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Chest X-Ray Findings in HIV Infected Children Starting HAART at a Tertiary Institution in South Africa

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

Johannesburg, 2013

DECLARATION

I, Nasreen Mahomed, declare that this research report is my own work. It is being submitted for the degree of Masters of Medicine (Diagnostic Radiology) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



_____

Signature of Candidate

9 day of September 2013

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

1. Mahomed N, Andronikou S, Naidoo J, Mbakaza M, Moultrie M, Van Rie A, Sawry S. Chest X-Ray Findings in HIV Infected Children Starting HAART at a Tertiary Institution in South Africa. Oral paper. First RSSA / SASPI Paediatric Imaging Congress 9-11 November 2012, Sandton, Gauteng. Abstracts published in SAJR 787 (pg 84)

ABSTRACT

INTRODUCTION: There is limited information on the radiographic presentation of children eligible to start HAART in resource-limited settings. **OBJECTIVES:** Determine radiographic patterns on pre-HAART chest X-rays (CXRs) in children, compare findings in immune-suppressed vs. non immune-suppressed children, compare the percentage of children with radiographic features of pulmonary TB to the percentage of children on TB treatment and assess inter-observer agreement between 3 radiologists. **METHODS:** Children (0-8 years) participating in a cohort study of TB and BCG-IRIS who had an acceptable routine pre-HAART CXR were included. CXRs were independently assessed by 3 radiologists, blinded from clinical data, using a standardised assessment form. All 3 readings were used to create a majority consensus finding during the data analysis phase. **RESULTS:** Amongst 161 children, the median age at enrolment was 2.3 years (25% (41/161) were <1year), 54% (87/161) were on TB treatment and 65% (100/154) were immune-suppressed. The majority (71%) had an abnormal CXR finding, predominantly air space disease (42%) and parenchymal interstitial disease (21%). Of the sub-group of 112 (70%) CXRs that could be assessed for lymphadenopathy, 75(67%) had one or more features suggestive of TB (74 lymphadenopathy, 2 cavities, 18 miliary infiltration) and 65% (70/107) were immune-suppressed. Statistically significant differences between immune-suppressed and non-immune-suppressed children were noted for features of lymphadenopathy and radiographic pulmonary TB. Amongst the sub-group of 112 CXRs a high percentage 49/75 (65%) were on TB treatment, with 26/75 (35%) not on TB treatment. Inter-observer agreement between all 3 readers was fair for overall abnormal CXR findings (K=0.23), airspace disease (K=0.22), moderate for parenchymal interstitial disease (K=0.54) and slight for lymphadenopathy (K=0.05).

CONCLUSION: Among children eligible to start HAART, most (71%) presented with abnormal CXR findings and the majority (67%) had one or more CXR signs suggestive of TB. Of concern was the high proportion of CXRs (30%) that were of insufficient quality to be assessed for lymphadenopathy and the poor inter-observer agreement for lymphadenopathy.

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TABLE OF CONTENTS

DECLARATION i
PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY ii
ABSTRACT iii
ACKNOWLEDGEMENTS v
TABLE OF CONTENTS vi
LIST OF TABLES ix
LIST OF FIGURES x
NOMENCLATURE x
1 INTRODUCTION 1
1.1 HIV Burden in South Africa 1
1.2 Immune Suppression and HAART Eligibility in HIV Infected Children in South Africa 1
1.3 The Role of the Chest X-Ray in HIV Infected Children 2
1.4 Etiology and Presentation of Chest X-Ray Abnormalities in HIV Infected Children 2
1.4.1 Pulmonary Infections 2
1.4.2 Non- infective Pulmonary Disease 7
1.5 Critical Review of Chest X-Ray Findings in HIV Infected Children 9
1.5.1 Overall prevalence of abnormalities on chest X-ray in HIV infected children 9
1.5.1 Specific abnormalities detected on chest X-rays in HIV-infected children 9
1.5.2 Association between chest X-ray abnormalities and immune suppression 11
1.6 Inter-Observer Agreement of Chest X-Ray Readings in Children 12
1.7 Summary 13
1.8 Study Objectives 15
2 MATERIALS AND METHODS 16
2.1 Study Population and Study Site 16
2.2 Study Design 16
2.3 Study Period 16
2.4 Inclusion and Exclusion Criteria 16
2.4.1 Inclusion criteria 16
2.4.2 Exclusion criteria 17

2.5 Immune suppression 17
2.6 Pre-HAART chest X-ray: 18
2.7 Chest X-Ray Reading Procedures 18
2.8 Radiographic Parameters 18
2.9 Data Collection and Collation 19
2.10 Data Analysis 20
2.11 Ethical Clearance 21
3 RESULTS 22
3.1 Demographic and baseline characteristics 22
3.2 Radiographic Patterns in Paediatric HIV 24
3.3 Pre-HAART Chest X-Ray Findings in Immune Suppressed vs Non Immune Suppressed Children 25
3.4 Radiographic, clinical and immunological features of the subgroup of children evaluated for lymphadenopathy and radiographic PTB 26
3.5 Inter-Observer Agreement of Paediatric Chest X-ray Readings 27
3.5.1 Inter-Observer agreement between 3 readers 27
3.5.2 Inter-Observer Agreement between 2 readers 28
4 DISCUSSION 31
4.1 Radiographic Findings 31
4.1.1 Quality of Chest X-rays 31
4.1.2 Radiographic Patterns in Paediatric HIV 31
4.2 Pre-HAART Chest X-Ray Findings in Immune Suppressed vs. Non Immune Suppressed Children 32
4.3 Radiographic, clinical and immunological features of the subgroup of children evaluated for lymphadenopathy and radiographic PTB 32
4.4 Inter-Observer Agreement on Paediatric Chest X-Rays 34
4.5 Radiographic Findings in Comparison to Other Studies 36
4.6 Study Limitations 40
4.7 Recommendations 40
4.7.1 Improve the quality of paediatric chest radiographs. 40
4.7.2 Improve inter-reader agreement 41
5 CONCLUSIONS 42

6 APPENDICES 44
6.1 APPENDIX 1: WHO Clinical Staging of HIV/AIDS for children with confirmed HIV[8] 44
6.2 APPENDIX 2: Informed Consent form used in the THINK study 46
6.3 APPENDIX 3: Child Assent Form used in the THINK study 53
6.4 APPENDIX 4: Ethics Committee Clearance Certificate 56
6.5 APPENDIX 5: Data Collection Sheets 57
7 REFERENCES 59

LIST OF TABLES

Table #	Table Heading	Page #
Table 1.1	Comparison between the 2004 and 2010 South African National HAART guidelines for infants and children	2
Table 2.1	Radiographic parameters assessed on chest X-rays	19
Table 2.2	Kappa value interpretation by Landis and Koch, 1977	21
Table 3.1	Demographic and clinical characteristics of all children and the sub-group	23
Table 3.2	Radiographic findings using a majority consensus reading	24
Table 3.3	Comparison of immune suppressed vs. non-immune suppressed children for all radiographic findings (excluding lymphadenopathy and radiographic pulmonary TB)	25
Table 3.4	Comparison of immune suppressed vs. non-immune suppressed children for lymphadenopathy and radiographic pulmonary TB	26
Table 3.5	Radiographic, clinical and immunological features of the sub-group of children evaluated for radiographic pulmonary TB	27
Table 3.6	Inter-observer agreement between 3 readers for each radiographic parameter	28
Table 3.7	Inter-observer agreement between 2 readers (reader 1 and 2) for each radiographic parameter	29
Table 3.8	Inter-observer agreement between 2 readers (reader 2 and 3) for each radiographic parameter	29
Table 3.9	Inter-observer agreement between 2 readers (reader 1 and 3) for each radiographic parameter	30
Table 4.1	Inter-Observer Agreement of Paediatric Chest X-rays, a comparison to the literature	36
Table 4.2	Radiographic Findings in Comparison to Literature	39

LIST OF FIGURES

Fig #	Figure Heading	Page #
Figure 3.1	Flow diagram illustrating all children and the sub-group	23

NOMENCLATURE

CMV	Cytomegalo -virus
CT	Computerized Tomography
HAART	Highly Active Antiretroviral Treatment
IRIS	Immune Reconstitution Inflammatory Syndrome
IQR	Interquartile Ratio
K	Kappa
LIP	Lymphocytic Interstitial Pneumonitis
MAC	Mycobacterium Avium Complex
MDR	Multidrug resistant
MRI	Magnetic Resonance Imaging
NHLS	National Health Laboratory Service
PJP	*Pneumocystis Jiroveci* Pneumonia
RSV	Respiratory syncytial virus
SD	Standard Deviation
TB	Tuberculosis
THINK	TB, HIV, IRIS and Nutrition in Kids
WHO	World Health Organization

1 INTRODUCTION

1.1 HIV Burden in South Africa

HIV is a global pandemic. According to the World Health Organization (WHO) AIDS Epidemic Update 2008, 33.4 million people were living with HIV worldwide and 2.1 million were children younger than 15 years[1]. Of the 430 000 new infections in children younger than 15 years, 91% occurred in sub-Saharan Africa[1]. South Africa had the largest worldwide population living with HIV, at 5.7 million in 2009, including 280 000 children younger than 15 years[2, 3].

