Radiological progression of lung disease in human immunodeficiency virus (HIV)-infected children

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Declaration

I, Richard Denys Pitcher, hereby declare that the work on which this thesis is based is my original work, except where the acknowledgements indicate otherwise and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 2 May 2016

The journey is the destination

For Stevie, Sorrel and Sean, who shared the journey

In loving memory of Samuel James Pitcher
2 July 1996 – 27 February 1998

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Give thanks to the Lord for he is gracious
His mercy endures forever
Psalm 136

Acronyms

AP	Antero-posterior
ART	Anti-retroviral therapy
ARV	Anti-retroviral
BALT	Bronchus associated lymphoid tissue
BO	Bronchiolitis obliterans
CD4	Cluster of differentiation 4 cell
CDC	Centres for Disease Control and Prevention
CI	Confidence interval
CIP	Chronic interstitial pneumonitis
CRF	Case report form
CTR	Cardio-thoracic ratio
CXR	Chest X-ray
DIP	Desquamative interstitial pneumonitis
DoH	South African National Department of Health
EBV	Epstein-Barr virus
LMIC	Low- or middle-income country
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
HRCT	High resolution computerised tomography
ILO	International Labour Office
INH	Isoniazid
IQR	Inter-quartile range
IRIS	Immune reconstitution inflammatory syndrome
LIP	Lymphocytic interstitial pneumonitis
LOWESS	Locally weighted scatterpoint smoothing
LRTI	Lower respiratory tract infection
MAC	Mycobacterium avium complex
MDG	Millennium Development Goal
MRC	South African Medical Research Council
NRF	National Research Foundation
OR	Odds ratio
P2C2 HIV study	Prospective Study of Paediatric Pulmonary and Cardiovascular Complications of Vertically transmitted Human Immunodeficiency Virus Infection
PCP	*Pneumocystis* pneumonia
PCR	Polymerase chain reaction
PTB	Pulmonary tuberculosis
SA	South Africa
SSA	Sub-Saharan Africa
TB	Tuberculosis
WHO	World Health Organisation
WHOHAZ	Height-for-age z-score
WHOWAZ	Weigh-for-age z-score
WHOWHZ	Weight-for-height z-score

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Abstract

Introduction

There are limited data on the chest X-ray (CXR) abnormalities in human immunodeficiency virus (HIV)-infected children in low- and middle-income countries (LMIC's).

Aim

To investigate the evolution of CXR abnormalities in HIV-infected children in LMIC's, to correlate this with the severity of HIV-disease, and to assess the impact of anti-retroviral therapy (ART).

Method

A prospective longitudinal study evaluating clinical, immunological and radiographic parameters at regular intervals over a minimum of 24 months. CXR abnormalities were stratified by severity and deemed persistent if present for 6 consecutive months or longer. Univariate and multiple logistic regression analyses assessed associations between radiological and clinical/immunological parameters at enrolment. An ordinal multiple logistic regression model assessed the association of enrolment and time-dependent variables with CXR findings over time.

Results

330 children (m=53%; median age=24 months) underwent baseline evaluation; 169(51%) had severe CXR abnormalities. Baseline CXR severity was associated with more advanced clinical HIV-disease (OR=6.9; 95%CI=1.9-25.6), CD4+%<20 (OR=1.8; 95%CI=1.0-3.0) and age>24 months (OR=4.1; 95%CI=2.1-8.0).

258/330 children (78%; median age=28 months; median CD4+%=21) had radiographic follow-up. At enrolment, 233(90%) had moderate/advanced clinical HIV-disease, 70(27%) were on ART and 37(14%) had pulmonary tuberculosis (PTB).

130(50%) commenced ART and 36(14%) developed PTB during the study. 154(60%) had persistent, severe CXR abnormalities, with median duration 18 months. Lymphocytic interstitial pneumonitis (LIP) (n=71,46%) and PTB (n=47,31%) were the commonest causes. CXR severity over time was associated with CXR severity 6 months prior (OR=120.80; 95%CI=68.71–212.38), lack of ART (OR=1.72; 95%CI=1.29–2.27), enrolment age<18months (OR=1.39; 95%CI=1.06–1.83), diffuse, severe CXR abnormality at enrolment (OR=2.18; 95%CI=1.33–3.56), hospitalization for respiratory tract infection during the previous 6 months (OR=1.88; 95%CI=1.06–3.30) and length of follow-up: at 18-24 months (OR=0.66; 95%CI=0.49–0.90), and at 30-54 months (OR=0.42; 95%CI=0.32-0.56). Amongst children on ART, 69%(162/235) of changes in CXR status across transition periods were improvements and 31%(73/235) were deteriorations. Amongst those not on ART, 45%(54/120) of CXR changes were improvements and 55%(66/120) deteriorations. Compared to those not on ART, children on ART had 24% more improvements and 24% fewer deteriorations across the transition periods.

Conclusion

CXR abnormalities are common in HIV-infected children in LMIC's. Most children have severe CXR abnormalities persisting for at least 18 months. ART is beneficial, reducing the risk of radiographic deterioration or increasing the likelihood of radiological improvement.

Chapter One

Introduction

Respiratory disease is the leading cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected children without access to anti-retroviral therapy (ART). [Zar 2006, Zar 2008, Gray 2009, Morrow , Gray 2010, Punpanich 2011, Punpanich 2012]

The chest X-ray (CXR) is the most affordable and accessible imaging modality for the assessment of respiratory disease in children. [Mettler, Maru]

In HIV-infection, the CXR serves two main functions. It provides a *baseline* evaluation of the extent and nature of respiratory disease, allowing a working differential diagnosis and an assessment of any features of pulmonary tuberculosis (PTB). [Zimmermann, Marks, Jeena 1996, Mukadi 1997, Jeena 1998, Madhi 2000, Kattan, Jeena 2002] The CXR also *monitors* respiratory disease, documenting response to treatment and disease progression, which is important since several associations of HIV-infection in children without access the ART may predispose to persistent or progressive CXR abnormalities. [Chadwick, Marquis, Jeena 1996, Mukadi 1997, Sheik, Jeena 1998, Graham 2005, Meuller, Theron, Nel, Masekela]

The prevalence and radiographic features of CXR abnormalities in HIV-infected children have not been systematically documented. Furthermore, the relationship between the clinical severity of HIV disease, the degree of immune suppression and the extent of CXR abnormality is not well understood.

A single longitudinal study of North American children who were not on ART [Norton] reported a 29% cumulative prevalence of persistent CXR abnormalities by the age of

48 months. The most common abnormality was an increase in bronchovascular markings, which occurred in 18% of cases; persistent consolidation and nodules each occurred in 11% of cases, while 10% of patients showed a combination of features. Those with persistent changes had lower mean CD4 counts and the resolution of CXR abnormality was associated with further immune suppression.

However, there has been no comparable work in children from low- or middle-income countries (LMIC's). Several factors in resource-limited settings are distinct from those in North America and may influence the development of respiratory disease. [Ansari, Pitrez, Lodha, Mwiru, Jackson] In LMIC's, children with vertically transmitted HIV infection show more rapid disease progression. [Tudor-Williams] There is also an increased burden of respiratory illness in African children, particularly acute pneumonia and pulmonary tuberculosis. [Hesseling 2009, Zar 2006] Poorly developed healthcare infrastructure and sub-optimal access to care may impact on prevention, diagnosis and management of paediatric respiratory disease. [Graham 2003, Zar 2004, Zar 2013] In addition, other factors such as malnutrition, crowding and passive smoke exposure may impact on the incidence and severity of respiratory disease in such settings. [Mwiru, Jackson]

The early use of ART and pneumonia prophylaxis regimes has contributed to a reduction in acute respiratory morbidity and mortality amongst HIV-infected infants and children in both well- and poorly-resourced environments. [de Martino, Graham 2003, Violari, Chokephaibulkit] However, there has been no study of the impact of ART on the CXR findings in HIV-infected children.

Therefore, this prospective study, from 2002 to 2007 , was undertaken to investigate the radiological evolution of lung disease in HIV-infected children from a resource-limited environment, to correlate this with the degree of clinical and immunological dysfunction, and to assess the impact of ART.

The study was conducted in the epicenter of the paediatric HIV epidemic, as 90% of HIV-infected children reside in sub-Saharan Africa (SSA). Furthermore, South Africa (SA) has more people living with HIV than any other country in the world. [UNAIDS 2015] Moreover, in 2002, the Southern African HIV-epidemic was intensifying. Infection levels amongst pregnant women were 20% or higher in six Southern African countries and there were approximately 210,000 (190,000-230,000) South African children living with HIV. [UNAIDS 2015] In the period of this study, the number of South African children living with HIV-infection has increased substantially, peaking at an estimated 380,000 (350,000-400,000) children in 2008. [UNAIDS 2015]

Chapter Two

Review of the literature

RATIONALE FOR THE INCLUSION OF PUBLISHED WORK

The manuscript included in this chapter represents the first comprehensive review of the literature on the CXR features of chronic respiratory disease in HIV-infected children. It summarises the characteristics of HIV-infection which predispose to persistent paediatric respiratory illness and reviews the patterns of chronic CXR abnormality reported to date.

The manuscript also provides a critical analysis of published work in the field. It highlights the relative paucity of available data as well as the deficiencies in existing data, including an appraisal of radiological reporting methodology and terminology.

By outlining limitations in current knowledge and understanding, the chapter informs the remainder of this thesis, defining the research focus of succeeding chapters. It also specifies the requirements for systematic, standardized chest radiographic reporting which underpin the customized reporting template utilized throughout this work.

Paediatric Respiratory Reviews

Review

The chest X-ray features of chronic respiratory disease in HIV-infected children – a review

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INTRODUCTION

Several features of HIV-infection favour the development of chronic respiratory disease in children who are not on ART. [Meuller, Toro, Khunnawat, Phutanakit, Masekela, Nel]

Firstly, HIV–associated acute chest infections are characterized by their frequency, [CDC 1987, Kattan, Madhi 2000] severity, [Madhi 2000, Zar 2001, Madhi 2001, Madhi 2002] broad range of aetiological agents, [Madhi 2000, Zar 2001, Jeena 1996, Ruffini, Graham 2000, Chintu, Molyneux, Zampoli 2011, Goussard] high rate of co-infections, [Jeena 2005, Zar 2006, McNally, Pitcher 2011] and poor response to antimicrobial treatment. [Madhi 2000, Zar 2001, Jeena 1998] These factors prolong acute chest infections, delay CXR resolution, [Molyneux, Jeena 2005, Cherian] predispose to persistent [Madhi 2000] and recurrent pneumonia [Kattan, Molyneux, Jeena 2005, Zar 2006, Mofenson, Zar 2004] and the evolution of bronchiectasis. [Sheik, Berman, Amorosa] This is especially true in SSA, where there is a high incidence of childhood respiratory infections, a high prevalence of malnutrition and limited access to healthcare. [Gray 2010, Zar 2013] The early use of prophylaxis regimes, newer conjugate vaccines and/or highly active antiretroviral therapy (HAART) has reduced the incidence of acute respiratory morbidity and mortality, and has prolonged survival in young HIV-infected children. [Violari, Graham 2003] However, longer survival may increase the prevalence of chronic respiratory disease. [Amorosa, Berdon, Pitrez]

Secondly, HIV infection increases the risk of childhood tuberculosis (TB), [Luo, Mukadi 1997, Corbett, Hesseling 2009] while TB accelerates the progression of HIV disease [Goletti] and

TB in HIV-infected children has a less favourable outcome. [Madhi 2000, Jeena 1996, Luo, Mukadi 1997, Hesseling 2005, Palme, Schaaf]

Thirdly, HIV-related progressive encephalopathy (PE), [van Rie] esophagitis and gastro-oesophageal reflux predispose to oro-pharyngeal inco-ordination with micro-aspiration, [Nel, van Rie, Chiou, Thom] which may lead to aspiration pneumonia or recurrent wheezing.

Fourthly, there is a high prevalence of anaemia and cardiovascular disease, particularly HIV-related cardiomyopathy, which may manifest with cardiomegaly and chronic pulmonary congestion [Khunnawat, Adetifa, Eley, Keesler] and ultimately pulmonary hypertension.

Fifthly, the association of paediatric HIV-infection with lymphocytic interstitial pneumonitis (LIP) is well recognized. [Toro, Jeena 2005, Marquis, Marks, Khare, Lynch]

In addition, HIV-related pulmonary neoplasms, particularly Kaposi's sarcoma, non-Hodgkin's lymphoma and bronchial smooth-muscle tumours [Meuller, Theron, Chadwick, Sabatino] have been reported as rare causes of refractory CXR abnormalities, while pulmonary involvement in the immune reconstitution inflammatory syndrome (IRIS) is increasingly implicated in similar changes. [Phutanakit, Zampoli 2007, Kilborn 2009]

To our knowledge, there has been no comprehensive review of the published CXR features of chronic respiratory disease in HIV-infected children, and there has been

little documentation of the impact of ART on the radiological findings in these children. The two reviews of chronic respiratory disease in HIV-infected children published to date have focused on clinical rather than radiographic features. [Zar 2008, Weber]

The CXR remains the most accessible investigation for respiratory disease, and plays a pivotal role in the baseline assessment and follow-up of respiratory disease in HIV-infected children. A review of the current knowledge of the CXR features of chronic respiratory disease in HIV-infected children could assist in the clinical management of these children, while highlighting areas requiring additional research.

Soon after the onset of the HIV pandemic, guidelines for the systematic reporting of CXR abnormalities appeared in two landmark radiological publications. The first [McLoud] proposed a revised reporting tool for systematic CXR analysis. Although intended for epidemiological studies of diffuse pulmonary disease in adults, the principles outlined can be applied to CXR abnormalities in general. The second article suggested a standard terminology for CXR reporting. [Tuddenham] Used in conjunction, these two articles afford both a precise description of CXR features and a tool for defining the extent of disease.

The aim of this study is to review the reported CXR features of chronic respiratory disease in HIV-infected children and to assess whether these have been systematically analysed utilizing standard radiological terminology

METHODS

Medline and Google Advanced Scholar searches were conducted for English language articles published from 1981 through 2013 with descriptions of the CXR features of HIV-related chronic respiratory disease in children.

The initial search included the keywords: "chronic or persistent" and "pulmonary or lung" and "disease or illness" and "infant or child or children or paediatric or pediatric" and "HIV" and "chest X-ray" or "chest radiograph". Similar search iterations were then conducted using known predisposing factors to chronic respiratory disease in HIV-infected children as additional key words, namely "persistent or chronic pneumonia", "tuberculosis", "aspiration pneumonia", "bronchiectasis", "lymphocytic interstitial pneumonitis"; "pulmonary congestion", "pulmonary neoplasms" and "pulmonary IRIS". Finally, searches were conducted using "anti-retroviral therapy" or "combined anti-retroviral therapy" or "highly active anti-retroviral therapy" with "infant or child" and "chest X-ray".

The titles and abstracts of articles were reviewed and the full manuscripts of eligible articles were retrieved. Reference lists of the articles retrieved were examined for further eligible articles. Research articles, case series or case reports which reported the CXR findings of conditions associated with chronic respiratory disease in children aged 0-14 years, with vertically-transmitted HIV-infection were included. Chronic respiratory disease was defined as any condition with the potential to cause respiratory symptoms for three months or longer. [Jeena 1998, Singh] Only reports

including biopsy-proven LIP were considered. *Pneumocystis* pneumonia was analysed separately from other fungal pneumonias. Reports of cases in which HIV-infection was not acquired by vertical transmission were excluded.

Eligible articles were collated according to the main predisposing conditions and tabulated by journal, country of origin, publication date, authorship and main CXR findings.

CXR findings were critically assessed with respect to the use of a systematic method of analysis of the patterns and extent of radiological abnormalities and the consistent use of appropriate reporting terminology.

RESULTS

Forty-seven publications documented the CXR findings in 826 patients; 533 (65%) patients were from SSA. (Table 2.1)

Less than half the reports (n = 21; 45%) had a radiologist as co-author and less than a quarter (n = 10; 21%) were prospective studies.

Reporting methodology was defined in three studies (6%). [Oldham, Norton, Kumar] Norton [2001] utilized the forced-choice template of the Prospective Study of Paediatric Pulmonary and Cardiovascular Complications of Vertically transmitted Human Immunodeficiency Virus Infection (P2C2 HIV study). [Cleveland] Nodule dimension was

the basis of the documentation of LIP by Oldham, [1989] and Iriso [2005] invoked clinico-radiological criteria for the identification of PTB.

Pulmonary tuberculosis (PTB) (n = 581; 70%) and LIP (n = 128; 15%) together accounted for over 85% of cases.

The CXR features of less than a dozen cases each of chronic *Pneumocystis* pneumonia (PCP), pulmonary IRIS, mycobacterium avium complex (MAC) pneumonia, bronchiectasis, fungal pneumonia, interstitial pneumonitis, thoracic Kaposi's sarcoma, lymphoma and smooth-muscle tumours were recorded.

There were no reports of the CXR features of aspiration pneumonitis or pulmonary congestion and no studies of the chronic CXR features of children on ART.

PTB (studies = 14, patients = 581; Table 2.2)

Mediastinal lymphadenopathy (n = 266; 46%) and homogeneous segmental or lobar opacification (n = 244; 44%) have been the most consistently documented features, with pulmonary nodules recorded in a third of patients (n = 194; 33%).

The non-specific term "infiltrate" was used to describe the parenchymal opacification in almost one-fifth of cases (n = 108; 19%).

In all studies, a proportion showed more than one parenchymal abnormality. However, combinations of parenchymal involvement were reported in less than one-fifth of cases (n = 113; 19%) [Madhi 2000, Jeena 1998, Norton, Chan, Srinakarin] and no study systematically recorded the extent of parenchymal abnormality.

The distribution of mediastinal adenopathy was noted in less than forty percent of cases (n = 222; 38%) [Mukadi, Palme, Iriso, Chan] and the association of mediastinal adenopathy with parenchymal involvement in just over ten percent (n = 64; 11%). [Chan, Srinakarin]

Although eleven reports [Madhi 2000, Jeena 1996, Luo, Mukadi, Palme, Schaaf, Iriso, Srinakarin, Kiwanuka 2001, Kiwanuka 2002, Soeters] compared the CXR features of PTB in HIV-infected (n = 546) and HIV-uninfected children (n = 1205), and six studies [Jeena 1996, Mukadi, Palme, Iriso, Kiwanuka 2002, Soeters] found no significant difference, the prospective analysis of proven cases of PTB by Schaaf [2007] is the most comprehensive report to date. This study included 126 HIV-infected and 274 HIV–uninfected children with PTB and found that HIV-infected children had almost double the probability of segmental or lobar opacification and cavitation.

There are limited data on the radiological response of HIV-infected children to TB therapy. While radiographic improvement at 6-months of follow-up was reported in 52% and 68% of cases studied by Jeena [1996] and Mukadi [1997] respectively, there has been no systematic longitudinal study of the CXR features of HIV-infected

children on TB treatment. Furthermore, there has been no study of the impact of ART in this setting.

LIP (studies = 25, patients = 128; Tables. 2.3a, 2.3b)

All cases showed parenchymal abnormality, described as "diffuse" and "bilateral" in the large majority (n = 125; 98%). Twenty-five descriptors were used to characterize the parenchymal abnormalities. In 96 (75%), "nodular" or "reticulo-nodular" were used, while in 22 (17%), the descriptor was non-specific; examples included "interstitial infiltrates", "interstitial pattern", "interstitial densities", and "increased interstitial markings."

