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Isoniazid preventive therapy use among adult people living with HIV in Zimbabwe

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Abstract

We assessed the prevalence of isoniazid preventive therapy (IPT) uptake and explored factors associated with IPT non-uptake among people living with HIV (PLHIV) using nationally representative data from the Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA) 2015–2016. This was a cross-sectional study of 3418 PLHIV ZIMPHIA participants eligible for IPT, aged ≥15 years and in HIV care. Logistic regression modeling was performed to assess factors associated with self-reported IPT uptake. All analyses accounted for multistage survey design. IPT uptake among PLHIV was 12.7% (95% confidence interval (CI): 11.4–14.1). After adjusting for sex, age, rural/urban residence, TB screening at the last clinic visit, and hazardous alcohol use, rural residence was the strongest factor associated with IPT non-uptake (adjusted OR (aOR): 2.39, 95% CI: 1.82–3.12). Isoniazid preventive therapy non-uptake having significant associations with no TB screening at the last HIV care (aOR: 2.07, 95% CI: 1.54–2.78) and with hazardous alcohol use only in urban areas (aOR: 10.74, 95% CI: 3.60–32.0) might suggest suboptimal IPT eligibility screening regardless of residence, but more so in rural areas. Self-reported IPT use among PLHIV in Zimbabwe was low, 2 years after beginning national scale-up. This shows the importance of good TB screening procedures for successful IPT implementation.

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Supplementary material

Supplemental material for this article is available online.

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: The lead author affirms 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.

Keywords

Isoniazid preventive therapy; people living with HIV; HIV; TB/HIV coinfection; Zimbabwe; Zimbabwe Population-based HIV Impact Assessment; sub-Saharan Africa

Background

People living with HIV (PLHIV) are at 20–40 times higher risk of developing TB compared to people who do not have HIV. For this reason, TB remains a pressing global health priority particularly in sub-Saharan Africa (SSA) where the HIV epidemic persists.[1] Since 2011, the World Health Organization (WHO) has recommended that TB preventive therapy (TPT) be administered to PLHIV to reduce TB-related morbidity and mortality.[2] TB preventive therapy has been shown to reduce the incidence of TB disease among PLHIV by 33%–62%.[2] Isoniazid preventive therapy (IPT) reduces mortality among PLHIV by 37%, independent of antiretroviral therapy (ART).[3] The 2011 WHO guidelines conditionally recommend the use of IPT for at least 36 months for PLHIV in high TB- and HIV-prevalence settings. The WHO End TB Strategy aims to get 90% of PLHIV on TPT by 2025. However, uptake of TPT has been poor among PLHIV globally, especially in many countries with high TB and HIV burden.[4] In 2018, the TPT coverage among PLHIV who newly enrolled in HIV care was 49% globally and 60% in SSA.[1] Various barriers to high TPT coverage have been reported in high TB burden settings, such as lack of awareness and buy-in from healthcare workers, additional burden on clinic staff, commodity stock outs, and distance from health facilities.[5,6]

Zimbabwe is one of the 14 countries with high burdens of TB, multidrug resistant TB and HIV.[1] TB incidence among PLHIV in Zimbabwe is 19 estimated at (14–24)/ 1000/annum in 2018[1] and mortality among PLHIV remains 3-fold higher than among those not affected with HIV.[3] Given the WHO recommendations for on IPT scale-up among PLHIV, the Ministry of Health and Child Care (MOHCC) piloted implementation of isoniazid (INH) together with pyridoxine in 10 selected sites across five provinces to determine feasibility of scale-up between 2012 and 2013. The pilot showed a high rate of 6 months completion (81%) among 9924 PLHIV who initiated IPT.[7] In 2014, the Zimbabwe National ART Programme started nationwide scale-up of IPT, prioritizing IPT provision to PLHIV on ART.

With MOHCC-led initiatives to expand IPT coverage, the number of ART clients initiated on IPT increased from 98 in 2012 to 373,819 in 2018.[8] However, published literature on national IPT uptake in Zimbabwe is scarce. Here, we assessed the prevalence of self-reported IPT uptake among PLHIV and explored factors associated with IPT non-uptake using data from the nationally representative Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA) survey 2015–2016.