1.2 Immune Suppression and HAART Eligibility in HIV Infected Children in South Africa

In 2004, the South African government launched its accelerated national AIDS response, and as at 2012, South Africa had the largest Highly Active Antiretroviral Treatment (HAART) program in the world[2]. Between 2004 and 2012, the South African National HAART Guidelines have changed twice[4, 5]; reflecting and adapting to changes in the WHO guidelines[6] over the same time period. A comparison of the two sets of guidelines (Table 1.1) reveals a shift in the age of HAART initiation to much younger children and towards initiating HAART in children who are less immune-compromised to facilitate better clinical outcomes in HIV-infected children[4, 5, 7].

Despite the sophisticated nature of the HAART guidelines adopted by the South African National Government, resource limitations are still an impediment to treatment initiation, with limited access to treatment; an estimated 46% of HIV infected children younger than 15 years are not receiving HAART despite being eligible according to the latest South African National HAART guidelines[2, 3].

Table 1.1: Comparison between the 2004 and 2010 South African National HAART guidelines for infants and children[4, 5]

2004 Guidelines		2010 Guidelines	
<18 months	CD4 % <20%	<1 year	All children should initiate HAART
>18 months	CD4 % <15%	1-5 years	WHO Stage 3,4* or CD4%<25% or CD4 absolute count<750 cells/mm^3
All children	WHO Stage 2,3*	>5 years	WHO Stage 3,4* or CD4 absolute count < 350 cells/mm^3

*A comprehensive description of the WHO clinical staging criteria[8] is provided in Appendix 1

1.3 The Role of the Chest X-Ray in HIV Infected Children

Respiratory tract infections, in particular pulmonary TB, are common in HIV infected children who have been shown to have an eleven-fold risk of developing acute lower respiratory tract infections compared to uninfected children[9-12]. The primary cause of death in most HIV infected children is pulmonary disease[10,13,14]. The diagnosis of most pulmonary disease is confirmed using chest X-rays. As a result, the South African National HAART Guidelines recommend that chest X-rays are routinely performed before the initiation of HAART to provide a radiological baseline, to either exclude or diagnose pulmonary Tuberculosis (TB) and to assess acute and chronic lung disease[4,5]. In addition, follow up chest X-rays are used to monitor treatment response to HAART, which include the development of Immune Reconstitution Inflammatory Syndrome (IRIS)[15,16].

1.4 Etiology and Presentation of Chest X-Ray Abnormalities in HIV Infected Children

1.4.1 Pulmonary Infections

More than 70% of HIV infected children will suffer at least one episode of a pulmonary infection in the course of their illness[17]. While chest X-ray findings are non-specific for a

pathogen, a combination of clinical findings with pattern recognition on chest X-ray narrows the differential diagnosis and expedites disease management[17].

1.4.1.1 Pulmonary TB

TB is the most common opportunistic infection in HIV infected patients[3, 11]. The HIV epidemic has led to the resurgence of TB incidence by 300 to 400% in some sub-Saharan countries[3, 18]. South Africa has one of the highest HIV/TB co-infection rates (75%) in the world, with TB being the leading cause of death in HIV infected adults and children[3, 18, 19]. In children the risk of TB disease increases with severe immune suppression[16, 19]. HIV and TB co-infection results in increased HIV viral replication and disease progression with other associated co-infections. Therefore HIV infected children have an increased risk of developing complicated pulmonary TB or disseminated TB compared to uninfected children[19].

The diagnosis of TB is difficult in HIV infected children with non-specific clinical signs and limitations to the use of the tuberculin skin test[17, 19]. In addition, sputum smear microscopy from gastric washings and induced sputa have a low yield (4-7%),[20] with TB culture producing yields of 30-40%[21, 22, 23]. As a consequence of the difficulty in obtaining microbiological confirmation of TB in children, the diagnosis often relies on clinical and radiological investigations[22].

Chest X-rays are the standard radiologic modality in South Africa for excluding pulmonary TB[4, 5, 17 ,19]. However radiographic findings may be nonspecific for pulmonary TB[22]. Certain radiographic patterns such as lymphadenopathy with airway compression, miliary disease or pulmonary cavitation are associated with pulmonary TB[22]. While lymphadenopathy is the radiological hallmark of pulmonary TB on chest X-ray, an important limitation is the wide inter- and intra-observer variability, as reported in several studies[17, 19, 22, 24]. Computerized

Tomography (CT) is the international modality of choice for detection of lymphadenopathy but has a higher radiation exposure and has a limited role in countries with a high TB burden and limited resources[17, 19, 22]. The role of Magnetic Resonance Imaging (MRI) in the detection of lymphadenopathy in the chest is currently being investigated for sensitivity and feasibility in routine settings[17, 19].

Parenchymal involvement is a non-specific finding in primary PTB and most commonly appears as an area of homogeneous consolidation in a segmental or lobar distribution, with patchy linear, nodular and mass like forms described on chest X-ray and CT chest. Pleural effusions are an uncommon manifestation of primary TB in infants and young children[17].

1.4.1.2 Bacterial Pneumonia

The common causal agents of bacterial pneumonia in HIV infected children are *Streptococcus pneumonia* and *Staphylococcus aureus*, which also occur in immune competent children[17]. The radiological appearance of bacterial pneumonia is independent of immune status and has two classic patterns: 1) diffuse patchy air-space disease in bronchopneumonia, and 2) confluent air-space disease with air bronchograms in lobar pneumonia. In addition, HIV infected children present with complications of pneumonia such as abscess formation and empyema[17]. HIV infected children also present with atypical pneumonias caused by uncommon pathogens like *Salmonella, Klebsiella, Pseudomonas* and *Escherichia coli* and have the added complexity of polymicrobial infections. Atypical pneumonias can have a wide range of radiographic appearances including reticulo-nodular infiltration, patchy or confluent air-space disease or a combination thereof[17].

1.4.1.3 *Pneumocystis Jiroveci* Pneumonia (PJP)

Pneumocystis jiroveci pneumonia (PJP) formerly known as *pneumocystis carinii* pneumonia is a common cause of severe pneumonia and death in HIV infected infants (peak age

incidence of 4–5 months) in sub-Saharan Africa[17]. PJP is a rapidly progressive disease in young infants, with a mortality rate of 40–50%[17]. Most patients with PJP have severe immune suppression with CD4 counts of <100 cells/mm3. PJP was the most common opportunistic infection in HIV infected infants prior to widespread prenatal HIV screening, trimethoprim-sulphamethoxazole prophylaxis and widespread HAART initiation[17, 19, 25].

Clinically, children present acutely with cough, tachypnea, hypoxia and fever. PJP may be difficult to diagnose on chest X-ray alone as radiographs may appear normal or may demonstrate diffuse bilateral peri-hilar interstitial infiltrates which may progress into airspace disease and/or bilateral air trapping. Less common chest X-ray findings include lymphadenopathy, nodules and mass lesions[17, 25]. Complications of PJP include pneumothorax and pneumomediastinum while pleural effusions are uncommon. Differential diagnoses include Lymphocytic Interstitial Pneumonitis (LIP), *Mycobacterium Avium Complex* (MAC) and viral pneumonias, including Cytomegalovirus (CMV) and *Epstein-Barr virus*[17].

1.4.1.4 Viral pneumonias

HIV infected children demonstrate signs of consolidation on chest X-ray more frequently than non-infected children[17]. Viral pathogens responsible for pneumonia include *respiratory syncytial virus* (RSV), influenza, CMV, Varicella Zoster and measles[17].

RSV pneumonia infection is commonly complicated by secondary bacterial pneumonia and associated with a higher mortality rate in HIV infected compared to HIV uninfected children in Africa[17]. On chest X-ray the predominant finding is diffuse, patchy or nodular air-space disease; interstitial infiltrates are uncommon[17].

CMV pneumonia is the third most common finding after pneumonia and PJP in HIV infected infants [17]. PJP co-infection is common. Chest X-rays can be normal in early infection or may

demonstrate reticular patterns, reticulo-nodular patterns, air-space consolidation or combinations of these patterns. Complications include bronchiectasis, thick-walled cavities and pleural effusions[17].

Severely immune-suppressed HIV-infected children have a higher incidence of pneumonia due to measles. Chest X-rays demonstrate progressive bilateral diffuse interstitial and alveolar infiltrates [17].

The incidence of Varicella Zoster pneumonia in immune-compromised children is 40%. The most common chest X-ray finding is bilateral reticulo-nodular infiltrates. Other presentations include lobar pneumonia or military infiltrate[17].

Herpes simplex type 1 pneumonia is a rare infection and predominantly affects immune compromised patients. Polymicrobial infection occurs in up to 33% of patients. Chest X-ray findings include a diffuse segmental or sub-segmental mixed ground-glass opacities and nondependent consolidation. Pleural effusions can occur but cavitation is not a feature of herpes pneumonia[17].

1.4.1.5 Immune reconstitution inflammatory syndrome (IRIS)

IRIS is defined as a paradoxical worsening of symptoms and radiological signs due to recovery of the immune system, and is not due to recurrence or relapse of disease/infection[14, 19]. IRIS is commonly seen in patients with HIV and TB co-infection and may be seen with different mycobacterial organisms and CMV infection[14,19]. IRIS occurs secondary to HAART-related immune reconstitution that leads to an abnormal immune response to antigens from dead or dying bacilli. IRIS can occur weeks to months after HAART initiation[14, 19]. IRIS presents radiologically as new or worsening hilar or mediastinal lymph nodes in 73% of patients and about 55% of patients present with pulmonary nodule (<3 mm

in size) enlargement. Worsening of pulmonary infiltrates may also occur. It is important but radiologically difficult to distinguish IRIS from multidrug-resistant TB and other infections[14].

