# Factors Associated with Treatment Success among Pulmonary Tuberculosis and HIV Co-infected Patients in Oyo State, South West-Nigeria.

Type of Article: Original

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***ABSTRACT***

***BACKGROUND***

*The co-existence of Tuberculosis (TB) and Human immunodeficiency Virus (HIV) is known to increase morbidity and mortality in patients. The determinants of treatment success in TB-HIV co-infection are not yet well studied. Such information can help optimise treatment and reduce morbidity and mortality.*

***OBJECTIVE***

*To determine factors associated with anti-tubercular treatment success among TB/HIV co-infected patients.*

***METHODS***

*A cross sectional study was carried out in fifty three DOT clinics and treatment centres using tuberculosis patient's records from January 2009 to December 2010 in Oyo state, Nigeria. The study population consisted of 7905 tuberculosis patients. Information on variables of interest were obtained with the use of data extraction forms. Chi-square and logistic regression were used to test the relationship between TB/HIV co-infection and socio-demographic variables, clinical characteristics and treatment success.*

***RESULTS***

*Prevalence of TB/HIV co-infection was found to be 14.2%. Patients with TB-HIV co-infection were younger and more likely to be females. There were statistically significant association between treatment success and gender, marital status and patient point of care. After adjusting for other variables, it was found that patients receiving treatment in private facilities were independently less likely to be successfully treated compared with those receiving care in Public facilities. Female patients were also independently more likely to have better treatment outcome than male.*

***CONCLUSION***

*In addition to patients' point of care, gender of the patients can adversely impact on their treatment success. Efforts from the government to strengthening the private public mix, health education and media awareness on adherence to treatment to improve treatment success should be intensified in the country.*

***Keywords:*** *Tuberculosis; Human immunodeficiency virus, Directly observe therapy short-course; Treatment success, Co-infection.*

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## INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by the bacillus, Mycobacterium tuberculosis which can affect any part of the body but more commonly the lungs. TB has a worldwide distribution [1] and being a droplet infection has high infectivity rate, and is easily transmitted from person to person through droplet/droplet nuclei [2]. TB is a major public health concern globally and is one of the notifiable diseases in the world [3]. According to the 2012 version of World Health Organization's Global Burden of TB[4], in spite of the gains in TB control in the last two decades, there were still an estimated 8.7 million new cases of TB globally and 1.4 million people still died from TB globally in the year 2011 alone.

On the other hand, Human immunodeficiency virus (HIV) infection is caused by a retrovirus that spreads through body fluids. The virus attacks the immune system, thereby weakening it and increasing the susceptibility of the individual to opportunistic infections (OIs). TB is among the OIs that can arise in the course of HIV-induced immune-suppression as such patients are at a higher risk of latent TB activation [5]. One report puts the estimated annual risk of TB in HIV-positive patients at 7%-10%, compared with a total lifetime risk of 5%-10% in HIV-negative individuals [6]. Other studies found a 20-30 times higher risk of TB among persons living with HIV[7,8].

Yet, the co-existence of HIV infection and TB has been described as one of the most serious threats to human health since the Black Death, and has been described as 'the cursed duet'[1]. Maniar et al[9] aptly described the two disorders as 'partners in crime' while McShane[10] described same as 'double trouble' in reference to the lethality of their co-occurrence in a single patient. Several other studies, especially from sub-Saharan Africa (SSA), have found an increased risk of morbidity and mortality among TB/HIV co-infected patients [2, 11-14]. In addition to their combined lethality, TB-HIV co-infection remains the single biggest challenge to TB control efforts [2] as the co-existence of the duet makes the effective treatment of TB very difficult even in the directly observed short course (DOTS) regime [15-19]. This scenario continues to pose an increased risk of TB transmission in the community [20].

SSA has the highest burden of TB, accounting for about a quarter of global burden[4]. About 13% of TB cases in the region are HIV co-infected; a figure that represents close to 80% of global burden of TB-HIV co-infection [4]. Other than South-Africa, Nigeria has one of the highest burdens of TB in SSA There were more than 84,000 new cases of TB in Nigeria in the year 2011 alone, out of which 26% of those whose HIV status were known were HIV co-infected[4]. The lethality and the treatment challenges of the co-existence of the two diseases in the same person had been recognised by health authorities in Nigeria based on field experience [21]. This is not unconnected with the fact that field evaluations of treatment-success in TB programs in Nigeria has consistently yielded figures far below the WHO's 85% treatment-success target. For instance, field surveys in Nigeria has yielded a TB treatment success rates ranging from 42% in South-South Nigeria [16], through 64-76% in South-West[15,19] to 40% in Northern Nigeria[22]. The key factor responsible for the low success rate for TB control in the country had been reported to be HIV co-infection [19].

