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Tuberculosis preventive treatment uptake among adults living with human immunodeficiency virus: Analysis of Zimbabwe population-based human immunodeficiency virus impact assessment 2020

Talent Maphosa[1], **Kelsey Mirkovic**[1], **Rachel A. Weber**[1], **Godfrey Musuka**[2], **Munyaradzi P. Mapingure**[2], **Julia Ershova**[3], **Rebecca Laws**[3], **Trudy Dobbs**[3], **William Coggin**[3], **Charles Sandy**[4], **Tsitsi Apollo**[4], **Owen Mugurungi**[4], **Michael Melchior**[1], **Mansoor S. Farahani**[5]

[1]U.S. Centers for Disease Control and Prevention, Harare, Zimbabwe

[2]ICAP at Columbia University, Harare, Zimbabwe

[3]Division of Global HIV & TB, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[4]Ministry of Health and Child Care, Harare, Zimbabwe

[5]ICAP at Columbia University, New York City, NY, USA

Abstract

Background: Tuberculosis remains the leading cause of death by an infectious disease among people living with HIV (PLHIV). TB Preventive Treatment (TPT) is a cost-effective intervention known to reduce morbidity and mortality. We used data from ZIMPHIA 2020 to assess TPT uptake and factors associated with its use.

Methodology: ZIMPHIA a cross-sectional household survey, estimated HIV treatment outcomes among PLHIV aged ≥15 years. Randomly selected participants provided demographic and clinical information. We applied multivariable logistic regression models using survey weights. Variances were estimated via the Jackknife series to determine factors associated with TPT uptake.

Results: The sample of 2419 PLHIV ≥15 years had 65% females, 44% had no primary education, and 29% lived in urban centers. Overall, 38% had ever taken TPT, including 15% currently taking TPT. Controlling for other variables, those screened for TB at last HIV-related

Corresponding author: Talent Maphosa, U.S. Centers for Disease Control and Prevention, HIV Services Branch, Embassy Harare, 2 Lorraine Drive, Bluffhill, Harare, Zimbabwe. oxv9@cdc.gov.

Authors' contribution

The authors confirm contribution to the paper as follows: analysis and interpretation of results: T. Maphosa, K. Mirkovic, M. Farahani, and R. Laws. Draft manuscript preparation: T. Maphosa, K. Mirkovic, M. Farahani, R. Laws, T. Dobbs, and G. Musuka. All authors reviewed the results and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

[1]HIV treat all defined as initiation of antiretroviral therapy regardless CD4 count or clinical stage

visit, those who visited a TB clinic in the previous 12 months, and those who had HIV viral load suppression were more likely to take TPT.

Conclusion: The findings show suboptimal TPT coverage among PLHIV. There is a need for targeted interventions and policies to address the barriers to TPT uptake, to reduce TB morbidity and mortality among PLHIV.

Keywords

Tuberculosis preventive treatment; isoniazid preventive therapy; people living with human immunodeficiency virus; TB screening; tuberculosis screening; tuberculosis; human immunodeficiency virus; Zimbabwe; Leave out Zimbabwe population-based HIV impact assessment

Background

Globally, tuberculosis (TB) is the second leading cause of death from a single infectious agent, after coronavirus disease 2019 (COVID-19).[1] TB remains the leading cause of death by an infectious disease among people living with HIV (PLHIV) in Zimbabwe.[2] In 2021, 5900 PLHIV died from TB versus 2100 individuals without HIV.[1] Until 2021, Zimbabwe had been on the World Health Organization's (WHO) list of 30 countries with a high burden of TB. Despite recent improvements, the country remains on the high burden list for HIV-associated TB and multidrug-resistant TB.[3] While HIV-associated TB has been declining in Zimbabwe, 54% of TB clients have HIV, indicating that TB among PLHIV remains a challenge.[1] Among PLHIV in Zimbabwe, TB incidence is 104 per 100,000, and TB mortality rose from 31 per 100,000 in 2020 to 40 per 100,000 in 2021.[1,2] Both TB mortality and incidence are approximately three times higher among HIV-positive than HIV-negative persons. TB prevention interventions must be scaled up, targeting those at higher risk, to end the TB epidemic and reduce the burden of TB among PLHIV.

