**The author names of the manuscript that was published September 2009 issue of Turkish Thoracic Journal were printed mistakenly incomplete. This was corrected manuscript.**

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# Impact of Immunosuppression on Radiographic Features of HIV Related Pulmonary Tuberculosis among Nigerians

## Nijerya Halkında HIV ile İlişkili Bağışıklık Sisteminin Baskılanmasının Akciğer Tüberkülozunun Radyolojik Bulgularına Etkileri

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**ABSTRACT**

**Objective:** The impact of immunosuppression on radiographic manifestation of HIV related pulmonary tuberculosis among Nigerians was studied.

**Material and Method:** We recruited 127 cases of HIV related pulmonary tuberculosis at the Federal Medical Centre Yola Adamawa state, Nigeria. Demographic information, smoking history and results of sputum smear for AAFB, chest radiographic findings and blood CD4 counts were obtained. Subjects were subdivided into two groups: Group I (CD4 count < 200cell/mm$^3$) and Group II (CD4 count ≥ 200cell/mm$^3$).

**Results:** Of the 127 subjects, 74 were males and 53 were females. The mean age of the subjects was 35.1±8.4 years and the mean CD4 count was 166±100 cell/mm$^3$. There were 93(73.2%) in Group I and 34(26.8%) in Group II. Mediastinal lymphadenopathy, middle and lower lung zone involvement, bilateral lung involvement, miliary or disseminated patterns as well as normal chest radiographs were found more frequently in Group I. Cavitations, upper lung zone involvement, pleural effusion and bilateral lung infiltrate were found more frequently in Group II.

**Conclusion:** Severe immunosuppression was significantly associated with atypical radiological findings of TB, while mild immunosuppression was significantly associated with typical pulmonary tuberculosis. The physician needs to be aware of the impact of immunosuppression on radiographic manifestation of HIV related pulmonary tuberculosis.

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**Key words:** Immunosuppression, radiographic, AIDS manifestation, HIV, tuberculosis, Nigerians

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**ÖZET**

**Amaç:** Bu çalışmada, Nijerya halkında HIV ile ilişkili bağışıklık sisteminin baskılanmasının akciğer tüberkülozunun radyolojik bulgularına etkileri değerlendirildi.

**Gereç ve Yöntem:** Yola Adamawa eyaletinde Federal Tıp Merkezinde HIV ile ilişkili akciğer tüberkülozu tanısı ile izlenen 127 olgu çalışmaya dahil edildi. Olguların demografik özellikleri, sigara öyküleri, akciğer grafileri, CD4 düzeyleri ve aside rezistan basil yönünden yayma-kültür sonuçları incelendi. Olgular CD4 sayılarına göre iki gruba ayrıldı: I. Grupta CD4 sayısı <200/mm$^3$ ve II.Grupta da CD4 sayısı ≥200/mm$^3$ idi.

**Bulgular:** Olguların 74'ü erkek ve 53'ü kadındı. Ortalama yaşları 35.1±8.4 ve ortalama CD4 sayısı da 166±100/mm$^3$ idi. Gruplarda yer alan hasta sayıları sırasıyla 93(%73.2) ve 34 (%26.8) idi. Birinci gruptaki hastaların akciğer grafilerinde; mediastinal lenfadenopati, orta ve alt zon tutulumu, bilateral akciğer tutulumu, milier ve yaygın infiltrasyonlar sık karşılaşılan patolojilerdi. İkinci grupta yer alan hastaların akciğer grafilerinde; kavitasyon, üst zon tutulumu, plevral efüzyon ve bilateral akciğer tutulumu daha sık karşılaşılan patolojilerdi.

**Sonuç:** Ciddi derecelerde bağışıklık sistemi baskılanması tüberküloza bağlı atipik radyolojik değişikliklere neden olurken, daha hafif seviyede olan bağışıklık sistemi baskılanması akciğer tüberkülozunun tipik radyolojik değişiklikleri ile karşımıza çıkmaktadır. HIV ile ilişkili bağışıklık sistemi baskılanması ile ortaya çıkan akciğer tüberkülozu olgularında klinisyenler hastalığın derecesi hakkında radyolojik bulgulardan da bilgi edinebilir.