In ten patients (8%), focal confluent opacification was super-imposed on a diffuse nodular pattern, accounting for some asymmetry. [Jeena 1998, Amorosa, Marquis, Oldham, Zimmermann, Bradford] Only three cases (2%) showed focal parenchymal abnormality, with "cysts", [Schroeder] "consolidation" [Norton] and "consolidation with effusion" [Jeena 1998] recorded in one case each.

Twenty-five patients (20%) had mediastinal adenopathy, [Marquis, Rubinstein 1986, Andiman, Zimmermann, Rubinstein 1988, Bradford, Zuckier, Haney] one having bronchial narrowing. [Bradford]

Nodule size was recorded in two reports, involving 11 patients (9%). [Oldham, Bradford] Bradford [1988] found nodules most easily visible in the lung bases and periphery, that

these were first discerned when approximately 1 mm in diameter and rarely exceeded 3 mm in diameter.

Evolution of radiological features was recorded in 43 patients (34%) followed for 18–84 months, [Amorosa, Marquis, Lynch, Oldham, Rubinstein 1988, Bradford, Izraeli] showing that LIP may be radiographically occult in the earliest stages of lymphocytic infiltration of the interstitium. [Marquis] With progressive infiltration, features evolve sequentially as i. bronchial wall thickening [Marquis] ii. a fine reticular pattern [Jeena 1998] iii. A reticulo-nodular pattern, with nodule dimensions increasing from 1–5 mm in diameter [Oldham, Bradford, Izraeli] and iv. coalescence of nodules to form areas of confluent opacification. [Jeena 1998, Marquis, Oldham] Bradford [1988] documented a single case where an increase in nodule size was discernible on radiographs taken one month apart. In all other cases, radiographic change was only documented over more than two months.

Where interstitial infiltration was sufficient to compromise adjacent bronchi, bronchiectasis could evolve distally. [Amorosa] Four patients (3%) developed bronchiectasis in follow-up periods from 36 to 84 months.

With the exception of bronchiectasis, all features were potentially reversible, either in response to therapy or in the natural evolution of the disease. [Marquis] In a retrospective analysis, Lynch [2001] showed radiographic resolution in 13 of 20 patients (65%) within 1–4 years, and that this was not due to decreasing immune function. Rubinstein [1988] showed that 10 of 15 patients (60%) on steroid therapy demonstrated a decrease in nodule size and number over 16 months.

Chronic PCP (studies = 6; patients = 11) [Norton, Schroeder, Izraeli, Evlogias, Solomon, Holland]

A small number of cases have been reported, showing focal (n = 6; 55%) and multifocal/diffuse (n = 5; 45%) parenchymal abnormality in similar proportions.

Focal abnormality manifested as confluent lobar or segmental opacification in 5 cases and as a cyst in one case. Multifocal or diffuse abnormality was characterised only as parenchymal "infiltrates".

Pneumothoraces (one with an associated pneumomediastinum) [Schroeder, Evlogias, Solomon, Holland] and pneumatocoeles [Evlogias, Solomon, Holland] were documented in 36% (n = 4) and 27% (n = 3) of cases, respectively.

IRIS (studies = 1; patients = 9) [Zampoli 2007]

A single study included cases of both "paradoxical" and "unmasking" TB IRIS. The median duration of ART at diagnosis was 25 days (range: 8–54 days).

Cases of paradoxical IRIS (n = 3) showed progression of baseline radiological features, manifesting as more extensive mediastinal adenopathy and parenchymal opacification in all cases. An enlarging effusion and bronchial compression were each seen in two cases (67%).

In "unmasking" IRIS (n = 6), the majority developed new radiological features. Mediastinal adenopathy and parenchymal opacification evolved in 67% (n = 4) and

50% (n = 3) of cases respectively, increased in extent in one case each and were unchanged in the remainder. Bronchial compression and pleural effusions developed in 50% (n = 3) and 33% (n = 2) respectively.

There was no analysis of the distribution of mediastinal adenopathy or the nature and extent of parenchymal abnormality pre- and post-IRIS.

Bronchiectasis (studies = 1; patients = 4) [Amorosa]

A single small series (n = 4) reported LIP-associated bronchiectasis, which was focal in three cases (75%) showing dilated bronchi surrounded by homogeneous lobar opacification and multifocal in one case with bilateral basal ring shadows and atelectasis.

MAC infection (studies = 2; patients = 9) [Izraeli, Pursner]

Mediastinal adenopathy, diffuse pulmonary nodules, cavitation and bronchiectasis have each been reported in almost eighty percent of cases (n = 7; 78%). However, radiographic descriptions have not been comprehensive; the pattern of mediastinal adenopathy, the size and distribution of pulmonary cavities and the radiographic features of the associated bronchiectasis have not been systematically recorded.

Fungal pneumonia (studies = 2; patients = 3) [Izraeli, Pillay]

Persistent pneumonia due to Histoplasmosis, Cryptococcus and *Bipolaris* have been described. Those due to Histoplasmosis and Cryptococcus showed homogeneous lobar opacification and breakdown, with the latter having an associated pneumothorax. The *Bipolaris* pneumonia showed diffuse bilateral nodules.

Pulmonary neoplasia

Kaposi sarcoma (studies = 2; patients = 7) [Theron, Marais 2003]

Multifocal homogeneous opacification (n = 6; 86%) associated with a diffuse reticular or nodular pattern (n = 5; 71%), pleural effusions (n = 6; 86%) and mediastinal adenopathy (n = 4; 43%) have been characteristic. The extent of parenchymal pathology was systematically reported using recommended radiological terminology.

Lymphoma: (studies = 4; patients = 6) [Scott, Izraeli, Teruya-Feldstein, Gray 2013]

The reported cases represent a heterogeneous group including B-cell lymphoma of bronchus-associated lymphoid tissue (BALT) origin (n = 2), large-cell lymphoma, lymphomatoid granulomatosis and immunoblastic lymphosarcoma.

All patients presented with a pulmonary mass. Multiple lesions were seen in one case (17%) and in two cases (34%) masses showed central breakdown. There was

associated mediastinal adenopathy in one case (17%). The size of the mass was reported in only 3 cases (50%) and ranged from 3-5 cm in diameter.

Smooth muscle tumours: (studies = 1; patients = 1) [Sabatino]

There has been a single report of a 7-year-old with synchronous tumours of the trachea (leiomyoma) and left main bronchus (leiomyosarcoma), manifesting with tracheal narrowing and left lower lobe collapse respectively.

Chronic interstitial pneumonitis (studies = 3; patients = 7) [Jeena 1998, Zimmermann, Mauskar]

This group included five patients with chronic interstitial pneumonitis (CIP) and one case each with desquamative interstitial pneumonitis (DIP) and bronchiolitis obliterans (BO).

All cases presented with diffuse reticular or reticulo-nodular patterns. Two patients (29%; DIP, CIP) showed focal areas of superimposed segmental homogeneous opacification.

Unknown aetiology (studies = 1; patients = 60) [Norton]

Norton [2001] conducted a 4-year prospective longitudinal study of 287 HIV-infected USA children who were not on ART. Eighty-three patients (29%) showed chronic

CXR abnormality, defined as increased bronchovascular markings persisting for 6 months or longer, or consolidation or nodules present for 3 months or longer. The aetiology of the chronic CXR changes was established in 23 patients (23/83; 28%), being LIP (n = 16; 19%), chronic *Pneumocystis* pneumonia (n = 5; 6%) and PTB (n = 2; 2%).

Amongst those with no defined cause for the chronic CXR abnormality (n = 60; 72%), an increase in bronchovascular markings was the most common finding (n = 52; 87%), while focal consolidation (n = 24; 40%) and pulmonary nodules (n = 17; 28%) were also seen, although the combinations of parenchymal involvement were not reported.

DISCUSSION

Globally, approximately 3.3 million children under the age of 15 years are living with HIV infection, of whom 2.9 million (88%) are in SSA. [UNAIDS 2013] Considering that acute and chronic respiratory illness is the leading cause of morbidity and mortality in HIV-infected children [Gray 2010, Weber, Zar 2008, Punpanich 2011] and that the estimated prevalence of LIP in HIV-infected children is 30-40%, and that the estimated incidence of culture-confirmed TB amongst infants living in areas of high HIV and TB prevalence is 1,596 cases per 100,000 population, [Hesseling 2009] the CXR features of a relatively small number of cases of chronic respiratory illness have been recorded.

Factors contributing to this paucity of radiographic data include difficulties diagnosing PTB in HIV-infected children, [Osborne] the challenge of accurately identifying paediatric TB IRIS [Boulware] or LIP, [Jeena 1998] the limitations of CXR's in demonstrating bronchiectasis [Silverman 1987] and the high incidence of co-infection in HIV-related chronic pneumonia, [Zar 2006, Zar 2008] which precludes implication of a single causative organism. Furthermore, healthcare infrastructure in SSA is constrained, limiting definitive diagnosis of HIV-associated infections and co-morbidities. [UNAIDS]

The published CXR data often lack important detail, with no record of the extent and/or precise nature of parenchymal abnormality, and/or the presence or absence or distribution of mediastinal adenopathy. Notwithstanding this, existing studies have enhanced our understanding of CXR findings in HIV-related chronic respiratory disease. In LIP, a spectrum of features has been elucidated. Presentation findings have been diffuse, bilateral, and symmetrical in approximately 90% of cases and the parenchymal pattern has been "nodular" or "reticulo-nodular" in 75 percent. Pulmonary changes have been diffuse but asymmetrical in approximately 8 percent and focal in less than 2 percent. Consolidation, mediastinal adenopathy, and bronchiectasis are recognized associations.

The available data (Table 2.1) also allow appreciation of potential patterns of CXR abnormality. Thus, in an HIV-infected child with persistent pulmonary nodularity, with or without focal homogeneous opacification, and with or without mediastinal adenopathy, LIP must always be considered a diagnosis of exclusion, since PTB,

IRIS, MAC pneumonia, fungal pneumonia and other forms of interstitial pneumonitis may have a similar radiological appearance. Careful clinical correlation is thus required.

Diffuse pulmonary nodularity accompanied by parenchymal breakdown/cavitation has not been described in LIP and would suggest either PTB or MAC, while chronic PCP should be the first consideration if nodules are seen in conjunction with thin-walled cysts, especially if there is an associated pneumothorax. Pleural effusions are most unlikely in LIP; an effusion in association with diffuse nodularity favours PTB, IRIS or Kaposi's sarcoma, the latter being particularly associated with large, bilateral effusions. In a child with chronic, focal, homogeneous opacification TB, bronchiectasis or chronic PCP should be considered, while a discreet pulmonary mass is suggestive of lymphoma.

The absence of data on the CXR features of children receiving ART most likely reflects relatively limited access to treatment amongst children from LMIC's. As recently as 2005, only 75,000 children from resource-limited environments were receiving ART. [Unicef] Although this figure had increased to 647,000 by 2012, this only represents 34 percent current coverage of eligible children. [UNAIDS 2013]

This study was limited by broad inclusion criteria for reported radiological features, contributing to inclusion of articles with only cursory radiological descriptions amongst the less common causes of chronic respiratory disease. Conversely, excluded were those articles documenting either predisposing factors to the

development of chronic CXR changes in HIV-infected children, or the complications of chronic HIV-related chest infection in which the chronic CXR features were broadly outlined in the inclusion criteria or methodology, but not critically analysed within the results section. This applied particularly to two studies of bronchiectasis in HIV-infected children, involving a total of 45 patients. [Sheik, Berman] A further limitation of the study is the inclusion of English language articles only.

CONCLUSION

This review highlights the need for further, prospective work on the CXR features of HIV-related chronic respiratory disease in children. In particular, the natural history, pathophysiology, clinical determinants and immunological correlates of LIP remain poorly elucidated, the radiological response of HIV-infected children to PTB treatment has not been analysed and there is a striking paucity of data on the radiographic features of HIV-related bronchiectasis.

RECOMMENDED FUTURE RESEARCH INITIATIVES

i. Standardisation of CXR reporting terminology and systematic CXR reporting methodology.

ii. Longitudinal studies of the response of HIV infected children to anti-tuberculous therapy.

iii. Elucidation of the natural history, pathophysiology, clinical determinants and immunological correlates of lymphatic interstitial pneumonitis.

iv. Evaluation of the impact of anti-retroviral therapy on chronic HIV-related CXR changes.

v. Elaboration of the clinical and immunological determinants, as well as the radiological features, of HIV related bronchiectasis.

condition	TB	LIP	PCP	IRIS	MAC	bronchiec-tasis	Kaposi	lymphoma	smooth muscle tumour	pneumonitis	fungal pneumonia	unknown etiology
	n(%), median (IQR)	n(%), median IQR	n(%), median (IQR)	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR	n(%), median IQR
studies	14	25	7	1	2	1	2	4	1	3	2	1
radiologist as author	3	14	4	1	2	1	1	2	0	0	2	1
patients	581	128	11	9	9	4	7	6	1	7	3	60
age (months)	ns	ns	ns	ns	Ns	68	ns	ns	84	Ns	ns	Ns
mediastinum												
adenopathy	266(46)	25(18)	0	9(100)	7(78)	0	3(43)	1(17)	0	0	ns	Ns
airway compression	Ns	1(1)	0	5(56)	Ns	0	2(29)	0	1	0	ns	Ns
parenchyma												
parenchymal involvement	Ns	128(100)	11(100)	9(100)	9(100)	4(100)0	7(100)	6(100)	1(100)	7(100)	3(100)	60(100)
opacification	254(44)	16(13)	5(45)	ns	Ns	3(75)	7(100)	0	1(100)	2(29)	2(67)	24(40)
non-specific descriptor	108(19)	22(17)	5(45)	9(100)	0	0	0	0	0	0	0	0
nodules	194(33)	108(84)	0	ns	7(78)	Ns	5(71)	0	0	4(58)	1(33)	17(28)
ring shadows/ reticular pattern	7(1)	4(3)	0	0	0	1(25)	5(71)	0	0	3(43)	0	52(87)
cavities	70(12)	0	0	ns	7(78)	0	ns	2(33)	0	0	2(67)	0
cysts	0	1(1)	3(27)	ns	0	0	ns	0	0	0	0	0
atelectasis	32(6)	ns	0	ns	Ns	3(75)	ns	0	1(100)	0	0	Ns
calcification	10(2)	0	0	ns	Ns	0	0	0	0	0	0	0
mass	0	0	0	0	0	0	0	6(100)	0	0	0	0
bronchiectasis	Ns	4(3)	0	ns	7(78)	4(100)	ns	0	0	0	0	Ns
pleura												
pleural involvement	49(8)	1(1)	4(36)	4(44)	Ns	0	6(86)	1(17)	0	0	1(33)	Ns
effusion	48(8)	1(1)	0	4(44)	Ns	0	6(86)	1(17)	0	0	0	Ns
pneumothorax	1(0)	1(1)	4(36)	0	Ns	0	0	0	0	0	1(33)	Ns

Table 2.1. Publications on the chest radiographic features of chronic respiratory disease in HIV-infected children, by co-morbidity

author	Luo	Chan	Mukadi	Jeena	Madhi	Norton	Kiwanuka	Palme	Kiwanuka	Soeters	Iriso	Schaaf	Kumar	Srinakarin
radiologist as author	no	no	no	no	no	Yes	yes	No	no	no	no	no	no	Yes
country of origin	Zambia	USA	Cote d'Ivoire	SA	SA	USA	Uganda	Ethiopia	Uganda	SA	Uganda	SA	West Indies	Thailand
year	1994	1996	1997	1998	2000	2001	2001	2002	2002	2005	2005	2007	2007	2012
study type	pro-spective	retro-spective	pro-spective	pro-spective	pro-spective	pro-spective	pro-spective	pro-spective	pro-spective	retro-spective	pro-spective	pro spective	retro-spective	retro-spective
total patients	67	12	22	8	39	2	26	58	43	43	62	126	21	52
method of TB diagnosis	clinical	culture	clinical/ culture	culture	clinical/ culture	Culture	clinical	clinical/ culture	clinical/ culture	clinical/ culture	clinical/ culture	culture	culture	clinical
TB culture confirmed	ns	12(100)	5(23)	8(100)	12(31)	2(100)	ns	14(24)	4(9)	23(53)	19	126(100)	21(100)	0
median age	ns	36 m	49 m	Ns	12 m	Ns	ns	Ns	36 m	29 m	26 m	31 m	21 m	84 m
mediastinum														
adenopathy	20(30)	4(33)	9(41)	4(50)	17(44)	Ns	15(58)	10(17)	24(56)	18(42)	44(71)	71(56)	13(62)	17(33)
airway compression	ns	ns	ns	0	ns	Ns	0	Ns	ns	ns	ns	17(13)	ns	0
parenchyma														
parenchymal involvement	ns	10(83)	ns	8(100)	ns	2(100)	ns	Ns	ns	ns	ns	ns	ns	52(100)
homogeneous opacification	ns	3(25)	3(14)	6(75)	26(67)	1(50)	17(65)	Ns	28(65)	25(58)	37(60)	84(67)	12(57)	12(23)
non-specific descriptor	0	0	18(82)	0	3(8)	0	14(54)	44(76)	32(74)	0	0	8(63)	4(19)	0
total with nodules	46(69)	9(75)	ns	1(13)	12(31)	1(50)	ns	Ns	ns	17(40)	23(37)	31(25)	7(33)	47(90)
ring shadows	ns	ns	ns	2(25)	ns	0	ns	Ns	ns	ns	5(8)	ns	ns	Ns
total with cavities	ns	ns	2(9)	0	12(31)	0	4(15)	1(2)	3(7)	9(21)	2(3)	33(26)	3(14)	1(2)
atelectasis	ns	ns	0	0	10(26)	0	0	Ns	ns	ns	4(6)	14(11)	4(19)	0
total with calcification	ns	ns	ns	0	ns	0	2(8)	ns	ns	0	0	4(3)	4(19)	ns
bronchiectasis	ns	ns	ns	2(25)	0	Ns	ns	Ns	ns	ns	ns	ns	ns	5(10)
pleura														
pleural involvement	1(1)	1(8)	2(9)	0	9(23)	Ns	ns	2(3)	1(2)	13(30)	3(5)	17(13)	0	0
effusion	1(1)	0	2(9)	0	9(23)	Ns	ns	2(3)	1(2)	13(30)	3(5)	17(13)	0	0
pneumothorax	0	1(8)	0	0	0	Ns	ns	Ns	0	0	0	0	0	0

Table 2.2. Publications on the chest radiographic features of PTB in HIV-infected children

