Tuberculosis Treatment Outcomes: A Fifteen Year Retrospective Study In Jos North And Mangu, Plateau State, North - Central Nigeria

CURRENT STATUS: UNDER REVISION

BMC Public Health  ▻ BMC Series

Comfort Nanbam Sariem
University of Jos

Corresponding Author
sariemcn@gmail.com
ORCiD: https://orcid.org/0000-0002-4915-7936

Patricia Odumosu
University of Jos, Plateau State

Maxwell Patrick Dapar
University of Jos, Plateau State

Jonah Musa
University of Jos, Plateau State

Luka Ibrahim
Public Health Department, Plateau State Ministry of Health

John Chinyere Aguiyi
University of Jos, Plateau State

DOI:
10.21203/rs.2.11227/v2

SUBJECT AREAS
Health Economics & Outcomes Research  Health Policy

KEYWORDS
Tuberculosis, Treatment Outcomes, Retrospective Study, Nigeria
Abstract
Background Tuberculosis (TB) disease is the leading cause of death from a single infectious agent globally. Medication adherence will be more valuable if it improves clinical/treatment outcomes of the patient because treatment outcomes are major indicators for evaluating TB therapy. Objective To examine a fifteen-year record of tuberculosis treatment outcomes in Jos North and Mangu Local Government Areas of Plateau State. Methods The retrospective registry based study was done in five TB treatment centers which account for more than half of data for tuberculosis patients in Plateau State, North-Central Nigeria. Data were collected from 10,156 TB patient’s health records from 2001 to 2015. Treatment outcomes were classified as successful (cured, treatment completed) or unsuccessful (non-adherent, treatment failure or death). Analysis was done descriptively and factors associated with treatment outcomes were determined using multiple logistic regression with the aid of Stata version 11. Results Males were 58.1% of the population (10,156). Mean age ±SD was 35.5±15.5 years. The overall treatment success rate was 67.4%; non-adherence(defaulting rate was 18.5%, with majority of patients defaulting at the end of intensive phase of treatment; sputum conversion rate was 72.8% and mortality rate was 7.5%. A decrease in successful treatment outcomes from 83.8% to 64.4%, with a corresponding increase in unsuccessful treatment outcomes was observed. After adjusting for sex, and TB category, being HIV positive was 2.8 times (95% CI: 1.11-6.83, p =0.028) more likely to be associated with treatment success than having an unknown status. TALF/RAD, relapse and MDR-TB were less likely associated with treatment success than newly diagnosed TB patients Conclusion Underlying reasons for medication non-adherence and treatment failure identified should be resolved by the patient, treatment supporter and health system through adherence counseling, increased education on voluntary counseling and testing of HIV among TB patients. Keywords: Tuberculosis, Treatment Outcomes, Retrospective Study, Nigeria

Introduction
Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis*. It remains a major global health problem being the tenth leading cause of death worldwide, and the leading cause of death from a single infectious agent since 2011, ahead of the Human Immunodeficiency Virus.
Globally, 10 million people (0.13 %) were estimated to have fallen ill with TB in 2017, with 9 % of the 10 million people HIV- positive. Death toll globally from TB disease was 1.3 million, with an additional 300,000 deaths from TB among HIV positive patients in 2017. In Nigeria, TB mortality, including HIV associated TB death was 155,000 in 2017; the second highest reported mortality globally, after India.\textsuperscript{2} The global treatment success rate was 82 % among all new TB cases.\textsuperscript{1} TB treatment saved 53 million lives globally (including HIV positive TB patients) and 11 million lives were saved in Africa.

Nigeria recorded a treatment success of 86 % in 2017. However, Nigeria was 6\textsuperscript{th} among the high TB burden countries after India, China, Indonesia, Philippines and Pakistan.\textsuperscript{1} There are 30 high TB burden countries (HBCs) which collectively have about 87 % of the world’s TB cases (HBC is defined as Nigeria is also among the 14 countries with overlap high burden of TB, TB/HIV and multidrug resistant-TB (MDR-TB).around 100 or more cases per 100,000 population).\textsuperscript{3} \textsuperscript{1} The total TB incidence rate in Nigeria was 219/100,000 population (population of 191 million people), out of which of 14 % were HIV positive.\textsuperscript{1}

\textit{Mycobacterium tuberculosis} is an intracellular microorganism that replicates very slowly, therefore prolonged multi-drug treatment regimen (6 months) is the recommended treatment strategy implemented through the Directly Observed Therapy (DOT).\textsuperscript{4} Because of this treatment regimen, medication non-adherence remains a potential and actual challenge. Prevention of new TB infections and their progression to (TB) disease is crucial in reducing the burden of disease and death caused by TB, and in achieving the End TB Strategy targets set for 2030 and 2035, which is linked with the target of the Sustainable Development Goal-SDG; to reduce the number of TB deaths by 90 % by 2030, cut new cases by 80 % between 2015 and 2030, and to ensure no family is burdened with catastrophic cost due to TB.\textsuperscript{5} Current health interventions for TB prevention include: treatment of latent TB infection (LTBI), with particular attention to children aged less than 5 years and HIV positive TB patients, prevention of transmission of \textit{M. TB} through infection control especially among health workers; and vaccination of children with the Bacille Calmette-Guérin (BCG) vaccine.\textsuperscript{1}
Efforts have been made to identify factors influencing medication adherence,\textsuperscript{6-12} from which interventions \textsuperscript{12-16} have been developed to improve adherence. This is because adherence has been shown to have profound effect on other treatment outcomes.\textsuperscript{17} A study observed that most intervention studies targetted only adherence, but improving adherence would be more valuable if it improves clinical/treatment outcomes of the patient.\textsuperscript{18} Treatment outcomes of TB patients are major indicators for evaluating TB therapy. A study of the pattern of treatment outcomes over the years can be done to identify specific areas in TB management that require intervention in order to improve these outcomes and health services. Treatment outcomes of TB patients in this study were classified as successful (cure or treatment completed) or unsuccessful (default, treatment failure or death), as defined from the World Health Organization (WHO) and National TB and Leprosy Control Program (NTBLCP) guidelines.\textsuperscript{1,4} Non-adherence and mortality have been shown to account for 64 \% and 32 \% poor/unsucceesfull treatment outcomes respectively.\textsuperscript{19}

