BURDEN OF RESPIRATORY DISEASE AMONG PAEDIATRIC PATIENTS INFECTED WITH HIV/AIDS

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ABSTRACT

HIV is a prominent infection in society and its health implications are seen in the paediatric wards daily. Despite its multi-system effect on the body, it particularly results in many respiratory infections. Effective understanding of the disease profile and management of patients with HIV relies on correct statistics and proper use of resources.

Since the introduction of anti-retrovirals in 2004 in South Africa, the impact of HIV/AIDS on respiratory disease needs to be re-evaluated. The purpose of the study is to understand the disease profile of children with HIV/AIDS with regard to the presence of respiratory conditions with which they present, the need for chest physiotherapy and their health status.

Of the 125 patients recruited in this study 55% were boys, average age was 20.55 months (SD= 23.64), average length of hospital stay of 2 ½ weeks (mean=18.76, SD=19.19), 80% discharged and 9.6% died. The most common respiratory conditions presented included bacterial pneumonia (66.4%), tuberculosis (48%) and pneumocystis jirovecii pneumonia (23.2%). The least common condition was lymphoid interstitial pneumonitis (4.8%). Two thirds of the children (68.8%) presented with a high burden of disease. Physiotherapy treatment was indicated for 96% of the patients mainly due to excess secretions and poor air entry. About forty percent (40.8%) of children were taking anti-retrovirals with an average length of use of 9.81 months (SD=11.61). Three out of four (75%) mothers were not involved in a PMTCT program. The analysis of immune status revealed a mean CD4 percentage 17.33% (SD=10.96), CD4 absolute 631.36 cell/mm^3 (SD=610.36) and viral load 2.6 million copies /ml (SD=9.08 million copies/ml).

A higher burden of disease was related to the use of anti-retrovirals, a lower immunity, female patients, longer length of hospital stay and incidences of mortality occuring at later periods of hospital stay.

Results of this study highlight the characteristics of respiratory disease burden among children with HIV in a South African setting in a post HAART era.

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DECLARATION

I declare that this Research Report is my own work which I have prepared individually, except where otherwise indicated in the reference citation and acknowledgements.

I submit this report in partial fulfilment of the requirements for the Degree of Master of Science (Physiotherapy) at the University of the Witwatersrand.

It has not been submitted before for any other degree or examination in any other University.

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LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ARV	anti-retroviral
ARI	acute respiratory infection
BCG	bacillus calmette gurin
CHER	children with HIV early anti-retroviral therapy
CMV	cytomegalovirus
DOT	directly observed therapy
HAART	highly active anti-retroviral therapy
Hib	haemophilus influenza B
HIV	human immunodeficiency virus
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LIP	lymphoid interstitial pneumonitis
MAC	mycobacterium avium complex
MRSA	methicillan resistant staphylococcus aureus
NTM	non-tuberculous mycobacterium
NVP	neviripine
PCR	polymerase chain reaction
PEP	positive expiratory pressure
PJP	pneumocystis jirovecii pneumonia
PMTCT	prevention of mother to child transmission
PTB	pulmonary tuberculosis
PZA	pyrazinamide

RMP	rifampicin
RSV	respiratory syncytial virus
TB	tuberculosis
TST	tuberculin skin test
V/Q	ventilation/perfusion ratio
WHO	world health organisation

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CHAPTER ONE

Introduction

1.1 Introduction

This chapter discusses the background of the study and its significance, statement of the problem, the research questions, the purpose and objectives of the study, definition of terms used and an overview of the remaining chapters of the study.

Physiotherapists practising in the paediatric field observe many patients infected by HIV/AIDS. This disease contributes to the incidence of many other opportunistic infections of which those respiratory in nature, are the most common. Respiratory disease remains a major cause of morbidity and mortality amongst HIV-infected children (Zar, 2008).

According to the UNICEF global report in 2006, South Africa had the sixth highest prevalence of HIV in the world, later reporting in 2008 that South Africa has the highest incidence in the world with an estimated five point seven million people living with the disease - 25% of the Sub-Sahara-African statistics (UNAIDS, 2009). The 2008 reports mention that of two point one million children infected worldwide, Sub-Saharan Africa accounts for one point eight million of those. An estimated 240 000 children aged zero to fourteen were living with HIV in South Africa in 2005 according to statistics calculated by UNICEF (2010).

The impact of HIV/AIDS on the health system is immense, hence it is of particular value to our country and to the physiotherapy profession to conduct research in this field. This study has determined the distribution of respiratory conditions among children with HIV/AIDS and their indication for physiotherapy as an in-hospital service. There are relevant factors which influence a HIV positive child's health status including the use of anti-retrovirals, the CD4 count and viral loads, age, gender and length of hospital stay. These factors have been investigated to determine their influence on the burden of respiratory disease.

1.2 Background

HIV/AIDS is a prominent disease that is observed within the South African health care environment on a daily basis. The disease in South Africa is defined as being hyper-endemic due to the high rate of HIV prevalence and the modes of HIV transmission of which mother-to-child transmission is the major cause of childhood infection (UNAIDS, 2010).

Zar & Mulholland reported in 2003 that of more than one point five million HIV infected children, 90% will develop a respiratory illness sometime in the course of their HIV condition. In contrast, in developed countries, early diagnosis of HIV infection in infants, and use of pneumocystis jirovecii prophylaxis, and highly active anti-retroviral therapy (HAART) have led to a substantial decline in HIV associated respiratory infections (Zar, 2008). The management of HIV has made progress in South Africa and thus, the incidence of acute and opportunistic respiratory infections has declined while HIV-associated chronic lung disease has increasingly emerged (Zar, 2008). Respiratory disease in children infected with HIV/AIDS thus remains pertinent.

1.2.1 Incidence of respiratory disease

The incidence of acute pneumonia is much higher in HIV infected than uninfected children ([a]Madhi et al, 2000) and chronic lung diseases are much more common owing to a wider range of pulmonary diseases (Graham, 2005). Literature reiterates that pneumocystis jirovecii pneumonia (PJP) is by far the most common opportunistic infection and serves as a HIV marker and many other studies have shown that PJP, cytomegalovirus (CMV), mycobacterium avium complex (MAC) and pulmonary tuberculosis (PTB) are among the most common opportunistic infections (Parker et al, 1998). The probability of developing PJP rises markedly as the CD4 count falls below 200cells/mm3 (Lubis et al, 2003), however the use of HAART may decrease its incidence up to 86-100% according to Nesheim et al (2007). Lymphoid interstitial pneumonitis (LIP) is a condition which, despite its prevalence,

receives little attention. In children with HIV infection, LIP has been designated as an AIDS-defining illness by the US Center for Disease Control and Prevention (1994). A study done by Gona et al (2006) established that bacterial pneumonia and lymphoid interstitial pneumonitis have a prevalence of 25% and 12% respectively. Pulmonary infection may develop chronicity illustrated by the significant occurrence of bronchiectasis in children with AIDS particularly in children developing LIP, recurrent pneumonia and unresolved pneumonia (Sheikh et al, 1997).

1.2.2 Influence of other factors on the burden of respiratory disease

There are many other factors which may contribute towards the prevalence of respiratory conditions including age and health status. In the pre-HAART era the 0-3 year old group had the highest incidence of a first opportunistic infection (87%), whereas in the post-HAART era this was found in the 0-7 year old group (33%), in a study completed by Nesheim et al (2007). Graham (2007) and Gona et al (2006) support this trend as survival rates have increased with improved treatment strategies.

Health status may be evaluated through CD4 count and viral load testing. The CD4 count is a good immunological marker of disease progression. Thus >25% means that there is no immune suppression; 15–24% means moderate suppression and <15% means severe suppression (World Health Organisation, 2005).

1.2.3 Initiation of anti-retrovirals

The South African Government's response to the epidemic is grounded in the HIV/AIDS strategic plan for the period 2000-2005. "An operational plan for Comprehensive Treatment and Care" (National Department of Health, 2003) was adopted in November 2003 to begin the roll out of an ARV programme. At the end of 2005 Gauteng had nearly 10 000 patients on ARVs.

In the United States the roll out of anti-retrovirals commenced in 1994 and since then, the incidence of opportunistic infections including pneumocystis jirovecii pneumonia (PJP) has declined considerably (Kaplan et al, 2000).

Prior to the introduction of anti-retrovirals in 2004 in South Africa, respiratory tract infections were found in over 90% of HIV infected African children at post mortem and accounted for 30-40% of paediatric inpatient admissions in HIV endemic regions with case fatality rates of between 15-28% (Zwi et al, 2000). This was confirmed in a study by Langston et al (2001). A prospective study conducted at a Durban hospital in 2000, established that 60% of the admitted children were HIV-1 infected (Pillay et al, 2001).

The high prevalence of respiratory conditions (Zwi et al, 2000) may have been partly attributable to many children not on HAART or had an undiagnosed HIV infection. Decision-making about starting treatment is particularly important for children aged under 12 months as the probability of death in untreated HIV-infected children is high: mortality rates of up to 40% by the age of one year have been reported (World Health Organisation, 2007).

The prevalence of respiratory infections may be quite different since the introduction of HAART. However it may also be possible that studies may find similar results as respiratory conditions may remain prevalent due to poor adherence to the proper use of HAART. Poor adherence may be due to poor access to health care services, inadequate nutrition, unstable living conditions, or commonly discomfort with disclosure (Cowburn et al, 2004).

1.2.4 The role of physiotherapy

A study completed at Chris Hani Baragwanath Hospital in 2005 revealed that of the HIV infected adult patients suitable for physiotherapy only two percent were actually referred (Myezwa, 2007). This is alarming as physiotherapy has a role to play in the management of HIV infected patients particularly those with respiratory conditions (McClure, 1993; Wallis et al, 1999; Graham, 2007).

A study by Cowburn (2004) completed in Cape Town raised an issue that health care workers cannot adopt a deontological approach when treating patients infected with HIV due to “a high incidence of HIV infection and lack of access to HAART, coupled with resource constraints”. Jeena (2005) discusses that in developing countries a much more utilitarian view has to apply until such time that resources to practise at optimum levels become available. However the question to be raised should be whether these health care workers are using the resources that are available optimally. It was emphasized that data are urgently required to guide policy, resource allocation and ethical decision making in this setting. Research with regard to HIV and respiratory care is scant and is thus required in order to develop data upon which policies can be built.

1.3 Purpose of study

The purpose of the study is to understand the disease profile of hospitalised children with HIV/AIDS with regard to the presence of respiratory conditions with which they present, the indication for chest physiotherapy and their health status.

1.4 Research question

The study sought to explore the following question:

What is the prevalence of respiratory conditions among paediatric patients infected with HIV/AIDS who are admitted to hospital?

What is the indication for chest physiotherapy among these patients?

What is the relationship between the burden of respiratory disease with certain influencing factors?

1.5 Aim

To determine the burden of disease with regard to the prevalence of respiratory conditions among paediatric patients infected with HIV/AIDS and to establish the indication for chest physiotherapy.

1.6 Objectives

1. To establish the profile of respiratory conditions presented by paediatric patients infected with HIV/AIDS admitted to medical wards with a respiratory condition.
2. To establish the prevalence of paediatric patients infected with HIV/AIDS and presenting with a respiratory infection requiring chest physiotherapy
3. To establish whether a relationship exists between the burden of respiratory disease and influencing factors including the use of antiretroviral drug combinations, length of drug use, CD4 counts and viral load.

1.7 Significance of study

With the prevalence of HIV/AIDS in our country, it is important that physiotherapists are informed about the condition and its clinical manifestations. This may assist physiotherapists working with these patients with their clinical decision making. An understanding of the medical and physiotherapy management may contribute to improved service delivery in our hospitals.

The results of this study will help the appropriate allocation of physiotherapists based on the need for more physiotherapists and the establishment of protocols regarding improved holistic management of patients infected with HIV.

HIV is a prominent infection in society and its health implications are seen in the paediatric wards daily. Despite its multi-system effect on the body, it particularly results in many respiratory infections. Effective understanding of the disease profile and management of patients with HIV relies on correct statistics and proper use of

resources. It is thus necessary to establish the health status of paediatric patients infected with HIV, the prevalence of respiratory infections presented and whether there is a indication for physiotherapy.

CHAPTER TWO

Literature Review

2.1 Introduction

The first presentation of HIV-related lung disease is usually in infants or children younger than five years of age (Graham, 2005). Girls tend to be better protected against acute respiratory tract infections than boys, although the difference is not significant nor well understood (Kristensen et al, 2006).

The distribution of respiratory disease relevant to HIV, indication of physiotherapy, anti-retroviral treatment, prevention of mother to child transmission and the burden of respiratory disease will be covered.

The literature reviewed included published articles dated from 1994 to the present. Key words used included paediatric HIV/AIDS, opportunistic respiratory infections, anti-retroviral drugs, chest physiotherapy, burden of respiratory disease, CD4 counts and viral loads. Search engines explored included Pubmed, Pedro and article reference lists.

2.2 Distribution of respiratory conditions

The HIV/AIDS epidemic has directly impacted on the epidemiology and spectrum of childhood respiratory illness and the efficacy of therapeutic and preventative strategies (Zar, 2008). There is an escalation of pulmonary disease among the patients infected with HIV/AIDS, particularly in Sub-Saharan Africa.

To an extent the incidence of acute infections has declined due to improved survival and management (Zar 2008), however the incidence of chronic infections has increased as the children infected with HIV/AIDS are living longer. This is directly influenced by the introduction of anti-retrovirals. Despite this Zar (2008) states that

respiratory disease still remains a major cause of morbidity and mortality amongst HIV-infected children.

During the pre-HAART era, acute infections such as bacterial pneumonia, pneumocyctis jirovecii pneumonia (PJP) and disseminated mycobacterium avium complex were amongst the most frequent conditions diagnosed (Zar, 2008). This distribution is rapidly shifting towards the chronic spectrum with conditions such as lymphocytic interstitial pneumonia (LIP), immune reconstitution inflammatory syndrome (IRIS), bronchiectasis, malignancies, and interstitial pneumonitis receiving attention (Zar, 2008).

Due to the nature of the disease and an increased susceptibility to infections mixed infections are common such as bacterial pneumonia or cytomegalovirus (CMV) with PJP, or bacterial pneumonia complicating viral pneumonia, PTB, or LIP (Graham, 2003). This occurence contributes to the burden of disease, affects the health status and complicates the management process. With the introduction of anti-retrovirals and the incidence of mixed infections, the occurence of an immune reconstitution inflammatory syndrome has been reported (Zar, 2008), particularly associated with mycobacterial and cytomegalovirus infections.

In developing countries such as South Africa it is of value to note the multi-factorial forces that impact on health. Economic disparity, with resultant widespread poverty, poor living conditions, and malnutrition occurring in children in developing countries, leads to poor respiratory health as reported by Zar et al (2003). This is illustrated in the statistics that 35–59% of HIV-infected African children die within the first two years of life.

Respiratory disease in the HIV/AIDS infected population thus remains a burden on the health system and as physiotherapists it is important that this disease and all its clinical associations be understood.

