A comparison of Chest Radiographic Findings in HIV-infected and HIV-uninfected Children with Pulmonary Tuberculosis

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

Johannesburg, 2020

Declaration

I, Thandi Eunice Buthelezi declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Thandi Eunice Buthelezi

On this 18th day of August 2020.

To the love of my life, Themba kaThandi Buthelezi, and to my inspiration, Khethelo, Sisekelo and Hlumokuhle.

Publications and presentations

This work has never been published.

Part of this work has been presented in the form of an electronic scientific poster at the European Society of Paediatric Radiology (ESPR) Congress in Graz, Austria, from the 2nd – 6th of June 2015.

Abstract

The incidence of pulmonary tuberculosis (PTB) has increased globally with the HIV epidemic. Chest X-ray (CXR) plays a primary role in the diagnosis of PTB in children; however, co-infection with HIV may pose additional diagnostic complexity.

AIM: To compare CXR findings in HIV-infected and HIV-uninfected children who had laboratory-proven PTB. A secondary aim was to investigate the impact of nutritional status on these CXR findings and within the study population.

METHOD: Retrospective analysis of CXRs from children with known HIV status and proven PTB (culture and GeneXpert® Xpert® MTB/RIF positive), who were hospitalised at Red Cross War Memorial Children's Hospital or seen at Nolungile Primary Health Care Centre from Feb 2009 to April 2014. Children underwent anteroposterior (AP) and lateral CXR as part of a routine initial assessment. These CXRs were interpreted for this study by two independent readers. A third independent reader was used as a tie-breaker if there was no consensus. A standardised reporting form was used, and all readers were blinded to HIV-status, clinical data and other laboratory results of all the patients. Radiological findings were subsequently compared according to HIV and nutritional status.

RESULTS: A total of 130 CXRs were analysed from 35 (27 %) HIV-infected and 95 (73 %) HIV-uninfected children, median age 45.7 months, interquartile range 18.0 - 81.3 months.

CXR changes consistent with PTB were reported in 21/35 (60%) of HIV-infected and 58/95 (61%) of HIV-uninfected patients. Normal CXR was identified in 3/35 (8.6%) of HIV-infected and 5/95 (5.3%) of HIV-uninfected patients. Airway compression was present in 3/35 (8.6%) of HIV-infected and 7/95 (7.4%) of HIV-uninfected patients. Hilar lymphadenopathy was present in 8/35 (23%) of HIV-infected and 25/95 (26%) of HIV-uninfected patients, while mediastinal lymphadenopathy occurred in 8/35 (23%) of HIV-infected and 20/95 (21.1%) of HIV-uninfected children. Airspace consolidation was present in 60% of both HIV-infected (21/35) and HIV-uninfected patients (57/95). Only 1/35 (3%) of the HIV-infected cases compared with 12/95(13%) of the HIV-uninfected cases had lung cavities; similarly, 1/35 (3%) of HIV-infected and 11/95 (11.6%) of HIV-uninfected patients had interstitial nodular infiltrates. Pleural effusion was present in 2/35 (5.7 %) of HIV-infected and 9/95 (9.5 %) of HIV-uninfected patients. However, *p*-values for all of these results indicated no significant difference between the CXR findings according to HIV status.

Thirty-nine (30.0%) patients were underweight-for-age, 74 (56.9%) adequately nourished and 17 (13.1%) had unknown nutritional status. Pleural effusion was present in 9/74 (12.2%)

of the adequately nourished patients, while none of the malnourished patients had this feature, $p = 0.025$. Most underweight-for age patients (38/39 patients, 97.4%) were hospitalised, $p = 0.004$, and were male (28/39 patients, 72%), $p = 0.046$. Underweight-for-age occurred more commonly in HIV-infected patients (17/31, 48.6%) versus HIV-uninfected patients (22/95, 23.3%), $p = 0.008$.

CONCLUSIONS: More than 90% of chest radiographs in both HIV-infected and HIV-uninfected children with confirmed PTB were abnormal but there were no significant differences in the CXR findings between the groups. Concerning nutritional status, pleural effusion was found only in adequately nourished patients and underweight-for-age occurred more commonly in the children who were HIV-infected, hospitalised or male.

Acknowledgements

I would like to acknowledge the following team of supportive people for their love and encouragement. Without them, I would never have achieved all of this:

Dr Susan Lucas, my supervisor. Thank you for being patient and believing in me even when I doubted myself. You taught me all the baby steps of research.

Prof Heather Zar, my co-supervisor, for sharing your outstanding research experiences with me and monitoring the clinical side of things as well. You held my hand all the way.

Prof Savvas Andronikou, my mentor, for the push (literally and figuratively) in the right direction. Your exceptional experience in research and Paediatric Radiology is amazing.

Prof Victor Mngomezulu, my Head of Department, for allocating dedicated research time, making research the priority and always being available to help.

Ms Noleen Gordon for helping with data analysis and upgrading my Excel knowledge.

Lesley Workman and the Cape Town Team, for providing the database and always being available to help and clarify. Lesley, your commitment to this project was noticed.

Dr Petra Gaylard, for helping with statistical analysis.

My Family, for the undying support all the time.

My Friends and colleagues, for the love and encouragement.

Themba, for the endless love and support. I love you, Shenge!

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AP view – anteroposterior view

ARV – antiretroviral

BI – bronchus intermedius

CT scan – computed tomography scan

CXR – chest X-ray

CXRN – normal chest X-ray

CXRTB – chest X-ray consistent with tuberculosis

ELISA – enzyme-linked immunosorbent assay

GeneXpert® Xpert® MTB/RIF – diagnostic test (PCR) for MTB and rifampicin resistance

HAART – highly active antiretroviral therapy

HIV – human immunodeficiency virus

IQR – interquartile range

IRIS – immune reconstitution inflammatory syndrome

Laboratory-proven TB – in this study, TB proven by both culture and PCR

Lat view – lateral view

LMB – left main bronchus

MDR – multidrug-resistant

MTB – *Mycobacterium tuberculosis*

MRI – magnetic resonance imaging

NG – Nolungile Primary Health Care Centre

PACS – picture archiving and communication system

PCR – polymerase chain reaction

PMTCT – prevention of mother-to-child transmission

PTB – pulmonary tuberculosis

RIF – rifampicin

RMB – right main bronchus

RPT – right paratracheal

RX – Red Cross War Memorial Children's Hospital

TB – tuberculosis

WHO – Word Health Organisation

1. Rationale

The impact of human immunodeficiency virus (HIV) and co-infections, including tuberculosis (TB), continues to place a major burden on healthcare systems worldwide, especially in sub-Saharan Africa. In children, vertical transmission is still the predominant mechanism behind HIV infection(1-3).

HIV-infected children have a three-fold higher risk of contracting respiratory infections, especially TB, not only because of their immature immune systems (4) and HIV-related immune suppression but also from poor maternal immunity and lack of protective maternal antibodies (5, 6). Pulmonary TB (PTB) is one of the commonest infections in both HIV-infected and HIV-uninfected children living in sub-Saharan Africa (6-8). TB commonly co-exists with malnutrition, contributing to the high TB-associated mortality(5, 9).

Chest X-ray (CXR) forms part of the workup in all patients with TB and malnutrition. CXR is the most easily available radiological tool in a resource-limited setting like South Africa (10, 11). HIV-infected children may develop more severe PTB compared to HIV-uninfected children, as reflected by more extensive and specific CXR findings (10). Small studies have described a higher incidence of cavity or miliary disease in HIV-infected compared to HIV-uninfected children (12-15). However, these studies are limited by small sample sizes and lack of a gold standard diagnosis for PTB. Malnutrition in children confers an increased risk for PTB but also for other lower respiratory tract infections (5, 6). This study, therefore, aims to compare CXR findings in HIV-infected and HIV-uninfected children who had laboratory-proven PTB. A secondary aim was to investigate the impact of nutritional status on these CXR findings and within the study population.

1.1. Background

The worldwide prevalence of TB has increased exponentially with the HIV epidemic (16, 17). South Africa is amongst the countries with the highest rates of TB and HIV co-infection (6). About 1.2 million of the 10.4 million people who developed TB in 2015 were HIV-positive; South Africa together with just five other countries constituted 60% of these patients (6). The burden of TB is highest in Asia and Africa (6, 18, 19). The burden of TB amongst children has been underestimated due to difficulties in confirming the diagnosis and the reliance on

smear-positivity for reporting (20-22). However, despite these restrictions, children are still estimated to account for a substantial proportion of the TB caseload: 15 - 20% in high TB prevalence areas (22, 23). In 2015, it was estimated that there were about 1.0 million new TB cases globally among children under the age of 15 years and 170 000 TB deaths in HIV-negative children were reported (6).

1.2. Epidemiology of TB

According to the World Health Organisation (WHO) report for 2016, the estimated prevalence of TB globally has been declining for the period 2007-2014 (24). Africa still has very high mortality and prevalence rate, but this is also now stabilising according to this latest report (24). TB incidence rate (including adults and children, HIV-positive and HIV-negative) in South Africa is around 834 per 100 000 population, as compared to 275 per 100 000 population in Africa and 142 per 100 000 population globally (6).
Notably, South Africa still had the highest TB prevalence of 696 per 100 000 population per year in 2014 amongst the African countries, a set-back from 466 per 100 000 population per year in 1990 (24).

