

A descriptive case series of HIV-positive infants started on antiretroviral treatment within the first six weeks of life at Rahima Moosa Mother and Child Hospital

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DECLARATION

I, Carice Ann Goossens, declare that this research report is my own work. It is being submitted for completion of the degree of Master of Medicine in the branch of paediatrics at the University of Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination at this or any other University.



.....
on the 20th day of November, 2018

To all children who are living with HIV:
May your lives be enriched and prolonged with advances that the department of
medicine makes with the treatment of this illness. I wish you happy, beautiful lives
without pain or suffering.

PRESENTATIONS ARISING FROM THIS PROJECT

1. WITS Pediatric Research Day. June 2014. Register oral presentation.
Goossens CA. "A Descriptive Case Series Of HIV Positive Infants Started on Antiretroviral Treatment Within The First Six Weeks Of Life At Rahima Moosa Mother And Child Hospital".

2. Southern African HIV Clinicians Society 2nd Biennial Conference (SA HIV 2014). September 24-27 September. CTICC in Cape Town South Africa.
Poster presentation of abstract "A Descriptive Case Series Of HIV Positive Infants Started on Antiretroviral Treatment Within The First Six Weeks Of Life At Rahima Moosa Mother And Child Hospital". Goossens CA.

ABSTRACT

Background: Human Immunodeficiency Virus (HIV) progresses rapidly in neonates (babies younger than 28 days of life), often before, the previously recommended, routine HIV testing at six weeks and subsequent treatment initiation. Recent South African treatment guidelines recommend HIV polymerase chain reaction (PCR) testing on all HIV-exposed babies at birth and recommend starting antiretroviral treatment (ART) within one week of diagnosis. This results in babies being diagnosed and treated much earlier than previously. There is inadequate evidence around the safe and effective use of ART in neonates, especially in premature infants. The presence of concurrent illnesses complicates the initiation of ART and affects treatment outcomes. The effectiveness and adverse effects of ART in infants where the pharmacokinetics and pharmacodynamics of ART are poorly understood need to be documented.

The aim of this study was to describe the diagnosis, treatment and outcomes of HIV-infected neonates initiated on ART within the first six weeks of life at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa.

Subjects and Methods: Records of neonates initiated on ART prior to 6 weeks of age between 2004 -2013 were reviewed. These neonates were tested earlier than prevailing national guidelines due to their being symptomatic for HIV infection, being premature or having low birth weight (LBW). Sixty two files where neonates had a positive PCR test prior to 6 weeks of life were reviewed. Cases were excluded if either they were started on ART in the first six weeks of life at a different institution or if they were not cared for at RMMCH in their first year of life. A number of patients were excluded due to initiation after 6 weeks even though diagnosed prior. Baseline pretreatment characteristics (PMTCT exposure, clinical parameters and clinical conditions at ART initiation) were reviewed. Outcomes to the end of one year of life with regards to follow-up status, clinical parameters (weight and height Z-scores), immunological and virological results (CD4 and VL) were reviewed.

Results: Twenty records were eligible and reviewed. The median age of ART initiation was 27 days. The majority of patients fulfilling the study criteria were premature, LBW infants who had received inadequate PMTCT. Fourteen neonates required treatment for illnesses prior to or during the period of ART initiation. Two of these newborns required ventilation. Illnesses requiring treatment were: necrotizing enterocolitis (n=2), neonatal hepatitis (n=1), congenital pneumonia (n=3), congenital syphilis (n=2), cytomegalovirus infection (CMV) (n=2), pneumocystis jirovecii pneumonia (PCP) (n=2), tuberculosis (n=2) and Group B Streptococcus meningitis (n=1). Other pre-treatment characteristics such as adequate PMTCT (n=3), prematurity (n=12), LBW(n=10), thrombocytopenia (n=6), anemia (n=8) and renal dysfunction (n=2) were evident. Viral load (VL) pre-ART ranged from 1295-10 000 000 copies/ml. One nevirapine-exposed infant had an undetectable VL immediately pre-ART even though HIV was confirmed virologically in prior and later tests. Abacavir (ABC), 3TC and LPV/r was the most common regimen initiated. (n=10). Two patients demised. Lipodystrophy was an adverse effect experienced by one patient on stavudine (d4T).

Conclusion: In our study of mainly premature and LBW neonates who initiated ART at a mean age of 28 days (SD: 11 days) we saw that many of them had significant co-morbidities. Majority of patients initiated early in this study survived until 1 year follow up, two demised. This study highlights the need for consideration and further research of co morbid conditions at time of ART initiation as well as adverse effects of medication and polypharmacy. Reduced diagnostic sensitivity in nevirapine-exposed infants may be a concern in infants tested after birth.

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NOMENCLATURE

Abacavir – ABC

Acid fast bacilli – AFB

Antenatal clinic - ANC

Anti Retroviral Treatment - ART

Antiretroviral – ARV

Appearance, Pulse, Grimace, Activity, Respiration – APGAR

Appropriate for gestational age - AGA

Caesarian Section – C/S

Cytomegalovirus - CMV

Didanosine – Ddi

Efavirenz – EFV

Food and Drug Administration –FDA

Gestational age - GA

Half-life - $t_{1/2}$

Human immunodeficiency virus - HIV

Intrauterine growth restricted - IUGR

Johannesburg - JHB

Kaletra – KLT

Lamivudine - 3TC

Lopinavir/Ritonavir – LPV/r (Kaletra)

Loss to follow up – LTFU

Low birth weight - LBW

Lower than detectable level – LDL

Necrotizing enterocolitis - NEC

Nevirapine – NVP

Nil per os - NPO

Normal Vaginal Delivery – NVD

Patent ductus arteriosus - PDA

Pharmacokinetic - PK

Pneumocystis jirovecii pneumonia - PCP

Polymerase chain reaction - PCR

Postmenstrual age - PMA

Prevention of Mother to Child Transmission - PMTCT

Rahima Moosa Mother and Child - RMMCH

Respiratory distress syndrome - RDS

Severe acute malnutrition – SAM

Small for gestational age - SGA

South African - SA

Stavudine - d4T

Tuberculosis - TB

Twice daily - bd

Viral Load –VL

World Health Organization -WHO

Zidovudine – AZT

CHAPTER 1 – INTRODUCTION

Human immunodeficiency virus (HIV) infection is unfortunately still a far too common condition in neonates in South Africa. Despite aggressive Prevention of Mother to Child Transmission (PMTCT) programmes, there is still a significant burden of HIV disease in children. With efficacious interventions the risk of mother to child HIV transmission can be reduced to below 2% [1]. In South Africa the coverage (the percentage of mothers and neonates that required PMTCT and actually received it) was 61% in 2009 with a 14% transmission rate. In 2012 the coverage increased to 87% with a 5% transmission rate and the transmission rate dropped to 3.5% in 2013 [2]. At the end of 2013, it was estimated that 3.2 million children were living with HIV, mostly residing in sub-Saharan Africa [1]. In the period between 2000 and 2010, 35.5% of deaths in children less than 5 years of age were attributed to HIV [1].

1.1 PMTCT and Early Testing

1.1.1 WHO Guidelines and Early Disease Progression

At the time of this study (prior to 2015) the World Health Organization (WHO) Guidelines did not recommend testing babies at birth and therefore early diagnosis and antiretroviral treatment was not common practice. The 2004 WHO Guidelines recommended a qualitative polymerase chain reaction (PCR) test at 4-6 weeks of age in infants who were HIV-exposed [3], or earlier if ill or signs of symptomatic disease were present. This therefore allowed for treatment initiation at approximately 10-12 weeks of age (usually later). Neonates were however being tested and treated more regularly prior to 6 weeks of life due to symptomatic disease or prematurity or low birth weight (LBW).

Guidelines were adjusted, as over the years research has shown that HIV infected neonates are at risk of early disease progression. This was highlighted in a study by Marston et al in 2011 which showed a mortality of 20% by 90 days of life if HIV infected infants were left untreated [4]. It was again made evident in a study by Lillian et al in 2013 where they found a 13-25% mortality in the first year of life when HIV

infected infants were initiated on ART where possible. The average age of ART initiation, in their study, was 16 weeks [5].

The Children with HIV Early Antiretroviral Therapy (CHER) Study is one of the hallmarks of research conducted on early initiation of ART. In this study HIV infected infants were either initiated < 12 weeks of age (early) or when immunological or clinical criteria were met (delayed). The early initiation group (average = 7.1 weeks) had a reduction in mortality of 76%. This study showed that HIV-infected infants had an increased mortality and morbidity irrespective of their clinical or immunological staging [6]. Based on the CHER study, in 2010 WHO recommended that all HIV-infected infants should start treatment after diagnosis irrespective of their immunologic or clinical stage [7]. Research has demonstrated that the initiation of ART in early infancy reduces the risk of death and disease progression [6;8].

In 2013, the South African PMTCT guidelines further recommended testing at birth for all low birth weight and premature infants[9]. New PMTCT guidelines were released in 2015. These guidelines currently recommend that all HIV exposed infants should undergo HIV PCR testing at birth and at ten weeks of age, with the understanding that this will result in earlier initiation of ART and a resultant decrease in mortality and morbidity[10]. These new guidelines will result in early initiation of ART.

In accordance with guidelines between 2004 and 2008, early diagnosis and treatment of HIV in neonates at this time was limited to neonates presenting with symptoms and/or meeting immunological criteria. This resulted in neonates less than six weeks of life very rarely starting on ART. With the most recent guidelines recommending birth PCR testing it is important to describe the outcomes of infants that have previously been tested and treated earlier than six weeks of life. This will allow understanding of the difficulties that may be faced with the initiation of ART in premature infants and in infants less than 6 weeks of age.

1.1.2 PMTCT concerns

There are concerns that nevirapine (NVP) and zidovudine (AZT), as part of PMTCT, may lead to reduced diagnostic sensitivity as well as to resistance to treatment.

