

**Original Article****Open Access****Active tuberculosis among adult HIV-infected patients accessing antiretroviral therapy in a tertiary health facility in Lafia, northcentral Nigeria**\*<sup>1</sup>Audu, E. S., <sup>2</sup>Adiukwu, C., <sup>3</sup>Bello, S., <sup>4</sup>Abdulmajid, S., <sup>4</sup>Anyuabaga, B., <sup>5</sup>Ashuku, Y. A., and <sup>6</sup>Anazodo, M.<sup>1</sup>Department of Medical Microbiology/Special Treatment Clinic, Dalhatu Araf Specialist Hospital, Lafia<sup>2</sup>Department of Internal Medicine, Dalhatu Araf Specialist Hospital, Lafia<sup>3</sup>Department of Paediatrics/Special Treatment Clinic, Dalhatu Araf Specialist Hospital, Lafia<sup>4</sup>Special Treatment Clinic, Dalhatu Araf Specialist Hospital, Lafia<sup>5</sup>College of Medicine, Federal University, Lafia<sup>6</sup>Research Unit, Dalhatu Araf Specialist Hospital, Lafia\*Correspondence to: [estanamo@gmail.com](mailto:estanamo@gmail.com)**Abstract:****Background:** Tuberculosis and Human Immunodeficiency Virus (HIV) co-infection is a major problem in Nigeria and other countries that are ravaged by a high burden of both diseases. The World Health Organization (WHO) reports that the risk of developing active tuberculosis (TB) among people living with HIV is 16-27 times that of HIV negative persons. Although antiretroviral therapy (ART) reduces the risk of developing TB, there are factors which predispose those on ART to TB. This study sought to determine the prevalence of TB among adults on ART in our facility and identify the predisposing factors.**Methodology:** This was a retrospective study utilizing data from clinical records (folders and electronic) of adult HIV patients who are accessing ART in our facility and have been on ART for at least 6 months. A proforma was used to collect data including demographic, clinical, ART and laboratory information of the patients. The data were entered into SPSS version 23 and analyzed using descriptive statistics and bivariate analysis. Associations were tested using Chi square with 95% confidence level.**Results:** A total of 457 patients were studied, aged 18-69 years (mean age 38.3± 10 years), and 72.4% females. Majority were married (81%), unemployed (53.8%), had mean baseline CD4 cell count of 267.4 ± 185 cells/mm<sup>3</sup> and a mean duration on ART of 100.9± 39 months. Seventeen point three percent of the patients had a previous history of TB before or within 6 months of commencement of ART. Thirteen (2.8%) of the patients had active TB while on ART. Majority of those who had active TB were females (76.9%), married (76.9%), unemployed (46%), had no previous history of TB (53.8%), baseline CD4 cell count of ≤ 350 cells/mm<sup>3</sup> and were on first line ART medication. There was however no significant statistical association of active TB with any of these factors.**Conclusion:** Few patients had active TB while on ART in this study. The high frequency of TB in those who had low baseline CD4 cell count and baseline WHO stage shows the importance of early initiation of ART in people living with HIV (PLHIV). There is need for regular screening of PLHIV for TB and innovative approaches to get people with HIV to know their TB status as well as early commencement of ART.**Keywords:** Human immunodeficiency virus, Active Tuberculosis, Antiretroviral therapy.

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**Tuberculose active chez des patients adultes infectés par le VIH ayant accès à un traitement antirétroviral dans un établissement de santé tertiaire à Lafia, au centre-nord du Nigéria**\*<sup>1</sup>Audu, E. S., <sup>2</sup>Adiukwu, C., <sup>3</sup>Bello, S., <sup>4</sup>Abdulmajid, S., <sup>4</sup>Anyuabaga, B., <sup>5</sup>Ashuku, Y. A., et <sup>6</sup>Anazodo, M.

