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Substance use disorders and adherence to antituberculosis medications in Southwest Ethiopia: a prospective cohort study

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ABSTRACT

Objectives In Ethiopia, little is known about the association between substance use disorders and adherence to antituberculosis (anti-TB) medications. Therefore, the objective of this study was to assess the effect of substance use disorders on adherence to anti-TB medications in Southwest Ethiopia.

Design Prospective cohort study.

Settings Patients were recruited from 22 health centres and four hospitals in Southwest Ethiopia.

Participants This study was conducted among 268 patients with TB, aged 18–80 in Southwest Ethiopia between October 2017 and October 2018. At baseline, patients who were exposed substance use disorders (134 patients) and unexposed to substance use disorders (134 patients) were recruited. Patients were followed for 6 months, and data were collected on three occasions.

Main outcome measure Adherence to anti-TB medications.

Results Patients with substance use disorders had consistently higher prevalence of non-adherence than those without, 16.4% versus 3.0% at baseline, 41.7% versus 14.4% at 2-month follow-up and 45.7% versus 10.8% at 6-month follow-up assessments. Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder (Adjusted odds ratio (aOR)=3.8, 95% CI 1.8 to 8.0). Patients who had alcohol use disorder (AUD) were also 3.2 times likely to have poor adherence compared with their counterparts (aOR=3.2, 95% CI 1.6 to 6.6). In addition, being educated (aOR=4.4, 95% CI 1.7 to 11.3), and being merchant (aOR=6.1, 95% CI 1.2 to 30.8) were associated with non-adherence to anti-TB medications.

Conclusion Khat and AUDs predict greater likelihood of non-adherence to anti-TB medication. This implies the need to integrate the management for substance use disorders into the existing TB treatment services.

Strengths and limitations of this study

- The strengths of this study are the prospective cohort design, longitudinal data collection, including patients from urban and rural health institutions, intensive training for data collectors, multi-centre data collection and use of standardised instruments.
- Due to social desirability, patients might minimise reporting of the amount and frequency of the substances they were using.
- Measuring adherence based on pills count may not reflect the real adherence situation, since patients may not bring all leftover medications during the follow-up.
- Follow-up and data collections have been carried out by health professionals working in the respective tuberculosis (TB) clinic. As a result, their assessment of adherence might be biased.
- Hospitalised patients, patients on retreatment and patients with multidrug-resistant-TB were not included in this study, and this may limit the generalisability of the result for these patients.

INTRODUCTION

Tuberculosis (TB) is a preventable and treatable disease but it remains one of the major diseases leading to death worldwide.[1 2] WHO estimates that 1.6 million persons died of TB in 2017[1]; almost 20% of them were HIV positive.[1] The number of patients with TB is estimated at about 10 million with an annual incidence of 6.4%. TB remains the main reason for premature mortality among HIV positive patients.[1]

TB is most prevalent in middle-income and low-income countries. This exerts enormous pressure on societies as TB mainly affects mostly adults in the economically productive age groups.[1 3 4] In fact, 87% of cases worldwide are from Asia, Africa and the Russian Federation.[1 5] TB-related morbidity and mortality also remain high in low-income and middle-income countries. Because these countries have poor nutrition, unfavourable housing conditions and unstable healthcare.[1] Notably, 117 705 new cases were registered in 2017 in Ethiopia, corresponding to an annual incidence of 164 per 100 000 habitants.[1] Ethiopia remains

one of the top 22 countries having the highest TB mortality with an estimated mortality rate of 24 per 100 000 inhabitants in 2017.[1]

Long-term adherence to standardised medication is the key to successful treatment of TB as non-adherence may lead to the emergence of multidrug-resistant TB (MDR-TB), an increasing global health threat.[1 6 7] Non-adherence to anti-TB medication could also lead to a lower treatment success rate,[8 9] default and death.[10 11] Thus, Ethiopia has developed a national TB treatment guideline to ensure adherence through regular appointments and supervised drug administration, and to reduce poor treatment outcomes.[12]

In Ethiopia, the prevalence of non-adherence among patients with TB has been estimated to range from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia.[13] To counteract this, the Ethiopian has implemented direct observed treatment (DOT) services in almost all health institutions,[12] but its impact on medication adherence is unclear and the reasons for non-adherence are still poorly understood.

