Part 0: Preamble

Title Page

Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics

University of Cape Town

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UCT MPH (Epidemiology) Mini-dissertation

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Dedications

To my husband, David – I love you for taking us on an incredible journey abroad, filling my life with laughter, and always knowing the perfect way to be a supportive friend. Go team “MorshEdwards”!

To my American family – I love you for always being my cheerleaders.

To my South African family – I love you for welcoming me into your homes, teaching me about your beautiful country, and inspiring me with your unflagging strength.

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Thesis Abstract: **Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics**

Background: South Africa faces the world's largest pediatric HIV epidemic. Combination antiretroviral therapy (ART) is the only effective treatment for HIV virus suppression. Pediatric HIV care has traditionally been provided in academic research and tertiary care facilities, however efforts to improve ART availability for children are ongoing through decentralization. Tygerberg Hospital physicians with training in pediatric HIV management are providing care in seven community-based primary health care (PHC) clinics in the greater Cape Town region. ART initiation and ongoing ART management for those down-referred from tertiary and district level facilities are provided. The HIV-related outcomes of this cohort have yet to be reported.

Methods: Research ethics approval from the South African Provincial Government of the Western Cape Department of Health, University of Cape Town and Stellenbosch University were acquired. PHC HIV clinic rosters identified 848 patients under the age of 14, 613 of whom received at least one visit for ART management between 2004 and 2009. A retrospective chart review was performed to collect baseline characteristics, site and date of ART initiation, serial CD4 and viral load levels, TB co-infection status, ART regimen changes, and clinical status at study closure. Data was compiled in Excel spreadsheets and analyzed with STATA Statistical Software.

Results: Nearly 80% of the PHC cohort initiated ART when diagnosed with WHO clinical stage III or IV disease; 60% had laboratory findings of either advanced or severe immunosuppression. Those down-referred from tertiary and secondary care sites had significantly lower baseline CD4% ($p=0.016$), higher viral loads ($p<0.001$), and greater likelihood of TB co-infection ($p=0.013$) at the time of ART initiation. Virological suppression was accomplished in 85% at the last study visit. Peak CD4 count reconstitution was seen after 36 months on ART. Documented mortality was 2.2%; maximal mortality (inclusive of those lost to follow-up) was 6.2%. Highest maximal mortality risk was in the first three months of ART initiation. All early deaths were in infants less than 6 months of age, or young children (11-15 months) with severe immunological suppression (CD4%-8.2%). Nearly half of these children were receiving treatment for TB co-infection. Eighty percent of down-referred children had virological suppression at the time of transfer; 96% maintained suppression. Nearly 80% of unsuppressed patients achieved suppression within 6 months of transfer; 75% of these children had previously been diagnosed with clinically significant virologic failure.

Conclusions: Annually increasing numbers of less severely-ill ART initiates within the PHC network suggests successful ART roll-out in the Cape Town region. Long-term ART management by physicians in PHC clinics yields high rates of viral load suppression and immune reconstitution, and low mortality. Highest mortality risk is in the first 3 months of ART among those <15 months of age. Down-referral for adherence-related virologic failure may allow recovery of suppression and spare use of second-line medications.

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Angela Dramowski, my research partner and Fogarty International Clinical Research Fellowship "twin", shared equally in the inception and data collection aspect of this research project. Her unflagging work ethic and enthusiastic spirit were the driving forces behind making many months of data cleaning bearable.

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Prof Cotton's consistent encouragement to persevere despite a busy pediatrics residency and fellowship schedule resulted in completion of this project.

Landon Myer's biostatistics lessons provided the foundation that lead to the realization of this Epidemiology paper. His kindness to serve as my UCT mentor, while my work was predominantly at Tygerberg Hospital (TBH), will always be appreciated.

This project would not be possible without the cooperation of the IDC outreach pediatric clinicians. Their expertise in HIV management is apparent by the stellar outcomes of their patients.

Angela and I would like to acknowledge the National Institutes of Health Fogarty International Clinical Research Fellows Program for supporting our initial collaboration and those that follow.

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DECLARATION

MPH Course: Mini-dissertation

Assignment Title: Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics

I, Megan Morsheimer (Student No. MRSMEG002) declare that the work I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowleged.

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Signature: Signed by candidate

Date: 13 February 2013

Senate requires all students to make a declaration when submitting written work; they declare that the work submitted is their own and that where the work of others has been used (whether it has been quoted verbatim or paraphrased or referred to) it has been attributed and acknowledged using a standard references convention.

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Part A: Protocol

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Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African Community-based clinics

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ABSTRACT:

Many HIV-infected children in South Africa initiate antiretroviral therapy (ART) in a hospital based setting. However, with increasing demand for chronic HIV services and expanding expertise in paediatric HIV management, a large proportion of children now initiate or continue ART at community-based and primary health care facilities. There are few descriptions in the literature of paediatric cohorts receiving community-based HIV care. This audit will describe the survival rate, virological and clinical outcomes of children who received paediatric HIV care at seven community-based ART facilities supported by the Tygerberg Children's Hospital Infectious Disease outreach service in

South Africa's Western Cape Province between January 2004 and January 2009. Baseline WHO HIV staging, immunological and virological characteristics will be described. Antiretroviral treatment regimen type and duration, as well as immunological and virological outcomes will be analysed 6 monthly from ART initiation. Median survival and time to virological suppression will also be calculated. Confounding variables such as TB co-infection, ongoing WHO staging, and site of initiation and ongoing care will be taken into consideration.

BACKGROUND AND SIGNIFICANCE

WHO estimates that of the 2 million children living with HIV, 90% reside in sub-Saharan Africa[i]. South Africa faces the world's largest HIV epidemic with a staggering 280,000 children affected[ii]. Perinatally acquired HIV infection in developing countries results in high mortality rates; without intervention approximately half of all HIV-infected children will die by their second birthday[iii,iv,v].

Combination antiretroviral therapy (ART) is the only effective treatment available for the suppression of the HIV virus, and it is credited with the prevention of AIDS-related morbidity and mortality[vi,vii]. Children in developed countries receive ART as the standard of care, however it is estimated that less than ten percent of those living in resource-limited settings receive this life-sustaining treatment[viii]. Barriers to treatment abound in sub-Saharan Africa: delayed diagnosis, limited number of paediatric clinicians, and lack of paediatric ART drug formulations in the public sector are among the most common cited. Management and provision of paediatric ART services requires sophisticated laboratory resources, clinical expertise, and reliable pharmaceutical distribution capacity. Due to the high level of health care human resources and logistical coordination needed, paediatric ART distribution is commonly located at established research units and tertiary hospitals. For a predominantly rural-based

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population like South Africa, access to urban-based ART treatment facilities is associated with significant direct and indirect costs and contributes to the high rates of untreated children.

In recent years, South Africa has expanded public sector HIV services and ART roll-out activities by addressing barriers to access. Through the National Health Laboratory Service (NHLS), most clinicians now have access to rapid and accurate HIV diagnosis techniques (HIV Elisa and PCR), as well as CD4+ T-lymphocyte and HIV viral load quantification monitoring tests. Due to international funding sources such as PEPFAR and the Global Fund, training in paediatric ART management and stock of paediatric drug formulations has been increasingly available.

In the Western Cape Province of South Africa, paediatric ART first became available to public sector patients in 2004. Although children with complicated medical and social backgrounds maintain clinical follow-up at tertiary facilities, a decentralized approach for chronic HIV care has been adopted to increase community penetrance and availability of services for rural populations. The Infectious Disease Clinic (IDC) at Tygerberg Children's Hospital (TBH) supports a down-referral system by sending skilled paediatric clinicians to seven community-based clinics located in the suburbs and rural areas surrounding Cape Town: Ikwezi, Grabouw, Kraaifontein, and Delft clinics; Eerste River, Helderberg and Karl Bremer Hospitals.

ART efficacy is traditionally evaluated in three ways: repopulation of CD4+ T-lymphocyces, suppression of HIV viral load, and clinical recovery. Many research studies have documented paediatric ART efficacy in the form of immunological, virological and clinical outcomes among those enrolled in programs based in developed countries, and tertiary hospital/research settings

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within developing countries[ix,x,xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx,xxi,xxii]. Only two published accounts of community-based ART efficacy in a developing country have been identified to date[xxiii,xxiv].

Implementation of a community-based ART program proved successful in the Zambian cohort as demonstrated by a doubling of CD4+ T-lymphocyte cell counts during the first year of ART. Unlike our Cape Town-based study population, the Zambian cohort was cared for by non-physician clinicians (nurses and physician assistants), and viral load testing was unavailable. The treatment and monitoring strategy used for this population is therefore significantly different from the South African paediatric ART approach.

The second assessment of paediatric ART outcomes in a developing country was performed in the Western Cape Province of South Africa. Bock *et al*. utilized the PGWC ART monitoring system to compare immunological and virological outcomes among HIV-infected children during the first 18 months of ART treatment at differential levels of health system facilities (tertiary, secondary and community hospitals, and PHC clinics). Aggregate data was used to document deaths, loss to follow-up, trends in CD4 and HIV viral load levels, and initiation of second-line therapy for all children initiating ART in the Province.

Although this study provided an excellent assessment of short-term outcomes, this proposal aims to provide a temporally extended assessment (potentially up to 5 years of follow-up) and address some of the limitations identified by the authors of the aforementioned study. Bock *et al.* were able to glean a great amount of meaningful data from the monitoring system, yet their data was limited to elements captured by this electronic register. Baseline characteristics (age, CD4, VL, WHO stage) as well as longitudinal information about clinical disease progression (serial WHO staging, development of TB) were

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therefore not available. These characteristics, however, are well known to influence the survival, immunological and virological outcomes of HIV-infected children.

The monitoring system data analyzed in Bock *et al.*'s publication was appropriate for an assessment of a province-wide program and ART roll-out strategy as the aggregated data at the clinic and hospital level provided facility-averaged outcomes. This study of paediatric ART outcomes among the TBH-IDC outreach cohort will allow for an outcome analysis that takes into account baseline and clinical data, and provides information on the individual patient level. An analysis of this type will yield novel data that will add to the breadth and depth of the paediatric HIV literature. With the expansion of chronic ART services for paediatric patients, it is essential to document ART response in developing countries' community-based clinics. Documentation of the success of these programs at the provincial (Bock *et al.*) and individual level (this proposal) will provide valuable information to the PGWC management.

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HYPOTHESES

HIV-infected children in PHC clinics receiving care from paediatric clinicians attain high levels of survival, immunological and virological outcomes.

AIM

To describe the survival, immunological and virological outcomes of children receiving ART at seven community-based facilities in the Western Cape Province of South Africa between January 2004 and January 2009.

OBJECTIVES

1. To describe the number of children registered at each of the seven paediatric HIV clinics supported by the TBH-IDC community-based outreach service between January 2004 and January 2009.

