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Factors associated with pulmonary tuberculosis treatment failure in Togo, 2015-2016

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Tuberculosis (TB) treatment failure compromises its elimination as recommended by Sustainable Development Goals. The purpose of this study is to determine the factors associated with pulmonary TB treatment failure in Togo between 2015 and 2016. An unmatched case-control study was conducted on cases of pulmonary TB under treatment at all of 47 TB Diagnostic and Treatment Centers (DTC) in Togo between 2015 and 2016. Treatment failure of TB was defined as any patient whose sputum smear or culture was positive at the fifth month or later during treatment. Controls were patients whose smear sputum was negative at the fifth month of treatment or later. Logistic regression model was performed to identify independently associated factors by calculating Adjusted Odds Ratio (AOR). In multivariate analysis, factors associated with treatment failure were: Positive sputum result in second month (AOR = 38.75; 95% CI [10.52-142.76], p≤0.001), occurrence of side effects [AOR=3, 61; 95% CI (1.06-12.22), p=0.038], treatment interruption for at least 14 days [AOR=8.15; 95% CI (2.35-28.28), p≤0.001], absence of family-based Directly Observed Treatment practice (AOR=23.76; 95% CI [5.66-99.64], p≤0.001). The study identified the socio-demographic and clinical factors of TB treatment failure whose inclusion in action plans would contribute to achieve TB elimination in Togo.

Key words: Tuberculosis, treatment failure, directly observed treatment short-course, Togo.

INTRODUCTION

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis, also known as Koch's Bacillus. It can affect all organs, but the lungs are affected in most cases. One third of the world's population is infected with Kock's Bacillus, but only a small proportion will develop TB (Dye et al., 1999). The

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Global TB report estimated that 10.0 million people developed TB disease in 2017, with 1.3 million deaths among HIV-negative people and with an additional 300 000 deaths from TB among HIV-positive people (WHO, 2018). It is one of the top 10 causes of death in the world (European Centre for Disease Control and Prevention, WHO – European Region; WHO, 2018). Low and middle-income countries are the most affected and accounted for 97% of reported TB cases globally (WHO, 2018).

Tuberculosis incidence, which declined sharply around 1980, increased with HIV epidemic emergence and contributed to a further increase in the burden of TB (Mlotshwa et al., 2016; Adamu et al., 2017; Pefura-Yone et al., 2017; Workicho et al., 2017). Indeed, TB and HIV co-infection is a deadly combination (Shuldiner et al., 2014; Baghaei et al., 2016; Cui et al., 2017; Heunis et al., 2017; Takarinda et al., 2017; Nagu et al., 2017). According to WHO report, 0.4 million of the 1.2 million deaths from TB in 2015 were due to TB/HIV co-infection. The new vision for TB control is in line with the Sustainable Development Goals (SDGs). It aims to end the global TB epidemic by reducing the number of TB deaths due by 90% and reducing TB incidence rate by 80% by 2030. Tuberculosis treatment regimen is a multidrug therapy that lasts six months and treatment outcomes are often marked by unwanted events such as death, lost to follow-up, but also treatment failures. Tuberculosis control interventions have contributed to reduce TB incidence by an average of 1.5% per year since 2000. Mortality also declined by 47% between 1990 and 2015, saving 49 million lives (WHO, 2018).

According to WHO estimates, TB incidence in Togo decreased from 77 cases per 100,000 inhabitants in 2010 to 52 cases per 100,000 inhabitants in 2015. The notification rate remained low at 58 and 69% between 2010 and 2015 (WHO, 2015). Treatment success rate has increased from 85% in 2010 to 88% in 2014. Treatment failure rate, although stable at 2%, almost doubled significantly ($p = 0.0014$) in one year, from 34 cases to 67 cases (unpublished data).

Tuberculosis studies conducted in Togo between 1990 and 2016 were based on the analysis of secondary data from universities hospitals registers. They covered the epidemiological profile of peritoneal TB (Darré et al., 2015), TB in children (Segbedji et al., 2016), miliary TB (Hounkpati et al., 2008) and radiological features (Tchaou et al., 2012). None addressed the analytical aspects of TB cases treatment outcome in general and treatment failure in particular, despite the doubling of the number of cases between 2015 and 2016 and the threat they pose to TB elimination. It is in response to this lack of control of the determinants influencing the treatment outcome of positive microscopy pulmonary TB cases in Togo that this study was conducted to identify the clinical and socio-demographic factors associated with pulmonary TB in Togo from 2015 to 2016.

MATERIALS AND METHODS

Type of study

An unmatched case-control study in Togo was conducted.

Study population

Study population was all patients of positive microscopy pulmonary TB recorded in 2015 and 2016 by TB Diagnostic and Treatment Centres (DTC) of Togo. All selected patients who consented to participate in the study were included.

