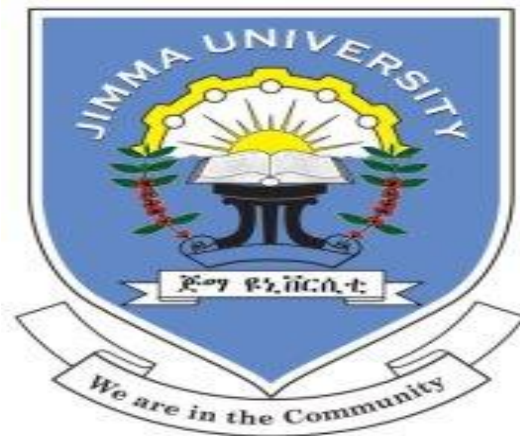


Determinants of non adherence to Tuberculosis Treatment among
TB patients in four public health facilities of Gambella Region,
Southwest Ethiopia



By: Wiw Gach Jing (BSc)

A Research Project submitted to Jimma University Institute of Health, Faculty of Public Health, Department of Epidemiology; in Partial Fulfillment for the Requirements for Master of Public Health (MPH)

June, 2017

Jimma, Ethiopia

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By: Wiw Gach Jing (BSc)

Advisors:

1. Professor Kifle Woldemichael (MD, MPH, Professor of Epidemiology)
2. Abiot Girma (Bsc, MPHE, Lecturer)

ABSTRACT

Background: Ethiopia is among 30 TB/HIV high burden countries and has encountered the emergence of MDR-TB. In Gambella Region, low treatment success rate and high default rate raised the concerns for determining various determinants of non adherence to TB treatment. Therefore; the objective was to determine the determinants of non adherence to TB treatment among patients treated in four public health facilities of Gambella Region, Southwest Ethiopia.

Methods: A case control study was conducted on a sample of TB patients who were on DOTs program in four public health facilities of Gambella Region, starting from March 1-27/201. The total sample size was 288 patients, (72 cases and 216 controls). A ratio of 1:3 was used to obtain sufficient sample for the purpose of inference. Cases were TB patients who missed 10% of the doses (18 days and above) while controls were those who completed 90% or more doses (162 days and above) during the treatment period. Both cases and controls were selected using systematic random sampling techniques from the lists of TB patients. Data collectors (students) from Gambella college and university traced the patients at their home and interviewed them using a structured questionnaires. Data were defined and double entered into Epidata 3.1 version and exported to SPSS version 20 and analyzed. Proportions, bivariate (crude odd ratios) and multivariate analysis (adjusted odd ratios) were reported. Ethical clearance was given from the IRB of Jimma University, College of Health Sciences.

Results: Perception of being stigmatized (AOR=2.7); 95% CI (1.1, 6.6), not believing in the benefit of regular medication (AOR=6.8), 95% CI (1.8, 24.9), perceiving TB as not severe (AOR=8.4), 95% CI (2, 34.6), having not been ever counseled (AOR=35.5), 95% CI (10, 122), and being smoker (AOR=10.9), 95% CI (4, 29) were independently associated with non adherence to TB treatment.

Conclusion and recommendation: Patient and provider related factors were found to be the predictors of non-adherence to TB treatment. Therefore, **capacity** building by providing a training and supervision to health care providers is highly recommended.

KEY WORDS: Non adherence, adherence, TB medication, Gambella, TB patients

ACKNOWLEDGMENTS

Foremost, I would like to thank Professor Kifle Woldemichael for his kindness, sincerity, friendly manner and valuable comments that motivated me to complete my entire thesis preparation. It would be unforgettable job done by Mr. Abiot Girma, handling his work as well commenting and providing me very constructive suggestions that reflected his directness and committed character during my research work.

I would like to thank the patients involved in this study for their cooperation, and the health facilities staffs, directly observed therapy (DOT) clinic involved, and data collectors for their assistance in facilitating access to the target population.

My grateful thanks goes to my mother Nyantey Gatkuoth Jenyang who dedicated me an advice during my school life. Her words has encouraged, strengthened and made me to stand firmly on my footsteps.

Last but not least, I would like to thank Jimma University and Gambella Region Health Bureau for financing this Research Project. Indeed, it would have never been easy without their financial aid.

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ABBREVIATIONS/ACRONYMS

AIDS	Acquired Immunodeficiency Syndromes
CNS	Central nervous system
CSA	Central Statistical Agency of Ethiopia
DOTS	Directly Observed Treatment short course
E	Ethambutol
EFY	Ethiopian Fiscal Year
EPTB	Extra pulmonary Tuberculosis
FDRE	Federal Democratic Republic of Ethiopia
H	Isoniazid
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MDGs	Millennium Development Goals
MDR-TB	Multi-Drug Resistant Tuberculosis
PTB	Pulmonary Tuberculosis
R	Rifampicin
RR-TB	Rifampicin Resistant Tuberculosis
RX	Treatment
S	Streptomycin
SDGs	Sustainable Development Goals
SNNPR	Southern nations, nationalities and Peoples' Region
SPSS	Statistical Package for Social Science
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug resistant Tuberculosis
Z	Pyrazinamide

1. INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Pulmonary Tuberculosis is the most common form that mainly affects the lungs. Sporadically, the disease can be caused by *Mycobacterium bovis* and *Mycobacterium africanum* (1). Pulmonary TB is transmittable (1). Any form of Tuberculosis involving other organs than the lungs such as pleura, lymph nodes, spine, joints, genito-urinary tract, nervous system and abdomen is called extra pulmonary Tuberculosis (2).

Tuberculosis is a global public health concern. In 2015, the disease accounted for incidence of 10.4 million TB cases where 5.9, 3.5 and 1.0 million new cases were among men, women and children respectively (3). In addition to this; an estimate of 480,000 new cases of multi-drug resistant TB (MDR-TB) were reported worldwide in the same year with additional 100, 000 People with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment (4). About 45% of MDR TB new cases were in India, China and Russia Federation (3). Furthermore, Human Immunodeficiency Virus (HIV) exacerbated the condition by increasing susceptibility to TB infection, progression to disease; facilitate the reactivation rate and increased re-infection rate (2). There is also a high chance of developing TB disease in HIV infected people compared with HIV negative person (5).

Although the Millennium Development Goal of having lowered TB burden had been met in many regions of the world between 2000 and 2015, TB remained one of the top ten causes of death globally. For instance, one year ahead of the final year of Millennium Development Goal (MDGs), TB killed an estimated number of 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890 000 men, 480 000 women and 140 000 children respectively (4).

In Ethiopia, Tuberculosis is a leading cause of death among communicable diseases. According to World Health Organization (WHO) 2014 report, the prevalence and incidence of all forms of TB were 211 and 224 /100,000 population, respectively (6). Apart from HIV associated deaths, TB mortality was estimated to be 32 per 100,000 population in 2013. Among all the estimated new TB cases, 13% were HIV co-infected. According to recent WHO 2016 report, Ethiopia is among the lists of 30 countries with high burden of TB/HIV and multi-drug resistant TB (MDR TB) (7). The prevalence rate of MDR-TB in the country has increased alarmingly from baseline of 1.6 % since 2005 (8).

In 2014, the national TB drug resistance surveillance report showed that 2.3% of new TB cases and 17.8% re-treated TB cases were estimated to have MDR TB in 2014 (9). The newly adopted Sustainable Development Goals (SDGs) demand to "achieve universal health coverage" in which effective treatment for all TB infected people has been stipulated under its target. In this regard, TB treatment coverage is one of the top priority indicators to monitor the progress toward the End TB Strategy by 2030 and 2035 (4).

1.2 Problem Statement

Tuberculosis is a major economic setback for many developing regions of the world. Tuberculosis in Ethiopia mostly affects the productive or young age group, for instance, 58% TB prevalence were under 35 years of age (10). Thirty-nine percent of 32,000 death per year were also under 15 to 64 years of ages (11). Consequently, this is associated with the income lost for the affected family. Health Sector transformation plan (HSTP) clearly argued that effective treatment TB is one of the key health interventions for addressing poverty and inequality" (12).

Adherence to treatment is defined as the "extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (13). In terms of TB control, adherence to treatment may be defined as the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment (14). Hence, adherence to TB medication is one of the areas of concern for reducing TB burden (15). The national strategy is aligned with global TB end strategy with the goal of ending TB epidemic by 2035 (4). Besides active surveillance and prevention of TB, adherence to medication is one of the crucial factors that results in positive treatment outcome as well as realization of TB program goal (16).

Contrary to that, poor adherence to treatment prolonged the illness, increased chance of transmitting the disease and death (17). Inappropriate treatment and irregular use of anti TB drugs trigger the widespread of multi-drug resistant TB strains; an emerging public health threat worldwide (18). Likewise, improper treatment regimen for MDR-TB also aggravates the development of extensively drug resistant TB (XDR-TB) which requires a very expensive chemotherapy using less potent and effective drugs for curing (19). As per the MDGs, Ethiopia has made a significant progress in reducing TB prevalence and mortality by 50% (20). Despite the remarkable achievement, Tuberculosis still shares a significant contribution toward the total communicable disease burden (21). The rise in this prevalence was coupled with low detection rate of MDR TB cases; a huge concern to health sector which requires urgent means of averting (22). An effective treatment of all

forms of TB cases with rigorous adherence to medication is the one of the key intervention strategies. However, barriers to adherence are complex. Moreover, solutions to improve adherence also needs a multi-factorial approach of assessing and understanding of barriers and facilitators to adherence (23). The patients' ability to follow the recommended regimen usually link with various determinants such as social and economic factors, the health care team/system, the characteristics of the disease, disease therapies and patient-related factors (15). Consequently, ensuring patient adherence to treatment can be quite challenging because TB disease is a long term illness that requires long duration of treatment for at least six month (24).