2. To describe baseline WHO HIV staging, immunological and virological characteristics of these children.

3. To describe the ART regimen type and duration of treatment in this cohort of children.

4. To describe the immunological and virological outcomes at 6 monthly intervals post-ART initiation, with stratification by baseline characteristics and place of treatment initiation (hospital versus clinic).

5. To describe the numbers of children who died or were lost to follow-up during the study period.

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METHODOLOGY

This retrospective audit will document the number of children accessing ART at the seven paediatric ART clinics supported by the TBH-IDC outreach service: Ikwezi, Grabouw, Kraaifontein, and Delft clinics; Eerste River, Helderberg and Karl Bremer Hospitals. The electronic patient register for each clinic will be acquired from the clinic database manager, and this document will be used to identify all children (< 14 years of age) newly started on ART or down-referred from TBH for continued treatment between January 2004 and January 2009. For each child identified from the register, data will be extracted from the IDC database (an electronic register of clinical and outcome data for children at the seven TBH-IDC supported ART clinics) for the following variables: DOB, first visit date at HIV clinic, ART initiation date,

ART initiation site, baseline WHO HIV stage, 6 monthly CD4 count and viral loads, and TB diagnoses. Loss to follow-up and deaths will also be recorded. Data unavailable through electronic databases will be acquired through manual file acquisition (Appendix 1: Data Collection Tool).

STUDY DESIGN

A retrospective, descriptive cohort study of HIV-infected children accessing care at seven community-based ART clinics in the Western Cape Province: Ikwezi, Grabouw, Kraaifontein, and Delft clinics; Eerste River, Helderberg and Karl Bremer Hospitals.

STUDY POPULATION

All HIV-infected children (less than 14 years of age) receiving ART at any one of the seven aforementioned paediatric community-based ART clinics supported by the TBH-IDC outreach service between January 2004 and January 2009. Recent estimates suggest that the study population will include approximately 700 children.

STUDY SITES AND IMPACT ON RESOURCES

TBH is a referral centre for complicated cases of paediatric HIV infection, with both inpatient and outpatient services offered. An outreach service supports seven HIV clinics, providing the expertise to initiate ART and accept down-referrals from TBH for follow-up care.

The TBH outreach clinicians who visit these sites weekly will introduce the study and provide the PGWC approval letter to the Clinic Director and/or Hospital Superintendent. Once the institutional head agrees to participate, investigators will identify missing data points and provide a list of patients requiring manual folder search to the TBH-IDC outreach doctors. The TBH-IDC doctors will assist

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in obtaining files and capturing data after completion of their clinical duties. We anticipate that we will require minimal time on-site to obtain missing data directly from the clinic files.

If additional research staff are utilized to supplement to the IDC doctors' efforts (i.e. Drs. Morsheimer and Dramowski), one or two days of data collection will be planned for each site. The outreach doctor will liaise with the head matron to identify a workspace for investigators that does not interfere with the flow of patient care or impose upon existing personnel. Laptop computers are available so that investigators will not compete with staff for computing resources. It is not expected for existing staff to identify patient files on our behalf, as we do not want to increase their workload. However, assistance from hospital clerks to locate and pull patient files may be requested if the site prefers not to allow clinical or research staff in the file room.

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INCLUSION CRITERIA

Any HIV-infected child (less than 14 years of age) receiving ART and attending the paediatric HIV clinic at any one of the seven facilities supported by the TBH-IDC outreach service between January 2004 and January 2009. Any child transferred from TBH-IDC to a community-based ART clinic for follow-up.

EXCLUSION CRITERIA

Any HIV-infected child (less than 14 years of age) at a community-based HIV clinic NOT receiving ART between January 2004 and January 2009. Any child exclusively followed at TBH-IDC without down-referral to a community-based ART clinic.

DATA COLLECTION

The current TBH-IDC database includes data from patients followed at all seven

ART clinics supported by their clinicians. This database is part of an umbrella data collection and interpretation project on pediatric HIV (ART-LINC Collaboration). Ethical approval has previously been granted for collection and use of the ART-LINC data set. This analysis will seek to specifically describe and assess the pediatric outcomes of those attending the seven clinics.

Unlinked data will be extracted from the clinic database. Where there are discrepancies in the data or possible queries, the patient will be identified and the paper records traced to verify information. A coded and de-identified data collection form will be used manually to extract data from the source document when necessary[i]. The investigators will personally complete each data collection form thus helping to maintain data quality. No patient identifiers will be used on the forms so as to protect the confidentiality of all cases.

The primary risk to patients is a breach of confidentiality. To minimize this, several steps will be undertaken:

- An arbitrary anonymization key has been developed to remove any identifying information of the patients prior to data transfer
- This key is held under strict secure conditions by the local collaborating clinician
- Data entered in electronic databases will be password protected
- Hard copies of the data will be stored in a locked, steel filing cabinet in a locked office.

It is anticipated that the aforementioned system will work efficienty. The use of depersonalized data from the ART-LINC Collaboration database has not yielded a breach of confidentiality to date.

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[i] Please see Thesis Part D: Appendices, Data Capture Instrument

ANALYSIS

Data will be exported from the database and cleaned in Microsoft Excel. Data quality will be checked by performing frequencies on categorical variables such as clinic name and by checking the range of continuous variables such as age and weight. Data will be exported to STATA version 10 for more in-depth data analysis.

Continuous variables will be compared using the Wilcoxon rank-sum test, and categorical variables will be compared using the Pearson Chi 2 test statistic. Kaplan-Meier curves will be fit to assess survival functions stratified by baseline CD4+ T-lymphocyte count (absolute count and percentage of total lymphocytes), WHO stage, age at ART-initiation, and site of ART initiation (TBH-IDC or PHC clinic). The log-rank test will be used to assess statistical difference among groups.

Hazard ratios (HRs) for mortality will be estimated using Cox proportional hazards regression. For children receiving ART, we will calculate overall mortality rates, at 90 days of therapy, and after 90 days of therapy with exact 95% confidence limits.

Multiple logistic regression modeling will be used to explore the association of certain characteristics (eg. baseline viral load, clinic site, site of ART initiation, TB co-infection) with attainment of virological suppression. Change in CD4 percentage from ART initiation and HIV-1 RNA suppression below 400 copies/ml at 12 months will be modeled using linear and logistic regression, respectively, adjusting for values before ART, age at ART initiation and mode of presentation.

Antiretroviral treatment regimen type and duration, as well as immunological and virological outcomes will be analysed 6 monthly post-initiation

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of antiretroviral therapy. Median time to virological suppression will also be calculated.

STUDY TIMELINE

Protocol development:	February 2009
Ethical clearance:	March 2009
Data collection:	May 2009
Data analysis/Write up:	June 2009 – February 2012
Mentor review:	February 2012 - February 2013
Submit for publishing:	March 2013

BUDGET

700 data collection forms @ 50c per page x 2 pages =	R700
General printing costs =	R250
Travel costs to each of the seven study sites =	R1000
Database extraction and data cleaning =	R5000
Total costs =	R6950

These costs were covered by a pre-existing administrative grant from the Fogarty International Center, National Institutes of Health, USA.

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ETHICAL CONSIDERATIONS

This protocol has been approved by the Human Research Ethics Committees at Stellenbosch University and the University of Cape Town. A waiver of patient consent has been granted by SU and UCT as a part of the ethics application. Permission has also been granted by the PGWC Department of Health.

Every effort will be made to ensure confidentiality of the patients' electronic

and physical medical records. Electronic data will be kept on password protected computers, and forms containing identifying data will be stored in a locked, steel filing cabinet within a locked office at the University of Stellenbosch Faculty of Health Sciences Teaching Block.

All research will be conducted in agreement with Good Clinical Practice guidelines (Dr. Morsheimer received GCP Certification in November 2008 with recertification in April 2013) and the Declaration of Helsinki version 2000[xxv].

APPLICATION OF STUDY FINDINGS

Depersonalized data and aggregated analyses will be published in a peer-reviewed journal. A report of results will also be provided to the PGWC.

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Part B: Structured Literature Review

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A: Objectives of the literature review

- Acquire a series of papers and documents that are credible, relevant, and up-to-date with regards to pediatric HIV/AIDS treatment outcomes.
- Identify outcome-related papers that include populations of HIV-infected children on ART in developing countries.
- Discover whether published evidence of long-term pediatric HIV treatment outcomes among PHC or down-referred patients has been published to date.
- Attain manuscripts and documents from large-scale organizations (WHO, UNAIDS) for background epidemiology.

B & C: Literature search strategy, Quality review for inclusion

A systematic literature review was performed using the PICO strategy (P: population, I/E: intervention/exposure, C: comparison group, O: outcomes) to identify literature regarding pediatric ART treatment outcomes (Richardson et al., 1995). PubMed MeSH terms were used, and search filters were applied to maximize effective identification of literature while limiting the study type ("Humans, Clinical Trial, Meta-analysis, Randomized Clinical Trial, Review") and subject age ("All Infant: birth-23 months, All Child: 0-18 years"). Initial searches yielded large numbers of applicable studies (4,503 to 189,247 hits), therefore boolean terms were used to layer search outcomes so as to create an aggregate search that was most specific to my research topic. (Please see "Part D: Appendices" for complete details of systematic literature review, including MeSH search terms and outcomes for the primary search performed). Despite using a "venn diagram"-type approach to narrow search results, over 1200 papers were identified. Exploration with further limitation of

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terms failed to yield sentinel and desired publications; therefore manual review was performed on this large number of citations. A methodical review of all abstracts was performed with care to identify relevant literature (Please see “Part D: Appendicies” for topics excluded to improve quality/relevance of search engine output) and classify literature into the following categories: epidemiology, barriers to care, long-term outcomes (further delineated as developed countries/international multisite organized trials, resource-limited academic settings, resource-limited community-based settings, PHC’s, comparison of settings), and public health perspectives.

An additional focused search aimed at papers addressing outcomes among individuals receiving care in a decentralized or down-referral program was performed. The UNAIDS publications website (http://www.unaids.org/en/resources/publications/unaidspublications/2012/) was utilized to download policy and epidemiology resources. Research collaborators provided a few resources, and reading the references of highly relevant papers identified further desired citations.

Full publications were downloaded as pdf files through academic access provided by the University of California, San Francisco library. References were ultimately uploaded into RefWorks Web Based Bibliographic Management Software.