The challenges of managing TB-HIV co-infection have since been recognised by the WHO and collaborative efforts with nations have been put in place since 2004[10]. As a global partner in TB control, the main goal of Nigeria's National TB control program had been to reduce the burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the STOP TB Partnership targets [19]. Among the strategies for achieving this is the development of further capacity in the effective treatment of TB-HIV co-infection. Prior efforts at scaling-up TB the effectiveness of TB control programmes in Nigeria had

focused on the determinants of treatment success in TB without emphasis of patients with TB-HIV co-infection [15.19]. The sample size and the catchment areas of these studies were also small, and as such, limiting the degree to which the conclusions can be reliably drawn. Understanding the determinants of treatment success among patients with TB-HIV co-infection can influence policies that can enhance the treatment-success of TB-HIV co-infection in particular. This study therefore aimed at studying the socio-demographic and clinical determinants of treatment success among a large cohort of TB-HIV co-infected patients receiving DOTS therapy within Oyo state, Nigeria.

## METHODS

Setting and Target Population: The setting is a total of fifty three approved DOTS centres located in public and private hospital in Oyo state of Nigeria. This comprise of all the facilities in the state. It is a standard procedure for all approved DOTS centres to keep a pre-designed record-sheet (National Tuberculosis and Leprosy Control Program (NTBLCP) standardised reporting profoma) containing the bio-data and clinical variables like sputum-smear and HIV statuses, radiological findings, type of TB (extra- or intra-pulmonary), treatment outcome among others, for all patients. These records are filled by previously trained health workers and are actively supervised by health authorities. Data were extracted from records of diagnosed TB patients who had completed DOTS. It is also a standard procedure in the study sites to check the HIV status of all patients with confirmed TB.

## PROCEDURES

The socio-demographic variables assessed consisted of age, gender, marital status, educational status and occupation. The clinical variables included HIV status, site of TB, sputum smear result before commencement of treatment, type of treatment facility (public or private), treatment regimen, and anti-retroviral therapy status. The main outcome variable in this study is treatment success categorised as successful and unsuccessful.

Inclusion and exclusion criteria: For an individual registered for treatment to be eligible, she/he must be older than fifteen years of age, must be registered in any of the DOT clinics or treatment centres and must have also been screened for the diagnosis of TB and HIV.

Data management and Analysis: Data was obtained from the patients NTBLCP standardised reporting and recording forms using a data extraction form. The treatment outcome were recorded in six categories which include cured, treatment completed, defaulted, failed treatment, dead or and transferred-out. The definitions of the treatment outcome variables are as follows:

- Is Cured: TB Patient who was smear positive at diagnosis, who completed 6 or 8 months of treatment and who is smear-negative at the end of $6^{th}$ or $7^{th}$ month of treatment and in at least one previous occasion.
- Treatment Completed: TB patient who was smear-positive at diagnosis and who completed treatment but in whom smear examination results are not available at the end of treatment. Or, all smear-negative and extra pulmonary TB patients who completed treatment.
- Failure: TB patient who remains or becomes smear-positive at the end of fifth month or later during ant-tuberculosis chemotherapy.
- Died: TB patient who died for any reason during the course of ant-tuberculosis therapy.
- Defaulted: TB patient who has interrupted for 8 consecutive weeks or more after the date of the last attendance during the course of treatment.
- Transferred out: TB patient who has been transferred to another treatment centre in another state and whose treatment result is not known.

For the purpose of this study, treatment success was defined as treatment completed and cured. All other categories were classified

as treatment failure. Data were checked for completeness, consistency and accuracy. The data set was omitted for patients with no record of treatment outcome and HIV or TB test results.

Data analysis was carried out using Statistical Package for Social Sciences (SPSS) version 16. Frequency tables, charts, mean and standard deviation were used to summarise the variables of interest. Proportion was used to summarise the care received by co-infected and non co- infected patients. Chi-square, as a test statistic was used to investigate if there were differences between the treatment success and explanatory variables. Statistical significance was set at 5% level. Logistic regression was used to determine the degree of relationship between dependent variables and its predictors. Cut off used for independent variables in the logistic regression model was 10%.

## ETHICAL CONSIDERATION:

Ethical exemption to use patients' records for the study was obtained from Oyo state Ministry of Health and permission was sought from Damien foundation Belgium- Nigeria TB Project.

