intervals is in Table 4.6.18.

Table 4.6.17: Sign Tests for differences between pre- and post-successful down-referral viral load levels of suppression

	Negative Differences[a]	Positive Differences[b]	Ties[c]	Total	Exact sig. (2-tailed)
(VL levels at 6mo) - (VL levels pre-transfer)	1	4	56	61	0.375
(VL levels at 12mo) - (VL levels pre-transfer)	0	5	59	64	0.063
(VL levels in 2-14mo) - (VL levels pre-transfer)	1	7	125	133	0.070

Abbreviations: sig. – significance; VL – viral load
a. Post-transfer viral load < Pre-transfer viral load
b. Post-transfer viral load > Pre-transfer viral load
c. Post-transfer viral load = Pre-transfer viral load

Table 4.6.18: Viral Load Suppression Comparison at the Different Study Time Interval

	VL Suppression Pre-transfer		VL Suppression at 6 months		VL Suppression at 12 months		VL Suppression in 2-14 month period	
	With Results (n)	%	With Results (n)	%	With Results (n)	%	With Results (n)	%
Unsuppressed	0	0.0	2	3.3	5	7.8	5	3.8
Suppressed	173	100.0	59	96.7	59	92.2	128	96.2
Total	173	100.0	61	100.0	64	100.0	133	100.0

Abbreviations: VL – viral load.

4.7. Immunological Outcomes

For those who were retained in care at 6 months post successful down-referral, only 24.2% (40/165) had recorded CD4 results (CD4 count and/or percentage); 75.8% (125/165) had no result recorded (neither a CD4 count nor percentage). In the 12 month window period, 21.7% (35/161) of the patients that had recorded CD4 results and 78.3% (126/161) had no CD4 results recorded.

As for VL, it was determined what proportion of patients had at least one CD4 result (CD4 count and/or percentage) in the 2-14 month period post successful down-referral. Again, if there was more than one, the later result was used in the analyses. It was found that, 50.3% (87/173) had at least one CD4 result recorded during this period; 42.8% (74/173) did not have any recorded CD4 results (neither CD4 count nor percentage); 3.5% (6/173) were LTFU; 2.9% (5/173) defaulted and 0.6% (1/173) was transferred out. Proportions of results obtained for CD4 measurements are presented in Table 4.7.1.

In terms of whether the patients had CD4 counts or CD4 percentages recorded, the following was found. Of those with CD4 results recorded 23% (38/165) had CD4 count results at 6 months, and only 2.4% (4/165) had CD4 percentage results. The mean and median CD4 count at 6 months was 957.71 (95% CI: 855.46-1059.96) and 892.50 (IQR: 689.25-1142.50), respectively. The mean and median CD4 percentage for this time interval was 27.16% (95% CI: 21.92-32.39%) and 27.77% (IQR: 23.78-29.93) respectively. In the 12 month window period, 20.5% (33/161) of the patients had CD4 count results, and only 1.9% (3/161) had CD4 percentage results. The mean and median CD4 count at 12months was 920.30 (95% CI: 778.69-1061.92) and 892 (IQR: 654-1174), respectively. The mean and median CD4 percentage were 38.86% (95% CI: 36.32-41.40%) and 38.59% (IQR: 38.00-no value calculated), respectively.

In the 2-14 month period post successful down-referral a total of 47.4% (82/173) patients had at least one recorded CD4 count result, with a mean and median CD4 count of 916.48 (95% CI: 837.15-995.80) and 872.50 (IQR: 646.75-1130.75), respectively. The number of patients with a recorded CD4 percentage results remained low at 4.6% (8/173), with a mean and median CD4 percentage of 31.93% (95% CI: 26.71-37.15%) and 30.14% (IQR: 26.88-38.44) respectively. All the CD4 means and medians are presented in Table 4.7.1.

Of value is the proportion of patients that continued to exhibit an IR to treatment with ART following successful down-referral. A 100% (all 40) of the patients with recorded CD4 results (CD4 count and/or CD4 percentage) at 6 months had ongoing IR to ART. At 12 months 94.3% (33/35) of the patients showed ongoing IR, with 5.7% (2/35) reverting to a PIR to ART. When looking at the 2-14 month period post successful down-referral, of the 87 patients with results, 97.7% (85) had ongoing IR and 2.3% (2) had reverted to a PIR. These results for immunological outcomes are summarized in Table 4.7.1.

Table 4.7.1: Immunological outcomes including results obtained, central tendency and immune response – Descriptive Statistics

	N	Percent (%)	95% CI or IQR	
			Lower	Upper
CD4 Results obtained =Yes				
6 month interval (% of retained in care)	40	24.2	.	.
6 month interval (% of total)	40	23.1	17.1	30.1
12 month interval (% of retained in care)	35	21.7	.	.
12 month interval (% of total)	35	20.2	14.5	27.0
2-14 month period (% of total)	87	50.3	42.6	58.0
CD4 count at 6 months				
Mean (CI)	957.71	.	855.46	1059.96
Median (IQR)	892.50	.	689.25	1142.50
CD4 percentage at 6 months				
Mean (CI)	27.16	.	21.92	32.39
Median (IQR)	27.77	.	23.78	29.93
IR maintained at 6 months				
Yes (% of those with results)	40	100.0	91.2	100.0
No (% of those with results)	.	.	.	.
CD4 count at 12 months				
Mean (CI)	920.30	.	778.69	1061.92
Median (IQR)	892.00	.	654.00	1174.00
CD4 percentage at 12 months				
Mean (CI)	38.86	.	36.32	41.40
Median (IQR)	38.59	.	38.00	.
IR maintained at 12 months				
Yes (% of those with results)	33	94.3	80.8	99.3
No (% of those with results)	2	5.7	0.7	19.2
CD4 count in 2-14 months				
Mean (CI)	916.48	.	837.15	995.80

Median (IQR)	872.50	.	646.75	1130.75
CD4 percentage in 2-14 months				
Mean (CI)	31.93	.	26.71	37.15
Median (IQR)	30.14	.	26.88	38.44
IR maintained in 2-14 months				
Yes (% of those with results)	85	97.7	91.9	99.7
No (% of those with results)	2	2.3	0.3	8.1

Abbreviations: N – count/number; CI – Confidence Interval; IQR – Inter-quartile range; IR – immune response.

4.7.1 Immunological Outcomes by Age Categories

The uptake for CD4 results was low in all age groups. At 6 months 57.1% (4/7), 67.1% (57/85) and 79% (64/81) had no CD4 results available for the 1-4 years, 5-9 years and 10-14 years age groups respectively. The 12 month interval had no CD4 results available for 85.7% (6/7), 71.8% (61/85) and 72.8% (59/81) for the 1-4 years, 5-9 years and 10-14 years age groups respectively. Those without any CD4 results, neither CD4 count nor percentage, were lower when looking at the entire post down-referral period of 2-14 months, compared with the 6 and 12 month intervals above, with 28.6% (2/7), 40% (34/85) and 46.9% (38/81) having no CD4 results in the 1-4, 5-9 and 10-14 years age groups respectively (Table 4.7.2).

Table 4.7.2: CD4 results obtained for each post down-referral time interval by age at time of down-referral in categories

Age Categories	Results Available	CD4 at 6months		CD4 at 12months		CD4 in 2-14months	
		N	Percent (%)	N	Percent (%)	N	Percent (%)
1-4 years	With Results	3	42.9	1	14.3	5	71.4
	No Results	4	57.1	6	85.7	2	28.6
	Not Retained	.	.	.	.	.	.
	Total	7	100.0	7	100.0	7	100.0
5-9 years	With Results	25	29.4	20	23.5	47	55.3
	No Results	57	67.1	61	71.8	34	40.0
	Not Retained	3	3.5	4	4.7	4	4.7
	Total	85	100.0	85	100.0	85	100.0
10-14 years	With Results	12	14.8	14	17.3	35	43.2
	No Results	64	79.0	59	72.8	38	46.9
	Not Retained	5	6.2	8	9.9	8	9.9
	Total	81	100.0	81	100.0	81	100.0

Abbreviations: N – count/number.

There were discrepancies as to whether the CD4 count or the CD4 percentage was recorded in the electronic database at the PHC facilities. For those with results 42.9% (3/7), 27.1%

(23/85) and 14.8% (12/81) had CD4 counts for the 1-4, 5-9 and 10-14 year age groups respectively at the 6 month time interval. The mean CD4 count was higher in the 1-4 year old patients when compared to the other groups. For instance, for each age group the means were as follows: 1103.00 for the 1-4 year group; 1014.04 for the 5-9 year group and 813.42 for the 10-14 year group. Similarly, the median CD4 count was higher in the 1-4 year old patients when compared to the other groups. For instance, the median was 1126 for 1-4 year, 1026 for the 5-9 year and 815.5 for the 10-14 year age groups. However when a Kruskal-Wallis test was performed there were no significant differences in the distribution of CD4 count at 6 months across the categories of age at down-referral (p=0.158) (Table 4.7.5).

At 12 months 0% (0/7), 22.4% (19/85) and 17.3% (14/81) had CD4 counts for the 1-4, 5-9 and 10-14 year group respectively. The mean and median CD4 count were higher in the 5-9 years age group at this interval as seen by mean values of 1055.89 for 5-9 years and 736.29 for 10-14 years of age; and median values of was 927 for the 5-9 year and 671.5 for the 10-14 year age groups. In this case there were significant differences observed between these two age groups, based on the Kruskal-Wallis test (p=0.018) (Table 4.7.5).

Similarly, in the entire period, post successful down-referral (2-14 months) 57.1% (4/7), 50.6% (43/85) and 43.2% (35/81) had recorded CD4 counts. Again there was a higher mean of 1067.25 and a higher median of 1043 in the younger group (1-4 year olds) when compared to the mean of 1018.26 and 774.20, and median of 927 and 721 for the 5-9 year and 10-14 year age groups, respectively. A Kruskal-Wallis test did demonstrate a significant difference between the age groups (p=0.011) (Table 4.7.5). Furthermore it demonstrated that the difference that was significant was between the 5-9 year and 10-14 year age groups (Adj. Sig, p=0.017), whereas it was not significant between the other groups (1-4 years and 10-14 years had p=0.211; 1-4 years and 5-9 years had p=1.000) (Table 4.7.6). The CD4 count data by age category is summarized in Tables 4.7.3 and 4.7.4.

