Tuberculosis preventive treatment opportunities at antiretroviral therapy initiation and follow-up visits

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Setting: Twenty-two clinics providing HIV care and treatment in Botswana where tuberculosis (TB) and HIV comorbidity is as high as 49%.

Objectives: To assess eligibility of TB preventive treatment (TPT) at antiretroviral therapy (ART) initiation and at four follow-up visits (FUVs), and to describe the TB prevalence and associated factors at baseline and yield of TB diagnoses at each FUV.

Design: A prospective study of routinely collected data on people living with HIV (PLHIV) enrolled into care for the Xpert® MTB/RIF Package Rollout Evaluation Study between 2012 and 2015.

Results: Of 6041 PLHIV initiating ART, eligibility for TPT was 69% (4177/6041) at baseline and 93% (5408/5815); 95% (5234/5514); 96% (4869/5079); and 97% (3925/4055) at FUV1, FUV2, FUV3, and FUV4, respectively. TB prevalence at baseline was 11% and 2%, 3%, 3% and 6% at each subsequent FUV. At baseline, independent risk factors for prevalent TB were CD4 <200 cells/mm³ (aOR = 1.4, *P* = 0.030); anemia (aOR = 2.39, *P* < 0.001); cough (aOR = 11.21, *P* < 0.001); fever (aOR = 2.15, *P* = 0.001); and weight loss (aOR = 2.60, *P* = 0.002).

Conclusion: Eligibility for TPT initiation is higher at visits post-ART initiation, while most cases of active TB were identified at ART initiation. Missed opportunities for TB further compromises TB control effort among PLHIV in Botswana.

Tuberculosis (TB), a preventable and curable disease, remains the leading cause of death among people living with HIV (PLHIV).¹ Post-mortem studies in high HIV incidence settings indicate that nearly 40% of all deaths among PLHIV are due to TB.^{2,3} In Botswana, the TB epidemic continues to be driven by HIV as 49% of TB patients with known HIV status were HIV-positive in 2018.⁴ To prevent TB in PLHIV, both antiretroviral therapy (ART) and chemoprophylaxis regimens, such as isoniazid preventive therapy (IPT), are recommended. ART has been shown to reduce the development of TB by 65% regardless of CD4 count.^{5,6} IPT provides an additional 37% reduction in the risk of developing TB in PLHIV on ART compared to those on ART alone, even among PLHIV who are clinically stable and have high CD4 counts.^{5,6} Historically, IPT has been the only chemoprophylaxis option for PLHIV since prior studies used only isoniazid; however, newer, shorter regimens, such as isoniazid and rifampentine, are now available for PLHIV and these are collectively referred to as TB preventive treatment (TPT).^{7,8}

Eligibility to start TPT among PLHIV begins with a TB symptom screen (cough, fever, night sweats, or weight loss). PLHIV who lack any duration of TB symptoms (i.e. screen negative) are unlikely to have active TB disease and are eligible for TPT if no contraindications exist.⁷ For PLHIV who have any one of the four symptoms, (i.e., screen positive or have presumptive TB), additional diagnostic testing is indicated to evaluate for TB disease.⁷

Although screening PLHIV for TB symptoms is recommended at every clinic visit,⁷ few studies describe the proportion of PLHIV expected to screen negative at ART initiation compared to subsequent clinic visits post-ART initiation. One study from South Africa demonstrated a higher proportion of TB symptoms among PLHIV who were ART naïve (23.7%), compared to those on ART (6.6%).⁹ Other studies often use cross-sectional study designs and only capture screening results among ART naïve patients^{10,11} or use screening algorithms that are different from the WHO recommended algorithms.¹² In April 2019, the Botswana HIV program included TPT in its guidelines and began implementation later that year. As Botswana continues scale-up of TPT, understanding expected TB screening results among PLHIV newly starting ART, compared to those on ART, is needed to interpret programmatic data and inform subsequent TPT scale-up. We used routine, programmatic data to assess eligibility for TPT based on 1) a negative TB symptom screen among a cohort of PLHIV at ART initiation (enrolment) and at follow-up visits (FUVs), and 2) among those with an initial positive symptom screen who subsequently had negative TB diagnostic tests. We also described the TB prevalence and associated factors at enrolment and yield of TB diagnoses at each of FUVs.