Among the reasons for non-adherence, substance use disorders have been found to play a dominant role.[8 14–16] Substances such as alcohol, tobacco, khat and illicit drugs are commonly used among patients with TB.[17–19] Patients with TB are also at risk of increased morbidity, and premature mortality due to substance use disorders.[20] Because, substance use disorders such as alcohol and tobacco are associated with MDR-TB.[21 22]

Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids, cathinone and cathine cause the stimulating effect, and lead to craving and dependency.[23–26] There is evidence that khat use increases susceptibility to TB,[27–31] and maybe associated with poor TB treatment outcomes,[14 32] prolonged duration of treatment[33] and high load of bacteria in patients with TB.[34] In Yemen, khat use has been shown to be associated with non-adherence to anti-TB medications,[35] probably because khat disrupts patients' sleep patterns and causes them to miss their appointments.[35 36] Ethiopia, like Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an important but unrecognised threat to anti-TB medication adherence. Filling the information gaps about the effect of substance use disorders will help to improve TB treatment outcomes and inform decision-makers about the need for an integration of substance use disorder treatment in TB control programmes in the future. Therefore, the objective of this study is to assess the effect of substance use disorders (including khat and alcohol) on adherence to anti-TB medications in Southwest Ethiopia. Specifically, we examined the association of the most frequently used substances, namely khat and/or alcohol, on adherence to guideline compatible TB treatment.

METHODS

Study area, period and patients

We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma city special zone is the capital city of Jimma zone and located in the Southwestern part of Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital and a zonal hospital, as well as four functional health centres those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than 3 million inhabitants. During the period of this study, Jimma Zone had 112 health centres and three hospitals. Out of these government's public health facilities, 91 health centres and all hospitals were providing services to patients with TB. In this study, data were collected from a total of 26 health institutions (22 health centres and four hospitals). From Jimma city, we randomly selected two health centres and one hospital. We also randomly selected 20 health centres and three hospitals from the Jimma Zone. Patients were included if they had initiated anti-TB treatment within a month of start of the study at the selected health centres and hospitals between October 2017 and October 2018. Patients were recruited over the first 6 months. Follow-ups were done at the end of 2 and 6 months of treatment.

Study design

This study is a multicentre prospective cohort study. We did not pair exposed and non-exposed patients by a certain character. Patients recruited to the cohort were interviewed on three occasions, namely, baseline (starting treatment), first follow-up (after 2 months) and second follow-up (at the end of 6 months).

Sample size assumption and sampling procedure

In Ethiopia and other African countries, we could not find a study done regarding substance use disorders (alcohol, tobacco, cannabis, amphetamine and others) and adherence to anti-TB. So, we were forced to calculate the sample based on the proportion of adherence to anti-TB among khat users patients with TB. The prevalence of non-adherence among patients with TB who also used khat from previous studies was 62.4%.[35] The prevalence of non-adherence among non-khat user patients with TB was 43.6%.[35] We have included 111 exposed (with substance use) and 111 unexposed (without substance use) individuals to detect a difference of non-adherence to anti-TB medication at an alpha level of 0.05 and with a power of 80% using the corrected Fleiss sample size calculation (EPInfo).[37] The total sample size was calculated considering a 20% of drop out rate and the final sample size was 134 in each group which totals 268 patients with TB. New patients with TB who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than 1 month, patients on retreatment, and MDR-TB cases were not included in the study.

Instruments

Exposure variables

In this study, the exposure variable is substance use disorder which includes khat and/or alcohol use disorder (AUD).

Substance use disorder

In this study substance use disorder was defined as having khat and/or AUD. Data on tobacco, shisha and cannabis use were collected for explorative data analysis.

