Smear Negative Tuberculosis in HIV-Infected Patients: Treatment Outcomes and Factors Associated with Delay in Initiating Treatment Peru 2005-2010

Lilian Saavedra Sevillano

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2012

Committee:

Joseph R. Zunt, Chair

Mark A. Micek

Program Authorized to Offer Degree:

Global Health

University of Washington

Abstract

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Peru 2005-2010

Lilian Saavedra Sevillano

Chair of the Supervisory Committee:

Associate Professor Joseph R. Zunt

Objectives: The primary aims of this study were to estimate the proportion of SnPTB in HIV co-infected patients, to identify the clinical, demographic, and radiographic factors associated with SnPTB, and to compare TB treatment outcomes and survival rates between patients diagnosed with SnPTB and SpPTB.

Methods: A retrospective cohort of TB/HIV co-infected patients who started TB treatment between 2005 and 2010 under the TB control Program at posts, health centers, hospitals, or at one of five reference hospitals providing care for HIV-infected patients under the Ministry of Health system in three regions of the Peruvian Amazon.

Results: Of the 332 patients with TB and HIV co-infection, 220 patients were included in this study. 56.8% patients were diagnosed with SnPTB and in the multivariate model, three factors were associated with a diagnosis of SnPTB: concurrent opportunistic infection (OR=4.8, 95%CI: 1.4-16.4), and alveolar infiltrate (OR=7.9, 95%CI: 1.9-31.8) or miliary infiltrate (OR=29.3, 95%CI: 4.3-199.7) on chest radiography. Forty-five percent of patients had an unsuccessful. Treatment at a level II or III health facility (OR=4.8, 95%CI: 2.1-10.8), and a history of addictive habits (OR=5.7, 95%CI: 1.8-18.2) were associated with increased likelihood of unsuccessful TB treatment outcome. Compared to SpPTB, SnPTB was associated with an 85% increased risk of death at one year (HR=1.85, 95%CI: 1.1-3.24), after adjusting for CD4 cell count, completed treatment, age, concurrent opportunistic infection, chronic pre-existing conditions, and use of HAART. The majority of

deaths (74%) occurred while receiving TB treatment. Among patients with SnPTB, the median delay between diagnosis and initiation of TB treatment was two days (IQR=0-5). In the multivariate analysis, treatment delay was higher among patients with a history of addictive habits (OR=3.6, 95%CI: 1.1-12.1) and in patients living farther from the health facility.

Conclusions: More aggressive TB surveillance and treatment monitoring activities should be routinely performed in smear negative patients. Further studies are needed to develop and evaluate innovative and inexpensive methods to ensure that patients living distant from health facilities or affected by alcohol abuse receive appropriate monitoring and therapy.

Key words: smear negative pulmonary tuberculosis, treatment outcome, HIV infection.

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Chapter One

Introduction

Worldwide, there were 8.8 million incident cases of Tuberculosis (TB) in 2010, with approximately 1.0 -1.2 million (12 -14%) cases occurring in people with HIV infection [1]. In Peru, TB is the most common opportunistic infection in people living with HIV/AIDS. The prevalence of TB is high and there is a concentrated HIV epidemic among men who have sex with men (MSM) [2]. Furthermore, TB is the AIDS defining illness in approximately 28% of AIDS cases, and 50% of persons with AIDS develop TB at some point during their infection [3]. The Peruvian Tuberculosis Control Program reported that the incidence rate of TB among HIV-infected people rose from 28 cases per 100,000 HIV-infected inhabitants in 2004 to 30 cases in 2006 [4].

Although direct sputum microscopy for detection of acid fast bacilli (AFB) is widely used throughout the world, its usefulness in patients with TB and HIV co-infection is limited because of the high proportion of smear-negative pulmonary tuberculosis (SnPTB) and the lower prevalence of cavitary pulmonary disease among HIV-positive patients [5] [6]. The reported proportion of cases of SnPTB in HIV positive patients ranges from 24% to 61% [7] [8] [9] [10].

The clinical characteristics of TB depend on the stage of HIV infection and its associated degree of immunodeficiency, as determined by the CD4 cell count [11]. Although patients with TB and HIV co-infection may have classic symptoms of TB such as cough, weight loss or fever, these symptoms have lower sensitivity for the diagnosis of TB in this population. For example, cough of any duration is 70-90% sensitive for detection of TB in the general population; however this sensitivity falls to 50% in patients with TB and HIV co-infection [12] [13]. Around 80% of pulmonary tuberculosis (PTB) in patients with advanced HIV infection and low CD4+ T lymphocyte counts have atypical chest radiograph

findings [14] [15]. In a study of HIV-infected patients in Botswana, only 0.2% of those screened for TB had chest radiographic findings suggestive of TB [16]. A multicenter trial for the treatment of pulmonary TB in HIV-infected persons in the United States found that patients with negative sputum smears had a higher frequency of normal chest radiographic findings compared to patients with positive sputum smears (15.0% vs. 4.6%; p=0.07) [17] .

Among HIV positive patients with PTB, SnPTB patients have poorer treatment outcomes and a higher early mortality rate, likely due to their high degree of underlying immunosuppression, as well as delays in prompt diagnosis, leading to delays in initiation of anti-TB treatment [18] [19] [20]. A study conducted in Malawi documented a mortality rate of 40% over 8 months in HIV-infected patients with SnPTB compared with a mortality rate of 21% in smear-positive patients (SpPTB) [19].

Several studies have identified factors associated with an eventual diagnosis of TB in smear-negative HIV-infected patients, including older age, male gender, previous diagnosis of pulmonary TB, alcohol abuse, and the presence of chronic medical illnesses [8] [21] [22]. However, few studies have examined the clinical and radiological characteristics associated with smear negativity in HIV co-infected patients or whether such factors vary by geographical location [11] [23].

