Risk factors for pulmonary tuberculosis treatment failure in rural settings in Benin, West Africa: a cohort study

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Abstract

Tuberculosis (TB) remains a public health issue particularly in the north-east of Benin where there is a high frequency of TB treatment failure. The aim of our study was to identify the risk factors of TB treatment failure in rural north-east settings, Bembèrèkè, Benin (West Africa). This was a retrospective cohort study. We included smear-positive pulmonary TB patients who began TB treatment between 1 January 2007 and 31 January 2011 as extracted from the TB registry. The outcomes of TB treatment were defined according to 2007 the World Health Organization (WHO) guidelines. Failure was defined as remaining smear positive at month five or later during TB treatment for smear-positive pulmonary TB cases. Treatment successes was defined as being either smear negative (cured) at month five or later of treatment or having completed TB treatment in situations where sputum smear microscopy was not done. Those who died for any reason during TB treatment were also recorded. For reasons of analysis, we also defined composite outcome (failure or death). After univariate analysis, multivariate analysis with 0.05 as the level of significance was carried out, focusing on socio-demographic variables, HIV status, and acid-fast bacilli score at baseline.

Of the 270 pulmonary TB patients, 264 were included in the final analysis. The median age was 35 years (interquartile range, 28–46 years); 23 patients failed on TB treatment with a frequency of 8.6% (5.5–12.6%). In the multivariate analysis, positive HIV status (OR, 10.38; 95% CI, 1.77–60.91; p=0.01) and male gender (OR, 4.34; 95% CI, 1.03–18.28; p=0.046) were each significantly associated with increased risk of TB treatment failure. Only positive HIV status (OR, 12.86; 95% CI, 4.27–8.27; p<0.0001) remained significantly associated with composite outcome. In conclusion, positive HIV status and male gender are the potential risks factors of TB treatment failure. The association between positive HIV status and composite outcome confirmed the deadly association between TB and HIV. There is a need to truly integrate HIV and TB activities in all levels of the health system.

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Introduction

Tuberculosis (TB) is one of the oldest preventable and curable diseases.[1] However, TB remains an important public health problem in the world, as evidenced by the 10.4 million new TB cases and the 1.4 million deaths from the disease in 2015,[2] the majority of cases occurring in resource-limited settings. Benin Republic (West Africa) has a low TB burden, with 32 cases per 100 000 inhabitants and a death rate of 5% for smear-positive pulmonary TB cases (PTB+).[3] The treatment of PTB+ cases in Benin Republic is free of charge and is based on a four-drug regimen according to the World Health Organization (WHO) TB treatment guidelines 2010.[4]

The whole country has achieved the WHO minimum acceptable threshold for treatment success which was 85% for PTB+;[5] the high rate of treatment failure of about 8% in two areas of north-east Benin could be a factor in the emergence of multidrug resistant (MDR) TB in these settings.[6] Those authors reported a 12% occurrence of MDR strains among retreatment cases.[7]

Many approaches have been proposed to increase TB treatment success and reduce failure, such as Directly Observed Treatment Short course (DOTS),[5,8] which is implemented nationwide in Benin.[9,10] Many factors (such as age ≥35 years, body mass index (BMI) ≤18.5, diabetes, MDR TB,[11] and non-conversion of sputum smear after intensive phase) have been reported to be significantly associated with TB treatment failure.[12] However, it is unknown to what extent these or other factors contribute to treatment failure in north-east Benin and in West African rural settings.

We present the results of a study designed to assess risk factors for anti-TB treatment failure in PTB+ cases in north-east Benin.