2.2.1 Pneumocystis jirovecii pneumonia (PJP)

Pneumocystis jirovecii formerly known as pneumocystis carinii pneumonia (PCP) was the most common opportunistic infection in HIV-infected infants prior to widespread prenatal HIV screening, prophylaxis, and HAART (Zar, 2008). It has now become clear that HIV-infected individuals who respond to HAART with immunological improvement have a substantially decreased risk of developing PJP (Beck et al, 2001).

However, its presence still remains for several reasons. Patients may not be aware of a positive status until they have acquired PJP, some may not adhere to taking anti-retrovirals and in some cases anti-retrovirals are ineffective or HAART and PJP prophylaxis is not available (Beck et al, 2001).

Pneumocystis is an atypical fungus, with a global distribution that usually first causes infection early in childhood (Graham, 2005). Clinical findings depicting the presence of PJP include significant tachypnoea and hypoxia, cyanosis (Jeena, 2005), mild intermittent fever, a dry cough and minimal auscultatory findings with bilateral diffuse alveolar infiltrates (Marais, Rabie et al, 2006) or hyperinflation (Graham, 2005) on chest xray. Radiological findings may progress to features compatible with the acute respiratory distress syndrome (Jeena, 2005). It usually presents as an acute severe pneumonia however chronic infection may manifest into a cystic disease or develop a pneumatocoele (Zar, 2008). Lactate dehydrogenase (LDH) level is usually markedly elevated, although this is not specific. Diagnosis may also be made upon the discovery of immunofluorescent stained cysts in induced sputum or by polymerase chain reaction (PCR) testing (Graham, 2005).

Currently PJP is less frequent than bacterial pneumonia as a cause of severe lung disease in HIV-infected children but is still the most important opportunistic infection in infants (Graham, 2005). It is regarded as a HIV defining illness and is categorised as a stage four disease according to the World Health Organisation's clinical staging guidelines (2005). PJP is the indicator disease for AIDS in 20–40% of South African children. The

prevalence of PJP in children with ARI varies between 10% and 17% according to Jeena (2005). PJP remains an exceedingly common cause of death among HIV-infected infants in Africa, particularly in children under six months of age ([b]Marais et al, 2006). Graham (2003) reports that PJP presents with severe pneumonia, in infants between two to seven months old. However the incidence of PJP is much lower in HIV-infected children after one year of age and in countries where PJP prophylaxis is routine for infants born to HIV-infected mothers (Graham, 2005).

Response to therapy is relatively slow ([b]Marais et al, 2006). Management includes the use of a high-dose intravenous cotrimoxazole for a total duration of two to three weeks ([b]Marais et al, 2006), oxygen therapy and in the absence of CMV- steroids (Graham, 2005). Cotrimoxazole prophylaxis reduced mortality by 43% and the hospital admission rate by 23% in a cohort of children followed-up over 19 months (Chintu et al, 2004). Mechanical ventilation may be required and this poses a problem in a resource-constrained environment. However, the benefit of oxygen therapy in reducing case fatality rates is likely to be lower for PJP than for bacterial pneumonia (Graham, 2005) - posing a dilemma for doctors in deciding which patient would benefit more.

The current status of PJP prophylaxis in our country is commenced four to six weeks after birth (National Department of Health, 2010) or as soon as HIV is diagnosed but may be discontinued when the CD4 percentage is consistently > 20% for more than six months (National Department of Health, 2004).

2.2.2 Bacterial pneumonia

Bacterial pneumonia is common in all stages of HIV infection and at all ages (Jeena, 2005). Streptococcus pneumonia is consistently the most common cause of bacterial pneumonia while haemophilus influenza pneumonia is also common in HIV-infected children, however its prevalence has been reduced in countries where routine immunisation with Hib vaccine has been introduced

(Mulholland, 2003; Jeena, 2005). Children with advanced HIV disease are at greater risk of recurrent infection and death (Graham, 2003).

The Hib vaccine was introduced in 1990 and is currently administered at six, 10 and 14 weeks of age (KZN Department of Health). The effectiveness of the vaccine is significantly reduced in HIV-infected compared with uninfected children (Madhi et al, 2002). The first pneumococcal vaccine was introduced in South Africa in April 2009 in an effort to reduce staphylococcal pneumonia infections (Madhi, 2008).

Staphylococcus aureus, particularly methicillan resistant staphyloccal aureus (MRSA) strains have become common in children infected with HIV/AIDS (Graham, 2003; Zar, 2008). Staphylococcal pneumonia may be complicated by the development of an empyema, pneumatocoele or lung abscess (Zar, 2008). Severe, destructive, persistent or recurrent bacterial pneumonia may lead to chronic lung disease such as bronchiectasis (Zar, 2008).

The definition of pneumonia has been debated, however the ‘‘gold standard’’ investigation to define pneumonia is the chest radiograph (Mulholland, 2003). Unfortunately there has been little agreement between radiologists on the interpretation of what constitutes significant consolidation on a paediatric chest radiograph and this leads to exclusion of many pneumonia events that do not produce sufficient radiological changes (Mulholland, 2003).

Major questions have remained unanswered, particularly in relation to the mortality burden of pneumonia (Mulholland, 2003). Thus studies are required to understand the patterns of pneumonia and its mortality within and between communities.

2.2.3 Viral pneumonia

Viral pneumonia is less common than bacterial pneumonia however the persistence of a viral infection or chronic sequelae of an acute infection may lead to chronic lung disease (Zar, 2008).

Other respiratory viruses such as respiratory syncytial virus (RSV), measles, influenza, parainfluenza and adenovirus are commonly seen in HIV-infected children with pneumonia (Jeena, 2005). Mulholland (2003) recognises that respiratory syncytial virus is the main viral cause of pneumonia. RSV is not limited by season in HIV infected children ([b]Madhi et al, 2000). The absolute burden of hospitalization for viral associated pneumonia is two to eight-fold greater in HIV-infected children (Zar, 2008).

Measles pneumonia is categorised as a viral pneumonia. It may present in children with advanced immunosuppression without the typical mucocutaneous features, making diagnosis difficult (Graham, 2005). In children presenting with measles, the administration of vitamin A significantly reduces the likelihood of severe pneumonia and death (Graham, 2005). There are effective programmes that immunise around 80% of infants against measles at nine months of age and the provision of vitamin A to infants at six months of age has reduced both the incidence of measles and measles-related mortality (Graham, 2005).

Adenovirus and herpes viruses have been described as causes of severe and fatal pneumonia in HIV-infected children, however autopsy studies generally find them to be uncommon (Graham, 2005).

2.2.4 Tuberculosis

Tuberculosis poses a large burden to the Sub-Saharan population and it is fuelled by the immune compromise that results from HIV infection ([b]Marais et al, 2006). HIV-infected children have an increased risk of developing pulmonary TB and complicated or disseminated disease compared to uninfected children (Zar, 2008). HIV infected children are not only more vulnerable to progress to disease, but are also more likely to be exposed to TB and become infected or re-infected ([b]Marais et al, 2006).

A recent report by [a]Marais et al (2006) from Cape Town indicated that children under 13 years of age contributed 13.7% of the total TB disease burden, with a calculated TB incidence rate of more than 400/100 000 per year. TB can present at any age, even in neonates. An increased incidence of congenital TB has been associated with maternal HIV-infection ([b]Marais et al, 2006). In a prospective study from Côte d'Ivoire, the risk of TB was four times higher in children with CD4 percentage below 15% than in those with CD4 % above 15% ([b]Marais et al, 2006).

Clinical findings according to the WHO criteria for diagnosis of TB is a cough of more than two weeks, failure to thrive and weight loss ([b]Marais et al, 2006), however these symptoms are usually already present in the HIV-infected child. Less specific signs include coughing, wheezing, tiredness and or failure to thrive.

One of the diagnostic tools such as the tuberculin skin test (TST) is of reduced value in HIV-infected children (Zar, 2008), as a compromised immune system due to severe malnutrition, low CD4 counts and progressive HIV disease are associated with false negative TST results ([b]Marais et al, 2006). Induced sputum and gastric aspirates may assist in yielding a positive culture, however a study reports that the yield in one induced sputum is equal to three gastric aspirates (Zar et al, 2005). Induced sputum using hypertonic saline should therefore be the primary diagnostic procedure in a child with suspected pulmonary TB (Zar, 2008). Chest radiographs are done to assist in the diagnosis but are not confirmatory, rather assistive towards a diagnosis (Marais et al, 2007). Statistics may be under or over evaluated due to the typical miliary picture of disseminated TB which may be mimicked by the reticulonodular pattern of lymphoid interstitial pneumonitis (LIP) ([b]Marais et al, 2006).

Prevention of TB in this country has been of priority and widespread education has been conducted. BCG or Bacillus Calmette Gurin vaccination against TB is given to all infants at birth. In HIV-infected children, there is an

increased risk of developing BCG associated complications, such as local or disseminated BCG disease ([b]Marais et al, 2006). Disseminated BCG disease has a poor prognosis with a case fatality rate of approximately 50% (Zar, 2008). Despite this, the current recommendation is to vaccinate all children irrespective of HIV-exposure, but to remain vigilant of BCG-associated complications as the benefits of BCG vaccination outweigh the risks (World Health Organisation, 2006).

The treatment regimen for TB consists of isoniazid (INH), rifampicin and pyrazinamide (PZA), given as fixed dose combination therapy, during two month intensive phase followed by INH and RMP during the four month continuation phase ([b]Marais et al, 2006). Treatment should be closely observed to promote adherence and reduce the chances of treatment relapse or failure. Directly observed therapy (DOT) should be used as poor adherence manifests multi-drug resistant forms that pose a grave risk, particularly to vulnerable HIV-infected children (Zar, 2008).

Co-infection with tuberculosis and HIV results in more rapid deterioration of immune dysfunction, viral replication, and HIV progression and more frequently other severe infections (Zar, 2008). Due to the strong association between TB and HIV, it is often required that treatment be initiated simultaneously. Immune reconstitution inflammatory syndrome (IRIS) may occur as the side-effects of TB treatment are exacerbated by the anti-retrovirals ([b]Marais et al, 2006). IRIS usually manifests within two to six months after the initiation of HAART and subsides spontaneously, although severe cases may require treatment with corticosteroids.

2.2.5 Mycobacterium avium complex

MAC is a non-tuberculous mycobacterium (NTM) of which the risk of infection is associated with CD4 counts less than 50 cells/mL in adults, but this threshold is less well established in young children (Zar, 2008). In a study done by Langston et al (2001), it was found that MAC is the underlying or

contributing cause of death in 42% of all HIV-related mortalities. The use of HAART dramatically reduces the incidence of NTM disease in children. Primary prophylaxis for children is given according to the age and CD4 counts and secondary prophylaxis to children with a history of NTM to prevent reoccurrence (Zar, 2008). Respiratory symptoms may occur but are uncommon, the usual presentation being weight loss, fever, abdominal pain and diarrhoea (Graham, 2005).

2.2.6 Lymphoid interstitial pneumonitis

Lymphoid interstitial pneumonitis (LIP) is a common cause of chronic respiratory disease in HIV-infected African children (Graham, 2003). LIP occurs in approximately 20–30% of HIV-infected children, usually presents after two years of age, and is associated with pneumonia and bronchiectasis (Graham, 2003). Swigris et al (2002) confirms that LIP occurs most often in the second or third year of life. Lynch et al (2001) and Becciolini et al (2001) both support the statistics in stating that 30-40% of patients infected perinatally will develop LIP.

LIP is not associated with as poor an outcome as PJP. Rather, children with LIP can survive for years with a clinical course characterised by intermittent episodes of superimposed bacterial pneumonia and eventual bronchiectasis or cor pulmonale. (Graham, 2005 ; Rabie et al, 2007).

LIP presents as a slowly progressing interstitial disease with mild hypoxaemia and is usually characterized by a cough, generalised lymphadenopathy, digital clubbing (Lynch et al, 2001), respiratory distress, failure to thrive (Swigris et al, 2002), hepatosplenomegaly and parotid enlargement (Rabie et al, 2007).

Lymphoid interstitial pneumonitis presents with reticular, nodular or recticulonodular parenchymal changes (Jeena, 2005). Chest radiographs often show a diffuse reticulonodular pattern, more pronounced centrally which

may be difficult to distinguish from pulmonary or miliary TB (Zar, 2008). If there is clinical suspicion of TB despite negative skin test and sputum culture results, the child should be treated with anti-tuberculous therapy for six months before the diagnosis of LIP is made (Simmank et al, 2001).

A lung biopsy is suggested as a means of correctly diagnosing LIP (Oldham et al, 1989). In some lung biopsy specimens Epstein-Barr virus has been found (Swigris et al, 2002). In view of the fact that LIP is often misdiagnosed as TB (Graham, 2003), the accuracy of LIP statistics should be questioned.

2.2.7 Bronchiectasis

Bronchiectasis is a irreversible dilatation of the airways that disrupts normal airway functioning and usually results from severe and recurrent infections (Rabie et al, 2007) such as recurrent bacterial pneumonia, LIP and PTB (Graham, 2005) leading to the damage of the bronchial wall beyond repair (Sheikh et al, 1997). It is a common problem and occurs in up to 16% of children (Rabie et al, 2007). This is supported by Sheikh et al (1997), where 15,8% of patients with a mean age seven point five years developed bronchiectasis.

Classically the production of copious amounts of purulent sputum is described, but young children frequently swallow their sputum, making this a less obvious symptom (Rabie et al, 2007). Coughing is often worse at night, while other classical signs include clubbing, halitosis and coarse crackles (Graham, 2005; Zar, 2008).

Chest radiographs show focal abnormalities with bronchial dilatation (Graham, 2005). These abnormalities are often displayed by a honeycomb appearance with small cysts, persistent areas of opacification or widespread lung destruction, usually with fibrosis and volume loss (Rabie et al, 2007).

Treatment includes broad-spectrum antibiotics and chest physiotherapy (Rabie et al, 2007; Graham, 2005).

2.2.8 CMV pneumonitis

Cytomegalovirus infection is common in HIV-infected children, but its role in causing disease is difficult to assess (Graham, 2005). An autopsy study of Zambian infants and children who died of pneumonia reported CMV as the third commonest finding in HIV-infected infants, after pyogenic pneumonia and PJP (Graham, 2005). CMV is common in HIV-infected infants with pneumonia, often in association with PJP (Graham, 2003).

Co-infection with CMV and HIV results in more rapid progression of HIV disease (Zar, 2008). The use of HAART has resulted in a substantial decrease in the incidence of CMV infection (Gona et al, 2006).

Radiographic abnormalities due to CMV are typically diffuse, interstitial infiltrates similar to PJP (Graham, 2005). Treatment with gancyclovir is advocated for patients with CMV retinitis, gastrointestinal involvement and severe lung disease (Jeena, 2005).

2.3 Indication for physiotherapy

A group of expert physiotherapists lead a movement towards leaving the term “chest physiotherapy” behind and to replace it by “airway clearance techniques” as a group name for all of the techniques and devices that have been developed (De Boeck et al, 2008).