The primary aims of this study were to estimate the proportion of SnPTB in HIV co-infected patients in the Peruvian Amazon between 2005 and 2010, to identify the clinical, demographic, and radiographic factors associated with SnPTB, and to compare TB treatment outcomes and survival rates between patients diagnosed with SnPTB and SpPTB.

Chapter Two

Methods

1. Study Design and Population

This retrospective cohort study was conducted in three regions of the Peruvian Amazon: Loreto, Ucayali, and San Martin. All consecutive medical records of patients starting TB treatment between 2005 and 2010 under the TB control Program at posts, health centers, hospitals or at one of five reference hospitals providing care for HIV-infected patients in the three regions under study were evaluated for eligibility. In addition, we reviewed the medical records of all patients with a diagnosis of HIV/TB who were registered at the National Strategy of Prevention and Control of HIV/AIDS. Patients' identification numbers were identified from TB and HIV case record books. Inclusion criteria for the study included: 1) age 15 years or older; 2) confirmed HIV-1 infection; 3) admission to a Peruvian Ministry of Health hospital, health center, or post for treatment of TB; and 4) initiation of TB treatment between 2005 and 2010. Patients with extrapulmonary TB or without a medical chart or health facility admission note were excluded. The study was reviewed and approved by the institutional review boards (IRB) of the Asociacion Civil Impacta Salud y Educación Lima-Peru and the University of Washington.

2. Measures and Data collection

Diagnosis of TB in Peru

The gold standard for diagnosis of TB is the bacteriological identification of *Mycobacterium tuberculosis* [10] [24]. The AFB smear of sputum samples is the most common method for the prompt diagnosis of PTB, but has a very low sensitivity in HIV co-infected patients, with some studies suggesting a sensitivity of 35-38% among HIV positive

patients [5] [6]. Culture of tuberculous bacilli is more sensitive (80-85%) and has a specificity of approximately 98%. However it usually takes 3-6 weeks to obtain results and because of expense and technical requirements, is often reserved in resource-limited settings for surveillance of drug resistance or for evaluation of suspected pulmonary TB in patients with repeatedly negative smear results [22]. Therefore, if a bacteriological diagnosis cannot be readily established by sputum smear, a presumptive diagnosis of SnPTB is typically made on clinical and radiological grounds and anti-TB treatment is initiated [25] [26].

According to Peruvian National Guidelines, confirmation of SpPTB requires identification of AFB on one or more sputum smear examinations (direct smear microscopy). However, a diagnosis of SnPTB is made if the patient has respiratory symptoms, two negative AFB sputum smear exams and a radiographic chest X-ray (CXR) suggestive of TB.

TB Treatment outcomes

The Peruvian National Guidelines define five mutually exclusive categories of treatment outcomes: 1) “Cured” - when a patient completes treatment and has a negative sputum smear or has no symptoms (if the patient is not able to produce a sputum sample), and has completed treatment; 2) “Died” - when a patient dies from any cause during treatment; 3) “Failed” - when a patient remains smear-positive after four or more months of treatment or has two positive sputum smears after two months of negative smears under directly observed treatment short-course (DOTS); 4) “Lost to follow-up” - when a patient does not receive treatment for more than 30 consecutive days or transfers care to a health facility that does not confirm accepting care of the patient; and 5) “Transferred out” - when the patient transfers to another health facility but no information is available regarding health condition. The World Health Organization (WHO) includes an additional category

"Treatment completed" for patients who complete treatment but do not have documentation of smear negativity, and defines "Treatment success" as the total number of patients who are cured or completed treatment. In the case of SnPTB patients, Peruvian standards define "cured" as patients who have no symptoms and have completed treatment. In this study, "successful outcome" included patients meeting the criteria for cured. "Unsuccessful outcome" included those patients meeting the criteria of death, lost to follow-up, failed or transferred out. Information regarding treatment outcome was recorded from the time of TB diagnosis to the end of treatment and at least one year of follow-up after diagnosis.

Other variables

We gathered retrospective data on standard risk factors for acquiring TB infection including gender, age, region, drug, tobacco and alcohol use, crowding (more than three people per bedroom) and prior TB, among others. Clinical information abstracted included presence of cough, fever, hemoptysis, weight loss, CDC Classification of HIV infection, CD4 lymphocyte count and HIV viral load most recent to initiation of TB treatment (no more than a year old), prescription of cotrimoxazole prophylaxis, tobacco use, and other chronic pre-existing comorbidities such as diabetes mellitus, rheumatoid arthritis, dyslipidemias or chronic renal failure. The results of CXR were obtained from clinical charts. We also recorded the number of sputum smears analyzed for each patient. The current number of physicians and nurses or technicians working at the TB program was provided by the person in charge of the TB program at each facility. Distance from the health facility providing treatment to the patient's home was obtained through a Global Position System (GPS). Physicians and nurses with training on HIV/TB and ethical conduct of human subject research abstracted information from the medical charts.

3. Statistical analysis

Basic descriptive statistics were performed, including proportions and medians (interquartile ranges) for discrete and continuous variables, respectively (Table 1). A Multivariate logistic regression model was used to assess for potential associations between SnPTB and demographic, behavioral and clinical risk factors. Factors considered in this analysis included gender, drug use, chronic pre-existing conditions, use of HAART at the time of admission, previous AIDS-defining illnesses, opportunistic infections, TB status at the time of admission (new, relapse or treatment after loss to follow-up), CD4 cell count, plasma HIV viral load, and miliary and alveolar patterns on the CXR.

A multivariate logistic regression model was also used to assess the association between TB treatment outcomes and demographic, behavioral, and clinical risk factors. Factors considered in this analysis included sputum smear result on admission, being on HAART or initiating HAART within two months of starting TB treatment, history of addictive habits (alcohol, drugs, and tobacco), CD4 cell count, TB status at the time of admission (new, relapse or treatment after loss to follow-up), and alveolar pattern on CXR. We also included the level of health facility where the patient received TB treatment, categorized as level I (health posts), level II (health centers or hospitals), and level III (reference hospitals).