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## Abstrait:

**Contexte:** La co-infection tuberculose et virus de l'immunodéficience humaine (VIH) est un problème majeur au Nigéria et dans d'autres pays qui sont ravagés par un fardeau élevé des deux maladies. L'Organisation mondiale de la santé (OMS) signale que le risque de développer une tuberculose active (TB) chez les personnes vivant avec le VIH est de 16 à 27 fois supérieur à celui des personnes séronégatives. Bien que la thérapie antirétrovirale (TAR) réduise le risque de développer la TB, il existe des facteurs qui prédisposent les personnes sous TAR à la TB. Cette étude visait à déterminer la prévalence de la tuberculose chez les adultes sous TAR dans notre établissement et à identifier les facteurs prédisposants.

**Méthodologie:** Il s'agissait d'une étude rétrospective utilisant des données provenant de dossiers cliniques (dossiers et électroniques) de patients adultes atteints du VIH qui accèdent au TAR dans notre établissement et qui sont sous TAR depuis au moins 6 mois. Un formulaire a été utilisé pour recueillir des données, y compris des informations démographiques, cliniques, ART et de laboratoire des patients. Les données ont été saisies dans SPSS version 23 et analysées à l'aide de statistiques descriptives et d'une analyse bivariée. Les associations ont été testées en utilisant le chi carré avec un niveau de confiance de 95%.

**Résultats:** Un total de 457 patients ont été étudiés, âgés de 18 à 69 ans (âge moyen 38,3 ± 10 ans) et 72,4% de femmes. La majorité était mariée (81%), sans emploi (53,8%), avait un nombre moyen de cellules CD4 de base de 267,4 ± 185 cellules/mm<sup>3</sup> et une durée moyenne sous TAR de 100,9 ± 39 mois. Dix-sept virgule trois pour cent des patients avaient des antécédents de tuberculose avant ou dans les 6 mois suivant le début du TAR. Treize (2,8%) des patients avaient une tuberculose active pendant le TAR. La majorité de ceux qui avaient une tuberculose active étaient des femmes (76,9%), mariées (76,9%), sans emploi (46%), sans antécédents de tuberculose (53,8%), le nombre initial de cellules CD4 ≤ 350 cellules/mm<sup>3</sup> et étaient médicaments antirétroviraux de première ligne. Il n'y avait cependant pas d'association statistique significative de la TB active avec aucun de ces facteurs.

**Conclusion:** Peu de patients avaient une tuberculose active pendant le TAR dans cette étude. La fréquence élevée de la tuberculose chez ceux qui avaient un faible nombre de cellules CD4 de base et un stade de base de l'OMS montre l'importance de l'initiation précoce du TAR chez les personnes vivant avec le VIH (PVVIH). Il est nécessaire de procéder à un dépistage régulier des PVVIH pour la tuberculose et à des approches innovantes pour permettre aux personnes vivant avec le VIH de connaître leur statut antituberculeux ainsi que le début précoce du TAR.

**Mots-clés:** virus de l'immunodéficience humaine, tuberculose active, thérapie antirétrovirale.

## Introduction:

Tuberculosis (TB) remains one of today's global health challenges ranking as one of the leading infectious cause of death in the world. Tuberculosis and human immunodeficiency virus (HIV) co-infection also remain a major problem especially in sub-Saharan Africa which carries a high burden of both diseases. According to the World Health Organization (WHO), approximately 36.9 million people are living with HIV globally in 2017, 66% of them in sub-Saharan Africa (1,2). The WHO reports that the risk of developing TB is estimated to be 16-27 times greater in PLWHA than HIV negative persons (3-5). HIV has been reported to increase the incidence of TB as well as the morbidity and mortality associated with the disease (4).

The introduction of antiretroviral therapy (ART) has decreased the incidence of TB in PLWHA. However, patients on ART are still at risk of TB. Reports have associated different factors with the risk of TB in patients who are

on ART (4, 5). Such factors including previous exposure to TB and low immune status as indicated by their baseline CD4 cell count have been reported to contribute to the development of active TB in HIV patients on ART. Other factors include low socio-economic status with poverty and poor nutritional status. All these can also lead to poor adherence to anti-retroviral drugs (ARVs) which can lead to further deterioration of health in HIV patients (6).