In Nigeria, studies have reported trends in tuberculosis treatment outcomes for the country,\textsuperscript{1} and for different states within the country.\textsuperscript{20,21} However assessment of treatment outcomes in individual DOT centers is lacking.\textsuperscript{22} This will enable treatment centre-specific interventions to be implemented. This study was done to examine the factors associated with TB treatment outcomes in five DOT centers in Jos-North and Mangu Local government Areas of Plateau state, North-Central Nigeria through a fifteen year retrospective study.

Methods

\textbf{Study Design}

A retrospective registry-based study of TB patient’s from January 2001 to December 2015 was done.

\textbf{Study Setting}

The study was done in five DOT centers in Jos - North and Mangu Local Government Areas of Plateau State, North-Central Nigeria. The TB centers were chosen conveniently because they account for more than 50 \% of all TB cases in Plateau State, and health records of TB patients were available from
inception of the DOT programme in 2001. Plateau State has a land mass area of 26,899 square
kilometers with a population of 3,206,531 people. The study centers were: Faith Alive Foundation Hospital (FAF), Our Lady of Apostles (OLA), COCIN Hospital and Rehabilitation Centre (CHRC) Mangu and Bingham University Teaching Hospital (BUTH), which are faith based hospitals. Plateau State Specialist Hospital (PSSH) is a tertiary health care institution owned by Plateau State Government. CHRC, FAF and OLA are secondary health care institutions, while BUTH is a tertiary health care institution.

Ethical approval was sought and obtained form the various hospital’s Institutional review boards/Ethical Committees. Permission to collect data was also obtained from the unit heads. All information obtained were treated confidentially. De-identified patient data were collected and used for analyses, so that anonymity of the patients was maintained throughout the study.

Data Collection

Data (10,156) were collected from TB registers and treatment cards of patients who accessed TB treatment from 2001 to 2015 by the researcher and a trained research assistant. Data were collected manually, using a pre-designed form before transferring to a personal computer. Data collected include TB patient’s demographic (sex, age, address, year of enrollment) and clinical characteristics (diagnosis, TB category, retreatment, sputum Acid Fast Bacilli-AFB analysis, period of defaulting), as well as their treatment outcomes. Socioeconomic data were not recorded at the registries during the study period. Incomplete and missing data, especially those without recorded treatment outcomes were excluded from the study.

Data Analysis

Data checking and cleaning was done in Microsoft Excel before exporting to STATA® version 11.0 (College Station Texas, USA) for analysis. Demographic and clinical characteristics of the TB patients were described by proportions. Categorical variable proportions were compared using Chi-square test and when appropriate, Fisher’s exact test was used. Bivariate analysis was used to determine patient and clinical characteristics factors associated with treatment outcomes. For the multivariate analysis factors with $p$ values $\leq 0.2$ were included in the model, taking into account all the potential
confounders. Missing values, which were determined to be missing at random were managed using complete case analysis.

**Definition of Terms**

**Cured** refers to a pulmonary TB patient who was smear or culture positive at the beginning of treatment and is smear or culture negative upon completion of treatment.\(^4\)

**Completed Treatment** is a TB patient who completed treatment but without evidence (no laboratory test) at the end of treatment.\(^{24}\)

**Successful treatment outcome**: Cured and completed treatment together make up successful treatment outcomes which should increase towards 100 % and reach at least 85 % with good case management.\(^4\)

**Unsuccessful Treatment outcome** include: default/lost to follow-up, treatment failure or death.

**Treatment Failure** is a PTB patient who was smear or culture positive at beginning of treatment and remains positive at month 5 or later during their most recent course of treatment.\(^4\)

**Lost to follow-up** is a TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.\(^4\)

**Default** is defined by the WHO as missing more than 20 % of the prescribed doses during the treatment period i.e. a treatment interruption of two consecutive months or more after at least one month on treatment.\(^{25}\) The definition of defaulters however can vary within national programs, for example, the Federal Ministry of Health in Nigeria, defined defaulting as not taking anti-TB medications consecutively for more than two days intensive phase and more than two consecutive weeks continuation phase.\(^{24}\)

**Retreatment** is a sputum AFB positive TB patient who had a one or more month extension of intensive phase due to sputum inconversion.\(^{24}\)

**Relapse** is a patient who was cured or completed treatment, but returned sputum positive or with clinical symptoms of TB (either a true relapse or a new episode of TB caused by reinfection).\(^4\)
**Died** refers to a TB patient who died for any reason during the course of treatment.\textsuperscript{24}

**Results**

The mean age ± SD was 35.5±15.5. The proportion of males was more (58 %) than the females (Table 1). Majority of the TB patients were in the productive age of 24-35 years of age (33.4 %) and were HIV positive (38.4 %). Patient enrollment increased from 22.0 % to 39.6 % over the 15-year period, with the enrollment of HIV positive TB patients also increasing from 2.3 % to 57.7 %. Mean time-outcome ± SD was 5.4 ± 3.0 (time in months).