In Gambella region, few studied have been focusing on the trend and treatment outcome (25). A recent study conducted at the Regional Hospital indicated that, the treatment successful rate was 70.76% and the defaulted rate was 8.4% (26). This was an indication of the problem that might arise due to non adherence to TB medication.

Beside this, most studies used cross-sectional study design to assess adherence level of patients. This study has used a case control study design to assess multiple exposures that associate with adherence to TB treatment. In addition to other patient related factors, the study also has encompassed patient's perception about the severity of the disease, perception about the susceptibility to disease as result of interrupting the medication, perceived benefits of taking drug and belief about curability when taking medication.

2. LITERATURE REVIEW

2.1 Introduction

2.1.1 Treatment of Tuberculosis

The treatment for Tuberculosis is standardized with the following objectives; (a) To cure the patients by rapidly eliminating the bacilli from the body, (b) To prevent death from active tuberculosis, (c) To prevent relapse of tuberculosis, (d) To prevent the development of drug resistance by using a combination of drugs, (e) To decrease transmission of tuberculosis to others. The drugs used as first line treatment of tuberculosis both in the intensive phase and continuation phase are: Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) (1). WHO recommended two phases in TB treatment:

The initial (intensive) phase consists of four combination of drugs for two months for new cases, and with combination of five drugs for the first two months followed by four drugs for the next one month for re-treatment cases. This makes the patient non-infectious by rapidly reducing the load of bacilli in the sputum, usually within 2-3 weeks except in case of drug resistance. At this phase the drugs must be collected daily by the patient and swallowed under the direct supervision of provider. This may help patients to adhere to medication as they are not yet familiar with the treatment (2).

The continuation phase immediately follows the intensive phase with two or more drugs for four to six months with the assumption of making the patient permanently cured and prevent relapse (27). Studies revealed that during the continuation phase, patients felt that they are cured and reluctant to continue medication. Therefore, patient's knowledge about the treatment schedule, benefits and disadvantage of discontinuing medication is an integral part of improving adherence to treatment (25).

2.1.2 Adherence to TB treatment in Ethiopia

In order to have a successful TB treatment outcome, WHO recommended adherence to TB treatment to be high. Preferably, TB patients should take 90% or more than 90% of the prescribed anti TB drugs. A cross-sectional study conducted in Tigray, northern Ethiopia for 278 TB patients using self reported missed doses and record reviews showed that 97% of the patients adhered to their medication (28). Study conducted in Alamata district in northeastern Ethiopia on 200 TB patients showed an overall adherence level of 88.5% which is slightly below WHO standard (29).

2.1.3 Measurement of adherence to TB treatment

Adherence to TB treatment is measured either by process-oriented or outcome-oriented definitions. Process oriented makes use of intermediate variables which can be measured through subjective approach (a) by asking the patients, family members, caregivers, and physicians about the patient's medication or appointment keeping; (b) objective measurements obtained by counting pills, examining pharmacy refill records, or using electronic medication event monitoring systems, biochemical measurements obtained by adding a nontoxic marker to the medication and detecting its presence in blood or urine or measurement of serum drug levels. Currently, a combination of approaches is preferable for reliability. However, feasibility issue in term of time, cost and man power hampers the applicability of those approaches (30).

Hence, adherence has been commonly measured by counting the pills/doses of drugs taken by the patient. A patient is considered as adherent if adherence percentage defined as the number of pills absent in a given time period ("X") divided by the number of pills prescribed by the physician in the same time period is greater than or equal to 90%. $\frac{\text{No.of Pills Absent in Time X}}{\text{No.of Pills prescribed for Time X}} 100 \geq 90\%$. Some findings reported the adherence level should be 95% or more in order to facilitated the cure for TB disease (31). Most prevalence studies usually use pills or doses counting method to assess the adherence level at specific point in time during the treatment schedule. One limitation of this method is that, temporary relationship between risk factors and adherence level cannot be ensured because the researcher investigates the adherence level and its associated factors at specific moment.

Recent studies have used case control studies where cases have been defined, according to WHO as TB patients who interrupt the treatment for two or more consecutive months during the recommended schedule and controls as those TB patients who complete the recommended treatment schedule for TB diseases (32). Study conducted in TB clinics of urban Morocco on 91 cases and 186 controls has applied this standard definition (33). Another case control study conducted in all provinces of Khartoum state on 105 cases and 210 controls also used similar definition (34).

2.2 Factors that affect medication adherence

2.2.1 Patient's behavioral factors

Patient-related factors comprised of knowledge about disease and benefits of treatment, patient's perception about the severity and susceptibility to disease, perception about stigmatization, patient's smoking habit and substance use, patient's perception about the cost/expense related to the

treatment (35). Belief that TB is not curable, not preventable, or stopping anti TB drugs will not result in difficulty of treating TB and lack of awareness about the duration of TB treatment were associated with lower adherence (28). The patient's beliefs and perception concerning the effectiveness of the treatment also affect the degree of medication adherence (24). A community based case control study conducted at district of India for 47 case and 94 controls showed that hazardous use of alcohol as one of the significant factors for interrupting the treatment (36). Another case control study conducted in India on 90 TB patients, 30 defaulters (cases) and 60 treatment completed patients showed that lack of motivation, lack of self confidence to adhere to duration of treatment were associated with non adherence (37).

2.2.2 Provider-related factors

Patient satisfaction with the “significant” provider of health care is considered to be an important determinant of adherence. But empathic relationships are difficult to forge in situations where health providers are untrained, overworked, inadequately supervised or unsupported in their tasks, provider often fail to build their relationship with their patients (38). As a result, provider fall short to provide valuable information regarding the prescribed drugs, the consequence of stopping the drug, drug side effects as well as addressing patient's emotional and spiritual aspect due to TB disease, and also fail to keep the privacy of their patients (35).

2.2.3 Socio economic related factors

TB usually affects people who are hard to reach, poor and unemployed people. Lack of effective social support networks for patients and low monthly income were found to be associated with lower adherence (28). Lack of transportation to far health facility has been revealed as a barrier to adherence among TB patients with low socioeconomic level in Argentina (39). Another study conducted in Nigeria has revealed transport problem, low educational level, average monthly income as the determinants TB medication (40).

2.2.4 Disease characteristics and complexity of treatment

TB disease is a long term illness that requires a long duration to eliminate bacteria from infected host. Thus, factors related to the nature of disease and its treatment affect the adherence level of the patients (30). A study conducted in northern Ethiopia, Tigray region pointed out that an adverse effects of TB drugs as one of the risk factors non adherence (41). Another study on 77 patients (treatment failure) (and 153 controls (treatment completed) within the same region revealed the

similar reason treatment failure (42). Other study in Sudan, Kassala state showed that patient's feeling better after completing TB treatment intensive phase was the main determinant of treatment discontinuation (43).

2.2.5 Health system-related factors

The organization of clinical services, including availability of expertise, links with patient support systems and flexibility in the hours of operation, also affects adherence to treatment. In many health care settings, health workers are busy with other works such as managing patients with acute illness. This increases the waiting time for TB patients to get the services that could result in missing the drugs. Other factors are Lack of drugs, distance from health care unit, lack of incentive for TB patient, treatment strategy also impede the adherence level (30).

2.3 Conclusion of the literature review

Numerous literatures have acknowledged adherence to TB treatment as a complex behavior that is influenced by various factors. WHO guideline broadly classified them into patient's factors, provider's factors, Health care/system related factors and social/economic related factors. Many researchers had overlooked other behavioral (patient's) factors such as perceived seriousness perceived risk, perceived benefit of treatment and perceived barriers to TB medication. In order to improve adherence, a holistic approach to address those factors was required. This also required the establishment of strong association between determinants and adherence using a case control study design.