Nigeria was reported in 2017 to have about 1.9 million people living with HIV and AIDS (PLWHA) (7, 8). In addition, Nigeria rank seventh among 30 high TB burden countries and second in Africa (3, 9, 10), and is among the top 14 high burden countries for TB, TB/HIV and multidrug resistant (MDR) TB (3, 9). The need to place all HIV infected patients on ART and to ensure they are virally suppressed through administration of appropriate ARV regimen with adherence to medication is sacrosanct as this has been reported to improve outcomes and reduce risk of developing active TB (11-13).

While studies on prevalence of TB and

HIV infections have been conducted in many other centers, no such study has been done in our facility which serves a large population across many states in northcentral Nigeria. This study therefore sought to highlight the occurrence of TB in HIV infected individuals who are already on antiretroviral therapy and factors associated with the development of the disease. The aim is to determine the prevalence of active tuberculosis and associated risk factors among adult HIV patient receiving ART in Dalhatu Araf Specialist Hospital (DASH), Lafia, northcentral Nigeria.

## Materials and methods:

### Study area:

The study was conducted in a tertiary health facility located in Lafia, northcentral Nigeria. Lafia is the capital of Nasarawa State which has boundaries with Plateau, Kaduna, Benue, Kogi and Taraba states as well as the Federal Capital Territory. The facility receives patients from the state and border communities from all the neighboring states.

### Study design:

This was a descriptive cross sectional and retrospective study utilizing records of HIV infected patients registered for care at the ART clinic of Dalhatu Araf Specialist Hospital, Lafia.

### Study population:

The study population were adult HIV patients receiving antiretroviral therapy (ART) at the ART clinic of the Dalhatu Araf Specialist Hospital, Lafia. A total of 5,000 adult patients were accessing ART at the clinic at the time of the study.

### Sample size:

The sample size was determined using the Kish Lisle formula;  $n = z^2pq/d^2$ , where 'n' is the minimum sample size, 'z' is the standard normal deviate (1.96), a 'p' value of 50% was used, 'd' is the degree of confidence which is 5%, and 'q' is 1-p. This gives a sample size of 384. Since the study population is less than 10,000 and the sample size is more than 5% of the study population of 5,000, the Cochran correlation formula which is  $N = n/1 + (n/\text{study population})$  was used to obtain the final sample size (N). This gave 352 and with a 15% attrition, the minimum calculated sample size (N) was 420, which was increased to 457.

### Inclusion criteria:

All consenting adult HIV infected patients who are receiving antiretroviral therapy in the facility during the study period were included.

### Exclusion criteria:

Adult HIV infected patients who are newly initiated on ART (less than 6 months on ART) and those with incomplete data were excluded from analysis.

### Sampling method and duration:

The systematic random sampling was used. The sampling frame consisted of 5,000 adult patients. The patients' unique ART enrolment numbers were arranged serially and every 11<sup>th</sup> number was selected to make up the sample size. The study was carried out between April and October 2019.

### Data collection:

Permission was sought from the Medical Records Department to have access to the sampled case notes (physical folders and electronic medical records (EMR)). Data were extracted from the case notes and EMR and entered in a proforma. The extracted data included Patients' age, sex, marital status, occupation, ethnicity, history of TB prior to commencing ART or within the first 6 months on ART, baseline CD4 cell count, whether patient had active tuberculosis or not from 6 months of commencement of ART, duration of patient on ART before diagnosis of active TB, patients' CD4 count at time of TB diagnosis, patients' ART adherence history and the ART regimen. Active TB was defined as patients who met the criteria for TB diagnosis including positive sputum microscopy or positive GeneXpert or radiological evidence of pulmonary TB in the presence of clinical symptoms and clinical diagnosis with or without laboratory support for extra pulmonary TB. Data on the type of TB was also recorded.

### Data management and statistical analysis:

Data were entered in the Statistical Package for the Social Sciences (SPSS) version 23 and analyzed using univariate analysis to describe the study population. Bivariate analysis was done with Chi square test used to establish association of categorical variables.

