

Full Length Research Paper

Directly observed treatment short-course compliance and associated factors among adult tuberculosis cases in public health institutions of Hadiya zone, Southern Ethiopia

Lonsako Abute¹, Yohannes Kebede², Tigist Astale², Bayu Begashaw Bekele³ and Tegene Legese⁴

¹Department of Public Health, School of Public Health, College of Medicine and Health Sciences, Wachemo University, Hossana, Ethiopia.

²Institute of Health Science, Faculty of Public Health, Behavior and Society, Jimma University, P.O. Box, 378, Jimma, Ethiopia.

³Public Health Department, College of Health Sciences, Mizan-Tepi University, P.O. Box, 260, Mizan -Aman, Ethiopia.

⁴School of Public Health, College of Health Sciences and Medicine, Hawassa University, Hawassa, Ethiopia.

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Tuberculosis (TB) is a major public health problem in Ethiopia. This is at various levels of prevention; connected to early detection, prompt treatment seeking and compliance behavior of patients. DOTS is important strategy to tackle its prevalence and severity among public. In addition, development of MDR-TB is another emerging agenda which mainly happens as a result of poor compliance to treatment regimen. The main aim of this study is assessing DOT treatment compliance and associated factors among adult patients of TB treatment service. Facility based cross-sectional study triangulated with in-depth interview was conducted between March and April, 2015 in public health facilities of Hadiya zone. Data were collected from 203 respondents selected by simple random sampling using pre-tested structured questionnaire. Ethical clearance was collected from the ethical clearance committee of Jimma University, College of health science. We used adapted instrument composed of behavioral, therapy, social and facility related variables. Descriptive statistic and logistic regression analysis were employed to identify factors associated with DOTS compliance in TB patients. We used odds ratio and 95%CI to declare significant factor fits. Then quantitative data were triangulated with qualitative data. Finally, the findings were presented in narrative texts, tables and graphs. A total of 203 tuberculosis patients were interviewed; nearly three quarters (75.9) were rural dwellers. 142 (70%) of the respondents were compliant with in the last seven days. Majority (84%) of the respondents were morning time compliant. Average number of day that patient takes the drug in 1 week is 6.6 and most of them (72.50%) takes seven days. Phase of treatment, knowledge, getting encouragement, perceived severity, distance from health facility and getting advice were significantly associated at p -value <0.05 with DOTS compliance. Moreover distance and getting advice in intensive phase and absence of symptom, waiting time and getting encouragement in continuation phase were significantly associated. DOTS compliance in this study is poor relative to other studies. Special attention on compliance counseling should be given for those patients who have no symptom in continuation phase, distant patients in intensive phase and those who did not get social support.

Key words: Adult patients, compliance, DOTS treatment.

INTRODUCTION

Tuberculosis is a chronic infectious disease which is caused by an acid-fast bacillus, belongs to the

Mycobacterium tuberculosis complex. Tuberculosis transmission begins with a human source, most often a person with cavitary, pulmonary TB through coughing and sneezing (Dye et al., 2005). Tuberculosis is still a major cause of death worldwide, especially in sub-Saharan Africa (FMOH, 2012). There were an estimated 9 million new TB cases, from which 7.4 million occurs in south-east Asia and sub-Saharan Africa. Tuberculosis is a major public health problem, with an estimated global incidence rate of 137 cases per 100,000 populations (WHO, 2013).

Directly observed treatment short-course for tuberculosis are under development to improve treatment outcomes and reduce costs (Trajman et al., 2016). Between 1995 and 2009, a total of 41 million tuberculosis patients were successfully treated according to the DOTS/Stop TB Strategy and up to 6 million lives were saved as a result (Bayu et al., 2016).

Even though it takes more than a century after the discovery of the infectious agent and five decades after introducing effective chemotherapy, tuberculosis remains a major cause of death in the world. One-third of the world's population is infected with *M. tuberculosis*, and the socio-economic outcomes of the disease are huge (FMOH, 2014). Thus in total, approximately 1.45 million people died of TB this equates to a best estimate of 15 deaths per 100,000 population. Tuberculosis hinders socioeconomic development: 75% of people with TB are within the economically productive age group of 15 to 54 years (Harries et al., 2007).