NVP as part of PMTCT has been shown to reduce the sensitivity of the HIV PCR test done at 6 weeks of age. In a study by Mphatswe et al it was noted that a single dose of NVP reduced infant viral load to below the detectable limit in 38% of cases at 5 days of age and in 17% of cases at 2 weeks of age [11]. This resultant viral suppression could result in false negative HIV PCR results with resultant delay in diagnosis of HIV infection and initiation of ART [12]. If infants are tested at birth, those infants that are prenatally infected will not be misdiagnosed and will be initiated on treatment earlier resulting in improved mortality and morbidity. To avoid misdiagnosis by an early false negative result it is therefore recommended to do a second PCR test at ten weeks to diagnose perinatal transmission of HIV after the infant has been off NVP for four weeks [5].

The recommended HIV deoxyribonucleic acid (DNA) PCR is a sensitive test used to detect HIV viral DNA in peripheral blood mononuclear cells. The specificity of this test at birth is 99.8%, and 100% at one, three, and six months [13]. If the PCR is performed at birth it has a sensitivity of only 55% but this increases to more than 90% by two to four weeks of age, and 100% at three months and six months of age [14].

Another benefit of early testing and treatment is that it diminishes the chance of developing resistance to NVP, as a consequence of taking NVP for six weeks as part of the PMTCT programme, despite already being HIV-infected.

1.2 ART (antiretroviral therapy)

1.2.1 The Safety and Efficacy of ART

Despite the wide use of ART in HIV-exposed neonates as prophylaxis and as treatment in HIV infected infants, there is limited evidence about the correct dosage and choice of drugs for initiation of ART in this population. The dosing guidelines and

pharmacokinetic (PK) data on neonatal antiretroviral (ARV) use are limited to a handful of ARV drugs used for PMTCT.

Zidovudine (AZT) is the only drug with available PK and dosing data for premature infants [15].

In term neonates, there is sufficient data to provide dosing recommendations appropriate for the treatment of HIV infection with AZT, lamivudine (3TC), emtricitabine, and stavudine (d4T). From a chronological age of two weeks in term neonates; didanosine (DDI), nevirapine (NVP), and ritonavir-boosted lopinavir also have sufficient data available to provide dosage recommendations. There is no dosing data for abacavir (ABC) in infants less than three months of age. DDI and emtricitabine are generally not used in neonatal treatment regimens. Stavudine (d4T) has dosage recommendations in term neonates but there is no data available for dosing in premature infants. It is not included in the SA treatment guidelines as there is no liquid formulation available in the public sector. Stavudine may be a good alternative to AZT if contraindicated or if there are side effects from AZT such as hematological toxicities [16]. The PK and safety data are insufficient for all other antiretrovirals to allow recommendations for safe doses appropriate for use in HIV infected neonates [16].

Lopinavir/Ritonavir (LPV/r), with trade name Kaletra, has a black box warning for infants with a postmenstrual age (PMA) less than 42 weeks. The liquid formulation contains 42.4% alcohol and 15.3% propylene glycol. The FDA (Food and Drug Administration) received a report where ten neonatal cases (after being given LPV/r liquid formulation) experienced severe metabolic and/or cardiac toxicities. A single fatality was also reported. A recommendation was then issued to avoid LPV/r until two weeks of age and 42 weeks post-conception [15]. There is however some data to guide dosage in premature and term infants, should the potential benefit be thought to outweigh the risk [16].

It is currently recommended that neonates be started on AZT, 3TC and NVP until they are greater than 42 weeks PMA. NVP is then changed to LPV/r due to the P1060 trial showing greater efficacy of LPV/r when compared to NVP [17].

Infants are then changed from AZT to ABC once they are greater than 3 months of age and preferentially virally suppressed [18].

In a study by Saik Urien, Firtion, Anerson et al, seven neonates were treated for HIV infection, the median age of treatment initiation was two weeks and the median weight was 3.3kg. The most suited doses of LPV/r that kept the trough level within a normal range were suggested to be 40mg 12 hourly in the 1-2kg group, 80mg 12 hourly in the 2-6kg group and 120mg 12 hourly in the 6-10kg group [17].

Various other factors need to be considered in neonates and small infants. Neonates and infants have delayed absorption, reduced liver metabolism as well as decreased renal elimination of drugs [15]. Dosing of ART in neonates is challenging due to the fact that during the first few days of life there are significant changes in renal function. There is immature glucuronide conjugation and glomerular filtration in the early neonatal period and this affects the elimination and clearance of some of the drugs [15].

Adult levels of elimination of orally administered AZT in infants are only reached by four to eight weeks of life. Premature infants require a significant increase in the dosing interval to avoid potentially toxic exposure as the clearance of AZT is even more decreased in premature infants [15]. Lamivudine clearance is also prolonged immediately after birth and it requires a 50% dose reduction in younger (<1 month) infants. A similar dose reduction is required for d4T [15].

Among all ART used in the neonatal period, NVP has the longest elimination half-life ($t_{1/2}$) [17]. The median $t_{1/2}$ is 43.6 hours (range: 23.6–81.6 hours) following the administration of a single dose of NVP to infants at 48 to 72 hours after birth. NVP is a substrate and inducer of hepatic metabolism by enzymes of the CYP450 family and therefore chronic (not single dose) maternal NVP use before delivery may produce induction of NVP metabolism in utero and accelerate NVP elimination in the infant after birth. Adequate NVP concentrations in infants born to mothers with chronic NVP therapy can be achieved with additional NVP doses postpartum (48 and 96 hours) [15].

1.2.2 Hematological considerations and opportunistic infections

There are numerous opportunistic infections that often coexist with HIV. These infections may require single or even multiple drug therapies. This results in exposure to combinations of drugs which, at times, may enhance side effects such as myelosuppression. For example AZT, trimethoprim-sulfamethoxazole (Bactrim), and ganciclovir all may cause defective hematopoiesis [20].

In neonates, opportunistic infections such as cytomegalovirus (CMV), group B streptococcus, syphilis and disseminated tuberculosis can also cause defective hematopoiesis.

Thrombocytopenia occurs in 20 - 33% of pediatric patients with HIV some time during the course of their disease[19] and is a fairly common finding in neonates who are HIV exposed [20].

1.2.3 Early ART

The Mississippi baby was an infant born in 2010 who was thought to have been “cured” of HIV in 2013. This led to thoughts that ART initiated within hours of birth could cure HIV infection. In July 2014 however, it was reported that the child had developed a detectable viral load again and was unfortunately still HIV infected [21]. The alleged cure of the “Mississippi baby” led to suggestions that “very early ART may interfere with either the quantities or qualities of persistent reservoirs of replication-competent virus”[22]. In this infant a 3 drug prophylactic regimen to provide high-risk prophylaxis was initiated at 30 hours of life, using AZT, 3TC and NVP. HIV infection of the infant (positive HIV – DNA at 30 hours and HIV-1 RNA of 19 812 copies/milliliter) was confirmed at 31 hours of age and therefore ART was continued. At 1 week of age LPV/r replaced NVP.

The viral load (VL) was repeated and found to be 2617 copies/ml at six days, 516 copies/ml at 11 days and 265 copies/ml at 19 days and lower than detectable level (LDL) at 29 days of life. The patient defaulted follow up between 18 to 23 months of age. The mother claimed to have stopped administering ART at 18 months of age

and the last documented collected script was at 15 months of age. The VL was still undetectable at 23 and 24 months of age after this period of defaulting. A repeat HIV PCR and ELISA at 24 months were both negative too [22]. The child later however developed a detectable viral load and was restarted on ART.

It is hoped that earlier ART initiation will result in better controlled HIV infection and in better clinical outcomes such as less neurological impairment of perinatally HIV infected children.

1.3 Summary

Not much is known about the safety and effectiveness of ART in neonates and premature infants. The outcomes of infants who have been started on ART prior to a corrected age of 42 weeks PMA need to be described. Drug doses and side effects as well as drug regimens, drug efficacy and resistance are all important aspects that still need to be clarified.

Despite the uncertainties and lack of evidence around dosing, drug regimens and side effects, most clinicians initiate ART soon after making a diagnosis of HIV in neonates due to the major concern around potential disease progression. With the most recent ART guidelines being implemented this will now become common practice. It is important that infant outcomes such as drug toxicity, drug resistance, infant mortality, neurodevelopment and long term virological suppression following early diagnosis and treatment of HIV positive neonates are clearly documented.

1.4 Aims and Objectives

The aim of this study is to describe the diagnosis, treatment and outcomes of HIV-infected neonates initiated on ART within the first six weeks of life at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa.

The objectives of this study are:

1. To describe pre-treatment characteristics of infants in terms of obstetric PMTCT exposure history and clinical parameters at age of diagnosis and ART initiation.

2. To describe outcomes to the end of one year of life with regards to vital and follow-up status, clinical parameters (weight and height Z-scores), immunological and virological results (CD4 and VL)

3. To describe all associations recorded that can be attributed to ART.

CHAPTER 2 – MATERIALS AND METHODS

2.1 Study type

The study is a retrospective descriptive study.

2.2 Study setting

Rahima Moosa Mother and Child (RMMCH) is a maternity and pediatric, government hospital in Johannesburg (JHB), South Africa. RMMCH is located approximately seven kilometers west of the JHB CBD. It has its own HIV clinic, Empilweni Clinic, where children infected with HIV are followed up and managed. It is one of the larger pediatric cohorts in South Africa. The clinic plays a major role in PMTCT and pediatric ART and diagnosis, follow up and research. The pediatric section of RMMCH has a 35 bed neonatal unit (ward 16B) with a ten bed neonatal intensive care unit (six ICU beds and four high care beds). The doctors from Empilweni are consulted for any neonates who are diagnosed as HIV-infected. They regularly follow up these neonates whilst admitted and then if feasible for the parents, they will be followed up at Empilweni Clinic subsequent to being discharged.

2.3 Study population

- Inclusion criteria:
 - HIV-infected neonates initiated on ART < 6 weeks of chronological age
 - Patients must have started ART between January 2004 up to and including August 2013.
- Exclusion criteria:
 - Patients that started ART in the first six weeks of life at a different institution and those that were not cared for at RMMCH in their first year of life.