METHODS

Study design

We conducted a prospective study using routinely collected data on PLHIV enrolled in care for the Xpert MTB/RIF Package Rollout Evaluation Study (XPRES) between 2012 and 2015, in Botswana.¹³

Settings and study population

This is a sub-analysis of the XPRES study, registered at ClinicalTrials.gov, NCT02538952. In summary, XPRES is a clustered randomized trial, comparing sputum-smear microscopy (smear) and Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) diagnostic algo-

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rhythms, in which all persons with HIV who initiated ART for the first time (i.e., ART naïve) were enrolled prospectively at one of the 22 HIV clinics from August 1, 2012 to March 31, 2015. These clinics were purposefully selected by the Ministry of Health and Wellness based on a high number of newly registered HIV-positive patients on a monthly basis. Both adults and children were included. Patients were screened for TB symptoms at ART enrolment and at each FUV, which occurred monthly for the first three months (30 days, 60 days, 90 days) and then quarterly (after 210 days for the fourth follow-up visit). Full details of the study protocol can be accessed in the published protocol.¹³

Tuberculosis screening and diagnosis

Adolescents and adults (combined into one adult group and defined as persons ≥ 12 years) were screened for the presence of any of four TB symptoms (cough, fever, night sweats, or weight loss) of any duration. Children (< 12 years old) were screened for weight loss or failure to thrive (no weight gain within 3 months), enlarged lymph nodes (more than 1×1 cm), cough for ≥ 2 weeks, fever for ≥ 2 weeks, fatigue/reduced playfulness ≥ 2 weeks, and profuse night sweats ≥ 2 weeks. Persons who screened negative for TB symptoms, or who were determined not to have TB disease after further diagnostic evaluation, were eligible for TPT. Per World Health Organization (WHO) guidelines, confirmation of latent TB infection with a tuberculin skin-test or interferon-gamma-release assay was not required.⁸ Since clinics participating in XPRES followed national HIV guidelines for patient management, and Botswana had not yet included TPT in its guidelines or implemented TPT programmatically during the study period, PLHIV who screened negative for TB symptoms were not offered TPT in this study. Additionally, since TPT was not actually given, we did not assess for exclusion criteria such as prior history of hypersensitivity to isoniazid, hepatitis, or peripheral neuropathy. The only exclusion criterion was active TB.

PLHIV with any duration of at least one symptom were presumed to have TB and were eligible for additional testing.⁷ PLHIV with presumptive TB received a chest x-ray and provided sputum for subsequent testing by smear or Xpert, had already been introduced in the clinic. PLHIV who had negative smear or Xpert results, but clinicians still strongly suspected TB based on chest X-ray, were clinically diagnosed with TB. Similarly, children who screened positive for TB received gastric lavage, which was evaluated via smear or Xpert. They also received chest X-rays and could be clinically diagnosed with TB based on those findings.

Data collection and analysis

Data were prospectively collected by interview using standardized case report forms (CRF). Data were double-entered into a Clindex database (Fortress Medical Systems, Minneapolis, MN, USA). Inconsistencies were identified through logic checks, and once identified, were checked against the original CRF. Where possible, inconsistencies and missing data were corrected through review of patient charts.

Data were analysed using STATA (StataCorp, College Station, TX, USA) to describe demographic data in proportions, to fit univariate and multivariate regression models, and to describe and compare demographic and clinical characteristics among patients with TB and without TB at baseline.¹⁴ All analysis were adjusted for within-clinic correlation. We calculated numbers and proportions of PLHIV screened for TB symptoms and their results at baseline and subsequent FUVs. The numerator was defined as 1) PLHIV who screened negative for TB symptoms, or 2) those who initially had a positive symptom screen, but had active TB ruled out following further diagnostic examinations. The denominator was PLHIV enrolled at baseline and those who completed the respective FUVs (1, 2, 3 or 4). PLHIV who were diagnosed with TB at baseline (ART start) and initiated on TB treatment, were excluded from the denominator for subsequent FUVs.

