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Khat and alcohol use disorders predict poorer adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study

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Abstract

Introduction: Non-adherence to anti tuberculosis (anti-TB) medication greatly contributes to the rise in multi-drug resistance tuberculosis which is associated with high rates of mortality. Substance use is frequently seen among patients with poor adherence, however, little is known about the effect of substance use on adherence to anti-TB medications in Ethiopia. The objective of this study was to assess the effect of substance use disorders on adherence to anti-TB medications in Southwest Ethiopia.

Methods: A prospective cohort study was conducted among 268 patients with tuberculosis in Southwest Ethiopia between October 2017 and 2018. A structured questionnaire translated to local language was used to assess substance use disorders, adherence and other potential risk factors. Patients were followed for six months and data were collected on three occasions. Generalized linear mixed model was used to identify the effect of substance use disorder on adherence to anti-TB medications. The model fitting was checked using Bayesian Information Criterion (BIC) while the covariate selection was based on a directed acyclic graph (DAG).

Results: The overall prevalence of non-adherence among patients with substance use disorders was 16·4% (n=22), 41·7 % (n=48), and 45·7% (n=59) at baseline, two month, and six month respectively. The odds of non-adherence to anti-TB medications among patients with khat use disorder was nearly four times that of patients who did not use khat (aOR 3·8, 95%CI=1·8-8·0). Also patients who have alcohol use disorder were 3·2 times likely to have poor adherence compared to their counterparts (aOR=3·2, 95%CI=1·6-6·6). In addition, being educated (aOR =4·4, 95%CI=1·7-11·3), and being merchant (aOR=6·1, 95%CI=1·2-3·0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-TB medication. This implies that there is a need to integrate management for substance use disorders into the existing tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, food insecurity, Ethiopia, sub-Saharan Africa

Strengths and limitations

- The strength 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-center data collection, and the use of standardized instruments.
- Due to social desirability, patients might minimize reporting of the amount and frequency of substance they were using.
- Measuring adherence based on pills count may not reflect the real adherence situation, because patients might not bring all left over of medications during the follow up.
- Follow up and data collections have been carried out by health professional working in the respective TB clinic, so their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment and patients with MDR-TB were not included in this study, so that the results cannot be generalized 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). According to World Health Organization (WHO) estimates, 1.6 million persons died of TB in 2017 (1), almost 20% of them were HIV positive (1). The number of TB is estimated at about 10 million people with an annual incidence of 6·4%. TB remains the main reason for premature mortality in HIV positive patients (1).

TB is most prevalent in middle and low income countries. This exerts an enormous pressure on societies as TB mainly affects mostly adults in the economically most productive age groups (1, 3, 4). In fact, 87% of cases worldwide from Asia, Africa, and the Russian Federation (1, 5). Tuberculosis related morbidity and mortality also remain high in low and middle income countries due to poor nutrition, unfavorable housing conditions, and unstable health care (1). Notably, in Ethiopia, 117,705 new cases were registered in 2017, corresponding to an annual incidence of 164 per 100,000 habitants (1). Ethiopia remains one of the 22 countries with the highest TB mortality with an estimated mortality rate of 24 per 100, 000 inhabitants in 2017 (1).

Long-term adherence to standardized medication is the key to successful treatment of TB as non-adherence may lead to the emergence of multi drug resistant TB (MDR TB), which is 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 TB patients 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 health system 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, 9, 14-16). Use of substances such as alcohol, tobacco, khat, and illicit drugs is common in persons with TB compared to general population (17-19). Patients with TB are also at risk to increased morbidity, and premature mortality due to substance use disorders (20). Alcohol use disorder and tobacco smoking are associated with the risk of MDR-TB (21, 22).

Khat is a natural stimulant with over 40 active compounds. Among these, the psychoactive alkaloids, cathinone, and cathine cause the stimulating effect, craving and dependency (23-26). There is evidence that khat use increases susceptibility to tuberculosis (27-31), and may be associated with poor TB treatment outcomes (14, 32), a prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti- tuberculosis 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 unrecognized threat to anti-TB medication adherence. Filling the information gap about the effect of khat and alcohol 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 program in the future.