2.4 Data collection

The patients who were less than six weeks chronological age when started on ART between 2004 – 2013 at RMMCH were identified as follows:

1. A list was compiled of all children fulfilling the inclusion criteria from the existing Empilweni clinic database.
2. Once the ethics committee granted their approval, the NHLS laboratory was approached for permission to print out all PCR positive results for infants aged less than six weeks, from RMMCH from January 2004 up to and including August 2013 NHLS (Appendix A).

We received a list with 272 names from the NHLS and 25 names from the Empilweni database. Five patient names from the Empilweni database did not appear on the NHLS list. After reviewing the lists, duplicates were removed as well as patients that were diagnosed after 36 days of life, as they wouldn't have been initiated on therapy prior to the criteria of six weeks. This was assumed for all, because some (approximately 15) of the files were reviewed and none of these patients were initiated prior to six weeks of life.

The list of patients' names was then used to obtain the files from the hospital records (filing) department for record review. 154 names on a list were given to the filing clerks. A large number of files were not found or missing. When files were not found at records, the patient's were searched for on the electronic Empilweni database (Gatekeeper permission below, Appendix B).

Of those 154 names only 62 files were found and formally reviewed. 92 files were not found. This is outlined in Figure 2.1 below. These files had either been destroyed, misplaced or the patients were not actually tested at RMMCH and were therefore unable to be reviewed for the study. The researcher conducted a thorough review of the 62 files located.

A data capturing form was drawn up (Appendix C), prior to file review, which allowed for documentation of each patient's data that was vital to the study. The patient data was entered onto the pre formulated data sheet.

Only 20 patients of the 62 files reviewed fitted the study criteria. The major reason for not fulfilling the study criteria was due to advanced age of initiation of ART followed by initiation or follow up at another institution. On review of the actual files and dates of ART commencement, it was found that the majority of the patients only started ART after six weeks of life. Therefore the numbers of eligible patients decreased from 62 to 20. The other reason the number of eligible cases diminished even further was due to initiation records not found due to diagnosis at RMMCH and then follow up at another institution.

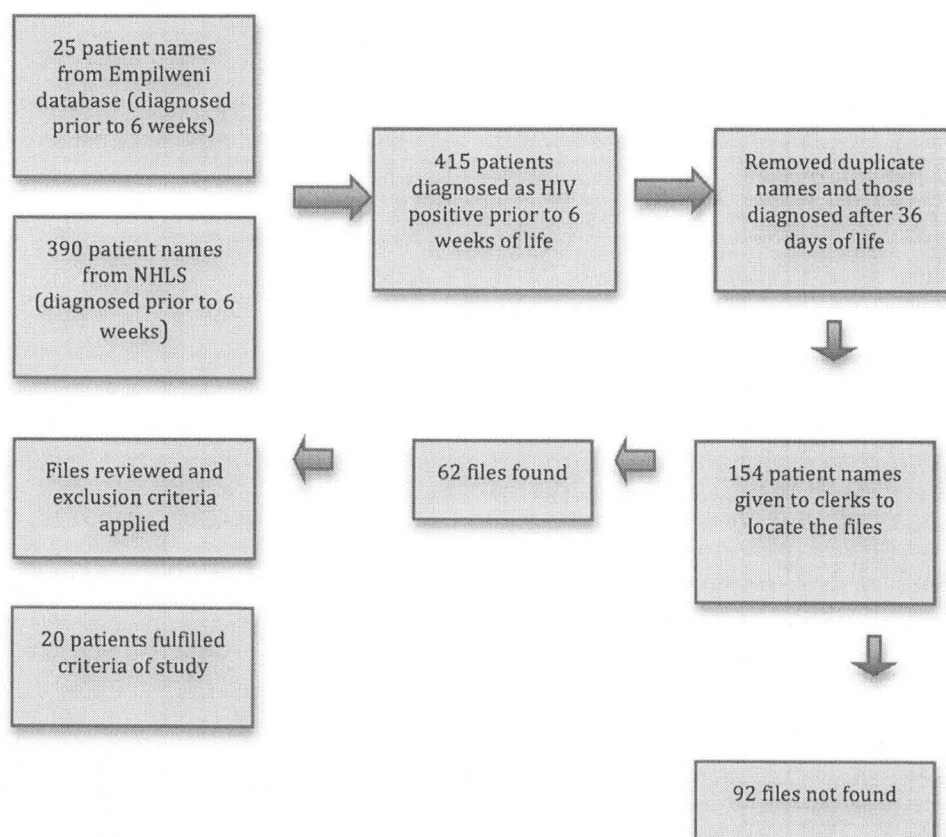


Figure 2.1 The data collection process

Measuring tool or instrument:

The following data elements were abstracted from patient files: Infant age at diagnosis, obstetric and birth history (PMTCT, gestational age, birth weight, type of

delivery) and age at initiation of ART. The course over one year was then reviewed and documented. The following was also documented: mortality, follow up status, CD4 and VL, weight and length measures for the first year of follow up.

Information was taken from the hospital notes. Adverse events were documented. Weight, height and weight for height Z-scores were calculated from the documented weights and heights in the patients' files. If patients had been lost to follow up, it was reflected in the follow up status.

Once all data was obtained it was entered onto the RedCap (Research Electronic Data Capture) database, which is a secure, web-based application [23]. It was accessed through the WITS website. Data can be entered onto this system and then reviewed in different formats highlighting specifically requested aspects.

2.5 Statistical analysis

Normally distributed continuous data was reported as a mean, while non-normally distributed continuous data was reported as a median and interquartile range (IQR) [or range]. Categorical data was described using frequencies and percentages. Analyses were performed using REDCAP.

2.6 Ethics and institutional approval

An approval from the Ethics committee was required to gain access to the NHLS blood results from 2004-2013 for positive PCR tests, following which an application was made to the NHLS (Appendix A). No identifying details were used to document data from the files. Age at diagnosis and age at treatment initiation rather than date of birth was used. Year of birth was recorded. No data was collected prior to ethics approval.

Prior to ethics approval, approval was received from the hospital medical superintendent and from the gatekeeper of Empilweni HIV treatment clinic (Sr A Jordan – Appendix B).

Empilweni Clinic has an existing approval for the analysis of routinely collected data (M090501 – Appendix D). All patients and their caregivers are routinely invited to sign a consent allowing the use of anonymous data for analysis pending ethics approval (Appendix E). This consent form was introduced in 2007 and there is a system in place in the clinic to ensure that all patients/parents are invited to participate. Those caregivers who have specifically declined their contribution were automatically excluded. This study was a retrospective review so no informed consent was requested from patients additional to the consent mentioned above.

The data capturing form did not contain any patient identifiers e.g. the patients name or date of birth but only a study number assigned specifically for this review. Only the principal investigator (Dr Goossens) had access to a list that links names with study numbers. This was to ensure confidentiality. From then on the study number was used as a means to identify the patient.

The Ethics committee reviewed the above documentation and study protocol. The Human Research Ethics Committee (Medical) at the University of the Witwatersrand, JHB approved the study on 04/11/2013. (Appendix F)

CHAPTER 3 – RESULTS

Twenty patients (of the 62 files reviewed) fitted the study criteria. The results are outlined below.

The dates of ART initiation of the patients that fitted the study criteria ranged from 12th May 2005 to the 5th June 2013. The dates of birth ranged from April 2005 to May 2013. The majority of infants in this study (70%) were born in or after 2010.

3.1 Baseline characteristics

The patient characteristics before and after initiation of ART were reviewed. A portion of the data was unable to be captured due to inadequate recording keeping or missing files. This is highlighted in the text below. The baseline characteristics that were reviewed were gestational age at delivery, birth weight, mode of delivery, maternal age at delivery as well as PMTCT and the adequacy of it. Table 3.1 documents the results of these baseline characteristics.

Table 3.1: Baseline characteristics prior to initiation of ART

Characteristic	All (N=20)
Sex, N (%)	
Male	8 (40 %)
Female	11(55%)
Unknown	1 (5%)
Preterm, N (%)	
Term (>37 weeks)	5 (25)
Preterm	12 (60)
Unknown	3 (15)
Birth Weight (g), Mean	1931
Birth Weight, N (%)	
<2500	13 (76.5%)
≥2500	4 (23.5%)
Unknown	3 (15%)
Gestational Age (weeks), Range	27.0, 36.0
Gestational Age (weeks), Median (IQR)	29.5 (28.0, 35.0)

Mode of Delivery, N (%)		
NVD		7 (43.8%)
C/Section		9 (56.3%)
Unknown		4 (20%)
Maternal Age at Delivery (years), Mean $\pm$ SD		29.9 $\pm$ 5.6
Maternal CD4 Count (cells/mm ³), Mean $\pm$ SD		294 $\pm$ 191
Maternal PMTCT		
No Treatment		6 (32%)
Adequate		3 (16%)
Inadequate		4 (21%)
Not Documented		7 (35%)
Baby PMTCT		
No treatment		1 (6%)
NVP		13 (81%)
AZT		2 (13%)
Unknown		4 (20%)
Was PMTCT adequate? [†]		
NO		9 (75.0%)
YES		3 (15.0%)
Unknown		8 (40%)

[†] PMTCT was described as adequate if it was in keeping with the PMTCT guidelines recommended at that specific time

Once the HIV-positive neonates were identified, specific characteristics relating to initiation of treatment were reviewed. The age, weight and VL at initiation of treatment were documented. The treatment regimen that was decided upon was also documented.

3.2 Treatment initiation status/characteristics (post-diagnosis)

Table 3.2.1: Characteristics at Initiation of Treatment

Characteristic		All (N=20)
Age at ART Initiation (days), Range		9.0, 47.0
Age at ART Initiation (days), Median (IQR)		27.0 (20.0, 38.0)
Age at ART Initiation (days), N (%)	≥ 28 days	10 (50.0)
	< 28 days	10 (50.0)

Corrected Gestational age at initiation	≥ 42 weeks	5
	< 42 weeks	11
	Unknown	4
Weight at Initiation (grams), Mean ± SD		2343 ± 1025
Infant CD4 at Initiation (cells/mm ³), Range		42, 2571
Infant CD4 at Initiation (cells/mm ³), Median (IQR)		1120 (268, 2146)
Infant VL at Initiation (copies/mL), Median		83773
Infant VL at Initiation (copies/mL), Range		25, 10 million

One NVP exposed infant had an undetectable viral load pre-treatment at day 16 of life, but the repeat VL was 23 600 copies/mL 1 week later (day 22 of life). ART was initiated at day 27 of life. The VL then decreased to 62 copies/mL by 19 weeks of life.