The WHO has identified South Africa as a country with a high TB burden, high HIV burden and high multidrug-resistant tuberculosis (MDR-TB) burden (6). The Western Cape is a region with a particularly high incidence of TB and children under 15 years of age form 15 - 20% of this burden (25).

1.3. Diagnosis of TB in children

TB may be difficult to diagnose in children as the signs and symptoms are non-specific and definitive confirmation may be difficult, especially in young children and HIV-infected children (14, 21, 22, 26). However, there have been recent improvements in diagnostic strategies for paediatric TB with improved specimen collection techniques and rapid molecular diagnostic tests (21, 22). Culture or positive polymerase chain reaction (PCR) (GeneXpert® Xpert® MTB/RIF) of *M. tuberculosis* are the gold standards for the diagnosis of definite PTB (6, 22, 27). However, children are frequently culture-negative and as timely initiation of therapy is important to prevent disease progression in children, therapy is often started based on clinical and radiological features (20). Diagnosing TB can also be challenging

in the presence of malnutrition as the clinical presentation, disease spectrum and/or diagnostic yield may be altered (28).

1.3.1. WHO criteria

The WHO-recommended approach to diagnose TB in children is as follows (29):

i. Careful history (including the history of TB contact and symptoms consistent with TB);

ii. Clinical examination (including growth assessment);

iii. Tuberculin skin testing (TST);

iv. Bacteriological confirmation whenever possible;

v. Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB;

vi. HIV testing (in high HIV prevalence areas).

1.3.2. Tuberculin test

The TST or Mantoux test is a screening tool for *M. tuberculosis* infection (29). A positive result, as evidenced by an induration seen on the skin 48 to 72 hours post intradermal injection of 0.1 mL of tuberculin purified protein derivative (PPD), indicates infection with *M. tuberculosis*. Induration of 5 mm or more in diameter in an HIV-positive / immunocompromised/malnourished child or of 10 mm or more in diameter in an immunocompetent child is considered to be positive (28, 29). This test is widely used as part of the workup for TB. A negative TST does not exclude TB infection or active disease as false-negative results may occur due to any of the following: recent TB exposure (window period), severe malnutrition , immunosuppression (due to drugs or HIV), disseminated TB and TB meningitis (28-30).

1.3.3. Laboratory tests (microscopy, culture and biochemistry)

Gastric lavage, aspirates, bronchoscopy, nasopharyngeal aspirates and sputum induction are different methods that can be used to obtain specimens in young children who cannot produce sputum (31). Obtaining a good specimen may be challenging in young children because of many factors ranging from the technique used and experience of the caregiver, transportation of the specimen, invasiveness and costs of some tests (31). For most specimens, two or more samples must be obtained to increase diagnostic yield. Children are

invariably sputum smear-negative (20). Culture or GeneXpert® Xpert® MTB/RIF is the gold standard; culture may take up to six weeks to obtain the results(29, 30, 32).

In 2010, the WHO endorsed the GeneXpert® Xpert® MTB/RIF for the use in TB-endemic countries like South Africa. Xpert® MTB/RIF is a molecular test (polymerase chain reaction, PCR) which detects *M. tuberculosis* and rifampicin resistance. It has high specificity and sensitivity, especially if more than one sample is used (20, 33). It is a valuable testing tool in children, including those with HIV-infection. This test has improved rapid diagnosis and identification of PTB and rifampicin resistance (20, 21, 33). Its availability in the district and sub-district regions is an added advantage in resource-constrained areas (33). Its advantages over culture are quick specimen turnaround time, cost effectiveness and decreased technical complexity (20, 21).

1.4. Epidemiology of HIV

Increased survival of the HIV-infected population due to significant improvement of the local antiretroviral (ARV) roll-out has contributed to the estimated increase in people living with HIV in South Africa, from 4.6 million in 2008 to 6.8 million in 2014 (34). This HIV prevalence is the highest among other developing countries, which in turn have an increased prevalence compared to high-income countries (34). According to WHO Africa Statistics 2016, South Africa has achieved the Millennium Development Goal target on HIV incidence, with reduction in the country's HIV incidence from 2.23% in 2000 to 1.27% in 2014 (24). Worldwide, 36.7 million individuals were estimated to be living with HIV in 2015, of which 1.8 million were children (34). Encouragingly, there has been a notable decline in AIDS-related deaths globally from about 1.5 million in 2010 to about 1.1 million in 2015 (34).

There is a growing population of HIV-exposed but uninfected children as prevention of mother-to-child transmission (PMTCT) programmes are strengthened and the number of HIV-infected children declines (1, 35). Many studies in sub-Saharan countries, particularly in South Africa, have shown this positive impact of PMTCT programmes (1, 2, 35, 36). One South African study demonstrated a ten-fold reduction in mother-to-child transmission from 2004 to 2012 (1).

1.4.1. Diagnosis of HIV in children

From high-quality evidence, the WHO recommends the following regarding the diagnosis of HIV in children (37):

i. Infants below 18 months – HIV virology testing or screening assay to determine HIV exposure (PCR for testing and diagnosis; enzyme-linked immunosorbent assay (ELISA) for exposure);

ii. All HIV-exposed infants - HIV virology testing at four to six weeks of age or at the earliest opportunity thereafter (PCR);

iii. Infants with unknown and uncertain HIV status seen at primary health clinic – HIV exposure has to be determined (ELISA);

iv. Children older than 18 months - diagnostic assay (e.g. ELISA).

There are further indications for HIV testing based on breastfeeding and the use of antiretroviral treatment (37).

1.5. TB and HIV

TB is common in HIV-infected children (11, 14, 15, 29, 38, 39). It may cause severe, rapidly progressive disease and is associated with worsening of HIV disease (10, 39). According to the WHO Global Tuberculosis Report 2013, HIV-positive TB patients have worse treatment outcomes than HIV-negative TB cases (40). Treatment of TB disease in HIV-infected children can be complex due to drug interactions and the need to adjust ARV doses (29, 41). Also, adherence to multiple drugs is more challenging (29, 41). Confirming the diagnosis of TB would be useful to prevent unnecessary treatment and to ensure that children who do have TB are treated quickly.

1.6. TB and Malnutrition

Studies have shown that severely malnourished children are at high risk for severe lower respiratory tract diseases (38, 42-44). A study by Wafula *et al*. demonstrated high prevalence of lower respiratory tract infection among severely malnourished children (42). Other studies also showed an association with higher mortality (28, 42, 43). Malnutrition and TB may co-exist, making it difficult to diagnose TB due to non-specific clinical presentations, false-negative diagnostic tests and sometimes unremarkable chest X-ray findings (28, 44).

1.7. Radiology in pulmonary TB in children

1.7.1. CXR

CXR plays a vital role in the diagnosis of PTB especially in children (28). CXR features that are suggestive of TB include: enlarged hilar lymph nodes, lung opacification, miliary pattern opacification and persistent opacification not responding to treatment (29). Normal CXR findings have also been reported in children with TB, including those who are HIV-infected (45, 46). Adult features suggestive of TB on CXR, such as cavitatory disease, pleural effusions or lung collapse may also occur, especially in older children (26, 29). However, CXR interpretation may be difficult in children (21, 22, 47) due to anatomical differences that come with age, technical factors that may result in poor quality CXR (such as poor inspiration, suboptimal positioning and moving) and wide inter- and intra-observer variability in the interpretation of paediatric CXRs (28, 47).

HIV-infected children may present with atypical findings and a normal CXR (45, 46) and cavitation is apparently less common in this group (31). In a study by Srinakarin, that compared the CXRs of HIV-infected and HIV-uninfected children with PTB (26), the majority (75%) of HIV-infected and of HIV-uninfected (73%) children had interstitial (reticulonodular) infiltrates, while a third had hilar/mediastinal lymphadenopathy and only 2% of HIV-infected patients had miliary infiltrate. Pleural effusion and cavitatory disease were not seen in HIV-infected patients. Radiological changes were similar in HIV-infected and HIV-uninfected patients. In the HIV-uninfected group, 4.8% had pleural effusion and 2.4% showed cavitation. However, the study was small (93 children: 52 HIV-infected and 41 HIV-uninfected) and only three children had microbiologically-confirmed TB, all three of whom were HIV-uninfected(26).