Author	Rubinstein	Oleske	Scott	Goldman	Fackler	Andiman	Rubinstein	Pahwa	Boccon	Kornstein	Zimmermann	Schiff
radiologist author	no	No	no	yes	No	no	yes	No	no	no	yes	yes
Country	USA	USA	USA	USA	USA	USA	USA	USA	France	USA	USA	USA
study type	series	Series	Series	retro-spective	Report	series	retro-spective	retro-spective	series	series	Series	series
Year	1983	1983	1984	1985	1985	1985	1986	1986	1986	1986	1987	1987
total patients	1	2	6	8	1	2	11	8	4	2	3	2
age/mean age	13 m	27 m	ns	ns	15 m	33m	ns	Ns	3 y	16 m	15 m	35 m
mediastinum												
mediastinal nodes	ns	Ns	ns	ns	Ns	2(100)	11(100)	Ns	ns	ns	1(33)	ns
airway narrowing	ns	Ns	ns	ns	Ns	0	0	Ns	ns	ns	0	ns
parenchyma												
parenchymal involvement	1(100)	2(100)	6(100)	8(100)	1(100)	2(100)	11(100)	8(100)	4(100)	2(100)	3(100)	2(100)
opacification	0	0	0	0	0	0	0	0	0	0	1(33)	0
non-specific descriptor	1(100)	2(100)	6(100)	0	1(100)	1(50)	0	8(100)	4(100)	2(100)	1(33)	1(50)
Nodules	0	0	0	8(100)	0	1(50)	11(100)	0	0	0	1(33)	0
ring shadows	0	0	0	0	0	0	0	0	0	0	0	0
atelectasis	0	0	0	0	0	0	0	0	0	0	0	0
calcification	0	0	0	0	0	0	0	0	0	0	0	0
Cysts	0	0	0	0	0	0	0	0	0	0	0	0
bronchiectasis	0	0	0	0	0	0	0	0	0	0	0	0
Pleura												
pleural involvement	0	0	0	0	0	0	0	0	0	0	0	0
Effusion	0	0	0	0	0	0	0	0	0	0	0	0
pneumothorax	0	0	0	0	0	0	0	0	0	0	0	0

Table 2.3a. Publications on the chest radiographic features of LIP in HIV-infected children: 1983 - 1987

Author	Rubinstein	Bradford	Zuckier	Oldham	Haney	Amorosa	Marquis	Schroeder	Izraeli	Sharland	Jeena	Norton	Lynch
radiologist author	yes	yes	yes	yes	yes	yes	yes	no	no	no	no	yes	yes
Country	USA	USA	USA	USA	USA	USA	USA	USA	USA	UK	SA	USA	USA
study type	series	review	report	series	review	retro	retro	report	series	retro	pro	pro	retro
Year	1988	1988	1988	1989	1989	1992	1993	1995	1996	1997	1998	2001	2001
total patients	5	3	1	1	2	4	3	1	5	1	16	16	20
age/mean age	30 m	16 m	3 y	27 m	20 m	21m	ns	ns	ns	5 y	Ns	ns	4 y
Mediastinum													
mediastinal nodes	5(100)	1(33)	1 (100)	ns	2(100)	Ns	2(67)	ns	ns	ns	Ns	ns	2(10)
airway narrowing	0	1(33)	0	ns	0	Ns	0	ns	ns	ns	Ns	ns	0
Parenchyma													
parenchymal involvement	5(100)	3(100)	1(100)	1(100)	2(100)	4(100)	3(100)	1(100)	5(100)	1(100)	16(100)	16(100)	20(100)
Opacification	0	1(33)	1(100)	1(100)	0	0	1(33)	0	0	0	5(31)	1(6)	1(5)
non-specific descriptor	0	0	0	0	1(50)	0	0	0	1(20)	0	2(13)	0	1(5)
Nodules	5(100)	2(33)	1(100)	1(100)	1(50)	4(100)	2(67)	0	4(80)	1(100)	8(50)	15(94)	19(95)
ring shadows	0	0	0	0	0	0	1(33)	0	0	0	1(6)	0	0
Atelectasis	0	0	0	0	0	0	0	0	0	0	0	0	0
Calcification	0	0	0	0	0	0	0	0	0	0	0	0	0
Cysts	0	0	0	0	0	0	0	1(100)	0	0	0	0	0
Bronchiectasis	0	0	0	0	0	4/32(13)	0	0	0	0	0	0	0
Pleura													
pleural involvement	0	0	0	0	0	0	0	1(100)	0	0	1(6)	0	0
Effusion	0	0	0	0	0	0	0	0	0	0	1(6)	0	0
Pneumothorax	0	0	0	0	0	0	0	1(100)	0	0	0	0	0

Table 2.3b. Publications on the chest radiographic features of LIP in HIV-infected children: 1988 - 2001

Chapter Three

Aim, objectives and chest radiographic reporting methods

AIM

To investigate persistent CXR abnormalities in HIV-infected children, to correlate these with the clinical severity of HIV-infection and the degree of immunological compromise, and to assess the impact of ART.

OBJECTIVES

i. Describe the enrolment CXR findings in a cohort of HIV-infected South African children

ii. Investigate the association between CXR features and clinical or immunological markers of severity

iii. Describe the radiological progression of lung disease in HIV-infected children

iv. Investigate the relationship between CXR changes over time and specific respiratory diseases, in particular PTB and LIP

v. Investigate the impact of ART on CXR abnormalities

CHEST RADIOGRAPHIC REPORTING METHODS

Introduction

The concept of systematic reporting of chest radiographic changes for epidemiological purposes was introduced by the International Labour Office (ILO) in 1930, thereby standardising radiological reporting in silicosis. [ILO 1930]

In 1968, the United States Public Health Service recommended modifications to the ILO system, to facilitate its use in asbestos exposure. Within three years international uniformity in the reporting of industrial lung disease had been achieved through the ILO U-C 1971 Classification. [Shipley]

It was not until the work of Greene in 1978 that systematic chest radiographic reporting was considered for other clinical settings. Through the introduction of the Minimum Standardised Radiographic Reporting System, the ILO U/C 1971 Classification was adapted for utilisation in the broad spectrum of adult chronic lung disease. [Greene] Further modifications were recommended in 1983, especially with respect to terminology. [McLoud]

The first semi-quantitative reporting system for evaluation of acute lung pathology was introduced in 1988, in the setting of the adult respiratory distress syndrome.[Pistolese] A similar system was first used in paediatrics in 1991, in the

context of neonatal intensive care unit reporting, [Maconochie] and was subsequently invoked by Sivit for documenting PCP in children. [Sivit]

In 1997 Cleveland and co-workers developed a radiographic reporting tool for large population paediatric chest studies, which was utilised to document chronic lung abnormalities in HIV-infected children [Cleveland, Norton] and in 2001, the World Health Organisation (WHO) Pneumonia Vaccine Trial Investigator's Group utilised systematic reporting for large population acute paediatric respiratory disease. [WHO 2001]

Against this background, a customised reporting tool was developed for use in this study. It was designed to document the broad spectrum of acute and chronic CXR changes in HIV-infected South African children with a disease burden distinct from previous studies of HIV-infected children.

Terminology

Although international consensus has been reached on the semi-quantitative analysis of industrial lung disease through the use of accepted terminology and a standard set of comparative radiographs, there is no such formal consensus on terminology applicable to the broader spectrum of pulmonary pathology. [McLoud, Cleveland] Terms used in this study are thus clearly defined and referenced. Radiological interpretation was based on the radiological signs of Fraser and Pare, [Fraser] the pattern recognition

defined by Gould [1958] and Groskin [1993] and the terminology of the Fleischner Society. [Tuddenham, Hansell]

Inter-observer variation

Inter-observer variation is a limitation in any study where radiographic outcomes are assessed by a single observer. However, recent studies have shown that standardised reporting yields moderate inter-observer agreement on the majority of significant radiological endpoints in both acute [Cherian] and chronic [Cleveland] paediatric respiratory illness, achieving kappa indices > 0.56.

Radiographic technique

Routine CXR examinations in this study included erect, antero-posterior (AP) and lateral projections, acquired at a focus-film distance of 150 cm.

In acutely ill children, whose clinical condition precluded the standard imaging protocol, a single supine projection was obtained.

Reporting tool

The customised evaluation form required forced choice qualitative or semi-quantitative graded responses. (Table 3.1) In cases showing parenchymal disease, the distribution of the abnormality was further analysed on the AP radiograph by

dividing each lung into three zones. Disease was considered focal if confined to one zone, multifocal if involving two to four zones and diffuse if present in more than four zones. [McCloud 1983]

The following features were analysed:

Technical quality

Optimal radiographic quality is essential for accurate interpretation. [Shipley, Greene, WHO 2001, Jessen, Alt, Kohda] The following technical factors were evaluated by way of quality assurance:

i. Movement artefact

Identified by subtle loss of definition of anatomical structures, particularly the ribs, hemidiaphragm(s) and/or cardiac silhouette on AP and lateral projections.

Exclusion criterion: Any movement artefact.

ii. Vertical rotation

AP projection: Discrepancy in the lengths of the anterior ribs is indicative of rotation on the vertical axis. The anterior ribs appear foreshortened on the

side to which the patient is turned. Vertical rotation may result in increased radiolucency on the side to which the patient is turned. [Joseph]

Lateral projection: Absence of vertical rotation demonstrated by superimposition of the posterior ribs of left and right sides.

Exclusion criterion:

AP projection: Greater than 4:1 discrepancy in anterior rib length between the left and right sides.

Lateral projection: Failure to project both sets of posterior ribs dorsal to the posterior vertebral body line.

iii. Horizontal rotation (AP view only)

Horizontal rotation results in a lordotic projection, identified by positioning of the anterior ends of the ribs above the posterior ends, and projection of the medial ends of the clavicles above the first thoracic vertebral segment. Rotation on the horizontal axis may distort the cardiac contour, resulting in spurious prominence to the cardiac apex. [Burton, Donoghue]

Exclusion criterion: The medial ends of the clavicles projected above the level of the third cervical segment.

iv. Penetration

AP projection: Adequate penetration affords visualization of the vertebral column, intervertebral discs and pulmonary vasculature behind the heart, and

the pulmonary vessels in the proximal two thirds of the lung fields, but not in the peripheral third. [Burton 1999]

Exclusion criteria:

Under penetration: Inability to discern the vertebral column behind the heart.

Over penetration: Inability to discern pulmonary vessels in the parahilar region.

v. Lung volumes

AP projection: Optimal inspiratory excursion affords visualization of five or six anterior ribs above the right hemidiaphragm in the mid-clavicular line. Demonstration of seven or more anterior ribs was attributed to hyperinflation, while the visualization of four or less anterior ribs was attributed to poor inspiratory excursion or small volume lungs. [Lloyd, Greene, McLoud, Schlesinger, Burton, Silverman 1985]

Lateral projection: Evaluation of inspiratory excursion is more subjective on the lateral projection. The signs of hyperinflation are flattening of the hemidiaphragms and an increase in the retro-sternal space, [Griscom, Erikson, Dawson] while a poorly inspired film shows marked cephalad convexity of the hemidiaphragms, with the domes approximating the carina.

Exclusion criterion:

AP projection: Visualisation of less than three anterior ribs above the right hemidiaphragm in the mid-clavicular line.

Lateral projection: Hemidiaphragms superimposed on hilar structures

Heart size

In children younger than forty-eight months, a cardiothoracic ratio (CTR) up to 60% was regarded as normal on a technically satisfactory, well inspired AP chest radiograph. In children forty eight months and older a CTR up to 50% was regarded as normal. [Burton, Donoghue]

Bronchial wall thickening

Bronchial wall thickening was recorded if parahilar "ring" or "tramline" opacities were visualized, with normal intervening pulmonary parenchyma. [Erikson, Tuddenham, Swischuk]

Pulmonary opacification

Pulmonary opacification was recorded if either of the following was identified. [Fleischner, Felson, Tuddenham, Hansell]

> *"Ground-glass" opacification:* an area of poorly defined, hazy increase in pulmonary parenchymal attenuation within which pulmonary vessels and airway walls remain visible, but with indistinct margins.
>
> *"Consolidation"*: an area of homogeneously increased pulmonary parenchymal attenuation which effaces vessel margins and airway walls, and which may contain air bronchograms.

Nodules

The presence of small, discrete, rounded opacities measuring 2-10 mm in diameter. For reporting purposes, a miliary pattern was regarded as a nodular pattern. [Shipley, Cleveland, Tuddenham, McLoud]

Reticular pattern

The presence of widespread, countless small linear opacities, which combine to produce an appearance similar to a net. [Tuddenham, McCloud, Cleveland, Hansell]

Atelectasis

Evidence of diminished volume involving all or part of a segment or lobe. Stratification was as follows: [Fraser]

Mild: Bronchovascular crowding alone,

Moderate: Bronchovascular crowding with displacement of the hilar point and/or adjacent pleural fissure, and/or mediastinal deviation and/or elevation of a hemidiaphragm and/or compensatory hyperinflation of the adjacent lung and/or ipsilateral rib crowding,

Severe: Complete lobar collapse.

Bronchiectasis

Chest radiographs have limitations in defining both the presence and extent of early bronchiectasis. High resolution computerized tomography (HRCT) is recognized as the diagnostic reference standard. [Gudbjerg, Currie, Munro, Fall, Bayramoglu] Notwithstanding this, a presumptive diagnosis of bronchiectasis was based on identification of cylindrical, varicose or cystic dilatation of the bronchi, extending towards the periphery of the lung, in association with bronchial wall thickening and atelectasis. [Gudbjerg , Vandevivere, Westcott, Fraser, Hansell]

Pulmonary cyst or cavity

A *pulmonary air cyst* was defined as a round, gas-containing pulmonary space with either a thin (< 2mm), well-defined and regular wall, or no discernible wall. A *cavity* was a gas-filled space (as shown by the presence of decreased attenuation) within a mass, a nodule or an area of consolidation. [Feuerstein, Tuddenham, Hansell]

Thymus gland

Criteria for identification of a normal thymus gland were an anterior mediastinal structure of homogeneous attenuation which blended imperceptibly with the middle mediastinal structures in a child younger than 48 months of age, causing no mediastinal displacement or trachea-bronchial narrowing; lateral margins on the AP projection may show gentle undulation, representing impressions from the costal

cartilages, while the anterior margin as seen on the lateral view was completely smooth, conforming with the sternal margin. [Silverman 1985]

Mediastinal adenopathy

To identify mediastinal adenopathy, and other mediastinal masses, knowledge of normal paediatric plain radiographic mediastinal anatomy was used in conjunction with established radiographic signs of mediastinal pathology on AP and lateral CXR's. [Chang, Silverman 1985]

AP projection: A lobulated and/or widened mediastinal contour with or without bronchial displacement and/or narrowing.

Lateral projection: Increased attenuation postero-inferior to the carina, constituting the so-called "doughnut" or "hamburger" sign; and/or an anterior mediastinal mass with a lobulated anterior margin not conforming to the sternal contour.

STUDY NUMBER	
X-RAY DATE	
X-RAY NUMBER	
1(a) TECHNICAL FACTORS SATISFACTORY: 0 = NO; 1= YES	
1(b) IF NO: 1 = MOVEMENT; 2 = VERTICAL ROTATION; 3 = HORIZONTAL ROTATION; 4 = PENETRATION; 5 = INSPIRATION	
2. HEARTSIZE: 0 = CTR < 60% below 48 months ; CTR < 50% 48 months or older 1= ENLARGED	
3. BRONCHIAL WALL THICKENING: 0 = ABSENT; 1 = PRESENT; 2 = OBSCURED	
4(a) PULMONARY OPACIFICATION: 0 = ABSENT; 1 = PRESENT	
4(b) IF PRESENT: 1 = FOCAL; 2 = MULTIFOCAL; 3 = DIFFUSE	
5(a) RETICULAR PATTERN: 0 = ABSENT; 1 = PRESENT; 2 = OBSCURED	
5(b) IF PRESENT: 1 = FOCAL; 2 = MULTIFOCAL; 3 = DIFFUSE	
6(a) NODULAR/RETICULO-NODULAR PATTERN: 0 = ABSENT; 1 = PRESENT 2 = OBSCURED	
6(b) IF PRESENT: 1 = FOCAL; 2 = MULTIFOCAL; 3 = DIFFUSE	
6I IF PRESENT: NODULE SIZE: 1 = < 2mm; 2 = 2-4 mm; 3 = > 4 mm	
7(a) ATELECTASIS: 0 = ABSENT; 1 = PRESENT	
7(b) IF PRESENT: 1 = SUBSEGMENTAL; 2 = SEGMENTAL; 3 = LOBAR	
8(a) BRONCHIECTASIS: 0 = ABSENT; 1 = PRESENT	
8(b) IF PRESENT: 1 = FOCAL; 2 = MULTIFOCAL	
9. THYMUS: 0 = NOT VISUALISED ; 1 = VISUALISED; 2 = OBSCURED	
10(a) MEDIASTINAL ADENOPATHY: 0 = ABSENT; 1 = PRESENT; 2 = OBSCURED	
10(b) IF PRESENT: BRONCHIAL NARROWING: 0 = ABSENT; 1 = PRESENT	
11(a) CYST/CAVITY: 0 = ABSENT; 1 = PRESENT	
11(b) IF PRESENT: 1 = FOCAL; 2 = MULTIFOCAL	
12. PLEURAL PATHOLOGY: 0 = ABSENT;1 = PRESENT (SPECIFY)	
13. CHEST WALL PATHOLOGY: 0 = ABSENT; 1 = PRESENT (SPECIFY)	
14. OVERALL ASSESSMENT: 0 = NORMAL; 1 = MILD ABNORMALITY; 2 = SEVERE ABNORMALITY	

Table 3.1. Customised chest radiograph reporting template

Chapter Four

Baseline chest radiographic features

RATIONALE FOR THE INCLUSION OF PUBLISHED WORK

The manuscript included in this chapter addresses two key thesis objectives.

It provides a detailed analysis of the enrolment CXR findings in the study cohort, defining the main patterns of radiographic abnormality. It also provides the first evidence of an association between the extent of radiological abnormality, the clinical severity of HIV-disease and the degree of immune suppression.

Furthermore, foundation data are provided for the evaluation of CXR abnormalities over time, which are reported and analysed in later chapters.

PEDIATRIC PULMONOLOGY

Clinical and immunological correlates of chest X-ray abnormalities in HIV-infected South African children with limited access to anti-retroviral therapy

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INTRODUCTION

Respiratory illness is the leading cause of morbidity and mortality in HIV-infected children. [Ansari, Graham 2007, Jeena 2008, Zar 2010, Gray 2010] The major burden of paediatric HIV-associated respiratory disease is in LMIC's, especially SSA. [UNAIDS 2012]

The CXR is the most readily available and most common imaging modality for assessing paediatric respiratory disease. [Maru, Mettler, Mehta, Frush] However, there is little information on the spectrum of CXR abnormalities in HIV-infected children in LMIC's, where access to care may be sub-optimal. Furthermore, there are limited data on the relationship between CXR abnormalities and clinical severity or immune dysfunction in HIV-infected children in LMIC's.

Because of the scarcity of radiologists worldwide, especially in LMIC's, clinicians interpret most CXR's. [Mettler, Cockshott] A better understanding of the CXR patterns in HIV-infected children may thus be of broad benefit.

The aim of this study was to describe baseline CXR findings in a cohort of HIV-infected South African children and to investigate the association between CXR features and clinical or immunological markers of severity.

MATERIALS AND METHODS

Study population

We undertook a cross-sectional study of HIV-infected children enrolled in an isoniazid (INH) prophylaxis trial at the Tygerberg and Red Cross War Memorial Children's Hospitals in Cape Town, South Africa. Inclusion criteria were age between 8 weeks and 12 years, a weight greater than 2.5 kg, and ability to attend regular follow-up visits. Exclusion criteria were current use or need for isoniazid preventive therapy, prior hypersensitivity to sulphur drugs or INH, severe anaemia (haemoglobin <70 g/litre), neutropaenia (absolute neutrophil count <400 cells/ml), thrombocytopenia (platelet count < 50 000×10^9/l) and non-reversible renal failure. Children were recruited over a 5-year period, from December 2002 through November 2007. All children were from socio-economically deprived settings, attended public healthcare facilities and were assumed to have mother-to-child transmission of HIV-infection, on the basis of a history of parental infection. Enrolment was at a routine outpatient clinic visit when children showed no features of acute pneumonia. Although most children were not on ART at enrolment, the majority commenced treatment after enrolment, through public access programs beginning in 2004.

