Depression, stigma, social and family support and nutritional status in Filipino TB patients:

Impact on adherence to anti-TB treatment

A mixed-methods study

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Abstract

Background:

The Philippines has the third highest TB incidence worldwide. In the Philippines, limited data exist on the prevalence and effects of depression in Filipinos with TB on adherence to treatment. This study investigated the reasons for nonadherence among Filipinos enrolled in public TB-DOTS centres.

Methods:

A sequential explanatory mixed-methods study nested within the Starting Anti-TB Treatment (St-ATT) cohort study. Filipino adult participants were enrolled in public facilities from St-ATT study in Metro Manila, Cebu, and Negros Occidental within 5 days of starting ATT. Depression and Anxiety symptoms were assessed using The Hospital Anxiety and Depression Scale, Social-family support using the Multidimensional scale of perceived social support, Stigma using TB-related stigma scale, and adherence using the Morisky Medication Adherence scale at baseline, end of intensive phase of treatment, mid- and end of continuation phase in participants. For the qualitative study, 15 key informants within the St-AAT cohort study only in Negros Occidental were purposively selected using criteria based on the quantitative results.

Results:

356 persons were enrolled between 26th April 2019 to 20th February 2020 and had been followed-up until 27th December 2020. The prevalence of depression (HADS depression ≥8) was highest at end of the intensive phase (N=27, 12%) while the prevalence of anxiety (HADS

anxiety ≥8) was highest at enrolment (N=93, 33%). Similarly, of 149 with complete data at all time points, the prevalence of depression was highest at the end of intensive phase (8%) as was nonadherence (Morisky score <6; 21%). In multivariable mixed-effects analysis using all available data, participants on ATT for multi-drug resistant TB (MDR-TB) (β=--0.679, 95% CI: -1.17 -0.186) and from Metro Manila (β = -0.219, 95%CI: -0.392 -0.060) had at any given time-point lower mean Morisky scores of adherence compared to those on drug-sensitive ATT or participants from Western Visayas. Independent of these effects, increased depressive symptoms (β = -048, 95% CI: -0.068 -0.002), and modelled separately, anxiety symptoms (β = -0.066, 95% CI: -0.0801 -0.047), were also associated with lower adherence scores. The qualitative findings showed that participants were depressed after their diagnosis of TB due to lack of TB knowledge, and personal beliefs while financial reasons, severe weight loss, and the fear of contaminating others were the most identifiable reasons behind being anxious. Also, this study found that participants from urban areas were afraid of stigma compared to rural areas who had high social and family support.

Conclusions:

This study found an association between depression/ anxiety and nonadherence to TB medication in Filipino persons undergoing routine treatment at government facilities, especially within the intensive phase. Also, Patients who are taking MDR-TB treatment are more at risk of being non-adherent compared to DS-TB. These findings indicate that mental health evaluation and treatment adherence should be regularly incorporated in the management of TB patients. Social and psychological interventions may improve medication compliance levels especially at end of the intensive phase. Health promotion and providing

financial incentives may improve adherence especially among patients who are taking MDR-TB treatment.

Abbreviations

ATT: Anti-TB Treatment

CP: Continuation Phase

DALYs: Disability-Adjusted Life Years

DAT: Digital Adherence Technologies

DOTS: Direct Observed Treatment

DS-TB: Drug Susceptible TB

ECP: End of Continuation Phase

HADS: Hospital Anxiety Depression scale

HCP: Health Care providers

HIV: Human Immunodeficiency Virus

HRQOL: Health-Related Quality of Life

ICF: Informed consent Form

INH: Isoniazid

IP: Intensive Phase

LMIC: Low and Middle-Income Countries

LSHTM: London School of Hygiene &Tropical Medicine

MCP: Middle of Continuation phase

MDR-TB: Multi-Drug Resistant TB

MHO: Medical Health Officers

MSPSS: Multidimensional scale of perceived social support

NCP: Nutrition Center of the Philippines

NTP: National TB Program

PHQ-9: Patient Health Questionnaire

ODK: Open Data Kit

PMHA: Philippines Mental Health Association

RIF: Rifampicin

SMS: Short Messaging Systems

TB: Tuberculosis

VOT: Video observed treatment

WHO: World Health Organization

Chapter 1

1. Background & literature review

1.1. Global and regional issues of TB

Tuberculosis (TB) remains a major and evolving health challenge globally. In many low and middle-income countries, TB has reached epidemic proportions, with a third of the world's population being infected[1]. TB is one of the top 10 causes of death worldwide and ranked as one of the diseases with a heavy burden of disability-adjusted life years (DALYs), calculated as over 40 million in 2017[2]. The World Health Organization (WHO) estimated that there was 10 million TB incident with 1.6 deaths worldwide in 2019, and 1.8 million of them were in the Western Pacific Region[3]. Among 1.8 million incident cases in the region, 77% of them were detected and notified to National TB Program (NTP), and the treatment success rate was 91%[3]. This shows that a considerable number of individuals with TB do not seek care, or do not complete treatment successfully[4]. TB can be curable if appropriate, effective, uninterrupted anti-tuberculosis therapy is given[5]. Therefore ensuring high adherence to anti-TB treatment (ATT) is considered an essential behavior towards achieving TB elimination through increased cure rates, reduced transmission, and minimizing the development of drug resistance[6].

1.2. TB in the Philippines

In the Philippines, TB is a major health problem. It is ranked as the sixth leading cause of death[3]. In 2019, WHO estimated there were 591,000 incident cases in the Philippines (**Figure 1**), and 26, 000 died in a year[3]. In 2016, the National Prevalence Survey showed that the Philippines has the third-highest TB incidence worldwide at 554 per 100,000 and a prevalence of 1,159/100,000 population[7]. Thus the Philippines is classified as a high TB burden country, both for drug-susceptible TB (DS-TB) and multi-drug resistant TB (MDR-TB) with an estimated 18,000 MDR-TB cases in 2019 (**Figure 1**)[3]. Generally, TB prevalence is high among high-risk groups such as the elderly, urban poor, smokers, and those with compromised immune systems such as people living with HIV, malnutrition, and diabetes[8]. In the Philippines, TB is more prevalent among males compared to females and among the working-age 22-55 years old age group[7].

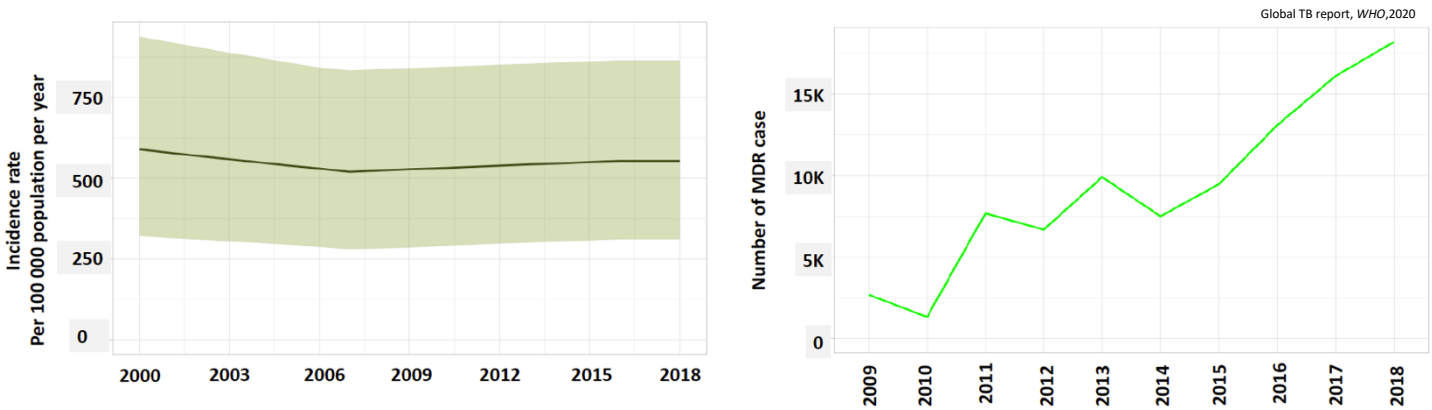


Figure 1: Estimated TB incidence rate & the number of MDR/RR TB Cases detected in TB-MDR

1.3. Adherence

WHO defines treatment adherence as "the extent to which a person's behavior – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider"[9]. In terms of TB control, adherence can be measured using either process-oriented (defined as relying on indicators of intermediate variables (e.g. appointment keeping or pill counts)) or outcome-oriented definitions (defined as the end result of treatment to indicate adherence (e.g. cure rate))[9]. One of the critical elements of successful TB control programs is adherence to the treatment[6]. Multiple factors can lead to nonadherence to medications. Those factors can be categorized as factors related to financial constraints, psychological issues, co-morbidities including malnutrition, medications, access to food, patient behavior, and health systems[10] (**Figure 2**). Incomplete adherence to ATT regimens has been identified as one of the most serious limitations in current TB control activities, resulting in increased rates of drug resistance and poses a major barrier to the elimination of TB[11].

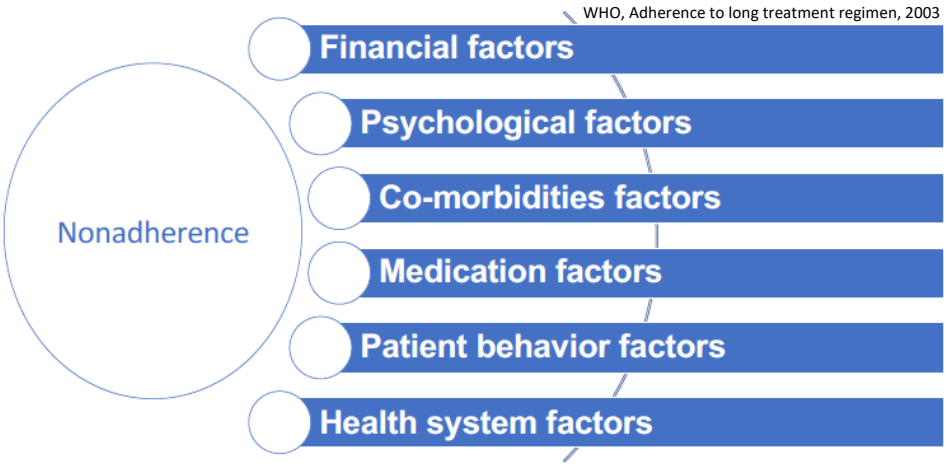


Figure 2 Categories of the reason for nonadherence by WHO

1.4. Adherence and drug resistance

Adherence to ATT is difficult due to the long duration of TB treatment, normally at least 6 months and up to 24 months in those with identified MDR-TB[6]. Poor adherence during the long treatment regimen has been documented as one of the main reasons leading to the development of drug resistance. This was confirmed in a seminal retrospective study in New York in 184 TB patients. There were 88 (48%) had incomplete adherence to their medication, resulting in a long time to culture conversion (254 versus 64 days), increased risk of developing drug resistance (OR=5.6) and increased total treatment duration (560 versus 324 days)[12]. The multiple drugs and tablets which comprise ATT, with commonly occurring side effects and interactions with other medications also, present significant challenges to patients and health care providers to ensure adherence[13]. Finally, patients can often experience rapid improvement in symptoms, which may result in patients perceiving continued treatment as unnecessary[5,13]. Of equal note, lack of knowledge, stigma, depression, and lack of social family support are other barriers to adherence (outlined in section 1.7).