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D: Summary of the Literature

Although 2009 global prevalence estimates of children living with HIV has risen to 2.5 million [1.7 million–3.4 million], mortality among those under 15 appears to have fallen 19% over a period of 5 years (Joint United Nations

Programme on HIV/AIDS (UNAIDS), 2010). Rising prevalence and decreasing mortality is likely secondary to efforts to improve pediatric access to life-saving ART. Overall, incidence rates are decreasing, with vertical transmission resulting in 370,000 children born with HIV in 2009 (decreased from 500,000 cases in 2001) and 1200 new infections every day (WHO, 2010). Sub-Saharan Africa continues to shoulder the largest share of the HIV disease burden with 68% of the overall global patient load and 90% of the pediatric cases (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010). 2.3 million [1.4-3.1 million] children are estimated to live with HIV in sub-Saharan Africa. Sub-Saharan Africa reached 54% PMTCT coverage in 2009, which indicates interval improvement (15% in 2005) with room for further roll-out. HIV treatment expansion activities are reaching larger numbers of adults and children in need of pharmacologic intervention with every passing year; an estimated 37% of all eligible patients in Southern Africa in 2009 received ART, compared to 2% in 2002 (U. a. U. WHO, 2010). ART access among children in need is estimated at 26% (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010).

South Africa continues to have the largest national HIV epidemic, with an estimated 5.6 million [5.4 million–5.8 million] individuals living with HIV, including 330,000 [190,000 – 440,000] children. Despite achieving a nearly 90% PMTCT coverage rate by 2009 (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010), children continue to be born with and die from HIV at alarming rates. Perinatally acquired HIV infection results in high mortality rates; without intervention approximately one third of HIV-infected children will die by their first birthday (WHO, 2010), and half of all HIV-infected

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children will not celebrate their second (Dabis et al., 2001; Dunn & HIV Paediatric Prognostic Markers Collaborative Study Group, 2003; Spira et al., 1999). Thirty five percent of South African children who die before their fifth birthday fall victim to an AIDS-related demise (Shisana, 2010). Combination antiretroviral therapy (ART) is the only effective treatment available for the suppression of the HIV virus, and this pharmacologic intervention is credited with the prevention of AIDS-related morbidity and mortality (de Martino et al., 2000; Gibb et al., 2003). The majority of children in developed countries receive ART as the standard of care upon initial diagnosis, however it is estimated that only one in four children living in sub-Saharan Africa receives this life-sustaining treatment (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010). Despite substantial evidence that early intervention with ART is life and morbidity sparing (Berk et al., 2005; Johnson et al., 2011; Violari et al., 2008), the age of those accessing ART services remains high in developing countries (M. Davies et al., 2011; KIDS-ART-LINC Collaboration, 2008).

Although generally the political will is present for countries to roll-out HIV therapy, barriers to ART programs in developing countries abound: inadequate infrastructure, archaic laboratories, paucity of adequately-trained health care human resources, patented medications and vulnerable pharmacy supply chain, disconnected care provision models (i.e. separate tuberculosis, ART, PHC and pediatric clinics), and a marked disparity between rural and urban access to care sites (Ojikutu, 2007; Ojikutu, Jack, & Ramjee, 2007). ART roll-out activities in South Africa have come under particular criticism due to the slow rate of implementation and concern for governmental commitment

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(Ojikutu et al., 2007). Although some endorse volitional prolongation to ART scale-up (Nattrass, 2006), unique political, cultural and infrastructural deficits must be considered as contributing factors. Addressing the magnitude of the need for services within a public health system with limited means to mend long-standing inequities in health care provision has proven a formidable task. South Africa, now home to 5.6 million individuals living with HIV (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010), has taken up partnerships with numerous multinational charitable organizations and NGOs to hasten roll-out services. As a reflection of improved ART access, preliminary death registry analysis performed by the Medical Research Council of South Africa suggests decreasing annual mortality rates attributable to HIV (Pillay-van Wyk et al., 2013)

Although larger proportions of South Africans are accessing life-saving ART, services for pediatric patients lag behind. Delayed diagnosis due to lack of capacity for HIV DNA PCR testing, limited number of clinicians and staff trained to provide pediatric HIV management, scarcity of pediatric ART drug formulations, and limited access to birth certificates for rural-born children (required for enrollment) are among the most common pediatric-specific barriers cited (Balcha & Jeppsson, 2010; Fredlund & Nash, 2007; Meyers et al., 2007). Successful provision of pediatric ART services ultimately requires sophisticated laboratory resources, clinical expertise, and reliable pharmaceutical distribution capacity – resources often lacking at primary and secondary care facilities. Due to the high level of health care human resources and logistical coordination needed, pediatric ART distribution has therefore historically been located at established research units, tertiary

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centers and more recently, district-level hospitals. As of 2007, the majority of children in Gauteng Province continued to receive ART care in tertiary facilities due to lack of pediatric clinicians with HIV care expertise (Meyers et al., 2007). For a predominantly rural-based population like South Africa, access to urban tertiary ART treatment facilities is associated with significant direct and indirect costs, which undoubtedly contribute to the high rates of untreated children.

In the Western Cape Province of South Africa, pediatric ART first became available to public sector patients in 2004. Barriers to diagnosis and monitoring were addressed with expansion of National Health Laboratory Service (NHLS) capacity; access to rapid and accurate HIV diagnosis techniques (HIV Elisa and PCR), as well as CD4+ T-lymphocyte and HIV viral load quantification monitoring became routinely available (given the care site to laboratory transportation chain was intact). International funding sources such as PEPFAR and the Global Fund not only ensured a reliable supply-chain of pediatric drug formulations, but also expanded access to heath-worker training in pediatric ART management. Although the WHO has been recommending a decentralized, public health-centered approach for ART delivery in resource-limited settings since 2000 (Gilks et al., 2006; Qazi & Muhe, 2006), it was only in conjunction with the aforementioned advancements many years later that an integrated, primary health care (PHC) model for pediatric ART delivery became feasible.

As evidence of the Western Cape Province's commitment to WHO recommendations for community-based ART delivery, the proportion of pediatric ART care at tertiary care centers (Red Cross War Memorial

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Children's Hospital, Groote Schuur Hospital at the University of Cape Town, and Tygerberg Children's Hospital at Stellenbosch University) dropped from 78.4% in 2004 to 38% in 2006 (Meyers et al., 2007) . Training in routine pediatric care, as well as the complexities of ART management, was identified as a rate-limiting step for rapid expansion of pediatric community-based care in Cape Town by international funders. In order to overcome this barrier and expedite access to high quality pediatric ART care for those in the suburbs and rural areas surrounding Cape Town, pediatric clinicians from the Infectious Disease Clinic at Tygerberg Children's Hospital (TBH) were funded by PEPFAR to travel weekly to seven PHC clinics: Ikwezi, Grabouw, Kraaifontein, and Delft clinics; Eerste River, Helderberg and Karl Bremer Hospitals.

Three distinct groups of HIV-infected children receive care from TBH pediatric clinicians within the PHC network: individuals not on ART undergoing periodic evaluation for clinical or immunological qualification for ART; those initiating and continuing ART within the PHC network; and children down-referred on ART from tertiary, secondary and research-affiliated facilities. Long-term outcomes among ART naïve pediatric patients who initiate care in PHC clinics, as well as those who are down-referred between tiered levels of the healthcare delivery system (Please see Part D: Appendices, Supplementary Tables and Figures, Figure 1, for a reproduction of the "Health Services Pyramid", demonstrating the hierarchical levels of healthcare provision within Provincial Health Systems) (Gold et al., 1994; Turnock, 2009) are of particular interest to public health stakeholders as this represents a larger absolute number and proportion of HIV-infected children

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every year.

ART efficacy is traditionally evaluated in three ways: repopulation of CD4+ T-lymphocytes, suppression of HIV viral load, and survival. Numerous research studies have documented pediatric ART efficacy in the form of immunological, virological and clinical outcomes among those enrolled in programs based in developed countries (DC), however these outcomes are thought to be significantly different from those documented in resource-limited settings (RLC). A recent large-scale meta-analysis of published pediatric outcomes (including both papers and conference abstracts) was performed to compare pediatric ART outcomes stratified by United Nations designation as resource-limited (Peacock- Villada, Richardson, & John-Stewart, 2011). Baseline higher viral load and lower CD4 levels were identified in RLC cohorts. After 12 months of ART, mean CD4% was found to be 24% among RLC and 27% in DC children (p=0.03); VL suppression (<400 copies per ml) was 65% among RLC and 49% of DC patients (p=0.4); and mortality rates were 5-9 times higher (p=0.002) in RLC studies ("7.6% vs 1.6% and 8 vs 0.9 for motality percentage and DPCY", p<0.001).

Efforts preceding Peacock's study (Peacock-Villada et al., 2011) took either a more focused approach to pooled data from RLC publications (Ciaranello et al., 2009) or findings originating from sub-Saharan Africa (Sutcliffe, van Dijk, Bolton, Persaud, & Moss, 2008). As many of the papers utilized data included in Peacock's study it is not surprising that results were similar. Ciaranello et.al. estimate one year CD4% improvement of 13.7%, virologic suppression among 70%, and mortality rates ranging from 0 to 18.8%. Sutcliffe et.al. noted severe immunosuppression with advanced or

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severe clinical disease upon initiation of ART. The median rise in CD4% T lymphocytes while on ART was reported at 6-monthly intervals: “7-13.8% at 6-8 months, 10-16% at 12-15 months, 10% at 24 months and 21% at 36 months”. Serial viral loads were also included in longitudinal analysis: “viral suppression [<400 copies/ml] was…46-81% at 6 months…49-81% at 12 months…50% of children at 24 months, 47-83% at 36 months, and 45% at 42 months”.

Inclusive of cohorts of patients representing the majority of South Africa’s Provinces, a prospective database created by the NIH-funded “International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration” (IeDEA-SA) aims to provide insight into treatment outcomes within the South African national ART programme (Cornell et al., 2009). According to results reportedly representative of 20% of children enrolled in the South African national treatment program, most children were severely ill at the onset of ART treatment. Viral load suppression (<400 copies/ml) rates were consistently over 80% throughout the 36 month monitoring period and a mortality rate at 3 years of 7.7% was observed (M. A. Davies et al., 2009). Additionally the 3-year probability of developing virologic failure (as defined by “2 consecutive unsuppressed viral loads with the second being >1000 copies/ml, after more than 24 weeks of therapy”, and to be hereby denoted as VF) was 19.3% with independent association between VF and PI-containing regimens (M. Davies et al., 2011).

The vast majority of the aforementioned analyses, despite inclusion of RLC’s and African children, included data pooled from research studies where ART was provided to patients at tertiary centers and research units. In a

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unique approach to gain insight into more generalizable outcomes, Bock et.al. published the first African study utilizing aggregate public health data (routine data collected between 2004 and 2006 by the provincial ART monitoring system) to compare pediatric ART outcomes within the tiered healthcare delivery model (Bock, Boulle, White, Osler, & Eley, 2008). Stratification by academic or tertiary hospitals, regional referral hospitals, as well as district-level hospitals and PHC clinics revealed comparable outcomes. Proportions of children with CD4% greater than 20% rose from 60.6% at 6 months to 96.8% at 18 months, while VL suppression rates were similar to those noted in other studies (72.3% at 6 months, 76.8% at 18 months). Low rates of regimen change were observed overall without any PHC-enrolled children changing to second line ART.