Ethical considerations

The study protocol was approved by the Botswana Health Research and Development Committee (Gaborone, Botswana), the United States Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) Institutional Review Board (IRB), the University of Pennsylvania IRB (Philadelphia, PA, USA), and the University of Witwatersrand IRB (Johannesburg, South Africa). Written informed consent was obtained from adults aged ≥ 18 years old. Assent was obtained from participants aged 7–17 years old in addition to consent obtained from a parent or guardian.

RESULTS

A total of 6041 patients presenting for ART initiation were enrolled and completed 20 463 visits equating to 5495 person-years of follow-up. Table 1 shows at baseline, prior to ART initiation, 67% (4030/6041) were female and 99.5% (6010/6040) were adolescents or adults. Of the study participants, 39% (2320/5921) had advanced HIV with a CD4 cell count < 200 cells/mm³. A history of previous TB was noted by 19% (1162/6025) of participants and 22% (1321/6026) reported alcohol use.

Figure 1 shows the number of PLHIV screened at each visit decreased from 6041 PLHIV at baseline (ART initiation) to 4055 PLHIV at FUV4. At the baseline visit, 69% (4177/6041) of PLHIV reported no TB symptoms and were therefore eligible for TPT. This proportion increased after ART initiation at follow-up visits as follows: 93% (5408/5815) at FUV1; 95% (5234/5514) at FUV2; 96% (4869/5079) at FUV3; and 97% (3925/4055) at FUV4. By contrast, Figure 2A shows the proportion of PLHIV who had a positive symptom screen (i.e. presumptive TB) was highest at the baseline ART initiation visit (31%, 1864/6041) and then decreased post-ART initiation at FUVs 1, 2, 3, and 4, respectively, as follows: 7% (407/5815), 5% (280/5514), 4% (210/5079) and 3% (130/4055).

Figure 2B shows results from TB diagnostic tests performed on those with presumptive TB. Of those who underwent diagnostic evaluation for TB, but were

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TABLE 1 Baseline characteristics of antiretroviral therapy-naïve patients at 22 HIV clinics, Botswana, 2012–2015

Characteristics	N	n	%
Age, years			
<12	6040	21	0.3
12–<18	6040	62	1.0
18–<25	6040	663	11.0
25–<35	6040	2548	42.2
≥35	6040	2746	45.5
Female sex	6041	4030	66.7
CD4 count, cells/mm ³			
<100	5921	1035	17.5
100–<200	5921	1285	21.7
200–<350	5921	2855	48.2
≥350	5921	746	12.6
Body mass index, kg			
<18.5	6008	1234	20.5
18.5–<25	6008	3277	54.5
25–<30	6008	1039	17.3
≥30	6008	458	7.6
Previous history of TB	6033	646	10.7
Smoking*	6025	1162	19.3
Alcohol use	6026	1321	21.9
Miner†	6026	303	5.0

*Current or former smoker.

†Current or former miner.

HIV = human immunodeficiency virus; TB = tuberculosis.

not diagnosed with TB, the proportion eligible for TPT were: 89% (1661/1864) at baseline; 98% (398/407) at FUV1; 97% (272/280) at FUV2; 97% (204/210) at FUV3; and 94% (122/130) at FUV4. After further inclusion of those with TB symptom/s who tested negative for TB (i.e. after ruling-out TB), the proportion of eligible for TPT ranged from 96.6%–99.9%. At baseline, 96.6% (5838/6041) were overall eligible for TPT, followed by 99.8%

(5806/5815) at FUV1, 99.9% (5506/5514) at FUV2, 99.9% (5073/5079) at FUV3, and 99.8% (4067/4075) at FUV4. A total of 234 TB cases were diagnosed within the four follow-up periods. The proportion of persons with TB disease among presumptive TB cases were 11% (203/1864) at baseline and 2% (9/407), 3% (8/280), 3% (6/210) and 6% (8/130) at subsequent FUVs. Table 2 shows the base line rate of TB was 3360 per 100000 patients; those with CD4 <200 (aOR = 1.4, $P = 0.030$), anaemia (aOR = 2.39, $P < 0.001$), cough (aOR = 11.21, $P \leq 0.001$), fever (aOR = 2.15, $P = 0.001$), and weight loss (aOR = 2.60, $P = 0.002$) had a higher odds of TB.