This study aimed to examine the effect of substance use disorders on adherence to anti TB medications. Specifically, we have examined the association of the most frequently used substances, namely khat and 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 centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers 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 centers and hospitals between October 2017 and October 2018.

Study design

This study is a multicenter prospective cohort study. 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 six months).

Sample size assumption and sampling procedure

The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients 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 TB patients. New TB patients who were 18years older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment and MDR-TB were not included in the study.

Instruments

Exposure variables

Substance use disorder: In this study substance use disorder was defined as the summation of having disorder related to alcohol, and khat. Data on tobacco, shisha, and cannabis use were collected for explorative data analysis.

Alcohol use disorders (AUDs):-Alcohol use disorder identification test (AUDIT) was used to collected 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 eight 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 the questions number two and three regarding standard drink 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 0-10 to measure nicotine dependence. A total FTND score of five 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: Using both substances and their frequency were assessed.

Khat use: - Khat use was assessed by self-reported questionnaire. Since there is no standardized 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 one month was considered as current khat use. Frequent khat use and using more than one bundle of khat per day was considered as khat use disorder.

Outcome variable

Adherence: Adherence status of tuberculosis patients was assessed by Direct Observed Treatment (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 tuberculosis in Ethiopia (12). In this study non-adherence is defined as missing at least one follow-up appointment during DOT. Also, 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 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: 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 categorized considering that the minimum monthly wage for employees of a governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

Factors related to health facilities: Health professionals who were working in TB clinics were asked whether there is addiction counseling services for patients with tuberculosis.

Disease related factors: Types of TB diagnosis (smear positive, smear negative, extra pulmonary 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 (43). The scale had been was validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at baseline, second month (at first follow up), and six month (at the completion of anti-TB treatment or second follow up).

Food insecurity: It was assessed by using 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 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at baseline, second month (at first follow up), and six 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 center. Those patients who participated in the pretest were not included in the main cohort study. Data was collected by trained health professionals working in the respective TB clinics. Also, district tuberculosis 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 (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of substance use disorders 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 alcohol use disorders 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 an analytical method for visualizing hypotheses about causal relationships between exposure (substance use) and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (50).

Ethical considerations

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 participants. The anonymity of the study participants was kept at all stages of data processing and write-up of the manuscript.

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

Socio-demographic characteristic

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32·4, SD 14·4, 60·1% male) with tuberculosis were recruited. 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.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	2nd 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 laborer	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	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	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)

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. This percentage increased to 26·1% (n=70) who were missing at least one dose of their medication at two month assessment and 27·6% (n=74) who were missing at least one dose at the six month assessment.

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 table2).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (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 laborer	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	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	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)
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)

Effect of substance use disorder on the adherence to anti 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=2·1-8·6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3·3 times that of patients free of AUDs (OR=3·3, 95%CI=1·6-6·6). Adding covariates did not substantially change this association (OR= 2·8,

95%CI=2·0-3·8) and further improved model fit (BIC= 642·2). In the final model khat use disorder (aOR= 3·8, 95%CI=1·8-8·0), or alcohol use disorder (aOR= 3·2, 95%CI=1·6-6·6), being educated (aOR=4·4, 95%CI=1·7-11·3), and being merchant (aOR=6·1, 95%CI= 1·2-30·8) 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 to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis 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	aOR	95%CI
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-
	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-
Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					

	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9
Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis 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 (51), Northwest (52), and Addis Ababa (53) Ethiopia. Possible reasons for non-compliance included distance from the health institution that dispenses medications (13, 51), lack of knowledge about tuberculosis (51, 52), psychological distress (53), being busy with work (52), and alcohol intake (52). To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs 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 during the first (26·1%) and second (27·6%) follow up was slightly higher than findings from South (24·5%) (51), Northwest (21·2%) (52), and Addis Ababa (19·5%) (53) Ethiopia. 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 SUD to maximize

power. The discrepancy may be due to patients in our study were using substance 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 US (39%) (52, 55, 56).