Informed consent was obtained from a parent or legal guardian. The study was approved by the Research Ethics Committees of the Faculties of Health Sciences of the Universities of Cape Town and Stellenbosch.

Baseline investigations

A detailed history was taken, physical examination, CXR and blood tests done, including a full blood count with CD4+%. HIV staging was according to the Centre for Disease Control and Prevention (CDC) clinical and immunological categories. [CDC 1994]

Where there was clinical suspicion of PTB children underwent at least two induced sputa for smear and liquid culture. Children were classified as having confirmed tuberculosis if they were culture positive for *M tuberculosis*. Probable pulmonary tuberculosis was diagnosed when chest radiography suggested tuberculosis (lymphadenopathy, miliary pattern, pleural effusion, bronchial compression, or parenchymal infiltrate) and the child had at least one of: a positive tuberculin skin test result, a history of a close contact with tuberculosis, loss of weight or failure to gain weight within the previous three months, or a positive smear result for acid fast bacilli. The diagnosis of probable tuberculosis was subject to independent review by a blinded investigator.

CXR's

AP and lateral CXRs were taken at enrolment and reported by a paediatric radiologist blinded to clinical details other than HIV status. Standard radiological quality control criteria, [Greene] defined signs, [Fraser] pattern recognition [Gould, Groskin] and terminology [Tuddenham, Hansell] were utilized to evaluate thirteen CXR features, including technical factors, heart size, the major airways, lung parenchyma, mediastinum, pleural

spaces and chest wall. Radiological findings were recorded on a customized force-choice reporting sheet.

To assess the severity of pulmonary parenchymal abnormality, the radiological end-points of the WHO Radiology Working Group on Paediatric Pneumonia [Cherian] were modified and overall radiological severity was stratified as:

Grade 1: Normal or only minor abnormality, such as bronchial wall thickening.

Grade 2: Moderate or severe abnormality, defined as one or more of the following features: pulmonary opacification, a reticular/nodular/reticulo-nodular pattern, cavities, cysts or bronchiectasis

In cases where bronchial wall thickening (grade 1) occurred in conjunction with a more severe abnormality such as pulmonary opacification (grade 2), overall radiographic severity was assigned according to the most advanced abnormality demonstrated.

The distribution of grade 2 features was further analysed on the AP radiograph by dividing each lung into three zones. Disease was considered focal if confined to one zone, multifocal if involving two to four zones and diffuse if in more than four zones. [McLoud]

Statistical analysis

Descriptive statistics were calculated. Univariate and multiple logistic regression analyses were performed for the association of age, gender, cotrimoxazole prophylaxis, CDC clinical and immunological stages, previous or current TB, nutritional status, haematological parameters and ART with severity of radiological disease.

To facilitate the formulation of multiple logistic regression models, continuous variables were analysed utilising locally weighted scatterpoint smoothing (LOWESS) curves, thus allowing identification of thresholds for increased risk of more severe radiological abnormality.

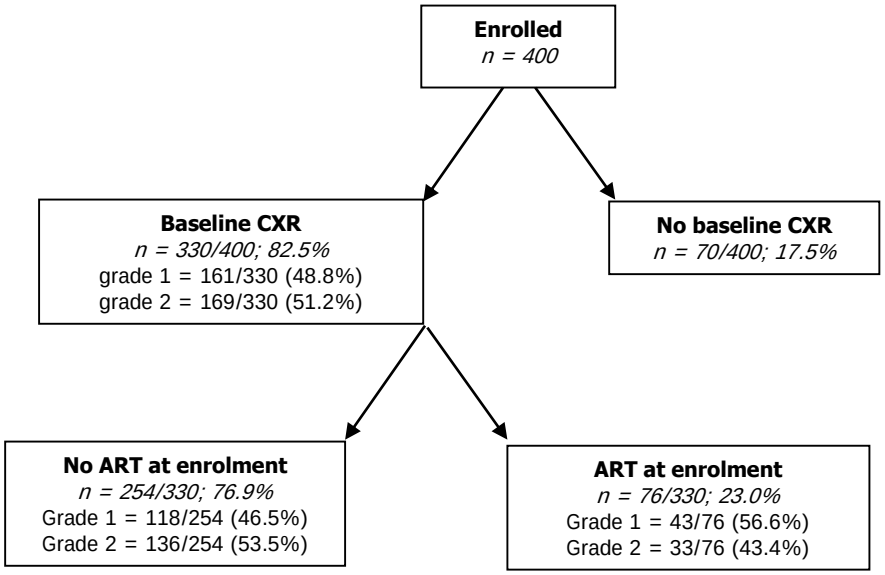
Odds ratios with 95% confidence intervals (CI) were reported.

RESULTS

Study population

Four hundred children were enrolled, of whom 82.5%, (n = 330; median age: 23.8 months; range 1.1 – 141.7 months) had retrievable baseline CXR's. (Table 4.1)

All retrieved radiographs were considered technically satisfactory. There was no difference between those with and without radiographs by age, gender, HIV-staging, nutritional status, cotrimoxazole prophylaxis or ART.



Most children (n = 303, 91.8%) had moderate or advanced clinical disease; 203 (61.5%) were CDC clinical category B and 100 (30.3%) clinical category C.

The defining clinical conditions for category B were:

(i) Previous severe infection (n = 66/203; 32.5%), including thirty (30/203; 14.8%) with a history of pneumonia

(ii) Anaemia (n = 52/203; 25.6%),

(iii) Diarrhoea (n = 32/203; 15.8%),

(iv) LIP (n = 17/203; 8.3%) and

(v) Cardiomyopathy (n = 7/203; 3.4%).

In 29 cases (14.3%), the defining condition was not recorded.

The defining category C conditions were:

(i) Recurrent serious infections (n = 45; 45%); including twenty-seven (27/100; 27%) with recurrent severe pneumonia,

(ii) Wasting (n = 28; 28%)

(iii) A history of disseminated or extra-pulmonary tuberculosis (n = 9; 9%)

(iv) Encephalopathy (n = 4; 4%)

(v) Previous PCP (n = 2; 2%) and

(vi) Previous Cryptococcal meningitis (n = 1; 1%).

In eleven cases (n = 11; 11%), the defining category C condition was not recorded.

More than two-thirds of the cohort (n = 225; 68.1%) had moderate or advanced immune suppression (immunological category 2 or 3). Almost three-quarters (n = 239, 72.4%) were on cotrimoxazole prophylaxis and twenty-three percent (n = 76) were on ART.

One hundred and twenty-one patients (n = 121; 37%) had respiratory signs at enrolment. Thirty-six patients (n = 36, 11%) had a solitary respiratory sign, while 85 (26%) showed a combination of features. Chest retraction (n = 71; 22%) was the most common finding. Tachypnoea and crepitations were each documented in 59

cases (18%), while rhochi and crepitations were each found in 47 cases (14%) and bronchial breathing was present in 23 subjects (7%).

Forty six patients (n = 46, 13.9%) were diagnosed with PTB at enrolment, with 18 (39%) being culture-confirmed. Respiratory signs were present in 36 patients (78%), of whom 29 (63%) showed multiple signs. Retraction was most commonly seen, occurring in 23 patients (50%).

Twenty five patients (n = 25; 7.5%) had been treated for an acute chest infection in the month preceding enrolment. The median time from commencement of treatment to enrolment was 10 days (IQR: 7-15 days).

Radiological findings (Table 4.2)

Overall radiographic severity was grade 1 in 161 cases (48.8%) and grade 2 in 169 cases (51.2%).

Grade 1 findings (n = 161; 48.8%)

Fifty two patients (15.8%) had a normal CXR and one-hundred and nine (33.0%) showed bronchial wall thickening (Figure 1).

Grade 2 findings (n = 169; 51.2%)

Three main patterns occurred (Figures 2, 3, 4):

i. Pulmonary opacification alone (n = 91; 27.5%)

ii. A nodular/reticulo-nodular pattern with areas of opacification (n = 41; 12.4%) and

iii. A nodular/reticulo-nodular pattern alone (n = 37; 11.2%).

The distribution of grade 2 abnormalities was multifocal or diffuse in most cases (n = 128; 75%). Opacification was the most common pattern in children under 24 months of age, while a nodular or reticular-nodular pattern was the predominant finding in those older than 48 months. Children aged 24 to 48 months, showed opacification alone and a mixed pattern of nodules with opacification in similar proportions.

Other grade 2 features such as atelectasis (n = 38; 11.5%), bronchiectasis (n=13; 3.9%) and isolated thin-walled pulmonary cysts (n = 6; 1.8%) occurred in association with one of the three main grade 2 parenchymal patterns.

Eighty nine patients (89/169; 53%) with grade 2 features had respiratory signs. Conversely, almost half of those with grade 2 radiographic features had no respiratory signs.

Additional findings:

Overall, bronchial wall thickening (n= 230; 69.6%) was the most common radiographic abnormality.

Cardiomegaly (n = 49; 14.8%) was more common in older children, with 39/49 (79.5%) above 48 months of age (OR = 8.2, 95% CI: 4.7-14.4, p<0.001). Amongst those with cardiomegaly, 28 (57%) showed grade 2 abnormality, manifest as nodules alone in 12 cases (24%), opacification alone in 10 subjects (20%), and a combination of features in 6 patients (12%).

Mediastinal adenopathy (n = 19; 5.8%) was uncommon, was mostly associated with grade 2 parenchymal abnormality (17/19; 89.5%) and rarely resulted in bronchial narrowing (3/19; 15.8%)

Pleural abnormality was also uncommon (n = 11; 3.3%), with mild focal basal thickening the only abnormality demonstrated.

All 46 patients (13.9%; median age 18.7 months; IQR: 10.1 – 49.0 months) diagnosed with PTB at enrolment had abnormal CXR's. In twelve cases (26%), bronchial wall thickening (grade 1) was the only abnormality. Thirty-six (78%) demonstrated grade 2 findings, which were multifocal or diffuse in 86% (31/36); 20 (43.5%) had pulmonary nodules, either alone or in association with opacification; 9 (19.5%) had mediastinal adenopathy, all with grade 2 parenchymal abnormality.

Amongst the four subjects with encephalopathy, two had respiratory signs, of whom one had severe radiographic abnormality, manifest as multifocal opacification.

Risk factors for radiological abnormality

Univariate analysis (Table 4.3)

More severe radiological abnormality was associated with more advanced clinical HIV disease, greater immune suppression, poor nutritional status, lower haemoglobin, higher white cell count and PTB diagnosed at enrolment. No association was demonstrated with age, gender, use of cotrimoxazole prophylaxis, prior treatment for TB or ART.

Multiple logistic regression analysis (Table 4.4)

Grade 2 radiological features were independently associated with CDC clinical categories B or C, CD4+ less than 20%, and age more than 24 months. The likelihood of grade 2 abnormalities was four-times higher in children between 24 and 48 months, compared to those younger than 24 months, and almost double that of patients older than 48 months.

DISCUSSION

This study provides the most comprehensive evaluation to date of the spectrum of CXR abnormalities in HIV-infected children in a LMIC setting. It highlights the high prevalence of CXR abnormalities in the absence of associated acute respiratory symptoms. More advanced HIV disease was associated with three predominant

radiological patterns, namely pulmonary opacification alone, opacification with nodules, or pulmonary nodules alone. These patterns were multifocal or diffuse in most cases, and therefore potentially easily identifiable by a broad spectrum of healthcare providers. Our study further defined the CD4+ threshold (20%) below which there is an increased probability of finding these patterns.

Our finding that more severe radiological abnormality is associated with more advanced clinical HIV disease may reflect that many conditions defining the CDC clinical categories of "moderate" or "severe" HIV disease manifest with CXR changes. Foremost amongst these is *pneumonia*, which typically shows consolidation, but which may demonstrate a combined pattern of consolidation with nodules or even a predominant nodular pattern due to acinar involvement. Although none of our cohort showed clinical features of acute pneumonia, a history of severe pneumonia defined the clinical category in fifty-seven cases (n = 57; 17.2%), with 30 (9.0%) having a single previous infection and 27 (8.2%) multiple preceding episodes. Twenty five patients (7.5%) were treated for acute chest infection in the month preceding enrolment. Post-infective changes could thus potentially account for more than a third (57/161; 35.4%) of the grade 2 abnormalities in our cohort. Our observation that opacification alone is the most common grade 2 pattern in children younger than 24 months may reflect the high incidence of pneumonia in this population. [Gray 2010] *LIP* (category B) usually causes a reticulo-nodular pattern, but nodules may coalesce to form areas of superimposed confluent opacification. LIP has an estimated prevalence of 30-40% [Khare] and is more common in older children. [Zar 2008] The predominance of a nodular grade 2 pattern in children older than 48

months may reflect LIP prevalence in this population. [Pitcher 2010] *HIV-encephalopathy*, *oropharyngitis or oesophagitis* can cause swallowing inco-ordination with aspiration pneumonitis and multifocal confluent basal opacification. Severe anaemia, *cardiomyopathy or HIV nephropathy* may precipitate pulmonary congestion and oedema, with confluent bilateral parahilar opacification or a nodular pattern presumed to be due to acinar opacification. [Pitcher 2009]

The high prevalence of bronchial wall thickening may reflect mucosal oedema or inflammation as a result of lower-respiratory tract infection, micro-aspiration or pulmonary congestion. However, this may also be an early feature of LIP, preceding the characteristic reticulo-nodular pattern. [Pitcher 2010]

Our results differ from those of a recently published retrospective study of a smaller cohort of 92 older HIV-infected South African children (mean age 5.4 years) at commencement of ART. [du Plessis] This study investigated CXR abnormalities, WHO clinical staging and CDC immunological category. In contrast to our findings, most children had a normal CXR and no association was found between radiological abnormality and clinical staging or degree of immune suppression. However, this study is limited by the small sample of older ART-naïve children, representing a selected population of survivors. Furthermore, the broad "moderate" CDC immunological stage 2 may be insensitive for predicting radiological abnormality. This is supported by our finding of an increased probability of grade 2 radiological abnormalities only in children with CD4+ less than 20%. This threshold falls in the middle of the CD4+% stage 2 range (15%-24%) for "moderate" suppression.

Children with "moderate" immune suppression but a CD4+ of 20%-24% have a prevalence of grade 2 radiological abnormality similar to those with no immune suppression.

A strength of our study is the consistent reporting of CXR's by the same observer throughout the five-year study period. Reporting methodology was rigorous and standardized with inclusion criteria for each feature clearly defined by radiological igns and according to published international norms. Furthermore, reporting was by a paediatric radiologist with more than twenty years of clinical experience who was blinded to the clinical and immunological parameters of the children.

Paradoxically, a limitation of the current study is that reporting was by a single observer. The potential for inter-observer variation in the interpretation of CXR features is well recognized, especially for mild changes. [Cleveland] Therefore some observer-dependent under- or over-reporting of grade 1 findings may have occurred. However, inter-observer variation is less likely to impact on the reported prevalence of the more overt grade 2 findings, which had a multifocal or diffuse distribution in most cases. Good inter-observer agreement can be achieved when there is systematic and standardized reporting of such features, [Cherian] as was done in our study. Another limitation is the potential for under-reporting of features such as adenopathy or bronchiectasis, which generally require computerized tomography for definitive diagnosis. Resource limitations and ethical concern about unnecessary exposure of children to radiation precluded the use of this modality in most children. Lastly, definitive diagnosis of some HIV-associated lung diseases such as LIP

requires biopsy. We were unable to correlate CXR changes with histological changes, as ethical concerns and resource limitations precluded the use of diagnostic biopsy in these children.

The association of age with grade 2 radiological abnormalities warrants a further longitudinal study, as our cross-sectional design does not distinguish transient from persistent changes. The peak prevalence of grade 2 abnormalities in children aged 24-48 months has not been documented previously, but may reflect a combination of transient post-infective abnormalities, with persistent changes from LIP, chronic infections, aspiration syndromes, congestion and bronchiectasis. This is supported by findings of a 4-year longitudinal birth-cohort study of 86 HIV-infected North American children [Norton] showing that persistent radiographic changes had a cumulative prevalence of 14.6% by 18 months of age and 29% by 48 months, with the median age of onset 18 months. The lower prevalence of CXR abnormalities in children older than 48 months most likely reflects survival of those with less advanced disease.

CONCLUSION

CXR abnormalities in the absence of acute respiratory symptoms are common in HIV-infected children in LMIC's. These abnormalities may be due to previous infection, PTB, LIP, congestion or chronic aspiration. The extent of radiological abnormality correlates with age and clinical and immunological severity of HIV-disease.

