Chest X-Ray Findings in Drug Sensitive and Drug Resistant Pulmonary Tuberculosis Patients in Uganda

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Abstract

Background: Tuberculosis (TB) is one of the leading causes of death worldwide. Radiology has an important role in the diagnosis of both drug-sensitive (DS) and drug-resistant (DR) pulmonary TB (PTB). This study aimed at comparing the chest x-ray (CXR) patterns of microbiologically confirmed cases of DS and DR PTB in Uganda.

Methods: We conducted a hospital based retrospective study at the Mulago National Referral Hospital (MNRH) TB wards. All participants had microbiologically confirmed diagnosis of PTB. CXR findings extracted included infiltrate, consolidation, cavity, fibrosis, bronchiectasis, atelectasis and other non-lung parenchymal findings. All films were independently examined by two experienced radiologists blinded to clinical diagnosis.

Results: We analyzed CXR findings of 165 participants: 139 DS- and 26 DR-TB cases. Majority (n=118, 71.7%) of the participants were seronegative for HIV. Overall, 5/165 (3%) participants had normal CXR. There was no statistically significant difference in the proportion of participants with consolidations (74.8% versus 88.5%; p – 0.203), bronchopneumonic opacities (56.1% versus 42.3%, p=0.207) and cavities (38.1% versus 46.2%, p=0.514), across drug susceptibility status (DS versus DR TB). Among HIV infected participants, consolidations were predominantly in the middle lung zone in the DS TB group and in the lower lung zone in the DR TB group (42.5% versus 12.8%, p – 0.66). HIV infected participants with DR TB had statistically significantly larger cavity sizes compared to their HIV uninfected counterparts with DR TB (7.7 ± 6.8cm versus 4.2 ± 1.3cm, p – 0.004).

Conclusion- We observed that a vast majority of participants had similar CXR changes, irrespective of drug susceptibility status. However, HIV infected DR PTB had larger cavities.

The diagnostic utility of cavity sizes for the differentiation of DR from DS TB could be investigated further.

Background

Tuberculosis (TB) is one of the leading causes of mortality globally (1). In 2019, an estimated 10 million people were diagnosed with TB globally and of these 4 million died from the disease and its complications (1). In the same year, an estimated 206,030 cases of drug-resistant (DR) TB were reported, reflecting a 10% increase from the year 2018 (1).

Chest X-ray (CXR) is the primary radiologic evaluation of suspected or proven pulmonary TB (PTB) (2). When combined with clinical symptoms and signs, CXR has a high sensitivity in the diagnosis of PTB (3). However, several factors have been shown to affect CXR findings in patients with PTB; namely, human immunodeficiency virus (HIV) infection and the degree of immunosuppression, previous treatment for PTB and microbiological profile, that is drug-sensitive (DS) or DR-TB (4). Though, some studies suggest that DS and DR-TB present differently on the CXR in terms of morphology, size and location of the

lesions, a detailed description of the difference in CXR findings between DS- and DR-TB is not widely published(4, 5).

Among immunocompetent patients in Indonesia, patients with DR TB had CXR features predominantly of consolidations, infiltrates, cavities, fibrosis, bronchiectasis, calcifications, nodes, with accompanying extra pulmonary lesions such as effusions and empyema (4). The lesions were larger in size and usually more than one. On the other hand, DS-TB patients presented with majorly infiltrates and lesions which were generally smaller in size (4).

Among HIV-infected multi-drug resistant (MDR) TB patients in South Africa, CXR features of hilar and mediastinal lymphadenopathy, consolidations, volume loss, bronchiectasis and pleural effusions were the commonest findings in decreasing frequency (6).

Despite the fact that CXR are widely available and do play a central role in the screening and diagnosis of PTB (7), in sub-Saharan Africa where the burden of DS and DR TB as well as HIV is disproportionately high, there is a scarcity of literature on similarities and differences in radiological features of DS and DR TB patients. In this study therefore, we sought to address this critical knowledge gap by describing CXR findings of DS TB and DR TB patients and stratified findings by HIV status.

Methods

Study design and setting

This was hospital based retrospective comparative study conducted at TB ward of Mulago National Referral Hospital, Kampala, Ugandan, between 1st January 2018 and 31st December 2018. Mulago National Referral Hospital is located in Mulago hill road 2km from Kampala city center. The TB ward in the hospital runs both inpatient and outpatient clinics for patients being managed for TB. It is the largest DR TB referral and treatment center serving about 10 districts in central Uganda and is considered a center of excellence. In 2018, 137 and 713 patients were diagnosed with DR-TB and DS-TB respectively.