A multivariate Cox proportional hazard model was created to determine whether SnPTB was associated with prolonged survival compared to SpPTB, after adjusting for confounding factors such as CD4 cell count, completion of TB treatment (yes or no), age, concurrent opportunistic infections, chronic pre-existing conditions, and being on HAART at the time of TB diagnosis. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated.

A Multivariate logistic regression model was also used to evaluate factors potentially associated with delay of TB treatment, defined as the difference between date

of starting treatment and date of TB diagnosis. Delayed TB treatment was considered when a patient initiated TB treatment more than one day after the date of diagnosis. Factors considered in this analysis included gender, employment status, history of addictive habits (alcohol, drugs, and tobacco), level of health facility where the patient received TB treatment, ratio of physicians to nurses or technicians, distance from the health facility, being on HAART at the time of TB diagnosis, CD4 cell count, and presence of other opportunistic infections. All analyses were performed using STATA version 11.1 (Stata Corporation, College Station, TX).

Chapter Three

Results

A total of 332 HIV-infected patients 15 years age or older were diagnosed with TB between 2005 and 2010 according to the annual operational reports at the five facilities of the Ministry of Health providing care for HIV-infected patients in the three regions of Peru included in this analysis. There was no information available from the San Martin region between 2005 and 2006. One hundred and twelve patients were excluded because of missing medical records from the health facility (n=75, 67%), diagnosis of extrapulmonary TB (n=32, 29%), age younger than 15 years of age (n=3, 3%) or without confirmed HIV infection (n=2, 1%). Two hundred twenty patients receiving TB treatment at forty five health facilities (posts, health centers, hospitals and reference hospitals) were included in this study. Among them, 137 (62%) received care at a level I health facility and 83 (38%) at a level II or III health facility.

Most patients included in the study were from the Loreto region (n=160, 73%), were male (n=184, 84%), and had completed some high school education (n=191, 89%). Median age was 33 years (IQR= 27-38); history of some alcohol use at the time of TB diagnosis was common (n=177, 81%); the majority had newly diagnosed TB infection (n= 177, 81%), and were classified as having CDC Stage 3 HIV infection (n= 159, 72%) (Table 1). Only 13 (10%) SnPTB cases were confirmed by culture, and the majority were started on TB treatment based on clinic and radiographic criteria (n=100, 80%).

Factors associated with SnPTB diagnosis

One hundred twenty-five (56.8%) patients were diagnosed with SnPTB. In the multivariate model, three factors were independently associated with a diagnosis of SnPTB: concurrent opportunistic infection (OR=4.8, 95%CI: 1.4-16.4), and alveolar

infiltrate (OR=7.9, 95%CI: 1.9-31.8) or miliary infiltrate on chest radiography (OR=29.3, 95%CI: 4.3-199.7). Chronic pre-existing conditions (OR=3.9, 95%CI: 0.8-18.3, p= 0.08), taking HAART at the time of TB diagnosis (OR=3.8, 95%CI: 0.7-19.1, p=0.11), and plasma HIV viral load (OR=1.8, 95%CI: 0.9-3.4, p=0.09) showed borderline statistically significant associations with diagnosis of SnPTB (Table 2).

Factors associated with TB treatment outcome

In this cohort, 98 (45%) patients had an unsuccessful TB treatment outcome. In the multivariate analysis, treatment at a level II or III health facility (OR=4.8, 95%CI: 2.1-10.8), and a history of addictive habits (OR=5.7, 95%CI: 1.8-18.2) were associated with increased likelihood of unsuccessful TB treatment outcome. In addition, compared to patients with CD4 cell counts less than or equal to 50 cells/mm3, patients with higher CD4 cell counts were less likely to have an unsuccessful TB treatment outcome: OR=0.3 (95%CI: 0.1-0.8) for CD4 counts between 51-200 cells/mm3, OR=0.2 (95%CI: 0.1-0.8) for CD4 counts between 201-350 cells/mm3, and OR=0.1 (95%CI: 0.02-0.7) for CD4 counts >350 cells/mm3. Likewise, patients with an alveolar infiltrate on CXR were less likely to have an unsuccessful treatment outcome (OR=0.4, 95%CI: 0.2 -0.9) (Table 3).

Association of survival and SnPTB

Of the 220 patients who started TB treatment, 122 (55%) patients completed treatment and 74 (34%) died within one year of starting treatment. Among participants who died, 46 (62%) had SnPTB, and the majority of deaths occurred while receiving TB treatment (74% vs. 26%), the majority within the first two months of starting TB treatment (n=39, 71%).

The probability of survival after TB diagnosis estimated by the Kaplan-Meier method is shown in Figure 1. In a bivariate analysis, smear-negativity increased the risk of death by

45% when compared to smear positive patients (HR=1.45, 95%CI: 0.9-2.3). In the multivariate analysis, SnPTB was associated with an 85% increased risk of death in comparison with SpPTB at one year (HR=1.85, 95%CI: 1.1-3.24), after adjusting for CD4 cell count, completed treatment, age, concurrent opportunistic infections, chronic pre-existing conditions, and HAART use (either taking HAART at the time of TB diagnosis or starting HAART within two months of starting TB treatment).

Factors associated with TB treatment delay among SnPTB cases

Among SnPTB cases, the median delay between diagnosis and the initiation of TB treatment was 2 days (IQR=0-5). In the multivariate analysis, treatment delay was higher among those with a history of addictive habits (OR=3.6, 95%CI: 1.1-12.1), and among those living farther from the health facility. In addition, employed patients were less likely to start TB treatment late (OR=0.2, 95%CI: 0.04-0.8) (Table 4).