Table 1: Demographic Characteristics of TB Patients by HIV Status (n=10156)

| Variable                  | HIV Negative (n=3,733) | HIV Positive (n=2,968) | Unknown HIV Status (n=3455) | Total Freq.(%) |
|---------------------------|------------------------|------------------------|-----------------------------|---------------|
| **Sex**                   |                        |                        |                             |               |
| Male                      | 2467(66.1)             | 1343(45.2)             | 2094(60.6)                  | 5904(58.1)    |
| Female                    | 1266(33.9)             | 1625(54.8)             | 1361(39.4)                  | 4252(41.1)    |
| **Age (Years)**           |                        |                        |                             |               |
| 0-14                      | 159(4.5)               | 93(3.3)                | 297(14.5)                   | 549(6.5)      |
| 15-24                     | 503(14.2)              | 237(8.5)               | 261(12.7)                   | 1001(11.1)    |
| 25-34                     | 1135(31.9)             | 1069(38.4)             | 598(29.2)                   | 2802(33.4)    |
| 35-44                     | 686(19.3)              | 856(30.8)              | 431(21.0)                   | 1973(23.3)    |
| 45-54                     | 489(13.8)              | 364(13.1)              | 238(11.6)                   | 1091(13.0)    |
| >54                       | 582(16.4)              | 163(5.9)               | 228(11.1)                   | 972(11.6)     |
| Not Recorded              |                        |                        |                             | 1768(17.4)    |
| **Patient Residence**     |                        |                        |                             |               |
| Jos North                 | 1393(37.3)             | 1188(40.0)             | 1992(57.7)                  | 4573(45.0)    |
| Jos South                 | 390(10.4)              | 446(15.0)              | 594(17.2)                   | 1430(14.1)    |
| Jos East                  | 139(3.7)               | 127(4.3)               | 194(5.6)                    | 460(4.5)      |
| Other LGAs in Plateau     | 992(26.6)              | 531(17.9)              | 540(15.6)                   | 2063(20.3)    |
| Other States Outside Plateau | 133(3.6)             | 138(4.6)               | 134(3.9)                    | 405(4.0)      |
| Not recorded              |                        |                        |                             | 1229(12.1)    |
| **Year of Enrollment**    |                        |                        |                             |               |
| 2001-2005                 | 0(0.0)                 | 67(2.3)                | 2169(62.8)                  | 2236(22.0)    |
| 2006-2010                 | 1531(41.0)             | 1188(40.0)             | 1179(34.1)                  | 3898(38.4)    |
| 2011-2015                 | 2202(59.0)             | 1713(57.7)             | 107(3.1)                    | 4022(39.6)    |

Freq.=Frequency, LGAs=Local Government Areas

Majority of the patients were new (93.3 %), pulmonary TB (92.4 %) patients. Most of the patients that returned after default, relapsed, developed multidrug resistance, or needed retreatment TB were HIV negative TB Patients. Non-adherence/defaulting rate was 18.5 %, with majority of the patients, especially those with unknown HIV status defaulting at the end of intensive phase. The sputum conversion rate was 72.8 % (Table 2).

Table 2: Clinical Characteristics of Tuberculosis Patients by HIV Status (n = 10,156)
### Table 1: Patient Enrollment and Treatment Outcomes

| Variable                      | HIV Negative (n=3,733) | HIV Positive (n=2968) | Unknown HIV Status (n=3455) | Total Freq. (%) |
|-------------------------------|------------------------|-----------------------|-----------------------------|----------------|
| **TB Diagnosis**              |                        |                       |                             | T F            |
| Pulmonary TB                  | 3311 (88.7)            | 2818 (94.9)           | 3258 (94.3)                 | 9              |
| TB Spine                      | 227 (6.1)              | 29 (1.0)              | 19 (0.5)                    | 3              |
| TB Adenitis                   | 39 (1.0)               | 22 (0.7)              | 61 (1.8)                    | 2              |
| TB Abdomen                    | 135 (3.6)              | 91 (3.1)              | 25 (0.7)                    | 5              |
| Others*                       | 21 (0.6)               | 8 (0.3)               |                             |                |
| **TB Category**               |                        |                       |                             | T F            |
| New                           | 3405 (91.2)            | 2778 (93.6)           | 3290 (95.2)                 | 9              |
| RAD/TALF                      | 104 (2.8)              | 59 (2.0)              | 55 (1.6)                    | 2              |
| Relapse                       | 161 (4.3)              | 72 (2.4)              | 49 (1.4)                    | 2              |
| MDR-TB                        | 11 (0.3)               | 7 (0.2)               | 1 (0.0)                     | 1              |
| Transfer-In                   | 52 (1.4)               | 52 (1.8)              | 60 (1.7)                    | 1              |
| **Neddind Retreatment**       |                        |                       |                             | T F            |
| No                            | 3290 (88.1)            | 2704 (91.1)           | 2979 (86.2)                 | 8              |
| Yes                           | 282 (7.6)              | 136 (4.6)             | 104 (3.0)                   | 5              |
| Indeterminate*                | 161 (4.3)              | 128 (4.3)             | 372 (10.8)                  | 6              |
| **Sputum AFB on Diagnosis**   |                        |                       |                             | T F            |
| Sputum Negative               | 2355 (63.1)            | 2398 (80.8)           | 2480 (71.8)                 | 7              |
| Sputum AFB Positive           | 1378 (36.9)            | 570 (19.2)            | 975 (28.2)                  | 2              |
| **Sputum AFB After Intensive Phase** |                |                       |                             | T F            |
| Sputum Negative               | 3510 (94.0)            | 2806 (94.5)           | 3044 (88.1)                 | 9              |
| Sputum AFB Positive           | 39 (1.0)               | 18 (0.6)              | 12 (0.3)                    | 6              |
| Indeterminate*                | 184 (4.9)              | 144 (4.9)             | 398 (11.5)                  | 7              |
| **Defaulting Period (n=1874)**|                        |                       |                             | T F            |
| During Intensive Phase        | 97 (2.6)               | 65 (2.2)              | 271 (7.8)                   | 4              |
| End of Intensive Phase        | 190 (5.1)              | 191 (6.4)             | 559 (16.2)                  | 9              |
| Continuation Phase            | 96 (2.6)               | 62 (2.1)              | 343 (9.9)                   | 5              |
| **Binary Outcome**            |                        |                       |                             | T F            |
| Unsuccessful                  | 919 (24.6)             | 781 (26.3)            | 1599 (46.3)                 | 3              |
| Successful                    | 2814 (75.4)            | 2187 (73.7)           | 1855 (53.7)                 | 6              |