Alcohol use disorders

AUD identification test (AUDIT) was used to collect data on AUDs.[38] The AUDIT was evaluated over a period of two decades, and provides an accurate measure of risk of AUDs across gender, age and cultures. With a cut-off score of 8 or more, the sensitivity, and specificity of AUDIT for AUDs was 0.90 and 0.80, respectively.[39] AUDIT was used in Ethiopian context and questions number two and three regarding standard drinks were adapted to a more locally appropriate question.[40]

Nicotine dependence

The Fagerstrom test for nicotine dependence (FTND) was used to assess tobacco dependence. A total score of FTND ≥5 was considered as tobacco dependence.[41] At a cut-off score ≥5, the FTND has good sensitivity (0.75), and specificity (0.80). The FTND has six items, with a total score ranging from 0 to 10 to measure nicotine dependence. A total FTND score of 5 indicates moderate nicotine dependence, a score of 6–7 indicates high nicotine dependence and a score of 8–10 indicates very high nicotine dependence. Patients were also asked about their reasons for smoking tobacco.[41]

Cannabis and shisha use

Use of both substances and their frequency were assessed.

Khat use

Khat use was assessed by self-reported questionnaire. Since there is no standardised questionnaire for khat use, patterns and reasons of khat use were assessed by using a structured questionnaire which was developed in the context of a literature review. Any consumption of khat in the last 1 month was considered as current khat use.

In this study, frequent khat use (using khat daily and 2–3 times per week) and using more than one bundle of khat per day was considered as khat use disorder. The term 'khat use disorder' is also supported by previous study.[42]

Outcome variable

Adherence

Adherence status of patients with TB was assessed by DOT (based on missing appointments) and pills counts. In this study, adherence is defined as taking medication regularly and attending follow-up according to appointments and national guideline for TB in Ethiopia.[12] In this study, non-adherence is defined as missing at least one follow-up appointment during DOT. Non-adherence during intensive phase is defined as missing at least one dose of the prescribed anti-TB medication and noted separately. Adherence was assessed at baseline (beginning of intensive phase), at second month (end of intensive phase) and at end of sixth month (end of continuation phase).

Explanatory variables

Socio-demographic characteristic

Age, sex, marital status, level of education, religion, ethnicity, income, household size, occupation, place of residence and living conditions were assessed using a structured questionnaire. Income was categorised considering that the minimum monthly wage for employees of governmental organisation in Ethiopia of 1214 Ethiopian birr (€36.67).[43] Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cut-off 14 568 Ethiopian birr (€439.98).

Disease related factors

Types of TB diagnosis (smear positive, smear negative, extrapulmonary TB and MDR-TB) were collected from patients' charts.

Comorbidities

All confirmed diagnoses of HIV, previous mental illness, hypertension and diabetes mellitus were collected from patients' charts.

Social support

Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the strength of social support. The Oslo-3 total score 3–8 indicate poor social support, 9–11 indicate moderate social support and 12–14 indicate strong social support.[44] The scale had been validated in Ethiopia among patients with TB.[45] Social support was assessed at baseline, second month (at first follow-up) and sixth month (at the completion of anti-TB treatment or second follow-up).

Food insecurity

It was assessed using the Household Food Insecurity Access Scale (HFIAS) to determine whether the respondent has experienced any of the indicators of food insecurity in the previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity if the respondent endorsed any of the items 1, 2, 3 and/or 4 but not the items 5–9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7–9, and 'severe food insecurity' if the respondent has endorsed items 7, 8 and/or 9.[46] This tool had been validated in Ethiopia among people living with HIV.[47 48] Food insecurity assessed at baseline, second month (at first follow-up) and sixth month (at the completion of anti-TB treatment or second follow-up).