The data from studies that have investigated CXR changes in children with suspected TB and/or HIV are summarised in Table 1.1. below

Table 1.1. Summary of studies comparing chest X-ray findings of children based on their TB or HIV status

Study	N	HIV Status	TB Status	Major CXR Findings	Comment
Srinakarin, J. *et al.* 2012 (26)	93	52 HIV-infected 41 HIV-uninfected	93 (90 mainly clinically and radiologically diagnosed / 3 microbiologically diagnosed)	HIV-infected group: i) 75% interstitial infiltration ii) 33% hilar/mediastinal lymphadenopathy HIV-uninfected group: i) 73% interstitial infiltration ii) 32% hilar/mediastinal lymphadenopathy	i) Radiographic findings were similar in both HIV-infected and HIV-uninfected groups.
Pitcher, R.D. *et al.* 2013 (45)	330	330 HIV-infected (303 moderate / severe clinical disease 225 moderate / severe immune suppression)	46 confirmed microbiologically at enrolment	i) 16% normal CXR ii) 28% pulmonary opacities iii) 13% reticulo-nodular pattern iv) 11% nodular (alone) pattern v) 5.8% mediastinal lymphadenopathy	i) HIV-infected children demonstrate CXR abnormalities commonly. ii) Extent of radiological abnormality is associated with age and clinical and immunological severity of HIV disease.
du Plessis, V. *et al.* 2011 (46)	92	92 HIV-infected	8 radiologically consistent with TB	i) 54% normal CXR ii) 34% parenchymal disease (28% airspace) iii) 21% cardiomegaly iv) 1% lymphadenopathy v) 1% pleural disease	i) Baseline CXR in outpatient is mostly normal. ii) Airspace disease is less likely to be seen in moderate or severe immune suppression.
Soeters, M. *et al.* 2005 (25)	238	95 HIV-uninfected 43 HIV-infected 100 unknown status	184 PTB (total) 80 HIV-infected 35 HIV-uninfected 69 unknown status	i) 58% opacification (HIV-infected group) ii) 42% mediastinal lymphadenopathy (HIV-infected group) iii) 30% pleural effusion (HIV-infected group)	i) Intrathoracic findings of TB in children were most common in the HIV-infected group as compared to other groups.

1.7.2. Definition of radiological terms

Radiological terms used in this study are defined as follows:

Airspace consolidation: alveolar filling disease, alveoli filled with thick material appearing as white (high density) with air bronchograms (low density) on CXR.

Ghon focus: round opacity which may have an overlying pleural reaction with cavity formation and resultant intra-bronchial spread with broncho-pneumonic consolidation as complications (48).

Lymphadenopathy: the presence of enlarged lymph nodes in the perihilar and mediastinal regions seen in AP and/or Lat views. Hilar lymphadenopathy is evidenced by the presence of an outwardly convex soft tissue density mass obscuring the hilar point, giving a doughnut sign on the lateral view. Mediastinal lymphadenopathy, including paratracheal and subcarinal regions, is seen by the mass effect into the airway with/without obstruction, right-sided shift of the para-oesophageal line and/or multi-shadowed density below the carina (48, 49). Careful consideration of the presence of the thymus in the mediastinum, which should not cause any mass effect, is of paramount importance.

Pleural and pericardial effusion: fluid in the pleural space and pericardium. In pericardial effusion, the heart shadow may be enlarged with a globular heart.

Nodular infiltration: diffuse, larger than 2 mm nodular infiltrates.

Miliary infiltration: diffuse, smaller than 2 mm nodular infiltrates.

Hyperinflation: the presence of seven or more anterior ribs visible above the diaphragm in the midclavicular line on an AP CXR, flattened diaphragms, and retrosternal air trapping on Lat CXR.

Heart enlargement: cardio-thoracic ratio is more than 60% in patients younger than two years and more than 50% in older children (46).

1.7.3. CT Scan, MRI and ultrasound in TB

Chest X-ray forms part of the workup in respiratory tract infection, especially TB, in both adults and children. It is the first-line imaging modality because it is easily accessible and available and has low radiation dose. Other imaging modalities can be used to assess the chest. Computed tomography (CT) scan does not form a standard part of the workup in the diagnosis of TB, especially in children due to higher radiation doses and higher costs of CT scan in comparison to CXR (31). CT may offer additional, more comprehensive images and

more information in some TB cases (31). Chest CT is more useful in lymphobronchial TB for both diagnosis and treatment planning (50). It is the gold standard for assessing the morphology of lung parenchyma (51).

Rizzi *et al.* identified that both CT and magnetic resonance imaging (MRI) were able to diagnose PTB (51). MRI does not use ionising radiation and was found to better identify parenchymal inhomogeneity, caseating necrosis, pleural involvement and lymphadenopathy due to its better contrast resolution (51). In South Africa and other developing countries, using MRI for the diagnosis of PTB is not feasible due to high costs and long MRI waiting times.

Ultrasound can identify superior mediastinal lymph nodes (52) but it is limited by depth, acoustic impedance of thoracic structures, especially ribs/bone and subjectivity. Its major role is appreciated when an easily-accessible pulmonary or mediastinal lesion needs to be biopsied (53). An ultrasound-guided aspiration biopsy of accessible lesions improves diagnostic yield and lessens the possibility of procedure-related complications (52). It is easily available, non-invasive, radiation- free and not expensive (52, 53).

1.8. Study aims and objectives

This study aims to compare the chest X-ray findings in HIV-infected and HIV-uninfected children with definite, laboratory- confirmed PTB.

1.8.1 Objectives

1. To describe and compare the frequency of CXR findings between children who are HIV-infected and those who are HIV-uninfected and have laboratory-confirmed PTB.
2. To investigate the impact of nutritional status on these CXR findings and within the study population.

2. Methods

2.1. Research paradigm

Secondary analysis of CXR data collected as part of a parent prospective study *"Diagnosis of tuberculosis in HIV-infected children – development of microbiological and immunological strategies".* The parent study was a study protocol, hitherto unpublished. The primary investigator for the parent study was Professor Heather Zar, Head of Department: Paediatrics and Child Health, University of Cape Town, who provided access to this database for the current study.

2.2. Sample

The parent prospective study was conducted at Red Cross War Memorial Children's Hospital (RX) and Nolungile Primary Health Care Centre (NG) in the Western Cape of South Africa. The patients from RX were all inpatient population and their CXRs were performed on admission or within 48 hours of admission. All NG patients were outpatients. Inclusion criteria for the parent study were children aged 13 years and younger with suspected pulmonary TB where informed consent was provided.

TB cases were suspected based on clinical and radiological findings, and the case findings were active.

The HIV status of the patients was documented if known or was obtained as part of the study. CXRs were performed as part of the routine management of these patients at enrolment. Ethics approval from the HREC of Faculty of Health Sciences, University of Cape Town, had been obtained for the parent study (ethics clearance number **Ref No: 045/2008)**. For the current study, the Ethics Clearance Certificate No: M140128 was obtained from the University of the Witwatersrand, see Appendix A.

2.2.1. Inclusion criteria for the current study

For the current study, only children (aged 13 years and less) with laboratory-confirmed, **proven** TB (positive TB culture and positive GeneXpert® Xpert® MTB/RIF) and with known HIV status were considered for inclusion into the study.

2.2.2. Exclusion criteria

i) Unreadable / unacceptable radiographs (as recorded by the majority of the readers).

ii) Patients with only a single available CXR view.

iii) Incorrect data.

Figure 2.1. below demonstrates how the sample size of the current study was obtained from the database of the parent study.

Children enrolled between 01 February 2009 and 30 April 2014 were included in this analysis (N = 1693), of these 137 were laboratory-confirmed TB; 20 of the children presented at a clinic, 110 were hospitalised and 7 were excluded.

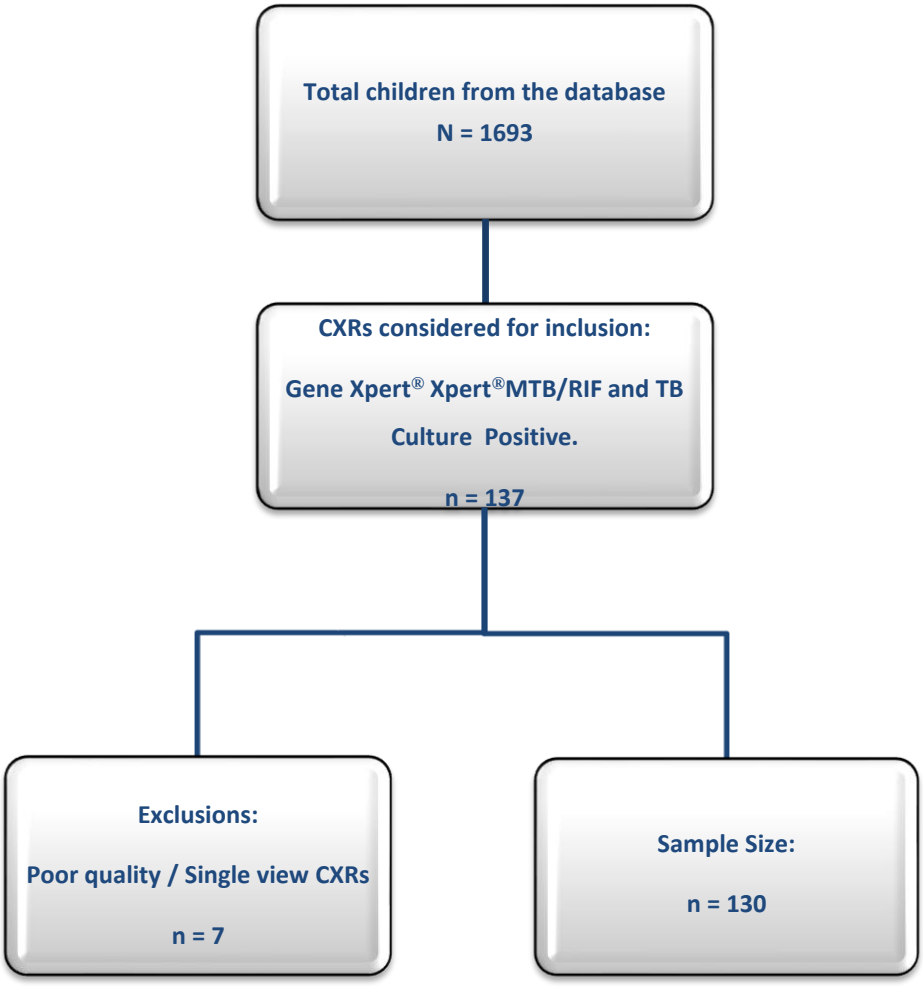

Figure 2.1 Derivation of final sample for the current study after application of exclusion criteria to chest X-rays selected from database