Examples of such techniques include manual chest compression during expiration, autogenic drainage, active cycle of breathing, manual cough assist techniques, devices directed at huff coughing, high-frequency chest wall compression, intrapulmonary percussive ventilation, oscillatory devices such as flutter, and positive expiratory pressure (PEP) mask and their derivatives (De Boeck et al, 2008).

De Boeck et al (2008) reviewed literature that shows that airway clearance techniques are not useful on previously healthy children and believe that children

have the ability to cope and heal independently. However, should patients be selected according to their ability to cope with treatment and their need to improve gaseous exchange and reduce fatigue of removing secretions then it may be beneficial.

Positioning to optimize V/Q matching, ease work of breathing, relaxation techniques and breathing control are aspects of treatment that physiotherapists may provide patients presenting with PJP (McClure, 1993). Confirmation of PJP and TB may be assisted via induced sputum (Graham, 2007). Positive expiratory pressure (PEP) has been shown to be useful in improving ventilation and reducing the volume of trapped gas while collateral ventilation is recruited to expand airways and mobilise secretions (Lannefors et al, 2004).

Lymphocytic interstitial pneumonitis (LIP) presents clinically with a productive cough, poor posture and reduced exercise tolerance all of which physiotherapists can manage with manual chest techniques, posture analysis and exercise prescription.

During the acute stages of bronchiectasis, patients can be treated with chest techniques, positioning and exercise endurance and then with postural drainage and effective coughing exercises during the chronic phase (Sheikh et al, 1997). Airway clearance therapy is traditionally considered the cornerstone of therapy for the prevention and treatment of cystic fibrosis lung disease or other causes of bronchiectasis (Schechter, 2007) but efficacy is somewhat an article of faith, backed by voluminous clinical experience and moderately convincing but by no means definitive evidence.

Patients with diseases known to cause clearance abnormalities can have sputum clearance with some techniques, such as positive expiratory pressure, autogenic drainage, and active cycle of breathing techniques (Wallis et al, 1999). Bronchodilators and manual chest therapy may also be helpful (Graham, 2005).

In ventilated children, chest physiotherapy with saline lavage and stimulated cough was successful in improving lung expansion in 84% of patients (Galvis et al, 1994).

This has been confirmed by Peroni and Boner (2000). The prescription of physical exercise proves helpful in patients with chronic lung disease as it improves airway clearance and breathing volumes (Lannefors et al, 2004).

Indications or contraindications for or against chest physiotherapy should never be formulated on the basis of diagnostic entities but should rather stem from a detailed analysis of the prevailing individual pathophysiology (Oberwaldner, 2000).

2.4 Anti-retrovirals

Since the introduction of anti-retrovirals in South Africa in 2004, there has been a large upscale in treatment programmes. The South African anti-retroviral treatment programme reached 81% of children in need of anti-retrovirals in 2009 (Republic of South Africa, 2010). In a sample of 270 patients in Ivory Coast, fifty-seven percent were on anti-retrovirals (Kouakoussui et al, 2004).

According to the National Antiretroviral Treatment Guideline (2004) patients are eligible for anti-retroviral therapy when they present with recurrent hospitalisations (i.e. more than two admissions per year) for a HIV-related disease, or a prolonged hospitalisation regarded as more than four weeks. Treatment may also commence should the child present with a modified WHO stage two or three disease, a CD4 percentage < 20% in a child under 18 months old or a CD4 percentage < 15% in a child over 18 months old. This has been recognised in an article by Rabie et al (2006). According to the National Department of Health South Africa (2010), the current guidelines state, anti-retroviral treatment may begin immediately in children under one, when the CD4 % is under 25 in children aged one to five years, or the CD4 count is under 350 in children above five years.

The normal CD4 cell count varies with age, starting high and then declining slowly to reach adult values around 5 years of age, however, the number of CD4 cells expressed as a percentage of the total lymphocyte count remains fairly stable (Rabie et al, 2006). Hence CD4 % is a stronger predictor of immune status.

In both adults and children starting anti-retrovirals, mortality was highest in the first six months of therapy, however after two years of use, 85.7% of children had achieved a CD4 greater than 20% of lymphocytes (Boulle et al, 2008).

Zolopa et al (2009) randomised a sample of 282 subjects into early and late initiation of ARV groups. The 'early group' regarded as receiving ARV's during the presence of an opportunistic infection instead of after, spent less time with CD4 counts below 50 cells/ml and therefore the ''window of vulnerability'' to additional AIDS-related complications was shortened. A European Collaborative Study (2006) suggests that there is a benefit of initiating ARV's before the age of five months.

Another study demonstrated that after highly active anti-retroviral treatment (HAART) the incidence of respiratory infections decreased dramatically compared to before HAART. It was, however, only statistically significant in children over five years old and those severely immunocompromised regarded as a CD4 percentage under five percent (Kouakoussui et al, 2004).

After one year of HAART a study demonstrated that 69.7% of children had a viral load < 400 copies/ml thus the comparative analysis showed significant improvements in growth, immunological status and virological control (Eley et al, 2006). A South African study (CHER) demonstrated that the early diagnosis of HIV and early antiretroviral therapy reduced early infant mortality by 76% and HIV progression by 75% compared to children with a deferred treatment program (Violari et al, 2008).

For children infected with HIV/AIDS, the timing of HAART after initiation of TB therapy depends on the clinical and immunological severity of disease. In those with severe clinical illness or advanced HIV, HAART should be started two to eight weeks after TB therapy to minimize the risk of immune reconstitution syndrome, optimize adherence, and differentiate potential side effects due to TB or antiretroviral drugs (Zar, 2008). Immune reconstitution syndrome is a paradoxical clinical deterioration after starting HAART, due to the improving immune system interacting with organisms that have colonised the body during the early stages of HIV infection

(National Antiretroviral Treatment Guideline, 2004). For instance, rifampicin is a TB drug that induces hepatic cytochrome P450 enzymes which may reduce levels of antiretroviral agents (Zar, 2008).

To improve the survival of young, HIV-infected children in Africa, early diagnosis must be coupled with comprehensive monitoring and care, including the timely introduction of HAART (Eley et al, 2007). HIV-infected children who adhere to a regimen of HAART are likely to enjoy suppression of HIV replication, and preservation or improvement in immunological function, with a reduced incidence of opportunistic events and mortality (Beck et al, 2001).

2.5 Prevention of mother to child transmission

Of the approximately 800,000 public sector births in South Africa in 2006, about 580,880 pregnant women were offered PMTCT services (Department of Health, 2007). In 2002 there were almost 339 000 orphans in South Africa, as a direct result of HIV/AIDS and the ASSA 2000 model predicted that in 2010 this number would increase to 1,5 million (Doherty et al, 2002).

Maternal death early in childhood is very common in the African context (Graham, 2003) and major risk factor for poor survival in HIV-exposed infants (Graham, 2005) as morbidity and mortality are affected by poor adherance to medication and nutritional care. Poor compliance may be an additional factor to incidence of acute respiratory infections, as social disruption due to death of a parent is common for HIV-infected children (Graham et al, 2001).

Breastfeeding remains a topic of debate in transmission of HIV/AIDS however findings in a Soweto based study tends to support suggestions that breastfeeding may confer protection against the severity rather than the incidence of acute respiratory infections. Breastfeeding showed a tendency towards protection against more severe acute respiratory infections (Kristensen et al, 2006). A study based in Malawi, demonstrated that breastfeeding by women infected with HIV was not

associated with mortality or morbidity; rather it was associated with highly significant reductions in mortality among their children (Taha et al, 2006).

A Cochrane review (Volmink et al, 2009) confirms that antiretroviral treatment administered in the perinatal period compared with placebo lowers the risk of mother-to-child transmission of HIV. The length of treatment appears to influence transmission rates with a longer antenatal component being the most important (Volmink et al, 2009).

Current guidelines recommend that all HIV-exposed infants should receive single dose Neviripine (NVP) post-delivery and the low-dose NVP for six weeks. At six weeks if the mother is on lifelong anti-retrovirals or the baby is not receiving any breast milk, then NVP may be stopped otherwise continue or as long as infant is receiving any breast milk (National Department of Health, 2010).

2.6 Burden of respiratory disease

From a global perspective, children from sub-Saharan Africa carry by far the heaviest burden of HIV-related respiratory disease (Graham et al, 2001). Acute respiratory infections account for 20% of the global under five years mortality in childhood (Jeena, 2005). Another study mentioned mortality rates of 26% by one year and of 62% by five years (Graham et al, 2001).

The prevalence of HIV infection is less than five percent among children aged under five years, however children this age accounted for 45% of those hospitalized and 84.7% of those who died because of severe lower respiratory tract infections (Madhi et al, 2000). Children with HIV who survive longer are less likely to die of pulmonary disease or infection and more likely to die of cardiac causes or with wasting syndrome (Langston et al, 2001).

Immune status and respiratory disease may influence the burden of disease among infected children. A CD4 cell count of under $50mm^3$ was a significant predicator of mortality in a group of 309 adult patients in Durban (Ojikutu et al, 2008) yet in a study

of 151 children at the same clinic the CD4 count was not a predictor (Reddi et al, 2007). Autopsy studies show, as in Zambia, that among respiratory causes of death the three major causes are acute pyogenic pneumonia, pneumocystis carinii and cytomegalovirus in HIV-1 infected children (Kouakoussui et al, 2004). Pneumocystis jirovecii pneumonia (PJP) and bacterial pneumonia have become a major cause of hospitalization and death in HIV-infected children according to Zar et al (2003). A longer duration of illness and greater case fatality rate in both well-nourished and malnourished HIV-1–infected children may be related to PJP ([b]Madhi et al, 2000). The admission rate for acute lower respiratory tract infections in children with LIP was approximately twice that of children without (Simmank et al, 2001). In a 2000 study by [b]Madhi et al, the overall case fatality rate was 13.1%.

2.7 Conclusion

The HIV/AIDS epidemic has had a large impact on Sub-Saharan African children, which subsequently affects the health system. Respiratory disease is a common cause of morbidity associated with HIV/AIDS. Since the introduction of anti-retrovirals in 2004 in South Africa, the impact of HIV/AIDS on respiratory disease needs to be re-evaluated with further studies. Identifying the prevalence and variety of respiratory conditions and identifying its relationship with factors such as age, immune status and the indication for physiotherapy may provide evidence on the burden of respiratory disease among children under the age of seven, most of whom were born within the post-HAART era.

CHAPTER THREE

Methodology

In this chapter, the methodology used in this cross sectional study will be discussed. The location of the study, ethical clearance, sample collection, study population, assessment tools, procedure and statistical analysis have been included.

3.1 Location

This study was conducted at Steve Biko Academic Hospital (Pretoria) in all paediatric wards and at Chris Hani Baragwanath Hospital (Johannesburg) in three paediatric wards. All the paediatric wards at Steve Biko Academic Hospital admit medical patients whereas at Chris Hani Baragwanath Hospital there are three assigned wards that admit medical patients. Both hospitals are large tertiary, academic hospitals situated in urban Gauteng, South Africa.

3.2 Ethical clearance

Ethical clearance was obtained from the Human Research Medical Ethics Committee at the University of the Witwatersrand – protocol number M080955 (Appendix I) and from the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria- protocol number 214/2008 (Appendix II).

Permission was granted from the CEO at Steve Biko Academic Hospital (2008/10/13) (Appendix III) and the Medical Superintendent at Chris Hani Baragwanath Hospital (2009/08/06) (Appendix IV) as well as both Heads of Department of Paediatrics to conduct the study at these hospitals .

3.3 Sample collection

One hundred and twenty-five consecutive patients (63 from Steve Biko Academic and 62 from Chris Hani Baragwanath Hospital) infected with HIV/AIDS admitted to the hospitals with a respiratory condition were recruited once informed consent was obtained from the caregivers.

3.3.1 Inclusion criteria

- Patients under seven years of age admitted to the paediatric medical wards with a respiratory condition and infected with HIV/AIDS

3.3.2 Exclusion criteria

- Patients who are not infected with HIV/AIDS
- Patients whose caregivers did not provide informed consent

3.4 Study population

Steve Biko Academic and Chris Hani Baragwanath are both tertiary hospitals and hence admit patients according to similar protocols. All patients are managed by paediatric pulmonology consultants, registrars and rotating intern and student doctors. One hundred and twenty five patients were assessed and the children's files were reviewed for data which were analysed to meet the research objectives.

3.5 Assessment tool

A data collection form (Appendix V) was completed by the researcher and used to note information extracted from the patients files. The form identified:

- Diagnosis of the respiratory condition(s)
- Whether physiotherapy intervention was necessary
- Reason for physiotherapy intervention according to a check list (Appendix VIII)
- Whether the patient was receiving or not receiving antiretroviral therapy, which combination was administered and the length of drug use
- The patients' history of ARV drug combination use and whether the mother was on ARV's
- The CD4 count and viral load
- Age and gender of patient
- Length of hospital stay

3.6 Procedure

During the research period, a list of new patients was created upon admission. The files of the patients were screened for subject recruitment following inclusion and exclusion criteria.

The caregiver was then approached and the information sheet (Appendix VI) read and discussed. The meeting with the caregiver was completed in a private room so that the caregiver did not feel compelled to provide consent in the presence of other caregivers in the ward. A translator was utilised in the event that the caregiver could not understand English or if the caregiver was not able to read the information sheet. The third person would therefore sign the verbal consent form as a witness. In the event of the caregivers' absence, telephone calls were made and consent was requested. The caregivers were requested to sign consent (Appendix VII) when visiting the hospital. In the event of after-hours visits the sister in charge of the ward was asked to obtain consent from the caregivers.

Once consent was achieved, the information in the file was read to complete the data collection form and an objective respiratory assessment was completed to evaluate whether physiotherapy was necessary. This was done by following guidelines on a tick list (Appendix VIII). A percentage of patients were also evaluated objectively by a research assistant who was another member of staff. The research assistant was blinded to the researcher's findings in order to serve as an inter-rater reliability test. Physiotherapy treatment was commenced on the day of evaluation if it was deemed necessary. Treatment was either provided by the researcher, a physiotherapy student under the researcher's supervision or by another qualified physiotherapist. The data collection form was completed at different intervals – two days post admission, five to seven days post admission and repeatedly five to seven days later until discharge and then at discharge.

During the data collection procedure, all respiratory conditions presented by the patients enrolled in the study were documented. The conditions were reviewed and it was documented whether the respiratory condition presented was treatable by chest physiotherapy according to literature, findings of the evaluation and guidelines set by the researcher. Data collection sheets were stored in a safe in the physiotherapy department until discharge of the patient after which they were kept in a safe place.

The relationship between the burden of respiratory disease and influencing factors such as the use of anti-retrovirals, ARV combinations and length of use, the CD4 count and viral load according to laboratory results was analysed. The age, gender and length of hospital stay of each patient was recorded for demographic analysis. The results were statistically reviewed once the findings were collated.