1.5. Approach to measure adherence

1.5.1. The possible ways to assessing adherence through quantitative approaches

Adherence to medication can be measured in a variety of different ways, most commonly by self-report (e.g., Questionnaire, interview), objective measures (e.g., pill counts, pharmacy refill or electronic medication monitors), and biological endpoints (e.g., drug levels in sputum, urine, blood samples), and health related quality of life measures (e.g., multi-dimensional domains including physical, mental, and social domains) (**Table 1**).

A. Self-report

Many authors believe that self-report methods are subjective and the least reliable among all approaches to measure adherence[14]. Nevertheless, there are many advantages to this method such as easy to administer and availability of real-time feedback[15,16]. The drawbacks of this method are that it is the least reliable, has relatively poor sensitivity and specificity and can be affected by communication skills of interviewers, and the questions used to elicit the desired information[17]. Referring to previous systematic review studies, the most self-reported questionnaires have been used are:

I. Morisky Medication Adherence Scale (MMAS-8)

The eight items of (MMAS-8) is a structured self-reported measure of medication-taking behaviour[18]. It's known as the most commonly used scales to measure adherence[14]. It's widely used in different study design especially in Randomized Control Trials (RCT) to develop medication adherence intervention among patients with numerous chronic diseases[19]. It is consist of 8 Items, the first 7 of which are yes/no and the last item which is 5 point Likert scale[20]. The advantages of this scale are: identifies barriers to nonadherence clearly form 3 dimensions (forgetting to take medications, stopping medications when feeling better or worse, and the complexity of the drug regimen)[21], short, easy to apply as well as score, very adaptable for various medication group, can estimates the patient's medication-taking behavior and has outstanding validity, stability and reliability[21,14] .The sensitivity of this scale is 93% and 60% specificity was reported while validated with several chronic and infectious diseases[22].

II. Self- efficacy for appropriate medication use (SEAMS)

This scale was developed by a multidisciplinary team with expertise in medication adherence and health literacy. It consists of 16 questions with a three point Likert scale [14]. The main advantage of this scale is providing an assessment of the self-efficacy which focuses on measuring the positive attitude toward drug compliance, patient belief in medication, and social influence that encourage adherence[23]. It is good to explain patient's health preventive behavior (barriers to be non-adherent)[24]. However, it cannot measure the patient's actually medication-taking behavior such as the actual missed doses in a specific duration[24 25]. It is a good tool to predict patient's health behavior as it can hypothesize through patient's beliefs on their capacity toward medications[25].

III. Brief Medication Questionnaire (BMQ)

This scale can screen adherence and its barriers. It has three main questions headings and multi-sub questions under each heading. This tool includes 5 items regimen asking the patient about the name and dose of medication that patient takes. A 2-item measuring the common barriers facing patient to take medication, and a 2-items which evaluates the patient difficulty in buying and refilling their medications in time[14]. This scale is good at measuring adherence in the patient with chronic disease who are taking more than 3 different types of medicines[26]. It is recommended to be used in cross-sectional studies[14]. It is only validated with high validity and reliability to measure compliance with antihypertensive medications but not for other medications[14,26].

IV. The Hill-Bone Compliance scale

This scale is also focusing only on hypertensive patients. It assesses patient behavior from 3 important behavior domains (reduce sodium intake, appointment keeping, and medication taking)[27]. This scale consists of 14 items in three subscales with 4 Likert scales for each item. This scale was validated only among South African and Turkish primary health care setting[14,28]. This scale can address barriers and self-efficacy for hypertensive patients but has a limitation in their generalizability since it targets patients with hypertension only and focuses on 3 behaviors which it can be different from person to other and from culture to another[27,28].

V. The medication adherence rating scale (MARS)

This scale was developed from the Morisky medication adherence scale, Drug attitude inventory (DAI), and a common psychiatric adherence survey [29]. This scale assess both beliefs and barriers to medication adherence quickly and without intervention[29]. It consists of 10 items with yes/ no choices. It was designed and first validated for patients with schizophrenia[30].

VI. TBMAS

This scale is designed to measure adherence among TB patients only. It can identify nine factors conceptually associated with medication adherence in TB patients: communication with healthcare providers, personal traits, confidence in curing TB, social support, mood disorders, lifestyle and habits, coping style, access to healthcare, and forgetfulness[31]. It consists of 41 questions with 5 points Likert scale. This scale has high sensitivity to detect nonadherence with 82.9%[31,32]. It can detect the barrier and reasons of being nonadherent.

However, It is relatively long especially if the patient asked to answer it every month (in follow-up visits)[31].

B. Pill count

It is an indirect method to count the number of dosage units that have been taken between two schedule appointments or clinical visits. The number is then compared to the total number of units received by the patient to calculate the adherence ratio[33]. The main features of this method are low cost and simplicity which contribute to its popularity. However, the accuracy of pill counts in estimating actual adherence to a medication regimen can vary as it does not record actual taking of the medication[16,33,34]

C. Biomedical adherence measurements

For some drugs, adherence can be assessed by measuring drug concentrations in the blood or urine[16]. However, there are many potential drawbacks, including expensive, difficult to perform as many technical and professionals skills are required to carry out and monitor this process[35], time taken for analysis. Moreover, drug metabolism should be considered as some medications can be detected even after long period of stopping. However, others reflecting only the recent treatment adherence (e.g. within the previous 24 hrs.)[35,36]. Also, this method cannot be used to monitor many drugs. Additionally, drug- drug interactions and drug- food interactions can restrain accurate assessment[37,38].

D. Electronic monitoring measurements:

Digital adherence technologies can include those utilizing phone-based short messaging systems (SMS) such as 99-DOTS[39], smartphone-based technologies (Video observed treatment VOT) [40,41], digital pillboxes, and ingestible sensors[40]. SMS methods such as 99 DOTS work by wrapping each anti-TB blister in a custom envelope, which includes hidden phone numbers that are visible only when doses are dispensed[35] (outlined in section 1.10.2). Digital pillboxes methods monitor adherence by recording the time of opening medication bottles or the pillbox to take medication. whilst VOT actually records patients actually taking the medications, so is a replacement for directly observed therapy, by observing remotely, either in real-time or close to real time[40]. These approaches provide the most accurate and detailed data on adherence especially in difficult clinical cases including with multiple medications. However, these methods is expensive, may require expert technical support , e.g. for the software require reliable cellular communication networks, digital adherence technologies (DAT), and potentially expensive equipment (smart-phones, digital pill boxes) and running costs of using data networks, or staff required for monitoring of incoming data[39].

1.5.2. The possible ways to assessing adherence through qualitative approaches:

Although quantitative methods can provide some measurements of nonadherence and quantify potential reasons for nonadherence such as the incidence of drug-related side effects, or distance from treatment centers and determine if these are correlated. Generally, qualitative research methods are better suited to investigate the context-specific motivations of patients and health providers underlying why and how people undertake particular behaviors (e.g. nonadherence) within specific populations[42,43]. Thus, although qualitative approaches are

generally not used to classify patients as adherent or non-adherent[44]. they can be used to discover the barriers preventing adherence among specific populations[45] and from different perspectives, e.g. from patients compared to health care providers or patient's household contact[46]. The most common methods used in qualitative studies are recorded interviewing (structured or unstructured interviews) and observational[47].

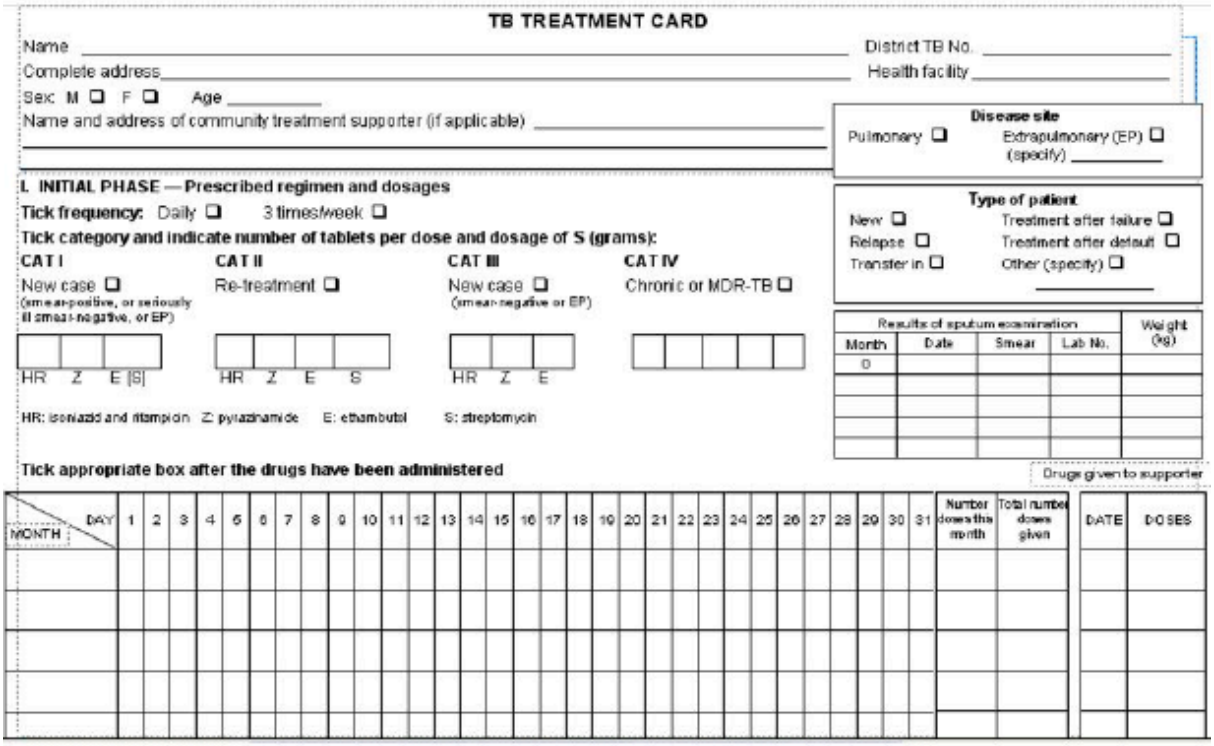
Method of measuring adherence	Pros	Cons
Direct Method		
Obesrving therapy taken by patient	- Most accurate method	- Delusion from patient by hiding the pills in the mouth and then discard them
Biochemical measurment	- Objevtive	- Different in metabolism, absorption and rate of excreation from person to another - Drug- drug and drug- food interaction - Bias occure if patient know the schedule of the test (white coat adherence)
Indirect Method		
Patient self report	- Simple - Inexpensive - Real time fedback available - Flexible to accommodate different conditions - Well validated - Identify belief and barriers to adherence - The most useful method in clinical setting	- Leatest reliable - Relatively poor sensetivity and specificity - Affecting by communication skills - Patient desirability can bias
Pill count	- Objective - Quantifiable - Simple and canbe used in varias formulation - Easy to perform	- Underestimation due to early refill - Unable to identify medication taking pattern - Data easily altered by patient (pill duming)
Electronic medication device	- Able to identify patient at risk for treatment failure - Precise - Result are easily quantified - Provide medication refilling pattern - Track patterns of talking medication	- Expensive - Techniqual support require - Require routine visits and downloading data from medication vials - Overestimation if patient actuate the countainers - Pressure for patient
Assessment of the patient clinical response	- Simple - Easily to perform	- Factors other than medication adherence can affect clinical response
(Culing and Leppee 2014; Hill, kendall and fernandez 2003; Osterberg and Blaschke, 2005)		

