

Risk Factors for Tuberculosis in HIV-Infected Patients on Combination Antiretroviral Therapy in General Hospital, Lafiagi, Kwara State, Nigeria

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ABSTRACT

Background: Tuberculosis (TB) leads to substantial morbidity and mortality in human immunodeficiency virus (HIV) positive people in Africa. During the period of combination antiretroviral (cARV) drugs, plummeting TB burden globally is of utmost importance to human health. **Aim:** This study established issues related to the incidence of TB among patients on cARV drugs. **Subjects and Methods:** A cross-sectional study of two hundred and thirty HIV-positive patients on cARV ranging from one to seven years in General Hospital, Lafiagi was carried out. Clinical symptomology, GeneXpert and Sputum Smear Microscopy tests were performed to make a diagnosis of patients with TB. Logistic regression analysis was exploited to outline issues related to the incidence of TB. Results: Two hundred (87 %) were women. The incidence of TB was 4.8 % (11) and only pulmonary TB was discovered. The rate of co-infection was significantly lesser in females, (4.0 %) than males, (10.0 %). Patients with CD4 counts under 200 cells/ml, had a greater co-infection rate (14.3%) and problem of co-infection (63.6 %) than patients with CD4 counts larger than 200 cells/ml (2.2 %, 36.4 % respectively). The highest risk factor linked with the incidence of TB in these patients was inappropriate adherence to cARV drugs (OR=7.32, 11.012-23.678; 95 % confidence interval). Others included low CD₄ count (OR=4.90, 1.431-11.302; 95 % confidence interval), advanced WHO clinical stage (OR=3.11, 0.231-0.611; 95 % confidence interval), Low Body Mass Index (OR=2.33, 1.2711-9.2021; 95 % confidence interval) and gender (OR=1.22, 0.1444-1.1933; 95 % confidence interval). Age of the patients had the lowermost effect on the co-infection (OR=0.70, 3.3321-1.2423; 95% confidence interval). Conclusion: Factors associated with the incidence of TB were inappropriate adherence to cARV drugs, advanced WHO clinical stage, age, gender and malnutrition. More studies are necessary to identify the incidence of TB amongst HIV positive patients to decrease the threat.

Keywords: Human Immunodeficiency Virus, Tuberculosis, Combination antiretroviral therapy, General Hospital, Lafiagi, Nigeria

INTRODUCTION

Mycobacterium tuberculosis (TB) disease is triggered by bacteria in the air. TB can arise at any time in the course of human immunodeficiency virus (HIV) infection, however, most frequently when CD4 counts are at a low level. The association of HIV and TB pandemics persist to exact major morbidity and mortality globally (Mohajan, 2015). Universally, tuberculosis is the commonest severe opportunistic infection in people living with HIV. The World Health Organization (WHO) showed that 8.7 million people acquired tuberculosis in 2011; 1.1 million of them were co-infected with HIV (WHO, 2012). In 2015, Nigeria had the highest TB burden in Africa and second highest HIV burden worldwide (NACA, 2015; UNAIDS, 2015). In spite of the advantages of combination antiretroviral therapy (cART), TB is the

most prominent reason for mortality among human immunodeficiency virus (HIV)-infected people in Africa (Chang et al., 2015). In accordance with WHO and Nigerian clinical guidelines, adolescents and adults showing for HIV care must be tested for symptoms of TB at first and afterward with the clinical algorithm of a four-symptom test. Patients with dormant TB need to be offered Isoniazid Preventative Therapy (IPT) to avoid future stimulation of latent infection, whereas a positive TB screen would promote potential diagnostic workup (FMOH, 2008, WHO, 2011).

The incidence of TB among patients who were infected with human immunodeficiency virus accelerated from 2.2 % to 19.1 % and then 25 % in the years 1991, 2001 2010 respectively which proposes

that state of Tuberculosis is intensely HIV-driven (Roetzindu et al., 2016). A survey performed in Abidjan by Seyler et al (2005) reported 19.4 % of TB in HIV patients which are adults. In addition, Gjergj et al. (2017) stated high rate of 32.2 % cases of TB among HIV patients in Albania. Iroetzindu et al. 2015 in Nigeria observed the incidence of active TB in HIV subjects as 7.7 % while Anelies et al., 2011 in South Africa recorded prevalence rate of 6.6 %.

