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Review Article

Pulmonary Tuberculosis among HIV/AIDS Patients: Chest X-Ray Characteristics

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Abstract

Pulmonary Tuberculosis (PTB) and human immunodeficiency virus (HIV) constitute the main burden of infectious disease worldwide. Infection with HIV increases an individual's risk to 20-fold of developing active TB. Chest X-ray (CXR) is one of the important tools used in the diagnosis of pulmonary tuberculosis among people living with HIV/AIDS. The spectrum of radiological findings varies according to HIV status and immunological status. This review designed to identify the common CXR findings encountered in pulmonary TB-HIV coinfection. The electronic search was in three main databases PubMed, Scopus, and Google Scholar were conducted using the search term: "Chest X-ray/radiological features/ Findings/ characteristics, pulmonary TB and HIV/AIDS co-infection". Typical radiological finding was found to be closely related to the immunological status, where the atypical presentations were commonly reported in PTB-HIV confection. It could be included that interpretation of CXR in areas with a high prevalence of HIV-related TB necessitates interpreters to be provided with HIV status and the degree of immunosuppression.

Key words: Pulmonary TB, HIV/AIDS, Chest X-ray

Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) constitute the main burden of infectious disease worldwide. World Health Organization (WHO) estimated that TB remains a global epidemic with 10 million new cases worldwide, of which 8.6% of them were people living with HIV/AIDS (PLWHA)[1]. Globally , 2.1 million new HIV cases were reported in 2018, and by end of 2018 the total number of PLWHA were 37.9 million[2]. By end of 2017 , 9% of PLWHA developed TB, where 49% of PLWHA were unaware of their coinfection and are therefore not receiving care[2]. Infection with HIV increases an individual's risk to 20-fold of developing active TB[3]. The lifetime risk of TB activation among non-HIV-infected persons is reported between 5-10%, however, the risk of TB activation among PLWHA increases to 5-10% per year[4]. TB is the most frequent cause of AIDS-related deaths worldwide, despite progress in access to antiretroviral therapy (ART)[5]. TB caused about 251,000 deaths

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among PLWHA in 2018, representing about one third of all HIV deaths[3]. Global data indicate that PLWHA are about 20 times more likely to develop active TB than those without HIV infection[6]. This increased number due to multidrug-resistant (MDR) or extensively drug-resistant (XDR) compared to the non-HIV-infected population[7]. TB-HIV co-infection augment each other's, that result in difficult diagnostic and therapeutic challenges, and contribute to atypical presentations, accelerated disease course, and specific treatment challenges[8]. HIV infection decreases the number of CD4 T lymphocytes, which play an important role in cellular-mediate immunity the result in TB granuloma formation, which is essential for pulmonary TB (PTB) sequestration in the latent stage, and failure of this process increases the risk of PTB reactivation. For that, the rate of progression to active TB increases by decreasing CD4 count[8]. There are two methods of TB screening, active and passive screening. Passive screening is initiated by the patient and based on the symptomatic presentation that brought him to seek medical advice, which is more unreliable in HIV-infected cases where atypical presentations are not uncommon. Active screening is healthcare provider driven, and in resource-limited settings generally include symptoms screening followed by sputum microscopy and/or Chest X-ray (CXR)[9]. The chest radiographic findings of tuberculosis in HIV-positive patients have been described to differ from the HIV-negative population and inversely with CD4 cell counts[10]. Recognition of the atypical radiographic appearances of tuberculosis in HIV-infected patients is crucial to the timely initiation of effective therapy, both for the benefit of the individual patient and for his contacts[10]. However, there is a paucity of radiology literature describing the CXR finding among PLWHA. The aim of the current article is to review available literature on CXR characteristics among PLWHA. Is the immune status based on CD4 T lymphocyte count affect radiological features? To answer this question and looking for the radiological characteristics of TB among PLWHA; we searched the PubMed, Scopus and google scholar database using different search strategies to search for article on PTB CXR findings among PLWHA.