*= Disseminated TB, Miliary TB, Ovarian TB, Pleural TB, Skin TB, Heart TB;  
Indeterminate due to lost to follow-up or death during intensive phase of treatment  
TALF = Treatment after lost to follow up, RAD = Return after Default

The patient enrollment in 2001 was 360 patients, which rose to a peak of 983 patients in 2013, but decreased to 721 in 2015 (Figure 1).

Treatment success was highest in OLA hospital (86.2 %), and non-adherence/defaulting rate was highest in Plateau State Specialist Hospital (26.4 %). Mortality rate was highest (10.5 %) in CHRC Mangu (Table 3).

Table 3: Treatment Outcomes from DOT Centers
Distribution of Tuberculosis Treatment Outcomes by HIV Status

TB patients with known HIV status had higher treatment success rates than those with unknown HIV status. Non-adherence/defaulting rate was highest (34.0 %) among TB patients with unknown HIV status and mortality was highest (11.2 %) among HIV positive TB patients (Table 4)

Table 4: Distribution of Tuberculosis Treatment Outcomes by HIV Status

| Treatment Outcome       | HIV Negative (n=7,169) Freq. (%) | HIV Positive (n=2,967) Freq. (%) | Unknown HIV Status (n=20) Freq. (%) | Total Freq.(%) |
|-------------------------|----------------------------------|----------------------------------|-------------------------------------|--------------|
| Transfer-Out            | 227(6.1)                         | 117(3.9)                         | 251(7.3)                            | 595(5.9)     |
| Cured                   | 1,037(27.8)                      | 488(16.4)                        | 514(14.9)                           | 2039(20.1)   |
| Treatment Completed     | 1777(47.6)                       | 1,699(57.2)                      | 1341(38.8)                          | 4817(47.4)   |
| Treatment Success       | 2,814(75.4)                      | 2,187(73.7)                      | 1855(53.7)                          | 6856(67.5)   |
| Defaulted               | 383(10.3)                        | 318(10.7)                        | 1173(34.0)                          | 1874(18.5)   |
| Treatment Failure       | 33(0.9)                          | 11(0.4)                          | 9(0.3)                              | 53(0.5)      |
| Died                    | 266(7.1)                         | 331(11.2)                        | 162(4.7)                            | 759(7.5)     |
| Discontinued Trt.       | 10(0.3)                          | 4(0.1)                           | 4(0.1)                              | 18(0.2)      |

Trt=Treatment, Freq.=Frequency

The trend of treatment outcomes in figure 2 showed a steady increase in treatment success over the years was seen with a peak at 83.8 % in 2011, but dropped to a low 64.4% in 2015. A consequent reverse trend was seen in unsuccessful treatment, with a peak in 2002 (59.9%) and 30.5% in 2015.

Factors Associated with Tuberculosis Medication Non-adherence

Compared to HIV positive TB patients, TB patients were 4.3 times more likely to default/not adhere if they did not know their HIV status in the course of their TB treatment (CI: 3.74-4.91, p < 0.001).
Males had a 1.15 times likelihood of medication non-adherence than females (CI: 1.036-1.272, \( p = 0.008 \)). TB patients with a history of non-adherence had a 2.3 higher likelihood to default again from taking their anti-TB medicines (CI: 1.34-3.87, \( p = 0.002 \)) (Table 5).

Table 5: Factors Associated with Tuberculosis Medication Non-adherence

| Variable               | df | \( P \)  | OR    | 95 % Confidence Interval |
|------------------------|----|----------|-------|--------------------------|
|                        |    |          |       | Upper                    | Lower        |
| Sex                    |    |          |       |                          |              |
| Male                   | 1  | 0.008*   | 1.150 | 1.036                    | 1.272        |
| Female                 |    |          |       |                          |              |
| HIV Status             |    |          |       |                          |              |
| Negative              | 1  | 0.546    | 0.950 | 0.810                    | 1.110        |
| Unknown                | 1  | 0.001*   | 4.290 | 3.740                    | 4.910        |
| Positive               | 2  |          |       |                          |              |
| TB Category            |    |          |       |                          |              |
| New                   | 1  | 0.147    | 1.380 | 0.890                    | 2.160        |
| TALF/RAD              | 1  | 0.002*   | 2.270 | 1.340                    | 3.870        |
| Relapse               | 1  | 0.871    | 0.950 | 0.550                    | 1.670        |
| MDR-TB                | 1  | 0.055    | 2.830 | 0.980                    | 8.190        |
| Others                | 4  |          |       |                          |              |

\( TALF/RAD = \text{Treatment After Lost to Follow-up/Return After Default}; \) \( MDR-TB = \text{Multi-Drug Resistant TB}; \) \( OR = \text{Odds ratio}; \) *Statistically significant at \( p<0.05; \) Others=Transfer-In

Factors Associated with Mortality

HIV negative TB patients and those not needing retreatment were less likely to be associated with mortality than HIV positive TB patients. Extra pulmonary TB patients were 2.3 times more likely to be associated with mortality than pulmonary TB patients (Table 6).