3.7 Statistical analysis

The following objectives would be analysed during a statistical appraisal of this study:

- proportion of paediatric patients with HIV/AIDS admitted to the medical wards with respiratory conditions requiring physiotherapy
- distribution of respiratory conditions in paediatric patients with HIV/AIDS
- proportion of patients on ARV's
- among the patients using ARV's find the length of use
- determine the relationship between the burden of respiratory disease (categories: one condition only, between two to three conditions and four or more conditions) and the influencing factors (ARV use, CD4 count, viral load, age, gender)
- relationship between length of hospital stay and respiratory disease category with the influencing factors

- Sample size was determined with reference to the proportion of patients with respiratory conditions requiring physiotherapy. It was conservatively assumed that the expected proportion of patients that required physiotherapy would be 50 %, then a sample of at least 97 patients would estimate the proportion to an accuracy of at least 10% with a 95% confidence interval. It was then assumed that 80% of all patients with respiratory disease would require physiotherapy then at least 125 patients would need to be screened.

The data of 125 patients was thus reviewed and analysed as follows:

- The proportion of subjects that require physiotherapy along with a 95% confidence interval and similarly for the proportion of those patients on anti-retrovirals was found.
- The relationship between the respiratory categories and influencing factors was investigated using logistic or polytomous logistic regression.
- The relationship between length of stay and the influencing factors employed time to event (survival) analysis. Interpretation was performed at a 0.05 level of significance.

The results of this study will be presented in chapter four.

CHAPTER FOUR

Results

In this chapter, the results of the study will be presented. The results are presented under the following topics: demographic information, distribution of respiratory conditions in paediatric patients with HIV, proportion of patients with respiratory conditions requiring physiotherapy, status of anti-retroviral use, patient immune status, relationship between the burden of respiratory disease and the influencing factors and the relationship between the burden of respiratory disease and the length of hospital stay.

4.1 Demographic information

4.1.1 Age distribution

The age distribution of the sample is presented in table 4.1.

Table 4.1 Age distribution (n=125)

	Mean	*SD**	*Median*	*IQR***
Age in months	***20.55***	***23.64***	***11***	***4 - 29***

** SD - standard deviation*

*** IQR – inter-quartile range*

The average age of all the children recruited who were all under seven years (84 months) was 20.55 months (SD=23.64).

4.1.2 Gender distribution

The gender distribution of the sample is presented in Figure 4.1.

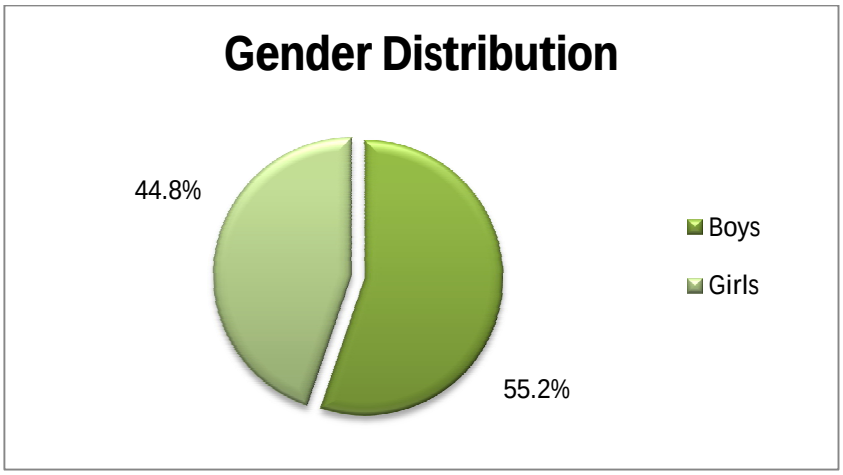

Figure 4.1 Gender distribution (n=125)

The total number of patients n=125 was represented by slightly more boys (55.2%) than girls (44.8%).

4.1.3 Length of hospital stay distribution

The length of hospital stay of the sample is presented in table 4.2.

Table 4.2 Length of stay distribution (n=125)

	Mean	*SD**	*Median*	*IQR***
Hospital stay in days	***18.76***	***19.19***	***13***	***8 - 23***

** SD - standard deviation*

*** IQR – inter-quartile range*

The average length of admission to hospital was 18.76 days (SD=19.19), approximately 2 ½ weeks. The median was approximately 2 weeks (13 days).

4.1.4 Outcome post admission distribution

The outcome of the sample (n=125) after admission is presented in figure 4.2

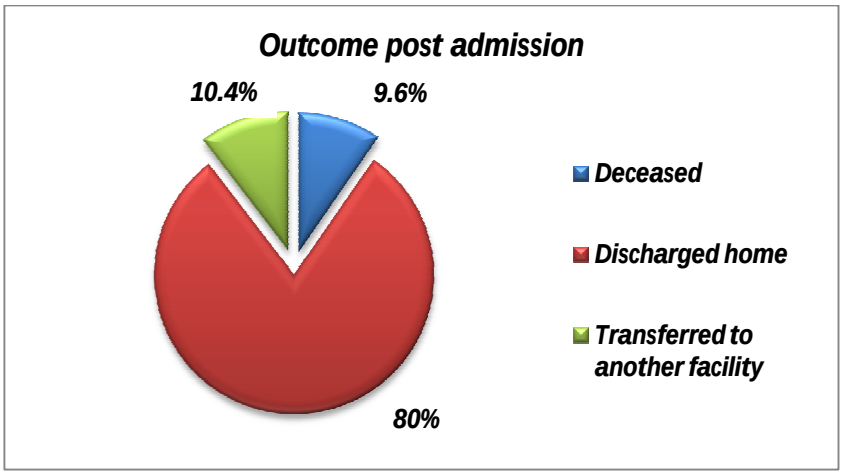

Figure 4.2 Outcome post admission distribution

The majority (80%) of the patients were discharged home, followed by 10.4% transfer to another medical facility. Just less than ten percent (9.6%) of patients died in hospital.

4.2 Distribution of respiratory conditions in paediatric patients with HIV

4.2.1 Respiratory disease distribution

The distribution of respiratory conditions was collated and categorised into eight groups. This is shown in figure 4.3.

'Bacterial pneumonia' included all forms of bronchopneumonia, pneumonia, community and hospital acquired. '*Viral pneumonia'* included bronchiolitis and all types of influenza. The '*Other'* group included interstitial lung disease, emphyema, pleural effusion, laryngomalacia, bronchopulmonary dysplasia, mycobacterium avium complex (MAC), swine flu (H1N1) and lung fibrosis.

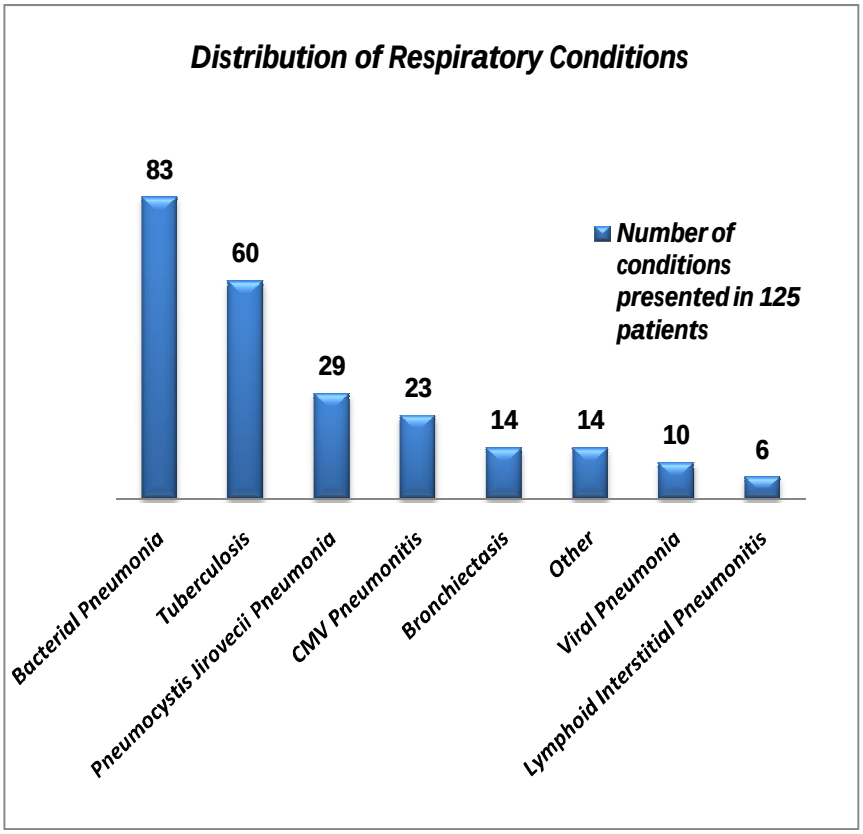

Figure 4.3 Distribution of respiratory conditions (n=239 conditions)

The distribution of disease category expressed as a percentage of the total patients presenting with each is demonstrated in figure 4.4.

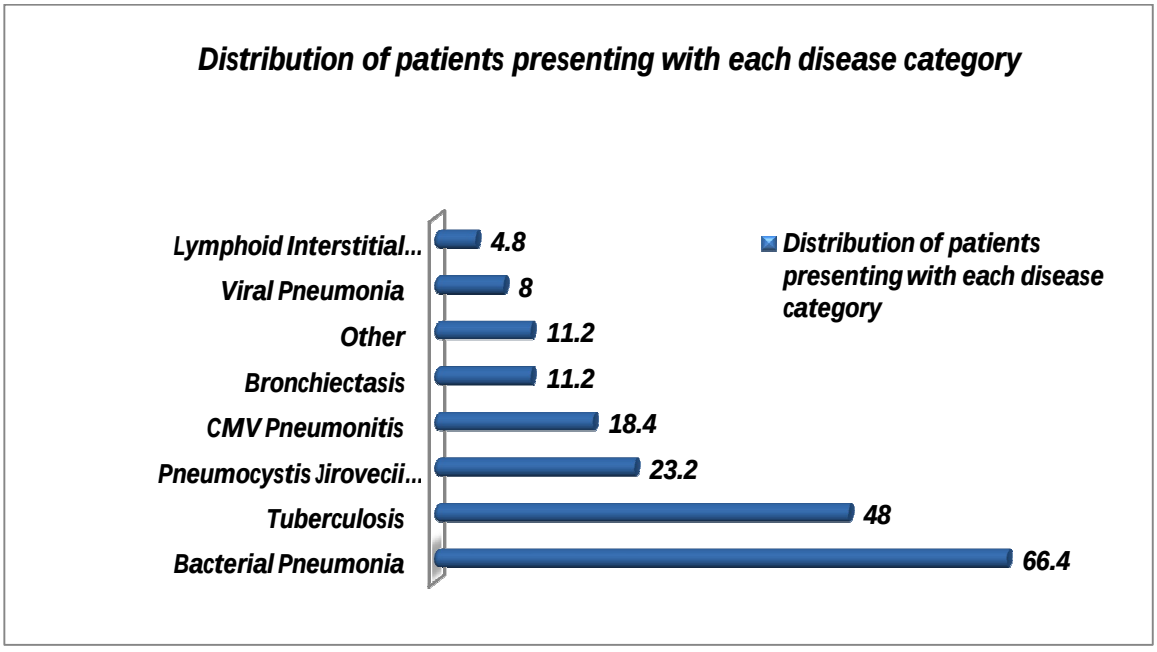

***Figure 4.4** Percentage of patients presenting with each disease category*

Bacterial pneumonia was the most commonly diagnosed respiratory condition (66.4%), followed by tuberculosis (48%) and pneumocystis jirovecii pneumonia (23.2%). Lymphoid interstitial pneumonitis was the least frequently diagnosed with only a 4.8 % presentation.

4.2.2 Burden of disease

Patients presented with one to four respiratory conditions as depicted in figure 4.5.

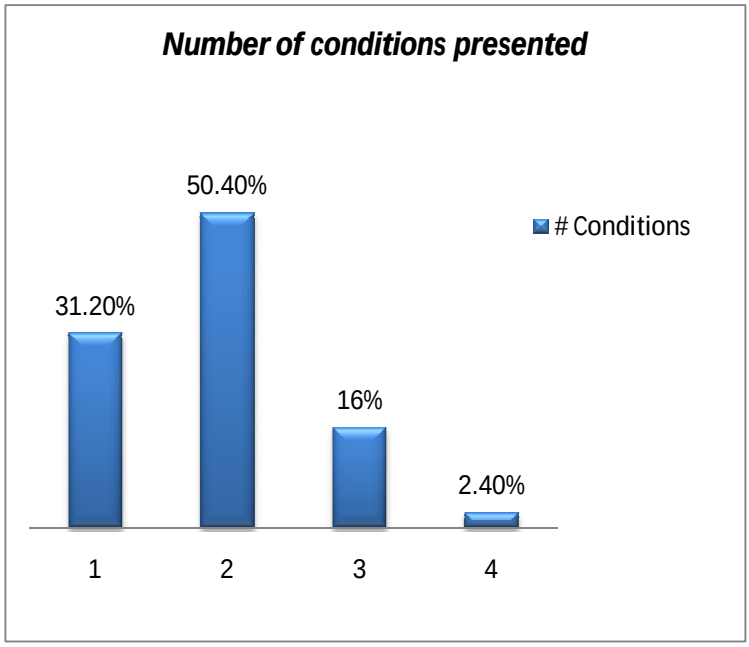

Figure 4.5 Distribution of the number of conditions presented

These were then categorised as a 'Low burden' (only one condition) or a 'High Burden' (more than one condition) as shown in figure 4.6.

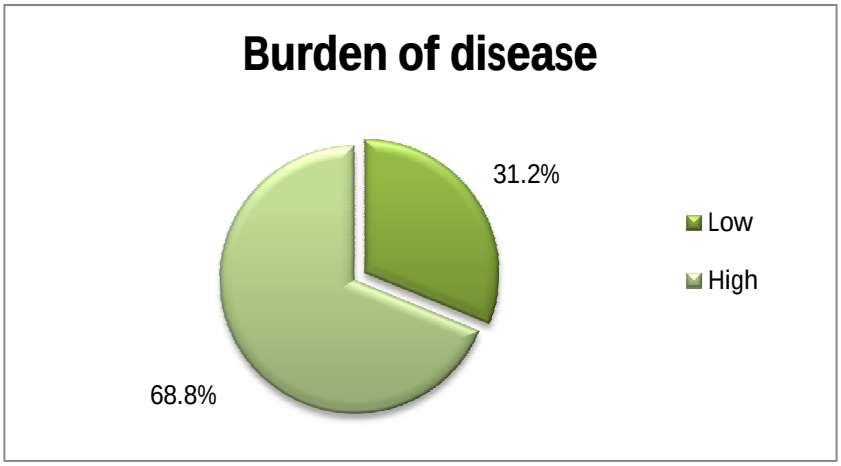

Figure 4.6 Low versus High burden of disease

Two thirds (68.8%) of all the patients can thus be classified as having a high burden of respiratory disease.

4.3 Proportion of patients with respiratory conditions requiring physiotherapy

The proportion of patients requiring physiotherapy is shown in table 4.3.

Table 4.3 Indication for physiotherapy

	Mean	*SD*	*Median*	*IQR*
Maximum # days requiring physiotherapy	***14.23***	***11.94***	***11***	***7 - 17***
Minimum # days requiring physiotherapy	***11.11***	***11.98***	***7.5***	***4 – 12.75***
Average # days requiring physiotherapy	***13***	***13.34***	***9.5***	***5 - 15***

** SD - standard deviation*

*** IQR – inter-quartile range*

Physiotherapy was indicated in 96 % of all the patients (n=125), therefore only five patients did not require physiotherapy at all. For the 120 patients who did

require physiotherapy the average indication for treatment was 13 days (SD=13.34).

