

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043050
Article Type:	Original research
Date Submitted by the Author:	24-Jul-2020
Complete List of Authors:	Daba, Matiwas; Jimma University College of Public Health and Medical Sciences, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Markos ; Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Adorjan, Kristina; Department of Psychiatry and Psychotherapy, LMU Munich, Germany; Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany Krahl, Wolfgang ; Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany, Forensic Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Elias ; Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Psychiatry Yitayih, Yimenu; Jimma University College of Public Health and Medical Sciences, Psychiatry Strobl, Ralf; Ludwig-Maximilians-Universitat Munchen, Institute for Medical Information Processing, Biometrics and Epidemiology Grill, Eva; Ludwig Maximilians University Munich, Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany ; Center for International Health, Ludwig Maxmillians University, Munich, Germany
Keywords:	Substance misuse < PSYCHIATRY, Tuberculosis < INFECTIOUS DISEASES, INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Khat and alcohol use disorders predict poorer adherence to anti-tuberculosis medications**
6
7 **in Southwest Ethiopia: A prospective cohort study**
8

9
10 Matiws Soboka^{1*,8}, Markos Tesfaye^{2,8}, Kristina Adorjan^{3,4,8}, Wolfgang Krahl^{5,8}, Elias
11
12 Tesfaye¹, Yimenu Yitayih¹, Ralf Strobl⁶, Eva Grill^{6,8}
13
14
15
16
17
18
19
20

21 *** Corresponding author:** Matiws Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma
22
23 Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany
24

25
26 **Email:** matiws2004@yahoo.com
27

28
29 **Phone:** +251913792348
30

31 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
32

33
34 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
35

36
37 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
38

39
40 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
41

42
43 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
44

45
46 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
47

48
49 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
50

51
52 ⁸Center for International Health, Ludwig Maxmillians University, Munich, Germany
53
54
55
56
57

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.

1
2
3 **Conclusion:** Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-
4 TB medication. This implies that there is a need to integrate management for substance use
5 disorders into the existing tuberculosis treatment services.
6
7
8
9

10
11 **Keywords:** Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, food
12 insecurity, Ethiopia, sub-Saharan Africa
13
14
15

16 **Strengths and limitations**

- 17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 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

1
2
3 counteract this, the Ethiopian health system has implemented Direct Observed Treatment (DOT)
4 services in almost all health institutions (12), but its impact on medication adherence is unclear
5 and the reasons for non-adherence are still poorly understood.
6
7
8

9
10 Among the reasons for non-adherence, substance use disorders have been found to play a
11 dominant role (8, 9, 14-16). Use of substances such as alcohol, tobacco, khat, and illicit drugs is
12 common in persons with TB compared to general population (17-19). Patients with TB are also
13 at risk to increased morbidity, and premature mortality due to substance use disorders (20).
14 Alcohol use disorder and tobacco smoking are associated with the risk of MDR-TB (21, 22).
15
16
17
18
19

20
21
22
23 Khat is a natural stimulant with over 40 active compounds. Among these, the psychoactive
24 alkaloids, cathinone, and cathine cause the stimulating effect, craving and dependency (23-26).
25 There is evidence that khat use increases susceptibility to tuberculosis (27-31), and may be
26 associated with poor TB treatment outcomes (14, 32), a prolonged duration of treatment (33),
27 and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be
28 associated with non-adherence to anti-tuberculosis medications (35), probably because khat
29 disrupts patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia,
30 like Yemen, counts among the few countries where khat use is legal. Khat use disorder may be
31 an important but unrecognized threat to anti-TB medication adherence. Filling the information
32 gap about the effect of khat and alcohol use disorders will help to improve TB treatment
33 outcomes and inform decision makers about the need for an integration of substance use disorder
34 treatment in TB control program in the future.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 This study aimed to examine the effect of substance use disorders on adherence to anti TB
4 medications. Specifically, we have examined the association of the most frequently used
5 substances, namely khat and alcohol, on adherence to guideline compatible TB treatment.
6
7
8
9

10 **Methods**

11 **Study area, period and patients**

12
13
14
15 We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma
16 city special zone is the capital city of Jimma zone and located in the Southwestern part of
17 Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital
18 and a zonal hospital as well as four functional health centers those currently providing services.
19
20 Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the
21 zone has more than three million inhabitants. During the period of this study, Jimma Zone had
22 112 health centers and three hospitals. Out of these government's public health facilities, 91
23 health centers and all hospitals were providing services to TB patients. In this study, data was
24 collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma
25 city we randomly selected 2 health centers and one hospital. We also randomly selected 20
26 health centers and three hospitals from the Jimma Zone. Patients were included if they had
27 initiated anti-TB treatment within a month of start of the study at the selected health centers and
28 hospitals between October 2017 and October 2018.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Study design**

49
50
51 This study is a multicenter prospective cohort study. Patients recruited to the cohort were
52 interviewed on three occasions, namely, baseline (starting treatment), first follow up (after 2
53 months), and second follow up (at the end of six months).
54
55
56
57

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 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 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 the questions number two and three regarding standard drink were adapted to a more locally appropriate question (40).

1
2
3 *Nicotine dependence:* The Fagerstrom test for nicotine dependence (FTND) was used to assess
4 tobacco dependence. A total score of FTND ≥ 5 was considered as tobacco dependence (41). At
5 a cut-off score ≥ 5 , the FTND has good sensitivity (0.75), and specificity (0.80). The FTND has
6 six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND
7 score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine
8 dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also
9 asked about their reasons for smoking tobacco (41).

10
11
12
13
14
15
16
17
18
19
20 *Cannabis and shisha use:* Using both substances and their frequency were assessed.

21
22
23 *Khat use:* - Khat use was assessed by self-reported questionnaire. Since there is no standardized
24 questionnaire for khat use, patterns and reasons of khat use were assessed by using a structured
25 questionnaire which was developed in the context of a literature review. Any consumption of
26 khat in the last one month was considered as current khat use. Frequent khat use and using more
27 than one bundle of khat per day was considered as khat use disorder.

28 29 30 31 32 33 34 35 **Outcome variable**

36
37
38 *Adherence:* Adherence status of tuberculosis patients was assessed by Direct Observed
39 Treatment (DOT) (based on missing appointments) and pills counts. In this study adherence is
40 defined as taking medication regularly and attending follow-up according to appointments and
41 national guideline for tuberculosis in Ethiopia (12). In this study non-adherence is defined as
42 missing at least one follow-up appointment during DOT. Also, non-adherence during intensive
43 phase is defined as missing at least one dose of the prescribed anti-TB medication and noted
44 separately. Adherence was assessed at baseline (beginning of intensive phase), at second month
45 (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 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

1
2
3 previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity
4 if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate
5 food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and
6
7
8 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had
9
10 been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at
11
12 baseline, second month (at first follow up), and six month (at the completion of anti-TB
13
14 treatment or second follow up).
15
16
17
18
19

20 **Data collection procedures**

21
22
23 Before starting data collection the questionnaires were pretested on a sample (5% of the total
24 sample) of patients with TB who were on treatment at Agaro health center. Those patients who
25 participated in the pretest were not included in the main cohort study. Data was collected by
26
27 trained health professionals working in the respective TB clinics. Also, district tuberculosis focal
28
29 persons and other health professionals specifically trained for this purpose participated in the
30
31 supervision of data collection.
32
33
34
35
36
37

38 **Data analysis**

39
40
41 Data were entered to Epi Data (version 3.1) and analyzed using R studio (1.2.1335). Missing
42 values of income were excluded from the analysis. Participants' characteristics and study
43 variables were presented using descriptive statistics. Generalized linear model was used to
44
45 examine the longitudinal effect of substance use disorders on medication adherence (binary
46
47 outcome). We used an intercept only model to investigate the trajectory of adherence over time
48
49 (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat and
50
51 alcohol use disorders on adherence without adjusting for covariates, model 2 investigated the
52
53
54
55
56
57

1
2
3 longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates.
4
5 Model fit was examined with the Bayesian Information Criterion (BIC).
6
7

8 The covariate selection was based on a directed acyclic graph (DAG). DAGs are an analytical
9 method for visualizing hypotheses about causal relationships between exposure (substance use)
10 and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets
11 of variables and to avoid bias (50).
12
13
14
15
16

17 **Ethical considerations**

18
19 Ethical clearance was obtained from the Ethical Review Board of Jimma University
20 (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written
21 informed consent was obtained from each participants. The anonymity of the study participants
22 was kept at all stages of data processing and write-up of the manuscript.
23
24
25
26
27
28
29
30

31 **Patient and public involvement**

32
33 Patients were not involved in development of the research questions, study design, interpretation
34 of results or writing of the manuscript.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (%)	2 nd 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	

For peer review only

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

1
2
3 power. The discrepancy may be due to patients in our study were using substance whereas in the
4
5 systematic review there was no data regarding substance use.
6
7

8
9 In this study the prevalence of non-adherence among patients with substance use disorder at
10
11 baseline, first, and second follow up was 16·4%, 41·7%, and 45·7% respectively. This is in line
12
13 with a study from the US (39%) (52, 55, 56).
14
15

16
17 Moreover, this study provides the evidence that substance use disorders have significant negative
18
19 effect on adherence to anti-TB medications among patients with tuberculosis, which supports
20
21 earlier findings from previous studies that found alcohol use disorder, tobacco dependence, and
22
23 illicit drug use have negative impact on adherence in Uzbekistan, Spain, and Morocco (57-59).
24
25 This is also, in line with retrospective studies conducted in Russia and New York which found
26
27 that alcohol use disorder and drug addiction were significantly associated with non-adherence to
28
29 anti-TB medications (8, 9). Likewise, the finding of this study is in line with studies conducted in
30
31 different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-
32
33 adherence to anti-TB medications (52, 56, 60). In our study patients with substance use disorder
34
35 were more than two times more likely not to follow their medication plan than patients without
36
37 substance use disorders. This finding is in line with finding of a study from US that found the
38
39 risk of missing a DOT appointment was 2.6 times higher among patients with substance use
40
41 disorder than in patients without drug consumption (55).
42
43
44
45
46

47
48 In our study, khat use disorder turned out to be the most stringent factor that decreased
49
50 adherence. This confirms earlier findings from Yemen (61) and Ethiopia (14, 60). A plausible
51
52 explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which
53
54 may lead to missing the DOT appointments at the health facility. Another reason may be that
55
56
57
58
59
60

1
2
3 khat is omnipresent in Ethiopia, and therefore less attention is paid to the use of khat. Since little
4
5 is known about the effect of khat on patients with tuberculosis (14), khat may be considered as
6
7 part of a normal social interaction (61).
8
9

10
11 A higher level of education was associated with non-adherence to anti-TB medications in our
12
13 study. This result confirms the findings from Yemen that found more educated patients were
14
15 19% times less likely to be adherent to their medication (61). Also, a study from Ethiopia
16
17 showed that attending primary education was associated with non-adherence to anti-TB
18
19 medications (60). Our findings are contrary to previous studies which have suggested that lower
20
21 or no formal education decreases adherence to TB medication (13, 63). Our finding seems
22
23 counterintuitive. However, our results are likely to be related to findings from a study indicating
24
25 that persons with higher educational attainment might be reluctant to accept DOTS regimes (64).
26
27 Daily visits to the health facility have been reported as too time consuming and probably
28
29 stigmatizing for patients with a job (65). In this study, being merchant was associated with poor
30
31 adherence to anti-TB medications. This might be due to patients miss their medications because
32
33 of busy working time, but it needs further investigation.
34
35
36
37
38

39 **Limitations**

40
41
42 This study has some limitations. Due to social desirability, patients might minimize reporting of
43
44 the amount and frequency of substance they were using. Also, measuring adherence based on
45
46 pills count may not reflect the real adherence situation for the same reason as some patients
47
48 might not bring all left over of medications during the follow up. Likewise, follow up and data
49
50 collections have been carried out by health professional working in the respective TB clinic, so
51
52 their assessment of adherence might be biased. However, overestimating adherence may have
53
54
55
56
57

1
2
3 biased our results towards a null effect and led to underestimating the effect of substance use
4 disorders, so we are confident that our estimates are conservative. The participation of district
5 tuberculosis focal persons and other health professionals in the supervision of data collection
6 might also introduce bias.
7
8
9
10
11

12
13 Also, hospitalized patients, patients on re-treatment and patients with MDR-TB were not
14 included in this study, so that the results cannot be generalized for these patients. However,
15 MDR-TB patients are under special treatment and surveillance so that including this group of
16 patients might have biased the results. Finally, we did not assess the reasons for non-adherence.
17 This should be part of a separate study going more into the details of the situation of persons
18 with khat and alcohol problems.
19
20
21
22
23
24
25
26

27 28 **Strengths**

29
30
31 The specific strength of this study are the prospective cohort design, longitudinal data collection,
32 including patients from urban and rural health institutions, intensive training given for data
33 collectors, multi-center data collection, and the use of standardized instruments to assess
34 exposure, outcomes and explanatory variables.
35
36
37
38
39
40

41 **Conclusions**

42
43
44 Substance use disorders predict greater likelihood of anti-TB medication non-adherence among
45 TB patients. Also in our study, khat and alcohol use disorders were the main risk factors for anti-
46 TB medications adherence. This finding implies the importance integrating of substance use
47 disorder screening and treatment in to the existing tuberculosis services to reduce the effect of
48 substance on treatment outcomes including adherence.
49
50
51
52
53
54
55
56
57

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.

Funding

The study was funded by Jimma University Institute of Health with the grant number of IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant number of 15106202/2018, and individual throughout data collection. The funders had no role in this study including interpretation and preparation of the manuscript.

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.

Author affiliations

¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.

² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany

⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany

⁵ Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany

⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

⁸ Center for International Health, Ludwig Maxmillians University, Munich, Germany

Acknowledgement

We are grateful to the study participants for compromising their time to participate in the study. Our gratitude is extended for Jimma University for funding the project. We are also grateful to IPPG for funding part of the project. Our gratitude extended to Dr. Michael Odenwald, who contributed money from his pocket to support the project.

Availability of data

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

References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019
2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet Infect Dis.* 2018; 18(12):1291-3.
3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.
4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. *Lancet Respir Med.* 2018; 6(4):299-314.
5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016. <https://apps.who.int/medicinedocs/en/d/Js23098en/> accessed on 24/07/2019.
6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-Nkwanta Regional Hospital: a 2-year experience. *Int J Tuberc Lung Dis.* 2004; 8(11):1337-41.
7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on 25/07/2019
8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence,

1
2
3 default and the acquisition of multidrug resistance. Bulletin of the World Health Organization.
4
5 2007; 85(9):703-11.
6

7
8
9 9. Pablos-Mendez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Non-adherence in
10
11 tuberculosis treatment: predictors and consequences in New York City. The American journal of
12
13 medicine, 1997; 102(2):164-70.
14

15
16 10. Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant
17
18 tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to
19
20 2013. J Glob Antimicrob Resist. 2016; 6:102-7.
21
22

23
24 11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and
25
26 after tuberculosis treatment. Int J Tuberc Lung Dis. 2011; 15(7):871-85.
27
28

29
30 12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic
31
32 management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.
33

34
35 13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and
36
37 determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and
38
39 meta-analysis. PLoS One. 2019; 14(1):e0210422.
40
41

42
43 14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and
44
45 tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bulletin of the World
46
47 Health Organization. 2018; 96(4):243-55.
48
49

50
51 15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on
52
53 tuberculosis treatment outcomes: a retrospective cohort study. Arch Public Health. 2018; 76:45.
54
55
56
57

- 1
2
3 16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction
4 and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort
5 study. *Epidemiol Infect.* 2017; 145(16):3516-24.
6
7
8
9
10
11 17. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, Warndorff D, et al. Investigation
12 of the risk factors for tuberculosis: a case-control study in three countries in West Africa.
13 *International journal of epidemiology.* 2005; 34(4):914-23.
14
15
16
17
18 18. Lynch JB. Multidrug-resistant Tuberculosis. *The Medical clinics of North America.*
19 2013; 97(4):553-79, ix-x.
20
21
22
23
24 19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence
25 and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia.
26 *PloS one.* 2013; 8(9):e74406.
27
28
29
30
31
32 20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in
33 patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study.
34 *Clinical epidemiology.* 2014; 6:405-21.
35
36
37
38
39
40 21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al.
41 Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB
42 patients. *The international journal of tuberculosis and lung disease: the official journal of the*
43 *International Union against Tuberculosis and Lung Disease.* 2006; 10(5):565-70.
44
45
46
47
48
49
50 22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al.
51 Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.
52 *Bulletin of the World Health Organization.* 2013; 91(1):36-45.
53
54
55
56
57
58
59
60