Attempts have been progressively made to address this double burden of disease by collaborative HIV/TB programs, as defined in WHO policy and guidelines (WHO, 2012). Significant interventions suggested to diminish the TB burden among patients Living with HIV comprised isoniazid preventative therapy, intensified TB case-finding and treatment, early combination antiretroviral therapy (cART) initiation and TB infection control (FMOH, 2008, WHO, 2011, Howard et al., 2012).

On the basis of aforementioned concerns, it is necessary to review the incidence of TB in HIV positive patients on Combination Antiretroviral Therapy in the society. Therefore, the objectives of the research were to determine the incidence rate of TB and to recognize risk factors related to TB among patients on combination ART.

Subjects and Methods

Study site

This research was performed in the Comprehensive Human Immunodeficiency Virus (HIV) Centre of General Hospital (GH), Lafiagi. General Hospital Lafiagi, a government-owned Secondary Healthcare Facility in Edu Local Government Area of Kwara State, Nigeria, was established in 1973. The healthcare facility delivers medical services to the people of Kwara, Nasarawa, Niger and suburbs. The Comprehensive HIV Centre commenced services in the hospital in 2009 by Friends for Global Health (FGH) while Management Science for Health (MSH) took over the centre in 2013. These American based Non-Governmental Organizations made available to the patients free antiretroviral, anti-tuberculosis and other opportunistic infectious drugs, free laboratory test reagents and equipment, and employment of supportive staff. As at 17th October 2017, nine hundred and forty HIV infected patients are receiving care for HIV infection in the facility, of which five hundred and seventy-five were on combination antiretroviral therapy (cART).

Study Design

In the centre of study, all the patients who have been infected with human immunodeficiency virus are tested for TB on routine basis, based on clinical *symptomatology*, Sputum Smear Microscopy and

geneXpert technology test before initiation of cART.

Sample size determination

Using a single population proportion formula as reported by Moges and Kassa, 2014, a sample size of 383 patients was obtained. In the study site, the total population of HIV positive patients on cARV drugs was 575. The desired sample size (nf) = 230, was calculated by Araoye statistical formula.

Therefore, two hundred and thirty patients were enrolled into the study. The study sample consists of 230 HIV-infected patients that enrolled and commenced combination ART between November 2010 and October 2017. The two hundred and thirty patients were made up of 200 females and 30 males, aged between 20 and 55 years, screened negative for TB before initiation of cARV drugs and who received Isoniazid Preventive Therapy for the first six months of cART. Those on cARV drugs for less than a year and patients diagnosed to have TB earlier than the initiation of cARV drugs were omitted from the study. The 230 patients enrolled in this study were further screened for TB with the diagnostic tests described above. All the patients who tested positive to Sputum Smear Microscopy were diagnosed as active TB.

Data collection process

Demographic and clinical profiles of the patients were retrieved from patients' medical folders and personal interview. Adherence level to cARV drugs was assessed by self-reporting method. In data collection method to check adherence level based on self-reporting, patients were questioned on the level of adherence to the therapy for the past thirty days. Taking 95 % of cARV drugs prescribed doses was considered as Adherence. Non-adherent patients were identified if more than 5 % of cARV drugs doses omitted (Bello et al., 2011).

Ethics Approval

Ethical approval to conduct the study was obtained from Health Ethical Research Committee of Kwara State Ministry of Health. Before patients' enrollment into the study, written and oral informed consents were collected. All the patients among whom TB was newly detected were asked for the referral to TB centre within the facility for appropriate treatment.

Statistical Analysis

With the help of using percentages & frequencies, categorical variables were then tabulated. The significance of differences between categorical variables was tested by using chi-square test. The factors linked with the prevalence of tuberculosis were evaluated by using odd ratios.