### Ethical consideration:

Ethical approval was obtained from the Research Ethics Committee of the Dalhatu Araf Specialist Hospital, Lafia. Information obtained were treated confidentially by de-identification of patient information before sharing of data, hard copies of the data which had patient identifier were kept in a locked cabinet accessible only by the researchers and electronic copies of the data were kept in a personal computer which was pass worded and only used by the researchers.

## Results:

The records of a total of 457 patients were analyzed. The study population was aged between 18 and 69 years with a mean age of  $38.3 \pm 10$  years; 72.4% were females while 27.6% were males. Majority of the patients were married (81%), unemployed (53.8%), had baseline WHO stage 2 and 3 (81%), on first line ART regimen (86.9%) and had good ART average adherence (84%). The mean baseline CD4 count was  $267.4 \pm 185$  cells/mm<sup>3</sup> and majority had baseline CD4 cell count of  $\leq 350$  cells/mm<sup>3</sup>. The mean duration on ART was  $100.9 \pm 39$  months with a range of 7 to 204 months. A total of 79 (17.3%) patients had previous history of TB before or within 6 months of commencement of ART.

Patients who developed active TB while on ART were 13 (2.8%). Active TB occurred more frequently among patients who were married, female gender, unemployed, those who had a baseline WHO stage 2 and 3, and those who had no previous history of TB. However, bivariate analysis shows no statistically significant association between active TB and any of these factors (Table 2). Ninety-two percent (12/13) of those who

developed active TB had pulmonary TB while only 1 (7.7%) had extra pulmonary TB.

## Discussion:

The prevalence of active TB among HIV infected patients receiving antiretroviral therapy in the current study is 2.8%. This rate is comparable to the 4% reported by Chang et al., in a study from a large HIV program in Nigeria (14). Other studies also from Nigeria and Ethiopia reported higher prevalence of TB in patients at commencement of ARVs (15-18). A prevalence of 7.7% was reported in a study from southeast Nigeria (7). Studies from other African countries also show varying prevalence rates ranging from 11% to 27.7% (16, 18, 19). The low prevalence of active TB in our study may be due to the exclusion of those who had TB at commencement and within the first 6 months of ART. Those who had TB before or within the first 6 months of ART were 17.3%, which is similar to the rates from other studies such as the one from Asia where 17% of HIV patients had active TB within the first 6 months of commencement of ART (20). Other studies from Africa and around the world which included all those with TB at commencement of ART also

Table 1: Demographic, clinical and laboratory characteristics of the study population

Variable	Category	Number	%	Mean
Age (years)				38.31
Gender	Male	126	27.6	
	Female	331	72.4	
Marital status	Single	49	10.7	
	Married	369	80.7	
	Widowed	25	5.5	
	Divorced/seperated	14	3.1	
Occupation	Unemployed	246	53.8	
	Civil servants	77	16.8	
	Farmer	35	7.7	
	Trader	32	7.0	
	Artisans	21	4.6	
	Others	20	4.4	
Baseline WHO stage	Stage 1	71	15.5	
	Stage 2	207	45.3	
	Stage 3	165	36.1	
	Stage 4	14	3.1	
Baseline CD4 cell count (cells/mm <sup>3</sup> )				267.4
Duration on ART (months)				39.6
Average adherence to ART	Good (>95%)	386	84.5	
	Fair (85-95%)	46	10.1	
	Poor (<85%)	25	5.5	
Previous history of TB	Yes	81	17.7	
	No	354	77.5	
	Don't know	22	4.8	
Active TB while on ART	Yes	13	2.8	
	No	444	97.2	

Table 2: Frequency distribution of active TB patients by demographic and clinical characteristics

