National Profile and Treatment Outcomes of Patients with Extrapulmonary Tuberculosis in Bénin

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Abstract

Background: In sub-Saharan Africa, there is a dearth of published literature on extrapulmonary tuberculosis (EPTB).

Objective: To describe demographic, diagnostic and HIV-status characteristics of patients with EPTB in Bénin, their treatment outcomes, and among those who completed their treatment in the Centre National Hospitalier de Pneumophthisiologie (CNHP-P), the proportion whose bodyweight increased during treatment.

Material and Findings: This was a retrospective cohort study with comparisons made between EPTB and new smear-positive pulmonary tuberculosis (NPTB) patients diagnosed in the country from January to December 2011. There were 383 EPTB patients (9% of all TB cases) with a mean age of 35 years, male/female ratio of 1.3 and important regional variation. There were significantly more females (p = 0.001), children <15 years (p < 0.001) and HIV-positive patients (p = 0.005) with EPTB compared with NPTB. Pleural effusion, spinal and lymph node tuberculosis accounted for 66% of all EPTB. Children < 15 years represented 16% of cases, with lymph node disease being most common among them (p < 0.001). Of 130 EPTB patients registered in CNHP-P, 7% had a confirmed bacteriological/histological diagnosis. There were 331 (86%) patients with all these patients from one region. The best treatment completion rates were in children < 15 years (OR:3.5, 95%CI:1.0–14.8) while patients with pleural effusion and ascites had the worst outcomes. Of 72 HIV-coinfected patients, 88% were on antiretroviral therapy (ART). HIV-positive status was associated with poor outcomes while those on ART fared better. In the CNHP-P, more than 80% who completed their treatment showed an increase in bodyweight and this was more evident in HIV-positive compared with HIV-negative patients (p = 0.03).

Conclusion: Patients with EPTB generally do well in Bénin, although the TB Programme would benefit through more attention to accurate diagnosis and earlier start of ART in HIV-infected patients.

Introduction

Patients with extrapulmonary tuberculosis (EPTB), i.e., tuberculosis (TB) without associated lung involvement, usually receive less priority in national TB Programmes. However, in many countries, their numbers remain either stable or are increasing while numbers of patients with pulmonary disease are decreasing [1]. In populations with a low prevalence of HIV infection, these patients usually represent 15% to 20% of all TB cases. However, this proportion is thought to be higher in populations with a high prevalence of HIV infection [2], the latter mostly occurring in sub-Saharan Africa.

Confirmation of the diagnosis of EPTB, as recommended by the World Health Organization (WHO) [3], is not easy. Diagnosis in many low income countries is often based on presumptive and circumstantial evidence, with the consequence of a possible misdiagnosis [4].

In Bénin, information is limited about this type of TB, especially with regard to epidemiological characteristics and the most predominant forms of EPTB. Furthermore, the treatment outcomes of patients with EPTB are analyzed in the routine programme together with those of patients with smear-negative pulmonary tuberculosis, the latter in a recent study showing higher rates of unsuccessful treatment compared with new smear-positive pulmonary tuberculosis (NPTB) [5]. These treatment outcomes are usually reported quarterly, using standard classifications; and a “treatment completion” is considered a successful outcome [3]. However, treatment can be completed without improvement of the patient’s health condition, particularly if the diagnosis of EPTB is wrong. The disappearance of initial symptoms along with weight
gain in patients who have completed treatment might be a better
gauge of successful treatment.

In this study, we aimed to describe the pattern of disease in
patients registered as EPTB, their treatment outcomes and
among those who completed their treatment in the Centre
National Hospitalier de Pneumo-Phthisiologie (CNHP-P), the
proportion whose weight increased during the course of
treatment. Specific objectives were to determine in Bénin for
2011: i) the number (and proportion) of patients recorded as
EPTB and NPTB among all TB cases, ii) demographic, clinical
characteristics and HIV-status of patients with EPTB and NPTB,
iii) treatment outcomes of patients with EPTB and NPTB and
the influence of HIV-infection and antiretroviral therapy and iv)
the proportion who increased in weight among those who
completed their treatment in the CNHP-P.