Study population

Records of all patients aged 15 years and above that had been diagnosed with PTB by GeneXpert, also who had baseline frontal chest radiograph and were managed from TB ward were retrieved. Patients with poor quality radiographs and additional respiratory co-morbidities such as chronic pulmonary obstructive disease, pulmonary cancer, interstitial lung disease, heart failure and sarcoidosis were excluded. Patients younger than 15 years of age were also excluded since bedaquiline, which is used in the management of MDR TB in Uganda is contraindicated in these patients.

Sample size

A sample size of 167 participants was determined using the formula proposed by Kelsey and colleagues. The following assumptions were used, P = Proportion of patients with DR-TB who have large lesions to be

average of 96% and proportion of patients with DS-TB who have large lesions to be average of 27%. Z value of 1.96 at 95% confidence level and a margin of sampling error of 5%

Study procedure

During the study period, 713 DS-TB and 137 DR-TB patient files were accessible to investigator. Stratified sampling was used in order to maintain the ratio of DS-TB to DR-TB considered in the sample size. A total of 139 files with DS-TB were then obtained using systematic random sampling using a sampling interval of (713/139) = 5 and 28 patient files with DR-TB using the sampling interval (137/28) = 5. The first DR-TB and DS-TB files to be enrolled into the study were selected randomly from the first five DR-TB and five DS-TB records using ballot papers. After enrolling the first patient file for each group, every other 5th DS-TB and DR-TB file was recruited into their respective groups. Records that were excluded were replaced by the next consecutive eligible record. Using a structured data collection tool bio-demographic and relevant history were obtained (Appendix 1).

The baseline CXR were then read independently in a systematic manner by the principal investigator and two senior radiologist and findings recorded. An Ewen-Janus viewing box Model D94405 Landau was used. The readers of the chest radiographs were blinded to the clinical information including the drug sensitivity. The CXR were reviewed for the presence of the following pathologies using a structured data collecting tool (Appendix 2), hilar/mediastinal lymphadenopathy, bronchopneumonic opacification, segmental/lobar consolidation, cavities, miliary opacification, pleural effusion, bronchiectasis, atelectasis, fibrotic bands, and pneumothorax. A chest radiograph lacking all the above features was considered to be normal. The location of the lesion was described by side and zone. The zones were; upper (between 1st and 2nd anterior ribs), middle (between 2nd and 4th anterior ribs) and lower (between the 4th and last anterior rib). The widest dimension of a lesion was taken as its size. Measurement was done using a HACO ruler that is factory calibrated.

Statistical analysis

Data was entered into EPIDATA version 4.4.2 and thereafter exported to SPPSS version 26 for analysis. Patient characteristics were summarized using mean and standard deviation for normally distributed continuous variables or median and range for skewed continuous variables. Categorical variables were summarized using frequencies and proportion. Normality was tested using Shapiro wilk test and normal distribution probability plots. The outcome of the study was CXR findings. The primary independent variable was drug sensitivity. The potential confounders in this study were age, sex, Immunological status and history of PTB treatment. To describe CXR findings of pulmonary DS-TB and DR-TB among patients in Mulago Hospital pulmonary DS-TB among patients in Mulago, we used frequencies and proportion. The CXR findings were grouped into three categories namely Morphology, size, number of zones affected and location; each with a number of indicator variables. To compare the proportions of CXR findings in patients with DR-TB and DS-TB we used Chi square test for cell counts above 5 or Fischer exact test for cells counts less than 5. Continuous variables such as age were categorized as per existing literature to

increase clinical significance. Mean for independent data were compared using the independent t-test. Statistical significance was set at $p < 0.05$.

Results

Characteristics of the study participants

A total of 165 participants, 139 DS and 26 DR-TB of which 106 (63.9%) males were recruited in the study. Overall, 118 (71.7%) participants were HIV uninfected. Of the 118, 103 (87.3%) had DS and 15 (12.7%) DR TB. Overall, 37 (22.4%) participants had a history of previous TB treatment with 9 defaulting and 3 failing on treatment. The proportion of participants with previous history of PTB was higher among DR TB compared to DS TB group (46.2% versus 18%, $p = 0.04$). (Table 1. Summarizes the baseline characteristics of the study participants.

