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A PROFILE OF HIV-RELATED PAEDIATRIC ADMISSIONS AT CHRIS HANI BARAGWANATH HOSPITAL, JOHANNESBURG, SOUTH AFRICA

ANGELA DRAMOWSKI

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Paediatrics

Johannesburg 2008

Declaration

I, Angela Dramowski declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

_____

_____ day of _____, 2009

Dedication

For my husband, Craig and my parents, Elizabeth and Josef

Publications and presentations arising from this research

- Presentation of research and feedback to the Department of Paediatrics at Chris Hani Baragwanath Hospital (CHBH), 24 June 2008
- Presentation of research and feedback to the Neonatal Unit, Department of Paediatrics at CHBH, 27 June 2008
- Presented at the 4th South African AIDS conference, Durban, South Africa, 31 March - 3 April 2009

Abstract

Aim: To describe the prevalence of HIV infection, and the disease profile and outcome of 440 HIV-infected children admitted to the general paediatric wards at Chris Hani Baragwanath Hospital (CHBH).

Methods: A comprehensive list of all paediatic patients admitted to the general wards between October and December 2007 was compiled using hospital admission records. Hospital folder and laboratory records were used to determine HIV prevalence. A retrospective review of inpatient hospital records was conducted for all confirmed HIV-infected paediatric patients admitted during the study period.

Results: The prevalence of confirmed HIV infection amongst paediatric admissions at CHBH during the study period was 29.5% (95% CI 27.2 -31.9%). Of these children, 54.1% were newly diagnosed with HIV during the current hospital admission. Despite the majority (92.7%) of admissions having advanced HIV disease (WHO Stage 3 or 4), only 17% were accessing ART. Of the 202/440 (45.9%) children known to be HIV-infected before hospital admission, only 74/202 (36.6%) were currently receiving ART. Of the remaining 128/202 children known to be HIV-infected before hospital admission, 121/128 (94.5%) had WHO HIV stage 3 or 4 disease and thus were eligible for ART. Only 19% of children had a normal weight. Amongst infants aged less than 6 months uptake of PMTCT interventions was poor - only 36% of mother-infant pairs received single dose nevirapine and 28% of infants received cotrimoxazole prophylaxis. Respiratory illness was the principal reason for hospitalization in 37.5% of admissions. Gastroenteritis, sepsis and tuberculosis accounted for 22%, 19.5% and 21% of principal diagnoses respectively. The overall case fatality rate was 12% (95% CI 9.2–15.5%), with deaths in HIV-infected children contributing 58% of all deaths in the general paediatric wards. Over half (52%) of all deaths in the HIV-infected group occurred in infants younger than 6 months of age.

Conclusion: HIV infection remains a major contributor to morbidity and mortality among paediatric admissions at CHBH. Poor uptake of PMTCT interventions, late diagnosis of HIV infection and delay in accessing ART are immediate barriers to improved care in HIV-infected children at CHBH. The underlying reasons for poor accessibility and under-utilisation of paediatric HIV-related services requires further investigation. Efforts to reduce mortality amongst HIV-infected paediatric admissions at CHBH should focus on early diagnosis of HIV infection and prompt initiation of antiretroviral treatment, especially in infants under 6 months of age.

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Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
CDC	Centers for Disease Control
CHBH	Chris Hani Baragwanath Hospital
CHER	Children with HIV Early Antiretroviral Therapy trial
Child PIP	Child Healthcare Problem Identification Programme
CI	Confidence interval
CSF	Cerebrospinal fluid
CTX	Cotrimoxazole
EPTB	Extrapulmonary tuberculosis
ESBL	Extended-spectrum beta-lactamase producing organism
FTT	Failure to thrive
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HIVISS	HIV Impact Surveillance Study
ICU	Intensive care unit
IQR	Interquartile range
IRIS	Immune reconstitution inflammatory syndrome
MAC	Mycobacterium avium complex
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHL	Non-Hodgkins lymphoma
NHLS	National Health Laboratory Service
NVP	Nevirapine

PCR	Polymerase Chain Reaction test
PHRU	Perinatal HIV Research Unit
PJP	*Pneumocystis jiroveci* pneumonia
PMTCT	Prevention of mother to child transmission
RTHC	Road to Health Card
TB	Tuberculosis
pTB	Pulmonary Tuberculosis
VCT	Voluntary counselling and testing
Wits	University of the Witwatersrand
WHO	World Health Organisation

Study Definitions

Several definitions for the following terms can be found in the medical literature. However for the purposes of this dissertation the definitions listed below were utilized.

HIV-exposed: mother known to be HIV-infected and infant's status as yet unknown.

HIV-unknown: no confirmed HIV result available for mother or child from laboratory and hospital records.

HIV-negative: a non-reactive HIV PCR in an infant less than 18 months old or a non-reactive HIV Elisa test in a child greater than 18 months old. Since this study was retrospective, only mothers' self-reported HIV status could be recorded. Thus it was not possible to accurately document what proportion of the HIV negative children had been HIV-exposed.

HIV-infected: a reactive HIV PCR in an infant less than 18 months old or a reactive HIV Elisa test in a child greater than 18 months old.

Maternal HIV status**:** Owing to the retrospective study design, only mothers' self-reported HIV status could be recorded.

Nevirapine exposure: NVP exposure was said to have occurred if it was documented in the hospital record that either mother or infant or both had received NVP.

Cotrimoxazole prophylaxis: A child was considered to be receiving CTX prophylaxis if the hospital record documented that the child was on CTX immediately prior to the hospital admission.

Reference classifications

Wellcome classification: This classification developed by the Wellcome Trust International Working Party on childhood malnutrition was utilised for categorization of nutritional status of HIV-infected children in this study.[1]

WHO Clinical staging: (see Appendix 2) This staging system can be used for all children aged under 15 years with confirmed laboratory evidence of HIV infection. The revised 2004 version (as it appears in the "Guidelines for the management of HIV-infected children" was utilised for classification of children in this study.[2]

WHO growth references: This study utilised the 2006 WHO standards for assessing the growth and development of children from birth to 5 years of age.[3, 4]

Case definitions

Pneumocytsis jiroveci Pneumonia (PJP): A working clinical diagnosis of PJP at CHBH was considered in HIV-infected infants who fulfilled two or more of the following criteria: oxygen saturations less than 90% on admission or if ventilated, requirement of FiO2 >0.4 for 4 or more consecutive days plus a respiratory rate > 60/minute, minimal findings on chest auscultation and a reticulonodular infiltrate on chest radiograph. These criteria are based on local teaching and the WHO clinical case definition of PJP.[5]

Pulmonary Tuberculosis (pTB): A working clinical diagnosis of pTB at CHBH was considered in HIV-infected infants and children who fulfilled at least 2 of the following criteria: persistent cough for more than 2 weeks and/or fever for more than 1 week and/or recent failure to thrive, a history of a current TB contact, a positive tuberculin skin test (defined as induration > or equal to 5mm) and a suggestive chest radiograph or persistent infiltrates or lymphadenopathy on serial chest radiographs.

Immune reconstitution inflammatory syndrome (IRIS): A working clinical diagnosis of IRIS at CHBH was considered in HIV-infected infants and children who fulfilled the IRIS case definition recommended in the "Guidelines for the management of HIV-infected children": a paradoxical clinical deterioration within 6 weeks of starting ART, with new symptomatic infection with pathogens reported to be associated with IRIS, particularly *Mycobacterium tuberculosis*, *Mycobacterium avium complex* , *Mycobacterium bovis* (BCG reactions) and Cytomegalovirus (CMV) infections amongst others.[2]

1. Introduction and literature review

1.1 Paediatric HIV – the International experience

Internationally, low-income, high-HIV prevalence countries have documented the adverse impact of paediatric HIV/AIDS on child health indicators. Under-five mortality rates are high in Malawi and India at 188 and 78 respectively, with paediatric HIV being a major contributor to child deaths.[6] A prospective study of HIV infection among paediatric in-patients in Blantyre, Malawi, documented HIV prevalence of 18.9% and high rates of malnutrition, lower respiratory tract infections and sepsis.[7] Mortality rates approached 30% among HIV-infected children in the study, a three fold higher rate than that observed among HIV-uninfected children in the same cohort.[7] A prospective study of the clinical profile of paediatric HIV infection from India described very high rates of protein-energy malnutrition among a group of 42 HIV-infected children.[8] Gastrointestinal and respiratory system illnesses were the principal reasons for hospitalisation among these HIV-infected children.[8]

In high-income, low-HIV burden countries such as the United Kingdom (UK) and Ireland, HIV has had much less of an impact on the profile of paediatric hospital admissions. A well-functioning prevention of mother to child transmission (PMTCT) programme and an increasing proportion of HIV-infected children accessing antiretroviral therapy (ART), resulted in an absolute decrease in hospital admissions of 26% between 1997 and 2002.[90] Data showed that up to 60% of HIV-infected children from a cohort of 944 had been born abroad.[9] In a review of advances in paediatric HIV management, Sharland et al report that at the time of publication in 2002, there were around 600 children living with HIV in the UK.[10] With the routine availability and high uptake of ART, the authors state that in the UK, HIV has become another treatable chronic disease of childhood.[10]

1.2 Paediatric HIV in South Africa – the scope of the epidemic

The 2006 UNAIDS report on HIV/AIDS states that South Africa has one of the highest HIV seroprevalence rates in sub-Saharan Africa.[11] At an 18.8% HIV seroprevalence rate, this translates into an estimated infected population of 5,4 million people.[11] Of these cases, approximately 240 000 are HIV-infected children[11], who suffer a disproportionately high burden of HIV-related morbidity and experience mortality rates double that of their HIV-negative counterparts.[7, 12] Past advances in child mortality rates have been reversed by the paediatric HIV epidemic in South Africa, making attainment of the Millennium Development Goals for Child Health improbable, if not impossible.[12]

1.3 Paediatric HIV in South Africa – impact on hospital admission profiles

The impact of paediatric HIV on hospital admission rates and profiles has been documented at many public hospitals in South Africa. In Kwa-Zulu Natal, Pillay et al recorded a 62.5% HIV prevalence rate among children admitted to a tertiary general paediatric ward during a cross-sectional study of one month's duration.[13] A 20% case fatality rate was reported among HIV-infected infants during the same period.[13] In the Western Cape, a retrospective review of HIV-infected infants admitted at a tertiary hospital noted that infants under 6 months of age contributed 43% of all paediatric HIV-related admissions and suffered a high case-fatality rate of 13.5%.[14] In both studies pneumonia was the main reason for hospitalisation. At a tertiary hospital in Bloemfontein, a review of admission data from the years 1991 and 2001 was compared. Substantial increases in rates of pneumonia, malnutrition and overall mortality were attributed to the effect of HIV disease on the paediatric patient population.[15] Similar findings have been published from a rural, district hospital in Hlabisa, Kwa-Zulu Natal, where a prospective study of paediatric admissions documented a 25% HIV prevalence rate.[16] The same study also

described higher rates of malnutrition and death from diarrhoeal disease and pneumonia in HIV-infected children.

1.4 Previous studies of Paediatric HIV infection at CHBH

Three previous studies at CHBH have described the local impact of HIV on paediatric hospital admission patterns. Zwi et al conducted a retrospective study in the Department of Paediatrics at CHBH that documented the rapid rise of HIV prevalence among hospitalised children from 3% in 1992 to 19% in1996. It was also demonstrated that over the same period, although mortality rates among HIV-uninfected children had declined, mortality in HIV-infected children increased dramatically from 6.7% to 46.1%.[17] This study used computerized hospital discharge summary data only and at the time of the study HIV PCR testing was not available, thus limiting the reliability of the data used for HIV prevalence calculations. The study lacked a comprehensive description of the HIV-infected sub-population, but did include information on a comparison group of HIV-negative and HIV-unknown children

In 1996 - before the commencement of the national Department of Health's PMTCT programme and before ART became available in the public sector - Meyers et al conducted a prospective study to determine paediatric HIV prevalence and clinical spectrum of disease at CHBH. Over a 6 month period, serial pediatric admissions to a single ward were screened for HIV, enrolling a total of 549 patients. The study documented an estimated HIV prevalence among hospitalized children of 29%, recorded a mortality rate of 17% among the HIV-infected children and cited infectious diseases (pneumonia and gastroenteritis) as the most common reason for hospital admission.[18] A comparison group of HIV-uninfected children was included. HIV PCR results were missing or indeterminate

in up to 50% of HIV Elisa-positive children aged 15 months or younger and thus again, the prevalence calculations for this study were based on incomplete data.

The cross-sectional HIV Impact Surveillance System (HIVISS) study was conducted in 2005 by the University of the Witwatersrand (Wits) School of Public Health and the Gauteng Department of Health. The study aimed to establish a surveillance system for monitoring the impact of HIV/AIDS on health services in Gauteng. Sentinel sites for collection of data on adult and paediatric admission profiles were established at several provincial clinics and hospitals including CHBH. Unpublished data from this study reflected a 31.5% HIV prevalence and a high mortality rate of 24.3% among HIV-infected children admitted to the general wards at CHBH. [19] One of the strengths of this study was that a 95% uptake of HIV testing was achieved at CHBH for paediatric admissions during the study period and that in only 2% of cases, a diagnosis of HIV-infection was based only on a history of HIV-exposure and clinical stigmata. The study was designed to calculate HIV prevalence and quantify the impact of HIV on paediatric services. There was very limited descriptive data available for HIV-infected children.

1.5 Paediatric HIV in South Africa – role of the Child Healthcare Problem Identification Programme (Child PIP)

In response to the increasing burden of care and child mortality rates in South Africa (largely attributable to paediatric HIV) the concept of the Child Healthcare Problem Identification Programme (Child PIP) was developed. Child PIP assists in monitoring the quality of care delivered to South African children by documenting all inpatient paediatric deaths, assigning cause of death, recording nutritional and HIV status and identifying modifiable factors for each child death. There are currently 57 hospitals from district to

tertiary level participating in the programme and contributing data which is analysed at local and national level to identify problems and generate recommendations for paediatric healthcare improvements.

Recent data from countrywide Child PIP (2005-2007) – which is used in more than 50 health facilities in South Africa - showed that of hospitalised children tested for HIV, 80% were either HIV-exposed or HIV-infected.[20] However, many hospitalised children did not receive HIV testing and HIV status was recorded as unknown in 46% of all deaths at Child PIP sites. Of known cases of paediatric HIV, 50% of children who died were assessed as WHO stage 3 or 4 and were thus eligible for ART, yet only 3% of these children were accessing ART.[20] Child PIP data from 28 sites showed that HIV/AIDS was responsible for 35% of under-five deaths.[12] Notwithstanding the availability of Child PIP data, information regarding paediatric HIV-related morbidity and mortality in South Africa is incomplete; for example, CHBH – the largest tertiary, public hospital in the country with a sizeable paediatric HIV/AIDS service – does not contribute data to the Child PIP records. Thus for clinicians and public health personnel working at CHBH, it is important to document the prevalence and impact of paediatric HIV at this large hospital.

1.6 Prevention of Paediatric HIV in South Africa – the PMTCT programme

The South African approach to preventing infant HIV infection is based on the 4-pronged comprehensive approach suggested by World Health Organisation and UNAIDS: primary prevention of HIV in parents-to-be; reduction of unwanted pregnancies; intensification of programmes to prevent mother-to-child transmission of HIV and provision of appropriate treatment and care to women living with HIV as well as their children and families.[21]

Most HIV-infected children are vertically infected by mother-to-child transmission both perinatally (during labour and delivery) and postnatally (through breastfeeding.)[22] In South Africa the antenatal HIV prevalence in the 2007 national survey was estimated at 28%.[23] In the absence of any preventative interventions, the risk of HIV transmission to the baby is about 25-35%.[24] In developed countries with established prevention programmes, that include dual therapy, modified obstetric practices (mainly caesarean section deliveries), and replacement feeding, the rate of HIV transmission from mother to child has been curtailed to less than 2%.[25] This statistic reinforces the fact that paediatric HIV is an eminently preventable disease. However, in South Africa, as in the rest of sub-Saharan Africa, the burden of paediatric HIV continues to grow as a result of the uncontrolled adult HIV epidemic and poor functioning of the prevention of mother-to-child transmission (PMTCT) programmes.[26] According to The United Nations Children's Fund (UNICEF), 300,000 infants are born to HIV-infected mothers annually, resulting in approximately 93,000 new paediatric HIV infections in South Africa each year.[26]

Universal access to PMTCT in South Africa is not a reality and even in regions where PMTCT progammes are established, multiple programmatic weaknesses are identified. Some of these problems include low uptake of PMTCT amongst HIV-positive pregnant women, poor record keeping and high loss to follow-up of HIV-exposed infants.[27, 28] From the perspective of South African paediatricians and researchers who seek to prevent new cases of paediatric HIV, universal coverage and intensification of current PMTCT programmes could achieve a radical reduction in the numbers of newly HIV-infected children in South Africa.[29] For infants born to HIV-infected mothers, early testing would afford the opportunity to provide cotrimoxazole prophylaxis (to prevent early mortality from *Pneumocystis jirovecii* pneumonia) and ART to infected infants.