4.4 Status of anti-retroviral use

4.4.1 Proportion of patients taking anti-retrovirals

The proportion of children taking anti-retrovirals is demonstrated in figure 4.7.

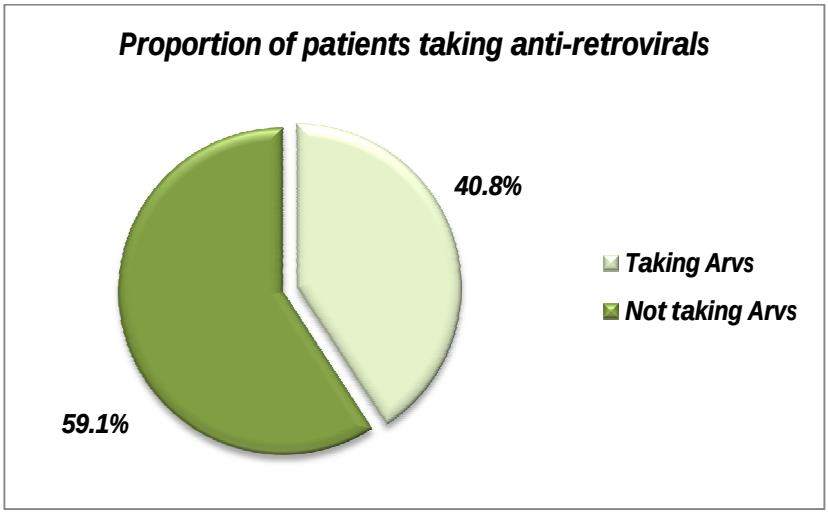

Figure 4.7 Proportion of patients taking anti-retrovirals

The number of children taking anti-retroviral medication was 51 (40.8%), while the number of those children not on anti-retroviral medication was 74 (59.1%).

Figure 4.8 demonstrates the breakdown of the status of anti-retroviral use.

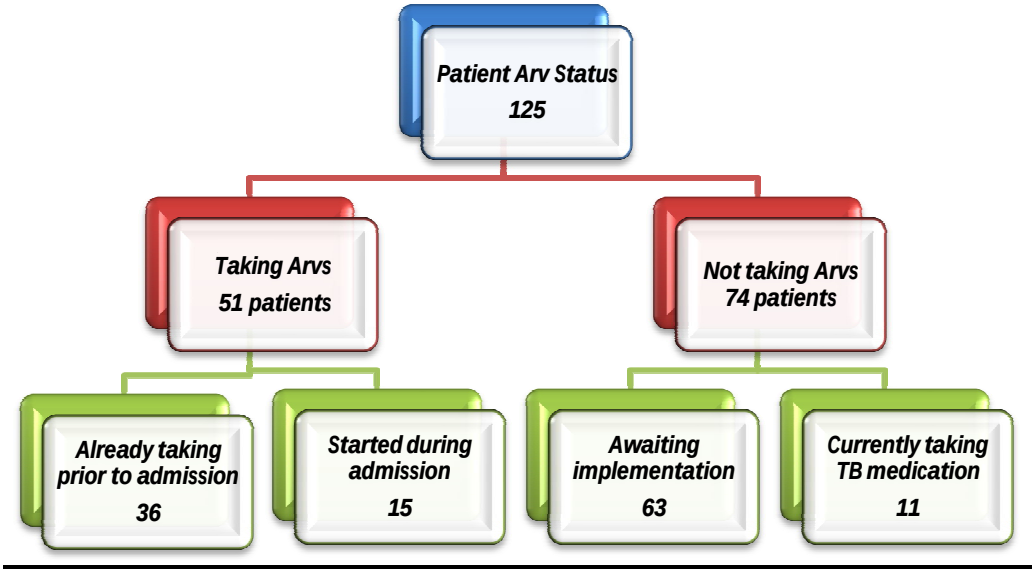

Figure 4.8 Breakdown of reasons for the status of ARV use

The distribution of patients receiving anti-retrovirals was divided into those already taking the medication prior to admission (28.8% of all patients n=125) and those starting the medication during admission (12%). The patients not taking medication was either due to awaiting Arv initiation (50.4%) or because the child was receiving TB medication (8.8%).

4.4.2 Average length of anti-retroviral use

Table 4.4 depicts the average length of anti-retroviral drug use (n=36) of the children already taking anti-retrovirals prior to admission.

Table 4.4 Average length of anti-retroviral drug use (n=36)

	Mean	SD	Median	IQR
Length of anti-retroviral use in months	*9.81*	*11.61*	*4.50*	*1– 15.25*

* SD - standard deviation

** IQR – inter-quartile range

The average length of anti-retroviral use for the 36 patients that were already taking anti-retrovirals prior to admission was 9.81 months (SD=11.61).

4.4.3 Distribution of anti-retroviral medication

Figure 4.9 exhibits the anti-retroviral medication used by the children taking anti-retroviral medication (n=51).

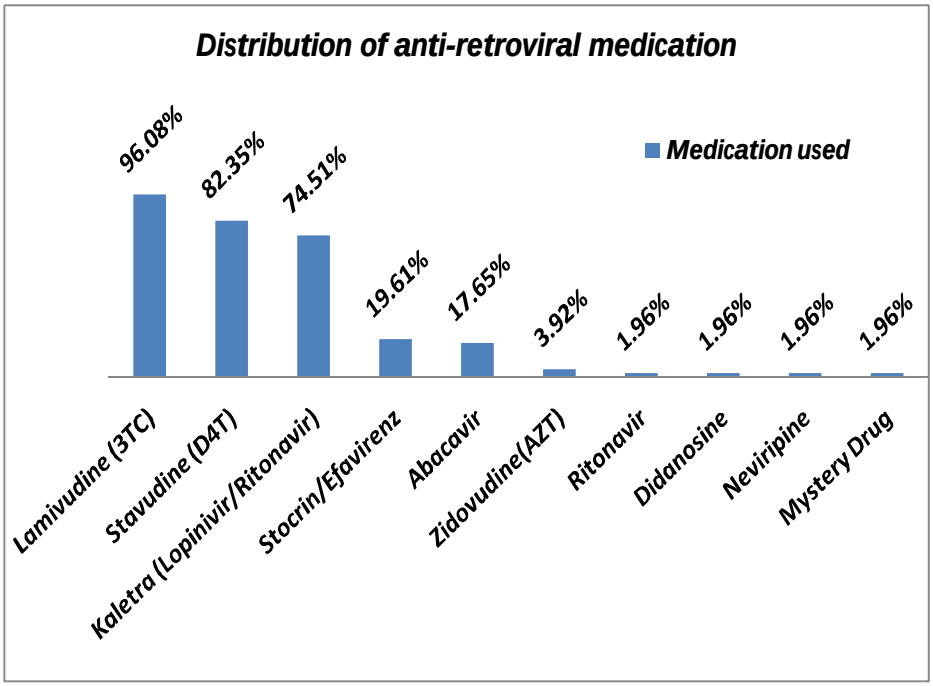

Figure 4.9 Distribution of anti-retroviral medication

Nucleoside analogues such as Lamivudine and Stavudine were the most commonly prescribed drugs among ARV users. Abacavir (a first line drug) was used in 17.65% of patients on ARVs while Zidovudine and Didanosine were used in a small percent of patients (3.92% and 1.96% respectively) as second line drugs. Kaletra was the protease inhibitor drug of choice (74.51%) with Ritonavir used in a small portion of patients (1.96%). Efavirenz was used as a non-nucleoside reverse transcriptase inhibitor in 19.61% of patients. Only one patient was still

taking neviripine and one patient was enrolled in another study which required administration of a “mystery drug”.

4.4.4 Status of maternal anti-retroviral use during pregnancy (PMTCT)

The breakdown of the status of anti-retroviral medication taken by the mothers during pregnancy is depicted in figure 4.10.

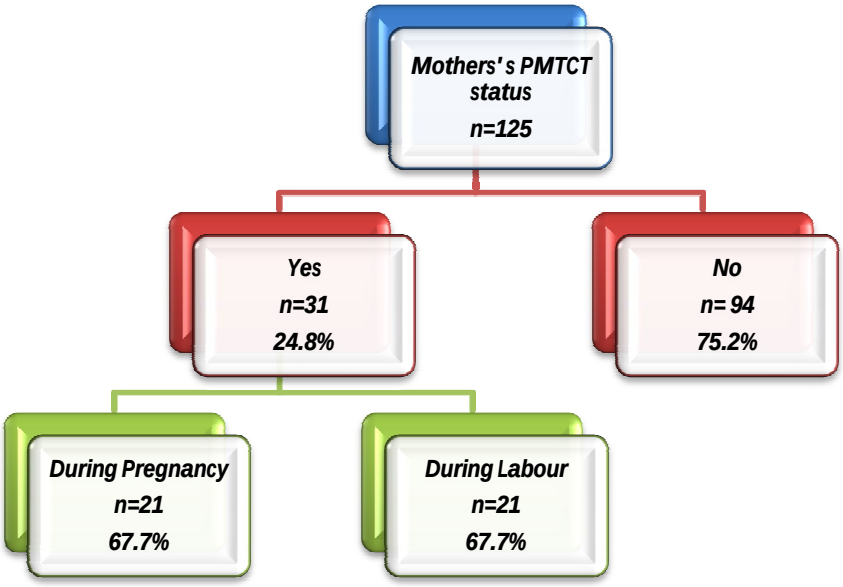

Figure 4.10 Breakdown of the status of PMTCT use

Of all the mothers there were only 31 (24.8%) who were involved in a PMTCT programme whereby approximately two thirds (67.7%) received either during pregnancy or labour or both. Ninety-four mothers were not involved in a PMTCT programme.

4.5 Patient immune status

4.5.1 CD4 count and viral load values

Information regarding the immunity of the children is included in table 4.5.

Table 4.5 Immunological status

	Mean	SD	Median	IQR
CD4 percentage	17.33	10.96	16.7	8.94 – 21.3
CD4 absolute (cell/mm^3)	631.36	610.36	417	233.5 – 811.5
Viral Load (copies/ mL)	2664420	9080406	350000	33000 - 1550000

* SD - standard deviation

** IQR – inter-quartile range

The average CD4 count was 17.33% (SD=10.96) and 631.36 mm^3 (SD=610.36) while the average viral load was 2.6 million copies per mL (SD=9.1).

4.5.2 Level of immunosuppression

The level of immunosuppression was categorised into four stages (figure 4.11) according to the WHO staging which accounts for age and CD4 percentage (for children under 5 years) or CD4 absolute count (for children 5 years and older) .

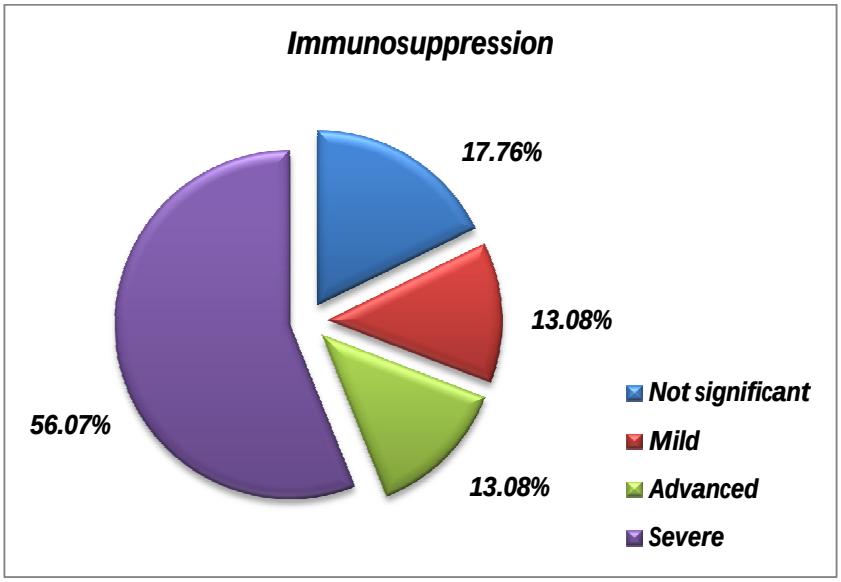

Figure 4.11 Level of immunosuppression

It is of importance to note that the immune status was assessed on the the basis of 107 patients' results. Eighteen patients had missing CD4 results.

For the purpose of statistical analysis the advanced and severe categories were grouped together. The immunosupression distribution was thus modified (figure 4.12).

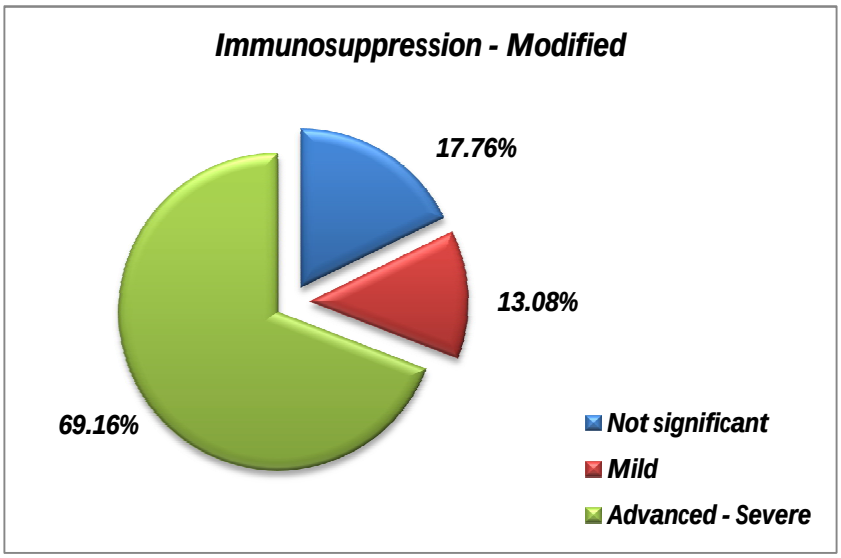

Figure 4.12 Modified level of immunosuppression

4.6 Relationship between the burden of respiratory disease and the influencing factors

The burden of respiratory disease was regarded as low or high burden as described above. The influencing factors include: Anti-retroviral use, CD4 count, viral load, age and gender.

A relationship was discovered with ARV use, CD4 count and gender (table 4.6).

No relationship was found with regard to viral load and age.

4.6.1 Logistic regression of burden versus ARV use

With a crudes odd ratio of 0.54, it can be said that children not on ARVs have half the risk of having a higher burden of respiratory disease than children using ARVs.
P value = 0.13.
Therefore: there is a higher burden of disease among patients using anti-retrovirals – no statistical significance.

4.6.2 Logistic regression of burden of disease versus CD4 count

With a crudes odd ratio of 1.66, it can be said that patients with a mild immunosuppression have one and a half times the risk of having a higher burden of respiratory disease than patients with a non-significant immunosuppression.
P value = 0.50.

