Outcomes of Human Immunodeficiency Virus infected children admitted to a Paediatric Intensive Care Unit in Cape Town, South Africa

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DECLARATION

I, Mogamat Shamiel Salie, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part thereof has been, is currently being, or is to be submitted for another degree at this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Medicine in Public Health Medicine.

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Thesis Abstract

During the mid to late 1990's, nearly all HIV infected children admitted to South African paediatric intensive care units died. This was in the context of an increasing HIV epidemic in Sub-Saharan Africa, a limited number of intensive care beds in public hospitals and the South African government refusing to supply antiretroviral medication to public sector patients. HIV infected children all die without ARV medication, and it resulted in an increase in the South African under-5 mortality rate. In this context critically ill HIV infected children were often denied PICU admission. Developed countries introduced ARV medication in the early 1990's and the South African government only started supplying ARV medication in late 2003.

When ARV medication became available in South Africa, it was started on the basis of the individual child's clinical and immunological status and there was not much published data on initiation of ARV therapy in critical ill children in intensive care units. Many HIV infected children had recurrent hospital admissions and many children died before initiating ARV medication. HIV infected children are not only susceptible to the normal bacteria and viruses, but at increased risk of opportunistic and mycobacterial infections. CMV has increasingly been recognized as a common co-infection with PCP, but has been difficult to diagnose and treat effectively.

We retrospectively reviewed all HIV exposed and infected children admitted to our PICU in 2009. In addition to our standard treatment, we initiated ARV medication as soon as logistically possible and children with suspected CMV infections were empirically treated with gancyclovir.

There were 1231 PICU admissions during the 1-year study period, with 144 (11.7%) deaths. The standardized mortality ratio (PIM2) was 0.74. There were 123 HIV related admissions; 75 HIV infected children had 85 admissions, there were 24 HIV exposed but HIV negative

admissions and 14 HIV exposed children had no confirmatory tests. Respiratory failure was the main reason for PICU admission in 68% of cases. Only 29% of HIV infected children were known to have received PMTCT. HIV infected children had a median age of 4 months (IQR 3-7), were admitted for a median of 6 days (IQR 3-12) and spent a median of 16 days (IQR 9-28) in hospital after PICU discharge. On admission, 24 children were on ARV medication and 31 children (61% of the children eligible for ARV medication) commenced ARV's on PICU. The PCP immunofluorescence test was positive in 25% of children not on ARV's. Thirty-eight percent of children admitted on ARV's and 57% of the HIV infected children not on ARV's on admission had a CMV viral load > log 4 copies/ml. Fourteen (29%) children who started ARV's during the admission developed IRIS. Seventy-nine percent of HIV infected children survived to PICU discharge and 69% of children survived to hospital discharge. Thirty-one HIV infected children, which is 60% of the children discharged home, or 89% of the children with follow up data, were known to be alive 1 year later.

Conclusions:

This retrospective study shows that increasing numbers of critically ill HIV infected children are surviving PICU and hospital admissions. Antiretroviral therapy was successfully initiated in PICU and apart from the risk of IRIS, there were no obvious side effects to commencing ARV's in critically ill children. CMV is a common opportunistic infection in HIV infected children and empiric therapy with Gancyclovir should be considered whilst confirmatory blood results are awaited.

HIV infection per se, should no longer be an exclusion criterion for PICU admission

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Abbreviations

AIDS	acquired immune deficiency syndrome
ARV	anti retroviral
BCG	Bacillus Calmette-Guerin
CD4	cluster difference 4
CMV	cytomegalovirus
ELISA	enzyme-linked immunosorbent assay
HIV	human immunodeficiency virus
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
PCP	*Pneumocystis jiroveci* pneumonia
PICU	paediatric intensive care unit
PIM2	paediatric index of mortality
PMTCT	prevention of mother-to-child transmission
PTB	pulmonary tuberculosis
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS

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Part A: Protocol

Outcomes of Human Immunodeficiency Virus infected children admitted to a Paediatric Intensive Care Unit in Cape Town, South Africa

Introduction:

The World Health Organization and the joint United Nations programme on HIV/AIDS (UNAIDS) estimated that in 2009, there were 2.5 million Human immunodeficiency virus (HIV) infected children in the world, with 2.3 million or 92% of these children living in Sub-Saharan Africa(1) .

The survival of critically ill HIV infected children has changed dramatically over the past 20 years. In the mid to late 1990's, nearly all HIV infected children admitted to paediatric intensive care units in South Africa (PICU's) died (2,3). There were also reports that the mortality of HIV infected children was similar with and without the availability of intensive care treatment (4). This was in the context of a growing HIV epidemic (5,6), a limited number of PICU beds in state hospitals (7) and the refusal of the South African government to supply anti-retroviral medication to public sector patients (8,9). This resulted in many units refusing admission to HIV infected children with life-threatening illnesses. With the passage of time and increased understanding of disease processes, PICU's have subsequently reported survival rates of >70% of HIV infected children (10,11).

This improved survival can be attributed to a number of factors; effective treatment of *Pneumocystis jirovecci* pneumonia (PCP), the availability of anti-retroviral (ARV) drugs and improvements in the management strategies and technology available to treat critically ill children with septic shock and acute respiratory distress syndrome (12).

The optimal time for starting ARV's has not been determined, but recent research has clearly shown improved survival from early initiation of ARV therapy. The Children with HIV Early Antiretroviral Therapy CHER study group was able to demonstrate a 76% reduction in mortality and 75% reduction in HIV progression by early diagnosis of HIV with immediate commencement of ARV therapy (13).

The majority of children currently commence ARV therapy from outpatient clinics or hospital wards. There is very little data on the initiation of ARV's in critically ill children. The hesitancy in initiating ARV medication in critically ill children was related to the fact that ARV medication is thought not to improve the child's condition immediately and there is potential for drug toxicity in critically ill children (14). An additional concern about starting ARV's in acutely ill children is the potential for developing immune reconstitution inflammatory syndrome (IRIS). The incidence of IRIS in children starting ARV's has been reported to be approximately 20%, with a BCG reaction being the most common (15,16).

HIV infected children are also at increased risk of Cytomegalovirus (CMV) infection, with an increased risk of death (17,18). Goussard et al (19) estimated the incidence of CMV infection in HIV infected children admitted to a PICU as 72%, whilst Zampoli et al (18) reported a CMV incidence of 36% in HIV infected children hospitalized with severe pneumonia. The diagnosis of CMV infection is not easy, with the PP65 antigen test having a high false negative rate (19) and CMV viral load results usually only available days after admission.

Our current management strategy for children with severe sepsis or pneumonia and suspected HIV infection includes the following; broad spectrum antibiotics, co-trimoxazole and prednisone for suspected PCP, and since 2008, empiric gancyclovir treatment for possible CMV infection, prior to confirmation of an elevated plasma CMV viral load or detection of CMV in TA or BAL, as well as initiating ARV's as early as possible after HIV infection has been confirmed.

Aim:

To report the 1-year experience of initiating ARV's and the empiric use of gancyclovir therapy in HIV infected children admitted to our PICU during 2009.

Specific objectives are to report on:

1. The numbers of HIV exposed and infected children admitted to PICU
2. The reason HIV exposed/infected children are admitted to PICU
3. The proportion of children receiving PMTCT
4. Incidence of CMV Infection in HIV exposed and infected children
5. The numbers of children starting ARV's in PICU
6. Complications relating to initiating ARV's in PICU
7. Length of PICU and hospital stay
8. PICU and hospital survival rates
9. The 1 year follow up of HIV infected children

Methodology:

All HIV exposed and infected children admitted to the PICU during 2009 will be included in the study. HIV exposed and infected children admitted to the PICU during 2009 will be identified from the intensive care unit's electronic patient database and cross referenced with the hospital's admission system.

The following investigations are routinely requested on children admitted with severe sepsis or pneumonia; blood culture, full blood count, serum electrolytes and renal function, urinalysis, tracheal aspirate (TA) or broncho-alveolar lavage (BAL) for respiratory viral screen (multiplex PCR kit, Seeplex RV 7 Detection kit; Seegene, Rockville, MD), microscopy and culture, and PCP immune-fluorescence testing (IF: Detect IF PC, Axis-Shield, UK).

Children who have not previously been tested for HIV are screened with an HIV rapid test (Determine HIV 1/2, Abbot Laboratories, Abbot Park, IL). HIV infection is confirmed in HIV exposed children with an HIV PCR test (Amplicor HIV-1 DNA test version 1.5, Roche Diagnostics, GmbH, Mannheim, Germany) if they are under 18 months and with an HIV Elisa test (Architect HIV Ag/Ab Combo ELISA, Abbott Laboratories, Abbott Park, IL) if they are older than 18 months of age.