Ninety-five percent (95%) of all cases and 99% of deaths occur in developing countries, with the greatest burden in sub-Saharan Africa and South East Asia (12). According to the WHO global TB report 2011, there were an estimated 220,000 (261 per 100,000) incident and 330,000 (394 per 100,000) prevalence of TB cases with an estimated 29,000 deaths (35 per 100,000) occurs in Ethiopia due to TB (WHO, 2011). Now a days co-infection HIV/AIDS and newly emerging drug-resistant TB, especially multidrug resistant TB (MDR-TB) poses a great challenge of reducing human misery from this deadly disease and makes it major issue of WHO agenda. Household costs of TB are substantial; estimates suggest that tuberculosis costs the average patient three or four months of lost earnings, which can represent up to 30% of annual household income (John et al., 2011). Even though there are a lot of problems associated by tuberculosis; compliance is top urgent that plays the major role in the prevention and control program of TB and which is affected by many different factors (WHO, 2008).

Compliance to anti-tuberculosis treatment and risk

factors in Sub Saharan African countries shows that the proportion of patients non-compliant for treatment is unacceptably varied and high (WHO, 2011). Non-compliance with TB treatment poses a significant public health threat, as it is associated with increases in transmission rates, morbidity, and costs to TB control programs. Moreover, it leads to persistence and resurgence of TB and is regarded as the chief cause of relapse and development of MDR-TB (Tadesse et al., 2013). Therefore, this study will lay emphasis on the factors that affect patient compliance with anti TB treatment to alleviate the above problems in the study area.

METHODS

Study setting

Community based cross sectional study was conducted in Hadiya zone health facilities south Ethiopia between March to April, 2015. The zone comprises of 11 districts with a total population of 1,547,846 with 49.47% of male and 50.53% of female. As to health infrastructures one Hospital, sixty one functional health centers which delivers routine health services to the community including DOTS program. DOTS were initiated in Hadiya zone in 1996 Hossanna hospital and one health centre, with potential population coverage of 25%. Health facilities providing DOTS increased to 31% in 1997, and 100% in 2011 making the population coverage by DOTS (Hadya zone, 2015).

Population

The study was conducted on adult TB patients of age ≥ 15 years old who were on anti-TB drug for at least three weeks of treatment. But those patients on anti-TB drug and severely ill TB patients, who were not able to respond from attendants of TB treatment clinic during data collection period were excluded.

Sample size

The sample size was calculated using single population proportion formula ($n = (Z \cdot 1-a/2)^2 \cdot p \cdot (1-p) / d^2$) with the following assumptions: 74% proportion of compliance level according to previous similar study from Sidama south Ethiopia was used (Zekariyas et al., 2013), marginal error (d) 5% and confidence interval of 95%. Using correction formula and considering 10% non-response rate the final sample size was determined to be 209.

For the qualitative part of the study, 12 key-informant in-depth interviews were conducted (6 HEW and 6 treatment supporters).

Sampling technique

Six districts were selected by simple random sampling technique

*Corresponding author. E-mail: baybeg121@gmail.com.

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using lottery method. Sample was proportionally allocated to selected districts. There are 32 health institutions in six districts (District 1(7 HF), District 2(7HF), District 3(6HF), District 4(4HF), District 5(4HF) and District 6(4HF)) and all institutions from selected districts were included in the study. Then sample was also proportionally allocated for all institutions in the districts. Finally patients were included in the study by using computer generated simple random sampling technique by using list of the patient on registration book as sampling frame. Key-informant in-depth interview participants were HEW those takes training on national guideline of TB and treatment supporters other than health professionals, selected purposively.