In 2012, Zimbabwe's Ministry of Health and Child Care (MoHCC) introduced TB Preventive Treatment (TPT) — 6 months of isoniazid (6H) — for PLHIV to mitigate the impact of HIV-associated TB.[4] TPT is a cost-effective method to reduce morbidity, mortality, and incidence of TB among PLHIV.[5] Antiretroviral therapy (ART) and TPT, independent of one another, reduce the likelihood of developing TB by 65% and 33%–44%, respectively,[4–8] among PLHIV, emphasizing the need for TPT to be an integral part of HIV care and treatment. Despite these overwhelming benefits of TPT, implementation has been slow. According to the Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA) 2015–2016, conducted three to 4 years after the TPT rollout in 2012, TPT uptake among PLHIV was estimated to be 13.%.[6] When the second ZIMPHIA (ZIMPHIA 2020) was conducted, the following PLHIV were eligible for TPT: those who (1) did not have active TB, and (2) had no signs or symptoms of liver disease. This was also a period of transition from the old to new guidelines which recommended ART and TPT be started on the same day for new clients enrolling in HIV care, where possible. The MoHCC recommends that during each visit to a health facility, all PLHIV are screened for TB using the WHO symptom (cough, night sweats, fever, and weight loss) tool.[7] Those who are asymptomatic are then assessed for TPT eligibility. Patients who screen positive are considered to have

a presumptive TB diagnosis and tested. Patients with negative test results are subsequently assessed for TPT eligibility, while those who test positive are immediately started on anti-TB treatment and then considered eligible for TPT at the end of their treatment.

During a United Nations High-Level Meeting on TB in 2018, member countries, including Zimbabwe, committed to providing TPT to 30 million people by 2022 to expedite TPT implementation. For Zimbabwe this meant initiating ART among all eligible persons by the end of 2022. The Office of the U.S. Global AIDS Coordinator also committed to delivering TPT to all 13.6 million ART patients supported by the President's Emergency Plan For AIDS Relief (PEPFAR) by 2021.[8] Globally, the PEPFAR initiative led to the integration of TPT into standard HIV care and provided resources for drug procurement and implementation (4). These events triggered a drive to scale up TPT in the country, and according to the WHO Global TB Report 2020, 89% of patients with new HIV diagnoses in Zimbabwe started TPT.[2] However, the prevalence of TPT uptake among all PLHIV remains unknown.

In this analysis, we used ZIMPHIA 2020 data to assess the prevalence of self-reported TPT uptake among PLHIV and explored factors associated with its use. Ours is a follow up to a similar analysis done by Takamiya et.al.[9] using ZIMPHIA 2015–2016 data.

Methods

Study design and population

Survey methods.—ZIMPHIA 2020 is a nationally-representative, cross-sectional, household-based survey to estimate HIV prevalence, national incidence, and provincial viral load suppression in Zimbabwe. Data collection was conducted between November 2019 and March 2020. A two-stage stratified cluster sample design was used. In the first stage, within each province, EAs were selected systematically with probability proportional to size, where the size of an EA is defined by the number of households in that EA based on population projections for 2020 derived from the 2012 census. Within each province, EAs were sorted by urban-rural status and then geographically within urban-rural status prior to sample selection. Such sorting induces an implicit stratification that ensured that the number of urban and rural EAs in the sample was proportional to their distribution in the census. In the second stage, an average of 35 dwelling units were selected in every selected EA within each stratum. In total, 356 EAs were selected for this survey. Complete survey methods for ZIMPHIA have been published.[10]

Study participants.—Adults 15 years and older living in residential households and visitors who slept in the household the night before the survey, were eligible to participate if they were willing and cognitively able to provide consent after household consent was obtained from the head of household. Consenting participants were asked questions about demographic characteristics, HIV testing history, ART initiation date and adherence, TB screening during the previous ART visit, and TPT initiation and duration of use.

Whole blood was collected, and HIV testing was conducted in the household using serological tests according to the national algorithm with results returned to participants

for further management. For HIV seropositive samples a supplemental assay, Genius HIV 1/2 Supplemental Assay (Bio-Rad, Hercules, California, United States), was used as a confirmatory test in the laboratory. CD4 count and HIV viral load (HIV RNA copies per mL) measurements among all adults living with HIV were done using a battery-operated Pima™ CD4 Analyzer (Abbott Molecular Inc., Chicago, Illinois, United States, formerly Alere) and COBAS AmpliPrep/Taqman 96 assay on the COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) HIV-1, v2.0 Test (Roche Molecular Diagnostics, Branchburg, New Jersey, United States) respectively, both laboratory-based. In cases where plasma samples were not available, HIV-1 VL was performed on dried blood spot (DBS) samples using the COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) Free Virus Elution (FVE) Protocol (Roche Molecular Diagnostics, Branchburg, New Jersey, United States).