2.4 Conceptual framework

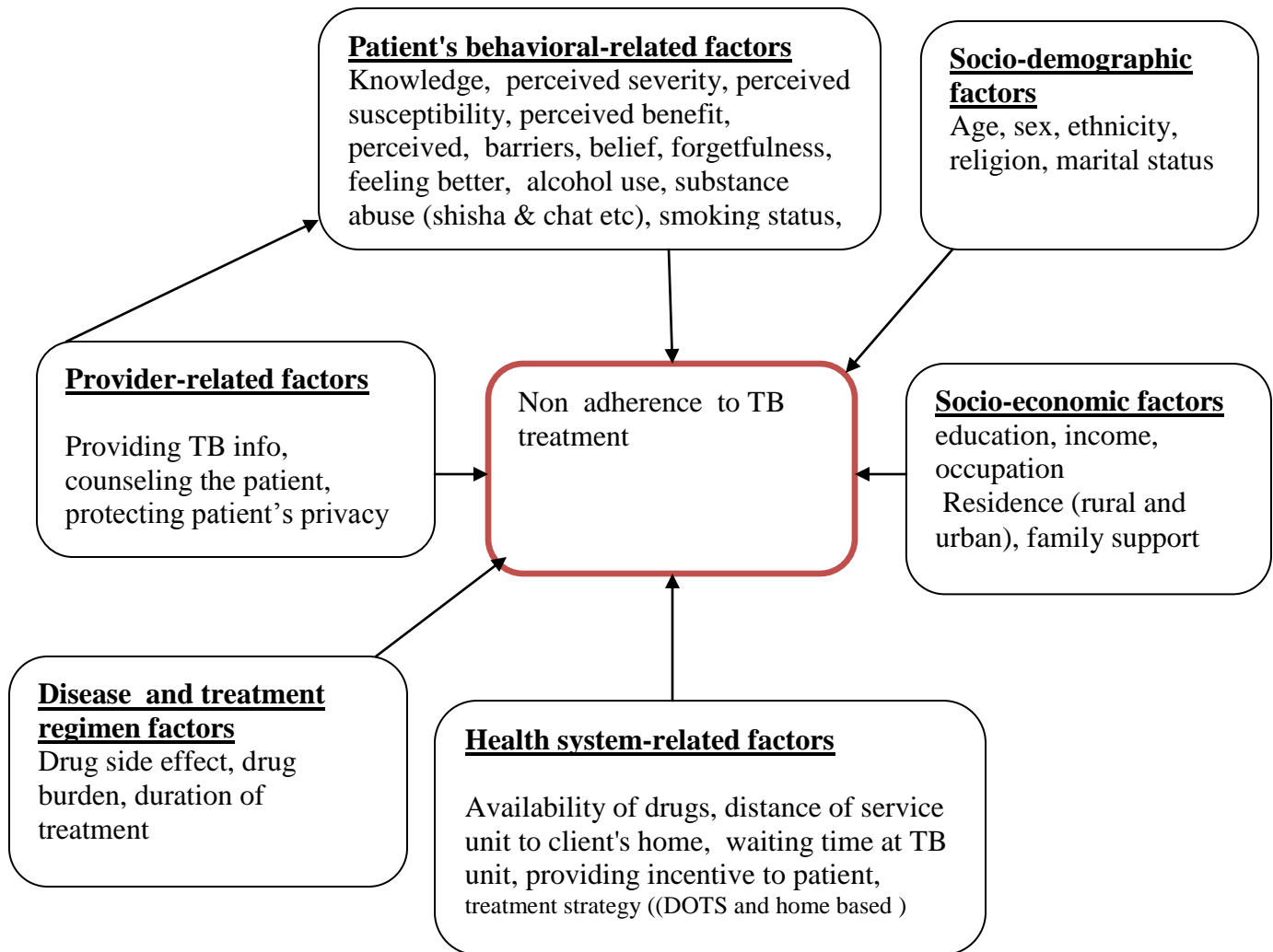


Figure 1. Conceptual framework showing various determinants of non adherence to TB treatment adapted from (30).

2.5 Significance of the study

Tuberculosis being a worldwide public health concern, particularly developing countries of the world shared the biggest burden of the diseases in term of prevalence, incidence and mortality. In Ethiopia TB is still among the top causes of death among communicable diseases. Beside this, multi-drug resistant TB is on the alarming rate of increasing. It is necessary to channel research projects toward preventing and controlling the spread of the diseases, by reducing its burden through effective treatment strategy so that disease will no longer be a public health threat. This study had helped us in determining the determinants of adherence to TB treatment; one of the critical issues in determining treatment outcome.

This finding may help and aware clinicians and policy makers about prominent factors contributed to non adherence to TB medication, especially those clinicians working in the specific public health facilities selected for the study purpose.

3. OBJECTIVES OF THE STUDY

3.1 General Objective

To assess determinants of non adherence to TB treatment among patients of four public health facilities of Gambella region, Southwest Ethiopia, March 1-27 /2017.

3.2 Specific Objectives

To identify patient related factors that influence non adherence to TB treatment in four public health facilities of Gambella Region, Southwest Ethiopia.

To find out provider related factors that influence non adherence to TB treatment in four public health facilities of Gambella region, Southwest Ethiopia.

To determine health care system related factors that affect non adherence to TB treatment in four public health facilities of Gambella region, Southwest Ethiopia.

4. METHODS

4.1 Study area and period

Gambella is one of the regional states in Ethiopia, located in Southwest of the country about 768km away from Addis Ababa. According to 2009 EFY population projection, estimated total population was 423,278 (Male 220,601, Female 202,677). There is major influx of refugee population from the unstable southern Sudan. It is bounded by Oromiya region in the Northern and Eastern Part, SNNPR in the South and Southern Sudan in the West. The Region has an area of 29,782.82 sq Km. Gambella region temperature ranges from 21.1.°C to 40.9°C. Average rainfall tends to be 600mm. Gambella is divided into three Zones namely Anywaak, Nuer and Mejeng. The formation of zones is based on the major tribes that inhabit the specific localities. There is one special Woreda/Itang and 13 Woredas and 158 Kebele. Gambella Town is the capital city of the region (44).

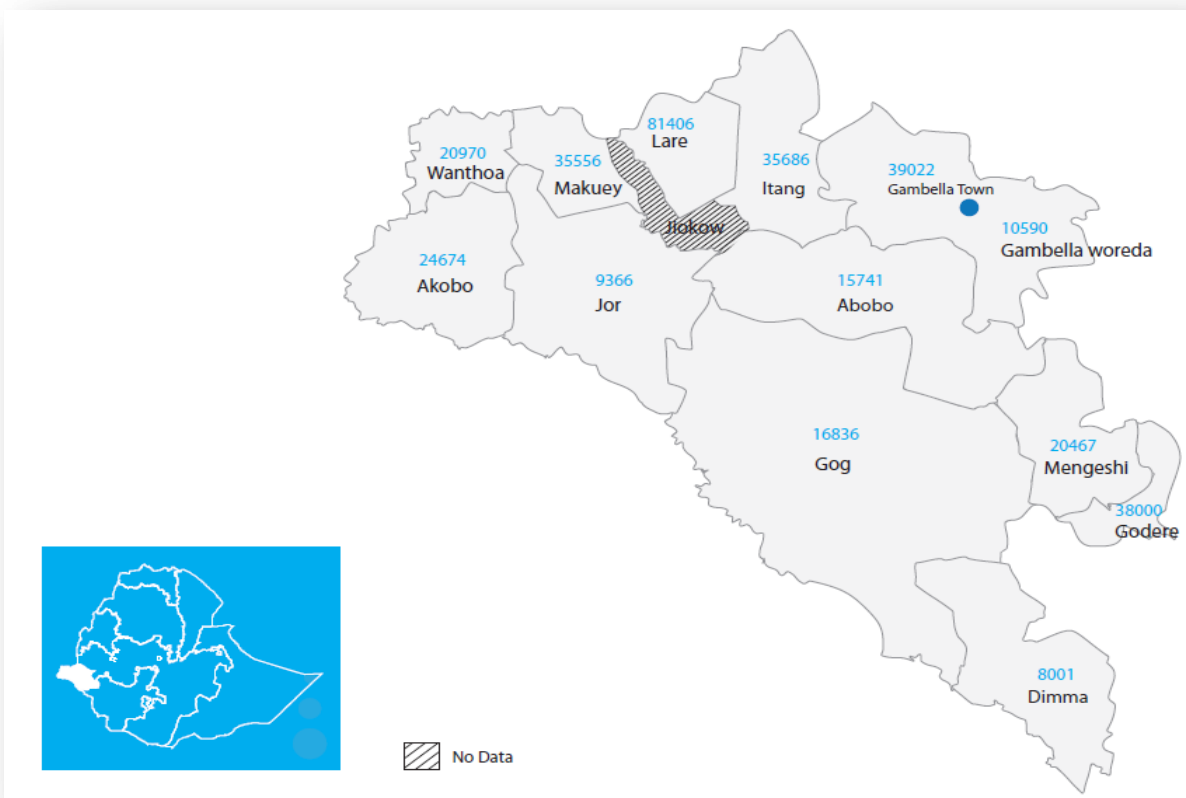


Figure 2. Gambella Map indicating the districts and 1 special district (Itang) (44)

Gambella region has 32 public health facilities functioning at different levels. There is 1 regional hospital, 3 newly built primary hospitals/ two are providing service and one under construction. The total health centers that provide TB diagnosis and treatment services in the region are 20. Beside this, five HCs that serve refuge population are providing diagnostic and TB treatment services. Currently the region has 53 private health facilities in which none of them provides TB service. Thirteen of them are higher and specialty clinics whereas 40 of them are lower or primary clinics. There is no MDR TB treatment initiation center in the region (44).

According to Gambella regional Health Bureau annual report of 2008 (E.C), 1,134 TB cases were reported. About 932 TB patients were tested for HIV of which 97 (10.4%) were positive. Based on the category of TB patients from the total of 1131, 537 were pulmonary TB (smear positive), 409 were clinically diagnosed as pulmonary TB (smear negative ones) and 188 were extra pulmonary TB cases (source Gambella Regional Health Bureau, TB/HIV Global fund). In the year 2016, recent report from Gambella Hospital showed that 46, 26 and 26 new cases of TB were diagnosed and registered at the month of September, October and November respectively (sources from TB clinic, Gambella Hospital, December 2016).

Study period: Study was conducted starting from March 1-27, 2017.

4.2 Study design

A case control study was conducted for TB patients of all forms (Pulmonary with smear positive and negative) as well as extra pulmonary TB.