Although aggregate surveillance data yields representative and highly powered outcomes, this study design is limited in its analysis of those who change levels of care during the duration of their ART therapy (i.e. down referral from tertiary care center to PHC clinic). As South African roll-out activities allow for larger numbers of young, less severely-ill patients to enroll for services in a decentralized system over time (Fatti, Bock, Eley, Mothibi, & Grimwood, 2011), a growing proportion of patients will also become eligible for down-referral from specialized sites for continuation of care in PHC clinics. Two large, recently published studies were identified and directly address the long-term outcomes of those down-referred from tertiary to PHC clinics for ongoing ART management.

A retrospective cohort analysis of Malawian adults and children receiving ART services in the public health sector was performed to evaluate

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differential outcomes depending on whether patients continued care at a tertiary hospital clinic or were down-referred to PHC clinics (Chan et al., 2010). In order to qualify for decentralized care, patients were required to be stable on first-line ART for at least three months without drug toxicity, active opportunistic infections, or adherence issues. Those down-referred ultimately had lower mortality and default rates. Although community-based clinical expertise was provided every 1-2 months by Baylor Pediatric AIDS Corps Consultants, larger proportions of children continued to receive ongoing care in the tertiary facility.

A recent prospective, case-controlled South African study of the down-referral of stable adult patients from a large, university-associated clinic to nurse-run PHC clinics yielded encouraging results: those down-referred had comparable, in cases better, outcomes than those continuing care at the treatment-initiation clinic (Brennan et al., 2011). Those down-referred had lower motality and loss to follow-up rates. Although these adult down-referred patients were heavily screened (more than 11 months on ART, at least two sequential VL levels <400 copies/ml, no opportunistic infections, and full immune reconstitution with CD4>200 cells/ul), the findings of this large-scale, rigorously-designed study of down-referral outcomes are encouraging.

As evidence mounts for successful initiation of pediatric ART care in rural and urban community-based PHC clinics (Barth et al., 2011; Bekker, Myer, Orrell, Lawn, & Wood, 2006; Bock et al., 2008; Bolton-Moore et al., 2007; van Griensven et al., 2008), the need for study of pediatric down-referral outcomes remains. Although children with complicated medical and social backgrounds will likely continue to receive care at tertiary facilities, a

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decentralized approach for chronic HIV care has been successfully adopted in RLC's, including South Africa, to increase community penetrance and availability of services for urban and rural populations alike.

E: Identification of gaps in the literature

Although data from some of the patients included in the "Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African Community-based clinics" study have already been published in the pediatric ART Western Cape Province analysis by Bock et.al., this study provides additional insight into outcomes among Cape Town children. Our data set includes a further 3 years of follow-up data, reflecting the ability to report 5-year outcomes, as well as the unique capacity to analyze children who cross health-system strata through a down-referral process for ongoing ART management. Unlike nurse-run PHC studies, pediatric clinicians provide direct care to PHC network patients, thus allowing capacity to manage unstable down-referred patients as well as those requiring second line therapy. Additionally, a gap of literature exists describing the side-by-side longitudinal care of evolving dual-cohorts – those who initiate ART in a PHC, and those down-referred – within a PHC.

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Part C: Manuscript

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Manuscript Title Page

(a) Full Title: Successful pediatric HIV management within a South African decentralization model of ART Delivery

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(f) Key words: Pediatric, HIV, ART, decentralized, primary health care

(g) Pediatric ART Outcomes within a Decentralization Model

(h) Decentralized Pediatric ART Outcomes

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Manuscript Abstract

Successful pediatric HIV management within a South African decentralization model of ART delivery

Background: South Africa faces the world's largest pediatric HIV epidemic. Efforts to expand antiretroviral therapy (ART) access are ongoing through decentralization of care to primary health care (PHC) clinics. Tygerberg Hospital physicians provide ART initiation and long-term management for pediatric patients in seven PHC clinics in the Cape Town region. HIV-related outcomes of this cohort have yet to be reported.

Methods: Clinic rosters identified 613 children <14 years of age who received ART management between 2004 and 2009. A retrospective chart review collected baseline characteristics, site and date of ART initiation, serial CD4 and viral load levels, TB co-infection status, ART regimen changes, and clinical status at study closure.

Results: Sustained virologic suppression and CD4 reconstitution was seen in over 80% of patients. Documented mortality was 2.2%. All early deaths were among infants <15 months of age. Nearly 80% of those with unsuppressed VL at the time of down-referral achieved suppression within 6 months; 75% of these children had clinically significant virologic failure at transfer.

Conclusions: Annually increasing numbers of less severely-ill ART initiates within the PHC network suggests successful ART roll-out in the Cape Town region. Long-term ART management by physicians in PHC clinics yields high rates of viral load suppression and immune reconstitution, and low mortality. Highest mortality risk is in the first 3 months of ART among those <15 months of age. Down-referral for adherence-related virologic failure may allow recovery of VL suppression and spare use of second-line medications.

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Introduction

WHO estimates that of the 2.5 million children living with HIV, 90% reside in sub-Saharan Africa [1]. South Africa faces the world's largest HIV epidemic with a staggering 330,000 children affected [1]. Perinatally acquired HIV infection results in high mortality rates; without intervention approximately half of all HIV-infected children will die by their second birthday [2-4]. 35% of South African children who die before their fifth birthday fall victim to an AIDS-related demise [5].

Combination antiretroviral therapy (ART) is the only effective treatment available for the suppression of the HIV virus, and it is credited with the prevention of AIDS-related morbidity and mortality [6, 7]. Children in developed countries receive ART as the standard of care upon initial diagnosis, however it is estimated that only one in four children living in sub-Saharan Africa receives this life-sustaining treatment [1]. Barriers to pediatric treatment abound in sub-Saharan Africa: delayed diagnosis due to lack of capacity for HIV DNA PCR testing, inadequate number of clinicians and staff trained to provide pediatric HIV management, and scarcity of pediatric ART drug formulations are among the most commonly cited systemic obstacles [8-10].

WHO has been recommending a decentralized, public health-centered approach for HIV care in resource-limited settings since 2000 [11, 12]. Due to the high level of health care human resources and logistical coordination needed to maintain a pediatric clinical practice and pharmacy, pediatric ART distribution has historically been located at tertiary centers and established research units in urban settings. For a predominantly rural and peri-urban based population like that in South Africa, access to urban tertiary care ART treatment facilities is associated with significant direct and indirect costs.

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In the Western Cape Province of South Africa, pediatric ART first became available to public sector patients in 2004. With concurrent expansion of the National Health Laboratory Service (NHLS) capacity and international funding for infrastructure and healthcare workforce training, a decentralized approach to ART delivery was actualized. International funders, however, identified mastering the complexities of ART management in addition to routine pediatric care as a surmountable rate-limiting step. To expedite access to high quality care for HIV-infected children in the suburbs and rural areas surrounding Cape Town, PEPFAR and the South African government funded pediatric clinicians from the Infectious Disease Clinic (IDC) at Tygerberg Children's Hospital (TBH) to provide direct care within seven primary health care (PHC) outreach clinics: Ikwezi, Grabouw, Kraaifontein, and Delft clinics; Eerste River, Helderberg and Karl Bremer Hospitals. Between 2004 and 2006 a decentralized approach to care resulted in a decrease in the proportion of Cape Town children receiving services at tertiary centers (Red Cross War Memorial Children's Hospital, Groote Schuur Hospital at the University of Cape Town, and Tygerberg Children's Hospital at Stellenbosch University) from 78.4% to 38% [10] .

As evidence mounts for successful initiation of pediatric ART care in rural and urban community-based PHC clinics [13-17], the need to evaluate pediatric down-referral outcomes remains. Two large studies performed in sub-Saharan Africa demonstrated lower mortality and default rates among down-referred patients; it is notable, however, that the option of down-referral was only offered to stable, compliant patients on first-line ART [18, 19]. Chan et al.'s Malawian cohort study was the only down-referral study inclusive of children, yet the authors

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acknowledge that the majority of children remained in the tertiary clinic at the end of the study period.

A unique cohort of children has developed within the PHC network as clinician-driven longitudinal care was provided for both ART-naïve initiates and those down-referred from tertiary facilities. Characterization of this cohort provides insight into long-term immunologic and virologic outcomes of PHC-managed children. Analysis of the outcomes of children who cross health-system strata through a down-referral process to initiate community-based ART management may identify characteristics predictive of success.

MATERIALS AND METHODS

Patients seeking HIV management at PHC clinics received opportunistic infection screening, ART regimen oversight and dose adjustment for growth, adverse event monitoring with clinical examination and routine blood work, and referral for nutritional support as needed. Services were performed in accordance with South African National protocols, which are based on WHO guidelines.

Children under 14 years of age who were either newly started on ART or down-referred for continued ART management between January 2004 and January 2009 within one of seven PHC clinics supported by the TBH outreach physicians was identified by PHC HIV clinic register for inclusion. Retrospective cohort data was gleaned from the IDC database (an electronic register of clinical and outcome data for children at the seven outreach clinics) so as to create a novel database including date of birth, first visit date at an HIV clinic, ART initiation date, ART initiation site, baseline WHO clinical stage, 6 monthly CD4 count and viral loads. Dates of TB treatment, loss to follow-up

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and deaths were also extracted. Data not available within the IDC database was either retrieved from the NHLS laboratory server or through clinic-based paper chart evaluation[i]. Patients identified without follow-up data (due to ART initiation, transfer-in or transfer-out, death, or loss to follow-up within 6 months of identification within the PHC network) were categorized as "baseline"; those with at least 6 months of follow-up data within the PHC network were assigned to the "longitudinal" cohort.

Serial CD4 counts and HIV viral loads were ordered by physicians at 6 month intervals as part of standard HIV-care protocols in the Western Cape Province. Lab values identified within three months of each 6-monthly evaluation period after ART initiation were included in the database. All laboratory testing was performed by NHLS with public funds. Within the NHLS lab, CD4 percentages are measured through the application of a dual-platform, dual-color PanLeucogating CD45-assisted flow cytometry machine [20]. Viral loads were initially performed using the NucliSens HIV-1 QT assay (bio-Merieux, Boxtel, the Netherlands), which yielded viral loads undetectable below 400 copies/ml. Advances in sensitivity with the introduction of the NucliSens EasyQ HIV-q assay allowed more precise quantification of low-level viremia, however all viral load values less than 400 copies/ml will be considered "suppressed".

Clinically significant virologic failure (VF) was defined as two sequential viral load values greater than 1,000 copies/ml. Once patients with VF were identified, pediatric clinicians were asked to provide a clinical vignette describing adherence issues or the presumed underlying cause for failure.

