

# National profile and treatment outcomes of adult smear-negative pulmonary TB patients in Benin

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**Background:** In Benin, patients with smear-negative pulmonary TB (SNPTB) are of low priority in the National Tuberculosis Programme (NTP) and little is known about their profile or treatment outcomes.

**Methods:** A retrospective cohort study was carried out to determine characteristics and treatment outcomes in all adults registered with SNPTB in 2009. Findings were compared with patients with new smear-positive pulmonary tuberculosis (PTB) diagnosed in the same period.

**Results:** Of 3140 patients with PTB, 273 (8.7%) had SNPTB, with higher rates in northern and southwestern regions. SNPTB was associated with female gender, older age and HIV-positive status ( $p < 0.01$ ). Patients with SNPTB had a higher proportion of unsuccessful treatment outcomes compared with smear-positive PTB owing to death and loss to follow-up (LFU) ( $p < 0.01$ ). The region with the capital city had the highest rate of LFU. Differences in unsuccessful outcomes between SNPTB and smear-positive PTB were more apparent in persons who were HIV-negative, and among HIV-positives not on antiretroviral treatment.

**Conclusion:** In Benin, treatment outcomes of SNPTB patients were inferior to those with smear-positive PTB, with LFU being a major problem. The Benin NTP needs to better address the problem of patients with SNPTB in terms of monitoring and reporting, treatment management including that associated with HIV care, and reducing LFU.

**Keywords:** Smear-negative pulmonary TB, Benin, Treatment outcome, Loss to follow-up, HIV

## Introduction

Adult patients with sputum smear-negative pulmonary TB (SNPTB) are diagnosed according to international standards if they have a cough for more than 2–3 weeks, negative sputum smears, chest radiographic findings consistent with active TB, and lack of response to a trial of broad-spectrum antimicrobials.<sup>1</sup> Such patients receive lower priority from National Tuberculosis Programmes (NTPs) in terms of follow-up, recording and reporting because they are perceived to be less contagious and therefore less of a risk to the community than smear-positive pulmonary TB (PTB) patients.

In high HIV prevalence countries, especially in sub-Saharan Africa, the number of patients with SNPTB has increased significantly and their outcomes are reported to be worse than those of patients with smear-positive PTB.<sup>2–6</sup> The reasons for this include HIV-related immunosuppression, misdiagnosis and stigma, the latter causing delays in presentation, diagnosis and treatment. In contrast, in countries with a low prevalence of HIV

and TB, outcomes in patients with SNPTB are reported to be no different to those of other patients.<sup>7,8</sup>

Benin is a low-income country in West Africa with an intermediate HIV prevalence.<sup>9</sup> Benin has a functional NTP that is responsible for the management of all TB patients. The NTP registers in total approximately 3500–4000 TB patients per year, of whom only 7–10% are recorded as SNPTB. Although the NTP reports quarterly on cases and outcomes, these reports are focused on smear-positive patients and there is no information on demographic and clinical characteristics, HIV status or treatment outcomes of those with SNPTB. In addition, these patients do not receive directly observed treatment, short course (DOTS). It is therefore important to obtain more information about SNPTB in Benin because of the need to provide optimum individual case management for all TB cases and because the WHO now reports on treatment success for new smear-positive and all newly diagnosed TB patients.<sup>10</sup>

The aim of this study was therefore to describe the epidemiological characteristics and treatment outcomes of patients

registered with SNPTB in Benin and to compare these with patients who were diagnosed as having smear-positive PTB. Specific objectives were to determine among adults (age  $\geq 15$  years) with PTB in the whole population of Benin in 2009: (i) the number and proportion registered as SNPTB; (ii) demographic and HIV-related characteristics of SNPTB and smear-positive PTB; and (iii) treatment outcomes of patients with SNPTB and new smear-positive PTB, stratified by gender, age, region, HIV status and HIV treatment.

## Materials and methods

### Study design

This was a retrospective cohort study of all adult patients recorded as SNPTB and smear-positive PTB in Benin between 1 January and 31 December 2009.