A baseline CXR is thus recommended in all children, irrespective of respiratory symptoms, to serve as a comparison when the child presents with an acute respiratory complaint.

population summary	n (%) or median (IQR)
Demographics	
N	330
age (months)	23.8 (11.1 – 47.4)
Male	175 (53)
respiratory signs	
No	209 (63.3)
Yes	121 (36.7)
cotrimoxazole prophylaxis	
no	91 (27.6)
Yes	239 (72.4)
ART	
no	254 (77.0)
Yes	76 (23.0)
> 2 months	72 (21.8)
PTB	
No	234 (70.9)
prior treatment	50 (15.2)
diagnosis at enrolment	46 (13.9)
CDC clinical stage	
N	4 (1.2)
A	23 (7.0)
B	203 (61.5)
C	100 (30.3)
CDC immunological stage	
1	104 (31.5)
2	121 (36.7)
3	104 (31.5)
haematological parameters	
CD4+%	20.3 (14.0-27.2)
haemoglobin concentration (gm/dL)	10.5 (9.4-11.4)
white cell count ($x10^9$/L)	10.0 (7.4-13.5)
WHO anthropometric parameters	
height for age z-score (WHOHAZ)	-1.9 (-2.9 - - 0.9)
weight for age z-score (WHOWAZ)	-1.4 (-2.9 - -0.43)
weight for height z-score (WHOWHZ)	-0.21 (-1.1 - -0.72)

Table 4.1 Baseline study population summary

radiographic finding	n (%)	median age in months (IQR)	median CD4+%(IQR)
lung parenchyma			
grade 1 features (n = 161, 48.8%)			
Normal	52 (15.8)	19.5 (8.7 – 43.9)	27.2 (19.0 – 33.0)
bronchial wall thickening	109 (33.0)	24.6 (11.3 – 54.4)	21 (15.6 - 27.3)
grade 2 features (n = 169, 51.2%)			
confluent opacification alone	91 (27.5)	15.5 (8.5-30.1)	19.0 (13.3-25.5)
nodular/reticulo-nodular pattern with opacification	41 (12.4)	35.0 (20.5-44.7)	15.9 (12.4-22.0)
nodular/reticulo-nodular pattern alone	37 (11.2)	42.4 (19.3-79.0)	17.5 (13.0-25.0)
Atelectasis	38 (11.5)	38.2 (20.7 – 60.2)	16.1 (13.2 – 21.2)
Bronchiectasis	13 (3.9)	28.1 (18.6 – 62.5)	19.9 (17.0 – 21.7)
Cyst	6 (1.8)	31.8 (19.6 – 67.1)	19.4 (17.3 – 24.5)
inspiratory excursion			
Poor	62 (18.8)	42.5 (20.6 – 56.5)	20.4(14.0-26.9)
Normal	207 (62.7)	24.6 (12.4 – 48.5)	21.0 (15.2-28.4)
Hyperinflation	61 (18.5)	10.5 (6.0 – 21.4)	17.9(11.9-22.4)
Heart			
Cardiomegaly	49 (14.8)	61.8 (51.4 – 79.0)	21.7 (14.0 – 24.0)
Mediastinum			
thymus visualised	43 (13.0)	12.5 (7.0 – 20.6)	21.0 (17.3 – 28.0)
Adenopathy	19 (5.8)	31.0 (22.7 – 76.7)	16.6 (12.6 – 27.0)
Pleura			
Thickening	11 (3.3)	29.0 (13.6 – 69.0)	24.0 (14.7 – 28.0)
trachea and main bronchi			
bronchial narrowing	3 (0.9)	21.2 (7.8 – 83.4)	14.3 (4.9 – 23.0)

Table 4.2. Baseline chest radiographic findings

Univariate analysis				
Parameter	**Grade 1 n (%) or median (IQR)**	**Grade 2 n (%) or median (IQR)**	**Odds ratio (95% CI)**	**p-value**
Demographics				
age (months)	21.9 (10.3-51.4)	24.6 (11.9-44.8)		0.48
Male	80 (45.7)	95 (54.3)	1.30 (0.84-2.00)	0.24
cotrimoxazole prophylaxis				
No	50 (54.1)	41 (45.9)	1.0	
Yes	111 (46.4)	128 (53.6)	1.40 (0.87 – 2.28)	0.255
ART				
none	120 (47.2)	134 (52.7)	1.0	
< 2 months	42 (55.3)	34 (44.7)	0.7 (0.44 – 1.22)	0.2
> 2 months	42 (58.3)	30 (41.7)	0.6 (0.35 – 1.02)	0.1
PTB				
No	120 (51.3)	114 (48.7)	1.0	
prior treatment	18	32	1.9 (1.0 – 3.5)	0.052
diagnosis at enrolment	12 (26.0)	34 (73.9)	3.1 (1.6 – 6.3)	0.001
CDC clinical stage				
A + N	20 (74.1)	7 (25.1)	1.0	
B	101 (49.7)	102 (50.3)	2.8 (1.16 – 7.12)	0.02
C	40 (40)	60 (60)	4.2 (1.65 – 11.07)	0.003
CDC immunological stage				
1	67 (64.4)	37 (35.6)	1.0	
2	54 (44.6)	67 (55.4)	2.24 (1.31 – 3.84)	0.003
3	39 (37.5)	65 (62.5)	3.01 (1.71 – 5.30)	0.000
haematological parameters				
median CD4+%	22.0 (16.1-29.9)	18.1 (13.0 – 24.5)		0.004
median haemoglobin	11.1 (9.6-11.8)	10.0 (8.8-11.1)		0.000
median white cell count	9.4 (6.9-12.1)	10.7 (8.0-14.6)		0.000
WHO anthropometric parameters				
height-for-age z-score	-1.7 (-2.6 - -0.7)	-2.1 (-3.2 - - 1.3)		0.033
weight-for-age z-score	-1.1 (-2.3 - - 0.12)	-1.8 (-2.7 - - 0.9)		0.006
weight-for-height z-score	0.06 (-0.78 - - 0. 9)	-0.4 (- 0.79 – 0.9)		0.007

Table 4.3. Baseline univariate analysis

multiple logistic regression analysis		
Parameter	**Odds ratio (95% CI)**	**p-value**
CD4+%		
>20	1.0	
< 20	1.8 (1.0 – 3.0)	0.028
CDC clinical category		
A + N	1.0	
B	3.8 (1.1 – 13.0)	0.032
C	6.9 (1.9 – 25.6)	0.004
age (months)		
0-24	1.0	
24-48	4.1 (2.1 – 8.0)	0.000
> 48	1.9 (1.0 – 3.8)	0.049

Table 4.4. Baseline multiple logistic regression analysis

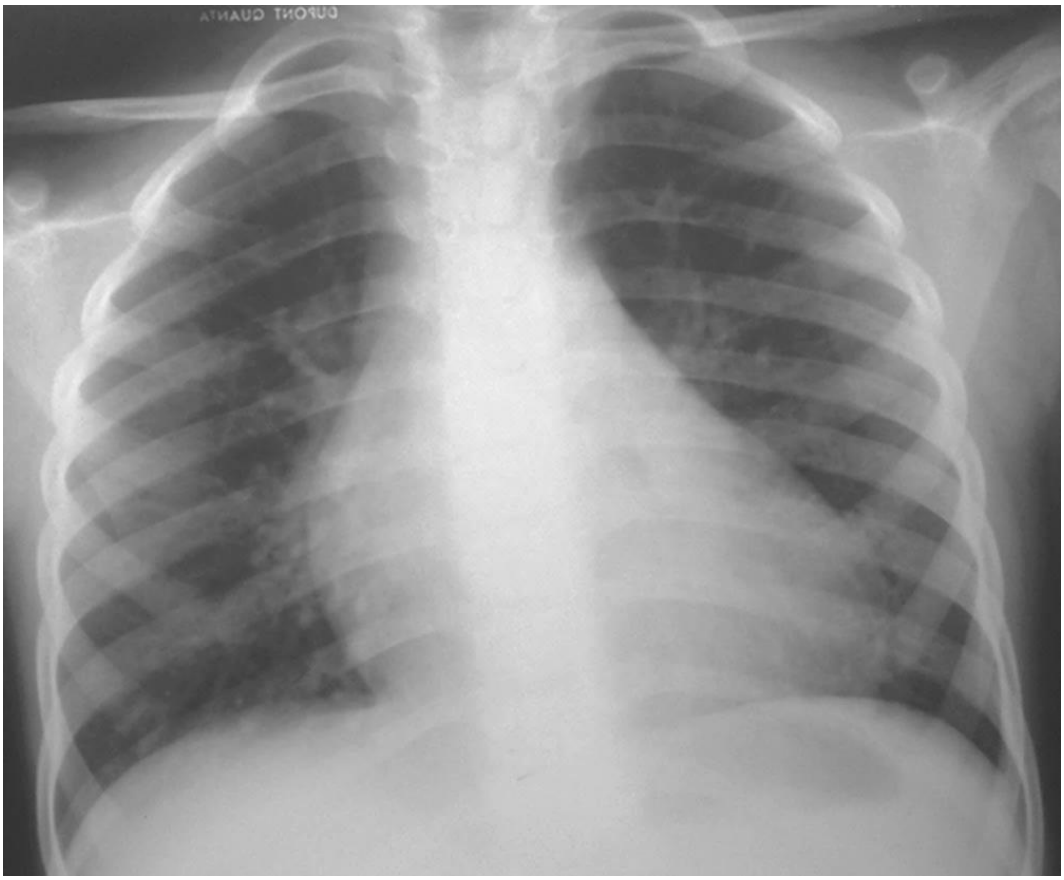


Figure 1. AP chest radiograph showing parahilar ring shadows consistent with bronchial wall thickening

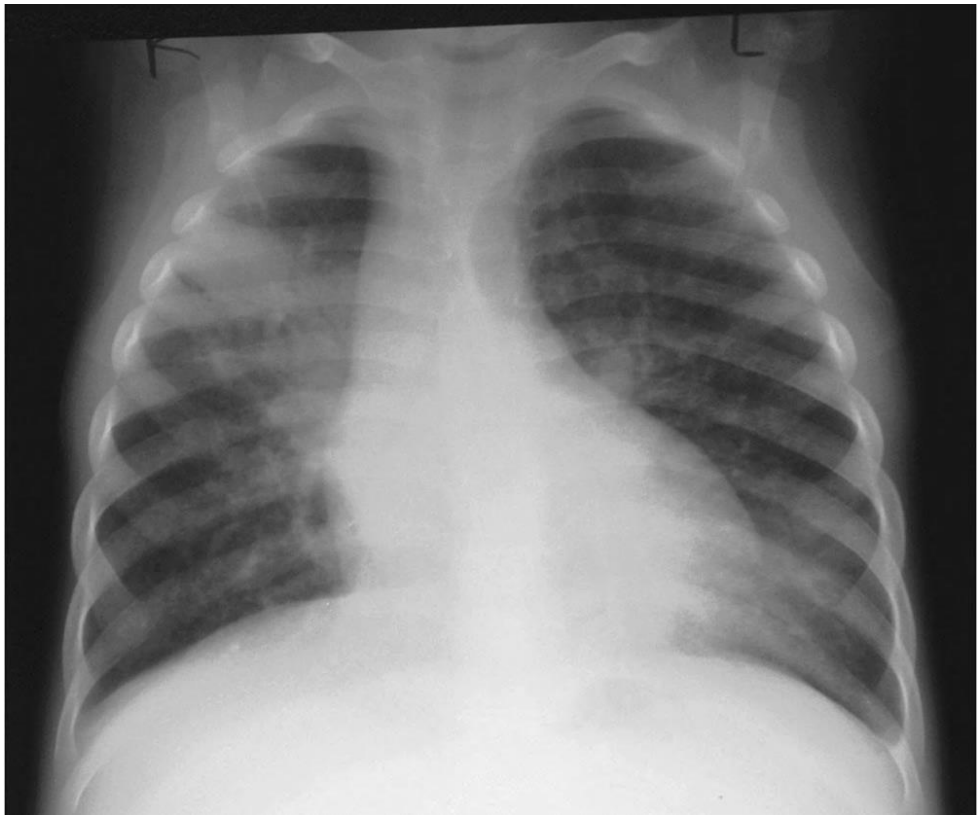


Figure 2. AP chest radiograph demonstrating multifocal opacification involving the right upper and left lower zones

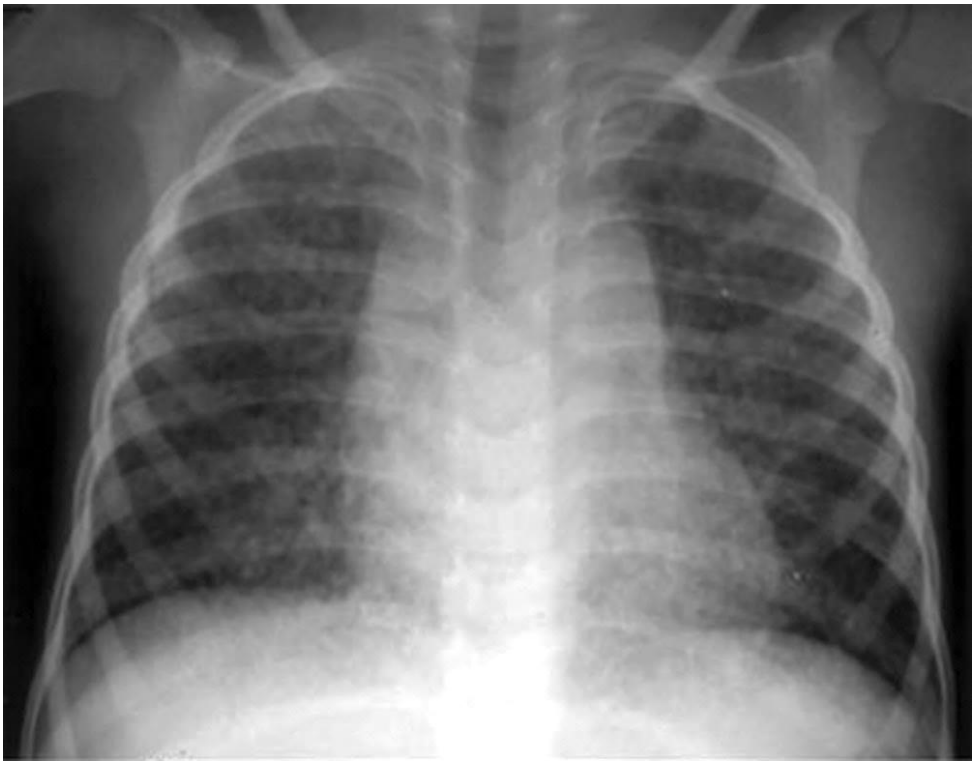


Figure 3. AP chest radiograph demonstrating a diffuse bilateral nodular pattern

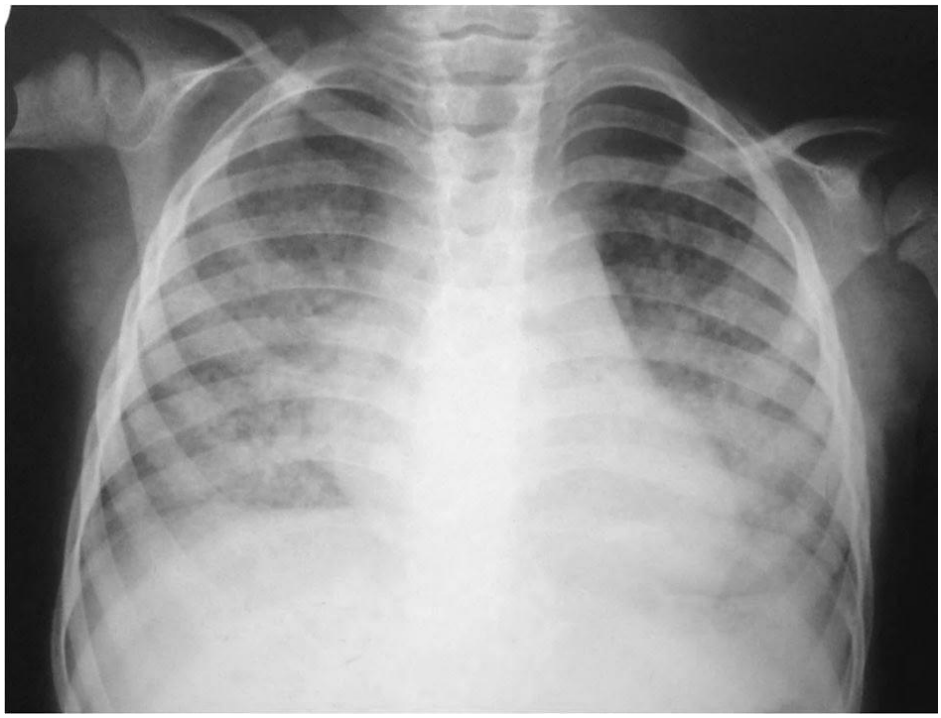


Figure 4. AP chest radiograph demonstrating a diffuse nodular pattern with areas of mid and lower zone opacification

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Chapter Five

Chest radiographic findings over time

RATIONALE FOR THE INCLUSION OF PUBLISHED WORK

The published manuscript included in this chapter reports the longitudinal component of this study and thereby addresses three key thesis objectives.

This paper describes the evolution of persistent CXR abnormalities in HIV-infected children in a resource-limited setting, defining the common abnormal radiographic patterns encountered, as well as their causes and associations. The manuscript also presents a detailed evaluation of the impact of ART.

Thorax

Chest radiographic abnormalities in HIV-infected African children – a longitudinal study

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INTRODUCTION:

Acute and chronic respiratory illness is the leading cause of morbidity and mortality in HIV-infected children. [Punpanich 2011, Gray 2010, Weber 2013, Zar 2008] This high burden of respiratory disease is reflected in abnormalities of the chest radiograph, a common investigation for respiratory illness. Although combination ART programs reduce incidence and severity of respiratory disease in HIV-infected children, there are limited longitudinal data on the chest radiographic abnormalities in HIV-infected children in LMIC's, especially where access to ART has been sub-optimal. [WHO 2002, DOH 2004, WHO 2006, Prasitsuebsai, Micheloud, Nunes, Walters]

We have previously reported that amongst a group of HIV-infected South African children with late access to ART, over 50% demonstrated severe chest radiographic abnormalities, either confluent opacification, a nodular pattern, or in combination. These radiographic patterns were most common in children aged 24-48 months and were associated with advanced HIV-disease and immune suppression. [Pitcher 2014]

Prior to the availability of ART comprising 3 antiretrovirals (ARVs), a 4-year longitudinal study of 287 HIV-infected North American children, some of whom were receiving one or two ARVs, reported a 29% (n = 87) cumulative prevalence of persistent chest radiographic abnormalities, with 23% (n = 64) having severe abnormalities, manifesting as persistent consolidation or nodules. [Norton] There is no comparable study in LMIC's where a high burden of paediatric HIV-disease, limited

access to healthcare, malnutrition, poverty and a high incidence of respiratory infections such as PTB contribute to respiratory morbidity. [UNAIDS 2013]

The aim of this study was to longitudinally investigate the prevalence, features and progression of chest radiographic abnormalities, and the impact of ART, in HIV-infected African children.

METHODS:

Study population

We conducted a prospective longitudinal study of HIV-infected children enrolled in an INH prophylaxis trial at the Red Cross War Memorial Children's Hospital and Tygerberg Children's Hospital in Cape Town, South Africa. [Zar 2007, Frigati] Children were recruited over a 5-year period, from December 2002 through November 2007. All children attended public healthcare facilities and were vertically infected. Informed consent was obtained from a parent or legal guardian. The Research Ethics Committees of the Faculties of Health Sciences of the University of Cape Town and Stellenbosch University approved the study.

Clinical assessment

Baseline

At enrolment, study investigators recorded a standardized baseline assessment on a customized case report form (CRF). This included a detailed history incorporating socio-economic parameters, and a physical examination. CD4 count and percentage were measured. HIV-staging was according to the CDC clinical and immunological categories. [CDC 1994] For clinical suspicion of PTB, children had at least two induced sputa for smear and liquid culture. [Zar 2007, Frigati]

Follow-up:

Patients were seen at monthly intervals for the first six months, six-weekly for the next six months and three-monthly thereafter. At each visit, an abbreviated history and physical examination, including height and weight, were undertaken. CD4+ cells and percentage were measured twelve-monthly. Tuberculin skin testing was repeated six-monthly if prior tests were negative.

Caregivers kept diaries of intercurrent illnesses and clinic attendance between study visits and a questionnaire reflecting diary entries was completed at each study visit. When a child was hospitalized, caregivers contacted a study investigator, thereby facilitating recording of hospitalization data. Children hospitalized for acute lower respiratory tract infection (LRTI) were investigated for bacterial, viral, mycobacterial

and fungal pathogens and treated according to current South African public sector guidelines. All hospitalizations for lower respiratory tract infections were included on the study database.

Access to ART through public programs became available from 2004. Follow-up for children commencing ART was according to standard guidelines for ART safety and compliance. ART adherence was assessed at each visit as percentage compliance, based on medication dispensed and returned.

Throughout the study, nutritional supplements (multivitamin syrup, elemental iron and folic acid) were prescribed as standard of care. In addition, Primary Health Care facilities provided food supplementation to moderately malnourished children. Severely malnourished children were hospitalized for initial management.

Radiological assessment:

AP and lateral chest radiographs were acquired at enrolment and then six-monthly. Additional radiographs were performed prior to initiating ART or if hospitalized for LRTI, if PTB was suspected, or at the discretion of the treating doctor.

Reporting

A paediatric radiologist blinded to the clinical details undertook chest radiographic interpretation. The standardized reporting methodology and customized force-choice

reporting template have been previously described.[Table 3.1, Pitcher 2014] Overall radiographic severity was assigned according to the most advanced radiographic abnormality and stratified as *grade 0* (normal), *grade 1* (mild/moderate abnormality – bronchial wall thickening and/or mild atelectasis) or *grade 2* (severe abnormality – confluent opacification, a nodular/reticulo-nodular/reticular pattern, moderate/severe atelectasis, bronchiectasis, cysts or cavities).