4.3 Population

4.3.1 Source population

The reference population for this study comprised all Tuberculosis patients registered at Tuberculosis treatment centers of Gambella Region between March 2016 and March 2017. The recommended standard treatment schedule for all form of TB cases (pulmonary and extra pulmonary TB) is six months with exception of MDR-TB patients which requires 18 or more month (45). However, some form of extra pulmonary TB such as the ones that involve central nervous system (CNS), TB meningitis, Musculoskeletal TB and TB pericarditis require 12 months duration of

treatment. Therefore, those TB patients whose duration of treatment was 6 months and 12 were traced.

4.3.2 Study Population

4.3.2.1 Study population for cases and controls

Cases (non adhered) and controls (adhered) were defined based on the missed days (doses) during the entire treatment period (28). Cases were defined as those TB patients who missed 10% or more doses (18 days and above) during the entire treatment period in four public health facilities of Gambella Region. Controls were those TB patients who completed 90% or more (162days) during the entire treatment period in the aforementioned health facilities.

4.3.3 Inclusion criteria

The inclusion criteria for both cases and controls were; TB patients with age 18 years or more, who had been treated under Gambella, Kuergeng, Pugnido and Nyinennyang health center respectively. The age limit was based on the legal age to consent for participation in research activities (46). It has also been clearly stated under National Research Ethics Review Guideline for Ethiopia as the legal age for adults who have a right to informed consent and can participate in research activities (47).

4.3.4 Exclusion criteria

- TB patients who are treatment failures;
- TB patients whose contacts have been lost and difficult to contact;
- TB patients who are mentally and physically unstable to give a proper answer

4.4 Sample size determination

Sample size was determined using the following formula for calculating independent case control study (Unmatched case control study) (48). In order to minimize calculation errors, the sample size was automatically verified using Epi Info 7-Stat Calc for calculating sample size and power.

$$n = \frac{(Z\alpha + Z\beta)^2 \times 2P(1 - P)}{(P_1 - P_2)^2} \times \frac{(C + 1)}{2C}$$

$$P = \frac{P_1 + P_2}{2}$$

$$P_1 = \frac{P_2^2 * r}{1 + P_2 * (r - 1)}$$

Number of cases (n)

r, is the odds ratio (odds ratio of exposures between cases and controls)

c, is the number of control subjects per case subjects was 3. The most efficient ratio of cases to controls is 1, but cost or design considerations may dictate the use of a different ratio. In particular, for the purpose of greater generalizability, sometimes multiple control groups are used in a study. But beyond 4 control per case does not improve precision (49).

Number of controls (cn)

Total sample size (n+cn)

Z_α , represents the desired level of statistical significance at 95% confidence

Z_β , represents the desired statistical power at 95%

P_1 is the proportion of exposure among cases

P_2 is proportion of exposure among controls

P is the average exposure between the case and control subjects

According to the study conducted in Gambella region Itang special district almost 42 % of the participants from the community had poor level of knowledge on TB disease (50). Therefore, the exposure level among the control, was estimated as the population prevalence of exposure (P_2) which was estimated to be 42% (0.42).

Odds ratio (r) of exposures between the cases and controls was estimated to be 2.72 from previous study conducted in Mekelle city, Ethiopia, which showed that TB patients who had felt ashamed or stigmatized were 2.72 times more likely to be non adhered to anti TB drug compared to those who did not feel stigmatized (41).

Therefore, $P1 = \frac{P2 * r}{1 + P2 * (r - 1)}$

By substitution, $P1 = (0.42 * 2.72) / (1 + (0.42) * (2.72 - 1))$

$$P1 = \frac{1.1424}{1.7224}$$

P1= 0.66 (66%), the exposure prevalence among cases

q1=0.34

Therefore, $P = \frac{P1 + P2}{2}$, an average of P1 and P2

$P = \frac{0.66 + 0.42}{2} = 0.54$, the average exposure rate between the cases and controls.

q=0.46

Hence, the sample size in case group will be determined as;

$$n = \frac{(Z\alpha + Z\beta)^2 \times 2 \times 0.54(1 - 0.54)}{(0.66 - 0.42)^2} \times \frac{(3 + 1)}{2 \times 3}$$

n=74

Thus, number of controls is (cn) which is equal to 74*3=222

Total sample size is (n+cn) which is equal 74+22=296

4.5 Sampling procedures

Four public health facilities were purposely selected based on the TB patients load. Proportional to population size ratio allocation was used to allocate the number of cases and controls to each health facility. Cases and controls were obtained from the lists of TB patients at health facilities during study period based on inclusion and exclusion criteria.

Both cases and controls were selected using systematic random sampling techniques from the lists of TB patients. Since study subjects were at home after completing the continuation phase, they

were traced using their contact addresses/telephone number found at their treatment records in TB treatment units.

Table 1. Proportional size allocation of the sample to four health facilities

S/No	Health Center (HC)	Patients load in 2008 E.C 1st quarter (pi)	No of cases in HC	No of cases needed (ni)	No of controls needed(c)
1	Gambella Health center	497	68	44	132
2	Punyido Health center	124	21	11	33
3	Kuergeng Health center	136	18	12	36
4	Nyinengang Health center	56	15	5	15
5	Subtotal	813	122	72	216
6	Total sample size (n+cn)				288

Note: (n) is the number of cases required, (c) is the number of control per case, (c*n) is the number of controls, (n+c*n) is the total number of sample size and (p) is the TB patient load in each Health facility or district.

The number of cases was allocated using proportional allocation of sample size to population of patient in each facility. It is calculated as $ni = \frac{pi*n}{Tp}$

Where ni is the number of cases required from each facility

pi is the TB patient load in each facility

Tp is the total number TB patient load in four health facility (the 2008 E.C first quarter report from Gambella Regional Health Bureau) .

n is total calculated number of case to be proportionally distributed (n=72).

4.6 Variables

Independent variables

Socio-demographic factors

- Age
- Sex
- Ethnicity

- Religion
- Marital status

Socio-economic factors

- Income
- Occupational status
- Educational status
- Family support for patient
- Residence (urban and rural)

Patients behavioral factors

- Knowledge about TB disease and its treatment duration
- Perception about the cost related to TB disease
- Perceived susceptibility to MDR TB
- Perceived severity of TB
- Belief about the modern TB medicine
- Belief about the benefit of regular medication
- Perceived stigma
- Forgetfulness
- Alcohol use
- Substance abuse
- Smoking status

Provider-related factors

- Instruction on how to take medicine,
- Information on the importance treatment
- Information on side effect and consequence of missing drugs
- Protecting privacy of patients
- Counseling patient during TB treatment

Health care system related factors

- Availability and accessibility of the drug
- Treatment strategy (DOTS and home based)
- Waiting time for receiving drug
- Distance from health care service unit

Disease characteristic and complexity of treatment regimen

- Drug side effect

- Drug burden
- Duration of treatment

Outcome variable

- **Non-adherence**

4.7 Data collection procedures and Instruments

Graduate students of Gambella Teacher and Health Science college were selected as data collectors. Experience about data collection was given due consideration during data collectors' selection. In addition to this, knowledge of local language was also considered to avoid language barriers. A two day training of the data collectors and field supervisor was conducted on Feb 25-26, 2017. The training had covered the following topics; General knowledge on TB disease and treatment as per the National guidelines; TB program, objectives and importance of the study, orientation about the questionnaires. Beside this, communication skills was included for data collectors to obtain a reliable information from study participants. A facility visit was arranged as a part of training and pre-testing for the questionnaires was done on 9 individual TB patients who follow DOTS at Gambella hospital, the subjects were contacted at their home for interview. The result was analyzed manually to check the consistency of the questionnaires. After that, minor modification on the tools was done based on the pre-test result.

Structured questionnaire/tool was used for face to face interview. It was first prepared in English by the principal investigator and checked by the two advisors. Then it was translated into (Nuer and Amharic). The translation was done by experienced University instructors. Similarly, the translation back to English was done by another college teacher who is experienced in translation.

4.8 Data quality control

Training of data collectors and pre-testing of questionnaire had contributed to the data quality assurance. Beside this, the completeness and consistency of data was checked at field by the data collectors, then checked again by the supervisor and principal investigator at the end of each session. Double entry of data into Epi-Data version 3.1 was done to minimize the errors during data entry time.

4.9 Data entry and analysis procedure

After completion of the data entry, data were exported to SPSS version 20. For categorical variables, bivariate analyses or cross-tabulation of each independent variable with the outcome was performed using χ^2 test. Where a cell value was below 5, Fisher's exact test for two-way tables was applied. The criterion for significance was set at p-value less than 0.05 on a two sided-test. All the variables that were not significantly associated with outcome at χ^2 test were not entered for bivariate analysis.

All the independent variables that have a significant association with adherence status were analyzed using bivariate analysis. All variables with p-value less than 0.25 qualified as a candidate for multivariable logistic regression model. The use of p-value 0.25 as a screening criteria was based on the work of Bendel and Afifi (1977) on linear regression and the work of Mickey and Greenland (1989) on logistic regression. These authors argued that the use of significance level as p-value less than 0.05 often fails to identify the important variables. After the completion of bivariate analysis, multi-co linearity among the variables which qualified for multiple logistic regression was diagnosed and checked by considering Pearson correlation coefficient (r), the cutoff point was that $r=0.8$ and above, indicated multicollinearity, otherwise, no concern (51). If two or more variables have multicollinearity effect, one of them was removed and only one was retained to reduce redundancies.