Table 6: Factors Associated with Mortality

| Variable               | df | \( P \)  | OR    | 95 % Confidence Interval |
|------------------------|----|----------|-------|--------------------------|
|                        |    |          |       | Upper                    | Lower        |
| Sex                    |    |          |       |                          |              |
| Female                 | 1  | 0.104    | 0.879 | 0.752                    | 1.027        |
| Male                   |    |          |       |                          |              |
| HIV Status             |    |          |       |                          |              |
| HIV negative           | 1  | 0.001*   | 0.434 | 0.371                    | 0.508        |
| HIV Positive           | 1  | 0.068    | 0.312 | 0.089                    | 1.092        |
| Unknown status         | 2  |          |       |                          |              |
| TB Category            |    |          |       |                          |              |
| RAD                   | 1  | 0.472    | 1.535 | 0.478                    | 4.930        |
| Relapse               | 1  | 0.011*   | 5.131 | 1.459                    | 18.045       |
| Treatment Failure     | 1  | 0.015*   | 4.191 | 1.323                    | 13.273       |
| New                   | 3  |          |       |                          |              |
| TB Diagnosis           |    |          |       |                          |              |
| EPTB                  | 1  | 0.001*   | 2.346 | 1.848                    | 2.978        |
| PTB                   |    |          |       |                          |              |
| Needing Retreatment   |    |          |       |                          |              |
| No                    | 1  | 0.913    | 1.022 | 0.687                    | 1.522        |
| Yes                   | 1  | 0.001*   | 0.239 | 0.192                    | 0.297        |
| Indeterminate\(^1\)   | 2  |          |       |                          |              |

\(^1\) Indeterminate
Factors Associated with Treatment Success

A significant association between HIV status and treatment outcome was obtained after adjusting for sex and TB category. Being HIV positive was 2.8 times more likely to be associated with treatment success than having an unknown status. TALF/RAD, relapse and MDR-TB were less likely to be associated with treatment success than newly diagnosed TB patients (Table 7).

Table 7: Factors Associated with Treatment Success

| Variable          | df | P     | OR   | 95% Confidence Interval Upper | 95% Confidence Interval Lower |
|-------------------|----|-------|------|-------------------------------|------------------------------|
| Sex               |    |       |      |                               |                              |
| Female            | 1  | 0.243 | 1.060| 0.961                         | 1.170                        |
| Male              |    |       |      |                               |                              |
| HIV Status        |    |       |      |                               |                              |
| HIV negative      | 1  | 0.132 | 2.003| 0.811                         | 4.946                        |
| HIV Positive      | 1  | 0.028*| 2.758| 1.114                         | 6.826                        |
| Unknown status    | 2  |       |      |                               |                              |
| TB Category       |    |       |      |                               |                              |
| TALF/RAD          | 1  | 0.024*| 0.351| 0.142                         | 0.869                        |
| Relapse           | 1  | 0.029*| 0.757| 0.589                         | 0.972                        |
| MDR-TB            | 1  | 0.001*| 0.627| 0.475                         | 0.827                        |
| New               | 3  |       |      |                               |                              |

TALF/RAD = Treatment After Lost to Follow-up/Return After Default
MDR-TB = Multi-Drug Resistant TB

Discussion

This study examined treatment outcomes among TB patients retrospectively from registers and patient records over a 15-year period. An overall treatment success rate of 67.4 %, less than the Nigerian and global success rate of 86 % \(^1\) was observed. A drop in the overall treatment success rate from 83.8% in 2011 to 64.4 % in 2015 was also observed. The factors associated with successful treatment outcomes was HIV status (being HIV positive), while having a history of non-adherence, treatment failure/MDR-TB and relapse were less likely to be associated with treatment success.

Tuberculosis disease was more in males than females as similarly observed in other studies.\(^{26,27}\) The possible reasons given were; women experiencing barriers to service access, longer clinical delays in diagnosis or producing sputum of poor quality than men.\(^{28}\) A community based intervention study however reported significantly more women diagnosed with TB at community level than in the health facilities because the interventions reduced barriers to services with poor women who had previously
faced difficulties travelling to health centres particularly benefitting.\textsuperscript{28} TB was found more in the productive age group (sexually active group), particularly among HIV positive TB patients as similarly observed in other studies and consistent with global epidemiological findings.\textsuperscript{20,29-33} Majority of the patients were from Jos North Local Government Area of Plateau State, where most of the data was collected. These centers were chosen because they had records of TB patients from the inception of the Directly Observed Treatment strategy for TB in Plateau State in 2001. They also constitute about more than half of the population of TB patients in Plateau state.