Materials and methods

We conducted a retrospective cohort study of PTB+ cases in order to assess risk factors for treatment failure. The study was carried out at the Evangelic Hospital of Bembèrèkè (EHB), a rural setting situated in north-east Benin about 700 km away from the capital city of Cotonou. We selected Bembèrèkè because it has a much higher TB treatment failure rate than the rest of Benin. EHB is an intermediary referral hospital for all patients

Variables	Overall	TB treatment success	TB treatment failure	Died	P-value[3]
	n=264	n=205	n=23	n=36	
Ages (years)[1]	38.0 (±14.3)	37.2 (±14.2)	41.3 (±15.3)	40.9 (14.2)	0.19
Male gender	67.80%	65.4%	87.0%	69.4%	0.11
HIV positive	08.71%	5.0%	13.6%	30.3%	<0.001
Benin resident	72.26%	73.7%	52.2%	77.8%	0.068
AFB smear (++ or +++)[2]	80.70%	86.3%	95.7%	88.9%	0.485

[1] Data expressed as mean (±SD).
[2] AFB result at baseline.
[3] T-tailed unadjusted p-value based on one-way analysis of variance (for age) or Pearson's chi-square test.

Table 1: Characteristics of tuberculosis treatment outcome group

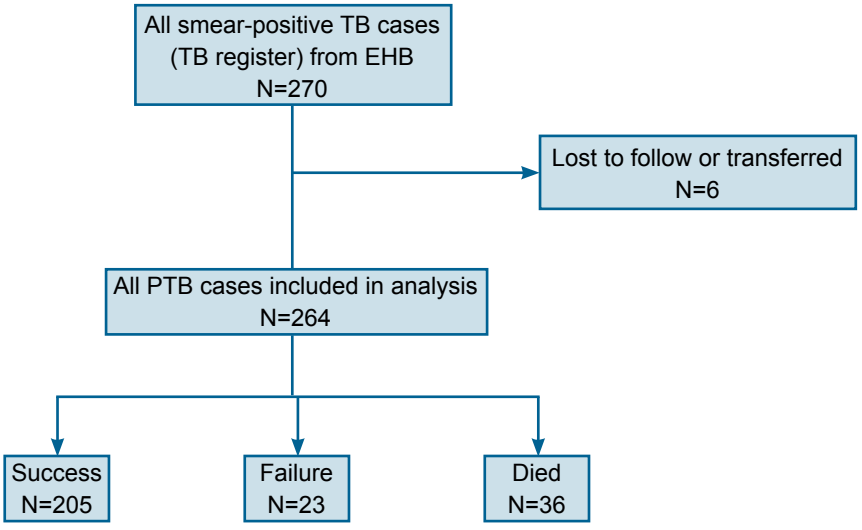

Figure 1: Flow chart of new pulmonary tuberculosis-positive cases registered in EHB between 2007-2011

Variables		Success vs failure	
	OR[1]	95% CI	p value[3]
Ages (years)	1.15	0.83–1.58	0.40
Male gender	4.34	1.03–18.28	0.046
HIV positive	10.38	1.77–60.91	0.010
Resident	0.43	0.17–1.11	0.080
AFB (++ or +++)[2]	6.26	0.66–39.23	0.11

[1] Adjusted odd ratio.
[2] AFB result at baseline.
[3] Adjusted p value.

Table 2: Logistic regression of TB treatment failure vs TB treatment success

from the upper north-east of Benin and to residents of neighbouring Niger and Nigeria.

Using the EHB registry of TB patients, we identified all new cases of PTB+ occurring between 1 January 2007 and 31 December 2011, among individuals aged 10 years of age or older. We defined PTB+ as the presence of cough and fever (temperature ≥39°C) for more than 2 weeks, loss of body weight, and the presence of acid-fast bacilli (AFB) sputum. Prior to 2010, three smear sputum samples were required to diagnose PTB+. The patient was considered positive for PTB+ if two or more of the samples were positive for AFB. After 2010, only two smear sputum were required, and patients were considered positive for PTB+ if at least one smear sputum sample was positive for AFB.

For the purposes of analysis, we excluded five patients who were lost to follow-up and one patient who transferred to a different facility for treatment before the six-months follow-up interval was completed, leaving a final analysis sample of 264 individuals (Figure 1). The study was approved by the ethics panel of Parakou University in Benin.