[i] Please see Part D: Appendices; Data Collection Tool

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Maximal mortality was defined as documented deaths in addition to those lost to follow-up. Survival analyses were calculated using the time to actual event or date of last evaluation.

Research Ethics Committees at Stellenbosch University and the University of Cape Town provided approval of this project. Additionally, permission to access patient health information was granted by the Deputy-Director General of District Health Services and Programmes within the Provincial Government of the Western Cape's Department of Health.

Statistical Analysis

Data were compiled into Excel spreadsheets and uploaded to Stata Statistical Software version 10.0 (StataCorp. LP. College Station, TX, United States of America) for analysis. Continuous variables were categorized by both ART initiation site (PHC vs. down-referred) and longevity within the PHC network ("baseline" vs. "longitudinal") and explored for normalcy; all values were accordingly analyzed with non-parametric Wilcoxon sum rank test for sub-cohort comparisons. Categorical frequencies were also stratified by ART initiation site and duration of care within the PHC network. A two-sample test of proportion was utilized to detect differences between sub-group frequencies.

Cox proportional hazards regression was performed to assess risk factors for maximal mortality (documented mortality and those lost to follow-up); a model including the age at ART initiation and days on ART at censorship was statistically significant. Kaplan-Meier survival analysis was performed to identify median time to VL suppression with stratification with categorical variables hypothesized to influence time to suppression. Multiple

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logistic regression was performed to explore variables (including protease inhibitor-containing ART and TB co-infection) that may be related to the risk of developing VF [21]. Manual and automated model building were performed to create a best-fit model, which ultimately included ART initiation site and baseline viral load log. Model diagnostics identified one patient that was both an outlier and influential point; the data for this patient was omitted from the model. Although his exclusion did not alter the significance of variables included in the model, the child had clinical and laboratory characteristics consistent with long-term non-progression which was felt to be phenotypically disparate from the general cohort.

RESULTS

Cohort Characteristics

A total of 848 patients were identified within the seven PHC ART clinics; 613 met the inclusion criteria. Two unique cohorts exist within the group of children cared for within the PHC network: those who initiated ART in one of the study clinics, and those who were down-referred from a higher level of care. The majority of those ineligible for analysis were HIV infected patients who had not initiated ART before the end of our study period (*see Figure 1*).

Baseline illness severity at the time of ART initiation, as measured by WHO clinical categorization, was significantly different between initiation sites; a larger proportion of severely ill children were started on ART at a higher level of care than a PHC clinic ($p<0.001$). Additionally, those who were ultimately down-referred had significantly lower baseline CD4 percentages ($p=0.016$), higher viral loads ($p<0.001$), and greater likelihood of TB co-infection at the time ART was initiated ($p=0.013$).

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Figure 1: Study cohort profile

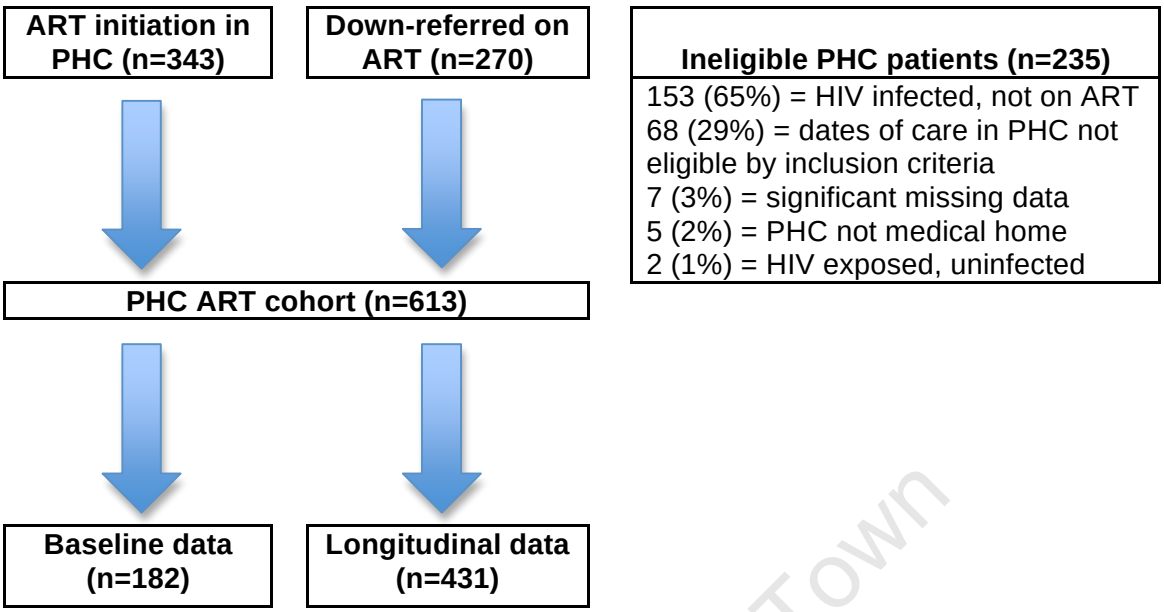

Table 1: PHC ART cohort characteristics stratified by ART initiation site

Variable	PHC cohort	ART initiation in PHC	Down-referred on ART	p-values
Number of Children	613	343	270	
Gender	46% male	48% male	44% male	0.359
Age at ART start *Median (IQR)*	26.4 months (10.2-63)	29.6 months (10-68.4)	25.1 months (10.5-59.3)	0.386
WHO clinical stage				
I	7%	10%	2.9%	<0.001
II	14.2%	19.2%	7.4%	<0.001
III/IV (Severe)	78.9%	70.7%	89.8%	<0.001
Baseline abs CD4 *Median (IQR)*	619 (323-1119)	608 (313-1151)	650 (340-1051)	0.879
Baseline CD4% *Median (IQR)*	16.7 (10.7-23.3)	17.8 (11-24.2)	16 (10-21.8)	0.016
Immunological Category				
No IS	22.5%	19%	27%	0.017
Mild IS	18%	21%	14.1%	0.027
Advanced IS	21.7%	23.6%	19.3%	0.194
Severe IS	37.9%	36.4%	39.6%	0.419
Baseline Viral Load *Median (IQR)*	270000 (49182 - 1000000)	230000 (32000 - 830000)	326969 (87841 – 1554457)	<0.001
Baseline Viral Load log *Median (IQR)*	5.4 (4.69 – 6)	5.4 (4.4 – 6)	5.5 (4.8 - 6)	<0.001
TB at ART initiation	20.5%	16.9%	25.3%	0.013

Similar trends in increased clinical severity (p<0.001) and higher baseline viral load (p=0.01) is present among those whose data is available

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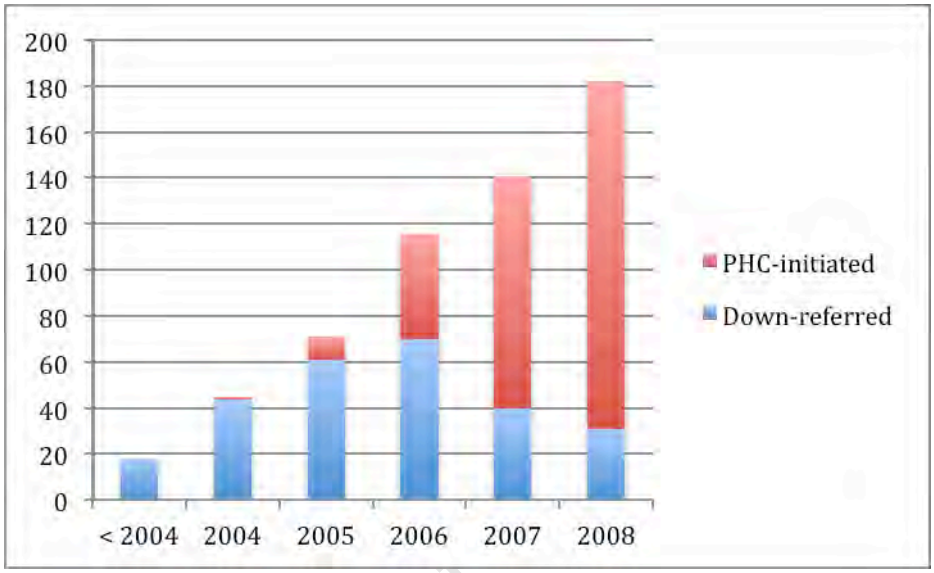
for longitudinal analysis. Due to the intensification of ART roll-out activities in the later half of the study period, the baseline cohort has a larger proportion of PHC-initiated patients, while the longitudinal cohort is skewed towards those down-referred (p<0.001) (*see Figure 2*).

Figure 2: ART initiation by year and site



Initial combination ART regimens were comprised of either two nucleoside reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI) (54%), or two NRTI drugs and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (46%). Lamivudine and stavudine were the most common NRTI drugs included in 99.5% and 86.7% of regimens respectively. Lopinavir/ritonavir was the preferred PI, and efavirenz was the primary NNRTI. Those who were down-referred for ongoing care were on ART for a median of 23.2 months (IQR 13.6-34 months) at the time of transfer.

The majority of children started on ART at any location had laboratory evidence of advanced or severe immunosuppression[ii]. Those without

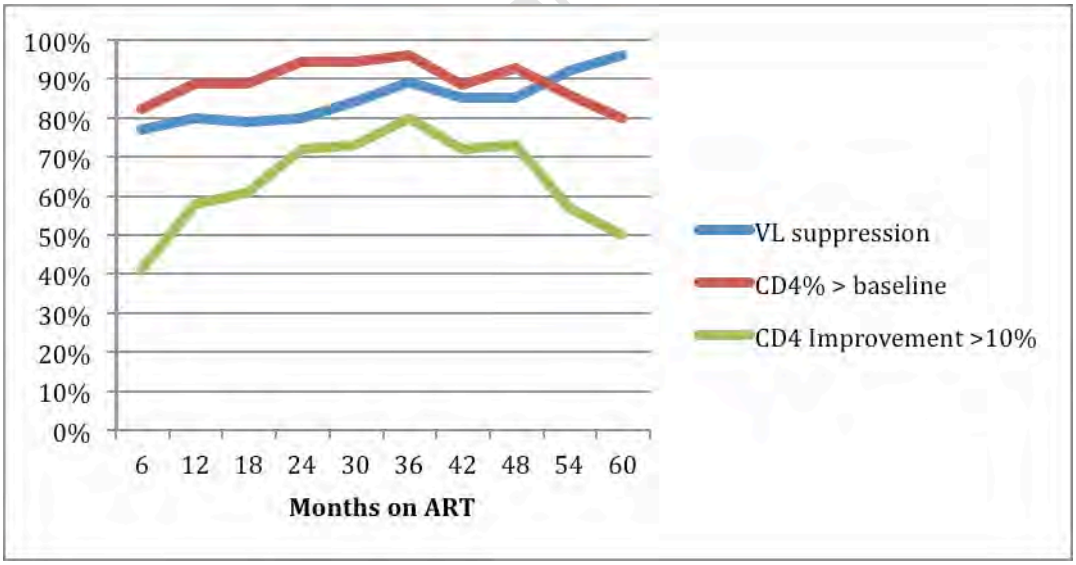
[ii] Please see Part D: Appendices; Supplementary Tables, Figures; Table 1 for age-related WHO Immunological Categories

immunosuppression, however, were significantly more likely to have initiated ART outside of the PHC system (p=0.017). Infants in particular were more likely to receive ART without immunosuppression when care was initiated at the tertiary or district hospital level (p=0.027).