Moreover, this study provides the evidence that substance use disorders have significant negative effect on adherence to anti-TB medications among patients with tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, tobacco dependence, and illicit drug use have negative impact on adherence in Uzbekistan, Spain, and Morocco (57-59). This is also, in line with retrospective studies conducted in Russia and New York which found that alcohol use disorder 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 studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (52, 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 disordes. This finding is in line with finding of a study from US 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 (61) and Ethiopia (14, 60). A plausible explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which may lead to missing the DOT appointments at the health facility. Another reason may be that

khat is omnipresent in Ethiopia, and therefore less attention is paid to the use of khat. Since little is known about the effect of khat on patients with tuberculosis (14), khat may be considered as part of a normal social interaction (61).

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 (61). 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, 63). 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 (64). Daily visits to the health facility have been reported as too time consuming and probably stigmatizing for patients with a job (65). 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 time, but it needs further investigation.

Limitations

This study has some limitations. Due to social desirability, patients might minimize reporting of the amount and frequency of substance they were using. Also, measuring adherence based on pills count may not reflect the real adherence situation for the same reason as some patients might not bring all left over of medications during the follow up. Likewise, follow up and data collections have been carried out by health professional working in the respective TB clinic, so their assessment of adherence might be biased. 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 tuberculosis focal persons and other health professionals in the supervision of data collection might also introduce bias.

Also, hospitalized patients, patients on re-treatment and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients 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 strength 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-center data collection, and the use of standardized instruments to assess exposure, outcomes and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also in our study, khat and alcohol use disorders were the main risk factors for anti-TB medications adherence. This finding implies the importance integrating of substance use disorder screening and treatment in to the existing tuberculosis services to reduce the effect of substance on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

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Authors' contribution

MS contributed to the conceptualization, design, statistical analysis and manuscript preparation. MT, KA, WK, ET, YY, RS and EG contributed to the design, analysis and the review of the manuscript.

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Availability of data

It will be available up on official request from the interested individuals or organization.

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2,3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10

Bias	#9	Describe any efforts to address potential sources of bias	10,11
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10, 11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10,11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	10
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	

Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12, 13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	14, 15
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	

Discussion

Key results	#18	Summarise key results with reference to study objectives	19-21
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	21
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-21
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

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Substance use disorders and adherence to anti-tuberculosis 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 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 centers and four hospitals in Southwest Ethiopia.

Participants: This study was conducted among 268 patients with tuberculosis, 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 six 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% vs. 3.0% at baseline, 41.7% vs 14.4% at two month follow up, and 45.7% vs 10.8% at six month follow up assessments. The odds of non-adherence to anti-TB medications among patients with khat use disorder was nearly four times that of patients who did not use khat (aOR 3.8, 95%CI=1.8-8.0). Patients who had alcohol use disorder were also 3.2 times likely to have poor adherence compared to their counterparts (aOR=3.2, 95%CI=1.6-6.6). In addition, being educated (aOR =4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI=1.2-3.0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders 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 tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.

Strengths and limitations

- 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-center data collection, and use of standardized instruments.
- Due to social desirability, patients might minimize 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 TB clinic. As a result, their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, and this may limit the generalizability 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). World Health Organization (WHO) estimates that 1.6 million persons died of TB in 2017 (1); almost 20% of them were HIV positive (1). The number of TB patients 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 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). Tuberculosis related morbidity and mortality also remain high in low and middle-income countries. Because these countries have poor nutrition, unfavorable housing conditions, and unstable health care (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 standardized 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 TB patients 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 tuberculosis (27-31), and maybe associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis 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 unrecognized 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 programs in the future.

This study aimed to examine the effect of substance use disorders on adherence to anti TB medications. Specifically, we examined the association of the most frequently used substances, namely khat and 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 centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers 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 centers and hospitals between October 2017 and October 2018.