### Setting: general and study site

#### Country

Benin is a West African country with a population of 9 million inhabitants. The country shares borders with Togo in the west, Nigeria in the east, and Burkina Faso and Niger in the north. In this part of Africa, it is notable that the notified TB incidence rate largely varies according to countries. In 2011, it ranged from 57 per 100 000 population in Burkina Faso to 118 per 100 000 population in Nigeria, and was 70 per 100 000 population in Benin. In comparison with its neighbouring countries, Benin has reported the highest treatment success rate among new smear positive and/or culture-positive cases (91% vs  $\leq 84\%$  for the others).<sup>10</sup> The TB programme follows the DOTS strategy and uses recognised international criteria for the diagnosis and treatment of patients with TB.<sup>11,12</sup> Diagnosis, registration and care of TB patients are decentralised to 57 basic management units in the country.

#### TB control

An adult patient is suspected of having TB when he/she coughs for more than 3 weeks and is then asked to provide two sputum samples for acid-fast bacilli (AFB) microscopy. Sputum samples are examined using either auramine phenol staining and fluorescence microscopy, or using Ziehl-Neelsen staining with light microscopy. Patients with at least one sputum smear-positive for AFB are registered as smear-positive PTB. Patients with smear-negative sputum, provided another diagnosis is unlikely, are given a trial of broad-spectrum antibiotics for 2 weeks. If symptoms persist, new sputum samples are taken for smear microscopy and if they are again negative for AFB, chest radiography is done. The presence of radiological signs of TB allows a doctor to consider the patient as having SNPTB and to start TB treatment. No further investigations are routinely undertaken, and culture of sputum for *Mycobacterium tuberculosis* is not done. A similar routine is followed for HIV co-infected patients, with an exception being for those with severe disease in whom there is a lower threshold for starting TB treatment.<sup>1</sup> Almost 100% of adults with suspected PTB submit sputum specimens for smear microscopy.

All SNPTB patients are classified as new cases in the Benin NTP. A positive smear or culture is mandatory for the diagnosis of

re-treatment TB. Bacteriological proof is required for these re-treatment cases to avoid TB treatment wrongly given to patients who may have other respiratory diseases. All new smear-positive PTB and SNPTB patients are treated using the same standardised regimen, consisting of daily rifampicin, pyrazinamide, isoniazid and ethambutol for 2 months (initial phase) followed by daily rifampicin and isoniazid for 4 months (continuation phase). Treatment of smear-positive PTB is directly observed by a healthcare worker during the initial phase, but this does not apply for patients with SNPTB. Treatment is free of charge and is only provided by the NTP. Treatment outcomes are monitored through the use of treatment cards and registers, and cases and their standardised outcomes are reported through quarterly reports. The NTP also has a department with responsibility for looking for patients with smear-positive PTB who discontinue during treatment, but this does not apply to SNPTB.

#### Management of TB/HIV co-infection

All registered TB patients are systematically offered an HIV test, and 99% of them have known HIV status.<sup>13,14</sup> Those who are HIV-positive (17% in the last national report) are offered trimethoprim/sulfamethoxazole (SXT) to prevent other opportunistic infections. For HIV treatment, since 2011 the country follows the 2010 WHO recommendations for the administration of antiretroviral therapy (ART). The regimen usually prescribed is efavirenz, zidovudine and lamivudine, and all co-infected patients can receive ART regardless of their CD4 counts.<sup>15</sup>

### Patients

All adult patients in Benin aged  $\geq 15$  years registered with new pulmonary PTB (SNPTB or new smear-positive PTB) between 1 January and 31 December 2009 were included in the study.

### Data variables, sources of data, and data collection tool

Data variables that were collected included epidemiological characteristics, HIV serological status, sputum smear result, standardised treatment outcomes, TB treatment regimen, and SXT and ART administration. Sources of data were TB registers, co-infection registers and quarterly reports. Data were collected into paper-based study questionnaires.

### Analysis and statistics

Data from the questionnaires were double-entered into an EpiData file (EpiData Software, CDC, Atlanta, GA, USA). Data were analysed by frequencies and percentages for demographic and HIV-associated characteristics and treatment outcomes. Findings in patients with SNPTB were compared with patients who had smear-positive PTB using the  $\chi^2$  test, with RR and 95% CI as appropriate. Levels of significance were set at 5%.