Virological Outcomes

The median duration of follow-up was 28 months (IQR 16.5 – 42.6) including over 6 years of available data[iii] for some children and a total of 1206 observed child-years. Sustained high levels of viral load suppression were achieved at each time point (Figure 3), with approximately than 80% of the cohort suppressed from the 12-month visit. At the last viral load measurement during the study period, 85% of the longitudinal cohort was suppressed.

Figure 3: Virological, Immunological Outcomes over 5 years of ART

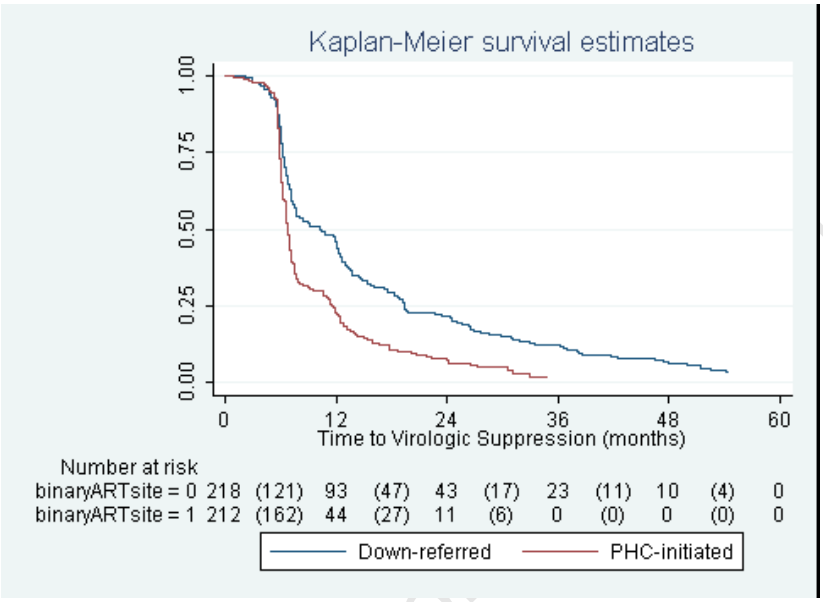


Kaplan-Meier survival analysis reveals a statistically significant difference in median time to VL suppression by ART initiation site: ART naïve patients who initiated care in the PHC system had a median time to

[iii] Please see Part D: Appendices; Supplementary Tables, Figures; Table 3 for full longitudinal dataset outcomes

suppression of 29 weeks, while those down-referred required 44 weeks (p<0.0001) (*Figure 4*). Stratification by sex, age, baseline WHO immune categorization, modified South African WHO clinical stage, and TB co-infection were not found to influence time to VL suppression.

Figure 4: Time to Viral Load Suppression by ART Initiation Site



Sixty patients (13.9%) met our criteria for clinically significant virological failure, representing an incidence of 5.4 cases per 100 child-years. Multiple logistic regression modeling revealed that patients who initiate ART in the PHC system are 66% [95% CI = 31%, 84%] less likely than those down-referred to develop VF. Additionally, for every one log increase in baseline VL the odds of developing VF doubles [95% CI = 1.3, 3.2]. Age, history of TB disease, protease inhibitor-based ART regimen with TB treatment, and baseline immune category were not found to be predictive of VF within the model; baseline WHO clinical classification, however, was so significantly predictive that the variable was restricted from the model due to colinearity.

Immunological Outcomes

Over 80% of the longitudinal cohort maintained a CD4% above baseline at each sequential monitoring period; a peak prevalence of 96% was achieved at 36 months of ART (*Figure 3*). The average percentage improvement over baseline CD4% was 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. Additionally, the largest proportion of those with more than 10% improvement in CD4% above baseline was achieved at 36 months. Although CD4% gains drop off after three years of therapy, lower age-related norms over time are more likely underlying this finding rather than poor response to therapy given ever-rising VL suppression rates.

Thirteen cases, two percent of children (1 per 100 child-years), had evidence of immunologic failure (IF)[iv] after at least 24 weeks of adherent ART treatment. Delayed immune reconstitution occurred in five IF children (38.5%); in this subgroup CD4 counts were recovered in 80% by 12 months and all children by 18 months of ART. An additional five cases (38.5%) experienced transient IF despite concurrent VL suppression. Although IF resolved by the subsequent interval evaluation, it should be noted that forty percent were undergoing concurrent TB treatment. It is therefore possible that intercurrent illnesses, TB or otherwise, may contribute to IF. The remaining three children with IF (23%) had persistent failure despite ongoing VL suppression. One persistent IF case experienced immune reconstitution after changing the protease inhibitor in her ART regimen from ritonavir to lopinavir/ritonavir.

[iv] Please see Part D: Appendices; Supplementary Tables, Figures; Table 2 for age-related WHO Immunologic Failure criteria

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Mortality

Documented mortality among the PHC cohort was 2.2% with a maximal mortality estimate (documented deaths and those lost to follow-up) of 6.2%. The relative risk of maximal mortality was found to decrease by 14.4% for every 3 months on ART, and by 15% for every 6 month increase in age at ART initiation. A skewed temporal distribution of documented deaths was noted with near-equal numbers experiencing early (<3months on ART) and late (7-30 months on ART) mortality. Similarly, a disproportionate number of children were lost to follow-up (LTFU) in the PHC-initiated group (p=0.028) concerning for undocumented early death after starting ART (*Figure 5*). Long-term maximal mortality rates (>6 months of care in a PHC clinic) did not differ by ART initiation site (p=0.091).

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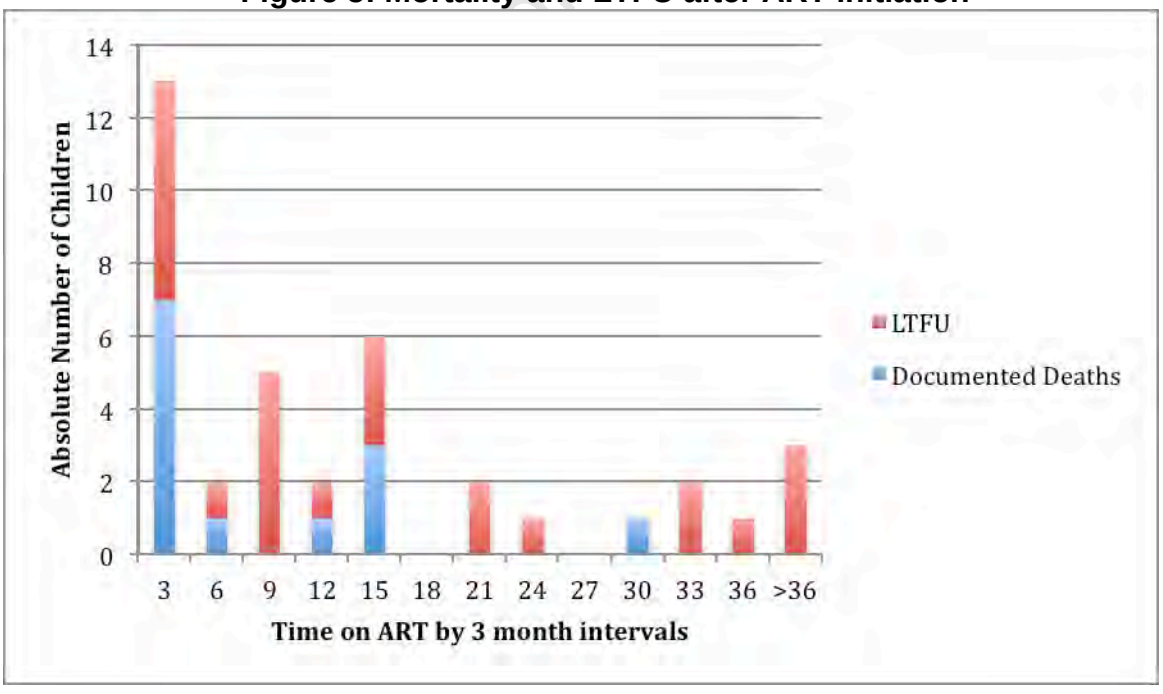
Figure 5: Mortality and LTFU after ART initiation



Due to left censoring of early deaths among the down-referred cohort, early deaths were only noted in those who initiated ART in the PHC system.

Early deaths occurred in either infants under 6 months of age, or young children (11-15 months old) with severe immunological suppression (CD4% 3-8.2%). Over half of the early mortality group (57%) died within the first 9 days of ART treatment. Nearly half of those with early mortality were receiving dual therapy for HIV and TB disease (43%); TB treatment was started from 1 week to 3 months before ART initiation.

Outcomes Among Children Down-referred from Tertiary Hospitals

After a median of 2 years (IQR 13.6 – 34 months) on ART, 153 patients were down-referred from a tertiary facility to a PHC clinic. Approximately 80% had a suppressed VL at the time of down-referral, and 96% of these patients remained suppressed at the last measured study evaluation. Of the 26 patients transferred with sub-therapeutic response to ART, 77% achieved virologic suppression after 6 months of support and treatment within the PHC system. Three quarters of the newly suppressed individuals met the criteria for VF at the time of transfer, yet only one third of these children required medication change to second line therapy to achieve successful suppression. Of the remaining 6 patients (23%) with ongoing VF, two were changed to 3TC mono-therapy; one was started on second line therapy immediately prior to the end of the study period whereby response to the intervention cannot be assessed; two made a lateral transfer to the adult ART roster within the same clinic; and only one patient required back-transfer to a tertiary care center. One down-referred child died within three months of transfer from a tertiary care site (0.6%).

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DISCUSSION

Cohort characteristics reveal ART initiation site strongly correlates with WHO clinical severity, findings consistent with appropriate acuity triage within the public health services pyramid model[v]. Annually increasing absolute numbers of ART initiates, particularly less severely ill children within the PHC network, suggests successful ART roll-out strategies for pediatric patients in the Cape Town region [22]. Children receiving ongoing treatment within the PHC network demonstrated sustained indices of effective HIV management (high VL suppression rates, rapid immune reconstitution, low mortality rates) that are comparable, if not better, than those previously published studies of similar cohorts [15, 23-26].