- 1
2
3 23. Luqman W, Danowski TS. The use of khat (*Catha edulis*) in Yemen. Social and medical
4 observations. *Ann Intern Med.* 1976;85(2):246-9.
5
6
7
8 24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. *J*
9 *Ethnopharmacol.* 2010; 132(3):607-14.
10
11
12
13 25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. *Biomed*
14 *Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2004; 148(1):11-5.
15
16
17 26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al.
18 *Catha edulis* Forsk. (Khat): Evaluation of its Antidepressant-like Activity. *Pharmacognosy*
19 *magazine.* 2017; 13(Suppl 2):S354-s8.
20
21
22
23 27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University
24 Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-
25 Cross-Sectional Study. *Int J Bacteriol.* 2017;9840670.
26
27
28 28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected
29 adults in Northwest Ethiopia: a multicentre case-control study. *BMJ Open.* 2016; 6(4):e009058.
30
31
32 29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on
33 tuberculosis outcome in Yemen. *International journal of mycobacteriology.* 2016; 5(1):S20.
34
35
36 30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and
37 perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash
38 Valley of Afar region, Ethiopia. *BMC Public Health.* 2010; 10:187.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of
4 Mycobacterium tuberculosis infection by macrophage immune modulation? Med Hypotheses.
5 2014; 82(6):667-9.
6
7
8
9
10
11 32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-
12 Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. PLoS One. 2016;
13 11(6):e0156258.
14
15
16
17
18 33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations
19 among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study.
20 J Pharm Policy Pract. 2017; 10:36.
21
22
23
24
25
26 34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation
27 between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of
28 Saudi Arabia. PLoS One. 2015; 10(10):e0140245.
29
30
31
32
33
34 35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to
35 anti-tuberculosis treatment in Yemen: JPHSR; 2013.
36
37
38
39 36. Cox G, Rampes H. Adverse effects of khat: a review. Advances in Psychiatric Treatment.
40 2018; 9(6):456-63.
41
42
43
44
45 37. EPIInfoTM. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on
46 19/08/2019
47
48
49
50 38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
51 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.
52
53
54
55
56
57
58
59
60

1
2
3 [https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MS_D_MSB_01.6a.pdf;jsessionid=](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MS_D_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1)
4
5 [B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MS_D_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1) accessed on 20/07/2019.
6
7

8
9 39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
10 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.
11
12

13
14 40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated
15 factors among people living with HIV who are attending services in south west Ethiopia. BMC
16 research notes. 2014; 7:828.
17
18

19
20
21 41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for
22 nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research
23 : Gann. 1999; 90(10):1071-5.
24
25
26

27
28
29 42. Average Salary in Ethiopia. [http://www.salaryexplorer.com/salary-](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1)
30 [survey.php?loc=69&loctype=1](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1) accessed on 09/07/2019.
31
32

33
34
35 43. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.
36 [https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_e](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf)
37 [his/development/instruments/Manual_OSS_3.pdf](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf) , Accessed on 08/06/2019
38
39

40
41
42 44. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety
43 among patients with tuberculosis at Wolaita Sodo University Hospital and Sodo Health Center,
44 Wolaita Sodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.
45
46
47

48
49
50 45. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for
51 measurement of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.
52
53
54

1
2
3 http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on
4
5 10/01/2017
6

7
8 46. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity,
9 mental health and quality of life among people living with HIV commencing antiretroviral
10 treatment in Ethiopia: a cross-sectional study. *Health and quality of life outcomes*. 2016; 14:37.
11
12

13
14
15 47. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among
16 volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the
17 2008 food crisis. *The Journal of nutrition*. 2009; 139(9):1758-64.
18
19
20
21

22
23 48. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.
24 *Epidemiology*. 1999; 10(1):37-48.
25
26

27
28 49. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams.
29 *Epidemiology*. 2011; 22(5):745.
30
31
32

33
34 50. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res*
35 *Methodol*. 2008; 8:70.
36
37

38
39 51. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for
40 anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public
41 health care facilities in South Ethiopia: a cross-sectional study. *BMC Public Health*. 2017;
42 17(1):269.
43
44
45
46
47

48
49 52. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
50 associated factors among TB patients attending at Gondar town health centers, Northwest
51 Ethiopia. *BMC research notes*. 2018; 11(1):691.
52
53
54
55

- 1
2
3 53. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The
4 Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-
5 Adherence in Addis Ababa, Ethiopia. *Ethiopian journal of health sciences*. 2017; 27(5):447-58.
6
7
8
9
10
11 54. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis
12 treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. *PLoS*
13 *One*. 2013; 8(11):e78791.
14
15
16
17
18 55. Ricks PM, Hershov RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A
19 randomized trial comparing standard outcomes in two treatment models for substance users with
20 tuberculosis. *Int J Tuberc Lung Dis*. 2015; 19(3):326-32.
21
22
23
24
25
26 56. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB
27 treatment adherence: a qualitative study on DOTS service in public health centers in Addis
28 Ababa, Ethiopia. *BMC Public Health*. 2018; 18(1):462.
29
30
31
32
33
34 57. Hasker E, Khodjikhhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ,
35 et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and
36 why do they default? *BMC Infect Dis*. 2008; 8:97.
37
38
39
40
41
42 58. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of
43 treatment completion and fatality among tuberculosis patients in Spain. *Int J Tuberc Lung Dis*.
44 2004; 8(4):458-64.
45
46
47
48
49 59. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk
50 factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in
51 Morocco. *BMC Public Health*. 2011; 11:140.
52
53
54
55
56
57
58
59
60

- 1
2
3 60. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and
4 treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. BMC
5 research notes. 2015; 8:503.
6
7
8
9
10
11 61. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting
12 patients' compliance to anti-tuberculosis treatment in Yemen. Journal of Pharmaceutical Health
13 Services Research. 2013; 4(2):115-22.
14
15
16
17
18 62. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary
19 Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia:
20 Implications for Tuberculosis Control. PLoS One. 2016; 11(2):e0149453.
21
22
23
24
25
26 63. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing
27 completion of treatment among pulmonary tuberculosis patients. Patient Prefer Adherence. 2019;
28 13:491-6.
29
30
31
32
33
34 64. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and
35 qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in
36 Japan - Are physicians and nurses at a particular risk? PLoS One. 2018; 13(6):e0198075.
37
38
39
40
41
42 65. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et
43 al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative
44 study. J Health Popul Nutr. 2018; 37(1):1.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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 / [#2](#) Explain the scientific background and rationale for the 4-6
rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 6
hypotheses

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 6
periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 6
selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of
exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 7-10
confounders, and effect modifiers. Give diagnostic criteria, if
applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 7-10
measurement 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.

1	Bias	#9	Describe any efforts to address potential sources of bias	10,11
2				
3				
4	Study size	#10	Explain how the study size was arrived at	7
5				
6				
7	Quantitative	#11	Explain how quantitative variables were handled in the	10, 11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
10				
11				
12				
13				
14				
15	Statistical	#12a	Describe all statistical methods, including those used to control	10,11
16	methods		for confounding	
17				
18				
19				
20	Statistical	#12b	Describe any methods used to examine subgroups and	
21	methods		interactions	
22				
23				
24				
25				
26	Statistical	#12c	Explain how missing data were addressed	10
27	methods			
28				
29				
30				
31	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	
32	methods			
33				
34				
35				
36	Statistical	#12e	Describe any sensitivity analyses	
37	methods			
38				
39				
40				
41				
42	Results			
43				
44				
45	Participants	#13a	Report numbers of individuals at each stage of study—eg	12
46			numbers potentially eligible, examined for eligibility, confirmed	
47			eligible, included in the study, completing follow-up, and	
48			analysed. Give information separately for for exposed and	
49			unexposed groups if applicable.	
50				
51				
52				
53				
54				
55				
56				
57	Participants	#13b	Give reasons for non-participation at each stage	
58				
59				
60				

1	Participants	#13c	Consider use of a flow diagram	
2				
3				
4	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	12, 13
5			clinical, social) and information on exposures and potential	
6			confounders. Give information separately for exposed and	
7			unexposed groups if applicable.	
8				
9				
10				
11				
12				
13				
14	Descriptive data	#14b	Indicate number of participants with missing data for each	12
15			variable of interest	
16				
17				
18				
19	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
20				
21				
22				
23	Outcome data	#15	Report numbers of outcome events or summary measures	14, 15
24			over time. Give information separately for exposed and	
25			unexposed groups if applicable.	
26				
27				
28				
29				
30	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	14-18
31			adjusted estimates and their precision (eg, 95% confidence	
32			interval). Make clear which confounders were adjusted for and	
33			why they were included	
34				
35				
36				
37				
38				
39				
40	Main results	#16b	Report category boundaries when continuous variables were	
41			categorized	
42				
43				
44				
45	Main results	#16c	If relevant, consider translating estimates of relative risk into	
46			absolute risk for a meaningful time period	
47				
48				
49				
50				
51	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	
52			interactions, and sensitivity analyses	
53				
54				
55				
56	Discussion			
57				
58				
59				
60				

1	Key results	#18	Summarise key results with reference to study objectives	19-21
2				
3				
4	Limitations	#19	Discuss limitations of the study, taking into account sources of	21
5			potential bias or imprecision. Discuss both direction and	
6			magnitude of any potential bias.	
7				
8				
9				
10				
11				
12	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19-21
13			limitations, multiplicity of analyses, results from similar studies,	
14			and other relevant evidence.	
15				
16				
17				
18				
19	Generalisability	#21	Discuss the generalisability (external validity) of the study	
20			results	
21				
22				
23				
24				
25	Other Information			
26				
27				
28	Funding	#22	Give the source of funding and the role of the funders for the	23
29			present study and, if applicable, for the original study on which	
30			the present article is based	
31				
32				
33				
34				
35				

36 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution
37 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool
38 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043050.R1
Article Type:	Original research
Date Submitted by the Author:	03-Feb-2021
Complete List of Authors:	Daba, Matiwos; Jimma University College of Public Health and Medical Sciences, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Markos ; Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Adorjan, Kristina; Department of Psychiatry and Psychotherapy, LMU Munich, Germany; Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany Krahl, Wolfgang ; Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany, Forensic Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Elias ; Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Psychiatry Yitayih, Yimenu; Jimma University College of Public Health and Medical Sciences, Psychiatry Strobl, Ralf; Ludwig-Maximilians-Universitat Munchen, Institute for Medical Information Processing, Biometrics and Epidemiology Grill, Eva; Ludwig Maximilians University Munich, Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany ; Center for International Health, Ludwig Maxmillians University, Munich, Germany
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Infectious diseases, Mental health
Keywords:	Substance misuse < PSYCHIATRY, Tuberculosis < INFECTIOUS DISEASES, INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Substance use disorders and adherence to anti-tuberculosis medications in Southwest**
6
7 **Ethiopia: A prospective cohort study**
8

9
10 Matiws Soboka^{1*,8}, Markos Tesfaye^{2,8}, Kristina Adorjan^{3,4,8}, Wolfgang Krahl^{5,8}, Elias
11
12 Tesfaye¹, Yimenu Yitayih¹, Ralf Strobl⁶, Eva Grill^{6,8}
13
14
15
16
17
18
19
20

21 *** Corresponding author:** Matiws Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma
22
23 Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany
24

25
26 **Email:** matiws2004@yahoo.com
27

28
29 **Phone:** +251913792348
30

31 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
32

33
34 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
35

36
37 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
38

39
40 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
41

42
43 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
44

45
46 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
47

48
49 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
50

51
52 ⁸Center for International Health, Ludwig Maxmillians University, Munich, Germany
53
54
55
56
57
58
59
60

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.

1
2
3 **Conclusion:** Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-
4 TB medication. This implies the need to integrate the management for substance use disorders
5 into the existing tuberculosis treatment services.
6
7
8
9

10
11 **Keywords:** Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.
12
13

14 **Strengths and limitations**

- 15
16
17 ➤ The strengths of this study are the prospective cohort design, longitudinal data collection,
18 including patients from urban and rural health institutions, intensive training for data
19 collectors, multi-center data collection, and use of standardized instruments.
20
21
22
23
24
25 ➤ Due to social desirability, patients might minimize reporting of the amount and frequency
26 of the substances they were using.
27
28
29
30
31 ➤ Measuring adherence based on pills count may not reflect the real adherence situation,
32 since patients may not bring all leftover medications during the follow up.
33
34
35
36 ➤ Follow up and data collections have been carried out by health professionals working in
37 the respective TB clinic. As a result, their assessment of adherence might be biased.
38
39
40
41 ➤ Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
42 included in this study, and this may limit the generalizability of the result for these
43 patients.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 inhabitants (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).

1
2
3 In Ethiopia, the prevalence of non-adherence among TB patients has been estimated to range
4 from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (13). To
5
6 counteract this, the Ethiopian has implemented Direct Observed Treatment (DOT) services in
7
8 almost all health institutions (12), but its impact on medication adherence is unclear and the
9
10 reasons for non-adherence are still poorly understood.
11
12
13

14
15 Among the reasons for non-adherence, substance use disorders have been found to play a
16
17 dominant role (8, 14-16). Substances such as alcohol, tobacco, khat, and illicit drugs are
18
19 commonly used among patients with TB (17-19). Patients with TB are also at risk of increased
20
21 morbidity, and premature mortality due to substance use disorders (20). Because, substance use
22
23 disorders such as alcohol and tobacco are associated with MDR-TB (21, 22).
24
25
26

27
28 Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids,
29
30 cathinone, and cathine cause the stimulating effect, and lead to craving and dependency (23-26).
31
32 There is evidence that khat use increases susceptibility to tuberculosis (27-31), and maybe
33
34 associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and
35
36 high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated
37
38 with non-adherence to anti-tuberculosis medications (35), probably because khat disrupts
39
40 patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia, like
41
42 Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an
43
44 important but unrecognized threat to anti-TB medication adherence. Filling the information gaps
45
46 about the effect of substance use disorders will help to improve TB treatment outcomes and
47
48 inform decision makers about the need for an integration of substance use disorder treatment in
49
50 TB control programs in the future.
51
52
53
54
55
56
57
58
59
60

1
2
3 This study aimed to examine the effect of substance use disorders on adherence to anti TB
4 medications. Specifically, we examined the association of the most frequently used substances,
5
6 namely khat and alcohol, on adherence to guideline compatible TB treatment.
7
8
9

10 **Methods**

11 **Study area, period, and patients**

12
13
14
15 We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma
16 city special zone is the capital city of Jimma zone and located in the Southwestern part of
17 Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital
18 and a zonal hospital, as well as four functional health centers those currently providing services.
19
20 Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the
21 zone has more than three million inhabitants. During the period of this study, Jimma Zone had
22 112 health centers and three hospitals. Out of these government's public health facilities, 91
23 health centers and all hospitals were providing services to TB patients. In this study, data was
24 collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma
25 city, we randomly selected 2 health centers and one hospital. We also randomly selected 20
26 health centers and three hospitals from the Jimma Zone. Patients were included if they had
27 initiated anti-TB treatment within a month of start of the study at the selected health centers and
28 hospitals between October 2017 and October 2018.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Study design**

49
50
51 This study is a multicenter prospective cohort study. Patients recruited to the cohort were
52 interviewed on three occasions, namely, baseline (starting treatment), first follow up (after 2
53 months), and second follow up (at the end of six months).
54
55
56
57

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).

1
2
3 *Nicotine dependence:* The Fagerstrom test for nicotine dependence (FTND) was used to assess
4 tobacco dependence. A total score of FTND ≥ 5 was considered as tobacco dependence (41). At
5
6 a cut-off score ≥ 5 , the FTND has good sensitivity (0.75), and specificity (0.80). The FTND has
7
8 six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND
9
10 score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine
11
12 dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also
13
14 asked about their reasons for smoking tobacco (41).
15
16
17
18
19

20 *Cannabis and shisha use:* Use of both substances and their frequency were assessed.
21
22

23 *Khat use:* - Khat use was assessed by self-reported questionnaire. Since there is no standardized
24
25 questionnaire for khat use, patterns, and reasons of khat use were assessed by using a structured
26
27 questionnaire which was developed in the context of a literature review. Any consumption of
28
29 khat in the last one month was considered as current khat use. Frequent khat use (using khat
30
31 daily and 2-3 times per week) and using more than one bundle of khat per day was considered as
32
33 khat use disorder.
34
35
36
37

38 **Outcome variable**

39
40

41 *Adherence:* Adherence status of tuberculosis patients was assessed by Direct Observed
42
43 Treatment (DOT) (based on missing appointments) and pills counts. In this study, adherence is
44
45 defined as taking medication regularly and attending follow-up according to appointments and
46
47 national guideline for tuberculosis in Ethiopia (12). In this study, non-adherence is defined as
48
49 missing at least one follow-up appointment during DOT. Non-adherence during intensive phase
50
51 is defined as missing at least one dose of the prescribed anti-TB medication and noted separately.
52
53
54
55
56
57

1
2
3 Adherence was assessed at baseline (beginning of intensive phase), at second month (end of
4 intensive phase), and at end of 6 month (end of continuation phase).
5
6
7

8 **Explanatory variables**

9

10
11 *Socio-demographic variables:* Age, sex, marital status, level of education, religion, ethnicity,
12 income, household size, occupation, place of residence, and living conditions were assessed
13 using a structured questionnaire. Income was categorized considering that the minimum monthly
14 wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36.67
15 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the
16 annual income, and we used a cutoff 14,568 Ethiopian birr (439.98 Euros).
17
18
19
20
21
22
23
24
25

26 *Disease related factors:* Types of TB diagnosis (smear positive, smear negative, extrapulmonary
27 TB, and MDR-TB) were collected from patients' charts.
28
29
30

31 *Comorbidities:* All confirmed diagnoses of HIV, previous mental illness, hypertension, and
32 diabetes mellitus were collected from patients' charts.
33
34
35
36

37 *Social support:* Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the
38 strength of social support. The Oslo-3 total score 3-8 indicate poor social support, 9-11 indicate
39 moderate social support, and 12-14 indicate strong social support (43). The scale had been
40 validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at
41 baseline, second month (at first follow up), and six month (at the completion of anti-TB
42 treatment or second follow up).
43
44
45
46
47
48
49
50

51 *Food insecurity:* It was assessed using the Household Food Insecurity Access Scale (HFIAS) to
52 determine whether the respondent has experienced any of the indicators of food insecurity in the
53
54
55
56
57