Chapter Four

Discussion

More than half (56.8%) of HIV-infected patients diagnosed with TB in a Ministry of Health post, health center or hospital in the Peruvian Amazon had smear-negative pulmonary TB (SnPTB), which is similar to the prevalence reported in other countries [7]. The majority of SnPTB patients had severe immunosuppression (as determined by the CD4 cell count) at the time of TB diagnosis, and the risk of death for SnPTB cases was 85% greater than in patients with smear-positive pulmonary TB (SpPTB).

We also observed that concurrent opportunistic infection, and alveolar or miliary infiltrate on chest radiography were associated with a higher probability of SnPTB; these associations support a previous report that SnPTB was more likely (OR=2.5, 95%CI: 1.1-5.6) in patients with concurrent bacterial or parasitic opportunistic infections [8]. One potential explanation could be that other opportunistic infections indicate a higher level of immunosuppression that increases the likelihood of a smear-negative result [10]. Further studies are needed to examine this association and the effect of concomitant infections on the replication of *Mycobacterium tb*. Alveolar and miliary infiltrates are common during TB infection. Miliary infiltrates are also common in immunocompromised patients and 81% of SnPTB patients in this study had advanced immunosuppression at the time of TB diagnosis (stage 3 CDC Classification and a median CD4 cell count of 87 cells/mm3).

Unsuccessful treatment outcomes were associated with receiving treatment at a level II or III health facility and with a history of addictive habits. Level I health facilities (rural medical posts) had higher successful treatment rates than level II or III facilities, even though the complexity of services offered was lower. This could be explained by the shorter distance between these facilities and patients' homes that permitted better follow-

up of patients who did not adhere to treatment, or because most patients with severe immunosuppression received care at level II or III health facilities.

The median delay between diagnosis and initiation of treatment in SnPTB cases was 2 days (IQR= 0-5) and living more than 1.26 miles from a health facility increased the odds of starting treatment late by a factor of 8 ($p<0.01$). It is difficult to compare our results with other published studies that focused on factors associated with overall delay, which included delay in diagnosis (onset of symptoms to date of diagnosis), and reported a median total health system delay of 36-42 days [28] [29].

Despite optimal implementation of a DOTS program in Peru and the provision of ancillary social services to patients undergoing TB therapy, loss to follow-up and death were still very high for PTB patients co-infected with HIV (16% and 25%, respectively). Several studies have linked alcohol use to treatment outcomes, finding that alcohol consumption was a strong predictor of poor treatment outcome [30] [31] [32]. According to the WHO, alcohol use was an independent risk factor for non-adherence and default, and may lead to emergence of drug resistant strains of TB and to poor treatment outcomes [33]. People in our study had a high percentage (81%) of alcohol consumption. Our results suggest that DOTS programs should include services for the diagnosis and treatment of addictive habits concurrent with standard TB therapy.

There were 35 (34%) patients with a new case of SnPTB and 3 (17 %) patients with history of TB treatment who died during TB treatment. These proportions are higher than the national goals [34]. The Peruvian National TB Control Program (NTCP) has prioritized the monitoring of SpPTB and has not established goals for SnPTB. Our study found that more than half of patients with PTB and co-infected with HIV had SnPTB and the proportion of patients dying in this group was considerably higher than goals established by the NTCP, suggesting that SnPTB cases should be given higher priority, especially in areas such as the Peruvian Amazon, where HIV seroprevalence is high.

It was not possible to obtain post-mortem reports that would have allowed us to determine the final cause of death. However, this study reported that 71% of patients died within two months of starting TB treatment, so these early deaths were likely directly related to TB infection or to the effects of TB coinfection upon HIV infection.

Our study has several limitations. First, we excluded patients treated in health facilities outside the Ministry of Health system (approximately 11% of all TB infected patients) thus limiting the generalizability of our findings. Second, missing medical records from health facilities was common (23%) and limited our power to detect small differences or determine precise estimates of association. Finally, one of the regions under study, San Martin, only had information available since 2007 further limiting our power to detect associations.

The diagnosis of SnPTB is also subject to misclassification because 90% of SnPTB cases were not confirmed by culture. Even though the NTCP requests culture for all patients with TB/HIV, in resource-limited settings the diagnosis is most often based on a combination of CXR and clinical judgment.

In summary, concurrent opportunistic infection and miliary or alveolar pattern on CXR were associated with SnPTB. Receiving TB treatment in a level II or III health facility and history of addictive habits were found to increase the likelihood of unsuccessful treatment outcome. Patients with SnPTB had an increased risk of death compared to patients with SpPTB, and living a greater distance from a health facility increased the risk for delayed TB treatment. Further studies are needed to develop and evaluate innovative and inexpensive methods to more rapidly diagnose SnPTB and ensure that patients living distant from health facilities or affected by alcohol abuse receive appropriate monitoring and therapy. In addition, although the relative rate of TB transmission in SnPTB patients has been reported to be 22% of the transmission rate in SpPTB patients, given the high concentration of the HIV epidemic in the MSM population in Peru, the potential contribution

to TB transmission among HIV-infected MSM by patients with SnPTB in the Peruvian Amazon suggests that more aggressive TB surveillance and treatment monitoring activities should be routinely performed in this marginalized population.