Measurements

Pretested and semi structured questionnaire was adapted from different relevant literatures and modified to the local context for quantitative study. The questionnaire was prepared in English and then translated into Amharic and Hadiyigna by those who are native to Amharic and Hadiyigna language then back to English by other individual to insure consistency. The questionnaire consisted of five main parts: The first part was composed of socio-demographic information of the respondents. The second part consisted of items related to behavioral factors, includes comprehensive knowledge about TB and individual perception. Knowledge part consisted of 22 item (Yes/No) questions that focused mainly on the cause, transmission, treatment, prevention of tuberculosis and awareness on MDR/TB. The questions that measure perception consisted of five points Likert scale items, with 1 and 5 indicating the lowest and highest level of agreement, respectively. The response categories for Likert scale items have four or more categories to maximize variation. Each of the responses was scored: strongly disagree = 1, disagree = 2, undecided/not sure = 3, agree = 4, strongly agree = 5. After reversed for negatively worded items to positively worded items, score was summed for each respective factor. Variables of knowledge and perceptions (perceived severity, barrier and benefit) were treated as continuous variable Social influence consists of 9 items and focuses on the type and source of support. Facility related factors have 10 items to identify distance, waiting time, service providers' approach and their advice for clients on TB treatment. Nature of therapy includes phase of treatment and symptom during interview.

Outcome variable

To assess DOTS compliance level

The recent compliance during the last 7 day before the survey was assessed by patient's report. The patient is expected to take RHZE in intensive phase for two months and RH in continuation phase for four months. This is based on the number of pills which is consistent with treatment regimen weight (<39 kg = 2 pills, 39-55 kg = 3 pills and >55 kg = 4 pills) (following TB treatment standard guideline). The classifications of the patient as compliance when the number of pills reported by the patient was consistent with the treatment regimen weight for all seven days and non-compliance when the number of pills reported by the patient was not consistent with the treatment regimen weight even for one day in a week. (FMOH., 2012, Partha Sardar., 2009). The seven day compliance was checked for its compliance for 24 h.

The in-depth interview guide was prepared to explore information for qualitative data from HEW and treatment supporters on the factors that affect treatment compliance of TB patients like social, cultural, financial, facility related factors and traditional beliefs. It was conducted and transcribed by principal investigator by

Hadiyigna (local language). Key-informant interview was tape-recorded besides taking the notes.

Statistical analysis

Data was entered into EPI-DATA version 3.1 and exported to SPSS 16.0 statistical software to edit, clean for inconsistencies and missing values and finally to analyze. Different frequency tables, graphs and descriptive summaries were used to describe the study variables. Analysis of logistic regression was done to determine the predictors of DOTS compliance in TB patient. In binary logistic regression analysis those variables having a p-value ≤ 0.25 was considered as a candidate for multivariable analysis. In Multivariable Logistic regression adjusted odds ratio with 95% confidence interval that not include 1 and p-value at <0.05 was computed to assess the statistical significance, strength of association and to get final model. Model fitness was checked by Hosmer and Lemeshow test and it was >0.05 (0.161). Finally, the qualitative data were narrated and triangulated together with the quantitative findings.

Ethical consideration

Ethical clearance was obtained from the Ethical Committee of the College of Health Sciences, Jimma University. All respondents were given detailed information about the objective of the study and verbal consent was obtained from each respondent before the interview.

RESULTS

Socio-demographic characteristics

Two hundred three respondents were participated in the study producing response rate of 97.0%. Accordingly, 120(59.1%) of them were married. The mean age of the respondents was 33.04 ± 11.174 years. In terms of religion, 146(71.9%) of the respondents were protestant. Nearly all, 375 (98.9%) of the respondents, were farmers and the dominant ethnic group was Hadiya 174(85.7%). 63(31%) of respondents attended Grade 1 to 8 followed by 45(22.2%) secondary school attendants. Concerning employment status of respondents 27.1% were house wife followed by 22.7% were farmers. Most of the respondents (75.9%) live in rural areas.

Level of DOTS compliance

Out of 203 respondents 142(70%) were exhibiting compliance for DOTS irrespective of the phase they were. In fact, this compliance rate showed variation intensive and continuation treatment phase (PV<0.05).