Variable definition

Cases

Any patient with positive pulmonary TB in 2015 or 2016 in whose sputum smears at or after the fifth month of treatment was positive. It is a case of treatment failure.

Controls

Any patient with positive pulmonary TB in 2015 or 2016 whose sputum smears at or after the fifth month of treatment was negative. It is a cured case.

Sampling and sample size

Due to the rarity of the phenomenon of treatment failure and the difficulty in finding ex patients treated for TB, all cases of treatment failure of TB that occurred in Togo between 2015 and 2016 were enrolled. For one treatment failure case, two (02) controls were sampled. The controls were the two (02) cured patients who immediately followed the treatment failure case in the order of recording in the registry. Between 2015 and 2016, of the 101 cases of TB treatment failure, 81 cases were found and 168 controls were sampled.

Study variables

The dependent variable was treatment failure or cure. The independent variables were the socio-demographic and clinical characteristics associated with TB treatment failure. Socio-demographic characteristics were: age, sex, level of education, socio-professional category, distance between the Diagnostic and Treatment Center and patient's residence place, marital status, residence area (rural or urban). Clinical characteristics described were serological status of the Human Immunodeficiency Virus (HIV) stratified by sex, Cotrimoxazole prophylaxis in HIV-positive individuals, Anti-Retroviral Treatment (ART) for HIV-positive patients, the use of traditional medicine during TB treatment, Follow-up by home visit of care provider during the intensive phase (first two months) of treatment, Follow-up by home visit of care provider during continuation phase (from the 3rd to 6th month) of treatment.

Data collection

Interviewers were trained on the use of data collection

questionnaire. It was person in charge of the DTCs. This questionnaire was tested, reviewed and validated before being used during the survey. Data were collected by TB registers review and treatment cards to identify patients to be interviewed and report data on clinical and socio-demographic characteristics. Patients identified were thereafter sought in community or invited to the DTC where an individual interview was conducted using a semi-structured questionnaire to record information on compliance, occurrence of side effects, family-based Directly Observed Treatment (DOT) and follow-up.

Data processing

After the survey, each questionnaire was reviewed to ensure the completeness and quality of the information provided. For missing data and outliers, interviewers were contacted by telephone to complete the missing information and correct misreported information.
After this first check, a database was set up by entering data collected during the survey on a "97-2003" Excel sheet format. A second verification was conducted to correct entry errors and ensure consistency and conformance between data entered and those collected during the survey.

Data analysis

For analysis, Excel database was imported into the Epi Info software version 7.2.1.0. In descriptive analysis, proportions, ratios, means and standard deviations were calculated to describe the socio-demographic, clinical and treatment characteristics of the cases and controls. Statistical difference was appreciated using Chi^2, Fisher Exact and ANOVA tests. A univariate logistics regression was used to select variables with a p-value of <0.25 for inclusion in the baseline model in multivariate analysis. In a top-down multivariate logistics regression model, Adjusted Odd Ratios (AOR) were calculated and tested by the uncorrected Chi^2 test to identify association with treatment failure of pulmonary TB. A *p* value <0.05 was used for the significance interpretation.

Ethical considerations

The Bioethics Clearance Committee in Health and the Ministry of Health of Togo gave their approval for the study before it was carried out (N°012/2016/CBRS June 22 2017). Participants expressed their written informed consent to take part to the study and received information on TB.

RESULTS

Socio-demographic characteristics

The mean age was 38.64 years ± 13.25 years in cases and 38.90 ± 11.47 years in controls. These mean ages were significantly similar between cases and controls (p = 0.14). The overall female to male sex (F/M) ratio was 0.7 was similar in cases (sex F/M ratio = 0.5) and in controls (sex F/M ratio = 0.8) (p = 0.15). There was any difference between levels of education of cases and controls with p = 0.34.

Clinical characteristics

The proportion of TB/HIV co-infected patients in treatment failure and control cases was statistically similar at p = 0.83. However, for both home visits in the 2^{nd} month of treatment and between the 3^{rd} and 6^{th} month of treatment, there was a statistically significant difference between cases and controls for a value of p = 10^{-7}.

Univariate analysis

In univariate analysis, factors associated with treatment failure were: Socio-demographic characteristics (Table 1) :1) Rural residence; 2) Lack of money to travel to the DTC; 3) Lack of patient awareness on TB; 4) Lack of financial support and 5) food or other support from family members.

Clinical characteristics

Clinical features associated with treatment failure were: Presence of co-morbidity associated with TB (HIV, diabetes, asthma, hypertension): Positive result of microscopic examination in the 2^{nd} month of treatment; Occurrence of adverse reactions during treatment; Absence of at least one home visit during the first two (02) months of treatment; Use of traditional medicine; interruption of anti TB medication for at least 14 consecutive days.