When there is a clinical concern about possible *Mycobacterium tuberculosis* infection, a Mantoux (purified protein derivative, Statens Serum Institute, Copenhagen, Denmark) is done in children younger than 7 years and either gastric washings or tracheal aspirates are sent for microscopy and culture

Gancyclovir is started empirically in all HIV exposed and infected children admitted with severe pneumonia or suspected of having CMV intestinal infection. A systemic CMV viral load (Artus

RealArt LC CMV PCR, Qiagen, Germany) greater than 4.0 log copies /ml, is considered to be indicative of active CMV infection (18,20). Gancyclovir is stopped if the systemic CMV viral load is less than 4.0 log copies / ml.

Complications thought to be related to ARV drug administration e.g. IRIS, will be recorded as per treating clinicians' documentation.

The data shown in Appendix 1, will be retrospectively collected from the intensive care unit database, patient folders, the hospital laboratory result system and the hospital patient information system.

Statistical Analysis:

Data will be stored in a secure stata file and data analysis will be performed using Stata 11, (StataCorp. 2009. College Station, TX: StataCorp LP). The distribution of numerical variables will be determined by histograms and the Shapiro-Wilkes test. Numerical variables will be expressed as either means with standard deviations or medians and interquartile ranges depending on the data distribution. Categorical variables will be expressed as proportions.

Ethical considerations:

Approval will be obtained from the Departmental Research Committee, School of Child and Adolescent Health, the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town and the research review committee of the Red Cross War Memorial Children's Hospital. Informed consent will not be obtained from patients or their caregivers, as this is a retrospective audit of clinical practice and no interventions are planned. Patient confidentiality will be maintained throughout. All research will adhere to the requirements stated in the Declaration of Helsinki, 2000.

Potential Benefits of the study:

Documentation of the PICU and hospital survival rates with 1-year follow-up. The response to early initiation of ARV's and the incidence of CMV infection in critically ill HIV-infected children admitted to our unit.

This information will help clinicians to make rational decisions about the most appropriate care for patients with HIV infections and related diseases who are referred to the PICU for management.

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Part B: Structured Literature review:

a) Objectives:

The aim of this literature review is to focus on the following management aspects of HIV infected children:

- Initiation of ARV's in intensive care and critically ill children
- Immune reconstitution inflammatory syndrome (IRIS):
- The prevalence of CMV infection in HIV infected children
- PICU and hospital survival rates

b) Search strategy

I searched Pubmed and Google scholar for studies published between the years 1990 and 2014. The search was done using both keywords and Medical Subject Headings with the following terms: "HIV", "outcome", "antiretroviral therapy", "treatment", "HAART", "CMV", "Cytomegalovirus", "PCP", "IRIS", "PICU", "intensive care", "child", "paediatrics", "pediatrics", I also searched the references of selected articles and included relevant studies.
All study designs were included and articles not relevant to the literature review objectives were excluded.

c) Summary and interpretation of literature

<u>Initiation of ARV's in intensive care and critically ill children:</u>

The 2013 World Health Organization (WHO) guidelines (1) suggested that all HIV infected children under 5 years of age should be treated with ARV therapy, irrespective of their CD4 count or clinical stage of disease. The question of when to start ARV therapy in children was addressed in a 2012 Cochrane Collaboration review (2), examining the effectiveness of ARV therapy in HIV infected children under 2 years of age. The paucity of literature on the subject is reflected by the inclusion of only 2 articles to answer this question.

The Children with HIV Early Antiretroviral Therapy (CHER) study team (3) randomized HIV infants, with a median age of 7.4 week and CD4 percentage of 35%, to receive either immediate ARV therapy or deferred ARV therapy, when the CD4 percentage dropped to below 20% (25% in infants under 1 year) or until clinical criteria for disease progression were met. The study included 125 infants in the deferred ARV group and 252 infants received immediate ARV therapy between August 2005 and February 2007. According to the study protocol, 66% (83/125) of infants in the deferred ARV group commenced ARV therapy, after a median follow up period of 40 weeks. There were 20 infant deaths (16%) in the deferred ARV group compared to 10 infants (4%) in the early ARV group. There was disease progression in 32 infants (26%) in the deferred ARV group, compared to 16 infants (16%) in the early ARV treatment group. The study was stopped at the second review of the data and safety board, when it became clear that in this study, early initiation of ARV treatment in infants reduced mortality by 76% and HIV disease progression by 75%.

The second study by Prendergast et al (4) investigated the efficacy of early ARV therapy on viral suppression, in a group of infants who had received nevirapine perinatally. They randomized HIV infected infants to either immediate ARV therapy or deferred ARV therapy, when CD4 counts dropped below 20%. They included 43 infants in the immediate ARV group and 20 infants in the deferred ARV group. In the deferred ARV group, the CD4 counts of 17 children dropped below 20% in the first year and were eligible for ARV treatment. 1-year post initiating ARV therapy, 94 % of children had suppressed viral load with less than 50 copies/ml. They also reported that infants randomized to receive immediate ARV had significantly fewer illness episodes compared to infants in the deferred ARV group.

Cowburn et al (5) reported the short term outcomes of a group of HIV infected children who commenced ARV therapy shortly after PICU discharge. They conducted a prospective observational study over a 16-month period starting in February 2003. They screened all PICU admissions and confirmed HIV infection in 68 children, of which 51 survived to PICU discharge. ARV treatment was commenced in 21 of these children. Of the children that commenced ARV treatment, 3 died in the wards, 4 died after hospital discharge, 3 children were not compliant with medication and 11 children were known to be well at a median of 350 days. Thirteen children died in the wards prior to commencing ARV's, 2 children had previously been started on ARV therapy and 9 children did not meet the criteria for initiating ARV treatment.

Our study is a retrospective review of patients admitted to the PICU in 2009, a period when there was very little published data on initiating ARV therapy. There is now clear evidence that starting ARV therapy in early infancy improves survival. However, there is very little data on initiating ARV therapy in critically ill children during a PICU admission.

Immune reconstitution inflammatory syndrome (IRIS):

The immune reconstitution inflammatory syndrome refers to the paradoxical deterioration in clinical status of some patients, following initiation of antiretroviral therapy, with suppression of the HIV viral load and increasing CD4 counts.

Smith et al (6) prospectively reported the incidence, clinical manifestation and risk factors in a cohort of HIV infected children initiating ARV therapy between April 2005 and November 2006. They report that 21% (34/162) of HIV infected children developed IRIS at a median of 16 days (range 7 – 115 days) post ARV initiation. BCG adenitis occurred in 71% (24/34) of children, 12 children were diagnosed with Tuberculosis, whilst single cases of

CMV pneumonia, streptococcus pneumonia and severe seborrheic dermatitis were described. IRIS occurred more frequently in younger children with severe immunosuppression, median CD4 count 13.9.

Puthanakit et al (7) prospectively reported the incidence and spectrum of IRIS in a cohort of severely immunosuppressed HIV infected children in Thailand, commencing ARV therapy between May 2002 and November 2004. They enrolled 153 children and described the incidence of IRIS to be 19% (32/153), which occurred at a median of 4 weeks (range 2 – 31 weeks), after initiating ARV therapy. Mycobacterial organisms caused 14 episodes of IRIS, varicella zoster virus and herpes simplex virus were each implicated in 7 episodes, there were 3 episodes of *Cryptococcus neoformans* and 1 episode of Guillan-Barre' syndrome. Two children with IRIS were treated with short courses of steroids and 3 children died from complications of IRIS. They also found that the children who developed IRIS had lower baseline CD4 counts, compared to the children who did not develop IRIS.

Rabie et al (8) prospectively reported the incidence of BCG-IRIS (regional adenitis) in relation to children randomized to either early or deferred ARV initiation in the CHER study (3). Early treatment referred to children who commenced ARV treatment before 12 weeks of age and who had CD4 counts greater than 25%. Deferred treatment referred to infants who only commenced ARV treatment once their CD4 counts dropped below 25%, or developed CDC stage C or severe stage B disease. They included 369 infants, reporting that 28 infants developed BCG IRIS within 2 months and 32 (8.7%) children developed BCG IRIS within 6 months of commencing ARV treatment. They reported that the incidence of BCG IRIS in children who commenced early ARV's was 10.9 per 100 person-years, compared to 54.3 per 100 person-years in children with deferred ARV treatment. They also reported that low CD4 counts and high HIV viral loads were associated with an increased risk of

developing IRIS. They concluded that initiating ARV therapy before children deteriorated immunologically or clinically, reduced the risk of BCG IRIS.