CHRC Mangu, a rural DOT secondary facility had the lowest failure rate (0.2\%) and defaulting rate (2.9\%) but recorded the highest transfer-out (9.1\%) and mortality rates (10.5\%) than the urban DOT facilities. Training of health staff and treatment supporters should be encouraged so the community is more aware and educated on tuberculosis disease in order to increase case detection and decrease late reporting when the disease is advanced. Medication education and adherence counseling would further reduce treatment failure and defaulting rates. CHRC Mangu was receiving support from the Netherlands TB and Leprosy Relief. This drew a lot of patients from both Mangu and other Local Government Areas around the state because it was an active TB diagnostic and treatment centre. The Netherlands support was however withdrawn in 2016, now making Mangu more of a diagnostic and less of a treatment centre. Therefore patients diagnosed with TB in Mangu were referred to DOT centers closest to their residence for treatment; the probable reason behind the high transfer-out rates.

\textbf{Patient Enrollment and Treatment Outcomes}

The number of TB patients that accessed treatment significantly increased from 360 patients in 2001 to 983 in 2013, especially among HIV positive TB patients. This could likely be due to the increase in prevalence (from 2.2\% in 1991 to 25 \% in 2010) of HIV disease among TB patients\textsuperscript{33} and improved documentation processes. DOT expansion resulting to an increase in DOT facilities also increased the case detection rate.\textsuperscript{29,30} The number of TB patients that accessed TB treatment in the DOT centres however dropped between 2014 and 2015, probably due to lack of training and update of trends in TB
management. The trend in treatment outcomes followed a similar pattern where the treatment success increased steadily from 2001 (52.2%) to a peak in 2011 (83.8%) but decreased to 64.4% in 2015. The Nigerian National TB and Leprosy control programme is presently training and re-training TB DOT officers to improve TB health care services.

The non-adherence/defaulting rate pattern observed a sharp increase (from 30.6% to 54.2%) in 2002, which was the highest defaulting rate observed over the years. This could be as a result of the strict compliance of DOT, where TB patients came everyday for 2-3 months (initial phase of treatment) with the DOT officers observing them take their medicines. This resulted to the high defaulting rate as the patients became tired of coming everyday (most being very sick) and most patients could not afford transportation cost to the DOT centers. Recommendations were made to modify the DOT system of accessing TB treatment.\textsuperscript{34,35} This probably led to the subsequent decrease in defaulting rate as contact tracing, community DOT and decrease in number of visits to the DOT center from daily to weekly is being practiced.

**Factors Associated with Treatment Outcomes**

Treatment default was significantly associated with unknown HIV status. Socioeconomic characteristics may have contributed to this, however, it was not determined in this study due to unavailability of the records. This finding was not consistent with that of Central Ethiopia and Abuja-Nigeria, where TB/HIV co-infected patients had less likelihood of having successful treatment outcomes\textsuperscript{29,33}

TB patients with a history of defaulting/ non-adherence had a 2.3 times higher likelihood to default again from taking their anti-TB medicines and less likely to have successful treatment outcomes, consistent with findings from this study and other studies\textsuperscript{29,32} A strengthening of adherence counseling is encouraged so that factors responsible can be identified and resolved. This is important because non-adherence and regular treatment interruptions can lead to development of resistant TB, treatment failure, relapse, longer infections or even death\textsuperscript{29} - a finding similarly reported by WHO that Nigeria is among the 14 countries with overlap high burden of TB, TB/HIV and multidrug resistant-TB
HIV negative TB patients were associated with lower odds of mortality than HIV positive TB patients, similar to studies reported in other states in Nigeria,\(^\text{33,36}\) and other countries.\(^\text{37-39}\) Though it not clear if the reason is due to TB treatment failure or complication of HIV disease,\(^\text{33}\) possible reasons given in other studies include; late diagnosis of HIV,\(^\text{36}\) unavailability/inaccessibility of anti-retrovirals-ARVs,\(^\text{40}\) immunosuppression,\(^\text{41}\) lack of treatment supporters,\(^\text{42}\) and other co-morbidities such as cardiovascular diseases and diabetes mellitus,\(^\text{41}\) in HIV positive TB patients. If ARVs are procured, supplied and dispensed without disruption, it may go a long way to reduce the high mortality rate in Nigeria.\(^\text{2}\) Mortality was significantly associated with extra-pulmonary TB compared to pulmonary TB patients. This was explained in previous studies that extra-pulmonary TB may be associated with immunosuppression more than pulmonary TB.\(^\text{43-45}\) Being HIV positive was 2.8 times more likely to be associated with TB treatment success. A possible explanation for this finding is that HIV infected patients who have TB co-infection were likely to have received more/reinforced adherence counseling from trained adherence counselors prior to commencement of therapy, as with HIV treatment, TB therapy also requires high (> 90 %) adherence to facilitate cure.\(^\text{46}\) Thus, they may be more aware of the consequences of non-adherence in TB/HIV co-infection. This is however not consistent with other findings,\(^\text{33,36}\) where HIV positive TB patients were significantly associated with poor TB treatment outcomes due to malabsorption of anti-TB medicines, high pill burden and poor knowledge about the diseases.\(^\text{26}\) In conclusion, findings from this research have revealed an increase in the number of enrolments of TB and HIV positive TB patients in Plateau State. TB treatment outcomes from five DOT facilities were evaluated to show a decrease in tuberculosis treatment success rates in Plateau State from a fifteen year retrospective study. Appropriate interventions that would detect and resolve underlying reasons for non-adherence in TB patients with a history of defaulting, especially at the end of the intensive phase is advocated.
This study was limited was lack of socioeconomic records such as educational status, occupation and income of the TB patients, which were not collected at the initiation of DOT programme.