24 hour and seven-day compliance

This seven day compliance was checked by 24 h

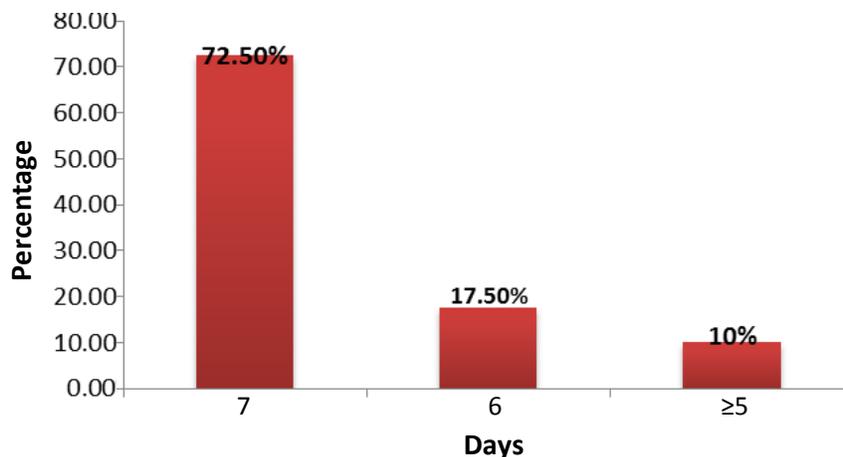


Figure 1. Average number of days TB patient takes drug per week.

compliance with their respective weight. That means all the patients who comply in the last seven days were comply for DOTS in the 24 h.

Reason for non-compliance

When we see reason for non-compliance 29(47.5%) reported that facility is far from home, 19(31.5%) is due to absence of symptom, fear of side effect 14.7% and not being at home, 6.5.

Compliance level by drug taking time

Majority (84%) of the respondents were morning time compliant followed by 10.4% evening.

Number of days the TB patient takes the drug a week

Average number of day that patient takes the drug in 1 week is 6.6 and majority of the patient (72.50%) takes seven days (Figure 1).

Psycho-social/behavioral variables

Comprehensive knowledge

The mean score of knowledge was 9.14 with $SD\pm 2.84$. Regard to the cause of the TB only 29.8% responds microbe as a cause of tuberculosis and the rest 70.2% responds other things (cold=35%, wind=20.8%, hardworking=9.8% and bad smell=4.6%). Above the half 109(53.7%) of the patients report as coughing and sneezing of the patient transmit TB where as 26% responds eating together followed by 11% working

together transmit TB disease.

Perceptions related to TB and its treatment

The mean perceived severity of TB was 48% with $SD\pm 3.87$, the mean perceived barrier for TB treatment was 48% with $SD\pm 2.52$ and the mean perceived benefit of TB treatment was 54% with $SD\pm 3.94$.

Nature of therapy and facility related variables

61.1% were on continuation phase of treatment. 79.3% travel less than 30 min before reaching health facility and 82.3% waits less than 30 min before getting service. An overwhelming majority 84.7% comes to health facility on foot and 84.7% responds that TB drug is available always in the facility. Regard to patient-service provider approach, 94.1% responds that health care providers have good approach and 75.9% gets advice from health professional on anti TB drug. Majority 143(94.7%) gets advice on daily and timely taking of anti TB drug (Table 1).

Social factors

145(71.4%) were received encouragement to be on anti-TB drug and majority 63% gets support by food, reminding to take TB drug daily and consistently. Majority (63%) of them get support from their families followed by 26% from relative.

Key-informant interview also supports this finding; different individuals and groups (husbands, family members, neighbors and peers) provide varying ranges of support for TB patients regarding compliance to treatment. These supports include talking about side-

Table 1. Distribution of respondents by therapy and facility related variables of TB patients Hadiya zone health facilities, June, 2015.