Methods

Study setting

The 2015–2016 ZIMPHIA assessed the prevalence of HIV and key HIV-related health indicators and behaviors in a nationally representative sample of individuals from randomly selected households across Zimbabwe. In stage one of the two-stage stratified cluster sampling design, 500 enumeration areas were selected from the Zimbabwe Population Census 2012, using a probability proportional to size method. In stage two, a sample of households was randomly selected from each cluster, using an equal probability method with an average sample of 30 households per cluster (range: 15–60). A total of 11,717 households responded to household questionnaires, from which 25,131 individuals aged 15 years or older completed individual questionnaires and participated in biomarker testing. Biomarker testing included genius HIV-1/2 confirmatory assay, CD4 cell count, HIV viral load (VL), syphilis point-of-care rapid test, assays for recent HIV infection (LAg Avidity enzyme immunoassay), presence of ART and drug resistance testing. Prior to administering questionnaires and drawing blood for biomarker testing, electronic informed consent was obtained from individuals aged 16 years and above and emancipated minors aged 15 years who slept in the household the night before the survey.

Eligibility for IPT initiation among PLHIV

The 2015–2016 ZIMPHIA was conducted before adoption of the “Treat All” HIV strategy where all persons diagnosed with HIV are immediately started on ART, regardless of CD4 count or WHO clinical staging.[9] At the time of the survey, national guidelines considered PLHIV eligible for 6 months of IPT administration if they (1) did not have active TB, or (2) were on ART for more than 3 months (this was revised in 2018/19 to allow IPT administration at the time of ART initiation), or (3) had no signs or symptoms of liver disease.[10] Per the national IPT guidelines in Zimbabwe, all PLHIV are screened for TB symptoms (cough, night sweats, fever, and weight loss) at each HIV care visit (including ART pickup). Patients who screen negative for TB symptoms are potentially eligible for the 6 months regimen of IPT. Patients who present with any of the four symptoms (cough of any duration, night sweats, fever, and weight loss) are considered as presumptive TB patients and referred for sputum examination using the Xpert MTB/RIF assay or smear microscopy. However, the guideline in 2015–2016 also did not include Xpert MTB/RIF assay for TB investigation, which was incorporated in late 2016, shortly after the ZIMPHIA data collection.

Study design and population

This was a cross-sectional study of data collected from 3507 participants in the ZIMPHIA 2015–2016 who met our eligibility criteria for analysis. The eligibility criteria for analysis were (1) being adult PLHIV (i.e. aged 15 years and above), (2) being in HIV care, and (3) having completed both the individual questionnaire and biomarker testing in the ZIMPHIA 2015–2016 (see Figure 1; flow diagram for analytic sample). For bivariate and multiple variable analyses, PLHIV who were on ART for less than 3 months were excluded from the analysis as they would have been ineligible for IPT based on national guidelines at the time of the ZIMPHIA survey.

Measurement

Sociodemographic and behavioral variables considered in the analysis were sex, age, education level, religion, province and location of residence (urban vs rural), current pregnancy status (female only), TB symptom screening at their last HIV care visit, ART status, taking cotrimoxazole, CD4 counts, VL, and hazardous drinking. Hazardous drinking is a variable composed of three alcohol drinking questions of The Alcohol Use Disorders Identification Test for Consumption (AUDIT-C) designed by WHO[11] and dichotomized into hazardous or nonhazardous drinkers. All the variables except CD4 count and VL were self-reported. Outcome variable, self-reported IPT uptake was defined as a "yes" response to the questions "Have you ever taken IPT or INH for TB prevention."