Declarations

**Ethics approval and consent to participate**

Ethical approval and permission to collect data was obtained form the institutional review board before data collection:

Jos University Teaching Hospital: Institutional Health Research Ethical Committee Reference Number: JUTH/DCS/ADM/127/XIX/6058,

All information obtained were treated with confidentiality. De-identified patient data were used for analyses, so that anonymity of the patients was maintained.

**Consent for Publication**

Not Applicable

**Availability of Data and Materials**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

**Competing Interest**

The authors declare that they have no competing interests.

**Funding**

This research was funded by the African Centre of Excellence in Phytomedicine Research and Development (ACEPRD) with grant award number 126974 from the World Bank.

**Author Contributions**

CS and PO conceptualized the research idea, CS designed the study, MD and JA supervised the research, JM analyzed most of the data and LI read and reviewed the manuscript.

**Acknowledgements**

This publication was supported by the Fogarty International Center of the National Institutes of Health under Award Number D43TW010130. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The support of Joshua
Dung in data collection data is highly appreciated. The contribution of Dr. Adamu Onu of Garki Specialist Hospital, Abuja in data analysis is acknowledged.

**Author Information**

1. Comfort Nanbam Sariem: sariemcn@gmail.com
2. Patricia Odumosu: patodumosu@gmail.com
3. Maxwell Patrick Dapar: xwelldapar@yahoo.com
4. Jonah Musa: drmusaj@yahoo.com
5. Luka Ibrahim: lukaimangveep@yahoo.com
6. John Chinyere Aguiyi: jca757@yahoo.com

**References**

1. World Health Organization-WHO. Global Tuberculosis Report. https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf. (2018). Accessed 1 March 2019.

2. Reid MJA, Arinaminpathy N, Bloom A, Boehme C, Chaisson R, Chin DP, et al. Building a tuberculosis-free world: The Lancet Commission on tuberculosis. The Lancet. 2019:7-10. http://dx.doi.org/10.1016/s0140-6736(19)30433-7. Accessed 16 October 2019.

3. World Health Organization-WHO. Global Tuberculosis Report. www.who.int. (2015). Accessed 3 March 2017.

4. Federal Ministry of Health-FMOH. National Tuberculosis, Leprosy and Buruli ulcer Management and Control Guidelines. 6th ed. Abuja: NTBLCP 2015.

5. World Health Organization-WHO. Tuberculosis. https://www.who.int/news-room/fact-sheets/detail/tuberculosis. (2018). Accessed 16 September 2019.

6. Bam TS, Gunneberg C, Bam D S, Alberg O, Kasland O, Shiyalap K, et al. Factors affecting patient adherence to DOTs in urban Kathmandu, Nepal. Int J Tuberc Lung
7. Bello SI, Itiola O. Drug adherence amongst tuberculosis patients in the University of Ilorin Teaching Hospital, Ilorin. Nigeria. Afr J Pharmacy and Pharmacology. 2010;4(3):109-14. Accessed 13 Mar 2012.

8. Erhabor GE, Aghanwa H S, Yusuph M, Adebayo R A, Arogundade F A, Amidiora O. Factors Influencing compliance in patients with tuberculosis on Directly Observed Therapy at Ile-Ife, Nigeria. East Afr Med J. 2000;77(5):235-9. Accessed 20 Jun 2010.

9. Kaona FAD, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. BMC Public Health. 2004;4(68). Accessed 20 Jun 2010.

10. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: A systematic review of qualitative research. PLoS Med. 2007;4(7):238.

11. Sariem CN, Gyang SS, Tayo F, Auta A, Omale S, Ndukwe HC. Factors influencing tuberculosis medication adherence in a tertiary health institution in Nigeria. West Afr J Pharm. 2013;24(2):66-75.

12. Sariem CN, Nanlir ZS, Banwat SB, Dapar MP. Factors influencing tuberculosis medication adherence: A cognitive intervention in a resource limited setting. World J Pharm Sci. 2015;3(9):1912-20.

13. Roter DL, Hall A, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. Medical Care. 1998;36:1138-61.

14. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients follow prescriptions for medications. The Cochrane Database of Systematic Reviews. 2002(2).
15. Borgdroff MW, Floyd K, Broekmans JF. Intervention to reduce tuberculosis mortality and transmission in low- and middle-income countries. Bulletin WHO. 2002;80:217-27.

16. Munro S. Theoretical models to support long-term medication adherence in TB and HIV. 3rd International Conference on ARV treatment adherence; NJ, USA. New Jersey: South African Medical Research Council; 2008.

17. Chisholm-Burns MA, Spivey CA. Pharmacoadherence: A new term for a significant problem. Am J Health-System Pharm. 2008;65(7):661-7.

18. Horne R, Weinman J, Barber N, Elliot R, Morgan M. Concordance, Adherence and Compliance in Medicine taking. (2005). Retrieved July 7, 2010, from London: www.epha.org/IMG/pdf/Rob_Horne_EP_handouts.pdf.

19. Arentz M, Narita M, Sangaré L, Kah JF, Low D, Mandaliya K, Walson JL. Impact of smear microscopy results and observed therapy on tuberculosis treatment in Mombasa, Kenya. Int J Tuberc Lung Dis. 2011;15(12), 1656-1663. doi:10.5588/ijtld.10.0625.

20. Dim CC, Dim NR. Trends of tuberculosis prevalence and treatment outcome in an under-resourced setting: The case of Enugu state, South East Nigeria. NMJ. 2014;54(6):392-7.

21. Ukwaja KN, Alobu I, Ifebunandu NA, Osakwe C, Igwenyi C. Trend in case detection rate for all tuberculosis cases notified in Ebonyi, Southeastern Nigeria during 1999 – 2009. The Pan Afr Med J. 2013;16(11). Accessed 13 Jul 2017.