Then multivariate logistic regression model built using backward LR by removing all the insignificant until a simple model with main predictors was obtained. Adequacy of the model to fit the outcome variable with the predictors was checked using Hosmer and Lemeshow Test for goodness of fit. With the p-value less than 0.05, the model would not fit the data very well. Otherwise, it would be adequate to fit the data (52). The model has indicated the goodness of fit (Hosmer & Lemeshow test, p-value=0.725).

Finally, the interaction terms were added to the model containing all the main effects and their significance was assessed using likelihood ratio test. Then the two models were compared to check the effect of interaction terms.

4.10 Ethical consideration

Ethical approval was provided by the IRB of Faculty of Public Health, Jimma University. Formal letter of permission was obtained from Jimma university and communicated to Gambella Regional health Bureau. Then letter of permission was also obtained from Gambella regional Health Bureau to all districts included under this study where they offered a permission to health facilities where the patients' records were reviewed. Beside this, the district offered a letter of permission to kebele where the patients were tracked at the community level.

Finally verbal consent was secured from the subjects included under the study before data collection. Before leaving the interviewed participants, health information messages was provided to those patients who had interrupted their treatment in order to seek the TB treatment again and those who completed their treatment were appreciated and encouraged to forge the same health seeking behavior for other medication of the diseases.

4.11 Operational definitions

Non adherent: TB patients who missed 10% of the doses during the duration of the treatment. For six months treatment period, 10% of the doses is equivalent to 18 days. Meaning that 10% of 180 days of the entire treatment duration. For 12 months duration of treatment, 10% of the missed doses is equivalent to 36 days. This information can be found from the patients' record at TB treatment units(28)

Adherents: TB patients who completed 90% or more of the recommended doses during the entire duration of the treatment (28).

Smear-positive pulmonary TB (PTB+): patient with at least two initial sputum smear examinations positive for AFB by direct microscopy, or

A patient with one initial smear examination positive for AFB by direct microscopy and culture positive, or

A patient with one initial smear examination positive for AFB by direct microscope and radiographic abnormalities consistent with active TB as determined by a clinician.

Smear-negative pulmonary TB (PTB-): A patient having symptoms suggestive of TB with at least 3 initial smear examinations negative for AFB by direct microscopy, and (a) no response to a course of broad-spectrum antibiotics, and (b) again three negative smear examinations by direct microscopy, and (c) radiological abnormalities consistent with pulmonary tuberculosis, and (d) decision by a clinician to treat with a full course of anti- tuberculosis Or a patient whose diagnosis is based on culture positive for M. tuberculosis but three initial smear examinations negative by direct microscopy.

Treatment failure (F): A patient who, while on treatment, is smear-positive at the end of the fifth month or later, after commencing. Treatment failure also includes a patient who was initially sputum smear-negative but who becomes smear-positive during treatment.

Treatment default: An interruption of TB treatment for two or more consecutive months during the intended treatment period.

Treatment duration. The time recommended to treat/cure TB. It is 6 months for pulmonary TB and extra pulmonary TB without involvement of central nervous system (CNS) and 12 months for extra pulmonary TB which involves CNS, TB Meningitis, TB Pericarditis and 18 months and above for MDR-TB patients.

Waiting Time: The time spent by patients to receive drugs at TB service unit.

Distance. The distance (km) of health facility from TB patient's home.

Knowledge: Patient's knowledge about the TB disease. It can be assessed by knowing the cause of TB, preventability, curability, duration of TB treatment in months as well as knowing the consequences of stopping treatment.

Patient's family support: A kind of support a patient received from family or friends during the treatment period. This support can be reminder about the date of appointment, reminder to take the drug, or spiritual support.

Perceived severity: Patient's personal feeling of how serious the disease is. It can be assessed as very low if the patient perceive the disease as not highly severe, medium if perceived as moderately severe, high if perceived as severe and very high if perceived as highly severe.

Perceived susceptibility: Patient's feeling or perception about how vulnerable or risk he/she is to TB which is difficult to cure as result of stopping taking TB medication. It can be measured as very low risk if a patient perceived him/herself as not highly at risk, medium if perceived as moderately at risk, high if perceived as at risk and very high if perceived as high susceptible or at risk.

Perceived stigmatization: Patient's personal feeling of being stigmatized/discriminated by other community members because of having TB disease.

Perceived benefits: Patient's belief about benefits of taking drug to cure his/her diseases. It is measured as very low if a patient believes that taking doses will not totally cure him/her, medium if he/she believes that the drug will moderately/partially cure the disease, high if he/she believes the drug will cure him/her, and very high if he/she believes that the drug will totally cure him/her.

Perceived barriers to treatment: Patient's fear about what could stop him/her from taking TB drugs. It can be measured by assessing the barriers of adherence to TB treatment (drug side effect, drug burden, waiting time to get services, distance to health facility, cost related to diseases treatment, patient's privacy, stigma). In order for health behavior (adherence to medication) to be adopted, a person needs to believe that the benefit of taking medication outweigh the consequences of stopping medication. This enables the barriers to be overcome and health behavior (adherence to TB medication) to be adopted.

Smoking status: Patient's smoking status during the entire treatment period of TB.

Alcohol use: Patient's alcohol drinking status during the entire treatment period of TB

Substance use: Patient's use of substance (chat, shisha, marijuana etc.) during the treatment period of TB.

Drug side effects: The effects such as dizziness, crumpling, nausea due to anti TB drugs experienced by the patients

Drugs burden: Taking anti -TB drugs along with other drugs such as Anti retroviral therapy (ART)

Treatment strategy during initial phase: Patient's treatment strategy (home base and DOTS) during the initial phase of TB treatment.

Health information: TB disease treatment information provides to patients by provider during the treatment period.

Incentives/enablers: Those things a patients receive from health facility and enable/or motivate them to continue their treatment (e.g transport voucher, reimbursement of transport money, money, others such as soap, food etc..).

4.12 Dissemination of findings

The findings will be submitted to the Department of Epidemiology, Jimma University and Gambella Regional Health Bureau, and public health facilities involved in the study or woreda/district health offices. It will be published in a peer reviewed scientific journal. It will also be printed and used by health staffs, policy makers and as well as clinicians working at TB treatment service units at the specific study area.

5. RESULTS

5.1 Descriptions of socio-demographic characteristics

Of the total sample size of 296 TB patients, the response rate was 97.3%. Hence, the sample population interviewed was 288 (72 cases and 216 controls). The study revealed that forty three (59.7%) cases (non adhered patients) and 137 (63.4%) controls (adhered patients) were male participants. The mean age for both sexes was 39.95 ± 13.4 years for cases and 35.4 ± 10.5 years for controls. Thirty one (43.1%) cases and 133 (61.6%) controls were in the age of 18-37. Fifty one (70.8%) cases and 174 (80.6%) controls were married. Among the study participants, twenty nine (40.3%) cases and 81 (37.5%) controls were Nuer. Sixty six (91.7%) cases and 195 (90.3%) controls followed Christianity. Forty seven (65.3%) cases and 198 (91.7%) controls had attended formal education. Seventeen (23.6%) cases and 120 (55.6%) controls were employed. The mean income of the study cases and controls was 1691.8 and 2128.5 and the overall mean income was 2019.337 Birr. Fifty (69.9%) cases and 198 (91.7%) controls resided in urban area during the entire treatment period (Table 2).

Table 2. Socio-demographic and economic factors for TB patients at Gambella, Kuergeng, Pugnido and Nyinenyang Health centre respectively, Gambella Region, March, 2017

Socio-demographic characteristics		cases no (%)	controls no (%)
Sex	Male	43 (59.7%)	137 (63.4%)
	Female	29 (40.3%)	79 (36.6%)
Age	18-37	31 (43.1%)	133 (61.6%)
	38-57	34 (47.2%)	72(33.3%)
	>=58	7 (9.7%)	11 (5.1%)
	Marital status	Married	51 (70.8%)
	Unmarried	21 (29.2%)	42 (19.4%)
Education	Formal education	47 (65.3%)	198 (91.7%)
	No formal education	25 (34.7%)	18 (8.3%)
Occupation	Employed	17 (23.6%)	120 (55.6%)
	Unemployed	55 (76.4%)	96 (44.4%)
Religion	Christian	66 (91.7%)	195 (90.3%)
	Muslim	6 (8.3%)	21 (9.7%)
Ethnicity	Nuer	29 (40.3%)	81 (37.5%)
	Anywaak	20 (27.8%)	51 (23.6%)
	Others	23 (31.9%)	84 (38.9%)
	Income (Birr)	<501Birr	34 (47.2%)
	>=501Birr	38 (52.8%)	181 (83.8%)
Residence	Urban	50 (69.4%)	198 (91.7%)
	Rural	22 (30.6%)	18 (8.3%)

5.2 Descriptions of patient's behavioral factors

Forty three (59.7%) of the cases and all controls know the causative agent of TB as bacteria. Similarly, forty eight (66.7%) of the cases and 215 (99.5%) controls also knew that TB could be prevented. Sixty seven (93.1%) cases and all controls believed that modern medicine could cure TB. Forty one (56.9%) cases and 206 (95.4%) controls believed the advantage of regular medication to cure TB. The study has revealed that forty seven (65.3%) cases and 177 (81.9%) controls knew the duration of TB treatment. The current study has also indicated that fifty three (73.6%) cases and 2012 (98.1%) controls know the consequence of missing TB medication. Forty one (56.9%) cases and 4 (1.9%) controls missed their anti TB drugs because of having not felt any improvement sign after starting the medication. More than half (55.6%) cases and 205 (94.9%) controls perceived TB as severe. Fifty four (75%) cases and 46 (21.3%) controls do not perceive that they would be susceptible to MDR-TB as a result of discontinuing treatment. Regarding TB stigma, forty two (58.6%) cases and 30 (13.9%) controls perceived that they were stigmatized because of having TB. Forty eight (66.7%) cases and 103 (47.7%) controls perceived that their privacy had never been protected/kept while receiving TB services. Forty two (58.3%) cases and 18 (8.3%) controls reported that they had been smoking during treatment schedule. Fifty one (70.8%) cases and 11 (5.1%) controls had been drinking alcohol while on TB medication. Fifty one (70.8%) of the cases and 203 (94%) controls had reported that they had never used substances such as chat, marijuana and hashish during their treatment period. Regarding patient's support (reminder of medication time, and appointment date) from family or friends, fifty one (70.8%) cases and 197 (91.2%) controls stated that they had received support. Other behavioral factors of the study participants are displayed (Table 3).