Statistical analysis.—The analysis was restricted to participants who had laboratory-confirmed HIV after a self-reported awareness of their HIV-positive status during the interview and had complete risk-factor data. The outcome variable used in this analysis was “Having received TPT” and “Screened for TB at the last ART visit,” treated as an exposure variable. Following the literature, we identified the variables selected for the model. We included sociodemographic variables, for example, age, sex, urbanicity, education, marital status, wealth index, the CD4, and viral load suppression as a proxy for the HIV disease progression in the data analysis. The time trend was captured by three indicator variables: “1985–2010; 2011–2015; 2016–2020.”

The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) statistical tests for model selection were used. Using these criteria, we redefined marital status to “Not in union” for the singles, divorced and widow (er)s. We used the wealth quintiles as a proxy for the household’s socio-economic status (SES). The quintiles were regrouped into “upper 60%,” which included the top three wealth quintiles, and “lower 40%,” which included the bottom two wealth quintiles. We divided the participant’s age into two groups (below 35 and 35+).

TPT prevalence was calculated for different sociodemographic and risky behavior variables. Bivariate associations between TPT uptake and sociodemographic characteristics were described using the Rao-Scott $\chi 2$ tests of association to account for the survey design. Jackknife replicate weights and survey estimation procedures were used to compute confidence intervals for all estimates, accounting for the complex sampling design and weighting adjustments.

PHIA data incorporated weights to adjust for selection probabilities, nonresponse, and noncoverage. These weights were calculated at different levels, including enumeration areas, households, individual interviews, and blood draws, considering various factors like response predictors and HIV status. All analyses were conducted using Stata 16 (Stata Corp., College Station, TX).

Nine individuals who responded, “don’t know” to questions about TPT use were classified as “not having taken,” and five individuals unsure of current TPT use were classified as “not

currently using TPT." One individual unsure of having visited a TB clinic in the previous 12 months was classified as "not having visited a TB clinic."

Ethical approval.—ZIMPHIA 2020 received ethical approval from the Medical Research Council of Zimbabwe, the Research Council of Zimbabwe, the U.S. Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB), Columbia University IRB, and Westat IRB. The study was reviewed following the U.S. CDC human research protection procedures and determined to meet ethical standards. Written informed consent in English, Shona or Ndebele was obtained from all participants.

Results

A total of 19,535 study participants aged ≥15 years from ZIMPHIA 2020 were interviewed and consented to biomarker testing, of which 2511 self-disclosed a positive HIV status which was laboratory confirmed. Five individuals were excluded for missing CD4 results, 3 individuals excluded for missing education information and 2 individuals excluded for missing marital status 2501 individuals.

Characteristics of the analytic population

Among the 2501 PLHIV ≥15 years; 36% were male, 74% were 35 years or older, 44% had no education or primary education, and 29% were living in urban centers. Sixty-seven percent had initiated ART before the "Treat All"[1] initiative in 2015, and 88% of all PLHIV were virally suppressed. Overall, 43% were reportedly screened for TB at their most recent ART visit and 37% had ever taken TPT. Among those who had ever taken TPT, 15% were currently taking TPT (Table 1).

Predictors of having received TPT

In unadjusted models, PLHIV who were male, who screened for TB at the last ART visit, who visited a TB clinic in the previous 12 months, who were ≥35 years of age, and who had a suppressed HIV viral load (VL <1000 copies/ml) were more likely to have taken TPT compared with reference groups. Those who had initiated ART from 2011 to 2015 and 2016–2020 were less likely to have taken TPT than those who initiated ART earlier before 2010. In the adjusted model, having screened for TB at the last ART visit (aPR: 1.21; 95% CI: 1.06–1.38) and, having visited a TB clinic in the previous 12 months (aPR: 1.71; 95% CI: 1.47–1.99), remained predictors of having taken TPT. Timing of ART initiation also remained significant in the adjusted model where those having initiated ART from 2011 to 2015 were less likely to have taken TPT than those who initiated ART from 1985 to 2010 (aPR: 0.86; 95% CI: 0.75–0.98) (Table 2).