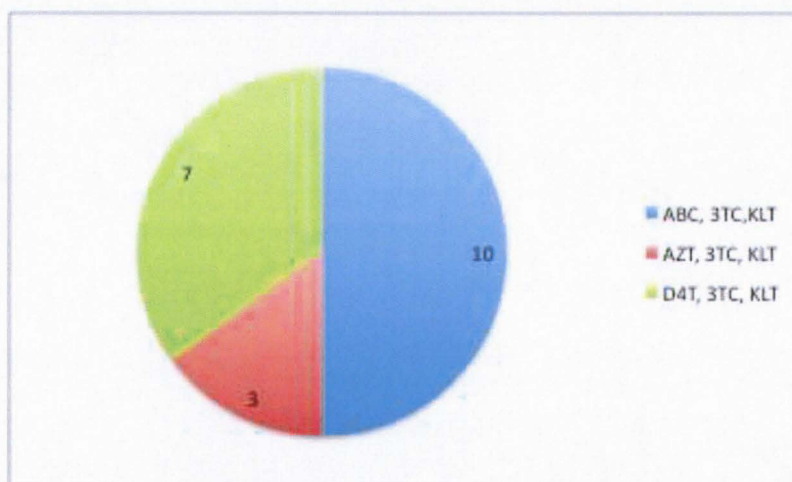


Figure 3.2.2 Antiretroviral regimen initiated

The median age of treatment initiation in our study was 27 days. This equates to a mean gestational age of 31 weeks, this accounts to an average corrected gestational age of 35 weeks.

The patients initiated on the ABC, 3TC and LPV/r regimen were started in the years from February 2010 until 2013. Those initiated on AZT, 3TC and KLT ranged from

December 2011 to May 2013. Those initiated on D4T, 3TC and KLT ranged from April 2005 to February 2011.

Some patients were initiated during their postnatal admission in ward 16B or neonatal ICU. These patients had not been home since birth. Other patients were initiated when they were admitted to the general wards with another condition after being discharged home after delivery. This is shown in Table 3.2.3 below.

Table 3.2.3 Ward/place patient was initiated on ARVS

WHERE INITIATED	NUMBER OF PATIENTS
In post natal ward after birth (Ward16B/NICU)	13 (69%)
When admitted to General Wards from home	4 (21%)
Empilweni Clinic after being discharged home after birth	1 (5%)
Unknown	1 (5%)

The illnesses and problems experienced in the postnatal period in the study group were then documented as noted in Table 3.2.4 below. This was done to note if there were any relevant similarities or common conditions amongst the study sample.

The reason why the majority of the patients in this review were actually diagnosed early was either due to postnatal illness or low birth weight (which enabled them to qualify for earlier HIV testing) Due to this a large amount of patients in this group had postnatal illnesses or low birth weight (LBW).

Table 3.2.4 Problems in the postnatal period

Characteristic	All (N=20)
Anemia	8 (40.0)
Prematurity	7 (35.0)
Mom ill, lodger	2 (10.0)
Thrombocytopenia	6 (30.0)
RDS (respiratory distress syndrome)	5 (25.0)
VLBW	5 (25.0)
LBW	3 (15.0)
Congenital Pneumonia	3 (15.0)

Necrotising enterocolitis (NEC)	2 (10.0)
Congenital syphilis	2 (10.0)
Ventilation	2 (10.0)
Congenital hepatitis	1 (5.0)
Hypoglycemia	1 (5.0)
Cytomegalovirus (CMV)	1 (5.0)
Fungal sepsis	1 (5.0)
ELBW	1 (5.0)
Nosocomial sepsis	1 (5.0)
Patent ductus arteriosus (PDA)	1 (5.0)
Group B Streptococcus meningitis (GBS)	1 (5.0)
No problems	2 (10.0)

One of the patients had perinatal asphyxia and required resuscitation at birth. The patient with confirmed nosocomial sepsis cultured *Klebsiella pneumoniae* which was not an Extended spectrum B-lactamase producing organism. This same patient was treated for fungal sepsis with fluconazole. These drugs were all administered during the time of ART initiation.

Considering the small study size, a large percentage of the patients had a condition that required treatment in the postnatal period, around the time of HIV diagnosis and initiation of treatment.

Both the NEC patients were non-surgical types and they were kept nil per os (NPO) for 3-5 days but they were not on ART yet. Another patient had suspected NEC and was kept NPO for 1 day on day 5 of ART.

The patient with the patent ductus arteriosus (PDA) received 2 doses of ibuprofen whilst on ART. Of significance two of the patients in this study developed chronic lung disease. The polypharmacy experienced during ART initiation is highlighted in Figure 3.2.6 below.

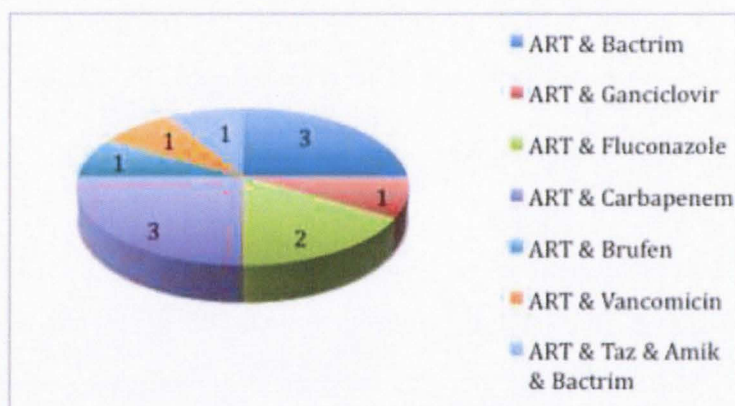


Figure 3.2.5 Drugs required in treating illnesses at the time of ART initiation

3.3 Follow up

Follow up was monitored until the first year of life. Three patients' follow up data were not found at all. It was documented whether the other 17 patients were still in care, transferred out to another facility, lost to follow up or if they demised at the time of this study. This is shown in Table 3.3.1 below.

At each follow up visit the weight, height, CD4 count, VL, treatment given, adherence and any medical problems at the visits were noted.

Table 3.3.1 Follow up status at time of study (whether over 1 year of age or not)

Status	All (N=20)
In follow up care	7 (41.2)
Transferred out	5 (29.4)
Lost to follow up	3 (17.7)
Demised	2 (11.8)
Missing all follow up data	3

3.3.1 In Follow Up Care

Four patients had incomplete follow up data until one year of age. Three of those four had no follow up data. Seven of the 16 patients (43.8%) who had complete follow up data (41.2%) were still in follow up care at the time of review of the files.

Nine of the 16 patients with complete data were not followed up to one year (Table 3.3.2) because of the following reasons:

One had not reached one year by the time of file review. Four were lost to follow up, one of whom never returned after initiation, the other three attended follow up visits before becoming lost to follow up. Two patients were transferred out before one year completed. Two patients demised prior to one year of age.

Table 3.3.2 Adequacy of Follow up

Adequate follow up to one year?	All (N=20)
Yes	7 (43.8)
No	9 (56.3)
Missing up to date data until one year	4

3.3.2 Lost to Follow up

Four (25%) of the 16 patients with complete follow up records were lost to follow up.

3.3.3 Transfer

Four patients at the time of the review had been transferred out to other facilities for follow up. Two were transferred out after a year, one to Witkoppen Clinic (at 12 months) and the other to Kwa Zulu Natal (at 13 months). The other two patients were transferred out at 19 weeks and 24 weeks to Limpopo and Kwa Zulu Natal respectively.

3.3.4 Deaths

Two (10%) of the patients in the study demised and case study reviews on the two deaths are presented to highlight pertinent findings from each patient.

Case 1

The first case was a female infant who was delivered at term via NVD (normal vaginal delivery) with a birth weight of 2780g in November 2012. She had normal APGAR scores. The mother was diagnosed as having HIV prior to the pregnancy and was on ARV treatment four years prior to conception. There was no documentation of the mother's most recent VL or CD4 count. The baby received NVP for four weeks postnatally. She was exclusively breastfed.

The infant was initiated on ART in the main wards at RMMCH at 28 days of life. There is no documentation as to why she was admitted. Her weight at initiation was 2.9kg. She was started on ABC, 3TC and LPV/r. She had poor weight gain and a dietician was consulted.

She had three follow up visits at 10, 19 and 32 weeks. At the 10 week visit she was started on co-trimoxazole and INH prophylaxis as her mother had been on TB treatment for three months. At her visit at 32 weeks she had no adverse effects of treatment but had a suppurative otitis media. This was the last follow up appointment she attended.

Table 3.3.2A – Case 1: VL trend during follow up

Chronological Age	Time VL tested relating to ART initiation	VL (copies/mL)
3 weeks	3 days prior	4 936 335
28 weeks	24 weeks later	7 592 199

She was admitted to the ward at 5 months of age for acute gastroenteritis. A tuberculosis (TB) workup was performed, she was not started on TB treatment. She had just completed 6 months of INH prophylaxis. The gastric washings that were sent for TB workup came back as positive for acid fast bacilli (AFB). This report

only came out after her demise. We were unable to find the final culture and DST results

Her persistently high viral load would suggest that there was non-adherence to ART as well as to INH prophylaxis. Resistance (both to HIV and TB) may have been a problem but is less likely. The patient demised on July 2013. The information that she had died was acquired telephonically from her mother and no further details were given.

In summary she was a term infant with presumed inadequate PMTCT who was initiated on ART at 28 days of life. She was never virally suppressed and adherence with treatment was questionable. She demised at seven months of age of TB disease which was only diagnosed posthumously and therefore never treated.

Case 2

The second case was a female infant who was delivered at 35 weeks gestational age (GA). She weighed 1620g. It was a breech delivery with cord prolapse. The APGAR scores were 7,8 and 10 at 1, 5 and 10 minutes. No resuscitation was required at birth. She was admitted to the postnatal ward (ward 16B) due to the low birth weight as well as mild respiratory distress.