Statistical analysis

Demographic and behavioral characteristics of survey respondents, stratified by self-reported IPT uptake, were summarized with unweighted counts and weighted percentages. Associations between the covariates and the outcome were assessed using the chi-square test and odds ratios (cORs) with 95% confidence intervals (CI). The covariates were assessed in univariate regression models for the reduction in 2 log likelihoods using chi-square tests. In multiple variable analysis, covariates of which cOR with $p < 0.25$ in bivariate analysis including confounders were added to a weighted logistic regression model (model 1). Because the factors associated with IPT uptake were different by urban/rural contexts, two models were built to illustrate differential effects of rural/urban residence. Logistic regression model 1 included sex, age, urban/rural residence, TB symptoms screening at the last HIV care visit, viral suppression, and hazardous alcohol use. Model 2 was stratified by urban/rural residence while keeping the same covariates from model 1. Hazardous drinking, which is often linked with active liver disease, was added to the regression model as a conceptually important covariate. All analyses were weighted for complex survey design, non-coverage, and nonresponse. All analyses were performed on SAS 9.4 statistical software (*SAS Institute Inc., Cary, NC, USA)*.

Ethical approval

Ethical approval was obtained from Medical Research Council of Zimbabwe, Research Council of Zimbabwe, US Centers for Disease Control and Prevention, Columbia University, and Westat. Written informed consent was obtained from eligible participants in Shona or Ndebele.

Results

Characteristics of adult PLHIV eligible for IPT

The sociodemographic and clinical characteristics of the study population are summarized in Tables 1 and 2. Of 3418 adult PLHIV in HIV care who were eligible for IPT, 40.0% were male and 63.3% lived in rural areas. The median age was 38 years old (interquartile range (IQR): 30–46). The majority completed either up to primary education (37.9%) or up to secondary education (57.6%). Only half (51.4%) were screened for TB symptoms at their

last HIV care visit. One in ten (10.2%) were hazardous drinkers. The median CD4 count was 387 cells/μl (IQR: 251–558), and 39.5% were not virally suppressed.

Factors associated with self-reported IPT non-uptake: Bivariate analysis

Among PLHIV who were eligible for IPT, the IPT uptake was 12.7% (95% CI: 11.4–14.1). Among 3418 PLHIV who were eligible for IPT, 3331 participants responded to the IPT question and were included in further analyses. Isoniazid preventive therapy non-uptake was associated with being virally unsuppressed (cOR: 3.51, 95% CI: 2.60–4.73), being 15–19 years old (cOR: 2.55, 95% CI: 1.41–4.61), no TB symptom screening at the last HIV care visit (cOR: 2.27, 95% CI: 1.71–3.01), living in rural areas (cOR: 2.09, 95% CI: 1.63–2.67), hazardous alcohol use (cOR: 1.65, 95% CI: 1.05–2.60).There was a dose–response relationship between education level and receiving IPT. The odds of not receiving IPT increase as the education level decreases (Supplementary Material Table 1).

Logistic regression analysis

After adjusting for covariates in model 1, IPT non-uptake was associated with living in rural areas (aOR: 2.39, 95% CI: 1.82–3.12), no TB screening at the last HIV care visit (aOR: 2.07, 95% CI: 1.54–2.78), and not being virally suppressed (aOR: 1.69, 95% CI: 1.14–2.52) (Table 3).

In model 2, which is stratified by urban/rural residence, those who were not screened for TB symptoms at the last HIV care visit were approximately twice less likely to have ever received IPT in both urban and rural areas (Table 3). Among those only residing in rural areas, 15–19 year olds were associated with IPT non-uptake compared to 60+ year olds (aOR for 15–19 year olds: 6.23, 95% CI: 1.33–29.17). On the other hand, among those residing in urban areas, hazardous drinking was associated with IPT non-uptake (aOR: 10.74, 95% CI: 3.60–32.0) (Table 3).