1.7 Management of Paediatric HIV infection in South Africa – the impact of the ART programme

Although comprehensive paediatric HIV care, including access to ART is available at selected, largely urban-based centres in South Africa, the vast majority of HIV-infected children in South Africa are not accessing ART.[30] In 2006, Department of Health estimated that over 21000 children under 14 years of age in South Africa were accessing ART. This reflects 10% of the total population on ART in the country, falling short of the 15 % target set for proportional representation of children in ART programme coverage.[31] Access to paediatric ART programmes also varies widely between provinces and districts within provinces of South Africa. Of particular concern is the fact that many paediatric ART programmes are based at tertiary hospitals and are run primarily by paediatricians and medical officers. In order to make paediatric ART more accessible, it is necessary to decentralise services and train primary care nurses to initiate and monitor children on ART. Although the National Department of Health is implementing the IMCI Complementary Course on HIV for nurses this has not translated into shifting or sharing the task of paediatric ART initiation and monitoring to nurses or to primary care level, nationally. The latter model, however, has been successfully achieved in the Western Cape, where the proportion of children receiving ART at tertiary hospital level has decreased from 78% in 2004 to 38% in 2006, due to ART initiation and monitoring at lower levels of the health care system.[30]

An international study in a resource-poor setting (Thailand) has reported significant reductions in admission rates and mortality rates in children commenced on highly active anti-retroviral therapy (HAART).[32] Similarly, the Children with HIV Early Antiretroviral Therapy (CHER) study, demonstrated that ART initiated before clinical and immunological

HIV disease progression, reduces early mortality in HIV-infected infants.[33] Thus urgent scaling up of paediatric ART provision is needed so that all children in need of ART are able to access it timeously. Even in older children with advanced HIV disease, ART has been shown to improve survival.[34]

Although some paediatric ART programmes in South Africa have published service audit data, few have commented on the effect of ART in reducing paediatric hospital admission rates.[35-37] More data on the impact of ART provision on hospital admission trends in paediatric wards is needed in order to advocate for urgent upscaling of paediatric ART provision and better PMTCT services.

1.8 Chris Hani Baragwanath Hospital and Harriet Shezi Children's Clinic

The study site, CHBH, is a tertiary government (public) hospital situated in Johannesburg, in the Gauteng province of South Africa. CHBH is one of the largest hospitals in the southern hemisphere and provides services to the burgeoning urban township population of Soweto (last official population estimation of 1 million in 1996.)[38] A significant proportion of paediatric inpatients at CHBH originate from other areas of Johannesburg and from beyond the Gauteng provincial boundaries. The hospital has a total of 140 beds for general medical paediatric admissions under 14 years of age, with approximately 6000 paediatric admissions annually. (J.M.Pettifor, Head of Paediatrics Department, CHBH, personal communication, May 2008)

A dedicated paediatric HIV clinic, Harriet Shezi Children's Clinic (part of the Wits Paediatric HIV Clinics) operates from the hospital. This clinic provides outpatient services to 3356 HIV-positive children, of whom 2383 are presently on ART. (L. Fairlie, Head of

Clinical Services, Harriet Shezi Children's Clinic, CHBH, personal communication, April 2008) HIV-infected children who are found to be in need of hospitalisation during their clinic follow-up consultations or at an outpatient clinic, are referred to CHBH general paediatric admission ward and, following discharge, are then followed up by the HIV clinic.

1.9 Motivation for this study of the profile of Paediatric HIV infection at CHBH

Continued surveillance of the prevalence and disease profile of HIV-related paediatric admissions at CHBH is an important task. CHBH is the only state hospital delivering tertiary care to the population of Soweto. Thus monitoring of the paediatric admission profile at this sentinel site provides valuable information about the impact of HIV/AIDS on the wider Soweto community. With scaling-up of ART and PMTCT provision, useful information regarding the impact of these programmes may be gained by continued monitoring of inpatient paediatric HIV-related morbidity and mortality.

In order to assess Gauteng province's success in implementing the goals of the HIV & AIDS National Strategic Plan for 2007 - 2011, detailed information on specific health targets will be needed. Data from ongoing surveillance of the paediatric HIV profile at CHBH (and other Gauteng hospitals) is an exercise that could assist with planning of services and contribute to a provincial database. This resource could be used to identify programmatic problems and measure progress in facilities providing paediatric HIV care. For example, monitoring the incidence of paediatric HIV (as measured by the number of new cases diagnosed at CHBH) would reflect on the effectiveness and coverage of the local PMTCT programme. Data on rates of PCR testing of HIV-exposed infants and provision of CTX prophylaxis can provide insight into the coverage and quality of health services for

infants. Data on rates of paediatric HIV testing, ART initiation and case fatality would also be valuable indicators in the assessment of HIV treatment programmes for children.[39]

Single cross-sectional and retrospective studies can only provide "snap-shots" of the impact of HIV on paediatric health services at CHBH at specific points in time. Collectively, however, such studies are indispensable in allowing for data comparison and establishment of long-term trends, as long as study methods and definitions used are similar. Data from periodic surveillance of paediatric HIV at CHBH should be used to assist with strategic planning and improvement of paediatric HIV services, both locally and at provincial level.

This study is needed to provide more recent information on the profile of HIV-infected children admitted at CHBH, in the context of a national programme to prevent mother-to-child transmission of HIV, and a national antiretroviral treatment programme. Prior to this study, the 1996 study by Meyers et al was the most recent study documenting HIV prevalence amongst children at CHBH. Although previous studies[17, 18] at CHBH included information on HIV-uninfected comparison groups, none provided in-depth and comprehensive data on the profile of HIV-infected children. Furthermore these previous studies were conducted prior to the roll out of a national programme to prevent mother-to-child transmission of HIV, and a national antiretroviral treatment programme. This study includes analysis of information regarding access to and utilisation of PMTCT interventions (although limited by lack of data) and access to HAART and this is an important difference between previous studies and this study.

1.10 Aim of the study

To determine the prevalence of HIV infection amongst paediatric inpatients and to describe the disease and demographic profile of HIV-infected children admitted to the general paediatric ward at CHBH.

2. Materials and Methods

2.1 Study design

A retrospective, descriptive survey with analytic components was conducted between 1st April and 1st May 2008, using the hospital records of all HIV-infected children admitted at CHBH from 1st October 2007 to 31st December 2007. The prevalence of HIV infection and the disease and demographic profile of HIV-infected children admitted to the general paediatric wards at CHBH during the study period was described.

2.2 Study population, methods and sampling

All consecutive admissions to the CHBH general paediatric wards from 1st October 2007 to 31st December 2007 were eligible for inclusion in the study. There were two populations of interest, firstly the larger population of all children admitted to CHBH during the study period (used to calculate period HIV prevalence) and secondly, the HIV-infected paediatric population – which was a sub-sample of the larger population of all children admitted during the study period.

The three month study period was chosen for several reasons:

1. A convenience sample was selected in order to describe a recent cohort of consecutive HIV-infected inpatients.

2. A recent sample would allow calculation of period prevalence so that recommendations could be made based on current practice.
3. Data was captured from a single paediatric registrar rotation period (October – January) giving greater consistency in hospital admission notes.
4. The study investigator wanted to ensure a yield of at least 300 records of HIV-infected children and (based on past admission statistics) estimated that at least 3 month's data was required to achieve that number.
5. The number of children admitted and the mortality rate during this period was not very different from other quarters in the same year.

Study methods and sampling

To define the first study population of interest, the study investigator obtained the patient admission lists (with names and hospital numbers) for the study period from the comprehensive register of all paediatric admissions located in the acute admission ward (ward 36A.) All children being admitted pass through this ward before being transferred to one of the four general paediatric wards. This data was checked against the intake list of admissions from each ward from 1 October to 31 December 2007. The list of names and hospital numbers was used to identify and locate the laboratory data for every child admitted during the study period. The NHLS laboratory-linked computerised results programme was searched to identify the HIV status of each child admitted during this study period.

If no confirmatory HIV test result appeared in the laboratory results for the current or prior admissions to CHBH, then the study investigator attempted to obtain the child's hospital record. The hospital record was then consulted to check if a confirmed HIV test result

from current or previous visits was documented in the medical notes and results flow chart. If no evidence of HIV testing could be found in the laboratory results or medical notes, then the HIV status was recorded as HIV-unknown. If the hospital file could not be located (this occurred in less than 20 cases) then the status remained classified as HIV-unknown.

HIV-exposure at the outset was determined from laboratory results by either a reactive maternal HIV Elisa or a reactive HIV Elisa in a child less than 18 months old. Thereafter, review of the hospital record for all HIV-unknown and HIV-exposed children was performed looking for documentation of HIV-infected maternal status in the hospital admission notes. If maternal status was HIV-infected and child had no HIV PCR result, then the child's status was classified as HIV-exposed. If maternal status was unknown or negative and the child had no HIV test result, then the child's status was classified as HIV-unknown. Thus the HIV prevalence was calculated using both laboratory data and hospital record review.

All HIV test results accessed retrospectively for the study were processed by the NHLS as part of the routine laboratory service and were therefore subject to a standardized NHLS protocol for laboratory testing of HIV status.

To define the second population of interest, the study investigator obtained the hospital records of all confirmed HIV-infected children (confirmed using the procedures described above) from the records department and then captured selected data on a standardized study tool by the study investigator (see Appendix 1.) Hospital records for HIV-negative, HIV-unknown and HIV-exposed children were not analysed further, apart from the initial determination of HIV status (if no HIV test result had been found on laboratory search.)

because the main aim of the study was to describe period HIV prevalence, and then to describe disease profile and outcome amongst HIV-infected children. Although comparison group/s (i.e. HIV-negative/HIV-exposed) would have been useful, the study investigator chose to focus only on confirmed HIV-infected children in order to determine access to, coverage and impact of the antiretroviral programme amongst a group of HIV-infected inpatients. However, further studies would be helpful in assessing missed opportunities for PMTCT interventions and HIV screening amongst the larger group of paediatric inpatients. Furthermore, a restricted study population was chosen due to funding and time constraints.

Data regarding deaths among the HIV-infected group were obtained from hospital record review. However, mortality data for the HIV-negative, HIV-unknown and HIV-exposed groups (admitted during the study period) was collected from the monthly morbidity and mortality reports for each of the four general paediatric wards at CHBH.

2.2.1 Inclusion and exclusion criteria

All children (from birth to 14 years of age) who presented to CHBH acute (general medical) paediatric admission ward between 1st October 2007 and 31st December 2007 were included in the study sampling frame to determine HIV prevalence. Only those children who had a documented positive HIV status (laboratory or hospital record) were included in the analysis of disease profile amongst HIV-infected children.

All HIV-negative, HIV-exposed children (where no final HIV status could be determined from the hospital and laboratory records) and children of unknown HIV status were excluded from the second part of the study that described disease profile amongst

confirmed HIV-infected children. The six HIV-infected children who were identified using the computerized laboratory record system but whose hospital records could not be located were included in the prevalence calculations but were excluded from all other study analyses.

2.3 Materials and Data collection

A pilot study was performed to assess the accessibility of records and the feasibility of collecting the required data on a pro-forma standardized study tool. (Appendix 1) Based on the results of this pilot and on the advice of the postgraduate committee reviewing the protocol, some detailed data on the socio-demographics and clinical history of each child was omitted from the final data collection. This data included information on feeding history, maternal CD4 cell count, paternal and sibling HIV status, immunization record, area of residence, presenting symptoms, household income and social grant uptake. This data collection tool is explained in greater detail below.

Although a computerised database of paediatric admission records exists, the data is incomplete since many of the paper copies of hospital discharge summaries have not been submitted for data capturing. Thus the only way to obtain complete data for the children identified as HIV-infected was to physically locate each hospital file in the CHBH Records Department. The study investigator (researcher) visited the CHBH Records Department and physically obtained all hospital records for children with unknown HIV status (to confirm that status was truly unknown) and for all HIV-infected children (as confirmed by hospital records). The researcher personally reviewed all data of interest and captured data on a standardized study tool. (Appendix 1) The study tool was developed after a pilot

study to ensure ease of data extraction, coding for simplified analysis and gathered mainly closed-ended quantitative data.

The following information was collected (where available from the hospital record) for each HIV-infected child:

- Demographics: age in months (Ethics committee would not allow recording of date of birth) and gender
- HIV testing (whether newly-diagnosed in this admission)
- PMTCT Details: self-reported HIV status of the biological mother, NVP prophylaxis to mother in labour and/or child at birth, place of birth
- ART treatment history: Current treatment, need for ART, duration of ART, usage of CTX prophylaxis at time of admission.
- Growth parameters: weight, height and Wellcome classification[1]
- HIV Staging: WHO stage and clinical criteria for staging
- Immunological indices: CD4 count and CD4 percentage
- Primary diagnoses or reason for hospital admission: one primary and two secondary diagnoses could be recorded
- Infectious pathogens: microbiology culture results and organisms identified via post-mortem biopsy results could be recorded
- Clinical outcome: discharged home – no ICU admission, discharged home after ICU admission, died in ICU, died in ward, transferred back to referring hospital, transferred to step-down hospital facility
- Duration of hospital stay

2.4 HIV testing/HIV status

As this was a retrospective study, laboratory and hospital records, as explained above, were used to determine HIV status. HIV infection status was documented based on the NHLS laboratory system test result (using either a positive HIV-DNA polymerase chain reaction test (PCR) in children < 18 months or a positive HIV enzyme-linked immunosorbent assay (ELISA) in children > 18 months of age). The NHLS laboratory records database contained records of all paediatric HIV PCR and HIV Elisa tests done at CHBH for at least the preceding 5 years. The NHLS uses routine, standardised protocols in laboratory testing of HIV PCR and HIV Elisa specimens.

In cases where no laboratory testing results were available, hospital records were obtained and HIV results documented therein were used to classify HIV status. The clinicians documenting these results would have considered a positive virological test in children < 18 months old or a positive antibody test in children ≥18 months old as proof of HIV infection. This interpretation of HIV test results is in accordance with the National Department of Health's Guidelines 2005 guidelines for HIV testing of infants and children.[32]

2.5 Reference classifications

Wellcome classification: This classification developed by the Wellcome Trust International Working Party on childhood malnutrition was utilised for categorization of nutritional status of HIV-infected children in this study.[1]

WHO Clinical staging: (see Appendix 2) This staging system can be used for all children aged under 15 years with confirmed laboratory evidence of HIV infection. The revised

2004 version (as it appears in the "Guidelines for the management of HIV-infected children" was utilised for classification of children in this study.[2]

WHO growth references: This study utilised the 2006 WHO standards for assessing the growth and development of children from birth to 5 years of age.[3, 4]

2.6 Case definitions

Pneumocytsis jiroveci pneumonia (PJP): A working clinical diagnosis of PJP at CHBH was considered in HIV-infected infants who fulfilled two or more of the following criteria: oxygen saturations less than 90% on admission or if ventilated, requirement of FiO2 >0.4 for 4 or more consecutive days plus a respiratory rate > 60/minute, minimal findings on chest auscultation and a reticulonodular infiltrate on chest radiograph. These criteria are based on local teaching and the WHO clinical case definition of PJP.[5]

Pulmonary Tuberculosis (pTB): A working clinical diagnosis of pTB at CHBH was considered in HIV-infected infants and children who fulfilled at least 2 of the following criteria: persistent cough for more than 2 weeks and/or fever for more than 1 week and/or recent failure to thrive, a history of a current TB contact, a positive tuberculin skin test (defined as induration > or equal to 5mm) and a suggestive chest radiograph or persistent infiltrates or lymphadenopathy on serial chest radiographs.

Immune reconstitution inflammatory syndrome (IRIS): A working clinical diagnosis of IRIS at CHBH was considered in HIV-infected infants and children who fulfilled the IRIS case definition recommended in the "Guidelines for the management of HIV-infected children": a paradoxical clinical deterioration within 6 weeks of starting ART, with new

symptomatic infection with pathogens reported to be associated with IRIS, particularly *Mycobacterium tuberculosis, Mycobacterium avium complex , Mycobacterium bovis* (BCG reactions) and Cytomegalovirus (CMV) infections amongst others.[2]

2.7 Statistical analysis plan

2.7.1 Determination of HIV prevalence

The total number of paediatric admissions over the study period 1 October to 31 December 2007 was identified from the hospital admission register and ward admission records. Laboratory results and hospital folder search was performed in order to determine HIV status. Crude HIV prevalence was calculated using the formula: crude period prevalence = total HIV-infected admissions / total admissions. The total number of HIV-infected children (446) was used for the prevalence calculations, whereas for the secondary analyses (see below), data was only available for 440/446 HIV-infected children. The same formula was used to calculate the crude period prevalence of HIV-negative, HIV-exposed and HIV-unknown status. The 95% confidence interval was calculated using statistical software, SAS version 9.1 (SAS Institute Inc., Cary NC, USA).[40]

2.7.2 Data entry and management for the HIV-infected sub-population

Four hundred and forty hospital files in the CHBH records department were analysed. The study investigator entered data into EpiData v3.1.[41] Data quality was checked by performing frequencies on categorical variables such as HIV status and by checking the range of continuous variables such as age and weight. The study investigator exported data to SAS version 9.1 (SAS Institute Inc., Cary NC, USA) for further quantitative analysis.[40]

2.7.3 Statistical Methods

Data was analysed and described by calculating frequencies, means, medians and standard deviations (for parametric data) and median values and interquartile range or ranges (for non-parametric data). Where groups were compared, student t-tests were used for continuous variables with normal distribution and Wilcoxon-Rank Sum tests were used for non-normally distributed data. Pearson chi-squared test was used to determine the association between non-ordinal categorical data; where expected cell count was less than 5 Fischer exact test was used to determine association between groups. A p-value of < 0.05 was considered to be statistically significant.