DISCUSSION

Our analysis shows that at ART initiation, 69% of PLHIV could be considered candidates for TPT. This proportion increases to 93% at subsequent FUVs. By contrast, opportunities to diagnose active TB in PLHIV are greatest at ART initiation with almost a third of PLHIV having presumptive TB at baseline, and of these, 11% being diagnosed with TB compared to 2–3% diagnosed at clinic visits post-ART initiation. The present study results illustrate the value of repeat TB screening at every ART visit to continuously maximize opportunities for TPT initiation and TB case-finding. Our findings of a high TB prevalence at ART initiation followed by a reduced risk for TB at subsequent visits are consistent with the WHO-led meta-analysis that revealed a protective effect of ART.¹⁵ The exact causal effect of ART on reduction of TB infectious or disease at subsequent visits is less clear. One could argue that, with the immune reconstitution, the proportion of symptomatic patients would decrease because of the effect of ART. However, among those symptomatic, the proportion of TB cases should be same. Further research is needed to understand better the effect of ART with immune recovery on reduction of TB incidence.

The proportions of symptomatic PLHIV at ART initiation that we observed in our analysis are similar to findings from other countries that used the same TB symptom screen.^{9–11,16} Results

FIGURE 1 Enrolment, follow-up and screening of people living with HIV, Botswana, 2012–2015. TB = tuberculosis; HIV = human immunodeficiency virus.

FIGURE 2 Proportion of people living with HIV with A) negative or positive TB symptom screen results or B) among those with presumptive TB, negative TB diagnostic test results or confirmed TB at ART initiation and FUVs, Botswana, 2012–2015. * *Baseline = clinic visit for ART initiation; after ART initiation, FUV1 = 30 days; FUV2 = 60 days; FUV3 = 90 days; and FUV4 = 210 days; median days for FUVs 1, 2, 3 and 4: 35 [IQR 28–42], 97 [IQR 65–126], 173 [IQR 121–218] and 243 [IQR 189–314], respectively; † the number of people with HIV screened for A) TB symptoms and B) with presumptive TB at each clinic visit. HIV = human immunodeficiency virus; TB = tuberculosis; ART = antiretroviral therapy; FUV = follow-up visit.

from South Africa, Rwanda, Zimbabwe, and Uganda also showed approximately 23–28% of PLHIV with TB symptoms prior to starting ART.^{9–11,16} The higher proportion of symptomatic patients observed at baseline is likely due to the higher degree of immuno-

suppression, making them more susceptible to a variety of infections, including TB. Indeed, in our study, ART-naïve PLHIV were diagnosed with TB at a rate approximately ten times higher (3360 versus 385/100 000) than the estimated national annual TB

TABLE 2 Characteristics of patients with TB vs. without TB at baseline in a multilevel logistic regression model at 22 HIV clinics, Botswana, 2012–2015