Discussion

In this population-based study of adult PLHIV in Zimbabwe, the self-reported IPT uptake among PLHIV in HIV care was low 2 years post-national scale-up. This is much lower than uptake reported from other Zimbabwe studies with smaller cohorts. Isoniazid preventive therapy uptake among PLHIV was 54% at sixteen health facilities in Midlands Province in 2013 and 52% at four clinics in Bulawayo.[12,13] However, Zimbabwe has achieved rapid progress in expanding IPT coverage in the more recent years. The number of ART clinics offering IPT and new IPT initiations increased exponentially across the country, with decentralization of IPT services to clinics in rural areas. By 2018, 82% of ART clinics offer IPT.[8] Zimbabwe needs to continue efforts in scaling IPT by addressing the current bottlenecks toward ending TB by 2035. To help design future interventions to improve the IPT uptake in the community, we explored factors associated with IPT non-uptake. Rural/urban residence was the strongest factor associated with IPT uptake, after adjustment for other covariates: IPT uptake was significantly lower in rural areas than in urban areas. Given that by end of 2016, only 611 (35%) of all public health facilities were offering IPT,[14] this is likely a result of IPT being available in district hospitals which are the largest hospital in

these settings and tend to offer ART services to larger PLHIV cohorts. It is therefore likely that there are bottlenecks in information dissemination to slower level uptake of services in rural areas in addition to variation in IPT stock availability.

Suboptimal TB symptom screening may be another factor related to the IPT non-uptake. Associations between TB screening at the last HIV care visit and IPT uptake were ubiquitous regardless of residence. Although the survey question was specific to the TB screening at the last clinic visit, this variable may serve as a proxy for on-site TB symptom screening practices in general. In fact, the low proportion of PLHIV screened for TB at their last HIV care visit (48.6%) suggests uneven TB symptom screening practices, although the national guideline recommends all PLHIV are to be screened for TB symptoms at every HIV care visit. Poor IPT coverage related to a failure to screen for TB symptoms has been reported in other African contexts. In a cross-sectional study among PLHIV in Ethiopia, only 68% of symptomatic PLHIV were investigated for TB, which may be attributed by provider barriers such as the absence of IPT guidelines on site, inadequate TB/HIV case management training, and clinicians' concerns regarding IPT safety (i.e. perceived side effects and increased risk of drug-resistant TB).[15] A qualitative study in Nairobi, Kenya, also emphasized the importance of provider training on IPT, clarity of IPT guidelines, and high-level commitment and support for the IPT program.[16]

In this study, we also found different factors have differentiated associations with IPT non-uptake by rural and urban areas. In rural areas, IPT non-uptake was associated with 15–19 year olds. Suggested by consistent reports on poor retention in HIV care among young adult PLHIV,[17] young adults particularly in rural areas might have poor retention in care and be less likely to initiate IPT. On the other hand, in urban areas, IPT non-uptake was significantly associated with hazardous alcohol use. This association was expected because those with a liver disease are not to be given IPT based on adverse effects of hepatotoxicity from IPT use.[18,19] However, it is unclear why the same association was not found in rural areas. This may highlight suboptimal screening practices on IPT eligibility in rural areas. Future interventions should strengthen knowledge and capacity building on IPT scale-up among health workers in rural areas.

Once IPT initiated, reported completion rates are often high, ranging from 69% to 96.8% in high HIV-prevalence and resource-constrained settings.[20–24] In a pilot study in Zimbabwe, 89% of PLHIV who initiated IPT completed a 6-month course.[25] Ensuring that all eligible PLHIV receive TPT reduce TB-related morbidity and mortality among PLHIV and help reduce the global TB burden. Maximizing IPT initiation both on provider- and patient-end is critical to enhance public health benefits of IPT.

One of the strengths of this study is use of the nationally representative data from the population-based survey. To our knowledge, this is the first study attempting to assess the prevalence of IPT use across Zimbabwe outside the realm of the pilot program. On the other hand, there are limitations pertaining to self-reported surveys, such as recall bias and social desirability bias. Also, given that the survey was conducted only 2 years after the national scale-up, it is unclear whether participants had a good grasp of understanding on TB preventive treatment, and distinguished it from TB treatment, without any prefatory briefings

on TB preventive treatment during the survey. For this reason, the low IPT uptake in this study may need cautious interpretation. However, our figure is similar to the WHO-reported estimate of TPT uptake among PLHIV in 2017 (11%).[14]