Methodology

Searching Strategies

A literature search was performed for the present study on the lines of searches for any papers fit with the review question. The electronic search in two main databases PubMed, Scopus, and Google Scholar that's 3 databases were conducted using the search term: "Chest X-ray/radiological features/ Findings/ characteristics, Pulmonary TB and HIV/AIDS co-infection". The inclusion criteria included all types of articles published in English and related only to humans. The date is open for searching medical literature. The exclusion criteria included articles for which full text was not available and was not in English. Generally, only articles describing the selected topic had been reviewed and included.

Results

From an initial screen of 3466 titles and abstracts, which were retrieved from PubMed, Scopus, and Google Scholar (509, 148 and 2809 respectively), only 25 studies were included in the final review as shown in (Figure 1). The excluded articles in the first cycle due to irrelevance to the research questions or duplication of the results. In the second cycle 45 articles were excluded because 7 of them were conducted on children and the rest were mixed studies PTB and non-tuberculous

mycobacterial infections. This review based on 25 articles after extensive screen process of literature as illustrated in Figure 1, which all of them are hospital-based and were classified according to their study design into: 14 cross-sectional, 4 retrospective study, 4 cohort; 2 comparative study and only one descriptive, prospective study.

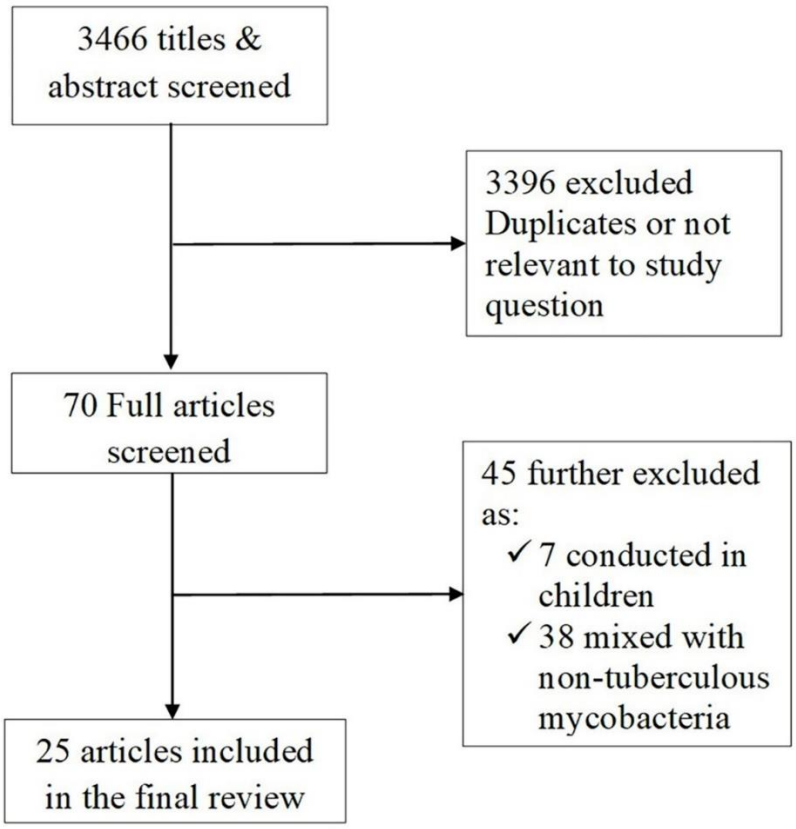

Figure 1: Algorithm of the included Studies

Discussion

Radiological Characteristics

CXR is one of the important tools in diagnosis of PTB, determining the extent and character of the disease, and evaluating the response to therapy[11]. The degree of immunosuppression and HIV disease progression is based mainly on the $CD4^+$ lymphocytes count[12]. In HIV, TB can present with both typical and atypical radiological features depending on the level of immunosuppression[12]. A normal CXR was more common in the HIV-positive group, which may be related to decrease cell-mediated immunity in those patients, as the impaired cell-mediated immunity results in reduced granuloma formation, caseation, liquefaction, and eventually cavitation[13]. In contrast, pulmonary infiltration, cavity, and fibrosis were more frequent in HIV-negative patients, which is related to the robust inflammatory response in this group[13]. An educational exhibit by European Society of Radiology in 2013 stated that the radiographic findings of TB in PLWHA depends on the severity of immune system reactions and the number of bacilli in the lung,

