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Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa

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SUMMARY

Objective: To determine and describe the factors influencing treatment default of tuberculosis (TB) patients in the Free State Province of South Africa.

Methods: A retrospective records review of pulmonary TB cases captured in the ETR.Net electronic TB register between 2003 and 2012 was performed. Subjects were >15 years of age and had a recorded pre-treatment smear result. The demographic and clinical characteristics of defaulters were described. Multivariate logistic regression analysis was used to determine factors associated with treatment default. The odds ratios (OR) together with their corresponding 95% confidence intervals (CI) were estimated. Statistical significance was considered at 0.05.

Results: A total of 7980 out of 110 349 (7.2%) cases defaulted treatment. Significantly higher proportions of cases were male (8.3% vs. female: 5.8%; $p < 0.001$), <25 years old (9.1% vs. 25–34 years: 8.7%; 35–44 years: 7.0%; 45–54 years: 5.2%; 55–64 years: 4.4%; >64 years: 3.9%; $p < 0.001$), undergoing TB retreatment (11.0% vs. new cases: 6.3%; $p < 0.001$), had a negative pre-treatment sputum smear result (7.8% vs. positive smear results: 7.1%; $p < 0.001$), were in the first 2 months of treatment (95.5% vs. >2 months: 4.8%; $p < 0.001$), and had unknown HIV status (7.8% vs. HIV-positive: 7.0% and HIV-negative: 5.7%; $p < 0.001$). After controlling for potential confounders, multivariate analysis revealed a two-fold increased risk of defaulting treatment when being retreated compared to being treated for the first time for TB (adjusted OR (AOR) 2.0, 95% CI 1.85–2.25). Female cases were 40% less likely to default treatment compared to their male counterparts (AOR 0.6, 95% CI 0.51–0.71). Treatment default was less likely among cases >24 years old compared to younger cases (25–34 years: AOR 0.8, 95% CI 0.77–0.87; 35–44 years: AOR 0.6, 95% CI 0.50–0.64; 45–54 years: AOR 0.4, 95% CI 0.32–0.49; 55–64 years: AOR 0.3, 95% CI 0.21–0.43; >64 years: AOR 0.3, 95% CI 0.19–0.35). Co-infected cases receiving antiretroviral therapy (ART) were 40% less likely to default TB treatment relative to those whose ART status was unknown (AOR 0.6, 95% CI 0.46–0.57).

Conclusions: Salient factors influence TB patient treatment default in the Free State Province. Therefore, the strengthening of clinical and programmatic interventions for patients at high risk of treatment default is recommended. In particular, ART provision to co-infected cases facilitates TB treatment adherence and outcomes.

1. Introduction

Tuberculosis (TB) remains a significant public health problem in South Africa, a country that is prominent among the 22 high-burden countries with the largest numbers of incident TB cases globally. Despite a 1.3-fold countrywide decline, from 576 per 100 000 population in 2000 to 430 per 100 000 population in 2012, the TB incidence in South Africa remains high.[1] In 2014, the TB incidence rate was estimated at 834 per 100 000 population among HIV-positive cases compared to 509 per 100 000 population among their HIV-negative counterparts.[2]

As with most African countries, the directly observed therapy short-course (DOTS) strategy is the mainstay of TB control in South Africa. In 2015, the country adopted the Stop TB Plan to guide TB

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control activities towards meeting the World Health Organization (WHO) target to end TB by 2035. The Plan entails an ambitious drive to diagnose and successfully treat at least 90% of all notified TB cases.[3] However, excessive default rates constrain the successful treatment of these patients. Despite rapid diagnosis and treatment initiation, some patients subsequently default, largely due to weak follow-up and management systems in the community.[3] From 2003 to 2011, patient default rates among new smear-positive TB cases remained higher than the <5% national target, fluctuating between 6.1% and 11.2%.[4–7] Simultaneously, successful treatment outcomes ranging from 58.0% to 79.0% between 1995 and 2011 have remained below the global target of >85%.[1,2]

For TB treatment to be effective, it is crucial to initiate patients on the correct treatment regimen in a timely manner (within 2 days of diagnosis) and to sustain such treatment for the correct period of time.[8] According to the South African TB management guidelines, patients should become less infectious within 2 weeks of initiating treatment.[8] Thus, treatment interruption presents serious implications not only for the patients themselves (including prolonged illness, development of clinical complications, development of drug resistance, and premature death), but also for their families, communities, and health service providers who may become infected with TB.[8–10] Knowledge of the drivers of patient treatment default is therefore essential for successful TB control and the optimal delivery of healthcare services in resource-poor settings like the Free State. Previous research conducted in Africa has reported varying impacts of demographic factors on treatment default. Some studies have reported a higher likelihood of treatment default among patients aged >25 years relative to their younger counterparts,[11,12] while others have reported that patients aged >25 years are less likely to default compared to younger patients.[13,14] Then again, some studies have reported no significant association between the demographic variables of age and sex, and treatment default.[15,16]