Walters et al (9) retrospectively reviewed the records of HIV infected children initiating ARV therapy between January 2003 and December 2005. They included 290 children and described Tuberculosis in 48% (136/290) of the children. One hundred and sixteen of the Tuberculosis episodes occurred before initiation of ARV's, and 10 of the 21 episodes that occurred after initiating ARV's were considered to be related to IRIS. They postulated that early initiation of ARV therapy would most likely reduce Tuberculosis related morbidity and mortality in Tuberculosis endemic areas.

A systematic literature review (10) reported on Tuberculosis associated IRIS (TB-IRIS) in children commencing ARV therapy. They included 13 studies of which 6 were retrospective, 2 prospective, 1 cross-sectional, 3 case reports and 1 case series. They described 303 cases of TB-IRIS, with the median time from ARV initiation to IRIS diagnosis ranging from 8 days to 16 weeks. Treatment was only described in 2 cases, and both received steroids. Few deaths were described, and it was difficult attributing the cause of death to the underlying disease or a complication of IRIS. They concluded that there was limited information on TB-IRIS, with research needed to assess the risk factors, incidence and optimum treatment.

IRIS is a recognized complication following initiation of ARV therapy. The available paediatric data on the risk factors, treatment and outcome of children with IRIS is limited. The majority of children described to have developed IRIS were from outpatient settings and not from initiating ARV therapy in intensive care. Severe immunosuppression is a well described risk factor for developing IRIS, which means that children initiating ARV therapy

whilst critically ill, may have a higher incidence of IRIS. Only 1 study reported the use of steroid treatment for IRIS and the mortality associated with IRIS appears to be low. With the high incidence of Tuberculosis in South Africa, BCG adenitis and pulmonary tuberculosis is a particular concern after initiating ARV therapy in HIV infected children.

The prevalence of CMV infection in HIV infected children

HIV infected children are at high risk of opportunistic infections. PCP was commonly described in HIV infected children and has been associated with high mortality(11). However, CMV infection has gradually also been recognized as being a major pathogen causing lung disease and death in immunosuppressed HIV infected children.

Ikeogu et al (12) reported the autopsy findings of a group of Zimbabwean children, under 5 years of age, who died at home or shortly after hospital admission. The aim of the study was to describe the spectrum of lung disease in HIV infected children from a developing country. Over a 10 month period between July 1992 and April 1993, they reported HIV infection in 66% (122/184) of these children, positive bacterial cultures in 86% (106/122) of children, Tuberculosis in 5% of children (6/122), 19% of the HIV infected children had PCP and 7% had evidence of CMV infection.

Chintu et al (13) performed autopsies in order to determine the cause of death in a group of hospitalized Zambian children, who died from respiratory illness. This descriptive study was performed between June 1997 and September 2000, and included 180 HIV infected children and 84 HIV negative children. The commonest cause of death in both groups of children was acute pyogenic pneumonia. In the group of HIV infected children, PCP was identified in 29%, CMV in 22% and tuberculosis in 18% of the cases. They reported that

only 3 of the 40 children had evidence of necrotizing CMV pneumonia, suggested that the majority of children had mild CMV infections and that treatment with Gancyclovir was toxic and too expensive for most African countries.

Goussard et al (14) prospectively described the role of CMV co-infection in ventilated HIV infected children with possible PCP, using the pp65 test for CMV antigen and lung biopsies. Twenty-five children were recruited between April 2001 and April 2005, with 17 of them having lung biopsies and 8 children had post mortem lung tissue biopsies. They diagnosed CMV pneumonia in 72% of the children. Thirty-six percent of children were infected with both CMV and PCP, whilst 24 % of children had only PCP isolated. The pp65 antigen test for CMV had a false negative rate of 24%. All of the children were treated for PCP and only 1 of these children were treated with gancyclovir. The PICU mortality rate in this study was 72% and overall hospital mortality rate in this group of children was 88%.

Kitchen et al (15) prospectively studied a group of HIV infected and exposed children admitted to their PICU with respiratory failure. They recruited 63 children, of which 53 were HIV infected and 10 were HIV exposed but not infected. All children were empirically treated with broad-spectrum antibiotics, cotrimoxazole/prednisone for suspected PCP and with Gancyclovir for suspected CMV infection. PCP was diagnosed in 33% of these infants and 38% of these children had a CMV viral load greater than log 4.0 copies/ml.
They reported that 32% of HIV infected children and 20% of HIV uninfected children died in this study, with the risk of death significantly higher in children with CMV disease.

Zampoli et al (16) prospectively investigated the prevalence and outcomes CMV associated pneumonia in hospitalized children from December 2006 to June 2008. They considered children to have active CMV infection if either blood or respiratory tract secretions had a

CMV viral load greater than or equal to log 4.0 copies/ml. The study recruited 124 HIV infected children and 76 HIV uninfected children. They diagnosed PCP in 27% of the children, CMV associated pneumonia in 28% of the children, with a prevalence of 36% in HIV infected children and 15% in HIV negative children. HIV infected children had a reported mortality of 35% compared to 11% in HIV uninfected children. Gancyclovir use was not consistent, with 68% (25/37) of HIV infected children and 80% (8/10) HIV uninfected children with CMV associated pneumonia receiving gancyclovir. They reported a mortality of 43% (9/21 children) in HIV infected children with CMV associated pneumonia treated with Gancyclovir, compared to 88% (7/8 children) in children not treated with Gancyclovir. The authors concluded that empiric Gancyclovir may be indicated in immune-suppressed, HIV infected children presenting with pneumonia.

Hsiao et al (17) performed a cross-sectional study, comparing the prevalence and level of CMV viraemia in asymptomatic HIV exposed infants and symptomatic HIV exposed infants hospitalized with suspected PCP between December 2006 and June 2008. They included 283 asymptomatic HIV exposed infants and 142 HIV exposed infants with severe pneumonia. They found that 68% of symptomatic HIV exposed infants with pneumonia had a high CMV viral load compared to only 24% of asymptomatic HIV exposed infants and that prevalence and level of CMV viraemia peaked at 3-4 months of age.

The above-mentioned studies confirm that CMV is a common opportunistic infection in HIV infected children. Performing a lung biopsy in order to diagnose CMV pneumonitis, is not practical in critically ill ventilated children. A quantitative CMV viral load with a cut-off of greater than or equal to log 4.0 copies/ml appears to be a good alternative diagnostic test to diagnose active CMV infection. However, whilst a positive CMV viral load might indicate

active CMV disease, and likely CMV pneumonitis in a HIV infected children presenting with pneumonia, it does not equate to a diagnosis of CMV pneumonitis.

PICU and hospital survival rates

In 2009, UNAIDS estimated that there were 33.3 million HIV infected people in the world, of which 22.5 million people lived in Sub-Saharan Africa(18). The HIV epidemic overwhelmed health systems in Sub-Saharan Africa, and many children died with limited access to healthcare and anti-retroviral medication(19).

In the mid 1990's, before the availability of effective PCP treatment and ARV therapy, most HIV infected children admitted to intensive care units in South Africa died. Mathivha et al (20) described the outcome of HIV infected and HIV negative children requiring mechanical ventilation for community acquired pneumonia in a 2 year period between 1992 and 1993. They admitted 93 HIV negative children during this period and had 29 deaths (31%). There were 17 HIV infected children admitted with respiratory failure, of which 15 died, representing a PICU mortality rate of 88%.

Thirsk et al (19) reported on the outcome of HIV exposed and infected children with respiratory failure. They compared the outcomes of children who were offered mechanical ventilation at a tertiary referral centre and with those of children who were refused PICU admission from a regional hospital, with limited capacity to ventilate children. They recruited 49 children in the mechanical ventilation arm and 67 children, who were refused ventilation. Forty-one percent of the ventilated children survived to hospital discharge compared to 24 % of children who were refused ventilation. They concluded that in the context of their small study, mechanical ventilation provided little survival benefit in HIV infected children admitted with acute respiratory failure.

Rabie et al (21) retrospectively described the outcomes of HIV infected children admitted to their PICU over a 1 year period in 2003, prior to the availability of ARV treatment. They had 47 HIV infected admissions with 17 children (36%) dying in PICU, and another 4 children died shortly after PICU discharge., for an overall hospital mortality rate of nearly 50%.