1
2
3 previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity
4 if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate
5 food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and
6
7
8 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had
9
10 been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at
11
12 baseline, second month (at first follow up), and six month (at the completion of anti-TB
13
14 treatment or second follow up).
15
16
17
18
19

20 **Data collection procedures**

21
22
23 Before starting data collection, the questionnaires were pretested on a sample (5% of the total
24 sample) of patients with TB who were on treatment at Agaro health center. Those patients who
25 participated in the pretest were not included in the main cohort study. Data were collected by
26
27 trained health professionals working in the respective TB clinics. Also, district tuberculosis focal
28 persons and other health professionals specifically trained for this purpose participated in the
29
30 supervision of data collection.
31
32
33
34
35
36
37

38 **Data analysis**

39
40
41 Data were entered to Epi Data (version 3.1) and analyzed using R studio (1.2.1335). Missing
42 values of income were excluded from the analysis. Participants' characteristics and study
43 variables were presented using descriptive statistics. Generalized linear model was used to
44
45 examine the longitudinal effect of substance use disorders on medication adherence (binary
46
47 outcome). We used an intercept only model to investigate the trajectory of adherence over time
48
49 (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat and
50
51 alcohol use disorders on adherence without adjusting for covariates, model 2 investigated the
52
53
54
55
56
57
58
59
60

1
2
3 longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates.
4
5 Model fit was examined with the Bayesian Information Criterion (BIC).
6
7

8 The covariate selection was based on a directed acyclic graph (DAG). DAGs are analytical
9 method for visualizing hypotheses about causal relationships between exposure (substance use)
10 and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets
11 of variables and to avoid bias (50).
12
13
14
15
16

17 **Ethical considerations**

18
19 Ethical clearance was obtained from the Ethical Review Board of Jimma University
20 (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written
21 informed consent was obtained from each participant. The anonymity of the study participants
22 was kept at all stages of data processing and write-up of the manuscript. Patients who had
23 alcohol and khat use disorder were advised to contact a mental health professional for further
24 evaluation and treatment.
25
26
27
28
29
30
31
32
33
34
35
36
37

38 **Patient and public involvement**

39 Patients were not involved in development of the research questions, study design, interpretation
40 of results or writing of the manuscript.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (%)	2 nd 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-

1
2
3 adherence in the Amhara region (13, 54). The proportion of non-adherence to anti-TB
4 medications during the first (26.1%) and second (27.6%) follow up was slightly higher than
5 findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), and Addis Ababa
6 (19.5%) (53). This might be explained by the high proportion of persons with a substance use
7 disorder in our study, in which we deliberately oversampled persons with SUD to maximize
8 power. The discrepancy may be also due to patients in our study were using substances whereas
9 in the systematic review there was no data regarding substance use.
10
11
12
13
14
15
16
17
18
19

20 In this study, the prevalence of non-adherence among patients with substance use disorder at
21 baseline, first, and second follow up was 16.4%, 41.7%, and 45.7% respectively. This is in line
22 with a study from the US (39%) (52, 55, 56).
23
24
25
26
27

28 Moreover, this study provides the evidence that substance use disorders have a significant
29 negative effect on adherence to anti-TB medications among patients with tuberculosis, which
30 supports earlier findings from previous studies that found alcohol use disorder, tobacco
31 dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and
32 Morocco (57-59). This is also comparable with retrospective studies conducted in Russia and
33 New York which found that alcohol use disorder and drug addiction were significantly
34 associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study
35 is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and
36 tobacco are the main factors for non-adherence to anti-TB medications (52, 56, 60). In our study,
37 patients with substance use disorder were more than two times more likely not to follow their
38 medication plan than patients without substance use disorders. This finding is in line with the
39 finding of a study conducted in US that found the risk of missing a DOT appointment was 2.6
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 times higher among patients with substance use disorder than in patients without drug
4
5 consumption (55).
6

7
8 In our study, khat use disorder turned out to be the most stringent factor that decreased
9 adherence. This confirms earlier findings from Yemen (61) and Ethiopia (14, 60). A plausible
10 explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which
11 may lead to missing of the DOT appointments at the health facility. Another reason may be that
12 khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is
13 known about the effect of khat on patients with tuberculosis (14), it may be considered as part of
14 a normal social interaction (61).
15
16
17
18
19
20
21
22
23

24
25 A higher level of education was associated with non-adherence to anti-TB medications in our
26 study. This result confirms the findings from Yemen that found more educated patients were
27 19% times less likely to be adherent to their medication (61). Also, a study from Ethiopia
28 showed that attending primary education was associated with non-adherence to anti-TB
29 medications (60). Our findings are contrary to previous studies which have suggested that lower
30 or no formal education decreases adherence to TB medication (13, 63). Our finding seems
31 counterintuitive. However, our results are likely to be related to findings from a study indicating
32 that persons with higher educational attainment might be reluctant to accept DOTS regimes (64).
33
34 Daily visits to the health facility have been reported as time consuming and probably
35 stigmatizing for patients with a job (65). In this study, being merchant was associated with poor
36 adherence to anti-TB medications. This might be due to patients miss their medications because
37 of busy working schedule, but this needs further investigation.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Funding

The study was funded by Jimma University Institute of Health with the grant number of IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant number of 15106202/2018, and individual throughout data collection. The funders had no role in this study including interpretation and preparation of the manuscript.

Authors' contribution

1
2
3 MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation.
4
5 MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the
6
7 manuscript.
8
9

10 **Author affiliations**

11
12
13
14 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.

15
16
17 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

18
19
20 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany

21
22 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany

23
24
25 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany

26
27
28 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

29
30
31 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

32
33
34 ⁸Center for International Health, Ludwig Maxmillians University, Munich, Germany

35 **Acknowledgment**

36
37
38
39 We are grateful to the study participants for sacrificing their time to participate in the study. Our
40
41 gratitude is extended to Jimma University for funding the project. We are also grateful to IPPG
42
43 for funding part of the project. Our gratitude also extends to Dr. Michael Odenwald, who
44
45 contributed money from his pocket to support the project.
46
47
48

49 **Availability of data**

50
51
52 It will be available upon official request from interested individuals or organizations.
53
54
55
56
57

References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019
2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet Infect Dis.* 2018; 18(12):1291-3.
3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.
4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. *Lancet Respir Med.* 2018; 6(4):299-314.
5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016. <https://apps.who.int/medicinedocs/en/d/Js23098en/> accessed on 24/07/2019.
6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-Nkwanta Regional Hospital: a 2-year experience. *Int J Tuberc Lung Dis.* 2004; 8(11):1337-41.
7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on 25/07/2019

- 1
2
3 8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al.
4
5 Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence,
6
7 default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization*.
8
9 2007; 85(9):703-11.
10
11
- 12
13 9. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
14
15 associated factors among TB patients attending at Gondar town health centers, Northwest
16
17 Ethiopia. *BMC Res Notes*. 2018; 11: 691.
18
19
- 20
21 10. Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant
22
23 tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to
24
25 2013. *J Glob Antimicrob Resist*. 2016; 6:102-7.
26
27
- 28
29 11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and
30
31 after tuberculosis treatment. *Int J Tuberc Lung Dis*. 2011; 15(7):871-85.
32
33
- 34
35 12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic
36
37 management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.
38
39
- 40
41 13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and
42
43 determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and
44
45 meta-analysis. *PLoS One*. 2019; 14(1):e0210422.
46
47
- 48
49 14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and
50
51 tuberculosis treatment outcomes, quality of life and disability, Ethiopia. *Bulletin of the World*
52
53 *Health Organization*. 2018; 96(4):243-55.
54
55
56
57

- 1
2
3 15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on
4 tuberculosis treatment outcomes: a retrospective cohort study. *Arch Public Health*. 2018; 76:45.
5
6
7
8
9 16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction
10 and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort
11 study. *Epidemiol Infect*. 2017; 145(16):3516-24.
12
13
14
15
16 17. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update.
17 *Clin Infect Dis*. 2009 ;48(1):72-82.
18
19
20
21 18. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in
22 the United States, 1997-2006. *Arch Intern Med*. 2009. 26;169(2):189-97
23
24
25
26
27 19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence
28 and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia.
29 *PloS one*. 2013; 8(9):e74406.
30
31
32
33
34
35 20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in
36 patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study.
37 *Clinical epidemiology*. 2014; 6:405-21.
38
39
40
41
42
43 21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al.
44 Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB
45 patients. *The international journal of tuberculosis and lung disease: the official journal of the*
46 *International Union against Tuberculosis and Lung Disease*. 2006; 10(5):565-70.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al.
4
5 Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.
6
7 Bulletin of the World Health Organization. 2013; 91(1):36-45.
8
9
10
11 23. Luqman W, Danowski TS. The use of khat (*Catha edulis*) in Yemen. Social and medical
12
13 observations. *Ann Intern Med*. 1976;85(2):246-9.
14
15
16 24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. *J*
17
18 *Ethnopharmacol*. 2010; 132(3):607-14.
19
20
21 25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. *Biomed*
22
23 *Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2004; 148(1):11-5.
24
25
26
27 26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al.
28
29 *Catha edulis* Forsk. (Khat): Evaluation of its Antidepressant-like Activity. *Pharmacognosy*
30
31 *magazine*. 2017; 13(Suppl 2):S354-s8.
32
33
34
35 27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University
36
37 Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-
38
39 Cross-Sectional Study. *Int J Bacteriol*. 2017;9840670.
40
41
42
43 28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected
44
45 adults in Northwest Ethiopia: a multicentre case-control study. *BMJ Open*. 2016; 6(4):e009058.
46
47
48 29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on
49
50 tuberculosis outcome in Yemen. *International journal of mycobacteriology*. 2016; 5(1):S20.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and
4 perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash
5 Valley of Afar region, Ethiopia. *BMC Public Health*. 2010; 10:187.
6
7
8
9
10
11 31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of
12 *Mycobacterium tuberculosis* infection by macrophage immune modulation? *Med Hypotheses*.
13 2014; 82(6):667-9.
14
15
16
17
18 32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-
19 Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One*. 2016;
20 11(6):e0156258.
21
22
23
24
25
26 33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations
27 among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study.
28 *J Pharm Policy Pract*. 2017; 10:36.
29
30
31
32
33
34 34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation
35 between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of
36 Saudi Arabia. *PLoS One*. 2015; 10(10):e0140245.
37
38
39
40
41
42 35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to
43 anti-tuberculosis treatment in Yemen: *JPHSR*; 2013.
44
45
46
47 36. Cox G, Rampes H. Adverse effects of khat: a review. *Advances in Psychiatric Treatment*.
48 2018; 9(6):456-63.
49
50
51
52 37. EPIInfoTM. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on
53 19/08/2019
54
55
56
57
58
59
60

1
2
3 38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
4 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

5
6
7
8 [https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=
9 B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1) accessed on 20/07/2019.

10
11
12
13
14 39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
15 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

16
17
18
19 40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated
20 factors among people living with HIV who are attending services in south west Ethiopia. BMC
21 research notes. 2014; 7:828.

22
23
24
25
26
27 41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for
28 nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research
29 : Gann. 1999; 90(10):1071-5.

30
31
32
33
34
35 42. Average Salary in Ethiopia. [http://www.salaryexplorer.com/salary-
36 survey.php?loc=69&loctype=1](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1) accessed on 09/07/2019.

37
38
39
40 43. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.
41 [https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_e
42 his/development/instruments/Manual_OSS_3.pdf](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf) , Accessed on 08/06/2019

43
44
45
46
47
48 44. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety
49 among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center,
50 WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.

- 1
2
3 45. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for
4 measurement of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.
5
6
7
8 http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on
9
10 10/01/2017
11
12
13
14 46. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity,
15 mental health and quality of life among people living with HIV commencing antiretroviral
16 treatment in Ethiopia: a cross-sectional study. *Health and quality of life outcomes*. 2016; 14:37.
17
18
19
20
21 47. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among
22 volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the
23 2008 food crisis. *The Journal of nutrition*. 2009; 139(9):1758-64.
24
25
26
27
28
29 48. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.
30 *Epidemiology*. 1999; 10(1):37-48.
31
32
33
34
35 49. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams.
36 *Epidemiology*. 2011; 22(5):745.
37
38
39
40 50. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res*
41 *Methodol*. 2008; 8:70.
42
43
44
45 51. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for
46 anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public
47 health care facilities in South Ethiopia: a cross-sectional study. *BMC Public Health*. 2017;
48 17(1):269.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 52. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
4 associated factors among TB patients attending at Gondar town health centers, Northwest
5 Ethiopia. *BMC research notes*. 2018; 11(1):691.
6
7
8
9
10
11 53. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The
12 Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-
13 Adherence in Addis Ababa, Ethiopia. *Ethiopian journal of health sciences*. 2017; 27(5):447-58.
14
15
16
17
18 54. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis
19 treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. *PLoS*
20 *One*. 2013; 8(11):e78791.
21
22
23
24
25
26 55. Ricks PM, Hershov RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A
27 randomized trial comparing standard outcomes in two treatment models for substance users with
28 tuberculosis. *Int J Tuberc Lung Dis*. 2015; 19(3):326-32.
29
30
31
32
33
34 56. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB
35 treatment adherence: a qualitative study on DOTS service in public health centers in Addis
36 Ababa, Ethiopia. *BMC Public Health*. 2018; 18(1):462.
37
38
39
40
41
42 57. Hasker E, Khodjikhhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ,
43 et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and
44 why do they default? *BMC Infect Dis*. 2008; 8:97.
45
46
47
48
49
50 58. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of
51 treatment completion and fatality among tuberculosis patients in Spain. *Int J Tuberc Lung Dis*.
52 2004; 8(4):458-64.
53
54
55
56
57

- 1
2
3 59. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk
4 factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in
5 Morocco. *BMC Public Health*. 2011; 11:140.
6
7
8
9
10
11 60. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and
12 treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. *BMC*
13 *research notes*. 2015; 8:503.
14
15
16
17
18 61. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting
19 patients' compliance to anti-tuberculosis treatment in Yemen. *Journal of Pharmaceutical Health*
20 *Services Research*. 2013; 4(2):115-22.
21
22
23
24
25
26 62. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary
27 Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia:
28 Implications for Tuberculosis Control. *PLoS One*. 2016; 11(2):e0149453.
29
30
31
32
33
34 63. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing
35 completion of treatment among pulmonary tuberculosis patients. *Patient Prefer Adherence*. 2019;
36 13:491-6.
37
38
39
40
41
42 64. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and
43 qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in
44 Japan - Are physicians and nurses at a particular risk? *PLoS One*. 2018; 13(6):e0198075.
45
46
47
48
49
50 65. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et
51 al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative
52 study. *J Health Popul Nutr*. 2018; 37(1):1.
53
54
55
56
57
58
59
60

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			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 / [#2](#) Explain the scientific background and rationale for the 4-6
 rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 6
 hypotheses

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 6
 periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 6
 selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of
 exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 7-10
 confounders, and effect modifiers. Give diagnostic criteria, if
 applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 7-10
 measurement 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.

1	Bias	#9	Describe any efforts to address potential sources of bias	10,11
2				
3				
4	Study size	#10	Explain how the study size was arrived at	7
5				
6				
7	Quantitative	#11	Explain how quantitative variables were handled in the	10, 11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
10				
11				
12				
13				
14				
15	Statistical	#12a	Describe all statistical methods, including those used to control	10,11
16	methods		for confounding	
17				
18				
19				
20	Statistical	#12b	Describe any methods used to examine subgroups and	
21	methods		interactions	
22				
23				
24				
25				
26	Statistical	#12c	Explain how missing data were addressed	10
27	methods			
28				
29				
30				
31	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	
32	methods			
33				
34				
35				
36	Statistical	#12e	Describe any sensitivity analyses	
37	methods			
38				
39				
40				
41				
42	Results			
43				
44				
45	Participants	#13a	Report numbers of individuals at each stage of study—eg	12
46			numbers potentially eligible, examined for eligibility, confirmed	
47			eligible, included in the study, completing follow-up, and	
48			analysed. Give information separately for for exposed and	
49			unexposed groups if applicable.	
50				
51				
52				
53				
54				
55				
56				
57	Participants	#13b	Give reasons for non-participation at each stage	
58				
59				
60				

1	Participants	#13c	Consider use of a flow diagram	
2				
3				
4	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	12, 13
5			clinical, social) and information on exposures and potential	
6			confounders. Give information separately for exposed and	
7			unexposed groups if applicable.	
8				
9				
10				
11				
12				
13				
14	Descriptive data	#14b	Indicate number of participants with missing data for each	12
15			variable of interest	
16				
17				
18				
19	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
20				
21				
22				
23	Outcome data	#15	Report numbers of outcome events or summary measures	14, 15
24			over time. Give information separately for exposed and	
25			unexposed groups if applicable.	
26				
27				
28				
29				
30	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	14-18
31			adjusted estimates and their precision (eg, 95% confidence	
32			interval). Make clear which confounders were adjusted for and	
33			why they were included	
34				
35				
36				
37				
38				
39				
40	Main results	#16b	Report category boundaries when continuous variables were	
41			categorized	
42				
43				
44				
45	Main results	#16c	If relevant, consider translating estimates of relative risk into	
46			absolute risk for a meaningful time period	
47				
48				
49				
50				
51	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	
52			interactions, and sensitivity analyses	
53				
54				
55				
56	Discussion			
57				
58				
59				
60				

1	Key results	#18	Summarise key results with reference to study objectives	19-21
2				
3				
4	Limitations	#19	Discuss limitations of the study, taking into account sources of	21
5			potential bias or imprecision. Discuss both direction and	
6			magnitude of any potential bias.	
7				
8				
9				
10				
11				
12	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19-21
13			limitations, multiplicity of analyses, results from similar studies,	
14			and other relevant evidence.	
15				
16				
17				
18				
19	Generalisability	#21	Discuss the generalisability (external validity) of the study	
20			results	
21				
22				
23				
24				
25	Other Information			
26				
27				
28	Funding	#22	Give the source of funding and the role of the funders for the	23
29			present study and, if applicable, for the original study on which	
30			the present article is based	
31				
32				
33				
34				
35				

36 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution
37 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool
38 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043050.R2
Article Type:	Original research
Date Submitted by the Author:	31-Mar-2021
Complete List of Authors:	Daba, Matiwas; Jimma University College of Public Health and Medical Sciences, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tsfaye, Markos ; Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Adorjan, Kristina; Department of Psychiatry and Psychotherapy, LMU Munich, Germany; Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany Krahl, Wolfgang ; Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany, Forensic Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tsfaye, Elias ; Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Psychiatry Yitayih, Yimenu; Jimma University College of Public Health and Medical Sciences, Psychiatry Strobl, Ralf; Ludwig-Maximilians-Universitat Munchen, Institute for Medical Information Processing, Biometrics and Epidemiology Grill, Eva; Ludwig Maximilians University Munich, Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany ; Center for International Health, Ludwig Maxmillians University, Munich, Germany
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Infectious diseases, Mental health
Keywords:	Substance misuse < PSYCHIATRY, Tuberculosis < INFECTIOUS DISEASES, INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Substance use disorders and adherence to anti-tuberculosis medications in Southwest**
6
7 **Ethiopia: A prospective cohort study**
8

9
10 Matiws Soboka^{1*,8}, Markos Tesfaye^{2,8}, Kristina Adorjan^{3,4,8}, Wolfgang Krahl^{5,8}, Elias
11
12 Tesfaye¹, Yimenu Yitayih¹, Ralf Strobl⁶, Eva Grill^{6,8}
13
14
15
16
17
18
19
20

21 *** Corresponding author:** Matiws Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma
22
23 Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany
24

25
26 **Email:** matiws2004@yahoo.com
27

28
29 **Phone:** +251913792348
30

31 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
32

33
34 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
35

36
37 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
38

39
40 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
41

42
43 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
44

45
46 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
47

48
49 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
50

51
52 ⁸Center for International Health, Ludwig Maxmillians University, Munich, Germany
53
54
55
56
57

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.