Materials and Methods

Ethics Statements

This study was approved by “Ethics Advisory Group” of the
International Union against Tuberculosis and Lung Disease, Paris,
France and “Bénin TB Control Programme Coordination”.
Because of its retrospective nature, the local Ethics Committee
approval (“Comité National d’Ethique pour la Recherche en
Santé”) was not required according to the country’s recommen-
dations.

This study uses already collected data, and written informed
consent -given by participants was not possible to obtain. Patient
records/Information was collected anonymously. Each participant
of this study was attributed a unique identifier number, in order to
compare data files that have been double entered. After checking
and cleaning the database, the unique identifier numbers have
been removed and participants were de-identified prior to analysis.
There was no way to recognize them. All databases were kept
confidential and have been protected with a password, with only
access by authorized persons.

Study Design

This was a retrospective cohort study of all patients recorded as
EPTB and NPTB between 1st January and 31st December 2011 in
Bénin.

Setting – General and Study Site, Including TB
Programme

Bénin is a West-African country with a population of 9 million
and a HIV prevalence rate of 1.1% [6]. Seven to 10% of the 4000
TB patients registered each year have EPTB. There is a national
TB Programme which follows the DOTs strategy and uses
recognised international criteria for the diagnosis and treatment of
TB patients [7]. Diagnosis, registration and care are decentralised
to 57 Basic Management Units in the country. Of them, the largest
is the CNHP-P of Cotonou, the economic capital. It houses the
Mycobacteria Reference Laboratory where culture and molecular
diagnostics can be performed for the whole the country.

Diagnosis and management of NPTB and EPTB in the
Bénin TB control Programme. Pulmonary TB diagnosis is
made with respect of WHO recommandations [2]. A person who
coughs more than 3 weeks is regarded as having presumptive
pulmonary tuberculosis. He/she is requested to provide two
sputum samples for acid-fast bacilli microscopy. Sputum samples
are examined using either auramine-phenol staining and fluores-
cence microscopy or Ziehl-Neelsen staining with light microscopy.
Patients with at least one sputum smear positive for acid-fast bacilli
and who have never been previously treated for TB (or less than
one month) are registered as NPTB.

A patient is considered as having presumptive EPTB if he/she
has symptoms suggestive of TB related to an extrapulmonary site,
with a decision then made by a medical doctor to treat with a full
course of anti-tuberculosis treatment. Usually, because of difficul-
ties in accessing and obtaining specimens from different biological
sites, TB treatment is started based on symptoms and other
circumstantial evidence that includes laboratory investigations and
radiographic abnormalities. Whenever possible, specimens col-
lected should be submitted for bacteriological investigation (direct
microscopy examination or standard culture, or molecular tests).
Rarely, these specimens are also analysed in histology laboratories.
In terms of registration, for patients who have TB in both
pulmonary and extrapulmonary sites, they are classified as having
“pulmonary TB”. For patients with TB in several extrapulmonary
sites (e.g., lymph nodes and pleural effusion), they are registered
according to the most severe form of disease.

All NPTB and EPTB cases are treated with the same
standardized first-line anti-tuberculosis regimen. Patients receive
daily rifampicin, pyrazinamide, isoniazid and ethambutol for 2
months (initial phase) followed by daily rifampicin and isoniazid
for 4 months (continuation phase). Contrary to the treatment of
NPTB, EPTB treatment is not directly observed during the
intensive phase and anti-tuberculosis drugs are given every two
weeks for self administration. Treatment is free and is only
provided by the Programme for all TB patients. TB drugs are not
available in private pharmacies in the city or country. While
sputum microscopy examination is performed during follow-up
of NPTB patients, those with EPTB are monitored clinically and in
particular body weight is measured and recorded during treatment
on personal treatment cards (at two, five and six months).

Standardized treatment outcomes are monitored through the
use of treatment cards and registers, and number of cases and
outcomes are quarterly reported.

TB/HIV co-infection management. Every patient who is
diagnosed with TB (including EPTB) is systematically offered an
HIV test using rapid tests and following national guidelines [8].
Those who are found to be HIV positive receive in addition
cotrimoxazole. Since 2011 and according to recent WHO
guidelines, all TB cases (including EPTB) are eligible for antiretroviral therapy (ART) [9]. The first line ART regimen is
elavirenz and two other drugs, zidovudine and lamivudine. If
there is anemia (Haemoglobin <7 g/dl) or a low platelet count (<
75000/l) zidovudine is replaced by stavudine. Cotrimoxazole and
ART are provided free of charge.