Cooper et al (22) retrospectively reported the 10 year experience of HIV infected children admitted to a PICU in the United Kingdom between 1992 and 2002. During this period, 42 HIV infected children had 66 admission episodes. Sixteen (38%) children died in PICU, 5 children died after PICU discharge and 21 (50%) children were alive at the time of reporting. Seventy-seven percent of the children were admitted for respiratory failure and 11% had elective admissions following surgery. They reported good growth and development outcomes in 80% of surviving children.

In developed countries, ARV therapy was introduced in the mid 1990's for HIV infected children. de Martino et al (23) conducted a multi-centered, population based, longitudinal study of HIV infected children in the Italian registry. They included 1142 HIV infected children born between 1980 and 1997, specifically reporting on the time to death of birth cohorts and related them to the administered ARV therapy. They found improved survival in HIV infected children in 1996 – 1998, concluding that it was related to combined ARV therapy. Similarly, Resino et al (24) reported on the effect of ARV therapy on the outcomes of 427 HIV infected Spanish children from 1980 until 2003.
From 1980 to 1989 ARV therapy was not available, monotherapy was used between 1990 and 1993, combined therapy was introduced between 1994 and 1996, with increasing numbers of children established on ARV therapy over the following years. They concluded

that effective ARV therapy for HIV children reduced the number of hospital admissions, reduced disease progression and death.

The intensive care and hospital outcomes of HIV infected children have historically been affected by access to appropriate treatment as well as treatment limitations based on their severity of illness and poor long term prognosis. What has become clear is that HIV infected children who do not start ARV therapy, have a high mortality rate. With the availability of effective ARV treatment programmes, paediatric intensive care and hospital survival rates of critically ill HIV infected children have steadily improved over the past 2 decades. Thus, HIV infection per se, should not be an exclusion criterion for admission to intensive care units in developing countries.

c) Needs for further research

i) An effective PMTCT programme currently offers the only hope of preventing HIV disease in children. Early initiation of ARV medication has clearly been associated with increased survival. There is an ongoing need to develop new ARV drugs and specifically intravenous formulations.

ii) There is a need to develop more reliable tests to diagnose PCP and CMV, which would allow more directed treatment of critically ill HIV infected children.

iii) IRIS is a poorly understood complication of ARV therapy and the risk factors and optimal management thereof still needs to be elucidated

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Part C: Journal 'ready' manuscript

I prepared the article for publication in the journal Pediatric Critical Care Medicine (PCCM). PCCM is a peer-reviewed journal that focuses exclusively on neonatal and paediatric critical care. PCCM is an official publication of the Society of Critical Care Medicine (SCCM) and the World Federation of Pediatric Intensive and Critical Care Society (WFPICCS).

The PCCM requirements for publication are in appendix 4.

Outcomes of Human Immunodeficiency Virus infected children admitted to a Paediatric Intensive Care Unit in Cape Town, South Africa

Abstract

Objectives: The aim of the study was to report the 1-year experience of initiating ARV's and the empiric use of gancyclovir therapy in HIV infected children admitted to our PICU.

Design: Retrospective cohort study

Setting: PICU, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Patients: All HIV infected and HIV exposed children admitted to the PICU in 2009

Intervention: None

Measurements and Main Results: There were 1231 PICU admissions during the 1-year study period, with 144 (11.7%) deaths. The standardized mortality ratio (PIM2) was 0.74. There were 123 HIV related admissions; 75 HIV infected children had 85 admissions, there were 24 HIV exposed but HIV negative admissions and 14 HIV exposed children had no confirmatory tests. Respiratory failure was the main reason for PICU admission in 68% of cases. Only 29% of HIV infected children were known to have received PMTCT. HIV infected children had a median age of 4 months (IQR 3-7), were admitted for a median of 6 days (IQR 3-12) and spent a median of 16 days (IQR 9-28) in hospital after PICU discharge. On admission, 24 children were on ARV's and 31 children commenced ARV's on PICU. The PCP immunofluorescence test was positive in 25% of children not on ARV's. Thirty-eight percent of children admitted on ARV's had a positive CMV viral load, and 57% of the HIV infected children not on ARV's on admission had a positive CMV viral load. Fourteen (29%) children who started ARV's during the

admission developed IRIS. Seventy-nine percent of HIV infected children survived to PICU discharge and 69% of children survived to hospital discharge. Thirty-one HIV infected children, 61% of the children discharged home, were known to be alive 1 year later.

Conclusions: The numbers of HIV infected children surviving PICU and hospital admissions have increased. Antiretroviral therapy was successfully initiated in PICU and apart from the risk of IRIS, there were no obvious side effects to commencing ARV's in critically ill children. CMV is a common opportunistic infection in HIV infected children and empiric therapy with Gancyclovir should be considered whilst confirmatory blood results are awaited.

Key Words: HIV; PICU; mortality; antiretroviral; cytomegalovirus, PCP, children, gancyclovir

INTRODUCTION

The survival of critically ill, HIV infected children in South Africa has changed dramatically over the past 20 years. During the mid to late 1990's, nearly all HIV infected children admitted to paediatric intensive care units (PICU's) in South Africa died (1,2). There were also reports that the mortality of HIV infected children was similar with and without the availability of paediatric intensive care treatment (3). This was in the context of an increasing HIV epidemic (4-6), a limited number of PICU beds in state hospitals (7) and the South African government refusing to supply anti- retroviral (ARV) medication to public sector patients (4,8). This resulted in most intensive care units refusing admission to HIV infected children with life-threatening illnesses.

The reality was that HIV infected children without access to ARV therapy were doomed to die. Hussey et al (9) demonstrated that the median survival in 193 newly diagnosed HIV infected children was 32 months from the time of diagnosis. The lack of ARV medication resulted in an increase in the number of children dying in hospitals (6) and an increase in the national under 5 childhood mortality rates (10).

From the early 2000's, with an increased understanding of disease processes, and the availability of private donor funded ARV's South African PICU's subsequently reported survival rates of HIV infected children at about 75%, with approximately 50% of children surviving to hospital discharge (11,12)(Salie unpublished data). This was not too dissimilar to the survival of HIV infected children admitted to resource rich intensive care units in developed countries(13).

This improved survival could be attributed to a number of factors including; effective treatment of *Pneumocystis jirovecci* Pneumonia (PCP), improvements in ventilator management strategies

(14) and technology available to treat critically ill children with septic shock and acute respiratory distress syndrome (15).

The South African government made ARV drugs available to public sector patients in November 2003 (16). There have been several approaches to commencing ARV medication, but the optimal time for initiating ARV's in critically ill children in PICU has not been determined.

Recent research has clearly shown improved survival from early initiation of ARV's (17). The CHER study group (18) was able to demonstrate a 76% reduction in early infant mortality and 75% reduction in HIV progression by diagnosing HIV early and commencing ARV's immediately.

The majority of children currently commence ARV's from outpatient clinics or hospital wards. There is very little data on the initiation of ARV's in critically ill children in intensive care units. The hesitancy in initiating ARV's in critically ill children was related to the fact, that ARVS's were thought not to improve the child's condition in the short term and there was the potential for drug toxicity (19), particularly in critically ill children. An additional concern about starting ARV's in acutely ill children has been the potential for developing immune reconstitution inflammatory syndrome (IRIS) (20,21), with associated deterioration in clinical condition.

Respiratory failure is probably the commonest reason for PICU admission in HIV infected children (11,13,22). HIV infected children are not only susceptible to the usual viral and bacterial pathogens, but are also at increased risk of opportunistic infections (23). PCP has been the commonest described opportunistic infection, but Cytomegalovirus (CMV) infection has increasingly been recognized as a common co-infection in HIV infected children (22,24-26).

In developing countries, with a high Tuberculosis prevalence, HIV infected children are also at increased risk of Pulmonary Tuberculosis (27).

Diagnosing CMV infection in resource-limited settings is challenging, with confirmatory tests often only available several days after admission. Treatment for CMV is also problematic as gancyclovir is not widely available.

Since 2008, our PICU and infectious diseases teams changed the management approach to critically ill HIV infected children. ARV medication was started in PICU as soon as the diagnosis of HIV infection was confirmed and the child's caregivers had been counseled. In addition, gancyclovir was started empirically on admission, in all HIV infected children with severe pneumonia and sepsis.

The aim of this retrospective study was to review the outcome of HIV infected children admitted to our PICU during 2009, who had ARV's initiated as soon as the diagnosis was confirmed and who were empirically treated with Gancyclovir for suspected CMV infection.