1.4.2 Non- infective Pulmonary Disease

Non-infective, chronic pulmonary disease is common in HIV infected children, increases with age and involves a wide variety of diseases and imaging findings[14].

1.4.2.1 Lymphocytic Interstitial Pneumonia (LIP)

LIP is common in HIV-infected children, occurring in 30-40% of children[14, 19], typically older than 2 years[14]. The etiology is unknown but serological data suggests that co-infection with Epstein-Barr virus produces a lympho-proliferative response. Children develop chronic coughs, tachypnea, clubbing and hypoxia[14, 19].

Lympho-proliferation also occurs in other organs resulting in generalized lymphadenopathy, bilateral non-tender parotid enlargement and hepatosplenomegaly. Pathologically there is chronic CD8 lymphocytic infiltration of the lungs and associated organs. Corpulmonale, bronchiectasis or cysts may complicate LIP[14, 19].

Chest X-rays often show a centrally pronounced diffuse, symmetrical reticulo-nodular or nodular pattern which may be difficult to distinguish from pulmonary or miliary TB[14, 19, 20]. This can progress to air-space consolidation. There may be associated lymphadenopathy but unlike TB there is no airway compression[14]. Isolated peri-bronchiolar thickening or normal chest X-rays may also occur in LIP [19]. Improvement of the reticulo-nodular opacification may be either due to HAART, corticosteroid therapy or due to immunological deterioration and progression of HIV disease[14, 19].

The role of nuclear scanning in confirming the diagnosis has not been well studied, but diffuse pulmonary gallium uptake has been reported in children with LIP. Definitive

diagnosis is by lung biopsy; demonstrating interstitial infiltrate of lymphocytes and lymphoid aggregates surrounding the airways[19].

1.4.2.2 Pulmonary Kaposi's sarcoma

Pulmonary Kaposi's sarcoma is rare in children[14]. However in HIV infected African children Kaposi's sarcoma is a common AIDS defining malignancy, due to the high prevalence of human herpes virus 8 infections[19]. Kaposi's sarcoma can affect the lung parenchyma, trachea, bronchi, pleura, hilar or mediastinal lymph nodes. Chest X-ray findings include lymphadenopathy (with airway compression), diffuse bilateral peri-hilar and lower zone infiltration (either air-space or interstitial reticular opacification) and pleural effusions[14, 19].

1.4.2.3 Lymphoma

The most common AIDS related neoplasm is non-Hodgkin B cell lymphoma, and is considered to be the malignant variety of B cell proliferative disorders such as LIP. Clinically, patients present with dyspnea, cough and recurrent pneumonia[14]. Extra-nodal disease, including lung involvement is more common in immune-compromised patients compared to immune-competent patients. Intra-thoracic lymphoma is part of disseminated disease[14]. Children usually present with hilar or mediastinal masses on chest X-rays, usually without parenchymal involvement. Reticulo-nodular involvement is more common in adults and is due to direct extension from mediastinal lymph nodes[14].

1.4.2.4 Aspiration pneumonia

HIV infected children can have a nonspecific motility disorder associated with dysfunctional swallowing that causes aspiration[14] and they also have an increased incidence of gastro-esophageal reflux[14, 26]. Chronic aspiration causes segmental or sub-segmental pulmonary infiltrates, peri-bronchial thickening and hyperinflation on the chest X-ray; most commonly

seen in the apical and basal segments of the lower lobes and the posterior segment of the upper lobes. Chronic aspiration may cause bronchiectasis[14].

1.5 Critical Review of Chest X-Ray Findings in HIV Infected Children

1.5.1 Overall prevalence of abnormalities on chest X-ray in HIV infected children

Very few studies have been published on the prevalence of chest X-ray abnormalities in children initiating HAART. Two studies in Africa investigating pre-HAART chest X-ray findings by Du Plessis *et al* (South Africa) and Kouakoussui *et al* (Ivory Coast) found a similar overall prevalence of chest X-ray abnormalities of 46 %[16] and 51%[10], respectively. Whilst Sheik *et al* (USA) reported a comparable prevalence of 45.7%, the HAART status of the participants was unreported at the time of abnormality detection[27]. In these 3 studies the commonest finding was air space consolidation [10, 16, 27]. In the prospective study by Nortan *et al* (USA), where 90% of children where on HAART during some time of the study, a cumulative incidence of 32.8% chronic lung changes by age 4 years was found[12]. In adolescent children (aged 10 to 18 years) with vertically-acquired HIV, where 36% of children were on HAART, Desai *et al* (Zimbabwe) reported a 68% prevalence of chest X-ray abnormalities, with 56.0% presenting with bronchiectasis and ring/tram line opacities [28].

1.5.1 Specific abnormalities detected on chest X-rays in HIV-infected children

Du Plessis *et al* found a high prevalence of parenchymal disease (34%), which was predominantly air space disease (28%) and mediastinal disease (22%) which was predominantly cardiomegaly in (21%) of children. Focal air space disease was present in (15%), diffuse air space disease in (13%), air trapping (10%), and bronchial disease (7%). Lymphadenopathy and pleural disease was very low at (1%) each[16]. Du Plessis *et a*l defined radiographic pulmonary TB as the presence of lymphadenopathy (with or without calcification), and/or nodular disease (miliary or larger), and/or cavitation (including

bronchiectasis). They found radiological appearances of TB in (9%) of children, all of whom were in the more severe clinical categories (WHO stages 3 and 4)[16].

Nortan *et al* defined chronic lung changes as either focal or diffuse parenchymal consolidation or nodular disease that lasted more than 3 months, increased broncho-vascular markings or reticular densities that lasted more than 6 months. Transient increased interstitial changes were the commonest overall finding, present in (41.8%) of children[12]. LIP (nodular densities on chest X-ray) was reported in (19.3%) of children, followed by PJP (consolidation on chest X-ray) in (6%) of children. Pulmonary TB was reported in only (2.4%) of patients, presenting with nodular densities on chest X-ray. In children with chronic lung disease there was an increased incidence of parenchymal consolidations (37.5% versus 36.8%) and nodular densities (40.6% versus 36.8%) in the group older than 28 days compared to a decreased incidence of broncho-vascular markings or reticular densities (62.5% versus 63.2%)[12].

Desai *et al*, investigating adolescents with HIV, found that the prevalence of consolidation was associated with hospitalization for respiratory distress (p value <0.005) whereas ring/tramline opacities did not differ significantly (p=0.21) between in- and out-patient subgroups suggesting that this pattern, which was the predominant finding in this study, may represent a form of chronic lung disease[28].The authors used the Fleischner Society: Glossary of Terms for Thoracic Imaging criteria for Chest X-ray reporting and the overall inter-observer agreement was good (K =0.87-0.91). The study findings are not generalizable to non-hospitalized patients as the majority of the patients included were hospitalized (78.6%)[28].

In the study by Sheik *et al*, bronchiectasis on chest X-ray was defined as an increase of pulmonary markings, loss of lung volume, bronchial wall thickening with dilatation, honeycombing or cystic spaces. Bronchiectasis was found in (15.8%) of chest X-rays. The

commonest association with bronchiectasis was with LIP followed by unresolved pneumonia and recurrent pneumonia. One child developed bronchiectasis after *PJP* and TB [27].

1.5.2 Association between chest X-ray abnormalities and immune suppression

Du Plessis *et al* described a statistically significant negative association between immune suppression and air space disease (p=0.049) with a relative risk of 0.46 (95 % CI 0.24-0.88) on pre-HAART chest X-rays[16]. The presence of air space disease correlated with a higher level of immunity which implied that patients with immune suppression were less likely to present with parenchymal air space disease[16].

In the prospective study by Nortan *et al* where 90% of patients were on HAART at some time during the study, a 3 month time interval was used to correlate radiographic findings with CD4 counts and viral loads[12]. Viral loads remained stable after children were 2 months old while CD4 counts declined after 15 months and were stable by 21 months. Initially Nortan *et al* found that HIV infected children with significantly lower mean CD4 counts and higher viral loads had an increased incidence of chronic radiographic lung changes. However, these changes resolved over time in many children with significantly lower CD4 counts, suggesting that the ability to mount an immune response within the lungs and resultant radiographic changes may decrease over time. This resolution of radiographic findings was not associated with any clinical improvement[12].

In contrast Kouakoussui *et al* found a lower incidence of respiratory infection in children on HAART that was statistically significant in severe immune suppressed children (CD4 <5%) and children > 5 years old[10]. Sheik *at al* also found that the development of bronchiectasis was associated with the severity of immune suppression; among the 23 children with bronchiectasis, all had CD4counts less than 100 cells/mm [27].

1.6 Inter-Observer Agreement of Chest X-Ray Readings in Children

Inter-observer agreement is based on the calculated kappa (*K*) values with its 95% confidence interval. The *K* test measures agreement between observers, ignoring the possibility that the observers agree by chance[29].

Inter-observer agreement in radiology is dependent on the experience and degree of training of the reader, standardization of techniques and the quality of chest X-rays[30-32]. Overall inter-observer agreement of paediatric chest X-ray readings is fair to moderate (*K*=0.21-0.60) while variability of individual radiographic features is slight (*K*=0.01-0.20)[30-33]. Inter-observer agreement is better between trained radiologists compared to the inter-observer agreement between radiologists and clinicians[30-32].