Multivariate analysis

In multivariate analysis, in the logistic regression model, the following factors were independently associated with treatment failure (Table 2).

Socio-demographic factors

It appeared that cases had 5.80 times [95% CI (1.51-22.21), p=0.010] the odds of not having money for transport to the DTC than controls. Family-based DOTS practice was 23.76 times [95% CI (5.66-99.64), p≤0.001] more associated with treatment failure occurrence.

Clinical factors

Study results revealed that patients with history of anti-TB treatment were 13 times [95% CI (1.44-118.17), p=0.022] more likely to have treatment failure than those without history of anti-TB treatment. Results had also shown that

Table 1. Sociodemographic and clinical factors associated with pulmonary TB treatment failure in univariate analysis, Togo, 2015 - 2016.

Factors considered	Cases n (%)	Controls n (%)	OR	95% CI	p-value
Socio-demographic factors					
Area of residence					
Urban (Ref)	45 (55.56)	116 (69.46)	1.00		
Rural	36 (44.44)	51 (30.54)	1.81	1.05 - 3.14	0.0300
Lack of money for transport to DTC for anti-TB drug supply					
No (Ref)	31 (50.00)	138 (86.25)	1.00		
Yes	31 (50.00)	22 (13.75)	6.27	3.20 - 12.27	0.0000
Forgot to travel to the Diagnostic and Treatment Center to obtain medication					
No (Ref)	29 (36.25)	143 (88.27)	1.00		
Yes	51 (63.75)	19 (11.73)	13.23	6.83 - 25.63	0.0000
Family members' support to the patient in financial resources, food or other					
No (Ref)	22 (27.85)	23 (14.37)	1.00		
Yes	57 (72.15)	137 (85.63)	0.43	0.22 - 0.84	0.0100
Patient's history of TB awareness					
No (Ref)	46 (57.50)	57 (33.93)	1.00		
Yes	34 (42.50)	111 (66.07)	0.37	0.22 - 0.63	0.0005
Clinical factors					
Presence of co-morbidity including HIV					
No (Ref)	43 (53.09)	112 (66.67)	1.00		
Yes	38 (46.91)	56 (33.33)	1.76	1.02 - 3.03	0.0500
Use of traditional medicine or herbs/auto medication					
No (Ref)	36 (45.00)	140 (84.34)	1.00		
Yes	44 (55.00)	26 (15.66)	6.58	3.5 - 12.08	0.0000
Occurrence of side effects during TB treatment					
No (Ref)	16 (20.25)	67 (42.68)	1.00		
Yes	63 (79.75)	90 (57.32)	2.93	1.55 - 5.52	0.0000
Result of sputum control during the 2nd month of treatment					
Negative (Ref)	17 (22.08)	151 (90.42)	1.00		
Positive	60 (77.92)	16 (9.58)	33.30	15.80 - 70.18	0.0000

Table 1 ContD.

Absence of family-based directly observed treatment practice					
No (Ref)	71 (87.65)	64 (38.55)	1.00		
Yes	10 (12.35)	102 (61.45)	0.08	0.04 – 0.18	0.0000
Forgot to take anti TB drugs					
No (Ref)	28 (34.57)	139 (85.28)	1.00		
Yes	53 (65.43)	24 (14.72)	10.96	5.83 – 20.59	0.0000
Absence to follow up by home visit during the first two (02) months of treatment					
No (Ref)	16 (19.75)	99 (59.28)	1.00		
Yes	65 (80.25)	68 (40.72)	5.91	3.15 – 11. 08	0.0000

patients that smear sputum result was positive at second month of treatment were 38.75 times [95% CI (10.52-142.76), p ≤ 0.001] likely to develop treatment failure. In addition, patients who had developed side effects had 3.61 times [95% CI (1.06-12.22), p=0.038] the odds to develop TB treatment failure than those who did not develop side effects. Furthermore, having interrupted anti TB drugs taking for at least 14 days were 8.15 times [95% CI (2.35-28.28), p≤0.001] more likely associated with treatment failure. Cases of treatment failure were 3.27 times [95% CI (1.03-10.40), p=0.044] more likely to have not been visited by a health care provider than those who were cured.