When it came to CD4 percentage at 6 months 0% (0/7), 3.5% (3/85) and 1.2% (1/81) had a recorded result for the 1-4, 5-9 and 10-14 year age group respectively. Both mean and median values were higher in the older age group (10-14 years) for this time interval. The mean values were 26.19% for the 5-9 years group, and 30.05% for the 10-14 years group. The median values were 25.98% and 30.05% for the 5-9 year and 10-14 year age groups respectively. However, a Kruskal-Wallis test showed no significant difference in distribution

of CD4 percentage at 6 months across the categories of age at the time of down-referral (p=0.180) (Table 4.7.5).

At 12 months 14.3% (1/7), 2.4% (2/85) and 0% (0/81) had a CD4 percentage recorded for the 1-4, 5-9 and 10-14 year age groups respectively, with very similar values found in both age groups. The mean and median was the same: 38.59% for those1-4 years of age; and was also the same: 39% for those 5-9 years of age. There was again no significant difference in the distribution across the age categories for CD4 percentage at 12 months according to a Kruskal-Wallis test (p= 1.000) (Table 4.7.5).

Finally, in the entire post down-referral period of 2-14 months 14.3% (1/7), 7.1% (6/85) and 1.2% (1/81) had a CD4 percentage recorded for the 1-4, 5-9 and 10-14 year age groups respectively. Again the mean and median CD4 percentage was higher for the 1-4 year old group as compared to the older age groups. The mean CD4 percentage was 38.59%, 31.13% and 30.05% for 1-4 year, 5-9 year and 10-14 year age groups respectively; and the median was 38.59%, 29.9% and 30.05% for the 1-4, 5-9 and 10-14 year age groups respectively. However a Kruskal-Wallis test showed no significant difference of distribution of CD4 percentage across categories of age for this time period (p=0.550) (Table 4.7.5). The CD4 percentage data by age category is summarized in Tables 4.7.3 and 4.7.4.

Table 4.7.3: CD4 Mean values at the different study time intervals as per age category

Age Categories		6 months		12 months		2-14 months	
		CD4 count	CD4%	CD4 Count	CD4%	CD4 count	CD4%
1-4 years	With Results	3	0	0	1	4	1
	Mean	1103.00	.	.	38.59	1067.25	38.59
	95% CI Lower	404.44	.	.	.	684.59	.
	95% CI Upper	1801.56	.	.	.	1449.91	.
5-9 years	With Results	23	3	19	2	43	6
	Mean	1014.04	26.19	1055.89	39.00	1018.26	31.13
	95% CI Lower	858.67	18.08	879.74	26.35	904.99	24.16
	95% CI Upper	1169.41	34.31	1232.05	51.64	1131.52	38.11
10-14 years	With Results	12	1	14	0	35	1
	Mean	813.42	30.05	736.29	.	774.2	30.05
	95% CI Lower	728.56	.	516.91	.	664.79	.
	95% CI Upper	898.27	.	955.66	.	883.61	.

Abbreviations: CI – Confidence Interval.

Table 4.7.4: CD4 Median values at the different study time intervals as per age category

Age Categories		6 months		12 months		2-14 months	
		CD4 count	CD4%	CD4 Count	CD4%	CD4 count	CD4%
1-4 years	With Results	3	0	0	1	4	1
	Median	1126.00	.	.	38.59	1043.00	38.59
	IQR Lower	811.00	.	.	38.59	848.25	38.59
	IQR Upper	.	.	.	38.59	1310.50	38.59
5-9 years	With Results	23	3	19	2	43	6
	Median	1026.00	25.98	927.00	39.00	927.00	29.90
	IQR Lower	678.00	23.04	810.00	38.00	724.00	25.25
	IQR Upper	1294.00	.	1248.00	.	1248.00	38.50
10-14 years	With Results	12	1	14	0	35	1
	Median	815.50	30.05	671.50	.	721.00	30.05
	IQR Lower	668.25	30.05	579.50	.	606.00	30.05
	IQR Upper	934.75	30.05	962.00	.	964.00	30.05

Abbreviations: IQR – Inter-quartile range.

Table 4.7.5: Independent-samples Kruskal-Wallis Test Summary for post down-referral CD4 results across age categories at the different study time intervals

Distribution of post down-referral CD4 result across categories of age at down-referral	N	Test Statistic	df	Asymp. Sig. (2-sided test)
CD4 count at 6 months	38	3.695	2	0.158
CD4 percentage at 6 months	4	1.800	1	0.180
CD4 count at 12 months	33	5.606	1	0.018
CD4 percentage at 12 months	3	0.000	1	1.000
CD4 count in 2-14 months	82	9.104	2	0.011
CD4 percentage in 2-14 months	8	1.194	2	0.550

Abbreviations: N – count/number; df – degrees of freedom; Asymp. Sig. – Asymptotic significance.

Table 4.7.6: Pairwise comparisons for CD4 count in 2-14 month post down-referral across age categories

	Test Statistic	Std. Error	Std. Error Statistic	Sig.	Adj. Sig.
10-14 years - 5-9 years	15.047	5.422	2.775	0.006	0.017
10-14 years - 1-4 years	22.750	12.569	1.810	0.070	0.211
5-9 years - 1-4 years	7.703	12.449	0.619	0.536	1.000

Abbreviations: Sig. – significance; adj. – adjusted.

4.7.2 Immunological Outcomes Associations

i. Effect of age at time of down-referral on immunological status

Spearman's correlation test was performed to assess for a correlation between age at the time of down-referral and CD4 count/percentage at the different post-transfer time intervals (6, 12 and 2-14 months). Monotonicity of the relationship between the variables was satisfied for all, except CD4 percentage at 12 months, thus no correlation was done for CD4 percentage at that time interval. A moderate negative correlation was found between age at the time of down-referral and CD4 count at 6 months, and this was statistically significant (Spearman's coeff: -0.484, p=0.002, significance for this test was p=0.01). This indicates that as age increased CD4 count decreased, in keeping with the findings by age category earlier in this chapter. There was no statistically significant correlation between age at time of down-referral and CD4 percentage at 6 months post successful down-referral (Spearman's coeff: 0.800; p=0.200). A moderate statistically significant negative correlation was found between age at the time of transfer and CD4 count at 12 months (Spearman's coeff: -0.511; p= 0.002), as well as for age at time of transfer and CD4 count in the 2-14 months period post successful down-referral (Spearman's coeff: -0.500; p=0.000). Again these findings indicate that as age increases CD4 counts decreases, in keeping with findings categorized by age earlier in this chapter. No significant correlation was found between age at the time of transfer and CD4 percentage in the 2-14 month period (Spearman's coeff: -0.048; p=0.910). These results are not presented in a figure or table format.

Fisher's Exact test was used to examine the relationship between IR and age at time of down-referral as categorized into child (0-9 years) and adolescent (10-14 years). For IR at 6 months post successful down-referral all those with CD4 results were classified as immune responders and so no test of association was necessary. Tables 4.7.7 and 4.7.8 show that there were more poor immune responders in the 10-14 years age group as compared to 0-9 years age group. However, for IR at 12 months post successful down-referral there was no significant association with age category (child vs. adolescent) as per Fisher's Exact test (p=0.153), nor was there for the IR in the 2-14 month period post successful down-referral (p=0.159).

Table 4.7.7: Age at transfer by Immune Response at 12 months post successful down-referral Cross-tabulation

		Immune Response at 12 months % (n)		Total % (n)
		IR	PIR	
Age at transfer	0-9 years	60.0 (21)	0.0 (0)	60.0 (21)
	10-14 years	34.3 (12)	5.7 (2)	40.0 (14)
Total		94.3 (33)	5.7 (2)	100.0 (35)

Abbreviations: IR – Immune Response; PIR – Poor Immune Response

Table 4.7.8: Age at transfer by Immune Response within 2-14months post successful down-referral as per latest CD4 result Cross-tabulation

		Immune Response within 2-14 months % (n)		Total % (n)
		IR	PIR	
Age at transfer	0-9 years	59.8 (52)	0.0 (0)	59.8 (52)
	10-14 years	37.9 (33)	2.3 (2)	40.2 (35)
Total % (n)		97.7 (85)	2.3 (2)	100.0 (87)

Abbreviations: IR – Immune Response; PIR – Poor Immune Response

ii. Effect of gender on immunological status

CD4 count at 6 months post successful down-referral was not normally distributed for each category of gender as the female category had a significant Shapiro Wilks test, however $Z_{skewness} = 1.95$ which indicates normal distribution as per skewness. The male category did have outliers. Levene's test showed equality of variances for CD4 counts at 6 months. A Point-Biserial correlation was thus performed and showed no statistically significant correlation between gender and CD4 count at 6 months post successful down-referral (Pearson correlation: 0.163; p= 0.329). Levene's test of homogeneity of variance could not be calculated for CD4 percentage at 6 months, and as there was only 1 female in the variable, normality could not be ascertained for females. For males the distribution was normal as per Shapiro Wilks and there were no outliers. When a Point-Biserial correlation test was performed, no significant correlation between CD4 percentage at 6 months and gender were found (Pearson correlation: -0.487; p=0.513). These findings are not presented in a figure or table format.

For CD4 count at 12 months post successful down-referral, assumption of normality for each category of gender was satisfied as per Shapiro Wilks test and there were no outliers for either category. Levene's test showed homogeneity of variances. A Point-Biserial correlation was run and confirmed there was no correlation between gender and CD4 count at 12 months (Pearson correlation: -0.011; p=0.954). There were only females with results for CD4 percentage at the 12 month interval therefore no test for correlation was performed. These findings are also not presented in a figure or table format.

For 2-14 months CD4 count satisfied the normality assumption for each category of gender as per the Shapiro Wilks test. There was one outlier for the female category. Levene's test indicated equality of variances. However, there was no correlation found between gender and

latest CD4 count in the 2-14momth period post successful down-referral (Pearson correlation: 0.097; p=0.387). CD4 percentage for the 2-14 month period was normally distributed according to the Shapiro Wilks test, and had no outliers for either gender. Levene's test indicated equality of variances. A Point- Biserial correlation found that there was a statistically significant strong negative correlation between gender and CD4 percentage at 2-14months, with males more likely to have a lower CD4 percentage (Pearson correlation: -0.740; p=0.036) as seen in Figure 4.7.1.

Figure 4.7.1: Simple Scatter for latest CD4 percentage in the 2-14 month period by gender

iii. Paired samples t-test for CD4 measurements

A paired samples t-test was run for CD4 counts and percentages at the 6 months interval, the 12 month interval, and for the 2-14 month period post successful down-referral. All assumptions, including those of approximately normal distribution of differences and no significant outliers in the differences between the two related variables (Lund Research Ltd, 2018a), were met unless otherwise indicated.