The distribution of severe (grade 2) features was further analysed on the AP radiograph by dividing each lung into three zones. Focal disease was confined to one zone, multifocal to between two and four zones, and diffuse when in more than four zones. [McLoud]

Statistical analysis:

Descriptive statistics (frequencies, medians, inter-quartile ranges and proportions) were calculated at baseline and across time. To assess the differences between the subgroup without follow-up radiographs and the study cohort with follow-up radiographs, baseline demographic and clinical characteristics were compared using 2-sample t-tests and chi-square tests.

The cumulative prevalence and median duration of persistent, severe radiographic abnormality was calculated by analysis of the longitudinal radiographic status of individual patients. Any child showing severe abnormality on consecutive 6-monthly follow-up radiographs was considered to have persistent severe abnormality. The

number of consecutive radiographs demonstrating severe abnormality determined its duration. Descriptive tables of transition in the radiographic status of the cohort were compiled at each six-monthly point of follow-up and stratified by ART status. As a summary descriptive metric, the cumulative total of transitions (improvement and deterioration) was calculated for ART and non-ART periods.

To assess radiographic severity over time, an ordinal multiple logistic regression model included independent variables from two components of the study, a) *enrolment variables* (gender, age in months, anthropometric data, CDC clinical classification, CD4+%, radiographic severity, active PTB, hospitalization for LRTI, INH prophylaxis, ART status) and b) *time dependent variables* (radiographic severity 6 months prior, hospitalization for LRTI within the preceding 6 months, diagnosis of active PTB in the preceding 6 months, INH status at the preceding 6-monthly clinical evaluation, ART status, CD4+% and anthropometric data at each point of follow-up). Using radiographic findings in the preceding 6-months as a variable in the model made this a transitional model for radiographic severity.

In addition, changes in the composition and chest radiographic severity risk of the cohort due to withdrawals, death, or duration of follow-up were accommodated by incorporating a time factor termed "length of follow-up". This key model component was defined by the three time periods, 6-12 months, 18-24 months and 30-54 months and used to evaluate the differential effects over time of risk factors such as anthropometric data, CD4+%, use of ART, INH treatment status and prior radiographic severity. The evaluation was performed by incorporating various

interaction terms into the model and testing them for significance; none was significant.

The model accounted for the dependency of repeated measures for each participant by using a robust cluster variance approach. Multiple imputations (n = 20) of missing covariate values for ART (1% missing), CD4+% (13% missing), and the weight-for-age z-score (24% missing) were done for the model. For the imputations, logistic and multivariate normal regression models were used with complete baseline covariates such as age, sex, INH status and radiological class.

To evaluate the proportional odds assumption as the outcome in the ordinal multiple logistic regression model, an approximate likelihood ratio test was applied across the radiographic severity categories as follows: grade 0 vs grade1/2 and grade 0/1 vs grade 2.

RESULTS:

Study population

Of 330 children enrolled, 24 (7%) died and 24 (7%) were withdrawn in the first 6 months, while 24 (7%) did not have retrievable follow-up radiographs. The remaining 258 children [78%; m = 138, 53%; median (IQR) age: 28 (13-51) months] had at least one follow-up radiograph and were included in this analysis,

contributing 2024 radiographic studies. During follow-up 8 children (3%) died, while 74 (29%) were withdrawn from the study. (Table 5.1)

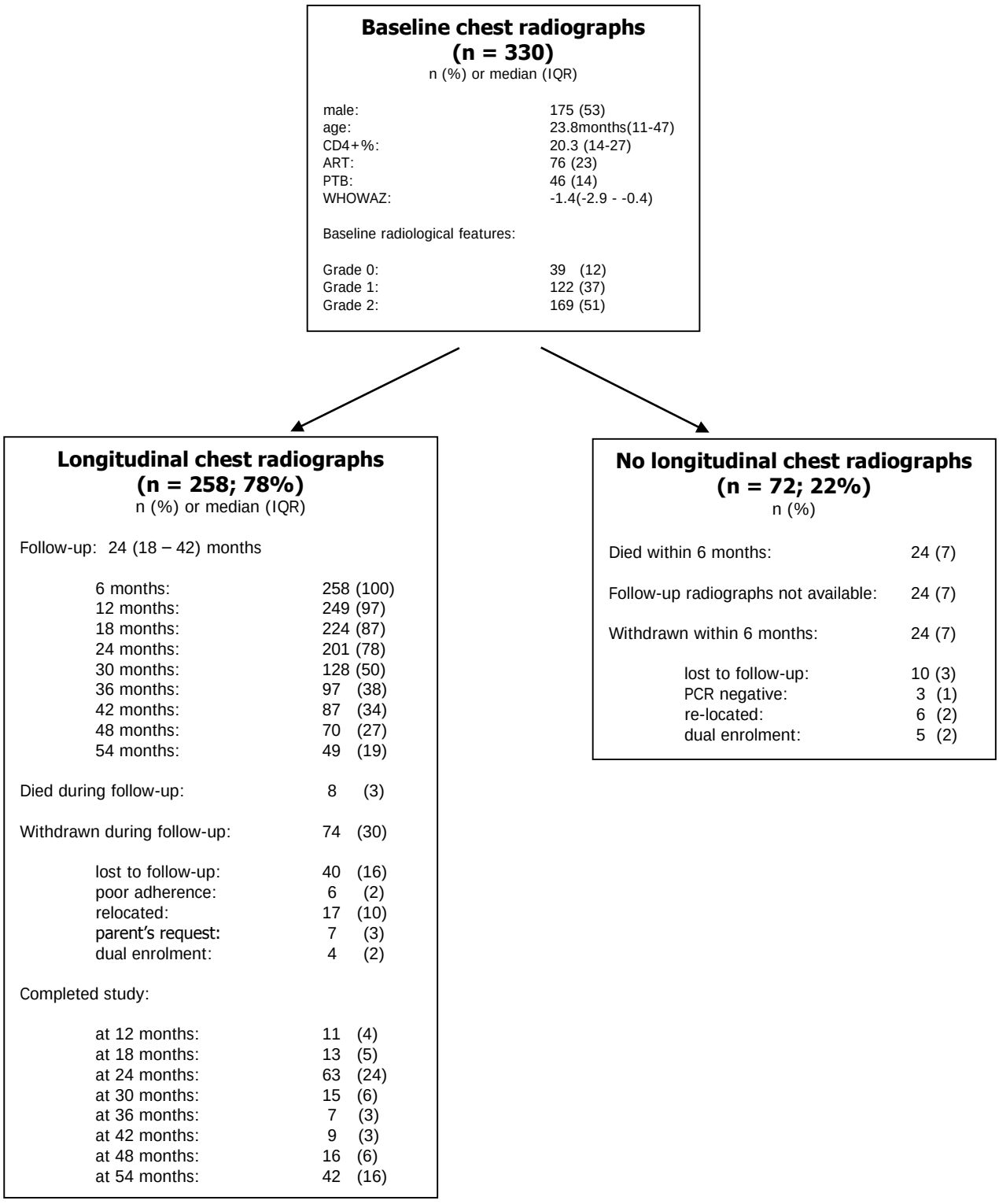

Table 5.1. Longitudinal study population summary

Comparison between the subgroup with no radiographic follow-up (n=72) and the study cohort (n=258) showed no significant difference in radiographic profile at enrolment. However, those without follow-up radiographs were younger, malnourished and had more advanced HIV disease.

Socio-economic features

All 258 children were from poor urban or peri-urban backgrounds. Almost half (120, 47%) lived in informal housing, more than half (141, 55%) were without running water in their homes, while 146 (57%) used outside toilet facilities.

Clinical features

At enrolment, 233(90%) had moderate or advanced clinical HIV-disease and most had moderate immune suppression [median (IQR) CD4+% = 21(15-28)]. Thirty-seven (14%) had PTB at enrolment, 3 being culture-confirmed and 34 clinically diagnosed. Seventy children (27%) were already on ART at enrolment, for a median of 7(5-15) months. (Table 5.2) During the study, an additional 130 children (50%), median age 33(18-56) months, commenced ART. At study end, 200(78%) were on ART, having received treatment for a median of 16(9-25) months.

Median length of follow-up was 24(18-42) months, during which 72 children (28%) required at least one hospitalization for acute LRTI, with 39(15%) having multiple admissions. Sixty-one patients (24%) had disease progression by CDC clinical

category. On final analysis, 250(97%) had moderate or advanced clinical HIV-disease. An additional 36 children (14%) developed PTB during the study, of whom, 14 were culture-confirmed and 22 diagnosed on clinical criteria. The immunological status of children followed for 54 months [median CD4+% = 32(26-36)] showed sustained improvement from enrolment [median CD4+% = 21(15-28)].

At enrolment, one third of the cohort (n = 84, 33%) had a weight-for-age z-score (WHOWAZ) below -2. For the first two years of follow-up there was steady improvement in nutritional status. By 24 months, the WHOWAZ was below -2 in only 33 subjects (17%). Thereafter, there was little further nutritional improvement. Persistent failure to thrive was ascribed to late diagnosis of HIV-infection and delayed access to ART.

parameter	Baseline n (%)	6 months n (%)	12 months n (%)	18 months n (%)	24 months n (%)	30 months n (%)	36 months n (%)	42 months n (%)	48 months n (%)	54 months n (%)
total	258 (100)	258 (100)	249 (97)	224 (87)	201 (78)	128 (50)	97 (38)	86 (33)	70 (27)	49 (19)
male	138 (53)	138 (53)	131 (53)	118 (53)	109 (54)	63 (49)	48 (49)	42 (49)	35 (50)	22 (45)
age in months	28 (13–51)	33 (19-56)	39 (25-62)	45 (30-70)	50 (34-75)	52 (40-73)	60 (47-76)	64 (52-83)	70 (59-89)	79 (65-96)
on ART	70 (27)	115 (45)	159 (64)	163 (73)	157 (78)	101 (82)	80 (82)	71 (83)	58 (83)	38 (78)
CD4+%	21 (15-28)	21 (15-29)	24 (18-30)	25 (18-31)	27 (20-33)	26 (20-32)	27 (21-34)	29 (23-35)	30 (25-37)	32 (25-35)
weight-for-age z-score <2	84 (33)	73 (28)	62 (25)	43 (19)	33 (16)	18 (14)	15 (15)	14 (16)	11 (16)	9 (18)
PTB diagnosed in period	37 (14)	16 (6)	11 (4)	5 (2)	0	2 (1)	1 (0)	1 (0)	0	0
hospitalised in period	n/a	48 (19)	34 (13)	11 (4)	9 (3)	3 (1)	5 (2)	1 (0)	0	0
CDC clinical category										
N	3 (1)	2 (1)	2 (1)	0 (0)	0	0	0	0	0	0
A	22 (9)	12 (5)	10 (4)	4(2)	2	0	0	0	0	0
B	163 (63)	158 (61)	145 (58)	127 (57)	109 (54)	56 (44)	45 (46)	36 (42)	26 (37)	16 (33)
C	70 (27)	86 (33)	92 (37)	93 (42)	90 (45)	72 (56)	52 (54)	50 (58)	44 (63)	33 (67)

Table 5.2. Demographic and clinical findings over time

Radiological progression (Table 5.3, Supplementary file 1)

At enrolment, 229(89%) children had a chest radiographic abnormality, with 130(50%) showing severe (grade 2) abnormality. In the first 6 months, the proportion with severe abnormality increased slightly from 50% to 54%, remaining unchanged at 12 months. Subsequently, slow but sustained radiological improvement was noted, with 40%, 28%, 19% and 16% showing severe abnormality at 24, 36, 48 and 54 months respectively. The cumulative prevalence of persistent, severe abnormality was 154(60%), with a median duration of 18(12-24) months.

radiological parameters	baseline n (%)	6 months n (%)	12 months n (%)	18 months n (%)	24 months n (%)	30 months n (%)	36 months n (%)	42 months n (%)	48 months n (%)	54 months n (%)
same	-	182 (70)	186 (75)	166 (74)	155 (77)	94 (74)	71 (73)	63 (73)	52 (74)	37 (78)
Improved	-	28 (11)	40 (16)	46 (21)	22 (11)	27 (21)	18 (19)	17 (20)	10 (14)	8 (14)
Deteriorated	-	48 (19)	23 (9)	12 (5)	24 (12)	6 (5)	8 (8)	6 (7)	8 (11)	4 (8)
grade 0	28 (11)	13 (5)	33 (13)	37 (17)	34 (17)	35 (27)	28 (29)	35 (41)	29 (41)	23 (43)
grade 1	100 (39)	107 (41)	83 (33)	95 (42)	86 (43)	45 (35)	42 (43)	33 (38)	28 (40)	218 (41)
grade 2	130 (50)	138 (54)	133 (54)	92 (41)	81 (40)	47 (37)	27 (28)	18 (21)	13 (19)	8 (16)
nodules alone	30 (12)	47 (18)	48 (19)	45 (20)	40 (20)	22 (17)	11 (11)	8 (9)	4 (6)	5 (10)
opacification alone	59 (23)	41 (16)	41 (16)	16 (7)	20 (10)	15 (12)	7 (7)	6 (7)	6 (9)	1 (2)
nodules with opacification	41 (16)	50 (19)	44 (18)	29 (13)	20 (10)	13 (10)	5 (5)	1 (1)	2 (3)	0 (0)
Bronchiectasis	7(3)	13 (5)	17(7)	14 (6)	22 (11)	13 (10)	9 (9)	7 (8)	7 (10)	4 (8)

Table 5.3. Chest radiographic findings over time

Nodules alone (n = 49), or with homogeneous opacification (n = 73), accounted for 122 (79%) cases of persistent, severe abnormality, visualized for a median of 18(12-

24) months. Nodule distribution was predominantly symmetrical and either multifocal or diffuse (n = 107; 97%), with a mean nodule diameter of 2mm.

Seventy-one patients (28%) with persistent nodules met CDC criteria for LIP, being persistence of diffuse, symmetrical, reticulo-nodular, or nodular pulmonary opacification, with or without mediastinal adenopathy, for at least two months, with neither an identifiable pathogen nor a response to antibiotic therapy. [CDC 1987] Of these, 46 (65%) had a purely nodular chest radiographic pattern, while 25 (35%) had areas of superimposed persistent confluent opacification during follow-up. Thirty-six patients [median CD4+% = 18(14-30); median age: 43(31-69) months] had LIP at enrolment and 35 [median CD4+% = 20(16-27); median age: 35(23-54) months] developed LIP during the study.

Persistent homogeneous opacification occurred in 32 cases (21%) and was present for a median of 12(6-18) months.

Of the 73 children diagnosed with PTB, 47 (64%) had persistent severe abnormality, with a median duration of 24(18-30) months. Homogeneous opacification alone or nodules with opacification were each noted in 19 cases (40%), while nodules alone occurred in 9 cases (19%). The median age at the time of PTB diagnosis was 31(13-61) months and the median CD4+% at diagnosis was 18(13-25).

Repeated hospitalization for acute LRTI was implicated in persistent severe radiographic abnormality in 8 patients (3%).

At enrolment, 7(3%) patients [median age: 19(17-38) months; median CD4+% = 21(19-22)] had features of bronchiectasis. A further 24(9%) patients [median age:

27(24-67) months; median CD4+% = 20(13-28)] developed radiographic signs of bronchiectasis during the study. Twenty-nine of these 31 patients (94%) also had persistent nodules and/or opacification. Thus, bronchiectasis alone accounted for less than 1% of the persistent severe radiographic abnormalities in our cohort, but in combination with other severe abnormalities was implicated in 12% of cases. Eleven patients with LIP (15%) developed features of bronchiectasis at a median of 12 (6-12) months after the onset of LIP and 10 PTB patients (10/47; 21%) developed such features at a median of 6(0-12) months after the PTB diagnosis. Bronchiectasis was basal in 28 cases (90%) and multifocal in 25 (80%). Tubular bronchiectasis (n =25, 81%) predominated with 6 (19%) showing cystic features.

Impact of ART (Supplementary file 2)

There was good adherence to ART, with 246 children (95%) reaching at least 90% compliance. Amongst children on ART, 69% (162/235) of changes in chest radiographic status across all the 6-month transition periods were improvements, and 31% (73/235) were deteriorations. By comparison, amongst those not on ART, 45% (54/120) of all changes were improvements and 55% (66/120) deteriorations. Thus, compared to those not on ART, children on ART had 24% more improvements and 24% fewer deteriorations across the transition periods.

Ordinal multiple logistic regression analysis (Table 5.4)

risk factor	Odds ratio (95% CI)	p-value
age below 18 months at enrolment		
No	1.00	
Yes	1.40 (1.06 – 1.83)	0.016
diffuse, severe, radiological abnormality at enrolment		
No	1.00	
Yes	2.18 (1.34 – 3.56)	<0.002
radiological severity 6 months prior		<0.001
grade 0	1.00	
grade 1	10.71 (6.92 – 16.55)	<0.001
grade 2	120.80 (68.71 – 212.38)	<0.002
hospitalised in the last 6 months		
No	1.00	
Yes	1.87 (1.07 – 3.30)	0.029
on ART		
Yes	1.00	
No	1.72 (1.29 – 2.27)	<0.001
months on the study		<0.0001
6- 12 months	1.00	
18-24 months	0.66 (0.49 – 0.90)	0.008
30 – 54 months	0.37 (0.28 – 0.51)	<0.001
diagnosed with TB		
No	1.00	
Yes	2.87 (0.95 – 8.64)	0.060
gender		
male	1.00	
female	0.97 (0.75 – 1.25)	0.811
CD4+%	0.99 (0.90 – 1.00)	0.062
CDC clinical classification		0.211
A + N	1.00	
B	1.63 (0.78 – 3.38)	0.192
C	1.91 (0.88 – 4.12)	0.101
INH at visit 6 months prior		
yes	1.0	
no	1.39 (0.99 – 1.96)	0.056
weight-for-age z-score	98 (0.90 – 1.08)	0.747

Table 5.4. Longitudinal ordinal multiple logistic regression analysis

A main-effects model is presented, since evaluation of the interaction of follow-up time with prior chest radiographic severity and ART status revealed that neither was significant (p=0.1551 and p=0.1219 respectively). The approximate likelihood ratio test of proportionality of odds across radiographic severity categories confirmed the assumption that the estimated regression coefficients were equal across categories (p=0.1666).

Chest radiographic severity was associated with radiographic abnormality on the previous film, absence of ART, enrolment age less than 18 months, diffuse severe radiographic abnormality at enrolment, hospitalization for acute respiratory tract infection in the preceding six months and the duration of follow-up (Table 5.4).

The influence of prior chest radiographic severity was most striking when the previous radiograph demonstrated severe (grade 2) abnormality. Here, the odds for remaining in the severe abnormality class were 120 times greater than a child with a normal radiograph at the preceding visit (OR=120.80; 95%CI: 68.71–212.38). Similarly, a mild (grade 1) abnormality on the previous film increased the probability of progression to severe abnormality on the subsequent film by 10-fold (OR=10.70; 95%CI: 6.93–16.55).

For a child not on ART, the odds of having a more severe abnormality were almost double that of a child on ART (OR=1.72; 95%CI: 1.29–2.27) independent of the period of follow-up. At each point of follow-up, children younger than 18 months at enrolment had an almost 40% increased risk of being in a higher severity category compared to children older than 18 months at enrolment (OR=1.39; 95%CI: 1.06–1.83).

Diffuse, severe radiographic abnormality at enrolment had a detrimental effect over the whole study period, more than doubling the odds of increased radiological severity, compared to children without this feature (OR=2.18; 95% CI: 1.33–3.56).

Hospitalization for LRTI in the preceding 6 months almost doubled the risk of being in a more severe category, compared to a child not hospitalized (OR=1.88; 95%CI: 1.06–3.30).