Data collection procedures

Before starting data collection, the questionnaires were pretested on a sample (5% of the total sample) of patients

with TB who were on treatment at Agaro health centre. Those patients who participated in the pretest were not included in the main cohort study. Data were collected by trained health professionals working in the respective TB clinics. Data collectors were not blind to exposure status of the patients. Also, district TB focal persons and other health professionals specifically trained for this purpose participated in the supervision of data collection.

Data analysis

Data were entered to Epi Data (V.3.1) and analysed using R studio (V.1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalised linear model was used to examine the longitudinal effect of khat and AUDs on medication adherence (binary outcome). We used an intercept only model to investigate the trajectory of adherence over time (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat and AUDs on adherence without adjusting for covariates, model 2 investigated the longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates. Model fit was examined with the Bayesian information criterion (BIC).

The covariate selection was based on a directed acyclic graph (DAG). DAGs are analytical method for visualising hypotheses about causal relationships between exposure (substance use disorders) and outcome (adherence).[49 50] This approach has been shown to yield valid adjustment sets of variables and to avoid bias.[51]

Patient and public involvement

Patients were not involved in development of the research questions, study design, interpretation of results or writing of the manuscript.

RESULTS

Sociodemographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% men) with TB were recruited. There was no loss to follow-up.

Of all patients, 10.8% (n=29), and 39.2% (n=105) had alcohol and khat use disorders, respectively. No participant had tobacco, shisha or cannabis use disorders. Age range was 18–80 years with 35% under 25 years (refer to table 1). There were 22 missing data of annual income which we excluded from the analysis.

Clinical characteristics and non-adherence

Out of all patients, 40.3% (n=108), 32.5% (n=87) and 27.2% (n=73) were diagnosed with smear positive, smear negative and extra pulmonary TB, respectively. At baseline, 3.7% (n=10) patients were diagnosed with HIV, and 7.1% (n=19) with other comorbidities. At baseline 9.7% (n=26) were non-adherent to TB medication. At 2 and 6 months of assessment, 26.1% (n=70) and 27.6% (n=74) missed at least one dose of their medications, respectively.

The prevalence of non-adherence among patients with substance use disorder was 16.4% (n=22), 41.7% (n=48) and 45.7% (n=59) at baseline, first and second follow-up, respectively (see table 2).

Effect of substance use disorder on the adherence to anti-TB medications

The intercept only model (model 0) showed a significant decrease in the percentage of adherence over time (BIC=642.5). Adding alcohol and khat use disorders (model 1) improved model fit (BIC=627.6): patients with khat use disorder had a significantly higher probability of non-adherence over time (OR=4.2, 95% CI 2.1 to 8.6). The odds of non-adherence among patients with AUD was 3.3 times that of patients free of AUDs (OR=3.3, 95% CI 1.6 to 6.6). Adding covariates did not substantially change this association (OR=2.8, 95% CI 2.0 to 3.8) and further improved model fit (BIC=642.2). In the final model, khat use disorder (aOR=3.8, 95% CI 1.8 to 8.0), or AUD (aOR=3.2, 95% CI 1.6 to 6.6), being educated (aOR=4.4, 95% CI 1.7 to 11.3), and being merchant (aOR=6.1, 95% CI 1.2 to 30.8) were associated with decreasing adherence (see table 3). Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder. Also, participants whose occupation was merchant were 6.1 times more likely to be non-adherent to anti-TB medications compared with daily labourers.

DISCUSSION

This study conducted in patients undergoing standardised treatment for TB in Southwest Ethiopia revealed three important findings: (1) adherence to medication decreased over the course of treatment; (2) substance use disorders, particularly khat and alcohol contributed to this non-adherence and (3) this association was independent of other factors such as education, social support and occupation.