MATERIALS AND METHODS

Setting

The study was conducted in the PICU of the Red Cross War Memorial Children's Hospital, situated in Cape Town, South Africa. It is a 20 bed, multidisciplinary unit with approximately 1250 admissions per year. Approximately 60% of admissions are for acute emergencies and about 70% of admissions require ventilatory support. This is the largest PICU in South Africa and a team of paediatric intensivists, rotating registrars and nursing staff, delivers patient care. The expertise of the PICU team is broadened by the availability of an interested infectious diseases department, supported by reliable microbiology and virology laboratories.

Design and Patients

Approval for the study was obtained from the Human Research Ethics Committee of the University of Cape Town and the Red Cross War Memorial Children's Hospital research review committee.

We conducted a retrospective cohort study of all HIV exposed and infected children admitted to the PICU during 2009. These children were identified from the intensive care unit's patient database. Data was collected from the intensive care unit database, patient folders, the hospital laboratory result system and the hospital patient information system.

All emergency and elective admissions to the PICU were discussed with the PICU Consultant on call, who was responsible for the care of all children admitted to the intensive care unit.
In 2009, HIV infection per se, was not an exclusion criterion for PICU admission. However, HIV infected children with prolonged hospital admissions and those children who had not responded to appropriate therapy were denied admission on the basis of having a poor chance of surviving long term. This was done on the basis of a carefully considered hospital policy, which was developed in consultation with clinical teams throughout the hospital (28).

All children admitted to the PICU, who had not previously been tested for HIV, were screened with a Rapid HIV test (Determine HIV 1/2, Abbot Laboratories, Abbot Park, IL). HIV infection was confirmed in HIV exposed children with an HIV polymerase chain reaction test (Amplicor HIV-1 DNA test version 1.5, Roche Diagnostics, GmbH, Mannheim, Germany) if they were younger than 18 months and with an HIV enzyme-linked immunosorbent assay (Architect HIV Ag/Ab Combo ELISA, Abbott Laboratories, Abbott Park, IL) if they were older than 18 months

of age. The infectious diseases department commenced antiretroviral drugs as soon as possible, once HIV infection was confirmed and the child's caregiver had received the appropriate counseling

The following investigations were routinely requested on children admitted with severe sepsis or pneumonia: full blood count, serum electrolytes and renal function, blood culture, urinalysis, tracheal aspirate (TA) or non-bronchoscopic broncho-alveolar lavage(BAL) for a respiratory viral screen (multiplex PCR kit, Seeplex RV 7 Detection kit; Seegene, Rockville, MD), microscopy and culture and PCP immune-fluorescence testing (IF: Detect IF PC, Axis-Shield, UK).

When there was a clinical concern about possible tuberculosis, a Mantoux test (purified protein derivative, Statens Serum Institute, Copenhagen, Denmark) was done in children younger than 7 years and either gastric washings or tracheal aspirate were sent for *Mycobacterium tuberculosis* microscopy and culture. The diagnosis of Pulmonary Tuberculosis after initiating ARV therapy was made on the basis of either a positive Mantoux, identification of acid-fast bacilli on microscopy and culture or clinically in children with persistent respiratory symptoms.

Our management strategy for children with severe sepsis or pneumonia and suspected HIV infection included the following; broad-spectrum antibiotics, co-trimoxazole and prednisone for suspected PCP, and since 2008, empiric gancyclovir treatment for possible CMV infection. A systemic CMV viral load greater than 4.0 log copies/ml was considered to be indicative of active CMV infection (25,29). Gancyclovir was stopped if the systemic CMV viral load was less than 4.0 log copies/ml. Children with suspected or proven PCP received 21 days therapy with intravenous co-trimoxazole and oral prednisone. Children with active CMV infection were

treated for a total of 42 days with gancyclovir initially and changed to oral valgancyclovir when they were discharged home.

Non-invasive ventilatory support was delivered with bubble nasal continuous positive airway pressure (Fisher & Paykel Healthcare, Auckland, NZ). Pressure control was the main mode of ventilation for mechanical ventilation and the unit practiced lung protective ventilator strategies (30). High frequency oscillatory ventilation with the Sensormedics 3100A (Carefusion, Yorba Linda, CA), was used as a rescue mode of ventilation for children with refractory hypoxaemia and hypercapnoea.

The total daily fluid allowance was restricted to 80ml/kg/day, including intravenous drug volumes. Enteral feeds were started as soon as the child was haemodynamically stable and able to tolerate feeds. Diuretics were used if patients were cumulatively fluid positive or developed peripheral oedema.

Data Analysis

Data were stored in a secure stata file and analyzed using Stata 11 (StataCorp, 2009. College Station, TX). The distribution of numerical variables was determined by histograms and the Shapiro-Wilk test. Numerical variables were expressed as medians and interquartile ranges, as most did not have a normal distribution. The Wilcoxon sum rank test was used for continuous variables. Categorical variables were expressed as proportions.

RESULTS

During the 1-year study period in 2009, there were 1231 admissions to the PICU, figure 1. Of these admissions, 144 (11.7%) children died and the Standardized mortality ratio, using the Paediatric Index of Mortality 2 (PIM2) (31)was 0.74.

Of the total number of admissions, 123 (10%) admissions were HIV associated. On admission, 44 of the children were known to be HIV infected and 79 children were known to be HIV exposed, but had not had definitive HIV testing. Twenty-four HIV exposed children were found to be HIV uninfected and 14 HIV exposed children had no confirmatory tests. Of these 14 children with no confirmatory tests, 5 died and the remaining 9 were transferred to other hospitals. Seventy-five HIV infected children had 85 admissions. Eight children had 2 admissions and 1 child had 3 admissions. There was no data on the number of HIV infected children refused PICU.

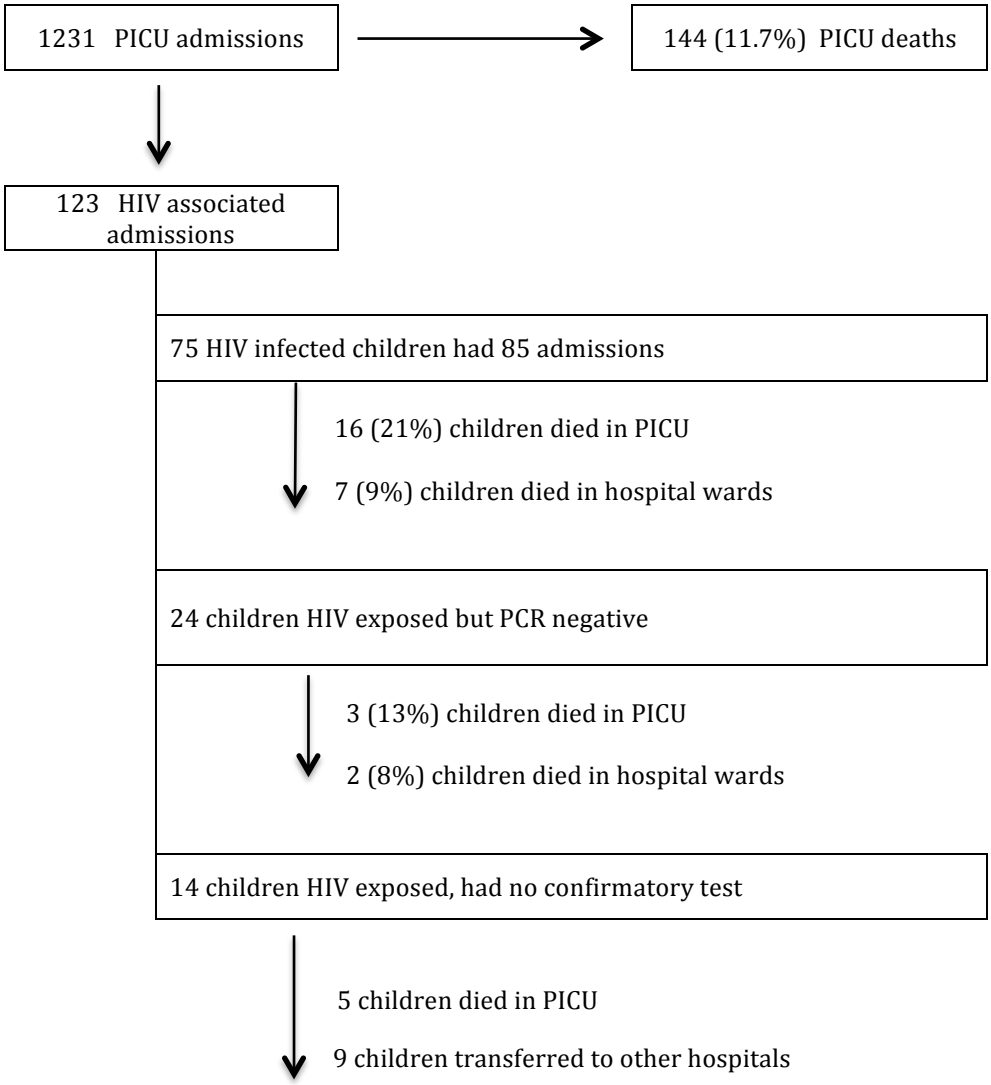

Figure 1: 2009 PICU admissions

Table 1 shows the PICU and hospital characteristics of HIV infected and HIV exposed children admitted during the 1-year study period. The reasons for admission in HIV infected children were predominantly for respiratory failure. Only 29% of HIV infected children had documented PMTCT compared to 71% of HIV exposed but HIV negative children. Only 22% of PCP immunofluorescence tests and 61% of CMV viral load tests performed on HIV infected children were positive.