Characteristics	TB			Without TB			aOR	95%CI	P value
	n	N	%	n	N	%			
Age <35 years	79	203	38.9	3215	5837	55.1	0.93	0.67–1.29	0.641
Female sex	92	203	45.3	3938	5838	67.5	0.57	0.30–1.08	0.084
CD4 count <200 cells/mm ³	130	199	65.3	2190	5722	38.3	1.40	1.04–1.90	0.030
Haemoglobin <10 mg/dl	70	171	40.9	848	5333	15.9	2.39	1.80–3.16	<0.001
BMI <18.5 kg/m ²	89	203	43.8	1131	5838	19.4	1.43	0.88–2.33	0.138
Smoking ever, yes	61	203	30.1	1101	5822	18.9	1.14	0.69–1.88	0.594
Alcohol use, yes	44	203	21.7	1277	5823	21.9	0.75	0.48–1.15	0.178
Miner ever, yes	22	203	10.8	281	5823	4.8	1.45	0.77–2.73	0.233
History of TB, yes	25	202	12.4	621	5831	10.7	0.68	0.43–1.07	0.094
TB symptoms									
Cough	175	203	86.2	997	5838	17.1	11.21	5.38–23.38	<0.001
Fever	103	203	50.7	460	5838	7.9	2.15	1.46–3.18	0.001
Night sweats	94	203	46.3	490	5838	8.4	1.23	0.79–1.92	0.337
Weight loss	156	203	76.9	1138	5838	19.5	2.60	1.51–4.49	0.002

*Without TB at baseline.

TB = tuberculosis; aOR = adjusted odds ratio; CI = confidence interval.

incidence. Unsurprisingly, patients with CD4 cell count <200 cells/mm³ had higher odds of TB at baseline in addition to other risk factors such as anaemia, cough, fever or weight loss. Although Botswana provided free ART access (eligibility for ART was CD4 count ≤ 350 /mm³ in the study period),¹³ nearly 40% of PLHIV had advanced HIV with CD4 cell count <200 /mm³. Evidence from other countries in sub-Saharan Africa confirm late-stage presentations of PLHIV to care.^{17,18} Immune reconstitution after starting ART appears to occur quickly such that the proportion of symptomatic patients in our cohort dramatically reduced from 31% at baseline to 4–7% at clinic visits thereafter.

Our study had limitations. First, we noted a high number of lost to follow-up in this study of almost 2000 participants. The proportion of participants lost to follow-up increased at each subsequent visit. As such, we may have overestimated TPT eligibility at subsequent visits because these participants were likely sicker than those retained in care and would have otherwise contributed a higher proportion of symptomatic participants or active TB cases. Second, since TPT was not implemented programmatically in Botswana during the period of our study, we could not follow the TPT cascade through TPT completion. Thus, the opportunities for TPT eligibility at subsequent ART visits shown in our study could have been different for countries that are implementing TPT, as prior history of receiving TPT will affect subsequent TPT eligibility. For the same reason, we did not evaluate how other exclusion criteria, such as hypersensitivities to isoniazid, hepatitis and peripheral neuropathy, might have influenced TPT eligibility at each visit. Third, we did not perform diagnostic testing among symptom-free PLHIV. We therefore likely missed some cases of TB in this group. Fourth, since TB patients were diagnosed variably using smear or Expert, it is likely that TB diagnoses among symptomatic PLHIV were also missed due to the lower sensitivity of smear compared to Xpert.¹⁷ Additionally, not all patients with TB symptoms were tested for TB since some might have not submitted sputum or not returned for an X-ray. As a result, we might have missed some TB patients, especially if patients did not return for FUVs, which may have inflated the TPT eligible patients at baseline and FUVs. Fifth, since children were often seen at a centralized children's clinic other than study clinics, we were unable to enrol more than 21 (0.3%) children in this study and thus were unable to draw any meaningful conclusions about their TPT eligibility across ART visits.

In conclusion, despite these limitations, our analysis provides useful descriptions of eligibility for TPT and TB case-finding potential by duration of ART exposure. In April 2019, Botswana changed its HIV guidelines to include the provision of TPT for eligible PLHIV and began implementation later that year. Since HIV is a major driver of the TB epidemic in Botswana,^{1,4} expanded TPT implementation in the country is expected to reduce the burden of TB among PLHIV in the coming years. Additionally, as the

country scales-up implementation of TPT, planning TPT procurements based on expected TPT eligibility by duration of ART exposure will become increasingly important. Finally, these results remind us not only of the value of continuous TB screenings for active-case finding, but of the ongoing opportunities to provide TPT throughout the lifelong course of ART.