Table 1
Baseline demographic Characteristics of 165 participants.

Baseline characteristics	All	Drug sensitivity		P-value
		DS TB(n = 139), %	DR TB (n = 26), %	
Gender	59 (36.1)	49 (35.3)	10 (38.5)	0.8
Female	106 (63.9)	90 (64.7)	16 (61.5)	
Male				
Age, median (range), years	30 (15–65)	30 (15–65)	33 (20–65)	0.103
HIV serostatus	118 (71.7)	103 (74.1)	15 (57.7)	0.099
Negative	47 (28.3)	36 (25.8)	11 (42.3)	
Positive				
CD4 counts, median (range)	218 (2–896)	208.5 (2-896)	218.0 (61–783)	0.268
History of smoking	36 (21.7)	31 (22.3)	5 (19.2)	1.0
Yes	129 (78.3)	108 (77.6)	21 (80.8)	
No				
History of PTB	37 (22.3)	25 (18.0)	12 (46.2)	**0.04**
Yes	128 (77.7)	114 (82.0)	14 (53.8)	
No				
Treatment outcomes (n = 37)	3 (8.1)	0 (0.0)	3 (25.0)	**0.037**
Failure	7 (18.9)	4 (16.0)	3 (25.0)	
Completed	9 (24.3)	7 (28.0)	2 (16.7)	
Defaulted	18 (48.8)	14 (56.0)	4 (33.3)	
Cure				
Extrapulmonary TB	14 (8.4)	14 (10.1)	0 (0.0)	0.130
Yes	151 (91.6)	125 (90.0)	26 (100.0)	
No				
Current or previous alcohol use	91 (54.8)	71 (51.1)	20 (76.9)	**0.018**
Yes	74 (45.2)	68 (49.0)	6 (23.1)	
No				

Chest X-ray findings

Five (3%) participants, 3 DS and 2 DR TB, had normal CXR. The most dominant feature of active PTB was consolidations (77%, n = 127). There was no statistically significant difference in the proportion of consolidation among DR compared to DS TB participants (88.5% versus 74.8%, p = 0.2). The participants with miliary pattern opacities on CXR were 3 (1.8%) and all of them were from DS-TB group (Table 2).

Table 2
Chest X-ray Findings of 165 participants

Radiological findings (N = 165)	Total	Drug sensitivity		P-value
	n (%)	DS-TB (%)	DR-TB (%)	
Normal	5 (3.0)	3 (2.2)	2 (7.7)	0.177
Bronchopneumonic process	89 (53.3)	78 (56.1)	11 (42.3)	0.207
Consolidation	127 (77.0)	104 (74.8)	23 (88.5)	0.203
Cavities	65 (39.4)	53 (38.1)	12 (46.2)	0.514
Miliary	3 (1.8)	3 (2.2)	0 (0.0)	> 0.999
Bronchiectasis	50 (30.3)	44 (31.7)	6 (23.1)	0.488
Atelectasis	17 (10.3)	13 (9.4)	4 (15.4)	0.314
Fibrotic bands	50 (30.3)	43 (30.9)	7 (26.9)	0.818

Participants with DS TB had consolidation as the commonest (104, 74.8%) CXR finding of active PTB followed by bronchopneumonic opacities (78, 56.1%) and cavities (53, 38.1%). A similar proportion of HIV uninfected compared to HIV infected had cavities (41.7 versus 27.8%, p = 0.165) (Table 3).

Table 3
Chest X-ray Findings in DS TB stratified by HIV status.

Radiological findings (N = 139)	Total	HIV status		P-value
	n (%)	Negative	Positive	
Bronchopneumonic process	78 (56.1)	55 (53.4)	23 (63.9)	0.331
Consolidation	104 (74.8)	77 (74.8)	27 (75.0)	> 0.999
Cavities	53 (38.1)	43 (41.7))	10 (27.8)	0.165
Bronchiectasis	44 (31.7)	29 (28.2)	15 (41.7)	0.149
Atelectasis	13 (9.4)	11 (10.7)	2 (5.6)	0.514
Fibrotic bands	43 (30.9)	32 (31.1)	11 (30.6)	> 0.999

Of the 26 participants with DR TB, 23 (88.5%) had consolidations followed by cavities and bronchopneumonic opacities respectively. Stratified by HIV status, there was no statistically significant

difference in the proportion of participants with cavities (53.3% for HIV negative versus 36.4% for HIV positive, p = 0.45) (Table 4).