Study design

This study is a multicenter prospective cohort study. 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 six months).

Sample size assumption and sampling procedure

The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients 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 TB patients. New TB patients who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment, and MDR-TB cases were not included in the study.

Instruments

Exposure variables

Substance use disorder: In this study substance use disorder was defined as the summation of having disorder related to alcohol and khat. Data on tobacco, shisha, and cannabis use were collected for explorative data analysis.

Alcohol use disorders (AUDs):-Alcohol use disorder 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 eight 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 0-10 to measure nicotine dependence. A total FTND score of five 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 standardized 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 one month was considered as current khat use. 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.

Outcome variable

Adherence: Adherence status of tuberculosis patients was assessed by Direct Observed Treatment (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 tuberculosis 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 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: 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 categorized considering that the minimum monthly wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

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 (43). The scale had been validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at baseline, second month (at first follow up), and six 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 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at baseline, second month (at first follow up), and six 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 center. 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. Also, district tuberculosis 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 (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of substance use disorders 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 alcohol use disorders 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 visualizing hypotheses about causal relationships between exposure (substance use) and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (50).

Ethical considerations

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.

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

Socio-demographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% male) with tuberculosis were recruited. 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.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	2nd 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 laborer	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	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	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)

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 two and six 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).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (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 laborer	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	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	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)
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)

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=2.1-8.6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model, khat use disorder (aOR= 3.8,

95%CI=1.8-8.0), or alcohol use disorder (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) 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 to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis 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	aOR	95%CI
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-
	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-
Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					
	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9

Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis 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 (51), Northwest Ethiopia (52), and Addis Ababa (53) Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications (13, 51), lack of knowledge about tuberculosis (51, 52), psychological distress (53), being busy with work (52), and alcohol intake (52). To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs 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 during the first (26.1%) and second (27.6%) follow up was slightly higher than findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), 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 SUD to maximize 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 US (39%) (52, 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 tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, 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 alcohol use disorder 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 studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (52, 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 US 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 (61) and Ethiopia (14, 60). A plausible explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which may lead to missing of the DOT appointments at the health facility. 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 tuberculosis (14), it may be considered as part of a normal social interaction (61).

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 (61). 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, 63). 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 (64). Daily visits to the health facility have been reported as time consuming and probably stigmatizing for patients with a job (65). 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 minimize reporting of the amount and frequency of substance they were using. 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 tuberculosis focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients 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-center data collection, and the use of standardized instruments to assess exposure, outcomes, and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also, khat and alcohol use disorders 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 tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

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Authors' contribution

MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation. MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the manuscript.

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Availability of data

It will be available upon official request from interested individuals or organizations.

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2,3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10

Bias	#9	Describe any efforts to address potential sources of bias	10,11
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10, 11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10,11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	10
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	

Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12, 13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	14, 15
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	

Discussion

Key results	#18	Summarise key results with reference to study objectives	19-21
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	21
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-21
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

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Substance use disorders and adherence to anti-tuberculosis 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 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 centers and four hospitals in Southwest Ethiopia.

Participants: This study was conducted among 268 patients with tuberculosis, 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 six 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% vs. 3.0% at baseline, 41.7% vs 14.4% at two month follow up, and 45.7% vs 10.8% at six 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 (aOR 3.8, 95%CI=1.8-8.0). Patients who had alcohol use disorder were also 3.2 times likely to have poor adherence compared to their counterparts (aOR=3.2, 95%CI=1.6-6.6). In addition, being educated (aOR =4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI=1.2-3.0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders 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 tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.

Strengths and limitations

- 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-center data collection, and use of standardized instruments.
- Due to social desirability, patients might minimize 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 TB clinic. As a result, their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, and this may limit the generalizability 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). World Health Organization (WHO) estimates that 1.6 million persons died of TB in 2017 (1); almost 20% of them were HIV positive (1). The number of TB patients 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 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). Tuberculosis related morbidity and mortality also remain high in low and middle-income countries. Because these countries have poor nutrition, unfavorable housing conditions, and unstable health care (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 standardized 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 TB patients 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 tuberculosis (27-31), and maybe associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis 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 unrecognized 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 programs 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 centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers 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 centers and hospitals between October 2017 and October 2018. Patients were recruited over the first six months.