Discussion

Here, we show TPT uptake among PLHIV marginally increased from 13% in 2016.[9] at the time of the first ZIMPHIA to 37%; suggesting the need for urgent scaling up of this critical intervention to achieve United Nations High Level Meeting (UNHLM) targets. PLHIV who had been screened for TB at their previous visit, and those who had visited a TB clinic in the previous 12 months were more likely to have initiated TPT. These results suggest

the need for integration of prevention and treatment interventions within TB and ART clinics. Patients with a presumptive TB diagnosis referred to TB clinics for investigations are eventually initiating TPT after test results indicate the absence of active TB disease.

There was no association between TPT uptake and level of education, socioeconomic status, rural/urban residency nor marital status. However, these have been found to impact TPT uptake in other Sub-Saharan African studies.[9,11–14] with similar settings. PLHIV who have initiated ART from 2011 were less likely to have taken TPT, compared with PLHIV who initiated ART before 2010, probably due to treatment guidelines. Zimbabwe's TPT guidelines recommended a 3-month waiting period for newly diagnosed PLHIV before TPT initiation. Therefore, during the first years of TPT rollout the program might have focused on actively tracking and initiating TPT among patients already on ART and have gone past the 3-month waiting period. Whereas new clients on ART might not have been prioritized. We recommend a further study to understand why timing of ART initiation is a significant factor for TPT uptake.

One of the main findings from Takamiya et. al, 2021 indicated that factors associated with TPT non-uptake did not vary between men and women[9]; our analysis had a similar finding. Additionally, in the previous study, clients between 15 and 19 years of age residing in rural areas were least likely to take up TPT,[9] potentially related to the poor retention in this age group during that time. Rural versus urban residency was not a factor in TPT uptake for this study, possibly showing an improvement in provision of service in both settings. To achieve UNHLM targets on TB, Zimbabwe must address the TPT uptake gaps among adolescents and young adults. Messaging tailored to make TPT attractive for these populations must be developed. Shorter TPT regimens that improve adherence and completion must be prioritized among the younger population groups who are busy and highly active. A study in Botswana reported low TPT completion among men and younger patients, with the groups citing work commitments as a barrier.[12] Hence targeted outreach and expansion of service delivery hours could improve uptake of TPT.

The standard practice recommends all PLHIV be screened for TB at every visit to the health facility because screening is an entry point for both TB prevention and treatment. In this survey, only 43% of PLHIV self-reported TB screening at their most recent visit, highlighting an area needing strengthening. Given the association between TB screening and TPT uptake, this may be why TPT coverage is low. Others have also noted the association between low TPT coverage and suboptimal TB screening practices. Roscoe et.al. observed that irregular TB screening practices were a barrier to TPT uptake and scale-up in Namibia.[11]

This study was based on a nationally representative sample of Zimbabweans thus producing generalizable results. However, weaknesses include reliance on self-reported TB screening, TPT uptake, and attendance ata TB clinic which are subjective and prone to recall bias. There are other factors that play a key role in health seeking behavior among PLHIV. Among these is religion,[15–17] our study did not collect and analyze data on religion as a factor influencing TPT uptake. HIV care is evolving to became more client centered

with differentiated service delivery (DSD) being scaled up. TPT integrated with DSD is acceptable[18]; we did not collect data to determine the influence of DSD on TPT uptake.

Conclusion

Our study is the second population-based study showing a marginal improvement in TPT uptake among PLHIV when compared with the first study. Despite the progress, the uptake is too low to achieve the UNHLM on TB targets of universal TPT coverage among the eligible clients by the end of 2022 and experience the desired impact. Without addressing the barriers and factors associated with the non-uptake of TPT it will be challenging for Zimbabwe to achieve UNHLM TPT targets. Roll out of shorter TPT regimens might improve patient choice and convenience, enhancing uptake and completion. Zimbabwe has a dual burden of TB and HIV; hence integrated interventions might be beneficial including testing of all TB clients for HIV.

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Data availability statement

Data for this manuscript is publicly available on ICAP Web site https://phia-data.icap.columbia.edu/

List of abbreviations

ART	Antiretroviral treatment
HIV	Human immunodeficiency virus
IPT	Isoniazid preventive treatment
MOHCC	Ministry of Health and Child Care
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
TB	Tuberculosis
TPT	TB preventive therapy
UNHLM	United Nations High Level Meeting
WHO	World Health Organization

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Table 1.