2.3. Materials and methods

All children enrolled in the parent TB diagnostic study who were aged 13 years and younger, who had culture-confirmed TB and a positive GeneXpert® Xpert® MTB/RIF on a respiratory specimen and who had a known HIV status were included. The clinical and laboratory data were recorded on an Excel spreadsheet as part of the larger study within which the current study is nested. The CXRs of 130 patients, who met the inclusion and exclusion criteria, as shown in Figure 2.1, were analysed. The CXRs, including both anteroposterior (AP) and lateral (Lat) views were read for each patient by two paediatricians (primary readers), each with more than 20 years of clinical experience, using a standardised reporting form (see Appendix B). The CXRs were interpreted from JPEG images and not from the picture archiving and communication systems (PACS) monitors. If there was disagreement in their final assessment of the CXR i.e. 'consistent with TB' or 'NOT' and 'CXR Normal' or 'NOT', (as shown in Appendix B), a senior paediatric radiologist acted as a tie-breaker. The majority answer was taken as the final answer. In the case where all three readers had different final assessments the radiographs were recorded as "Inconclusive".

The tie-breaker was not used for disagreements in the minor findings between the two primary readers. In the other parameters, a blank was regarded as a "No", if the final assessment was "normal CXR". All the readers of X-rays in the original database were given instructions and blinded to HIV status, clinical data and other laboratory results of all the patients, including TB and nutritional status of the patients. Z-scores of children younger than 120 months were provided, however, for the children over 120 months Z-scores were not provided and therefore not analysed. They were allocated into the unknown nutritional status group.

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2.4. Data collection

Data available from the parent study included demographic information, clinical information (e.g. nutritional status) and laboratory results (e.g. TB diagnosis and HIV status for each patient). Data on the CXR findings was documented on the standardised baseline CXR reporting form (Appendix B). This form had six defined categories – Lung parenchyma, Airway, Nodes, Pleura, Heart and Technical Quality. The tick sheet allowed for the

documentation of the presence of enlarged nodes at the paratracheal, hilar and subcarinal regions only, as well as calcification of these nodes.

2.4.1. Nutritional status

Nutritional status of a child is defined by the Centers for Disease Control and Prevention as follows (54):

- Adequately nourished: a Z-score between-2 and +2 using weight-for-height, height-for-age, or weight-for-age.
- Moderately malnourished: a Z-score between-3 and -2 using weight-for-height, height-for-age, or weight-for-age.
- Severely malnourished: a Z-score below -3 using weight-for-height, height-for-age, or weight-for-age. (54).

For the purposes of this study malnutrition (underweight-for-age) was defined as the weight-for-age with the Z-score of less than -2. Z-scores were only available for children under 120 months of age. Heights of the children were not available, hence Z-scores for weight-for-height and height-for-age were not obtained; weight for age was used to obtain the Z-score.

2.5. Outcome

A possible outcome of this study was to be able to define the features of PTB for HIV-infected patients (as compared to HIV-uninfected), in order to develop guidelines for X-ray interpretation to facilitate diagnosis of PTB in these patients.

2.6. Statistical analysis

2.6.1. Sample size calculation

The key research questions relate to the association between individual CXR features and HIV status. For this study, its demographics and its sample size, there was no prior knowledge of the expected differences in proportions of features identified between the two HIV groups before statistical analysis. A sample size calculation was based on 80% power, the 5% significance level and a two-tailed z-test for the difference in proportions.

Starting with a worst-case proportion of 50% for one group, the following illustrative sample size estimates, shown in Table 2.1, were obtained:

Table 2.1. Sample size estimates

Proportion (Group 1)	Proportion (Group 2)	Sample size
0.5	0.4 or 0.6	776
0.5	0.35 or 0.65	340
0.5	0.3 or 0.7	186
0.5	0.25 or 0.75	116

The sample size of 130 used in this study is thus quite low, and only fairly large differences in proportion can be detected with 80% power. Sample size calculations were carried out using G*Power software (55). The calculation assumes equal group sizes; sample size requirements increase further for unbalanced groups such as this study. It is clear from these calculations that the sample size for this study was too small for statistical significance to be detected where differences in proportions were small. This study was limited, however, by the number of patients in the original database.

2.6.2. Data analysis

Data analysis was carried out using SAS (SAS Institute Inc., *SAS Software, version 9.3 for Windows,* Cary, NC, USA: SAS Institute Inc. (2002-2010)).

Between-group differences for HIV status were tested as follows:
The X^2 test was used to assess the relationships between categorical variables. Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively.
The following scale of interpretation was used:

0.50 and above	high/strong association
0.30 to 0.49	moderate association
0.10 to 0.29	weak association
below 0.10	little if any association

The relationship between continuous and categorical variables was assessed by the t-test. Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank sum test was used. The strength of the associations was measured by the Cohen's d for parametric tests and the r-value for the non-parametric tests.

0.80 and above	large effect
0.50 to 0.79	moderate effect
0.20 to 0.49	small effect
below 0.20	near zero effect

For the between-group testing for underweight-for-age, HIV status was included as a covariate. For categorical variables, this was accomplished by using the Cochran-Mantel-Haenszel test, while for continuous variables, a general linear model with HIV status and nutritional status as fixed effects was used.

The 5% significance level was used throughout, unless specified otherwise.
Results were expressed as frequencies and percentages for categorical variables.

3. Results

3.1. Study population

The CXRs of 130 children were included in the study, see Figure 2.1. There were 110 (84.6%) patients from Red Cross War Memorial Children's Hospital (RX) and 20 (15.4%) from Nolungile Primary Health Care Centre (NG). Fifty-four patients (41.5%) were females with a male to female ratio of 1.4:1.

The ages ranged from 2 – 156 months with a median age of 45.7 months, interquartile range (IQR) 18.0 - 81.3 months.

There were 35 (26.9%) HIV-infected patients and 95 (73.1%) HIV-uninfected patients.

Table 3.1. below compares the HIV-infected and HIV-uninfected children with regards to health care site, gender and age. There was no statistically significant association between HIV status and health care site or HIV status and gender, however there was a statistically significant association between the HIV status and age. HIV-infected children were older, median age of 64.7months, IQR 44.2 – 91.3 months, than those who were HIV-uninfected, median age 27.3 months, IQR 16.6 – 62.4 months,

p = 0.005.

Table 3.1. Comparison of HIV-infected and HIV-uninfected patients in relation to health care site, gender, age and nutritional status

Variable	Category	Overall	Infected	Uninfected	*p*-value (effect size)
		Number of patients (%) N = 130	Number of patients (%) N = 35	Number of patients (%) N = 95	
Health care site	NG	20 (15.4)	4 (11.4)	16 (16.8)	0.59
	RX	110 (84.6)	31 (88.6)	79 (83.2)	
Gender	F	54 (41.5)	17 (48.6)	37 (38.9)	0.42
	M	76 (58.5)	18 (51.4)	58 (61.1)	
Age (months)	Median	45.7	64.7	27.3	0.005 (r = 0.25)
	IQR	18.0 to 81.3	44.2 to 91.3	16.6 to 62.4	
Underweight -for-age	No	74 (56.9)	14 (40)	60 (63.2)	0.008 (phi = 0.26)
	Yes	39 (30)	17 (48.6)	22 (23.2)	

NG-Nolungile Primary Health Care Centre; RX-Red Cross War Memorial Children's Hospital; phi: 0.10 – 0.29 = weak association; r-value 0.20 to 0.49 = small effect

3.2. CXR findings

The findings from the CXRs are summarised in Tables 3.2 to 3.5 below.

3.2.1. Overall

A total of 122 (94%) CXRs were found to be abnormal, while the remaining 8 (6%) were normal. Eighty (62%) CXRs were consistent with PTB, while 42 (32%) were considered to be inconclusive. None of these outcomes were significantly associated with HIV status or nutritional status.

The summary of the frequencies and the percentages of the CXR findings and their consistency with PTB are shown in Table 3.2 below.

3.2.2. Lung parenchymal findings

The most prevalent CXR finding was airspace consolidation, seen in 78 (60%) of the patients. No CXRs demonstrated a Ghon focus or parenchymal calcification. There were no significant associations between any of these findings and HIV status or nutritional status. The summary of the frequencies and the percentages of the positive lung parenchymal findings are shown in Table 3.3 below.

3.2.3. Lymphadenopathy findings

The commonest site of enlarged lymph nodes was in the perihilar region of 33 CXRs (25.4%). No CXRs demonstrated any calcified lymph nodes. There were no significant associations between the presence and location of lymphadenopathy and HIV status or nutritional status. The summary of the frequencies and the percentages of the presence and the location of lymphadenopathy are shown in Table 3.4 below.