In terms of the association between clinical factors and treatment default, some African studies have reported that HIV co-infected patients[17,18] and/or those with an unknown HIV status[15] are at a higher risk of treatment default compared to HIV-negative patients. However, few African studies have investigated the impact of other important routinely collected clinical factors, including the type of TB diagnosis (new vs. retreatment) and pre-treatment sputum smear status, on treatment default. In this study, population-level TB surveillance data for adult pulmonary TB (PTB) patients aged 15 years and older in the Free State Province of South Africa were analyzed. The objective was to ascertain the demographic and clinical factors that influence treatment default.

2. Methods

2.1. Study design and population

A retrospective population-based study was conducted using routinely captured data for the years 2003–2012. The study population was defined as PTB cases older than 15 years of age with a recorded pre-treatment smear result registered in the ETR.Net electronic register over the period 2003–2012. Cases with 'defaulted' as the recorded treatment outcome were assessed against those with successful outcomes (i.e., completed treatment/cured). According to the South African national TB management guidelines, treatment 'default' is defined as the interruption of treatment for two or more consecutive months during the treatment period.[8] The same guidelines define 'treatment success' as patients who are cured or have completed the prescribed course of treatment and show a clinical improvement. Cases with 'transferred out', 'moved-out', 'died', and 'failed' as the recorded treatment outcome were excluded from the final analysis. As the absence of diagnostic smears raises concerns about the validity of treatment outcomes,[19] only PTB cases with a recorded pre-treatment smear result were considered for analysis (Figure 1). Cases without recorded pre-treatment sputum smear results and those with extrapulmonary TB (EPTB) (which is difficult to diagnose especially in HIV-positive populations[20]) were thus excluded. A sensitivity analysis was performed in which PTB cases with a recorded pre-treatment smear result were analyzed together with cases with no recorded pre-treatment smear and EPTB cases. The results were then compared to those with the latter two groups excluded from the analysis. No significant differences were established in the estimated odds ratios across all parameters, implying minimal bias.

2.2. Data management and validation

Information on TB is routinely captured in the electronic TB register ETR.Net. This tool is valuable for collating and analyzing TB surveillance data and for monitoring programme performance.[21] At the facility level, the TB nurse collates patient information from clinic cards and enters this in a paper-based TB register on a daily basis. The same nurse reviews the patient data for completeness and correctness at the clinic level. Information from the paper-based TB register is then sent from the clinic to the sub-district level for electronic capturing. The sub-district office is responsible for further data validation and analysis at the end of a cohort period; i.e. the sub-district TB coordinator, in conjunction with data capturers at this level, performs random data checks to ensure that the data are captured completely and accurately.[8] Previous studies have reported that data on key demographic and TB clinical indicators recorded in ETR.Net were generally complete and largely corresponded to the case information in other patient records, including paper-based TB registers and patient clinic cards.[22,23]

Following the global launch of the WHO Interim Policy on Collaborative TB–HIV Activities in 2004[24] – advocating the surveillance of HIV prevalence among TB cases – ETR.Net was modified to include HIV-related information, i.e. uptake of HIV testing, CD4 count review, co-trimoxazole prophylactic treatment (CPT), and antiretroviral therapy (ART).[4,20] The systematic capturing and recording of HIV data in the provincial TB register began in earnest in 2009 with the launch of new TB management guidelines.[25] It should be noted that previous studies have reported low concordance on key HIV indicators between ETR.Net and other data sources.[22,26]

In this study, two authors inspected and deleted duplicate case entries and removed outliers and patient names before the data were analyzed. In addition, they performed spot checks on ETR.Net data for completeness and consistency, and cross-verified the data with clinical records. In the case of inconsistent or incomplete information, one author contacted the district, sub-district, and facility-level TB coordinators to cross-verify the data with information captured in paper-based TB registers and patient clinic cards as far as was possible.

2.3. Measures and data analysis

Independent variables considered for analysis included sex (male or female), age (categorized as 15–24, 25–34, 35–44, 45–54, 55–64, or ≥65 years), HIV status (positive, negative, or unknown), and pre-treatment sputum smear result (negative, positive, or 'no smear'), and CD4 count (≤200 cells/mm^3, 201–350 cells/mm^3, or ≥351 cells/mm^3), CPT uptake (unknown or yes), and ART uptake (unknown or yes) for TB–HIV co-infected cases. Data for multidrug-resistant TB cases were not considered, as these are captured in a separate electronic database.[8]