Two Year Review of Tuberculosis Preventive Therapy in HIV Clients Accessing Antiretroviral Therapy in A Tertiary Hospital, North -West Nigeria

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ABSTRACT

Background:
Tuberculosis (TB) is responsible for a considerable number of human immunodeficiency virus (HIV) related deaths. Recent inclusion of isoniazid, as one of the preventive therapies in HIV management, is one of the public health interventions for the prevention of TB among People Living with HIV (PLHIV). In Nigeria, the programme implementation has not been optimal. The objective of this study is to assess the effectiveness of tuberculosis preventive therapy (TPT) and review the incidence of TB among PLHIV.

Methods:
A retrospective cohort study of clients who assessed TPT in 2015 was conducted in a tertiary hospital, Kaduna, Northwest Nigeria. The clients were followed for a period of two (2) consecutive years, 2016-2018. Data was analysed using IBM SPSS version 23.0.

Results:
A total of 376 clients were enrolled, 259 (68.9%) were females while 117(31.1%) were male, 257 (76.9%) were married. There were 8 cases of TB with 2.13 per 100 person-years (PY).
There were statistically significant increases in mean CD4+ cell count, weight and haemoglobin. Bivariate analysis showed no significant association between age, sex, marital status, religion and development of TB. Multivariate logistic regression showed completion of TPT significantly reduced risk of developing TB (p= 0.000). (AOR 16.48, 95% CI = 4.85 – 56.01).

Conclusion:
TPT use and completion in PLHIV significantly reduced risk of TB over a 2-year period. All efforts should be made to ensure its availability, usage and adherence in these individuals.

Keywords: Tuberculosis, human immunodeficiency virus, highly active antiretroviral therapy, tuberculosis preventive therapy

INTRODUCTION

Tuberculosis (TB), a major public health problem, is responsible for a considerable number of human immunodeficiency virus (HIV) related deaths.[1] In the world health organisation (WHO) report of 2019, Nigeria ranks among the countries with a high burden of TB and co-infection with HIV with an incidence rate of 27/100,000 for TB/HIV.[2] HIV is the strongest risk factor for developing TB disease among those infected with *mycobacterium tuberculosis* (MTB). The risk of developing TB is 20 to 37 times greater in people living with HIV (PLHIV) than among those who do not have HIV infection.[3] In 2019, despite the global reduction in the incidence of TB, about 10 million people developed TB, it caused 1.4 million deaths out of which 208 000 were PLHIV.[1] Also, among 10.4 million new TB cases in 2015, HIV co-disease was highest in sub-Saharan Africa.[1]

If not adequately addressed, TB has the potential to undermine the great strides made globally in rapidly expanding HIV care and treatment.[4] Therefore prevention of TB is one of the most important measures needed to reduce morbidity and mortality among PLHIV, especially in countries with a high TB and HIV burden.[5] Multiple strategies are available for preventing TB disease in these high risk group including early initiation of highly active antiretroviral therapy (HAART) being the most effective TB prevention intervention among PLHIV.[6] The WHO, as part of the plans to reduce the TB/HIV burden, issued guidelines including the implementation of the 'Three I's' (infection control, Tuberculosis Preventive therapy [TPT] and intensified TB case finding [ICF]) and ART in PLHIV.[7,8,9] In 2011, the ICF/TPT guidelines added a symptom based algorithm screening for TB which is sufficient to start TPT for PLHIV; also noted that chest xray (CXR) and tuberculin skin test (TST) were not mandatory for commencement of TPT.[10]

Gupta et al in their study suggested that despite the dramatic reduction in TB risk among PLHIV on long-term ART, this risk remains several times higher than the risk of TB among persons without HIV infection living in the same communities.[11] This further highlights the importance of including other adjunctive strategies such as TPT in the management of clients.[11]

The effectiveness of INH in the treatment and prevention of TB were demonstrated as early as in the late 1950s and early 1960s,[12] earliest among immunocompetent adults demonstrating up to 90% protection from TB using a 6 to 12 month course of INH.[13,14] Evidence of same benefit in PLHIV started in early 1990s and it is also now a cornerstone of the WHO End TB strategy among high risk group.[7] Several other studies have demonstrated various levels of effectiveness of TPT more so in combination with HAART in PLHIV.[5,15,16,17,18] Despite the existing WHO recommendations, implementation of TPT remains sub-optimal, with various uptakes levels in newly enrolled clients in different counties especially in resource poor countries.[19,20,21] Even where TPT programs were implemented, completion rates ranged between 36%-98%.[5]

This study therefore aimed to evaluate the effectiveness of TPT in our clients in preventing TB disease over a 2-year

period and assessing its completion rate and other possible outcomes. This will enhance its cascade in the national roll-outs programmes, program planning and implementation in Nigeria and other high TB/HIV burden countries.

METHODOLOGY

This was a retrospective study in a tertiary facility in Kaduna state, North-western Nigeria, that offers general out-patient, specialised medical services and referral services to more than the six (6) million people of the state. It also has a special clinic that offers HIV care and follow up services.