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Contexte : Vingt-deux centres de santé offrant une prise en charge de l'infection par le virus de l'immunodéficience humaine (VIH) au Botswana où la comorbidité tuberculose (TB) et VIH atteint 49%.

Objectif : Evaluer l'éligibilité du traitement préventif de la TB (TPT) lors de la mise en route du traitement antirétroviral (TAR) et lors des consultations de suivi (FUV), et décrire la prévalence de la TB et les facteurs associés au départ ainsi que le rendement du diagnostic de TB lors de chaque consultation de suivi.

Schéma : Une étude prospective de données recueillies en routine chez des personnes vivant avec le VIH (PLHIV) enrôlées en soins dans le Xpert® MTB/RIF Package Rollout Evaluation Study (étude d'évaluation du lancement du paquet Xpert) entre 2012 et 2015.

Résultats : Sur 6041 PLHIV débutant le TAR, l'éligibilité au TPT a été

de 69% (4177/6041) au départ et de 93% (5408/5815) ; 95% (5234/5514) ; 96% (4869/5079) ; et 97% (3925/4075) lors des FUV1, FUV2, FUV3 et FUV4, respectivement. La prévalence de la TB au départ était de 11% et de 2%, 3%, 3% et 6% lors des FUV. Au départ, les facteurs de risque indépendants de TB ont été un CD4 <200 cellules/mm³ (ORa 1,4 ; $P = 0,030$), une anémie (ORa 2,39 ; $P < 0,001$), une toux (ORa 11,21 ; $P \leq 0,001$), une fièvre (ORa 2,15 ; $P = 0,001$) et une perte de poids (ORa 2,60 ; $P = 0,002$).

Conclusions : L'éligibilité à l'initiation du TPT est plus élevée lors des consultations postérieures à la mise en route du TAR alors que de nombreux cas de TB active ont été identifiés lors de l'initiation du TAR. Les occasions manquées de TPT compromettent davantage les efforts de lutte contre la TB parmi les PLHIV au Botswana.

Marco de Referencia: Veintidós consultorios que prestan atención y tratamiento relacionados con la infección por el virus de la inmunodeficiencia humana (VIH) en Botswana, donde la comorbilidad por tuberculosis (TB) e infección por el VIH puede alcanzar 49%.

Objetivos: Evaluar los criterios para recibir el tratamiento preventivo de la TB (TPT) durante las consultas de iniciación y seguimiento del tratamiento antirretrovírico (TAR) y describir la prevalencia de TB y los factores asociados en el momento del inicio y el rendimiento del diagnóstico de TB en cada cita de seguimiento del TAR.

Método: Fue este un estudio prospectivo de los datos obtenidos sistemáticamente en las personas con infección por el VIH (PLHIV), inscritas en la atención para el estudio de evaluación del despliegue de la prueba Xpert® MTB/RIF del 2012 al 2015.

Resultados: De los 6041 PLHIV que iniciaron el TAR, 69% (4177/6041) cumplía los criterios para recibir el TPT al comienzo;

93% (5408/5815) en la primera consulta de seguimiento; 95% (5234/5514) en la segunda; 96% (4869/5079) en la tercera; y 97% (3925/4075) en la cuarta cita de seguimiento. La prevalencia inicial de TB fue 11% y durante el seguimiento fue 2%, 3%, 3% y 6%, respectivamente. Al comienzo del TAR, los factores de riesgo independientes de diagnóstico de TB fueron una cifra de linfocitos CD4 <200 células/mm³ (aOR 1,4; $P = 0,030$), la anemia (aOR 2,39; $P < 0,001$), la tos (aOR 11,21; $P = <0,001$), la fiebre (aOR 2,15; $P = 0,001$) y la pérdida de peso (aOR 2,60; $P = 0,002$).

Conclusión: Los pacientes cumplen las condiciones para recibir el TPT con mayor frecuencia en las consultas posteriores al comienzo del TAR, pero la mayoría de los casos de TB activa se detecta al iniciarlo. Las oportunidades desaprovechadas para detectar casos de TB dificultan aún más el control de esta enfermedad en las PLHIV en Botswana.