At the 6 month interval the t(21)=1.288, p=0.212. This indicates that the decline in CD4 count at 6 months post successful down-referral was not statistically significant. At the 12 month interval post successful down-referral the t(17)=2.475, p=0.024. This indicates a statistically significant decline in CD4 count at 12 months post successful down-referral. In the 2-14 month period post successful down-referral the t(43)=2.725, p=0.009. This also indicates that there was a statistically significant decline in CD4 count in the 2-14 month

period post successful compared with pre-transfer. These findings are summarized in Tables 4.7.9 and 4.7.10.

For CD4 percentage at the 6 month interval, the t(3)=5.949, p=0.009. This indicates that the decline in CD4 percentage at 6 months post successful down-referral was statistically significant. The distribution of the difference between the pre-transfer CD4 percentage and the 12month CD4 percentage, as well as the 2-14 month CD4 percentage, was not normal as per the Shapiro Wilks test, but as it was approximately normal, the test was run anyway as the paired samples t-test is robust to violations of normality (Lund Research Ltd, 2018a). For CD4 percentage at the 12 month interval post successful down-referral the t(2)= -0.062, p=0.956. This indicates a small non-statistically significant improvement in CD4 percentage at 12 months post successful down-referral. In the 2-14 month period post successful down-referral the t(7)=0,848, p=0.425. This indicates that there was a non-statistically significant decline in CD4 percentage in the 2-14 month period post successful down-referral. These findings are summarized in Tables 4.7.11 and 4.7.12.

iv. Sign test for CD4 measurements

Even though the t-test is robust to violations of normality, a non-parametric test was also done for the differences between CD4 measurements at the different time intervals. A Sign Test was used as the distributions of differences were also not symmetrical and so a Wilcoxan Signed Rank test could not be used (Lund Research Ltd, 2018c).

For the 6 month interval there was a non-significant decrease in median CD4 count when compared to the median pre-transfer CD4 count as per the exact sign test (p=0.134). For the 12 month interval there was also a non-significant decrease in the median CD4 count when compared to the pre-transfer CD4 count as per the exact sign test (p=0.096). For the 2-14 month period post successful down-referral, there was a statistically significant decrease in the median CD4 count as compared to the median pre-transfer CD4 count as per the asymptotic sign test (Z= -2.440; p=0.015). These findings are summarized in Tables 4.7.13 and 4.7.14.

When testing the CD4 percentages, a non-significant decrease in median CD4 percentage at 6 months compared to the median pre-transfer CD4 percentage was noted as per exact sign test (p=0.125). For the 12 month interval there was no significant difference noted in median CD4 percentages (p=1.000). For the 2-14 month period post successful down-referral there

was a non-significant decrease in the median CD4 percentage compared to the median pre-transfer CD4 percentage as per exact sign test (p=0.070). It should be noted that the sample sizes for the CD4 percentages were very small in the post-transfer time intervals. These findings are summarized in Tables 4.7.15 and 4.7.16.

Thus comparing results from the paired samples t-test to the sign test, only the difference in CD4 count between the 2-14 month period and pre-transfer CD4 count remains significant.

Table 4.7.9: Paired samples t-test for pre- and post-successful down-referral CD4 count

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% CI of the Difference				
					Lower	Upper			
Pair 1	(Pre-transfer CD4 count) - (CD4 count at 6months)	112.27	409.00	87.20	-69.07	293.61	1.288	21	0.212
Pair 2	(Pre-transfer CD4 count) - (CD4 count at 12months)	259.06	444.02	104.66	38.25	479.86	2.475	17	0.024
Pair 3	(Pre-transfer CD4 count) - (CD4 count in 2-14month)	198.34	482.84	72.79	51.54	345.14	2.725	43	0.009

Abbreviations: CI – Confidence Interval; df – degrees of freedom; sig. – significance.

Table 4.7.10: Mean values for differences in CD4 counts pre- and post-successful down-referral

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-transfer CD4 count	1099.50	22	431.19	91.93
	CD4 count at 6months	987.23	22	340.88	72.68
Pair 2	Pre-transfer CD4 count	1149.78	18	428.36	100.97
	CD4 Count at 12months	890.72	18	443.72	104.59
Pair 3	Pre-transfer CD4 count	1127.36	44	501.16	75.55
	CD4 count in 2-14month period	929.02	44	399.92	60.29

Abbreviations: N – count/number.

Table 4.7.11: Paired samples t-test for pre- and post-successful down-referral CD4 percentage

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% CI of the Difference				
					Lower	Upper			
Pair 1	(Pre-transfer CD4%) - (CD4% at 6months)	2.19	0.74	0.37	1.02	3.37	5.949	3	0.009
Pair 2	(Pre-transfer CD4%) - (CD4% at 12months)	-0.35	9.74	5.62	-24.55	23.85	-0.062	2	0.956
Pair 3	(Pre-transfer CD4%) - (CD4% in 2-14month)	1.69	5.63	1.99	-3.02	6.39	0.848	7	0.425

Abbreviations: CI – Confidence Interval; df – degrees of freedom; sig. – significance.

Table 4.7.12: Mean values for differences in CD4 percentages pre- and post-successful down-referral

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-transfer CD4 Percentage	29.35	4	3.62	1.81
	CD4 percentage at 6months	27.16	4	3.29	1.65
Pair 2	Pre-transfer CD4 Percentage	38.51	3	9.99	5.77
	CD4 Percentage at 12months	38.86	3	1.02	0.59
Pair 3	Pre-transfer CD4 Percentage	33.62	8	7.46	2.64
	CD4 percentage in 2-14month period	31.93	8	6.24	2.21

Abbreviations: N – count/number.

Table 4.7.13: Sign test for pre- and post-successful down-referral CD4 count

	Negative Differences[a]	Positive Differences[b]	Ties[c]	Total	Exact sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)
(CD4 count at 6mo) - (CD4 count pre-transfer)	15	7	0	22	0.134	.	.
(CD4 count at 12mo) - (CD4 count pre-transfer)	13	5	0	18	0.096	.	.
(CD4 count in 2-14mo) - (CD4 count pre-transfer)	30	13	1	44	.	-2.440	0.015

Abbreviations: sig. – significance; Asymp. Sig.- Asymptotic significance.
a. Post-transfer CD4 count < Pre-transfer CD4 count
b. Post-transfer CD4 count > Pre-transfer CD4 count
c. Post-transfer CD4 count = Pre-transfer CD4 count

Table 4.7.14: Median values for CD4 counts pre- and post-successful down-referral

	N	Median	IQR	
			Lower	Upper
Pre-transfer CD4 count	80	897.00	677.25	1243.00
CD4 count at 6 months	38	892.50	689.25	1142.50
CD4 Count at 12 months	33	892.00	654.00	1174.00
CD4 count in 2-14 month period	82	872.50	646.75	1130.75

Abbreviations: N – count/number; IQR – Inter-quartile range.

Table 4.7.15: Sign test for pre- and post-successful down-referral CD4 percentage

	Negative Differences[a]	Positive Differences[b]	Ties[c]	Total	Exact sig. (2-tailed)
(CD4% at 6mo) - (CD4% pre-transfer)	4	0	0	4	0.125
(CD4% at 12mo) - (CD4% pre-transfer)	2	1	0	3	1.000
(CD4% in 2-14mo) - (CD4% pre-transfer)	7	1	0	8	0.070

Abbreviations: sig.- significance.
a. Post-transfer CD4 percentage < Pre-transfer CD4 percentage
b. Post-transfer CD4 percentage > Pre-transfer CD4 percentage
c. Post-transfer CD4 percentage = Pre-transfer CD4 percentage

Table 4.7.16: Median values for CD4 percentages pre- and post-successful down-referral

	N	Median	IQR	
			Lower	Upper
Pre-transfer CD4 Percentage	167	32.30	28.00	37.90
CD4 percentage at 6 months	4	27.77	23.78	29.93
CD4 Percentage at 12 months	3	38.59	38.00	39.99
CD4 percentage in 2-14 month period	8	30.14	26.88	38.44

Abbreviations: N – count/number; IQR – Inter-quartile range.

4.8. Summary of Results

To summarize, the major outcomes of the current research highlighted that decentralization through down-referral of paediatric ART patients, is a viable option for increasing access to paediatric HIV care in the BCM district of the EC. This is shown by the fact that more than ninety percent of patients are retained in care at 6 and 12 months after arrival at the PHC facility. In addition, for those who had results, virological suppression was maintained in more than ninety percent of patients at all time intervals for the study. The level of viral suppression was also lower than the detectable limit (<400 copies/ml) in more than ninety percent of patients with VL results, at all time intervals. The immunological outcomes show that, for those with CD4 results, IR to ART was maintained in more than ninety percent of patients at all time intervals.

However, this study also highlights a few factors that need to be addressed in both the down-referral process, and at PHC level. Firstly LTFU and treatment interruption at the point of down-referral pose significant risks to continuity of care in these patients. This is demonstrated by the fact that just over eighty percent of patients are known to have arrived at a PHC facility in BCM, at a median of 42 days post down-referral. Secondly, rates of VL monitoring at the PHC level are suboptimal, as are the rates of CD4 monitoring. Looking at the post down-referral period of 2-14 months, still only 76.9% of patients actually had at least one VL result from that entire period. As virological suppression is one of the key outputs for the 90-90-90 strategy, the low rates of VL monitoring mean that progress towards these goals cannot be optimally assessed. These findings are discussed in more detail in the sections to follow.

CHAPTER 5: DISCUSSION

5.1. Introduction

Provision of paediatric ART has many unique challenges such as the perceived complexity of treating paediatric HIV patients (Copelyn *et al.*, 2018); few highly potent paediatric ART formulations or fixed dose combinations (Teasdale *et al.*, 2017); side effects of medications and the skills required (e.g. drawing blood from a baby) (Williams *et al.*, 2018). These factors have in some instances produced a fear of treating paediatric HIV patients at PHC level, as described in an EC study by Williams *et al.* (2018) and potentially slowed the progress of down-referring paediatric HIV patients (Copelyn *et al.*, 2018). Decentralization is one of the main strategies for increasing access to HIV care and treatment for paediatric patients (Department of Health, 2010). Moreover, down-referring patients initiated at higher levels of care, is one of the options for implementing decentralization that is outlined by the WHO (2013). It is thus important to know how these paediatric patients fare once down-referred in order to inform both those down-referring the patients, as well as those taking over their management at a PHC level. This study sought to address the paucity of EC data on the outcomes of paediatric HIV patients who are initiated on ART in a hospital setting and subsequently down-referred to PHC facilities.