Conclusion

To our knowledge, this is the first population-based study assessing IPT uptake and exploring factors associated with IPT non-uptake in SSA. The self-reported IPT uptake among PLHIV in Zimbabwe was low 2 years post-national scale-up with challenges observed with IPT uptake in rural areas; among young adult PLHIV and prescribing TB/HIV care practices including TB symptom screening. Six decades since the discovery of TB treatment, the world has learned that treating people with TB alone is not enough to end the global TB epidemic. At the first-ever United Nations High-Level Meeting on TB in September 2018, 120 countries signed a declaration to accelerate the global TB response to eliminate TB by 2030, which includes substantial scale-up of TPT. Future interventions aimed at reducing patient, provider, and health system barriers to ensure delivery of TPT to all eligible PLHIV in the country would help Zimbabwe achieve its targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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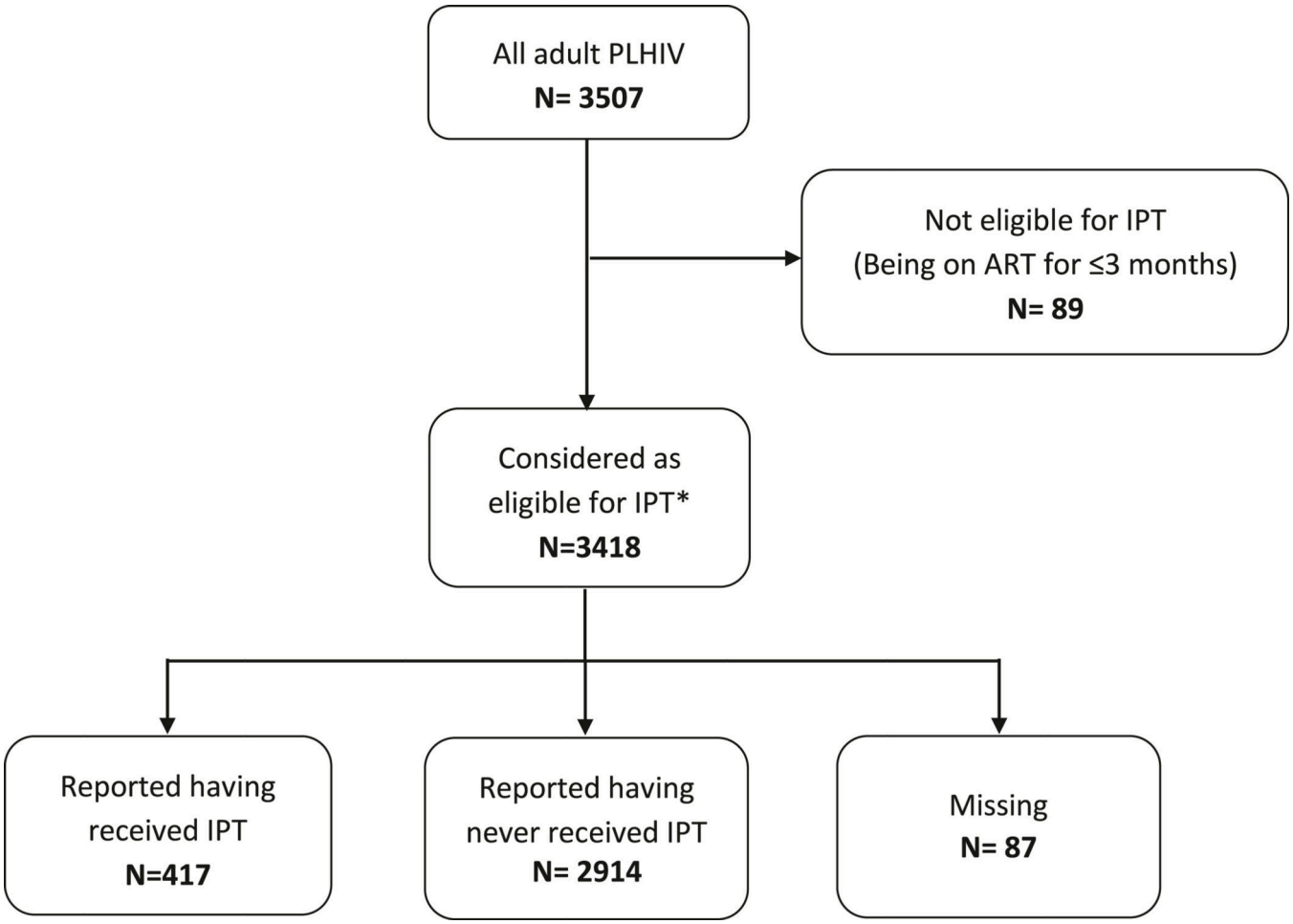

Figure 1.