Table 1: Comparison between different method of Measuring Adherence

1.6. TB treatment adherence and its measurement in the Philippines

The recommended regimen by WHO for adults newly diagnosed with TB at the intensive phase (for the first 2 months) are isoniazid (INH) with 56 doses/8 weeks/7 days per week and rifampicin (RIF) with 40 doses/8weeks/5 days a week. This will be followed by a continuation phase (for 4 months) of isoniazid with 125 doses/18 weeks and rifampicin 90 doses/18 weeks[48,49]. For the MDR-TB regimen, the WHO shorter regimen consists of high-dose of gatifloxacin or moxifloxacin, kanamycin, protionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol for intensive phase (Four months and can be extended to six months in case of delayed sputum smear conversion). This is followed by a continuation phase of five months containing gatifloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide[48,50]. Direct Observed Treatment (DOTS) became common practice for DS-TB patients to ensure treatment compliance[51]. In the Philippines, DOT has been implemented since 1995 and became part of the National TB Program (NTP)[52]. According to the NTP policies and guidelines, patients take their medication either by going to the DOT to collect medications and being observed taking the treatment by the assigned TB nurse or doctor or through treatment partner supervisior[53]. Patients are considered adherent if they receive the medication from DOT by themselves or through his/ her treatment partner[54]. However, in reality, full community-based or facility-based DOTS is not always occurring or is not accurately recorded. The number of treatment doses is recorded on the NTP treatment card (**Figure 3**), but it is common practice that when patients are not attending TB-DOTs facilities on a daily basis, as is the case for the majority of DS-TB, doses are recorded in the TB treatment card for all dates either up to the date of dispensing, or for the number of doses dispensed by the TB-DOTs nurse, which may not reflect actual behavior in taking the

treatment doses received. When treatment partners are involved, they are often not involved in the actual recording[53]. This is also what we have observed in our ongoing TB treatment cohort (St-ATT, section 2.1). Therefore, the documented treatment success rate in the Philippines of 90% for drug-susceptible (DS-TB) patients may be an overestimate of the true treatment success[51]. Also, there is no routine monitoring for the reasons for nonadherence to ATT[53]. It is important to find a way to accurately monitor ATT adherence and to investigate and document the reasons underlying nonadherence.


TB TREATMENT CARD

Name _____ District TB No. _____

Complete address _____ Health facility _____

Sex: M ☐ F ☐ Age _____

Name and address of community treatment supporter (if applicable) _____

Disease site
Pulmonary ☐ Extrapulmonary (EP) ☐ (specify) _____

Type of patient
New ☐ Treatment after failure ☐
Relapse ☐ Treatment after default ☐
Transfer in ☐ Other (specify) ☐ _____

I. INITIAL PHASE — Prescribed regimen and dosages

Tick frequency: Daily ☐ 3 times/week ☐

Tick category and indicate number of tablets per dose and dosage of S (grams):

CAT I	CAT II	CAT III	CAT IV
New case ☐ (smear-positive, or seriously ill smear-negative, or EP)	Re-treatment ☐	New case ☐ (smear-negative or EP)	Chronic or MDR-TB ☐
HR Z E [S]	HR Z E S	HR Z E	

HR: isoniazid and rifampicin Z: pyrazinamide E: ethambutol S: streptomycin

Results of sputum examination

Month	Date	Smear	Lab No.	Weight (kg)
0				

Tick appropriate box after the drugs have been administered

Drugs given to supporter

MONTH \ DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Number doses this month	Total number doses given	DATE	DOSES

Figure 3: TB Treatment card in the Philippines

1.7. Factors influencing adherence

1.7.1. Depression

Depression is one of the most serious health challenges in the world. The DALYs of depressive disorder is over 43 million in 2017[2]. More than 350 million people worldwide suffer from depression. Nearly half of those people living in South-East Asia and Western pacific Region[55]. However, the majority of people with depression are not diagnosed or are not effectively treated in low and middle-income countries(LMIC)[56]. One in five people will experience a period of depression in their lives[57]. Globally, over 78% of suicides under the age of 70 occurred in LMIC was because of depression[58,59]. Also, 8.5% of suicides among young adults aged 15–29 years occurred and is the second leading cause of death in this group after road traffic injuries[59]. It is well known that depression is common in people with chronic diseases[60]. Limited studies, mostly small, cross-sectional, have reported high psychiatric morbidity in TB patients[61,62] (**Table 2**). Including in LMIC: Nigeria (41.1%)[63], Cameroon (61.1%)[64], Pakistan (56%)[65], Ethiopia (54%)[66], and India (23.6%)[67]. A meta-analysis of data from American patients with chronic diseases, across 31 studies and 18,245 participants estimated that depression is significantly associated with nonadherence (OR=1.76; 95% CI 1.33-2.57)[68]. Patients with TB are more likely to be depressed due to several factors, such as the long duration of treatment for TB, the side effect of the medication, stigmatization faced by the patient due to the disease, and lack of social & family support[67,69] (**Figure 4**). Very little data exists for the Philippines, with to our knowledge only one published study. A cross-sectional survey in 561 TB patients in 10 public facilities in Manila between September and November 2012. This study reported that a depressive state was observed in 17% of participants (using PHQ-9 questionnaire, score of ≥10) which was independently associated

with malnutrition, treatment side effects, low perceived social support and symptom severity[70]. In the Philippines, there is insufficient data available regarding depression in TB patients, especially in rural areas.

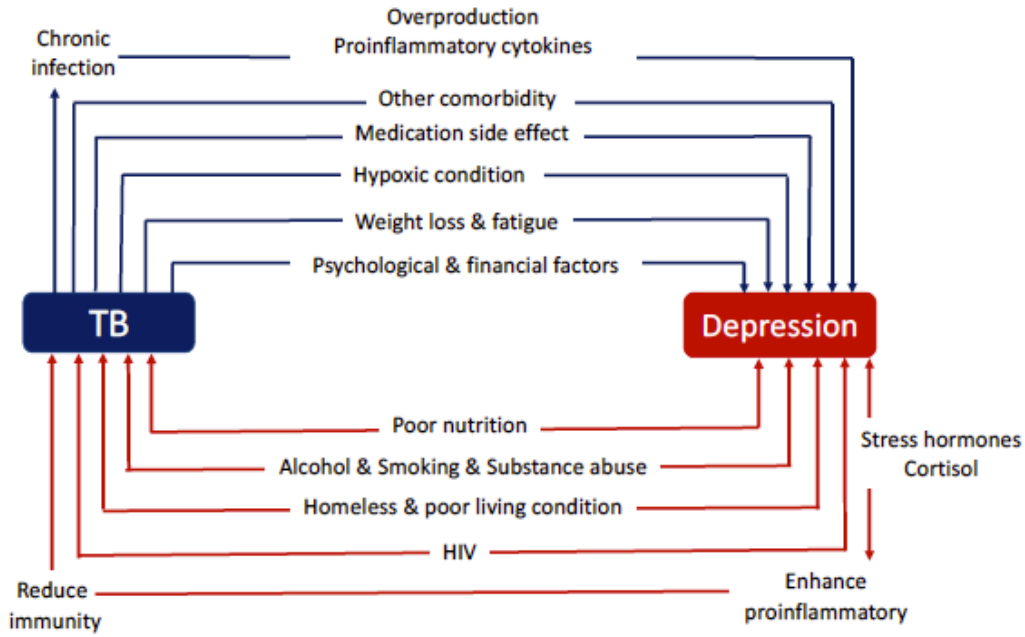


Figure 4: Pathway between TB and depression

Study location	Study design	Year	TB-TX type	Sample size	Depression measurement tools	Depression prevalence
Nepal	Cross-sectional	2005	DS-TB	250	PHQ-9	10%
Eithiopia	Cohort stud	2015	DS-TB	648	PHQ-9	7.40%
Pakistan	Cross-sectional	2005	Hospitalized TB	50	BDI-II	80%
Brazil	Cross-sectional	2017	MDR-TB	86	HADS	31.4
Pakistan	Cross-sectional	2018	TB	108	HADS	46.3
Turkey	Cross-sectional	2008	TB	208	HADS	60.5
India	Cross-sectional	2017	MDR-TB	100	HADS	55
Ethiopia	Cross-sectional	2015	TB	417	HADS	43.3
Cameroon	Cross-sectional	2016	TB	265	PHQ-9	61.1
Nigeria	Cross-sectional	2011	TB	65	PHQ-9	27.7
Ethiopia	Cross-sectional	2008	TB	403	PHQ-9	51.9
China	Cross-sectional	2018	TB	1252	PHQ-9	17.7
Botswana	Cross-sectional	2020	TB	180	PHQ-9	47.2
Pakistan	Cross-sectional	2016	TB	289	HDRS	49.4
India	Cross-sectional	2013	TB	200	HDRS	39.5
Nigeria	Cross-sectional	2010	TB	88	HDRS	45.5
Philippines	Cross-sectional	2014	DS-TB	561	PHQ-9	16.8

Table 2: The prevalence of depression in previous studies

1.7.2. Stigma

WHO described stigma as a "hidden" burden of disease[71]. This is due to how stigma adversely impacts individual health outcomes as well as related 'life chances', including educational opportunities, employment, housing, and social relationships[72]. It has also been shown the negative effect of stigma on health seeking behaviors and adherence to the treatment[73]. Most of the tools used to measure stigma in TB are focused on 3 main types of stigma, (1) ***Experienced stigma*** (the experience of exclusion and/or discrimination), (2***) anticipated stigma*** (the perception, expectation and/or fear of stigma), and (3) ***internalized stigma*** (a loss of self-esteem, dignity, fear and/ or shame)[74,75]. A prospective observational study in South Africa concluded that psychological factors, including stigma are associated with

nonadherence to the TB medication[76]. Stigma is likely to be an important predictor of adherence, as patients may tend to hide their symptoms and withdraw from interpersonal contact for fear of discrimination, isolating themselves to avoid negative public attitudes, which may consequently affect medication adherence[74]. Furthermore, TB related stigma can lead to poor self-esteem and lack of self-confidence which are common symptoms of depression[77,78]. This is supported by a recent, relatively large study in China which showed TB related stigma to be negatively correlated with medication adherence ($r=0.31$, $p < 0.01$), and which was partially mediated by depressive symptoms[79].