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Tables

Table 1: Characteristics of patients with PTB and HIV co-infection in Peru. 2005-2010

	SpPTB (n= 95, 43.2%)	SnPTB (n=125, 56.8%)	p-value
Demographics			
Region			
Loreto	68 (72%)	92 (74%)	(Ref)
Ucayali	20 (21%)	21 (17%)	0.47
San Martin	7 (7%)	12 (10%)	0.64
Age (Years)*	32 [26-38]	33 [28-39]	0.19
Gender (Male)	86 (91%)	98 (78%)	0.02
Education			
Less than High school	0 (0%)	3 (2%)	(Ref)
Some High school	83 (90%)	108 (88%)	0.37
More than High school	9 (10%)	12 (10%)	0.45
Health facility level			
I	66 (69%)	71 (57%)	(Ref)
II or III	29 (31%)	54 (43%)	0.06
Behavioral characteristics			
Alcoholism	79 (83%)	98 (78%)	0.38
Drug use	20 (23%)	17 (15%)	0.12
Tobacco use	56 (59%)	72 (58%)	0.45
Clinical characteristics			
AIDS Stage (CDC)**			
Stage 1	2 (2%)	2 (2%)	(Ref)
Stage 2	16 (17%)	20 (16%)	0.83
Stage 3	66 (70%)	93 (74%)	0.74
CD4 count (cells/mm3) *	74 [31- 190]	87 [29-173]	0.53
HIV Plasma load (log 10 copies/ml)*	5.0 [4.4-5.4]	5.3 [4.8-5.8]	0.54
Co-trimoxazole prophylaxis	39 (41%)	62 (50%)	0.21
TB Diagnosis - TB treatment (Days)*	2 [0-5]	1 [0-4]	0.92
Status on admission			
New	74 (78%)	103 (82%)	(Ref)
Relapse	11 (12%)	18 (14%)	0.69
Treatment after loss to follow-up	10 (11%)	4 (3%)	0.04
CXR			
Normal	5 (12%)	2 (2%)	(Ref)
Cavitary lesión	4 (4%)	3 (2%)	0.58
Alveolar infiltrate	21 (22%)	52 (42%)	0.04
Miliary infiltrate	6 (6%)	54 (43%)	<0.01
Other	6 (6%)	6 (5%)	0.37
Not performed	53 (56%)	8 (6%)	<0.01
Signs and Symptoms			
Cough	88 (93%)	113 (90%)	0.56
Weight loss	82 (86%)	99 (79%)	0.17
Fever	76 (80%)	95 (76%)	0.48
Hyporexia	65 (68%)	90 (72%)	0.50
Chest pain	15 (16%)	13 (10%)	0.25
Hemoptysis	7 (7%)	8 (6%)	0.76
TB treatment outcome			
Cure	57 (60%)	66 (53%)	_
Death	18 (19%)	37 (30%)	_
Lost to follow-up	15 (16%)	20 (16%)	_
Treatment failure	4 (4%)	0 (0%)	_
Transfer out	1 (1%)	2 (2%)	_

* Median [IQR= Interquertile range]

** CD4+ cell count was not performed in 21 patients

Table 2: Factors associated with a diagnosis of smear negative pulmonary TB

	SpPTB (n= 95, 43.2%)	SnPTB (n=125, 56.8%)	Multivariate analysis* OR (CI 95%)	P-value
Demographics				
Male gender	86 (91%)	98 (78%)	0.2 (0.02 - 1.4)	0.1
Behavioral characteristics				
Drug use (Yes)	20 (21%)	17 (14%)	3.4 (0.6 - 19.2)	0.16
Clinical characteristics**				
Chronic pre-existing conditions***				
Yes	21 (22%)	45 (36%)	3.9 (0.8 -18.3)	0.08
Concurrent opportunistic Infections				
Yes	34 (36%)	67 (54%)	4.8 (1.4 - 16.4)	0.01
Previous AIDS				
Yes	35 (37%)	46 (37%)	0.4 (0.1 - 1.5)	0.17
HAART****	12 (13%)	31 (25%)	3.8 (0.7 - 19.1)	0.11
CD4 count (cells/mm3)*****	74 [31- 190]	87 [29-173]	1.0 (0.99 - 1.0)	0.27
HIV plasma load (log 10 copies/ml)*****	5.0 [4.4-5.4]	5.3 [4.8-5.8]	1.8 (0.9 - 3.4)	0.09
TB Status				
New	74 (78%)	103 (82%)	1	
Relapse	11 (12%)	18 (14%)	0.4 (0.1 -2.6)	0.33
Treatment after default	10 (11%)	4 (3%)	0.3 (0.03 - 2.7)	0.28
CXR				
Alveolar infiltrate	21 (22%)	52 (42%)	7.9 (1.9 - 31.8)	< 0.01
Miliary infiltrate	6 (6%)	54 (43%)	29.3 (4.3 - 199.7)	< 0.01

* Adjusted for male gender, drug use, chronic pre-existing conditions, concurrent opportunistic infections, previous AIDS, HAART, CD4 count, HIV plasma load, TB status and alveolar and miliary infiltrate on CXR.
** On admission
*** Chronic medical conditions experienced up to TB treatment initiation (controlled or not controlled by treatment)
**** Taking HAART at least one month before TB diagnosis
***** Median [IQR= Interquartile range]

Table 3: Factors associated with an unsuccessful TB treatment outcome

	Successful (n= 122, 55%)	Unsuccessful (n= 98, 45%)	Multivariate analysis* OR (CI 95%)	P-value
Demographics				
Health facility level				
I	88 (72%)	49 (50%)	1	
II or III	34 (28%)	49 (50%)	4.8 (2.1 - 10.8)	<0.01
Behavioral characteristics				
Addictive habits				
No	27 (22%)	8 (8%)	1	
Yes	95 (78%)	90 (92%)	5.7 (1.8 - 18.3)	< 001
Clinical characteristics**				
Sputum smear result				
SpPTB	57 (47%)	38 (39%)	1	
SnPTB	65 (53%)	60 (61%)	0.8 (0.3 – 2.2)	0.72
HAART***				
No	79 (65%)	54 (55%)	1	
Yes	43 (35%)	44 (45%)	1.5 (0.7 - 3.4)	0.28
CD4 count (cells/mm3)				
0-50	26 (23%)	44 (51%)	1	
51-200	58 (51%)	31 (36%)	0.3 (0.1 - 0.8)	0.02
201-350	21 (19%)	8 (9%)	0.2 (0.1 - 0.8)	0.03
>350	8 (7%)	3 (3%)	0.1 (0.02 - 0.7)	0.02
Status				
New	100 (82%)	77 (79%)	1	
Relapse	18 (15%)	11 (11%)	2.1 (0.6 - 7.0)	0.21
Treatment after default	4 (3%)	10 (10%)	1.2 (0.1 - 11.4)	0.87
CXR				
Alveolar infiltrate	47 (39%)	26 (27%)	0.4 (0.2 - 0.9)	0.04