Study Patients

All patients recorded as EPTB and NPTB between 1st January
and 31st December 2011 in Bénin were included in the study.

Data Variables, Sources of Data and Data Collection

Variables for NPTB and EPTB patients included: sex, age,
residence by region, HIV-status (positive, negative, unknown),
cotrimoxazole and ART administration, treatment outcomes
(completion, death, loss-to-follow-up, not evaluated). Variables
for EPTB patients included in addition:- sites of disease (pleural
effusion, spinal, lymph node, bone or joint, ascites, other and not
recorded) and weight change during treatment for patients
managed in the CNHP-P. Individual data for EPTB patients
were collected from TB registers, laboratory TB registers,
treatment cards and TB medical personal files into a standardized
paper-based study questionnaire. For NPTB patients, data were
collected from quarterly and annual reports.
Results

Numbers, Epidemiological and Diagnostic Characteristics of TB Patients

The number and proportion of patients with EPTB and NPTB diagnosed in the same time period are shown in Table 1. Overall, EPTB patients represented 9% of all TB cases (mean age: 34.5 years, male/female ratio: 1.3), with a large variation between regions from 23% in Borgou (North of the country) to 5% in Ouémé (South of the country). All patients were new cases. Demographic characteristics and HIV-status of patients with EPTB and NPTB are shown in Table 2. There were significantly more females (p = 0.001), children under 15 years (p < 0.001) and HIV-positive patients (p = 0.005) diagnosed with EPTB compared with NPTB.

The different sites of EPTB are presented in Table 3. Pleural effusion, spinal disease and lymph node disease accounted for 66% of all EPTB cases. Demographic characteristics and HIV-status in relation to the different sites of EPTB are shown in Table 4. There was no association between gender and different types of EPTB. Children (under 15 years) represented 16% (62/383) of all EPTB cases diagnosed. Lymph node TB was more common in children than adults (p < 0.001) while TB pleural effusion was more common in adults (p < 0.001). Otherwise, there were no significant associations between age and other sites of EPTB. Compared with other regions, there was significantly more lymph node TB (OR: 2.6, 95%CI: 1.4–4.7, p = 0.001) and bone or joint TB (OR: 4.9, 95%CI: 2.1–11.6, p < 0.001) in Zou while there was significantly more TB pleural effusion in the Atlantique region. TB pleural effusion was significantly more common in HIV-positive patients compared with HIV-negative patients (p < 0.001).

The only health facility where confirmation of diagnosis has been assessed was CNHP-P. Of 130 EPTB patients registered and followed-up in this centre, the diagnosis was confirmed for 9 cases (7%): 2 with positive Mycobacterium tuberculosis culture and direct smear examination, 1 with positive culture alone, 1 with positive direct smear examination alone and 5 with histology showing tuberculous granuloma. For aspirates of pleural or peritoneal fluid, measurements of protein concentration and cytological analysis were performed for all cases.

Treatment Outcomes

Treatment outcomes of patients with EPTB and NPTB are presented in Table 5. Overall, 86% of patients successfully completed treatment. There were significantly more patients with EPTB who were lost-to-follow-up compared with NPTB (p < 0.001). Treatment outcomes in relation to demographic characteristics, sites of disease, HIV-status and ART administration to co-infected patients are shown in Table 6. No association was found between gender and treatment outcomes. However, treatment success was higher in children aged <15 years (OR: 3.5, 95%CI: 1.0–14.8, p = 0.02). All patients who were lost-to-follow-up during treatment were from the Atlantique region and patients with pleural effusion or ascites had the worst completion rates.

Finally, of 72 HIV-TB co-infected patients, 99% received cotrimoxazole and 88% were given ART. HIV-positive patients were at higher risk of death than HIV-negative patients during treatment (OR: 2.5, 95%CI: 1.0–5.7, p = 0.02). In HIV-positive patients, those on ART had much better outcomes than those not on ART (82.5% versus 44.4%, p = 0.03). The concomitant administration of ART was also associated with a lower loss-to-follow-up rate (OR: 31, 95%CI: 2.2–922, p = 0.005). There were no other significant differences.