Table 4
Chest X-ray Finding in DR TB stratified by HIV status

Radiological findings (N = 26)	Total n (%)	HIV status		P-value
		Negative	Positive	
Bronchopneumonic process	11 (42.3)	7 (46.7)	4 (36.4)	0.701
Consolidation	23 (88.5)	14 (93.3)	9 (81.8)	0.556
Cavities	12 (46.2)	8 (53.3)	4 (36.4)	0.453
Bronchiectasis	6 (23.1)	5 (33.3)	1 (9.1)	0.197
Atelectasis	4 (15.4)	1 (6.7)	3 (27.3)	0.279
Fibrotic bands	7 (26.9)	6 (40.0)	1 (9.1)	0.178

Location and number of lesions

Among HIV uninfected participants, consolidations were predominantly in the upper lung zones (47.1% in DS versus 9.2% in DR TB, p = 0.38) and middle lung zones (48.7% in DS Vs 7.6% in DR TB, p = 0.27). The bronchopneumonic opacifications were predominantly in the middle lung zones (37% in DS versus 5.9% in DR p = 0.59).

Of the HIV infected participants, the consolidations were predominantly in the middle lung zone (42.5%) in the DS TB group and in the lower lung zone (12.8%) in the DR TB group (p = 0.48). Bronchopneumonic opacities were mostly seen in the middle and lower lung zones (34% versus 32%, p = 0.46) in the DS TB group and in the three lung zones unilaterally in DR TB group.

The average number of zones affected by signs of active disease was comparable between the DS TB and DR TB groups (2.7 versus 3, p = 0,46) (Table 5).

Table 5
Average Number of Zones affected by Active disease

Drug sensitivity	Average number of zones with active disease (SD)	P-value
DS TB	2.7 (1.9)	0.46
DR TB	3 (1.8)	

Among the HIV infected participants, cavity sizes were statistically significantly large in those with DR TB compared to HIV uninfected participants with DR TB (7.7 ± 6.8 cm versus 4.2 ± 1.3 cm, p = 0.004). There was no statistically significant difference in the mean consolidation sizes (p = 0.8) and the mean number of cavities (p = 0.4) among HIV uninfected participants with DR TB compared to HIV infected participants

with DR TB. The commonest extrapulmonary findings were pleural effusion followed by fibrosis and lymphadenopathy with no statistically significant difference between the DS and DR TB groups (Table 6).

Table 6
Extrapulmonary findings

	HIV negative n = 118			HIV positive n = 47		
X-ray features	DS TB n(%)	DR TB n(%)	p-value	DS TB n(%)	DR TB n(%)	p-value
Lymphadenopathy	3 (2.5)	1 (0.8)	0.52	1 (2.1)	4 (8.5)	0.43
Unilateral	2 (1.7)	1 (0.8)	0.86	1 (2.1)	1 (2.1)	0.22
Bilateral	1 (0.8)	0 (0)	0.40	0 (0)	3 (6.4)	0.33
Pleural effusion	21 (17.6)	3 (2.5)		4 (8.5)	5 (10.6)	
Unilateral	19 (16.0)	3 (2.5)		3 (6.4)	3 (6.4)	
Bilateral	2 (1.7)	0 (0)		1 (2.1)	2 (4.3)	
Fibrosis	6 (5.0)	2 (1.7)		0 (0)	4 (8.5)	
Unilateral	5 (4.2)	2 (1.7)		0 (0)	4 (8.5)	
Bilateral	1 (0.8)	0 (0)		0 (0)	0 (0)	

CXR of HIV uninfected and HIV infected participants are demonstrated in Fig. 1 and Fig. 2 respectively.

Discussion

In this retrospective study aimed at comparing the CXR patterns of DS and DR TB participants, we showed no difference in radiological presentation. This is in keeping with a study done in Indonesia and another done in India (4, 8).

Due to acquired mutations of mycobacterium during treatment (9), previous history of treatment was significantly higher among participants diagnosed with DR TB 12(46.2%) compared to 25(18%) among DS TB. A metanalysis done in Ethiopia showed similar results (9).

With the emergence of DR TB, few studies have been done and published that shows CXR finding in DS TB, with majority being done DR TB (4, 10). Moreover less have been done comparing finding among adult with HIV coinfection (11).