The study involved HIV infected clients who were 18years and above, enrolled and accessing HAARTs and TPT care in 2015 in the facility. Most of the clients were on the tenofovir/lamivudine/efavirenz combination regimen for HAART and were commenced on TPT (300mg oral isoniazid daily for six months) after symptom screening was done. Any client that was considered to have presumptive TB then had further investigations including GenXpert and chest x-ray to exclude TB. Iif results were negative, the patient was then commenced on TPT. They were followed up during the period 2016-2018 for possible occurrence of active TB. The disease diagnosis was based on the national guidelines for clinical management of TB.[22] Criteria included positive GenXpert test, radiological abnormalities consistent with active TB, decision by a clinician to treat with full course of anti-TB chemotherapy or a smear positive TB. Extrapulmonary TB diagnosis was based on histological or strong clinical evidence consistent with active extra pulmonary TB. Pulmonary and extrapulmonary TB were included in this analysis. Clients below 18years, a past history of TB diagnosis or patients currently on TB medications were excluded from the study. Important data related to socio-demographic characteristics age, sex, and marital status, clinical, laboratory and TPT information, WHO staging, CD4+ cell count, weight, haemoglobin and functional status were extracted using a structured questionnaire and entered into the computer for both descriptive and inferential analysis using the IBM SPSS Statistics for Windows, Version 23.0. The student t-test, chi-square, bivariate and multivariate regression analysis were used for inferential analysis and level of statistical significance was set at $p<0.05$.

The study was approved by the ethical committee of the xyz hospital. Clients' information was stored anonymously and kept confidentially. Furthermore, personal identification was excluded from the data collected.

RESULTS

A total of 376 clients were enrolled for the study. As shown in table 1, 259 (68.9%) were females ; 257 (76.9%) were married a; 359 (95.5%) were between the ages of 21 to 60years of which 256 (68.1%) were in the 21-40years age group. Most were in WHO clinical stages I (156; 41.5%) and III (118; 31.4%). In table 2, 11(2.9%) of the clients were lost to follow, 17 (4.5%) died and there were 8 cases of TB during this study period with an overall incidence of 2.13 per 100 person-years (PY). 327 (87.0%) completed TPT but 49 (13.0%) discontinued treatment. Of those who

discontinued, reasons for this were not documented in 25 (51%) and only 4 (8.2%) was due to side effects though 2 other clients had mild reactions but still completed the treatment. The commonest side effect was dermatitis. Also, 3 (6.1%) developed active TB and had to be discontinued.

Table 3 shows the median CD4+ cell count at start of TPT was 394.0 cell/µl (IQR 228.0 - 571.3) with a mean of 437.8 cell/µl while at the end was 457.0 cells/µl (IQR 317.5 – 645.0) with mean of 507.0 cells/µl (p-value <0.005). Also, there were significant improvements in the pre-treatment and post- treatment means of their weights and haemoglobin levels.

In the bivariate analysis shown in table 5, there was no significant association between age, sex, marital status and religion on development of TB (p > 0.05). Multivariate logistic regression in table 6 also showed that completion of TPT was significantly associated preventing full blown TB, (p= 0.000, AOR 16.48, 95% CI = 4.85 – 56.01).

Table 1: Demographics of the study participants in TPT follow up in Kaduna (N = 376)

Variables	**Number (%)**
AGE (Years)	
≤ 20	3 (0.8)
21 - 40	256 (68.1)
41 - 60	103 (27.4)
≥ 61	14 (3.7)
Mean age (±SD)	37.3 (± 10.9)
SEX	
Male	117 (31.1)
Female	259 (68.9)
MARITAL STATUS	
Single	56 (16.8)
Married	257 (76.9)
Widowed/Divorced/separated	21 (6.3)
WHO stage	
I	156 (41.5)
II	90 (23.9)
III	118 (31.4)
IV	9 (2.4)
Not classified	3 (0.8)

Table 2: Completion of TPT and outcome of clients in Kaduna (2018)

Completion of TPT	No (%)
Yes	327 (87.0)
No	49 (13.0)
Outcome	
Lost to follow up	11 (2.9)
Died	17 (4.5)
Developed TB	8 (2.1)
No TB	337 (89.6)
Started anti-koch during TPT	3 (0.8)
Overall incidence of TB 2.13 per 100 person-year	

Table 3: Clinical and laboratory characteristic and follow up outcome in Kaduna (2018)

Variables (Unit)	Start of TPT (No)	End of TPT (No)	p value (t-test)
Haemoglobin (g/dl)	11.7 (IQR 10.6 – 12.8)	12.1 (IQR 11.1- 13.3)	0.000
Cd4+ Cell Count (Cells/µl)	394.0(IQR 228.0 - 571.3)	457.0(IQR 317.5 – 645.0)	0.000
Weight (Kg)	63.0 (IQR 55.0 – 75.0)	66.0 (IQR 58.0 – 75.0)	0.000

Table 4: Causes of non- completion of TPT among clients in Kaduna (N= 49)