Table 3. Patient's behavioral factors at Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, Gambella Region, March, 2017

Patient's behavioral factors		Cases no (%)	Controls no (%)
The cause of TB	Bacteria	43 (59.7%)	216 (100%)
	Do not know	29 (40.3%)	0 (0.0%)
TB preventable	Yes	48 (66.7%)	215 (99.5%)
	No	24 (33.3%)	1 (0.5%)
Modern medicine cure TB	yes	67 (93.1%)	216 (100%)
	No	5 (6.9%)	0 (0.0%)
Benefit of regular medication	Cure	41 (56.9%)	206 (95.4%)
	not cure	31 (43.1%)	10 (4.6%)
Duration of TB treatment	Know	47 (65.3%)	177 (81.9%)
	Did not know	25 (34.7%)	39 (18.1%)
Patient- knows the consequence of missing drugs	yes	53 (73.6%)	212 (98.1%)
	No	19 (26.4%)	4 (1.9%)
Patient's reasons for missing drugs	No improvement	41(56.9%)	4 (1.9%)
	Feeling ashamed	31 (43.1%)	2 (0.9%)
	Never missed drugs for any personal reasons	0 (0.0%)	210 (97.2%)
Perceived severity of TB	Severe	40 (55.6%)	205 (94.9%)
	Not severe	32 (44.4%)	11 (5.1%)
Perceived susceptibility to MDR-TB	Susceptible	18 (25%)	170 (78.7%)
	Not susceptible	54 (75%)	46 (21.3%)
Perceived Stigma	Not stigmatized	30 (41.7%)	186 (86.1%)
	Stigmatized	42 (58.3%)	30 (13.9%)
Perceived privacy	Protected	24 (33.3%)	113 (52.3%)
	unprotected	48 (66.7%)	103 (47.7%)
Smoking habit	Non smoker	30 (41.7%)	198 (91.7%)
	Smoker	42 (58.3%)	18 (8.3%)
Alcohol habit	Non drinker	21 (29.2%)	205 (94.9%)
	Drunker	51 (70.8%)	11 (5.1%)
Substance habit	non user	51 (70.8%)	203 (94%)
	User	21 (29.2%)	13 (6%)
Whether received family support	Received support	51 (70.8%)	197 (91.2%)
	Did not received support	21 (29.2%)	19 (8.8%)

5.3 Description of health care and provider's related factors

Thirty six (50%) cases and sixty five (30.1%) controls used to take home their anti TB drugs during initial phase of TB treatment. Thirty eight (52.8%) cases and 77 (35.7%) controls had reported an additional expenses related to TB test. Forty two (58.3%) cases and 3 (1.4%) controls had reported that, health service provider being so busy with other works had been one of the reasons for missing medication. Forty (55.6%) cases and 6 (2.8%) controls had pointed out the drug burden/side effect as one of the contributing factors for missing drugs. Seventy one (98.6%) cases and 202 (93.5%) controls had reported that they had received information about TB treatment. Fifty two (72.2%) cases and 55 (25.5%) controls had not ever received counseling during TB treatment.

Sixty three (87.5%) cases and 183 (87.7%) controls had not received incentives (food, transport voucher, money or cloth) during the course of therapy. Fifty four (75%) cases and 207 (95.8%) controls lived in less than 5km away from TB services unit. Fifty three (73.6%) cases and 120 (55.6%) controls used public transports (Minibus and Bajaj) to access TB treatment services.

Table 4. Health care and provider's factors for study subjects at Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, Gambella Region, March, 2017

Exposure factors		Cases no (%)	Controls no (%)
Treatment strategy	DOTS	36 (50%)	151 (69.9%)
	Home based	36 (50%)	65 (30.1%)
Reasons for related cost of TB treatment	no incurred cost	31(43%)	111 (51.4%)
	Test for TB	38 (52.8%)	77 (35.7)
	Managing drug side effect	3 (4.2%)	28 (13%)
Health care factors for missing drugs	no reasons	12 (16.7%)	210 (97.2%)
	Provider being busy	42 (58.3%)	3 (1.4%)
	Waiting Time	18 (25%)	3 (1.4%)
Disease and treatment factors for missing drugs	No reasons	32 (44.4%)	210 (97.2%)
	Drug side effect	40 (55.6%)	6 (2.8%)
Health Information	Received	71 (98.6%)	202 (93.5%)
	Did not received	1 (1.4%)	14 (6.5%)
Incentives	Not received	63 (87.5%)	183 (87.7%)
	Received	9 (12.5%)	33 (15.3%)
Distance TB Clinic	<5km	54 (75%)	207 (95.8%)
	>=5km	18 (25%)	9 (4.2%)
Transport means	Footing	19 (26.4%)	96 (44.4%)
	Public transport	53 (73.6%)	120 (55.6%)
Whether patient had been counseled	Yes	20 (27.8%)	161(74.5%)
	No	52 (72.2%)	55 (25.5%)

5.4 Socio-demographic factors associated with non adherence to anti-TB treatment in bi-variable analysis

The result of bivariate analysis indicated that, age 38-57 years old, having no formal education, unemployed, income, rural residence and having not supported by family or friends were associated with non adherence to medication (Table 5).

Table 5. Socio-demographic factors associated with non adherence to TB treatment in bi-variate analysis at Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, Gambella Region, March, 2017

Socio-demographic characteristics		non adhered no (%)	adhered no (%)	OR	95% CI	P-value
Age	18-37	31(43.1)	133 (61.6%)	1		
	38-57	34 (47.2%)	72 (33.3%)	2.14	1.152-3.56	0.014*
	>=58	7 (9.7%)	11 (5.1%)	2.73	0.98-7.61	0.055*
Educational status	No formal education	25 (34.7%)	18 (8.3%)	5.85	2.95-11.6	0.001*
	Formal Education	47 (65.3%)	198 (91.7%)	1		
Occupation	Employed	17 (23.6%)	120 (55.6%)	1		
	Unemployed	55 (76.4%)	96(44.4%)	4.05	2.21-7.42	0.001*
Income	<501Birr	34 (47.2%)	35 (16.2%)	4.63	2.57-8.33	0.001*
	>=501Birr	38 (52.8%)	181 (83.8%)	1		
Residence	Urban	50 (69.4%)	198 (91.7%)	1		
	Rural	22 (30.6%)	18 (8.3%)	4.84	2.4-9.71	0.001*
Patient's family support	Received support	51 (70.8%)	197 (91.2%)	1		
	No support	21 (29.2%)	19 (8.8%)	4.27	2.14-8.54	0.001*

Note: (*) indicates (the p-value less 0.25), 1 indicates the reference variable; OR=crude odds ratio, CI=confidence interval at 95% significance level

5.5 Behavioral factors associated with non adherence to anti-TB treatment in bi-variable analysis

Bivariate analysis results indicated that having not believed in the benefit of regular medication, . having not knowing the consequence of missing TB medication, perceiving TB as not severe, perceiving of being not susceptible to MDR-TB, not knowing the duration of TB treatment, perceiving of being stigmatized, perceiving privacy as not confidential/protected and being not counseled during TB treatment, being smoker, alcohol drinking, drug users were associated with non adherence to anti-TB treatment(Table 6).