3.2.4. Pleural and cardiac pathology

Eleven (8.5%) of the CXRs showed pleural effusion. There was no significant association between pleural effusion and HIV status. The summary of the frequencies and the percentages of the presence of the pleural effusion are shown in Table 3.3 below. No patients had cardiomegaly or pericardial effusion.

3.2.5. Airway compression

Ten (7.7%) of the CXRs showed airway compression. There was no significant association between airway compression and HIV status or underweight-for-age. The commonest site of airway compression was the left main bronchus, found in 8 CXRs (6.2%).

The summary of the frequencies and the percentages of the positive findings in airway compression with comparison to HIV and underweight-for-age are shown in Table 3.5 below.

Table 3.2. Final assessment of chest X-rays as well as final status of radiological diagnosis of TB in relation to HIV and nutritional status

Variable	Category	Overall	HIV status (N = 130)			Nutritional status (N = 113)		
			Infected	Uninfected	*p*-value	Adequately nourished	Underweight-for-age	*p*-value
Total		**Number (%) n = 130**	**Number (%) n = 35**	**Number (%) n = 95**		**Number (%) n = 74**	**Number (%) n = 39**	
CXRN	Normal	8 (6.2)	3 (8.6)	5 (5.3)	0.81	6 (8.1)	2 (5.1)	0.91
CXRTB	Yes	80 (61.5)	21 (60)	59 (62.1)		46 (62.2)	28 (71.8)	
	Inconclusive	42 (32.3)	11 (31.4)	31 (32.6)		22 (29.7)	9 (23.1)	

CXRN *- Normal chest X-ray;* ***CXRTB*** *- Chest X-ray abnormal and consistent with PTB; N-overall population*

Table 3.3. Comparison of chest X-ray positive lung parenchymal findings in relation to HIV and nutritional status

Variable	Category	Overall	HIV status (N = 130)			Nutritional status (N = 113)		
			Infected	Uninfected	*p*-value	Adequately nourished	Underweight-for-age	*p*-value
Total		Number (%) n = 130	Number (%) n = 35	Number (%) n = 95		Number (%) n = 74	Number (%) n = 39	
Airspace consolidation	No	50 (38.5)	13 (37.1)	37 (38.9)	> 0.99	29 (39.2)	15 (38.5)	0.81
	Yes	78 (60)	21 (60)	57 (60)		45 (60.8)	22 (56.4)	
	Inconclusive	2 (1.5)	1 (2.9)	1 (1.1)	-	0 (00)	2 (5.1)	-
Hyperinflation	Yes	3 (2.3)	1 (2.9)	2 (2.1)	> 0.99	3 (4.1)	0 (0)	0.17
Cavitation	Yes	13 (10)	1 (2.9)	12 (12.6)	0.18	7 (9.5)	1 (2.6)	0.34
Nodular infiltration	Yes	8 (6.2)	1 (2.9)	7 (7.4)	0.68	4 (5.4)	3 (7.7)	0.47
Miliary infiltration	Yes	4 (3.1)	0 (0)	4 (4.2)	0.57	2 (2.7)	2 (5.1)	0.29
Volume loss	Yes	4 (3.1)	0 (0)	4 (4.2)	0.57	3 (4.1)	0 (0)	0.29
Air trapping	Yes	1 (0.8)	0 (0)	1 (1.1)	> 0.99	0 (0)	1 (2.6)	0.1
Perihilar streakiness	Yes	10 (7.7)	4 (11.4)	6 (6.3)	0.46	3 (4.1)	5 (12.8)	0.11
Pleural effusion	Yes	11 (8.5)	2 (5.7)	9 (9.5)	0.73	9 (12.2)	0 (0)	0.025

Table 3.4. Comparison of the presence and location of lymphadenopathy in chest X-rays in relation to HIV and nutritional status

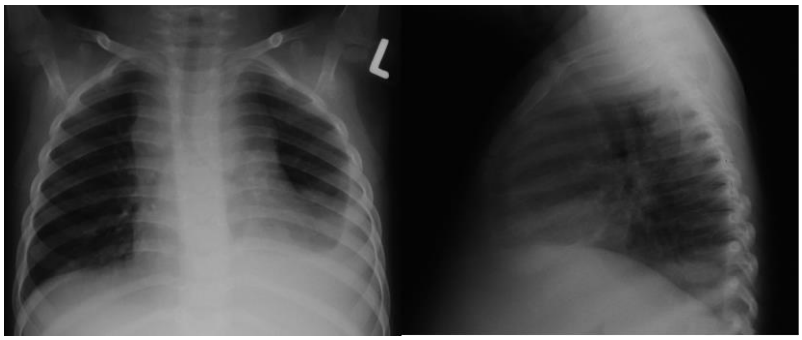
Variable	Category	Overall	HIV status (N = 130)			Nutritional status (N = 113)		
			Infected	Uninfected	*p*-value	Adequately nourished	Underweight-for-age	*p*-value
Total		**Number (%) n = 130**	**Number (%) n = 35**	**Number (%) n = 95**		**Number (%) n = 74**	**Number (%) n = 39**	
Lymph adenopathy	Yes	42 (32.3)	11 (31.4)	31 (32.6)		29 (39.2)	12 (30.8)	
Perihilar adenopathy	Yes	33 (25.4)	8 (22.9)	25 (26.3)	0.82	23 (31.1)	9 (23.1)	0.41
Subcarinal adenopathy	Yes	6 (4.6)	1 (2.9)	5 (5.3)	> 0.99	5 (6.8)	1 (2.6)	0.41
Paratracheal adenopathy	Yes	22 (16.9)	7 (20)	15 (15.8)	0.6	16 (21.6)	6 (15.4)	0.34

Table 3.5. Comparison of chest X-ray airway compression findings in relation to HIV and nutritional status

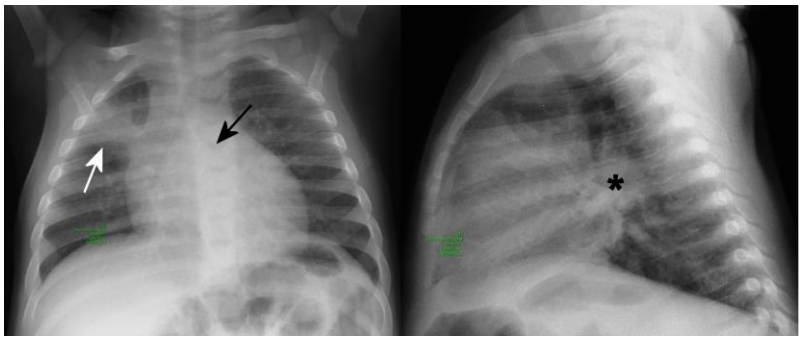
Variable	Category	Overall	HIV status (N = 130)			Nutritional status (N = 113)		
			Infected	Uninfected	*p*-value	Adequately nourished	Underweight-for-age	*p*-value
Total		**Number (%) n = 130**	**Number (%) n = 35**	**Number (%) n = 95**		**Number (%) n = 74**	**Number (%) n = 39**	
Airway compression	Yes	10 (7.7)	3 (8.6)	7 (7.4)	>0.99	7 (9.5)	3 (7.7)	0.71
RPT airway compression	Yes	1 (0.8)	1 (2.9)	0 (0)	0.27	1 (1.4)	0 (0)	0.27
RMB airway compression	Yes	5 (3.8)	2 (5.7)	3 (3.2)	0.61	4 (5.4)	1 (2.6)	0.38
BI airway compression	Yes	2 (1.5)	1 (2.9)	1 (1.1)	0.47	1 (1.4)	1 (2.6)	0.78
LMB airway compression	Yes	8 (6.2)	3 (8.6)	5 (5.3)	0.43	6 (8.1)	2 (5.1)	0.41

RPT *- Right paratracheal;* ***RMB*** *- Right main bronchus;* ***BI*** *- Bronchus intermedius;* ***LMB*** *- Left main bronchus*

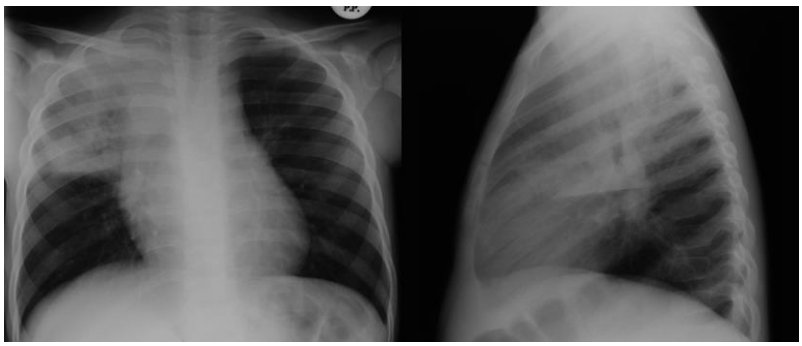
Typical radiological findings are shown in the CXR images below in Figure 3.1:



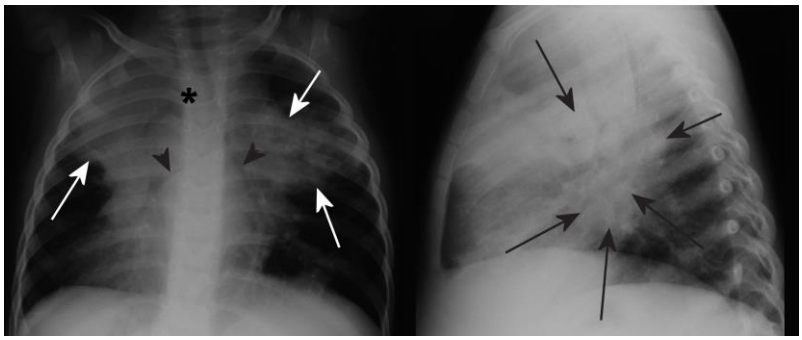
18-month-old girl.
Well nourished, HIV–uninfected.
Left pleural effusion.