Weight Variation during Treatment

The change in body weight among patients who completed their treatment in relation to HIV-status in the CNHP-P, the largest basic management unit in Bénin, is shown in Table 7. Up to 80% of patients who successfully completed treatment showed an increase in body weight, and this was more apparent among HIV-positive than HIV-negative patients (p = 0.03).

Discussion

This is the first study in Bénin to describe the epidemiological and diagnostic characteristics and treatment outcomes of EPTB patients. Patients with EPTB constituted less than 10% of all notifications, with some parts of the country showing higher prevalence than others. EPTB appeared to be more common in females, children under the age of 15 years and in those who were HIV-positive. Predominant sites of disease were pleural, spinal and...
lymph node, with TB lymph node disease being more common in children and pleural effusion being more common in adults, especially those HIV-positive. Diagnostic confirmation was rare even in the largest basic management unit in the country.

Successful treatment completion was good especially in children, although there was a higher rate of loss-to-follow-up when compared with patients who had NPTB. Interestingly, all patients lost to follow-up were from a specific region of Benin. Patients with pleural effusion and ascites had the worst treatment completion rates. Patients with HIV-associated TB remained at higher risk of death compared with those who did not have HIV-infection, although those on ART fared much better. Finally, in CNHP-P where weight during the treatment has been collected, there was a significant weight gain amongst those who completed treatment, with the change in weight being more evident in patients who were HIV-positive compared with those who were not HIV-infected.

The strengths of this study were that it involved the whole population and it was therefore nationally representative of the epidemiology of EPTB in Benin. There was no need for any sampling framework. In addition, basic management units are regularly supervised every three months by the TB control Programme coordination, and during these supervisory visits, quarterly reports and patients’ personal data are systematically reviewed and if necessary, corrections are made. Limitations related to the operational nature of the study which used already collected data from registers, medical files and quarterly reports which are difficult to validate when conducting a retrospective record review. In spite of regular supervision, some errors could also remain in the consulted documents.

There were important variations in the proportion of EPTB patients in the different regions of the country; and this could be related to the implication of medical doctors in the diagnosis of this form of TB. In Borgou region, where the highest proportion of EPTB cases was reported from, the large majority of these patients were diagnosed in two well frequented hospitals because of their good reputation (a confessional centre and a teaching hospital).

The proportion of patients diagnosed with EPTB in Benin was lower than that reported from other parts of the world [1,10–15], and few diagnoses were confirmed. Lack of appropriate and specific diagnosis in EPTB in sub-Saharan Africa remains a continuing source of debate [4]. There are recommendations that the diagnosis of EPTB should be based on at least one specimen with confirmed *Mycobacterium tuberculosis* (using microscopy examination, culture or rapid molecular testing), histological or strong clinical evidence consistent with active EPTB, followed by a clinician decision to treat with a full course of tuberculosis chemotherapy [3].

However, in resource-poor countries like Benin, following these recommendations is difficult. Obtaining the diagnosis is difficult for several reasons, such as lack of specialised physicians, microbiologists and pathologists, weak laboratory infrastructure and poor access to radiography and other more sophisticated imaging technologies such as ultrasound and computerised tomography scans.

The finding of females, children and HIV-positive patients having a higher prevalence of EPTB is in line with reports from other countries [1,12,16,17]. For children, the predominant site of TB reported in the literature is usually lymph node disease [1], although in adults a wide variety of patterns is reported from other countries which may depend to a large extent on resources