On admission 24 HIV infected children were on ARV's. Thirty-one HIV infected children commenced ARV treatment in PICU, which is 61% of those who were eligible for treatment. Two children died in PICU and 1 child following PICU discharge without starting ARV's. Seventeen children commenced ARV's in the hospital ward prior to discharge. HIV infected children spent a median of 16 days in the hospital wards before discharge, compared to a median of 4 days in the HIV exposed children. Seventy –nine percent of HIV infected children survived the PICU admission. Fifty-two (69%) HIV infected children survived to hospital discharge. Eight HIV infected children were referred for follow up at local hospitals or community health clinics and no follow up data was available for these children. Nine HIV infected children did not return for follow up visits. Four HIV infected children are known to have died following hospital discharge. Thirty-one HIV infected children were known to be alive 1 year after hospital discharge, which represents 60% of the children discharged from hospital and 89% of the children with follow up data 1 year later. There was no long-term follow up data for HIV exposed children.

Five (21%) of the HIV exposed children died during the hospital admission. Two of these children died from respiratory failure, 1 child from hypovolaemic/septic shock in PICU and 2 children died in the hospital wards from complications of necrotizing enterocolitis and

haemolytic uraemic syndrome. None of the 7 HIV exposed children diagnosed with pneumonia had a positive CMV viral load.

Table 1: All HIV infected and exposed PICU admissions and outcome data

	HIV infected admission (n=75 children with 85 admissions)	HIV exposed admissions (n=24)	p
Male : Female	45 : 40	11 : 13	
Age (months)	4 (3 – 7)	1 (0 – 3)	0.0000
Weight (kilograms)	4.6 (4 – 6.2)	3.4 (2.4 – 5.2)	0.0019
PIM2	0.23 (0.09 – 0.41)	0.09 (0.03 – 0.19)	0.008
Reasons for admission:			
• respiratory failure	58 (68%)	7 (29%)	0.0006
• cardiovascular / shock	15 (18%)	9 (38%)	0.038
• neurological	6 (7%)	0	0.182
• other	6 (7%)	8 (33%)	0.0007
PMTCT			
• received PMTCT	22 (29%) children	17 (71%) children	0.0002
• no PMTCT	26 (35%) children	1	0.0031
• unknown	27 (36%) children	7 (29%) children	0.529
CD4 count	15.4% (9.4 – 21.4)	-	-
CMV viral load			
• positive	43	0	-
• negative	27	7	-
PCP immunofluorescence			
• positive	14	1	
• negative	49	6	-
Anti-retroviral drugs			
• admitted on ARV's	24	-	-
• started ARV's in PICU	31	-	-
Length of ventilation (days)	5 (2 – 11)	2 (1 – 3.5)	0.0002
Length of PICU stay (days)	6 (3 – 12)	3 (2 – 4.5)	00005
Hospital stay post PICU discharge (days)	16 (9 – 28)	4 (3 – 8)	0.000
IRIS			
• BCG adenitis	8 children	-	-
• Pulmonary Tuberculosis	6 children	-	-
Discharge Diagnoses			
• Pneumonia	60 (71%)	7 (29%)	0.0002
• Septicaemia	9 (11%)	5 (21%)	0.201
• Gastroenteritis	3	3	00872
• Pneumococcal meningitis	3	-	0.352
• 0ther	10 (12%)	8 (33%)	0.0147
Mortality			
• PICU deaths	16 (21%) children	3 (13%)	0.385
• Hospital ward deaths	7 (9%) children	2 (8%) children	0.88
12 month survival	31 children	-	-
Data are presented as median (interquartile range) unless otherwise stated			

Table 2 shows the outcomes of HIV infected children who were admitted on ARV's, those that started ARV's in PICU and following PICU discharge. Children admitted on ARV's were older than those starting ARV's in PICU or the wards. None of the children, who were admitted on ARV's, were diagnosed with IRIS. Children who started ARV's in PICU were ventilated for longer, and had the longest PICU stay. A positive CMV viral load was found in 38% of children admitted on ARV's, in 58% of children starting ARV's in PICU and in 59% of children starting ARV's post PICU. Twenty-six percent of children starting ARV's in PICU and 35% of children starting ARV's post PICU discharge developed IRIS. Fifty percent of children who were admitted on ARV's died and 25% of children starting ARV's in PICU died. No deaths were documented as related to IRIS

Table 2: Outcomes of HIV infected children admitted on ARV's, those starting ARV's in PICU and children starting ARV's post PICU discharge

	Admitted on ARV's (n=24)	PICU ARV's (n=31)	ARV's post PICU (n=17)	p
Age (months)	13 (5 – 24)	3 (2 – 4)	3 (2 – 5)	0.00 *
PIM2	0.23 (0.08 – 0.46)	0.26 (0.08 – 0.32)	0.17 (0.12 – 0.44)	0.915
CD4 count	17 (6 - 26)	12 (8 – 18)	15 (12 – 21)	0.23
CMV viral load positive	9	18	10	
PCP positive	0	9	3	
Length of ventilation (days)	2 (1 – 6)	7 (4 – 14)	5 (2 – 6)	0.001*
Length of PICU stay (days)	4 (3 – 9)	10 (6 – 15)	6(3 – 8)	0.003*
Hospital stay post PICU discharge (days)	19 (5 – 30)	17 (9 – 23)	13 (10 – 21)	0.778
IRIS				
• BCG adenitis	0	5 (16%)	3 (18%)	0.85^
• Pulmonary Tuberculosis	0	3 (10%)	3 (18%)	0.42^
Mortality				
• PICU deaths	7 (29%)	7 (22%)	0	0.55*
• Hospital ward deaths	5 (21%)	1 (3%)	0	0.033*
12 month survival	8 (30%)	13 (43%)	10 (59%)	0.332*
Data are presented as median (interquartile range) unless otherwise stated				
• Denotes admitted on ARV's compared to PICU ARV's • ^ Denotes PICU ARV's compared to ARV's post PICU				

The Discharge diagnoses and outcomes of HIV infected children are shown in **Table 3**.

Fifty HIV infected children had 60 PICU admissions for Pneumonia. A positive CMV viral load was found in 34 (69%) of children and PCP in 13 (26%) of children with pneumonia. Twelve (24%) of children diagnosed with pneumonia were infected with both CMV and PCP. There were 7 deaths in PICU and a further 5 deaths in the hospital wards for an overall 76% survival rate in children diagnosed with pneumonia.

Nine children were diagnosed with septicaemia. Two of these children died in PICU, 1 child died in the hospital ward for an overall 67% survival rate in children diagnosed with septicaemia. Of the 3 children diagnosed with gastroenteritis, 1 died in PICU, another died in the hospital ward for an overall 33% survival rate. All 3 children diagnosed with pneumococcal meningitis died in PICU. Both children diagnosed with CMV enteritis died in PICU. The remaining children had a variety of discharge diagnoses including; myocarditis, poisoning, elective surgical admissions following patent ductus arterious closures, ventricular septal defect repairs and laryngeal cleft surgery

Table 3: Discharge diagnoses and outcomes of HIV infected children

Diagnosis	PICU mortality	Ward mortality	Survivors
Pneumonia (n=50)	7	5	38 (76%)
Septicaemia (n=9)	2	1	6 (67%)
Gastroenteritis (n=3)	1	1	1 (33%)
Pneumococcal Meningitis (n=3)	3	-	0
CMV enteritis (n=2)	2	-	0

Table 4 shows the characteristics of the 16 HIV infected children who died in PICU. The 3 children diagnosed with meningococcal meningitis died within 2 days of admission. Only 2 of the children who died were not on ARV drugs. Seven children who had ARV's commenced in PICU died during the admission episode. The 2 children diagnosed with CMV enteritis both died

and CMV was identified in another 2 children who died from pneumonia. Ten of these children had treatment withdrawn, as a result of not responding to appropriate care.