8-month-old girl.
Malnourished, HIV-uninfected.
Right upper lobe airspace consolidation ***(white arrow),*** perihilar lymphadenopathy ***(asterisk)*** and left main bronchus compression ***(black arrow).***



8-year-old boy.
Malnourished, HIV-infected.
Right upper lobe airspace consolidation with air bronchograms.



2.5-year-old girl.
Well nourished, HIV-uninfected.
Multilobar airspace consolidation ***(white arrows).*** Doughnut sign ***(black arrows)*** indicating perihilar adenopathy.
Paratracheal adenopathy ***(asterisk)*** as seen by tracheal displacement to the left.
Compression of bronchus intermedius as well as left main bronchus ***(arrow heads)***.

Figure 3.1. Examples of radiological features of PTB on frontal and lateral chest X-rays

3.3. Nutritional status

Thirty-nine of the 130 patients (30.0%) were classified as underweight-for age, while 74 (56.9%) were classified as adequately nourished. The nutritional status of the remaining 17 (13.1%) patients was not determined, since either weight data were missing (n = 2) or the patients were older than 120 months, where the weight-for-age Z-score could not be determined (n = 15). These patients were not included in the between-group analysis with regards to the nutritional status, reducing the sample size for this analysis from 130 to 113.

Table 3.6 below compares the adequately nourished and underweight-for-age patients with regards to health care site, gender and HIV status.

Table 3.6. Comparison of nutritional status of children with pulmonary TB in relation to health care site, gender and HIV status

Variable	Category	Adequately nourished	Underweight-for- age	*p*-value (effect size)
		Number of patients (%) N = 74	Number of patients (%) N = 39	
Health care site	NG	18 (24.3)	1 (2.6)	0.004
	RX	56 (75.7)	38 (97.4)	
Gender	F	32 (43.2)	11 (28.2)	0.046
	M	42 (56.8)	28 (71.8)	
Age (months)	Median	35.9	22.3	-
	IQR	18.0 to 56.5	13.5 to 80.7	
HIV status	Infected	14 (18.9)	17 (43.6)	0.008 (phi = 0.26)
	Uninfected	60 (81.1)	22 (56.4)	

NG-Nolungile Primary Health Care Centre; RX-Red Cross War Memorial Children's Hospital; (phi: 0.10 – 0.29 = weak association)

For those patients whose nutritional status was known, there was a significant association between health care site and nutritional status *(p* = 0.004*).* Underweight-for-age patients came almost entirely from the RX health care site (97.4%), the hospitalised population. There was also a significant association between HIV status and nutritional status (*p* = 0.008). Of the adequately nourished group, only 18.9% (14/74 patients) were HIV-infected, while this status constituted 43.6% (17/39 patients) of the underweight-for-age children.

Underweight-for-age children were younger, median age of 22.3 months, IQR 13.5 - 80.7, than the adequately nourished children, median age of 35.9 months, IQR 18.0 – 56.5.

There was no statistically significant association between gender and HIV status. However, a statistically significant association was found between gender and nutritional status, with boys (28/70 patients, 40%) more likely to be underweight-for-age than girls (11/ 43 patients, 26%), $p = 0.046$.

Tables 3.2. to 3.5 above also show the impact of nutritional status on CXR findings of children with PTB. There was no statistically significant difference between the well-nourished and the underweight-for-age group, except for the presence of pleural effusion. A significant association was noted between pleural effusion and adequate nutrition ($p = 0.025$); nine of the eleven patients with pleural effusion (12.2 %) were adequately nourished. Two (5.7%) of these patients were HIV-infected and 7 (7.3%) were HIV-uninfected.

4. Discussion

In this study, most children (94%) with laboratory- confirmed PTB had an abnormal CXR, with only 6% of children having a normal X-ray. However, there were no statistically significant differences in CXR findings between HIV-infected and HIV-uninfected children with PTB. A possible reason for this finding could be that the HIV-infected children were well-controlled on ARVs, with consequently higher CD4 counts and undetectable viral loads. Pitcher noted that the extent of radiological abnormality was associated with age, clinical and immunological severity of HIV disease and in his study, HIV infected patients had CXR abnormality commonly (45). A future project from this study could look at the effects of CD4+lymphocytes, viral load and ARV duration on these CXR findings.

Nutritional status was associated with HIV status and with hospitalisation (Table 3.6), but was not significantly associated with specific CXR findings other than pleural effusion, which occurred only in well-nourished children and was not identified in any of the underweight-for-age children. Most of underweight children came from the hospital setting; they were likely to be more severely ill whereas the clinic patients were outpatients in a better state of general health. Weight -for- age is a multifaceted indicator (56). It can reflect both stunting, wasting or both which means weight can be easily affected by multiple factors like acute and or chronic infection (56). Chronically ill child is more likely to be in the hospitalised population.

Normal chest X-ray findings are possible in patients with HIV and/or PTB. These results are consistent with other studies that investigated CXR changes in HIV-infected children; 16% of these children were found to have normal CXRs in one study (45) and an even higher percentage (54%) were identified in another (46). The higher percentage of normal CXRs in these studies in comparison to the current study (which showed only 6% normal CXRs) can be attributed to the fact that both of these studies examined outpatient clinic patients, whereas the majority of patients in the current study were hospitalised and were thus more likely to be acutely ill with abnormal CXR findings.

Table 4.1 below compares the current study with three other studies of CXR findings in children with PTB, and Table 4.2 compares the current study with seven other studies of CXR findings of HIV-infected and HIV-uninfected children with PTB.

Table 4.1. Comparison of the current study with other studies of chest X-ray findings of children with pulmonary TB

	Current Study South Africa	Boloursaz, M.R, *et al.* 2010 (57) Iran	Milkovic, D, *et al.* 2005 (58) Croatia	Pitcher R.D, *et al.* 2014 (11) South Africa
Age range (months)	2 - 156	5 - 180	< 168	1.1 - 141.7
Mean age (months)	53.3	Not stated	76.8	23.4
Modality	CXR	CXR and CT chest	CXR	CXR
Number of patients: **In-patient (HIV+/HIV-)** **Outpatient (HIV+/HIV-)**	130 110 (31/79) 20 (4/16)	70 All in-patients, HIV unknown	204 All in-patients, HIV unknown	330 All outpatients All HIV-infected
TB diagnosis	All proven positive by culture and PCR	Confirmed (clinically, radiologically and biochemically)	Clinically diagnosed 17% culture positive	46 Microbiologically diagnosed
HIV status: HIV+ **HIV-**	27% 73%	Unknown	Unknown	All HIV-infected
Normal CXR: **HIV+** **HIV-**	7.7% 11.4% 6.3%	None	None	16 % All HIV-infected None
Lymphadenopathy total **Commonest site**	32.3% Perihilar 25%	70% Right hilar	84% Right hilar 50.5%	19.5% Mediastinal
Parenchymal changes **(commonest pattern)** **HIV+** **HIV-**	Airspace consolidation 60% 60%	Airspace consolidation 26%	Airspace consolidation 61%	Bronchial wall thickening 69.6% None
Airway compression **(commonest site)** **HIV+** **HIV-**	Left main bronchus 6.2% 8.6% 5.3%	Right middle lobe 7%	Right lower lobe 4.4%	Not specified 15.8% None

Table 4.2. Comparison of this study with other studies comparing chest X-rays of HIV-infected and HIV-uninfected children with TB