*Adjusted for facility level, addictive habits, sputum smear result, HAART, CD4 count, status and CXR

** On admission
*** Taking HAART at the time of TB diagnosis or started HAART within 2 months of starting TB treatment

Table 4: Factors associated with delayed start of TB treatment among smear negative pulmonary TB patients

	Not delayed (n= 50, 40.0%)	Delayed (n=75, 60.0%)	Multivariate analysis*	
			OR (CI 95%)	P-value
Demographics				
Male gender	37 (74%)	61 (81%)	1.2 (0.3 – 4.4)	0.81
Occupation				
Employed	44 (91%)	57 (77%)	0.2 (0.04 – 0.8)	0.04
Health facility level				
I	30 (60%)	41 (55%)	1	
II or III	20 (40%)	34 (45%)	0.7 (0.2 – 1.8)	0.42
Ratio of Physicians to nurses or technicians**	1 [1-2]	1 [1-2]	0.9 (0.6 – 1.5)	0.88
Distance to health facility (miles)				
0-0.36	22 (44%)	9 (12%)	1	
0.36-0.76	12 (24%)	18 (24%)	4.5 (1.2 – 16.8)	0.03
0.76-1.26	8 (16%)	25 (33%)	10.9 (2.7 – 44.3)	< 0.01
> 1.26	8 (16%)	23 (31%0	9.3 (2.2 – 39.0)	< 0.01
Behavioral characteristics				
Addictive habits				
No	12 (24%)	11 (15%)	1	
Yes	38 (76%)	64 (85%)	3.6 (1.1 – 12.1)	0.04
Clinical characteristics				
Concurrent Opportunistic Infections				
Yes	29 (58%)	38 (51%)	0.5 (0.2 – 1.3)	0.17
CD4 count (cells/mm3)				
0-50	13 (30%)	26 (37%)	1	
51-200	21 (48%)	33 (47%)	1.1 (0.3 – 3.4)	0.82
201-350	8 (18%)	11 (15%)	0.6 (0.1 -2.7)	0.54
>350	2 (5%)	1 (1%)	0.1 (0.004 – 2.9)	0.19
HAART				
No	37 (74%)	57 (76%)	1	
Yes	13 (26%)	18 (24%)	0.8 (0.3 – 2.4)	0.82

*Adjusted for gender, occupation, facility level, ratio of physicians to nurses or technicians, distance to health facility, addictive habits, Concurrent opportunistic infections, CD4 count and HAART.
** Median [IQR= Interquertile range]

Figures

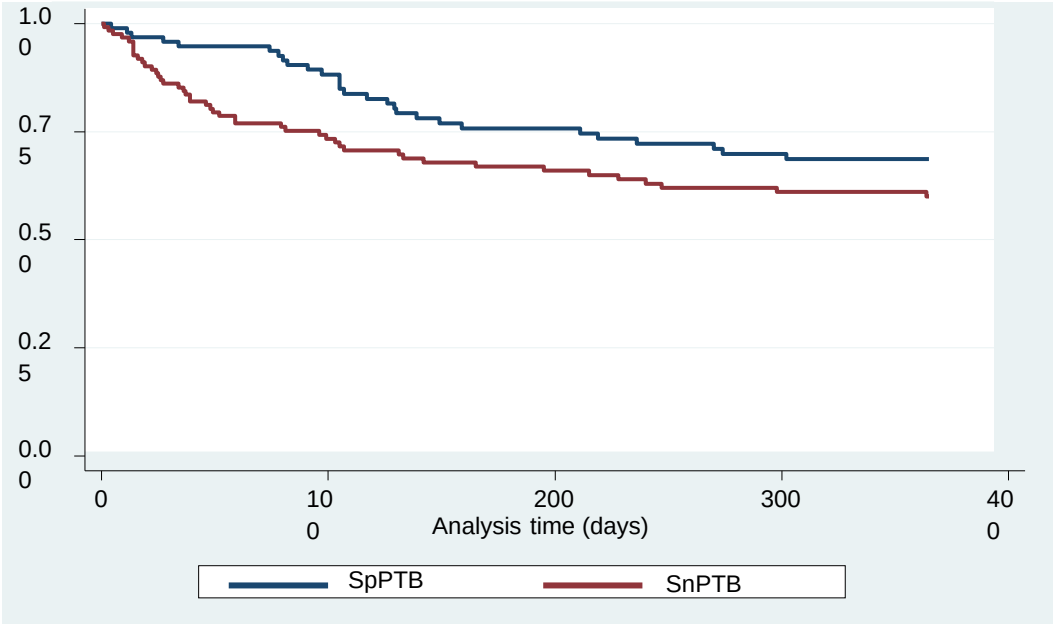

Figure 1. Kaplan-Meier estimators of survival function for SpPTB and SnPTB

Appendix A

Questionnaire

Smear Negative Tuberculosis in HIV-Infected Patients:
Treatment Outcomes and Factors Associated with Delay in Initiating Treatment
Peru 2005-2010

Identification Number: □□□
Name of person abstracting charts:
Date:
Region:

Section 1: Health Facility information:
1.1 Name of Health facility:
1.2 Level of Health facility:

I-1 (1)	□	II-1 (5)	□
I-2 (2)	□	II-2 (6)	□
I-3 (3)	□	III-1 (7)	□
I-4 (4)	□	III-2 (8)	□

1.3 Health facility Address:
1.4 Number of Physicians working at the TB program:
1.5 Number of Nurses working at the TB program:

Section 2: Patient Classification:

□ HIV-Infected patient + Smear-positive Pulmonary Tuberculosis (SpPTB) (1)
□ HIV-Infected patient + Smear-negative Pulmonary Tuberculosis (SnPTB) (2)

Section 3: Personal Information and Demographics:
3.1 TB Programme identification number: □□□□□□□□□□
3.2 HIV Programme identification number: □□□□□□□□□□
3.3 Province: 3.4 City: 3.5 District: 3.6 Address:
3.7 Date of birth:
3.8 Race

3.9 Gender:
□ Male (1)
□ Female (2)
□ Unknown (3)

3.10 Educational level:
□ Illiterate (1)
□ Primary School (2)
□ Secondary (3)
□ University (4)
□ Post-graduate (5)
□ Unknown (99)

3.11 Marital Status:
□ Married (1)
□ Single (2)
□ Divorced (3)
□ Widow (4)
□ Separated (5)
□ Living common law (6)
□ Unknown (99)

3.12 Occupation:
□ Fisherman (1)
□ Farmer (2)
□ Employee (3), specify…
□ Housewife (4)
□ Soldier/Police (5)
□ Driver (6)
□ Student (7)
□ Sex worker (8)
□ Unemployed (9)
□ Other (88)
□ Unknown (99)

Section 4: Personal History:

4.1 Alcoholism:
□ No (0)
□ Yes (1)
□ Unknown (99)

4.2 Drug use:
□ No (0)
□ Yes (1)
□ Unknown (99)

4.3 Crowding:
□ No (0)
□ Yes (1)
□ Unknown (99)

4.4 Tobacco:
□ No (0)
□ Yes (1), how long?.....
□ Unknown (99)

4.5 History of TB diagnoses previous to the last episode:
□ No (0), skip 4.6 and 4.7
□ Yes (1)
□ Unknown (99)

4.6 Outcome of TB treatment:
□ First Episode (1)
□ Cured (1)
□ Treatment failure (2)

□ Lost to follow-up (3)
□ Unknown (99)

If yes, how many times? (Without include last episode)

……..

□ Second episode (2)
□ Cured (1)
□ Treatment failure (2)
□ Lost to follow-up (3)
□ Not applicable (4)
□ Unknown (99)

Date of TB previous diagnosis:

--------/----------/---------- --------/---------/--------
day month year day month year

4.7 Previous TB treatment regimen received:
□ First Episode (1)
□ 2HREZ/4H_2R_2 (1)
□ 2HREZS-1HREZ/5$R_2H_2E_2$ (2)
□ Other (88), (Specify)…….
□ Unknown (99)

□ Second Episode (2)
□ 2HREZ/4H_2R_2 (1)
□ 2HREZS-1HREZ/5$R_2H_2E_2$ (2)
□ Not applicable (3
□ Other (88), (Specify)……. ……
□ Unknown (99)

4.8 BCG
□ No (0)
□ Yes (1)
□ Unknown (99)

4.9 Date of HIV diagnosis:

-------/---------/-------
day month year

4.10 How did the patient likely contract HIV?: check only one
□ Sex with male who have sex with men (1)
□ Sex with commercial sex worker (2)
□ Sex with a regular partner (3)
□ Heterosexual contact with spouse (4)
□ IDU (5)
□ HIV infected mother (6)
□ Multiple sex partners (7)
□ Other (88), specify……
□ Unknown (99)

4.11 History of AIDS-defining illness:
□ No (0)
□ Yes (1)
□ Unknown (99)

If yes, what symptoms or diseases (check all that apply):
□ Wasting syndrome (1)
□ CNS Toxoplasmosis (2)
□ P. jiroveci pneumonia (3)
□ TB (4)
□ Esophageal candidiasis (5)
□ HIV encephalopathy (6)
□ Chronic herpes simplex (7)
□ CMV disease (8)
□ Cryptococcal meningitis (9)
□ Kaposi Sarcoma (10)
□ Invasive cervical cancer (11)
□ Others (88), Specify ……

4.12 First ART regimen:
□ AZT + 3TC + NVP (1)
□ AZT + 3TC + EFV (2)
□ SQV/r + d4T + 3TC (3)
□ SQV/r +DDI +3TC (4)
□ LPV/r + d4T + 3TC (5)
□ LPV/r + DDI + 3TC (6)
□ Not applicable (7)
□ Others (88), specify ……
□ Unknown (99)

4.13 Other pre-existent conditions:
□ No (0)
□ Yes (1), specify …….
□ Unknown (99)

Section 5: TB Clinical Status

5.1 Date of admission:

----------/---------/--------
Day month year

5.2 Date of sputum smear test:

First specimen: ----------/---------/--------
Day month year

Result: □ Negative (0)
□ Positive (1)
□ Undetermined (2)

Second specimen: -------/--------/------
Day month year

Result: □ Negative (0)
□ Positive (1)
□ Undetermined (2)

5.3 Date initiation TB treatment:

--------/------------/-----------
Day month year

5.4 Person who made diagnosis:
□ Nurse (1)
□ Physician (2)
□ Technician (3)
□ Other (88)
□ Unknown (99)

5.5 DOT:
□ No (0) □ Yes (1) □ Unknown (99)

5.6 Date of Diagnosis ----------/---------/--------
Day month year

5.7 Registration Status:
□ New (1)
□ Relapse (2)
□ Treatment after default (3)
□ Transfer in (4)
□ Other (88), (Specify)…….