A South African study by Du Toit *et al* investigated inter-observer and intra-observer agreement of lymphadenopathy detection in chest X-rays of 100 children, amongst 4 paediatric pulmonologists. They found a fair inter-observer agreement (average *K* =0.33) and moderate intra-observer agreement (*K*=0.44-0.71) among paediatric pulmonologists in detecting lymphadenopathy on chest X-rays[24].

Inter-observer agreement for lymphadenopathy (*K* =0.33) was lower compared to other radiographic features of respiratory infection; with bronchial wall thickening (*K*=0.43-0.55) having moderate agreement and consolidation (*K*=0.46- 0.79) and hyperinflation (*K*=0.78-0.83) having substantial agreement[24]. Due to the high inter-observer and intra-observer variation of lymphadenopathy detection in chest X-rays, the authors suggested caution when basing clinical decisions on the presence of lymphadenopathy on chest X-rays[24]. However the authors reported a higher agreement for lymphadenopathy compared to the literature[30-33], since all readers had similar backgrounds and training, experience at assessing chest X-rays

and worked in the same institution which has one of the highest incidences of childhood TB in the world[24].

1.7 Summary

Respiratory tract infections, particularly pulmonary TB, are common in HIV infected children[3, 9-11]. The primary cause of death in HIV infected children is pulmonary disease and is the most common clinical feature of HIV[17]. Chest X-rays are routinely performed before the initiation of HAART to provide a radiological baseline, to exclude pulmonary TB and to assess acute and chronic lung disease. Follow up chest X-rays are used to monitor treatment response to HAART, which include the development of IRIS[14-16, 19].

The diagnosis of pulmonary TB in childhood is difficult with limited sensitivity of the tuberculin skin test, acid fast bacilli smear microscopy and TB culture. Hence the diagnosis is often made in conjunction with history of exposure, clinical findings, radiographic findings and laboratory data[17, 19-23]. Certain radiographic patterns such as lymphadenopathy with airway compression, miliary disease and pulmonary cavitation are associated with pulmonary TB[22]. In countries with a high prevalence of TB and HIV, pulmonary TB and LIP may co-exist. Both conditions may produce a bilateral symmetrical reticulo-nodular pattern on chest X-ray which may be difficult to distinguish from each other[17, 19].

There is significant overlap in the chest X-ray findings in HIV infected children from infectious and non-infectious causes[14, 17, 19, 20, 24]. While chest X-ray findings may be non-specific for a pathogen, a combination of clinical findings with pattern recognition on chest X-ray narrows the differential diagnosis and expedites disease management[17].

Published findings demonstrate a high prevalence (45%-68%) of chest X-ray abnormalities in HIV infected children[10, 12, 16, 27, 28]. The commonest finding is pneumonia (28%-45%), while the prevalence of radiographic pulmonary TB is low (2.4%-9%). The prevalence of chronic lung changes varies between studies (5%-56%)[10, 12, 16, 27, 28].

There is conflicting literature on the association between chest X-ray findings and immune suppression. A prospective study, where 90% of children were on HAART, demonstrated a negative association between immune suppression and chest X-ray abnormalities i.e lower immunity means a child is more likely to have a normal chest X-ray[12]. This study suggests that the ability to mount an immune response within the lungs and produce radiographic changes may decrease with immune suppression[12]. This is in contrast to the 2 studies that reported a lower incidence of respiratory infections and bronchiectasis in children on HAART i.e. children with lower immunity had increased chance of abnormal chest X-ray findings, with features of infection and bronchiectasis [10, 27].

Inter-observer agreement in radiology is dependent on the experience and degree of training of the reader, standardization of techniques and the quality of chest X-rays[30, 31, 32]. Inter-observer agreement of paediatric chest X-ray readings is fair to moderate, while agreement of individual radiographic features is slight[30, 31, 32, 33]. Lymphadenopathy has the poorest inter-observer agreement [24].

1.8 Study Objectives

1. To evaluate the pre-HAART chest X-rays in children at a tertiary HAART centre and determine the radiographic patterns in paediatric HIV

2. To compare the pre-HAART chest X-ray findings of immune suppressed vs. non immune suppressed children

3. To compare the percentage of children with radiographic features of pulmonary TB to the percentage of children on TB treatment

4. To determine inter-observer agreement of chest X-ray readings in children between 3 radiologists

2 MATERIALS AND METHODS

2.1 Study Population and Study Site

The study population is children initiating HAART at the Harriet Shezi Children's Clinic (a tertiary paediatric HAART centre) in Chris Hani Baragwanath Academic Hospital, Soweto (South Africa).

2.2 Study Design

This was a retrospective cross-sectional study nested within the THINK study (TB, HIV, Immune Reconstitution, and Nutrition in Kids)- a prospective cohort study investigating the incidence of TB- and BCG-IRIS in children initiating HAART at the Harriet Shezi Children's Clinic at Chris Hani Baragwanath Academic Hospital. The THINK study is ongoing and has enrolled children between the ages of 0-8 years at the time of initiating HAART and will follow them up for a period of 2 years. The pre-HAART chest X-rays from children enrolled in the THINK study were utilised for this study. The THINK study chest X-ray collection process commenced in September 2009.

2.3 Study Period

Pre-HAART chest X-rays were retrospectively read from 4 October 2011 to 2 May 2012

2.4 Inclusion and Exclusion Criteria

2.4.1 Inclusion criteria

a. Children enrolled in the THINK study aged 0 – 8 years. The age group of this study was limited by the inclusion criteria of the THINK study in which this study was nested. Eight years was used as the cut off for the THINK study as the incidence, clinical and radiological presentation of pulmonary TB is different in childhood compared to adolescence.

b. Available pre-HAART chest X-ray (frontal and lateral) during the study period.

2.4.2 Exclusion criteria

a. Chest X-rays were completely excluded if they were of an inadequate quality due to technical factors; i.e.: over- or under-exposed film, significant rotation, significant under-inspired film.

b. Chest X-rays were excluded for lymphadenopathy assessment when the airways, hilar or mediastinal areas were not visible.

2.5 Immune suppression

Immune suppression was determined using CD4% and CD4 absolute counts depending on the patient's age. CD4 percentage is defined as the number of CD4 cells expressed as a percentage of the total number of lymphocytes. In children, younger than 5 years, CD4 percentage is a better marker of level of immune suppression than the absolute CD4 count. Immune suppression was categorized as follows:

Children <5 years

- CD4 < 25% (immune suppressed)
- CD4 $\geq$25 % (not immune suppressed)

Children 5 years and older

- CD4 absolute count < 350 cells/mm^3 (immune suppressed)
- CD4 absolute count $\geq$350 cells/mm^3 (not immune suppressed)

2.6 Pre-HAART chest X-ray:

A pre-HAART chest X-ray was defined as a chest X-ray taken within 4 weeks of HAART initiation. As Harriet Shezi Clinic is a tertiary HAART center, children were generally referred from Chris Hani Baragwanath Academic hospital, where chest X-rays would have been taken at the time of hospitalization.

2.7 Chest X-Ray Reading Procedures

All available pre-HAART chest X-rays were read and reported on by 3 independent radiologists. The 3 chest X-ray readers were selected to represent paediatric radiologists in practice. The readers ranged in paediatric radiology experience from 3 years to 12 years of clinical practice. Chest X-rays were read by each reader independently, at separate sittings and all readers completed a standardised data collection form independently (Appendix 5). The readers were blinded to the level of immune-suppression, clinical signs, laboratory findings and to each other's findings. The readers were not given an opportunity to discuss their findings. A majority consensus reading (i.e. findings reported by at least 2 of the 3 readers per chest X-ray) was performed during the data analysis phase for each radiographic parameter.

2.8 Radiographic Parameters

Each reader evaluated the chest X-rays according to the parameters and sub-parameters defined in Table 2.1. They each indicated; on a standardised data collection form (Appendix 5), whether they detected the presence of any of the parameters.

Table 2.1: Radiographic parameters assessed on chest X-rays

Radiographic Parameters	Defined as one or more of the following sub-parameters
Air space disease	homogenous increase in parenchymal attenuation that obscures vessels and airway walls
Parenchymal interstitial disease	reticulo-nodular infiltrate or reticular infiltrate or large nodular infiltrate (nodules > 2mm) or miliary infiltrates (nodules < 2mm)
Bilateral air-trapping	more than 6 anterior ribs visible at mid-diaphragm
Chronic Lung Disease	bronchiectasis or cavities
Pleural reactions	blunting of costo-phrenic angles
Cardiomegaly	cardio-thoracic ratio >60% in children <2 years or >50% in children≥2 years
Lymphadenopathy	hilar or mediastinal masses or airway compressions or lobar collapses or unilateral air-trapping
Abnormal CXR*	Lymphadenopathy or Air space disease or Parenchymal interstitial disease or Chronic Lung Disease or Bilateral air-trapping or Pleural reactions or Cardiomegaly
Radiographic Pulmonary TB*	lymphadenopathy (+/- air-space disease) or miliary infiltrates (nodules <2mm) or cavities

***determined during data analysis phase**

2.9 Data Collection and Collation

All readers completed a standardised data collection form (Appendix 5) for each participant's set of frontal and lateral chest X-rays. At the end of the reading sessions, the reports were put into envelopes, sealed by the reader, collected by the principle investigator and delivered to an independent data capturer.

The data capturer captured all reports into an MS-Excel spread sheet.

Pre-HAART CD 4 results were obtained from the NHLS database or the patient's study file and data relating to age and TB treatment was obtained from the THINK study data base. Quality control of data entry was performed by the principle investigator after all the data was entered to verify the accuracy of the data.