Table 4: HIV infected children dying in PICU

PICU Deaths	Age (months)	PIM2 score	PICU days	ARV's started	Diagnosis / Cause of Death
1.	26	0.93	1	Previously	Pneumococcal meningitis
2.	24	0.23	2	Previously	MRSA sepsis, pneumonia
3.	10	0.66	5	Previously	Gut necrosis, Klebsiella/E. coli sepsis
4.	3	0.58	7	No	CMV enteritis, Klebsiella sepsis
5.	4	0.59	7	Previously	CMV enteritis, E. Coli sepsis
6.	4	0.61	5	PICU	Pneumonia, E.coli sepsis
7.	6	0.68	13	PICU	Klebsiella sepsis, septic shock
8.	4	0.23	22	Previously	Pneumonia, CMV
9.	2	0.92	2	No	Pneumococcal meningitis
10.	3	0.59	17	PICU	H1N1 Pneumonia
11.	3	0.28	26	PICU	PCP / rhinovirus pneumonia
12.	2	0.09	26	PICU	PCP, Klebsiella/ pseudomonas sepsis
13.	2	0.14	16	PICU	PCP, RSV, parainfluenzae
14.	2	0.46	1	Previously	Pneumococcal meningitis
15.	5	0.16	3	Previously	Klebsiella sepsis,
16.	7	0.25	17	PICU	CMV, RSV, MRSA sepsis

Table 5 shows the characteristics of the 7 HIV infected children who died in the hospital ward following a PICU admission. The majority of these children died from respiratory failure. Another child, who had commenced ARV's in PICU, died following PICU discharge. One child died prior to the initiation of ARV's. Six of the HIV infected children who died following PICU discharge were not considered for re-admission, on the basis of them not responding to appropriate treatment.

Table 5: HIV infected children Hospital deaths

Hospital Deaths	Age (months)	PICU days	ARV's started	Diagnosis / Cause of Death	Days post PICU discharge
1	78	16	Previously	Chronic lung disease	1
2	14	9	Previously	Myocarditis	3
3	7	42	PICU	Chronic lung disease	2
4	2	3	No	Pneumonia	13
5	1	24	Previously	Klebsiella Septicaemia	5
6	4	6	Previously	Pneumonia, PCP	31
7	8	38	Previously	Chronic lung disease	23

DISCUSSION

This retrospective review focused on critically ill, HIV infected children admitted to a paediatric intensive care unit in a developing country, who were commenced on antiretroviral medication as soon as logistically possible and empirically started on gancyclovir for suspected CMV infection. The survival rates of HIV infected children in our institution have increased, with 79% of children surviving the PICU admission and 69% of the children surviving to hospital discharge. We managed to initiate ARV's in PICU in 61% of children eligible for ARV's. CMV was a common opportunistic infection and a high CMV viral load was found in nearly 60% of children not previously on ARV medication. At least 60% of the children, who were discharged home, or 89 % of the children with follow up data, were known to be alive 1 year later.

Sub-Saharan Africa has been the epicenter of the HIV epidemic (32). The numbers of children with HIV have overwhelmed healthcare systems and increased the South African under 5 year mortality rate (10). A large PICU in London (13) only admitted 42 HIV infected children in a ten year period, which poignantly reflects the difference in disease burden faced by developing countries. Intensive care is an expensive, scarce resource in developing countries, and rationing resources (28,33,34) is a daily reality, which increases the emotional burden on clinicians caring for critically ill children with a high likelihood of dying.

HIV infection in childhood is preventable with access to medical care and appropriate interventions. According to the UNAIDS 2014 report (32), between 2009 and 2013, there has been a 43% decline in the number of new HIV infections in children, mainly as a result of HIV infected pregnant mothers receiving ARV medication and effective PMTCT programmes. In our cohort of children, only 29% of the HIV infected children were known to have been on the PMTCT programme. However, it is likely that this is an underestimation, as PMTCT was not

documented in the folders of 36% of the HIV infected children. It is concerning that 35% of HIV infected children did not receive PMTCT, which most likely reflects the challenges women face in accessing antenatal care and the deficiencies in our healthcare system (16).

Developed countries introduced ARV therapy in the early 1990's (35,36), whilst the huge burden of disease, cost of ARV therapy and political intrigue only saw ARV therapy introduced by the South African government in 2003. Our review focused on children admitted to PICU in 2009, a period in which eligibility for ARV therapy was based on clinical and immunological criteria.

Antiretroviral drug therapy has subsequently become standard treatment for HIV infected children (37). The 2013 guidelines from the Department of Health in South Africa (38) recommend that all children under 5 years of age are eligible for ARV treatment irrespective of their CD4 counts. Furthermore, children less than 1 year of age, children with WHO stage 4 disease, children with drug resistant TB and with CD4 counts less than 15% should be fast tracked and start ARV's within 7 days. A Cochrane review (39) of the effectiveness of ARV therapy in HIV infected children under 2 years of age, only included 2 studies in order to address the question of when to start ARV treatment. Their recommendations were in keeping with the included CHER study (18), advocating early ARV therapy in infants to prevent progression of disease and early death. The recommendations for initiating ARV therapy in children less than 2 years of age are less clear, however it is recognized that they have a high risk of dying.

However, there is little published data on initiating ARV drugs in critically ill children in PICU. Cowburn et al (11) reported the experience of initiating ARV treatment in children following PICU discharge. ARV therapy was only initiated in 21 of the 51 children who survived the PICU admission, with 11 of these children known to be well almost 1 year later. Thirteen children died in the wards before commencing ARV's, 11 children did not meet the criteria for commencing ARV's and 4 children were lost to follow up.

We only managed to initiate ARV therapy in 31 (61%) children eligible for ARV therapy during their intensive care stay. This was mainly related to a shorter PICU stay in this group of patients and logistic factors like delays in confirmatory HIV results and counseling of care-givers. It is reassuring that all children who survived the hospital admission were discharged home on ARV medication and hugely encouraging that 89% of the children with follow up data was alive 1 year later. There are many gaps in our health system (40) and another major challenge is ensuring that children starting ARV medication receive the appropriate follow up and support for this life long chronic illness.

The only complication related to initiation of ARV medication in this cohort of patients was IRIS. Twenty –nine percent of the children who commenced ARV's either in PICU or subsequently the ward developed IRIS, with BCG adenitis occurring slightly more commonly that pulmonary tuberculosis (some had AFB's isolated on sputum, but mostly on CXR changes and symptoms - treated empirically by the infectious diseases team). South Arica has one of the highest incidences of Tuberculosis in the world (41)and HIV infected children are particularly susceptible. Walters (27) reviewed 290 HIV infected children receiving ARV's over a 2-year period and reported that 48% of the children were treated for tuberculosis. The high burden of tuberculosis and susceptibility of HIV infected children is illustrated by 116 episodes of TB

diagnosed before the children commenced ARV's and only 21 episodes of TB diagnosed after initiating ARV's. Smith et al (42) prospectively followed up a group of HIV infected children commencing ARV's, found that 21% of children developed IRIS at a median of 16 days post ARV initiation. BCG adenitis and pulmonary tuberculosis was the commonest reactions, and they also described cases of CMV pneumonia, streptococcus pneumonia and seborrheic dermatitis. The development of IRIS was associated with younger children and children with low CD4 counts.

Puthanakit(43) reported the incidence of IRIS to be 19%, in a group of children in Thailand with advanced HIV commencing ARV's. Apart from IRIS secondary to mycobacterial organisms, Puthanakit also described reactions to Herpes simplex virus, *Cryptococcus neoformans* and an episode of Guillain Barre' syndrome. The children in this study who developed IRIS had lower baseline CD4 counts, compared to the children who did not develop IRIS. Rabie(44) reported a substantial reduction in the risk of developing BCG-IRIS in children who initiated ARV's under 12 weeks of age compared to children who only started ARV's once they had deteriorated immunologically or clinically.

The HIV infected children who commenced ARV's in our cohort had very low CD4 counts and were all severely immunosuppressed. This might explain the higher incidence of IRIS in our cohort compared to previous studies. The reported mortality with IRIS is relatively low, and in our setting the benefits of early initiation of ARV medication on long-term survival is of greater importance. None of the HIV infected children admitted to PICU on ARV therapy were diagnosed with IRIS, which is probably more reflective of our understanding of the condition. A recently published systematic literature review on tuberculosis IRIS only identified 13 studies, highlighting the lack of information and our limited understanding of this phenomenon(45).