	Current Study South Africa	Srinakarin, J. *et al.* 2012 (26) Thailand	Soeters, M. *et al.* 2005 (25) South Africa	Schaaf, HS 2007 (15) South Africa
Age (months)	2 – 156	4 – 144	<180	< 156
Mean / median (months)	52.8 / 45.6	86.4 (mean)	25.2 (median)	31 (median)
Patients: **In-patient (HIV+/HIV-/unknown)** **Out-Patient (HIV+/HIV-)**	130 110 (31/79/0) 20 (4/16)	93: Mostly outpatients	238 All (43/95/100) None	596 All (133/281/182) None
TB diagnosis	All proven positive by culture and PCR	Mainly clinically and radiologically proven TB	Total 124 Biochemically proven (52%) clinically suspected (48%)	Culture Proven TB
HIV status: HIV+ **HIV–** **Not tested**	35 (27%) 95 (73%) 0	52 (56%) 41 (44%) 0	43 (18%) 95 (40%) 100 (42%)	133 (22%) 281 (47.1%) 181 (30.5%)
Normal CXR: HIV+ **HIV-**	4 (11.4%) 6 (6.3%)	None	3* (7%) 14* (15%)	5 (4%) 32 (11.7%)
Lymphadenopathy (Overall) **HIV+** **HIV-** **Commonest site (HIV+/HIV-)**	42† (32.3%) 11† (31.4%) 31† (32.6%) Perihilar 25% (23% / 26%)	Hilar/mediastinal † 17† (32.6%) 13† (31.7%) Not specified	Mediastinal † 18*† (42%) 38*† (40%) Not specified	51.9% 56.3% 51.8% Perihilar 14.1% (36.5/33.2) %
Parenchymal changes (commonest pattern) **Total** **HIV+** **HIV-**	Airspace consolidation 78/130 (60%) 21/35 (60%) 57/95 (60%)	Interstitial (reticulonodular) infiltration 69/93 (74%) 39/52 (75%) 30/41 (73.1%)	Airspace consolidation 56/138* (40.6%) 18/43* (41.9%) 38/95* (40%)	Airspace consolidation 285 (51.4%) 128 (66.7%) 84 (46.7%)
Airway compression (commonest site) n/% **HIV+** **HIV-**	Left main bronchus: 8 (6.2%) 3 (8.6%) 5 (5.3%)	Not stated	Not stated	Not stated 17 (13.5 %) 54 (19.7%)

* Only patients with known HIV status, TB status and read CXR are tabulated here. Those with unknown HIV, TB status and CXR findings are not included in these calculations. † Overall finding.

Table 4.2. cont. Comparison of this study with other studies comparing chest X-rays of HIV-infected and HIV-uninfected children with TB

	Madhi, S. *et al.* 2000 (59) South Africa	**Iriso, R. 2005 (60) Uganda**	**Kiwanuka 2002 (61) Uganda**	**Palme, I.B. 2002 (62) Ethiopia**
Age (months)	2 - 144	2 - 60	< = 168	0 - 168
Mean / median (months)	12.5 (HIV+) and 20 (HIV-) (median)	25.5 (mean)	36 (median)	Not stated
Patients: **In-patient (HIV+/HIV-/unknown)** **Outpatient (HIV+/HIV-)**	98* All in-patients	126 All in-patients	88* All in-patients	517 (234 * with PTB) 72 (Not specified) 445 (Not specified)
TB diagnosis	Clinical, radiological and microbiological	Clinical, radiological and microbiological Culture-proven = 36(28.6%)	Clinical, radiological and microbiological	Mainly clinically. (190 culture-positive)
HIV Status: HIV+ **HIV–** **Not tested**	39* (39.8%) 59* (60.2%) 0	62 (49%) 64 (51%) 0	43* (49%) 45* (51%) 0	28* (48%) with PTB 206* (45%) with PTB 0
Normal CXR: HIV+ **HIV-**	Not stated.	None	None.	3% 18%
Lymphadenopathy (Overall) **HIV+** **HIV-** **Commonest site (HIV+/HIV-)**	Hilar adenopathy 46* (46.9%) 17* (43.6 %) 29* (49.2%) Not specified.	 44 (35%) 37 (29.4%) Perihilar 35% (39%/31%)	Hilar adenopathy 53*(60.2) 24* (56%) 29* (64%) Not specified.	Hilar adenopathy 10 (17%) 115 (25%) Not specified
Parenchymal changes **(commonest pattern)** **Total** **HIV+** **HIV-**	Airspace consolidation 54* (55.1%) 26* (66.7%) 28* (47.5%)	Airspace consolidation 72 (57.1%) 37 (60%) 35 (55%)	Airspace consolidation 47* (53.4%) 28* (65.1) 19* (42.2)	Not specified.
Airway compression **(commonest site) n/%** **HIV+** **HIV-**	Not stated.	Not stated.	Not stated.	Not stated.

* Only patients with known HIV status, TB status and read CXR are tabulated here. Those with unknown HIV, TB status and CXR findings are not included in these calculations. † Overall finding.

The most common CXR finding in both HIV-infected (60%) and HIV-uninfected (60%) children with PTB was airspace consolidation. This is consistent with prior studies where this finding was seen in the ranges of about 26% (57) - 61% (58) of patients. See Table 4.1 and 4.2 above. A study by Pitcher et al found bronchial wall thickening to be the commonest CXR finding, implicating lower respiratory tract infections and aspiration as possible causes for the bronchial wall thickening (11). That study had a younger population (median age 23.4 months, IQR 11.1-47.4) than the current study, and all their patients were HIV-infected with only 13.9 % of patients having PTB; that could account for the difference.

The current study showed that miliary and nodular infiltration, cavitation, hyperinflation, volume loss and perihilar streakiness were uncommon CXR findings regardless of the HIV or nutritional status. These features demonstrated low percentages in both HIV-infected and HIV-uninfected patients, with no statistical difference between all these findings in the two HIV groups (25, 60, 61).. In a study from Thailand similar to the current study of 93 children with PTB and known HIV status, Srinakarin reported that in the HIV-infected group, 2% of patients demonstrated miliary infiltration and **no** evidence of cavitation In the HIV-uninfected group, only 2.4% showed cavitation. However, the final assessment also showed no statistically significant difference between these two groups (26).

Cavitation is not a common feature of primary TB. It is usually seen in teenagers and adults as part of the postprimary spectrum, which includes reinfection and reactivation (63). The frequency of cavitation on CXR in children with PTB, varies greatly in the literature, from as low as 2.5% (Milkovic, 39) to 22% (25). These findings are in line with the current study, which found cavitation in only 10% (13 patients) of the patients and majority of them (7 out of 13) were in an older age group.

To our knowledge Schaaf *et al*, has the largest cohort to date (596 culture-positive TB children) with almost the same demographics and age distribution as the current study. They showed that HIV-infected children were more likely to demonstrate cavitation and airspace opacifications when compared to HIV-uninfected children (15). As high as 26.2 % of HIV-infected children showed cavitation in that study, as compared to 16.1 % of HIV-uninfected children (15). This study is summarised in Table 4.2 above. Madhi *et al*'s findings also

showed a difference between HIV-infected and HIV-uninfected children. These are the only studies that demonstrated such a difference (15, 59).

Lymphadenopathy is a common finding in children with PTB. The current study showed no statistically significant associations between HIV status or nutritional status and the presence of lymphadenopathy on radiographs. Lymphadenopathy was more likely to be located in the perihilar region, irrespective of the nutritional status and HIV status.
The current study and others mentioned in Table 1.1., Table 4.1. and Table 4.2. clearly confirm that hilar and mediastinal lymphadenopathy is common in both HIV and/or PTB patients with Milkovic and Boloursaz reporting as high as 80% and 70 % perihilar involvement respectively as compared (57, 58). All patients in the Milkovic *et al.* and Boloursaz *et al.* studies were hospitalised, TB-proven children with unknown HIV status and nutritional status. No study has shown that lymphadenopathy is more common in HIV-infected or HIV-uninfected patients.

Most CXR studies found that airway compression was not a common finding in children with PTB (26, 58, 64). However, when a superior modality like CT was used, detection of air way compression was reported more frequently. The current study found airway compression in 7.7% of the patients. This is comparable with the study by Boloursaz *et al.*, who found airway compression on CXR in 7% of patients (57). Patients in that study were also children and were clinically, radiologically and biochemically TB-proven with unknown HIV status (38). Patients from the Boloursaz *et al.* study were found to have higher airway compression percentage when CT was used (12.8%), as compared to CXR (7%) (57), confirming the superiority of CT over CXR for airway evaluation. There was no significant difference between HIV-infected and HIV-uninfected groups or between malnourished and adequately nourished groups with regard to airway compression in the current study.

There are differing reports of the commonest site of airway compression. The finding in the current study that the commonest site of airway compression was the left main bronchus is in keeping with a prior study by Andronikou, of 100 children from the same region who were clinically suspected of having PTB (65). In those children, CT scan was used to detect mediastinal and hilar adenopathy and the left main stem compression was found in 28% of cases with left hilar adenopathy (65).This may be explained by the anatomy of the left main

bronchus which is longer, narrower and more horizontal as compared to right main bronchus (66). However, Boloursaz et al found that right middle lobe demonstrated collapse more commonly than other lobes both on CT and CXR (57). They found that CT had a higher detection rate than CXR and CXR was a poor identifier of TB features in children when compared to CT (57). However, CT does not form part of the routine workup for TB in children and it is not recommended because of the high associated radiation dose.

No patient had pericardial effusion or cardiomegaly in this study. Studies by Srinakarin (26) and Boloursaz also did not show cardiac involvement in children, even when CT was used (57). These are not common presenting findings in the CXR of a child with TB (15, 26, 59, 60). Children normally present with radiological features of primary PTB.

There was no statistical significance between pleural effusion and HIV status. These findings are similar to those of prior studies (26, 59, 60).

Malnourished children are known to be prone to lower respiratory tract infections (38, 42, 44, 67). No studies were found that compared the CXR findings of well-nourished and malnourished or underweight for age children, with or without PTB. Most studies revealed that airspace consolidation was common in the CXR of a malnourished child (28, 38, 42-44, 68). These were not comparative studies and in most of them the HIV and/or TB status of the children was not known. The current study is in agreement that airspace consolidation was indeed common in a child with PTB irrespective, of the HIV and/or nutritional status.