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**Anahtar sözcükler:** Bağışıklık sistemi baskılanması, radyolojik, AIDS, HIV, tüberküloz, Nijerya

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## INTRODUCTION

At the end of 2000, about 11.5 million human immune deficiency viruses (HIV) -infected people worldwide were co- infected with Mycobacterium tuberculosis. Seventy percent of the co- infected people were in sub-Saharan Africa, 20% were in South-East Asia and 4% in Latin America and the Caribbean [1, 2]. Tuberculosis (TB) has a greater impact on morbidity and mortality in HIV-1-infected individuals than all other opportunistic infections (OI) [3]. TB accounts for 40 percent of acquired immune deficiency syndrome (AIDS) deaths in Africa and Asia and one-third of AIDS deaths worldwide [1]. TB and

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HIV infections have a synergistic influence on the host immunoregulation. HIV infection undermines cell-mediated immunity through depletion of CD4+ lymphocytes which leads to reactivation of TB in HIV-infected people and increases susceptibility to new infections [1-4]. TB can develop at any stage of immunodepression regardless of the levels of circulating CD4+ T-lymphocytes [4]. CD4+ T-lymphocytes count is one of the surrogate markers for evaluating the degree of immunosuppression and HIV disease progression [4].

The degree of immunosuppression in HIV infection has a greater impact on the radiographic pattern of TB. No radiographic pattern is specific to pulmonary tuberculosis, however in HIV infection, TB can produce typical and atypical radiological patterns depending on the degree of immunosuppression [5-9]. Atypical radiological presentations are lower frequency of cavitations and higher frequency of mediastinal lymphadenopathy, interstitial infiltrates in the lower zone and normal chest radiographs, while typical radiological presentations are upper lobe fibrosis, bilateral infiltrates, consolidation and cavitations [6-9]. There are few studies on the impact of immunosuppression on the radiographic manifestation of HIV related pulmonary tuberculosis in Nigeria. Our aim was to study the impact of immunosuppression on radiographic manifestation of HIV related pulmonary tuberculosis among Nigerians.

## SUBJECTS and METHODS

We conducted the study from May 2007 to July 2007 at the Federal Medical Centre Yola Adamawa state, Nigeria. The subjects were recruited from patients attending the HIV clinic and those admitted into hospital for HIV/AIDS treatment. The inclusion criteria were age ≥14 years, patients diagnosed with HIV related pulmonary tuberculosis, not taking antituberculous or antiretroviral therapy at the time of entry into the study. Indeterminate cases of pulmonary tuberculosis, suspected fungal pneumonia, pneumocystis jirovecii, confirmed diabetes mellitus, chronic renal failure, nephrotic syndrome and malignancies were excluded from the study. The HIV patients were diagnosed by antibody test ,initially using rapid immunobinding assay followed by enzyme immunoassay (EIA) Genscreen HIV1/HIV2 version 2 and confirmed by immonocomb II (Immunocombfirm) (HIV1/HIV2 combfirm Orgenics). Suspected TB patients were thoroughly reviewed by two specialist physicians and underwent sputum smear microscopy for acid and alcohol fast bacilli (AAFB) on three consecutive days.

Also, we carried out a baseline standard posterior anterior (PA) radiograph for all patients, and the radiographs were blindly reported by two radiologists without their knowledge of enrolment into the study. When a disagreement occurred in their evaluation, the two radiologists reached a consensus on radiological findings of that chest radiograph. The radiologists evaluated the radiograph for mediastinal lymphadenopathy, cavitations, infiltrates, localised or miliary shadows and pleural effusion. In addition, they also determined the predominantly affected lung zones.

The haematologist measured the recent baseline CD4 count by flow cytometry to determine the degree of immunosuppression and stage of HIV infection. Based on the CD4 T-lymphocytes count, subjects were divided into two groups, Group I had severe degrees of immunosuppression (CD4 count< 200) and Group II had mild to moderate degrees of immunosuppression (CD4+ ≥ 200cell/mm$^3$).

Demographic information, smoking history, and sputum smear results for AAFB and peripheral blood CD4 counts were obtained. The data were analysed using SPSS version 14 computer statistical software. Frequency and descriptive statistics were performed to examine the characteristics of the subjects and the radiological pattern of pulmonary tuberculosis. Pearson Chi- square, continuity correction was used to test significance. A P value <0.05 was considered significant.

### Case definition

The diagnosis of PTB/HIV co-infection was based on criteria for diagnosing TB in poor resource settings where there are no facilities and manpower for mycobacterium tuberculosis culture: (a) the diagnostic criteria of TB given in the World Health Organisation (WHO) treatment of tuberculosis guideline for national programmes [5]; (b) specificity of clinical criteria in diagnosing TB patient [6, 10]; (c) Although Mantoux is usually negative in HIV infection because of loss of cell mediated immunity due to depletion of CD4 count, HIV patients who were smear negative for AAFB, but had positive Mantoux test with an area of induration ≥10mm diameter were considered diagnostic for tuberculosis.