The commonest CXR findings in DS TB was consolidation. The distribution of consolidative lesions in both HIV negative and HIV positive participants with more upper and middle zone involvement compared to the lower zones. Mean consolidation size was higher among HIV positive participants when compared to HIV seronegative participants. Bronchopneumonic opacities were second commonest CXR finding with predominantly middle and lower lung zones distribution in both HIV seronegative and HIV seropositive

participants. Bronchopneumonic opacities followed by consolidation and cavities were the commonest findings among an HIV seronegative participants in Indonesia (4). Similar findings were found in an HIV seropositive group in South Africa (4, 12). However, in the south African study cavities were more dominant than infiltrates among the HIV negative patients (12).

The commonest CXR features among DR TB group were consolidations in the upper lung zones. A similar study done in India found that this was the second commonest finding after cavities (8). Among the HIV negative group majority had upper zone consolidations followed by middle zone and lower zone, which is consistent with comparable study done in India (8). In our study consolidations followed by cavities and bronchopneumonic opacities were the commonest finding among both HIV positive and HIV seronegative groups. This was in keeping with a study done among HIV seropositive participants where the commonest CXR findings were bronchopneumonic infiltrates and consolidations (4, 13). In HIV seropositive participants the majority of the lesions were in the lower lung zone. The mean consolidation size was bigger in HIV seronegative participants than in the HIV seropositive participants. The lower lung zone distribution among HIV seropositive participants was also seen in a study done by similar to a study done by Padyana et al. (13).

Cavities were the least common feature of active disease occurring most in the middle lung zones in both the HIV seronegative and HIV seropositive participants with DR TB. In a metanalysis done by Xiáng J and colleagues, the prevalence of cavities among HIV positive patients was as low as 9% which is similar to low prevalence in this study (10). However among immunocompetent patient cavitary disease was the commonest finding in most studies (4, 10). In the pathophysiology of PTB consolidations and bronchopneumonic opacities precede cavities (14). Therefore, the participants could have presented early before formation of cavities.

The cavity sizes were also larger among HIV seropositive patients than among HIV seronegative in DR TB group. The difference in cavities sizes between the groups is unusual since cavities are not common in immunosuppressed individuals. However, this can be explained by late diagnosis in HIV positive patients due to delayed clinical presentation and diagnostic challenges associated with immunodeficient patients (15–18).

The average number of zones with active disease in DR TB group was 3. Chuchottaworn and colleagues found that 59.8% of the patients with MDR had involvement of more than two lung zones (19).

This study showed that consolidations and bronchopneumonic opacities formed the largest proportions of CXR findings in both DR TB and DS TB with cavities formed least common findings. There was no significant difference in proportions of the different lesions between DR TB and DS TB from this study. In a study that used chest computed tomography, all the different lesions of active PTB were not significantly different between the two groups except for a higher proportion of cavities amongst the DR TB group($p = 0.007$) (20). Most authors stipulate those cavities facilitate development of resistance to antimicrobial treatment as the lining of the cavity prevents penetration of drugs and the high bacterial titers in the cavity facilitate development of resistance (20). It is not clear if primary infection with MDR

causes cavity formation. In some studies, patients with no previous history of MDR infection had a fewer proportion of cavities (10). This could explain why cavities were not so dominant in this population since only three patients had history of failed treatment.

Majority of findings were unilateral in both DR TB and DS TB with no significant difference between the two groups. Some studies demonstrated that there was a difference in distribution with DS TB showing a more bilateral distribution and was attributed to delayed diagnosis and initiation of treatment allowing for more spread of disease to involve both lungs (4, 10).

The limitation of the study was that it was a retrospective study looking at records as such some records were in complete. The chest x-rays were taken using various machines in the hospital.

Conclusion

The study found no statistically significant difference in chest x-ray patterns of PTB between DR TB and DS TB among immunocompetent patients. Among HIV positive patients, cavity sizes were significantly larger in DR TB compared to DS TB. CXR alone is not sufficient for risk stratification for DS TB. All patients with features of active PTB on the CXR should be screened for DR TB.