Pleural effusion was the only CXR finding found as a differentiating feature between the well-nourished and the underweight-for-age group. TB and malnutrition co-exist (28, 44), as do TB and HIV resulting in a “terrible disease triad” with treatment challenges, especially in paediatrics. The current study confirmed the co-existence of PTB, HIV and malnutrition, finding that 49% of HIV-infected children with confirmed PTB were underweight-for-age. This is in keeping the findings of prior studies (25, 59, 60, 62). There was a significant association between pleural effusion and nutritional status *(p = 0.025*). Pleural effusion was present in 12.2% of the adequately nourished patients, while none of the underweight-for-age patients had this feature. Pleural effusion represents a hypersensitivity reaction to *M. tuberculosis*; it is possible that malnourished children may have impaired immunity and may

not be able to mount a hypersensitivity reaction. Further studies of the pathogenesis of pleural effusion are indicated.

The majority of the underweight-for-age children in the current study were male (72%). This is consistent with other studies showing that boys were more likely to be malnourished (69, 70). A study conducted in seven sub-Saharan African countries (Benin, Burundi, Cameroon, Côte d'Ivoire, Mali, Chad and Togo) which examined the burden of malnutrition amongst HIV-infected children, TB status unknown, showed that boys were more likely to be malnourished with 63%, 55% and 67% of children demonstrating acute, chronic and mixed malnutrition respectively were shown to be boys (69). This study consisted of **older** children (median age ten years, IQR 7-13 years) (69). A meta-analysis conducted across ten sub-Saharan African countries investigating children **under** five years of age, TB and HIV status unknown, also found that boys were more likely to be malnourished than girls (70). Wells suggested that boys are more vulnerable to environmental stress than girls; this could be a possible explanation for this phenomenon (71).

The current study have clearly demonstrated the "vicious cycle" of causative effects between HIV and malnutrition, as described by Jesson *et al*. (62, 69, 72-74). The current study showed a significant association between HIV status and nutritional status ($p = 0.008$) and that an HIV-infected child is about twice as likely to be malnourished (48.6%) than an HIV uninfected child (23.2%). This is due to the immunological effects and opportunistic infections, especially gastrointestinal disease, associated with HIV (69, 75). Miller goes on to implicate changes in the metabolic state and socioeconomics of the HIV-infected children (75). A study similar to ours from Kampala, Uganda also showed that more HIV-infected children (65%) were malnourished than HIV-uninfected children (42%), $p = 0.020$ (60).

The current study showed that the underweight-for-age child was younger (median age 22.3 months) than the overall study population (median 45.7 months. This is in keeping with what Palme *at al*. found in a study done in Ethiopia (62). Both of these studies have almost similar socioeconomic status which could be attributed to this finding, over and above the underdeveloped immune system of the of a younger child.

Furthermore, we showed that an underweight-for-age child was more likely to be hospitalised shown by a significant association between health care site and nutritional status *(p* = 0.004). The underweight-for-age patients came almost exclusively from the hospital setting, most likely due to the fact that malnutrition affects the immune system, making a child prone to recurrent infections and failure to thrive and thereby needing hospital care.

4.1. Limitations of the current study

This study used a pre-existing database, hence the sample size for **this** study was limited by the number of patients that were GeneXpert® Xpert® MTB/RIF and culture **proven** PTB in the larger database. Patients in the original database that had clinically **suspected** PTB but not proven by both of these two modalities were excluded from the current study. This strict inclusion criterion limited the sample size but made this study unique. Only one other study of similar size or more, which had TB culture confirmed in **all** the patients could be found in the literature (15). The majority of patients in other studies had PTB mostly diagnosed on clinical grounds.

Regarding the ability of readers to record all information as comprehensively as possible, reading CXRs in JPEG format instead of Digital Imaging and Communications in Medicine (DICOM) images off PACS monitors may have limited the identification of some of the CXR features e.g. airway compression, as windowing and other specific features could not be applied to JPEG images. Additionally, the tick sheet was complex with many slots to fill and some of the slots were left blank by the readers.

4.2. Future applications

A further project arising from this study could look at the effects of CD4+lymphocytes, viral load, and ARV duration on these CXR findings.

A larger, prospective study could be considered, with an adequate sample size to demonstrate if there are indeed differences between the radiological findings of HIV-infected and HIV-uninfected children with PTB, and any relationship to nutritional status. However, the majority of the comparative studies done so far, including this study, have not

shown significant trends to imply that a different result could be expected from a larger study. Very few studies have shown some radiological differences between HIV-infected and HIV-uninfected children with PTB, and those that do were also limited by sample size (59), (15). No study has proven that a CXR of a child with PTB will have different radiological features based on the child's HIV status. The current approach where clinical, radiological and laboratory results are all taken into consideration when diagnosing TB in children, should still be followed, even though there are still TB diagnostic challenges, until such time that a better approach is identified (31).

Our finding that HIV-infected children with TB are more likely to be malnourished and needing hospitalisation emphasises the importance of better primary health care in preventing malnutrition, potentially avoiding the escalating health care costs associated with this "terrible disease triad".

5. Conclusion

This study showed that radiological features in children with laboratory-confirmed PTB are similar for HIV-infected and HIV-uninfected patients. This is in keeping with the majority of other similar studies performed.

In both HIV-infected and HIV-uninfected groups, the most common radiological abnormalities on CXR of children with PTB were airspace consolidation followed by hilar/mediastinal lymphadenopathy.

The inclusion of only patients with proven TB (GeneXpert® Xpert® MTB/RIF and culture positive) and the fact that most of the patients had their HIV status known makes this study significant, important and unique, despite small patient numbers.

Concerning nutritional status, pleural effusion was found only in adequately nourished patients and underweight-for-age occurred more commonly in the children who were HIV-infected, hospitalised or male.

Appendix A: Ethics Clearance Certificate

R14/49 Dr Thandi Eunice Buthelezi and Prof H Zar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140228

NAME: (Principal Investigator)	Dr Thandi Eunice Buthelezi and Prof H Zar
DEPARTMENT:	Radiation Science Red Cross Hospital, Western Cape University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Comparison of Chest Radiographic Findings in HIV-Infected, HIV-exposed and HIV-uninfected Children with Pulmonary Tuberculosis
DATE CONSIDERED:	28/02/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S Lucas
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/03/2014

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

DECLARATION OF INVESTIGATORS

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

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

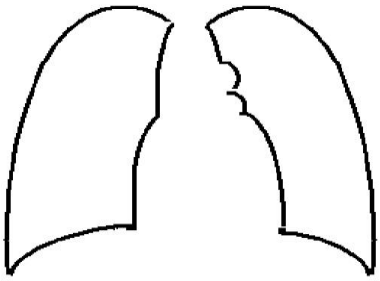
Principal Investigator Signature Date 10-04-2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Standardised Reporting Form

CXR CRF Baseline vs1
26-aug-2010

CXR results form Baseline (enrolment)

10.	Chest x-ray date		
11.	Is the chest x-ray **N**ormal (go to end) **A**bnormal (go to x)	**N**	**A**
12.	Indicate the distribution of abnormalities 		

Coder/Reporter:	**Name:**										
PARENCHYMA	**Lung area involved** (tick applicable boxes)										
Alveolar (consolidaton)	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Ghon focus	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Expansile	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Cavity (number, size, thickness)	Y	N	RUL	RML	RLL	LUL	LING	LLL			
Nodular infiltr (>2mm)	Y	N	Peri-hilar			Peripheral				Right	Left
Miliary infiltr (up to 2mm)	Y	N	Peri-hilar			Peripheral				Right	Left
Volume loss	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Hyperinflation	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Calcification (lung)	Y	N	RUL	RML	RLL	LUL	LING	LLL		Segm	Lobar
Peri-hilar streakiness	Y	N	Right	Left							
AIRWAY COMPRESSION AND OR TRACHEAL DISPLACEMENT											
Right paratraceal			y		n		maybe		Not visible		
Right main bronchus			y		n		maybe		Not visible		
Right bronchus intermedius			y		n		maybe		Not visible		
Left main bronchus			y		n		maybe		Not visible		
NODES											
Peri –hilar (P-H)	Y	N	R	L	SC	U					
Paratracheal (PT)	Y	N	R	L	U						
Calcification (nodes)	Y	N	P-H	PT							
PLEURA											
Effusion	Y	N	R	L	B-L	Sm	Lge		Loculated	Y	N

HEART							
Enlargement	Y	N	U	Pericardial Effusion	Y	N	U

TECHNICAL QUALITY				
AP view	Acceptable	Poor but readable	Not acceptable	Not readable
Lateral view	Acceptable	Poor but readable	Not acceptable	Not readable

REPORTER				
	Report completed by/ investigator code:			
	Has digital image been recorded	**Y**	**N**	**DK**
	Is the CXR consistent with TB?	**Y**	**N**	**Inconclusive**
Comments				

Appendix C: Note on referencing style

Please note that the referencing in this thesis is a modification of the Vancouver Referencing style, done according to the Faculty of Health Sciences Style Guide as set out by the Wits Health Sciences Library.

The information on this WHSL Vancouver Citation Style Guide for Theses, Dissertations and Research Reports is available from http://libguides.wits.ac.za/whsl-vancouver updated on 30 January 2017.

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