22. Fatiregun AA, Ojo AS, Bambgboyie AE. Treatment Outcomes among pulmonary tuberculosis patients at treatment centres in Ibadan, Nigeria. Annals Afr Med. 2009;8(2):100-4. Accessed 13 Jul 2017.

23. NPC. Abuja, Nigeria: National Population Commission.
http://www.population.gov.ng/index.php/state-population. 2017. Accessed 13 July 2017.

24. Federal Ministry of Health-FMOH. National Tuberculosis and Leprosy Control Program (NTBLCP) Workers Manual Final Draft. 2008; Abuja:Nigeria.

25. World Health Organization-WHO. Adherence to long term therapies: evidence for action. (2003). http://whqlibdoc.who.intpublications20039241545992.pdf. Accessed 1 March 2016.

26. Johansson E, Long NH, Diwan VK, Winkvist A. Gender and tuberculosis control. Health Policy. 2000;52(1):33-51. Accessed 13 Jul 2017.

27. Weiss MG, Sommerfeld J, Uplekar MW. Social and cultural dimensions of gender and tuberculosis Editorial. Int J Tuberc lung Dis. 2008;12(7):829-30. Accessed 27 Jul 2017.

28. Yassin MA, Datiko DG, Tulloch. O, Markos P, Aschalew M, Shargie EB, et al. Innovative Community-Based Approaches Doubled Tuberculosis Case Notification and Improve Treatment Outcome in Southern Ethiopia. PLoS ONE. 2013;8(5).

29. Hamusse SD, Demissie M, Teshome D, Lindtjørn B. Fifteen-year trend in treatment outcomes among patients with pulmonary smear-positive tuberculosis and its determinants in Arsi Zone, Central Ethiopia. Glob Health Action. 2014;7(25382):10.

30. Dangisso MH, Datiko DG, Lindtjørn B. Trends of Tuberculosis Case Notification and Treatment Outcomes in the Sidama Zone, Southern Ethiopia: Ten-Year Retrospective Trend Analysis in Urban-Rural Settings. PLoS ONE. 2014;9(12).

31. Hamid-Salim MA, Declercq E, Van-Deun A, Saki KAR. Gender differences in tuberculosis: a prevalence survey done in Bangladesh. Int J Tuberc lung Dis. 2004;8:952-7.

32. Shargie EB, Lindtjørn B. DOTS improves treatment outcomes and service coverage for
tuberculosis in South Ethiopia: a retrospective trend analysis. BMC Public Health. 2005;5(62).

33. Ofoegbu OS, Odume BB. Treatment outcome of tuberculosis patients at National Hospital Abuja Nigeria: a five year retrospective study. South Afri Fam Pract. 2015;57(1):50-6.

34. Sariem CN, Ndukwe HC, Dayom WD. Assessing the effectiveness of Directly Observed Therapy short-course (DOTs) for tuberculosis in a Nigerian hospital. J Pharm Biores. 2012;9(2):116-21.

35. MacLehose HG. Improving practice using systematic reviews: A series about evidence-based practice. Afri Health. 2002;11-7.

36. Ifebunandu NA, Ukwaja KN, Obi SN. Treatment outcome of HIV-associated tuberculosis in a resource-poor setting. Trop Doct. 2012;42:74-76. DOI:10.1258?td.2011.110421. Accessed 12 October 2019.

37. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. ‘Smear-negative’ pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. Int J Tuberc Lung Dis. 2001;5:847-54.

38. Lienhardt C, Manneh K, Bonchier V, Lahai G, Millian PJ, McAdam KP. Factors determining the outcome of treatment of adult smear positive tuberculosis cases in the Gambia. Int J Tuberc Lung Dis. 1998;2:712-8.

39. Marks SM, Magee E, Robison V. Patients diagnosed with tuberculosis at death or who died during therapy: association with the human immunodeficiency virus. Int J Tuberc Lung Dis. 2011;15(4):465-70.

40. King L, Munsiff SS, Ahuja SD. Achieving international targets for tuberculosis treatment success among HIV-positive patients in New York City. Int J Tuberc Lung Dis. 2010;14(12):1613-20.
41. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis.;15(7):871-85.

42. Burton NT, Forson A, Lurie MN, et al. Factors associated with mortality and default among patients with tuberculosis attending a teaching hospital clinic in Accra, Ghana. Trans R Soc Trop Med Hyg. 2011;105(12):675-82. http://dx.doi.org/10.1016/j.trstmh.2011.07.017.

43. Pang Y, An J, Shu W, Huo F, Chu N, Gao M, et al. Epidemiology of Extrapulmonary Tuberculosis among Inpatients, China, 2008–2017. Emerg Infect Dis. 2019;25(3):457-464. https://dx.doi.org/10.3201/eid2503.180572. Accessed 16 October 2019.

44. Sterling TR, Dorman SE, Chaisson RE, Ding L, Hackman J, Moore K, Holland SM. Human immunodeficiency virus-seronegative adults with extrapulmonary tuberculosis have abnormal innate immune responses. Clin Infect Dis. 2001;33:976–82. DOI:10.1086/322670. Accessed 15 October 2019.

45. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis. 1993;148:1292–7. DOI:10.1164/ajrccm/148.5.1292.

46. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. Bulletin of the World Health Organization. 2008; 86(3):161-240.

Figures
Figure 1

Tuberculosis Patient’s Enrollment Trend

Figure 2

Trend of Treatment Outcomes