It is alarming that adherence to TB medication decreased over the course of treatment, as already shown by studies done in South Ethiopia,[52] Northwest Ethiopia[9] and Addis Ababa,[53] Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications,[13 52] lack of knowledge about TB,[9 52] psychological distress,[53] being busy with work[9] and alcohol intake.[51] To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programmes throughout the whole treatment and all over the country starting from initiation to completion of treatment.[12]

In this study, the prevalence of non-adherence to anti-TB medication in the first month of treatment was 9.7% which is in line with a systematic review that found 10.0% of non-adherence in the Amhara region.[13 54] The proportion of non-adherence to anti-TB medications

Table 1 Sociodemographic characteristics and substance use disorder among a cohort of patients on antituberculosis treatment in Southwest Ethiopia, 2017/2018 (n=268)

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	Second follow-up N (%)
Gender	Female	39.9	40 (37.4)	35 (32.7)	45 (42.1)
	Male	60.1	94 (58.4)	80 (49.7)	84 (52.2)
Age	18–24	34.7	42 (45.2)	31 (33.3)	38 (40.9)
	25–34	32.5	35 (40.2)	34 (39.1)	35 (40.2)
	35–44	13.4	23 (63.9)	20 (55.6)	22 (61.1)
	45–54	10.1	17 (63.0)	16 (59.3)	18 (66.7)
	55–64	9.3	17 (68.0)	14 (56.0)	16 (64.0)
Occupation	Merchant	10.8	23 (79.3)	19 (65.5)	20 (69.0)
	Farmer	34.3	57 (62.0)	51 (55.4)	57 (62.0)
	Government employee	39.2	37 (35.2)	29 (27.6)	33 (31.4)
	Daily labourer	15.7	17 (40.5)	16 (38.1)	19 (45.2)
Education	No formal education	63.1	68 (40.2)	59 (34.9)	62 (36.7)
	Literate	36.9	66 (66.7)	56 (56.6)	67 (67.7)
Annual income in birr	<14 568	76.9	108 (52.4)	92 (44.7)	104 (50.5)
	≥14 568	14.9	16 (40.0)	17 (42.5)	18 (45.0)
Marital	Single	36.2	85 (54.1)	76 (48.4)	87 (55.4)
	Married	58.6	39 (40.2)	32 (33.0)	34 (35.1)
	Divorced/widowed	5.2	10 (71.4)	7 (50.0)	8 (57.1)
Religion	Orthodox	30.6	43 (52.4)	27 (32.9)	43 (52.4)
	Muslim	61.6	89 (53.9)	86 (52.1)	82 (49.7)
	Protestant/others	7.8	2 (9.5)	2 (9.5)	4 (19.0)
Ethnicity	Amhara	22.0	27 (45.8)	17 (28.8)	29 (49.2)
	Oromo	61.6	83 (50.3)	82 (49.7)	79 (47.9)
	Tigre/Gurage	16.4	24 (54.5)	16 (36.4)	21 (47.7)
Family size	Less than five	67.5	89 (49.2)	76 (42.0)	89 (49.2)
	Five or greater	32.5	45 (51.7)	39 (44.8)	40 (46.0)
Residence	Rural	47.4	72 (56.7)	59 (46.5)	68 (53.5)
	Urban	52.6	62 (44.0)	56 (39.7)	61 (43.3)
Type of tuberculosis	Smear positive	40.3	54 (50.0)	43 (39.8)	46 (42.6)
	Smear negative	32.5	43 (49.4)	39 (44.8)	46 (52.9)
	Extra pulmonary	27.2	37 (50.7)	33 (45.2)	37 (50.7)

during the first (26.1%) and second (27.6%) follow-up was slightly higher than findings from South Ethiopia (24.5%),[52] Northwest Ethiopia (21.2%)[9] and Addis Ababa (19.5%).[53] This might be explained by the high proportion of persons with a substance use disorder in our study, in which we deliberately oversampled persons with substance use disorder (SUD) to maximise power. The discrepancy may be also due to patients in our study were using substances whereas in the systematic review there was no data regarding substance use.