Study definitions. We used the EHB TB registry to abstract treatment outcomes. Consistent with WHO guidelines[13] the following definitions were used: 'TB treatment failure' - patients who were initially smear positive and who remained smear positive at month 5 or later during treatment; 'TB treatment cure' - patients who were initially smear positive and who were smear negative in the last month of treatment and on at least one previous occasion; 'TB treatment completed' - patients who completed treatment but did not meet the criteria for cure or failure; 'TB treatment success' - either TB treatment cure or TB treatment completed. 'Deaths' were patients who died from any cause during treatment. For the purposes of this analysis, we also define a 'composite adverse outcome' as the occurrence of either anti-TB treatment failure or death in first six months of treatment. Potential predictor variables for TB treatment failure and the composite adverse outcome include: socio-demographic factors (age, sex, country of residence Benin or not), HIV-related factors (HIV status), AFB result at baseline.

Statistical methods. We conducted separate analyses for TB treatment failure and the composite adverse outcome. For the former we excluded the 36 patients who died during the study (Figure 1). We used one-way ANOVA and Pearson chi-square tests to compare the baseline characteristics of patients in the three treatment outcome groups (TB treatment success, TB treatment failure, and deaths), and multiple logistic regression analysis to assess risk factors for TB treatment failure and for the composite adverse outcome. Analyses were conducted using Stata, version 12, and all reported p values are two-sided with a significance level <0.05.

Variables		Success vs composite outcome	
	OR[1]	95% CI	p value[3]
Ages (years)	1.21	0.96–1.57	0.11
Male gender	2.20	0.98–4.94	0.56
HIV positive	12.86	4.31–38.27	<.001
Resident	0.71	0.35–1.44	0.34
AFB (++ or +++)[2]	3.17	0.95–10.57	0.060

[1] Adjusted odd ratio.
[2] AFB result at baseline.
[3] Adjusted p value.

Table 3: Logistic regression of composite outcome vs TB treatment success

Results

General and socio-demographic characteristics of the study population. Of the 264 PTB+ cases, 23 (8.71%) had TB treatment failure, 36 (13.64%) died, and 205 (77.65%) had TB treatment success (Figure 1). The mean age of the cohort was 38.4 (±14.3) years, the majority were male (179, 67.80%). There were 23 (8.71%) HIV positive cases, 91 (72.6%) patients resided in Benin, and 213 (80.70%) had had high positivity of AFB (Table 1).

Univariate analysis. Positive HIV status was strongly associated with treatment outcome, accounting for 13.6% of TB treatment failures and 30.3% of deaths; only 5% of those successfully treated for TB were HIV positive. Although not significantly different, in our sample TB treatment failures were considerably more likely to be male and to not live in Benin. Of the 72 non-Benin residents attending EHB for treatment, 70 were from Nigeria and 2 were from Niger. They were also somewhat more likely to have higher initial AFB scores (Table 1).

Multivariate logistic regression models. Positive HIV status (OR, 10.38; 95%CI, 1.77–60.91) and male gender (OR, 4.34; 95%CI, 1.03–18.28) were each significantly associated with increased risk of TB treatment failure with respectively p=0.01 and p=0.046. An increased baseline AFB score was also associated with increased risk of TB treatment failure (OR, 6.26; 95%CI, 0.66–39.23) but this was not statistically significant (p=0.11). Finally, the data were suggestive of a reduced risk of TB treatment failure for Benin residents (OR, 0.43; 95%CI, 0.17–1.11), but this was not statistically significant (p=0.08) (Table 2).

Positive HIV status was significantly associated with composite outcome (OR, 12.86; 95%CI, 4.27–38.27; p<0.0001) with increased risk of the composite adverse outcome of treatment failure or death (Table 3). Increased baseline AFB score was also just significantly associated with composite outcomes (OR, 3.17; 95%CI, 0.95–10.57; p=0.06). Being resident in Benin appeared to be a protective factor against composite outcome, without statistical significance (OR, 0.71; 95%CI, 0.35–1.44; p=0.34).