RESULTS

Table 1: Social and Clinical Variables of HIV adult Patients

Parameter	Frequency (n = 230)	Percent (%)
Gender		
Male	30	13.0
Female	200	87.0
Age (years)		
Less than 40	173	75.2
Greater/equal 40	57	24.8
Occupation		
Employed	177	77.0
Not employed	53	23.0
Religion		
Muslim	210	91.2
Christian	20	8.8
Marital Status		
Married	204	88.8
Single	26	11.2
Educational Status		
No formal education	187	81.3
Quranic	22	9.6
Primary	21	9.1
WHO Staging		
Stage I	204	88.7
Stage II & III	26	11.3
Adherence to cARV drugs		
Good adherence ($\geq 95\%$)	211	91.7
Inappropriate adherence ($< 95\%$)	19	8.3
CD₄ Count (Cells/ml)		
Less than 200	49	21.3
Greater/equal 200	181	78.7
Body Mass Index (Kg/m²)		
Less than 18.5 (underweight)	11	4.8
18.5-24.9 (Normal)	140	60.9
25.0-29.9 (Overweight)	41	17.8
Greater than 30 (Obese)	38	16.5
Combination Antiretroviral Therapy		
Zidovudine/Lamuvudine/Nevirapine containing regimen	169	73.5
Tenofovir/Lamuvudine/Efavirenz containing regimen	61	26.5
HAART duration (Years)		
1-4	77	33.4
5-8	153	66.6
Isoniazid Preventative Therapy		
Patients Received Isoniazid during cART	224	97.4
Patients Without Isoniazid during cART	6	2.6

Among the 230 patients enrolled, 87.0 % (200) were females. Majority 75.2 % (173) were less than forty years and 77 % (177) engaged in trading of indigenous rice, millet, smoked fish, groundnut cake and farming. Muslims constituted 91.2 % (210) of the patients, and very few 18.7 % (43) had Quranic and primary education. The most frequent WHO clinical stage observed in the patients was stage 1, 88.7 % (204)

followed by stage II & III with 11.3 % (26). About 78.7 % (181) patients presented with significant CD4 count which was greater than 200 cells/microliter. Most 60.9 % (140) patients had Body Mass Index (BMI) within normal range while 34.3 % (79) of the participants had abnormal BMI. About 73.5 % (169) of patients were on Zidovudine containing regimen and 26.5 % (61) on Tenofovir regimen. The duration

of cARV drugs for most of the 66.6 % (153) patients was between 5 and 8 years. Good adherence to combination antiretroviral drug was recorded in 91.7 % (211) patients. Almost all the patients 224 (97.4 %)

received Isoniazid Preventive Therapy for six months while on cARV medications (Table 1).

Table 2: Presentation of HIV/TB co-infected Patients on ARV drugs

Parameter	Frequency (n)	Percentage (%)
Type of Tuberculosis		
Pulmonary tuberculosis	11	4.8
Extrapulmonary tuberculosis	0	0
Diagnosis		
Acid Fast Bacillus	200	86.9
GeneXpert Test	30	13.1
Clinical Presentation		
Prolonged fever	30	13.2
Unintentional weight loss	47	20.3
Persistent cough	146	63.3
Night sweats	7	3.2

Out of the 230 patients enrolled into the study, 11 (4.8 %) were co-infected with TB. In those with co-infection, all 11(4.8 %) had pulmonary tuberculosis. The screening of the patients for TB was conducted through Sputum Smear Microscopy (AFB sputum)

and geneXpert. The clinical symptoms presented that were suggestive of pulmonary tuberculosis included persistent cough 146 (63.3 %), followed by unintentional weight loss 47 (20.3 %), prolonged fever 30 (13.2 %) and night sweats 7 (3.2%) (Table 2

Table 3: HIV/TB co-infection among HIV infected Patients on combination antiretroviral drugs

Parameter	Co-infection n (%)	Not Co-infected n (%)	Total n (%)	Co-infection Burden (%)	Chi-square (x ²)	P-value
Gender						
Male	3 (10.0)	27 (90.0)	30 (100.0)	27.3	0.103	0.659
Female	8 (4.0)	192 (96.0)	200 (100.0)	72.7		
WHO staging						
Stage 1	4 (2.0)	200 (98.0)	204 (100.0)	36.4	5.567	0.922
Stage 2/3	7 (26.9)	19 (73.1)	26 (100.0)	63.6		
Body Mass Index						
< 18.5	8 (72.7)	3 (27.7)	11 (100.0)	72.7	1.822	0.414
18.5-24.9	1 (0.7)	139 (99.3)	140 (100.0)	9.1		
25.0-29.9	1 (2.4)	40 (97.6)	41 (100.0)	9.1		
≥ 30.0	1 (2.6)	37 (97.4)	38 (100.0)	9.1		
CD4 Cells Count						
< 200	7 (14.3)	42 (85.7)	49 (100.0)	63.6	2.661	0.725
> 200	4 (2.2)	177 (97.8)	181 (100.0)	36.4		