## RESULTS

Socio-demographic and clinical characteristics: A total of 7905 completed records were found for TB patients on DOTS, with 1122 (14.2%) patients recorded as HIV-positive. The mean age of the participants was 39.95±1.66 yrs wile that of the TB-HIV co-infected participants was 37.95±1.22yrs ($p<0.05$). About 60% of those who were HIV co-infected were in the age bracket 25-44 years compared with 50% of the HIV-negative patients ($p<0.05$). The HIV co-infected patients were also more likely to be females compared with the HIV-negative patients (59% vs. 44%; $p<0.05$). The socio-demographic and relevant clinical variables of all the TB-HIV co-infected are as shown in Table 1 and Figure 1 shows initial sputum AFB among co-infected patients prior anti tuberculosis treatment.

**Table-1: Distribution of socio-demographic and clinical characteristics of TB and TB/HIV co-infected patients.**

| Variables | TB-HIV Co-infected patients (n=1122) |
|---|---|
| **Age group** | |
| 15–24 | 103(9.2) |
| 25–34 | 365(32.5) |
| 35–44 | 358(31.9) |
| 45–54 | 185(16.5) |
| 55–64 | 66(5.9) |
| 65 and above | 45(40) |
| Sex | |
| Male | 464(41.4) |
| Female | 658(58.6) |
| Marital Status | 611(54.5) |
| Single | 511(45.5) |
| Married | |
| Educational status | |
| No formal education | 278(24.8) |
| Primary | 486(43.3) |
| Secondary | 225(20.1) |
| Tertiary | 133(11.8) |
| Occupation | |
| Unemployed | 12(1.1) |
| Employed | 1110(989) |
| Type of facility | |
| Public | 1029(92.0) |
| Private | 93(8.0) |
| Disease site | |
| Pulmonary | 986(87.9) |
| Extra pulmonary | 136(12.1) |
| Treatment regimen | |
| Category 1 (Newly treated) | 1088(97.0) |
| Category 2 (Previously treated) | 34(3.0) |

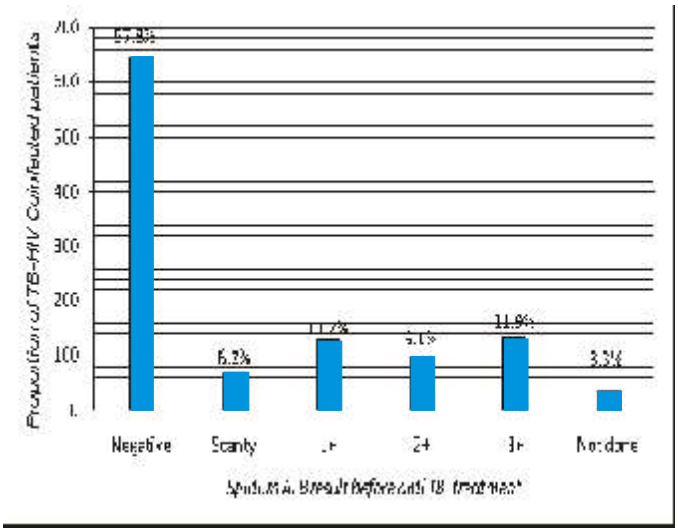


**Figure-1: Sputum AFB among TB-HIV co-infected patients prior anti TB Treatment**

**Determinants of treatment outcome:**
As shown in Table 2, there was a statistically significant association between treatment outcome and gender and patient's point of care (P<0.05). After controlling for other significant variables in a logistic regression model, females were 1.347 times more likely to have treatment success compared to TB/HIV co-infected males (CI= 1.010 – 1.795). Furthermore, it was also found that patients in private facilities were 1.613 times less likely to have treatment success compared to patients receiving care in public facilities (CI = 0.414 – 0.930). See table 3 for further details

**Table-2: Association between socio-demographic, clinical characteristics of TB/HIV co-infected patients and treatment success.**