An abnormal chest X-ray was defined by the presence of one or more of the chest X-ray parameters (Table 2.1) using a majority consensus reading – this was computed in MS-Excel. The MS-Excel spread sheet was exported to Epi Info 7 (CDC, 2012) for statistical analysis by the principle investigator.

2.10 Data Analysis

All analyses, besides Kappa values, were computed in Epi Info 7 by the principle investigator. These results were subsequently verified on Stata12 (StataCorp, College Station, Texas, USA) by the co-supervisor. All Kappa values were calculated by the co-supervisor on Stata 12.

The age range, median and inter-quartile range was calculated using a rank sum test for non-parametric data.

Radiographic parameter frequencies were computed with 95% confidence intervals.

Pre-HAART chest X-ray findings of immune suppressed vs. non immune suppressed children were compared using Pearson's Chi-square or Fisher's exact tests, as appropriate.

The Pearson's Chi-square test was used to compare the proportions of children on TB treatment to those children with radiographic features of pulmonary TB.

Kappa values were used to determine inter-observer agreement of chest X-ray readings between all 3 readers and between 2 readers.

Kappa values were interpreted according to Landis and Koch (1977) (Table 2.2).

Table 2.2: Kappa value interpretation by Landis and Koch, 1977 [29]

K value	Kappa Interpretation
K<0.00	Less than chance agreement
K=0.01–0.20	slight agreement
K=0.21–0.40	fair agreement
K=0.41–0.60	moderate agreement
K=0.61–0.80	substantial agreement
K=0.81–0,99	almost perfect agreement

2.11 Ethical Clearance

Ethics approval for this study was granted by the University of Witwatersrand Human Research Ethics Committee (Certificate #: M110729) (Appendix 4). Ethics approval for the THINK cohort study was granted by the University of Witwatersrand Human Research Ethics Committee (Certificate #: M081162).

3 RESULTS

3.1 Demographic and baseline characteristics

A total of 192 children enrolled in the prospective THINK study, were considered in this study for the chest X-ray reading period 4 October 2011 to 2 May 2012. Of these, 31 children were excluded: 7 children for inadequate chest X-rays as per the exclusion criteria and 24 children for not having pre-HAART chest X-rays available in the study or clinic file for reading.

Therefore, a total of 161 children were included for radiographic analysis. Of these, only 112 (70%) children could be assessed for lymphadenopathy as per the exclusion criteria: the airways, hilar or mediastinal areas were not visible on 49 chest X-rays. The 112 children that could be assessed for lymphadenopathy will henceforth be referred to as the sub-group. (Fig 3.1)

The mean age of the 161 included children was 3.1 years (SD: 2.4years) with 25% under 1 year at enrolment; 91 (57%) were male and 70 (43%) were female. The median age was 2.3 years (IQR: 1 - 4.8 years). Ages ranged from 0.1 to 8.6 years (Table 3.1).

Amongst the 161 children included in the full radiographic analysis, 7 (4.3%) had no pre-HAART CD4 results available. Of the 154 children with CD4 results available, 100 (65%) were immune suppressed (CD4% <25% in children less than 5 years or CD4 absolute count <350 cells/mm^3 in children 5 years and older) and 54 (35%) were non-immune suppressed. In the sub-group of 112 children where lymphadenopathy could be assessed, 5 (4.5%) children had no pre-HAART CD4 results available. Of those with available CD4 results, 70 (65%) were immune suppressed and 37 (35%) were non-immune suppressed (Table 3.1). Hence the percentage of immune suppressed children was the same for both groups.

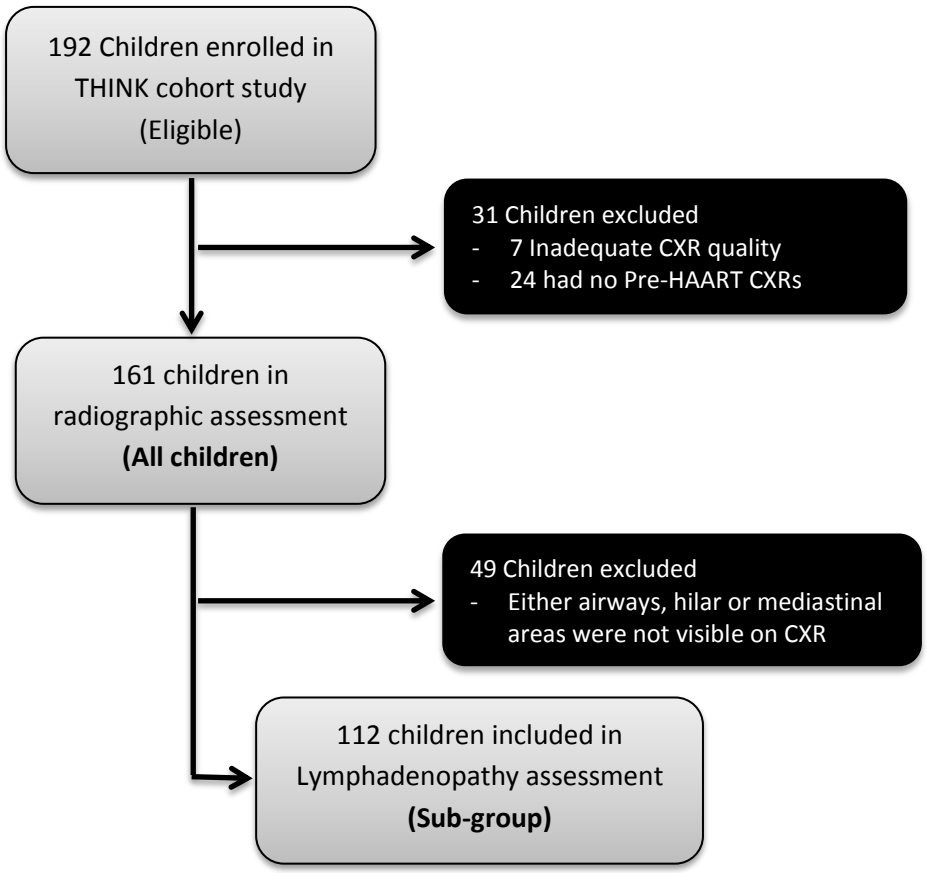


Fig 3.1: Flow diagram illustrating all children and the sub-group

Table 3.1: Demographic and clinical characteristics of all children and the sub-group*

Demographic and clinical characteristics	**All children N=161 n(%N)**	**Sub-group N=112 n(%N)**
Age		
Mean (SD)	3.1 years (2.4)	3.1 years (2.3)
Median (IQR)	2.3 years (1.0 to 4.8)	2.3 years (1.1 to 5.0)
Gender		
Males	91 (57%)	62 (55%)
Females	70 (43%)	50 (45%)
Immune suppressed	100[1] (65%)	70[2] (65%)

* Children evaluated for lymphadenopathy and pulmonary TB

[1] N=154; 7 children had no baseline CD4 counts available

[2] N=107; 5 children had no baseline CD4 counts available

3.2 Radiographic Patterns in Paediatric HIV

A majority consensus reading of 3 radiologists was used for all radiographic parameters during the date analysis phase. The findings for the radiographic parameters are summarised in Table 3.2.

The study demonstrated a high prevalence of (71.4%) of chest radiographic abnormalities in this group of HIV infected children. There was a high prevalence of air space disease (42.2%) followed by parenchymal interstitial disease (20.5%). There was a low prevalence of bilateral air trapping (4.4%), chronic lung disease (1.2%), pleural reactions (0.6%) and cardiomegaly (1.7%) (Table 3.2). Amongst the sub-group of 112 chest X-rays evaluated for lymphadenopathy and radiographic pulmonary TB, the commonest findings were lymphadenopathy (66.1%) and radiographic pulmonary TB (67.0%). Radiographic pulmonary TB comprised of lymphadenopathy 74/112, miliary infiltrate 18/112 and cavities 2/112. The frequencies of each of the radiographic parameters had narrow confidence intervals (Table 3.2).

Table 3.2: Radiographic findings using a majority consensus reading

	Radiographic Parameters	Frequency	%N	95% Confidence Interval
All Children (N=161)	Abnormal CXR*	115	71.4	63.8-78.2
	Air space disease	68	42.2	34.5-50.3
	Parenchymal interstitial disease	33	20.5	14.6-27.6
	Bilateral air trapping	7	4.4	1.8-8.8
	Chronic lung disease	2	1.2	0.2-4.4
	Pleural reactions	1	0.6	0.0-3.4
	Cardiomegaly	3	1.7	0.4-5.4
Sub-Group (N=112)	Lymphadenopathy	74	66.1	56.5-74.8
	Radiographic Pulmonary TB[#]	75	67.0	57.4-75.6

* Abnormal CXR includes lymphadenopathy

[#]Defined as the presence of either lymphadenopathy or miliary infiltrate or cavities

3.3 Pre-HAART Chest X-Ray Findings in Immune Suppressed vs Non Immune Suppressed Children

Of the 161 children that were evaluated for all radiographic parameters, 65% (100/154) were immune suppressed and there was no statistically significant difference (p >0.05) between the immune suppressed and the non-immune suppressed children for any of the parameters evaluated (Table 3.3).