In this chapter the major outcomes obtained from this research will be discussed. These outcomes will include the success of down-referral, RIC at 6 and 12 months post down-referral, virological suppression on ART and immunological response to ART. Available literature will be used to corroborate or contrast these outcomes. Both important positive and negative outcomes will be highlighted in order to potentially inform the current practice in the district of the EC regarding down-referral of paediatric ART patients. Moreover, gaps identified by the current research will also be highlighted as a form of motivation for future research.

5.2. Successful down-referral

In the current study it was found that 80.1% of patients successfully down-referred to a PHC facility in the BCM district. These findings are comparable to other studies done in the WCP, where it has been demonstrated that the proportions of successful transfer range between 76% (Arowosegbe, 2016) and 81% (Davies *et al.*, 2017). While the 80.1% of patients who successfully down-referred in the current study seems to be higher than the proportion of 67.2% demonstrated in another similar study done in the EC (Teasdale *et al.*, 2017), it

however falls short of the 90.6% observed in the Copelyn *et al.* (2018) study done in the WCP. The current research thus confirms that LTFU at the point of transfer is a significant risk, with 16.2% of patients falling into this category. Teasdale *et al.* (2017) found that 16.3% of all LTFU patients and 7.6% of unsuccessful transfers were likely to be "silent transfers" or undocumented transfers to another facility. Taking this into account, it is possible that successful down-referral in the BCM district could actually be closer 87.7% due to the possibility that patients had in fact silently transferred. Tracing of patients using the NHLS database, as was done in the Teasdale *et al.* (2017) study, would help determine the true rates of successful down-referral in this district and may present an area for future inquiry.

In order to compare the studies accurately, the time taken to transfer successfully or "transfer delay", should also be taken into account. For instance, although Arowosegbe (2016) demonstrated a proportion of successful transfer of 76%, only 68% were within 18 months of down-referral. Similarly, only 77% in the Davies *et al.* (2017) study transferred within 18 months of down-referral. Furthermore, Copelyn *et al.* (2018) found that 11.4% of patients took more than 8 weeks to present to the PHC facility. In the current study, 89.6% of those who successfully down-referred, had arrived within 2 calendar months of the down-referral date; and 99.4% (172/173) had arrived within 12 months of being down-referred. Thus, for the entire cohort that was originally down-referred in the current study (216 patients), this equates to 71.8% and 79.6% (172/216) arriving at PHC facilities in the BCM district within 2 and 12 months post down-referral respectively. Of note is that, the 71.8% of patients from the current study who arrived within 8 weeks, is lower than 88.6% that Copelyn *et al.* (2018) reported. Whereas, the 79.6% of patients in the current study who arrived at a PHC facility by 12 months, is higher than the 68% who arrived within 18 months found by Arowosegbe (2016). It must be taken into consideration that in the latter study only NHLS data was used. When used in isolation, NHLS data may underestimate the proportion of successful transfers (Davies *et al.*, 2017). However, when Davies *et al.* (2017) used all data sources, they found that 77% of patients down-referred within 18 months, which is comparable to the 79.6% in 12 months in the current study.

Furthermore, patients in the current study took a median of 42 days to present to the PHC facility. This was far better than the median of 5.4 months in the Arowosegbe (2016) study and it was comparable with the 56 days in the Davies *et al.* (2017) study. Finally, the median of 42 days to present to the PHC facility in the current study was not as good as the median of 27 days that Copelyn *et al.* (2018) found. While transfer times in the current study appear

comparatively good, treatment interruptions at transfer seemed to be a concern. Only 33.7% of those for whom it was recorded, arrived within the duration of their ART script. This may be an underestimation of those arriving within script duration, as 1 month was taken to be 28 days. The period of 28 days was used as it is often the duration written by doctors for a 1 month script. In reality, the pharmacy may have issued up to 30 days of treatment for a 1 month script, as the medication is often packaged in these amounts. Nonetheless, these findings still present probable treatment interruptions in a large proportion of patients that is likely to be clinically significant.

The early adolescent age group (10-14 years) had a slightly higher proportion of unsuccessful down-referrals (19.8%) as compared to the 1-4 year (12.5%) and 5-9 year age groups (14.1%). However when grouped into 0-9 year and 10-14 year age groups, the differences in proportions between groups was not statistically significant. There was also no significant relationship between gender, duration on ART pre-transfer or referring facility, and success of down-referral. Two other studies identified factors that had an effect on success of down-referral. Arowosegbe (2016) for instance found that having a recorded transfer out site was a strong predictor of successful transfer. Davies *et al.* (2017) on the other hand found that those who transferred from the tertiary institutions, those ≥15 years of age and those who were virologically suppressed at the time of transfer, were more likely to have a successful transfer.

In summary, the findings for the "success of down-referral" outcome in this study, confirm what has been found in other studies: that LTFU at the point of transfer is a significant risk. In addition to this, the findings confirm that "transfer delay" is also a risk and may result in treatment interruption. In both these instances, it is possible that the patients may be receiving care at another facility that is unknown to either the referring or receiving facility (silent transfer). The RCWMCH has a protocol for down-referral that requires the referring doctor to make the first appointment at the receiving PHC facility on behalf of the patient (Copelyn *et al.*, 2018). This would likely be of benefit in the EC as well, as there would be an early alert system if the patient did not present for care. Whether or not this telephonic appointment system would be logistically feasible in the EC setting is not known. Furthermore, in BCM the electronic databases (Tier.net) at PHC facilities and hospitals are not linked. Such linking would allow patients to be easily traced, should they not arrive for an appointment. This will therefore help to minimize possible treatment interruptions at the point of transfer. Finally, these findings highlight the need for future research into the factors affecting success of

down-referral/transfer. None were identified in this study or in the Copelyn *et al.* (2018) study, and only a few were identified in other similar studies (Arowosegbe, 2016; Davies *et al.*, 2017). This research may be of benefit in addressing these issues.

5.3. Retention in care

Of the 173 patients who successfully down-referred to PHC facilities in the BCM district, 95.4% were retained in care at 6 months and 93.1% were retained in care at 12 months after presentation to the PHC facility. This compares favourably to similar studies in which the RIC ranges from 62.6% of those successfully transferred in the EC study (Teasdale *et al.*, 2017) to 100% in the Thailand study (Hansudewechakul *et al.*, 2012). Copelyn *et al.* (2018) had a RIC of 81% at 12 months, with 64.7% of those at the designated PHC facilities and 16.4% at other sites in WCP. Their total reported RIC was thus higher than the EC study (Teasdale *et al.*, 2017) as they had the benefit of using the PHDC database to follow-up patients who had transferred to other sites in the WCP (Copelyn *et al.*, 2018). Nonetheless, the 81% RIC reported in their study (Copelyn *et al.*, 2018) is lower than the RIC proportions reported in the current study.

For the current study, of those who were not retained in care at 12 months, 3.5% (6/173) were LTFU after successful down-referral. A further 2.9% (5/173) had defaulted at 12 months, but later re-engaged in care. Using the NHLS database Teasdale *et al.* (2017) found that 31.3% of those who were LTFU after having successfully down-referred were also in fact "silent transfers". The implication of this for the current study is that around a third of those LTFU after a successful down-referral may have actually been in active care at another facility. Four of the six patients LTFU at 12 months were in the early adolescent age group but the numbers of LTFU were so small that the significance of this is unclear.

Adherence, in terms of attending clinic visits, was not as reassuring as the RIC rates, with only 69.9% of patients attending all scheduled monthly visits in the 14 month follow-up period. For those who did miss appointments, a median of 4 monthly visits (IQR: 3-7) were missed. Though not assessed in this study, consecutive visits missed could infer significant treatment interruptions, especially when 5.9% of patients missed 10 or more monthly visits. Those who missed all visits in the 6 month window period (4-8 months) and 12 month window period (10-14 months) were listed as defaulters for those intervals. The data from the Teasdale *et al.* (2017) study suggests that many children that appear to be LTFU often later re-engage in care after potential treatment interruptions. This is in-keeping with those who

were found to default at the designated time intervals in this study, as they too re-engaged in care at a later date. Four of the five defaulters at 12 months were in the early adolescent age group, but again the numbers were so small that the significance of this was unclear. Teasdale et al. (2017) reported that when they did community tracing for the children who were LTFU, they found that 40% of those children had missed more than one routine care visit. However, none of the other studies reported on clinic visit attendance in the detail presented in the current study.

In the current study, neither age categories, nor facility type had any association with RIC at 6 or 12 months. Duration on ART prior to transfer did have a weak correlation with retention in care at 12 months. This should be interpreted with caution, however this may indicate that there is a small possibility that RIC improves the longer a patient is on ART prior to down-referral. Copelyn *et al.* (2018:437) found that TB co-infection at ART initiation and caregivers receiving a social grant were "associated with non-retention in care". However, neither of these remained significant in a multivariable analysis. They also found that virological suppression had no association with RIC.

In summary the results of the current study demonstrate that once a patient has successfully down-referred to a PHC facility, the proportion of patients that are LTFU is low. Thus, at face value RIC for these down-referred paediatric ART patients, is good and compares favourably with similar research. However, if one takes into account attendance of scheduled clinic visits, just under a third of patients may have experienced treatment interruptions in the 14 month period post successful down-referral. The patients had to have demonstrated good attendance of scheduled visits at the hospital HIV clinic in order to be included in the current study. With this in mind it is unclear why these patients missed a median of 4 monthly visits at the PHC facilities during the study follow-up period. Particularly since one of the aims of decentralization is to bring HIV care closer to patients homes, with the ultimate goal of improving RIC and adherence to ART (van Dijk *et al.*, 2014). Teasdale *et al.* (2017) found in their study that the reasons most cited by caregivers for missed clinic visits included: the child refusing to take ART (25%); family disruption (20%); and the caregiver not having enough time to collect medication (16.7%). These reasons are largely beyond the control of the healthcare facilities.

5.4. Virological outcomes

Virological outcomes post down-referral appeared favourable for the current study. At 6 months post successful down-referral 96.7% of patients with viral load results maintained virological suppression and 93.4% had a VL lower than the detectable limit. At 12 months 92.2% of those with results maintained virological suppression, with all of these below detectable limit. In the 2-14 month period, 96.2% of those with results maintained virological suppression and 94.7% of these had a VL lower than detectable limit. Analysis found no statistically significant differences between pre-transfer VL levels (<400 copies/ml; 400-1000 copies/ml; and $\geq$ 1000 copies/ml) and VL levels at each of the post-transfer time intervals.