Table 6. Behavioral factors associated with non adherence to TB treatment in bivariate analysis, Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, Gambella Region, March, 2017

Behavioral factors		non adhered no (%)	adhered no (%)	OR	CI	p-value
The benefit of regular medication	Cure	41 (56.9%)	206 (95.4%)	1		
	Not cure	31 (43.1%)	10 (4.6%)	15.58	7.1-34.2	0.001*
Whether patient knows the duration of TB treatment	Know	47 (65.3%)	177 (81.9%)	1		
	Do not know	25 (34.7%)	39 (18.1%)	2.41	1.33-4.38	0.04*
Whether patient knows the consequence of missing drugs	Yes	53 (73.6%)	212 (98.1%)	1		
	No	19 (26.4%)	4 (1.9%)	19	6.2-58	0.001*
Patient's perceived severity of TB	Severe	40 (55.6%)	205 (94.9%)	1		
	Not severe	32 (44.4%)	11 (5.1%)	14.9	6.9-32	0.001*
Patient's perceived susceptibility to MDR-TB	Susceptible	18 (25%)	170 (78.7%)	1		
	Not susceptible	54 (75%)	46 (21.3%)	11.12	5.9-20.7	0.001*
Perceived stigma of being TB patient	Not stigmatized	30 (41.7%)	186 (86.1%)	1		
	Stigmatized	42 (58.3%)	30 (13.9%)	7.63	4.1-14.2	0.001*
Patient's perceived privacy	Protected	24 (33.3%)	113 (52.3%)	1		
	Unprotected	48 (66.7%)	103 (47.7%)	2.24	1.3-3.8	0.001*
Smoking habit	Non smoker	30 (41.7%)	198 (91.7%)	1		
	Smoker	42 (58.3%)	18(8.3%)	15.43	7.7-30	0.001*
Alcohol habit	Non drinker	21 (29.2%)	205(94.9%)	1		
	Drinker	51 (70.8%)	11(5.1%)	45.31	20.5-99.9	0.001*
Substance habit	Non user	51 (70.8%)	203(94%)	1		
	User	21 (29.2%)	13 (6%)	6.44	3-13.7	0.001*

Note: (*) indicates the p-value less 0.25), 1 indicates the reference variable; OR=crude odds ratio, CI=confidence interval

5.6 Health care system factors associated with non adherence to TB treatment in bivariate analysis

Bivariate analysis results indicated that taking anti-TB drugs home during intensive phase, living more than 5km away from TB service unit, using public transport as means of transport to access services, not being counseled during treatment were crudely associated with non adherence to TB treatment (Table 7).

Table 7. Health care and provider's factors associated with non adherence to TB treatment in bivariate analysis, Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, Gambella Region, March, 2017

Exposure factors		Non adhered no (%)	Adhered no (%)	OR	95% CI	p-value
Treatment strategy	DOTS	36 (50%)	151(69.9%)	1		
	Home based	36 (50%)	65 (30.1%)	2.32	1.33-4	0.002*
Disease treatment factors	No reason	32 (44.4%)	210 (97.2%)	1		
	Drug side effect	40 (55.6%)	6 (2.8%)	43.75	17-111	0.001*
Distance to TB Clinic	<5km	54 (75%)	207 (95.8%)	1		
	>=5km	18 (25%)	9 (4.2%)	7.67	3.2-18	0.001*
Transport mode	Footing	19 (26.4%)	96 (44.4%)	1		
	Public transport	53 (73.6%)	120 (55.6%)	2.23	1.2-4.0	0.008*
Whether patient had been counseled	Yes	20 (27.8%)	161(74.5%)	1		
	No	52 (72.2%)	55 (25.5%)	7.61	4.18-13.86	0.001*

Note: (*) indicates (the p-value less 0.25), 1 indicates the reference variable OR=crude odds ratio, CI =Confidence interval at 95% significance level

5.7 Factors independently associated with non adherence to anti-TB treatment

Five predictors were independently associated with non adherence to anti-TB treatment among TB patients who had been treated under four public health facilities. TB patients who perceived as being stigmatized were 2.74 times more likely to be not adhered than those who do not perceived stigma as a result of TB. TB patients who do not believe in the benefit of regular medication were 6.83 times more likely to be not adhered than those who believed in the benefit of regular medication.

perceiving TB as not severe was statistically significantly associated with non adherence to TB treatment (AOR,8.38); CI at 95% (2.1-34.6), with p-value =0.03. Having not been counseled during TB treatment (AOR, 35.52), at 95% CI (10-122), p-value =0.001 and being smoker during treatment schedule (AOR,11.13), at 95% CI (4-29), p-value =0.001 were also independently associated with non adherence to TB treatment(Table 8).

Table 8. Factors independently associated with non adherence to anti-TB treatment among TB patients treated at Gambella, Kuergeng, Pugnido and Nyinenyang Health center respectively, March 2017.

Exposure variables		Cases no (%)	Controls no (%)	AOR	CI	P-value
Perceived stigma	Not stigmatized	30 (41.7%)	186 (86.1%)	1		
	Stigmatized	42 (58.3%)	30 (13.9%)	2.74	1.1-6.6	0.03
Benefit of regular medication to cure TB	Cure	41 (56.9%)	206 (95.4%)	1		
	Not cure	31 (43.1%)	10 (4.6%)	6.83	1.8-24.9	0.04
Perceived severity of TB	Severe	40 (55.6%)	205 (94.9%)	1		
	Not severe	32 (44.4%)	11 (5.1%)	8.38	2-34.6	0.03
Whether patient had been counseled	Yes	20 (27.8%)	161(74.5%)	1		
	No	52 (72.2%)	55 (25.5%)	35.52	10-122	0.001
Smoking habit	Non smoker	30 (41.7%)	198 (91.7%)	1		
	Smoker	42 (58.3%)	18(8.3%)	11.13	4-29	0.001

Note: 1 indicates the reference variable, AOR= Adjusted odds ratio, CI =confidence interval at 95% significance level. Hosmer & Lemeshow test, indicated the goodness of fit for the model; p-value=0.725

6. DISCUSSION

TB treatment discontinuation often leads to poor final treatment outcome, multi-drug resistant TB as well as extensively drug resistant TB; the current concerns of the country and the region in particular. The current study indicated that non adherence to anti-TB treatment among TB patients who had followed DOTS under four public health facilities of Gambella Region was influenced by some components of patients and health care related factors; an issue which has been acknowledged by previous scholars (35). Hence; the study has thematically discussed the prominent determinants of non adherence to TB medication as follows.

The study has pointed out that, perceiving TB as not severe, and not believing in the benefits of regular medication were independently associated with non adherence to anti TB drugs among TB patients. The possible reasons for this could be the fact that, perceiving disease as not severe usually do not trigger or could not keep individuals to maintain health behavior, unless a patient perceived and believes the threat and difficulty the disease will impose on his/her life. These fears or threats could be physical suffering, financial burden and loss of income as a result of contracting the disease. Similarly, if patients do not believe in the benefit of taking action, the likelihood of adopting the new behavior (adhering to TB medication) will be less, unless the patient believed in the usefulness of adopting new behavior that it would decrease the risk of developing disease (for instance; progression or developing MDR-TB). Perceived severity of TB and perceived benefit of regular medication were the constructs of health belief model, which are common to influence healthy behavior. Researchers acknowledged their importance in TB control or TB treatment (53).

The study has divulged that perceiving stigmatized by others because of being TB patient was a significant predictor of non adherence to anti-TB drugs. Those patients who perceived as being stigmatized were 2.7 times more likely to be non adherent compared to those who did not perceive stigmatized. The possible explanation for this might relate to fear of stigma as TB disease is usually associated with HIV/AIDS. Similar observation was documented by other researchers who stated that, having TB has been attached with stigmatization or rejection by community members. Such a behavior of denial and social isolation could pave the gate for non adherence to anti-TB drugs, eventually could lead to poor treatment outcome, MDR-TB, death and transmission of the disease among community members (15,54). The finding is consistent with other findings conducted in Eastern Sudan Region (43).

In addition to patient's behavioral factors was the smoking habit which has a significant association with non adherence to TB medication. It showed that, being smoker during TB treatment was 15 times more likely to be non adherent to medication than being non smoker. This is consistent with study conducted in India (55). In general, patient related factors contributed most to non adherence to TB medication.

Apart from this, provider related factors also contributed to non adherence to TB treatment. Having not been counseled during treatment period had been significantly associated with non adherence to TB treatment. This clearly shows the importance of counseling as TB treatment goes for a relatively longer period of time that requires persistent follow-up and support so that patients strictly adhere to the treatment regimen. Researches indicated that adequate counseling that encompasses, healthcare needs, physical suffering, financial burden, nutritional needs, psycho-social or emotion as well as spiritual suffering of patients during the entire period of TB treatment has been an integral aspect of improving patients adherence to TB medication (56,57). The result conformed with other findings in Sudan and South Africa (34,58,59).

Despite the remarkable finding observed between the aforementioned predictors and non adherence, the current study has not shown a significant association between knowledge about duration of TB treatment and adherence. This is contrary to the previous findings observed in South Ethiopia (60) and finding of Khartoum State of Sudan (61). The discrepancy could be the fact that in the current study, almost 60% above of the cases and 95% and above of the controls knew the cause of TB, its preventability, curability using modern medicine, and well informed about the duration of TB treatment as well as the consequences of discontinuing the treatment. This could positively contribute to their awareness about the importance of TB treatment, eventually enhancing their adherence to TB medication.

Furthermore, finding has not manifested an association between illiteracy and non adherence to TB treatment; that is inconsistent with the study conducted in Brazilian Amazon area and Equatorial Guinea (62,63). The disagreement between the previous findings and the present study could be because in the latest study, most of the study subjects had formal education which might also contribute to their knowledge of the disease treatment and could be advantageous and protective reason for non adherence to TB medication.