Abbreviations

PTB- Pulmonary Tuberculosis

HIV- Human Immunodeficiency Virus

DS-TB – Drug sensitive tuberculosis

DR-TB – Drug resistant tuberculosis

MDR- Multidrug resistant tuberculosis

RR- Rifampicin Resistance

WHO- World Health Organisation

Declarations

Ethics approval and consent to participate

Waiver of informed consent was obtained. Ethical approval was obtained from Makerere University School of Medicine Research and Ethics committee and administrative clearance was sought from Mulago National Referral Hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

All authors made a significant contribution to the study, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Figures

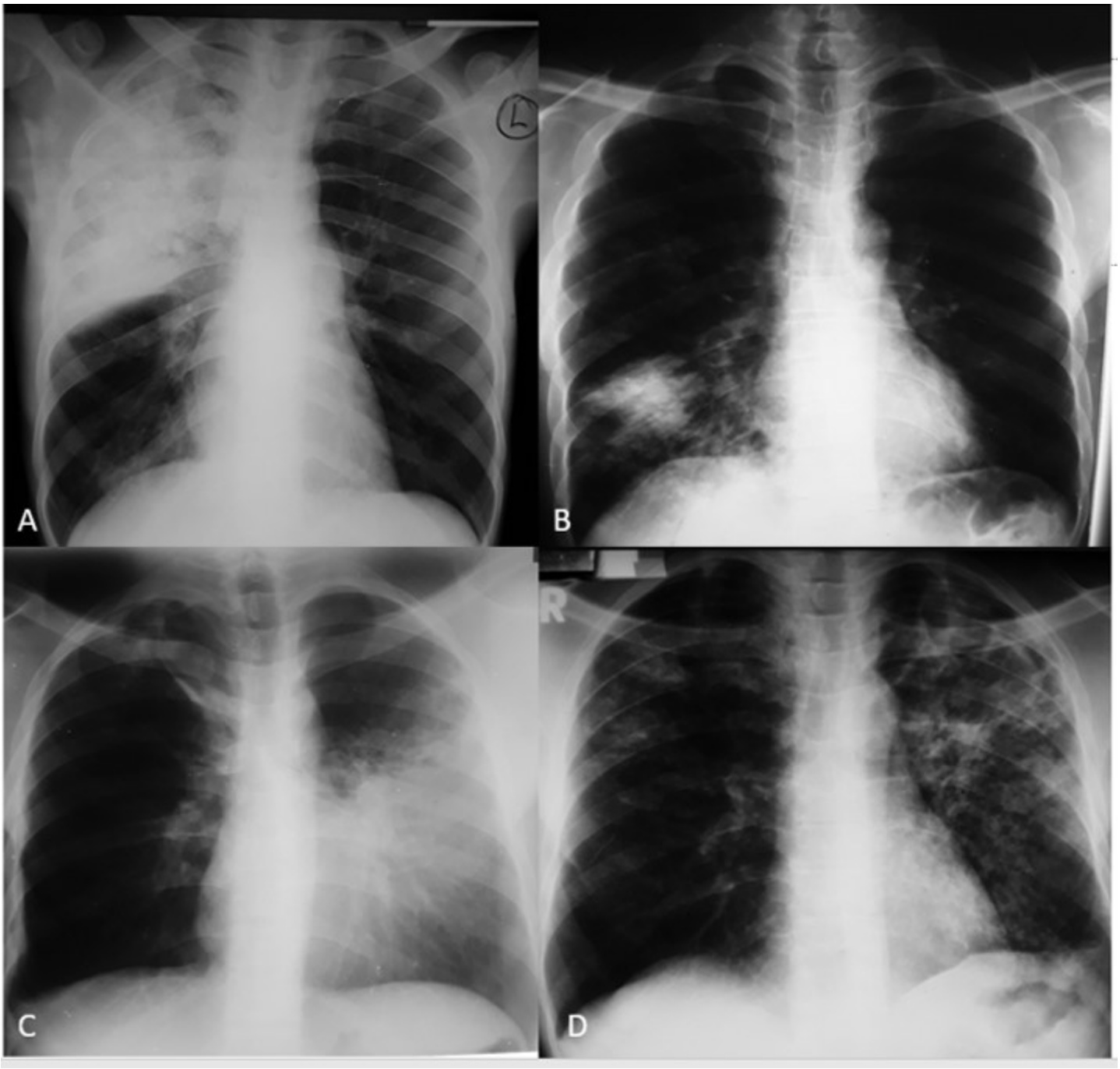

Figure 1

Frontal chest radiograph of HIV seronegative participants A) Of a 38 year old male patient with DS TB showing a consolidation involving the right upper and middle lung zones. B) Of a 26-year-old patient with DS TB showing consolidation in the right lower lung zone. C) Of a 26-year-old patient with a consolidation involving the left middle and lower lung zones. D) Of a 34 year old with DS TB showing

multiple left upper lobe cavities, bronchopneumonic opacities in the whole left lung and right upper and middle lung zones. There are also bilateral areas of bronchiectasis.