When comparing these results to those in other similar studies, Morsheimer *et al.* (2014) reported comparable findings. Of the 80% of children that were virally suppressed at the time of down-referral, 96% remained so at their last evaluation (Morsheimer *et al.*, 2014:152). Spicer and Krishna (2016) used pre-transfer virological suppression as an inclusion criterion for their study, and they reported that only 81% of those with results remained suppressed at approximately 12 months post down-referral. Copelyn *et al.* (2018) reported that the rates of virological suppression were similar pre- and post transfer for their study. They showed that of those with recorded VL results available, 86.4% were suppressed at down-referral and 75.9% were suppressed at 12 months post down-referral (Copelyn *et al.*, 2018). The current study thus compares favourably with other similar studies, as it demonstrates some of the highest proportions of ongoing virological suppression.

However, what is concerning in the current study is the low proportion of recorded VL results at the different time intervals. Only 37% of those retained in care had VL results at 6 months, and only 39.8% of those retained in care had VL results for the 12 months. There appeared to be little overlap between the groups at the different time intervals, thus those with a measurement at 6 months were unlikely to also have one at 12 months post down-referral.

Furthermore, it appeared that there was a lack of standardized protocol for the timing of the VL monitoring post down-referral at the PHC facilities in this study. The national HIV treatment guidelines of 2015 (Department of Health, 2015) require that after virological suppression is attained, VL should be measured annually. However, the timing of this annual VL is left to the discretion of the healthcare providers. Some of the PHC facilities in the current study appeared to have timed the VL measurement according to cohorts determined by the date of ART initiation. Others appeared to have timed it according to transfer dates,

while still others appeared to have timed it according to last VL taken, and so on. Thus, for the purpose of accurate reporting, the proportion of patients with at least one VL result recorded in the entire post-transfer period (2-14 months) was determined. It should be noted that RIC, as per the study definition, varied for individual patients over this time period. Therefore, those who were not retained in care in the 6 or 12 month window period may still have had a VL result in the 2-14 month period. For example, they may have had a VL taken at 3 or 9 months post arrival; or in the first half of this period, but be LTFU by the second half. Bearing this in mind, 76.9% of patients had at least one VL result in the 2-14 month period. No VL result was obtained for 17.3% of the patients. The remaining 5.8% had no available result as they were not retained in care or had no result outside the window periods described above.

These findings are also comparable to other studies. For instance, Spicer and Krishna (2016) found that only 73% of those down-referred had VL results at approximately 12 months post-transfer. However, as they used only NHLS data, a proportion of the missing results may be due to patients who were LTFU. Davies *et al.* (2017) found that 11% of patients had missing VL results at 1 year post-transfer and this increased to 20% at 3 years post-transfer. Copelyn *et al.* (2018), on the other hand, found that 20% of those retained in care had no VL results at 6 months and 28% had no VL results at 12 months post down-referral. Teasdale *et al.* (2017) showed that for the 2015/2016 period, of those who had successfully transferred and were known to be active in care at that point, only 40.2% had recent laboratory monitoring. Thus, the current study shows similar proportions of available VL results to the studies in the WCP. However, it does have better proportions of recorded VL results than the KZN and EC studies, when assessing the entire post-transfer period (2-14 months). This confirms the findings of the other literature, that VL monitoring will need be improved in order to make decent progress towards 90-90-90, and subsequently, 95-95-95 goals (UNAIDS, 2015). It also highlights areas of potential future inquiry, which include investigating which factors affect whether or not VL monitoring is performed correctly.

No association was found between age categories at the time of down-referral, gender, regimen type or facility type, and virological suppression. No correlation was found between duration on ART prior to transfer and virological suppression post transfer in the current study. There are no directly comparable findings in other literature. Nevertheless Davies *et al.* (2017:22) found that both virological and immunological outcomes were "consistently worse in the older adolescents" (15-19 years) in their study. However, this age group is not included

in the current study. Morsheimer *et al.* (2014) found that the group initiated on ART in the PHC were 66% (95% CI: 31-84) less likely to develop virological failure than those who were initiated in the hospital and subsequently down-referred. They also found that, for the entire study population (both cohorts); "age, history of TB disease, protease-inhibitor based ART regimen with TB treatment, and the baseline immune category" were not predictive of virological failure (Morsheimer *et al.*, 2014:151). This is a slightly different analysis than in the current study, as it looks at two different cohorts and from the perspective of the risk of virological failure, rather than virological suppression. Another study looking at virological outcomes in a rural hospital found that longer travel times and a nevirapine based ART regimen were associated with increased risk of viral suppression (van Dijk *et al.*, 2011). While these findings were not in a down-referred group of patients, the associations found in this study could be applied in such a setting as decentralization aims to decrease distance to facilities for ART patients (van Dijk *et al.*, 2014).

In summary, in this study, the virological outcomes of paediatric ART patients post down-referral were good. Both rates of virological suppression, and VL results lower than detectable limit (LDL), were above ninety percent at all study time intervals. However the proportion of recorded VL results was low. Less than eighty percent of the patients successfully down-referred had at least one VL result in the entire post-transfer period (2-14 months). And only 54.9% of these had results in the second half of that time period. These findings may suggest poor rates of VL monitoring at the PHC level. Further investigation into the reasons for the low proportions of available VL results could be an area for future research. It may also highlight the need for training on and clarity of the VL monitoirng guidelines in practice.

5.5. Immunological outcomes

For this study the majority of data were collected from facility electronic databases. These very seldom contained both the CD4 count and percentage for a patient, usually one or the other was recorded. Thus unlike in the comparative literature (Hansudewechakul *et al.*, 2012; van Dijk *et al.*, 2014; Morsheimer *et al.*, 2014; Arowosegbe, 2016; Spicer & Krishna, 2016; Davies *et al.*, 2017; Copelyn *et al.*, 2018) in which the researchers had access to actual laboratory results and could choose which parameter to present, this study relied on what had been recorded.

For those who successfully down-referred (173 patients) the median CD4 count values decreased by 4.5 points from a pre-transfer median of 897 (IQR: 677.25-1243.00) to post-transfer median of 892.5 (IQR: 689.25-1142.50) at 6 months; by 5 points from a pre-transfer median of 897 (IQR: 677.25-1243.00) to post-transfer medians of 892 (IQR: 654.00-1174.00) at 12 months; and by 24.5 points from a pre-transfer median of 897 (IQR: 677.25-1243.00) to post-transfer medians of 872.5 (IQR: 646.75-1130.75) in the entire post down-referral period of 2-14 months. Using t-test the differences in means between pre- and post-transfer CD4 counts were statistically significant for the 12 month and 2-14 month time intervals. However when a Sign test was performed, only the difference in median CD4 count between pre-transfer and the entire post-transfer period of 2-14 months remained statistically significant.

Similarly, in the current study, the median CD4 percentage values decreased by 4.53 points from a pre-transfer median of 32.3% (IQR: 28.00-37.90) to 27.77% (IQR: 23.78-29.93) at 6 months; and by 2.16 points from a pre-transfer median of 32.3% (IQR: 28.00-37.90) to 30.14% (IQR: 26.88-38.44) in the 2-14 month period post down-referral. However, the median increased by 6.26 points from a pre-transfer to median of 32.3% (IQR: 28.00-37.90) to 38.59% (IQR: 38.00-39.99) at the 12 month interval. Using the t-test the only statistically significant difference in the means was between pre-transfer CD4 percentage and CD4 percentage at 6 months post down-referral. However, using the Sign test there were no statistically significant differences in the medians between pre- and post-transfer measurements.

Despite these decreases in CD4 measurements, (only CD4 percentage at 12 months increased) all the post-transfer medians would be considered at a level that confers ongoing IR to ART as per the study definition. In addition, 100% (40) of patients with results at 6 months, 94.3% (33) at 12 months and 97.7% (85) in 2-14 months had sustained IR to ART post successful down-referral. Only 5.7% (2) at 12 months and 2.3% (2) in 2-14 months post down-referral had reversion to a PIR to ART. It is likely that these are the same 2 poor responders in both time periods, as the 2-14 month period includes the 12 month interval. Thus, this current study does show favourable immunological outcomes post down-referral.

In the related literature one study conducted in the adolescent age group showed a significant decrease in median post-transfer CD4 count as compared to the pre-transfer median (Davies *et al.*, 2017). While these medians were still above 500 cells/µl (the IR threshold for that study), the overall proportion of patients with a CD4 count >500 cell/µl decreased from 71%

at 1-2 years, to 59% at 3 years, inferring ongoing PIR to ART in some and reversion to PIR in others (Davies *et al.*, 2017). Copelyn *et al.* (2018) and Spicer and Krishna (2016) both showed maintenance in the post-transfer period of the IR achieved prior to down-referral. Arowosegbe (2016) on the other hand, showed improvements in both median CD4 count and percentage from those measurements at the time of transfer to the post-transfer results. The median CD4 count improved from 1026 cells/mm^3 (IQR: 563-1577) at the time of transfer to 1260 cells/mm^3 (IQR: 788-1802) post-transfer. The median CD4 percentage improved from 25.1% (IQR: 17.25-33.75) to 30.15% (IQR: 22.88-36.62) at the same time points (Arowosegbe, 2016). The current study shows maintenance of IR, similar to that in the Copelyn *et al.* (2018) and Spicer and Krishna (2016) studies; with better immunological outcomes than the Davies *et al.* (2017) study; and poorer outcomes than those found by Arowosegbe (2016).

The proportion with CD4 results obtained in the current study was low at all time points. Of those retained in care, 24.2% had results at 6 months and 21.7% had results at 12 months post down-referral. In the 2-14 month time period 50.3% (87/173) had at least one CD4 result; and 42.8% (74/173) had no CD4 results. These proportions are even lower than those for VL results.This may be explained by a change in the 2013 South African treatment guidelines (Davies *et al.*, 2017) which recommended that in clinically stable, virologically suppressed patients, CD4 monitoring is no longer indicated (Davies *et al.*, 2017). However, given that the VL monitoring was also poor, it wouldn't be possible to determine virological suppression in all patients without CD4 results. It is therefore likely that the missing CD4 results can only be partly attributed to this change in guidelines. The proportion of patients with CD4 results in the current study was also much lower than the proportion of patients with results in similar studies. Spicer and Krishna (2016) showed that 71% of patients in their study had CD4 results at approximately 12 months post down-referral. Davies *et al.* (2017) on the other hand reported that the 13% of participants with missing CD4 results at 1 year, increased to 28% at 3 years. Thus even at 3 years 72% of particpants in the Davies *et al.* (2017) study would have had CD4 results. Both the afore-mentioned studies showed a substantially higher proportion of patients with results than is shown in the current study.