2.7.4 Analysis describing the study population

Data for the 440 HIV-infected children was subdivided into four age categories for analysis PMTCT interventions in infants aged less than 6 months, immunological indices by age, breakdown of deaths by age and calculation of case fatality rates by age group. Frequency calculation was done to determine what proportion of the study population was newly-diagnosed and what proportion was known to be HIV-infected at the time of hospital admission. The study population was then assigned a Wellcome classification and the frequency of each weight category eg. marasmic, was calculated. Weight for age z-scores were calculated for age categories less than 60 months of age using a macro on SAS based on WHO references.[3] Frequency calculations were performed for WHO HIV staging, staging criteria, ART status, primary diagnosis, spectrum of infectious pathogens, and cause of death analyses. Median and interquartile ($25^{th} – 75^{th}$) ranges were calculated for immunological indices.

2.7.5 PMTCT Sub-analysis

Data concerning PMTCT interventions was analysed for a subgroup of the study population, namely the age category of HIV-infected infants less than 6 months old. Frequency calculations were performed for maternal HIV status, NVP exposure, CTX prophylaxis and place of birth. The uptake of PMTCT interventions was then compared by maternal HIV status grouping using the Pearson chi-squared test. Frequency calculation was performed to breakdown uptake of PMTCT interventions in infants less than 6 months of age.

2.7.6 Determination of Case fatality rates

The total number of deaths in the HIV-negative, HIV-unknown and HIV-exposed group was divided by the total number of admissions for each group over the same study period to obtain the case fatality rate data. Case fatality rates were also calculated by age category for HIV-infected children. . The 95% confidence interval was calculated using statistical software, SAS version 9.1 (SAS Institute Inc., Cary NC, USA).[40]

2.7.7 Comparison of HIV-infected patient characteristics by final outcome

Children who survived were compared with children who died, for variables such as age, weight for age z-score, median CD4 count, ART status, WHO HIV stage, CTX prophylaxis uptake and timing of HIV diagnosis. Pearson chi-squared tests were used for categorical data (Fischer exact test if expected cell count<5) , student t-tests for parametric continuous data, and Wilcoxon rank sum test for non-parametric continuous data.

2.7.8 Comparison of HIV-infected patient characteristics by ART status

Children receiving ART were compared to ART-naive children for variables such as age, weight for age z-score, median CD4 count, duration of hospital stay, WHO HIV stage, CTX prophylaxis uptake and inpatient mortality rate. Pearson chi-squared tests were used for categorical data (Fisher exact test if expected cell count<5), student t-tests for parametric continuous data, and Wilcoxon rank sum test for non-parametric continuous data.

2.8 Ethics clearance

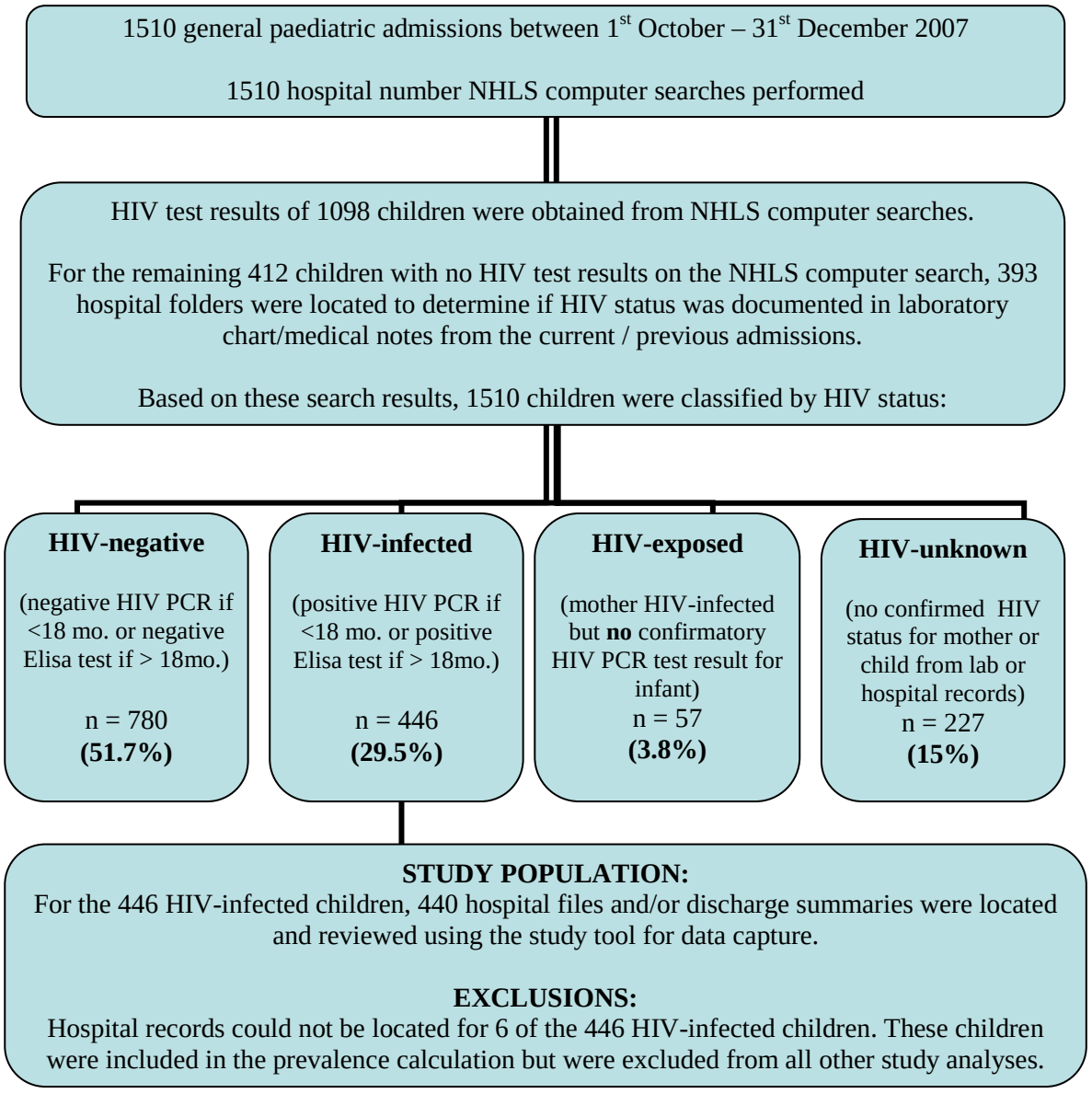
The study was approved by the University of the Witwatersrand Human Research Ethics Committee (reference no. M080202). Permission was obtained from the hospital administration to perform a retrospective review of hospital records. (see Appendix 3)

The protocol was also presented to the paediatric post-graduate committee. The latter recommended that the student limit the scope of this work, and subsequently approved the current protocol and focus as adequate for the MMed thesis.

3. Results

Figure 1. Schematic overview of the study population

The flow diagram in Figure 1. demonstrates how HIV status was determined for all 1510 children admitted to the paediatric wards between 1st October and 31st December 2008. The study population included all children identified to be HIV-infected after review of laboratory and hospital records. Six HIV-infected children whose hospital records could not be located were excluded from all further analyses after HIV prevalence had been calculated.



3.1 HIV prevalence

A total of 1510 children were admitted to the four general paediatric wards over the three month study period. Laboratory results from the NHLS data system were used to determine HIV status of paediatric inpatients admitted during the study period: The HIV status of 412 children was not documented in the NHLS database. Hospital records for 393 of these children were located and examined to obtain HIV status. Of these 1510 children, 446 (29.5% [95% CI 27.2-31.9]) were HIV-infected, 780 (51.7% [95% CI 49.1-54.2]) were HIV-negative, 57 (3.8% [95% CI 2.9-4.9]) were HIV-exposed and 227 (15% [95% CI 13.3-16.9]) were of unknown HIV status (see Table 1). HIV prevalence amongst paediatric admissions during the study period may have been higher than 29.5%, since some of the HIV-exposed infants and children of unknown HIV status may have been HIV-infected.

Table 1. HIV prevalence amongst paediatric admissions at CHBH

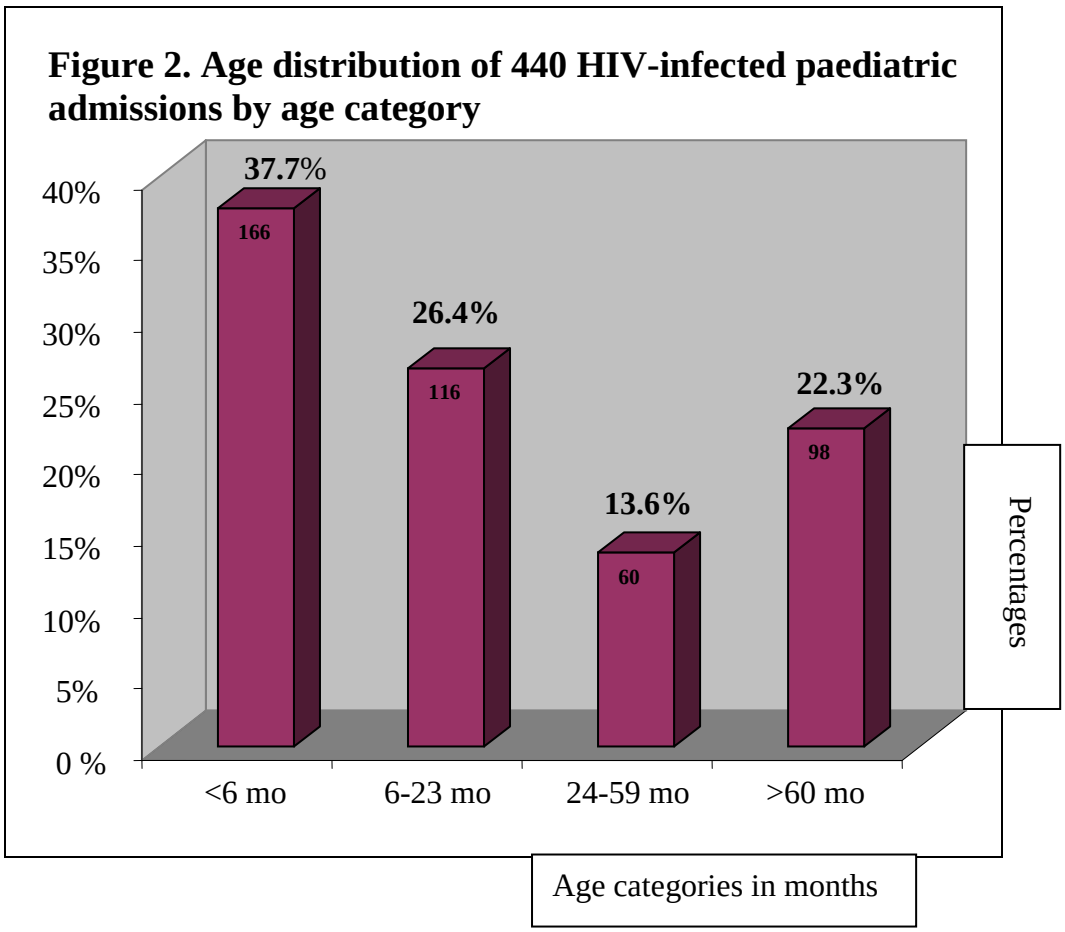
HIV Status	**Number admitted** n = 1510	**Percentage prevalence** Total = 100%	**95% Confidence Interval**
HIV-infected	446	29.5	27.2 – 31.9
HIV-negative	780	51.7	49.1 – 54.2
HIV-exposed	57	3.8	2.9 – 4.9
HIV-unknown	227	15	13.3 – 16.9

3.2 Characteristics and disease profile of confirmed HIV-infected paediatric admissions

3.2.1 Demographics

Four hundred and forty-six HIV-infected children were admitted during the study period. Six hospital records from the study sample of 446 HIV-infected children could not be located and these children were thus excluded from the study. Of the remaining 440 children, 234 (53.2%) were male and 206 (46.8%) were female. Their ages ranged from 1 month to 167 months with a median age of 10 months and an interquartile (IQR) [25th to 75th quartiles] range of 3 to 44.5 months. No other socio-demographical data was collected for these children. The age distribution of the 440 HIV-infected children was: 166 (37.7%) under 6 months of age, 116 (26.4%) 6 to 23 months of age, 60 (13.6%) 24 to 59 months of age and 98 (22.3%) over 60 months of age.

The age distribution of HIV-infected children is illustrated in Figure 2.



3.2.2 Timing of HIV diagnosis amongst HIV-infected children

Of the 440 children in the study population, 238 (54.1%) were newly diagnosed with HIV during ward admission. Two hundred and two children (45.9%) were known to be HIV-infected (of which more than 90% were currently attending hospital or community-based HIV clinics, although data on the breakdown of different HIV services attended was not formally collected.) The newly diagnosed children were more likely to be younger (median age of 6 months) whereas children known to be HIV-infected were older (median age of 20 months.) ($p = 0.001$) Data regarding timing and place of HIV diagnosis in the group known to be HIV-infected were not available from hospital records.

3.2.3 Self reported access to prevention of mother-to-child transmission (PMTCT) services amongst HIV-infected children less than 6 months of age

Data concerning PMTCT interventions was analysed for a subgroup of the study population, namely HIV-infected infants under the age of 6 months (n=166). Owing to the limited availability of data, review of PMTCT interventions was restricted to HIV-infected infants under 6 months of age, who were more likely to have PMTCT data recorded in their files. Self-reported maternal HIV status, Nevirapine (NVP) exposure and use of Cotrimoxazole (CTX) prophylaxis were determined for this subgroup.

3.2.3.1 Self reported maternal HIV status

Ninety of 166 (54.2%) mothers to HIV-infected infants less than 6 months old reported their status as HIV-positive and 25/166 (15.1%) reported their status as HIV-negative. A further 51/166 (30.7%) mothers reported their status as HIV-unknown or -untested or had no data regarding maternal HIV status available in their infant's hospital record. The latter group of HIV-infected infants whose mothers' HIV status was unknown included

abandoned infants, maternal orphans and infants brought to hospital by a caregiver other than the biological mother.

Of the 25 mothers reporting their status as HIV-negative, 13/25 (52%) had delivered at CHBH, 5/25 (20%) at a clinic, 3/25 (12%) at another hospital, 1/25 (4%) was born before arrival at hospital (BBA) and in 3/25 (12%) birthplace could not be determined from the hospital record. HIV was newly diagnosed in 22/25 (88%) of infants to these mothers (who reported their status as HIV-negative).

3.2.3.2 Nevirapine exposure

The frequency of NVP exposure as part of the PMTCT programme was calculated for this subgroup of HIV-infected infants less than 6 months of age. Sixty of 166 (36.2%) mother/infant pairs received NVP, 55/166 (33.1%) did not receive NVP and in 51/166 (30.7%) it could not be determined if NVP was received as either the required data had not been recorded or was unknown to the mother. In the latter (NVP unknown) group, the majority of cases had no PMTCT information recorded in the hospital file and a minority had documented in their hospital record that the primary caregiver or mother was unsure if NVP had been received.

3.2.3.3 Cotrimoxazole prophylaxis

Frequency of CTX prophylaxis usage at the time of hospital admission was determined by review of admission records for the subgroup of HIV-infected infants under 6 months of age. Forty-six of 166 (27.7%) infants were currently receiving CTX, 114/166 (68.7%) were not currently receiving CTX and in 6/166 (3.6%) infants CTX usage was unknown. Those infants that had received NVP at birth were significantly more likely to be receiving

CTX at the time of hospital admission, compared with infants who had not received NVP or had unknown NVP exposure. (p=0.008)

The 114/166 (68.7%) infants who were not receiving CTX prophylaxis at the time of hospital admission included 34 infants under the age of 2 months. As per a request from the Wits Ethics committee, age in months rather than exact date of birth was documented during data collection. Therefore it was not possible to calculate exactly how many infants were less than 6 weeks of age and therefore not yet commenced on CTX prophylaxis at the time of hospital admission. If these 34 infants under the age of 2 months are excluded from the analysis i.e. 166 - 34 = 132, then 40/132 (30.3%) infants were currently receiving CTX, 86/132 (65.2%) were not currently receiving CTX and in 6/132 (4.5%) infants CTX usage was unknown.

Among the same overall subgroup of infants (n = 166), 51/166 (30.7%) were known to be HIV-infected and 115/166 (69.3%) were newly diagnosed at the time of hospital admission. Of the 51 infants previously diagnosed/known to be HIV-infected, 39/51 (76.5%) were receiving CTX prophylaxis at the time of hospital admission. Among the 115 newly diagnosed infants, 7/115 (6.1%) were receiving CTX prophylaxis. The 7 infants newly diagnosed but already receiving CTX, were infants who were known to be HIV-exposed at birth. They had been correctly commenced on CTX prophylaxis from 6 weeks of age, but had not had HIV PCR testing before hospital admission.