Variable		Frequency	Percent
Treatment regimen	New	138	68
	Retreatment	65	32
Phase of treatment	Intensive	79	38.9
	Continuation	124	61.1
Time to reach health facility	≤30 min	161	79.3
	≥30 min	42	20.7
Waiting time in HF	≤30 min	72	82.2
	≥30 min	36	17.7
Transportation	On foot	172	84.7
	Public transportation	31	15.3
TB drug availability	Always	172	84.7
	Not always	31	15.3
Health care provider approach	Friendly	191	94.1
	Not friendly	12	5.9
Get advice	Yes	154	75.9
	No	49	24.1

effects of TB drugs at family and peer levels, preparing food for TB patients, lending traditional transportation services like horses. For instance an in-depth interview*"Once the patient starts TB drug he/she needs supporting by food ... reminding to take TB drug daily and appointment schedule is necessary. Not only this disease itself causes weakness, so even there is a need of traditional transportation like horse."*(Treatment supporter).

There are also structures in the community that plays major role in the success of DOTS compliance. In-depth interview explored from HEW indicates the role of community leaders, one to five network, health developmental army and treatment supporters as they are discussing about the prevention and control of tuberculosis disease, its treatment and consequence like development of MDR-TB.*"most of the times community leaders, one to five network, health developmental army and treatment supporters were discussing about the prevention and control as well as following the patients who are on anti-TB drug to complete the drug consistently (HEW).*

Predictors of DOTS compliance in TB patients

Phase of treatment, knowledge, getting social support, perceived severity, distance from health facility and getting advice from health professional were identified as significantly associated with patient compliance to TB

treatment. Those patients in intensive phase were three (AOR=3.25[1.13, 7.90]) times more likely comply than patients in continuation phase. Those respondents who get social support 6.5 (AOR=6.59[2.65, 16.41]) times more likely compliant than their counter parts. Those respondents who travel ≤30 min before reaching health facility 2.9 (AOR=2.99[1.06, 8.44]) times more likely comply as compared with those travel >30 min. Actually in-depth interview finding revealed that traveling daily to health institution is very difficult for TB patients while on treatment. When the patient comes from very distant areas, they come to be bored of travelling and as they are TB patient they might have body weakness that makes their daily travelling by foot very difficult and tedious. *"most of the time if the patient comes from very distant areas, he/she comes to be bored of travelling and as they are TB patient they have no power of daily travelling daily by foot (especially for rural communities it is very difficult and tedious) and it makes them not to comply"*(HEW).

A unit increase of patient's knowledge score would increase the level of compliance by an average of 1.3 (AOR=1.30[1.11, 1.51]). Those patients who get advice from health professional on TB drug was 6 (AOR=6.20 [2.46, 15.63]) times more likely comply as compared with not advised. A similar pattern was also observed in in-depth interview from HEW that health providers' advice during the initiation of anti-TB drug plays major role towards DOTS compliance. This finding indicates that provision of adequate health education on drug side

Table 2. Multivariable logistic regression that predict DOTS compliance in Intensive phase of treatment in TB patients Hadiya zone health facilities, June, 2015.

Variable		COR(95%CI)	AOR(95%CI)
Distance	≤30 min	7.32(2.16, 24.73)	6.69[1.83, 24.41]**
	≥30 min	1	1
Waiting time	≤30 min	2.45(0.96, 6.24)	1.10[0.38, 3.23]
	≥30 min	1	1
Getting advice	Yes	2.68(1.17,6.15)	2.43[1.03, 5.73]*
	No	1	1
Knowledge		1.08[0.96,1.21]	1.05(0.93, 1.17)

Table 3. Multivariable logistic regression that predict DOTS compliance in continuation phase of treatment in TB patients Hadiya zone health facilities, June, 2015.