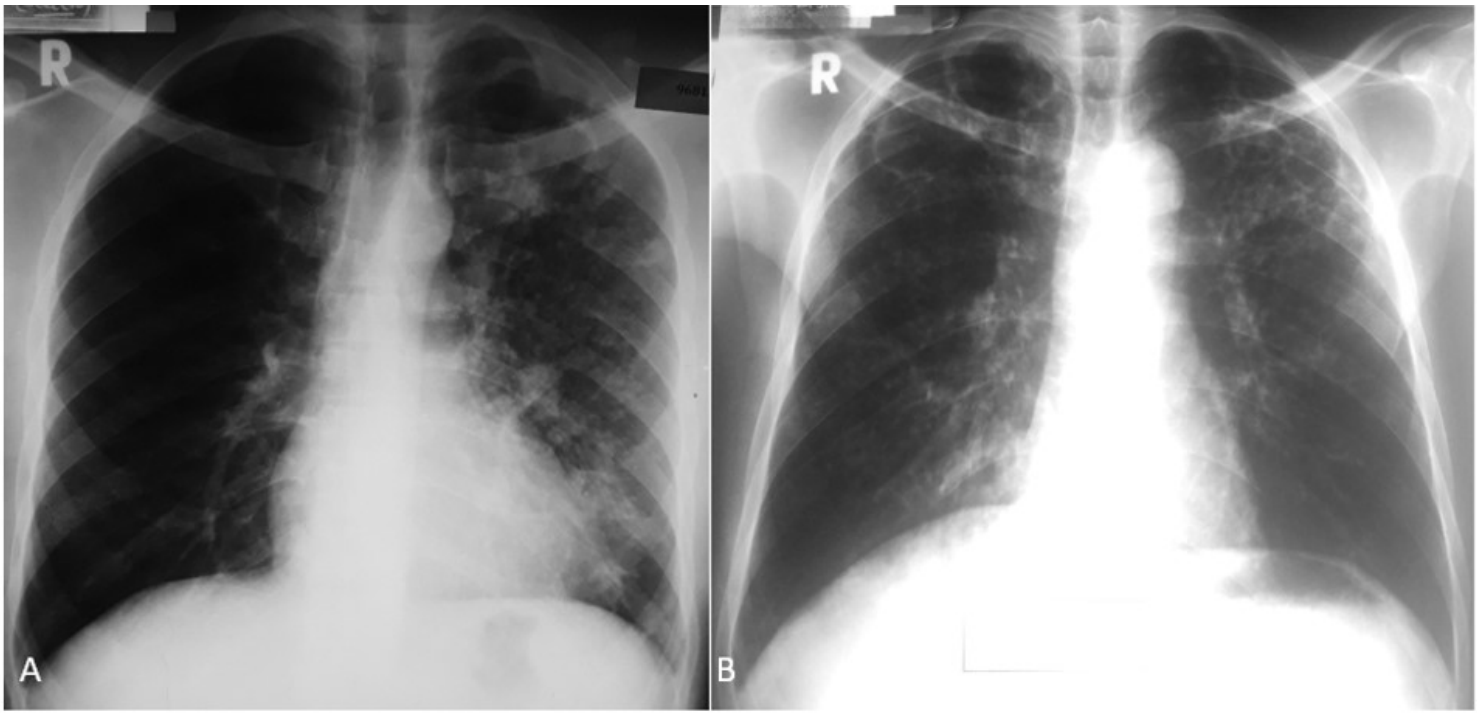

Figure 2

Frontal chest radiograph of HIV seropositive participants A) Of a 39-year-old patient with DS TB showing multiple cavities in the left upper and middle lung zones and bronchopneumonic opacities involving the whole left lung field. B) Of a 42 year old patient with DS TB with bilateral upper lung zone cavities, bilateral upper and middle lung zone bronchiectasis and bilateral upper and middle lung zone bronchopneumonic opacities.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- APPENDIX.docx