Factors associated with Tuberculosis among HIV individuals receiving combination antiretroviral therapy in General Hospital, Lafiagi, Nigeria

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Abstract

Tuberculosis (TB) leads to substantial deadly consequences in Human Immunodeficiency Virus (HIV) positive people in Africa, even with the free access to combination Antiretroviral Therapy (cART). This research was conducted to assess the risk factors associated with development of TB among HIV individuals receiving cART. A cross-sectional study was investigated among 230 HIV infected patients receiving cART in HIV Centre Lafiagi, Kwara State, Nigeria. Clinical symptomatology, GeneXpert and Sputum Smear Microscopy tests were used for diagnosis of TB among HIV infected patients. Logistic regression analysis was exploited to outline factors related to incidence of TB/HIV co-infection. Of the 230 HIV subjects enrolled, only (4.8 %) had pulmonary TB. The rate of co-infection was lesser in females, (4.0 %) than males, (10.0 %). Patients with CD4 count below 200 cells/ml had a greater co-infection rate (14.3%) and burden of co-infection (63.6 %) than patients with CD4 counts larger than 200 cells/ml (2.2 % and 36.4 %, respectively). The highest risk factor linked with the incidence of TB in these patients was inappropriate adherence to cART (Odds Ratio, 7.32; 11.012-23.678, 95 % CI). Other factors were low CD4 count cells (Odds Ratio, 4.90; 1.431-11.302, 95 % CI), advanced WHO clinical stage (Odds Ratio, 3.11; 0.231-0.611, 95 % CI), low Body Mass Index (Odds Ratio, 2.33; 1.271-9.202, 95 % CI) and gender (Odds Ratio, 1.22; 0.144-1.193, 95 % CI). Inappropriate drug adherence is a major risk factor for development of TB in HIV infected patients on cART. Concerted efforts on cART adherence should be intensified to improve therapy significantly and reduce the burden of TB/HIV co-infection.

Keywords: Inappropriate adherence, GeneXpert, Microscopy tests, Body Mass Index

Introduction

A bacterium named *Mycobacterium tuberculosis* causes Tuberculosis (TB) disease. TB infection arises when someone with active TB disease sneezes or coughs and another person inhales the droplets[1]. The infectious droplets can remain in the atmosphere for many hours in moisten enclosed environment with poor ventilation or illumination, including prisons and congested areas. Majority of healthy individuals can tolerate the TB infection as it does not always lead to active TB disease. Those with TB infection with no disease cannot transfer TB. Only active TB of the tracheal is contagious[2]. In addition, a range between 5 and 15 % of the 2–3 billion TB infected individuals acquire the disease throughout their lifetime[3,4]. However, as the immunity lessens and CD4 count lowers, the *Mycobacterium tuberculosis* multiplies rapidly, resulting in active disease. Meanwhile, there are cases of extrapulmonary TB that affects the rest of the body apart from the lungs[1].

A syndemic has been described as the synergistic interaction between two or more diseases that increases the burden of the

infections. The syndemic convergence of TB/HIV epidemics had caused the greatest deaths around the world[5]. According to World Health Organization (WHO)[6], TB disease is a major severe opportunistic infection in people living with HIV in 2016 with 1million deaths globally; of which 86% are from Africa. HIV infected individuals are 21 times more prone to TB disease than those with no HIV. However, about 60% of HIV-associated TB cases were neither diagnosed nor treated, causing 370 000 TB-HIV related deaths in the world. However, there are about 10.4 million TB cases in 2015, comprising 1.2 million (11%) of HIV infected individuals. However, the association of HIV and TB pandemics declines by 33% from 2005 to 2015[7]. Nigeria was the foremost on TB burden in Africa in 2015 and ranked second worldwide[8,9]. TB occurrence ranged from 2.2 % in 1991 to 19.1% in 2001, and 25% in 2010, when the HIV infection rate increased drastically, revealing that TB is intensely HIV driven[4]. World widely, Gjergjet al[10] reported 32.2 % TB-HIV co-infection in Albania and 6.6 % was recorded in South Africa[11]. In spite of the merits of combination Antiretroviral Therapy (cART), the association of TB and HIV is still pandemic in Africa[12,13].