## Results

### Epidemiological characteristics and HIV status

There were 19 782 patients suspected of TB who provided sputum for smear microscopy in 2009. Of these, 3140 were diagnosed and

**Table 1.** Patients with new smear-negative pulmonary TB (SNPTB) and smear-positive pulmonary TB (PTB) registered nationally and in the different regions of Benin in 2009

Region	Total	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]
Benin	3140	273 (8.7)	2867 (91.3)
Northern regions			
Atacora/Donga	200	24 (12.0)	176 (88.0)
Borgou/Alibori	241	33 (13.7)	208 (86.3)
Central region			
Zou/Collines	310	20 (6.5)	290 (93.5)
Southern regions			
Atlantique/Littoral	1256	107 (8.5)	1149 (91.5)
Mono/Couffo	482	55 (11.4)	427 (88.6)
Ouémé/Plateau	651	34 (5.2)	617 (94.8)

<sup>a</sup> The percentage was calculated from the total number of newly diagnosed pulmonary TB cases in each region.

**Table 2.** Demographic characteristics and HIV status of patients with new smear-negative pulmonary TB (SNPTB) and smear-positive pulmonary TB (PTB) in Benin in 2009

Characteristic	Total	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]	p-value
All	3140	273	2867	
Gender				
Male	2016	147 (53.8)	1869 (65.2)	<0.001
Female	1124	126 (46.2)	998 (34.8)	<0.001
Age (years)				
15–24	582	36 (13.2)	546 (19.0)	0.01
25–34	1021	59 (21.6)	962 (33.6)	<0.001
35–44	693	67 (24.5)	626 (21.8)	NS
45–54	449	49 (17.9)	400 (14.0)	NS
55–64	221	26 (9.5)	195 (6.8)	NS
≥65	174	36 (13.2)	138 (4.8)	<0.001
HIV status				
Positive	500	113 (41.4)	387 (13.5)	<0.001
Negative	2570	149 (54.6)	2421 (84.4)	<0.001
Indeterminate	19	1 (0.4)	18 (0.6)	NS
Not recorded	51	10 (3.7)	41 (1.4)	<0.01

<sup>a</sup> The percentage was calculated among new SNPTB and smear-positive PTB patients, respectively.

registered with new PTB. The number and proportion of these patients with new SNPTB and smear-positive PTB for the whole country and in the different regions are shown in Table 1. Of these, 273 adults (8.7%) had SNPTB (mean age 42.4 years). None reported a previous history of TB. A higher proportion of

**Table 3.** Treatment outcomes in patients with new smear-negative pulmonary TB (SNPTB) and smear-positive pulmonary TB (PTB) in Benin in 2009

Outcome	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]	p-value
Total enrolled for treatment	273	2867	
Successful outcome	204 (74.7)	2588 (90.3) <sup>b</sup>	<0.001
Unsuccessful outcome	69 (25.3)	279 (9.7)	<0.001
Failure	0	67 (2.3)	
Death	30 (11.0)	163 (5.7)	<0.001
Loss to follow-up	36 (13.2)	35 (1.2)	<0.001
Transfer out	3 (1.1)	14 (0.5)	NS

NS: not significant.

<sup>a</sup> The percentage was calculated among new SNPTB and smear-positive PTB patients, respectively.

<sup>b</sup> There were 2351 patients (82.0%) who were cured with negative sputum smears at the end of treatment.

SNPTB was found in the regions of Borgou, Atacora and Mono in the northern and southwestern parts of the country. Demographic characteristics and HIV status of patients with new SNPTB and smear-positive PTB are shown in Table 2. There were higher proportions of females, persons aged ≥65 years and persons with HIV-positive status among those with SNPTB compared with smear-positive PTB.

### Treatment outcomes

Treatment outcomes are shown in Table 3. There was a significantly higher rate of unsuccessful outcome in patients with SNPTB, in whom loss to follow-up (LFU) and death were significantly more frequent compared with patients who had smear-positive PTB. Failure rates were just above 2% for new smear-positive PTB: these are not determined for patients with SNPTB in whom follow-up smears in the continuation phase are not carried out. With regard to the high LFU and death in patients with SNPTB, there were no significant differences in relation to gender or age. However, in the Atlantique region, 35 (32.7%) of 107 patients with SNPTB were lost to follow-up, which was significantly higher than that observed in the other regions where there was one patient lost to follow-up ( $p < 0.001$ ).