Table 3 above showed that the co-infection rate was considerably lower in females, (4.0 %) than males, (10.0 %). A contrary result was obtained when the burden of the disease was evaluated (females, 72.7 % and males, 27.3 %). Both the rate and burden of co-

infection were greater in patients on HIV clinical stages 2/3, 26.9 % and 63.6 % respectively than those on stage 1 (2.0 %, 36.4 %). Patients with CD4 counts below 200 cells/ ml, had a higher co-infection rate (14.3%) and burden of co-infection (63.6%) than

patients with CD4 counts equal/greater than 200 cells/ml (2.2 %, 36.4 % respectively). As regards the BMI, patients with BMI less than 18.5 (malnourished) had higher co-infection rate (72.7 %)

and co-infection burden (72.7%) than their counterparts with BMI equal and greater than 18.5 (5.7 %, 27.3 %).

Table 4: Risk Factors in development of HIV/Tuberculosis co-infection

Parameter	Co-infection n (%)	Odd ratio	95 % Confidence Interval
Gender			
Male	3 (10.0)	1.22	0.1444-1.1933
Female	8 (4.0)		
Age (years)			
< 40	9 (9.6)	0.70	3.3321-1.2423
≥ 40	2 (8.7)		
Body Mass Index			
< 18.5-24.9	9 (73.4)	2.33	1.2711- 9.2021
> 24.9	2 (5.0)		
CD₄ Cells Count			
< 200	7 (14.3)	4.90	1.431-11.302
≥ 200	4 (2.2)		
WHO Staging			
Stage 1	4 (2.0)	3.11	0.231-0.611
Stage 2 & 3	7 (26.9)		
Adherence to cARV drugs			
Good adherence	1 (0.5)	7.32	11.012-23.678
Poor adherence	10 (52.6)		

The topmost risk factor for development of tuberculosis in these patients was inappropriate adherence to cARV drugs (OR= 7.32, 11.012-23.678; 95 % confidence interval), then low CD4 count (OR=4.90, 1.431-11.302; 95 % confidence interval), advanced WHO clinical staging (OR=3.11, 0.231-0.611; 95 % confidence interval), low Body Mass Index (malnutrition) (OR=2.33, 1.2711-9.2021; 95 % confidence interval) and gender (OR=1.22, 0.1444-1.1933; 95 % confidence interval). Age of the patients had the lowest influence on the co-infection (OR, 0.70, 3.3321-1.2423; 95 % confidence interval).

Discussion

Mortality among human immunodeficiency virus (HIV)-infected persons in Africa is known to be

expedited by the presence of tuberculosis (TB) in spite of Combination Antiretroviral Therapy (cART)'s availability,

Despite that, tuberculosis (TB) incidence among HIV-infected cohorts receiving cARV drugs is reduced by 70–90%, it remains significantly higher than among HIV-non infected patients (Lawn et al., 2005).

In this study, the incidence of TB was 4.8 %. This is similar to the incidence rate of 4.0 % found in the Harvard/APIN PEPFAR Nigeria program reported by Chang et al., 2015. However, the higher incidence rate of 7.7 % recorded by Iroezindu et al., 2013 in a study among HIV positive individuals on cART for a period of 3 years at a tertiary health facility in the South-East Nigeria, the higher rate of 12.5 % found in the study of Duru et al., 2014 conducted in Imo State University

Teaching Hospital, Nigeria on 128 HIV infected patients and 32.2% incidence of cases of TB among HIV patients in Albania by Gjergj et al., 2017 sharply contrasts with the much lower rate of 4.8% observed in the present study. The discrepancies observed in the incidence rate of TB in various studies could be attributed to differences in sample size, study design, duration on cARV drugs, type of cARV drugs, adherence level and differences in diagnostic criteria for TB.