Study design

This study is a multicenter prospective cohort study. 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 six months).

Sample size assumption and sampling procedure

The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients 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 TB patients. New TB patients who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment, 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.

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

Alcohol use disorders (AUDs):-Alcohol use disorder 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 eight 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 $\geq$ 5 was considered as tobacco dependence (41). At a cut-off score $\geq$5, the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND score of five 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 standardized 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 one month was considered as current khat use. 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.

Outcome variable

Adherence: Adherence status of tuberculosis patients was assessed by Direct Observed Treatment (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 tuberculosis 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 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: 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 categorized considering that the minimum monthly wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

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 (43). The scale had been validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at baseline, second month (at first follow up), and six 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 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at baseline, second month (at first follow up), and six 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 center. 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. Also, district tuberculosis 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 (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of substance use disorders 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 alcohol use disorders 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 visualizing hypotheses about causal relationships between exposure (substance use) and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (50).

Ethical considerations

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.

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

Socio-demographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% male) with tuberculosis were recruited. 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.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	2nd 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 laborer	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	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	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)

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 two and six 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).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (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 laborer	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	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	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)
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)

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=2.1-8.6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model, khat use disorder (aOR= 3.8,

95%CI=1.8-8.0), or alcohol use disorder (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) 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 to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis 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	aOR	95%CI
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-
	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-
Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					
	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9

Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis 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 (51), Northwest Ethiopia (52), and Addis Ababa (53) Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications (13, 51), lack of knowledge about tuberculosis (51, 52), psychological distress (53), being busy with work (52), and alcohol intake (52). To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs 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 during the first (26.1%) and second (27.6%) follow up was slightly higher than findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), 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 SUD to maximize 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 US (39%) (52, 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 tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, 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 alcohol use disorder 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 studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (52, 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 US 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 (61) and Ethiopia (14, 60). A plausible explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which may lead to missing of the DOT appointments at the health facility. 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 tuberculosis (14), it may be considered as part of a normal social interaction (61).

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 (61). 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, 63). 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 (64). Daily visits to the health facility have been reported as time consuming and probably stigmatizing for patients with a job (65). 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 minimize 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 tuberculosis focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients 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-center data collection, and the use of standardized instruments to assess exposure, outcomes, and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also, khat and alcohol use disorders 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 tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

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Authors' contribution

MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation. MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the manuscript.

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Availability of data

It will be available upon official request from interested individuals or organizations.

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2,3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10

Bias	#9	Describe any efforts to address potential sources of bias	10,11
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10, 11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10,11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	10
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	

Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12, 13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	14, 15
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	

Discussion

Key results	#18	Summarise key results with reference to study objectives	19-21
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	21
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-21
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

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Substance use disorders and adherence to anti-tuberculosis 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 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 centers and four hospitals in Southwest Ethiopia.

Participants: This study was conducted among 268 patients with tuberculosis, 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 six 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% vs. 3.0% at baseline, 41.7% vs 14.4% at two month follow up, and 45.7% vs 10.8% at six 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 (aOR 3.8, 95%CI=1.8-8.0). Patients who had alcohol use disorder were also 3.2 times likely to have poor adherence compared to their counterparts (aOR=3.2, 95%CI=1.6-6.6). In addition, being educated (aOR =4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI=1.2-3.0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders 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 tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.

Strengths and limitations

- 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-center data collection, and use of standardized instruments.
- Due to social desirability, patients might minimize 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 TB clinic. As a result, their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, and this may limit the generalizability 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). World Health Organization (WHO) estimates that 1.6 million persons died of TB in 2017 (1); almost 20% of them were HIV positive (1). The number of TB patients 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 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). Tuberculosis related morbidity and mortality also remain high in low and middle-income countries. Because these countries have poor nutrition, unfavorable housing conditions, and unstable health care (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 standardized 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 TB patients 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 tuberculosis (27-31), and maybe associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis 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 unrecognized 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 programs 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 centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers 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 centers and hospitals between October 2017 and October 2018. Patients were recruited over the first six months.