therefore HIV-seropositive patients may have radiographically atypical presentations[14]. The reported radiological features in PLWHA related to the CD4 T lymphocytes count, those with normal CD4 T lymphocytes count have findings like those described for immunocompetent individuals. The radiological findings of PTB in patients without HIV were summarized (Table 1). The CXR findings of PTB in PLWHA based on CD4 T lymphocytes count can be summarized as follow:

- All patients with $CD4^+$ T lymphocytes count < 200 cells/µL had normal CXR or can be similar to primary PTB radiological features. The interstitial infiltrates localized mainly in lower lobe rather than upper lobe, the air-space opacities similar to pneumonic consolidation without cavitation and fibrosis. Intrathoracic lymphadenopathy is often evident in these patients[15]. Diffuse pulmonary infiltrates/opacities are the dominant radiological findings. Miliary pattern and pleural effusion are more common[16](Figure 2).
- Patients with CD4 T lymphocytes count > 200 cells/µL showed post-primary or typical PTB radiological characteristics[14]. African showed high rate of cavitation as evident in many studies[14]. This can be explained by high prevalence rate of TB, and PTB occur at earlier stages of HIV infection[17] (Figure 3).

The overall sensitivity of CXR features was higher than of the symptom screens, 98% for any CXR abnormality, with 75% specificity, and 87% pooled sensitivity for TB abnormalities, with 89% specificity as reported in one of Cochrane Database of Systematic Reviews 2014[18]. CXR had a sensitivity and specificity of 72% and 57 %, respectively, with the positive predictive value of 21 % and negative predictive value of 93 % in diagnosing PTB[19]. In a community survey with high TB and HIV level, the specificity for any abnormal CXR was 67%, and when limited to typical features it was 83%[20]. The subjectivity of CXR interpretation is one of the challenges facing the diagnosis of TB radiologically. There are high levels of inter-observer variability among experienced radiologists and chest physicians. For that if certain CXR findings can be indicative of TB, it remains an insensitive and nonspecific tool[21]. Table 2 summarizes the common CXR findings from the top appropriate studies.

Table 1: Radiological features of PTB in patients without HIV

Primary PTB	Pos-Primary/Secondary PTB
Parenchymal infiltrates or opacities	Patchy bronchopneumonic opacities and fibrosis mainly in upper lobes
Lymphadenopathy	Cavitation
Segmental atelectasis	Secondary pleural effusion
Pleural effusion	Pneumothorax
Miliary TB	Hydropneumothorax