1.7.3. Social and Family Support (SFS)

TB patients may experience social isolation and a changing pattern of self-image. They may lose employment, financial resources, and even family and friends as major sources of support[80,81]. Family support includes financial assistance, support in the disclosure process, daily routine activities, medical assistance, and psychological support, which help patients to stick to treatment regimens[82]. The presence of support and strong ties with the patient's family and friends can play an important role in health behaviors such as sickness adaptation[83], lifestyle coping[84], and medical health care utilization[85]. In previous studies, a supportive environment has been found to decrease disease-related negative effects among TB patients, especially for those who are suffering from fear of being lonely and rejected by family, friends, and society[82,86]. Other recent studies in Ethiopia and Eretria showed that one of the main reasons for being non-adherent to the prescribed medication is the lack of social and family support, which considered a critical factor affects negatively on the patient's adherence behavior[5,87].

1.7.4. Malnutrition

Malnutrition is a common clinical finding in TB patients and might increase the risk of developing active TB[88]. Also, TB might contribute to develop malnutrition by changing the metabolism through increasing metabolic demands and inducing a catabolic state and reduce the appetite which can lead to severe weight lost[88].

1.8. Adherence in previous studies

In a previous systematic review of patient adherence to TB treatment which included 44 studies identifying barriers to adherence in Africa (14), North America (9), South (8) and East Asia (8), Latin America (2) and Europe (2)[89] barriers were categorized as:

- Structural Factors: Incorporating poverty, especially cost and financial burden
- Personal factors: Incorporating knowledge, beliefs, interpretations of illness, and attitude towards treatment.
- Social context: incorporating family, community, stigma, and household support
- Health services factors: incorporating organisation of care and treatment, disease progress, and side effects.

Two recent studies worth highlighting include a recent qualitative study in China, investigating TB patient perceptions of their engagement in healthcare and adherence[90] and a mixed methods study in Ethiopia[91]. In China, data were collected through in-depth interviews (face to face interview) with 23 participants (11 male, 12 female) using open-ended and semi-structured questions[90]. The result was summarized in four themes:

1- Devaluing engagement: This theme reflected the patient's negative attitude toward engaging in healthcare with patients describing engagement as "useless" and "meaningless".

2- Interacting with Health care providers (HCPs): This theme reflected limited opportunities for discussion, to have their questions answered and paternalistic approach leading to passive behaviour and unwillingness to engage.

3- Facing inability: Patients felt the side effects of the treatment were worse than the symptoms of TB and consequent limiting effects on daily living and psychological pressure such as concerns about the uncertainty of illness, long-term hospitalization, high financial expense, family commitments and missed work opportunities.

4- Seeking for external support: some patients acknowledged the significant role of their family members in supporting their treatment engagement. However, most reported distancing themselves from their family members due to fear of transmission and social isolation.

In Ethiopia, the first phase, involved a quantitative cross-sectional survey in 261 TB patients from 17 health centers and one general hospital. The second qualitative, explanatory phase involved in-depth interviews of 14 key informants. The prevalence of nonadherence (defined as patients who missed 10% or more of their prescribed doses of anti-Tb drugs) was 24.5% and was positively associated with poor knowledge of TB and its treatment (AOR = 4.6, 95%CI: 1.4-15.6), cost of medication other than TB (AOR = 4.7, 95%CI: 1.7-13.4), having health information at every visit (AOR = 3.0 95% CI: 1.1-8.4), and distance of DOTS center from residence (AOR = 5.7, 95%CI: 1.9-16.8). The qualitative findings supported the quantitative results with patients highlighting lack of service decentralization, drug stock-outs, distance of DOTS Centers, lack of awareness about the importance of completing the treatment course, stigma, and the cost of transportation.

1.9. Adherence in the Philippines

Adherence to TB medication has not been well assessed in the Philippines. There is only one published case control study assessing factors associated with loss to follow-up during treatment for MDR-TB (treatment interruption for >2 consecutive months) compared with controls (continued treatment 12 months or documented treatment outcome), independent risk factors included reported severity of drug-related vomiting, whilst increased TB knowledge, reported receipt of TB program support (either transport allowance, food or free medications for side effects), social-family support, and higher scores for level of trust and support from program staff were associated with decreased risk of loss to follow-up[92]. Analysis of In-depth interviews conducted with the same participants reflected the quantitative findings. The author concluding that patients felt that reducing patient travel or improving provision of patient transport costs, increase the social and family support, provision of food support and reduction of side effect, would improve adherence behavior to treatment. However, the retrospective case control design of this study limits the conclusions that can be drawn from this study as recall bias and sample bias are highly likely to contribute to these findings. Hence, further prospective investigations are needed to determine the key barriers to adherence for Filipino TB patients (DS-TB & MDR-TB) and to understand their relative interplay and importance in order to design context-specific, locally applicable interventions or improvements to services that are likely to have the biggest impact to reduce patient loss to follow-up and increase adherence level.

There is a wide range of factors affecting adherence levels in TB patients. Those factors are different by countries and populations. **Figure 5** is showing a summary of the most common barriers affecting adherence to TB treatment.

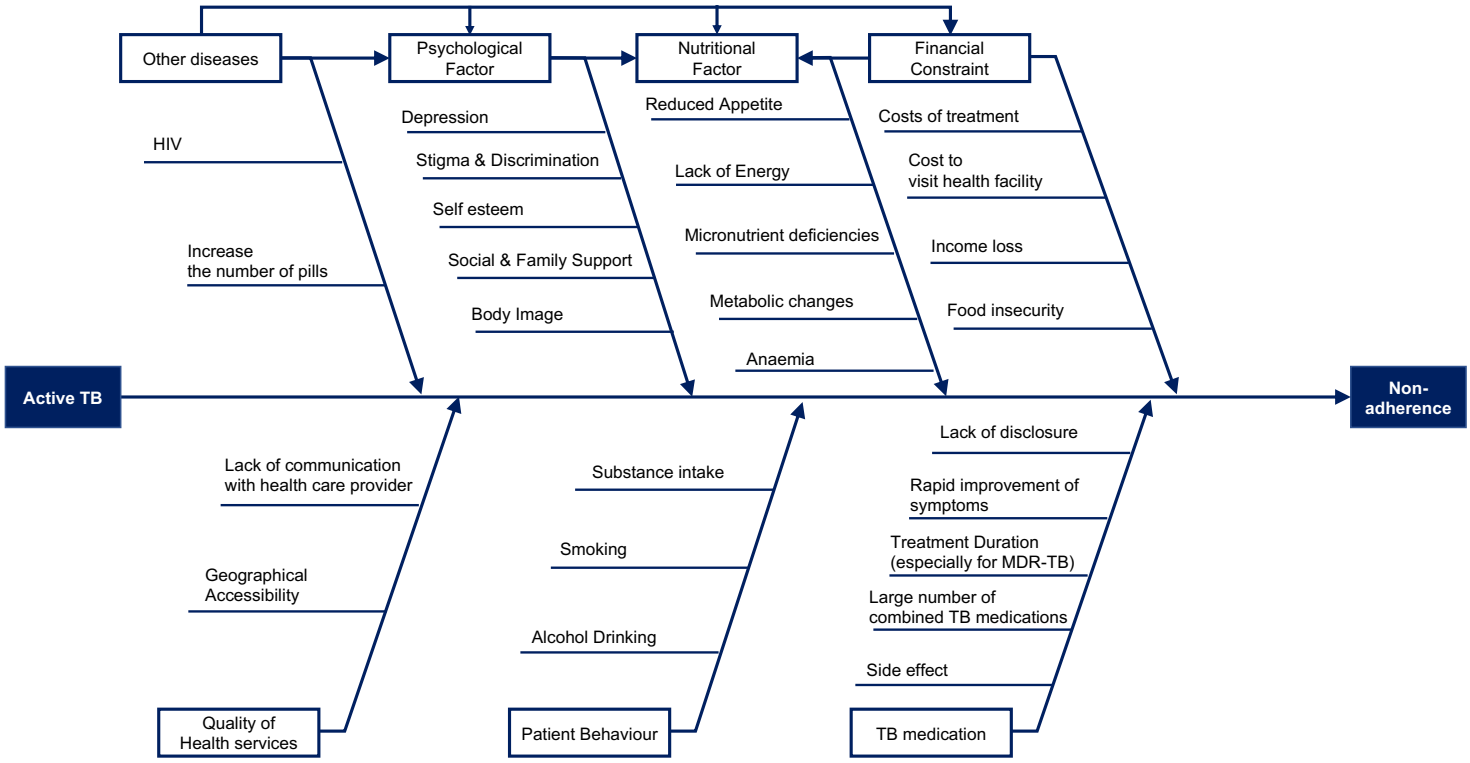


Figure 5: Summary of the most common barriers affecting adherence to TB treatment

1.10. The possible ways to manage TB

Uncompleted TB treatment demonstrate a public health challenges as it contributes to developing drug resistance and allow the patients to be infectious for long time. The most serious form of incomplete treatment is known as “treatment abandonment” or “treatment default”. For TB, such abandonment is represented by a break in treatment of at least two consecutive months[93]. To improve adherence behavior, there are many interventions strategies such as:

1.10.1. Training Health care Providers (HCP)

This intervention based on providing training to HCP on TB symptoms and transmission, how to identify TB suspects, how to collect, label, store and transport sputum specimens, types of TB regimen, administrating DOT, appointment scheduling, follow patients during treatment, and home visiting. This way ensures the deep understanding to the treatment procedure and improve the treatment success. Moreover, it will enhance the case detection rate. In Ethiopia, a community-randomized trial was done among fifty-one HCP who randomly allocated to intervention and control groups. The HCPs in the intervention advised people with productive cough of 2 weeks or more to visit health facilities. Two hundred and thirty smear-positive patients were identified from the intervention and 88 patients from the control. The mean case detection rate was higher in the intervention than in the control (122.2% vs 69.4%, $p<0.001$). The mean treatment success rate was higher in the intervention than in the control (89.3% vs83.1%, $p=0.012$)[94].

1.10.2. Electronic interventions:

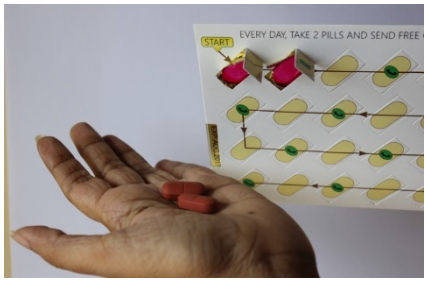
This method can improve adherence by reminding the patient to take the dose. It also can record and stamping the time of opening bottles to take medication. So, through using this way, HCP can detect a patient's behavior to take the medication[95]. The most famous interventions of this technologies are:

A. TB-DOTS method:

It is a low-cost intervention approach which can be easily utilized[95]. It enables remote observation of doses administered by patients or their family members. Using 99-DOTS, each anti-TB blister pack is wrapped in a custom envelope, which includes hidden phone numbers that are visible only when doses are dispensed. After taking daily medication, patients make a free call to the hidden phone number, yielding high confidence that the dose was "in-hand" and has been taken[95].