The risk of being in a more severe category declined significantly with time. Compared to children followed for 6-12 months, those followed for 18-24 months had reduced risk of severe radiographic disease (OR=0.66, 95%CI: 0.49–0.90), while those followed for 30-54 months had a further reduction (OR=0.37, 95%CI: 0.28–0.51). Gender, CDC clinical classification, PTB, anthropometric parameters, CD4+% and INH usage were not associated with radiographic severity (Table 5.4).

DISCUSSION

In this first longitudinal analysis of chest radiographic abnormalities in HIV-infected African children, we found a 60% cumulative prevalence of persistent severe abnormality, almost three-fold above HIV-infected North American children prior to the availability of ART. [Norton] In the USA study, persistent abnormality was defined as present for 3 consecutive months or longer, in contrast to our definition of 6 months or longer. The prevalence of persistent changes in our study therefore represents a conservative estimate. The high prevalence of persistent and severe radiographic abnormalities highlights the substantial burden of HIV-associated chronic respiratory disease in children in SSA.

LIP (45%) and PTB (31%) were the leading causes of persistent, severe abnormality, accounting for over three-quarters of cases. In the North American study, the cause of severe abnormality was established in 23 of 64 cases (35%); LIP (16/64; 25%) predominated, followed by chronic *Pneumocystis* infection (5/64; 8%) and PTB (2/64; 3%). [Norton] The 10-fold higher prevalence of PTB in our cohort underscores the significant PTB burden in SSA.[Hesseling 2009] The prevalence of LIP is also higher than reported by Norton [2001] (16/287;6%), but comparable to retrospective studies of symptomatic HIV-infected children in North America and the United Kingdom. [Marolda, Marquis, Sharland, Lynch] Reasons for the variable prevalence of LIP may relate to the epidemiology of EBV infection, which has been implicated in LIP pathogenesis, [Bhoopat 2010, Bhoopat 2011, Slyker] to the diagnostic criteria used, age range and selection of patient populations.

The preceding chest radiograph was the single most important predictor of subsequent radiological severity. This strong association reflects the intractability of the underlying lung disease, as exemplified by LIP and PTB, where severe abnormalities persisted for a median of 18 and 24 months respectively. This study therefore provides important new information on the persistence of severe radiological abnormality in HIV-associated pulmonary disease. The study also suggests that repeated chest radiographs are not indicated in HIV-infected children with severe radiological findings without clinical deterioration.

Importantly, we have shown that ART can both decrease the risk of progression to severe radiographic abnormality and ameliorate established abnormality. The

benefits of ART manifested within 6-months of commencing treatment and the beneficial effects were quantifiably sustained across all time periods. ART almost halved the burden of radiological severity at each time-point, especially in LIP and PTB. The impact of ART on LIP has, to our knowledge, not been previously described in children. Thus far, a single study documented complete resolution of LIP [Dufour] in 4 of 5 adults (80%) after 6 months of ART. Further study of the pathogenesis and immunological correlates of LIP are required to better understand the mechanism of radiological improvement. The ART-related radiographic response in PTB may be achieved through arresting clinical progression of HIV disease, [Sturt, Barry] enhancing immunity [Hansudewechakul] or increasing the efficacy of TB treatment. [Walters]

The findings of this study suggest that early initiation of ART may prevent the radiological abnormalities documented in this cohort. We found that young age and diffuse, severe radiographic abnormality at enrolment (when a minority of children was on ART) were associated with radiographic severity at each point of follow-up, that ART had a sustained capacity to both prevent and reverse radiological abnormality, and that there was a natural tendency to radiographic improvement beyond 12-months of follow-up.

Both a strength and a limitation of the study is that the same experienced paediatric radiologist undertook all of the reporting using standardized reporting methodology. [Pitcher 2014] The potential for inter-observer variation in the interpretation of grade 0 (normal) and grade 1 (mild/moderate) radiographic abnormalities is well recognized.

[Cleveland] However, inter-observer variation is less likely to impact on the reported prevalence of more radiographically overt severe findings which, in our study, were mostly multifocal or diffusely distributed. Good inter-observer agreement can be achieved by systematic and standardized reporting of such features, [Cherian] as in our study. A further limitation is the potential for under-reporting of features such as bronchiectasis, which usually require computerized tomography for definitive diagnosis. Resource limitations and ethical concerns regarding unnecessary exposure to radiation precluded its use in most children. The prevalence of chronic radiological disease in this study may therefore be underestimated.

Although clinical features such as cough, respiratory rate and chest auscultation findings were recorded for all children at each follow-up visit, correlation with radiographic findings is difficult and could not be included in this analysis. However, there was a marked reduction in hospitalization for acute LRTI over time, concomitant with clinical and radiological improvement.

Currently, an estimated 2.9 million children in SSA and 400 000 in other resource-limited settings are HIV-infected. [UN 2013] Our findings suggest that almost two million of these children may have persistent, severe chest radiographic abnormalities. Furthermore, in low- and middle-income countries, only a third of those eligible are receiving ART, well short of the Millennium Development Goal (MDG) of 100% ART coverage by 2015. [UN MDG] The finding that ART can either reduce the risk of radiographic progression or reverse established abnormality underscores the importance of universal, early access to treatment.

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AUTHOR CONTRIBUTIONS:

H. Zar and M. Cotton conceived the cohort study and supervised the cohort study staff at the respective sites. H. Zar obtained funding for the cohort study, was responsible for overall oversight of the cohort study and overall supervision of the radiological aspects.

L. Workman was responsible for development of the database, database quality control and contributed to the analysis of the cohort study.

C. Lombard contributed to study design and statistical analysis of the cohort study and the statistical analysis of the radiological study.

S. Beningfield co-supervised the radiological study.

R. Pitcher was responsible for the study design, literature search, data collection, data analysis, data interpretation, figures, tables, manuscript writing and editing of the radiological study.

All authors contributed to the final manuscript.

Chapter 6

Persistent, severe chest radiographic abnormalities in HIV-infected African children - Conclusions and recommendations

INTRODUCTION

The finding of a 60% cumulative prevalence of persistent, severe CXR abnormalities in this cohort of South African children with delayed access to ART [median age at initiation of treatment = 33 (IQR: 18-55) months] has potential implications for all HIV-infected children in SSA, where approximately ninety percent of all HIV-infected children reside, and where access to ART remains suboptimal. [UNAIDS, 2015]

Homogeneous opacification and pulmonary nodules, alone or in combination, were the predominant severe CXR abnormalities. However, these are non-specific radiological findings, with a broad differential diagnosis, and should always be interpreted in the appropriate clinical context. [Groskin] This relatively narrow spectrum of radiographic abnormality reflects the limited number of potential pulmonary responses to a variety of parenchymal insults. [Groskin, Peliso]

Most affected children had extensive pulmonary involvement, which was multifocal or diffuse in more than two-thirds of cases. This implies clinical severity, but also suggests relative ease of radiographic recognition. Most HIV-infected children in SSA have access to only basic imaging equipment and few specialist radiologists. The main radiological resource is the CXR, and interpretation is largely the clinician's responsibility. This study suggests that CXR's can serve a useful role in detecting and monitoring persistent pulmonary disease in HIV-infected African children. Given the relatively limited radiographic spectrum and the conspicuity of the CXR findings,

primary health care workers can be taught to recognise and diagnose these radiological patterns.

The fact that two conditions, LIP and PTB, together account for most cases (76%) of persistent severe abnormality has a number of implications. Firstly, this suggests that prevention of these two conditions may result in a substantial reduction in the burden of disease and that these conditions should be the focus of intervention strategies in SSA. Secondly, it underscores the need for a high index of suspicion for PTB in any HIV-infected African child with severe persistent CXR abnormalities. Thirdly, our study has shown that ART is effective in both preventing and improving radiological abnormalities, highlighting the importance of wider access to ART for all HIV-infected children in Africa.

MAIN CAUSES OF PERSISTENT SEVERE CXR ABNORMALITY

LIP (n = 71; 46%)

LIP has been shown to be the leading cause of persistent severe CXR abnormality in this cohort of HIV-infected African children, accounting for almost half of all cases. While LIP has long been recognised in HIV-infected children, [Oldham, Sharland, Jeena 1998, Gonzales] the prevalence in African children has not been well studied. Further, although LIP is recognised as a cause of significant pulmonary morbidity, [Sharland] it remains an under-researched and poorly understood condition, the natural history of which has not been fully elucidated. [Muthu]

The factors initiating LIP remain poorly understood. Infiltration of the interstitium is predominantly by CD8+ T lymphocytes and plasmocytes and mainly involves the alveolar septa along lymphatic vessels. [Dufour] The process is thought to be mediated by cytokines and to be a response to HIV antigens and/or other pathogens such as the Epstein-Barr virus. [Dufour] The HIV viral load within the pulmonary parenchyma is therefore considered an important determinant.

There have been conflicting reports of the significance of resolution of CXR abnormalities in LIP. Prosper reported that radiographic clearing was a poor prognostic sign, associated with absolute CD4 lymphocytopenia. [Prosper] Norton [2001] found that chronic CXR changes were associated with lower CD4 cell counts, and their resolution with further CD4 cell depletion. However, Gonzalez [2000] concluded that LIP had a natural tendency to gradual resolution, which was independent of the clinical severity of HIV disease. This was supported by Lynch, [2001] who showed that radiographic clearing of LIP was not associated with any change in immunological or clinical status.

The 71 children in this study represent the largest LIP cohort reported to date. This is also the first study to correlate CD4+% with longitudinal CXR features. The 35 patients who developed LIP during the course of the study afforded a unique opportunity for longitudinal observational analysis of the immunological correlates of LIP (Table 6.1).

Almost 75% of patients developing LIP during the study were more than 24 months of age (median age = 35 months, IQR: 23-54 months) and the majority had moderate immune suppression (median CD4+ = 20%, IQR: 16-27) at the time of first detection of CXR abnormality. [CDC] Almost half the patients (n = 17; 49%) showed radiographic clearing during the study, at a median CD4+ of 30% (IQR: 22 – 33). No patient relapsed. During the first 12 months after the onset of LIP, most of those with persistent nodules remained moderately immune suppressed; those with nodules still visible at 18 months showed borderline immune suppression, and the majority with nodules persisting beyond 18 months (n = 8; 23%) had normal CD4+ levels. (Table 6.1)

length of follow-up	nodules present		nodules resolved		completed study
	n (%)	CD4+% median(IQR)	n (%)	CD4+% median(IQR)	n (%)
6 months prior to appearance of nodules	35 (100)	22 (18-30)			
At appearance of LIP	35 (100)	20 (16-27)			
6 months	35 (100)	22 (16-28)			
12 months	24 (69)	22 (17-30)	5(14)	30 (23-33)	6(17)
18 months	17 (49)	24 (18-31)	5(14)	26 (21-29)	2(6)
24 months	8 (23)	32 (28-35)	3(9)	31 (30-32)	6(17)
30 months	4 (11)	32 (31-34)	3(9)	37 (26-38)	1(3)
36 months	2 (6)	n/a	1(3)	n/a	1(3)

Table 6.1. Chest radiographic features of LIP by CD4+ percentage

This analysis suggests that LIP is initiated during periods of moderate immune suppression and tends to resolve when the immune status improves. However, we have identified a subset of LIP patients (8/35; 23%) in whom the radiographic features persisted, despite normal CD4+ levels.

PTB (n = 47; 31%)

Of the 73 patients diagnosed with PTB, 17 (23%) were culture confirmed. All cases of probable PTB were subject to independent review by a blinded investigator. [Zar 2006] The proportion of culture-confirmed PTB in our cohort is similar to that documented by Mukadi [1997], Madhi [2000] and Palme [2002] and more than double that reported by Kiwanuka [2002]. Of note, the manuscripts of Luo [1994], Kiwanuka [2001] and Srinakarin [2012] did not distinguish confirmed from probable cases. The proportion of confirmed PTB in our cohort is thus in line with that of a number of LMIC publications and highlights the challenge of definitive PTB diagnosis in children.

Almost two-thirds of subjects with PTB (47/73; 64%) developed persistent, severe CXR abnormalities. Of these, 20/47 (43%) had PTB at enrolment (median CD4+% = 14, IQR: 10-19; median age = 17 months, IQR: 11-36); the remainder (27/47; 57%) were diagnosed during the study (median CD4+% = 19, IQR: 16-27; median age = 40 months, IQR: 26-65 months). Ten of 17 subjects (59%) with culture confirmed PTB demonstrated persistent severe changes; conversely, just over one-fifth (10/47; 21%) of subjects with suspected PTB-related persistent severe radiographic abnormality had a positive TB culture.

Patients with PTB at enrolment tended to be younger (median age = 19 months, IQR: 10-53) and to have more severe immune suppression (median CD4+ = 15%; IQR: 11-21) than those diagnosed during the study (median age = 40 months, IQR:

24-65; median CD4+ = 19%, IQR: 16-27). PTB in young children is known to be associated with greater clinical severity [Chisti] and a higher risk of radiographic complications. [Weber, Lamont, Palme] Furthermore, HIV-infected children with PTB have almost double the probability of homogeneous opacification and cavitation, when compared to HIV-uninfected children. [Schaaf] This may reflect higher risk for development of progressive primary disease. [Marais 2004]

Resolution of PTB-related CXR changes in appropriately treated, immune-competent children is known to be a slow process and may be incomplete. Factors influencing the rate of clearing in immune-competent children are poorly understood, but residual scarring has been associated with more extensive parenchymal opacification at presentation and delayed initiation of treatment. [Weber]

Prior to this study there had been no systematic longitudinal analysis of the CXR features of HIV-infected children on TB treatment. The limited available data were from the studies of Jeena [1996] and Mukadi, [1997] who documented some radiographic improvement at 6 months of follow-up in 52% and 68% of cases respectively. We found PTB-related severe abnormalities were particularly intractable, persisting for a median of 24 months (IQR: 18-30). This chronicity is best appreciated by comparison with findings in immune competent children. While 50% of TB cases in this study showed residual severe radiological disease at 24 months, Leung [1992] and Swaminathan [2005] respectively documented residual CXR abnormalities in only 17% and 29% of immune-competent children at the same stage of PTB follow-up. The findings in this study are consistent with clinical studies

which have shown HIV-infected children with TB to have a worse outcome than HIV-uninfected children, with a poorer response to treatment, higher recurrence rates and a higher incidence of complications. [Lou, Jeena 1996, Mukadi, Madhi, Kiwanuka, Palme, Hesseling, Soeters, Schaaf]

Analysis of PTB patients by CD4+% (Table 6.2), shows that most were moderately immune suppressed at the time of TB diagnosis. The level of immune suppression was similar for those with and without severe CXR abnormality. Although there was steady overall radiological and immunological improvement with time, one-fifth of PTB patients with persistent severe abnormality (10/47; 21%) who were followed for more than 30 months showed persistence of severe radiographic abnormalities, despite achieving normal CD4+ levels. Bronchiectasis could be implicated in 5/10 (50%) of these cases.

Length of follow-up	**Severe abnormality**		**normal/mild abnormality**	
	n (%)	CD4+% median (IQR)	n (%)	CD4+% median (IQR)
0 months	50 (68)	18 (13-22)	23 (32)	20 (14-27)
6 months	45 (62)	18 (9-24)	24 (33)	19 (16-22)
12 months	39 (53)	21 (13-26)	23 (32)	24 (19-33)
18 months	26 (36)	22 (15-27)	27(37)	24 (16-31)
24 months	20 (27)	23 (17-37)	22 (30)	20 (18-26)
30 months	14 (19)	24 (22-28)	25 (34)	26 (19-33)
36 months	10 (14)	27 (24-39)	22 (30)	27 (21-33)
42 months	6 (8)	35 (32-41)	20 (27)	29 (23-34)
48 months	6 (8)	40 (36-45)	17 (23)	30 (27-34)

Table 6.2. Chest radiographic abnormalities in PTB patients by CD4+ percentage

Bronchiectasis (n = 31; 20%)

Bronchiectasis is an important complication of HIV-related paediatric pulmonary disease [Holmes] and may be associated with LIP, unresolved pneumonia, recurrent pneumonia, PTB, PCP and profound immune suppression. [Sheik, Sharland, Berman] Prior to this study there were very limited data on the radiographic features of HIV-related paediatric bronchiectasis. This work represents the first prospective longitudinal analysis of bronchiectasis in this setting and is also the largest such cohort studied to date.

At enrolment, 7 children (7/258; 3%) had features of bronchiectasis, while 24 (9%) developed radiographic signs during follow-up. Most children who progressed to bronchiectasis were moderately immune suppressed (median CD4+ = 20%, IQR: 13-28) at the time of radiographic evolution. The overall prevalence of bronchiectasis (31/258; 12%) is similar to that recorded by Sheik [1997] in a study of HIV-infected children attending a New York paediatric pulmonology clinic between 1984 and 1996 (26/164; 16%), but more than double that reported from a general paediatric infectious diseases clinic in Florida from 1982 through 2000 (43/749; 5.7%). [Berman]

A feature of this cohort is the relatively early onset of bronchiectasis. Those diagnosed at enrolment and during follow-up had median ages of 19 (IQR: 17-38) and 27 months (IQR: 24–67) respectively. By comparison, the New York [Sheik] and Florida [Berman] cohorts were both diagnosed at a median age of 90 months.

A further striking feature of this cohort is the high proportion showing bilateral basal, tubular disease (80%). This pattern of involvement appeared to be independent of the underlying cause of bronchiectasis and has not been previously documented as a characteristic finding in HIV-related paediatric bronchiectasis.

The prevalence of bronchiectasis documented in this cohort was based on plain radiographic findings and may be an underestimate, since high-resolution computed tomography (HRCT), which is acknowledged as the reference standard for the diagnosis of bronchiectasis, was not performed. [Redding] Plain chest radiographs have limitations in defining both the presence and extent of early disease. [Gudbjerg, Currie, Munro, Fall, Bayramoglu] Resource limitations and ethical concerns about additional exposure of children to ionising radiation precluded the routine use of HRCT in our study.

The leading causes of bronchiectasis in this cohort reflect the major causes of persistent, severe radiographic abnormality, with LIP (11/31; 35%) and PTB (10/31; 32%) accounting for more than two-thirds of cases.

LIP-associated bronchiectasis

Approximately one-sixth of LIP patients (11/71; 15%) developed bronchiectasis. A similar proportion of New Jersey children with LIP (4/32, 13%) progressed to bronchiectasis in a retrospective study conducted in the pre-ART era (1981-1990).

[Amorosa] However, this SA cohort showed more rapid progression to bronchiectasis, with a median of 12 months (IQR: 6-12) between LIP diagnosis and the first features of bronchiectasis, compared to 29 months (IQR: 19-42) for the New Jersey children. Sheik reported a higher proportion of LIP-related bronchiectasis amongst New York children (16/47; 34%), [Sheik] which may reflect a longer period of follow-up (13 years), thereby allowing more time for the evolution of bronchiectasis in cases of persistent or progressive LIP.