With a crudes odd ratio of 2.01, it can be said that patients with an advanced/severe immunosuppression have twice the risk of having a higher burden of respiratory disease than patients with a non-significant immunosuppression.
P value = 0.20
Therefore: as the level of immunosuppression increases so does the burden of respiratory disease – with no statistical significance.

4.6.3 Logistic regression of burden of disease versus gender

With a crudes odd ratio of 2.23, it can be said that females have twice the risk of having a higher burden of respiratory disease than males.
P value = 0.05.
Therefore: there is a higher burden of disease among female patients – with statistical significance.

These data are summarised in table 4.6 below.

Table 4.6 Summary of findings

	Risk of increased Burden	***Crudes odd ratio***	***P value***
ARV non -users	***1/2***	***0.54***	***0.13***
Mild immunosuppression	***1 ½***	***1.66***	***0.50***
Advanced/Severe immunosuppression	***2***	***2.01***	***0.20***
Females	***2***	***2.23***	***0.05***

4.7 Relationship between the burden of respiratory disease and the length of hospital stay

Using the Kaplan Meier survival curves there was a marginally significant difference (p= 0.06) between a low burden of disease and high burden with respect to mortality.

- The low burden group died earlier but had a shorter length of stay
- The high burden group died later but had a longer length of stay

The relationship between burden of disease and the length of hospital stay was also significant (p=0.029) significance was tested in various ways:

- Students t test p = 0.03
- Welch t test p ≤ 0.01
- Mann-Whitney test p= 0.03

Therefore: the patients with a high burden of disease were admitted for longer and displayed incidents of mortality much later in admission compared to those with a low burden.

4.8 Conclusion

Of the 125 patients recruited in this study 55% were boys and the mean age was 20.55 months. The children stayed in hospital for an average of 2 ½ weeks, while 80% were discharged and 9.6% died. The most common respiratory conditions presented included bacterial pneumonia (66.4%), tuberculosis (48%) and pneumocystis jirovecii pneumonia (23.2%). The least common condition was lymphoid interstitial pneumonitis (4.8%). Two thirds of the children (68.8%) presented with more than one condition and thus a high burden of disease was more prevalent. Physiotherapy treatment was indicateded for 96% of the patients mainly due to excess secretions and poor air entry.

The use of anti-retrovirals was 40.8%, while 50% were awaiting initiation. The average length of anti-retroviral use was 9.81 months. The most common drugs used were lamivudine, stavudine and kaletra. Seventy-five percent of mothers were not involved in a PMTCT program. The average CD4 % was 17.33, CD4 absolute 631.36 cell/mm^3 . The average viral load 2.6 million copies /ml. Thus most children presented in the advanced to severe group of immunosupression. There was a higher burden of disease among patients using anti-retrovirals (p=0.13), children with a mild level of immunosupression (p=0.50) and advanced to severe (p=0.20), and with female patients (0.05) and had a longer length of stay.

These results will be discussed in the following chapter.

CHAPTER FIVE

Discussion

Introduction

The results obtained in this study will be discussed in this chapter and comparisons will be made with previous studies. Clinical and research implications and challenges of this study are described.

5.1 Demographics

The study population consisted of 125 children all diagnosed with perinatally acquired HIV and a respiratory illness. Of all these children under the age of seven, the average age was found to be just short of two years. This study therefore included younger children compared to some other studies which were conducted on children with average ages of seven and a half years (Sheikh et al, 1997); five and a half years (Becciolini et al, 2001); two and a half years (Schaaf et al, 2007) and two years (Langston et al, 2008). The distribution of males to females was nearly the same.

The length of hospital stay was approximately two and a half weeks and resulted in an 80% discharge rate. [a]Madhi et al (2000) found in a South African based study that the average length of hospitalisation was just under seven days. The mortality was found to be just under 10%. Similar results were found as in Jaspan et al (2008) with a nine percent mortality and greater mortality rates of 16% were found in a study by Ojikutu et al (2008) both of which were South African based studies. The large standard deviations are due to a wide range of results found in this study.

Of the twelve patients who died only three (25%) were taking anti-retrovirals, however all three had only started during the study so essentially all children who died were ARV naive, highlighting the problems arising as a result of late

initiation of anti-retrovirals. Nine of the twelve children who died were under the age of six months, the other three were 15, 16 and 58 months old . Of the patients who died – Pneumonia, PJP, CMV Pneumonitis and TB were the associated respiratory illnesses, concurring with a 2004 Zambian study by Kouakoussui et al.

5.2 Distribution of respiratory conditions in paediatric patients with HIV

Although Zar (2008) discusses a shift from acute to chronic exacerbations of respiratory disease, this state is not clearly depicted in this study due to the population age of under seven and an average age of just under two. Perhaps then, this study may offer more insight into acute respiratory diseases.

Pneumocystis Jirovecii Pneumonia varies between 10% and 17% of children according to Jeena (2005), however is represented by 23% of children in this study. It usually first causes infection early in childhood (Graham 2005). Graham (2003) reports that PJP presents with severe pneumonia, usually in infants between two and seven months old. This study supports this statement when looking at the age distribution of the children who presented with PJP. Of the twenty-nine children, 27 were seven months or younger. This demonstrates that PJP is one of the first presenting conditions in children with HIV and affects children at a very young age – supporting the need for proper ante-natal HIV testing and PJP prophylaxis post-natally.

With the current use of prophylaxis in the HIV clinics, this study further supports Graham's (2005) findings that bacterial pneumonia is now more common than PJP as an acute respiratory illness by almost three times as much. Lower respiratory tract infections (LRTI) are a major cause of morbidity and mortality in children aged under five years in developing countries ([a]Madhi et al, 2000; Zar et al, 2003). The average age of the children recruited in this study was just under two years. An immature immune system is a

factor which predisposes all children to infections and even more so due to the superimposed immunocompromised status.

Bacterial Pneumonia was found in two thirds of all patients. This is a high level and recognises that community and nosocomial pneumonias are a more common presenting feature among HIV children especially since the management of other specific diseases such as PJP have become better controlled. **CMV pneumonitis,** often associated with PJP (Graham, 2003) was found in 18.4% of children in this study.

Viral Pneumonia was not very common with only an eight percent presentation. This group included bronchiolitis and influenza viruses. Measles pneumonia was not seen in this group of patients. The swine flu epidemic occurred during this study. Despite low immunity among the study population, only two cases were diagnosed. The reasons for these values could indicate that perhaps this group in particular was not exposed to the swine flu and would not have taken into account the group of children that demised before the potential for admission. This group is still of importance to note as repeated viral infections may precipitate into chronic lung diseases of which HIV infected children are susceptible (Zar, 2008).

In almost half of the cases **Tuberculosis** was a presenting respiratory disease. Tuberculosis is thus still a major factor in our country and its management should be of importance because co-infection with HIV results in more rapid deterioration of immune dysfunction, viral replication, and HIV progression and more frequently other severe infections (Zar, 2008).

Tuberculosis has been associated as a co-infection in most HIV infected patients. The effects that TB has had in South Africa are vast. Diagnosis often requires a triad of investigations including chest xrays, skin tuberculin tests and sputum samples. Despite the use of these tests, some children still receive treatment in cases where the diagnosis is not confirmed. This is due to the nature of this epidemic – it is a prevalent community spread infection

that most children infected with HIV will be exposed to. It is therefore in the best interest of the children to receive TB treatment to reduce morbidity. This however impacts on the health budget as treatment is expensive as management should continue for at least six months and complications such as IRIS augments the need for health care.

Lymphoid Interstitial Pneumonitis (LIP) is a common cause of chronic respiratory disease in HIV-infected African children (Graham, 2003). It is usually seen in children over the age of two years (Swigris et al, 2002). In this study a low percentage of cases was discovered – slightly less than five percent. This occurence may be due to a few reasons. Firstly the study population was young – under seven years old. Since LIP is considered a chronic lung disease it may be more prevalent in children over the age of seven. Of the six children presenting with LIP, the average age was 42 months. The second reason may be due to improved care of acute respiratory exacerbations which long term may reduce the occurence of chronic lung diseases due to limited lung damage.

Since the roll out of anti-retrovirals and improved knowledge regarding HIV and the respiratory system, the management of conditions presenting in the acute stage may be better than before. Another possible and likely reason for the low prevalence of LIP in this study group is the underdiagnosis of LIP as a result of an overdiagnosis of TB, since the presenting features are very similar. On xrays a diffuse reticulonodular pattern, more pronounced centrally is present which may be difficult to distinguish from pulmonary or miliary TB (Zar, 2008).

Bronchiectasis is a common presenting condition among children infected with HIV and occurs as a result of repeated lung tissue damage. It occurs in up to 16% of children (Rabie et al, 2007). Just over eleven percent of children in this study presented with bronchiectasis. Sheikh et al (1997) report similar results however the children had a mean age of seven and a half years. This

recognises that the chronic lung diseases occur at a later age, maybe a reason for the relatively low numbers of children with bronchiectasis in this sample.

5.3 Burden of disease

The number of respiratory diseases presented was classified as low burden when only one condition was present and a high burden when two or more conditions were present. Due to the nature of the HIV disease and an increased susceptibility to infections – mixed infections are common such as bacterial pneumonia or cytomegalovirus (CMV) with PCP, or bacterial pneumonia complicating viral pneumonia, PTB, or LIP (Graham, 2003). This is clearly demonstrated in this study with a 68.8% rate of high disease burden.

Other studies (Graham, 2005; Rabie et al, 2007) have not classified the burden of disease into low and high categories but have rather discussed the array of conditions with which each child presented – which are very similar to the conditions found in this study. Graham (2003) discusses the burden as the scale of the problem and the lack of resources specific to the African setting and Zar and Mulholland (2003) discuss how lower respiratory tract infections place a burden on prevention and treatment. Zar and Mulholland (2003) also make references to other studies where the burden is described as the effect HIV has on mortality statistics. This study however has taken the burden of disease to signify the status of conditions presented and how they may co-exist – which in effect is a factor leading to poor immune status and poor health.

5.4 Indication for physiotherapy

The indication for physiotherapy for each child was based upon the need to provide treatment due to excess secretions, decreased air entry, weak cough,

poor exercise endurance, poor positioning or posture, poor breathing control or need for a home programme and caregiver education in the event of chronic lung diseases (McClure, 1993).

One hundred and twenty of the total number of patients (n=125) required physiotherapy mostly due to excess secretions and decreased air entry. Of the 120 patients the average indication for physiotherapy was thirteen days. There are no studies that have been done before to investigate the length of time that physiotherapy is required.

Physiotherapy was provided to all children who required it, however the frequency or techniques used was dependent upon the physiotherapist working in the relevant wards and whether or not weekend physiotherapy was applied. This could be viewed as an inconsistent variable which could affect the total number of days that a child would need physiotherapy based upon the efficacy of the physiotherapists' treatments. However, it may also be viewed as a natural occurence that each physiotherapist will treat in a different manner, and thus the results are based upon research in a natural setting.

5.5 Status of anti-retroviral use

Of all the patients (n=125) only 36 were already taking anti-retrovirals prior to admission for an average length of 9.81 months (SD=11.61). Almost 60% of the children were not taking anti-retrovirals. Many patients are only diagnosed with HIV during a hospital admission – this accounts for 62 patients diagnosed with HIV but still awaiting the initiation of anti-retroviral drug treatment. The most commonly administrated drugs include: Stavudine, Lamivudine and Kaletra. These proportions may change as new combinations are attempting to lower drug toxicity.

In 2010, the National Department of Health in South Africa published 'Guidelines for the Management of HIV in Children' and suggested that all

children under the age of one start anti-retrovirals immediately. Children between one and five years are eligible to start treatment if they are symptomatic stage III or IV, have a CD_4 count under 750 cells/mm^3 or percentage below 25%. Children over five may start ARV's when they too are symptomatic of stage III or IV or their CD_4 counts are below 350 cells/mm^3.

The 2004 guidelines from the National Department of Health were based on recurrent hospitalisations, a modified WHO stage II or III and CD4 percentages under 20% for children under 18 months of age and under 15% for children over 18 months of age .

Violari et al (2008) conducted a study which found that starting ARV's at an average age of seven weeks reduced early mortality by 76% when compared to children receiving ARV's based on CD4 percentage or clinical progression of HIV. Studies show that early anti-retroviral treatment initiation reduces the risk of opportunistic infections and lowers the viral load (Kouakoussui, et al. 2004; Eley et al. 2006). The initiation of early anti-retrovirals has shown a 69-94% reduction in mortality (Kitahata et al, 2009) and Boulle et al (2008) showed that ARV's reduced early mortality rates within the first six months. Ojikutu et al (2008) found that the strongest predictors of mortality in children who have initiated anti-retroviral drugs are CD_4 counts less than 50 and the presence of oral candidiasis.

Anti-retroviral drugs were introduced to South Africa in 2004 and since the children recruited in the study are under the age of seven, most were born in the post-HAART era. Despite this, a low number of children were on treatment. Perhaps then, there are still many problems facing HIV testing and anti-retroviral initiation. The identification of actively replicating virus by DNA polymerase chain reaction (PCR) is more reliable, but is difficult to obtain in most developing countries. Replication of this study in a few years may yield different results since the new 2010 revised guidelines on anti-retroviral treatment will recruit more patients into the anti-retroviral programme.

5.6 Prevention of mother to child transmission

Of all the mothers just under a quarter (24.8%) took anti-retrovirals during pregnancy. Of the infected children in this study it is shown that despite a quarter of the mothers undergoing PMTCT, their children tested positive. This identifies that the PMTCT programme is not yet reaching all settings in South Africa as there were many mothers who did not join the PMTCT programme. Ante-natal care should be widely promoted and PMTCT programmes need to be carefully monitored in order to reduce transmission rates.

The proportion of current maternal anti-retroviral use was not evaluated, however it is an important factor influencing the burden of childhood disease – with regard to administration of medication to children, nutrition, spread of disease and mortality. Maternal death is a major risk factor for poor survival in HIV-exposed infants (Graham, 2005). Seven intervention trials from sub-Saharan Africa in largely breastfeeding populations demonstrated that the death of children by age one is approximately seven times greater when the mothers are HIV infected compared to non-infected (Newell et al, 2004).

5.7 Patient immune status

The average CD_4 count was 17.33% and 631.36 mm^3, while the average viral load was 2.6 million copies/ml. This places almost 70% of the study population in the advanced to severe immune-compromised group. This directly increases the burden of respiratory disease which in turn impacts on the health system and need for hospital care.

Identifying the immune status is important for the initiation of anti-retroviral drugs. As seen in this study their immune systems are compromised and thus most children would classify for drug initiation – as discussed above with regard to CD_4 counts and percentages being eligibility criteria for the initiation of anti-retrovirals. The results with regard to immune status are only based on 107 children as not all viral load and CD4 counts were tested.

5.8 Relationship between the burden of respiratory disease and the influencing factors

This study set out to determine whether there was a relationship between the burden of respiratory disease and a variety of factors. No relationship was found with regard to viral load and age. However a relationship was found pertaining to the use of anti-retrovirals, level of immune suppression and gender.

