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Pulmonary Tuberculosis Diagnostic Practices among People Living with HIV in Lesotho

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Abstract

Setting—Twelve health facilities in Berea district, Lesotho participating in the START Study, a mixed-methods cluster-randomized trial evaluating a combination intervention package to improve early ART initiation and TB treatment success among TB/HIV patients.

Objective—To assess TB and HIV diagnostic practices among TB/HIV patients.

Design—A standardized survey assessed services at each facility at baseline. Routine clinical data were abstracted for all newly-registered adult TB/HIV patients during the study period. Descriptive statistics were used to assess TB diagnostic practices, timing of HIV diagnosis, and antiretroviral therapy (ART) status at TB treatment initiation.

Results—Between April 2013 and March 2015, 1233 TB/HIV patients were enrolled. Among 1215 with available data, 87.2% had pulmonary TB, of which 34.8% were bacteriologically confirmed, 40.9% tested negative and 24.3% were not tested. Among 1138 with available data, 53.3% had an existing HIV diagnosis, of which 39.3% were ART-naïve.

Conclusions—The majority of pulmonary TB patients were clinically diagnosed and many were unaware of their HIV status or were ART-naïve despite known status. The Test and Treat strategy holds promise to prevent TB and reduce TB-related mortality among people living with HIV; however, enhanced TB diagnostic capacity and improved HIV case detection are urgently needed.

Keywords

Tuberculosis-HIV integration; implementation science; Tuberculosis diagnosis

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Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

INTRODUCTION

Tuberculosis (TB) now outranks human immunodeficiency virus (HIV) as the leading cause of death from an infectious disease worldwide.[1] TB/HIV co-infection remains a significant challenge in the fight against TB, accounting for 400,000 of the 1.8 million TB deaths in 2015.[2] Timely and accurate diagnosis of TB, and timely diagnosis of HIV infection, are essential to reduce TB-related morbidity and mortality among people living with HIV (PLHIV).

Despite its lower sensitivity in immunocompromised individuals, smear microscopy often remains the primary diagnostic test for pulmonary TB (PTB) in resource-limited settings, where TB/HIV co-infection rates are high.[1,3,4] Reliance on smear microscopy in this population results in higher rates of clinical diagnosis of PTB, and may lead to poorer outcomes. When compared to clinical diagnosis, bacteriological diagnosis of PTB improves diagnostic accuracy, and is associated with a shorter time to treatment initiation and lower loss to follow-up rates.[5–8]

For PLHIV with presumptive TB, current World Health Organization (WHO) guidelines recommend the use of Xpert MTB/RIF, a rapid molecular diagnostic test with greater sensitivity than smear microscopy.[9] Additionally, the WHO now recommends early ART initiation for all PLHIV regardless of CD4 count.[10] Early ART maintains immunocompetence and has been shown to reduce TB incidence by 50–68%.[11–15] However, data from WHO and UNAIDS indicate that rates for bacteriological confirmation of PTB, HIV case detection and ART coverage remain low in sub-Saharan Africa.[2,16]

Because poor outcomes in TB/HIV patients have been linked to late or inaccurate diagnosis of TB and HIV, in this paper we sought to evaluate TB diagnostic practices among PLHIV in Lesotho, a country with the world's second highest TB incidence and HIV prevalence, and a co-infection rate of 72%.[2,17] In addition, we looked at timing of HIV diagnosis and ART status at the time of TB treatment initiation. We assessed these factors among newly-registered adult TB/HIV patients utilizing data from the START Study.

STUDY POPULATION AND METHODS

Study Setting and Population

The START Study is described in detail elsewhere.[18] Briefly, START was a mixed-methods cluster-randomized trial evaluating a novel combination intervention package (CIP) to improve early ART initiation and retention among TB/HIV patients in Lesotho. Twelve public health facilities (clusters) within Berea District, Lesotho were randomized to deliver the CIP or standard of care (SOC), stratified by facility type (hospital or health center). All TB/HIV patients at facilities assigned to the SOC condition received standard of care supported by the Lesotho Ministry of Health (MOH), while all those enrolled in facilities assigned to the CIP condition received the SOC plus the intervention package. CIP contained programmatic, structural and psychosocial components, and did not explicitly intervene on any diagnostic procedures.