Flow diagram depicting inclusion and exclusion of PLHIV in analyses. *Those who were on ART for >3 months or were not on ART were considered eligible for IPT per the then-IPT guidance in Zimbabwe. Note: PLHIV: people living with HIV; ART: antiretroviral therapy; IPT: isoniazid preventive therapy.

Table 1.

Demographic characteristics of adult PLHIV eligible for IPT (*N* = 3418), ZIMPHIA, 2015–2016.

		Weighted					Weighted		
Variable		***N***	**%**	**95% CI**	**Variable**		***N***	**%**	**95% CI**
Sex	Male	1179	40.0	(38.4–41.7)	Religion	Traditional	73	2.0	(1.4–2.5)
	Female	2239	60.0	(58.3–61.6)		Catholic/Protestant	803	23.6	(21.7–25.6)
Age in years	15–19	142	4.9	(4.1–5.8)		Pentecostal	636	19.2	(17.3–21.0)
	20–29	508	16.6	(15.1–18.1)		Apostolic	1402	39.4	(37.1–41.8)
	30–39	1060	32.5	(30.9–34.2)		Muslim/others	46	1.3	(0.8–1.8)
	40–49	939	27.2	(25.6–28.8)		None	456	14.5	(12.9–16.0)
	50–59	502	12.4	(11.2–13.5)		Missing	2		
	60+	267	6.3	(5.4–7.2)	Current pregnancy[a]	Yes	6521	3.2	(2.3–4.0)
Residence	Rural	2357	63.3	(60.8–65.8)		No	38	96.8	(96.0–97.7)
	Urban	1061	36.7	(34.2–39.2)		Missing	36		
Education secondary	No education	136	3.3	(2.6–4.0)					
	Primary	1312	34.6	(32.6–36.6)					
	Secondary	1843	57.6	(55.5–59.7)					
	More than secondary	125	4.4	(3.4–5.5)					
	Missing	2							

Note: PLHIV: people living with HIV; IPT: isoniazid preventive therapy; ZIMPHIA: Zimbabwe Population-based HIV Impact Assessmen

[a]Pregnant status was female only.

Table 2.

Clinical and behavioral characteristics of adult PLHIV eligible for IPT (*N* = 3418), ZIMPHIA, 2015–2016.

		Weighted					Weighted		
Variable		***N***	**%**	**95% CI**	**Variable**		***N***	**%**	**95% CI**
ART	Not on ART	1156	36.2	(34.2–38.2)	VL suppression	No	1260	39.5	(37.4–41.7)
	On ART for >3 months	2229	63.0	(60.9–65.0)		Yes	2153	60.5	(58.3–62.6)
	On ART for unknown duration	32	0.8	(0.5–1.2)		Missing	5		
Taking Septrin	Yes	1888	76.3	(74.2–78.3)	Hazardous alcohol	Yes	302	10.2	(8.8–11.5)
	No	610	23.7	(21.7–25.8)	use	No	3075	89.8	(88.5–91.2)
	Missing	920				Missing	41		
CD4 counts (cells/μl)	CD4 <200	526	16.6	(15.1–18.1)	Screened for TB	Yes	1155	48.6	(46.3–50.9)
	CD4 200–350	884	26.5	(24.9–28.1)	symptoms at their	No	1277	51.4	(49.1–53.7)
	CD4 350–500	877	24.8	(23.2–26.4)	last HIV care visit	Missing	986		
	CD4 >500	1128	32.1	(30.5–33.8)					
	Missing	3							

Note: PLHIV: people living with HIV; ART: antiretroviral therapy; IPT: isoniazid preventive therapy; ZIMPHIA: Zimbabwe Population-based HIV Impact Assessment; VL: viral load.