Table 3.3: Comparison of immune suppressed vs. non-immune suppressed children for all radiographic findings (excluding lymphadenopathy and radiographic pulmonary TB)

Radiographic Finding	Immune Suppressed N=100 n(%N)	Non-Immune Suppressed N=54 n(%N)	Total N=154 n(%N)	p-value
Abnormal CXR	76(76)	34(63)	110(71)	0.087**
Air Space Disease	42(42)	24(44)	66(43)	0.770**
Parenchymal Interstitial Disease	24(24)	8(15)	32(21)	0.180**
Bilateral Air Trapping	3(3)	2(4)	5(3)	1.000##
Chronic Lung Disease	0 (0)	1(2)	1(1)	0.351##
Pleural Reactions	1(1)	0(0)	1(1)	1.000##
Cardiomegaly	2(2)	1(2)	3(2)	1.000##

** Pearson χ^2 test

Fisher's exact test

In the sub-group of 112 children that were evaluated for lymphadenopathy and radiographic pulmonary TB, 65% (70/107) were immune suppressed (Table 3.1). There was a statistically significant difference for the presence of lymphadenopathy (p =0.041) and radiographic pulmonary TB (p =0.020) between the immune suppressed and the non- immune suppressed

children in this sub-group (Table 3.4). A statistically significant higher proportion of children who were non-immune suppressed had lymphadenopathy and radiographic pulmonary TB on chest X-ray, compared to immune suppressed children, probably because there is a decreased ability to mount an immune response and produce a radiographic abnormality in immune suppressed children.

Table 3.4: Comparison of immune suppressed vs. non-immune suppressed children for the sub-group, lymphadenopathy and radiographic pulmonary TB

Radiographic Finding	Immune Suppressed N=70 n(%N)	Non-Immune Suppressed N=37 n(%N)	Total N=107 n(%N)	p-value
Lymphadenopathy	41(59)	29 (78)	70 (65)	0.041**
Radiographic Pulmonary TB*	41(59)	30 (81)	71(66)	0.020**

**Pearson χ^2 test
* Defined as the presence of either lymphadenopathy or miliary infiltrate or cavities

3.4 Radiographic, clinical and immunological features of the subgroup of children evaluated for lymphadenopathy and radiographic PTB

Amongst the sub-group of 112 children, 75 had radiographic features of pulmonary TB. A high proportion of 65% (49/75) of these children were on TB treatment, with 35% (26/75) not on TB treatment (p=0.051). Of the 35% (26/75) of children with radiographic features of pulmonary TB and not on TB treatment; 22 (85%) had lymphadenopathy only, 3 (12%) had miliary infiltrate and lymphadenopathy and 1 (3%) had cavities only. Moreover, of the total of 66 children that were on TB treatment, 26% (17/66) had no radiographic features of pulmonary TB. (Table 3.5).

In this sub-group of 112 children, 107 had available CD4 results to determine their level of immune suppression. The immune suppressed group had a higher percentage of children on TB treatment 64% (45/70) compared to the non-immune suppressed group 51% (19/37). However there was no statistically significant difference (p=0.196) between the proportion of immune suppressed children and non-immune children who were on TB treatment. (Table 3.5).

Table 3.5: Radiographic, clinical and immunological features of the subgroup of children evaluated for radiographic pulmonary TB

	TB Treatment			**p-value**
Radiographic Pulmonary TB	**On TB treatment**	**Not on TB treatment**	**Total (N)**	
Present, n(%N)	49 (65)	26 (35)	75	0.051**
Absent, n(%N)	17 (46)	20 (54)	37	
Immune suppression	**On TB treatment**	**Not on TB treatment**	**Total (N)**	
Immune suppressed, n(%N)	45 (64)	25 (36)	70	0.196**
Non-immune suppressed, n(%N)	19 (51)	18 (49)	37	

**Pearson χ^2 test

3.5 Inter-Observer Agreement of Paediatric Chest X-ray Readings

3.5.1 Inter-Observer agreement between 3 readers

Inter-observer agreement between all 3 readers (Table 3.6) was fair *(K*=0.21–0.40) for overall abnormal chest X-ray findings, airspace disease, chronic lung disease and bilateral air trapping, moderate (*K*=0.41–0.60) for parenchymal interstitial disease and slight (*K*=0.01–0.20) for cardiomegaly, pleural reactions and lymphadenopathy.

Table 3.6: Inter-observer Agreement between 3 readers for each radiographic parameter

Radiographic Parameter	3-Reader Kappa	Interpretation of Kappa
Abnormal Chest X-Ray	0.23	Fair agreement
Air Space Disease	0.22	Fair agreement
Parenchymal Interstitial Disease	0.53	Moderate agreement
Bilateral Air Trapping	0.25	Fair agreement
Chronic Lung Disease	0.24	Fair agreement
Pleural Reactions	0.11	Slight agreement
Cardiomegaly	0.16	Slight agreement
Lymphadenopathy	0.05	Slight agreement

3.5.2 Inter-Observer Agreement between 2 readers

Inter-observer agreement between 2 readers (reader 1 and 2) (Table 3.7) was moderate for parenchymal interstitial disease, fair for abnormal chest X-ray, airspace disease and cardiomegaly, slight for lymphadenopathy, chronic lung disease, bilateral air trapping and less than chance agreement for pleural reactions.

In contrast to reader 1 and 2, the inter-observer agreement between reader 2 and 3 (Table 3.8) was moderate for abnormal chest X-ray, airspace disease and parenchymal interstitial disease, fair for chronic lung disease and bilateral air trapping and slight for lymphadenopathy but less than chance agreement for pleural reactions and cardiomegaly.

Inter-observer agreement between readers 1 and 3 was moderate for parenchymal interstitial disease, fair for chronic lung disease, bilateral air trapping and pleural reactions, slight for abnormal chest X-ray, lymphadenopathy and air space disease and less than chance agreement for cardiomegaly (Table 3.9).

Table 3.7: Inter-observer agreement between 2 readers (reader 1 and 2) for each radiographic parameter

Radiographic Parameter	2-Reader Kappa	Interpretation of Kappa
Abnormal Chest X-Ray	0.26	Fair agreement
Air Space Disease	0.21	Fair agreement
Parenchymal Interstitial Disease	0.54	Moderate agreement
Bilateral Air Trapping	0.09	Slight agreement
Chronic Lung Disease	0.18	Slight agreement
Pleural Reactions	-0.01	Less than chance agreement
Cardiomegaly	0.37	Fair agreement
Lymphadenopathy	0.21	Slight agreement

Table 3.8: Inter-observer agreement between 2 readers (reader 2 and 3) for each radiographic parameter

Radiographic Parameter	2-Reader Kappa	Interpretation of Kappa
Abnormal Chest X-Ray	0.45	Moderate agreement
Air Space Disease	0.54	Moderate agreement
Parenchymal Interstitial Disease	0.59	Moderate agreement
Bilateral Air Trapping	0.25	Fair agreement
Chronic Lung Disease	0.20	Fair agreement
Pleural Reactions	-0.02	Less than chance agreement
Cardiomegaly	-0.01	Less than chance agreement
Lymphadenopathy	0.16	Slight agreement

Table 3.9: Inter-observer agreement between 2 readers (reader 1 and 3) for each radiographic parameter

Radiographic Parameter	2-Reader Kappa	Interpretation of Kappa
Abnormal Chest X-Ray	0.10	Slight agreement
Air Space Disease	0.19	Slight agreement
Parenchymal Interstitial Disease	0.49	Moderate agreement
Bilateral Air Trapping	0.37	Fair agreement
Chronic Lung Disease	0.34	Fair agreement
Pleural Reactions	0.39	Fair agreement
Cardiomegaly	-0.01	Less than chance agreement
Lymphadenopathy	0.08	Slight agreement

4 DISCUSSION

4.1 Radiographic Findings

4.1.1 Quality of Chest X-rays

The overall quality of chest X-rays was poor with 49 (30%) children excluded from lymphadenopathy assessment as airways, hilar or mediastinal areas could not be evaluated. Chest X-rays were performed in an adult X-ray unit, with no dedicated paediatric trained radiographer. As this was a retrospective study, poor quality chest X-rays could not be repeated, thereby restricting the patient numbers and making this a potential limitation of the study.

4.1.2 Radiographic Patterns in Paediatric HIV

There was a high prevalence (71%) of chest X-ray abnormalities in this group of HIV infected children. While lymphadenopathy and radiographic pulmonary TB was only assessed in 112 children, they were the commonest findings; with lymphadenopathy prevalent in 66% and radiographic pulmonary TB in 67% of the 112 children. The rest of the radiographic findings were assessed in 161 patients and air space disease was common at 42% while parenchymal interstitial disease was prevalent in 21% of children. There was a low prevalence of bilateral air trapping (4%), chronic lung disease (1%), pleural reactions (1%) and cardiomegaly (2%). As serial chest X-rays were not compared in this study, chronic lung disease may have been under reported. This study represented a younger population group (median age of 2.3 years) so chronic lung disease and HIV-related cardiac disease may have had insufficient time to manifest.

4.2 Pre-HAART Chest X-Ray Findings in Immune Suppressed vs. Non Immune Suppressed Children

The only statistically significant difference between the immune suppressed and the non-immune suppressed groups was for lymphadenopathy (p =0.041) and radiographic pulmonary TB (p =0.020). A significantly higher percentage of children who were non-immune suppressed had lymphadenopathy and radiographic pulmonary TB on chest X-ray, compared to immune suppressed children. This is consistent with the literature that as the immunity decreases in HIV-infected children, there is both an increased risk of developing TB, but also a decreased ability to mount an immune response and therefore produce a radiographic abnormality [12,16]. This study's results could not be compared to the study by Sheik *at al* who found that bronchiectasis was associated with the severity of immune suppression as the prevalence of chronic lung disease (bronchiectasis and cavities) in this cohort was very low 1,2% (95% confidence interval of 0.2-4.4)[27].