1
2
3 **Conclusion:** Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-
4 TB medication. This implies the need to integrate the management for substance use disorders
5 into the existing tuberculosis treatment services.
6
7
8
9

10
11 **Keywords:** Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.
12
13

14 **Strengths and limitations**

- 15
16
17 ➤ The strengths of this study are the prospective cohort design, longitudinal data collection,
18 including patients from urban and rural health institutions, intensive training for data
19 collectors, multi-center data collection, and use of standardized instruments.
20
21
22
23
24
25 ➤ Due to social desirability, patients might minimize reporting of the amount and frequency
26 of the substances they were using.
27
28
29
30
31 ➤ Measuring adherence based on pills count may not reflect the real adherence situation,
32 since patients may not bring all leftover medications during the follow up.
33
34
35
36 ➤ Follow up and data collections have been carried out by health professionals working in
37 the respective TB clinic. As a result, their assessment of adherence might be biased.
38
39
40
41 ➤ Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
42 included in this study, and this may limit the generalizability of the result for these
43 patients.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 inhabitants (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).

1
2
3 In Ethiopia, the prevalence of non-adherence among TB patients has been estimated to range
4 from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (13). To
5
6 counteract this, the Ethiopian has implemented Direct Observed Treatment (DOT) services in
7
8 almost all health institutions (12), but its impact on medication adherence is unclear and the
9
10 reasons for non-adherence are still poorly understood.
11
12
13

14
15 Among the reasons for non-adherence, substance use disorders have been found to play a
16
17 dominant role (8, 14-16). Substances such as alcohol, tobacco, khat, and illicit drugs are
18
19 commonly used among patients with TB (17-19). Patients with TB are also at risk of increased
20
21 morbidity, and premature mortality due to substance use disorders (20). Because, substance use
22
23 disorders such as alcohol and tobacco are associated with MDR-TB (21, 22).
24
25
26

27
28 Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids,
29
30 cathinone, and cathine cause the stimulating effect, and lead to craving and dependency (23-26).
31
32 There is evidence that khat use increases susceptibility to tuberculosis (27-31), and maybe
33
34 associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and
35
36 high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated
37
38 with non-adherence to anti-tuberculosis medications (35), probably because khat disrupts
39
40 patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia, like
41
42 Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an
43
44 important but unrecognized threat to anti-TB medication adherence. Filling the information gaps
45
46 about the effect of substance use disorders will help to improve TB treatment outcomes and
47
48 inform decision makers about the need for an integration of substance use disorder treatment in
49
50 TB control programs in the future. Therefore, the objective of this study is to assess the effect of
51
52 substance use disorders (including khat and alcohol) on adherence to anti-TB medications in
53
54
55
56
57

1
2
3 Southwest Ethiopia. Specifically, we examined the association of the most frequently used
4 substances, namely khat and/or alcohol, on adherence to guideline compatible TB treatment.
5
6
7

8 **Methods**

9 **Study area, period, and patients**

10
11
12 We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma
13 city special zone is the capital city of Jimma zone and located in the Southwestern part of
14 Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital
15 and a zonal hospital, as well as four functional health centers those currently providing services.
16
17 Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the
18 zone has more than three million inhabitants. During the period of this study, Jimma Zone had
19 112 health centers and three hospitals. Out of these government's public health facilities, 91
20 health centers and all hospitals were providing services to TB patients. In this study, data was
21 collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma
22 city, we randomly selected 2 health centers and one hospital. We also randomly selected 20
23 health centers and three hospitals from the Jimma Zone. Patients were included if they had
24 initiated anti-TB treatment within a month of start of the study at the selected health centers and
25 hospitals between October 2017 and October 2018. Patients were recruited over the first six
26 months.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Study design**

49
50
51 This study is a multicenter prospective cohort study. Patients recruited to the cohort were
52 interviewed on three occasions, namely, baseline (starting treatment), first follow up (after 2
53 months), and second follow up (at the end of six months).
54
55
56
57

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

1
2
3 score of eight or more, the sensitivity, and specificity of AUDIT for AUDs was 0·90 and 0·80,
4
5 respectively (39). AUDIT was used in Ethiopian context and questions number two and three
6
7 regarding standard drinks were adapted to a more locally appropriate question (40).
8
9

10
11 *Nicotine dependence:* The Fagerstrom test for nicotine dependence (FTND) was used to assess
12
13 tobacco dependence. A total score of FTND ≥ 5 was considered as tobacco dependence (41). At
14
15 a cut-off score ≥ 5 , the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has
16
17 six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND
18
19 score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine
20
21 dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also
22
23 asked about their reasons for smoking tobacco (41).
24
25
26
27

28 *Cannabis and shisha use:* Use of both substances and their frequency were assessed.
29
30

31 *Khat use:* - Khat use was assessed by self-reported questionnaire. Since there is no standardized
32
33 questionnaire for khat use, patterns, and reasons of khat use were assessed by using a structured
34
35 questionnaire which was developed in the context of a literature review. Any consumption of
36
37 khat in the last one month was considered as current khat use. Frequent khat use (using khat
38
39 daily and 2-3 times per week) and using more than one bundle of khat per day was considered as
40
41 khat use disorder.
42
43
44

45 **Outcome variable**

46
47

48 *Adherence:* Adherence status of tuberculosis patients was assessed by Direct Observed
49
50 Treatment (DOT) (based on missing appointments) and pills counts. In this study, adherence is
51
52 defined as taking medication regularly and attending follow-up according to appointments and
53
54 national guideline for tuberculosis in Ethiopia (12). In this study, non-adherence is defined as
55
56
57

1
2
3 missing at least one follow-up appointment during DOT. Non-adherence during intensive phase
4
5 is defined as missing at least one dose of the prescribed anti-TB medication and noted separately.
6
7 Adherence was assessed at baseline (beginning of intensive phase), at second month (end of
8
9 intensive phase), and at end of 6 month (end of continuation phase).
10
11
12

13 **Explanatory variables**

14
15
16 *Socio-demographic variables:* Age, sex, marital status, level of education, religion, ethnicity,
17
18 income, household size, occupation, place of residence, and living conditions were assessed
19
20 using a structured questionnaire. Income was categorized considering that the minimum monthly
21
22 wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67
23
24 Euros) (42). Then the monthly income of each patient was multiplied by 12 months to obtain the
25
26 annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).
27
28
29

30
31 *Disease related factors:* Types of TB diagnosis (smear positive, smear negative, extrapulmonary
32
33 TB, and MDR-TB) were collected from patients' charts.
34
35

36
37 *Comorbidities:* All confirmed diagnoses of HIV, previous mental illness, hypertension, and
38
39 diabetes mellitus were collected from patients' charts.
40
41

42 *Social support:* Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the
43
44 strength of social support. The Oslo-3 total score 3-8 indicate poor social support, 9-11 indicate
45
46 moderate social support, and 12-14 indicate strong social support (43). The scale had been
47
48 validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at
49
50 baseline, second month (at first follow up), and six month (at the completion of anti-TB
51
52 treatment or second follow up).
53
54
55
56
57

1
2
3 *Food insecurity*: It was assessed using the Household Food Insecurity Access Scale (HFIAS) to
4 determine whether the respondent has experienced any of the indicators of food insecurity in the
5 previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity
6 if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate
7 food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and
8 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had
9 been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at
10 baseline, second month (at first follow up), and six month (at the completion of anti-TB
11 treatment or second follow up).
12
13
14
15
16
17
18
19
20
21
22
23
24

25 **Data collection procedures**

26
27
28 Before starting data collection, the questionnaires were pretested on a sample (5% of the total
29 sample) of patients with TB who were on treatment at Agaro health center. Those patients who
30 participated in the pretest were not included in the main cohort study. Data were collected by
31 trained health professionals working in the respective TB clinics. Also, district tuberculosis focal
32 persons and other health professionals specifically trained for this purpose participated in the
33 supervision of data collection.
34
35
36
37
38
39
40
41

42 **Data analysis**

43
44
45 Data were entered to Epi Data (version 3.1) and analyzed using R studio (1.2.1335). Missing
46 values of income were excluded from the analysis. Participants' characteristics and study
47 variables were presented using descriptive statistics. Generalized linear model was used to
48 examine the longitudinal effect of substance use disorders on medication adherence (binary
49 outcome). We used an intercept only model to investigate the trajectory of adherence over time
50
51
52
53
54
55
56
57

1
2
3 (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat and
4 alcohol use disorders on adherence without adjusting for covariates, model 2 investigated the
5 longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates.
6
7
8
9
10 Model fit was examined with the Bayesian Information Criterion (BIC).

11
12
13 The covariate selection was based on a directed acyclic graph (DAG). DAGs are analytical
14 method for visualizing hypotheses about causal relationships between exposure (substance use)
15 and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets
16 of variables and to avoid bias (50).
17
18
19
20
21
22

23 **Ethical considerations**

24
25
26 Ethical clearance was obtained from the Ethical Review Board of Jimma University
27 (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written
28 informed consent was obtained from each participant. The anonymity of the study participants
29 was kept at all stages of data processing and write-up of the manuscript. Patients who had
30 alcohol and khat use disorder were advised to contact a mental health professional for further
31 evaluation and treatment.
32
33
34
35
36
37
38
39
40
41

42 **Patient and public involvement**

43
44
45 Patients were not involved in development of the research questions, study design, interpretation
46 of results or writing of the manuscript.
47
48
49
50
51
52
53
54
55
56
57

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 (%)	2 nd 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-

1
2
3 adherence in the Amhara region (13, 54). The proportion of non-adherence to anti-TB
4 medications during the first (26.1%) and second (27.6%) follow up was slightly higher than
5 findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), and Addis Ababa
6 (19.5%) (53). This might be explained by the high proportion of persons with a substance use
7 disorder in our study, in which we deliberately oversampled persons with SUD to maximize
8 power. The discrepancy may be also due to patients in our study were using substances whereas
9 in the systematic review there was no data regarding substance use.
10
11
12
13
14
15
16
17
18
19

20 In this study, the prevalence of non-adherence among patients with substance use disorder at
21 baseline, first, and second follow up was 16.4%, 41.7%, and 45.7% respectively. This is in line
22 with a study from the US (39%) (52, 55, 56).
23
24
25
26
27

28 Moreover, this study provides the evidence that substance use disorders have a significant
29 negative effect on adherence to anti-TB medications among patients with tuberculosis, which
30 supports earlier findings from previous studies that found alcohol use disorder, tobacco
31 dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and
32 Morocco (57-59). This is also comparable with retrospective studies conducted in Russia and
33 New York which found that alcohol use disorder and drug addiction were significantly
34 associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study
35 is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and
36 tobacco are the main factors for non-adherence to anti-TB medications (52, 56, 60). In our study,
37 patients with substance use disorder were more than two times more likely not to follow their
38 medication plan than patients without substance use disorders. This finding is in line with the
39 finding of a study conducted in US that found the risk of missing a DOT appointment was 2.6
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 times higher among patients with substance use disorder than in patients without drug
4
5 consumption (55).
6

7
8 In our study, khat use disorder turned out to be the most stringent factor that decreased
9 adherence. This confirms earlier findings from Yemen (61) and Ethiopia (14, 60). A plausible
10 explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which
11 may lead to missing of the DOT appointments at the health facility. Another reason may be that
12 khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is
13 known about the effect of khat on patients with tuberculosis (14), it may be considered as part of
14 a normal social interaction (61).
15
16
17
18
19
20
21
22
23

24
25 A higher level of education was associated with non-adherence to anti-TB medications in our
26 study. This result confirms the findings from Yemen that found more educated patients were
27 19% times less likely to be adherent to their medication (61). Also, a study from Ethiopia
28 showed that attending primary education was associated with non-adherence to anti-TB
29 medications (60). Our findings are contrary to previous studies which have suggested that lower
30 or no formal education decreases adherence to TB medication (13, 63). Our finding seems
31 counterintuitive. However, our results are likely to be related to findings from a study indicating
32 that persons with higher educational attainment might be reluctant to accept DOTS regimes (64).
33
34 Daily visits to the health facility have been reported as time consuming and probably
35 stigmatizing for patients with a job (65). In this study, being merchant was associated with poor
36 adherence to anti-TB medications. This might be due to patients miss their medications because
37 of busy working schedule, but this needs further investigation.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 data collectors, multi-center data collection, and the use of standardized instruments to assess
4
5 exposure, outcomes, and explanatory variables.
6
7

8 **Conclusions**

9
10
11 Substance use disorders predict greater likelihood of anti-TB medication non-adherence among
12
13 TB patients. Also, khat and alcohol use disorders were the main risk factors for anti-TB
14
15 medication adherence. This finding implies the importance of integrating substance use disorders
16
17 screening and treatment into the existing tuberculosis services to reduce the effect of substances
18
19 on treatment outcomes including adherence.
20
21
22

23 **Ethics approval and consent to participate**

24
25
26
27 Ethical clearance was obtained from the ethical review committee of Jimma University, Institute
28
29 of Health. Written informed consent was obtained from each participant before participation.
30
31 Information obtained in due course was kept confidentially
32
33
34

35 **Consent for publication**

36
37
38 Not applicable.
39
40

41 **Competing of interest**

42
43
44 All authors declare that they have no conflict of interests.
45
46

47 **Funding**

48
49
50 The study was funded by Jimma University Institute of Health with the grant number of
51
52 IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant
53
54
55
56
57

1
2
3 number of 15106202/2018, and individual throughout data collection. The funders had no role in
4
5 this study including interpretation and preparation of the manuscript.
6
7

8 **Authors' contribution**

9
10 MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation.
11
12 MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the
13
14 manuscript.
15
16
17

18 **Author affiliations**

19
20
21
22 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
23

24
25 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
26

27
28 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
29

30
31 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
32

33
34 ⁵ Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
35

36
37 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
38

39
40 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
41

42
43 ⁸ Center for International Health, Ludwig Maxmillians University, Munich, Germany
44

45 **Acknowledgment**

46
47 We are grateful to the study participants for sacrificing their time to participate in the study. Our
48
49 gratitude is extended to Jimma University for funding the project. We are also grateful to IPPG
50
51 for funding part of the project. Our gratitude also extends to Dr. Michael Odenwald, who
52
53 contributed money from his pocket to support the project.
54
55
56

Availability of data

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

References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019
2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet Infect Dis.* 2018; 18(12):1291-3.
3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.
4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. *Lancet Respir Med.* 2018; 6(4):299-314.
5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016. <https://apps.who.int/medicinedocs/en/d/Js23098en/> accessed on 24/07/2019.
6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-Nkwanta Regional Hospital: a 2-year experience. *Int J Tuberc Lung Dis.* 2004; 8(11):1337-41.
7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on 25/07/2019

- 1
2
3 8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al.
4
5 Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence,
6
7 default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization*.
8
9 2007; 85(9):703-11.
10
11
- 12
13 9. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
14
15 associated factors among TB patients attending at Gondar town health centers, Northwest
16
17 Ethiopia. *BMC Res Notes*. 2018; 11: 691.
18
19
- 20
21 10. Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant
22
23 tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to
24
25 2013. *J Glob Antimicrob Resist*. 2016; 6:102-7.
26
27
- 28
29 11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and
30
31 after tuberculosis treatment. *Int J Tuberc Lung Dis*. 2011; 15(7):871-85.
32
33
- 34
35 12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic
36
37 management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.
38
39
- 40
41 13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and
42
43 determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and
44
45 meta-analysis. *PLoS One*. 2019; 14(1):e0210422.
46
47
- 48
49 14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and
50
51 tuberculosis treatment outcomes, quality of life and disability, Ethiopia. *Bulletin of the World
52
53 Health Organization*. 2018; 96(4):243-55.
54
55
56
57