Table 2. indicates the breakdown of PMTCT interventions amongst the subgroup of infants less than 6 months of age. (n = 166)

Table 2. Breakdown of PMTCT interventions in infants less than 6 months of age

PMTCT intervention/s	Frequency/Number (Total n = 166)	Percentage (Total = 100%)
No interventions	76	45.8
NVP + CTX + early diagnosis	20	12
NVP + CTX	4	2.4
NVP + early diagnosis	4	2.4
CTX + early diagnosis	19	11.5
NVP only	32	19.3
CTX only	3	1.8
Early diagnosis only	8	4.8

Seventy-six (45.8%) of all 166 infants less than 6 months of age received no PMTCT interventions. Only 20/166 (12%) of infants received all recommended interventions i.e. NVP and CTX prophylaxis and an early HIV PCR test to diagnose HIV infection.

3.2.3.4 Place of birth

Table 3. displays data on place of birth for the subgroup of HIV-infected infants less than 6 months old. Eighty-three of 166 (50.1%) infants were born at CHBH, 21/166 (12.6%) at a local clinic, 20/166 (12.0%) at another hospital, 4/166 (2.4%) at home/BBA and 38/166 (22.9%) of unknown birthplace. There was no statistically significant association between place of birth (CHBH versus clinic/other hospital/BBA) and access to NVP or CTX. ($p = 0.1288$ and $p = 0.5818$ respectively.)

Table 3. PMTCT interventions in infants less than 6 months of age by place of birth

Place of Birth	Number of infants n = 166 (100%)	Received NVP (%)	Received CTX (%)
CHBH	83 (50.1)	43/83 (51.8)	26/83 (31.3)
Clinic	21 (12.6)	6/21 (28.6)	4/21 (19)
Other hospital	20 (12)	9/20 (45)	7/20 (35)
BBA	4 (2.4)	2/4 (50)	1/4 (25)
Birthplace Unknown	38 (22.9)	0/38 (0)	8/38 (21)
All infants < 6 months of age	166 (100)	60/166 (36.2)	46/166 (27.7)

Data for NVP and CTX use was stratified and re-analysed by place of birth at local clinic and at other hospitals. When comparing infants born at CHBH versus birth at a clinic, the difference in documented NVP use approached statistical significance ($p = 0.057$) However, there was no difference in frequency of NVP usage between infants born at CHBH versus infants born at other hospitals ($p = 0.5847$). There was also no statistically significant association between place of birth and CTX usage when stratified for CHBH versus local clinic and CHBH versus other hospitals ($p = 0.2672$ and $p = 0.7519$ respectively.)

3.2.3.5 PMTCT interventions by maternal self-reported HIV status

Table 4. Comparison of NVP and CTX prophylaxis uptake in infants less than 6 months of age by self-reported maternal HIV status

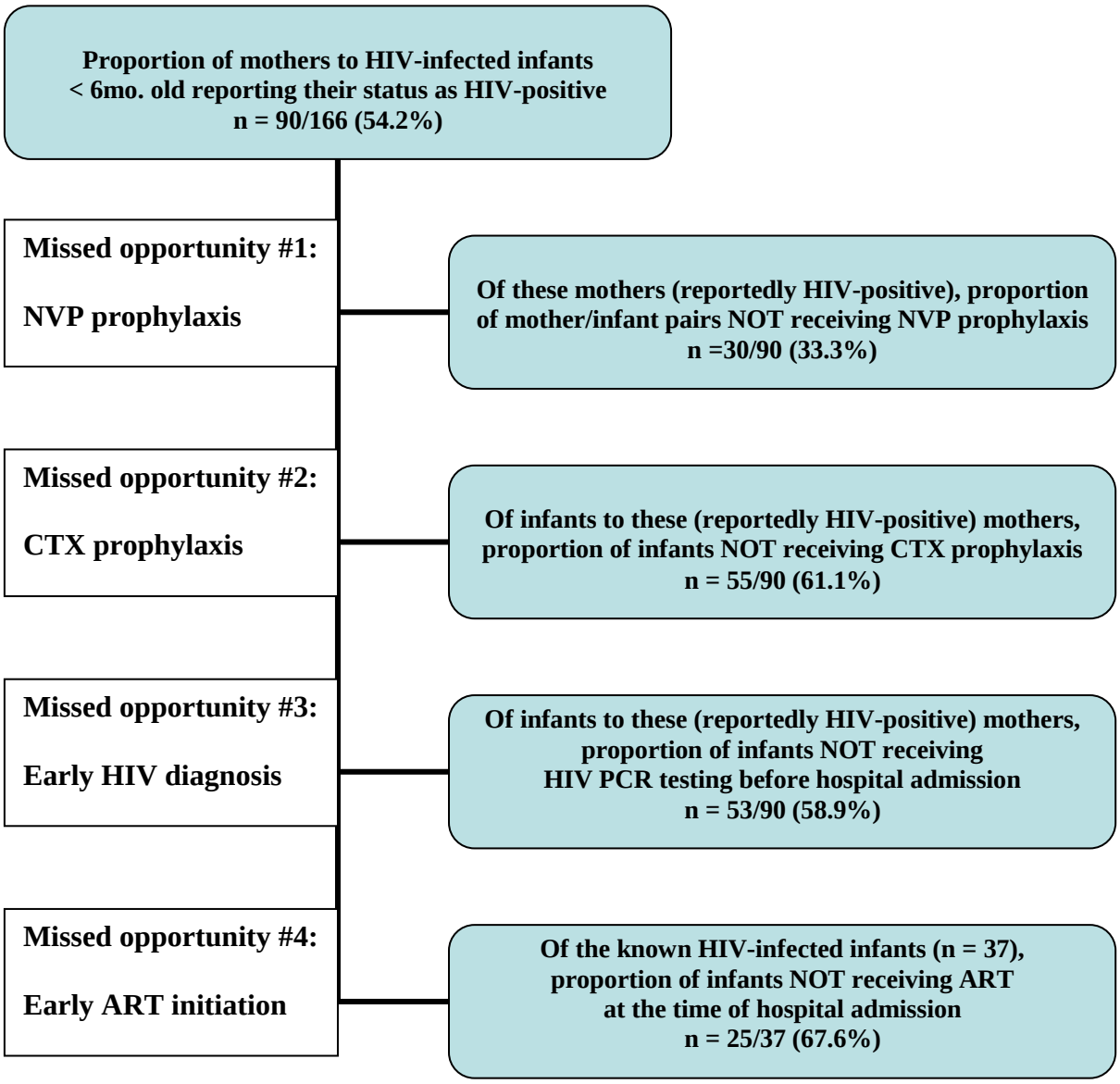
	Self-reported HIV status of mothers to infants < 6 mo. (n=166)			
PMTCT intervention	**Total (regardless of maternal HIV status) n = 166 (100%)**	**Mother reportedly HIV-positive n = 90 (54.2%)**	**Mother reportedly HIV -negative or HIV-unknown n = 76 (35.8%)**	**p-value**
Mother/infant pair received NVP				
Yes	60 (36.2)	60 (66.7)	0 (0)	
No	55 (33.1)	13 (14.4)	42 (55.2)	
Unknown	51 (30.7)	17 (18.9)	34 (44.8)	<0.0001
Infant receiving CTX prophylaxis				
Yes	46 (27.7)	35 (38.9)	11 (14.5)	
No	114 (68.7)	50 (55.6)	64 (84.2)	
Unknown	6 (3.6)	5 (5.5)	1 (1.3)	0.0001

Table 4. compares uptake of NVP and CTX prophylaxis among infants less than 6-months whose mothers were reportedly HIV-positive versus mothers reportedly HIV-negative or HIV-unknown. Infants whose mothers reported their status as HIV-positive were significantly more likely to have received NVP and CTX prophylaxis than infants whose mothers reported their status as HIV-negative or HIV-unknown. ($p = <0.0001$ and 0.0001 respectively)

3.2.3.6 Missed opportunities for PMTCT interventions

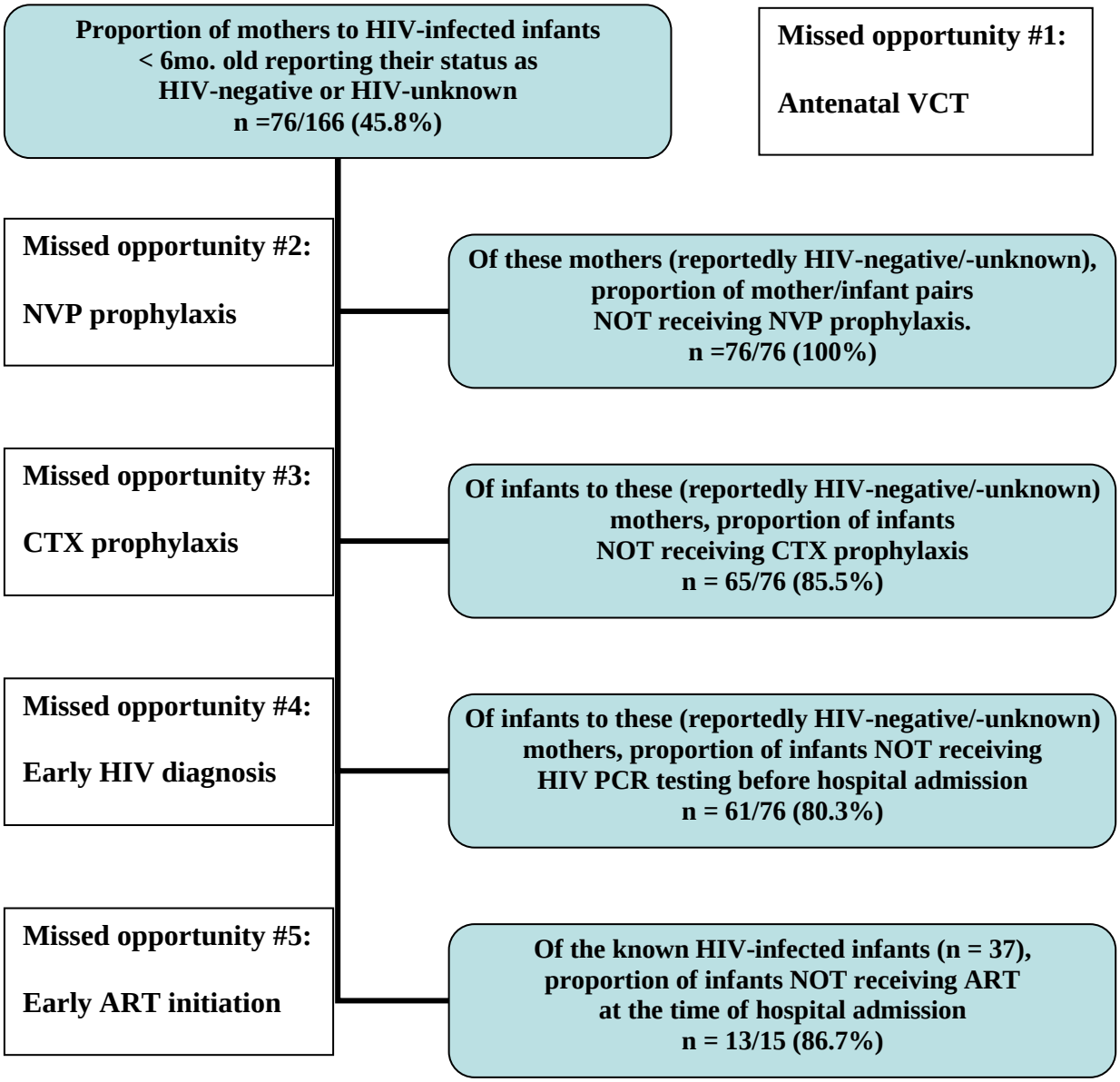
The flow chart below highlights the multiple levels of missed opportunities for PMTCT implementation in the subgroup of infants under 6 months of age whose mothers reported their status as HIV-positive.

Figure 3. Missed opportunities for PMTCT interventions in infants less than 6 months old born to mothers who self-reported their status as HIV-positive



The flow chart below highlights the multiple levels of missed opportunities for PMTCT implementation in the subgroup of infants under 6 months of age whose mothers reported their status as HIV-negative or HIV-unknown.

Figure 4. Missed opportunities for PMTCT interventions in infants less than 6 months old born to mothers who self-reported their status as HIV-negative or HIV-unknown.

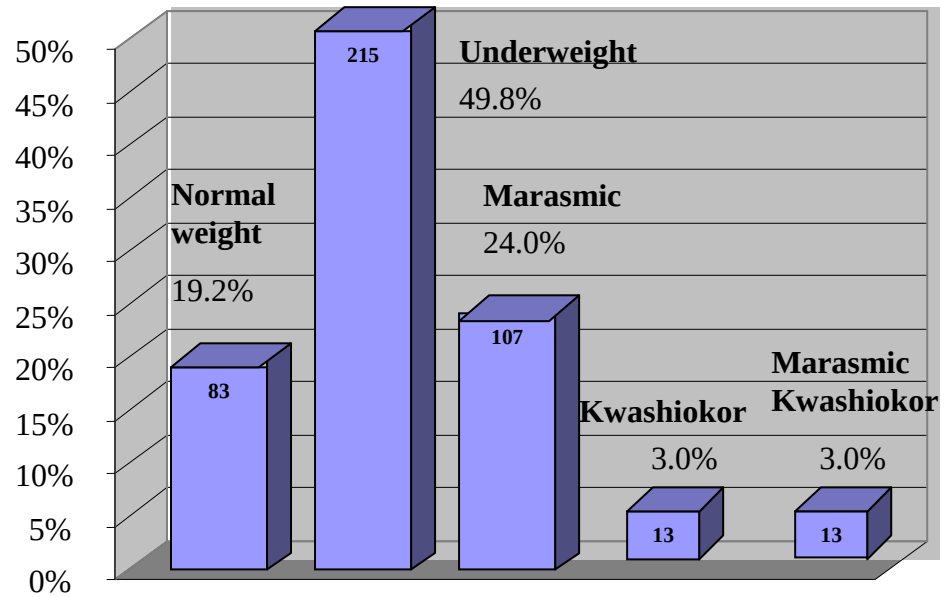


No detailed data was collected on whether mothers were actually tested for HIV, when they were tested and why in many cases, mothers with HIV-infected infants reported their own status as HIV-negative or HIV-unknown. This information, although interesting and important, was not available from the hospital records and was beyond the scope of the thesis.

3.2.4 Nutritional status

Of the 440 records found for HIV-infected children admitted during the study period, 9 records had no documentation of weight at the time of hospital admission and therefore n=431. For these 431 children, nutritional status was assessed using the Wellcome classification.

Figure 5. Wellcome classification of HIV-infected children (n = 431)



The majority (80.8%) of children were malnourished when assessed using the Wellcome classification. Only 19.2% of children had a normal weight for age (above the 3rd centile for expected weight for age on the WHO growth reference charts.)

Table 5. Median weight for age z-scores by age category in months

Age category	Number of children	Median weight for age z-score
< 6 months	163	-3.52
6 – 23 months	116	-3.29
24 – 60	68	-1.93
All children 60 months or less	347*	-3.23

*Total number of children aged 60 months or less for whom admission weight data was available.

Table 5. describes weight for age z-scores analysed for a subgroup of the study population who were 60 months or less of age and who had admission weight data recorded in the hospital file. (n = 347) Analysis was performed using WHO references that are only available for children 60 months of age or younger. Therefore no weight for age z-score analyses were performed for children above 60 months of age. The median weight for age z-score in children 60 months and younger was -3.23, with an interquartile (25th to 75th quartiles) range of -4.3 to -1.71. Older children (between 24 and 60 months of age) had a better, although still decreased median weight for age z-score of -1.93.

3.2.5 HIV staging

WHO HIV staging classification (Appendix 2) was determined by review of clinical parameters documented in the hospital record from the time of hospital admission. Almost 93% of all paediatric admissions had advanced HIV disease and were classified as WHO HIV stage 3 or 4.

Table 6. WHO Staging of 440 HIV-infected paediatric admissions at CHBH

WHO HIV Stage	Number (n = 440)	Percent (100%)
1	3	0.7
2	29	6.6
3	188	42.7
4	220	50

Table 7. documents the breakdown of criteria used to classify the 440 HIV-infected children by WHO HIV stage. On Wellcome classification, 348/431 children who had admission weight data available were malnourished. The number of children in whom failure to thrive (FTT) was used as a WHO HIV staging criterion is discrepant with the number of malnourished children (by Wellcome classification) because criteria other than FTT were used in many cases to assign WHO HIV stage.* Other than FTT, pulmonary TB and presumed HIV encephalopathy were the most common staging criteria used.

Table 7. Prevalence of specific WHO staging criteria amongst 440 HIV-infected paediatric admissions at CHBH

Staging Criteria	Number (n=440)	Percent (100%)
Stage 1: Generalized lymphadenopathy	3	0.7
Stage 2: Severe bacterial infection	6	1.4
Hepatosplenomegaly	23	5.2
Stage 3:** Pulmonary TB	74	16.8
Moderate FTT (60-80% expected weight for age)	105*	23.9
Stage 4:** Extrapulmonary TB	26	5.9
Severe FTT (< 60% expected weight for age)	102*	23.2
Presumed HIV encephalopathy	40	9.1
Severe FTT + encephalopathy	21	4.8
Pneumocystis jiroveci pneumonia	18	4.1
Cytomegalovirus infection	5	1.1
Other[#]	18	3.4

[#] cytopaenias, oesophageal candidiasis, HIVAN, NHL, disseminated MAC, recurrent pneumonia.

* The number of children in whom failure to thrive (FTT) was used as a WHO HIV staging criterion is discrepant with the number of malnourished children (by Wellcome classification) because criteria other than FTT were used in many cases to assign WHO HIV stage.