Process:

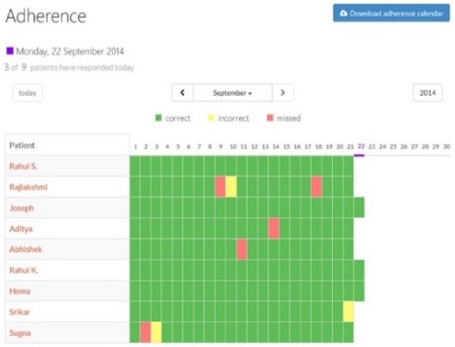
1- Patient medication is packaged in specific custom secondary envelopes which add dosage instruction, and a series of hidden numbers behind the pills.



2- Each time a patient takes a dose of medication, a hidden number is revealed which is unpredictable to the patient.

3- The revealed number completes a phone number, where the first part of the number is printed on the front side of the envelope. The patient then makes a free call to the completed phone number.

4- Adherence can be measured by tracking phone numbers which are packaged in an unpredictable way to the patients, and the only way for a patient to call the correct number is to dispense the pills. Therefore, accurate monitoring of adherence rate with high confidence that the patients have taken their medication for the day. With this real-time information, it will be easy to set reminders, incentives, and additional counselling for those patients with low adherence.



B. Electronic Pillbox:

These devices used to record the time when each lid was opened or closed. when the user opened a dispenser lid on the pillbox, the plunger would release a switch inside the device and sending a signal to the server indicating when the door was open (using date and time). This way is used to measure patient's compliance to the medication through common features: recorded dosing events and stored records of adherence, digital displays, real-time monitoring, and feedback on adherence performance[96].

Even though not all such features are available in all devices, for instance, some devices have an alarming feature which can be used to remind the patient with the next dose especially among old patients. The capacity of the memory can store up to 256 events[97].

1.10.3. Social protection and financial support

This way encourage TB patients to visit the health facility through providing a weekly or monthly food supplies[95], housing[99], medication coverage[100], recognition of the importance of employment[101] essential supplies for daily life[101] transport reimbursement and income-generation support[98].

1.10.4. Peer Support

This intervention relies on grouping TB patients living in a same area to visit the health facility together. This way makes patients know each other and began to form "TB clubs". Each club has leader, who is usually literate and has good communication skills. The leader ensures that all members of the TB club attend the follow-up visit at the health center on the appointed day and informs the staff of the reason if a member is absent. This contributes to the recording of patient attendance. This help patients to share their experiences and support each other which will reflect positively in their compliance[102].

1.10.5. Care delivery

The intervention here is through providing a home visits for the patients at their home. Patients who delay for collecting drug or refuse to attend, a community volunteer "treatment partner" is assigned to visit the patient at home and ask him/her to return to the center. Also, patients who are living far from the health facility or who cannot afford transpiration fees can make agreement with health facility to receive the DOT at home. The treatment partner delivering the medications to the patients and observe him/her taking their dose, then record that on

treatment card which will be delivered back to the health facility. This intervention is helping to improve the treatment success by 95%[103].

Chapter 2

2. Methodology

2.1. Main Cohort study (ST-ATT)

2.1.1. Aim & Objectives of the main cohort study (St-ATT)

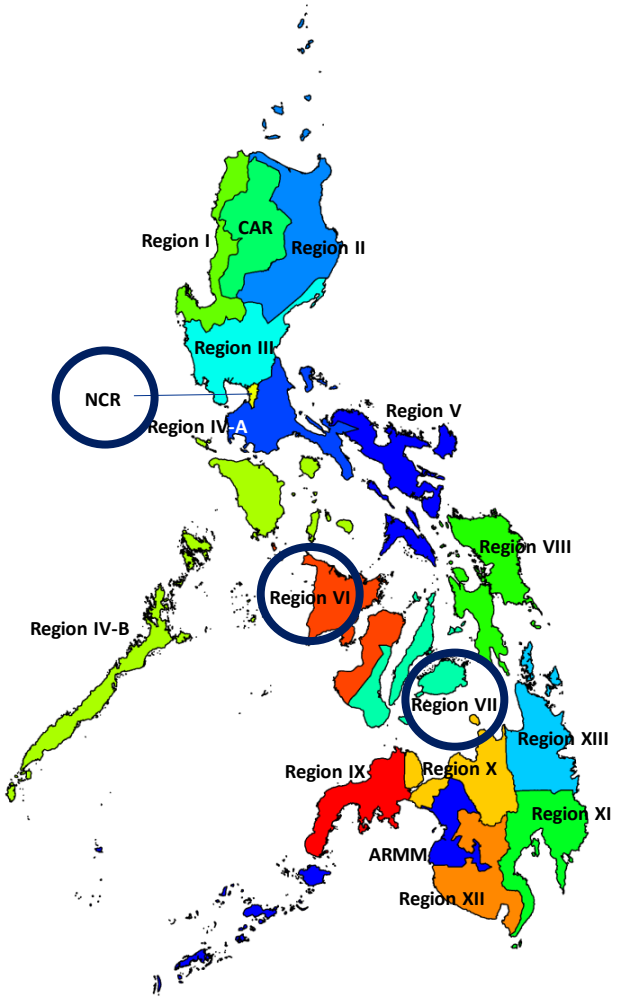
The aim of this study is to measure the effects of malnutrition and diabetes in patients with tuberculosis and investigate associations with treatment outcome through potential effects on treatment compliance, drug side effects, glycemic control, weight gain and nutrition during treatment and cell-mediated immune responses. The primary objective is to estimate the effect of malnutrition (BMI<17.0 kg/m2) and diabetes on risk of adverse treatment outcome (death, loss to follow-up, incomplete treatment or treatment failure) in adults newly starting a DS-TB or the WHO shorter (Bangladesh) regimen for MDR-TB in public facilities at Negros Occidental, Cebu, and Manila in the Philippines. All study participants were followed up at the registered TB-DOTS clinic where they were receiving treatment until treatment completion according to the type of their treatment regimen.

2.1.2. St-ATT study design & study population

The study is a facility-based prospective cohort study in TB DOTs facilities in the Philippines. The study targeting participants aged 18 or more who are initiating a new TB treatment regimen. Participants were recruited from NTP DOTs including those following the WHO shorter regimen within the National Capital Region, Negros Occidental and Cebu.

2.1.3. Study situation

The Philippines is an island nation located in southeast Asia bordered by the Celebes Sea. In addition, the Philippines has maritime borders with China (the west), Japan (the west), Vietnam (the west), Malaysia (the south), Taiwan (the west), Indonesia (the south), and Palau (the east)[104]. The Philippines has 7,641 islands with a total land area of 300,000 square kilometres. It is the world's 5th largest island country. The Philippines island chain is divided into 3 main islands group: Luzon, Visayas, and Mindanao[105]. This study conducted within St-ATT clinic sites located in:



1- Western Visayas Region

- Valladolid Health Centre
- Bacolod Health Centre
- La Carlota Health Centre (MDR-TB site)
- Riverside Hospital
- Bago Health Center

2- Central Visayas Region

- Consolacion Health Centre
- Carmen Health Centre
- Lapu Lapu Health Centre
- Compostela Health Centre.
- Eversley Hospital (MDR-TB site)

3- National Capital Region

- San Lazaro Hospital

2.1.4. St-ATT Eligible criteria

Subject Inclusion Criteria: Active TB cases

1- Patients initiating a new TB DOTS treatment regimen with bacteriologically confirmed or clinically diagnosed pulmonary TB, including new diagnoses, relapse, treatment after failure, treatment after loss to follow-up (TALF), and previous treatment unknown outcome (PTUO).

2- DR-TB cases who initiated the 9-12 month WHO shorter DR-TB regime and registered in DOTS.

3- intending to reside within the study area for the duration of their treatment.

4- Age ≥18 years old.

Subject Exclusion Criteria

1- Pregnant woman

2- Age <18 years old

3- imprisoned

4- Plan to move away from the study site or do not give consent to participate

5- Started the current ATT regimen more than 5 days before enrolment.

2.1.5. St-ATT Data collection

All study participants recruited by a study research nurse at enrolment and had been interviewed at monthly follow-up at the registered TB-DOTS clinic or Barangay health station where receiving/collecting treatment until treatment completion depending on TB treatment regimen. Study assessments samples and data collected are summarized below (**Table 3**). The St-ATT cohort study recruited newly diagnosed persons with TB at baseline from 1st August 2018 to 20th February 2020 and had been followed up until 27th December 2020.

Assessment Time points	0M	Monthly	3M	6M	9M	12M
Demographics, clinical history, household information	✓					
TB & Diabetes Medication History, adherence; adverse effects		✓				
TB Classification, diagnosis, regimen	✓					
Anthropometry [BMI, MUAC, waist & hip ratio]; grip strength, blood pressure, reported appetite	✓	✓				
HbA1c (after baseline for DM & pre-DM only)	✓		(✓)	(✓)	(✓)	(✓)
Oral Glucose Tolerance Test (if Hba1C ≥5.7% to < 6.5%)	✓					
TX history, diabetes co-morbidities in DM & pre-DM cases	✓		(✓)	(✓)	(✓)	(✓)

Source: ST-ATT protocol

Table 3: Summary of the variables collected through ST-ATT study

2.2. The nested cohort study

2.2.1. Aims & objectives

Aim: The aim of this study is to assess patients' adherence to TB medications, and explore the factors associated with adherence causing patients to be non-adherent to their medication.

The primary objective:

To assess adherence to TB treatment throughout planned treatment duration among Filipino TB patients and if associated with depression, anxiety, TB-stigma, malnutrition, social and family support.

The secondary objectives:

1- To explore the lived experiences of TB patients to identify perceived barriers which make them non-adherent to their medication.

2- To investigate treatment adherence patterns in TB patients

3- To determine the prevalence of depression among Filipino TB patients

2.2.2. Study design

An explanatory sequential mixed-methods cohort study nested within a 900-patient TB treatment cohort study (St-ATT) in Filipino adults to investigate potential pathways affecting TB treatment adherence including depression, anxiety, TB-stigma, social & family support and adherence. This study has two main components, the primary component of this study was quantitative conducted through standardized questionnaires to assess adherence and the mentioned risk factors. The second component was qualitative part which done using a topic guide with a semi structured and open-ended questions.

2.3. The quantitative study

A standardized questionnaire was used to assess depression, anxiety, SFS, stigma, and adherence following the St-ATT follow-up visits (**Table 4**). Only the demographic, nutrition, all the TB and clinical data were extracted from St-ATT study. Nutrition data was collected through Mid-Upper Arm Circumference (MUAC), Body Mass Index BMI. This nested study recruited participants from St-ATT cohort study from 26th April 2019 until 20th February 2020 then followed them until 27th December 2020.