In the current study the median CD4 count decreased with an increase in categories of age for all time periods assessed. The 10-14 year age group consistently had the lowest median CD4 counts. Furthermore, statistically significant and moderate negative correlations were found between age at the time of transfer and CD4 count at 6, 12 and in 2-14 months post down-

referral. However, as described by Morsheimer *et al.* (2014:151) this decrease is likely due to "lower age-related norms" rather than indicating poorer response to ART. This is confirmed by the fact that no significant associations were found between age categories (child vs. adolescent) and IR to ART at 12 and 2-14 months post down-referral. In fact, all patients at the 6 month interval were immune responders.

In summary immunological outcomes post down-referral were also good for all patients that had CD4 results in the current study. The proportion of patients with ongoing IR to ART was above ninety percent for all time intervals assessed. This indicates that the IR achieved prior to down-referral was maintained in the post transfer period, even though the actual mean and median CD4 values decreased (for all except CD4 percentage at 12 months). However, the proportion of patients with recorded CD4 results was very low. While this is likely to be driven, in part, by the guideline changes described above, it is also suggestive of low levels of monitoring of HIV outcomes for paediatric ART patients in this region. The latter finding has been confirmed in other literature for both VL and CD4 monitoring in KZN and WCP as well (Spicer & Krishna, 2016; Davies *et al.*, 2017).

5.6. Limitations

While this study has many important findings, it also has some limitations that require discussion. Due to the retrospective nature of the design utilised in the current study, the data used were the routine program data which were originally collected by health facility staff for purposes other than those for the current research. Hence, there are a number of missing or incomplete data. In addition, at the regional hospital and all the included PHC facilities, data were collected from the electronic database at the facility (Tier.net). The data in these databases are captured from patient files by non-clinical staff (data capturers) and thus the potential for errors in capturing may be present. Although where certain discrepancies were found, other sources, such as patient files, were checked in order to try and verify the information.

Those patients that were LTFU, either at the time of down-referral or post successful down-referral, were not traced in the current study. Thus, undocumented transfers (silent transfers) between facilities are not accounted for.

Furthermore, the sample size attained was smaller than the required sample size of 285 patients that was initially calculated based on the WC study by Morsheimer *et al.* (2014). Hence, the power of the study may be affected. This is beyond the control of the primary

researcher, since only 216 patient files were available at the time of research that fitted the criteria for patient selection.

The patients included in the current sample had to be virologically suppressed at the time of transfer as per inclusion criteria. Furthermore, they had to have demonstrated good hospital clinic attendance, and have IR to ART as per the definition for this study. All these criteria were used to ensure that the patients had the potential to develop the outcomes of interest. However, it could be argued that this pre-selected them for success. That said, when inquiring of one of the paediatric specialists at the hospital clinic, it was mentioned that in general those who are considered eligible for down-referral have uncomplicated HIV infection, are virologically suppressed and are tolerating their medication.

The lack of a unique patient identifier, as is used in the PHDC in the WCP, meant that the identity of certain patients could not be confirmed post down-referral necessitating that they be removed from further analysis. Finally, while this study did not select the down-referral facilities at which outcomes would be followed-up (all facilities in BCM to which patients were referred were included), it was limited to the BCM district of the EC and so the results may not be generalizeable.

5.7. Conclusion

In conclusion, all the objectives of the current study have been attained. This study successfully addressed the paucity of data on the current topic in the EC province of South Africa. In addition, it demonstrated the proportion of paediatric ART patients who were successfully down-referred from hospital level care to the PHC facilities in the BCM district of the EC. In doing so, it could be confirmed that LTFU and treatment interruption at the point of transfer are significant risks for these patients. The current study also demonstrated that there were high levels of RIC once patients had successfully down-referred to the PHC level. The proportion of patients LTFU after a successful down-referral was very low. Be that as it may, while clinic visit attendance was fair, the numbers of missed appointments could indicate significant treatment interruptions for many of the patients.

Furthermore, this study demonstrated that good virological and immunological responses to treatment with ART could be maintained when patients were down-referred from hospital level care to PHC facilities in the BCM district of the EC. The issue of suboptimal VL monitoring was highlighted by the paucity of available results in the current study. The same was true for availability of CD4 results. This is likely to be driven, in part, by the guideline

changes in South Africa as of 2013 in which virally suppressed patients do not need ongoing CD4 monitoring (Davies *et al.*, 2017). However, it is also suggestive of low levels of monitoring of HIV care in general for paediatric ART patients in this region.

CHAPTER 6: RECOMMENDATIONS

6.1. Recommendations

The down-referral process may be improved with more communication between the referring institution and receiving facility. For example, referring clinicians making telephonic contact with the receiving PHC facility to arrange the first appointment on behalf of the patients, as is done at RCWMCH (Copelyn *et al.*, 2018). One study, with high levels of support for lower level facilities by the referring institution, had no patients LTFU during the course of the study (Hansudewechakul *et al.*, 2012). Whether this level of support is feasible in lower resource settings is not certain. However, it would offer some form of an early warning system to alert healthcare providers that a patient had not arrived at the transfer facility.

It is highly desirable to have a means of tracing patients who do not arrive at their designated down-referral facility. The PHDC in the WCP, which uses a unique patient identifier in all health related services in order to track the outcomes of patients across disease programmes and health facilities (Davies *et al.*, 2017), is an ideal example of how this can be achieved. A similar database in the EC or even nationwide would allow patients to be traced at different facilities with ease. An existing tool that was successfully used to trace patients in other studies (Arowosegbe, 2016; Teasdale *et al.*, 2017) is the NHLS database. This can, however, be problematic when patient identifiying data is not accurately captured thus making it difficult to confirm the identity of the patients in the database (Teasdale *et al.*, 2017). The use of both of these databases still requires that someone from the referring institution take the time to follow-up on those patients that have been transferred out. Further research would be useful to ascertain the feasibility of such an undertaking. Further research is also needed into the factors that affect the success of down-referral in order to identify possible areas for future interventions.

Another area of future inquiry may be ascertaining the factors that affect whether or not viral load monitoring is performed correctly as per national treatment guidelines. These guidelines may not always be clear as to how to continue routine monitoring after an event such as: inter-facility transfer or after following up for an abnormal VL result. Ongoing training on these topics is particularly important in settings where the level of comfort with treating paediatric HIV patients is not yet optimal (Williams *et al.*, 2018).

6.2. Concluding comments

While there are a number of issues to address in the down-referral process, the current study confirms that down-referral is a feasible option for up-scaling paediatric HIV care, specifically in the EC. Furthermore, the current study provides additional EC data on this topic and highlights areas for potential intervention by those involved in training, support, research and management of paediatric HIV services in the province.

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APPENDICES

Appendix A – Data Collection Tool

		Appendix B1: Variables for Tertiary & Regional Hospital										Variables for Primary Care Facilities				
		Study Domains														
		patient characteristics								patient retention			viral load suppression			
Patient code	Facility down-referred to	Age (in years)	Sex (M/F)	ART start date	Current ART regimen start date	Current ART regimen (drug names)	VL prior to down-referral	CD4 prior to down-referral	TB co-infection	Date of down-referral	Duration of treatment issued	Date of presentation to PCF	VL at 6 Months post down-referral	CD4 at 6 months post down-referral	VL at 12 months post down-referral	CD4 at 12 months post-down-referral

Appendix B – Letters of Approval

UNIVERSITY of the WESTERN CAPE

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06 March 2019

Dr SJ Maughan
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM19/1/1

Project Title: Outcomes of paediatric ART patients down-referred from a tertiary and a regional hospital to a primary care facilities in Buffalo City Municipality, Eastern Cape.

Approval Period: 15 February 2019 – 15 February 2020

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

BMREC REGISTRATION NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

Province of the
EASTERN CAPE
HEALTH

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Date: 12 June 2019

RE: OUTCOMES OF PAEDIATRIC ART PATIENTS DOWN-REFERRED FROM A TERTIARY AND A REGIONAL HOSPITAL TO PRIMARY CARE FACILITIES IN BUFFALO CITY MUNICIPALITY, EASTERN CAPE. (EC_201905_019)

Dear Dr SJ. Maughan

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

Province of the
EASTERN CAPE
HEALTH

BUFFALO CITY METRO HEALTH DISTRICT
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INTERNAL MEMORANDUM

To:	BCMHD Health Facilities
From:	District Manager
Subject:	Permission to conduct Research Study: Dr S MAUGHAN
Date:	5 December 2019

Purpose
The purpose of this memorandum is to inform relevant Buffalo City Health District staff and patients of permission granted for research study to be conducted by Dr S MAUGHAN from the University of the Western Cape.

Background and Exposition of Facts
Dr Maughan is currently studying towards a Masters in Public Health with the University of the Western Cape. The title of their research project is **"Outcomes of Paediatric ART patients down-referred from a tertiary and a regional hospital to primary care facilities in Buffalo City Municipality, Eastern Cape".**

She has requested for permission to do research at BCMHD Health facilities. Dr Maughan has submitted all the required documents for a research study in Eastern Cape Department of Health facilities and as such permission has been granted to her by the Research Unit to conduct the study in terms of her research protocol and methodology.