| Variables | Treatment success | | Total | $\chi^2$ | P value |
|---|---|---|---|---|---|
| | Yes | No | | | |
| Age group | | | | | |
| 15 – 24 | 78(75.7) | 25(24.3) | 103 | | |
| 25 – 34 | 295(80.8) | 70(19.2) | 365 | | |
| 35 – 64 | 465(76.4) | 144(23.6) | 609 | 4.858 | 0.182 |
| 65 and above | 31(68.9) | 14(31.1) | 45 | | |
| Sex | | | | | |
| Male | 341(73.5) | 123(26.5) | 464 | | |
| Female | 528(80.2) | 130(19.8) | 658 | 7.103 | 0.008* |
| Marital Status | | | | | |
| Single | 486(79.5) | 125(20.5) | 611 | | |
| Married | 383(75.0) | 128(25.0) | 511 | 3.358 | 0.067 |
| Educational status | | | | | |
| No formal | 209(75.2) | 69(24.8) | 278 | | |
| education | 378(77.8) | 108(22.2) | 486 | | |
| Primary | 174(77.3) | 51(22.7) | 225 | 1.925 | 0.588 |
| Secondary | 108(81.2) | 25(18.8) | 133 | | |
| Tertiary | | | | | |
| Occupation | | | | | |
| Unemployed | 9(75.0) | 3(25.0) | 12 | | |
| Employed | 860(77.5) | 250(22.5) | 1110 | 0.042 | 0.838 |
| Type of facility | | | | | |
| Public | 773(78.4) | 213(21.6) | 986 | | |
| Private | 96(70.6) | 40(29.4) | 136 | 4.173 | 0.041* |
| Disease site | | | | | |
| Pulmonary | 844(77.6) | 244(22.4) | 1088 | | |
| Extra pulmonary | 25(73.5) | 9(26.5) | 34 | 0.309 | 0.578 |
| Treatment regimen | | | | | |
| Category 1 | 792(77.0) | 237(230) | 1029 | | |
| Category 2 | 77(82.8) | 16(17.2) | 93 | 1.659 | 0.198 |
| Anti-retroviral drug use | | | | | |
| Yes | 281(68.2) | 131(31.8) | 412 | | |
| No | 539(75.9) | 171(24.1) | 710 | 2.165 | 0.141 |

*P<0.05, Gender and type of facilities were statistically significant. Marital status considered for Logistic regression at 10%

**Table-3: Logistic regression analysis of TB/HIV co-infected patients' characteristics and treatment success**

| Variables | Odd's Ratio | 95% C.I | P-Value |
|---|---|---|---|
| Sex | | | |
| Male (Ref) | 1 | | |
| Female | 1.347 | 1.010-1.795 | 0.042* |
| Marital status | | | |
| Single (Ref) | 1 | | |
| Married | 0.761 | 0.573-1.011 | 0.060 |
| Type of facility | | | |
| Public (Ref) | 1 | | |
| Private | 0.620 | 0.414-0.930 | 0.021* |

*P<0.05

## DISCUSSION

The prevalence of HIV among patients with TB in this study was 14.2%. This is much lower than the figures ranging from 40-50% reported from other Sub Saharan Africa countries like Zambia, Kenya, Tanzania and South Africa [23-25]. A prevalence of 14.2% is however much higher than a prevalence of less than 2% of HIV co-infection among TB patients reported in other regions with lower HIV prevalence rates like China and the Netherlands[26,27]. Our finding of 14.2% prevalence of HIV co-infection among patients with TB in this study is similar to many studies in Nigeria. Okoh and Omuemu [28], reported a prevalence of 19.8% HIV co-infection among patients with TB in Benin (Southern Nigeria). Similarly, Onipede et al [29] and Daniel et al [17] reported 12.0% in Ile-Ife and 14.9% in Sagamu in South-West,Nigeria respectively, while Iliyasu [30] also reported a prevalence of 10% HIV co-infection among patients with TB in Kano (Northern Nigeria).

These rates are however low when compared to the 41.2% in Keffi Northern Nigeria [31]; 28% in Ibadan South-West Nigeria [32], and 25% in Port-Harcourt in Southern Nigeria[33]. These differences may however be explained by the lower sample size associated with this studies as most of this studies having samples of less than 250 patients compared to the over 7000 in this study. In addition the fact that

these other studies were conducted in tertiary healthcare facilities which are the main referral centres for complicated TB may also contribute to the disparity. A higher proportion of the co-infected patients in the present study were within the age group of 25–44 years and significantly more likely to be of the female gender. This pattern has previously been reported among patients with TB in Nigeria [33, 34]. The finding may just reflect the fact that HIV infection, with or without TB is commoner among women and the middle aged persons in Nigeria [35]. According to Sweet and Denison [36], social inequalities, including gender and power relations, have an important impact on HIV transmission. Recent reviews also suggest that women in many parts of the developing world are less likely to control how, when, and where sex takes place thereby increasing the likelihood of HIV infection[37]. It is also possible that whatever social disadvantage puts women at a higher risk of HIV also puts them at higher risk of TB infection, since they are both diseases of poverty and inequality.