- 1
2
3 15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on
4 tuberculosis treatment outcomes: a retrospective cohort study. *Arch Public Health*. 2018; 76:45.
5
6
7
8 16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction
9 and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort
10 study. *Epidemiol Infect*. 2017; 145(16):3516-24.
11
12
13 17. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update.
14 *Clin Infect Dis*. 2009 ;48(1):72-82.
15
16 18. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in
17 the United States, 1997-2006. *Arch Intern Med*. 2009. 26;169(2):189-97
18
19 19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence
20 and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia.
21 *PloS one*. 2013; 8(9):e74406.
22
23 20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in
24 patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study.
25 *Clinical epidemiology*. 2014; 6:405-21.
26
27 21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al.
28 Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB
29 patients. *The international journal of tuberculosis and lung disease: the official journal of the*
30 *International Union against Tuberculosis and Lung Disease*. 2006; 10(5):565-70.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al.
4
5 Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.
6
7 Bulletin of the World Health Organization. 2013; 91(1):36-45.
8
9
10
11 23. Luqman W, Danowski TS. The use of khat (*Catha edulis*) in Yemen. Social and medical
12
13 observations. *Ann Intern Med*. 1976;85(2):246-9.
14
15
16 24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. *J*
17
18 *Ethnopharmacol*. 2010; 132(3):607-14.
19
20
21 25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. *Biomed*
22
23 *Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2004; 148(1):11-5.
24
25
26 26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al.
27
28 *Catha edulis* Forsk. (Khat): Evaluation of its Antidepressant-like Activity. *Pharmacognosy*
29
30 *magazine*. 2017; 13(Suppl 2):S354-s8.
31
32
33 27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University
34
35 Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-
36
37 Cross-Sectional Study. *Int J Bacteriol*. 2017;9840670.
38
39
40
41 28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected
42
43 adults in Northwest Ethiopia: a multicentre case-control study. *BMJ Open*. 2016; 6(4):e009058.
44
45
46 29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on
47
48 tuberculosis outcome in Yemen. *International journal of mycobacteriology*. 2016; 5(1):S20.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and
4 perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash
5 Valley of Afar region, Ethiopia. *BMC Public Health*. 2010; 10:187.
6
7
8
9
10
11 31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of
12 *Mycobacterium tuberculosis* infection by macrophage immune modulation? *Med Hypotheses*.
13 2014; 82(6):667-9.
14
15
16
17
18 32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-
19 Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One*. 2016;
20 11(6):e0156258.
21
22
23
24
25
26 33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations
27 among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study.
28 *J Pharm Policy Pract*. 2017; 10:36.
29
30
31
32
33
34 34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation
35 between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of
36 Saudi Arabia. *PLoS One*. 2015; 10(10):e0140245.
37
38
39
40
41
42 35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to
43 anti-tuberculosis treatment in Yemen: *JPHSR*; 2013.
44
45
46
47 36. Cox G, Rampes H. Adverse effects of khat: a review. *Advances in Psychiatric Treatment*.
48 2018; 9(6):456-63.
49
50
51
52 37. EPIInfoTM. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on
53 19/08/2019
54
55
56
57
58
59
60

1
2
3 38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
4 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

5
6
7
8 [https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1)
9 [B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1) accessed on 20/07/2019.

10
11
12
13
14 39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
15 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

16
17
18
19 40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated
20 factors among people living with HIV who are attending services in south west Ethiopia. BMC
21 research notes. 2014; 7:828.

22
23
24
25
26
27 41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for
28 nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research
29 : Gann. 1999; 90(10):1071-5.

30
31
32
33
34
35 42. Average Salary in Ethiopia. [http://www.salaryexplorer.com/salary-](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1)
36 [survey.php?loc=69&loctype=1](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1) accessed on 09/07/2019.

37
38
39
40 43. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.
41 [https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_e](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf)
42 [his/development/instruments/Manual_OSS_3.pdf](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf) , Accessed on 08/06/2019

43
44
45
46
47
48 44. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety
49 among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center,
50 WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.

- 1
2
3 45. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for
4 measurement of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.
5
6
7
8 http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on
9
10 10/01/2017
11
12
13
14 46. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity,
15 mental health and quality of life among people living with HIV commencing antiretroviral
16 treatment in Ethiopia: a cross-sectional study. *Health and quality of life outcomes*. 2016; 14:37.
17
18
19
20
21 47. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among
22 volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the
23 2008 food crisis. *The Journal of nutrition*. 2009; 139(9):1758-64.
24
25
26
27
28
29 48. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.
30 *Epidemiology*. 1999; 10(1):37-48.
31
32
33
34
35 49. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams.
36 *Epidemiology*. 2011; 22(5):745.
37
38
39
40 50. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res*
41 *Methodol*. 2008; 8:70.
42
43
44
45 51. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for
46 anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public
47 health care facilities in South Ethiopia: a cross-sectional study. *BMC Public Health*. 2017;
48 17(1):269.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 52. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
4 associated factors among TB patients attending at Gondar town health centers, Northwest
5 Ethiopia. BMC research notes. 2018; 11(1):691.
6
7
8
9
10
11 53. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The
12 Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-
13 Adherence in Addis Ababa, Ethiopia. Ethiopian journal of health sciences. 2017; 27(5):447-58.
14
15
16
17
18 54. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis
19 treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. PLoS
20 One. 2013; 8(11):e78791.
21
22
23
24
25
26 55. Ricks PM, Hershov RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A
27 randomized trial comparing standard outcomes in two treatment models for substance users with
28 tuberculosis. Int J Tuberc Lung Dis. 2015; 19(3):326-32.
29
30
31
32
33
34 56. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB
35 treatment adherence: a qualitative study on DOTS service in public health centers in Addis
36 Ababa, Ethiopia. BMC Public Health. 2018; 18(1):462.
37
38
39
40
41
42 57. Hasker E, Khodjikhhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ,
43 et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and
44 why do they default? BMC Infect Dis. 2008; 8:97.
45
46
47
48
49
50 58. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of
51 treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis.
52 2004; 8(4):458-64.
53
54
55
56
57

- 1
2
3 59. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk
4 factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in
5 Morocco. *BMC Public Health*. 2011; 11:140.
6
7
8
9
10
11 60. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and
12 treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. *BMC*
13 *research notes*. 2015; 8:503.
14
15
16
17
18 61. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting
19 patients' compliance to anti-tuberculosis treatment in Yemen. *Journal of Pharmaceutical Health*
20 *Services Research*. 2013; 4(2):115-22.
21
22
23
24
25
26 62. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary
27 Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia:
28 Implications for Tuberculosis Control. *PLoS One*. 2016; 11(2):e0149453.
29
30
31
32
33
34 63. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing
35 completion of treatment among pulmonary tuberculosis patients. *Patient Prefer Adherence*. 2019;
36 13:491-6.
37
38
39
40
41
42 64. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and
43 qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in
44 Japan - Are physicians and nurses at a particular risk? *PLoS One*. 2018; 13(6):e0198075.
45
46
47
48
49 65. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et
50 al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative
51 study. *J Health Popul Nutr*. 2018; 37(1):1.
52
53
54
55
56
57
58
59
60

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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 / [#2](#) Explain the scientific background and rationale for the 4-6
 rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 6
 hypotheses

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 6
 periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 6
 selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of
 exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 7-10
 confounders, and effect modifiers. Give diagnostic criteria, if
 applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 7-10
 measurement 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.

1	Bias	#9	Describe any efforts to address potential sources of bias	10,11
2				
3				
4	Study size	#10	Explain how the study size was arrived at	7
5				
6				
7	Quantitative	#11	Explain how quantitative variables were handled in the	10, 11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
10				
11				
12				
13				
14				
15	Statistical	#12a	Describe all statistical methods, including those used to control	10,11
16	methods		for confounding	
17				
18				
19				
20	Statistical	#12b	Describe any methods used to examine subgroups and	
21	methods		interactions	
22				
23				
24				
25				
26	Statistical	#12c	Explain how missing data were addressed	10
27	methods			
28				
29				
30				
31	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	
32	methods			
33				
34				
35				
36	Statistical	#12e	Describe any sensitivity analyses	
37	methods			
38				
39				
40				
41				
42	Results			
43				
44				
45	Participants	#13a	Report numbers of individuals at each stage of study—eg	12
46			numbers potentially eligible, examined for eligibility, confirmed	
47			eligible, included in the study, completing follow-up, and	
48			analysed. Give information separately for for exposed and	
49			unexposed groups if applicable.	
50				
51				
52				
53				
54				
55				
56				
57	Participants	#13b	Give reasons for non-participation at each stage	
58				
59				
60				

1	Participants	#13c	Consider use of a flow diagram	
2				
3				
4	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	12, 13
5			clinical, social) and information on exposures and potential	
6			confounders. Give information separately for exposed and	
7			unexposed groups if applicable.	
8				
9				
10				
11				
12				
13				
14	Descriptive data	#14b	Indicate number of participants with missing data for each	12
15			variable of interest	
16				
17				
18				
19	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
20				
21				
22				
23	Outcome data	#15	Report numbers of outcome events or summary measures	14, 15
24			over time. Give information separately for exposed and	
25			unexposed groups if applicable.	
26				
27				
28				
29				
30	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	14-18
31			adjusted estimates and their precision (eg, 95% confidence	
32			interval). Make clear which confounders were adjusted for and	
33			why they were included	
34				
35				
36				
37				
38				
39				
40	Main results	#16b	Report category boundaries when continuous variables were	
41			categorized	
42				
43				
44				
45	Main results	#16c	If relevant, consider translating estimates of relative risk into	
46			absolute risk for a meaningful time period	
47				
48				
49				
50				
51	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	
52			interactions, and sensitivity analyses	
53				
54				
55				
56	Discussion			
57				
58				
59				
60				

1	Key results	#18	Summarise key results with reference to study objectives	19-21
2				
3				
4	Limitations	#19	Discuss limitations of the study, taking into account sources of	21
5			potential bias or imprecision. Discuss both direction and	
6			magnitude of any potential bias.	
7				
8				
9				
10				
11				
12	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19-21
13			limitations, multiplicity of analyses, results from similar studies,	
14			and other relevant evidence.	
15				
16				
17				
18				
19	Generalisability	#21	Discuss the generalisability (external validity) of the study	
20			results	
21				
22				
23				
24				
25	Other Information			
26				
27				
28	Funding	#22	Give the source of funding and the role of the funders for the	23
29			present study and, if applicable, for the original study on which	
30			the present article is based	
31				
32				
33				
34				
35				

36 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution
37 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool
38 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59

BMJ Open

Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043050.R3
Article Type:	Original research
Date Submitted by the Author:	26-May-2021
Complete List of Authors:	Daba, Matiwas; Jimma University College of Public Health and Medical Sciences, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Markos ; Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Adorjan, Kristina; Department of Psychiatry and Psychotherapy, LMU Munich, Germany; Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany Krahl, Wolfgang ; Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany, Forensic Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tesfaye, Elias ; Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Psychiatry Yitayih, Yimenu; Jimma University College of Public Health and Medical Sciences, Psychiatry Strobl, Ralf; Ludwig-Maximilians-Universitat Munchen, Institute for Medical Information Processing, Biometrics and Epidemiology Grill, Eva; Ludwig Maximilians University Munich, Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany ; Center for International Health, Ludwig Maxmillians University, Munich, Germany
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Infectious diseases, Mental health
Keywords:	Substance misuse < PSYCHIATRY, Tuberculosis < INFECTIOUS DISEASES, INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Substance use disorders and adherence to anti-tuberculosis medications in Southwest**
6
7 **Ethiopia: A prospective cohort study**
8

9
10 Matiws Soboka^{1*,8}, Markos Tesfaye^{2,8}, Kristina Adorjan^{3,4,8}, Wolfgang Krahl^{5,8}, Elias
11
12 Tesfaye¹, Yimenu Yitayih¹, Ralf Strobl⁶, Eva Grill^{6,8}
13
14
15
16
17
18
19
20

21 *** Corresponding author:** Matiws Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma
22
23 Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany
24

25
26 **Email:** matiwos2004@yahoo.com
27

28
29 **Phone:** +251913792348
30

31 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
32

33
34 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
35

36
37 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
38

39
40 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
41

42
43 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
44

45
46 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
47

48
49 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
50

51
52 ⁸Center for International Health, Ludwig Maxmillians University, Munich, Germany
53
54
55
56
57
58
59
60

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.

1
2
3 **Conclusion:** Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-
4 TB medication. This implies the need to integrate the management for substance use disorders
5 into the existing tuberculosis treatment services.
6
7
8
9

10
11 **Keywords:** Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.
12
13

14 **Strengths and limitations**

- 15
16
17 ➤ The strengths of this study are the prospective cohort design, longitudinal data collection,
18 including patients from urban and rural health institutions, intensive training for data
19 collectors, multi-center data collection, and use of standardized instruments.
20
21
22
23
24
25 ➤ Due to social desirability, patients might minimize reporting of the amount and frequency
26 of the substances they were using.
27
28
29
30
31 ➤ Measuring adherence based on pills count may not reflect the real adherence situation,
32 since patients may not bring all leftover medications during the follow up.
33
34
35
36 ➤ Follow up and data collections have been carried out by health professionals working in
37 the respective TB clinic. As a result, their assessment of adherence might be biased.
38
39
40
41 ➤ Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
42 included in this study, and this may limit the generalizability of the result for these
43 patients.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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).

1
2
3 In Ethiopia, the prevalence of non-adherence among TB patients has been estimated to range
4 from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (13). To
5
6 counteract this, the Ethiopian has implemented Direct Observed Treatment (DOT) services in
7
8 almost all health institutions (12), but its impact on medication adherence is unclear and the
9
10 reasons for non-adherence are still poorly understood.
11
12
13

14
15 Among the reasons for non-adherence, substance use disorders have been found to play a
16
17 dominant role (8, 14-16). Substances such as alcohol, tobacco, khat, and illicit drugs are
18
19 commonly used among patients with TB (17-19). Patients with TB are also at risk of increased
20
21 morbidity, and premature mortality due to substance use disorders (20). Because, substance use
22
23 disorders such as alcohol and tobacco are associated with MDR-TB (21, 22).
24
25
26

27
28 Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids,
29
30 cathinone, and cathine cause the stimulating effect, and lead to craving and dependency (23-26).
31
32 There is evidence that khat use increases susceptibility to tuberculosis (27-31), and maybe
33
34 associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and
35
36 high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated
37
38 with non-adherence to anti-tuberculosis medications (35), probably because khat disrupts
39
40 patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia, like
41
42 Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an
43
44 important but unrecognized threat to anti-TB medication adherence. Filling the information gaps
45
46 about the effect of substance use disorders will help to improve TB treatment outcomes and
47
48 inform decision makers about the need for an integration of substance use disorder treatment in
49
50 TB control programs in the future. Therefore, the objective of this study is to assess the effect of
51
52 substance use disorders (including khat and alcohol) on adherence to anti-TB medications in
53
54
55
56
57

1
2
3 Southwest Ethiopia. Specifically, we examined the association of the most frequently used
4 substances, namely khat and/or alcohol, on adherence to guideline compatible TB treatment.
5
6
7

8 **Methods**

9 **Study area, period, and patients**

10
11
12 We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma
13 city special zone is the capital city of Jimma zone and located in the Southwestern part of
14 Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital
15 and a zonal hospital, as well as four functional health centers those currently providing services.
16
17 Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the
18 zone has more than three million inhabitants. During the period of this study, Jimma Zone had
19 112 health centers and three hospitals. Out of these government's public health facilities, 91
20 health centers and all hospitals were providing services to TB patients. In this study, data was
21 collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma
22 city, we randomly selected 2 health centers and one hospital. We also randomly selected 20
23 health centers and three hospitals from the Jimma Zone. Patients were included if they had
24 initiated anti-TB treatment within a month of start of the study at the selected health centers and
25 hospitals between October 2017 and October 2018. Patients were recruited over the first six
26 months.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Study design**

49
50
51 This study is a multicenter prospective cohort study. We did not pair exposed and non-exposed
52 patients by a certain character. Patients recruited to the cohort were interviewed on three
53
54
55
56
57
58
59
60

1
2
3 occasions, namely, baseline (starting treatment), first follow up (after 2 months), and second
4
5 follow up (at the end of six months).
6
7

8 **Sample size assumption and sampling procedure**

9

10
11 The prevalence of non-adherence among TB patients who also used khat from previous studies
12 was 62.4% (35). The prevalence of non-adherence among non khat user TB patients was 43.6%
13 (35). We have included 111 exposed (with substance use) and 111 unexposed (without
14 substance use) individuals to detect a difference of non-adherence to anti-TB medication at an
15 alpha level of 0.05 and with a power of 80% using the corrected Fleiss sample size calculation
16 [EPInfo™] (37). The total sample size was calculated considering a 20% of drop out rate and the
17 final sample size was 134 in each group which totals 268 TB patients. New TB patients who
18 were 18 years or older were recruited to participate in the study. Patients who had been on
19 treatment for more than one month, patients on re-treatment, and MDR-TB cases were not
20 included in the study.
21
22
23
24
25
26
27
28
29
30
31
32
33
34