PERMISSION TO CONDUCT RESEARCH STUDY: DR S MAUGHAN

Approval by the District

1. Kindly note that this memorandum serves as an approval at district level for Dr Maughan to conduct her research study in terms of the approved research protocol, ethical clearance and permission letter from the research unit subject to producing all necessary supporting documentation on request to prospective participants in the research study and management of the district;
2. All posters advertising the research must first be tabled with the Sub-District Manager;

APPROVED

05/12/2019

DR MV NKOHLA
DISTRICT MANAGER
BUFFALO CITY METROHEALTH DISTRICT

DATE

Appendix C – Literature Review Summary Tables

Table 2.1: Literature Review Summary – Part 1

Author (Year)	Location	Study Design	Age Range	Sample size	Study/ Cohort Period	Eligible Patients	Facilities included	Median Age at ART start	Median Age at TFO	Study follow-up time period
Copelyn *et al.* (2018)	CT, South Africa	Retrospective Cohort	<15 years	116	1 January 2006 – 31 December 2012	• Initiated ART at RCWMCH • Down-referred in cohort time period • Down-referred to designated PHC clinics	RCWMCH and 2 PHC clinics (in drainage area of RCWMCH)	11 months (IQR: 4-38)	26 months (IQR: 12-52)	6 months (window of 4-8 months) & 12 months (window of 9-15 months)
Teasdale *et al.* (2017)	PE, South Africa	Retrospective Cohort Analysis	0-15 years	644 (TFO to assigned facilities) 1582 (initiated on ART)	1 January 2004 – 31 September 2015	• Initiated ART at DNH • Initiated ART in cohort time period • Transferred from DNH to assigned facilities	DNH and 16 PHC facilities in surrounding areas of PE, EC (and had ≥10 children referred to them)	4 years (IQR: 1-8)	8 years (IQR: 5-11) This was for all 901 children TFO.	FU after successful TF included data from the first and last visit at the TF facility. For LTFU patients that were traced using NHLS data, there was a cut off of 29 April 2016.
Hansudewechakul *et al.* (2012)	Chiangrai,Thailand	Retrospective Cohort Analysis	Children - not further defined	410 (initiated ART) Sub-group cohorts: 133 (FU at CRH); 154 (FU at CH)	1 February 2002 – 31 March 2008	• Initiated ART at CRH • And Followed up at CRH or a CH in the network in cohort time period • Children with no FU data were excluded • For sub-group comparison analysis, children excluded if: ART experienced; had FU <6 months; had opportunistic infections; or were on a PI based ART regimen	CRH and 16 CH's in the network	8.6 years (IQR: 6.5-10.7)	Not stated	12 monthly intervals for 48 months for Weight for age, CD4% and VL. FU: from ART initiation to earliest of following dates: death, LTFU or 31 March 2008.

Arowosegbe (2016)	CT, South Africa	Retrospective Cohort Analysis	<16 years	725 (TFO); 1127 (initiate on ART)	31 December 2007 – 1 January 2012	• Initiated on ART at RCWMCH • AND transferred to a lower level facility in WC in cohort time period	RCWMCH and all "lower level facilities" in WC	5.6 months (IQR: 3.1-19.9)	Not stated	Within 18 months and within 48months of TF date
Davies *et al.* (2017)	WC, South Africa	Retrospective Analysis	10 - <20 years	460	March 2004 – December 2014	• All adolescents on ART • With a valid WC province (WCP) DOH folder number • Recorded at TFO from 4 facility cohorts (see "Facilities Included") within study period.	TFO facilities: 2 tertiary (TAH & RCWMCH); 2 PHC (Gugulethu and Khayelitsha CHC's). TFI facilities: all in WCP	8.4 years (IQR: 5.4-10.9)	12.8 years (IQR: 11.4-15.3)	12, 24 and 36 months post TF date.
Spicer & Krishna (2016)	PMB, South Africa	Retrospective Descriptive Analysis	Children - not further defined	266	No time period specified	• Children down-referred from Edendale Hospital (EDH) to a local clinic after achieving VS	EDH and local clinics	Not stated	Not stated	12 months after down-referral
Morsheimer *et al.* (2014)	CT, South Africa	Retrospective Cohort Analysis	<14 years	613 343 initiated on ART at PHC; 270 down-referred	1 January 2004 – 30 January 2009	• Initiated on ART or down-referred for continued ART management at assigned clinics during cohort time period	7 TBH-supported, community-based paediatric ART clinics.	26.4 months (IQR:10.2-63)	Not stated	6 monthly intervals until end of study period.
van Dijk *et al.* (2014)	Macha, Zambia	Prospective Observational Cohort	<16 years	77 (TF to outreach clinics) Compariso	September 2007 – March 2012	• HIV-infected children registered at Macha Hospital HIV clinic. • Inclusion in first analysis (of transport and distance to	Macha HIV clinic & 3 rural health centres	Hospital-affiliated group: 5.9 years (IQR: 2.4-	Not stated	Children remained in the study until: death, TF to another site, LTFU or 1 March 2012.

		study		n groups receiving ART: 68 at outreach clinics vs. 41 at hospital-affiliated clinic.		clinics) was that caregiver completed a questionnaire at study entry and upon TF to outreach clinic. • Sub-group of these at the outreach clinic that were receiving ART were included in second analysis. These had to be TF before 1 September 2011 and have ≥1 visit post TF • Inclusion into comparison group at hospital-affiliated clinic were located in the vicinity of Macha HIV clinic and would not have been transferred (hence removing confounder of distance to clinic) • All children had to be initiated on ART before 1 September 2011, and have ≥ 1 visit post ART initiation.	(outreach clinics), namely Mapanza RHC, Chilala RHC & Moobola RHC	10.4); Outreach clinics: 2.9 years (IQR: 1.7-7.3)		

Abbreviations used in the table:

- Hospitals: RCWMCH – Red Cross War Memorial Children's Hospital; DNH – Dora Nginza Hospital; CRH – Chiangrai Prachanukroh Hospital; TAH – Tygerberg Academic Hospital; EDH – Edendale Hospital; TBH – Tygerberg Children's Hospital.
- Receiving facilities: PHC – Primary Healthcare; CH – Community Hospital; CHC – Community Health Centre; RHC – Rural Health Centre.
- Cities and Provinces: CT – Cape Town; PE – Port Elizabeth; PMB – Pietermaritzburg; WC – Western Cape; WCP – Western Cape Province; EC – Eastern Cape
- Government structures: DOH – Department of Health; NHLS – National Health Laboratory Service.
- HIV- related: ART – Antiretroviral therapy; PI – Protease Inhibitor; VL – Viral Load; LTFU – Lost to Follow-up; VS – Virological Suppression.
- Other: TF – Transfer; TFO – Transfer out; TFI – Transfer in; FU – Follow-up.

Table 2.2: Literature Review Summary – Part 2

Author (Year)	Results		Limitations	Implications for practice/research
Copelyn *et al.* (2018)	**RIC**	At point of down-referral: 19.8% either LTFU (11/116) or experienced possible treatment interruption (12/116). 12 months post down-referral: 18.1% (21/116) were LTFU, with 52.4% (11/21) not having attended a single PHC clinic visit At designated PHC after 12 months: 64.7% (75/116)	Single cohort. Small sample size. Data only collected at the two designated PHC clinics.	Identified that evidence is limited for criteria to guide down-referral or identify high risk patients for LTFU. Transition of down-referral is a vulnerable time in treatment of HIV positive children and more support should be offered to help navigate it.
	VS	VS at down-referral: 50.7% (38/75) VS at 12 moths post down-referral: 54.7% (41/75) If only patients with documented VL's are considered: • VS at down-referral: 86.4% (38/44) • VS at 12 months post down referral: 75.9% (41/54)		
	CD4 outcomes			
	Factors for successful down-referral	This study did not identify specific factors associated with successful down-referral.		
Teasdale *et al.* (2017)	**RIC**	Successful TF (at least 1 recorded visit at TF facility): 67.2% (433/644) Unsuccessful TF (no recorded visits at TF facility/LTFU at point of TF): 32.8% (211/644) Of Successful TF group (433): • 17.8% (77/433) subsequent TF to another facility • 62.6% (271/433) in active care • 19.2% (83/433) LTFU after successful TF (no recorded visit or medication pick up >6months) LTFU from DNH (no visit or medication pick up >6months): 105 patients (not part of 644) Community tracing: attempted to reach caregivers for 120/399 patients LTFU (in total). Located 55% (66/120), 53 noted located and 1 refused consent. • 29% (18/55) discontinued ART despite 10 claiming to be in care. • 87.1% reported by caregivers to be enrolled in HIV care NHLS monitoring: • 52.6% (210/399) had lab results after date of LTFU • 16.3% (65/399) had results within 18months of last recorded visit suggesting "silent" TF	Not all TF facilities were included in study. Reliance on names to identify records (these are subject to errors). Possibility children are engaged in care but have no lab results (only 40% of children confirmed in active care had recent lab results). Community tracing did not attempt to trace all children that were LTFU.	Suggestions made: Better recording of contact information. Better documentation of TF outcomes at referring and receiving facilities. Active tracing of children who don't attend care at TF facility. Unique medical record numbers across facilities (as in WC)

		• 28.1% (112/399) had results in 2015-2016 period suggesting current engagement in care.		

	VL monitoring	• 77.2% of 1582 patients initiated on ART at DNH had VL <400 copies/ml at last test before TF or last visit if not TF.
		• Of all children who TFO of DNH (644) and LTFU at DNH (105):
		  o 19.6% (147) had VL results in 2015-2016 period
		  o 49.7% had VL <50copies/ml		

	Barriers to RIC as per caregiver interviews in community tracing	For children not enrolled in care (8 children): • No time to take child for clinic visit • Not liking the facility • Not wanting child on ART • Child refusing to go For children discontinued ART (18 children): • Child reluctant to take medication • Not having time to collect medication • Not liking the facility • Family disruptions (housing insecurity, child abandonment or mother incarcerated)		
Hansudewechakul *et al.* (2012)	**Entire Cohort**	As of 31 March 2008: • 10% (42/410) had died • 90% (368/410) remained on ART • No LTFU documented during study period Adherence: adherence data available for 89-97% of children in FU. Of these 96-100% had at least 95% adherence. VL response in ART naive: at 12months 91% (158/174), at 24months 93% (173/186), at 36months 93% (143/154), and at 48months 86% (121/140) had VL <400 copies/ml. CD4 improvement: median at baseline 6% (IQR: 2-13%); improved to 24% (IQR: 20-29%) at 24months, and 26% (IQR: 22-31%) at 48months.	Missing data due to retrospective study design. Some data limited e.g. VL due to programmatic reasons. CRH and CH comparison affected by unmatched design, differences in baseline weight for age, referral decision based on clinician's judgement and willingness of caregiver to be referred to CH. Few young children and infants in entire cohort. Only ART naive included in comparison analysis. May	Special attention to adherence in paediatric groups is needed for caregiver support, paediatric drug formulations and palatability of ARV's. Intensive support of CH's was needed by CRH to facilitate success of decentralization.
	Comparison Analysis	Comparison groups: 154 FU at CH's and 133 FU at CRH (123 excluded from comparison analysis). Deaths: None of the children FU at the CH died. Adherence: for those with adherence data adherence was similar in the two groups ≥95% over 48months (CRH 95-100% and CH 93-100% of patients with data). CD4% gain: no difference in CD4% gain between CRH and CH (median difference 19% and 21% respectively). No correlation found between the duration of treatment received at CRH prior to referral and changes in weight for age and CD4%.		