PCP has been the most commonly associated opportunistic infection in HIV infected children(22,23). We only isolated PCP in 25% of HIV infected children presenting with pneumonia. Due to the limitation of the PCP immunofluorescence test, all our HIV infected children with severe pneumonia were treated for suspected PCP with 21 days of cotrimoxazole and prednisone, irrespective of the immunofluorescence test result. Morrow et al (46) recently demonstrated a 2.5 times increased diagnostic yield using a PCP PCR compared to immunofluorescence testing and using a Grocott stain.

The diagnosis of CMV infection in children is also problematic. A lung biopsy is the gold standard for diagnosing CMV pneumonitis, but is often not feasible in ventilated children with severe pneumonia. Chintu et al(47) reported the post mortem findings of a group of HIV infected Zambian children who died from pneumonia, finding histological evidence that 29% of the children had PCP and 22% of them had CMV pneumonitis. Goussard et al(24) reported the lung biopsy and post mortem histology of a group of HIV infected children admitted to a PICU with severe pneumonia, finding that 72% of them had histological evidence of CMV disease and the pp65 antigen for CMV was falsely negative in 24% of children. Kitchen et al(26) reported on the outcomes of 63 HIV infected and exposed children admitted to PICU with ARDS, finding positive PCP tests in 33%, a CMV viral load greater than log 4.0 in 38% of children and a mortality rate of 30%. Zampoli et al (25) investigated the prevalence of CMV associated pneumonia in hospitalized children using quantitative CMV PCR , using a cut off of greater than 4.0 log copies/ml to indicate a high CMV viraemia. Overall, they reported CMV associated pneumonia in 28% (47/169) of children, with a prevalence of 36% in HIV infected children compared to 15% in immune-competent children. In this study, HIV infected children with CMV associated pneumonia had a much higher mortality rate than immune-competent children.

Hsiao et al(29) investigated the prevalence of CMV viraemia in asymptomatic HIV exposed infants and compared them to HIV exposed children hospitalized with pneumonia. They showed that HIV exposed children hospitalized with pneumonia, had significantly higher CMV viral loads than asymptomatic HIV exposed children, with CMV viral loads peaking at 3 – 4 months of age.

In children admitted to our PICU with severe pneumonia, we considered a CMV viraemia of greater than 4.0 log copies/ml indicative of CMV pneumonia. Thirty-eight percent of children admitted on ARV's had a positive CMV viral load, and 57% of the HIV infected children not on ARV's on admission, had a positive CMV viral load. The decision to empirically start gancylovir in critically HIV infected children admitted to our PICU was taken on the context of the high prevalence of CMV disease in immunosuppressed children and the reality that CMV viral load results were only available 3 -5 days after the tests were requested.

We also isolated a number of respiratory tract viruses in conjunction with PCP and CMV from HIV infected children admitted with respiratory failure. In this setting, it is almost impossible to say how these viruses are contributing to the lung disease.

CMV enteritis was diagnosed histologically, and with a high CMV viral load, in 2 children who presented with intestinal perforation and necrotic bowel. These children were not established on ARV therapy, as no intravenous preparations are available. Treatment was withdrawn in both children because of ongoing bowel necrosis.

The overall PICU and hospital survival rates in our retrospective study is encouraging and an improvement on that reported previously from our institution (11,48). The individual child's risk of dying ultimately depends on the severity of their underlying illness. This is usually not clear not admission, as the disease is still evolving and the exact underlying condition is often not fully defined. Two-thirds of the HIV infected children in our cohort had a discharge diagnosis of pneumonia, with 76% of these children surviving to hospital discharge. Whilst all the children diagnosed with CMV enteritis and pneumococcal meningitis unfortunately died.

Study limitations - the data was collected retrospectively and limited to what was recorded in patient's clinical notes. The study design is not able to prove whether the increased survival of HIV infected children is related to the early initiation of ARV medication and empiric gancyclovir treatment. However, with the improvements in general PICU care, mortality rates of most diseases are decreasing.

CONCLUSIONS

This retrospective study shows that increasing numbers of critically ill HIV infected children are surviving PICU and hospital admissions. Antiretroviral therapy was successfully initiated in PICU and apart from the risk of IRIS, there were no obvious side effects to commencing ARV's in critically ill children. CMV is a common opportunistic infection in HIV infected children and empiric therapy with Gancyclovir should be considered whilst confirmatory blood results are awaited.

HIV infection per se, should no longer be an exclusion criterion for PICU admission

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APPENDICES:

Appendix 1: Data Collection Sheet

Data Sheet No:

Folder No: (

Sex: male / female

Age on admission to PICU:

Reason for admission: elective/ respiratory failure/ septic shock/ neurological/ other

Admitted from: community / other hospital / RXH hospital ward/ emergency unit

Hospital admission date:

PICU admission date

History of PMTCT: yes / no / unknown, if no, why not:

HIV diagnosis date:

Admission weight:

PIM2 / Predicted mortality:

Ventilation: date intubated: date extubated:

non-invasive ventilation / cpap: date started: date stopped:

CD4 count: absolute: %

CMV viral load / PCR: copies / ml log 10

Date ARV's started:

PICU survivor: yes / no

Treatment limited/withdrawn in PICU: yes / no

PICU discharge date:

PICU discharge diagnosis:

Hospital ward death: yes/ no if yes, Date:

IRIS/ complications related to ARV's: yes / no if yes, Details:

Hospital discharge date:

12 month follow up/ outcome: alive / dead / unknown / referred CHC

Appendix 2: Human Research Ethics Committee, University of Cape Town

HUMAN RESEARCH ETHICS COMMITTEE
26 FEB 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28.2.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	26/2/15

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	25/2/15		
HREC REF Number	080/2012	Current Ethics Approval was granted until	28/02/14
Protocol title	Paediatric Intensive Care Outcomes of HIV infected children in a developing country		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	☐ Yes ☒ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr. S. SALIE		
Department / Office Internal Mail Address			

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☒ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 3: Red Cross War Memorial Children's Hospital research review committee

Dr TA Blake
Chairperson Hospital Research Review Committee
Email: thomas.blake@westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
22 October 2014

DR S SALIE
PAEDIATRIC CONSULTANT
PICU
RCWMCH

Dear Dr Salie,

RE: RESEARCH: Paediatric Intensive Care outcomes of HIV infected children in a developing country

You may proceed with the above-mentioned study.

Yours faithfully,

DR T A BLAKE
CHAIRPERSON
HOSPITAL RESEARCH REVIEW COMMITTEE

Appendix 4: Pediatric Critical Care Medicine : Instructions for Authors

Pediatric Critical Care Medicine is an international, peer-reviewed journal that is interested in publishing the highest quality scientific studies in the field of pediatric critical care medicine.

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Conflicts of Interest and Source of Funding: "Author A" has received honoraria from "Company 1." "Author B" is currently receiving a grant (#12345) from "Organization Y," and is on the speaker's bureau for "Organization X" – the CME organizers for Company 1. For the remaining authors none were declared.

Human and Animal Subjects. All studies of human subjects must contain a statement within the Materials and Methods section indicating approval of the study by the Institutional Review Board (or institutional review body) that subjects have signed written informed consent, or that the Institutional Review Board waived the need for informed consent. ***Before* your submission can be sent out for peer review, it is necessary that you address this issue of institutional review approval.** This is in accordance with the International Committee of Journal Editors uniform requirements for manuscripts submitted to biomedical journals. Please see http://www.icmje.org for more details. All animal studies must contain a statement within the Materials and Methods section confirming approval by the Institutional Animal Care and Use Committee and that the care and handling of the animals were in accord with National Institutes of Health guidelines or other internationally recognized guideline for ethical animal treatment.

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MANUSCRIPT CONTENT

Title Page. The title page should contain 1) the title; 2) first name, middle initial, and last name of each author; 3) highest academic degrees, fellowship designations, and institutional affiliation for each author; 4) name of the institution(s) where the work was performed; 5) the address for reprints and a statement regarding whether reprints will be ordered; and 6) financial support used for the study, including any institutional departmental funds. The authors should also provide six key words for indexing, using terms from the Medical Subject Headings list of *Index Medicus*. Structured abstracts are required for all manuscripts (except editorials, letters, and book reviews) submitted to *Pediatric Critical Care Medicine*.

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Standard Book with Editors: Norman IJ, Refern SJ (Eds): Mental Health Care for Elderly People. New York, Churchill Livingstone, 1996

Standard Chapter in a Book: Phillips SJ, Whisnant JP: Hypertension and stroke. In: Hypertension: Pathophysiology, Diagnosis and Management. Laragh JH, Brenner BM (Eds). Second Edition. New York, Raven Press, 1995, pp 465-478

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