### Ethical approval

Verbal and informed consent from the subjects was obtained and the ethical committee of Federal Medical Centre Yola approved the study.

**Table 1.** Characteristic of patients in the study

| Characteristics | Frequency % |
|---|---|
| **Mean age** (years) | 35.1±8.4 |
| **Sex** | |
| Male | 53 (41.7) |
| Female | 74 (58.3) |
| **Education** | |
| None/primary | 33 (26.0) |
| Secondary | 82 (64.6) |
| Tertiary | 12 (9.4) |
| **Socioeconomic status** | |
| Low | 127 (100) |
| High | 0 (0) |
| **Smoking habits** | |
| Never | 97 (76.4) |
| Ever | 30 (23.6) |
| **Sputum microscopy (AAFB)** | |
| Negative | 77 (60.6) |
| Positive | 50 (39.4) |
| **CD4 count** | |
| <200cell/mm$^3$ | 93 (73.2) |
| ≥200cell/mm$^3$ | 34 (26.8) |

**Total=127**

**Table 2.** Radiological features of pulmonary tuberculosis in HIV patients

| Radiological features | Group I n (%) | Group II n (%) | P values |
|---|---|---|---|
| **Mediastinal lymphadenopathy** | 51 (54.8) | 16 (41.2) | 0.04 |
| **Cavitations** | 25 (30.9) | 23 (63.9) | <0.01 |
| **Upper lung zones involvement** | 8 (13.3) | 4 (14.8) | 0.85 |
| **Mid/lower lung zones involvement** | 52 (86.7) | 23 (85.2) | 0.85 |
| **Hemithorax affected** | 32 (49.2) | 19 (63.3) | 0.20 |
| **Both hemithorax affected** | 33 (50.8) | 11 (36.7) | 0.20 |
| **Miliary opacities** | 31 (44.9) | 8 (26.7) | 0.09 |
| **Pleural effusion** | 9 (12.9) | 8 (22.2) | 0.16 |
| **Bilateral Infiltrate** | 48 (69.9) | 18 (75.0) | 0.61 |
| **Normal chest x-rays** | 10 (11.0) | 0 (0) | 0.09 |
| **Typical pattern** | 7 (8.1) | 6 (18.2) | 0.02 |
| **Atypical pattern** | 79 (79.1) | 25(75.8) | 0.02 |
| **Mixed pattern** | 0 (0) | 2 (6.1) | 0.02 |

NB: (There may be more than one abnormality for the same patient). Group I N=93, Group II N = 34

## RESULTS

One hundred and twenty-seven subjects participated in the study, of whom 74 were males and 53 were females. The mean age of the subjects was 35.1±8.4 years and the mean CD4 count was 166±100 cell/mm$^3$. Table 1 shows the general characteristics of the participating subjects. All the subjects were in a low socioeconomic class, 97 (76.4%) had never smoked cigarettes while 30 (23.6%) had smoked cigarettes at some time. Only 50 (39.4%) had smear-positive tuberculosis while 77 (60.6) had smear-negative tuberculosis. By stratification of CD4 T-lymphocytes count, 93 (73.2%) had a CD4 count < 200cell/ mm$^3$ and 34 (26.8%) had a CD4 count ≥ 200cell/mm$^3$.

Table 2 shows the radiological findings of patients with HIV-related pulmonary tuberculosis. Subjects in Group I (CD4 count<200cell/mm$^3$) frequently had more mediastinal lymphadenopathy (64.1%vs.44.4%; p=0.04), middle and lower lung zone involvement (86.7%vs.85.2%; p=0.85), bilateral lung involvement (50% vs. 36.7%; p=0.20), miliary or disseminated pattern (44.9%vs.26.7%; p=0.09) than Group I subjects (CD4 count≥200cell/ mm$^3$). Likewise, normal chest radiographs (11.0%vs.0.0%; p=0.09) and atypical or primary tuberculosis findings (79.1% vs. 75.8%; p=0.02) were more frequent in subjects with CD4 counts of < 200cell/mm$^3$. Also subjects with CD4 count ≥ 200cell/mm had more cavitations (63.9% vs. 30.9%; p=<0.01), upper lung zone involvement (14.8% vs. 13.3%; p=0.85), pleural effusion (22.2% vs. 12.9%; p=0.16) bilateral infiltrates (75.5% vs. 69.9%; p=0.61) and typical or post primary tuberculosis (18.2% vs. 8.1%; p=0.02) than subjects with CD4 count < 200cell/mm$^3$.