The mother was not on treatment for HIV prior to the baby being initiated on treatment. The mother's CD4 count was 43 cells/mm³ whilst the baby was in the ward. The baby received stat doses of NVP and AZT. She was formula fed only on day 2 of life but thereafter she was exclusively breastfed.

She was treated with 7 days of Penicillin G and Gentamicin due to the diagnosis of congenital pneumonia. She had thrombocytopenia with her platelets initially 87 x 10⁹/L on day 1 of life. The platelets continued to decrease to a low of 49 x 10⁹/L on day 4 of life.

She was initiated on ART on the 12th day of life, 36 weeks PMA, with a weight of 1445g on ABC, 3TC and LPV/r .

The thrombocytopenia resolved once ARVs were initiated. She had a normal cranial ultrasound and her work up for CMV (done due to the thrombocytopenia) was negative too. Her weight gain was adequate prior to discharge.

Table 3.3.2B – Case 2: VL trend during follow up

Chronological age	Time VL tested relating to ART initiation	VL (copies/mL)
12 Days	1 day prior to	52 000
13 weeks	11 weeks later	1 600

The first and second follow up visits at nine and 13 weeks respectively were uneventful, and her weight was improving, and drug doses were increased according to her weight. At the third visit at 16 weeks she presented with an oral candidal infection. On her fourth and final visit at 24 weeks of age she still had candidiasis and had a history of two weeks of diarrhea, which had subsequently resolved. Her WHO z-scores were -0.9 and -0.13 for weight for age and weight for length respectively.

She never arrived for her next follow up date and when her mother was contacted telephonically it was found that she had demised a month after her last visit to Empilweni Clinic. No cause of death was documented.

She was classified as WHO stage 3 and her VL was improving (Table 3.3.2B) but she was not virologically suppressed before her demise at six months of life.

3.4 Resistance Testing

Three patients underwent testing for resistance. They were tested because they were not showing a virological response to their treatment. The cases are discussed below to assess if there are any similarities amongst the cases.

Case 1:

This male infant was delivered prematurely via a caesarian section (C/S) at 30 weeks GA and weighed 2070 grams. The baby received 7 days of NVP. The mother had not received treatment prior to delivery. This baby was initiated on ABC, 3TC and LPV/r and was exclusively breastfed. He received treatment for PCP at 5 weeks of life. He was not virally suppressed on his treatment; he had a high VL of 92 490 by 13 months (Table 3.4.1).

Table 3.4.1 Case 1: VL trend from time of initiation and follow up visits

Age	5 weeks	18 weeks	27 weeks	32 weeks	44 weeks	13 months
Viral Load (copies/mL)	4 100 000	790 000	190 000	120 000	150 000	92 490

The first drug resistance testing was conducted at one year one month of age. It showed no drug resistance and was repeated again six months later. The second resistance testing was done due to a VL of 13 208 copies/ml and it showed resistance to Nelfinavir. He was admitted at this age for failure to thrive and his mother also reported vomiting after medicine. The regimen was then changed from ABC, 3TC and LPV/r to d4T, 3TC and EFV. The patient was still in follow up care at the time of the review.

Case 2:

This infant was born before arrival (BBA) via a NVD prematurely but no gestational age was documented. The baby weighed 1500 grams. There was no documentation pertaining to the PMTCT. It is uncertain whether NVP was received or not. At 33 days of life the baby was initiated on d4T, 3TC and LPV/r. The baby was exclusively formula fed. The VL was 20 000 copies/mL prior to resistance testing (Table 3.4.2). The resistance testing at 11 months (45 weeks) was negative and the patient was noted to have developed lipodystrophy by 11 months of age.

Table 3.4.2 Case 2: VL trend from time of initiation and follow up visits

Age	12 weeks	18 weeks	50 weeks	18 months	22 months	51 months
Viral Load (copies/mL)	330 000	29 000	20 000	5 300	2 100	279

At 50 weeks of age the regimen was changed to AZT, 3TC and LPV/r in view of the lipodystrophy. This patient was then transferred out to another facility for follow up and it is unknown whether the patient became virologically suppressed or not on the new regimen.

Case 3:

This patient was delivered via a C/S prematurely at 28 weeks GA and weighed 1170 grams. The mother received no PMTCT but the baby received nine days of NVP. This baby was initiated on AZT, 3TC and LPV/r at day nine of life. She was exclusively breastfed. There is no record of the VL prior to resistance testing which showed resistance to NVP/EFV. This resistance testing was conducted at two weeks of life. It showed high-level resistance for EFV as well as high-level resistance for NVP. The regimen was not changed, as the patient was not on a NVP based regimen. The patient was then lost to follow up.

Table 3.4.3 Case 3: VL trend from time of initiation and follow up visits

Age	1 week	6 weeks	28 weeks
VL (copies/mL)	66 085	1295	265

In summary, three patients underwent resistance testing and of those, two had positive resistance test results but not to antiretrovirals that they were currently prescribed. It is unknown whether they became virologically suppressed later, as the one was not followed up for reasons stated above and the other one needed a repeat VL (which had not been done yet at the time of this review) to review the outcome.

3.5 Adverse Events

3.5.1 Readmissions

The amount of times a patient was admitted to hospital after their initial diagnosis was documented. Nine out of 16 (56%) patients (who had complete records) were readmitted. Three of these nine patients were initiated in the main wards (after being discharged after delivery) but still readmitted after that again. The other six were initiated in the postnatal ward and then readmitted at a later stage. As seen earlier, in Table 3.2.3, four patients were initially initiated when admitted to the main wards, after a period of being home postnatally. One of these four patients was therefore not readmitted again after being initiated. Four out of 20 (20%) patients had incomplete records to comment on readmissions. Seven of the patients were readmitted once, one was admitted twice and another readmitted three times. This comes to a total of twelve readmissions for nine patients.

The patient who had the most admissions was diagnosed as HIV-positive on her first admission. She had meningitis and was treated for PCP on her first admission. CMV treatment was initiated but stopped once the CMV result came back as negative. The other two admissions were for bronchiolitis and bronchopneumonia. She was initiated on ABC, 3TC and LPV/r. She was exclusively formula fed and at the time of the review was still in follow up care.

Table 3.5.1 Reasons for patient readmissions

Diagnosis	Number (percentage of 12 readmission episodes)
Bronchopneumonia	4 (33%)
Bronchiolitis	2 (16%)
Acute gastroenteritis	1 (8%)
Malnutrition	1 (8%)
Meningitis	1 (8%)
PCP	1 (8%)

Two of the patients who were readmitted did not have the reason for admission or the diagnosis documented. None of the patients who were readmitted had confirmed CMV. The patient with CMV was one of the patients who was treated on the first

admission. The patient who had severe acute malnutrition (SAM) initially had a weight for height z-score of -1.48 at the last visit. This same patient had lipodystrophy and was not virally suppressed. Resistance testing was negative. Treatment adherence was questionable in this patient.

3.5.2 Lipodystrophy

Two of the patients in this study developed lipodystrophy. It developed at 11 months of age in a patient who was initiated on 3TC, d4T and LPV/r. The regimen was then changed to AZT, 3TC and LPV/r. This patient was transferred out and was no longer in follow up care at RMMCH. The other patient was also initially on d4T, 3TC, LPV/r and was reported to have developed lipodystrophy at three years of age. Follow up in this study was only until one year of age but it was noted in the records of the file. Once the lipodystrophy was noted the regimen was changed to ABC, 3TC and LPV/r.

3.5.3 Cardiac toxicity

There was a concern regarding cardiac toxicity three weeks after ART initiation with one of the patients who was initiated on day eight of life on AZT, 3TC and LPV/r. The notes state “? cardiac toxicity” and it was not documented as to why it was questioned. An electrocardiograph was done and a cardiologist reviewed the patient and conducted an echocardiogram. Cardiac toxicity was excluded and LPV/r was continued. This was the same patient who had severe perinatal asphyxia. This patient was last seen at 39 weeks of life and was lost to follow up thereafter.

3.6 Follow up VL / CD4 / Weight / Height

The first VL documented once ART had been initiated varied depending on patient, adherence and length of time on treatment. There were eight patients whose first repeat VL was <500 copies/mL and there were five patients whose VL were > 500 copies/mL. Seven of the patients had missing documented information. This is shown in Table 3.6.1 below.

Of the five patients who had a VL > 500 copies/mL, four were on ABC, 3TC and LPV/r. Of those four patients, two demised and one's repeat VL later decreased to 38 copies/mL. The other patient whose VL was >500 copies/mL after initiation that was not on the above regimen but on the 3TC, D4T and LPV/r regimen. This patient developed lipodystrophy and had problems with adherence to treatment; resistance testing was negative.