** The difference between number and percentage of children with stage 3 and stage 4 criteria in Table 6. is made up by children with WHO HIV staging criteria shown in the category "Other".

3.2.6 Antiretroviral treatment (ART)

Of the 440 HIV-infected children in the study population, 76 (17.3%) were on ART and 364 (82.7%) were not currently on ART at the time of hospital admission. Of the 76 (17.3%) children receiving ART at the time of hospital admission, the median duration of treatment was 2 months, with an interquartile (25^{th} to 75^{th} quartile) range of 1 to 10 months and a minimum of 1 and maximum of 48 months. Of the 364 children not currently on

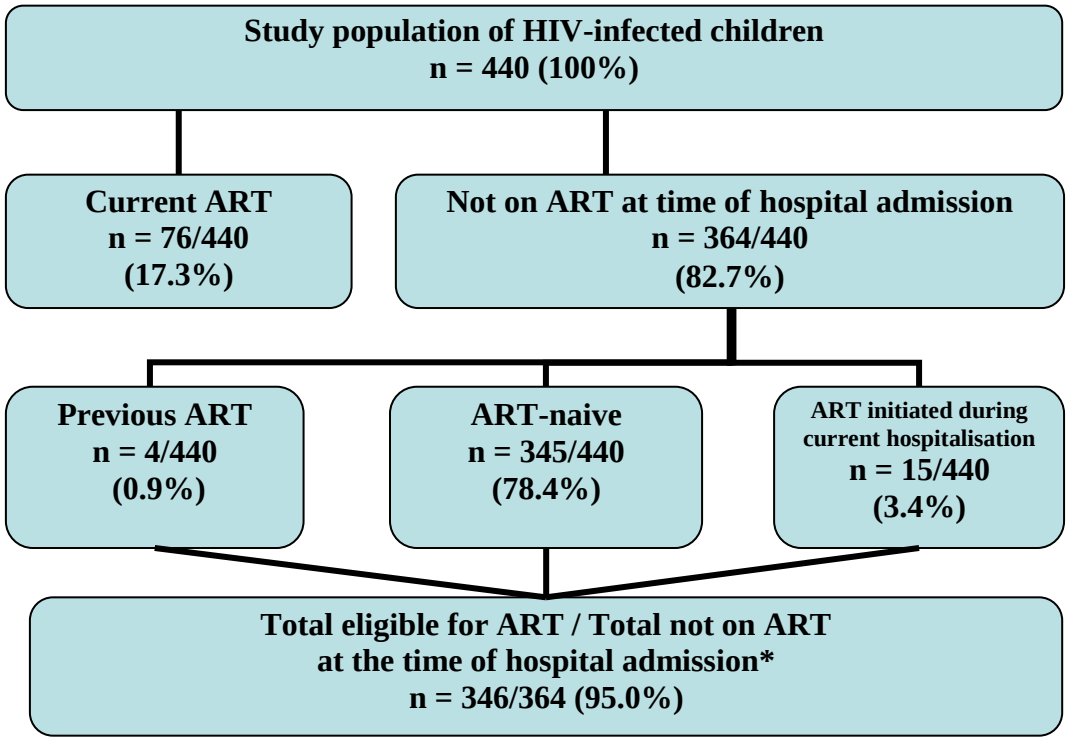
ART at the time of hospital admission, 345/364 (94.7%) had never been on ART, 4/364 (1.1%) had been previously treated but had stopped therapy and 15/364 (4.1%) had ART initiated as an inpatient during the course of their admission.

Of the 364 (82.7%) children not receiving ART at the time of hospital admission, 346 (95%) qualified for HAART. This calculation was based on the 2004 South African National Antiretroviral Treatment Guidelines for paediatric patients.[2] These guidelines recommended ART initiation in children less than 18 months of age with WHO stage 3 or 4 disease and/or CD4 < 20% and for children 18 months or older recommended ART initiation with WHO stage 3 or 4 disease and/or CD4 < 15%. There are other clinical (recurrent or prolonged hospitalisation) and social (identifiable caregiver and HIV disclosure) criteria for paediatric ART initiation which were not taken into account for this calculation owing to the lack of relevant information in hospital admission notes.

Of the 202/440 (45.9%) children known to be HIV-infected before hospital admission, 74/202 (36.6%) were currently receiving ART. Of the remaining 128/202 children known to be HIV-infected before hospital admission, 121/128 (94.5%) had WHO HIV stage 3 or 4 disease and thus were eligible for ART.

The flow chart in Figure 6.below illustrates the uptake of antiretroviral treatment amongst the 440 HIV-infected children in the study population.

Figure 6. Antiretroviral treatment status among 440 HIV-infected children



*Eligibility was determined during data analysis and was based on the criteria stipulated in the 2004 South African National Antiretroviral Treatment Guidelines for paediatric patients.[2]

3.2.7 Immunological indices

CD4 percentages and absolute CD4 counts were analysed in a subgroup of the study population who had CD4 testing performed within a month before or after the date of hospital admission. This subgroup was selected so that only CD4 counts from a timeframe close to that of the hospital admission date were analysed. The median CD4 percentage was 15% (IQR 18.2- 22.8) for the 320 children in whom recent results were available. Two hundred and fifty-four (79.4%) of the group had CD4 percentages of <25%, indicative of immune suppression. The median CD4 cell count was 485 cells/ul (IQR 192 - 932) for the

312 children in whom recent results were available. One hundred and sixty (51.3%) of the group had CD4 cell counts of <500 cells/ul, indicative of immune suppression.

Table 8. Median CD4 percentages classified by age group in months and proportion of CD4 percentages less than 25%

All age categories combined (n = 320)*		**<6mo** (n = 116)	**6-23mo** (n = 73)	**24-59mo** (n = 46)	**>= 60mo** (n = 85)
Median CD4 percentage (IQR)	**15.0%** (18.2- 22.8)	19.8% (13.7- 28.5)	15.9% (11.5 - 22.6)	12.6% (6.6 - 19.4)	8.0% (4.5 - 14.7)
CD4% < 25%# (percentage)	254/320 **(79.4)**	76/116 (65.5)	58/73 (79.5)	39/46 (84.8)	81/85 (95.3)

* Only 320/440 HIV-infected children had a CD4 percentage available that fell within the investigator-stipulated one month selection period on either side of the hospital admission date. # The CD4 percentage cut-off selected corresponds with the Centres for Disease Control (CDC) 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age which considered a CD4 percentage below 25% as evidence of immune suppression.[42]

Table 9. Median CD4 count classified by age group in months and proportion of absolute CD4 counts < 500 cells/ul

All age categories combined (n = 312)*		**<6mo** (n = 113)	**6-23mo** (n = 71)	**24-59mo** (n = 45)	**>= 60mo** (n = 83)
Median CD4 cell count - cells/ul (IQR)	485 (192-932)	796 (377 - 1474)	536 (395 - 889)	476 (208 - 875)	171 (44 - 389)
CD4 count < 500 cells/ul# (percentage)	160/312 (51.3)	35/113 (31.0)	32/71 (45.0)	24/45 (53.3)	69/83 (83.1)

* Only 312/440 HIV-infected children had an absolute CD4 count available that fell within the investigator stipulated one month selection period on either side of the hospital admission date. # The absolute CD4 count cut-off selected corresponds with the Centres for Disease Control (CDC) 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age which considered a CD4 count below 500 cells/ul as evidence of moderate immune suppression in children aged 6 – 12 years and as evidence of severe immunosuppression in children less than 5 years of age.[42]

3.2.8 Primary diagnosis

The primary diagnoses or main reasons for hospitalisation of HIV-infected paediatric admissions at CHBH are summarised in Table 10.

Table 10. Primary Diagnoses

Primary Diagnosis	**Number** (n = 440)	**Percent** (100%)
Pneumonia - other than *Pneumocystis jiroveci* pneumonia (PJP) and pulmonary tuberculosis (pTB)	125	28.4
Gastroenteritis	77	17.5
Pulmonary TB (pTB) - (45 presumed + 10 confirmed cases)	55	12.5
Other*	49	11.1
Septicaemia	42	9.6
Extrapulmonary TB (EPTB)	30	6.8
PJP/presumed PJP	24	5.5
Meningitis	23	5.2
Urinary Tract Infection	15	3.4

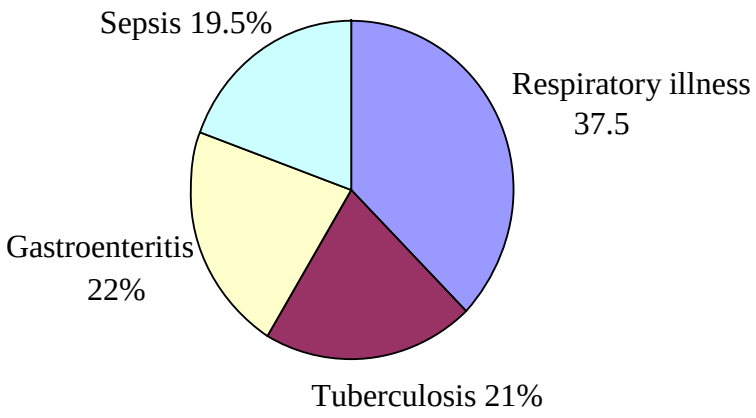
*anaemia, chronic lung disease, Cor pulmonale, IRIS, HIVAN

Pneumonia (other than PJP ad pTB) and gastroenteritis were the most frequent primary diagnoses at the time of hospital admission, accounting for 125/440 (28.45) and 77/440 (17.5%) respectively. Tuberculosis (pulmonary and extra-pulmonary) represented 55/440 (12.5%) and 30/440 (6.8%) of all primary diagnoses.

In some of the 440 HIV-infected children, the admitting doctor had recorded more than one diagnosis. Based on the ranking of the diagnoses in the hospital records, a primary and secondary diagnosis was recorded during data collection. Data on the primary and secondary diagnoses (reasons for hospitalization) were combined to produce Figure 7. which illustrates the proportional contribution of the four main reasons for hospital admission:

- Respiratory illness (including PJP and CMV pneumonitis) accounted for 37.5% of all admission diagnoses.
- Tuberculosis (including pulmonary and EPTB) accounted for 21% of all admission diagnoses.
- Gastroenteritis accounted for 22% of all admission diagnoses.
- Sepsis (including septicaemia, meningitis and urinary tract infection) accounted for 19.5% of all admission diagnoses.

Figure 7. Principal reasons for hospitalisation



3.2.9 Spectrum of infectious pathogens

One hundred and ten children (25%) of the HIV-infected study population had a confirmed bacterial, viral, protozoal or fungal infection during their hospital admission. The spectrum of pathogens that were encountered is represented in table 11. Percentage representation of each pathogen was calculated for the bacterial organisms only.

Table 11. Spectrum of infectious pathogens (bacterial and other)

Organism – Bacteria	**n = 86**	**Percentage of total bacterial pathogens**
Streptococcus pneumoniae	23	26.7
E coli species	16	18.6
Mycobacterium tuberculosis	10	11.6
Salmonella species	6	7.0
E coli extended spectrum B-lactamase producer (ESBL)	4	4.7
Klebsiella extended spectrum B-lactamase producer (ESBL)	4	4.7
Haemophilus influenza	3	3.5
Klebsiella species	3	3.5
Enterococcus faecalis	3	3.5
Methicillin-resistant Staphylococcus aureus (MRSA)	3	3.5
Acinetobacter baumanni	3	3.5
Mycobacterium avium intracellulare	1	1.2
Other bacterial: *Staphylococcus aureus, Proteus mirabilis, Pseudomonas aueruginosa, Enteropathogenic ecoli*	7	8
Organism – Viral/Other	**n = 24**	
Cytomegalovirus	14	
Varicella zoster	3	
Parvovirus	2	
Herpes zoster	2	
Measles	1	
Malaria falciparum	1	
Candida albicans	1	

Streptococcus pneumoniae was the most common bacterial isolate and *Cytomegalovirus* was the most common viral isolate among the 440 HIV-infected children. Of note was that many bacterial isolates from admission blood cultures were resistant to the empiric, first-line antibiotic regimen (Ampicillin and Gentamicin) employed at CHBH to treat presumed bacterial infections in immunocompromised (HIV-infected) children. Of all bacterial isolates (excluding *M. tuberculosis* and MAC) on blood, CSF and urine culture, 48% (36/75) were fully or intermediately resistant to one or both of these first line antibiotics. The proportion of isolates resistant to both antibiotics versus single antibiotic resistance was not recorded during the initial data collection and thus further analysis of resistance patterns is not possible with the existing dataset.

Table 12. Spectrum of infectious pathogens in the 53 HIV-infected children who died

Organism	**Number** (n = 24)	**Percentage** (100%)
Streptococcus pneumoniae	5	20.8
Cytomegalovirus	5	20.8
E coli species	3	12.5
Mycobacterium tuberculosis	3	12.5
Klebsiella extended spectrum B-lactamase producer (ESBL)	2	8.2
Salmonella species	1	4.2
E coli extended spectrum B-lactamase producer (ESBL)	1	4.2
Proteus mirabilis	1	4.2
Pseudomonas aueruginosa	1	4.2
Klebsiella species	1	4.2
Enterococcus faecalis	1	4.2

Table 12. lists the organisms cultured or proven on post-mortem biopsy specimens (in the case of CMV infection) among the 53 children who died. Of these children, 24/53 (45.3%) had a culture-confirmed infection in blood, urine or CSF culture at the time of death. The remaining 29/53 children who died had no growth on blood cultures. Children who died were significantly more likely to have a proven infection compared to children who survived (p=< 0.001). In 5/53 (9.4%) children who died, *Streptococcus pneumoniae* was isolated on culture of blood or CSF. In another 5/53 (9.4%) children who died, *Cytomegalovirus* infection was confirmed on post-mortem biopsy specimens.

3.2.10 Outcome of HIV-infected paediatric admissions at CHBH

Of the 440 HIV-infected children admitted during the study period, 309 (70.2%) were discharged home with no ICU stay, 10 (2.3%) were discharged home after a stay in ICU, 3 (0.6%) died in ICU, 50 (11.4%) died in the general wards and 68 (15.5%) were transferred to a step-down hospital facility to complete their treatment. The median duration of hospital stay was 7.0 days with an interquartile range of 4 to 10 days.

Table 13. lists the admission diagnoses and organism/s cultured for the 13 HIV-infected children who were admitted to ICU. Respiratory illness was the underlying diagnosis in 6 of the 13 (46.1%) children admitted to ICU. Only one out of the 13 ICU admissions was for a non-infectious illness (diabetic ketoacidosis.)

Table 13. Primary Diagnoses of 13 HIV-infected children admitted to ICU

Primary Diagnosis	**Number** (n = 13)	**Percent** (% = 100)	**Organism/s Cultured**
Pneumonia - other than *Pneumocystis jiroveci* pneumonia (PJP) and pulmonary tuberculosis (pTB)	2	15.4	*E coli* species
PJP/presumed PJP	3	23	None
Gastroenteritis	1	7.7	None
Pulmonary TB (pTB)	1	7.7	None
Septicaemia/UTI	1	7.7	*Haemophilus influenza and Candida albicans*
Extrapulmonary TB (EPTB)	1	7.7	None
Meningitis	1	7.7	*Streptococcus pneumoniae*
Epiglottitis	1	7.7	None
Diabetic ketoacidosis	1	7.7	None
Pericardial effusion	1	7.7	None

Figure 8. illustrates the distribution of deaths by age category in months among the 53 HIV-infected children who died. The greatest number of deaths in HIV-infected children (28/53 [52.8%]) occurred in young infants less than 6 months of age.