Treatment outcomes of patients with SNPTB and smear-positive PTB stratified by HIV status are shown in Table 4. In those who were HIV-positive, there was no difference in overall unsuccessful outcome between patients with SNPTB and smear-positive PTB, although there were more patients with SNPTB who were lost to follow-up ( $p < 0.001$ ). In those who were HIV-negative, significantly more patients with SNPTB had an overall unsuccessful outcome compared with smear-positive PTB patients ( $p < 0.001$ ), with the main outcomes significantly different being death (11.4% vs 3.8%;  $p < 0.001$ ) and LFU (10.1% vs 1.3%;  $p < 0.001$ ). For those with indeterminate HIV status ( $n = 19$ ) and HIV status not recorded ( $n = 51$ ), there were no differences in outcomes between the two types of TB.

**Table 4.** Treatment outcomes of new smear-negative pulmonary TB (SNPTB) and smear-positive pulmonary TB (PTB) patients stratified by HIV-positive or HIV-negative status in Benin in 2009

Outcome	HIV-positive		HIV-negative	
	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]
Patients evaluated	113	387	149	2421
Successful outcome	82 (72.6)	310 (80.1)	117 (78.5)	2233 (92.2)
Unsuccessful outcome	31 (27.4)	77 (19.9)	32 (21.5)	188 (7.8)
Failure	0	12 (3.1)	0	55 (2.3)
Death	10 (8.8)	57 (14.7)	17 (11.4)	92 (3.8)
Loss to follow-up	18 (15.9)	4 (1.0)	15 (10.1)	31 (1.3)
Transfer out	3 (2.7)	4 (1.0)	0	10 (0.4)

<sup>a</sup> The percentage was calculated among new SNPTB and smear-positive PTB patients, respectively.

**Table 5.** Treatment outcomes in HIV-infected patients with new smear-negative pulmonary TB (SNPTB) and new smear-positive pulmonary TB (PTB) stratified by antiretroviral treatment (ART) in Benin in 2009

	On ART		No ART	
	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]	SNPTB [n (% <sup>a</sup> )]	Smear-positive PTB [n (% <sup>a</sup> )]
Patients evaluated	59	157	54	230
Successful outcome	50 (84.7)	134 (85.4)	32 (59.3)	176 (76.5)
Unsuccessful outcome	9 (15.3)	23 (14.6)	22 (40.7)	54 (23.5)
Failure	0	6 (3.8)	0	6 (2.6)
Death	3 (5.1)	16 (10.2)	7 (13.0)	41 (17.8)
Loss to follow-up	6 (10.2)	1 (0.6)	12 (22.2)	3 (1.3)
Transfer out	0	0	3 (5.6)	4 (1.7)

<sup>a</sup> The percentage was calculated among new SNPTB and smear-positive PTB patients, respectively.

There were 500 HIV/TB co-infected patients, of whom 494 (98.8%) received SXT (99.7% of smear-positive PTB and 95.6% of SNPTB). Altogether 216 HIV-infected patients (43.2%) were treated with ART, which included 52.2% of HIV-positive SNPTB patients and 40.6% of HIV-positive smear-positive PTB patients. Treatment outcomes of HIV-infected patients with and without ART are shown in Table 5. Among those on ART, there was no difference overall in unsuccessful outcomes between SNPTB and smear-positive PTB. In those not on ART, there was a higher proportion of SNPTB patients overall with unsuccessful outcomes ( $p < 0.01$ ), and this was principally due to a higher LFU ( $p < 0.001$ ).

## Discussion

This is the first national study in Benin that has assessed the burden of SNPTB and its treatment outcomes in relation to baseline characteristics, HIV status, and HIV care and treatment. The

main findings were that almost 10% of patients with pulmonary disease had SNPTB, with higher rates seen in the northern and southwestern regions of the country. Being female, age  $\geq 65$  years and being HIV-positive were associated with SNPTB. In terms of treatment outcomes, patients with SNPTB experienced a higher overall rate of unsuccessful outcome compared with patients who had smear-positive PTB, and this was mainly due to a higher rate of death and LFU. There was no influence of age and gender on these findings. However, the majority of patients lost to follow-up resided in the Atlantique region, which houses the economic capital city of the country, Cotonou. Differences in unsuccessful outcome between SNPTB and smear-positive PTB patients were more apparent in persons who were HIV-negative and in persons who were HIV-positive but not on ART, with LFU being the major problem.

The strengths of this study are that it covered the whole population and it was therefore nationally representative of the

epidemiology of TB in Benin. All adults suspected of PTB submitted sputum specimens and all registered patients were included, thus there was no need for any sampling framework. The study report also followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>16</sup> Limitations include the operational nature of the study, the use of routine data from registers and quarterly reports which may be inaccurate, and lack of *M. tuberculosis* culture facilities to confirm whether or not patients truly had SNPTB.