Patients at participating health facilities were managed according to the Lesotho national HIV guidelines, which recommended intensified TB case finding for all PLHIV, with Xpert MTB/RIF as the diagnostic test of choice for all those with a positive TB symptom screen.[19] Sputum collection was performed at all health facilities, and samples were transported to the nearest district hospital or the National Reference Laboratory for Xpert MTB/RIF testing and smear microscopy. Sputum culture was not routinely used for TB diagnosis at the time of study implementation. Chest X-rays were recommended for sputum negative patients (those with a negative Xpert MTB/RIF test and/or smear), and were only available at district hospitals. Provider-initiated HIV counseling and testing was recommended for all patients with presumptive or active TB with an unknown HIV status. At the time of the study, the CD4 threshold for ART eligibility was 350 cells/mm^3, and national guidelines stipulated that all PLHIV with TB initiate ART within 2–4 weeks of TB treatment initiation regardless of CD4 count.[19]

All HIV-positive adults aged 18 or older who were newly registered for TB treatment at participating health facilities during the study period were eligible for the study. Patients newly diagnosed with HIV at the time of TB treatment initiation as well as those with a known HIV diagnosis were included. In Lesotho, patients diagnosed with drug-resistant TB are treated at a specialized facility and thus were excluded from the study.

Measures and Data Collection

A semi-structured survey was administered to the nurse in charge at each participating health facility at baseline to assess programmatic characteristics during the 30 days prior to study onset. A standardized tool was used to abstract demographic, clinical and laboratory data from the patient medical record, including age, sex, date of TB treatment initiation, site of TB disease, sputum test results, TB treatment category, date of HIV diagnosis, and date of ART initiation. In addition, the national laboratory database was searched in an effort to collect any missing laboratory data, including Xpert MTB/RIF results that were not documented in the patient record at the time of the study.

Bacteriologically confirmed PTB was defined as having one or more sputum specimens positive by Xpert MTB/RIF or smear microscopy at the time of TB treatment initiation.[20] *Clinically diagnosed PTB* was defined as being diagnosed with PTB by a medical officer, on the basis of clinical presentation and/or chest X-ray, in the absence of positive Xpert MTB/RIF or smear microscopy.[20] Timing of HIV diagnosis was categorized as *Known* or *New*, where *Known* included patients with either a documented HIV diagnosis prior to the onset of the current TB episode, or an ART initiation date prior to TB treatment initiation. O*nset of the current TB episode* was defined as 30 days prior to TB treatment initiation, in order to account for the lag time between having a positive TB screen and initiating TB treatment. Delays of up to 30 days were common in Lesotho, particularly when patients were sputum negative and required evaluation by a medical officer at the district hospital in order to initiate treatment. Patients without a documented ART initiation date were considered *ART-naïve.*

Data Analysis

The primary outcome of this analysis is proportion of TB cases with bacteriologically confirmed PTB, including Xpert MTB/RIF positive or sputum smear microscopy positive. Secondary outcomes include the proportions of newly registered TB/HIV patients previously diagnosed with HIV and on ART prior to TB treatment. Descriptive statistics were used to characterize participating health facilities and patients at baseline, using frequencies and proportions for categorical variables and means or medians for continuous variables. Differences in patient characteristics between study arms were assessed using unadjusted generalized linear mixed models with a random intercept for study site to account for violation of the independence assumption due to the cluster-randomized study design. All analyses were performed using SAS statistics software (version 9.4; SAS Institute Inc, Cary, NC).