Despite statistical significance as the p value was higher than 0,05, the study found that there was a higher burden of disease among patients using anti-retroviral medication. Although statistically this result has no bearing it does have clinical relevance. This result seems to be contradictory as the use of anti-retrovirals should improve the immune status and thus reduce the incidence of respiratory disease. The results found in this study may be due to a few reasons. The fact that some of the children were receiving anti-retrovirals did not distinguish those whom were on the drugs for a short period in which the effects have not yet taken place. It may also be that the children presenting with more conditions have been referred to the tertiary hospitals by secondary or primary institutions for more specialised care of complicated conditions – and thus already may have initiated anti-retrovirals at an earlier age.

There was a relationship between the level of immune suppression and the burden of disease. As the level of immunity decreases indicated by a reduction in the CD_4 percentage or absolute value, children are more predisposed to infection or acquiring respiratory conditions. A study has discussed that the CD_4 T cell determines host susceptibility to PCP in some animal models (Beck et al, 2001) and that it may also induce inflammation, lung injury and death.

The results did show that as the immune suppression changed from mild to advanced/severe, the risk of a high burden of disease increased from one and a half times (crudes odds ratio = 1.66) to two times (crudes odds ratio = 2.01) the risk. This is clinically relevant. Therefore as the immunity decreases it may be said that the burden of respiratory disease increases. Children infected with HIV have a lower immunity and are thus more susceptible to more infections and even more so to having a number of co-existing conditions.

With regard to gender the results show that girls are twice as likely to develop a higher burden of disease than boys. This contrasts with the findings by Kristensen et al (2006) that girls tended to be better protected against acute respiratory infections than boys. They studied a sample of children in Soweto who had an estimated HIV infection rate of five to six percent. There are no other studies that have looked at the difference between boys and girls with regard to the burden of disease and the distribution of respiratory conditions presented.

5.9 Relationship between the burden of respiratory disease and the length of hospital stay

The study sought to find if there was a relationship between the burden of disease and the length of hospital stay and with respect to mortality. With regard to mortality the children with a low burden of disease, that is with one condition, died at earlier stages of hospital admission. The patients with a high burden of disease were admitted for longer and displayed incidents of mortality much later in admission compared to those with a low burden.

There may be more than one reason for these findings. Of the children who died (n=12), nine were under the age of six months. Children who were admitted with only one condition such as pneumocystis jirovecii pneumonia which is severe in its presentation, may not have had enough time for adequate care and thus demised at an early stage of admission. The children

identified to have a higher burden of disease may have received a more intense program of care and thus their length of hospital stay was longer.

There was no relationship between the age of the child and the point of hospital stay when mortality occurred - the children who died earlier were not necessarily younger. Mortality was rather influenced by the number of conditions presented.

5.10 Challenges

The study chose to include children under the age of seven years. This has therefore not included a population of children who would have presented with more chronic lung diseases. This is seen with a low number of cases of LIP and bronchiectasis in this study. The study has therefore only given an idea of the burden of acute respiratory conditions.

The conditions presented were extracted from patient's files – the accuracy of the diagnosis was therefore out of the researcher's control.

Since the study recruited data from two tertiary hospitals the indication for physiotherapy may have been affected by factors which were uncontrollable. Physiotherapists recruit a variety of treatment strategies and frequencies of treatment.

This study did not distinguish the length of ARV use as a factor towards the development of a high burden of respiratory disease but rather whether the child was on treatment or not. Therefore the study demonstrated that the use of anti-retrovirals does not necessarily protect a child from developing a high burden of respiratory conditions – perhaps the length of use does.

5.11 Clinical and research implications

The average length of hospital stay was two and a half weeks which could be due to a number of reasons for prolonged care. It is however a risk for hospital acquired infections. It is also important to consider that this study recruited a sample of children under seven years of age with an average of 20.55 months of age (SD=23.64). This sample therefore is a vulnerable group with regard to acquiring respiratory infections, with age as a factor alone. HIV predisposes these children to be more susceptible. While this study has looked at the respiratory disease profile and its contributing factors in children infected with HIV, it might be interesting to conduct a comparison study between children infected and non-infected of the same age within the same setting.

PJP has shown to be less prevalent than before and is now less common than bacterial pneumonia. This has shown that efforts to introduce PJP prophylaxis has worked. The fact that PJP continues to contribute towards early mortality in the younger children recognises that the ante-natal prophylaxis programme is still not optimal.

This study assessed the burden of respiratory disease with regard to the respiratory conditions presented and the effects that ARV use, CD_4 counts and gender have. This is in contrast to other studies whereby the burden of disease was assessed by looking at the mortality rates alone. This therefore has presented data on the clinical features of children infected with HIV admitted to hospital. As the guidelines for anti-retroviral eligibility change and ante-natal testing improves – future studies may yield different results and the profile of respiratory diseases may be quite different.

A high burden of disease was clearly demonstrated with a 68,8% rate and this supports the indication for physiotherapy. Future studies may investigate which modalities and intensities of treatment are better suited to each

condition and thus further improve clinical understanding among physiotherapists treating children with HIV related respiratory conditions.

With an average age of just under two of all patients recruited, the study found that almost 60% of children were not on anti-retroviral therapy. This indicates that widespread testing during early infancy is not yet optimal. Similarly, the PMTCT program may not yet be as effective as just under a quarter of the mothers were involved in a PMTCT program and still transmitted the virus to their children.

Almost 70% of the study participants were placed in the advanced to severe immune-compromised group and thus our health care settings particularly tertiary institutions are dealing with a vulnerable group that requires specialised care. Since the immune suppression influenced the risk of the burden of respiratory disease it is important that the clinical profile of children be evaluated regularly to identify children most at risk. The intervention given by physiotherapists may then be influenced by identifying those patients most at risk quicker. This study has established basic characteristics of the respiratory disease burden among hospitalised children with HIV in a South African setting in a post HAART era.

CHAPTER SIX

Conclusion

The aim of the study was to determine the burden of disease with regard to the prevalence of respiratory conditions among paediatric patients infected with HIV/AIDS and to establish the indication for chest physiotherapy. The product of this study investigated the burden of respiratory disease with a focus on acute exacerbations due to the age group selected. Of the 125 children perinatally infected with HIV, there was just under a 10% mortality rate owing predominantly to children diagnosed with Pneumonia, PJP, CMV Pneumonitis and TB. Conditions observed were similar to previous studies, highlighting that PJP, bacterial and viral pneumonia, TB, LIP, CMV pneumonitis and bronchiectasis remain common conditions among children with HIV. A shift seen in recent years as described in this study is that bacterial pneumonia has overtaken PJP as the leading respiratory condition due to improved prophylactic measures. A large majority of patients presented with an indication for physiotherapy treatment, which highlights the importance of physiotherapists understanding this population of patients.

With regard to the relationships between the burden of disease and the influencing factors, it was found that a higher burden of disease was related to the use of anti-retrovirals, a higher immuno-suppression, female patients, longer length of stay and later mortality rates. Despite six years of anti-retroviral therapy roll-out there are still so many undiagnosed children who await initiation and thus in the interim, many respiratory conditions still prevail.

CHAPTER SEVEN

References

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APPENDICES

I. **Ethical clearance from the University of Witwatersrand**
II. **Ethics clearance from the University of Pretoria**
III. **Consent from superintendants to conduct research at Chris Hani Baragwanath Hospital**
IV. **Consent from superintendants to conduct research at Steve Biko Academic Hospital**
V. **Data collection form**
VI. **Information sheet for caregivers**
VII. **Consent form**
VIII. **Guidelines for the indication of physiotherapy treatment**

Appendix I: Ethical clearance from the University of Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 da Cunha

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080955**
PROJECT	Screening for the Need of Chest Physiotherapy among Paediatric Patients Infected with HIV/AIDS
INVESTIGATORS	Miss NCP da Cunha
DEPARTMENT	Physiotherapy Department
DATE CONSIDERED	08.09.26
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 08.09.29 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

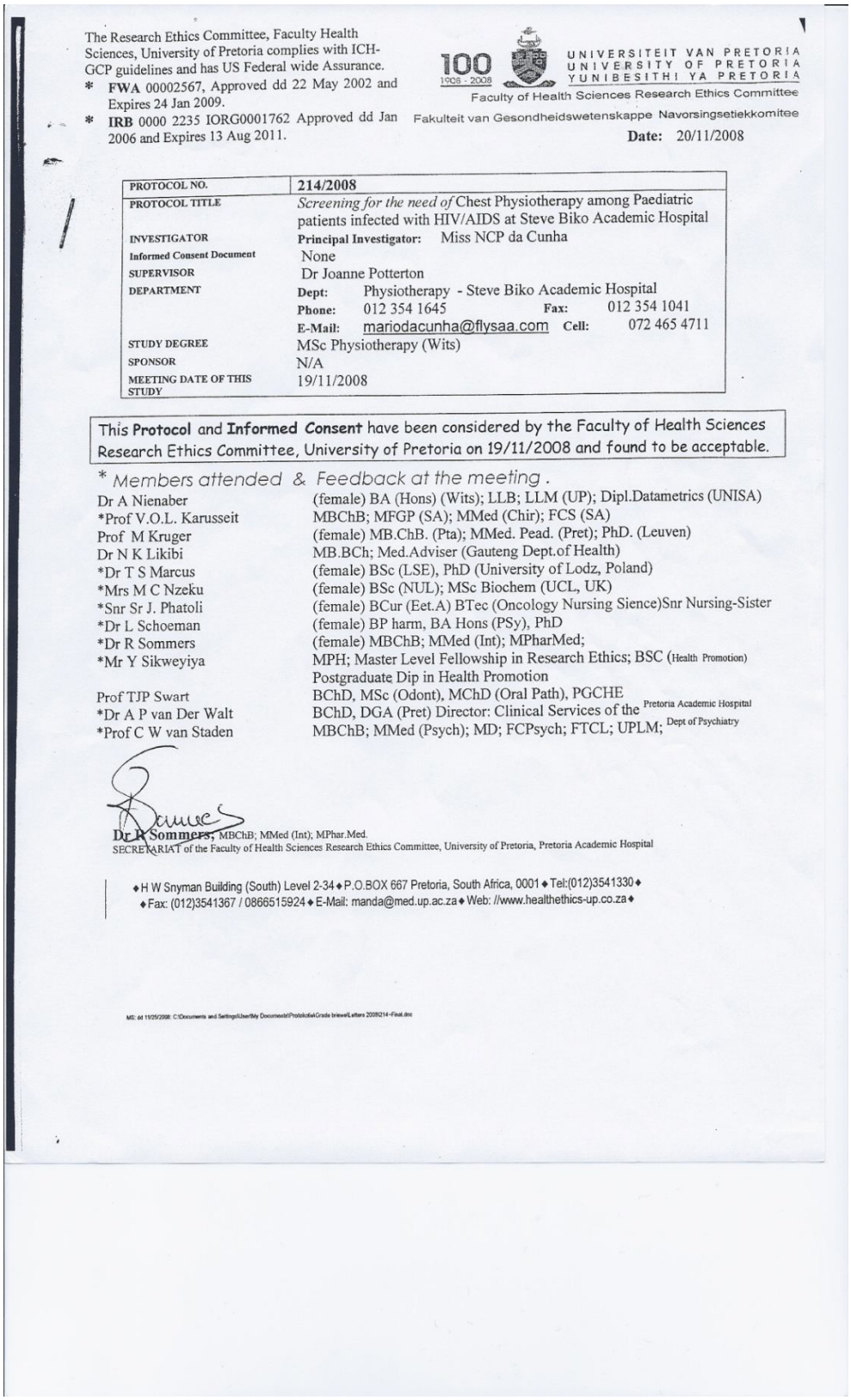
cc: Supervisor : Dr J Potterton

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix II: Ethics clearance from the University of Pretoria



The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

* **FWA** 00002567, Approved dd 22 May 2002 and Expires 24 Jan 2009.
* **IRB** 0000 2235 IORG0001762 Approved dd Jan 2006 and Expires 13 Aug 2011.

100 1906 - 2006

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

Fakulteit van Gesondheidswetenskappe Navorsingsetiekkomitee

Date: 20/11/2008

PROTOCOL NO.	**214/2008**
PROTOCOL TITLE	*Screening for the need of* Chest Physiotherapy among Paediatric patients infected with HIV/AIDS at Steve Biko Academic Hospital
INVESTIGATOR	**Principal Investigator:** Miss NCP da Cunha
Informed Consent Document	None
SUPERVISOR	Dr Joanne Potterton
DEPARTMENT	**Dept:** Physiotherapy - Steve Biko Academic Hospital **Phone:** 012 354 1645 **Fax:** 012 354 1041 **E-Mail:** mariodacunha@flysaa.com **Cell:** 072 465 4711
STUDY DEGREE	MSc Physiotherapy (Wits)
SPONSOR	N/A
MEETING DATE OF THIS STUDY	19/11/2008

This **Protocol** and **Informed Consent** have been considered by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria on 19/11/2008 and found to be acceptable.