In accordance with WHO and Nigerian clinical guidelines, TB screening with the clinical algorithm of a four-symptom test is to be carried out spasmodically on HIV-infected adolescents and adults to promote potential diagnostic workup[14]. Also, patients with dormant TB need to be offered Isoniazid Preventive Therapy (IPT) to avoid future stimulation of latent infection[14,15]. However, attempts had been progressively made to address this double burden disease by the collaborative TB/HIV programs, as defined in WHO policy and guidelines[16]. Significant health interventions that can reduce the TB eclipsed HIV is the use of IPT, strengthened TB case-finding and treatment, and early cART initiation with TB control[14,15,17]. On the basis of aforementioned concerns, it is necessary to understand the risk factors over time among TB/HIV co-infected clients on cART. This research was conducted to assess the risk factors of TB-associated with HIV infection among individuals receiving cART for the possibility of designing effective preventive and control strategies.

Subjects and Methods

Study site

This research was performed at the Comprehensive Human Immunodeficiency Virus (HIV) Centre of the General Hospital, Lafiagi. The Hospital is a government-owned Secondary Healthcare Facility in Edu Local Government Area of Kwara State, Nigeria and was established in 1973. The Centre delivers medical services to the people of Kwara, Nasarawa, Niger States and suburbs. The Centre commenced services in 2009 by Friends for Global Health and thereafter a Management Science for Health took over the Centre in 2013. Both are American based Non-Governmental Organizations which offered cART, anti-TB and other opportunistic infections drugs free of charge including free sputum microscopy, HIV, and GeneXpert tests. They equally recruited supportive staff in the Centre at no cost to the hospital. As at 17th October, 2017, nine hundred and forty (940) HIV infected patients were receiving care of which five hundred and seventy-five (575) were on cART.

Study design

This is a prospective and retrospective cross-sectional study.

Sample size determination

Using a single population proportion formula as reported by Moges and Kassa[18], a sample size of 383 patients was obtained. In the studied hospital, a total population of HIV positive patients on cART was 575. A convenient sample size of 230 HIV-infected patients that enrolled and commenced cART between November 2010 and October 2017 were studied.

Inclusion criteria

Patients included in the study were males and females, aged between 20 and 55 years. Those screened negative for TB before initiation of cART and patients who received Isoniazid Preventive Therapy (IPT) for the first six months of cART were also included.

Exclusion criteria
Patients on cART for less than a year and those diagnosed with TB before the commencement of cART were excluded from the study. Also, excluded were those patients with cancer, renal failure, diabetes mellitus and malnutrition.

Data collection process
Information on demographic parameters, WHO clinical staging, CD4 cells count and use of IPT were retrieved from patients' medical folders and through personal interview with the patients. Clinical profiles such as height, weight, TB diagnosis and patients' adherence to cART were assessed by standard procedures.The 230 HIVinfected patients enrolled into this study were screened for TB based on Clinical Symptomatology, Sputum Smear Microscopy, and GeneXpert technology tests. Those patients who tested positive to Sputum Smear Microscopy were diagnosed as having active TB.

Diagnosis of Tuberculosis
All the patients enrolled into HIV care and at cART commencement, underwent TB testing with acid-fast bacilli (AFB) sputum smear microscopy, which required collection of 3 sputum specimens over two consecutive days as previously described by Chang et al[12]. GeneXpert is nucleic acid amplification test that identify *Mycobacterium tuberculosis* DNA. The test is useful in diagnosis of TB in patients that are missed by conventional tests[19].TB diagnosis was made by symptom assessment such as persistent cough, night sweats, weight loss, fever, and history of contact with a person with chronic cough. At all clinic visits, patients were routinely clinically screened for TB, and those with symptoms suggestive of TB were tested with sputum AFB microscopy as previously described by Chang et al[12]. All AFB smear positive cases were diagnosed as active TB based on Nigerian National TB management guideline whereby sputum mycobacterial culture is highly prioritized[20].

Height and weight measurements
The weights and heights of the patients were evaluated while standing on a calibrated Dual weight and height measuring scale. The Body Mass Index (BMI) of the subjects was computed as the weight in kilogrammes divided by the height in metre squared. The values of BMI for the patients were grouped into four classes: Underweight/thin (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9kg/m^2), over weight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥ 30kg/m^2)[21].