Discussion

Positive HIV status was the first predictor of TB treatment failure. Male gender was the second predictor of TB treatment failure. These findings reinforce the necessity of HIV test screening in order to reach 100% of TB patients and to give further attention to those who are male and/or HIV positive in TB clinics. Perriëns et al[14] in Zaire, found an association between HIV and TB treatment failure among PTB+ patients with a risk ratio (RR) of 2.6, 95%CI of 1.4–4.9, p=0.002. Sanchez et al[15] found in a study in Brazil, that the risk of occurrence of unfavourable outcomes during TB treatment was 3.09 times higher among HIV-co-infected vs HIV-negative patients and underlined the necessity of screening TB patients for HIV. In Cameroon, Pefura Yone et al16 found that, being HIV positive was associated with an increased, but non- significant, risk of failure/defaulting of TB treatment (RR, 1.19; 95%CI, 0.88–1.59). The difference between these results and our study could be explained by the fact that their study included 1467 TB cases with 73.8% of them PTB+. In the same study, Pefura Yone et al found that ignorance of HIV status was associated with a statistically significant increased risk of failure/default (RR, 2.30; 95% CI, 1.65–3.21).[16] The role of HIV in TB treatment failure is linked to the active replication of HIV in the presence of Mycobacterium tuberculosis strains.[17,18] This active replication of HIV, induced lymphocyte T4 depletion in gut mucosae. This has been shown to cause chronic enteropathy and malabsorption of anti-TB drugs in PTB+ individuals co-infected with HIV.[19–21] The role of HIV in TB treatment failure could be attenuated by antiretroviral therapy (ART)[22] and many authors have shown the advantages of early initiation of ART after starting TB treatment.[23,24] In other study, HIV among TB patients was associated with low adherence to TB treatment.[25] In the current study, HIV also had a role in composite outcomes (i.e. treatment failure or death), with one third of PTB+ patients who died being HIV positive, and an increase in OR from treatment failure (OR, 10.38) to composite outcome (OR, 12.86). Male gender has also been shown to be a risk factor for unsuccessful TB treatment outcomes in a study in Malaysia.[26] In another study, Pefura Yone et al in Cameroon showed that TB treatment failure rates (28% among patients with Mycobacterium tuberculosis strains) were high among those with positive sputum cultures after the intensive phase of TB treatment.[12] The high failure rate in this study could be due to the fact that the test used to assess TB treatment outcomes among patients who remained positive for AFB after the intensive phase of TB was more sensitive than the AFB technique used in the current study.

There were several limitations to the current study. The retrospective data were incomplete and therefore it was not possible to assess the role of diabetes in TB treatment failure; this non-communicable disease is a public health problem in West Africa. In fact the role of diabetes in TB treatment failure is unclear; some authors, for example Jiménez-Corona et al,[27] have shown that diabetes is associated with a higher probability of TB treatment failure (OR, 2.93; 95%CI, 1.18–7.23; p=0.022), also a study from Guangzhou in China by Fengling et al28 reported a risk ratio (RR) of 4.46, 95%CI 1.46–10.98. In contrast, studies such as those by Duangrithi,[29] Dooley et al,[30] and Prasad et al[31] did not find any association between diabetes and TB treatment failure (p=0.51). However, the role of diabetes in increased risk of failure and death combined, was underlined in a meta-analysis by Baker et al.[32] (RR, 1.69; 95% CI, 1.36–2.12). Another limitation of the current study was a selection bias due to the AFB technique

used for PTB+ diagnosis and TB treatment failure assessment; AFB positivity did not mean the presence of Mycobacterium tuberculosis in every case.[33] Finally, the number of failures and deaths reported in the study limited the power of multivariate analysis, but the use of composite outcomes improved this.

Conclusion

In summary we have shown that risk factors for PTB+ treatment failure were co-infection with HIV and being of male gender; this suggests that national guidelines must emphasize the integration of HIV and TB clinics at all levels of the health system in order to enable collaborative activity. The fact that HIV remains a predictor risk of composite outcome (failure or death) confirms the deadly association between HIV and TB, and suggests that further studies are required in this area.

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Author declaration

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