Ethics

The START Study protocol was approved by the Columbia University Medical Center Institutional Review Board (Ref #IRB-AAAK7103) and the Lesotho MOH National Health Research and Ethics Committee (Ref ID68-2012), and registered at ClinicalTrials.gov (NCT01872390). Patient data collected for this analysis were covered under a waiver of informed consent for records review.

RESULTS

Characteristics of the 12 participating health facilities prior to study implementation are shown in Table 1. The majority of facilities (83.3%) were located in rural settings. Four (33.3%) facilities were managed by the MOH, seven (58.3%) by the Christian Health Association of Lesotho and one (8.3%) by the Red Cross. The nurse in charge at six (50.0%) facilities reported that nurses had received training and mentorship in TB/HIV co-treatment in the month prior to study implementation. At 11 (91.7%) facilities, TB/HIV patients received ART at the TB clinic for the duration of TB treatment. Facility characteristics were similar across study arms.

Between April 2013 and March 2015, a total of 1233 adult TB/HIV patients were newly registered for TB treatment across the 12 study sites, including 713 (57.8%) patients at CIP sites and 520 (42.2%) at SOC sites; demographic and clinical characteristics are shown in Table 2. Among 1215 patients with available data, 1059 (87.2%) were diagnosed with PTB. Among 1056 PTB cases with available data, 367 (34.8%) were bacteriologically confirmed (303 [82.6%] by smear microscopy only, 19 [5.2%] by Xpert MTB/RIF only and 45 [12.3%] by both) and 689 (65.2%) were clinically diagnosed (432 [62.7%] with negative test results and 257 [37.3%] without bacteriological examination).

Among 1138 patients with available data, 532 (46.8%) had a new HIV diagnosis. Among the 606 patients with a known HIV diagnosis, the median (IQR) time from HIV diagnosis to TB treatment initiation was 534.5 (93-1447) days and 238 (39.3%) were ART-naïve prior to the current TB episode. Of note, 79 patients initiated ART in the 30 days prior to TB treatment initiation.

Baseline patient characteristics were similar across study arms, with the exception of year of TB treatment initiation. The SOC arm had a lower proportion of patients enrolled in 2013 (37.7% vs 44.0%) and a higher proportion enrolled in 2015 (9.8% vs 3.7%; p=0.0009).

DISCUSSION

Despite significant investments by multilateral and bilateral funding agencies to enhance TB diagnostic capacity and improve access to bacteriological testing in Lesotho, the majority (65.2%) of patients with PTB in this study were clinically diagnosed. The sensitivity of sputum smear microscopy and Xpert MTB/RIF are reduced among PLHIV, particularly with advanced immunosuppression, which may partially account for the high proportion of clinically diagnosed cases in this cohort.[3,4] However, the finding that in over a third of clinically diagnosed PTB cases, a bacteriological test was not done suggests that underutilization of laboratory diagnostics was a major contributing factor. Health system challenges such as stock outs of commodities including sputum cups and reagents, understaffing at district laboratories, and problems with the specimen transport system, were common during the study period. Similar barriers exist nationwide and may explain why Lesotho has the highest clinical diagnosis rate among TB/HIV high-burden countries in southern Africa. According to the WHO, Lesotho had a 51% clinical diagnosis rate among new and relapse PTB patients in 2015, compared to 48% in Botswana, 40% in South Africa and 30% in Swaziland during the same period.[21]

Diagnosis based on Xpert MTB/RIF testing was extremely low in the study population, despite the fact that Xpert MTB/RIF is the recommended first-line test for all PLHIV with presumptive TB.[19] While a precise calculation of Xpert MTB/RIF use was not possible due to the fact that only positive results were available from the national laboratory database, the finding that only 6.0% of PTB cases in our study were confirmed by a positive Xpert MTB/RIF result strongly suggests underutilization. Reasons for Xpert MTB/RIF underutilization during the study period included poor adherence to national guidelines and an inadequate supply of cartridges. Improving adherence to the national diagnostic algorithm and the supply of laboratory commodities could significantly enhance diagnostic accuracy, reduce time to TB treatment initiation and improve treatment outcomes among PLHIV in Lesotho, and concurrent use of smear microscopy would allow for monitoring of treatment response.[5–8]