The major primary PTB CXR features, either occur alone or in combination

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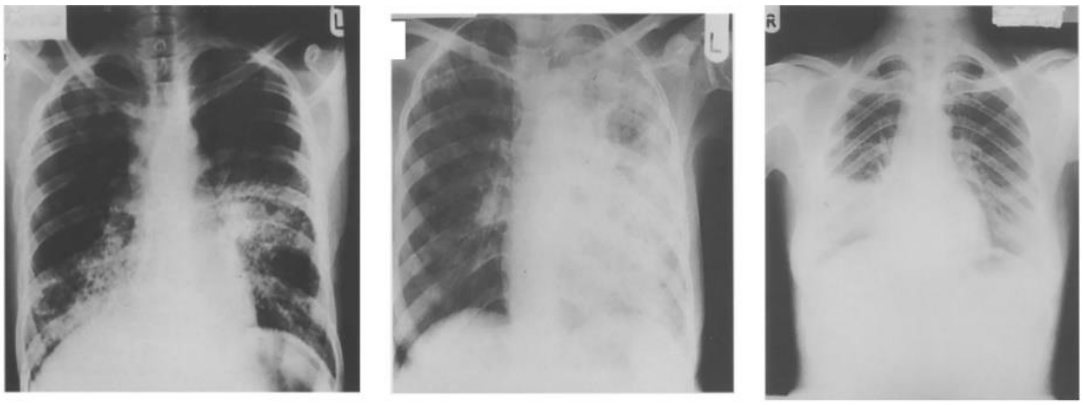
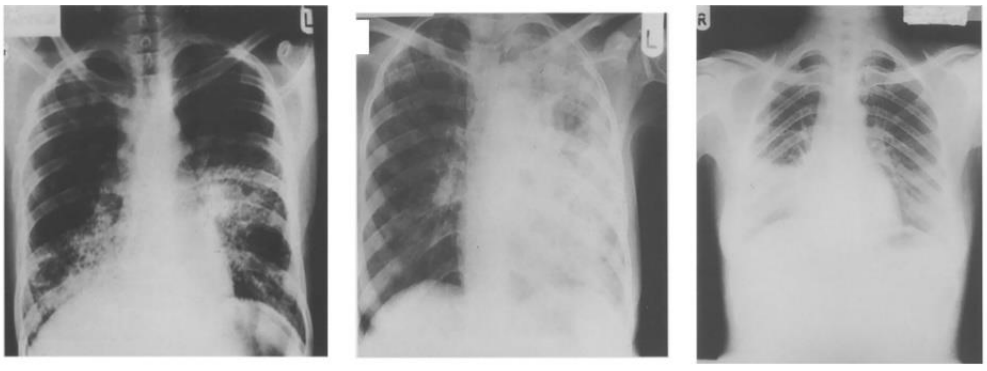


a. Middle and lower zone infiltrates (23)
b. Left lung Consolidation and cavity (23)
c. Bilateral Atypical tuberculous consolidation (23)

Figure 2: Miliary pattern and pleural effusion are more common



a. Middle and lower zone infiltrates (23)
b. Left lung Consolidation and cavity (23)
c. Bilateral Atypical tuberculous consolidation (23)

Figure 3: TB, and PTB at earlier stages of HIV infection

Table 2: Summaries of the findings of 25 articles

Author	Year	Country	Study design	Study area setting	Sample size	Main findings	Conclusion	No. of References in the article
Haramati, Jenny-Avital and Alterman [22]	1991-1993	USA	Retrospective descriptive	Hospital-based	98	HIV-positive patients had higher rate of mediastinal lymphadenopathy (60 vs. 23%) and atypical infiltrates (55 vs. 10%) than HIV- negative patients. Infiltrates in HIV-negative patients indicates reactivation tuberculosis (77 vs. 30%) and cavitation (52 vs. 18%) significantly more frequently than HIV-positive patients.	HIV-positive patients have high rate of atypical infiltrates and mediastinal lymphadenopathy, and less frequent cavitation and infiltrates typical for reactivation tuberculosis than in HIV-negative patients.	16
Tshibwabwa-Tumba [23]	1992-1995	Zaire & Zambia	Retrospective analysis of CXR with TB HIV coinfection	Hospital-based	1963	CXR findings in PTB with +ve HIV had a higher rate of lymphadenopathy (26 % vs 13 %), pleural effusions (16% vs 6.8%), miliary shadowing (9.8% vs 5%), an interstitial pattern (12% vs 7%) and consolidation (10% vs 3%). The less frequent features were cavitation (33% vs 78%) and atelectasis (12% vs 24%).	This study revealed a significantly increased incidence of lymphadenopathy, pleural effusions, parenchymal changes, consolidation and miliary disease, but significantly less cavitary disease and atelectasis, in PTB in H1V +ve.	16
San and Muhamad [24]	1995-1998	Malaysia	Retrospective analysis of CXR with TB HIV coinfection	Hospital-based	80	Typical CXR findings were only found in 16.2%. Atypical CXR findings were found in 83.3% of all cases, which include: normal CXR, middle and/ or lower zones involvement, intrathoracic lymphadenopathy, pleural effusion and miliary TB. Only 1.6% with CD4 count < 200, and 66.7% with CD4 count > 200 had typical pattern. Atypical CXR finding commonly seen when CD4 count < 200, which include: normal CXR, middle and /or lower zones involvement and mediastinal lymphadenopathy.	Typical CXR pattern commonly seen in CD4 count > 200, in comparison with atypical CXR finding commonly seen when CD4 count < 200.	26