Assessment Time points	Baseline	End-IP	Mid-CP	End-CP
Depression, Anxiety, SFS, Sigma	✓	✓	✓	✓
Adherence		✓	✓	✓

*__EIP__ = intensive phase of treatment; __CP__=continuation phase of treatment (✓) indicates conducted in subset of participants

Table 4 Summary of the variables collected in nested cohort study

2.3.1. Study population

The study population are a subset of the St-ATT cohort study (**Section 2.1.2**). This study followed the same inclusion and exclusion criteria of St-ATT cohort study which included adult TB patients who registered at public TB DOTs facilities in the mentioned participating TB-DOTs clinics with the same inclusion and exclusion criteria.

2.3.2. Data collection

Trained research nurses from Nutrition Centre of Philippines (NCP) were based in each study site for recruiting patients from the main cohort study (St-ATT). First, research nurses explained the study to the participants using a St-ATT written information sheet, which included assessment of depression, anxiety, stigma, SFS, and adherence (**Appendix 7.1**). Patients who accepted to participate were asked to sign the St-ATT informed consent (**Appendix 7.2**). Data collection for those risk factors were conducted by interview using a standardized questionnaire in local language (Cebuano, Hiligaynon, and Tagalog). The questions are designed and implemented using Open Data Kit (ODK) which answered by the patient using an Android electronic tablet. The emojis were used to ensure the patient's understanding of the choices to get accurate answers (**Figure 6**). The translation and content of the questionnaire was validated and modified according to the patients' response and feedback from research assistants. The first interview was conducted at the time of starting TB treatment. The second interview was conducted at the end of intensive phase (2 months for DS-TB and 5 months for MDR-TB). The third visit was conducted at the middle of continuation phase (4-5 months for DS-TB and 6-7 months for MDR-TB). The last visit was done at the end of continuation phase (6-8 months for DS-TB and 9-12 months for MDR-TB) (**Figure 7**). The questionnaire included different standardized scales (**details section 2.3.3**) to assess depression, anxiety, TB stigma, family and social support. All the data collection tools used are highly standardized and have been used in many countries and different populations, including the Philippines and in TB.

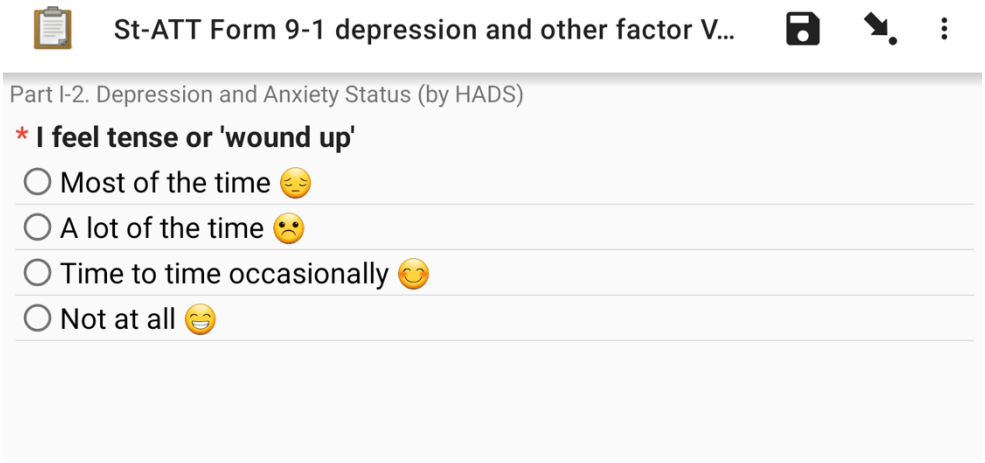


Figure 6: An example of collecting data using ODKFigure

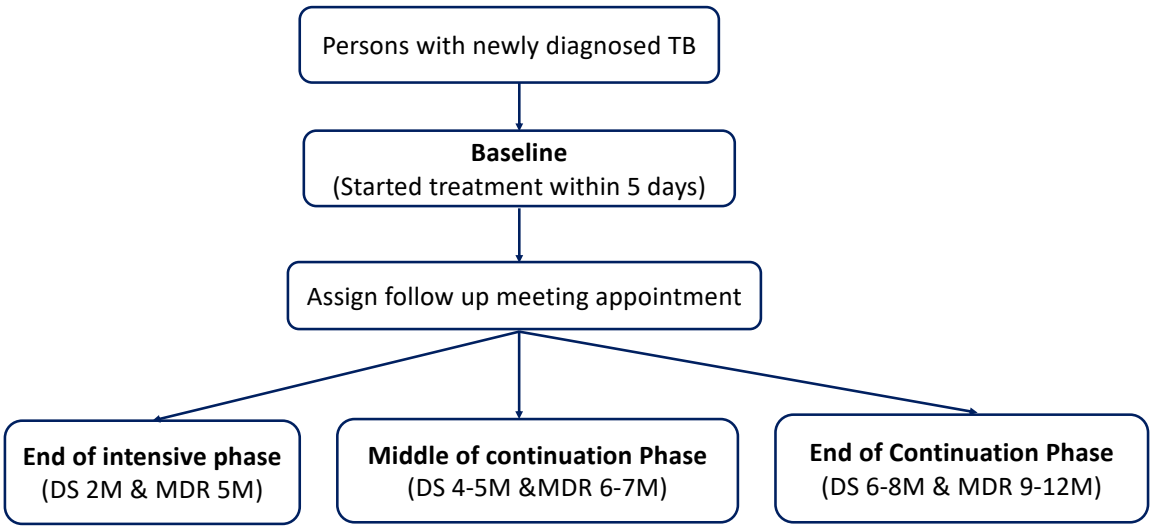


Figure 7: Interview timepoint

2.3.3. Data collection tools for quantitative study

a. Depression

The Hospital Anxiety and Depression Scale (HADS) is a widely used health-related quality of life (HRQOL) tool for measuring psychological distress. It was developed in 1983 by Zigmund and Snaith to screen patients for the presence of depression and anxiety symptoms in non-psychiatric hospital patients[106]. It consists of a 14-item questionnaire which includes seven questions to measure depression (7 items) and other seven questions to measure anxiety and each item contains four Likert scale (from 0 to 3). The subscales measure anxiety and depression with a range from 0 to 21, a high score represents the presence of either anxiety or depression symptoms. Specifically, scores of 0 to 7 in each subscale corresponds to a non-depressed and non-anxious, scores of 8 to 10 correspond to a mild depression and mild-anxiety, scores of 11 to 14 corresponds to a moderate depression and moderate anxiety, and score from 15-21 corresponds to severe depression and sever anxiety[107]. The presence of anxiety-depressive symptoms will be evaluated by the cut-off point= 8 (HADS≥ 8 (yes), versus HADS < 8 (no))[108]. The HADS questionnaire has been validated in several languages, countries including the Philippines[109]. It is useful for the initial diagnosis and to track the progression of psychological symptoms. It considers one of the National Institute for Health and Care Excellence (NICE) in the UK recommended tools for diagnosis of depression and anxiety[110]. According to previous studies, HADS appears to represent the best currently available self-report scale to diagnose anxiety and depression in TB-infected patients due to its simplicity and it's recommended to be easily implemented as a routine TB and HIV care[107–110].

b. Social and family support

The Multidimensional scale of perceived social support (MSPSS) is a tool designed to measure perceptions of support and the extent to which an individual perceives social support from 3 different sides: Family side (Question 3,4,8 and 11), Friends side (question 6,7,9 and 12), and a Significant another side (question 1,2,5 and 10)[111]. The scale is self-reported questionnaire comprising a total of 12 items, with 7 points Likert scale ranging from (1) strongly disagree to (7) very strongly agree[112]. Concerning other studies, MSPSS has proven a reliable factorial validity, reliability and psychometrically instruments to be used to measure social and family support in several countries for patients with depression[113–116]. The total score is dividing to 3 categories: (from 69 to 84) represent high support, (from 49 to 68) moderate support, (from 12 to 48) low support[117].

c. Stigma

TB related stigma scale is tools designed to detect stigma in TB patients. It can measure TB stigma from community (11 questions) and patient's perspectives (12 questions) through measuring fear, guilt and sorrow in coping with TB. The scale consists of four point Likert scale ranging from strongly agree to strongly disagree[118]. The item scores from the questionnaire are summed and the scores range from 11 to 44 for Community perspectives to 12–48 for Patient perspectives on tuberculosis. The highest score representing higher stigma[119]. TB-stigma scale showed a strong validity and consistency with psychometric prosperities in TB patients in different countries[118,120,121].

d. Adherence

The Morisky Medication Adherence scale (MMAS-8) was used to measure patient's medication-taking behavior. Each item measures a specific medication-taking behavior[122]. The responses for the items are yes/no except that the last item is on a five-point Likert scale. The range of MMAS-8 score ranges from 0 to 8. The cut-points could be categorized as high adherence (=8 points), medium adherence (6 or 7 points), low adherence (<6 points)[123]. Morisky scale has shown a high reliability and validity to measure adherence in TB patients[124,125].

2.3.4. Data collection tools for Qualitative study

As I followed an explanatory sequential mixed method design (**Figure 8**), I identified 15 key informants (TB patients) for interview only in Negros from the nested quantitative study. I chose Negros to explore what kind of risk factors affecting adherence behavior toward TB treatment in a more rural area since there are fewer studies assessing adherence among persons with TB in rural compared to urban areas and to the best of my knowledge, none outside of the National Capital Region for the Philippines. Also, this region has almost the same TB incidence rates as NCR, 381 vs 384/100,000 and is ranked 4th for the total number of TB cases contributing 9% compared to 16% for NCR, ranked 1st for number of TB cases and TB incidence[126]. The key informants within the St-ATT cohort were purposively selected using criteria based on the quantitative data comprising (**Figure 9**), but not limited to, adherent vs. non-adherent, depressed vs. non-depressed and where feasible, selected to represent the sex distribution of the patients (70% male), patients who are resident close to and far from the treatment centers. Based on quantitative result, Participants who were nonadherent were

considered for the interview. Not only that, but also participants who were nonadherent and had one or more risk factor. For example, participants who were nonadherent and depressed and/or stigmatized were considered. **Figure 9** illustrates the participants with a blue circle were eligible to participate in this study and were approached for interview. I chose to focus on nonadherent participants to get a broader range of risk factors affecting persons with TB adherence behavior. Accordingly, the topic guide was designed to specifically know the barriers affecting nonadherence.