Most TB/HIV patients (70.2%) had no documented history of ART use prior to TB treatment initiation. This finding is consistent with the well-documented increased risk of TB among PLHIV not receiving ART,[12–15] but is substantially higher than results from a large cross-sectional study from Malawi, in which 60% of HIV-positive PTB patients were ART-naïve.[22] Of the 606 patients with a known HIV diagnosis, 238 (39.3%) were ART-naïve prior to TB treatment initiation. Because CD4 count data at the time of HIV diagnosis were not collected, we do not know the proportion of patients with a known HIV diagnosis that was eligible for ART prior to TB diagnosis. However, it is likely that there was a large cohort of individuals who would have benefitted from the Test and Treat strategy recently recommended by the WHO, and adopted by the Lesotho MOH, which facilitates early initiation of ART among PLHIV regardless of CD4 count.[23] Randomized controlled trials

have shown that early initiation of ART substantially reduces the incidence of TB among PLHIV.[12–15] Of note, 79 (33.2%) patients who were ART-naïve prior to the current TB episode were started on ART within 30 days prior to initiating TB treatment, putting them at increased risk of developing immune reconstitution inflammatory syndrome.[24,25] While this may partially reflect poor implementation of TB screening prior to ART initiation, it is likely that many of these patients represent cases of unmasking of subclinical TB due to immune reconstitution.[26]

Notably, nearly half of all TB/HIV patients were diagnosed with HIV during the current TB episode. This finding highlights the importance of integrated TB/HIV services for ensuring HIV diagnosis among TB patients in settings with high rates of co-infection such as Lesotho. However, it also suggests that many PLHIV in Lesotho are not diagnosed until they become ill and therefore they may miss the prevention benefits of Test and Treat against acquiring TB. A large cross-sectional study in Ethiopia, which assessed HIV testing among TB patients, also found that a high proportion (57%) of TB/HIV patients were newly diagnosed with HIV during TB treatment.[27] Innovative strategies are needed to ensure that all PLHIV are diagnosed, and that those who are diagnosed are promptly initiated on ART and achieve viral suppression as outlined in the UNAIDS 90-90-90 treatment targets,[16] in order to mitigate the risk of TB in this high burden setting.

Our study had limitations. We relied on abstraction of routinely collected clinic data, and there was a substantial amount of missing data for some variables. Despite utilization of multiple sources within the medical record, a high proportion of patients (14.8%) were missing data for date of HIV diagnosis. Additionally, cases in which sputum testing was not documented were interpreted as "bacteriological testing not done", and cases in which ART initiation date was not documented were interpreted as "ART-naïve", which may have resulted in misclassification. There is no reason, however, to believe this misclassification would be nonrandom. A strong effort was made to mitigate this limitation by searching the national laboratory database as well as other data sources to retrieve clinical information on as many patients as possible.

Strengths of our study include the large cohort size, long study period and broad inclusion criteria, which enhance the generalizability of our findings. Additionally, data were collected under programmatic conditions at a diverse sample of facilities, which further enhances external validity.

CONCLUSIONS

The majority of TB patients in the START Study were clinically diagnosed, and many were either newly diagnosed with HIV infection during the current TB episode or ART-naïve despite known HIV infection. Recent adoption of the Test and Treat strategy in Lesotho holds promise to prevent TB and reduce TB-related morbidity and mortality among PLHIV; however, improved access to HIV testing and enhanced TB diagnostic capacity are urgently needed.