5.8 Criterion of TB diagnosis:
□ Sputum positive(1)
□ Culture positive (2)
□ Clinical (3)
□ Radiological (4)
□ Clinical and radiological (5)
□ Unknown (99)

5.9 Radiographic findings:
□ Cave (1) □ Nodule (7)
□ Fiber tracts (2) □ Bulla (8)
□ Pleural effusion (3) □ Miliary (9)
□ Pneumothorax (4)
□ Alveolar infiltrates (5)
□ Nodal Intratoraxica (6)
□ Other (88), (Specify)…….
□ Unknown (99)

5.10 Symptoms of TB at diagnosis (check all that apply):

□ Cough (1)
If yes, duration of cough:
□ Less than 1 week (1)
□ 1-2weeks (2)
□ More than 2 weeks (3)
□ More than 3 weeks (4)
□ More than 4 weeks (5)
□ Unknown (99)

□ Chest pain (2)
If yes, duration of chest pain:
□ Less than 1 week (1)
□ 1-2weeks (2)
□ More than 2 weeks (3)
□ More than 3 weeks (4)
□ More than 4 weeks (5)
□ Unknown (99)

□ Fever (3)
If yes, duration of fever:
□ Less than 1 week (1)
□ 1-2weeks (2)
□ More than 2 weeks (3)
□ More than 3 weeks (4)
□ More than 4 weeks (5)
□ Unknown (99)

□ Hemoptysis (4)
□ General weakness (7)
□ Shortness of breath (5)
□ Profuse sweating (8)
□ Weight lost (6)
□ Hyporexia (9)

5.11 Treatment Regimen:
□ 2HREZ/4H_2R_2 (1)
□ 2RHZES-1RHZE/5R_2H2E_2 (2)
□ Other (88), (Specify)…….
□ Unknown (99)

5.12 Did initial regimen change?
□ No (0), skip question 5.12
□ Yes (1)
□ Unknown (2)

If yes, specify new regimen:

……..

Regimen changed:

--------/------------/------------
day month year

5.13 Why TB treatment changed?
□ Adverse drug event (1)
□ Abandoned (2)
□ Change inTB guidelines (3)
□ Treatment failure (4)
□ Other (88), specify……
□ Unknown (99)

5.14 Were there adverse drug events during TB treatment?
□ No(0), skip question 5.14
□ Yes (1)
□ Unknown (99)

5.15 Adverse event were present during:
□ Phase 1
□ Phase 2
□ Unknown (99)

5.16 Type of adverse drug event:
□ Rash (1)
□ Peripheral neuropathy (2)
□ Abdominal pain/nausea (3)
□ Jaundice/Hepatitis (4)
□ Fever (5)
□ Arthralgia (6)
□ Other (88), specify……
□ Unknown (99)

5.17 Date stopped TB treatment:
--------/------------/------------
day month year

5.18 Bacteriological controls:

□ First month (1)	□ Third month (3)	□ Fifth month (5)	□ Seventh month (7)	□ Year (9)
□ Negative (0)	□ Negative (0)	□ Negative (0)	□ Negative (0)	□ Negative (0)
□ Positive (1)	□ Positive (1)	□ Positive (1)	□ Positive (1)	□ Positive (1)
□ Undetermined (2)	□ Undetermined (2)	□ Undetermined (2)	□ Undetermined (2)	□ Undetermined (2)
□ Not available (3)	□ Not available (3)	□ Not available (3)	□ Not available (3)	□ Not available (3)

□ Second month (2)	□ Fourth month (4)	□ Sixth month (6)	□ Eighth month (8)
□ Negative (0)	□ Negative (0)	□ Negative (0)	□ Negative (0)
□ Positive (1)	□ Positive (1)	□ Positive (1)	□ Positive (1)
□ Undetermined (2)	□ Undetermined (2)	□ Undetermined (2)	□ Undetermined (2)
□ Not available (3)	□ Not available (3)	□ Not available (3)	□ Not available (3)

5.19 TB treatment outcome:
□ Died (1)
□ Failed treatment (2)
□ Lost to follow-up (3)
□ Cured (4)
□ Unknown (99)

5.20 Adherence at the end of the TB treatment:
□ > 90% (1)
□ < 90% (2)
□ Unknown (3)

Section 6: HIV Clinical Status at TB diagnosis

6.1 Prophylaxis:
(Check all that apply)
□ Co-Trimoxazole (1)
□ Isoniazid (2)
□ Not taking prophylaxis (3)
□ Unknown (99)

6.2 CDC defined stage:
□ Stage 1 (1)
□ Stage 2 (2)
□ Stage 3 (3)

6.3 HAART
□ No (0)
□ Yes (1)
□ Unknown (99)

6.4 Treatment scheme
□ AZT+3TC+NVP (1)
□ AZT+3TC+EFV (2)
□ SQV/r+d4T+3TC (3)
□ SQV/r+DDI+3TC (4)
□ LPV/r+d4T+3TC (5)
□ LPV/r+DDI+3TC (6)
□ Other (88), specify…
□ Unknown (99)

6.5 Date of HAART initiation:
--------/------------/------------
day month year

6.6 Adherence:
□ >90% (1)
□ < 90% (2)
□ Unknown (99)

6.7 Opportunistic infections:
□ No (0)
□ Yes (1)
□ Unknown (99)
If yes, describe…….

6.8 Did initial regimen change?
□ No (0), skip question 6.8
□ Yes (1)
□ Unknown (99)

6.9 Why did initial HIV treatment changed?
□ Adverse drug event (1)
□ Change in national HIV treatment guidelines (2)
□ Treatment failure
□ Other (88), specify……
□ Unknown (99)

6.10 CD4 count (cells/mm3) and date: ……6.11 Plasma Viral Load (copies/ml and date): …….

6.12 Adverse drug events during HAART?
□ No (0), skip question 6.12
□ Yes (1)
□ Unknown (99) □ Other (88), specify

6.13 Type of adverse drug event:
□ Rash (1) □ Renal Insufficiency (2) □ Anemia (3)
□ Hepatotoxicity (4) □ Nausea (5) □ Lipodystrophy (6)
□ Peripheral neuropathy (7) □Unknown (99)