Figure 8. Distribution of deaths by age category in HIV-infected children. (n = 53)

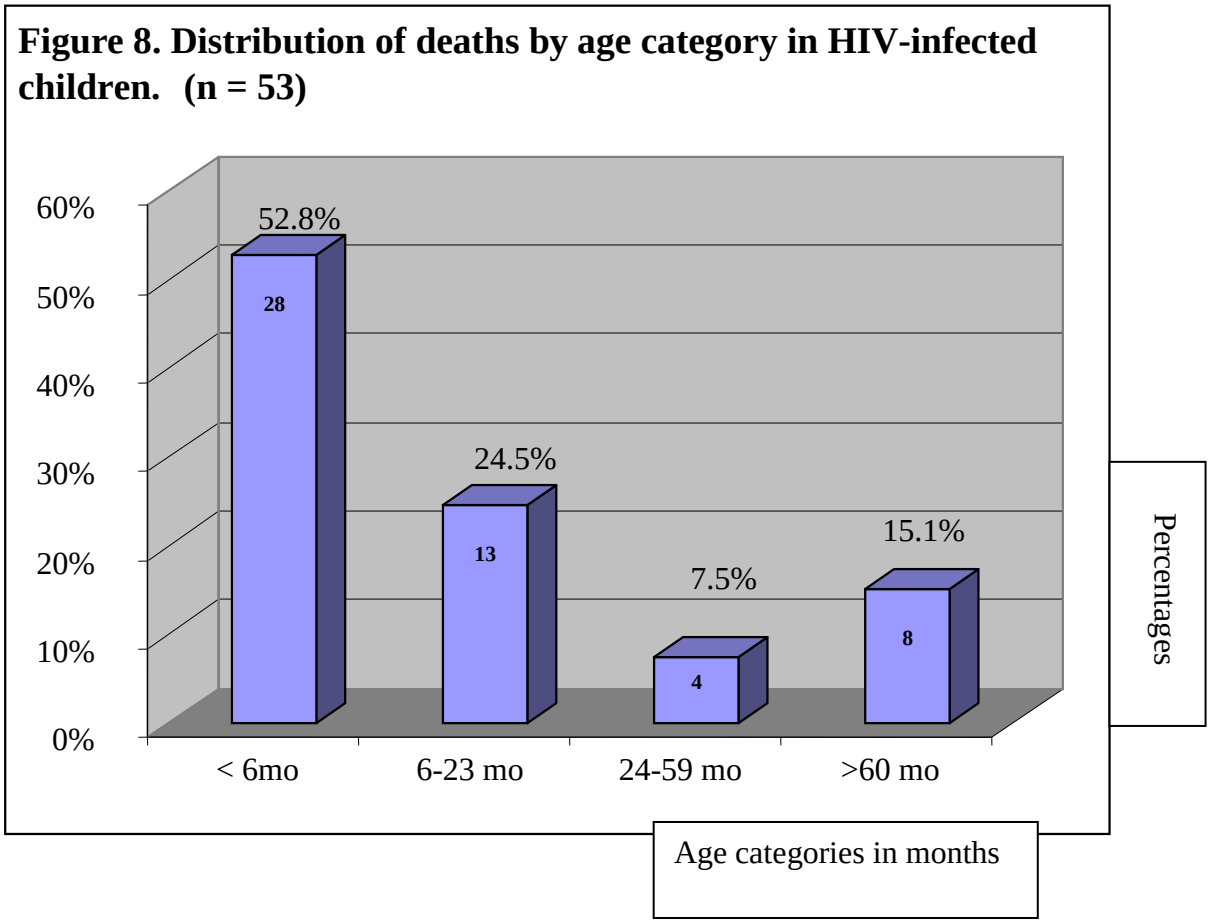


Table 14. Case fatality rate by age group in HIV-infected admissions

Age category	Deaths / Category total number	Percentage Case Fatality Rate	95% Confidence Intervals
Overall	53/440	12	9.2–15.5
<6mo	28/166	16.9	11.5-23.5
6-23mo	13/116	11.2	6.1-18.4
24-59mo	4/60	6.7	1.9-16.2
>60mo	8/98	8.2	3.6-15.5

HIV-related deaths contributed 53 of the total 91 deaths in the paediatric general wards during the study period (i.e. 58.2% of all paediatric deaths). The overall case fatality rate in the study population of HIV-infected children was 53/440. (12.0% [95% CI 9.2–15.5%]) In contrast, the risk of mortality in the HIV negative, HIV-exposed and HIV unknown group over the study period was 38/1064. (3.6% [95% CI 2.5-4.9%]) The highest case fatality rate by age category, occurred in infants aged less than 6 months, with 28 deaths among 116 infants. (16.9% [95% CI 11.5-23.5%])

Variables in the 53 children who died were compared to those in the 387 children who survived to hospital discharge to determine which features were associated with poorer outcomes.

Table 15. Comparison of HIV-infected patient characteristics by final outcome

Characteristic (Total n = 440)	**Outcome = Death (n = 53)**	**Outcome = Survival (n=387)**	**p-value**	**Odds Ratio**	**95% Confidence Interval**
Median age (IQR)	5 months (3 -13 mo.)	12 months (4 – 48 mo.)	0.2	-	-
Median weight for age z-score# (IQR)	-4.4 (-4.9 to -3.0)	-3.0 (-4.1 to -1.7)	0.005	-	-
Newly diagnosed	34/53 (64%)	204/387 (52.7%)	0.11	0.62	0.3-1.1
Receiving ART	6/53 (11.3%)	70/368* (19%)	0.17	0.54	0.2-1.3
WHO HIV Stage 3 or Stage 4	50/53 (94.4%)	358/387 (92.5%)	0.62	1.35	0.4-4.6
Median CD4 number (IQR)	401 cells/ul (99-711)	486 cells/ul (210-949)	0.18	-	-
Median CD4% (IQR)	13.9% (6.9-20.8%)	15.2% (8.3-23.0%)	0.32	-	-
Receiving CTX prophylaxis	17/53 (32.1%)	148/387 (38.2%)	0.43	0.78	0.4-1.5

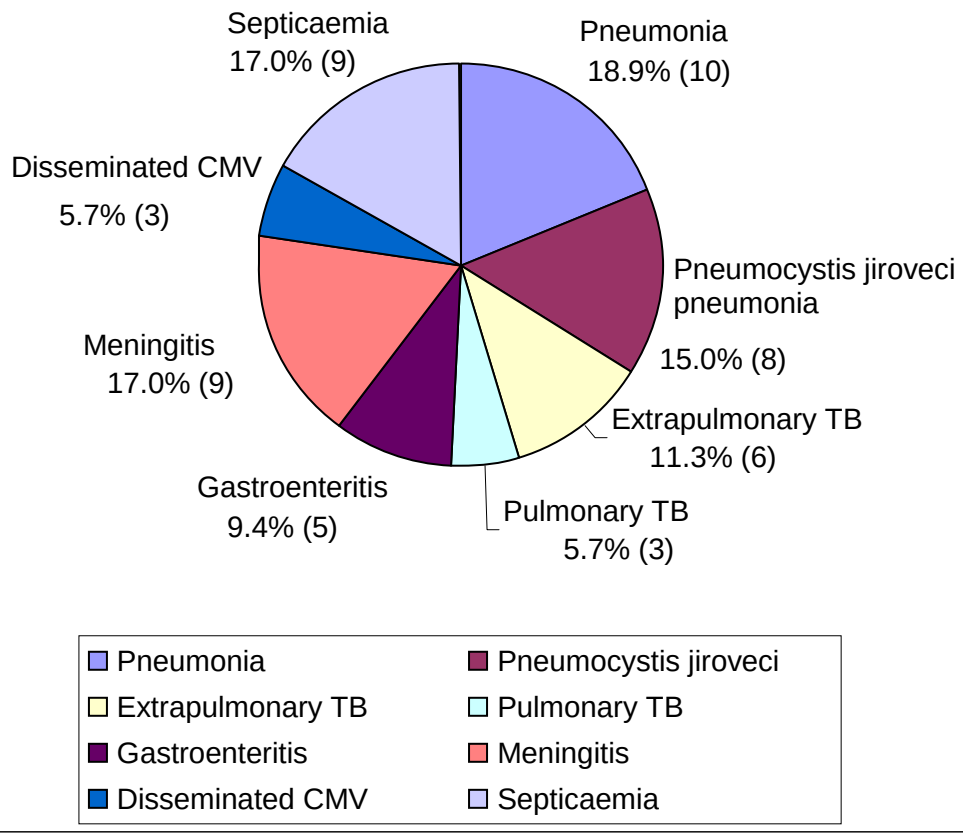
This calculation was only performed in patients aged 60 months or younger who had a documented weight in the hospital record, therefore in the death group n = 44 and in the survival group n = 303. * This denominator excludes patients who had received ART in the past, but were not receiving ART at the time of hospital admission and excludes patients who had inpatient initiation of ART. (n = 19)

There were no significant differences between median age, new HIV diagnosis, frequency of ART, WHO staging, immunological indices or frequency of CTX prophylaxis between HIV-infected children who died versus those who survived. However, median weight for age z-score was significantly lower in the group of children who died versus those who survived. (p = 0.005)

3.2.11 Cause of death in HIV-infected paediatric admissions at CHBH

Infections were associated with all 53 deaths amongst HIV-infected children. PJP, an illness largely preventable by CTX prophylaxis, accounted for 8/53 (15%) of all deaths. Figure 9 illustrates the proportional contribution of each aetiology.

Figure 9. Causes of death in HIV infected children (n = 53)



3.2.12 Comparison of groups by ART status

Differences in the subgroup of patients receiving ART at the time of hospital admission and the subgroup of ART-naive patients are tabulated below. Children who had inpatient initiation of ART during the current hospital admission and children who had received ART in the past were excluded from this analysis.

Table 16. Comparison of HIV-infected patient characteristics by population receiving ART versus ART-naive population

Characteristic (Total n = 421)	**Receiving ART (n = 76)**	**ART-naive (n = 345)**	**p-value**	**Odds Ratio**	**95% Confidence Interval**
Median age (IQR)	38 months (10.5 – 98 mo.)	7 months (3 – 32 mo.)	<0.0001	-	-
Median weight for age z-score (IQR)#	-2.8 (-4.1 to -1.6)	-3.3 (-4.4 to -1.9)	0.32	-	-
Receiving CTX Prophylaxis	71/76 (93.4%)	82/345 (23.8%)	<0.0001	0.01	0.002-0.04
WHO HIV Stage 3 or Stage 4	75/76 (98.7%)	314/345 (91.0%)	0.02	0.14	0.02-0.09
Median CD4 number (IQR)	403 cells/ul (94-682)	505 cells/ul (224-996)	0.09	-	-
Median CD4% (IQR)	13.3% (6.3-19.2%)	15.9% (9.4-23.9%)	0.008	-	-
Inpatient mortality rate	6/76 (7.9%)	47/345 (13.6%)	0.17	-	-
Median duration of hospital stay	6.5 days (4-10 days)	7.0 days (4-10 days)	0.93	-	-

This calculation was only performed in patients 60 months of age or younger who had a documented weight in the hospital record, therefore in the ART treatment group n = 49 and in the ART-naive group n = 284.

Significant differences between the patients receiving ART and ART-naive patients included: median age (p=<0.0001); frequency of CTX prophylaxis age (p=<0.0001); median CD4 percentage (p=<0.008) and the proportion with WHO HIV stage 3 or 4 disease. (p=0.02)

The table below (Table 17.) compares the proportion of children who died that were eligible for ART with the proportion of children receiving ART at the time of their death. The calculation of eligibility for ART was based on the South African national guidelines[2] for paediatric ART initiation at the time of the study - using immunological and clinical (WHO staging) criteria only.

Table 17. Eligibility for ART versus ART access in 53 HIV-infected children who died

Age categories	**Number and proportion with CD4 percentage qualifying for ART***	**Number and proportion with WHO HIV stage qualifying for ART**	**Number and proportion actually receiving ART at time of death**
All deaths	18/27**	50/53	6/53
(n = 53)	66.7%	94.3%	11.3%
Deaths < 18 months	10/17**	38/40	6/40
(n = 40)	58.8%	95%	15%
Deaths > 18 months	8/10**	12/13	0/13
(n = 13)	80%	92.3%	0%

* CD4 < 20% for children < 18 months old, CD4 < 15% for children > 18 months old

** The denominators differ from the overall group denominators because only a proportion of the 53 children HIV-infected children who died had recent CD4 percentage results available.

4. Discussion and Conclusion

4.1 Limitations

1. The retrospective study design did not allow for assessment of in-hospital quality of care or evaluation of access to paediatric HIV services during and post-admission. This information would be useful in assessment and planning of paediatric HIV service delivery at CHBH, but this type of operational research would be best obtained by a prospective study design.
2. Clinical data obtained for WHO HIV staging was subject to inter-observer variation as it had been collected by multiple doctors in the paediatric admission ward. However, the study investigator used the WHO HIV staging reference to ensure consistency in assigning HIV staging based on the clinical data recorded (in cases where no HIV stage was documented.)
3. The study site (tertiary hospital), small sample size, and limited time period limits the application of this study's findings i.e. it may not be appropriate to generalise the results of this study to the paediatric HIV population of Gauteng province. However the study provides a "snap-shot" of the impact of HIV on the paediatric wards at CHBH and in conjunction with previous studies can be used to inform planning of paediatric HIV service delivery at CHBH.
4. The short time period of the study may overlook seasonal variations in the spectrum of illnesses diagnosed in our paediatric inpatient population.
5. The data available on mothers' antenatal HIV status and usage of Nevirapine prophylaxis was limited – the PMTCT history was generally poorly documented in hospital files. Recall bias with regard to NVP usage may also have been present. Further prospective studies to determine the uptake and efficacy of PMTCT at CHBH are urgently needed.

6. The lack of an HIV-negative comparison group is a shortcoming of this study, but is in part compensated by the comprehensive documentation and analysis of data on the HIV-infected group of children, as the latter was the main aim of this study.

4.2. Strengths of the study

1. A detailed record review was completed for each HIV-infected child.
2. The study investigator was the only assessor for all of the hospital records thus ensuring consistency in completion of the study tool.
3. From all 446 HIV-infected children admitted during the study period, only 6 records could not be located.
4. Estimation of HIV prevalence was performed using data from both lab results and record review.
5. Data from the study period compared favourably (in terms of total number of admissions and HIV-related mortality) with the CHBH basic ward statistics collected during the preceding three quarters of 2007. It is therefore likely to be a true representation of HIV-infected paediatric admissions at CHBH.

In an attempt to contextualise the results of this study, the study period of the last quarter of 2007 was compared to the first three quarters of 2007 (using CHBH paediatric departmental statistics.) During the study period, 1510 paediatric admissions were recorded which compared closely to the 1677, 1542 and 1408 admissions in the first three quarters respectively.

The number of deaths amongst HIV-infected children was similar during the study period (at 53 deaths/440 HIV-infected paediatric admissions [12%]) and during the first three

quarters of 2007 with 50, 45 and 51 deaths recorded amongst HIV-infected paediatric admissions. It is not possible to calculate case fatality rates among HIV-infected children for the first three quarters of 2007 because the denominator [total number of HIV-infected children admitted each quarter] is not available/not known. The proportional contribution of HIV-related deaths to the overall number of paediatric deaths in the general wards was higher at 58.1% (53/91 total deaths) during the study period, compared to 50.5% (50/99), 46.4% (45/97) and 53.6% (51/95) during the first three quarters of 2007.

As the Child PIP programme is adopted at more hospitals, including CHBH, data on countrywide paediatric HIV-related in-hospital mortality will become more readily available for comparison. This study (with HIV-related deaths contributing 58.1% of all paediatric deaths) showed striking concordance with the South African national statistics from the Countdown to 2015 report which attributed 57% of all under-five mortality to HIV/AIDS.[43]

4.3 HIV prevalence

This study highlights the ongoing burden of disease from HIV-related paediatric admissions at CHBH and it is likely that this reflects the situation at many other state hospitals in South Africa. The HIV prevalence amongst paediatric admissions during the study period was 29.5%, but this figure may have been higher since 15% of all admissions had no documentation of HIV testing (ie of unknown HIV status) and another 3.8% were HIV-exposed but had not yet undergone HIV PCR testing.

Of the HIV unknown group of children, it is likely that the majority were not tested because they were considered highly unlikely to be HIV-infected, based on their history,

nutritional status and clinical presentation. However, it is possible that some children in this group were not tested because parental consent for HIV testing could not be obtained (in cases where parents were not available for counselling or where parents refused testing outright.) However, this possibility could not be verified as documentation of reasons for not performing HIV testing in children of unknown HIV status was lacking in most clinical records.

In the group of HIV-exposed infants who did not undergo HIV PCR testing during ward admission, the majority were less than 6 weeks of age. Although data on the reasons for admission in the HIV-exposed group was not collected, these infants were presumably admitted with illnesses that may have been indicative of symptomatic HIV infection. Currently, South Africa's paediatric HIV testing protocols do not routinely recommend HIV PCR testing before 6 weeks of age. It should be routine practice, however, to perform HIV DNA PCR for symptomatic HIV-exposed infants, in order to make an early diagnosis and expedite treatment for HIV-infected infants.[33] It is of concern that very young infants are not being investigated for HIV even when sick enough to be admitted, particularly since HIV-exposure status is often unknown.

Three previous studies at CHBH have assessed HIV ward prevalence and in-hospital mortality rates. Data from previous and current studies at CHBH is tabulated below (Table 18.) in order to identify trends in the paediatric admission profiles.

Table 18. HIV ward prevalence data from previous and current studies of paediatric admissions at CHBH

Study Period, Authors & Study Design	**Estimated HIV prevalence (%, absolute values and 95% CI)**	**In-hospital mortality rate (HIV + children)**	**In-hospital mortality rate (HIV - children)**
1992 – 1996 Zwi et al.[17] Retrospective	Increased from 3% (120/3800) to 19% (870/4694) -	Increased from 9.2% (11/120) to 12.9% (112/870) -	Decreased from 5.4 % (80/1472) to 4.5% (53/1187) -
1996 Meyers et al.[18] Prospective	29% 144/493 (25.2-33.2%)	16.5% 17/103 -	4.6% 15/326 -
2005 Schneider et al.[19] Cross-sectional	31.5% 181/575 -	24.3% 44/181 -	5.1% 20/394 -
2007 Dramowski et al. (this study – retrospective)	29.5% 446/1510 (27.2 – 31.9%)	12% 53/440 (9.2–15.5%)	3.6%* 38/1064 (2.5-4.9%)

*Mortality in this study considered all deaths in the HIV negative, HIV-exposed and HIV-unknown group.

The HIV prevalence during the study period was very similar to the prevalence rate of 29% amongst hospitalized children at CHBH in the 1996 survey. [18] Thus several years after the national roll-out of the Department of Health's PMTCT and ART programmes, the paediatric HIV epidemic shows no evidence of a decreasing impact on paediatric hospital admissions.