Variable		COR(95%CI)	AOR(95%CI)
Getting support	Yes	4.79(2.11, 10.87)	4.06(1.72, 9.54)**
	No	1	1
Waiting time	≤30 min	2.71(1.17, 6.31))	2.53(1.03, 6.18)*
	≥30 min	1	1
Absence of symptom	Yes	0.33(0.18, 0.61)	0.35(0.18,0.66)**
	No	1	1
Knowledge		1.17(1.04,1.31)	1.12(0.99, 1.26)

effect, absence of symptom while the patient on treatment and consequence of interrupting the drug like development of MDR-TB is mandatory. As an in-depth interview most of the patients did not getting adequate counseling on the above circumstances.

HEW.....health professionals play the major role on the success of DOTS program. From the beginning of the treatment health care provider did not give enough health education about the behavior of the drug. If the patient is not get advice initially as well as during on treatment, drug side effect only makes the patient not to comply”.

Predictors of DOTS compliance in Intensive phase of treatment

Distance and getting advice from health provider remained significantly and independently associated with intensive phase compliance at $p < 0.05$ (Table 2).

Respondents who comes from near to health facility 6.69 (AOR=6.69[1.83, 24.41]) times more likely comply as compared to patients who far to health facility. TB patients who gets advice from health provider from the beginning of treatment was 2.43 (AOR=2.43[1.03, 5.73]) times more likely comply than their counterparts.

Predictors of DOTS compliance in continuation phase of treatment

Absence of symptom while the patient is on treatment, waiting time and getting social support remained significantly and independently associated at $p < 0.05$ (Table 3)

Patients who get social support 4 (AOR=4.06[1.72, 9.54]) times more likely comply. Patients without symptom 65% (AOR=0.35[0.18, 0.66]) less likely comply as compared to symptomatic patients. In-depth interview from treatment supporter also supported this finding. There are patients who did not swallow TB drug daily. Once symptom of the disease is absent they did not want to swallow appropriately. Most of the patient’s response for interruption as they are cured from the disease and further swallowing is burning by its side effects. For example treatment supporter: ”there are some TB patients who do not swallow TB drug daily, once symptom of the disease is absent even they took it to their home. When we ask, they respond to as “I am healed and no symptom..... so daily swallowing is only burning by its side effects, no other benefit other than it.” Those patients who wait in health facility less than or equal to 30 min before getting service were 2.53 (AOR=2.53 (1.03, 6.18)) times more likely comply than

their counterparts.

DISCUSSION

Compliance to anti-TB treatment is a major determinant of treatment outcome. In developing countries where inequities in access to health care are high and health resources are scarce the magnitude and impact of non-compliance is assumed to be higher. It is undeniable that many patients experience difficulties in following treatment recommendations. Currently for the dangerous TB specious (MDR-TB) development this non-compliance takes majority part (Bernt Lindtjørn., 2005). Hence, this study assessed the level and determinant factors of compliance to anti-TB medications.

Though institution based study is assumed to be over-estimated, 70% of compliance in the last seven days before the survey was found in this study. The overall compliance in this study is consistent with the study done in Morocco (69.8%) (K. Slama., 2012). This finding is lower from the previous reports of the Jiangsu Province of China (87.8%), Uganda (75%) and Sidama (74%) (Zekariyas Sahile., 2013, Monica G Amuha, et al., 2009, Weiguo Xu, 2007). but it is higher than DOTS compliance level in India and Kolkata (59.5%) (Suparna Bagchi., 2003). The variation might be methodological difference like compliance for DOTS was measured by 7 in this study and participant difference between the countries.

Patients in intensive phase three times more likely compliance from those patients in continuation phase. This finding is consistent with study done in Zambia and northwest Ethiopia being in continuation phase of chemotherapy is high risk factor for non-compliance (Kaona FAD., 2004, Adane AA., 2013). The reason might be disappearance of symptoms in continuation phase of treatment since absence of symptom is an indication of clinical improvement from disease. In this study patients who came from distant areas less comply as compared to their counterparts. This finding is similar with the study conducted in Egypt and Sidama where being far away from the health institution was the major factor for non-compliance (Zekariyas Sahile., 2013, Partha Sardar., 2009).