4.3 Radiographic, clinical and immunological features of the subgroup of children evaluated for lymphadenopathy and radiographic PTB

The diagnosis of TB is difficult in HIV infected children with non-specific clinical signs, limitations to the use of the tuberculin skin test [17, 19] and low sensitivity of microbiological investigations (smear and culture) [20]. As a result, chest X-ray findings are often used in conjunction with clinical and laboratory findings for the diagnosis of TB in children [20, 22].

Despite a significantly higher proportion of non-immune suppressed children who had lymphadenopathy and radiographic pulmonary TB on chest X-ray compared to immune suppressed children, there was no statistically significant difference (p=0.196) between the proportion of immune suppressed children and non-immune suppressed children who were on TB treatment.

Amongst the 112 children, who had chest X-rays that could be assessed for lymphadenopathy and radiographic pulmonary TB, a high proportion were on TB treatment. Of the 35% (26/75) of children with radiographic features of pulmonary TB and not on TB treatment, lymphadenopathy was reported in 85% and a further 12% had both miliary infiltrate and lymphadenopathy.

The interpretation of these chest X-rays for clinical purposes (ie: for the diagnosis of TB and decision to start TB treatment) was performed by clinicians at the time of the clinical consultation and were not read by radiologists, nor were radiology reports provided due to a shortage of radiologists within this hospital. Treatment decisions were made by clinicians using a combination of clinical signs, contact history, microbiology and chest X-ray reading. Chest X-ray interpretation by clinicians may have been influenced by nonspecific radiographic findings for pulmonary TB [22], co-morbidity such as bacterial and viral pneumonia [17], inadequate quality of chest X-rays or clinicians who were not specifically trained to read chest X-rays in children may have used them inappropriately for the diagnosis of pulmonary TB.

There are several possible reasons why 26% of the children had no radiographic features of pulmonary TB but were on TB treatment. Firstly, in HIV infected children, who are about to initiate HAART, clinicians tend to err on the side of caution (i.e. treat for TB) when the index of suspicion is high, in order to decrease the risk of developing TB-IRIS [14,15,16,19]. Secondly, children presenting with malnutrition, or severe immune suppression may not have the ability to mount an immune response that will present on chest X-ray [12,16], but may present with other clinical signs consistent with childhood TB.

For children with radiographic features of pulmonary TB who were not on TB treatment, the presence of pulmonary co-morbidities[17] may have led to an over-diagnosis of radiographic pulmonary TB. Alternately, chest X-rays for this research study were read retrospectively by 3 paediatric radiologists, blinded to clinical data and outside of a busy clinical environment. Their readings were further consolidated using a majority consensus reading determined during the data analysis phase. As a result, their increased experience, expertise and lack of a pressured environment may have allowed them to assess the chest X-rays in-depth and therefore report more accurately. However, in both this study and the study by Du Plessis et al[16] where chest X-rays were read independent of clinical information, which is often not the case in routine clinical practice, both studies reported a lack of consensus between children on TB treatment and those with radiographic features of pulmonary TB. The radiographic features of pulmonary TB were also subject to very low inter-observer agreement in this study. So while the proportion of children with lymphadenopathy was high using a majority consensus reading, the agreement between the three paediatric radiologists was poor.

4.4 Inter-Observer Agreement on Paediatric Chest X-Rays

Inter-observer agreement between the 3 readers was *fair* for 'overall abnormal chest X-ray findings', airspace disease, chronic lung disease and bilateral air trapping; *moderate* for parenchymal interstitial disease and *slight* for lymphadenopathy, pleural reactions and cardiomegaly. Chronic lung disease, bilateral air trapping, pleural reactions and cardiomegaly had a very low prevalence, negatively affecting Kappa values. (Kappa depends on the proportions of subjects that have true values in each category. Kappa is maximum when the probability of a true yes is 0.5 and as the probability gets closer to zero, the expected kappa gets smaller) [29].

Inter-observer agreement in radiology is dependent on the quality of chest x-rays, standardization of techniques and experience and degree of training of the readers[30, 31, 32]. In this study, the quality of chest X-rays was poor (30% could not be assessed for features of lymphadenopathy). While a data collection sheet was used which identified radiographic parameters and sub-parameters, standardised training for the specific radiographic parameters and sub-parameters for the 3 readers was not performed prior to the reading period. The 3 readers were from different institutions with different levels of experience and scope of practice. Two readers were from a predominantly clinical background, while one reader was from a predominantly research background. Du Toit et al reported a fair inter-observer agreement amongst paediatric pulmonologists for lymphadenopathy detection on paediatric chest X-rays[24] compared to this study's slight inter-observer agreement amongst radiologists.

These authors had better agreement than this study probably because all readers had similar backgrounds and training, experience at assessing chest X-rays and worked in the same institution[24]. This is in contrast to the general literature where overall inter-observer agreement of paediatric chest X-ray readings is fair to moderate, while variability of individual radiographic features is slight or poor. With lymphadenopathy having the lowest inter-observer agreement this study results is comparable with the literature[24, 30, 31, 32, 33].

Table 4.1: Inter-observer Agreement of Paediatric Chest X-Rays; a comparison to the literature

Radiographic Parameter	Kappa Values				
	Mahomed*, 2013	**Correia, 2011** [30]	**Sarria, 2003** [31]	**DuToit, 2002** [24]	**Albaum, 1996** [32]
Abnormal Chest X-Ray	0.23	0.31	0.33	0.33	0.37
Air Space Disease	0.22	0.41–0.60	NR	NR	-0.11
Parenchymal Interstitial Disease	0.53	<0.20	0.29	NR	NR
Bilateral Air Trapping	0.25	0.21–0.40	0.45	NR	NR
Chronic Lung Disease	0.24		0.11	NR	0.76
Pleural Reactions	0.11	0.41–0.60	0.93	NR	0.46
Cardiomegaly	0.16	NR	NR	NR	NR
Lymphadenopathy	0.05	<0.20	0.12	0.40	0.09

* data from this research report
NR = not reported

4.5 Radiographic Findings in Comparison to Other Studies

Two studies in Africa investigating pre-HAART chest X-ray findings by Du Plessis *et al* (South Africa) and Kouakoussui *et al* (Ivory Coast) found a similar overall prevalence of chest X-ray abnormalities of 46 % [16] and 51%[10], respectively (Table 4.2). Whilst Sheik *et al* (USA) reported a comparable prevalence of 45.7%, where HAART was unknown [27]. In these 3 studies the commonest finding was air space consolidation (Table 4.2)[10, 16, 27]. In the prospective study by Nortan *et al* (USA), where 90% of children where on HAART during some time of the study, a cumulative incidence of 32.8% chronic lung changes by age 4 years was found[12]. In adolescent children with vertically-acquired HIV, where 36% of children were on HAART, Desai *et al* (Zimbabwe) reported a (68%) prevalence of chest X-ray abnormalities, with 56.0% presenting with bronchiectasis and ring/tram line opacities[28] (Table 4.2).

Limitations of the South African study by Du Plessis *et al* investigating pre-HAART chest X-rays included: a small sample size of only 92 patients which may have limited the ability to detect significant differences between groups; generalizability to acutely ill patients or the general population is limited by the selection of only chronically ill outpatients; use of a single reader resulting in an inability to measure inter-observer agreement of radiological findings; and the lack of correlation between the chest X-ray findings and the final clinical diagnosis[16].

Limitations of the study by Nortan *et al* included the use of non-conventional radiographic terminology such as "dense patchy opacities", "interstitial markings" and "patchy opacification", which are broad and open to interpretation. Nortan *et al* also combined the findings of broncho-vascular markings and reticular densities due to low inter-observer agreement. This approach is problematic since these 2 radiographic patterns represent different pathological processes[12].

Limitations of the study by Desai *et al*, investigating adolescents with HIV included that the study findings are not generalizable to non-hospitalized patients as the majority of the patients included were hospitalized (78.6%) [28].

Limitations of the study by Sheik *et al* was limited radiographic correlation of bronchiectasis with the gold standard of CT chest, which was only performed and confirmed in 10/26 children (38.5%) [27].

This study's high prevalence (71%) of chest X-ray abnormalities correlated well with previous studies in HIV infected. This study's prevalence of air space disease (42%), parenchymal interstitial disease (21%), and pleural disease (1%) is comparable to the current literature[10, 12, 16, 27, 28]. However this study found a very high prevalence of lymphadenopathy

(66%) and radiographic pulmonary TB (67%) compared to the literature; Du Plessis *et al* 9% pulmonary TB[16], Nortan *et al* 2.4% miliary TB[12] and Kouakoussui *et al* 7% miliary TB and 2% with pulmonary TB[10,]. This is because the pre-HAART chest X-rays in this study were generally taken at the time of an admission for an acute illness, within 4 weeks of HAART initiation. This group in reality represents the chest X-rays of HAART naïve children during an admission for an acute illness. These results also represent the high burden of paediatric TB in the Soweto population and the feeder areas.

The finding of very low chronic lung disease (1%) was comparable with the South African study by Du Plessis *et al* (7%) [16] but disproportionately lower compared to the studies by Nortan *et al (*28.9%) [12], Desai *et al* (56%) [28] and Sheik *et al* (15.8%) [27]. This study population had a significantly lower median age of 2.3 years, compared to the studies in the literature. Chronic lung disease may have had insufficient time to manifest. This study was also limited in the diagnoses of chronic lung disease as serial chest X-rays were not compared.