In this study, the prevalence of non-adherence among patients with substance use disorder at baseline, first and second follow-up was 16.4%, 41.7% and 45.7%, respectively. This is in line with a study from the USA (39%).[9 55 56]

Moreover, this study provides the evidence that substance use disorders have a significant negative effect on adherence to anti-TB medications among patients with TB, which supports earlier findings from previous studies that found AUD, tobacco dependence and illicit drug use have a negative impact on adherence in Uzbekistan, Spain and Morocco.[57–59] This is also comparable with retrospective studies conducted in Russia and New York which found that AUD and drug addiction were significantly associated with non-adherence to anti-TB medications.[8 9] Likewise, the finding of this study is in line with

Table 2 Various characteristics by adherence to antituberculosis (anti-TB) medications at the three time point assessments among patients with TB in Southwest Ethiopia 2017/2018 (n=268)

Variables		Adherence to anti-TB at baseline		Adherence to anti-TB at first follow-up		Adherence to anti-TB at second follow-up	
		Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)
Substance use disorder	No	130 (97.0)	4 (3.0)	131 (85.6)	22 (14.4)	124 (89.2)	15 (10.8)
	Yes	112 (83.6)	22 (16.4)	67 (58.3)	48 (41.7)	70 (54.3)	59 (45.7)
Gender	Male	143 (88.8)	18 (11.2)	112 (69.6)	49 (30.4)	83 (77.6)	24 (22.4)
	Female	99 (92.5)	8 (7.5)	86 (80.4)	21 (19.6)	111 (68.9)	50 (31.1)
Age	18–24	88 (94.6)	5 (5.4)	72 (77.3)	21 (22.7)	69 (74.2)	24 (25.8)
	25–34	79 (90.8)	8 (9.2)	64 (73.7)	23 (26.3)	67 (77.0)	20 (23.0)
	35–44	28 (77.8)	8 (22.2)	24 (66.7)	12 (33.3)	23 (63.9)	13 (36.1)
	45–54	24 (88.9)	3 (11.1)	21 (77.8)	6 (22.2)	19 (70.4)	8 (29.6)
	55–64	23 (92.0)	2 (8.0)	17 (68.0)	8 (32.0)	16 (64.0)	9 (36.0)
Occupation	Merchant	22 (75.9)	7 (24.1)	17 (58.6)	12 (41.4)	14 (48.3)	15 (51.7)
	Farmer	79 (85.9)	23 (14.1)	66 (71.7)	26 (28.3)	64 (69.6)	28 (30.4)
	Government employee	21 (95.5)	1 (4.5)	79 (75.2)	26 (24.8)	82 (78.1)	23 (21.9)
	Daily labourer	41 (97.6)	1 (2.4)	36 (85.0)	6 (14.3)	34 (81.0)	8 (19.0)
Education	No formal education	165 (97.6)	4 (2.4)	145 (85.8)	24 (14.2)	139 (82.2)	30 (17.8)
	Literate	77 (77.8)	22 (22.2)	53 (53.5)	46 (46.5)	55 (55.6)	44 (44.4)
	Tertiary	20 (71.4)	8 (28.6)	8 (28.6)	20 (71.4)	10 (35.7)	18 (64.3)
Annual income in birr	<14 568	185 (89.8)	21 (10.2)	154 (74.8)	52 (25.2)	149 (72.3)	57 (27.7)
	≥14 568	37 (92.5)	3 (7.5)	30 (75.0)	10 (25.0)	31 (77.5)	9 (22.5)
Food insecurity	No	129 (94.9)	7 (5.1)	105 (72.4)	40 (27.6)	118 (72.8)	44 (27.2)
	Middle/ moderate	46 (80.7)	11 (19.3)	29 (70.0)	12 (29.3)	26 (60.5)	17 (39.5)
	Severe	67 (89.3)	8 (10.7)	64 (78.0)	18 (22.0)	50 (79.4)	13 (20.6)
Marital status	Single	92 (94.8)	5 (5.2)	109 (69.4	48 (30.6)	80 (82.5)	17 (17.5)
	Married	140 (89.2)	17 (10.8)	80 (85.8)	17 (17.2)	104 (66.2)	53 (33.8)
	Divorced/ widowed	10 (71.4)	4 (28.6)	9 (64.6)	5 (37.4)	10 (71.4)	4 (28.6)
Religion	Orthodox	74 (90.2)	8 (9.8)	63 (76.8)	19 (23.2)	61 (74.4)	21 (25.6)
	Muslim	147 (89.7)	18 (10.3)	118 (71.5)	47 (28.5)	114 (69.1)	51 (39.9)
	Protestant and others	20 (95.2)	1 (4.8)	17 (81.0)	4 (19.0)	19 (90.5)	2 (9.5)
Ethnicity	Amhara	53 (89.8)	6 (10.2)	49 (83.1)	10 (16.9)	48 (81.4)	11 (18.6)
	Oromo	160 (90.9)	16 (9.1)	119 (72.1)	46 (27.9)	119 (72.1)	46 (27.9)
	Tigre/Gurage	29 (87.9)	4 (12.1)	30 (68.2)	14 (31.8)	27 (61.4)	17 (38.6)
Family size	Less than five	165 (91.2)	16 (8.8)	132 (72.9)	49 (27.1)	137 (75.7)	44 (24.3)
	Five or greater	77 (88.5)	10 (11.5)	66 (75.9)	21 (24.1)	57 (64.5)	30 (34.5)
Residence	Rural	113 (89.0)	14 (11.0)	94 (74.0)	33 (26.0)	93 (73.2)	34 (26.8)
	Urban	129 (91.5)	12 (8.5)	104 (73.0)	37 (26.2)	101 (71.6)	40 (28.4)
Type of TB	Smear positive	95 (91.9)	13 (8.1)	80 (74.1)	28 (25.9)	78 (72.2)	30 (27.8)
	Smear negative	81 (9.1)	6 (6.9)	66 (75.9)	21 (24.1)	64 (73.6)	23 (26.4)
	Extra pulmonary	66 (90.4)	7 (9.6)	52 (71.2)	21 (28.8)	52 (71.2)	21 (28.8)