Finding in this study indicates that as one unit increase in knowledge, patients' being compliance is averagely increases by 1.3. That is similar with the finding from the Nigeria, China and India where lack of knowledge of duration of treatment was significantly associated with non-compliance (Luka Mangveep Ibrahim et al, 2010, Weiguo Xu, et al 2009, Suparna Bagchi., 2003). In this study patients who get adequate counseling on TB medication complies six times more likely from those who did not counseled (at p -value<0.001). Similarly study conducted in South Africa and Kolkata shows that those who did not received enough education about tuberculosis and anti-TB drug at the beginning of

treatment, that they were not told why treatment would take 6 or more months and those lacked counseling were non-compliant (Matebesi Z., 2004, Partha Sardar et al., 2009). One possible explanation for this is inadequately counseled patients may mistake the feeling of improvement to cure, thus interrupt sometimes medication. There is association of getting social support with DOTS compliance in this study. This finding is in line with study conducted in Addis-Ababa and china, where family support was found to be crucial for patients' treatment success. Some patients had been seriously ill when treatment was initiated and needed someone to accompany them for treatment (Weiguo Xu, et al., 2009, Suparna Bagchi., 2003).

Getting adequate advice on TB treatment is significantly associated with DOTS compliance in intensive phase of treatment in this study. This finding is consistent with the study conducted in Kolkata where patients in intensive phase who lacks proper counseling were non-compliance (Partha Sardar et al., 2009). This implies that if the patient is not informed initially about the serious consequences of the interruption of TB drug like development of MDR-TB, he/she might come to be non-compliant. In this study (intensive phase of the treatment) patients who were near to the health institution complies more likely as compared to those comes from faraway to health facility. The reason may be in this phase there is traveling long distance daily to swallow anti-TB drug to the facility and there is symptom of the disease like weakness.

In this study especially in continuation phase patients who waits greater than 30 min before getting service complies less likely than their counterparts. This finding is parallel with the studies of Philadelphia and Burkina Faso where patients those wait for a long time in health facilities for getting service were non-compliant (George LJ., 2003) (Sanou A., 2004). The possible reason might be when the patient waits long time before getting service; they perceived that they are not respected beside health care providers. The possible reason might be when the patient waits long time before getting service, they perceived that they are not respected beside health care providers. Their trust on the HCP comes to be diminished and they will be exposed for non-compliance.

Patients without symptom at the time of data collection in this study comply less likely than those with symptom (continuation treatment phase). This finding is consistent with the study of Bolivia and Zambia where absence of symptom especially patients in continuation phase of treatment is high risk factor for non-compliance (Greene JA., 2004, Kaona FAD et al., 2004). It is known that patients after completing intensive phase they have no daily contact with health professional. So it needs serous supervision since they are taking drug into their home and swallowing is in question. In addition to that in this phase the patient became asymptomatic and may be

perceive as he/she is cured from the disease.

Since the study was institution base on self-report the results be might overestimated to be related to compliance. The study was not treatment phase based, that is, the study did not separate the intensive phase and continuation phase of the treatment. Finally, it shares the limitations of cross-sectional studies and hence it might suffer from temporal relationship establishment of predicting some variables.

Conclusion

In general compliance is a dynamic issue and barriers are also liable to change over time, which necessitates continuation of multi-disciplinary collaborative studies and interventions. Hence, in this study the level of DOTS compliance was relatively poor as compared to other studies and it is affected by many different factors. Phase of treatment, getting social support, distance, knowledge about TB, getting advice from health professional and perceived severity were the factors that affect DOTS compliance. There are social capitals in the community that ranges from encouraging patients to visit health facility, to tolerate side effects, fetching drugs and presenting traditional transportation systems which the TB control program shall foster. In fact, TB control programs shall consider patients on different phases of treatment as different segments as a result of differences on classes of factors affecting their compliance. Accordingly, distance and provision of adequate advice in initial phase and social support, waiting time and absence of symptom in later phase of treatment were factors that affect compliance on DOTS treatment.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files but any additional data required by the journal can be available anytime.

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Conflict of Interests

The authors have not declared any conflict of interests.

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