Fátima *et al* [25]	1997-1999	Brazil	Cross-sectional	Hospital-based	275	Miliary shadow, pleural effusion, lymphadenopathy and absence of cavities were more seen in HIV than HIV (7.7% vs 1.7%), (15.4% vs 8.1%), (10.3% vs 3.4%) and (82.1% vs 50.4%) respectively.	Most of TB HIV coinfection had no cavitation.	17
Picon *et al.* [26]	1997 - 2001	Brazil	cross-sectional	Hospital-based	231	PTB HIV coinfection presented with high frequency of atypical pulmonary tuberculosis as intrathoracic lymphadenopathy, disseminated TB and less cavitary lesions. It also associated with lower median CD4 counts.	Atypical presentation and disseminated TB commonly seen in patients with advanced immunosuppression.	30
SWAMINATHAN *et al.* [27]	1999 - 2002	India	cross-sectional	Hospital-based	181	Common CXR presentations of TB among +ve HIV than HIV -ve were: normal CXR (14.2% vs 0), miliary TB (10.7% vs 1%) and pleural effusion (16.6% vs 3%), and less likely to have cavitation (17.8% vs 39.4%). At the end of treatment, HIV +ve were likely to have normal CXR (42.8% vs 1.2%), and less likely to have fibrosis (17.8% vs 42.5%).	The CXR presentation of PTB in HIV +ve patients is atypical with less cavitation, and more dissemination. On completion of ATT, patients with HIV have less radiographic sequelae in the form of fibrosis.	18
Patel, Rami and Ghanchi [28]	2003 - 2006	India	prospective observational study	Hospital-based	43	CXR involvement of lower lung field more than upper (41.86% vs 23.26%), while 34.88% had extensive disease. Cavitation were more observed in extensive diseases (60%). Intrathoracic lymphadenopathy and pleural effusion were equal in upper lung field, but in the lower field intrathoracic lymphadenopathy was higher than pleural effusion.	PTB in HIV showed atypical presentations	11

Badie *et al.* [29]	2004-2007	Iran	comparative study	Hospital-based	196	The CXR findings which were more common in HIV +ve were diffuse pulmonary involvement were (27.7% vs 12%), Miliary pattern (17% vs 4.7%) and hilar lymphadenopathy (10.6 vs 7.4%). The less commonly seen findings were cavitary lesion (4.3% vs 20.1%), and pleural effusion (13% vs 23.5%)	The most common CXR features of PTB HIV coinfection were diffuse pulmonary consolidation followed by miliary shadows Involvement of lung field in tuberculosis was atypical as evidenced by bilateral lung involvement; middle and lower zone or diffuse involvement	17
Ahmadi, Salmanzadeh and Kimyai [11]	2004-2008	Iran	Descriptive epidemiological retrospective study	Hospital-based	204	Normal thoracic radiography, pleural effusion, miliary pattern, and hilar and mediastinal lymphadenopathy were more common in the HIV-seropositive group. Pulmonary infiltration and cavities were more frequent in the HIV-seronegative group. Fibrosis in HIV-seronegative patients was higher than in HIV-seropositive subjects. Upper lobe pulmonary involvement in HIV-seropositive patients was less frequent than HIV-seronegative.	Radiological presentation of pulmonary TB differs between HIV-seropositive and HIV-seronegative patients due to progressive immunodeficiency from HIV infection.	17
Tania *et al.* [30]	2004 - 2010	Cuba	cross-sectional	Hospital-based	120	CXR findings in patient with CD4 count < 200 was 5.70 times higher to develop a primary radiological pattern. When CD4 count > 200 the chance of normal CXR was1.96 times higher. There is no clear statistically significant association between the post-primary CXR pattern and CD4 count.	The relationship between CD4 count and CXR findings is well evident when CD$ count < 200.	18
Affusim *et al.* [12]	2007	Nigeria	Cross-sectional	Hospital-based	89	Atypical CXR findings reported in 62% of patients with CD4 count < 200, typical findings found in 18% of patient with CD4 count > 200 and 12% had normal CXR.	CXR of HIV coinfected with pulmonary TB are related to the level of immunosuppression (CD4 count).	13