Possible reasons for this may include:

1. An increased prevalence of HIV amongst women of childbearing age with consequently a larger number of HIV-infected infants born despite PMTCT interventions.
2. In 2005 the HIV prevalence among paediatric admissions was 31.5%. It is possible that even higher prevalence levels were reached during the period between 1996 and 2004 and that the levels documented in 2005 and now in 2007 actually represent a decrease from a higher peak level.
3. Improved survival rates (particularly in older HIV-infected children) may have resulted in more children surviving to hospital admission. In the 1996 CHBH study, the HIV prevalence in hospitalised children was also 29%, but mortality rates were higher at 17%. [18] Currently however, there may be a lower community-based prevalence of HIV but with increased numbers of hospital admissions, as HIV-infected children survive longer as a result of intervention programmes and provision of ART.

Despite the static HIV prevalence figures, mortality rates appear to have dropped both among HIV-infected and HIV-uninfected children. There may be several explanations for this apparent trend including: earlier HIV diagnosis with improved awareness and

availability of testing; improved access to ART with earlier age of ART initiation and in both groups, improved health services and nutritional status may play a role.

4.4 Prevention of mother to child transmission (PMTCT)

4.4.1 Poor record-keeping

Of great concern is the fact that data regarding PMTCT interventions was very poorly documented by the admitting doctors in many patients' hospital records. However, in instances where PMTCT history was specifically enquired about during admission history-taking, many primary caregivers were unable to provide the required information and had no documentation of these interventions. Owing to the limited availability of data, review of PMTCT interventions was restricted to the subgroup of HIV-infected infants under 6 months of age, who were more likely to have PMTCT data recorded in their files. It was also hoped that recall bias would be reduced by restricting PMTCT analyses to infants born less than 6 months ago.

4.4.2 Maternal self-reported HIV status

In the subgroup of HIV-infected infants under 6 months of age, only 54.2% of mothers self-reported their status as HIV positive at the time of their child's hospital admission. Of the remainder, 15.1% reported their status as HIV negative and 30.7% reported their status as HIV unknown or untested. It is possible that some of the mothers who reported their status as HIV negative may have undergone seroconversion during pregnancy (after initial antenatal HIV testing.) Others reporting their HIV status as negative or unknown may have been in denial or may have feared stigmatisation/prejudicial treatment if they had disclosed their status to health care workers.

In some cases where a child was known to be or newly diagnosed as HIV-infected, no maternal HIV test result could be located on the NHLS laboratory system or in the child's hospital admission file. It is unclear whether the HIV-status of the mother was already known but not documented in the hospital file or if maternal HIV status was unknown and HIV testing for the mother had not been performed during the child's hospital stay. Many of the mothers who reported their HIV status as negative or unknown would have been offered an HIV test in the paediatric wards, but their results were not always documented in their children's hospital records. However, it is unfortunately not routine practise at CHBH to confirm a mother's HIV status (when she reports herself to be HIV-negative or HIV unknown) after her infant or child has been newly diagnosed as HIV-infected.

4.4.3 Nevirapine exposure

The overall frequency of reported NVP exposure as part of the PMTCT programme in infants under 6 months old was 36.2%. Of infants born at CHBH, reported NVP exposure was marginally better at 51.8%. For infants born elsewhere (clinic/other hospital/BBA combined – excluding those with unknown birthplace) reported NVP exposure was lower at 37.8%. Thus it would appear that almost half of the CHBH-born infants (and almost two-thirds of infants born elsewhere) who presented for admission in their first 6 months of life had missed an opportunity to access NVP prophylaxis at birth through the existing PMTCT programme.

There are many possible factors that contribute to poor uptake of NVP prophylaxis in HIV-positive mothers. Some of these factors could include: mothers who test at a clinic and then deliver in hospital; the HIV coding system used by midwives which is difficult to interpret; women's reluctance to disclose HIV status owing to stigma, poor transfer of

information between health facilities and a reluctance on the part of health care workers to offer all mothers HIV testing or to enquire about HIV status.

Infants that had received NVP at birth were significantly more likely to be receiving CTX at the time of hospital admission compared with infants who had not received NVP or had unknown NVP exposure ($p = 0.008$.) This finding probably reflects better health seeking behaviour in this group of mothers. It may also reflect linkages in the healthcare system (i.e. a note on the Road to Health Card [RTHC] regarding NVP administration at birth acting as a reminder to commence CTX at 6 weeks) and an opportunity for improving uptake of CTX prophylaxis (i.e. enforcing documentation of HIV-exposure and reminders for CTX prophylaxis and HIV PCR testing on the RTHC.)

4.4.4 Cotrimoxazole prophylaxis

Of the total subgroup of HIV-infected infants under 6 months, only 27.7% were reportedly receiving CTX prophylaxis at the time of hospital admission. The reported CTX usage in infants born at CHBH (31.3%) was marginally better than CTX usage in infants born at clinics, other hospitals and unknown birthplace (combined). Failure to provide CTX prophylaxis to HIV-exposed and HIV-infected infants represents a missed opportunity to prevent early mortality from *Pneumocystis jirovecii* pneumonia. High loss to follow-up of HIV-exposed infants is a major problem in the PMTCT programme both at CHBH and at a national level as reported by previous studies.[27, 28]

4.4.5 Missed opportunities for PMTCT interventions

PMTCT interventions in the subset of infants less than 6 months old were analysed taking into consideration the self-reported HIV status of their mothers. The mothers who reported

their status as HIV-infected would have been expected to have benefited from access to the PMTCT programme. However, only 66.7% of these mothers received NVP and only 38.9% of their infants received CTX prophylaxis. Of these same infants, only 41.1% had been HIV PCR tested and diagnosed HIV-infected prior to hospital admission. The remainder, although known to be HIV-exposed, were not tested for HIV until they were ill and required admission in the CHBH paediatric wards. Of the infants known to be HIV-infected at the time of hospital admission, only 32.4% were accessing ART. Based on the findings of the CHER Study[33], the WHO has recommended that all HIV-infected infants be fast-tracked for ART.[44] In view of the high case fatality rate among infants less than 6 months of age documented by this study, the provision of early ART to HIV-infected infants should be prioritized at CHBH.

A similar sub-analysis for infants whose mothers reported their own status as HIV negative or HIV unknown demonstrated even greater numbers of missed opportunities for PMTCT intervention. As illustrated in Figures 3 and 4, poor uptake of VCT at antenatal clinics, lack of repeat HIV testing in labour, poor uptake of NVP prophylaxis and lack of infant follow-up for CTX prophylaxis and PCR testing represent missed opportunities for the prevention of paediatric HIV. An analysis of access to PMTCT for HIV-exposed, HIV-negative and HIV-unknown infants is required, but was beyond the scope of this study.

In general, uptake of all PMTCT interventions among the 166 infants less than 6 months old was poor. Seventy-six (45.8%) of all 166 infants less than 6 months of age received no PMTCT interventions whatsoever and only 20/166 (12%) of infants received all recommended interventions (NVP, CTX, early HIV PCR testing.) The fifth perinatal care survey of South Africa (2003-2005) identified several weaknesses in the PMTCT

programme which could result in missed opportunities for paediatric HIV prevention including: overemphasis on prevention of vertical HIV transmission without inclusion of strategies for child survival i.e. feeding support, HIV PCR testing and referral for ART where indicated; poor uptake of maternal antenatal HIV testing because of opt-in testing policies; reluctance of midwives to take responsibility for establishing maternal HIV status and limited participation of mothers in feeding choices.[45]

4.5 Nutritional status and HIV staging

As expected, a significant proportion of HIV-infected children were malnourished when assessed by means of the Wellcome classification. Unfortunately length for age/height for age and height for weight analyses (to assess for stunting and wasting) could not be performed because many hospital records had no data on height documented.

Assessment for evidence of malnutrition is also an integral part of the WHO HIV staging system. Therefore clinicians, particularly those working in the outpatient setting, should encourage routine HIV testing of all malnourished children in order to maximise the HIV detection rate. This study confirmed that most HIV-infected patients present with advanced disease (92.7% had stage 3 or 4 disease) and consequently more severe illnesses and poorer outcomes. This finding reinforces the need to identify infected children earlier in the course of their disease. This will require intensified follow-up of all children receiving routine child health care and intensified follow-up of all children whose mothers received PMTCT care. This follow-up should commence from as early as 4-6 weeks after birth and should continue monthly in the first year of life (given the high incidence of admissions in those under six months.)

Preliminary results form the Children with HIV Early Antiretroviral Therapy (CHER) trial show that HIV-exposed infants are at risk for disease and death early on (even if asymptomatic and even with high CD4 percentages).[33] These results imply that all infants in high prevalence areas should be tested for HIV, especially young infants who present unwell at a health service. Based on these significant findings the WHO has recently released (May 2008) revised Paediatric treatment recommendations and the Paediatric subcommittee of the Southern African HIV Clinicians Society has issued an Advisory statement (June 2008).[46] Both of these recommendations call for treatment of all HIV-infected infants irrespective of CD4 percentage or count.

4.6 Antiretroviral treatment (ART)

Of the 364 (82.7%) HIV-infected children not receiving ART at the time of hospital admission, 346 (95%) qualified for HAART based on current WHO clinical and immunological guidelines. Of these 346 children who qualified for ART, only 15 children (3.4%) were able to initiate inpatient ART. Multiple hurdles to inpatient ART initiation exist, such as absence of the primary caregiver, poor social circumstances, the severity or nature of the child's illness and clinician inexperience with or reluctance to commence HAART in the inpatient population. Despite these obstacles, many more children could be prepared for, or commenced on, ART during ward admission.

Most newly-diagnosed HIV-infected children are seen by clinical staff from the hospital-based HIV service (Harriet Shezi Children's Clinic), whilst admitted in the wards in order to begin preparations for ART. Once discharged from hospital, a follow-up appointment is booked at the clinic to complete pre-treatment investigations and counseling. However, in

view of the fact that 95% of the paediatric admissions at CHBH qualify for ART, there is an urgent need to expedite inpatient commencement of ART.

This recommendation is given further impetus in light of the preliminary findings of the CHER study that showed a 75% reduction in mortality with early ART initiation in children.[33] In view of this dramatic finding, our current national treatment guidelines are probably too conservative, resulting in delayed initiation of HAART and consequently excess infant mortality.

4.7 Immunological indices

Recent (within a month of hospitalization) CD4 percentage and cell count test results were available for a subset of the study population (320/440 and 312/440.) These indices confirmed that the majority of children had moderate to severe immunosuppression at the time of hospital admission. This finding was not unexpected in light of the fact that over 90% of children presented with advanced HIV disease. Of note is that in the subgroup of infants aged less than 6 months, 65.5% had CD4 percentages below the WHO's recommended 25% cut-off for ART initiation, yet only 7.2% were receiving ART at the time of hospital admission.

The remaining 34.5% of infants aged less than 6 months, had CD4 percentages >25% but were symptomatic from their HIV disease and required hospital admission. This finding emphasizes the fact that CD4 percentage is not reliably predictive of disease severity in young infants. Thus it is hoped that new national guidelines recommending ART initiation for infants with CD4 percentages < 35% or WHO stage 2 or greater, will be published soon.

4.8 Primary diagnosis

As expected, infections were the most common reason for hospital admission. Respiratory illnesses (pneumonia, PJP and pulmonary TB) accounted for 46.4% of all admission diagnoses. In most cases the diagnosis of PJP was presumptive (based on clinical presentation), owing to the difficulties in collecting nasopharyngeal aspirates on admission and the poor sensitivity of immunofluorescent staining tests. Commencement of TB treatment was done empirically in most cases given the well-described difficulties of confirming TB disease in HIV-infected children. [47]

In the group of children on ART, 10.5% of children (8/76) were admitted with a primary diagnosis of IRIS on clinical grounds. However, this point prevalence does not take into account the relevant denominator ie. the entire pool of children commenced on ART at the Harriet Shezi Childrens Clinic. There is limited data available on the prevalence of IRIS in HIV-infected children commenced on ART (both at national and international level.) [48] In our setting, we feel that many cases of paediatric IRIS remain undiagnosed either because clinicians are not familiar with the presentation of IRIS or because some children may demise at home or in other institutions.

4.9 Spectrum of infectious pathogens

A quarter (110/440) of the study population had a confirmed bacterial, viral, protozoal or fungal infection during their hospital admission. A wide spectrum of pathogens were encountered, but notably, *Streptococcus pneumoniae* was the most commonly cultured bacterium overall. *Streptococcus pneumoniae* was also the most common bacterial isolate in children who died. This result is of public health significance because infection with this organism is potentially vaccine-preventable in HIV-infected children. [49]

Cytomegalovirus infection was confirmed in 14 cases and disseminated CMV disease was responsible for 5 of the 53 deaths in HIV-infected children (9.4%). Some cases of CMV infection were confirmed on post-mortem histology of lung and/or liver biopsies and the remainder by a positive pp65 antigen test in combination with a compatible clinical picture.

Of the 53 children who died, 24 (45.3%) had a confirmed infection at the time of death. Also of note was that 48% (36/75) of bacterial isolates from blood, urine or CSF cultures were fully or intermediately resistant to one or both of the first-line antibiotics used at CHBH in HIV-infected children. Typically, organisms such as *E coli ESBL, Klebsiella ESBL, Methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas, Salmonella* species and *Staphylococcus aureus* are not sensitive to empiric treatment with Ampicillin and Gentamicin. Thus we should have a low threshold for initiating second line antibiotic regimens utilising broad-spectrum antibiotics (based on local antibiotic resistance patterns) in critically ill HIV-infected children who do not respond clinically to initial therapy or who may have acquired resistant nosocomial bacterial infections.

4.10 Outcome

4.10.1 Contribution of HIV-related deaths to overall paediatric mortality

Most notable was the fact that HIV-infected children had a case fatality rate more than threefold greater than that of the HIV negative, HIV-exposed and the HIV unknown group (12% % [95% CI 9.2–15.5]) vs. 3.6% [95% CI 2.5-4.9]). HIV-related deaths were the single largest group, contributing 58.1% of all paediatric deaths in the general wards during the study period. As mentioned previously, this is in line with national estimates from the Countdown to 2015 report which attributed 57% of all under-five mortality to HIV/AIDS.[43]

4.10.2 Outcome in young infants

Infants less than 6 months of age were at highest risk of death with a case fatality rate of 16.9% (95% CI 11.5-23.5). Over half of these infants under 6 months of age (50.8%) qualified for ART based on our national guidelines for initiating ART in infants with CD4 counts less than 20%. If WHO immunological criteria (CD4 < 25%) are used, 65.5% of this group qualified for ART. Despite the fact that the majority of infants less than 6 months old qualified for ART, only 7.2% of this group was receiving ART at the time of hospital admission.

A high mortality in young infants has been documented in the CHER study where even infants who were clinically well and had high CD4 percentages, had an excess mortality compared to their counterparts who started ART early.[33] In other cohorts, up to 50% of children die before 2 years of age.[50] In order to address the high mortality recorded in this age group, we need to prioritise early diagnosis and fast-tracking of infants for ART.

4.10.3 Outcome of ICU intervention in HIV-infected children

During the study period only 13 children (3.0%) were admitted to ICU or ventilated in the high care area of the acute admissions ward. Of these 13 children, 10 (76.9%) survived to hospital discharge and 3 (23.1%) died in ICU or high care. Overall, a 76.9% ICU/high care survival rate in HIV-infected children appears surprisingly good. However, data were not analysed or were not available to consider how these ICU candidates were selected and how their duration of stay, incidence of complications and long-term morbidity and mortality compared with that of HIV negative children admitted to ICU.

At present, in view of the high demand for intensive care facilities, many critically-ill HIV-infected children at CHBH cannot be accommodated in the ICU. Further studies are required to evaluate current policies and outcomes of HIV infected children admitted to ICU – especially now that ART is more accessible – with a view to developing consensus guidelines for the admission of HIV-infected children to ICU.

4.10.4 Step-down care at CHBH

A substantial proportion of HIV-infected children (15.5%) were transferred to a step-down hospital facility after stabilisation, investigations and interim management were completed, in order to reduce the burden on overcrowded paediatric wards at CHBH. The outcomes of these children are unknown. Of concern with this practice of down-referral is that in some cases, children may be transferred before HIV testing results have been confirmed and before post-test counseling of parents has occurred. This results in missed opportunities for diagnosis and further delay in referral of HIV-infected children for commencement of ART.

4.10.5 Comparison of HIV-infected patient characteristics by final outcome

Median weight for age z-scores were significantly lower in the group of children who died versus those who survived, reinforcing the observation that poor nutritional status is associated with poorer outcomes among hospitalised children. Thus particular attention should be paid to nutritional rehabilitation of ill, hospitalised HIV-infected children.

Although the difference in median age between children who died and those who survived was not significant, it is important to note that most deaths occurred in early infancy.

This implies that ART initiation in infants should be fast-tracked in order to prevent or reduce early mortality in this age group of HIV-infected infants.

Also of note is the observation that there was no statistically significant difference between children who died versus those who survived in terms of HIV Stage and CD4 number or percentage. This observation is valuable in reinforcing the fact that CD4 count is a poor predictor of HIV disease progression and risk of death, especially in infants.[51]
ART status was not associated with outcome (death vs. survival), however, the median duration of ART in the treatment group was only 2 months and thus any real effect on survival in the ART group would have been limited. Interestingly, only 1 death was recorded in the group of children that had received ART for more than 6 months (n = 30/76), whereas there were 5 deaths in children that had received ART for less than 6 months. (n = 46/76) [p =0.23] Further studies are required (with larger numbers of children who have been established on ART for 6 or more months) to show a statistically significant association between ART and survival benefit in hospitalised HIV-infected children.