Initial measures should focus on increasing adherence to the TB diagnostic algorithm and implementation of Xpert MTB/RIF, including provider training and mentorship, and strengthening of the laboratory commodity supply chain and sample transport systems. Additional measures should focus on improving laboratory staffing and infrastructure, including creation of designated TB microscopists within the MOH organogram, integration of medical and laboratory information systems, and establishment of laboratories at the health center level.

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Table 1

Characteristics of 12 Participating Health Facilities at START Study Onset, April 2013*

	All (N=12)	CIP (N=6)	SOC (N=6)
Characteristics	**N (%)**	**N (%)**	**N (%)**
Type of facility			
Health center	10 (83.3)	5 (83.3)	5 (83.3)
Hospital	2 (16.7)	1 (16.7)	1 (16.7)
Facility setting†			
Urban	2 (16.7)	2 (33.3)	0 (0.0)
Rural	10 (83.3)	4 (66.7)	6 (100.0)
Facility management			
Ministry of Health	4 (33.3)	2 (33.3)	2 (33.3)
Non-governmental organization‡	8 (66.7)	4 (66.7)	4 (66.7)
Median (IQR) number of TB/HIV patients per facility during the study period	57 (43–113)	58 (42–153)	57 (44–73)
Nurses received 'Three I's' training§	11 (91.7)	6 (100.0)	5 (83.3)
Nurses received training and mentorship in TB/HIV co-treatment in the past month	6 (50.0)	3 (50.0)	3 (50.0)
TB/HIV patients receive ART at TB clinic	11 (91.7)	5 (83.3)	6 (100.0)

*Abbreviations: CIP, combination intervention package; SOC, standard of care; IQR, interquartile range; ART, antiretroviral therapy.

†Source: Lesotho Bureau of Statistics.

‡Christian Health Association of Lesotho or Red Cross.

§Three I's: intensified case finding for TB; isoniazid preventive therapy; and infection control.

Table 2

Demographic and Clinical Characteristics of Newly Registered TB/HIV Patients in Berea District, Lesotho, April 2013 – March 2015[*,†]

	All (N=1233)	CIP (N=713)	SOC (N=520)
Characteristics	**N (%)**	**N (%)**	**N (%)**
Mean (SD) age, years	38.6 (10.9)	38.3 (10.8)	38.9 (11.0)
Male	699 (56.7)	418 (58.6)	281 (54.0)
Year of TB treatment initiation			
2013	510 (41.4)	314 (44.0)	196 (37.7)
2014	646 (52.4)	373 (52.3)	273 (52.5)
2015	77 (6.2)	26 (3.7)	51 (9.8)
Site of TB disease			
Extra-pulmonary	156 (12.8)	74 (10.6)	82 (15.9)
Pulmonary	1059 (87.2)	625 (89.4)	434 (84.1)
Bacteriologically confirmed[‡]	367 (34.8)	236 (37.9)	131 (30.2)
Clinically diagnosed			
Bacteriological test negative	432 (40.9)	283 (45.5)	149 (34.3)
Bacteriological test not done	257 (24.3)	103 (16.6)	154 (35.5)
TB treatment category			
New case	1040 (84.4)	580 (81.4)	460 (88.6)
Retreatment case	192 (15.6)	133 (18.7)	59 (11.4)
Known HIV diagnosis	606 (53.3)	360 (54.0)	246 (52.2)
Median (IQR) time from HIV diagnosis to TB treatment initiation, days[§]	534.5 (93–1447)	573 (115–1452)	517 (72–1370)
ART-naïve prior to current TB episode[§]	238 (39.3)	151 (41.9)	87 (35.4)

[*] Abbreviations: CIP, combination intervention package; SOC, standard of care; SD, standard deviation; IQR, interquartile range; ART, antiretroviral therapy.

[†] Number missing data: site of TB disease, 18; bacteriological confirmation, 3; TB treatment category, 1; timing of HIV diagnosis, 95.

[‡] Defined as positive sputum smear microscopy or Xpert MTB/RIF test.

[§] Among patients with known HIV diagnosis.