Desalu *et al.* [31]	2007	Nigeria	cross-sectional	Hospital-based	127	CXR findings in patient with CD4 count < 200 include: mediastinal lymphadenopathy, middle and lower lung zone involvement, bilateral lung involvement, miliary or disseminated patterns, and normal CXR. In those with CD4 count >200 CXR findings include: cavitations, upper lung zone involvement, pleural effusion and bilateral lung infiltrate.	Severe immunosuppression was significantly associated with atypical CXR findings of TB, while mild immunosuppression was significantly associated with typical findings.	23
Kisembo *et al* [13]	2007-2008	Uganda	Comparative studies to compare CXR findings in HIV +ve and HIV -ve	Hospital-based	408	Cavities were significantly more common in HIV-seronegative TB patients than in HIV-seropositive (48% vs 13%). Consolidation also occurred more frequently among HIV-seronegative patients (70% vs 42%). Miliary abnormalities were more common among HIV seropositive (0% vs 2%). Intrathoracic lymphadenopathy were more common among HIV seropositive (11% vs 24%).	In populations highly endemic for HIV–TB coinfection, the radiographic features of TB in patients with HIV differ from the typical patterns seen in non-immunosuppressed or less immunosuppressed individuals.	28
Huang and Davis [32]	2007-2008	Uganda	Cross-sectional	Hospital-based	491	Only 334 patients had CXR. Normal CXR reported in 16% and commonly seen in cD4 count < 50.	Normal CXR findings were common among HIV +ve patients, especially those who were young, and with low CD4 counts.	29
Aline Besen, Guilherme Jönck Staub [33]	2009-2010	Brazil	Cross-sectional	Hospital-based	52	50% of participants were HIV +ve. The common radiological finding in HIV +ve were cavitation (43% vs 10%) and interstitial infiltrates (78% vs 40%).	In our sample of tuberculosis patients, expectoration was less prevalent, HB levels were lower, and cavitation was less common, as was an interstitial pattern, among those co-infected with HIV than among those without HIV co-infection	28

Kitara *et al*[34]	2009 - 2010	Uganda	prospective co-hort	Hospital-based	320	In PTB HIV +ve coinfection: Atypical CXR features: reticulonodular infiltrates (69.7%); intrathoracic lymphadenopathy (40%); pleural effusion (27.5%) and miliary (20.6%). Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitations (27.5%) and normal CXR (2.2%).	Atypical CXR findings were well evident in PTB HIV coinfection.	37
Padyana *et al.* [35]	2099 - 2011	India	prospective cohort	Hospital-based	200	Infiltration (39%), consolidation (30%), cavity (11%), and lymphadenopathy (9%) were commonly seen with CD4 < 200. Infiltration (37.5%), cavity (25%) and miliary (25%) seen with CD4 above >200. Bilateral (68.5%) and mid and lower zones or all zone involvement more commonly seen.	CD4 count clearly affecting the CXR findings in PTB HIV coinfection.	11
de Albuquerque *et al* [36]	2009-2012	Brazil	Cross-sectional	Hospital-based	140	The most common isolated radiological findings were consolidation, diffuse infiltrates, miliary shadow and cavity (14.3%, 11.9% ,11.9% and 7.1% respectively). The mixed findings were: Interstitial infiltrate and consolidation (11.9%) and Consolidation and cavity (7.1%). Normal CXR reported in 2.4% of study population.	the typical CXR findings in PTB HIV coinfection consolidation, diffuse infiltrates, miliary TB and cavity.	21
Ikuabe [37]	2012-2013	Nigeria	retrospective co-hort analysis	Hospital-based	307	The commonest radiological feature in HIV +ve were cavitation (63.8%), patchy opacities (43.9%), hilar opacities (38.1%), Perihilar patchy opacities (18.9%), consolidation (5.2%) and pleural effusion (4.6%). Bilateral chest involvement was common.	The CXR presentation of PTB in HIV +ve include the usual, characteristic upper zone infiltrates, cavitation and hilar or Perihilar opacities.	18
Kistan *et al* [38]	2012-2015	South Africa	cross-sectional	Hospital-based	474	HIV +ve patients had a higher proportion of infiltrates (58.9% vs 46.8%), a lower proportion of cavitations (40.8% vs 68.3%), and a lower proportion of disease extent involving half or more of the lung area radiologically (25.9% vs 45.3%).	Patient with HIV co-infected with PTB have a higher proportion of infiltrates and a lower proportion of cavitation. The absence of classical upper lobe cavitatory lesion on CXR does not exclude PTB.	17