DISCUSSION

Taking anti-TB drugs for at least one month defined as history of anti-TB drugs treatment was associated with treatment failure. In Uzbekistan (Karo et al., 2015), Asia (Lee et al., 2012; Scheelbeek et al., 2014), America (Albuquerque et al., 2001) and Africa (Nimagan et al., 2015), the history of anti-TB treatment has been identified as a risk factor for treatment failure. This could be the fact that an incomplete initial treatment put under drug pressure, the microorganism, which subsequently developed resistance to anti-TB drugs. These cases of failure could also correspond to the inaugural occurrence of authentic cases of pharmaco-resistance (He et al., 2011; Lackey et al., 2015; Lema et al., 2016). Cases of treatment failure would have been nearly 39 times the odds of having a positive result during the microscopic examination of sputum control in the 2nd month of treatment than controls. This was also found in a study done in 2009 in Burkina Faso (Sawadogo et al., 2015), in China in 2011 (Wang et al., 2017) and in Ethiopia in 2010 (Muñoz-Sellart et al., 2010). This could be explained by irregularity in taking anti-TB drugs due to forgetfulness, the occurrence of side effects and especially the absence of family DOTS practice. This could also include cases with very high density of Acid-Fast Bacilli (AFB) at diagnosis or cases of bilateral pulmonary TB (Kuaban et al., 2009; Bouti et al., 2013; Mlotshwa et al., 2016). The occurrence of side effects during TB treatment was associated with treatment failure in cases compared to controls. This association was also found in Ethiopia (Sinshaw et al., 2017) and in Canada (Yee et al., 2003). The occurrence of side effects, whether serious or not, compromises the success of treatment, particularly TB, whose success is based on a long course of multidrug therapy. This multidrug therapy can also potentialize the risk of side effects occurring through drug interaction, especially in patients with co-morbidities such as HIV infection, arterial hypertension and many other conditions that require combination therapy. These side effects may also occur due to certain liver diseases and renal failure that compromise drug metabolism. In this study 21% (17/81) of treatment failure cases had co-morbidities such as diabetes, asthma, liver disease, sickle cell disease, kidney disease other than HIV infection.

Table 2. Factors independently associated with pulmonary TB treatment failure, Togo, 2015 – 2016.

Factor	Parameter	Odd ratios	95% CI		P-Value
Socio-demographic characteristics					
Lack of money for transport to DTC for anti-TB drug supply	No (Ref)	1.00			
	Yes	5.80	1.51	22.21	0.0102
Absence of family-based directly observed treatment practice	No (Ref)	1.00			
	Yes	23.76	5.66	99.64	0.0000
Clinical factors					
Interruption of anti-TB drugs take for at least 14 days	No (Ref)	1.00			
	Yes	8.15	2.35	28.28	0.0009
Occurrence of side effects during treatment	No (Ref)	1.00			
	Yes	3.61	1.06	12.22	0.0389
Positive sputum test result during the 2nd month of treatment	No (Ref)	1.00			
	Yes	38.75	10.52	142.76	0.0000
History of TB treatment	No (Ref)	1.00			
	Yes	13.06	1.44	118.17	0.0222
Absence of follow-up by home visits of care provider during the first two months of treatment	No (Ref)	1.00			
	Yes	3.27	1.03	10.40	0.0444

Of the 69 TB/HIV co-infection cases representing approximately 30% of all patients included in the study, respectively 97% and 90% were taking, in addition to anti-TB drugs, antiretroviral drugs (ARVs) and Cotrimoxazole. Dosage errors at the beginning of treatment due to lack or misjudgment of patient weight, or during treatment due to non-adjustment of the dose in a case of weight loss of the patient could also explain the occurrence of these side effects and compromise the continuation of anti-TB treatment. These side effects, when they occur, can lead to discontinuation of treatment due to their severity. Although not severe, their occurrence may create a feeling of fear and anxiety in patient about innocuousness and effectiveness of treatment, which may result in either an irregularity in taking or a complete interruption of the treatment. The lack of implementation of Directly Observed Treatment (DOTS) by a family member had 3 times the odds of developing treatment failure than cure. DOTS strategy at community level consists of the administration of anti-TB drugs to patients by a family member or a village community health worker. Because of the supervision of drugs taking by a trusted person, compliance with the treatment is assured and thus increases chances for successful treatment. This strategy has demonstrated its efficiency as reported in several studies worldwide: Europe (Juan et al., 2006; Balabanova et al., 2006; Siemion-Szcześniak and Kuś, 2009), Asia (Anuwatnonthakate et al., 2008; Shrivastava et al., 2014), America (Ferreira et al., 2011; Pasipanodya and Gumbo, 2013), Africa (Elmahalli and Abdel-Aziz, 2007; Ntshanga et al., 2009; Sisay et al., 2016). However, Nateniyom found that its practice was inadequate for TB treatment in prisons (Sinshaw et al., 2017).

Limitation of study

Because of the low number of cases of treatment failure, the difficulty in finding ex-TB patients to interview and the distribution of cases and controls to be included in the study across the country, the sample size was not enough large to give a great power to the tests.

Conclusion

Capacity building for DTC managers on treatment

education and the implementation of treatment supervision by a family member could optimize TB treatment compliance in Togo. The National TB Control Program should also mobilize financial and logistical resources for home visits of patients under treatment and set up microbiological surveillance of TB cases to determine the mycobacteriological profile of TB pathogens in Togo.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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