Study design

This study is a multicenter 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 six months).

Sample size assumption and sampling procedure

The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients 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 TB patients. New TB patients who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment, 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.

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

Alcohol use disorders (AUDs):-Alcohol use disorder 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 eight 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 $\geq$ 5 was considered as tobacco dependence (41). At a cut-off score $\geq$5, the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND score of five 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 standardized 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 one month was considered as current khat use. 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.

Outcome variable

Adherence: Adherence status of tuberculosis patients was assessed by Direct Observed Treatment (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 tuberculosis 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 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: 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 categorized considering that the minimum monthly wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

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 (43). The scale had been validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at baseline, second month (at first follow up), and six 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 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at baseline, second month (at first follow up), and six 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 center. 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 tuberculosis 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 (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of substance use disorders 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 alcohol use disorders 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 visualizing hypotheses about causal relationships between exposure (substance use) and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (50).

Ethical considerations

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.

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

Socio-demographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% male) with tuberculosis were recruited. 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.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	2nd 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 laborer	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	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	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)

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 two and six 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).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (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 laborer	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	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	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)
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)

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=2.1-8.6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model, khat use disorder (aOR= 3.8, 95%CI=1.8-8.0), or alcohol use disorder (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) 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 to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis 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	aOR	95%CI
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-
	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-

Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					
	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9
Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis 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 (51), Northwest Ethiopia (52), and Addis Ababa (53) Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications (13, 51), lack of knowledge about tuberculosis (51, 52), psychological distress (53), being busy with work (52), and alcohol intake (52). To solve the problem related to

adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs 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 during the first (26.1%) and second (27.6%) follow up was slightly higher than findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), 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 SUD to maximize 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 US (39%) (52, 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 tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, 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 alcohol use disorder 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 studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (52, 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 US 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 (61) and Ethiopia (14, 60). A plausible explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which may lead to missing of the DOT appointments at the health facility. 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 tuberculosis (14), it may be considered as part of a normal social interaction (61).

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 (61). 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, 63). 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 (64). Daily visits to the health facility have been reported as time consuming and probably

stigmatizing for patients with a job (65). 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 minimize 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 tuberculosis focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients 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-center data collection, and the use of standardized instruments to assess exposure, outcomes, and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also, khat and alcohol use disorders 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 tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

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Authors' contribution

MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation. MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the manuscript.

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Availability of data

It will be available upon official request from interested individuals or organizations.

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2,3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10

Bias	#9	Describe any efforts to address potential sources of bias	10,11
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10, 11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10,11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	10
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	

Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12, 13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	14, 15
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	

Discussion

Key results	#18	Summarise key results with reference to study objectives	19-21
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	21
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-21
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

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Substance use disorders and adherence to anti-tuberculosis 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 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 centers and four hospitals in Southwest Ethiopia.

Participants: This study was conducted among 268 patients with tuberculosis, 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 six 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% vs. 3.0% at baseline, 41.7% vs 14.4% at two month follow up, and 45.7% vs 10.8% at six 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 (aOR 3.8, 95%CI=1.8-8.0). Patients who had alcohol use disorder were also 3.2 times likely to have poor adherence compared to their counterparts (aOR=3.2, 95%CI=1.6-6.6). In addition, being educated (aOR =4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI=1.2-3.0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders 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 tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.