Continued

Table 2 Continued

Variables		Adherence to anti-TB at baseline		Adherence to anti-TB at first follow-up		Adherence to anti-TB at second follow-up	
		Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)
HIV	Seronegative	233 (90.3)	25 (9.7)	190 (74.2)	66 (25.8)	183 (73.5)	66 (26.5)
	Seropositive	9 (90.0)	1 (10.0)	8 (66.7)	4 (33.3)	11 (57.9)	8 (42.1)
Social support	Poor	83 (89.2)	10 (10.8)	83 (74.8)	28 (25.2)	96 (68.6)	44 (34.1)
	Moderate	101 (89.4)	12 (10.6)	68 (80.0)	17 (20.0)	58 (78.4)	16 (21.6)
	Good	58 (93.5)	4 (6.5)	47 (65.3)	25 (34.7)	40 (74.1)	14 (25.9)

studies conducted in different parts of Ethiopia which found khat, alcohol and tobacco are the main factors for non-adherence to anti-TB medications.[9 56 60] In our study, patients with substance use disorder were more than two times more likely not to follow their medication plan than patients without substance use disorders. This finding is in line with the finding of a study conducted in the USA that found the risk of missing a DOT appointment was 2.6 times higher among patients with substance use disorder than in patients without drug consumption.[55]

In our study, khat use disorder turned out to be the most stringent factor that decreased adherence. This confirms earlier findings from Yemen[35] and Ethiopia.[14 60] A plausible explanation is that khat chewing disrupts night sleep[61] causing patients to oversleep which may lead to missing of the DOT appointments at the health facility.