Reasons for non- completion	No (%)
Side effects	4 (8.2)
Defaulted	9 (18.4)
Died	8 (16.3)
Not documented	25 (51.0)
Start Anti TB	3 (6.1)
Total	49 (100)

Table 5: Bivariate analysis of predictor variables of TB among clients in Kaduna (2018)

	Developed Tuberculosis		χ^2	
Variables	No (%)	Yes (%)		P-value
Age				
≤40	253 (97.7)	6 (2.3)	3.192	0.122
>40	115 (98.3)	2 (1.7)		
Sex				
Male	115 (98.3)	2 (1.7)	3.353	0.311
Female	253 (97.7)	6 (2.3)		
Marital status				
Married	251 (97.7)	6 (2.3)	3.125	0.530
Single	75 (97.4)	2 (2.6)		
Religion				
Christianity	197 (97.5)	5 (2.5)	1.656	0.329
Islam	134 (97.8)	3 (2.2)		
Completed TPT				
Yes	322 (98.5)	5(1.5)	33.697	0.000
No	46 (93.9)	3 (6.1)		

Table 6: Multivariate logistic analysis of predictor variables of TB among clients in Kaduna (2018)

	Developed Tuberculosis		Adjusted	95% confidence	
Variables	No	Yes	odds ratio	interval	p-value
Age					
≤40	253 (97.7)	6 (2.3)	0.436	0.113-1.630	0.228
>40	115 (98.3)	2 (1.7)	Ref		
Sex					
Male	115 (98.3)	2 (1.7)	1.975	0.512 – 7.620	0.323
Female	253 (97.7)	6 (2.3)	Ref		
Marital status					
Married	251 (97.7)	6 (2.3)	3.344	0.392 – 28.547	0.270
Single	75 (97.4)	2 (2.6)	Ref		
Religion					
Christianity	197 (97.5)	5 (2.5)	2.81	0.686 - 11.519	0.151
Islam	134 (97.8)	3 (2.2)	Ref		

Completed TPT					
Yes	322 (98.5)	5(1.5)	16.48	4.85 -56.01	0.000
No	46 (93.9)	3 (6.1)	Ref		

DISCUSSION

Most of the clients (68.9%) were females and about 256 (68.1%) in the economically productive age group as also described by several authors.[2,19, 23] The overall incidence of tuberculosis was 2.13 per 100 person-years (PY) in the entire follow-up period. This result was consistent with study done in Brazil with TB incidence of 2.28 per 100PY.[6] other incidences recorded by different authors like in Ethiopia showed 3.76 incidence though their sample included all age groups.[24] However, a cohort study in Thailand showed benefits of TPT and ART only in the first 6 months of care.[25] The disparity might be explained by limiting the scope of study to pulmonary TB.[22] The relatively low incidence in our study might be attributed to the prevention of progression of latent infection to active disease or reduction in rate of acquiring a new infection by the TPT. It may also be due to improved immune constitution of the clients as evidenced by the significant increase in their mean CD4 count at the end of the study period and increase in mean weight. This will also mean improved wellbeing. Risk of developing TB is known to be high when the immune status of the individual is compromised consistent with cohort studies that show gradual increase of the risk of TB when CD4+ cell count falls.[18,22]

This study showed that TPT offers a long-term risk reduction to the clients against tuberculosis during the follow up period. It has been documented that the use of TPT during ART care shows higher decrease in cumulative risk and TB-free survival time of TB in HIV-infected clients.[26,27] It was also in agreement with other studies conducted in Namibia, Brazil and Ethiopia[18,28,29] Churchyard et al also in South Africa also noted that giving TPT with HAART for 12 months reduced TB incidence by 37% compared with ART alone in HIV clients.[30]

About 65% of our clients were in the WHO clinical stages of I and II with better immune status which will also mean a lower risk of developing TB more so if initiated on TPT. The result agreed with study conducted in South Africa and Ethiopia.[7,18,31] This may be due to the fact that HIV weakens the immune system in more advance stages and lead to more opportunistic infections.

It was noted that the completion rate was as high as 87% and only 1.6% had side effects indicating good tolerance of the therapy as also noted by Churchyard.[29]

This is one of the few studies in Northwest Nigeria that explored association of TPT provision with the development of TB in clients undergoing care but was limited by some undocumented cases and missing records. Similarly, clients who were lost to follow-up and especially those who died could not be accounted for as not to have developed TB since advanced stage of the HIV disease puts them at greater risk for TB.

CONCLUSION

This study showed that completion of TPT confers a significant reduction in TB

incidence among HIV infected clients and adjustment for potential confounder did not alter the estimate of its effectiveness. Efforts should be strengthened in implementing the widespread provision and use of TPT among adult HIV-infected clients and the integration with intensified case finding. Furthermore, operational guidelines for the implementation of TPT in HIV care and treatment settings should be closely monitored to improve the target of stopping TB. Further prospective studies might be needed to establish the optimal duration of its protective effect in these clients.

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