Clinical and demographic characteristics of the study population. $n = 2501$.

	Weighted percent	95% confidence interval
Sex		
Male	35.8	(34.0–37.7)
Female	64.2	(62.3–66.1)
Age		
<35	25.6	(23.6–27.6)
35+	74.4	(72.4–76.4)
Marital status		
Not in a union	42.3	(39.5–45.1)
In a union	57.8	(54.9–60.5)
Education		
No education/Primary	44.2	(41.4–47.1)
Secondary/More than secondary	55.8	(52.9–58.6)
Have taken TPT		
Yes	37.2	(34.7–39.8)
No	62.8	(60.2–65.3)
Currently taking TPT[a]		
Yes	14.5	(11.6–18.3)
No	85.5	(82.0–88.4)
Screened for TB at last ART visit		
Yes	42.5	(40.2–45.0)
No	57.5	(55.0–59.9)
Visited a TB clinic in the previous 12 months		
Yes	15.1	(13.7–16.8)
No	84.9	(83.3–86.3)
Wealth quintile		
Average and below	66.5	(63.4–69.5)
Higher than average	33.5	(30.5–36.6)
Rural/Urban		

	Weighted percent	95% confidence interval
Urban	29.1	(25.2–33.5)
Rural	70.9	(66.6–74.8)
Current pregnancy[b]		
Pregnant	2.7	(2.1–3.4)
Not pregnant	61.1	(59.1–63.1)
Missing	36.2	(34.4–38.2)
Year of ART initiation[c]		
1985–2010	27.4	(25.2–29.7)
2011–2015	39.8	(37.4–42.2)
2016–2020	32.8	(30.5–35.2)
CD4 count		
<500	46.1	(44.0–48.2)
500+	54.4	(51.8–56.0)
HIV VL suppression (VL <1000 copies/ml)		
Yes	88.0	(86.4–89.4)
No	12.0	(10.6–13.6)

[a] Among those who have taken TPT.

[b] Among women only.

[c] Missing $n = 26$ not on ART or unknown ART initiation year.

Table 2.

Crude and adjusted prevalence ratios of having received TPT by selected characteristics. $N = 2501$.

Characteristics	Received TPT (N)	Weighted %	*p*- value	Crude prevalence ratios (cPR)	Adjusted prevalence ratio (aPR)
Sex			0.02		
Male	301	38.8 (35.4–42.3)		1.14 (1.02–1.28)	1.10 (0.99–1.23)
Female	642	61.2 (57.7–64.3)		REF	REF
Age			<0.001		
<35	173	20.7 (17.8–24.0)		1.30 (1.12–1.55)	0.98 (0.75–1.04)
35+	770	79.3 (76.0–82.0)		REF	REF
Marital status			0.70		
Not in a union	411	58.4 (54.6–62.0)		0.97 (0.86–1.10)	
In a union	532	41.6 (38.0–45.4)		REF	
Education			0.50		
No education/Primary	449	42.9 (39.2–46.6)		1.06 (0.93–1.20)	
Secondary/More than secondary	494	57.1 (53.4–60.8)		REF	
Wealth quintile			0.20		
Average and below	643	64.9 (60.9–68.7)		1.08 (0.94–1.24)	
Higher than average	300	35.1 (31.3–39.2)		REF	
Rural/Urban			0.60		
Urban	251	29.8 (25.7–34.2)		0.97 (0.83–1.14)	
Rural	692	70.3 (65.8–74.3)		REF	
Year of ART initiation[a]			<0.001		
1985–2010	329	33.8 (30.3–37.6)		REF	REF
2011–2015	393	42.5 (38.6–46.5)		0.86 (0.75–0.99)	0.86 (0.75–0.98)
2016–2020	216	23.7 (20.5–27.3)		0.58 (0.49–0.69)	0.58 (0.64-l.0l)
CD4 count			0.97		
<500	401	54.9 (51.2–58.6)		0.96 (0.85–1.09)	
500+	542	45.1 (41.5–48.8)		REF	
HIV VL suppression (VL <1000 copies/ml)			0.11		
Yes	868	90.7 (88.0–92.9)		0.75 (0.58–0.97)	0.81 (0.64–1.10)
No	75	9.3 (7.2–12.0)		REF	REF

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[a] Missing $n = 26$ not on ART or unknown ART initiation year.