Strengths and limitations

- 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-center data collection, and use of standardized instruments.
- Due to social desirability, patients might minimize 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 TB clinic. As a result, their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, and this may limit the generalizability 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). World Health Organization (WHO) estimates that 1.6 million persons died of TB in 2017 (1); almost 20% of them were HIV positive (1). The number of TB patients 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 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). Tuberculosis related morbidity and mortality also remain high in low and middle-income countries. Because these countries have poor nutrition, unfavorable housing conditions, and unstable health care (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 standardized 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 TB patients 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 tuberculosis (27-31), and maybe associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis 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 unrecognized 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 programs 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 centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers 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 centers and hospitals between October 2017 and October 2018. Patients were recruited over the first six months. Follow-ups were done at the end of two and six months of treatment.

Study design

This study is a multicenter 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 six 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 TB patients. The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients 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 TB patients. New TB patients who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment, 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.

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

Alcohol use disorders (AUDs):-Alcohol use disorder 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 eight 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 $\geq$ 5 was considered as tobacco dependence (41). At a cut-off score $\geq$5, the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND score of five 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 standardized 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 one 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 tuberculosis patients was assessed by Direct Observed Treatment (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 tuberculosis 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 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: 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 categorized considering that the minimum monthly wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (43). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

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 tuberculosis (45). Social support was assessed at baseline, second month (at first follow up), and six 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 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 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 six 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 center. 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 tuberculosis 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 (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of khat and alcohol use disorders 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 alcohol use disorders 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 visualizing 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).

Ethical considerations

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.

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

Socio-demographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% male) with tuberculosis 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.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total (%)	Substance use disorder		
			Baseline N (%)	First follow-up N (%)	2nd 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 laborer	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	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	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	Smear positive,	40·3	54(50·0)	43(39·8)	46(42·6)

tuberculosis	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)

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 two and six 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).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (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 laborer	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	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	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)
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)

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=2.1-8.6). The odds of non-adherence among patients with

alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model, khat use disorder (aOR= 3.8, 95%CI=1.8-8.0), or alcohol use disorder (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) 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 to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis 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	aOR	95%CI
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-
	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-
Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					

	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					
	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9
Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis 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 (53), and Addis Ababa (54) Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications (13, 52), lack of knowledge about tuberculosis (52, 53), psychological distress (54), being busy with work (53), and alcohol intake (51). To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs

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, 55). The proportion of non-adherence to anti-TB medications 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%) (53), and Addis Ababa (19.5%) (54). 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 SUD to maximize 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 US (39%) (53, 56, 57).

Moreover, this study provides the evidence that substance use disorders have a significant negative effect on adherence to anti-TB medications among patients with tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, tobacco dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and Morocco (58-60). This is also comparable with retrospective studies conducted in Russia and New York which found that alcohol use disorder 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 studies conducted in different parts of Ethiopia which found khat, alcohol, and

tobacco are the main factors for non-adherence to anti-TB medications (53, 57, 61). 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 US 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 (56).

In our study, khat use disorder turned out to be the most stringent factor that decreased adherence. This confirms earlier findings from Yemen (62) and Ethiopia (14, 61). A plausible explanation is that khat chewing disrupts night sleep (63) causing patients to oversleep which may lead to missing of the DOT appointments at the health facility. 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 tuberculosis (14), it may be considered as part of a normal social interaction (62).

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 (62). Also, a study from Ethiopia showed that attending primary education was associated with non-adherence to anti-TB medications (61). Our findings are contrary to previous studies which have suggested that lower or no formal education decreases adherence to TB medication (13, 64). 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 (65). Daily visits to the health facility have been reported as time consuming and probably stigmatizing for patients with a job (66). 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 minimize 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 tuberculosis focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients 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-center data collection, and the use of standardized instruments to assess exposure, outcomes, and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also, khat and alcohol use disorders 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 tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

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Authors' contribution

MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation. MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the manuscript.

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Availability of data

It will be available upon official request from interested individuals or organizations.

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Reporting checklist for cohort study.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2,3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10

Bias	#9	Describe any efforts to address potential sources of bias	10,11
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10, 11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10,11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	10
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	

Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12, 13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	14, 15
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	

Discussion

Key results	#18	Summarise key results with reference to study objectives	19-21
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	21
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-21
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23