Anecdotally, there has been an impression in clinical out-patient practice (at Harriet Shezi Children's Clinic) that the number of HIV-infected children established on ART requiring hospital admission has decreased. Thus the fact that this study did not show a statistically significant association between ART and survival in hospitalised HIV-infected children, may relate more to the fact that the children who were admitted reflected the sickest children with the most advanced disease course and shorter duration of ART.

4.11 Comparison of HIV-infected patient characteristics by ART status

The group of children on ART were significantly older than the ART-naïve group (median age 38 versus 7 months.) This highlights the fact that few children admitted at CHBH have had the benefit of early ART initiation.

Children with advanced HIV disease were more likely to be receiving ART at the time of hospital admission ($p = 0.02$). However, in the ART-naïve group, 91% of children presented with WHO stage 3 or 4 HIV disease and thus already qualified for ART initiation.

Interestingly, children accessing ART had a significantly lower median CD4 percentage than children who were ART-naïve. This probably reflects the fact however, that the most immunosuppressed children are commenced on ART earlier and that their CD4 counts take time to improve on ART. (The median duration of ART in the 76 children receiving treatment at the time of hospital admission was only 2 months.) CD4 counts may also be transiently lowered during opportunistic infections and this may explain the low counts observed in the study population who were being admitted during periods of illness. However, one would expect this to affect both the group of children on ART as well as the ART-naïve, and thus does not fully explain the difference in median CD4 percentages.

Children on ART were much more likely to be receiving CTX prophylaxis (93.4 vs 23.8%), which aside from the ART itself, may have contributed to the lower case fatality rate in this group ($p < 0.0001$). Although a lower inpatient case fatality rate was recorded amongst children on ART versus the ART-naïve group, this finding was not statistically significant. ($p = 0.17$) However, the median duration of ART in the treatment group was

only 2 months and a longer observation period on ART may be needed to demonstrate survival benefit in the ART group.

There was no significant difference in the median duration of hospital stay between the group on ART and the ART-naive. In the future, however, it is hoped that increasing rates of paediatric ART coverage will reduce the HIV-related case burden at CHBH. Further studies are warranted to assess the impact of ART on rates of re-admission in the paediatric wards at CHBH.

4.12 Eligibility for ART in HIV-infected children who died

Table 17. compared the proportion of children who died that were eligible for ART (based on immunological and clinical criteria) with the proportion of children receiving ART at the time of their death. This data reinforces the fact that the majority of children who died during the study period qualified for ART initiation on immunological and clinical grounds. Overall, 94.3% of the children who died had advanced HIV (WHO stage 3 or 4 disease.) Of the children under 18 months of age, 58.8% qualified for ART based on a CD4% < 20% but only 15% were accessing ART. Of children over 18 months of age, 80% qualified for ART based on a CD4% < 15% but not one child in this group was accessing ART, despite 53.8% of these children being previously diagnosed as HIV-infected. (ie. known cases)

4.13 Conclusion

In 2006, HIV/AIDS related deaths accounted for 57% of under-five mortality in South Africa.[43] The paediatric HIV epidemic in South Africa has seen a reversal of the past advances made in childhood mortality rates. Without a co-ordinated approach to prevention, early detection and comprehensive care of paediatric HIV, our country cannot hope to achieve the Millennium Development Goal of a two-thirds reduction in child mortality by 2015.

This retrospective, descriptive study with analytic elements determined a 29.5% prevalence (95% CI 27.2 – 31.9%) of HIV infection amongst paediatric admissions at CHBH and described the clinical profile and outcome of 440 HIV-infected children. Of these children, 54.1% were newly diagnosed with HIV. Only 19% of children had a normal weight.

Uptake of PMTCT interventions among infants less than 6 months old was poor, with 76/166 (45.8%) receiving no PMTCT interventions whatsoever. Multiple missed opportunities for the prevention and treatment of paediatric HIV were highlighted including: lack of antenatal HIV testing; poor uptake of NVP prophylaxis; lack of infant follow-up for CTX prophylaxis and HIV PCR testing.

Infection, especially pulmonary infection, was the principal reason for hospitalisation. Despite the majority (92.7%) of admissions having advanced HIV disease (WHO Stage 3 or 4), only 17% were accessing ART. The overall case fatality rate was 12% (95% CI 9.2-15.5), with deaths in HIV-infected children contributing 58% of all deaths in the general paediatric wards. Over half (52%) of all deaths in the HIV-infected group occurred in infants younger than 6 months of age.

HIV infection is the major contributor to morbidity and mortality among paediatric admissions at CHBH. Poor uptake of PMTCT interventions, late diagnosis of HIV infection and slow rollout of ART are barriers to improved care in HIV-infected children at CHBH. Based on these findings, several pragmatic recommendations have been made which aim to improve management of paediatric HIV at CHBH. The goal of achieving maximal PMTCT coverage at CHBH must be prioritised. In order to reduce paediatric HIV-related mortality at CHBH, efforts should focus on early diagnosis of HIV infection and prompt initiation of ART in infants under 6 months of age.

Key research questions identified by this study include the need for prospective, operational research around the following problems: apparent poor uptake of PMTCT services at CHBH; maternal non-disclosure of positive HIV status; poor access to/under-utilisation of ART services. Another key area to research is identification of barriers to inpatient ART initiation and evaluation of treatment outcomes (clinical and virological) among children who commence ART in the wards. An audit of the paediatric HIV services at CHBH, including long-term data on the impact of ART initiation on ward admission profiles is also needed. Ongoing surveillance of HIV prevalence and disease profile will help us to determine whether our efforts in PMTCT and ART provision will achieve a decrease in paediatric HIV-related admission and mortality rates at CHBH in the future.

4.14 Recommendations for improving management of paediatric HIV at CHBH based on the findings of this study:

A. Recommendations for practitioners/clinicians at CHBH (hospital level)

- **Improve paediatric HIV-related history taking:** Train all ward doctors to take a comprehensive perinatal history including PMTCT interventions (maternal HIV status, maternal ART or NVP/AZT prophylaxis, infant NVP/AZT prophylaxis and CTX usage, HIV PCR testing, WHO HIV staging, previous ART regimens etc) in the admission clerking notes of every child.
- **Improve documention of HIV status in inpatient and outpatient records:** Document NVP and AZT, CTX prophylaxis and HIV PCR testing results on every HIV-exposed child's RTHC and handheld hospital record.
- **Facilitate early diagnosis of HIV:** Perform HIV PCR testing on any HIV-exposed 'symptomatic' infant in CHBH outpatient clinics and all infants admitted to the wards, even if less than 6 weeks of age.
- **Ensure mothers (parents) are also tested for HIV:** In mothers of unknown HIV status presenting with infants at the CHBH paediatric outpatient department or wards, offer rapid HIV testing to the mother and HIV PCR testing for the infant if mother's rapid HIV test is positive.
- **Reduce numbers of HIV-exposed CHBH-born babies who are lost to follow-up:** Provide routine referral of all HIV-exposed infants for HIV PCR testing from 6 weeks of age (or earlier if symptomatic) as is currently occuring between the CHBH maternity wards and the Nurses Home at the Perinatal HIV Research Unit. At this visit for HIV PCR testing, a sufficient supply of CTX should be issued to last until the next visit for PCR results. (A proforma referral letter with the date and place of appointment should be issued on discharge from maternity or neonatal ward.)

- **Scale-up paediatric ART initiation in the wards:** Prepare more children for ART as inpatients and increase the rate of inpatient ART initiation at CHBH.
- **Ensure continuity of care for HIV-infected children:** Ensure that wherever possible, no child is discharged or transferred to step-down hospital facilities before HIV test results have been conveyed to the primary caregiver, in order to avoid missed opportunities in diagnosis and referral. If a child known to be HIV-infected and not normally resident in the CHBH drainage area is discharged, ensure that a referral letter and appointment date is given for a paediatric ART clinic in the child's are of normal residence. Improve communication with step-down facility so that children are not lost to follow-up when discharged (preferably a booking should be made at an ART clinic with the family contact details provided before any child is sent to step-down facility.) In the event that a child has to be referred, it is incumbent on the referring doctor to ensure that the child's HIV results are communicated (and such communication documented) to the referral site.
- **Reduce loss to follow-up of children diagnosed as HIV-infected in the wards:** Ensure that every HIV-infected child discharged from the CHBH general paediatric wards or short-stay wards has written confirmation of a HIV clinic follow-up appointment date so as to expedite the process of preparation for ART.

A paper authored by several local experts on paediatric HIV, recommended similar interventions to improve PMTCT and to scale-up paediatric diagnosis and ART services. [30]

B. Recommendations for policy-makers at CHBH (hospital level)

- Recommend routine recording of NVP and AZT prophylaxis on every HIV-exposed child's RTHC and CHBH handheld hospital record.

- Implement mandatory repeat maternal HIV testing shortly before delivery in CHBH labour ward, to identify mothers who have recently seroconverted.
- Recommend HIV testing of women in postnatal wards in cases where a mother was not tested antenatally or had tested HIV-negative more than six weeks prior to delivery.
- Review all existing data on PMTCT interventions at CHBH to identify and address programmatic deficiencies.
- Join the list of hospitals that contribute mortality data to the CHIP database, so that data from paediatric ward outcomes at CHBH can be used to assist with paediatric health service auditing and planning.

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6. Appendix 1: STUDY TOOL DOA: ____/_____/____ Study no: _____

A	**DEMOGRAPHICS**					
1.	**Age in months**					
2.	**Gender (1=male; 2=female)**					
B	**HIV TESTING**	**1 = yes**	**2 = no**	**9 = unknown**		
3.	Child **newly diagnosed HIV+ during this admission?**					
C	**PMTCT DETAILS**	**1 = positive**	**2 = negative**	**9= unknown**		
4.	**Self-reported HIV status of the biological mother?**					
		1 = yes	**2 = no**	**9 = unknown**		
5.	**NVP prophylaxis** to mother in labour and/or child at birth?					
		1 = CHBH	**2 = clinic**	**3 = other hosp**	**4 = BBA**	**9 = unknown**
6.	**Place of birth:**					
D	**HIV MANAGEMENT**	**1 = never Rx**	**2= previous ART**	**3 = current ART**	**4= inpatient ART**	**9 = unknown**
7.	**ARV treatment history:**					
		1 = yes	**2 = no**	**9 = unknown**		
8.	**If not on ARVs, does child currently need ARVs?**					
9.	**If on ARVs, no. of months on treatment:**					
		1 = yes	**2 = no**	**3 = not indicated**	**9 = unknown**	
10.	**Child on CTX prophylaxis at time of admission?**					
E	**GROWTH PARAMETERS**					
11.	Weight (kg)					
12.	Length / Height (cm)					
13.	% expected wt for age					
14.	% expected ht for age					
		1 = normal	**2 = UWFA**	**3 = marasmic**	**4 = kwash**	**5 = mar.kwash**
15.	**Wellcome classification**					
F	**HIV STAGING**		**1 = stage 1**	**2 = stage 2**	**3 = stage 3**	**4 = stage 4**
16.	WHO clinical stage					
17.	Criteria for staging					
G	**IMMUNOLOGICAL STATUS**					
18.	CD4 count : #					
19.	CD4 count : %					

H	**ADMISSION DIAGNOSES**	
20.	Diagnosis 1	1=pneumonia 2=PJP 3=CMV pneumonitis 5=pTB empiric 6=pTB confirmed 7=gastroenteritis 8=EPTB 9=septicaemia 10=IRIS 11=anaemia 12=CLD 13=cor pulmonale 14=meningitis 15=UTI 16=RVD encephalopathy 20=other
21.	Diagnosis 2	
22.	Organism	
I	**CLINICAL OUTCOME**	
23.	1 = Discharged home – no ICU admission 2 = Discharged home after ICU admission 3 = Died in ICU 4 = Died in ward 5 = Refused hospital treatment 6 = Transferred back to referring hospital 7 = Transferred to step-down hospital facility	
J	**DURATION OF HOSPITAL STAY**	**dd/mm/yy**
24.	Date of admission	/ /
25.	Date of final outcome	/ /
26.	Stay (number of nights)	

Appendix 2: WHO HIV Staging Criteria

Stage 1
Asymptomatic
Persistent generalised lymphadenopathy

Stage 2
Hepatosplenomegaly
Recurrent or chronic RTI (otitis media, otorrrhoea, sinusitis)
Papular pruritic eruptions
Seborrheic dermatitis
Extensive human papilloma virus infection
Herpes zoster
Fungal nail infections
Recurrent oral ulcerations
Angular cheilitis
Parotid enlargement
Lymphoid Interstitial Pneumonitis
Recurrent or severe bacterial infection

Stage 3
Failure to thrive (60-80% expected body weight)
Oral candidiasis beyond the neonatal period
Unexplained chronic diarrhoea (>2 weeks)
Unexplained persistent fever
Pulmonary TB
Severe recurrent presumed bacterial pneumonia
Unexplained anaemia (<8g/dl), neutropaenia (<500/mm^3), throbocytopaenia (<50 000/mm^3) for more than one month
Chronic HIV-associaed lung disease including brochiectasis
Symptomatic lymphoid interstitial pneumonitis

Stage 4
Severe failure to thrive (<60% expected body weight)
Pneumocystis pneumonia
Recurrent severe presumed bacterial infections (excluding pneumonia)
Chronic herpes simplex infection > 1 month
Extrapulmonary TB
Kaposi's sarcoma
Oesophageal candidiasis
CNS toxoplasmosis
HIV encephalopathy
CMV infection
Extrapulmonary cryptococcosis
Any disseminated endemic mycosis
Cryptosporidiosis, Isosporiasis
Disseminated non-tuberculous mycobacterial infection
Candida of trachea, bronchi, lungs
Visceral HSV
Acquired HIV-associated rectal fistula
Non-Hodgkins lymphoma
PML
HIV-associated cardiomyopathy or nephropathy

Appendix 3: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dramowski

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080202**
PROJECT	A profile of HIV-related paediatric admissions at CH Baragwanath Hospital Johannesburg, South Africa
INVESTIGATORS	Dr A Dramowski
DEPARTMENT	Paediatrics & Child Health
DATE CONSIDERED	08.02.29
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 08.04.02 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr A Goga

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

CHRIS HANI
BARAGWANATH HOSPITAL
CEO

Caring Hearts
Bringing Hope

PO BERTSHAM
2013
TEL: 933 9145-
FAX: 938-1005
E-mail - amanning@mweb.co.za

22 February 2008

Dr Angela Dramowski
Department of Paediatrics
University Of Witwatersrand

RE: PERMISSION TO CARRY OUT A RESEARCH PROJECT FOR MMed AT CHBH FROM MARCH TO MAY 2008.

I, Dr A. Manning, in my capacity as CEO of Chris Hani Baragwanath hospital, grant Permission for the conduct of the MMed Research project entitled:

" A PROFILE OF HIV-RELATED PAEDIATRIC ADMISSIONS AT CHRIS HANI BARAGWANATH HOSPITAL, JOHANNESBURG, SOUTH AFRICA."

One postgraduate and ethics approval have been obtained from the University Of Witwatersrand.

Yours faithfully

Dr A. Manning
CEO
CHBH
rmn.

Postgraduate Office, Faculty of Health Sciences

Wits Medical School, 7 York Road, PARKTOWN, 2193, Johannesburg • Tel: (011) 717 2745 • Fax: (011) 717 2119 • e-mail: tania.vanleeve@.wits.ac.za

RE-EXAMINATION
CERTIFICATE OF SUBMISSION TO BE SIGNED BY ALL SUPERVISORS OF HIGHER DEGREE CANDIDATES

Dr Angela Dramowski	0503312F	0842401643	angela.dramowski@absamail.co.za
(Name)	(Student Number)	(Telephone)	(E-mail)

Candidate for the degree of Master of Medicine in Paediatrics has submitted his/her thesis/dissertation/research report

Entitled: A PROFILE OF HIV-RELATED PAEDIATRIC ADMISSIONS AT CHRIS HANI BARAGWANATH HOSPITAL, JOHANNESBURG, SOUTH AFRICA

---

1. Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?	xYes	No

2. To the best of your knowledge are you able to verify that:

2.1 this is the candidate's work except as otherwise stated by the candidate?	xYes	No
2.2 the substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university	xYes	No
2.3 the candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions?	xYes	No

PLEASE TICK THE APPROPRIATE WORD

3. I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee/ Committee for Research on Human Subjects and the Number of the Certificate of Approval is: M080202

Name of Supervisor:	Ameena Ebrahim Goga	Telephone:	082 302 3168
Signature:	AGoga	E-mail:	Ameena.Goga@mrc.ac.za
Date:	10 May 2009		

Certificate of Submission
TDB/28/02/2005

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PLEASE TICK THE APPROPRIATE WORD

1. I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee/ Committee for Research on Human Subjects and the Number of the Certificate of Approval is: M080202

Name of Supervisor: Tammy Meyers Telephone: 0833270066

Signature: TMeyers E-mail: tammy@meyers.net

Date: 10 May 2009

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PLEASE TICK THE APPROPRIATE WORD

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Name of Supervisor: Dr Ashraf Hassen Coovadia Telephone: 011 470 9290

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Date: 8 May 2009

Certificate of Submission
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