35 **Instruments**

36

37 **Exposure variables**

38
39
40
41

42 In this study, the exposure variable is substance use disorder which includes khat and/or alcohol
43 use disorder.
44
45

46
47 *Substance use disorder:* In this study substance use disorder was defined as having khat and/or
48 alcohol use disorder. Data on tobacco, shisha, and cannabis use were collected for explorative
49 data analysis.
50
51
52
53
54
55
56
57

1
2
3 *Alcohol use disorders (AUDs)*:-Alcohol use disorder identification test (AUDIT) was used to
4 collect data on AUDs (38). The AUDIT was evaluated over a period of two decades, and
5 provides an accurate measure of risk of AUDs across gender, age, and cultures. With a cut-off
6 score of eight or more, the sensitivity, and specificity of AUDIT for AUDs was 0·90 and 0·80,
7 respectively (39). AUDIT was used in Ethiopian context and questions number two and three
8 regarding standard drinks were adapted to a more locally appropriate question (40).
9

10
11
12
13
14
15
16
17
18 *Nicotine dependence*: The Fagerstrom test for nicotine dependence (FTND) was used to assess
19 tobacco dependence. A total score of FTND ≥ 5 was considered as tobacco dependence (41). At
20 a cut-off score ≥ 5 , the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has
21 six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND
22 score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine
23 dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also
24 asked about their reasons for smoking tobacco (41).
25
26
27
28
29
30
31
32

33
34
35 *Cannabis and shisha use*: Use of both substances and their frequency were assessed.
36
37

38 *Khat use*: - Khat use was assessed by self-reported questionnaire. Since there is no standardized
39 questionnaire for khat use, patterns, and reasons of khat use were assessed by using a structured
40 questionnaire which was developed in the context of a literature review. Any consumption of
41 khat in the last one month was considered as current khat use. Frequent khat use (using khat
42 daily and 2-3 times per week) and using more than one bundle of khat per day was considered as
43 khat use disorder.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 *Social support:* Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the
4 strength of social support. The Oslo-3 total score 3-8 indicate poor social support, 9-11 indicate
5 moderate social support, and 12-14 indicate strong social support (43). The scale had been
6 validated in Ethiopia among patients with tuberculosis (44). Social support was assessed at
7 baseline, second month (at first follow up), and six month (at the completion of anti-TB
8 treatment or second follow up).
9

10
11
12 *Food insecurity:* It was assessed using the Household Food Insecurity Access Scale (HFIAS) to
13 determine whether the respondent has experienced any of the indicators of food insecurity in the
14 previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity
15 if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate
16 food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and
17 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (45). This tool had
18 been validated in Ethiopia among people living with HIV (46, 47). Food insecurity assessed at
19 baseline, second month (at first follow up), and six month (at the completion of anti-TB
20 treatment or second follow up).
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 **Data collection procedures**

40
41
42 Before starting data collection, the questionnaires were pretested on a sample (5% of the total
43 sample) of patients with TB who were on treatment at Agaro health center. Those patients who
44 participated in the pretest were not included in the main cohort study. Data were collected by
45 trained health professionals working in the respective TB clinics. Data collectors were not blind
46 to exposure status of the patients. Also, district tuberculosis focal persons and other health
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (%)	2 nd 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

1
2
3 adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs
4 throughout the whole treatment and all over the country starting from initiation to completion of
5 treatment (12).
6
7
8
9

10
11 In this study, the prevalence of non-adherence to anti-TB medication in the first month of
12 treatment was 9.7 % which is in line with a systematic review that found 10.0% of non-
13 adherence in the Amhara region (13, 54). The proportion of non-adherence to anti-TB
14 medications during the first (26.1%) and second (27.6%) follow up was slightly higher than
15 findings from South Ethiopia (24.5%) (51), Northwest Ethiopia (21.2%) (52), and Addis Ababa
16 (19.5%) (53). This might be explained by the high proportion of persons with a substance use
17 disorder in our study, in which we deliberately oversampled persons with SUD to maximize
18 power. The discrepancy may be also due to patients in our study were using substances whereas
19 in the systematic review there was no data regarding substance use.
20
21
22
23
24
25
26
27
28
29
30
31

32 In this study, the prevalence of non-adherence among patients with substance use disorder at
33 baseline, first, and second follow up was 16.4%, 41.7%, and 45.7% respectively. This is in line
34 with a study from the US (39%) (52, 55, 56).
35
36
37
38
39

40 Moreover, this study provides the evidence that substance use disorders have a significant
41 negative effect on adherence to anti-TB medications among patients with tuberculosis, which
42 supports earlier findings from previous studies that found alcohol use disorder, tobacco
43 dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and
44 Morocco (57-59). This is also comparable with retrospective studies conducted in Russia and
45 New York which found that alcohol use disorder and drug addiction were significantly
46 associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and
4 tobacco are the main factors for non-adherence to anti-TB medications (52, 56, 60). In our study,
5 patients with substance use disorder were more than two times more likely not to follow their
6 medication plan than patients without substance use disorders. This finding is in line with the
7 finding of a study conducted in US that found the risk of missing a DOT appointment was 2.6
8 times higher among patients with substance use disorder than in patients without drug
9 consumption (55).

10
11
12 In our study, khat use disorder turned out to be the most stringent factor that decreased
13 adherence. This confirms earlier findings from Yemen (61) and Ethiopia (14, 60). A plausible
14 explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which
15 may lead to missing of the DOT appointments at the health facility. Another reason may be that
16 khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is
17 known about the effect of khat on patients with tuberculosis (14), it may be considered as part of
18 a normal social interaction (61).

19
20
21 A higher level of education was associated with non-adherence to anti-TB medications in our
22 study. This result confirms the findings from Yemen that found more educated patients were
23 19% times less likely to be adherent to their medication (61). Also, a study from Ethiopia
24 showed that attending primary education was associated with non-adherence to anti-TB
25 medications (60). Our findings are contrary to previous studies which have suggested that lower
26 or no formal education decreases adherence to TB medication (13, 63). Our finding seems
27 counterintuitive. However, our results are likely to be related to findings from a study indicating
28 that persons with higher educational attainment might be reluctant to accept DOTS regimes (64).
29 Daily visits to the health facility have been reported as time consuming and probably
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 stigmatizing for patients with a job (65). In this study, being merchant was associated with poor
4 adherence to anti-TB medications. This might be due to patients miss their medications because
5 of busy working schedule, but this needs further investigation.
6
7
8
9
10
11
12
13

14 **Limitations**

15
16
17 This study has some limitations. Due to social desirability, patients might minimize reporting of
18 the amount and frequency of substance they were using. The tools used for alcohol and khat use
19 disorder are not gold-standard diagnostic for the respective disorders. Also, measuring adherence
20 based on pills count may not reflect the real adherence situation since some patients might not
21 bring all leftover medications during the follow up. Likewise, follow up and data collections
22 have been carried out by health professionals working in the respective TB clinics which might
23 have biased their assessment of adherence. However, overestimating adherence may have biased
24 our results towards a null effect and led to underestimating the effect of substance use disorders,
25 so we are confident that our estimates are conservative. The participation of district tuberculosis
26 focal persons and other health professionals in the supervision of data collection might have also
27 introduced bias.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
44 included in this study, so that the results cannot be generalized for these patients. However,
45 MDR-TB patients are under special treatment and surveillance so that including this group of
46 patients might have biased the results. Finally, we did not assess the reasons for non-adherence.
47 This should be part of a separate study going more into the details of the situation of persons
48 with khat and alcohol problems.
49
50
51
52
53
54
55
56
57

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.

Funding

1
2
3 The study was funded by Jimma University Institute of Health with the grant number of
4 IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant
5 number of 15106202/2018, and individual throughout data collection. The funders had no role in
6 this study including interpretation and preparation of the manuscript.
7
8
9
10
11
12

13 **Authors' contribution**

14
15
16 MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation.
17
18 MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the
19 manuscript.
20
21
22
23

24 **Author affiliations**

25
26
27 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.

28
29
30 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

31
32
33 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany

34
35
36 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany

37
38
39 ⁵ Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany

40
41
42 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

43
44
45 ⁷ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

46
47
48 ⁸ Center for International Health, Ludwig Maxmillians University, Munich, Germany

49 **Acknowledgment**

50
51
52 We are grateful to the study participants for sacrificing their time to participate in the study. Our
53 gratitude is extended to Jimma University for funding the project. We are also grateful to IPPG
54
55
56

1
2
3 for funding part of the project. Our gratitude also extends to Dr. Michael Odenwald, who
4 contributed money from his pocket to support the project.
5
6
7

8 **Availability of data**

9
10
11 It will be available upon official request from interested individuals or organizations.
12
13

14 **References**

- 15
16
17
18 1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-
19 NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019
20
21
22
23 2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet*
24 *Infect Dis.* 2018; 18(12):1291-3.
25
26
27
28
29 3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and
30 Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington
31 (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.
32
33
34
35
36
37 4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress
38 in care, prevention, and research: an overview in year 3 of the end TB era. *Lancet Respir Med.*
39 2018; 6(4):299-314.
40
41
42
43
44 5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016.
45
46
47 <https://apps.who.int/medicinedocs/en/d/Js23098en/> accessed on 24/07/2019.
48
49
50
51 6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-
52 Nkwanta Regional Hospital: a 2-year experience. *Int J Tuberc Lung Dis.* 2004; 8(11):1337-41.
53
54
55
56
57

- 1
2
3 7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013.
4
5 <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on 25/07/2019
6
7
- 8
9 8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al.
10 Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence,
11 default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization*.
12 2007; 85(9):703-11.
13
14
- 15
16
17
18 9. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
19 associated factors among TB patients attending at Gondar town health centers, Northwest
20 Ethiopia. *BMC Res Notes*. 2018; 11: 691.
21
22
23
- 24
25
26 10. Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant
27 tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to
28 2013. *J Glob Antimicrob Resist*. 2016; 6:102-7.
29
30
31
- 32
33
34 11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and
35 after tuberculosis treatment. *Int J Tuberc Lung Dis*. 2011; 15(7):871-85.
36
37
38
- 39
40 12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic
41 management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.
42
43
44
- 45
46 13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and
47 determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and
48 meta-analysis. *PLoS One*. 2019; 14(1):e0210422.
49
50
51
52
53
54
55
56
57

- 1
2
3 14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and
4 tuberculosis treatment outcomes, quality of life and disability, Ethiopia. *Bulletin of the World*
5
6 *Health Organization*. 2018; 96(4):243-55.
7
8
9
- 10
11 15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on
12 tuberculosis treatment outcomes: a retrospective cohort study. *Arch Public Health*. 2018; 76:45.
13
14
15
- 16 16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction
17 and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort
18 study. *Epidemiol Infect*. 2017; 145(16):3516-24.
19
20
21
22
23
- 24 17. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update.
25 *Clin Infect Dis*. 2009 ;48(1):72-82.
26
27
28
- 29 18. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in
30 the United States, 1997-2006. *Arch Intern Med*. 2009. 26;169(2):189-97
31
32
33
34
- 35 19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence
36 and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia.
37 *PloS one*. 2013; 8(9):e74406.
38
39
40
41
42
- 43 20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in
44 patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study.
45 *Clinical epidemiology*. 2014; 6:405-21.
46
47
48
49
- 50 21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al.
51 Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB
52
53
54
55
56
57

1
2
3 patients. The international journal of tuberculosis and lung disease: the official journal of the
4
5 International Union against Tuberculosis and Lung Disease. 2006; 10(5):565-70.
6
7

8
9 22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al.
10
11 Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.
12
13 Bulletin of the World Health Organization. 2013; 91(1):36-45.
14
15

16
17 23. Luqman W, Danowski TS. The use of khat (*Catha edulis*) in Yemen. Social and medical
18
19 observations. *Ann Intern Med.* 1976;85(2):246-9.
20
21

22
23 24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. *J*
24
25 *Ethnopharmacol.* 2010; 132(3):607-14.
26
27

28
29 25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. *Biomed*
30
31 *Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2004; 148(1):11-5.
32
33

34
35 26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al.
36
37 *Catha edulis* Forsk. (Khat): Evaluation of its Antidepressant-like Activity. *Pharmacognosy*
38
39 *magazine.* 2017; 13(Suppl 2):S354-s8.
40
41

42
43 27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University
44
45 Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-
46
47 Cross-Sectional Study. *Int J Bacteriol.* 2017;9840670.
48
49

50
51 28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected
52
53 adults in Northwest Ethiopia: a multicentre case-control study. *BMJ Open.* 2016; 6(4):e009058.
54
55

56
57 29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on
58
59 tuberculosis outcome in Yemen. *International journal of mycobacteriology.* 2016; 5(1):S20.
60

- 1
2
3 30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and
4 perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash
5 Valley of Afar region, Ethiopia. *BMC Public Health*. 2010; 10:187.
6
7
8
9
10
11 31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of
12 *Mycobacterium tuberculosis* infection by macrophage immune modulation? *Med Hypotheses*.
13 2014; 82(6):667-9.
14
15
16
17
18 32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-
19 Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One*. 2016;
20 11(6):e0156258.
21
22
23
24
25
26 33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations
27 among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study.
28 *J Pharm Policy Pract*. 2017; 10:36.
29
30
31
32
33
34 34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation
35 between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of
36 Saudi Arabia. *PLoS One*. 2015; 10(10):e0140245.
37
38
39
40
41
42 35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to
43 anti-tuberculosis treatment in Yemen: *JPHSR*; 2013.
44
45
46
47 36. Cox G, Rampes H. Adverse effects of khat: a review. *Advances in Psychiatric Treatment*.
48 2018; 9(6):456-63.
49
50
51
52 37. EPIInfoTM. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on
53 19/08/2019
54
55
56
57
58
59
60

1
2
3 38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
4 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

5
6
7
8 [https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1)
9 [B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1) accessed on 20/07/2019.

10
11
12
13
14 39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
15 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

16
17
18
19 40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated
20 factors among people living with HIV who are attending services in south west Ethiopia. BMC
21 research notes. 2014; 7:828.

22
23
24
25
26
27 41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for
28 nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research
29 : Gann. 1999; 90(10):1071-5.

30
31
32
33
34
35 42. Average Salary in Ethiopia. [http://www.salaryexplorer.com/salary-](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1)
36 [survey.php?loc=69&loctype=1](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1) accessed on 09/07/2019.

37
38
39
40 43. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.
41 [https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_e](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf)
42 [his/development/instruments/Manual_OSS_3.pdf](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf) , Accessed on 08/06/2019

43
44
45
46
47
48 44. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety
49 among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center,
50 WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.

- 1
2
3 45. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for
4 measurement of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.
5
6
7
8 http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on
9
10 10/01/2017
11
12
13
14 46. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity,
15 mental health and quality of life among people living with HIV commencing antiretroviral
16 treatment in Ethiopia: a cross-sectional study. *Health and quality of life outcomes*. 2016; 14:37.
17
18
19
20
21 47. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among
22 volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the
23 2008 food crisis. *The Journal of nutrition*. 2009; 139(9):1758-64.
24
25
26
27
28
29 48. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.
30 *Epidemiology*. 1999; 10(1):37-48.
31
32
33
34
35 49. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams.
36 *Epidemiology*. 2011; 22(5):745.
37
38
39
40 50. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res*
41 *Methodol*. 2008; 8:70.
42
43
44
45 51. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for
46 anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public
47 health care facilities in South Ethiopia: a cross-sectional study. *BMC Public Health*. 2017;
48 17(1):269.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 52. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
4 associated factors among TB patients attending at Gondar town health centers, Northwest
5 Ethiopia. *BMC research notes*. 2018; 11(1):691.
6
7
8
9
10
11 53. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The
12 Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-
13 Adherence in Addis Ababa, Ethiopia. *Ethiopian journal of health sciences*. 2017; 27(5):447-58.
14
15
16
17
18 54. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis
19 treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. *PLoS*
20 *One*. 2013; 8(11):e78791.
21
22
23
24
25
26 55. Ricks PM, Hershov RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A
27 randomized trial comparing standard outcomes in two treatment models for substance users with
28 tuberculosis. *Int J Tuberc Lung Dis*. 2015; 19(3):326-32.
29
30
31
32
33
34 56. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB
35 treatment adherence: a qualitative study on DOTS service in public health centers in Addis
36 Ababa, Ethiopia. *BMC Public Health*. 2018; 18(1):462.
37
38
39
40
41
42 57. Hasker E, Khodjikhhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ,
43 et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and
44 why do they default? *BMC Infect Dis*. 2008; 8:97.
45
46
47
48
49
50 58. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of
51 treatment completion and fatality among tuberculosis patients in Spain. *Int J Tuberc Lung Dis*.
52 2004; 8(4):458-64.
53
54
55
56
57

- 1
2
3 59. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk
4 factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in
5 Morocco. *BMC Public Health*. 2011; 11:140.
6
7
8
9
10
11 60. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and
12 treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. *BMC*
13 *research notes*. 2015; 8:503.
14
15
16
17
18 61. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting
19 patients' compliance to anti-tuberculosis treatment in Yemen. *Journal of Pharmaceutical Health*
20 *Services Research*. 2013; 4(2):115-22.
21
22
23
24
25
26 62. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary
27 Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia:
28 Implications for Tuberculosis Control. *PLoS One*. 2016; 11(2):e0149453.
29
30
31
32
33
34 63. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing
35 completion of treatment among pulmonary tuberculosis patients. *Patient Prefer Adherence*. 2019;
36 13:491-6.
37
38
39
40
41
42 64. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and
43 qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in
44 Japan - Are physicians and nurses at a particular risk? *PLoS One*. 2018; 13(6):e0198075.
45
46
47
48
49 65. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et
50 al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative
51 study. *J Health Popul Nutr*. 2018; 37(1):1.
52
53
54
55
56
57
58
59
60

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			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 / [#2](#) Explain the scientific background and rationale for the 4-6
 rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 6
 hypotheses

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 6
 periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 6
 selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of
 exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 7-10
 confounders, and effect modifiers. Give diagnostic criteria, if
 applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 7-10
 measurement 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.