Table 3.6.1 – Virological responses, regimens and important clinical factors

Patient	Important Factor	First VL	VL - Once on treatment (age in weeks or year tested)	Latest VL (age in weeks or year tested)	Last visit weight for height z -score	Regimen
1		3340	583	58 (28 wks)	1.75	3tc, ABC, LPV/r
2		4 100000	790 000	13 208 (3yrs)	-1.73	ABC, 3TC, LPV/r, resistance so changed to D4T, 3TC, LPV/r at 3 years 5 months
3		?	62	LDL (44 wks)	-1.35	3TC, AZT, LPV/r
4		77 545	68	LDL (44 wks)	0.92	AZT, 3TC, LPV/r
5		?	260	260 (24 wks) LDL(4yrs)	1.51	D4T, 3TC, LPV/r, lipodystrophy so changed D4T to ABC
6	Congenital Syphilis	1255	328	328 (40 wks)	0.64	AZT, 3TC, LPV/r
7	Demised AFB +ve	4 936 335 (8 wks)	7 592 199 (24 wks)	7 592 199 (24 wks)	-3.18	ABC, 3TC, LPV/r
8		6 960 (3 wks)	352 (10 wks)	73 (38 wks)	-0.19	ABC, 3TC, LPV/r
9	CMV	330 000 (14 wks)	29 000 (18 wks) ? drug adherence problems	20 000 (50 wks) after changing to AZT VL= 279	-2.0	3TC, D4T, LPV/r changed due to lipodystrophy AZT, 3TC, LPV/r
10		?	320 (11 wks)	LDL (34 wks)	-0.72	ABC, 3TC, LPV/r
11	Demised	52 000 (1 wks)	1 600 (13 wks)	1 600	-0.58	ABC, 3TC, LPV/r
12	? NEC Severe perinatal asphyxia, lost to follow up	66 085	1295 (10 wks)	265 (39 wks)	-3.14	ABC, 3TC, LPV/r
13	Lost to follow up	4 000 000 (5 wks)	?	?	-1.35	3TC, d4T, LPV/r
14	Transfer	?	750 000 (14 wks)	?	3.65	3TC,d4T, LPV/r

	out					
15	PCP Transfer out	860 000 (5 wks)	210 (25 wks)	LDL (3yrs)	-1.84	3TC, d4T, LPV/r
16	Congenital Syphilis, awaiting f/u	?	?	?		ABC, 3TC, LPV/r
17		2 000 000	?	?	?	ABC, 3TC, LPV/r
18	Thrombocyt openia Congenital hepatitis	950 000 (3 wks)				3TC, d4T, LPV/r
19		90 000 (6 wks)	?	?	?	3TC, d4T, LPV/r
20	Congenital pneumonia, CLD	10 000000 (4 wks)	?	?	0.3	3TC, ABC, LPV/r

At the most recent follow up the WHO weight for height z-score was documented according to the WHO growth charts. Both of the patients with SAM had virological failure.

One patient had moderate acute malnutrition and was not virologically suppressed. This patient had adherence issues and developed lipodystrophy and had no evidence of resistance on testing.

3.6.1 Viral Suppression

Seven patients showed viral suppression (VL < 100copies/mL) at their most recent visit. Five of these seven patients were suppressed within the one-year follow up period. Six patients were not virologically suppressed. Seven patients had inadequate records or missing information to comment on viral suppression (due to factors such as loss to follow up, death or being transferred out).

CHAPTER 4 – DISCUSSION

With movement towards early diagnosis and treatment of HIV, many factors need to be taken into consideration. Although only a small number of patients (twenty) fitted the study criteria this study highlights the factors that could be problematic with early initiation of treatment. It also shows the benefits of early treatment.

A study conducted by Innes and Lazarus et al in Cape Town and Soweto, was published in 2014, where they reviewed patients initiated on treatment prior to three months of age. In this study there were also only a small number of infants (only 22 (5% of their sample size) that were initiated on ART prior to six weeks of age. Nine of their patients had advanced HIV disease at ART initiation, showing that early disease progresses rapidly and reiterating the need for early treatment. The number of infants initiating ART before six weeks of age was too small to allow meaningful stratification [24]. Our study only had a small sample size therefore a descriptive retrospective review was conducted.

The fact that a small number of patients were eligible showed that not many neonates were initiated early due to the guidelines at that time. Many of the neonates in our study had comorbid conditions, which are related to HIV, again showing the benefit of early treatment, to have better outcomes. The number of patients fulfilling the study criteria and being treated in each year ranged from one in 2003 to six in 2010 and four in 2012. This has significance in that the recommended regimens as well as PMTCT guidelines varied across the years. It was noted that neonatal initiations were more common from 2010 onwards; this may be related to guideline changes and also to increased awareness and testing which helped us to identify the babies.

4.1 Pretreatment/Baseline Characteristics

A review of the characteristics led to the formulation of similarities between study subjects being brought to the forefront. Certain pre-treatment characteristics such as

inadequate PMTCT, prematurity, low birth weight, thrombocytopenia, anemia and renal dysfunction were noted.

4.1.1 Sex

It was a female predominance in our study which could be purely due to chance due to the small sample size. In the study done by Innes and Lazarus et al, mentioned above, there was no significant gender difference among those with advanced HIV disease or among those initiating ART in an optimal state ($p=0.11$ for both) [24].

4.1.2 Birth weight and gestational age

The review consisted of a large number of LBW neonates. A patient is considered to be LBW if the weight is less than 2500 grams [25]. Guidelines during the period of this study allowed for early testing of LBW or ill infants. This could be a reason for the high number of LBW infants in the study (76.5%). It could also be due to the higher risk for progression, or if an infant is infected intrauterine it may lead to premature births.

Cotton et al also mention the fact that prematurity could also be as a result of other intrauterine infections for example syphilis and TB [25]. In this study two patients were treated for congenital syphilis and one for CMV and all three of them were LBW infants.

A study done in Botswana on HIV infected pregnant woman also showed that maternal ART during pregnancy was associated with increased premature delivery, SGA and stillbirths [26]. In this study only three mothers received adequate PMTCT therefore not many of them were on adequate ART during pregnancy and therefore this effect of maternal ART on LBW is not reflective. In 2010 an audit of HIV-exposed preterm infants at a neonatal unit in Cape Town showed that 3.3% of the HIV-exposed infants had a birth weight below 1000 g (extreme low birth weight)[27].

LBW infants have different co morbidities to appropriate for gestational age (AGA) infants. Infants less than 32 weeks of age are more prone to develop respiratory

distress syndrome (RDS), NEC and other infections due to the immaturity of their lungs and immune systems respectively. These are important aspects to consider as NEC for example requires a patient to be nil per mouth, which could be problematic once ART has been initiated as it would cause a period of missed treatment which could be a potential risk for resistance or poor control.

4.1.3 Maternal Factors

Only three patients' mothers received adequate maternal PMTCT according to the guidelines at the time. The average CD4 count of mothers in our review was 294 cells/mm³. Guidelines at that stage recommended maternal treatment with full ART for CD4 counts of less than 250 cells/mm³ [28;29].

The average maternal age at delivery of 30 years could be beneficial for compliance of the infants' treatment. Younger mothers may not be as adherent as older mothers.

4.1.4 PMTCT

Our study showed inadequate PMTCT. Only three out of 20 patients received adequate PMTCT. This group of infants was therefore at a high risk for acquiring HIV. Infants that could especially benefit from both enhanced prophylaxis and early diagnosis are those whose mothers either seroconverted late in pregnancy or had not attained viral suppression on ART.

The PMTCT guidelines changed a number of times in the duration of 2004-2013. PMTCT was gauged as being adequate or not taking into consideration the time period at which the PMTCT was prescribed. If it matched guidelines at the time it was prescribed it was recorded as being adequate. Only three out of 20 patients received adequate PMTCT. This included the maternal as well as neonatal component of PMTCT. When deciding if PMTCT was "completely" adequate or not, eight out of 20 patients had either no record of PMTCT or it was documented in the file as being unknown or perhaps the baby received NVP/AZT but the mothers' history of AZT or ART had not been documented or vice versa.

In this study the problem seemed to lie more with the implementation of the antenatal component of the PMTCT guidelines as six out of 20 documented cases of mothers did not receive PMTCT whereas only one out of 20 neonates were documented as not receiving PMTCT. This could be due to many reasons such as, if the mothers presented to an antenatal clinic (ANC) late, were unbooked, were not correctly managed by the ANC or if they had a BBA or if they did not adhere to their treatment.

The PROMISE (Promoting Maternal-Infant Survival Everywhere) study showed significantly decreased HIV transmission in infants of mothers with high CD4 counts who received triple ART during pregnancy compared to infants whose mothers only received zidovudine and NVP at delivery.[30]

With moves towards earlier and better treatment of mothers infected by HIV, the necessity of infant ART may significantly diminish. The numbers of infants infected with HIV via vertical transmission should approach zero with adequate PMTCT. The importance of adequate and appropriate treatment of the infants that are diagnosed early is crucial. With the new guidelines of early testing these numbers are likely to increase. We need to know what complications to look out for and what doses of treatment to use if we are going to make the new guideline recommending early testing a worthwhile and beneficial step in managing HIV. As the costs of early testing may be significantly more, the benefits of hospital expenses for rapid progressors and treatment costs of comorbid opportunistic infections may be diminished.

Diagnosis can be tricky in the presence of PMTCT especially if the neonate has been given six weeks of NVP [22]. Resistance to NVP or AZT based regimens may also become problematic if later diagnosis is made. In the Ban study 56% of infants who became infected after being on NVP prophylaxis had NVP resistance. Other studies such as the SWEN study and PEPI-Malawi study have found even higher rates of resistance to NVP after an infant has been on NVP prophylaxis. [31]

Previous studies have shown that the HIV viral load after exposure to NVP prophylaxis decreases and this may hamper diagnosis and lead to falsely negative PCR results in infected children. (13)

4.2 Treatment initiation status/characteristics (post-diagnosis)

The median age of ART initiation in the study group was 27 days. The VL pre-ART ranged from 25 to 10 000 000 copies/ml. One NVP-exposed infant had an undetectable VL immediately pre-ART even though HIV was confirmed virologically in prior and later tests.

4.2.1 Initiation of treatment

The illnesses and age at the initiation of treatment are very important. The median age of initiation was 27 days. One patient in the study is outside of 42 days (>6 weeks of life). This patient was in the sixth week of life (47 days old) and still added to the study due to the small sample size. The median treatment initiation age of twenty-seven days is much earlier than the recent practice. Previously neonates were tested at six weeks and only initiated on ART at approximately ten weeks of age at the soonest. The youngest age at initiation was nine days. The recent guidelines pertaining to birth PCR's [10] will allow for even earlier initiation than nine days of life. With the move towards this early diagnosis and treatment the results of this study are describing some of the outcomes of this select group of neonates. Reviewing the outcome of these neonates is of importance as we need to know the benefits as well as the risks of early initiation of treatment.

4.2.2 Regimen

ABC, 3TC and LPV/r was the regimen most commonly initiated in this study. Neonates and premature infants at our hospital were often started on LPV/r despite not being a PMA of greater than 42 weeks. It is important to describe outcomes in these patients due to Kaletra's black box warning [17]. The mean age of treatment initiation in our study was 27 days. This equates to a mean gestational age of 31

weeks, this accounts to an average corrected gestational age of 35 weeks, which is less than the recommended safe age for KLT use of 42 weeks PMA.