The very low prevalence of cardiomegaly (2%) reported here was comparable to the Ivory Coast study by Kouakoussui *et al* (4.7%) [10], but vastly different to the 21% reported by Du Plessis *et al* in Durban, South Africa[16]. This difference in proportion of children presenting with cardiomegaly could be due to the difference in the median age in this study (2.3 years) compared to the Du Plessis study[16] (4.6 years). A consequence of this difference could be that HIV related cardiac disease may have insufficient time to manifest in our younger sample.

Table 4.2 Radiographic Findings in Comparison to Literature

Study	Study Type	Population characteristics	Percentage with any CXR abnormalities	Airspace disease/ consolidation	Parenchymal Interstitial disease	Lymphadenopathy hilar/mediastinal	Cardiomegaly	Pleural disease	Bronchiectasis/ ring tram line opacities	Other information
Mahomed[#] *et al* 2013 (South Africa)	Retrospective, descriptive	Mean age 3.1 years Median age 2.3 years 0% on HAART (N=161)	71.4%	42.2%	20.5%	66.1%*	1.7%	0.6%	1.2%	67.0%* had radiographic features of pulmonary TB
Du Plessis *et al* 2011 (South Africa)[16]	Retrospective, descriptive	Mean age 5.4 years Median age 4.6 years 0% on HAART (N=92)	46.0%	28.0%	-	1.0%	21.0%	1.0%	7.0%	Parenchymal disease 34% Mediastinal disease 22%
				34%						
Desai *et a*l 2011 (Zimbabwe)[28]	Retrospective	59 hospitalized: mean age-13.7 years 16 outpatients: mean age-14.1 years 36% on HAART (N=75)	68.0%	39.0%	<15%	12.0%	-	11%	56.0%	Consolidation more common in hospitalized patients, while ring/tram line opacities equal in both groups
Kouakoussui *et al* 2004 (Ivory Coast)[10]	Observational, Cohort	Mean age- 6.2 years 0% on HAART (N=86)	51.0%	22.1%	17.4%	-	4.7%	-	5.0%	Pneumonia 22.1% Interstitial Pneumonitis 10.5% Miliary TB 6.9% Bronchitis 4.7%
Nortan *et al* 2001 (USA)[12]	Prospective	Median age at enrollment 23 months 90% on HAART (N=287)		31.4%	16.7%	-	-	-	28.9%	Cumulative incidence of chronic lung disease 32.8% by age 4 years Increased bronchovascular markings and reticular densities commonest finding
Sheikh *et al* 1997 (USA)[27]	Retrospective	Median age 7.5 years Unknown % on HAART (N=164)	45.7%	45.7%	34.0%	-	-	-	15,8%	Bronchiectasis associated with -LIP 34.0% -recurrent pneumonia 12.5% -unresolved pneumonia 27.7%

[#]data from this research report

*this percentage was calculated amongst the sub-group of 112 children in whom lymphadenopathy could be assessed

4.6 Study Limitations

1. The quality of chest X-rays were poor with 49 (30%) children excluded for lymphadenopathy assessment because airways, hilar or mediastinal areas could not be evaluated. The retrospective nature of this study meant that poor quality chest X-rays could not be repeated.

2. The sample size was limited by time constraints.

3. Lack of a gold standard comparison e.g. CT chest for correlation of chest X-ray findings. Lymphadenopathy had the poorest inter-observer agreement on chest X-ray [24], hence the gold standard post contrast CT chest correlation would have been more useful. Although CT is the international modality of choice for detection of lymphadenopathy, there is a limited role in countries with a high TB burden and limited resources like South Africa[17,19, 22].

4. The scope of this study limited the clinical correlation performed with radiographic findings. While chest radiographic findings were correlated with the number of patients on TB treatment, further correlation with the clinical history, clinical examination findings, tuberculin skin test, gastric washings, TB cultures or final clinical outcome of patients was not done. This is a planned future project.

4.7 Recommendations

4.7.1 Improve the quality of paediatric chest radiographs.

Poor quality chest X-rays may mimic disease where there is none (e.g. under-inspiration may look like air-space disease, rotation of patient may mimic widened mediastinum, over-exposure of the film may obscure parenchymal interstitial disease). The proposed outcome is to improve the quality of paediatric chest X-rays. This can be done by having a dedicated

paediatric trained radiographer leading radiographers in a dedicated paediatric radiology department. Using digital units allows for a wider margin of error, post processing and retrievability. Allocating a dedicated on-site radiologist to report all radiographs, point errors, and request repeats before chest X-rays leave the radiology department will address quality on the ground. It is further recommended that quality assurance be performed on every 10th X-ray and a quality assurance chart supplied after every 50th X-ray for monitoring quality of radiographs.

4.7.2 Improve inter-reader agreement

Inter-reader agreement and specificity of lymphadenopathy on chest X-ray would improve if criteria were set for recording only definite and prominent findings like very large soft tissue masses extending beyond the hilar. Therefore standardization of chest X-ray readings is recommended using the Fleischner Society: Glossary of Terms for Thoracic Imaging criteria for Chest X-ray reporting. Routine reporting of every X-ray in the radiology department by a radiologist may also improve inter-reader agreement and improve training within the department. This training should extend to clinicians within and outside of major tertiary centres (where most childhood TB is diagnosed) in order to decrease under-diagnosis and under-treatment of childhood TB, especially where radiological findings are able to assist with a differential diagnosis.

5 CONCLUSIONS

This study correlated well with previous studies in HIV infected children demonstrating a high prevalence (71%) of chest X-ray abnormalities. This study's prevalence of air space disease (42%), parenchymal interstitial disease (21%), and pleural disease (1%) is comparable to the literature [10,12,16, 27, 28]. However this study found a very high prevalence of lymphadenopathy (66%) and radiographic pulmonary TB (67%) compared to the literature[10,12,16, 27, 28] . This is due to the chest X-rays being generally taken at the time of admission for an acute illness, within 4 weeks of HAART initiation. The chest X-rays may not represent true baseline pre-HAART radiographs. The radiographs also represent the high burden of paediatric TB in the Soweto population and the feeder areas.

The findings of a very low prevalence of cardiomegaly (2%) and chronic lung disease (1%) represents a significantly younger demographic group (median age of 2.3 years) compared to the literature. Hence chronic conditions may have had insufficient time to manifest on chest X-ray. This study was limited in the diagnoses of chronic lung disease as serial chest X-rays were not compared.

Of the sub-group, the higher proportion of children who were non-immune suppressed and had lymphadenopathy and radiographic pulmonary TB on chest X-ray was likely due to a decreased ability, in immune suppressed children, to mount an immune response and produce a radiographic abnormality [12, 16].The lack of concordance between those with radiographic TB and those on TB treatment suggests a high reliance, in this environment, on clinical signs and/or microbiological investigations for the decision to start TB treatment.

Inter-observer agreement in radiology is dependent on the quality of chest X-rays, standardisation of techniques and experience and degree of training of the readers. The quality of chest X-rays was poor, 30% could not be assessed for features of lymphadenopathy

while the 3 readers were from different institutions with different levels of experience and scope of practice. Inter-observer agreement between the 3 readers was fair for overall abnormal chest X-ray findings, airspace disease, chronic lung disease and bilateral air trapping, moderate for parenchymal interstitial disease and the poorest for lymphadenopathy. Inter-observer agreement in this study is comparable to other literature and this suggests that X-ray reading requires further standardization particularly for the diagnosis of TB in children.

6 APPENDICES

6.1 APPENDIX 1: WHO Clinical Staging of HIV/AIDS for children with confirmed HIV[8]

WHO Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
WHO Clinical stage 2
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular cheilitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)
WHO Clinical stage 3
Unexplainedi moderate malnutrition or wasting not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month) Persistent oral candidiasis (after first 6–8 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis or periodontitis Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease including brochiectasis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre) and or chronic thrombocytopaenia (<50 × 109 per litre)
WHO Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than one month's

duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (coccidiomycosis or histoplasmosis)
Disseminated non-tuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Cerebral or B-cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

6.2 APPENDIX 2: Informed Consent form used in the THINK study

6.3 APPENDIX 3: Child Assent Form used in the THINK study

6.4 APPENDIX 4: Ethics Committee Clearance Certificate

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr N Mahomed

CLEARANCE CERTIFICATE	**M110729**
PROJECT	Chest X-Ray Findings in HIV-Infected Children Starting HAART at a Tertiary Institution in South Africa
INVESTIGATORS	Dr N Mahomed.
DEPARTMENT	Division of Diagnostic Radiology
DATE CONSIDERED	29/07/2011
DECISION OF THE COMMITTEE*	Approed unconditioally

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

DATE 29/07/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

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

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...

6.5 APPENDIX 5: Data Collection Sheets

STUDY NUMBER	Lymphadenopathy	Hilar Nodes	Mediastinal nodes	Airway compressions	Lobar collapses	Unilateral air-trapping	SITE	Air space disease	SITE

STUDY NUMBER	Parenchymal interstitial disease	reticulo-nodular infiltrate	reticular infiltrate	large nodular infiltrate (nodules > 2mm)	miliary infiltrates (nodules < 2mm)	Chronic Lung Disease	bronchiectasis	cavities	Bilateral air-trapping	Pleural rxns	Cardio megaly

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