1	Bias	#9	Describe any efforts to address potential sources of bias	10,11
2				
3				
4	Study size	#10	Explain how the study size was arrived at	7
5				
6				
7	Quantitative	#11	Explain how quantitative variables were handled in the	10, 11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
10				
11				
12				
13				
14				
15	Statistical	#12a	Describe all statistical methods, including those used to control	10,11
16	methods		for confounding	
17				
18				
19				
20	Statistical	#12b	Describe any methods used to examine subgroups and	
21	methods		interactions	
22				
23				
24				
25				
26	Statistical	#12c	Explain how missing data were addressed	10
27	methods			
28				
29				
30				
31	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	
32	methods			
33				
34				
35				
36	Statistical	#12e	Describe any sensitivity analyses	
37	methods			
38				
39				
40				
41				
42	Results			
43				
44				
45	Participants	#13a	Report numbers of individuals at each stage of study—eg	12
46			numbers potentially eligible, examined for eligibility, confirmed	
47			eligible, included in the study, completing follow-up, and	
48			analysed. Give information separately for for exposed and	
49			unexposed groups if applicable.	
50				
51				
52				
53				
54				
55				
56				
57	Participants	#13b	Give reasons for non-participation at each stage	
58				
59				
60				

1	Participants	#13c	Consider use of a flow diagram	
2				
3				
4	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	12, 13
5			clinical, social) and information on exposures and potential	
6			confounders. Give information separately for exposed and	
7			unexposed groups if applicable.	
8				
9				
10				
11				
12				
13				
14	Descriptive data	#14b	Indicate number of participants with missing data for each	12
15			variable of interest	
16				
17				
18				
19	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
20				
21				
22				
23	Outcome data	#15	Report numbers of outcome events or summary measures	14, 15
24			over time. Give information separately for exposed and	
25			unexposed groups if applicable.	
26				
27				
28				
29				
30	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	14-18
31			adjusted estimates and their precision (eg, 95% confidence	
32			interval). Make clear which confounders were adjusted for and	
33			why they were included	
34				
35				
36				
37				
38				
39				
40	Main results	#16b	Report category boundaries when continuous variables were	
41			categorized	
42				
43				
44				
45	Main results	#16c	If relevant, consider translating estimates of relative risk into	
46			absolute risk for a meaningful time period	
47				
48				
49				
50				
51	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	
52			interactions, and sensitivity analyses	
53				
54				
55				
56	Discussion			
57				
58				
59				
60				

1	Key results	#18	Summarise key results with reference to study objectives	19-21
2				
3				
4	Limitations	#19	Discuss limitations of the study, taking into account sources of	21
5			potential bias or imprecision. Discuss both direction and	
6			magnitude of any potential bias.	
7				
8				
9				
10				
11				
12	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19-21
13			limitations, multiplicity of analyses, results from similar studies,	
14			and other relevant evidence.	
15				
16				
17				
18				
19	Generalisability	#21	Discuss the generalisability (external validity) of the study	
20			results	
21				
22				
23				
24				
25	Other Information			
26				
27				
28	Funding	#22	Give the source of funding and the role of the funders for the	23
29			present study and, if applicable, for the original study on which	
30			the present article is based	
31				
32				
33				
34				
35				

36 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution
37 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool
38 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59

BMJ Open

Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043050.R4
Article Type:	Original research
Date Submitted by the Author:	31-May-2021
Complete List of Authors:	Daba, Mawitaw; Jimma University College of Public Health and Medical Sciences, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tsefaye, Markos ; Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Adorjan, Kristina; Department of Psychiatry and Psychotherapy, LMU Munich, Germany; Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany Krahl, Wolfgang ; Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany, Forensic Psychiatry; Center for International Health, Ludwig Maxmillians University, Munich, Germany Tsefaye, Elias ; Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Psychiatry Yitayih, Yimenu; Jimma University College of Public Health and Medical Sciences, Psychiatry Strobl, Ralf; Ludwig-Maximilians-Universitat Munchen, Institute for Medical Information Processing, Biometrics and Epidemiology Grill, Eva; Ludwig Maximilians University Munich, Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany ; Center for International Health, Ludwig Maxmillians University, Munich, Germany
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Infectious diseases, Mental health
Keywords:	Substance misuse < PSYCHIATRY, Tuberculosis < INFECTIOUS DISEASES, INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5 **Substance use disorders and adherence to anti-tuberculosis medications in Southwest**
6
7 **Ethiopia: A prospective cohort study**
8

9
10 Matiws Soboka^{1*,7}, Markos Tesfaye^{2,7}, Kristina Adorjan^{3,4,7}, Wolfgang Krahl^{5,7}, Elias
11
12 Tesfaye¹, Yimenu Yitayih¹, Ralf Strobl⁶, Eva Grill^{6,7}
13
14
15
16
17
18
19
20

21 *** Corresponding author:** Matiws Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma
22
23 Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany
24

25
26 **Email:** matiwos2004@yahoo.com
27

28
29 **Phone:** +251913792348
30

31 ¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.
32

33
34 ² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
35

36
37 ³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany
38

39
40 ⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
41

42
43 ⁵Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
44

45
46 ⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany
47

48
49 ⁷Center for International Health, Ludwig Maxmillians University, Munich, Germany
50
51
52
53
54
55
56
57

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.

1
2
3 **Conclusion:** Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-
4 TB medication. This implies the need to integrate the management for substance use disorders
5 into the existing tuberculosis treatment services.
6
7
8
9

10
11 **Keywords:** Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.
12
13

14 **Strengths and limitations**

- 15
16
17 ➤ The strengths of this study are the prospective cohort design, longitudinal data collection,
18 including patients from urban and rural health institutions, intensive training for data
19 collectors, multi-center data collection, and use of standardized instruments.
20
21
22
23
24
25 ➤ Due to social desirability, patients might minimize reporting of the amount and frequency
26 of the substances they were using.
27
28
29
30
31 ➤ Measuring adherence based on pills count may not reflect the real adherence situation,
32 since patients may not bring all leftover medications during the follow up.
33
34
35
36 ➤ Follow up and data collections have been carried out by health professionals working in
37 the respective TB clinic. As a result, their assessment of adherence might be biased.
38
39
40
41 ➤ Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
42 included in this study, and this may limit the generalizability of the result for these
43 patients.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 inhabitants (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).

1
2
3 In Ethiopia, the prevalence of non-adherence among TB patients has been estimated to range
4 from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (13). To
5
6 counteract this, the Ethiopian has implemented Direct Observed Treatment (DOT) services in
7
8 almost all health institutions (12), but its impact on medication adherence is unclear and the
9
10 reasons for non-adherence are still poorly understood.
11
12
13

14
15 Among the reasons for non-adherence, substance use disorders have been found to play a
16
17 dominant role (8, 14-16). Substances such as alcohol, tobacco, khat, and illicit drugs are
18
19 commonly used among patients with TB (17-19). Patients with TB are also at risk of increased
20
21 morbidity, and premature mortality due to substance use disorders (20). Because, substance use
22
23 disorders such as alcohol and tobacco are associated with MDR-TB (21, 22).
24
25
26

27
28 Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids,
29
30 cathinone, and cathine cause the stimulating effect, and lead to craving and dependency (23-26).
31
32 There is evidence that khat use increases susceptibility to tuberculosis (27-31), and maybe
33
34 associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and
35
36 high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated
37
38 with non-adherence to anti-tuberculosis medications (35), probably because khat disrupts
39
40 patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia, like
41
42 Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an
43
44 important but unrecognized threat to anti-TB medication adherence. Filling the information gaps
45
46 about the effect of substance use disorders will help to improve TB treatment outcomes and
47
48 inform decision makers about the need for an integration of substance use disorder treatment in
49
50 TB control programs in the future. Therefore, the objective of this study is to assess the effect of
51
52 substance use disorders (including khat and alcohol) on adherence to anti-TB medications in
53
54
55
56
57

1
2
3 Southwest Ethiopia. Specifically, we examined the association of the most frequently used
4 substances, namely khat and/or alcohol, on adherence to guideline compatible TB treatment.
5
6
7

8 **Methods**

9 **Study area, period, and patients**

10
11
12 We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma
13 city special zone is the capital city of Jimma zone and located in the Southwestern part of
14 Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital
15 and a zonal hospital, as well as four functional health centers those currently providing services.
16
17 Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the
18 zone has more than three million inhabitants. During the period of this study, Jimma Zone had
19 112 health centers and three hospitals. Out of these government's public health facilities, 91
20 health centers and all hospitals were providing services to TB patients. In this study, data was
21 collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma
22 city, we randomly selected 2 health centers and one hospital. We also randomly selected 20
23 health centers and three hospitals from the Jimma Zone. Patients were included if they had
24 initiated anti-TB treatment within a month of start of the study at the selected health centers and
25 hospitals between October 2017 and October 2018. Patients were recruited over the first six
26 months. Follow-ups were done at the end of two and six months of treatment.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Study design**

49
50
51 This study is a multicenter prospective cohort study. We did not pair exposed and non-exposed
52 patients by a certain character. Patients recruited to the cohort were interviewed on three
53
54
55
56
57

1
2
3 occasions, namely, baseline (starting treatment), first follow up (after 2 months), and second
4
5 follow up (at the end of six months).
6
7

8 **Sample size assumption and sampling procedure**

9

10
11 In Ethiopia and other African countries, we could not find a study done regarding substance use
12 disorders (alcohol, tobacco, cannabis, amphetamine and others) and adherence to anti-TB. So,
13 we were forced to calculate the sample based on the proportion of adherence to anti-TB among
14 khat users TB patients. The prevalence of non-adherence among TB patients who also used khat
15 from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user
16 TB patients was 43·6% (35). We have included 111 exposed (with substance use) and 111
17 unexposed (without substance use) individuals to detect a difference of non-adherence to anti-TB
18 medication at an alpha level of 0·05 and with a power of 80% using the corrected Fleiss sample
19 size calculation [EPIInfo™] (37). The total sample size was calculated considering a 20% of drop
20 out rate and the final sample size was 134 in each group which totals 268 TB patients. New TB
21 patients who were 18 years or older were recruited to participate in the study. Patients who had
22 been on treatment for more than one month, patients on re-treatment, and MDR-TB cases were
23 not included in the study.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **Instruments**

43

44 **Exposure variables**

45

46 In this study, the exposure variable is substance use disorder which includes khat and/or alcohol
47 use disorder.
48
49
50
51
52
53
54
55
56
57

1
2
3 *Substance use disorder*: In this study substance use disorder was defined as having khat and/or
4 alcohol use disorder. Data on tobacco, shisha, and cannabis use were collected for explorative
5 data analysis.
6
7
8

9
10
11 *Alcohol use disorders (AUDs)*:-Alcohol use disorder identification test (AUDIT) was used to
12 collect data on AUDs (38). The AUDIT was evaluated over a period of two decades, and
13 provides an accurate measure of risk of AUDs across gender, age, and cultures. With a cut-off
14 score of eight or more, the sensitivity, and specificity of AUDIT for AUDs was 0·90 and 0·80,
15 respectively (39). AUDIT was used in Ethiopian context and questions number two and three
16 regarding standard drinks were adapted to a more locally appropriate question (40).
17
18
19

20
21
22 *Nicotine dependence*: The Fagerstrom test for nicotine dependence (FTND) was used to assess
23 tobacco dependence. A total score of FTND ≥ 5 was considered as tobacco dependence (41). At
24 a cut-off score ≥ 5 , the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has
25 six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND
26 score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine
27 dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also
28 asked about their reasons for smoking tobacco (41).
29
30
31
32
33
34
35
36
37
38
39
40
41

42 *Cannabis and shisha use*: Use of both substances and their frequency were assessed.
43
44

45 *Khat use*: - Khat use was assessed by self-reported questionnaire. Since there is no standardized
46 questionnaire for khat use, patterns, and reasons of khat use were assessed by using a structured
47 questionnaire which was developed in the context of a literature review. Any consumption of
48 khat in the last one month was considered as current khat use.
49
50
51
52
53
54
55
56
57

1
2
3 In this study, frequent khat use (using khat daily and 2-3 times per week) and using more than
4 one bundle of khat per day was considered as khat use disorder. The term 'khat use disorder' is
5
6 also supported by previous study (42).
7
8
9

10 **Outcome variable**

11
12
13
14 *Adherence:* Adherence status of tuberculosis patients was assessed by Direct Observed
15 Treatment (DOT) (based on missing appointments) and pills counts. In this study, adherence is
16 defined as taking medication regularly and attending follow-up according to appointments and
17 national guideline for tuberculosis in Ethiopia (12). In this study, non-adherence is defined as
18 missing at least one follow-up appointment during DOT. Non-adherence during intensive phase
19 is defined as missing at least one dose of the prescribed anti-TB medication and noted separately.
20
21 Adherence was assessed at baseline (beginning of intensive phase), at second month (end of
22 intensive phase), and at end of 6 month (end of continuation phase).
23
24
25
26
27
28
29
30
31
32

33 **Explanatory variables**

34
35
36 *Socio-demographic variables:* Age, sex, marital status, level of education, religion, ethnicity,
37 income, household size, occupation, place of residence, and living conditions were assessed
38 using a structured questionnaire. Income was categorized considering that the minimum monthly
39 wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67
40 Euros) (43). Then the monthly income of each patient was multiplied by 12 months to obtain the
41 annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).
42
43
44
45
46
47
48
49
50

51 *Disease related factors:* Types of TB diagnosis (smear positive, smear negative, extrapulmonary
52 TB, and MDR-TB) were collected from patients' charts.
53
54
55
56
57

1
2
3 *Comorbidities:* All confirmed diagnoses of HIV, previous mental illness, hypertension, and
4 diabetes mellitus were collected from patients' charts.
5
6
7

8
9 *Social support:* Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the
10 strength of social support. The Oslo-3 total score 3-8 indicate poor social support, 9-11 indicate
11 moderate social support, and 12-14 indicate strong social support (44). The scale had been
12 validated in Ethiopia among patients with tuberculosis (45). Social support was assessed at
13 baseline, second month (at first follow up), and six month (at the completion of anti-TB
14 treatment or second follow up).
15
16
17
18
19
20
21
22

23 *Food insecurity:* It was assessed using the Household Food Insecurity Access Scale (HFIAS) to
24 determine whether the respondent has experienced any of the indicators of food insecurity in the
25 previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity
26 if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate
27 food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and
28 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (46). This tool had
29 been validated in Ethiopia among people living with HIV (47, 48). Food insecurity assessed at
30 baseline, second month (at first follow up), and six month (at the completion of anti-TB
31 treatment or second follow up).
32
33
34
35
36
37
38
39
40
41
42
43
44

45 **Data collection procedures**

46
47
48 Before starting data collection, the questionnaires were pretested on a sample (5% of the total
49 sample) of patients with TB who were on treatment at Agaro health center. Those patients who
50 participated in the pretest were not included in the main cohort study. Data were collected by
51 trained health professionals working in the respective TB clinics. Data collectors were not blind
52
53
54
55
56
57
58
59
60

1
2
3 to exposure status of the patients. Also, district tuberculosis focal persons and other health
4 professionals specifically trained for this purpose participated in the supervision of data
5 collection.
6
7
8
9

10 **Data analysis**

11
12
13
14 Data were entered to Epi Data (version 3.1) and analyzed using R studio (1.2.1335). Missing
15 values of income were excluded from the analysis. Participants' characteristics and study
16 variables were presented using descriptive statistics. Generalized linear model was used to
17 examine the longitudinal effect of khat and alcohol use disorders on medication adherence
18 (binary outcome). We used an intercept only model to investigate the trajectory of adherence
19 over time (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat
20 and alcohol use disorders on adherence without adjusting for covariates, model 2 investigated the
21 longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates.
22 Model fit was examined with the Bayesian Information Criterion (BIC).
23
24
25
26
27
28
29
30
31
32
33
34

35
36 The covariate selection was based on a directed acyclic graph (DAG). DAGs are analytical
37 method for visualizing hypotheses about causal relationships between exposure (substance use
38 disorders) and outcome (adherence) (49, 50). This approach has been shown to yield valid
39 adjustment sets of variables and to avoid bias (51).
40
41
42
43
44

45 **Ethical considerations**

46
47
48
49 Ethical clearance was obtained from the Ethical Review Board of Jimma University
50 (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written
51 informed consent was obtained from each participant. The anonymity of the study participants
52 was kept at all stages of data processing and write-up of the manuscript. Patients who had
53
54
55
56
57

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 (%)	2 nd 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

1
2
3 throughout the whole treatment and all over the country starting from initiation to completion of
4
5 treatment (12).
6
7

8
9 In this study, the prevalence of non-adherence to anti-TB medication in the first month of
10
11 treatment was 9.7 % which is in line with a systematic review that found 10.0% of non-
12
13 adherence in the Amhara region (13, 55). The proportion of non-adherence to anti-TB
14
15 medications during the first (26.1%) and second (27.6%) follow up was slightly higher than
16
17 findings from South Ethiopia (24.5%) (52), Northwest Ethiopia (21.2%) (53), and Addis Ababa
18
19 (19.5%) (54). This might be explained by the high proportion of persons with a substance use
20
21 disorder in our study, in which we deliberately oversampled persons with SUD to maximize
22
23 power. The discrepancy may be also due to patients in our study were using substances whereas
24
25 in the systematic review there was no data regarding substance use.
26
27
28
29

30
31 In this study, the prevalence of non-adherence among patients with substance use disorder at
32
33 baseline, first, and second follow up was 16.4%, 41.7%, and 45.7% respectively. This is in line
34
35 with a study from the US (39%) (53, 56, 57).
36
37

38
39 Moreover, this study provides the evidence that substance use disorders have a significant
40
41 negative effect on adherence to anti-TB medications among patients with tuberculosis, which
42
43 supports earlier findings from previous studies that found alcohol use disorder, tobacco
44
45 dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and
46
47 Morocco (58-60). This is also comparable with retrospective studies conducted in Russia and
48
49 New York which found that alcohol use disorder and drug addiction were significantly
50
51 associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study
52
53 is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and
54
55
56
57
58
59
60

1
2
3 tobacco are the main factors for non-adherence to anti-TB medications (53, 57, 61). In our study,
4 patients with substance use disorder were more than two times more likely not to follow their
5 medication plan than patients without substance use disorders. This finding is in line with the
6 finding of a study conducted in US that found the risk of missing a DOT appointment was 2.6
7 times higher among patients with substance use disorder than in patients without drug
8 consumption (56).