Adherence measurement
Adherence to cART was assessed by self-reporting method. The patients were interviewed on adherence level over the last thirty days. Adherence was defined as taking 95 % of the prescribed doses of combination Antiretroviral (cARV) drugs. Non-adherent patients were identified if more than 5 % of cARV drugs doses omitted[22].

Ethics approval
Ethical approval to conduct the study was obtained from the Department of Planning, Research and Statistics of Kwara State Ministry of Health, Ilorin, Nigeria. Before patients' enrollment into the study, written and oral informed consents were collected. All patients newly diagnosed with TB were referred to the TB Centre within the facility for appropriate treatment.

Statistical analysis
The data collected were analyzed with the Statistical Application Software (SAS) program version 9.2[23]. Frequency and percentage were used as descriptive analysis. Inferential statistics such as chi-square and logistic regression were exploited for analysis. P-value of 0.05% was considered significant. The confidence interval was at 95% for all the statistical tests.

Results
Of the 230 TB/HIV positive subjects enrolled, 87.0 % (200) were females (Table 1). Majority 75.2 % (173) were less than forty years of age and 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 among the patients was stage 1 with 88.7 % (204), followed by stage 2 with 7.8 % (18). One hundred and eighty-one (78.7 %) of the patients had the CD4 counts greater than 200 cells/ml. Most 60.9 % (140) patients had Body Mass Index (BMI) within normal range while

34.3 % (79) had abnormal BMI. About three quarters (169) of patients were on Zidovudine containing regimen and 26.5 % (61) on Tenofovir regimen. The duration of cART for most of the patients 66.2 % (153) was between 5 and 7 years. Good adherence to cART was obtained in 35.2 % (81) patients. All the patients 230 (100.0 %) received IPT for six months while on cART.

Table 1: Social and Clinical variables of Hiv-infected Patients on cart

Parameter	Frequency (n = 230)	Percentage (%)
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 1	204	88.7
Stage 2	18	7.8
Stage 3	8	3.5
Adherence to cART		
Good adherence (≥ 95 %)	81	35.2
Inappropriate adherence (< 95 %)	149	64.8
CD4 Count (cells/ml^3)		
Less than 200	49	21.3
Greater/equal 200	181	78.7
Body Mass Index (Kg/m^2)		
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
5-7	153	66.6
Isoniazid Preventive Therapy (IPT)		
Patients Received Isoniazid during cART	230	100.0

Out of the 230 patients enrolled into the study, 11 (4.8 %) were co-infected with pulmonary TB (Table 2). The clinical symptoms presented that were suggestive of pulmonary TB include a persistent cough 146 (63.3 %), followed by unintentional weight loss 47 (20.3 %), prolonged fever 30 (13.2 %) and night sweat 7 (3.2 %).

Table 2: Presentation of TB / Hiv Co-infected Patients on Cart

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 sweat	7	3. 2

In table 3, the TB/HIV co-infection was considerably lower (4.0%) in females than males (10.0%). For the burden of the disease, females had 72.7% while males possessed 27.3%. TB/ HIV synergistic rate and burden were higher in patients on HIV clinical stage 3, 26.9% and 63.6% respectively than those on stage 1 (2.0% and 36.4%). Patients with CD4 counts below 200 cells/ml not only had a higher co-infection rate (14.3%) but also the burden of co-infection (63.6%) than patients with CD4counts equal or greater than 200 cells per 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 burden (72.7%) than their counterparts with BMI equal or greater than 18.5 (5.7%, 27.3%).

Table 3: TB / HIV Co-infection among HIV infected Patients on Cart

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 and 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		
18.5-24.9	1 (0.7)	139 (99.3)	140 (100.0)	9.1	1.822	0.414
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		
CD4Cells 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		

The topmost risk factor for the development of TB in these patients was inappropriate adherence to cART (OR= 7.32, 11.012-23.678; 95 % confidence interval), followed by 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) (Table 4). However, age of the patients had the lowest influence on the co-infection (OR, 0.70, 3.3321-1.2423; 95 % confidence interval).