The link of nadir cell counts for CD4 and advanced stages of human immunodeficiency virus, low BMI, inappropriate drug adherence, age and gender as risk factors for TB co-infection discovered in this study has been consistently reported in many studies; Illiyasu and babashani 2009, Ugochukwu et al., 2010; Okechukwu and Okechukwu 2011; Srirangaraj and Venkatesha 2011, Venturini et al., 2014, Duru et al., 2014 and Gjergji et al., 2017. It was observed that the risk of TB among people living with human immunodeficiency virus infection significantly elevated as the CD₄ cells count falls below two hundred cells per litre. A decline in the CD₄ cells observed in advanced HIV infection weakens patient's response to TB, therefore accelerating the progression of recent infection and inactive TB to active disease (Akaubi et al., 2013).

The burden of TB/ HIV hinged on the females than males as reported in this study. This finding negates the reports observed in the studies of Balla et al. (2016) and Gjergj et al. (2017) whereby TB/HIV co-infection predominated in the male patients. The reason for the dominance of females in TB burden in present study may be that men with tuberculosis are not recognized for cultural reason or due to factor associated with penetration into health services and healthcare system. Contrarily to the findings of this study, Srirangaraj and Venkatesha (2011) reported overcrowding and poor hygiene as contributory factors to high burden of HIV-related TB in developing countries. Furthermore, Lin et al. (2013) described that no marked association between gender and the presence of TB among the patients studied. Nearly all the patients had good adherence to cARV drugs. This is similar to the findings of Iroezindu et al., 2011 who observed that the majority were adherent to cART. Also, Annelies et al., 2011 showed that the more patients stay on cART, adherence to cART to inhibit therapy failure will become increasingly necessary in curbing TB among people on cART. The positive association between inappropriate adherence to ARV drugs and occurrence of TB as documented in this study is very important. This indicated that it is necessary to focus on factors related to patient when issues on cART non-adherence are discussed in HIV treatment centres. Furthermore, Habteyes et al., 2015 noted that the major factors

linked to TB treatment non-adherence were insufficient fund for transportation, absence of social support and poor patient-health care provider relationship. Other factors were improvement in health condition while on few weeks' treatment, lack of information on length of cART as well as consumption of alcohol. Furthermore, the study of Gjergj et al., 2017 supported this study that if the period of treatment with cART is less than or equal to one year, the TB cases would be 8.7 %, 2-4 years (34.8 %), 5-7 years (30.4 %) cases, and 8-10 years (26.1%) cases. This shows that the longer the duration on cART, the higher the cases of TB identified due to inappropriate adherence to cART. Several studies have coherently evidenced increase in TB incidence in the few months of cART (Annelies et al., 2011). The upsurge in the prevalence of TB during early phase of cART may be attributed to initial speedy restitution of the immune response (Annelies et al., 2011). Majority of the studies showed that the incidence of TB waned afterwards, but remains greater than the background TB incidence rate in the overall population, despite years of being on ART (Brinkhof et al., 2007; Lawn et al., 2009). This increased long-term TB incidence has been discovered to be markedly associated with the period at which the patients were at CD₄ count < 500 cells/ml (Annelies et al., 2011). All the patients had pulmonary tuberculosis and diagnosis was made by clinical symptomatology and laboratory studies. In general, TB infection is airborne in nature which establishes in a pulmonary manner among 70.0% of the infectious cases while and barely in the extrapulmonary fashion, particularly if there is an impairment of human as seen in progressive phases of human immunodeficiency virus disease (Walker et al., 2013). Most (86.9%) of the TB cases was detected by Acid Fast Bacillus (AFB) test. In contrary to the results from Duru et al. (2014) showed that out of all the cases, Acid- Fast Bacilli test was positive among 25.0 % cases only whereas chest x-ray for the majority of cases around 62.5 % the indicated TB, Okechukwu and Okechukwu (2011) was 22.0 % and Cohen et al. (2008) was 20.0 % diagnosed by Acid Fast Bacillus (AFB) test.

Conclusion

Factors associated with the incidence of TB were inappropriate adherence to cARV drugs, advanced WHO clinical stage, age, gender and malnutrition. More studies are necessary to identify the incidence of TB amongst HIV positive patients to decline the threat to our society.

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