Table 3.

Factors associated with IPT non-uptake among eligible adult PLHIV (N = 3418), ZIMPHIA 2015–2016. (Variables with statistically significant association with the outcome are shown. Please see Supplementary Material Table 1 for all other variables included in the analysis).

				Model 1[a]	Model 2[b]	
Variable	**Never received IPT**	**Weighted % (95% CI)**	**OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI) rural**	**Adjusted OR (95% CI) urban**
Total	2914	100				
IPT uptake						
Have received IPT	417	12.7 (11.4–14.1)	—			
Never received	2914	87.3 (85.9–88.6)	—			
IPT	87					
Missing						
Characteristics						
Sex						
Male	987	86.3 (83.9–88.8)	(ref)	(ref)	(ref)	(ref)
Female	1927	87.9 (86.3–89.5)	1.15 (0.89–1.49)	1.32 (0.98–1.77)	1.26 (0.91–1.74)	1.45 (0.87–2.44)
Age in years						
15–19	132	93.8 (89.0–98.5)	2.28 (0.89–5.81)	2.23 (0.77–6.43)	6.23 (1.33–29.17)	0.96 (0.18–5.05)
20–29	471	94.4 (92.1–96.7)	2.55 (1.41–4.61)	1.53 (0.80–2.92)	1.56 (0.74–3.28)	1.24 (0.38–4.08)
30–39	916	88.1 (85.9–90.2)	1.12 (0.71–1.76)	0.99 (0.58–1.69)	1.16 (0.66–2.06)	0.68 (0.22–2.11)
40–49	765	82.1 (79.1–85.0)	0.69 (0.43–1.11)	0.72 (0.42–1.23)	1.15 (0.66–2.03)	0.36 (0.11–1.12)
50–59	401	84.5 (81.0–88.1)	0.83 (0.49–1.39)	0.89 (0.50–1.58)	1.29 (0.70–2.40)	0.48 (0.14–1.63)
60+	229	86.9 (82.2–91.5)	(ref)	(ref)	(ref)	(ref)
Rural/urban residence						
Rural	2072	90.4 (88.9–92.0)	2.09 (1.63–2.67)	2.39 (1.82–3.12)		
Urban	842	81.9 (79.4–84.4)	(ref)	(ref)		
TB symptom screening at the last HIV care visit						
Screened	875	77.2 (74.1–80.3)	(ref)	(ref)	(ref)	(ref)
Not screened	1100	88.5 (86.4–90.6)	2.27 (1.71–3.01)	2.07 (1.54–2.78)	2.25 (1.58–3.20)	1.82 (1.09–3.03)
Missing	939					
VL suppression*						
No	1176	94.3 (92.8–95.8)	3.51 (2.60–4.73)	1.69 (1.14–2.52)	1.63 (0.96–2.79)	1.79 (0.98–3.26)
Yes	1733	82.6 (80.6–84.5)	(ref)	(ref)	(ref)	(ref)
Missing	5					
Hazardous alcohol use						

				Model 1[a]	Model 2[b]	
Variable	**Never received IPT**	**Weighted % (95% CI)**	**OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI) rural**	**Adjusted OR (95% CI) urban**
Yes	266	91.5 (88.1–94.9)	1.65 (1.05–2.60)	5.14 (0.99–26.67)	1.79 (0.39–8.33)	10.74 (3.60–32.0)
No	2613	86.7 (85.3–88.2)	(ref)	(ref)	(ref)	(ref)
Missing	35					

Note: PLHIV: people living with HIV; IPT: isoniazid preventive therapy; VL: viral load. *VL suppression was defined as <1000 copies/ml.

[a]Model 1 included sex, age, urban/rural residence, TB symptoms screening at the last HIV care visit, viral suppression, and hazardous alcohol use.

[b]Model 2 was stratified by urban/rural residence while keeping the same covariates from model 1.