Table 3 Predictors of non-adherence to antituberculosis (anti-TB) medications among patients with TB in Southwest Ethiopia 2017/2018 (n=268)

Variables		Model 0 (intercept only)		Model 1 (khat and alcohol including age and gender)		Full model	
		OR	95% CI	OR	95% CI	Adjusted odds ratio (aOR)	95% CI
Khat UD	No	Reference					
	Yes	–	–	4.2	2.1 to 8.6	3.8	1.8 to 8.0
AUDs	No	Reference					
	Yes	–	–	3.3	1.6 to 6.6	3.2	1.6 to 6.6
Age	18–24	Reference					
	25–34	–	–	1.2	0.4 to 3.2	–	–
	35–44	–	–	1.8	0.5 to 6.4	–	–
	45–54	–	–	0.9	0.2 to 4.0	–	–
	≥55	–	–	1.2	0.3 to 5.1	–	–
Gender	Female	Reference					
	Male	–	–	1.6	0.7 to 3.6	–	–
Education	No formal education	Reference					
	Read and write/literate	–	–	–	–	4.4	1.7 to 11.3
Social support	Good	Reference					
	Moderate	–	–	–	–	0.5	0.2 to 1.2
	Poor	–	–	–	–	0.8	0.3 to 1.9
Occupation	Daily labourer	Reference					
	Farmer	–	–	–	–	2.1	0.5 to 8.0
	Government employee	–	–	–	–	2.1	0.6 to 8.0
	Merchant	–	–	–	–	6.1	1.2 to 30.8
Time T2		2.7	2.0 to 3.6	2.7	2.0 to 3.6	2.8	2.0 to 3.8
BIC		642.5		672.6		642.2	

Another reason may be that khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is known about the effect of khat on patients with TB,[14] it may be considered as part of a normal social interaction.[35]

A higher level of education was associated with non-adherence to anti-TB medications in our study. This result confirms the findings from Yemen that found more educated patients were 19% times less likely to be adherent to their medication.[35] Also, a study from Ethiopia showed that attending primary education was associated with non-adherence to anti-TB medications.[60] Our findings are contrary to previous studies which have suggested that lower or no formal education decreases adherence to TB medication.[13 62] Our finding seems counterintuitive. However, our results are likely to be related to findings from a study indicating that persons with higher educational attainment might be reluctant to accept DOTS regimes.[63] Daily visits to the health facility have been reported as time consuming and probably stigmatising for patients with a job.[64] In this study, being merchant was associated with poor adherence to anti-TB medications. This might be due to patients miss their medications because of busy working schedule, but this needs further investigation.

Limitations

This study has some limitations. Due to social desirability, patients might minimise reporting of the amount and frequency of substance they were using. The tools used for alcohol and khat use disorder are not gold-standard diagnostic for the respective disorders. Also, measuring adherence based on pills count may not reflect the real adherence situation since some patients might not bring all leftover medications during the follow-up. Likewise, follow-up and data collections have been carried out by health professionals working in the respective TB clinics which might have biased their assessment of adherence. However, overestimating adherence may have biased our results towards a null effect and led to underestimating the effect of substance use disorders, so we are confident that our estimates are conservative. The participation of district TB focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalised patients, patients on re-treatment and patients with MDR-TB were not included in this study, so that the results cannot be generalised for these patients. However, patients with MDR-TB are under special treatment and surveillance so that including this group of patients might have biased the results. Finally, we did not assess the reasons for non-adherence. This should be part of a separate study going more into the details of the situation of persons with khat and alcohol problems.

Strengths

The specific strengths of this study are the prospective cohort design, longitudinal data collection, including patients from urban and rural health institutions, intensive training given for data collectors, multi-centre data collection and the use of standardised instruments to assess exposure, outcomes and explanatory variables.

CONCLUSIONS

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among patients with TB. Also, khat and AUDs were the main risk factors for anti-TB medication adherence. This finding implies the importance of integrating substance use disorders screening and treatment into the existing TB services to reduce the effect of substances on treatment outcomes including adherence.

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Patient consent for publication Not required.

Ethics approval Ethical clearance was obtained from the Ethical Review Board of Jimma University (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written informed consent was obtained from each participant. The anonymity of the study participants was kept at all stages of data processing and write-up of the manuscript. Patients who had alcohol and khat use disorder were advised to contact a mental health professional for further evaluation and treatment.

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