### Table 2. Demographic characteristics and HIV-status in patients with extrapulmonary tuberculosis and new smear-positive pulmonary tuberculosis, Benin, 2011.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EPTB (%)</th>
<th>NPTB (%)</th>
<th>p (value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>216 (56.4)</td>
<td>2158 (64.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>167 (43.6)</td>
<td>1173 (35.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>00–14</td>
<td>62 (16.2)</td>
<td>62 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15–24</td>
<td>62 (16.2)</td>
<td>608 (18.3)</td>
<td>NS</td>
</tr>
<tr>
<td>25–34</td>
<td>75 (19.6)</td>
<td>1035 (31.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35–44</td>
<td>64 (16.7)</td>
<td>743 (22.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>45–54</td>
<td>58 (15.1)</td>
<td>472 (14.2)</td>
<td>NS</td>
</tr>
<tr>
<td>55–64</td>
<td>36 (9.4)</td>
<td>252 (7.6)</td>
<td>NS</td>
</tr>
<tr>
<td>≥65</td>
<td>26 (6.8)</td>
<td>159 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV-status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>72 (18.8)</td>
<td>449 (13.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Negative or unknown</td>
<td>312 (81.5)</td>
<td>2882 (86.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Total</td>
<td>383</td>
<td>3331</td>
<td></td>
</tr>
</tbody>
</table>

Note: EPTB: Extrapulmonary tuberculosis, NPTB: New smear positive pulmonary tuberculosis; TB: Tuberculosis.

doi:10.1371/journal.pone.0095603.t002

### Table 3. Different sites of extrapulmonary tuberculosis in Benin, 2011.

<table>
<thead>
<tr>
<th>Sites</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>94 (24.5)</td>
</tr>
<tr>
<td>Spine</td>
<td>82 (21.4)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>77 (20.1)</td>
</tr>
<tr>
<td>Bone and Joint</td>
<td>29 (7.6)</td>
</tr>
<tr>
<td>Ascites</td>
<td>15 (3.9)</td>
</tr>
<tr>
<td>Other*</td>
<td>17 (4.4)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>69 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>383</td>
</tr>
</tbody>
</table>

Note: * Others include pericardial TB (n = 10), cerebral TB (n = 1), meningeal TB (n = 1), female genital TB (n = 1), male genital TB (n = 3), skin TB (n = 1).

TB: Tuberculosis.

doi:10.1371/journal.pone.0095603.t003
Table 4. Epidemiological characteristics and HIV-status in relation to the different sites of extrapulmonary tuberculosis, Bénin, 2011.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Pleural effusion</th>
<th>Spine</th>
<th>Lymph node</th>
<th>Bone/Joint</th>
<th>Ascites</th>
<th>Other *</th>
<th>Not recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>216</td>
<td>58 (26.9)</td>
<td>39 (18.1)</td>
<td>42 (19.4)</td>
<td>16 (7.4)</td>
<td>8 (3.7)</td>
<td>12 (5.6)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Female</td>
<td>167</td>
<td>36 (21.6)</td>
<td>43 (25.7)</td>
<td>35 (21)</td>
<td>13 (7.8)</td>
<td>7 (4.2)</td>
<td>5 (3)</td>
<td>28 (16.8)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>62</td>
<td>3 (4.8)</td>
<td>12 (19.4)</td>
<td>24 (38.7)</td>
<td>8 (12.9)</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
<td>12 (19.4)</td>
</tr>
<tr>
<td>≥15</td>
<td>321</td>
<td>91 (28.3)</td>
<td>70 (21.8)</td>
<td>53 (16.5)</td>
<td>21 (6.5)</td>
<td>13 (4)</td>
<td>16 (5)</td>
<td>57 (17.8)</td>
</tr>
<tr>
<td>Region</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atacora</td>
<td>18</td>
<td>1 (5.6)</td>
<td>3 (16.7)</td>
<td>5 (27.8)</td>
<td>0 (0)</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Borgou</td>
<td>58</td>
<td>10 (17.2)</td>
<td>19 (32.8)</td>
<td>10 (17.2)</td>
<td>8 (13.8)</td>
<td>2 (3.4)</td>
<td>2 (3.4)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Zou</td>
<td>70</td>
<td>8 (11.4)</td>
<td>18 (25.7)</td>
<td>24 (34.3)</td>
<td>14 (20)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Mono</td>
<td>51</td>
<td>3 (5.9)</td>
<td>9 (17.6)</td>
<td>3 (5.9)</td>
<td>3 (5.9)</td>
<td>2 (3.9)</td>
<td>1 (2)</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td>Atlantique</td>
<td>146</td>
<td>69 (47.3)</td>
<td>27 (18.5)</td>
<td>23 (15.8)</td>
<td>1 (0.7)</td>
<td>8 (5.5)</td>
<td>12 (8.2)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Oulénié</td>
<td>40</td>
<td>3 (7.5)</td>
<td>6 (15)</td>
<td>12 (30)</td>
<td>3 (7.5)</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>72</td>
<td>29 (40.3)</td>
<td>4 (5.6)</td>
<td>15 (20.8)</td>
<td>0 (0)</td>
<td>5 (6.9)</td>
<td>3 (4.2)</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>306</td>
<td>65 (21.2)</td>
<td>74 (24.2)</td>
<td>61 (19.9)</td>
<td>29 (100)</td>
<td>10 (3.3)</td>
<td>14 (4.6)</td>
<td>53 (17.3)</td>
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<td>Unknown</td>
<td>5</td>
<td>0 (0)</td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>383</td>
<td>94</td>
<td>82</td>
<td>77</td>
<td>29</td>
<td>15</td>
<td>17</td>
<td>69</td>
</tr>
</tbody>
</table>