* *Members attended & Feedback at the meeting .*

Dr A Nienaber	(female) BA (Hons) (Wits); LLB; LLM (UP); Dipl.Datametrics (UNISA)
*Prof V.O.L. Karusseit	MBChB; MFGP (SA); MMed (Chir); FCS (SA)
Prof M Kruger	(female) MB.ChB. (Pta); MMed. Pead. (Pret); PhD. (Leuven)
Dr N K Likibi	MB.BCh; Med.Adviser (Gauteng Dept.of Health)
*Dr T S Marcus	(female) BSc (LSE), PhD (University of Lodz, Poland)
*Mrs M C Nzeku	(female) BSc (NUL); MSc Biochem (UCL, UK)
*Snr Sr J. Phatoli	(female) BCur (Eet.A) BTec (Oncology Nursing Sience)Snr Nursing-Sister
*Dr L Schoeman	(female) BP harm, BA Hons (PSy), PhD
*Dr R Sommers	(female) MBChB; MMed (Int); MPharMed;
*Mr Y Sikweyiya	MPH; Master Level Fellowship in Research Ethics; BSC (Health Promotion) Postgraduate Dip in Health Promotion
Prof TJP Swart	BChD, MSc (Odont), MChD (Oral Path), PGCHE
*Dr A P van Der Walt	BChD, DGA (Pret) Director: Clinical Services of the Pretoria Academic Hospital
*Prof C W van Staden	MBChB; MMed (Psych); MD; FCPsych; FTCL; UPLM; Dept of Psychiatry

Dr R Sommers; MBChB; MMed (Int); MPhar.Med.
SECRETARIAT of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, Pretoria Academic Hospital

♦H W Snyman Building (South) Level 2-34♦P.O.BOX 667 Pretoria, South Africa, 0001♦Tel:(012)3541330♦
♦Fax: (012)3541367 / 0866515924♦E-Mail: manda@med.up.ac.za♦Web: //www.healthethics-up.co.za♦

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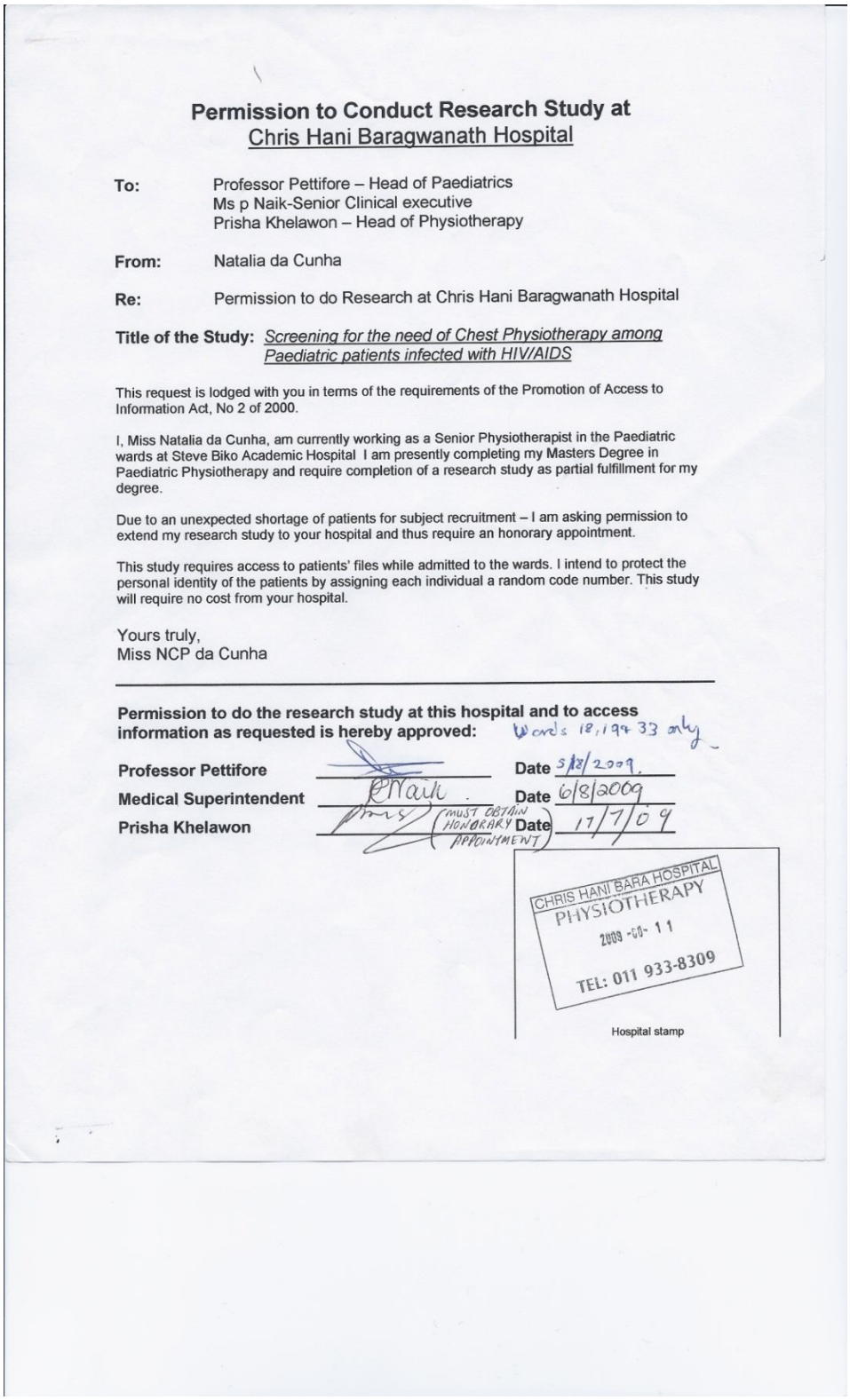
Appendix III: Consent from superintendants to conduct research at Chris Hani Baragwanath Hospital



Permission to Conduct Research Study at
Chris Hani Baragwanath Hospital

To: Professor Pettifore – Head of Paediatrics
Ms p Naik-Senior Clinical executive
Prisha Khelawon – Head of Physiotherapy

From: Natalia da Cunha

Re: Permission to do Research at Chris Hani Baragwanath Hospital

Title of the Study: *Screening for the need of Chest Physiotherapy among Paediatric patients infected with HIV/AIDS*

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act, No 2 of 2000.

I, Miss Natalia da Cunha, am currently working as a Senior Physiotherapist in the Paediatric wards at Steve Biko Academic Hospital I am presently completing my Masters Degree in Paediatric Physiotherapy and require completion of a research study as partial fulfillment for my degree.

Due to an unexpected shortage of patients for subject recruitment – I am asking permission to extend my research study to your hospital and thus require an honorary appointment.

This study requires access to patients' files while admitted to the wards. I intend to protect the personal identity of the patients by assigning each individual a random code number. This study will require no cost from your hospital.

Yours truly,
Miss NCP da Cunha

Permission to do the research study at this hospital and to access information as requested is hereby approved: Words 18,194 33 only

Professor Pettifore _____ **Date** 5/8/2009.

Medical Superintendent _____ **Date** 6/8/2009

Prisha Khelawon _____ (MUST OBTAIN HONORARY APPOINTMENT) **Date** 17/7/09

CHRIS HANI BARA HOSPITAL
PHYSIOTHERAPY
2009 -08- 11
TEL: 011 933-8309

Hospital stamp

Appendix IV: Consent from superintendants to conduct research at Steve Biko Academic Hospital

Permission to access Records / Files / Data base at

PRETORIA ACADEMIC Hospital / Clinic

TO: DR AP VD WALT [Name] FROM : MISS NCP DA CUNHA [Name]

Chief Executive Officer/Information Officer Investigator

PRETORIA ACADEMIC HOSPITAL
Hospital / Clinic

–
Hospital / Clinic OR University of Pretoria

Re: Permission to do research at PRETORIA ACADEMIC Hospital / Clinic

TITLE OF STUDY: RESPIRATORY CONDITIONS REQUIRING CHEST PHYSIOTHERAPY AMONG PAEDIATRIC PATIENTS INFECTED WITH HIV/AIDS AT PRETORIA ACADEMIC HOSPITAL

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a ~~researcher / student~~ SENIOR PHYSIOTHERAPIST at the Department of PHYSIOTHERAPY at the ~~University of Pretoria~~ / PRETORIA ACADEMIC Hospital. I am working with DR JOANNE POTTERTON (SUPERVISOR), I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. PATIENT FILES WHILST ADMITTED TO WARD

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria. & UNIVERSITY OF THE WITWATERSRAND.

Yours sincerely

N da Cunha
Signature of the Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved.

Title and name of Chief Executive Officer: DR MP MADIBELA

Name of hospital / clinic: STEVE BIKO ACADEMIC

Signature: _____

Date: 13.10.2008

, Title(s) and surname(s) of co-investigator(s) / supervisor(s)

GAUTENG PROVINCIAL GOVERNMENT
DEPARTMENT OF HEALTH
PRETORIA AKADEMIESE HOSPITAAL/ACADEMIC HOSPITAL
2008 -10- 13
PRIVAATSAK/PRIVATE BAG X169 PRETORIA 0001
GAUTENG PROVINCIAL GOVERNMENT
DEPARTMENT OF HEALTH

Appendix V: Data collection form

Entry number _____

Date of Admission _____

Age **Years** _____ **Months** _____

Gender **Male** _____ **Female** _____

Status of Current ARV therapy **Yes** _____ **No** _____

Drug combinations used _____

_____

_____

Length of drug use in months _____

Status of Previous ARV therapy **Yes** _____ **No** _____

Drug combinations used _____

_____

Mother's ARV use _____

_____

Patient's CD4 count _____

Viral load _____

Length of Hospital Stay in days _____

Date of Entry	Diagnosis of Respiratory Conditions	Need for Physio - according to Researcher	Need for Physio - according to Research Assistant

Appendix VI: Information sheet for caregivers

Information Sheet for Caregivers

Screening for the need of Chest Physiotherapy among Paediatric patients infected with HIV/AIDS

Dear Caregiver,

Thank you very much for taking the time to read this letter.

My name is Natalia da Cunha, I am a physiotherapist and I am doing research on children infected with HIV who also have lung illnesses. Research is the way that people, like me, working in the hospital can find the answer to a question about the patients' health. Physiotherapy can help with most lung illnesses because it can help loosen the secretions and help your child cough. This can be done by giving your child inhalations, clapping over the chest, vibrations and suctioning or assisted coughing, exercise and positioning correctly to improve the way your child breaths. In this study I want to learn what illness is affecting your child's lungs. This will help me understand the different illnesses that all the children have. I would like to learn this so that I, as a physiotherapist, can see which children need physiotherapy. I want to learn this from children with HIV because children with HIV have more chance of getting a lung illness. The answer to the question will help me or any other physiotherapist working with these children make sure that the children needing physiotherapy will receive it as soon as possible.

I am asking for your permission so that I can include your child in the research study. If you give me permission, then I would like to read the child's hospital file and then write down information that I can then use to find the answer to my question.

The child's name will not be used at all and I will not tell any person which children are part of the study. Only the child's hospital number will be written so that I do not mix the papers, but once I have added up all the results these papers will be destroyed.

No procedures will be done to your child except for normal physiotherapy if needed. As no procedures will be done there are no risks and no benefits involved if your child takes part in the study.

Participation in the study is voluntary – only if you want to. Physiotherapy is part of normal treatment for your child and should you not want to give permission for your child to take part in the study, your child will not be treated differently and will still receive normal physiotherapy treatment.

You will not be paid should your child be part of the study.

The Research Ethics Committee from the University of Witwatersrand and University of Pretoria have approved the study and will monitor the quality of the study.

You are encouraged to ask any questions throughout the study and if you would like to see the results of the study you are welcome to ask for them.

Please feel free to contact me 072 465 4711

Miss Natalia da Cunha

Physiotherapist

Appendix VII: Consent form

Consent documents for Caregivers

Title of Research: *Screening for the need of Chest Physiotherapy among Paediatric patients infected with HIV/AIDS*

I, the caregiver of the child, have read the attached information sheet and understand the procedure of the study and what is required of me. I understand that I am free to refuse or to withdraw my consent and discontinue the child's participation any time. I have had due chance to query any additional information and have had a reply. I understand that if I have any more questions at any time they will be answered. By refusing to take part in this study I understand that the child's treatment received in the hospital will not be affected. I also understand that I will not get paid for taking part in this study, and that the child's name will be kept confidential.

Entry number: _____

Caregiver:

Signiture: _____ Print name:_____ Date: _____

Witness :

Signiture: _____ Print name:_____ Date: _____

Investigator :

Signiture: _____ Print name:_____ Date: _____

Verbal Informed Consent

I, the undersigned, have read and have fully explained the information leaflet, which explains the nature and process of the study to the caregiver whom I have asked to provide consent for their child to partake in the study.

The caregiver indicates that s/he understands that the results of the study, including personal details will be anonymously processed into a research report. The caregiver indicates that s/he has had time to ask questions and has no objection to the inclusion of his/her child's medical information in the study.

S/he understands that should s/he wish to withdraw from the study the patient's treatment in hospital will not be affected in any way. I hereby certify that the caregiver has agreed to provide consent for the child to participate in the study.

Entry number: _____

Caregiver:

Signiture: _____ Print name:_____ Date: _____

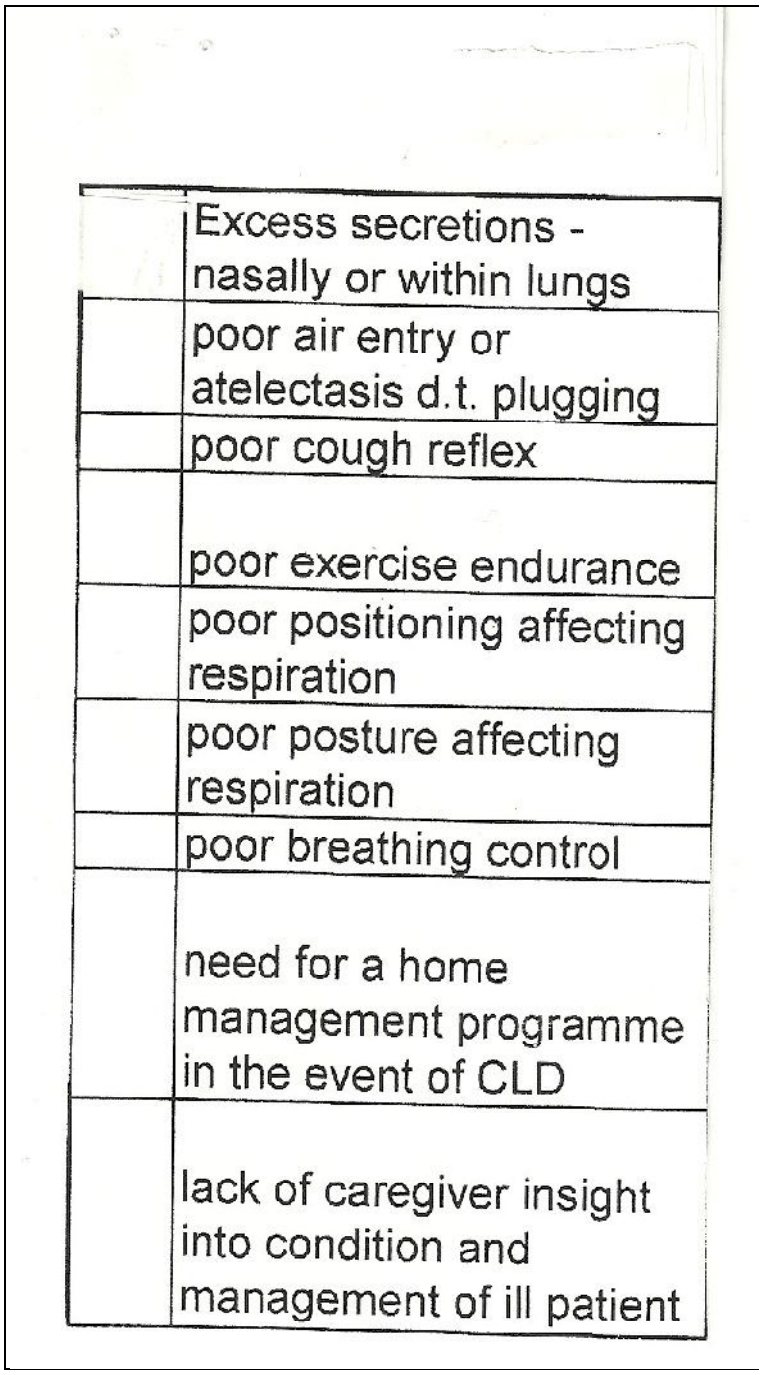
Witness :

Signiture: _____ Print name:_____ Date: _____

Investigator :

Signiture: _____ Print name:_____ Date: _____

Appendix VIII: Guidelines for the indication of physiotherapy treatment



	Excess secretions - nasally or within lungs
	poor air entry or atelectasis d.t. plugging
	poor cough reflex
	poor exercise endurance
	poor positioning affecting respiration
	poor posture affecting respiration
	poor breathing control
	need for a home management programme in the event of CLD
	lack of caregiver insight into condition and management of ill patient