Despite the South African (SA) ARV treatment guidelines recommendation that ABC should be used in all first-line ART regimens for children, there is insufficient safety data to recommend the use of ABC in infants less than three months old [10].

No regimen contained NVP. The majority of the babies in this study had a course of NVP as prophylaxis. The NVP was stopped at the time of diagnosis as ART was initiated. These babies could have acquired NVP resistance mutations. A regimen containing NVP may not be as effective and increase the risk of treatment failure but none of the ART regimens initiated contained NVP, so this could not be assessed in this review.

4.2.3 Coinciding postnatal problems

Fourty percent of the patients in our study had anemia. This is a concern when AZT is used in the treatment regimen as it has hematological toxicity and therefore AZT is usually switched to ABC at four weeks of age if the infant weighs 3kg or more.

Six of the patients had thrombocytopenia, which may be directly related to HIV. HIV-associated thrombocytopenia is mostly due to immune-mediated destruction of platelets or due to a defect in bone marrow production [21]. In children with advanced HIV disease, other causes of thrombocytopenia, such as opportunistic infections, medication side effects, and infiltrative malignancies, are more likely. Congenital infections can also cause thrombocytopenia. Medications most commonly used in patients with HIV which are associated with thrombocytopenia include ganciclovir (48%), pentamidine (18%), and trimethoprim-sulfamethoxazole (3%). Rifabutin, clarithromycin, zidovudine, and didanosine are less commonly associated with thrombocytopenia[32,21]. In this study ganciclovir, Ddi, AZT as well as trimethoprim were used.

Fourteen out of 20 patients had an illness or infection requiring treatment. The children in this study may have been ill because they were premature and ill and subsequently HIV was tested early and therefore a coincidental finding. Another

reason may be that these neonates are ill and in hospital because they are HIV positive at an early age and prone to infections due to lower immune function.

The majority of the patients were LBW which is in keeping with the higher numbers of prematurity. Thirteen out of 20 patients were less than 2500g and 12 out of 20 were premature with three unknown gestational age. One patient had a PDA, two had NEC and five had RDS, these are complications often associated with premature infants.

An important finding of the study shows that infants initiated less than six weeks of life had various serious co-morbidities. Therefore, antiretroviral treatment as well as the treatment of these illnesses may lead to polypharmacy. Treatment may also be interrupted with certain illnesses i.e. NEC kept *nil per os*. Co-morbidities including liver dysfunction and anemia may need flexibility with regimen choice. Monitoring their outcomes is complicated. Monitoring renal clearance and liver metabolism of Ganciclovir, Vancomycin and Gentamicin is important. Congenital infections and other illnesses requiring treatment (n=14) prior to or during the period of ART initiation were noted. Illnesses requiring treatment at the time of the HIV diagnosis were: NEC (n=2), congenital hepatitis (n=1), congenital pneumonia (n=3), congenital syphilis (n=2), CMV (n=2), PCP (n=2), TB (n=2) and GBS meningitis (n=1). These illnesses led to polypharmacy at the time of ART initiation.

Further research is required to describe the range of co-infections and co-morbidities in HIV-infected neonates presenting prior to six weeks of age. Initiating ART early may compound polypharmacy, as in this study, while some illnesses (i.e. PCP) may potentially be reduced.

4.3. Follow up

Four patients were lost to follow up. There are difficulties around neonatal ART initiation. Initiation of ART often took place at the institution where the baby was delivered. This central ART initiation may lead to difficulties for follow-up due to increased distances from home. There is a need to transfer out to more convenient sites for the mother, but this means that follow-up is harder to track in this group

although ideally, they are vulnerable and actually ideally would need continued central monitoring given that we know so little about their outcomes. In an analysis of routine data of greater than 13,000 children from Sub Saharan Africa and Asia, loss to follow-up (LTFU) by 18 months after ART initiation was higher in Sub Saharan Africa, ranging from 9.0% in Southern Africa to 21.8% in West Africa [32]. In addition to disease severity and young age, requirement to pay for services or medication as well as larger clinic size were associated with higher LTFU [33].

4.4 Adverse events

4.4.1 Deaths

Both of the patients that demised were not virologically suppressed. One had adequate PMTCT and the other did not. It cannot be said if any of the patients lost to follow up had demised, so this needs to be taken into consideration too.

4.4.2 Side effects

None of the neonates initiated on ARVs had significant side effects of LPV/r. In our study the most popular dosing formulation used was – ABC 3TC and LPV/r. With an average corrected gestational age of and the US HIV guidelines recommend that KLT should not be used before a post-menstrual age of 42 weeks, and a postnatal age of at least 14 days. It is only registered for use by US FDA in children of three months of age and older. No adverse effects of LPV/r or ABC were noted in this study even though the median age of treatment initiation in our study was 27 days. The mean gestational age of 31 weeks, accounts to an average corrected gestational age of 35 weeks. KLT is only recommended PMA of 42 weeks. KLT was initiated on all twenty patients in this study and a considerable number were less than the recommended PMA and no adverse effects until 1 year of age were noted. There was only a concern about cardiac toxicity in one patient. This patient was seen by a cardiologist and was confirmed as having no cardiac involvement and was said to have a normal heart, with normal function.

If we had a larger sample size, findings may have been different. The only adverse drug effect that was evident in this review was that of lipodystrophy. It was noted in

two patients that were initiated on d4T containing regimens. The d4T was changed AZT.

4.5 Viral Suppression

Sustained virologic suppression, especially from early infancy, is associated with better neurocognitive and growth outcomes as well as reduced viral reservoirs. Recent systematic reviews of mostly research cohorts suggest that viral failure is higher in children than adults [34,35]. The same review noted that 90% of children who had failed therapy had at least one resistance mutation, with 76% of children developing resistance within a year of failure. Even in children on lopinavir-based first-line with a high genetic barrier to resistance, 11% had lopinavir mutations [33]. This resistance to LPV/r, mentioned above, was not seen in our study.

4.6 Resistance

No patients were initiated on a NVP containing regimen and only three were initiated on an AZT containing regimen. Three patients underwent resistance testing due to a poor virological response to treatment. Two of the cases were on AZT based regimens and the other on ABC, 3TC and LPV/r. None of the patients were documented as having received AZT in the neonatal period as part of PMTCT. No cases of resistance to LPV/r were found. The resistance findings do not support drug resistance as a cause of poor virological suppression, therefore correct adherence should be supported and emphasized. Particularly adherence to the bitter tasting KLT syrup may be an underestimated problem.

4.7 Limitations

Without early diagnosis at the time of this study, many infants may have been missed and may have demised. This could have led to selection bias. A large proportion of neonates in the study were LBW (which was an indication for testing especially in the context of co-morbidity). Further research is needed to describe the range of co-morbidities and infections in AGA, SGA and premature infants.

All efforts were made to ensure that a representative sample was collected. The study aimed to identify all infants started on ART before six weeks of life at RMMCH. Patients may be lost to follow up and the reason for this may not be known, the patient may have demised and an accurate representation on the percentage of deaths may be skewed.

There were a large number of missing files that could not be retrieved from the records. 92 (59.7%) files were not found. The reasoning was that if a file had not been used within a five-year period it was discarded due to a shortage of space in the filing department. This may not show a true representation of the patients that will be diagnosed early in other institutions, as the study sample size is small.

There were various PMTCT guidelines throughout the period of testing and treating in the population sample. This could have led to different outcomes in the risk of transmission, as guidelines improved over time.

4.8. Conclusion

The largest gaps in the diagnosis and treatment of HIV remain in infants, children and adolescents. There has been an improvement in early infant diagnostic services. Despite this, in 2014, only half of HIV-exposed infants received a test before two months of age in twenty-two Global Plan priority countries [33].

In the absence of treatment, perinatally HIV-infected infants experience extraordinarily high mortality, which can be reduced by 75% with immediate ART in children less than three months of age [34]. This is undoubtedly the strongest evidence for the urgency of paediatric ART and immediate treatment of infants must be a priority [33]. There is no randomized controlled trial evidence of the benefit of starting ART within the first few weeks of life as addressed by Cotton *et al.*

Although our study had a small sample size it provides an important opportunity to review past cases. This aids in improving the monitoring and recording going forward with other cases. To achieve better outcomes, we would recommend the following:

1. An increase in awareness and the quality of antenatal care for HIV-infected women.
2. Development of guidelines for early ART initiation in neonates and standardized testing and follow up procedures.
3. Increased awareness and improved record keeping with collation of data countrywide, to ensure adequate sample sizes for drawing conclusions.

APPENDICES

APPENDIX A – NHLS Form

Q-Pulse5/docs/active/FMI0069v3

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NATIONAL HEALTH LABORATORY SERVICE HELPDESK
Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk1@nhls.ac.za

APPLICATION FOR DATA FROM NHLS INFORMATION SYSTEMS (Q-Pulse FMI0069)

Each application will be approved or rejected subject to the ability to extract this data and the availability of the data, and subject to the intended usage of the requested data. Applications that are incomplete and/or do not contain supporting documentation, will be rejected.

APPLICANT'S DETAILS

Applicant Name	DR CARICE OUSSENG	Tel No	(076) 941 9593	Email	info@carice.co.za
Business Role / Designation	PEDIATRIC REGISTRAR				
Laboratory / Department / Branch / Region (Internal applicants)	/				
Organisation (External applicants)	KAPPA MOUNTAIN TREC AND CHILD HOSPITAL				
Supervisor Name	DR KARL TEKMAN	Tel No	(011) 687 3633	Email	karltekman@gmail.com
Supervisor Designation	SENIOR MEDICAL OFFICER				

CONDITIONS

- Data / Information is not to be used in contravention of Sections 14, 15, 16 and 17 of the National Health Act 61 of 2004 and the Promotions of Access to information Act 2 of 2000.
- The applicant undertakes to ensure that the data supplied to it by the NHLS is used ethically and solely for the purposes for which it is provided as detailed in this application, and further acknowledges that it shall remain liable for any breaches of this clause by the end user.
- If the purpose for the data requested in this application is research or if patient identity linked data is required, ethics approval and a one page summary of the protocol shall be attached to this application form. It is the responsibility of the applicant to ensure that their institutions's Human Ethics approval includes explicit authorisation to access the requested NHLS data.
- The applicant undertakes to store the NHLS data in a confidential manner by separating patient identifying details from laboratory data and storing the masterlist that links patient identifying details to study patient identifiers in a separate, secure location.
- The information is for the private use of the applicant only, unless further approval is obtained from the NHLS. In the event of this, the applicant shall give due credit, including affiliation, of the participation of the NHLS in any such publications or presentations.
- The applicant undertakes to provide the Executive Manager: Academic Affairs, Research and Quality Assurance at the NHLS with a copy of any report, presentation or publication emanating from the use of this data.