Note: * Others include pericardial TB (n = 10), cerebral TB (n = 1), meningeal TB (n = 1), female genital track TB (n = 1), male genital track TB (n = 3), skin TB (n = 1).

TB: Tuberculosis.
doi:10.1371/journal.pone.0095603.t004
available for diagnosis [16,18–25]. In Bénin, we found few patients with TB meningitis, while the proportion diagnosed in others studies has been higher [23,24]. This may be due to good coverage of BCG immunization in Bénin and also the difficulties in establishing the diagnosis in this type of disease [22,26,27].

Although successful treatment completion was reasonable, this could be improved by reducing the losses-to-follow-up, especially in Atlantique region, where Cotonou, the economic capital city of the country, is located. One of the reasons for patients being lost-to-follow-up may be misdiagnosis, and this has been found in other parts of Africa. Patients with other pathology such as lung cancer, mesothelioma or systemic disease may be wrongly treated with anti-tuberculosis drugs without improvement, persuading them to seek alternative opinions and stopping treatment. Another reason is that some patients reported as lost-to-follow-up may have died, and this has also been found in other studies [28]. Finally more attention needs to be paid to accurate diagnosis of patients with pleural effusion and ascites, the latter especially having a wide differential diagnosis that includes chronic liver disease.

### Table 5. Treatment outcomes of patients with extrapulmonary tuberculosis and new smear-positive pulmonary tuberculosis in Bénin, 2011.

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>EPTB (%)</th>
<th>NPTB (%)</th>
<th>p (value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful completion</td>
<td>331 (86.4)</td>
<td>2988 (89.9)**</td>
<td>0.03</td>
</tr>
<tr>
<td>Failure</td>
<td>0 (0)</td>
<td>99 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>32 (8.4)</td>
<td>196 (5.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Loss-to-follow up</td>
<td>15 (3.9)</td>
<td>27 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>5 (1.3)</td>
<td>14 (0.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total evaluated</td>
<td>383</td>
<td>3324 *</td>
<td></td>
</tr>
</tbody>
</table>

Note: EPTB: Extrapulmonary tuberculosis; NPTB: New smear positive pulmonary tuberculosis.

* 7 patients of the 3331 were wrongly registered as new smear-positive TB and were removed from the cohort analysis one year later.
** 2800 of the 2988 patients were cured with negative sputum smear examination for acid-fast bacilli.
doi:10.1371/journal.pone.0095603.t005