In terms of treatment success, the fact that women with HIV-TB co-infection had better treatment outcomes suggest that the socio-cultural influence of gender on the HIV-TB spectrum is a bit complex. A recent study in Taiwan also found that women had better treatment outcomes in both TB[38] and HIV-therapy[39-41] independently. Gender differences in endogenous hormonal profiles among men and women may put them at differing risks of immune suppression and as such differing levels of response to treatment of immunity-related disorders like TB and HIV. Some in-vitro studies have found that oestrogen can enhance immune activation while testosterone may inhibit same [42,43]. In any case, animal studies have found that ovariectomized mice are vulnerable to Mycobacterium infection and that oestradiol replacement can reverse same [44]. Endogenous immune suppression may therefore explain the lower rate of success of HIV or TB treatment among males [41]. Health-care providers dealing with HIV-TB co-infection may want to be cognizant of this fact and may need to optimise the treatment of male patients early if there are signs of impending treatment failure.

The finding that patients receiving care in privately owned facilities had poorer outcomes in the current study reveals a disturbing angle in the HIV-TB control scheme in Nigeria. This suggest that privately owned health facilities are lacking in either the knowledge base or the rigour necessary to successfully treat HIV-TB co-infected patients. Though not among HIV co-infected patients, a cross-sectional descriptive study on the effectiveness of public private mix in the management of TB in Kaduna state, Nigeria, revealed that although the record documentation was relatively suboptimal in private facilities, they recorded a higher treatment success rate compared to the public health facilities (83.7% versus 78.6% respectively)[45]. This suggests that privately owned health facilities in Nigeria constitute an important complementary source for TB treatment in Nigeria as they account for 23% of total notified-TB cases in 2011[4] (WHO TB Global report 2012).

Private health facilities have also been observed to perform sub-optimally with respect to the adaptation of the WHO international standard of TB care (ISTC) and according to a recent study in Thailand, the unsuccessful treatment outcome was higher in private facilities compared with large public facilities [46]. The result of this study tends to suggest that the capacity of private health institutions to handle HIV/TB co-infection in Nigeria may be limited. The opportunities for training and re-training and the more rigorous supervision that is available to the public institutions might have made the difference. The policy implication of this finding if replicated includes extending further training and supervision on the management of TB-HIV co-infection to the private institutions. A notification system in which all cases of HIV-TB co-infection cases are reported to the nearest public-institution for co-management may also be useful. A more radical approach

will be to refer all cases of co-infection to a public institution, but this will have a lot of logistic problems and patients may be lost to treatment in the process. Additionally, this practice may further increase the burden on the already overstretched public health system with resultant negative effect.

However, before concluding on the issue of private/public facility dichotomy in TB-HIV co-infection treatment, it is important to note that the total number of patients treated in private facilities in the present study is too small to justify such assertions (<10%). This may be due to the fact that private facilities may prefer to refer HIV co-infected patients, who may have worse forms of the disease, to public facilities. There is however a need for further studies in this regard, to control for selection biases while determining the relative success of treatment among TB-HIV co-infected patients in public and private facilities.

There was a significant association between marital status and treatment outcome in this study with a higher proportion of treatment success among patients that were single compared with those that were married. Though this association was no longer present after logistic regression, the finding is still rather counter-intuitive as one will expect the married patients to leverage on the attendant social-support for better treatment outcome. However, being a highly stigmatised illness in Nigeria[47], it is possible that 'married' patients are experiencing additional stress of coping with stigma-driven marital difficulties that affected their treatment adherence. This thinking need to be further explored as it has implication for care of patients living with HIV-TB co-infection.

We did not find any association between social factors like education, income, employment status, and treatment outcome. Ditto for clinical variables like category of treatment (new or re-treatment cases) and use of anti-retroviral therapy. This finding is encouraging in the sense that it tends to suggest that these factors did not influence outcomes much. Therefore, efforts at scaling-up the success of the treatment of HIV-TB co-infection can still be universalised among patients irrespective of their socio-demographic or clinical group. However, overall efforts at reducing poverty and social inequalities especially among women still remain a germane issue in reducing the incidence of HIV and TB in the first instance.

## CONCLUSION

This study established that the prevalence of TB/HIV co-infection among tuberculosis patients enrolled on DOTS in Oyo state was 14.2% which is comparable to previous studies from the other parts of Nigeria. Gender and point of care were the key determinants of treatment outcome among the TB/HIV patients studied. There is a need for policy makers to strengthen the capacity of private health facilities in the care of patients with TB/HIV co-infection. Also women empowerment still remains an additional key strategy in TB control.

**Acknowledgments:**
I wish to acknowledge the entire Staff of Damien Foundation Belgium, Oyo state Tuberculosis and Leprosy Control Supervisors and Departmental staff of Epidemiology and Medical Statistics, University of Ibadan for their contributions toward the completion of this project

**Competing interests:** All authors declare no competing interest.

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