There has been concern that Benin under-reports the number of patients with SNPTB. However, a study in 2006 and 2007 in the largest basic management unit found a small proportion of patients with smear-negative culture-positive TB, indicating that there may not be a high prevalence of true smear-negative disease in the country.<sup>17</sup> The current study found higher rates of SNPTB in the northern and southwestern regions of the country where the incidence of TB is much lower than in the south.<sup>18</sup> It is possible that doctors are under less pressure of work in the north and southwestern regions of the country and therefore have more time to consider and follow the correct algorithms and procedures for the investigation of SNPTB.<sup>19</sup> There were higher rates of SNPTB in females and in those who were HIV-positive, and this is in agreement with other findings in Africa showing that HIV infection targets young women who then are at increased risk of TB.<sup>2,3</sup> The finding of SNPTB in older persons also makes sense. Older people may be at risk of chronic pulmonary disease due to fibrosis or occupational exposure and it is possible, as has been shown in other studies,<sup>5,19</sup> that SNPTB is wrongly diagnosed.

There were generally poor treatment outcomes in patients with SNPTB, especially in those who were HIV-negative and in those who were HIV-positive but not on ART. Treatment outcomes in HIV-positive patients with TB in programme settings before the advent of ART were very poor in sub-Saharan Africa, largely owing to HIV-related opportunistic infections as well as delays in diagnosis and treatment due to stigma and other factors causing an increase in mortality.<sup>19,20</sup> In HIV-negative patients, poor treatment outcomes were probably related to misdiagnosis or poor compliance with treatment.<sup>19,20</sup> In the current study, there were high rates of LFU, which compromised treatment outcomes especially in the Atlantique region. Previous research in Africa has identified death, transfer-out and discontinuation of treatment due to side effects or poor reception at health facilities as being responsible for LFU.<sup>21</sup> The reasons for LFU in SNPTB patients in Benin are not known, but it was more common in the region housing the capital city and probably relates to the challenges of urban TB control, a mobile urban population, lack of attention paid by the NTP to this category of patient, and death.

This study has important implications for the Benin NTP, whose outcome data reported from the treatment of new smear-positive PTB are excellent, with a success rate of 91% in 2010.<sup>13</sup> First, there is a need for SNPTB to assume a higher status within the programme and for treatment outcomes to be monitored, recorded and reported. Second, more attention needs to be paid to improving treatment outcomes of SNPTB. DOTS should be administered for SNPTB, and an active search made for those who discontinue therapy during treatment. Third, although there is good uptake of HIV testing and SXT, more patients need to access ART as this therapy improved TB treatment outcomes both in SNPTB and smear-positive PTB patients. This is not easy to do and may require better integration of HIV and TB services

as well as improvement in ART accessibility in the country. Finally, the programme must reduce the number of patients who are lost to follow-up and focus efforts around the Atlantique region and the capital city of Cotonou.

## Conclusion

This national study in Benin found that almost 10% of patients with pulmonary disease had SNPTB, with higher rates seen in the northern and southwestern regions of the country. Certain characteristics such as being female, age  $\geq 65$  years and being HIV-positive were associated with SNPTB, and treatment outcomes of these patients were in general inferior to those of patients with smear-positive PTB. LFU was a major cause of unsuccessful treatment outcome. The Benin NTP needs to pay more attention to the problem of SNPTB in terms of monitoring, recording and reporting, better treatment management including that associated with HIV care, and reducing LFU.

**Authors' contributions:** SAd, GAd and SAn conceived the study; ADH, AT and SAd designed the study protocol; GAg and SAd collected data on a standardised paper-based study questionnaire; SAd, DA and GAd collected data into EpiData files; ADH, SGH and SAd carried out analysis and interpretation of the data; ADH, SGH and SAd drafted the manuscript; DA, AT, GAd and SAn critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. SAd is guarantor of the paper.

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**Competing interests:** None declared.

**Ethical approval:** This study was approved by the Ethics Advisory Board of the International Union Against Tuberculosis and Lung Disease (Paris, France) and the Benin National Tuberculosis Programme (NTP) management team. Because of the retrospective nature of this study, approval of the Benin ethics committee was not required according to their policy.

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