Despite overall low mortality, clear high-risk characteristics among children with documented death were identified: those in the first three months of ART treatment, infants less than 6 months or children under 15 months of age with severe immunological suppression at ART initiation, and those undergoing dual treatment for HIV and TB disease. Similar trends in mortality have been noted in numerous studies [16, 25, 27, 28], providing further evidence of a focused time period among high-risk patients that may be ideal for a targeted intervention. Intensified surveillance of this population would ideally result in expedited referral to higher levels of care and decreased mortality, however research at the health system level would be required to validate this theory.

Although infants and young children are at higher risk for early mortality after ART initiation, evidence indicates that intervention before 12 weeks of

[v] Please see Part D: Appendices; Supplementary Tables, Figures; Figure 1 for an example of the Health Services Pyramid

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age reduces this risk by 76% [29]. As a marker of early adoption of research-based practice by physicians based in tertiary facilities (TBH was a CHER trial site), disproportionate amounts of non-immunosuppressed infants were found to be initiating ART at higher levels of care. Although data to support asymptomatic infant ART initiation was first presented in mid-2007 at the International AIDS Conference on HIV Pathogenesis, Treatment and Prevention, recommendations were more widely disseminated through journal and WHO publications near the end of the study period in 2008 [29, 30]. There is evidence of early adoption of infant ART roll-out in tertiary facilities, however the temporal nature of this study with respect to rapidly changing practice guidelines does not allow for true compliance evaluation.

Data from the PHC network is unique in that it arises from the first exclusively pediatric cohort with down-referral longitudinal data. Near perfect rates of sustained viral load suppression after tertiary-to-PHC down-referral is demonstrated among stable patients. Optimistic outcomes among predominantly adult down-referred patients are congruent with our findings, however these studies likely suffer from selection bias (those offered down-referral were pre-selected for success) [18, 19]. Unlike these studies, one out of every 5 down-referred child had an unsuppressed VL at the time of transfer. Among the unsuppressed, many had VF with clinicians noting adherence issues in most. Although down-referred children had more cumulative ART exposure with associated risk for resistance development, a high proportion achieved viral suppression after transfer into the PHC network without ART regimen change. Successful suppression on first line therapy for those previously failing indicates improved adherence, likely secondary to

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decreased barriers to care within communities-based clinics. PHC physicians demonstrated expertise in effectively managing those requiring second line therapy with rare referral back to tertiary care centers and low documented mortality rates. Substantial improvement in VL suppression rates among this sub-group was observed whether a focus on adherence or a change to second-line therapy was prescribed, thereby validating the efficacy of this model of care for all-comers.

Although results support favorable outcome measures, inherent characteristics of the study design may limit generalizability of findings to a larger health system. Initial patient identification from PHC rosters resulted in a cohort generally comprised of a stable down-referred population, and less severely ill children started on ART in the outpatient PHC setting. Children who suffer early mortality or are lost to follow-up prior to PHC down-referral are inherently unaccounted for in this analysis. Low mortality rates in this cohort may significantly underestimate those noted at a health system level due to sampling bias.

While many decentralization schemes aim to not only transfer care to community-based centers but to also task-shift care to non-physician staff, children in the PHC cohort received ongoing care by highly skilled physicians who specialize in pediatric HIV management. Weekly roundtable case review meetings between PHC clinicians, TBH IDC pediatric infectious disease specialists, and a social worker ensured that complex cases were routinely discussed. The majority of those down-referred from tertiary care sites in this cohort initiated ART at TBH and these children are therefore well known to the IDC physicians and social workers that attend weekly case conferences.

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While direct physician care of HIV management, weekly review of cases with subspecialists, and continuity of care for many down-referred patients may yield optimal medical outcomes, this approach is time and resource intensive. Prospective research on a health system level must be pursued to explore if favorable outcomes can be maintained as sustainable task-shifting to a non-physician workforce is implemented for ongoing PHC-based care.

Conclusion

Although the majority of children were severely ill at ART initiation, increasing proportions of less acutely unwell children are initiating ART annually. One of main anticipated demographic shifts among pediatric cohorts is the widespread provision of ART to asymptomatic infants; rapid adoption of this WHO recommendation has been observed at the tertiary care level in Cape Town.

While awaiting uniform adoption of early ART initiation for infants, our data suggests intensified surveillance of children under 15 months of age for the first three months of ART may improve mortality statistics. Reproducibly well-defined patient characteristics restricted to a discrete high-risk period yield a clear target for programmatic intervention.

Long term ART management within PHC clinics by pediatric clinicians yields successful outcomes. Down-referral of tertiary center-enrolled patients with VF, likely adherence-related, may be a first-line ART sparing strategy.

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Part D: Appendices

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Data Collection Tool

Study Number □□□
Patient's Initials □□□
Date of Birth □□/□□/□□□□ (dd/mm/yyyy)
Clinic register number □□□□□□□□
Clinic folder number □□□□□□□□
Data Capturer's Initials □□□

Demographics & Past Medical History:

Date of first PHC ART clinic attendance date □□/□□/□□□□ (dd/mm/yyyy)
Clinic Site: _____
Referral clinic/hospital: _____
Sex (m/f) □
Date of ART initiation □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Baseline CD4 □□□□ absolute
Baseline CD4 □□.□ %
Baseline VL □□□□□□□□
Baseline viral log □.□□
Baseline WHO Stage □

6 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

12 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

18 months on ART

University of Cape Town

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

24 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

30 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

36 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□

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viral log □.□□
WHO Stage □

42 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

48 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

54 months on ART

Date of visit □□/□□/□□□□ (dd/mm/yyyy)
ART regimen: 3TC□ d4T□ Kal□ EFV□ ABC□ AZT□ DdI□ Rtv□
Date of regimen change □□/□□/□□□□ (dd/mm/yyyy)
Reason for regimen change: policy change □ toxicity □ failure □ TB tx □ other
TB co-infection at this visit Yes □ No □ Unknown □
CD4 □□□□ absolute
CD4 □□.□ %
VL □□□□□□□□
viral log □.□□
WHO Stage □

Final Outcome

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Final Datapoint = Date of outcome □□/□□/□□□□ (dd/mm/yyyy)
□ Died □ lost to follow-up □ transferred out □ end of study period (Jan 09)

If alive and still at HIV clinic at final datapoint:

□ full virological suppression (VL=LDL)
□ incomplete virological suppression (VL < 1000 but > 400 [50] copies/ml)
□ virological failure (VL > 1000 c/ml)

Number of episodes TB treatment: □

1. □□/□□/□□□□ to □□/□□/□□□□
2. □□/□□/□□□□ to □□/□□/□□□□
3. □□/□□/□□□□ to □□/□□/□□□□

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Comprehensive Literature Review Methods
(Output as Performed on 7/12/11)

Topic	PubMed Search Terms	Results (search#)
Limits	Humans, Clinical Trial, Meta-analysis, Randomized Clinical Trial, Review, All Infant: birth-23 months, All Child: 0-18 years	n/a
HIV/AIDS *Cochrane Center's published search terms for HIV/AIDS*	"HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp]	7,835 #1
ART *Cochrane Center's published search terms for ART*	Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw])) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immunedeficiency[tw])) OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immune-deficiency[tw])) OR ((anti) AND (acquired immun*) AND (deficiency[tw]))	4,503 #2
Outcomes	viral load OR viral suppression OR virological suppression OR response OR immunologic* OR immune suppression OR immunosuppression OR survival OR death OR mortality OR CD4	75,258 #3
Setting	Developing country OR resource-limited OR community OR community-based OR primary care OR primary healthcare OR clinic OR public health	189,247 #4
Geographic Location	Africa	6,326 #5
Combine	#1 AND #2 AND #3	1,563 #6
Combine	#1 AND #2 AND #3 AND #4	1,214 #7

University of Washington

Combine	#1 AND #2 AND #3 AND #5	275 #8
Combine	#1 AND #2 AND #3 AND #4 AND #5	246 #9
Manual Review	Excluded themes: HIV-negative patients, studies of adult patients only, studies in HIV-infected patients whose primary outcomes are not VL/CD4/survival outcome related (lipodystrophy, metabolic changes, wt change, growth, neurologic/cognitive outcomes, etc), HIV-infected children's outcomes before starting ART, PMTCT outcomes, cost-effectiveness studies, adherence studies, resistance studies, opinion pieces without novel data, outcomes for novel meds not available on SA formulary, HepC co-infection, HepB co-infection, vaccine trials, Phase 1 Safety/PK studies, vaginal microbicides, studies of novel ART drugs for salvage therapy, outcomes after switch to 2nd line therapy after poor viral suppression, outcomes <6mo after ARTi, therapeutic drug level monitoring studies, mono or dual therapy drug therapy	
Additional Papers Identified	Additional literature was acquired from mentors, identified as appropriate resources within the references of related papers, WHO/UNAIDS website publications	

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Supplementary Tables, Figures

Figure 1: The Health Services Pyramid model demonstrates the theoretical proportion of hierarchical healthcare provision levels (ascension correlates with further specialization of health care providers and available services). Ideally primary and secondary prevention interventions result in smaller numbers of the population requiring access to higher-levels of more sub-specialized care {{140 Gold 1994; 141 Turnock 2009;}}. Within a context of pediatric ART management, population-based public health services refers to PMTCT and ABC campaign efforts; primary health care is the strata where our PHC network is located, and were we hope the majority of ART is eventually managed; the secondary health care level refers to district level hospitals where access to pediatric clinicians can likely be expected; and the tertiary health care summit references the three academic hospitals with pediatric infectious disease specialists in the Western Cape Province.

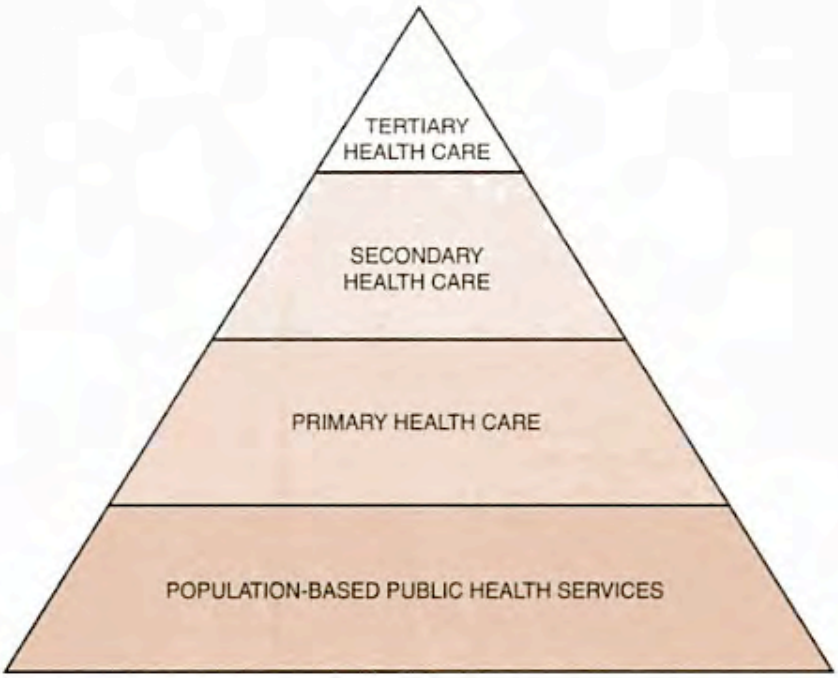

Figure 3-4 Health services pyramid. *Source:* Reprinted from U.S. Public Health Service. *For a Healthy Nation: Return on Investments in Public Health*. Hyattsville, MD: PHS; 1994.