Table 4: Regression analysis of Risk Factors in TB / HIV
Co-infected Patients

Variable	Co-infection (%)	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 3	7 (26.9)		
Adherence to cARV drugs			
Good adherence	1 (0.5)	7.32	11.012-23.678
Poor adherence	10 (52.6)		

DISCUSSION

This study showed that TB/HIV co-infected clients were below 40 years as earlier reported by several researchers[24-27]. The incidence of TB among HIV infected patients studied was low (4.8 %). This study is similar to 4.0 % found in the Harvard/APIN PEPFAR Nigeria program by Chang et al[12] and 7.7 % by Iroezindu et al[28] among HIV positive individuals on cART at a tertiary health facility in the South-East Nigeria. Contrarily, a rate of 12.5 % was found in the study of Duru et al[29] in Imo State University Teaching Hospital, Nigeria, 27.1% out of 155 HIV patients on cART by Veneranda et al[30]in Tanzania and 32.2 % detected in Albania by Gjergj et al[10]. The discrepancies observed in the incidence rates of TB in various studies could be attributed to differences in the sample size, study design, duration on cART, type of cART, level of ART adherence and diagnostic criteria for TB.

The association of CD4 cell counts, advanced stage of HIV, low BMI, inappropriate drug adherence, age and gender as risk factors for TB in HIV infected clients obtained in this study have been consistently reported by previous researchers[31-35]. It has been accentuated that the risk for TB, in people living with HIV infection markedly elevated as the CD4 cells count falls below 200 cells per ml[10]. Also, a decline in CD4 cells weakened patient's response to TB in advanced HIV infection. This, therefore, accelerated the progression from inactive TB to active one[36].

The burden of TB/HIV co-infection affected the females than the males in this study. This finding negates the report of Balla et al[37] and Gjergj et al[10] who reported that TB/HIV dominate among the male patients. The reason for the dominance of females in TB burden in the present study may be that men with TB are not recognized for cultural reasons or due to the factor associated with penetration into healthcare services. Also, contrary to the present findings, Srirangaraj and Venkatesha[34]observed overcrowding and poor hygiene as the contributory factors to the high burden of HIV-related TB in developing countries and Lin et al[38] reported no marked association between gender and TB disease. About two-thirds of the patients had inappropriate adherence to cART in this study. This is not in line with the findings of Isa et al[39] who reported that majority of the patients adhered to cART in Nigeria. The positive association between inappropriate adherence to cARV drugs and occurrence of TB as documented in this study is very important.

TB is an airborne infection that establishes in its pulmonary manner in up to 70.0 % of cases, and hardly in extrapulmonary form, particularly if the immune system is impaired in the progressive phases of HIV disease[1]. The deferral of treatment initiation could cause greater mortality in TB/HIV co-infected individuals. In the current study, most (86.9%) of the TB cases were detected by Acid-Fast Bacillus (AFB) test. Contrariwise, the findings of Duru et al[29] revealed 25.0% of TB cases

with the use of AFB test and most of the cases had chest X-ray suggestive of TB of 62.5%. In addition, Okechukwu and Okechukwu[33] reported 22.0 % and Cohen et al[40] obtained 20.0% diagnosed TB by AFB test. Also, a contrary report of Annelies et al[11] showed an increase in TB incidence in the early months of cART among HIV positive patients. The authors suggested that the upsurge of TB during the early phase of cART may be attributed to initial speedy restitution of the immune response. Meanwhile, this study established that most of the patients involved in this study were on cART for a longer duration of five to seven years. In support of this study, Gjergj et al[10] revealed that when the period of treatment with cART was less than or equal to one year, the TB cases obtained was 7.7%, 8.7% cases in 2-4 years, 34.8% in 5-7 years, and 26.1% cases in 8-10 years. This indicated that the longer a patient stays on cART, the higher the cases of TB identified due to drug fatigue leading to inappropriate adherence to cART. Majority of current researchers observed a decline in TB cases; nonetheless, TB still remained a very high burden despite years of being on cART[41,42]. Lawn and Wood[43] suggested that concurrent treatment of TB and HIV is complicated by the risk of immune reconstitution inflammatory syndrome, overlapping toxicities, poor adherence from high pill burden and drug-drug interactions.

CONCLUSION

The incidence of TB/HIV co-infection was low in this study and was related to the age group below 40 years. The most significant risk factor associated with the incidence of TB was inappropriate adherence to cART. For effective treatment strategy design, emphasis on ARV drug adherence should be intensified to reduce the burden of TB/HIV co-infection. Advance stage of HIV infection is a significant risk factor in HIV patients, thus a timely institution of cART could improve effective response to TB/HIV co-infection.

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