ACCEPTANCE OF CONDITIONS

By signing this document we accept the conditions stated above.

Applicant Signature		Date	6/12/2013
Supervisor Signature		Date	6/12/2013

In the event of a dispute concerning this document, the electronic version stored on Q-Pulse will be deemed to be the correct version.



NATIONAL HEALTH LABORATORY SERVICE HELPDESK
Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk1@nhls.ac.za

APPLICATION FOR DATA FROM NHLS INFORMATION SYSTEMS (Q-Pulse FMI0069)

All fields in this section must be completed

DATA REQUEST DETAILS

Request Type (Tick)	☒ New ☐ Modify	Data Format (Tick)	☐ Excel ☒ CSV	Data Delivery (Tick)	☒ CD / DVD or ☒ Email
Frequency of Extract (Tick)	☒ Once ☐ Repeat	If Repeat, specify frequency	☐ Daily ☐ Weekly	☐ Monthly ☐ Annually	
DESCRIPTION OF REQUIRED DATA EXTRACT					
Data required	All positive HIV PCR results for infants aged less than 6 weeks				
Region (for data extract, e.g. Province or Laboratory)	From Rahmon Moses Mother and Child Hospital				
Date range of extract	January 2006 up to and including August 2013				
Fields required (e.g. Patient name, Date of Birth, etc)	Patient's ^{Surrogate} name, age/date of birth, date of test RNA-PCR Result equals positive				
ADDITIONAL INFORMATION					
DESCRIPTION OF INTENDED USE OF DATA EXTRACT (e.g. research, epidemiology study, cost analysis of service, drug effectiveness, disease surveillance)					
For mmeo Research Project. A descriptive case series of HIV Positive Infants to identify infants diagnosed HIV positive early in life to describe treatment. Started on Antiretroviral Treatment within the first six weeks of life at Rahmon Moses Mother and Child Hospital.					
LIST WHO WILL HAVE ACCESS TO THIS DATA					
Principal Investigator + Supervisor (Dr CA Owsens + Dr R Tschirner)					
PROJECT NAME AND REGISTRATION NUMBER (if data is required for a registered research project. Please attach the Ethics Approval.)					
A descriptive case series of HIV Positive Infants started on Antiretroviral Treatment within the first six weeks of life at Rahmon Moses Mother and Child Hospital					

from KAMPEP
from 2006-2013



NATIONAL HEALTH LABORATORY SERVICE HELPDESK
Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk1@nhls.ac.za

APPLICATION FOR DATA FROM NHLS INFORMATION SYSTEMS (Q-Pulse FMI0069)

NHLS RESPONSIBILITIES

The NHLS will: • Ascertain if it is possible to extract the required data. • Register the application and issue a registration number. • Only release the requested data to the applicant whose name is specified on this application form.
After this application has been completed and approved, please raise a service request with the NHLS IT Service Desk (Contact Number: (011) 386-6125/6/7/9): • Send an email to helpdesk1@nhls.ac.za, and cc the CDW Manager (sue.candy@nhls.ac.za) • Scan this application form and attach it to the email, or fax it to (011) 386-6308.

FOR OFFICE USE			
APPROVAL BY BUSINESS			
(Approval will be obtained by the CDW Manager)			
INFORMATION MANAGEMENT UNIT APPROVAL (required for external requests and patient identifying data)			
Check list for external applicants	☐ Signed by Supervisor ☐ Ethics Approval attached, if applicable		
Executive Manager: Academic Affairs, Research and Quality Assurance		Signature	Date / /20
CEO APPROVAL (required for sensitive data requests)			
Chief Executive Officer		Signature	Date / /20
APPROVAL BY IT			
CDW Manager		Signature	Date / /20
REQUEST TRACKING			
Service Request Number			
Request Commence Date	/ /20		

In the event of a dispute concerning this document, the electronic version stored on Q-Pulse will be deemed to.

APPENDIX B – Gate Keeper Permission



Rahima Moosa Mother and Child Hospital, JHB

South Africa (Private Bag X20 Newclare 2112) • Tel: +27(0)11 470 9421
Fax: +27(0)11 470 9169 • E-mail: Annie.Jordan@wits.ac.za

Professor Cleaton-Jones
Chairman
Human Research Ethics Committee
University of the Witwatersrand

1st August 2013

Dear Professor Cleaton-Jones

Application: A Review of HIV Positive Infants Started on Antiretroviral Treatment within the first six weeks of life at Rahima Moosa Mother and Child Hospital

In my capacity as gatekeeper of the database of patients at Empilweni Clinic, Rahima Moosa Mother and Child Hospital, I hereby provide written permission for accessing the Empilweni database for the retrieval of patient's records required for the review. Use of this data is governed by the conditions set out in this protocol. Subject to these conditions being met and the approval of the ethics committee, I support the use of the available data for the review of HIV Positive Infants Started on ART within the first 6 weeks of life.

Yours sincerely,

A handwritten signature in cursive script, appearing to read "Annie Jordan".

Sr Annie Jordan, Project Manager and Gate Keeper
Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital

APPENDIX C – Data Capturing Form

BASELINE CHARACTERISTICS

YEAR OF BIRTH:	GESTATIONAL AGE AT BIRTH:	BIRTH WEIGHT:	MODE OF DELIVERY:	MATERNAL AGE AT DELIVERY:
.....	weeks	grams	 If C/section reason:	

ANTENATAL PROBLEMS:	PERINATAL PROBLEMS:	PMTCT:	MATERNAL:
			Timing of Dx:
			Treatment:
			
			
			
			
			CD4 and Date:

AGE AT INITIATION OF ART:	WEIGHT AND LENGTH AT INITIATION:	REGIMINE INITIATED:	FEEDING CHOICE:	DURATION OF BREAST FEEDING:
.....days	kg cm		Breast Formula Mixed Exclusive: Y/N	days

FOLLOW UP

VISIT DATE	REGIMINE	WEIGHT	LENGTH	ABSOLUTE CD4%	VIRAL LOAD	ADVERSE EFFECTS	OTHER PROBLEMS

LAST SEEN DATE:	STATUS AT TIME:	IN CARE
		TRANSFERRED OUT
		LOST TO FOLLOW UP
		DECEASED

APPENDIX D - Empilweni - analysis of routinely collected data

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Karl Technau

CLEARANCE CERTIFICATE

M090501

PROJECT

Multi-Centre Cohort Study of HIV-Infected
Children Receiving Care within Public Sector
Health Facilities supported by the Wits
Paediatric HIV Clinics and Participation in the
International Epidemiological Database.....(IeDEA)

INVESTIGATORS

Dr Karl Technau.

DEPARTMENT

Department of Paediatrics

DATE CONSIDERED

09.05.29.

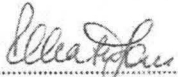
DECISION OF THE COMMITTEE*

Annual Renewal Approved
(See M070725-Dr T Meyers)

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08/06/2011

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX E - Empilweni – consent form

EMPILWENI Treatment Clinic - Consent

Version 3 June 2011

CONSENT FORM: USE OF CLINICAL INFORMATION

This document must be explained to the patient/family member/guardian by a member of the clinical staff and a copy of the signed document is to be given to the patient/family member/guardian.

Dear Guardian and Patient

You/your child are currently attending Rahima Moosa Mother and Child Hospital for treatment of problems you/your child are/is currently experiencing. The Hospital not only renders treatment but is also actively involved in conducting research aimed at improving the quality of care we deliver. From time to time such research involves the use of patient records from which information is extracted. The use of such information is subject to:

- 1 Approval from the Committee for Research on Human Subjects (University of the Witwatersrand)
- 2 Anonymity ie the identity of the patient from whose file information is extracted is never revealed to anyone but the researcher unless specific consent is obtained to do so.

Whilst we are not currently involved in research that requires us to use any information now, this may change in the future when you are already discharged. We would like to obtain your consent to use information from your file for the purpose of research, subject to the aforementioned conditions. If you choose not to give consent, this will not compromise your treatment in any way. If at any time you choose to withdraw consent you are free to do so and will not be prejudiced in any way.

Should you wish to contact us at any stage regarding this consent, contact Rahima Moosa Mother and Child Hospital, Empilweni Clinic at (011) 470 9421.

A. I.....hereby give consent for my/my child's records to be used as per the abovementioned conditions for the purposes of research: GUARDIAN NAME and RELATION:..... SIGNATURE:..... DATE:..... WITNESS:..... DATE:.....	B I.....DO NOT give consent for my/my child's records to be used as per the abovementioned conditions for the purposes of research: GUARDIAN NAME and RELATION:..... SIGNATURE:..... DATE:..... WITNESS:..... DATE:.....
---	--

APPENDIX F – ETHICS APPROVAL



HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130824

NAME: Dr Carice Ann Goossens
(Principal Investigator)

DEPARTMENT: Department of Paediatrics
Rahima Moosa Mother & Child Hospital

PROJECT TITLE: A Review of HIV Positive Infants Started on
Antiretroviral Treatment within the First Six
Weeks of Life at Rahima Moosa Mother and
Child Hospital

DATE CONSIDERED: 30/08/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Karl G Technau

APPROVED BY: 

Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 04/11/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____ M130824Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX G – TURNITIN REPORT

Turnitin Originality Report

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<http://www.jiasociety.org>

A descriptive case series of HIV-positive infants started on antiretroviral treatment within the first six weeks of life at Rahima Moosa Mother and Child Hospital Dr Carice Ann Goossens

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