In this particular study as well, income has not been found to associate with non adherence to anti TB drugs, unlike the previous studies in Kenya (64). Recent studies in Argentina and South East Nigeria had also pointed out that TB disease is generally associated with poverty and low income status, as a result, it mostly affected the poor section of the community, hard to reach people, and

those who cannot afford the transport cost for accessing TB treatment from far distant (39,40). However; in the current study, the monthly income for most participants was 501 Birr or greater compared with the study conducted in Northern Ethiopia (29). This could justify the reason for insignificant association of income with non adherence to TB treatment. Beside this, distance of patient's home to TB service unit was not independently related with non adherence to anti-TB drugs. The probable reason for this could be because most patients of the present study resided in urban area and lived within not more than 5km away from DOTs TB clinic. Hence, access to TB treatment services might be much easier for them than those who lived in rural area as well as within 5km or more away from the TB clinic (34). Other researchers in Nepal and Ethiopia have documented a similar findings that shorter distance of less than 5km was not a risk factor for non adherence to TB medication (29,65). Regarding barriers to access TB treatment services, transport means (using public transport), is also another factor which has not been found to be statistically significantly associated with non adherence to TB treatment. The main reasons could not differ from having income for patients and possibility to afford cost related to transport for obtaining medicine from TB clinic.

The current study has shown a significant association between the absence of family support and non adherence to TB medication. The possible implication for this could be because, most cases (71%) and 91% of the controls had received support from family during TB treatment. This may help them to strictly adhere to their medication. Moreover, the finding has contradicted with the previous findings which indicated the association between family support and non adherence to TB medication (34).

The bottom line is that, the study has addressed various determinants of non adherence to TB treatment by including behavioral components using constructs of health belief model, a public health model commonly used for improving TB treatment seeking behavior. This had helped in articulating and exploring other possible factors that affected non adherence to TB treatment. Most studies had exclusively dealt with socio-economic factors. Another strength was that the recall bias was minimized by reviewing the patient medical records and cross checking some variables that might intrude recall or difficulty in remembering by the patient. For instance; duration of TB treatment, TB treatment phases or months in which a patient interrupted/missed his/her drugs was retrieved from records.

However, there were some limitations and reservations. Thus, generalization of the finding to wider region is under question as the sample population was taken from only four public health

facilities because of resource limitations. In additions to this, sample size estimation from different areas due to lack of literatures from specific study areas might affect the reliability and precision, Beside this, recall bias in case control study is another limitation.

7. CONCLUSION

The study has profoundly addressed numerous factors that influenced non adherence to TB treatment in four public health care facilities of Gambella Regional State. The finding acknowledged that, the determinants of non adherence to TB treatment were patient's behavioral factors such as perceiving TB disease as not severe, not believing in the benefit of regular medication, perceiving as being stigmatized as a result of TB disease and being smoker during TB treatment period. In addition to this, lack of counseling during TB treatment was found to be determinant of non-adherence to treatment.

8. RECOMMENDATIONS

In order to improve TB treatment adherence in the studied public health facilities, Regional Health Bureau should build the capacity of service providers through training and supervise them at their respective work site. This will enhance their skill and help them to properly counsel their clients/patients. Consequently, patients would build confidence during their treatment schedule and follow medication without interruption. Apart from this, the system also should rigorously target the frontline community volunteer and health extension workers that would allow them to monitor their patients and advise them to refrain from smoking while on TB treatment. Further study is needed to screen MDR-TB among non adhered patients TB treatment.

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ANNEX II: QUESTIONNAIRES

JIMMA UNIVERSITY

INSTITUTE OF HEALTH

Postgraduate Program of MPH in Epidemiology

Name of principal investigator-----Name of data collector (s) -----

Dear Sir/madam;

As part of academic requirements, I am conducting assessment on factors that affect TB treatment/medication adherence. The-----Hospital/Health center has been selected for this purpose. You, as one of the patients under treatment in this health facility, are identified to be included in the study and your involvement is totally on voluntary basis. This will help us to understand the barriers for adherence to TB treatment.

The information obtained from you will not be disclosed to any other third body. Rather it will be used for research purpose only for solving the problems related to TB treatment.

Therefore, I am kindly asking your cooperation to participate in this interview and contribute for the improvement of TB disease control program.

Respondent's identification information

001. Health facility/ unit----- Zone.....Wordea/District.....Kebele.....

002 Case (non adherent) (1)TB patient who missed 10% of the doses and above (18 days and above for 6 months and 36 days and above for 12 months treatment period).

003. Control (adherent) (0).....TB patients who completed 90% of the doses and above during the entire treatment period.

Section 1: Socio-demographic Information of the respondent First, I would like to ask you some questions about yourself		
Q. #	Questions	Codes
1	Gender/sex	Male Female
2	How old are you ?	Age in years-----
3	What is your marital status	Single-----1 Married-----2 Widowed-----3 Divorced-----4 Separated-----5
4	What is your religion?	Orthodox.....1 Muslim.....2 Protestant.....3 Catholic.....4 Other specify97
5	What is your Ethnicity ?	Nuer.....1 Anuak.....2 Mejeng.....3 Oromo.....4 Amhara.....5 Other specify97
6	What is your occupation?	Employed.....1 Merchant2 Unemployed.....3 Farmer4 Housewife.....5 Other specify97
7	What is your average monthly income in Birr ?
8	What is your educational status?	Illiterate.....1 Read & write only2 Primary (G1-8 th).....3 Secondary (9-12 th).....4 Diploma and above.....5

9	What is your residence now ?	Urban1 Rural.....2
Section two: Questions pertaining to patients related factors that influence adherence to TB treatment		
10	What is the cause of TB ?	Bacteria1 Virus2 Parasites3 Other specify...97 Do not know.....99
11	Is TB a preventable disease ?	Yes.....1 No.....2
12	Is TB a curable disease?	Yes.....1 No.....2
13	Do you know how long your treatment had lasted ?	Yes1. No.....2
14	If yes for question No 13. For how many months?	Treatment duration in months -----
15	In which month(s) had you stop/ were you likely to stop your medication ?	First month.....1 Second month...2 Third month.....3 Forth month4 Fifth month.....5 Sixth month6 Seven month7 Eight month.....8 Nine month.....9 Tenth month10 Eleventh month....11 Twelve month.....12 None of them.....99
16	Which of the following conditions do you think could/had stop you from taking TB medicines?	TB drug side effects1 Forgetfulness2 Feeling better3 Feeling no improvement4 Taking other drugs along with TB drugs5 Other specify.....97

		None of them99
17	How do you rate the severity of TB disease?	Not highly severe1 Moderately severe.....2 Severe.....3 Highly severe4
18	Does stopping or missing the dose of TB medicines lead to a type of TB that is uncurable?	Yes1 No.....2
19	If yes for Q 18, rate your susceptibility to type of TB which is difficult to cure (MDR-TB)?	Not highly susceptible1 Moderately susceptible.....2 Susceptible.....3 Highly susceptible4
20	How do you rate your feeling of being stigmatized/discriminated because of having TB disease?	Not highly stigmatized.....1 Moderately stigmatized.....2 Stigmatized.....3 Highly stigmatized4
21	Circle/choose the following options about your believe of regular taking of TB medicines	Totally will not cure the disease.....1 Moderately will cure the disease2 Will cure the disease.....3 Totally will cure the disease.....4
22	Had/have you ever smoked during the treatment period ?	Yes1 No.....2
23	Had you ever used other drugs (Khat, Shisha etc...) during your the treatment period of your disease?	Yes.....1 No.....2
24	Had you ever drunk alcohol during your treatment period ?	Yes.....1 No.....2
Part Three. Health care/systems related factors, health services provider-patient and family support for patients		
25	During the initial phase (2-3 months) of your treatment, where did/do you use to take/swallow your medicine ?	At the TB services unit (DOTs).....1 At home (home based)2

26	During your treatment duration(s), what kind of support have you received from your family members or neighbor/friends?	Reminder about medication.....1 Spiritual support.....2 Reminder for the date of appointment....3 Other specify.....97 None of them99
27	What is the distance (on average) of your home from TB treatment unit ?	Less 5 km1 More than 5 km.....2
28	For Q 27, if the distance from TB treatment unit is more than 5 km, which means of transport do you used ?	On foot.....1 Public transport (Bus, Bajaj etc.).....2 Other specify97
29	Based on Q 28, which means of transport do you think that could/had discouraged you most from taking your drug regularly?	On foot b/c of the long distance1 Public transport due to high cost2 Other specify97 None of them.....99
30	How long on average do/did you wait to get your service from TB unit?	Time in minutes.....
31	Mention if you incur other cost/expense directly related to the following.	Tests for TB diseases.....1 Buying other medicines for managing side effects of the drug2 Other specify.....97 None of them.....99
32	What do/did you feel about your privacy while receiving TB medicines from your doctor/health worker?	Highly unprotected.....1 Moderately protected.....2 Protected3 Highly protected.....4
33	Rate your satisfaction about counseling if provider addresses your emotional and spiritual suffering as a result of TB disease and its treatment?	Strongly unsatisfied1 Moderately satisfied2 Satisfied.....3 Strongly satisfied4
34	Mention any of the following Health care system barriers that could discourage/had discouraged you from receiving drugs at TB services unit	Waiting time at TB treatment unit (average time Minutes.....) Minutes.....).....1 Absence of drug from TB clinic unit.....2 Health workers were busy with other works.....3 Other specify97 None of them.....99

35	Circle the following health information services if any of them was provided to you by your doctor	Instruction about how to take medicine1 Health information on the importance of TB treatment.....2 Health information about the bad consequence of stopping or missing medicine 3 Awareness on the common side effects of the drugs....4 Other specify.....97 None of them99
36	Had/had you ever received any incentive/enablers (for example, food, transport vouchers or money etc..) to continue your treatment ?	Yes1 No.....2