Variable	Active TB cases	Yes n (%)	No n (%)	p value		
Gender	Male	3 (23.1)	123 (27.6)	0.71		
	Female	10 (76.9)	321 (72.4)			
Marital status	Single	2 (15.4)	47	0.84		
	Married	10 (76.9)	359			
	Widowed	1 (7.7)	24			
	Divorced/seperated	0	14			
Occupation	Unemployed	6 (46)	240	0.67		
	Civil servants	2 (15.4)	75			
	Farmer	0	35			
	Trader	1 (7.7)	31			
	Artisans	1 (7.7)	20			
	Business	2 (15.4)	24			
	Others	1 (7.7)	19			
	Baseline who stage	Stage 1	0		71	0.17
		Stage 2	5 (38.5)		202	
Stage 3		8 (61.5)	157			
Stage 4		0	14			
Baseline CD4 cell count (cells/mm <sup>3</sup> )	1-200	7 (53.8)	178	0.26		
	201-350	6 (46.2)	166			
	351-500	0	0			
	501-1500	57	49			
ART regimen	First line	9 (69.2)	382	0.06		
	Second line	4 (30.8)	56			
Total duration on ART (months)	7-12	0	2	0.35		
	13-24	0	3			
	25-60	1 (7.7)	92			
	61-120	3 (23.1)	167			
	121-205	9 (69.2)	180			
	Average adherence to ART.	Good (>95%)	12 (92.3)		374	0.64
	Fair (85-95%)	1 (7.7)	45			
	Poor (<85%)	0	25			
Previous history of TB	Yes	5 (38.5)	74	0.11		
	No	7 (53.5)	344			
	Don't know	1 (7.7)	20			

had higher prevalence rates between 12%-34% (18, 19, 21-23). These findings show that the longer the patients are on ART, the less likely they are to develop active TB. This further buttress the need for early initiation of ART in HIV infected patients as a means to controlling the TB epidemic and reducing the morbidity and mortality associated with HIV in Nigeria and other countries with high burden of TB and HIV (6-8).

Although there was no significant association between gender and development of active TB in this study, more females than males had active TB. This finding is similar to other studies from Ethiopia that reported more females than males developing active TB (19-22). However, our finding is in contrast with the report from Tanzania where the male gender was found to be more frequently associated with active TB among HIV patients (16). Our findings may not be unconnected to the fact that

majority of the study participants (72%) were females and this is in line with many previous studies involving HIV infected patients which shows they are dominated by the female gender (1-4). The finding of more married patients having active TB in this study is in contrast with a study that reported single (unmarried) patients to be more likely to develop active TB while on ART (19, 21). This finding may be due to the majority of our study population being married (81%). The finding of more unemployed patients having active TB is also similar to studies that reported a higher TB prevalence in HIV population from low social class (17).

While our finding that active TB is more likely to occur in HIV patients with baseline WHO stage 2 or 3, those with baseline CD4 cell count less than 350 cells/mm<sup>3</sup> and those on first line Tenofovir based regimen, is similar to findings of other studies (14, 16, 17, 21, 22). It is worth

noting that we found no significant association between these factors and the development of active TB after 6 months of being on ART. Our study found that 69.2% of those who developed active TB had been on ART for more than 10 years and 92.3% had been on ART for more than 5 years. Most of these patients were initiated on ART late when their CD4 cell count was less than 350 cells/mm<sup>3</sup> in line with guidelines at that time.

This finding substantiates those from other studies that early initiation of ART can reduce the prevalence of TB in those living with HIV (14, 18, 19). Those who have remained on the same ART regimen for 5 – 10 years are likely to develop HIV drug resistance with possible risk of developing TB. This again is a further indication that early ART initiation and proper monitoring for development of drug resistance and appropriate change of ART regimen when there is resistance will go a long way in reducing the prevalence of TB in HIV patients.

## Conclusions:

Our study has established that people living with HIV who are on antiretroviral therapy can develop active tuberculosis in the course of their treatment. None of the factors examined was significantly associated. The morbidity and mortality associated with TB in HIV patients presents the health workers the challenge of proper and regular screening for TB especially in those with low baseline CD4 cell counts and those presenting in late stages. We recommend early initiation of ART as well as proper routine monitoring of the immune status of all people living with HIV as well as routine monitoring for ART resistance in those who have been on ART for more than 5 to 10 years.

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## Conflicts of interest:

No conflict of interest is declared

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