Variations in the time to evolution of bronchiectasis, and the proportion of LIP cases progressing to bronchiectasis may also relate to differences in the extent of lymphocytic infiltration of the pulmonary interstitium. It is known that LIP is radiographically occult in the earliest stages of lymphocytic infiltration [Marquis] and shows sequential radiographic evolution to bronchial wall thickening, [Marquis] a fine reticular pattern, [Jeena 1998] a reticulo-nodular pattern [Oldham, Bradford, Izraeli] and confluent opacification, as lymphocytic infiltration progresses. [Marquis, Oldham, Jeena 1998] Current understanding is that bronchiectasis evolves when interstitial infiltration is sufficient to compromise the adjacent bronchial lumen, [Amorosa] resulting in endobronchial bacterial infection. Such infection is considered the "final common pathway" for all causes of bronchiectasis and is thought to initiate a "vicious cycle" of damage to the supporting structure of the airway, with bronchial dilatation, muco-ciliary stasis, and further bacterial infection. [Cole] Published radiographic descriptions of LIP have documented confluent parenchymal opacification superimposed on a pulmonary nodular pattern in 8% of cases, [Zimmermann, Bradford, Oldham, Amorosa, Marquis, Jeena

1998] whereas 35% (25/71) of children with LIP in this study showed superimposed confluent opacification at some stage of follow-up.

TB-associated bronchiectasis

Overall, ten PTB patients (10/73; 14%) showed features of bronchiectasis at a median of 6 months (IQR: 0 – 12) after PTB diagnosis. All had associated persistent pulmonary opacification and/or nodules. Thus, more than one-fifth (10/47; 21%) of PTB patients with persistent severe radiographic abnormality progressed to bronchiectasis. Culture-confirmed PTB accounted for 40% (4/10) of PTB-related bronchiectasis; conversely almost a quarter (4/17; 24%) of those with culture-confirmed PTB developed bronchiectasis.

Pneumonia-associated bronchiectasis

Bronchiectasis evolved in three (38%) of the eight children with recurrent hospitalisation for severe respiratory tract infections. Two developed radiological signs 6 months after the first hospital admission and one at 12 months. The mean CD4+ at the time of hospitalisation was 15%.

Bronchiectasis of unknown aetiology

In all 7 patients (7/31, 23%) with features of bronchiectasis at enrolment, the underlying cause was not established.

Unknown aetiology (n = 21; 14%)

At enrolment, this group had a median age of 17 months (IQR: 7-34) and most were moderately immune suppressed (median CD4+ = 20%; IQR: 13-26). CXR abnormalities persisted for a median of 12 months (IQR: 6 – 17).

All children showed resolution of the severe abnormalities during the study. Aspiration syndromes, pulmonary congestion and recurrent/persistent chest infections not requiring hospitalization may be implicated in these cases.

NO PERSISTENT SEVERE CXR ABNORMALITY

Patients who did not develop persistent severe abnormality had a median age of 32 months (IQR: 16-55) and a median CD4+ of 25% (IQR: 18-33) at enrolment.

CONCLUSION

The major findings in this cohort of HIV-infected children with delayed access to ART and severe, persistent chest radiographic abnormalities are therefore:

i. Confirmation of the pivotal role of the CXR in detecting and monitoring HIV-associated paediatric pulmonary disease

ii. The high prevalence of persistent, severe chest radiographic abnormality

iii. The narrow spectrum and extent of persistent chest radiographic abnormality

iv. Most patients who developed persistent, severe abnormalities were immune suppressed at the time of first detection of severe CXR abnormality.

v. PTB or recurrent hospitalization for pneumonia were common causes of persistent severe CXR abnormalities in profoundly immunosuppressed patients under two years of age.

vi. In patients less than two years of age with moderate immune suppression, the specific cause of persistent severe abnormality could not generally be established, but aspiration syndromes, recurrent/persistent chest infections not requiring hospitalization, and pulmonary congestion are potential causes.

vii. LIP or PTB were implicated in most cases of persistent severe abnormalities in moderately immunosuppressed patients older than two years of age.

viii. Most patients with severe abnormalities showed radiographic clearing as CD4+ percentages normalized. However, in some patients severe radiographic abnormalities persisted despite normal CD4+ levels.

ix. The median age at the onset of bronchiectasis was lower than that documented amongst children from well-resourced environments in the pre-ART era, and the proportion of this cohort with bilateral basal bronchiectasis was higher than previously reported for HIV-infected children.

x. Most children who did not develop persistent severe CXR abnormalities maintained normal CD4+ levels.

xi. The dual role of ART in both reducing the risk of radiographic deterioration or increasing the likelihood of radiographic improvement, even if initiated late in the course of HIV-disease and in the face of established, severe radiographic abnormality.

RECOMMENDATIONS

Accordingly, the following recommendations are made for HIV-infected children in SSA:

Imaging strategies

i. In view of the pivotal role of the CXR in detecting and monitoring persistent, severe HIV-associated paediatric pulmonary disease, resource allocation and healthcare planning strategies in SSA should optimise access to this basic imaging service for HIV-infected children.

ii. Given the narrow spectrum and extent of persistent, severe CXR abnormalities in HIV-infected African children, and the resource-constraints in SSA, consideration should be given to training primary health care workers in the recognition and diagnosis of these radiographic patterns.

iii. Considering the high prevalence of severe CXR abnormality, a baseline radiograph is recommended in all HIV-infected children, irrespective of respiratory symptoms, to serve as a comparison when the child presents with an acute respiratory complaint.

iv. In children with severe abnormality on baseline imaging, repeated CXRs are not warranted unless there is clinical deterioration.

v. There should be a high index of suspicion for PTB in any HIV-infected African child with severe CXR abnormalities persisting for six months or longer

Clinical strategies

Clinical interventions should focus on prevention. A dual strategy is required, firstly to prevent paediatric HIV-infection and secondly to prevent respiratory disease amongst HIV-infected children.

The broad global initiatives aimed at containing and reversing the HIV pandemic in SSA have shown early success, as reflected in a decrease in the number of new adult and paediatric infections. [UNAIDS 2015] However, these programs require substantial expansion, with particular emphasis on decreasing the infection rate amongst pregnant women and eliminating mother-to-child transmission.

With respect to the prevention of severe, persistent CXR abnormalities, the findings of this study suggest three principal interventions:

i. *Prevention and careful monitoring for PTB.* Initiatives could include INH prophylaxis, regular TB surveillance, strengthened diagnostic strategies and early investigation and treatment of suspected PTB.

ii. *Prevention of pneumonia.* This could be achieved, through
    a. *general measures* such as avoidance of smoke exposure and nutritional programs, including breast feeding, and

b. *Specific initiatives* in the form of cotrimoxazole prophylaxis, immunization programs, and early diagnosis and appropriate treatment of infection.

iii. *Early diagnosis of HIV-infection and early initiation of ART.* Notwithstanding the relatively late initiation of ART in this cohort (median age at commencement of treatment = 33 months), the beneficial effects were manifest, even in the face of established, advanced radiographic abnormality. It is therefore recommended that existing programs be strengthened to allow diagnosis of HIV-infection early in life, and initiation of ART as soon as the diagnosis is confirmed, regardless of the stage of disease. Furthermore, where HIV-diagnosis and/or initiation of ART have been delayed, ART should nonetheless be commenced as soon as possible, regardless of the extent of immunological compromise or radiographic abnormality.

FUTURE RESEARCH

It is estimated that only one-third of HIV-infected children in SSA currently have access to ART. [UNAIDS 2015] As ART programs for children are strengthened in SSA, future research should focus on the elucidation of acute and chronic pulmonary disease in perinatally infected children who commence ART shortly after birth or during infancy.

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Appendices

Supplementary file 1

Descriptive transition table of chest radiographic severity

Diagonal cells:	no change in severity
Cells above diagonal:	increase in severity
Cells below diagonal:	decrease in severity

Time	month=6				
month = 0	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	10 (35.7)	14 (50.0)	4 (14.3)	28 (100.0)
	grade1	2 (2.0)	68 (68.0)	30 (30.0)	100 (100.0)
	grade 2	1 (0.8)	25 (19.2)	104 (80.0)	130 (100.0)
	total	13 (5.0)	107 (41.5)	138 (53.5)	258 (100.0)

Transition period: 0-6 months

time	month=12				
month=6	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	12 (100.0)	0 (0.0)	0 (0.0)	12 (100.0)
	grade1	17 (16.4)	64 (61.5)	23 (22.12)	104 (100.0)
	grade 2	4 (3.0)	19 (14.3)	110 (82.7)	133 (100.0)
	total	33 (13.3)	83 (33.3)	133 (53.4)	249 (100.0)

Transition period: 6-12 months

time	month=18				
month=12	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	22 (78.6)	5 (17.9)	1 (3.6)	28 (100.0)
	grade1	9 (12.0)	59 (80.0)	6 (8.0)	75 (100.0)
	grade 2	6 (5.0)	31 (25.6)	85 (69.4)	121 (100.0)
	total	37 (16.5)	95 (42.9)	92 (40.6)	224 (100.0)

Transition period: 12-18 months

time	month=24				
month=18	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	24 (68.6)	10 (28.6)	1 (2.9)	35 (100.0)
	grade1	9 (10.3)	64 (74.7)	13 (14.9)	87 (100.0)
	grade 2	1 (1.3)	12 (15.2)	67 (83.5)	79 (100.0)
	total	34 (16.9)	86 (43.3)	81 (39.8)	201 (100.0)

Transition period: 18-24 months

time	month=30				
month=24	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	21 (91.3)	1 (4.3)	1 (4.3)	23 (100.0)
	grade 1	14 (28.5)	31 (63.3)	4 (8.2)	49 (100.0)
	grade 2	0 (0.0)	13 (23.6)	42 (76.4)	55 (100.0)
	total	35 (27.6)	45 (35.4)	47 (37.0)	127 (100.0)

Transition period: 24-30 months

time	month=36				
month=30	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	21 (80.8)	4 (15.4)	1 (3.8)	26 (100.0)
	grade 1	6 (17.6)	27 (79.4)	3 (8.8)	34 (100.0)
	grade 2	1 (2.7)	11 (29.7)	23 (62.1)	37 (100.0)
	total	28 (28.9)	42 (43.3)	27 (27.8)	97 (100.0)

Transition period: 30-36 months

time	month=42				
month=36	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	20 (83.3)	2 (8.3)	2 (8.3)	24 (100.0)
	grade1	8 (20.5)	29 (74.4)	2 (5.1)	39 (100.0)
	grade 2	7 (30.4)	2 (8.7)	14 (60.9)	23 (100.0)
	total	35 (40.7)	33 (38.4)	18 (20.9)	86 (100.0)

Transition period: 36-42 months

time	month=48				
month=42	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	23 (79.3)	4 (13.8)	2 (6.9)	29 (100.0)
	grade1	5 (18.5)	20 (74.1)	2 (7.4)	27 (100.0)
	grade 2	1 (7.1)	4 (28.6)	9 (64.3)	14 (100.0)
	total	29 (41.4)	28 (40.0)	13 (18.6)	70 (100.0)

Transition period: 42-48 months

time	month=54				
month=48	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	18 (85.6)	2 (9.5)	1 (4.8)	21 (100.0)
	grade1	2 (12.5)	13 (81.3)	1 (6.3)	16 (100.0)
	grade 2	3 (25.0)	3 (25.0)	6 (50.0)	12 (100.0)
	total	23 (47.0)	18 (36.7)	8 (16.3)	49 (100.0)

Transition period: 48-54 months

Supplementary file 2

Descriptive transition tables of chest radiographic severity by ART status

Sub- tables and structure:

No ART: No ART up to transition time point.
On ART: On Art at start of transition period or commenced ART during transition period.

Diagonal cells: no change in severity
Cells above diagonal: increase in severity
Cells below diagonal: decrease in severity

Time	No ART month=6				
No ART month = 0	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	1 (9.1)	6 (54.6)	4 (36.4)	11 (100.0)
	grade1	0 (0.0)	39 (63.9)	22 (36.0)	61 (100.0)
	grade 2	1 (1.4)	11 (15.5)	59 (83.1)	71 (100.0)
	total	2 (1.4)	56 (39.2)	85 (59.4)	143 (100.0)
time	ART month=6				
ART month = 0	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	9 (53.0)	8 (47.0)	0 (0.0)	17 (100.0)
	grade1	2 (5.1)	29 (74.4)	8 (20.5)	39 (100.0)
	grade 2	0 (0.0)	14 (23.7)	45 (76.3)	59 (100.0)
	total	11 (9.6)	51 (44.3)	53 (46.1)	115 (100.0)

Transition period: 0-6 months

time	No ART month=12				
No ART month=6	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
	grade1	7 (15.2)	24 (52.2)	15 (32.6)	46 (100.0)
	grade 2	2 (4.7)	5 (11.9)	35 (83.3)	42 (100.0)
	total	11 (12.2)	29 (32.2)	50 (55.6)	90 (100.0)
time	ART month=12				
ART month=6	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
	grade1	10 (17.2)	40 (69.0)	8 (13.8)	58 (100.0)
	grade 2	2 (2.2)	14 (15.4)	75 (82.4)	91 (100.0)
	total	22 (13.8)	54 (34.0)	83 (52.2)	159 (100.0)

Transition period: 6-12 months

time	No ART month=18				
No ART month=12	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	5 (83.3)	1 (16.7)	0 (0.0)	6 (100.0)
	grade1	4 (20.0)	13 (65.0)	3 (15.0)	20 (100.0)
	grade 2	1 (3.0)	6 (17.6)	27 (79.4)	34 (100.0)
	total	10 (16.7)	20 (33.3)	30 (50)	60 (100.0)
time	ART month=18				
ART month=12	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	17 (77.3)	4 (18.1)	1 (4.5)	22 (100.0)
	grade1	5 (9.3)	46 (85.2)	3 (5.5)	54 (100.0)
	grade 2	5 (5.7)	25 (28.4)	58 (65.9)	88 (100.0)
	total	27 (16.5)	75 (45.7)	62 (37.8)	164 (100.0)

Transition period: 12-18 months

time	No ART month=24				
No ART month=18	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	5 (55.6)	3 (33.3)	1 (11.1)	9 (100.0)
	grade1	0 (0.0)	11 (73.3)	4 (26.7)	15 (100.0)
	grade 2	0 (0.0)	3 (15.0)	17 (85.0)	20 (100.0)
	total	5 (11.4)	17 (38.6)	22 (50.0)	44 (100.0)
time	ART month=24				
ART month=18	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	19 (73.1)	7 (26.9)	0 (0.0)	26 (100.0)
	grade1	9 (12.7)	53 (74.6)	9 (12.7)	71 (100.0)
	grade 2	1 (1.7)	9 (15.0)	50 (83.3)	60 (100.0)
	total	29 (18.5)	69 (43.9)	59 (37.6)	157 (100.0)

Transition period: 18-24 months

time	No ART month=30				
No ART month=24	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
	grade1	1 (12.5)	5 (62.5)	2 (25.0)	8 (100.0)
	grade 2	0 (0.0)	2 (15.4)	11 (84.6)	13 (100.00)
	total	2 (9.1)	7 (31.8)	13 (59.1)	22 (100.0)
time	ART month=30				
ART month=24	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	Total n (%)
	grade 0	20 (91.0)	1 (4.5)	1 (4.5)	22 (100.0)
	grade1	13 (31.7)	26 (63.4)	2 (4.9)	41 (100.0)
	grade 2	0 (0.0)	11 (26.2)	31 (73.8)	42 (100.0)
	total	33 (31.4)	38 (36.1)	34 (32.4)	105 (100.0)

Transition period: 24-30 months

time	No ART month=36				
No ART month=30	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
	grade1	1 (14.3)	5 (71.4)	1 (14.3)	7 (100.0)
	grade 2	0 (0.0)	3 (33.3)	6 (66.7)	9 (100.0)
	total	2 (11.8)	8 (47.1)	7 (41.2)	17 (100.0)
time	ART month=36				
ART month=30	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	20 (80.0)	4 (16.0)	1 (4.0)	25 (100.0)
	grade1	5 (17.2)	22 (75.9)	2 (6.9)	29 (100.0)
	grade 2	1 (3.8)	8 (30.8)	17 (65.4)	26 (100.0)
	total	26 (32.5)	34 (42.5)	20 (25.0)	80 (100.0)

Transition period: 30-36 months

time	No ART month=42				
No ART month=36	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	1 (50.0)	0 (0.0)	1 (50.0)	2 (100.0)
	grade1	1 (14.3)	5 (71.4)	1 (14.3)	7 (100.0)
	grade 2	4 (66.7)	1 (16.7)	1 (16.6)	6 (100.0)
	total	6 (40.0)	6 (40.0)	3 (20.0)	15 (100.00)
time	ART month=42				
ART month=36	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	19 (86.4)	2 (9.1)	1 (4.5)	22 (100.0)
	grade1	7 (21.9)	24 (75.0)	1 (3.1)	32 (100.0)
	grade 2	3 (17.6)	1 (5.9)	13 (76.5)	17 (100.0)
	total	29 (40.9)	27 (38.0)	15 (21.1)	71 (100.0)

Transition period: 36-42 months

time	ART month=48				
No ART month=42	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n(%)	total n (%)
	grade 0	6 (100.0)	0 (0.0)	0 (0.0)	6 (100.0)
	grade1	0 (0.0)	4 (80.0)	1 (20.0)	5 (100.)
	grade 2	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
	Total	7 (58.3)	4 (33.3)	1 (8.3)	12 (100.0)
time	ART month=48				
ART month=42	radiographic severity	grade 0 n (%)	grade 1 n (%)	grade 2 n (%)	total n (%)
	grade 0	17 (73.9)	4 (17.4)	2 (8.7)	23 (100.0)
	grade1	5 (22.7)	16 (72.7)	1 (4.5)	22 (100.0)
	grade 2	0 (0.0)	4 (30.8)	9 (69.2)	13 (100.0)
	Total	22 (37.9)	24 (41.4)	12 (20.7)	58 (100.00)

Transition period: 42-48 months

time		No ART month=54			
No ART month=48	**radiographic severity**	**grade 0** n (%)	**grade 1** n (%)	**grade 2 n (%)**	**total** n (%)
	grade 0	6 (85.7)	1 (14.3)	0 (0.0)	7 (100.0)
	grade1	0 (33.3)	2 (66.7)	0 (0.0)	2 (100.0)
	grade 2	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
	total	6 (70.0)	3 (30.0)	1 (0.0)	10 (100.0)
time	**ART month=54**				
ART month=48	**radiographic severity**	**grade 0** n (%)	**grade 1** n (%)	**grade 2** n (%)	**total** n (%)
	grade 0	12 (85.7)	1 (7.1)	1 (7.1)	14 (100.0)
	grade1	2 (14.3)	11 (78.6)	1 (7.1)	14 (100.0)
	grade 2	3 (27.3)	3 (27.3)	5 (45.4)	11 (100.0)
	Total	17 (43.6)	15 (38.5)	7 (17.9)	39 (100.0)

Transition period: 48-54 months

	No ART Transitions				**ART Transitions**		
	Improve	Deteriorate	percent improvement		Improve	Deteriorate	percent improvement
0-6 months	12	32	27%	0-6 months	16	16	50%
6-12 months	14	15	48%	6-12 months	26	8	76%
12-18 months	11	4	73%	12-18 months	35	8	81%
18-24 months	3	8	27%	18-24 months	19	16	54%
24-30 months	3	2	60%	24-30 months	24	4	86%
30-36 months	4	1	80%	30-36 months	14	7	67%
36-42 months	6	2	75%	36-42 months	11	4	73%
42-48 months	1	1	50%	42-48 months	9	7	56%
48-54 months	0	1	0%	48-54 months	8	3	73%
Total transitions	**54**	**66**	**45%**	**Total transitions**	**162**	**73**	**69%**

Cumulative totals of transitions across all periods by ART status

Give thanks to the Lord for he is gracious
His mercy endures forever
Psalm 136