## DISCUSSION

Our study revealed that radiographic manifestations of HIV related pulmonary tuberculosis have a relationship with the CD4 count; which is an indicator of immune status and stage of HIV infection. Severe immunosuppression and CD4 count <200/mm$^3$ were significantly associated with the presence of mediastinal lymphadenopathy. This confirms the report in other studies worldwide [10-14]. The middle and lower lung zone involvement, bilateral lung involvement, miliary pattern and normal chest radiograph were also more common in CD4 count <200/ mm$^3$ than in subjects having CD4 count≥200/mm$^3$ but, these radiographic findings were not statically significant (p >0.05). These findings agreed with and supported the observation of studies in Brazil, the USA and Côte d'Ivoire which relate the level of immunosuppression to radiographic manifestations [14-16].

We also found the cavities on chest radiographs to be frequent and significantly associated with less immunosuppression (CD4 count is ≥200/ mm$^3$). This result was consistent with several studies that reported the association between cavity formation and less immunosuppression [11,14,15,18,19]. Cavity formation mostly requires an adequate delayed-type of hypersensitivity response and intact cell mediated immunity in the host. Upper lung zones involvement occur more often in HIV subjects with less immunosuppression (CD4 count ≥200cell/mm$^3$) than in those with severe immunosuppression .TB in the upper zones is usually common in HIV seronegative patients who have high CD4 counts and are immunocompetent, therefore it is not surprising that HIV patients with high CD4 counts will have upper lung zone involvement.

**Figure 1.** Shows right hilar lymphadenopathy in a subject with CD4 count of 168cell/mm$^3$

**Figure 3.** Showing cavity in the left upper zone and streaky opacities in the right middle zone of a patient with CD4 count of 236 cell/mm$^3$

**Figure 2.** Showing atelectasis in the right lower zone and fluffy infiltrates in the middle zone in a subject having CD4 count of 189cell /mm$^3$

**Figure 4.** Showing infiltrate in the right upper zone of the lung in a patient with CD4 count of 275 cell /mm$^3$

Pleural effusion was significantly more closely associated with CD4 count >200cell/ mm$^3$ than in CD4 count <200cell/mm$^3$. Our result was comparable with other studies where pleural effusion was significantly associated with higher CD4 count [20-21]. In contrast, a study in Brazil reported pleural effusion to be associated with CD4 count <200 cell /mm$^3$ [15]. Pleural effusion in HIV-positive patients is due to a hypersensitive reaction in the pleura and this was responsible for most patients with a T-lymphocyte count of CD4 > 200 cell /mm$^3$ presenting with pleural effusion [20]. Only 11.0% of subjects having CD4 count <200 cells /mm$^3$ and none of those with CD4 count >200 cell /mm$^3$ had a normal chest radiograph, and this association was significant. One study in the USA also found no significant association between normal chest radiograph and CD4 level [14]. Some studies have noted an association of normal chest radiographs in HIV patients with CD4 count <200cell/mm$^3$ [12,17,22]. The increasing prevalence of PTB/HIV co- infection and the finding of a normal chest radiograph, negative Mantoux test and sputum smear microscopy poses a serious challenge for the diagnosis of pulmonary tuberculosis in countries with poor resources, where facilities for mycobacterium culture are non existent. It remains uncertain whether the absence of radiographic findings represents early stages of either primary disease or reactivation, or disease caused by intrathoracic lymphadenopathy not yet detected by simple radiographic examination [14-15]. In this study, atypical or primary pattern was common in patients with CD4 less than 200 cell /mm$^3$, while typical or post primary pattern was common in those with CD4 greater than 200 cell /mm$^3$ (p=0.02). This finding was similar to observations among African and American patients in whom there was significant asso ciation between low CD4 count and atypical or primary pattern of tuberculosis [12-14]. Patients with severe immune depression (CD4 count <200 cell /mm$^3$) had atypical or primary tuberculosis radiological features, while those with less severe immune depression (CD4 count ≥200 cell /mm$^3$) had typical or post primary pulmonary tuberculosis features. The various radiographic appearances have different pathogenesis that were greatly modified by the level of CD4 count, degree of immunosuppression and cell mediated immunity. Our study revealed that various radiographic manifestations of HIV related pulmonary tuberculosis are related to the level of immunosuppression. The physician needs to be aware of the impact of immunosuppression on radiographic manifestations of HIV related pulmonary tuberculosis.

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