### Table 6. Treatment outcomes of patients with extrapulmonary tuberculosis in relation to demographic characteristics, regions, HIV status and ART administration in those with HIV coinfection, Bénin, 2011.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Completion</th>
<th>Death</th>
<th>Loss-to-follow-up</th>
<th>Not evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>216</td>
<td>183 (84.7)</td>
<td>17 (7.9)</td>
<td>11 (5.1)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Female</td>
<td>167</td>
<td>148 (88.6)</td>
<td>15 (9)</td>
<td>4 (2.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>62</td>
<td>59 (95.2)</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>≥15</td>
<td>321</td>
<td>272 (84.7)</td>
<td>30 (9.3)</td>
<td>14 (4.4)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atacora</td>
<td>18</td>
<td>17 (94.4)</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Borgou</td>
<td>58</td>
<td>47 (81)</td>
<td>10 (17.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Zou</td>
<td>70</td>
<td>67 (95.7)</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Mono</td>
<td>51</td>
<td>47 (92.2)</td>
<td>4 (7.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atlantique</td>
<td>146</td>
<td>114 (78.1)</td>
<td>14 (9.6)</td>
<td>15 (10.3)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Oueumé</td>
<td>40</td>
<td>39 (97.5)</td>
<td>1 (2.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleurisy</td>
<td>94</td>
<td>73 (77.7)</td>
<td>11 (11.7)</td>
<td>7 (7.4)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Spine</td>
<td>82</td>
<td>75 (91.5)</td>
<td>4 (4.9)</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>77</td>
<td>70 (90.9)</td>
<td>4 (5.2)</td>
<td>3 (3.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bone and Joints</td>
<td>29</td>
<td>27 (93.1)</td>
<td>2 (6.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ascites</td>
<td>15</td>
<td>10 (66.7)</td>
<td>4 (26.7)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other*</td>
<td>17</td>
<td>14 (82.4)</td>
<td>1 (5.9)</td>
<td>2 (11.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>69</td>
<td>62 (89.9)</td>
<td>6 (8.7)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>HIV-Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>306</td>
<td>270 (88.2)</td>
<td>21 (6.9)</td>
<td>11 (3.6)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>HIV positive on ART</td>
<td>63</td>
<td>52 (82.5)</td>
<td>9 (14.3)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>HIV positive not on ART</td>
<td>9</td>
<td>4 (44.4)</td>
<td>2 (22.2)</td>
<td>3 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>383</td>
<td>331</td>
<td>32</td>
<td>15</td>
<td>5 (0)</td>
</tr>
</tbody>
</table>

Note: * Others include pericardial TB (n = 10), cerebral TB (n = 1), meningeal TB (n = 1), female genital track TB (n = 1), male genital track TB (n = 3), skin TB (n = 1). TB: Tuberculosis; ART: Antiretroviral therapy.
doi:10.1371/journal.pone.0095603.t006
HIV-positive patients with EPTB were at higher risk of death than HIV-negative patients, despite good coverage with ART. Often, HIV-infected patients with EPTB present with advanced immune suppression with CD4 counts <200 cells/µl, and hence their classification as a WHO Stage 4 AIDS defining disease. As a result, patients can also be affected by other opportunistic diseases that can result in death [29,30]. The time of start of ART in relation to start of anti-TB treatment is an important factor that determines mortality, and late initiation of ART is associated with increased case fatality [9]. A weakness of this study was the lack of information about when ART was started.

Finally, we assessed whether patients who completed treatment increased their weight, the latter adding to the evidence to support a successful treatment completion. The large majority of patients who completed their treatment showed an increase in body weight, especially in HIV-positive patients, and this has been found elsewhere. As recommended in guidelines, weight should be regularly measured during the course of treatment [4,31].

The findings of this study have several implications for the Bénin TB control Programme. First, there is a need to improve the regular follow-up of patients during treatment must improve especially in more difficult-to-diagnose cases of EPTB [32,33]. Second, the introduction of rapid molecular tests as Xpert MTB/RIF should be considered especially for the diagnosis of EPTB in the country and to perform appropriate examinations when needed such as mycobacterial culture on tissue specimens. The large majority of patients increased their weight, the latter adding to the evidence to support a successful treatment completion. The large majority of patients who completed their treatment showed an increase in body weight, especially in HIV-positive patients, and this has been found elsewhere. As recommended in guidelines, weight should be regularly measured during the course of treatment [4,31].

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Author Contributions

Conceived and designed the experiments: S. Ade ADH AT S. Anagonou. Performed the experiments: S. Ade G. Ade G. Agodokpessi S. Azon. Analyzed the data: S. Ade AT ADH. Contributed reagents/materials/analysis tools: G. Ade S. Anagonou S. Azon CA. Wrote the paper: S. Ade ADH AT G. Ade G. Agodokpessi CA S. Azon S. Anagonou.

References