The plan was to recruit the patients for interviews who were between 1-3 months of starting treatment, when I hypothesized that difficulties associated with adherence may be at their maximum, and when previous evidence suggests that longer term patterns of adherence may be defined. However, due to delays resulting from covid-19 some patients were in months 4-5 during the interview. The interview guides were built based on the themes identified from the literature as barriers to TB treatment adherence and in consultation with other researchers experienced in these methods and topics (Dr. Iliatha Papachristou, LSHTM & Professor Akiko Matsuyama, Tsuda university, Department of International Cooperation and Multicultural Studies). Questions were tested on some persons with TB and discussed with local investigators before starting the data collection and were modified according to key informant response and comments. The topic guide was first prepared in English and later translated to Hiligaynon (the local language)(**Appendix 7.3**). Each interview session lasted for about an average of 45 min. All interviews were recorded using a digital audio recorder. Due to the COVID-19 pandemic, which was preventing in-person contact with participants, and was causing delays in study progress. The interviews were conducted by telephone by the same

trained research assistant. An interview summary for participants was submitted daily to the primary investigator to ensure the quality of data collection until the transcription and translation process was completed. In this study, saturation was identified when there is no new information providing further insights.

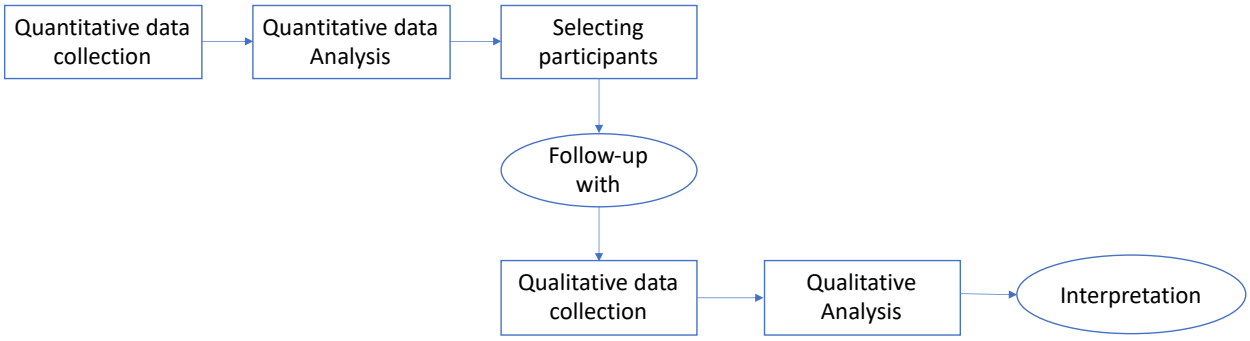


Figure 8: Data analysis process for explanatory sequential design

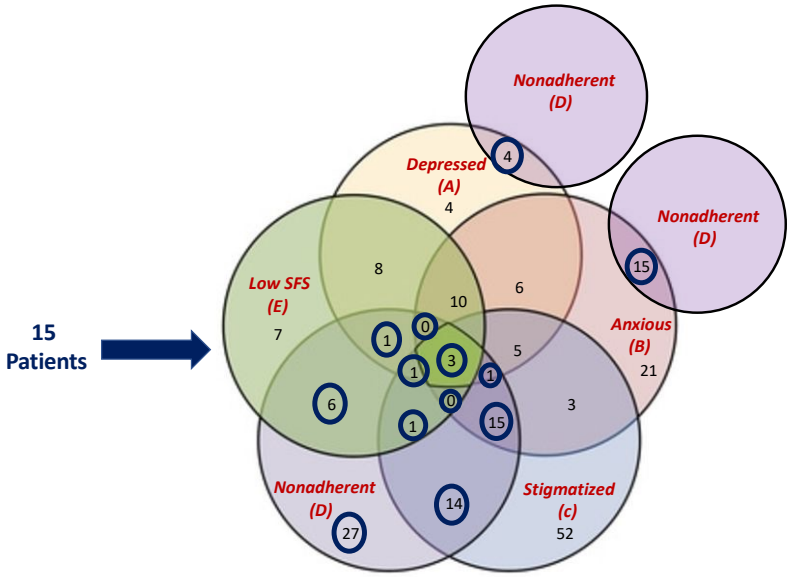


Figure 9: Procedure of s electing participants for qualitative data

2.4. Recruitment procedure

1- Participant invitation: Patients who met the initial inclusion criteria, were contacted by research nurses either by telephone or by asking them face to face to participate in the study. If the patient showing an interest, the research nurse assigned an appointment to meet the patient according to his/her availability and moving to the second step.

2- The initial introduction of study: A trained research nurses introduced the study to patients by using the study information sheet (**Appendix 7.4**). This introduction occurred in person at the safe and quite place.

3- Recruitment log: A recruitment log was kept documenting which patients have been approached and the outcome. If the patient indicated interest in the study, then the study staff continued to the next step. If the patient declined, this was recorded in the recruitment log and the process ended there. If the patient was unsure, s/he might take a copy of the study information sheet to review on his own, or he might speak to the study investigator to get further information.

4- Informed consent Form (ICF): the study staff reviewed the ICF with the patient and, if the participant gave an approval to join the study, they signed two ICF, one was kept in the research centre in the Philippines and other with the patient. Due to Covid-19, we got the approval from the patient through telephone (which was voice recorded). Written informed consent will be obtained from patients retrospectively (**Appendix 7.5**).

5- Screening: the potential participant was assigned a study ID number. The study staff determined patient eligibility using the inclusion and exclusion criteria on the screening checklist.

2.5. Ethics consideration

2.5.1. Potential risks and mitigation

There were no physical or biological hazards for patients and individuals involved in this research. Patients, however, might feel discomfort when discussing personal or emotional issues. We conducted the informed consent and interviews in a safe space where it is quiet and private. All persons involved in patient interviews were trained in sensitivity and patient/participant confidentiality. During interviews, participants could choose not to answer any particular questions or could terminate the interview at any time, without giving a reason. As part of the study information, all participants were provided with information about available mental health support services, including a 24-hour support hotline free service provided by the Philippines Mental Health Association "PMHA Bacolod Chapter". For patients who might suffer from involuntary recurrent memory (flashback syndrome) during the interview, we stopped the interview and if the patient wished, coordinate with the Medical Health Officer (MHO)/ municipal health center for referral or with the PMHA Bacolod chapter.

2.5.2. Informed consent and ethical consideration

Informed written consent was obtained from all study participants by trained research assistants in the language in which participants are most comfortable. All participants were provided with a written study information sheet in either Hiligaynon, Cebuano, English, or Tagalog which explained the study purpose, procedure, benefits, risks, personal confidentiality, and attribution and their right to withdraw from the study at any time, without

giving reasons and at no detriment to their usual care. Contact information was provided for any further questions. In the case of illiterate participants (which is not expected, based on previous experience with this patient population) the study was explained in the presence of an independent witness, who also signed the informed consent sheet, and the participant provided a thumbprint. Research assistants completed the informed consent in a quiet and private location to ensure patients have free and voluntary consent uninfluenced by health centre staff. Privacy was promoted to the highest possible level in the facilities where consent had been obtained but at a minimum, it would be asked that the regular staff of the health centre would not be present at the time of consent to avoid any possible perceived or real coercion into the study. Also, all the participants received a small reimbursement to thank them for their time of 250 PHP. All project staff signed non-disclosure forms and complete online Human Subjects Research Online Training, and Good clinical Practice Course (GCP). Also, the researchers abide by the Data Privacy Law of the Philippines.

2.6. Benefit of the study:

Patients did not have direct benefit from participation in this study. However, that participants might be released by talking about his/her experience. For patients who have recall problem or suffering from severe social problem such as stigma and discrimination, they were be referred for appropriate mental health services if they need and informed about 24 hrs., supporting hotline in the Philippines. For depressed patients, study staff discussed with them to understand the cause of depression and tried to figure out different ways to help them.

2.7. Patient confidentiality and data management:

All participants' data and information from the interviews are stored securely. For protection against data access by unauthorized individuals; several security measures were applied. Data collection devices (laptops/tablets/digital recorders) were password protected and stored data encrypted. Encrypted data including recordings, transcripts, and coded data were backed up to a secure University server. Access to electronic data on servers were protected using access controls including password protection. Access will only be available to research personnel through the authorization of the Primary/Co-Investigators. All staff were trained in the handling of personally identifiable data. Data was anonymized at the earliest opportunity. Data was used to inform future intervention development and process evaluation only. Generic identifiers (e.g., participant 1) was used from the transcription stage onwards. The key linking participants' names with study IDs were stored separately from other data in a double-locked file at the secure project office, with access restricted to appropriate study personnel. Paper consent forms stored similarly. Study reports, such as aggregated data in progress reports, did not contain identifying information. Project office computers were safeguarded from theft and damage (e.g., using locks, encryption, and antivirus software). Audio records were deleted after the transcripts are finalized. Fully anonymized data may be transferred for analysis to co-investigators. The participants personal information was not mentioned in any reports or publications. Anonymized dataset (not including transcripts, only coded quotes) stored in a database and then kept in LSHTM university research data repository for 10 years after completion of the project. After this period, it will be deleted. As the project has already approved by LSHTM ethics (approval number: 17416 on 26 July 2019), Professor Sharon Cox as LSHTM investigator will be responsible for ensuring the data is deleted after 10 years.

2.8. Ethical approval

There were two parts of ethical approval

1- The main cohort study (St-ATT) & quantitative part of this study:

- Ethical approval has been obtained from Nagasaki University School of Tropical Medicine and Global Health (REF: 50), by the Asian Eye Institute in the Philippines (REF ERC 2018-008), and the London School of Hygiene and Tropical Medicine (REF 14894) (**Appendix 7.6**).

- The COVID-19 amendment approval has been obtained from Nagasaki University School of Tropical Medicine and Global Health (REF: 050), the Asian Eye Institute in the Philippines (REF ERC 2018-008), and the London School of Hygiene and Tropical Medicine (REF 14894-3) (**Appendix 7.8**).

2- This mixed method study (Qualitative part):

- Ethical approval has been obtained from the Asian Eye Institute in the Philippines (REF ERC 2018-008), the London School of Hygiene and Tropical Medicine (REF 14894), and conditional ethical approval has been obtained from Nagasaki University School of Tropical Medicine and Global Health (REF: 73) (**Appendix 7.7**).

3- The COVID-19 amendment ethical approval has been obtained from the Asian Eye Institute in the Philippines (REF ERC-2019-017), the London School of Hygiene and Tropical Medicine (REF 17416-1), Nagasaki University School of Tropical Medicine and Global Health (REF: 073) (**Appendix 7.9**). This amendment was requested due to the community quarantine implemented in all areas in the Philippines because of the COVID-19 pandemic, which was preventing in-person contact with participants, and is causing delays in study

progress. The main purpose of this amendment was to get approval to conduct the in-depth interview through phone instead of face to face. Also, we requested to get participant's verbal consent to conduct the interview. The consent was voice recorded and once restrictions are lifted, the research nurses will seek to retrospectively obtain a written record of informed consent from participants.

2.9. Data analysis plan

2.9.1. For quantitative data

Analysis was conducted using R software. First, data was cleaned then, the prevalence of main exposure (depression) and outcome (adherence) presented as a percentage with 95% confidence intervals as overall, by region, and by each phase (baseline, End of Intensive Phase (EIP), Middle of Continuation Phase (MCP), End of Continuation Phase (ECP)).