Behera *et al* [39]	2013-2015	India	cross-sectional observational study	Hospital-based	162	Unilateral CXR findings of PTB are commonest in both HIV +ve and HIV -ve. These findings include infiltrates (53.3% vs 49%), Consolidation (10% vs 19.6%), fibrosis (0.0% vs 5.9%) and cavitation (6.7% vs 31.4). Radiological zones vary between seropositive vs seronegative; upper zone (30% vs 27.5%), middle zone (13.3% vs 11.8%), lower zones (16.7% vs 7.8%) and multiple zones (26.7% vs 47.1%).	CXR finding of PTB differ in HIV +ve than HIV -ve. Atypical radiological findings were common in HIV +ve.	20
Pandhi [40]	2015	India	Cross-sectional	Hospital-based	50	The CXR findings which were more common in HIV +ve were pulmonary infiltration (20% vs 16%), consolidation (16% vs 4%), pleural effusion (20% vs 8%), hyperinflation (8% vs 0%), Pneumothorax (4% vs 0%), lung abscess (4% vs 0%). The less common findings were cavitary lesions (8% vs 40%), hydropneumothorax (0% vs 4%). The presence of military pattern and hilar/mediastinal lymphadenopathy is similar in both groups.	The spectrum of CXR findings in TB HIV coinfection ranges from infiltration to military pattern. Radiological differences in HIV positive and negative patients were clearly stated.	7
Umar *et al.* [41]	2015-2017	Nigeria	A retrospective cross-sectional	Hospital-based	244	CXR findings in PTB HIV coinfections include: Normal CXR (60.0%), primary patterns as reticulonodular opacities (16.61%), typical post primary patterns as cystic/fibrotic changes (3.39%), and miliary pattern (2.73%).	Normal CXR constitute the major findings; primary and post-primary patterns of PTB account for the least findings.	24

MD *et al*.[42]	2016-2017	India	Cross-sectional	Hospital-based	90	Diffuse pulmonary involvement was more common in PTB HIV confection group than PTB without HIV infection (27.7% vs 12%). Mediastinal lymphadenopathy and lower zone infiltration are common HIV +ve than HIV-ve group (35.5% vs 0%). Cavitation is less in HIV +ve than HIV -ve (0% vs 57.69%). Typical CXR findings more seen when CD4 count >200.	Atypical chest x-ray findings are common in HIV- TB co infection and commonly seen when CD4 count <200. The most common atypical presentations are mediastinal lymphadenopathy, lower zone infiltrations and military shadow. Cavitation is less seen in TB- HIV coinfection	23
Rehan Ahmad[43]	2018	India	prospective cohort	Hospital-based	50	CXR in 80% of patients showed moderately or far advanced disease. The prevalence of typical radiological findings of post primary TB include upper zone infiltrate (24%), cavities (6%), fibrosis (4%). Cavitation commonly seen when CD4 count >100.	The most common CXR findings in TB HIV coinfection include parenchymal infiltration, consolidation, cavity, lymphadenopathy, pleural effusion, and miliary shadows.	12