Table 1:

WHO Immunological categories by CD4% and absolute CD4 count for pediatric HIV infection

Immune Status (severity, age category code)	**Age <12 mo (0)**	**Age >13 mo (1)**	**>5 yrs (2)**
No sig immunosuppression (1)	>35%	>25%	>500 cells/ul
Mild immunosuppression (2)	25-34%	20-24%	350-499 cells/ul
Advanced immunosuppression (3)	20-24%	15-19%	200-349 cells/ul
Severe immunosuppression (4)	<20%	<15%	<200 cells/ul

Table 2:

WHO Immunological failure is recognized as developing or returning to the following thresholds after at least 24 weeks on ART, in a treatment-adherent child:

≥2 years to <5 years of age	CD4 count of <200cells/mm3 or %CD4 < 10
≥5 years of age	CD4 count of <100 cells/mm3

Table 3:

Full longitudinal outcome data (n=431). NB: Not all individuals will have both CD4 and VL values available at each lab evaluation period (i.e. "n" is different for each measured event despite collection within the same time period)

Interval eval after ART initiation	**VL (n)**	**VL Supp**	**CD4 % (n)**	**Proportion of CD4%>BL**	**CD4% Imp >10%**	**WHO Imm Failure (n)**	**% with TB**
6 months	327	76.76%	300	82.33%	41%	7	14.89
12 months	317	80.44%	289	88.58%	58.13%	7	5.92
18 months	232	78.45%	204	88.73%	60.78%	2	3.36
24 months	212	80.19%	163	94.48%	72.39%	2	4.81
30 months	162	83.95%	125	94.4%	72.8%	2	4.43
36 months	137	89.05%	100	96%	80%	1	3.88
42 months	84	84.52%	61	88.52%	72.13%	1	3.61

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48 months	68	85.29%	41	92.68%	73.17%	2	6.25
54 months	39	92.31%	21	85.71%	57.14%	1	5.88
60 months	22	95.45%	10	80%	50%	1	0
66 months	10	90%	4	100%	100%	---	0
72 months	6	50%	0	---	---	---	0
78 months	1	100%	0	---	---	---	0
Last capture		84.69%					

*VL (n) = “n” obs available at each time point; VL Suppression defined as ≤400copies/ml; CD4% (n) = “n” obs available at each time point; CD4% Imp >10% = Percentage of follow-up CD4% levels that have risen more than 10% over baseline; %CD4%>BL = Percentage of follow-up CD4% levels that have maintained a value greater than baseline; WHO immunological failure is defined in Table 2 – these values do not include elimination of those non-adherent (i.e. with concurrent elevated VL); TB refers to the proportion of patients with concurrent TB tx at the time of f/u evaluation (according to TB Rx start and either documented or presumed – depending on type of TB disease – treatment termination dates).

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Journal article
1. Trujillo M, Correa N, Olsen K, et al. Cefprozil concentrations in middle ear fluid. *Pediatr Infect Dis J*. 2000;19:268 –270.

Book chapter
2. Grose C. Bacterial myositis and pyomyositis. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1998:704 –

708.

Entire book
3. Nelson JD, Bradley JS. *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

Proceedings
4. Harrigan PR, Dong W, Weber AE, et al. Highly mutated RT and protease [Abstract I-115]. In: 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September 24 to 27, 1998. Washington, DC: American Society for Microbiology; 1998.

Online journals
5. Friedman SA. Preeclampsia. Obstet Gynecol. [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

World Wide Web
6. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/ special/hiv/ethics. Accessed June 26, 1997.

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Financial disclosure: In the cover letter, indicate all affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials of the research discussed in the manuscript (e.g. employment, consultancies, stock ownership). All such information will be held in confidence during the review process. Should the manuscript be accepted, the Chief Editors will discuss with the author the extent of disclosure appropriate for publication.

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- Cover letter
- Title page (including conflicts of interest statement)
- Abstract
- Copyright Transfer & Disclosure form signed by all authors
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- References double-spaced in US National Library of Medicine style
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- Permission to reproduce copyrighted materials or signed patient consent forms
- Acknowledgments listed for grants and technical support
- High quality print of electronic art . Tables created using table software features
- Figures created/saved as TIFF, EPS, or PowerPoint files
- At least 3 suggested reviewers

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Department of Health
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7705
South Africa

FAX: 021 938 4153

Dear Dr Morsheimer

Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African community-based clinics

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact the following members of staff to assist you with access to the facilities:

1. Eerste River Hospital: Dr Visser tavisser@pgwc.gov.za Tel: 021 902 8000
2. Helderberg Hospital: Dr Erasmus clerasmu@pgwc.gov.za Tel: 021 851 1170
3. Karl Bremer Hospital: Dr Naude Lnaudc@pgwc.gov.za Tel: 021 918 1911
4. Grabouw Clinic: Mrs van Nelson 021 859 1301
5. Kraaifontein CHC: Mrs Steyn Lsteyn@pgwc.gov.za Tel: 021 9870080
6. Delft CHC: Mr van Heerden Javheerd@pgwc.gov.za Tel: 021 954 2237

We look forward to hearing from you.

Yours sincerely

DR J CUPIDO
DEPUTY-DIRECTOR GENERAL
DISTRICT HEALTH SERVICES AND PROGRAMMES
DATE: 21/5/2009

CC:
MS SMUTS — D: HIV/AIDS/TB DIRECTORATE
DR PEREZ — D: EASTERN AND KHAYELITSHA SUBSTRUCTURE
DR BITALO — D: TYGERBERG AND NORTHERN SUBSTRUCTURE
DR KRIGE — D: OVERBERG DISTRICT

UNIVERSITY OF CAPE TOWN

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

13 March 2009

REC REF: 120/2009

Dr MM Morsheimer
Public Health & Family Medicine

Dear Dr Morsheimer

PROJECT TITLE: SURVIVAL, VIROLOGICAL AND IMMUNOLOGICAL OUTCOMES OF HIV-INFECTED CHILDREN ACCESSING ART AT SOUTH AFRICAN PRIMARY HEALTH CARE CLINICS

Thank you for submitting your study to the Research Ethics Committee for review.

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

Approval is granted for one year till the 20th March 2010.

Approval is granted for a waiver of informed consent as participants' privacy and confidentiality will he protected and it would not be practical to obtain such consent.

Approval was granted using an expedited review according to Category Number 5 of the OHRP Guidance.

Please send us an annual progress report if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulations Part 50, 56 and 312.

Annual Progress Report

Date	2 August 2010
HREC REF Number	120/2009
Protocol number (if applicable) & Protocol title	Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics
Principal Investigator	Dr. Megan Morsheimer
Department / Office Internal Mail Address	megan.morsheimer@gmail.com

List of documentation

Annual Progress Report – Expedited review kindly requested

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	This serves as notification of annual approval, including all documentation described above.		
☐ Not approved	See attached comments.		
Type of review	☑ Expedited	☐ Full committee	
Expiry date	15/8/2011		
Signature Chairperson of the HREC		Date	6/8/2010

Annual Progress Report

Date	27 July 2011
HREC REF Number	120/2009
Protocol number (if applicable) & Protocol title	Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics
Principal Investigator	Megan Morsheimer, MD
Department / Office Internal Mail Address	Faculty of Health Sciences, School of Public Health Megan.morsheimer@gmail.com; morsheimerm@pds.ucsf.edu

List of documentation

Annual Progress Report – Expedited review kindly requested

5

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved ✓	This serves as notification of annual approval, including all documentation described above.		
☐ Not approved	See attached comments.		
Type of review	☐ Expedited ✓	☐ Full committee	
Expiry date	15 AUGUST 2012		
Signature Chairperson of the HREC		Date	5.8.11

24 March 2009

Dr MM Morsheimer

Department of Paediatrics

Stellenbosch University

Tygerberg

7505

Dear Dr Morsheimer

"Survival,virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics."

ETHICS REFERENCE NO: N09/03/082

RE : PROVISIONAL APPROVAL

It is my pleasure to inform you that the abovementioned project has been provisionally approved on 21 March 2009 for a period of one year from this date. You may start with the project, but this approval will however be submitted at the next meeting of the Committee for Human Research for ratification, after which we will contact you again.

Notwithstanding this approval, the Committee can request that work on this project be halted temporarily in anticipation of more information that they might deem necessary to make their final decision.

Please quote the abovementioned project number in all future correspondence.

Please note that a progress report (obtainable on the website of our Division) should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly and subjected to an external audit.

Please note that in line with the recent changes to research ethics guidelines, including the Declaration of Helsinki, the CHR requires that all researchers specifically request and motivate for a “waiver of informed consent” for retrospective clinical audits.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

University of Cape Town

The Committee for Human Research complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of

Fakulteit Gesondheidswetenskappe · Faculty of Health Sciences

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Yours faithfully

MRS MERTRUDE DAVIDS

RESEARCH DEVELOPMENT AND SUPPORT

Tel: 021 938 9207 / E-mail: mertrude@sun.ac.za

Fax: 021 931 3352

University of Cape Town

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University of Cape Town

15 March 2012

MAILED

Dr A Dramowski
Academic Unit: Infection Prevention & Control
Div Community Health
Stellenbosch University
Tygerberg campus
7505

Dear Dr Dramowski

"Survival, virological and immunological outcomes of HIV-infected children accessing ART at South African primary health care clinics."

ETHICS REFERENCE NO: N09/03/082

RE : PROGRESS REPORT

At a meeting of the Health Research Ethics Committee that was held on 14 March 2012, the progress report for the abovementioned project has been approved and the study has been granted an extension for a period of one year from this date.

Please remember to submit progress reports in good time for annual renewal in the standard HREC format.

Approval Date: 14 March 2012 Expiry Date: 14 March 2013

Yours faithfully

MRS MERTRUDE DAVIDS
RESEARCH DEVELOPMENT AND SUPPORT
Tel: 021 938 9207 / E-mail: mertrude@sun.ac.za
Fax: 021 931 3352