		VL data: 29% (38) of patients at CRH and 14% (22) of patients at CH had baseline VL. At CRH 1 patient out of 37 at 12months, 35 at 24months and 35 at 36months had VL >400copies/ml. And at the CH's 1 patient out of 18 had VL >400copies/ml at 48months.	affect generalizeability.	
Arowosegbe (2016)	**Successful TF**	Successful TF: 76% (541/725) within 48months of TFO date; 92% (496/541) within 18months of TFO date. Thus 68% of children successfully TF in 18month window.	Only able to identify successful TF if patient had undergone laboratory testing at TF site, therefore may underestimate this. Uses routinely captured data only and thus there was missing data. Could not assess effect of family socioeconomic and demographic characteristics or adherence on TF.	NHLS data provides easy efficient way to monitor pos TF outcomes especially in tracking patients. Decentralization of Paediatric HIV care is feasible and promising strategy to improve access to ART and RIC.
	VS	Proportion of children with VL <400 copies/ml: increased from 55.9% (265) at TFO to 81.4% (386) at first visit post TF.		
	Immunological response	Median CD4% improvement: from 25.1% (IQR: 17.3-33.8) at TFO to 30.2% (IQR: 22.9-36.6) at first visit post TF. Median CD4 count improvement: 1026 cells/mm^3 (IQR: 563-1577cells/mm^3) at TFO to 1260.5 cells/mm^3 (IQR: 788-1802cells/mm^3) at first visit post TF.		
	Factors associated with successful TF	• Having a recorded transfer out site. This may be because recording transfer site indicates better documentation and management of the TF process e.g. contacting the clinic to book. • Children transferred before 2010. This was expected because these children would have had more time to re-engage with lower level facilities.		
Davies *et al.* (2017)	**Successful TF**	• 81% (95% CI: 77-85%) of children TF successfully, of whom 95% linked to the TF site within 18months of TF date. • Most TF's were from tertiary hospitals (79%), and 72% were during early adolescence (<15 years of age). • Transfer delay: median TF delay for all data sources was 56 days (IQR: 27-134); using laboratory data only was 241 days (IQR: 142-388); and using visit data only was 73 (IQR:28-197) • Predictors of successful TF: TF out of tertiary institution; ≥15yeasr of age and VS.	Linkage data was limited to WCP. Thus no accurate measure of proportion of TF out of WCP Intended TF site not routinely recorded, so unable to assess if patients TF to intended site. Analysis limited to variables collected by routine health information systems, thus could not assess impact of socio-economic status, mental health or adherence on post-TF outcomes.	Enormous potential for using linked health information system data such as PHDC for assessing long term outcomes of adolescents. Laboratory data alone over-estimated time to successful TF. Outcomes of those not retained in care, need to be explored. Decline in VS and poorer outcomes in older
	RIC	• Median FU after successful TF was 3.3 years (IQR: 2.2-4.9) • Retention was 90% (95% CI: 86-93%) at 1 year, and dropped to 84% (95% CI: 79-89%) at 3 years. • Retention was lower in 15-19year olds vs. 10-14years olds at 1&2years, but similar at 3years.		
	VS	• Proportion HIV-RNA <400 copies/ml was 80% (95% CI: 75-84%) at 1year post TF and 75% (95% CI: 67-82%) at 3years post TF, for those assessed. • And was consistently lower for older adolescents TF at 1, 2 and 3yeasr post		

		TF.		adolescents are concerns.
	Immunological outcomes	• Proportion of CD4 >500 cells/µl was 71% (95% CI: 65-76% at 1year post TF and 59% (95% CI: 50-68%) at 3years post TF, for those assessed. • And was consistently lower for older adolescents TF at 1, 2 and 3years post TF.	Could not assess whether gaps in care identified were real or due to incomplete coverage of a particular data source. Small number of patients transferred limited ability to assess TF outcomes comprehensively. Could not assess whether mortality was an important reason for non-retention. Only examined outcomes for those recorded at TFO, thus possible some patients were incorrectly coded and thus excluded.	
Spicer & Krishna (2016)	**Adherence to guidelines for lab monitoring**	• 73% (194/266) had VL result from approximately 12 months post down-referral • 71% (188/266) had a CD4 results from approximately 12 months post down-referral	Not a lot of details on study as only the Abstract is available. It appears study was not complete at time of Abstract publication.	Evaluation of guideline adherence and VL response in patients remaining at the Regional Hospital Pediatric HIV clinic. Focus on factors (clinic and patient characteristics) associated with lack of guideline adherence and reversion to viral detection so as to develop intervention strategies.
	VS	• Of those with results: 81% (157/194) had persistent VS approximately 12 months post down-referral. Thus 19% (37/194) no longer had VS. • Percentage of those with reversion to virus detection could range from 14% (if all with unknown VL had remained suppressed) to 41% (if all with unknown VL were no longer suppressed)		
	CD4 results	• CD4 maintained/improved in 91% of those with results (172/188)		

Morsheimer *et al.* (2014)	**Virological outcomes**	• Median follow-up time 28 months (IQR: 16.5-42.6) • >80% on cohort suppressed from 12 month visit; 85% of longitudinal cohort suppressed at last VL in study period • Median time to VL suppression: 29 weeks for those initiated on ART in PHC, and 44weeks for those down-referred. • 13.9% (60/431 in longitudinal cohort) met criteria for clinically significant VF • Children initiated on ART in PHC were 66% less likely to develop VF	PHC clinics are physician run in this study. Retrospective study design may lead to missing data.	Intensified surveillance of children <15 months of age for their first 3 months on ART may improve mortality and thus should be a target for programmatic intervention. Long-term ART management at PHC clinics by paediatric clinicians yields successful outcomes.
	Immunological outcomes	• Improvement in CD4% rose from a median of 8.7% (IQR: 2.3-13.8) at 6 months to a mean of 17.4% (95% CI 15.5-19.2) at 36months. • 13 children (2%of cohort) had evidence of immunological failure after 24 weeks of ART. In 5 of these, CD4 counts had recovered in 80% (4/5) by 12 months and in all 5 by 18months. A further 5 had recovered by the subsequent interval evaluation. Remaining 3 had persistent IF despite suppressed VL.		
	Mortality	• Documented mortality: 2.2% for PHC cohort • Maximal mortality (documented deaths and LTFU cases): 6.2% • Disproportionate number of children were LTFU in PHC-initiated group • Early deaths (<3months on ART) (data only available for PHC initiated group) occurred in infants <6 months of age and young children (11-15months old) with severe immunological suppression.		
	Outcomes for down-referred cohort	• Down-referred after a median of 2 years (IQR: 13.6-34months) on ART • 80% VS at time of down-referral and 96% remained so at last evaluation • Of the 26 patients with sub therapeutic response to ART, 77% achieved VS by 6months at PHC. Of the newly suppressed patients 3/4 met criteria for VF at TF and only 1/3 required change to second line regimen.		
van Dijk *et al.* (2014)	**Access to facilities and quality of services**	• 99% of caretakers reported easier access to outreach clinics vs. Macha Hospital • 100% did not travel as far; 56% had lower transport costs; and 67% said transport was easier to the outreach clinics • Proportion of children travelling >5hours decreased from 29% to 4% • Proportion using public transport vs. walking or cycling decreased from 39% to 4% • 83% of caregivers reported overall quality of care as similar to the hospital • 85% reported shorter waiting times at the outreach clinics • 34% and 26% reported that counselling services and physical examination respectively, were of lower quality than at hospital clinic	Observational study where children were TF to outreach clinics at various times after starting treatment at the request of the caregiver and only if they had responded well to ART, thus they represent a select group. Unmeasured differences between groups may have impacted outcomes.	HIV care can be effectively administered in RHC's. Adequate resources and support are needed at outreach clinics to monitor adherence and manage treatment failure.
	CD4 data	• Mean CD4% did not differ between groups before TF, and was non-significantly lower in outreach group post TF • Changes in CD4 % for outreach group at last visit pre-TF vs. 6months post TF		

		did not differ significantly from changes in CD4% in hospital-affiliated group over the same time interval	Small sample size. Only included one hospital-affiliated clinic and 3 outreach clinics in a rural area, therefore findings may not be generalizeable.	
	VL data	• VS was assessed up 3 years post ART initiation • Proportion of children with undetectable VL was lower at each time point for outreach clinics (few statistically significant differences) • VL measures from outreach clinic were significantly more likely to be >400 copies/ml (17% vs. 8%); >1000 copies/ml (16% vs. 7%); and >10 000 copies/ml (10% vs. 3%).		
	Adherence	• Proportion with optimal adherence (>95%) at each study visit was lower for those at the outreach clinics vs. the hospital-affiliated clinic, with no significant differences observed. • Median % of visits with optimal adherence was poorer for outreach group (69.2% vs. 79.3%; p=0.01) • Median % of visits with optimal adherence for outreach group was 75% (IQR: 50-100) before TF; and 75% (IQR: 43-100) after TF (p=0.81) when stratified for location.		
	RIC	• In outreach group: 75% were active in program at a median of 34months on ART; 1.5% (1) had died from drowning; none were LTFU; 5.9% (4) had TF to other clinics; 17.6% (12) were TF to Chilala Clinic when it became an independent ART clinic. • In Hospital Clinic group: 95% were active in the program at a median of 34 months on ART; none died or were LTFU; 4.9% (2) TF to other clinics.		

Abbreviations used in the table:

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- Receiving facilities: PHC – Primary Healthcare; CH – Community Hospital; CHC – Community Health Centre; RHC – Rural Health Centre.
- Cities and Provinces: CT – Cape Town; PE – Port Elizabeth; PMB – Pietermaritzburg; WC – Western Cape; WCP – Western Cape Province; EC – Eastern Cape
- Government structures: DOH – Department of Health; NHLS – National Health Laboratory Service; PHDC – Provincial Health Data Centre.
- HIV- related: ART – Antiretroviral therapy; PI – Protease Inhibitor; VL – Viral Load; LTFU – Lost to Follow-up; VS – Virological Suppression; RIC – Retention in care; VF – Virological Failure; IF – Immunological Failure.
- Other: TF – Transfer; TFO – Transfer out; TFI – Transfer in; FU – Follow-up.