9
10 In our study, khat use disorder turned out to be the most stringent factor that decreased
11 adherence. This confirms earlier findings from Yemen (62) and Ethiopia (14, 61). A plausible
12 explanation is that khat chewing disrupts night sleep (63) causing patients to oversleep which
13 may lead to missing of the DOT appointments at the health facility. Another reason may be that
14 khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is
15 known about the effect of khat on patients with tuberculosis (14), it may be considered as part of
16 a normal social interaction (62).

17
18 A higher level of education was associated with non-adherence to anti-TB medications in our
19 study. This result confirms the findings from Yemen that found more educated patients were
20 19% times less likely to be adherent to their medication (62). Also, a study from Ethiopia
21 showed that attending primary education was associated with non-adherence to anti-TB
22 medications (61). Our findings are contrary to previous studies which have suggested that lower
23 or no formal education decreases adherence to TB medication (13, 64). Our finding seems
24 counterintuitive. However, our results are likely to be related to findings from a study indicating
25 that persons with higher educational attainment might be reluctant to accept DOTS regimes (65).
26 Daily visits to the health facility have been reported as time consuming and probably
27 stigmatizing for patients with a job (66). In this study, being merchant was associated with poor

1
2
3 adherence to anti-TB medications. This might be due to patients miss their medications because
4
5 of busy working schedule, but this needs further investigation.
6
7

8 **Limitations**

9
10
11 This study has some limitations. Due to social desirability, patients might minimize reporting of
12
13 the amount and frequency of substance they were using. The tools used for alcohol and khat use
14
15 disorder are not gold-standard diagnostic for the respective disorders. Also, measuring adherence
16
17 based on pills count may not reflect the real adherence situation since some patients might not
18
19 bring all leftover medications during the follow up. Likewise, follow up and data collections
20
21 have been carried out by health professionals working in the respective TB clinics which might
22
23 have biased their assessment of adherence. However, overestimating adherence may have biased
24
25 our results towards a null effect and led to underestimating the effect of substance use disorders,
26
27 so we are confident that our estimates are conservative. The participation of district tuberculosis
28
29 focal persons and other health professionals in the supervision of data collection might have also
30
31 introduced bias.
32
33
34
35
36
37

38 Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not
39
40 included in this study, so that the results cannot be generalized for these patients. However,
41
42 MDR-TB patients are under special treatment and surveillance so that including this group of
43
44 patients might have biased the results. Finally, we did not assess the reasons for non-adherence.
45
46 This should be part of a separate study going more into the details of the situation of persons
47
48 with khat and alcohol problems.
49
50
51
52
53
54
55
56
57
58
59
60

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.

Funding

The study was funded by Jimma University Institute of Health with the grant number of IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant number of 15106202/2018, and individual throughout data collection. The funders had no role in this study including interpretation and preparation of the manuscript.

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.

Author affiliations

¹ Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.

² Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

³ Department of Psychiatry and Psychotherapy, LMU Munich, Germany

⁴ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany

⁵ Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany

⁶ Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

⁷ Center for International Health, Ludwig Maxmillians University, Munich, Germany

Acknowledgment

We are grateful to the study participants for sacrificing their time to participate in the study. Our gratitude is extended to Jimma University for funding the project. We are also grateful to IPPG for funding part of the project. Our gratitude also extends to Dr. Michael Odenwald, who contributed money from his pocket to support the project.

Availability of data

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

References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019
2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet Infect Dis.* 2018; 18(12):1291-3.
3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.
4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. *Lancet Respir Med.* 2018; 6(4):299-314.
5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016. <https://apps.who.int/medicinedocs/en/d/Js23098en/> accessed on 24/07/2019.

- 1
2
3 6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-
4 Nkwanta Regional Hospital: a 2-year experience. *Int J Tuberc Lung Dis.* 2004; 8(11):1337-41.
5
6
- 7
8 7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013.
9
10 <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on 25/07/2019
11
12
- 13
14 8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al.
15
16 Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence,
17
18 default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization.*
19
20 2007; 85(9):703-11.
21
22
- 23
24 9. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
25
26 associated factors among TB patients attending at Gondar town health centers, Northwest
27
28 Ethiopia. *BMC Res Notes.* 2018; 11: 691.
29
30
- 31
32 10. Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant
33
34 tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to
35
36 2013. *J Glob Antimicrob Resist.* 2016; 6:102-7.
37
38
- 39
40 11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after
41
42 tuberculosis treatment. *Int J Tuberc Lung Dis.* 2011; 15(7):871-85.
43
44
- 45
46 12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic
47
48 management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.
49
- 50
51 13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and
52
53 determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and
54
55 meta-analysis. *PLoS One.* 2019; 14(1):e0210422.
56
57

- 1
2
3 14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis
4 treatment outcomes, quality of life and disability, Ethiopia. *Bulletin of the World Health*
5 *Organization*. 2018; 96(4):243-55.
6
7
- 8
9
10 15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on
11 tuberculosis treatment outcomes: a retrospective cohort study. *Arch Public Health*. 2018; 76:45.
12
13
- 14
15 16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction and
16 alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort study.
17 *Epidemiol Infect*. 2017; 145(16):3516-24.
18
19
- 20
21 17. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update.
22 *Clin Infect Dis*. 2009 ;48(1):72-82.
23
24
- 25
26 18. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in
27 the United States, 1997-2006. *Arch Intern Med*. 2009. 26;169(2):189-97
28
29
- 30
31 19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence and
32 correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia. *PloS*
33 *one*. 2013; 8(9):e74406.
34
35
- 36
37 20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in
38 patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study.
39 *Clinical epidemiology*. 2014; 6:405-21.
40
41
- 42
43 21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al. Alcohol
44 and drug use disorders, HIV status and drug resistance in a sample of Russian TB patients. *The*
45
46
47
48
49
50
51
52
53
54
55
56
57

1
2
3 international journal of tuberculosis and lung disease: the official journal of the International
4 Union against Tuberculosis and Lung Disease. 2006; 10(5):565-70.
5
6

7
8 22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al.
9 Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.
10 Bulletin of the World Health Organization. 2013; 91(1):36-45.
11
12
13

14
15 23. Luqman W, Danowski TS. The use of khat (*Catha edulis*) in Yemen. Social and medical
16 observations. *Ann Intern Med*. 1976;85(2):246-9.
17
18
19

20
21 24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. *J*
22 *Ethnopharmacol*. 2010; 132(3):607-14.
23
24
25

26
27 25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. *Biomed Pap*
28 *Med Fac Univ Palacky Olomouc Czech Repub*. 2004; 148(1):11-5.
29
30
31

32
33 26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al. *Catha*
34 *edulis* Forsk. (Khat): Evaluation of its Antidepressant-like Activity. *Pharmacognosy magazine*.
35 2017; 13(Suppl 2):S354-s8.
36
37
38

39
40 27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University
41 Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-
42 Cross-Sectional Study. *Int J Bacteriol*. 2017;9840670.
43
44
45

46
47 28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected
48 adults in Northwest Ethiopia: a multicentre case-control study. *BMJ Open*. 2016; 6(4):e009058.
49
50
51

52
53 29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on
54 tuberculosis outcome in Yemen. *International journal of mycobacteriology*. 2016; 5(1):S20.
55
56
57

- 1
2
3 30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and
4 perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash
5 Valley of Afar region, Ethiopia. *BMC Public Health*. 2010; 10:187.
6
7
8
9
10
11 31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of
12 *Mycobacterium tuberculosis* infection by macrophage immune modulation? *Med Hypotheses*.
13 2014; 82(6):667-9.
14
15
16
17
18 32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-
19 Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One*. 2016;
20 11(6):e0156258.
21
22
23
24
25
26 33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations among
27 cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study. *J*
28 *Pharm Policy Pract*. 2017; 10:36.
29
30
31
32
33
34 34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation between
35 Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of Saudi
36 Arabia. *PLoS One*. 2015; 10(10):e0140245.
37
38
39
40
41
42 35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-
43 tuberculosis treatment in Yemen: *JPHSR*; 2013.
44
45
46
47 36. Cox G, Rampes H. Adverse effects of khat: a review. *Advances in Psychiatric Treatment*.
48 2018; 9(6):456-63.
49
50
51
52 37. EPIInfoTM. <http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/> accessed on
53 19/08/2019
54
55
56
57
58
59
60

1
2
3 38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
4 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

5
6
7
8 [https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1)
9 [B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1) accessed on 20/07/2019.

10
11
12
13
14 39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders
15 Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

16
17
18
19 40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated factors
20 among people living with HIV who are attending services in south west Ethiopia. BMC research
21 notes. 2014; 7:828.

22
23
24
25
26
27 41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for
28 nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research
29 : Gann. 1999; 90(10):1071-5.

30
31
32
33
34
35 42. Duresso SW, Matthews AJ, Ferguson SG, Bruno R. Is khat use disorder a valid diagnostic
36 entity? Addiction. 2016; 111(9):1666-76.

37
38
39
40 43. Average Salary in Ethiopia. [http://www.salaryexplorer.com/salary-](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1)
41 [survey.php?loc=69&loctype=1](http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1) accessed on 09/07/2019.

42
43
44
45 44. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.
46 [https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_e](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf)
47 [his/development/instruments/Manual_OSS_3.pdf](https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf) , Accessed on 08/06/2019

- 1
2
3 45. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety among
4 patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center,
5 WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.
6
7
8
9
10
11 46. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement
12 of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.
13
14
15
16 http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on
17
18 10/01/2017
19
20
21 47. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity,
22 mental health and quality of life among people living with HIV commencing antiretroviral
23 treatment in Ethiopia: a cross-sectional study. Health and quality of life outcomes. 2016; 14:37.
24
25
26
27
28
29 48. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among volunteer
30 AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the 2008 food
31 crisis. The Journal of nutrition. 2009; 139(9):1758-64.
32
33
34
35
36
37 49. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.
38 Epidemiology. 1999; 10(1):37-48.
39
40
41
42 50. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams.
43 Epidemiology. 2011; 22(5):745.
44
45
46
47
48 51. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol.
49 2008; 8:70.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 52. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for anti-
4 tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public health
5 care facilities in South Ethiopia: a cross-sectional study. *BMC Public Health*. 2017; 17(1):269.
6
7
8
9
10
11 53. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and
12 associated factors among TB patients attending at Gondar town health centers, Northwest
13 Ethiopia. *BMC research notes*. 2018; 11(1):691.
14
15
16
17
18 54. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The
19 Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-
20 Adherence in Addis Ababa, Ethiopia. *Ethiopian journal of health sciences*. 2017; 27(5):447-58.
21
22
23
24
25
26 55. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis treatment
27 and determinant factors among patients with tuberculosis in northwest Ethiopia. *PLoS One*.
28 2013; 8(11):e78791.
29
30
31
32
33
34 56. Ricks PM, Hershov RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A randomized
35 trial comparing standard outcomes in two treatment models for substance users with
36 tuberculosis. *Int J Tuberc Lung Dis*. 2015; 19(3):326-32.
37
38
39
40
41
42 57. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB
43 treatment adherence: a qualitative study on DOTS service in public health centers in Addis
44 Ababa, Ethiopia. *BMC Public Health*. 2018; 18(1):462.
45
46
47
48
49
50 58. Hasker E, Khodjikhhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ, et
51 al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and
52 why do they default? *BMC Infect Dis*. 2008; 8:97.
53
54
55
56
57
58
59
60

- 1
2
3 59. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of
4 treatment completion and fatality among tuberculosis patients in Spain. *Int J Tuberc Lung Dis.*
5
6 2004; 8(4):458-64.
7
8
9
10
11 60. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk factors
12 for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco.
13 *BMC Public Health.* 2011; 11:140.
14
15
16
17
18 61. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and
19 treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. *BMC*
20 *research notes.* 2015; 8:503.
21
22
23
24
25
26 62. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting patients'
27 compliance to anti-tuberculosis treatment in Yemen. *Journal of Pharmaceutical Health Services*
28 *Research.* 2013; 4(2):115-22.
29
30
31
32
33
34 63. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary
35 Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia:
36 Implications for Tuberculosis Control. *PLoS One.* 2016; 11(2):e0149453.
37
38
39
40
41
42 64. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing completion of
43 treatment among pulmonary tuberculosis patients. *Patient Prefer Adherence.* 2019; 13:491-6.
44
45
46
47 65. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and qualitative
48 methods in investigating risk factors for lost to follow-up for tuberculosis treatment in Japan -
49 Are physicians and nurses at a particular risk? *PLoS One.* 2018; 13(6):e0198075.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 66. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et al.
4 Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study. J
5 Health Popul Nutr. 2018; 37(1):1.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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 / [#2](#) Explain the scientific background and rationale for the 4-6
rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 6
hypotheses

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 6
periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 6
selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of
exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 7-10
confounders, and effect modifiers. Give diagnostic criteria, if
applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 7-10
measurement 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.

1	Bias	#9	Describe any efforts to address potential sources of bias	10,11
2				
3				
4	Study size	#10	Explain how the study size was arrived at	7
5				
6				
7	Quantitative	#11	Explain how quantitative variables were handled in the	10, 11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
10				
11				
12				
13				
14				
15	Statistical	#12a	Describe all statistical methods, including those used to control	10,11
16	methods		for confounding	
17				
18				
19				
20	Statistical	#12b	Describe any methods used to examine subgroups and	
21	methods		interactions	
22				
23				
24				
25				
26	Statistical	#12c	Explain how missing data were addressed	10
27	methods			
28				
29				
30				
31	Statistical	#12d	If applicable, explain how loss to follow-up was addressed	
32	methods			
33				
34				
35				
36	Statistical	#12e	Describe any sensitivity analyses	
37	methods			
38				
39				
40				
41				
42	Results			
43				
44				
45	Participants	#13a	Report numbers of individuals at each stage of study—eg	12
46			numbers potentially eligible, examined for eligibility, confirmed	
47			eligible, included in the study, completing follow-up, and	
48			analysed. Give information separately for for exposed and	
49			unexposed groups if applicable.	
50				
51				
52				
53				
54				
55				
56				
57	Participants	#13b	Give reasons for non-participation at each stage	
58				
59				
60				

1	Participants	#13c	Consider use of a flow diagram	
2				
3				
4	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	12, 13
5			clinical, social) and information on exposures and potential	
6			confounders. Give information separately for exposed and	
7			unexposed groups if applicable.	
8				
9				
10				
11				
12				
13				
14	Descriptive data	#14b	Indicate number of participants with missing data for each	12
15			variable of interest	
16				
17				
18				
19	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
20				
21				
22				
23	Outcome data	#15	Report numbers of outcome events or summary measures	14, 15
24			over time. Give information separately for exposed and	
25			unexposed groups if applicable.	
26				
27				
28				
29				
30	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	14-18
31			adjusted estimates and their precision (eg, 95% confidence	
32			interval). Make clear which confounders were adjusted for and	
33			why they were included	
34				
35				
36				
37				
38				
39				
40	Main results	#16b	Report category boundaries when continuous variables were	
41			categorized	
42				
43				
44				
45	Main results	#16c	If relevant, consider translating estimates of relative risk into	
46			absolute risk for a meaningful time period	
47				
48				
49				
50				
51	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	
52			interactions, and sensitivity analyses	
53				
54				
55				
56	Discussion			
57				
58				
59				
60				

1	Key results	#18	Summarise key results with reference to study objectives	19-21
2				
3				
4	Limitations	#19	Discuss limitations of the study, taking into account sources of	21
5			potential bias or imprecision. Discuss both direction and	
6			magnitude of any potential bias.	
7				
8				
9				
10				
11				
12	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19-21
13			limitations, multiplicity of analyses, results from similar studies,	
14			and other relevant evidence.	
15				
16				
17				
18				
19	Generalisability	#21	Discuss the generalisability (external validity) of the study	
20			results	
21				
22				
23				
24				
25	Other Information			
26				
27				
28	Funding	#22	Give the source of funding and the role of the funders for the	23
29			present study and, if applicable, for the original study on which	
30			the present article is based	
31				
32				
33				
34				
35				

36 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution
37 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool
38 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60