Descriptive data summaries corresponded to data type, mean (SD) and median (range) for continuous data, percentage and raw numbers for categorical variables. A descriptive analysis of the adherence outcome data and depression the main exposure at each treatment phase was done, and trends over time within individuals described and tests for trend applied if appropriate after visual inspection. The study population was appropriately described according to age, level of education, employment status, marital status, nutrition status, and type of regimen by using appropriate charts and frequency tables with appropriate statistical tests applied as per data type (Chi-square test (or Fisher's exact test) for categorical variables;

Kruskal-Wallis test (for non-normally distributed), students' t-test (for normally distributed) continuous variables.

To start with, analysis of the exposures with nonadherence at each treatment timepoint were conducted using logistic regression, and trends over time within individuals investigated. For each treatment timepoint, I used the cut-off point 8 for both depression and anxiety to classify patients to depressed and anxious(≥8) or non-depressed and non-anxious (<8). For Social family support, the cut-off points 49 used to classify patients to either receiving high social/family support (≥49) or low social and family support (<49). Patients classified as adherent (≥ 6) or non- adherent (<6). For TB stigma, continuous data were used. A logistic regression model was made with the TB treatment adherence (high and below 6) and the change in exposure variables including demographic factors. Significant factors ($p<0.1$) obtained from univariable analysis entered into a multivariable regression model for investigation of potential confounders. Investigation of confounding and effect modification and development of a multivariable model was conducted using a forward stepwise approach and a variable included if the likelihood ratio test p-value comparing the model with and without the variable in question was significant ($p<0.05$) [and or the main exposure estimates were modified more than 10%]. The adjustment of potential confounders and effect modifier was considered to calculate the adjusted odds ratios.

Statistical analysis of the association between the exposures of interest and the outcome of nonadherence were conducted in order of increasing complexity, with the final analyses maximizing the value of the cohort design by incorporating all available data for all enrolled

individuals using mixed effects models to account for within individual covariance of repeated measures within individuals. Using repeated measures of time-varying exposures and outcomes were examined within-individual covariance of these variables over time. Longitudinal analyses were conducted with data from four assessments at baseline, end of the intensive phase, middle and end of continuation phase. During modeling, I included two variables for time. First, the number of days between baseline and the date of visit. Second, the difference between the planned visit and the actual visit which was treated the same as the other time varying covariates. The adherence score as outcome for these analyses was used.

2.9.2. A general overview of how risk factors were categorised in follow-up

For each phase, I calculated the change of risk factor's status between the baseline (as reference) and each follow-up time point (End if Intensive Phase, Mid and end of continuation phase). Each risk factor has 4-level categories. For example, if the participant's classification as non-depressed was unchanged from baseline to the follow-up time period a code of "0" was assigned, while "1" indicated their classification improved from depressed at baseline to non-depressed at follow-up, "2" indicated their status worsened from non-depressed at baseline to depressed at follow-up point, and "3" for classification as depressed was unchanged from baseline to the follow-up time. The same concept was assigned to anxiety, stigma, SFS, and BMI.

2.9.3. For qualitative data

In-depth interviews were conducted in the local language (Hiligaynon) and audio recorded. After that, transcription was done in local language by two different persons separately, a discussion occurred to finalized one transcript to be translated to English. Same procedure happened for translation by using two different persons to translate the final agreed transcript from Hiligaynon to English and then discuss again to get final English translated transcript. After that back translation (From English to Hiligaynon) was done by a different person to assure the translation accuracy. As a primary investigator, I started analysis by first familiarizing myself with the transcripts to find initial codes and patterns of the data. Then I completed an initial round of line-by-line open-coding to assign descriptive labels using NVIVO software from the analysis of transcripts to capture other relevant barriers to TB treatment. After finalizing coding, the emergent codes were discussed between the primary investigator and co-researchers who conducted the interviews until we agreed. After that, I grouped the codes into categories based on their relationships through constant comparison following thematic analysis using an inductive approach (**Figure 10**).

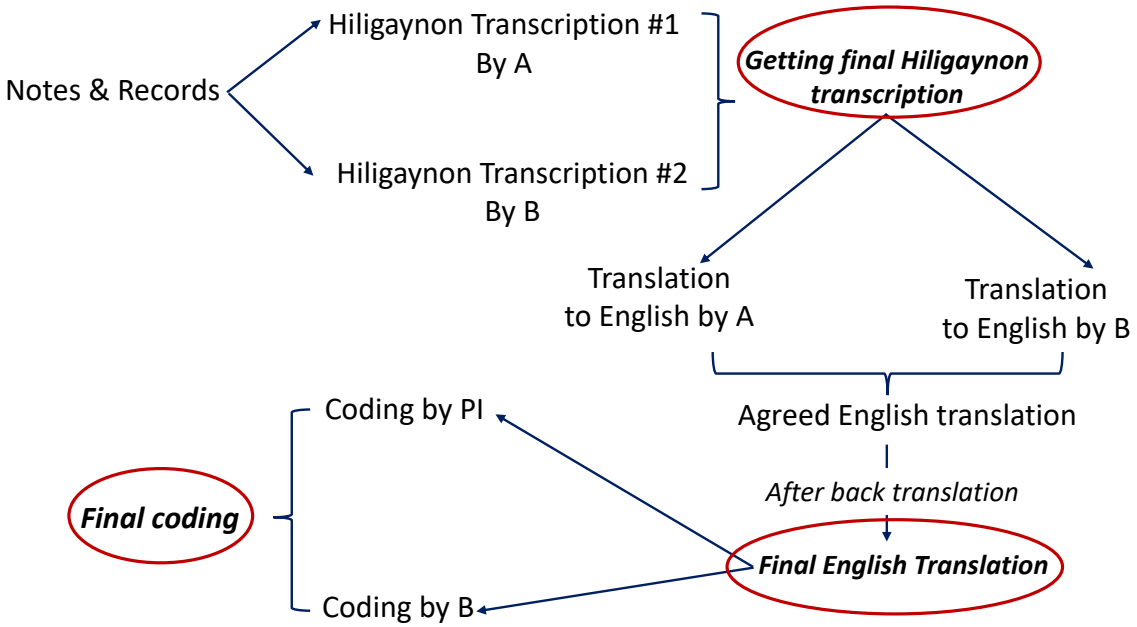


Figure 10: Qualitative analysis plan

2.10. Significance of the study

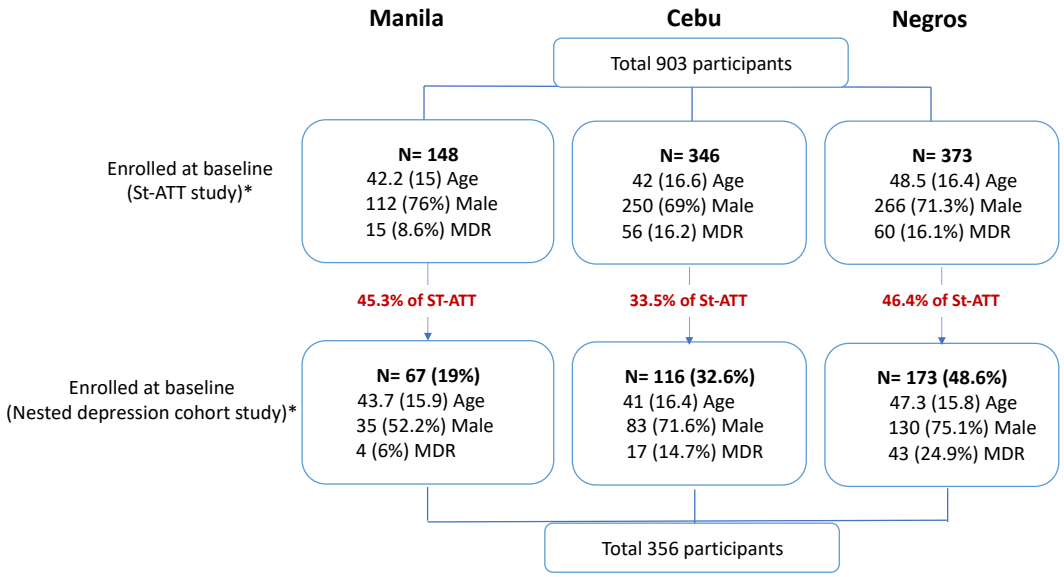
This study characterized the context specific barriers facing Filipino TB patients which can lead patients to be non-adherent to ATT regimens. Moreover, it may give the opportunity to spotlight on the impact of risk factors of TB medication adherence and investigate risk factors that affect adherence and disease progression which need to be further investigated. These results can then be used to inform the design of interventions or changes to Program operation to improve treatment adherence and thereby to reduce the development of drug resistance, poor patient outcomes, and reduce TB transmission from ineffectively treated TB cases.

Chapter 3

3. Results. Factors associated with nonadherence to TB-treatment: quantitative findings

3.1. Study participants

In the main St-ATT cohort study, 903 were enrolled in the period from 1st August 2018 to 20th Feb 2020 and followed up until the end of TB treatment, completing on 20th December 2020. There were 148 participants in Manila, 346 in Cebu, and 373 in Negros. In this nested cohort study, 356 participants participated in the period from 26th April 2019 to 20st Feb 2020. (**Figure 11**). The demographic characteristics of the total participants are shown in **Table 5**. The mean age was 44.6 years (range 18-87, SD 16.2). 30.3% were female while 69.7% are male. The highest number of participants were in Western Visayas with 173 persons (46.4% of St-ATT) followed by 116 in Central Visayas (33.5% of St-ATT), and 67 in National Capital region (45.3% of St-ATT). There were 42.7% reported being married. Only, 21.1% were highly educated at college or higher level, 62.6% were unemployed. Most participants had neither smoking experience nor drinking alcohol 45.5%, and 62.1% respectively. More than half of participants were registered on DS-TB treatment 82% while 18% were registered on MDR-TB treatment regimens. Most participants (65.7%) had no previous history of TB treatment and hence were registered as "New cases" **(Table 5)**.



* St-ATT study: Recruited participants from 1st Aug.2018 to 20th Feb.2020 & follow-up them until 27th Dec.2020. Nested depression cohort study: Recruited participants from St-ATT study from 26th Apr. 2019 to 20th Feb 2020& follow-up them until 27th Dec. 2020.

Figure 11: The distribution of nested study participants enrolled from the main St-ATT study

	Region VI (Western Visayas) N=173	Region VII (Central Visayas) N=116	National Capital Region (NCR) N=67	Overall N=356	P-value*
Age					
Mean (SD)	47.3 (15.8)	41.0 (16.4)	43.7 (15.9)	44.6 (16.2)	**0.007**
Median [Min, Max]	47.0 [18.0, 87.0]	39.5 [18.0, 75.0]	43.0 [19.0, 83.0]	45.0 [18.0, 87.0]	
Sex					
Female	43 (24.9%)	33 (28.4%)	32 (47.8%)	108 (30.3%)	**0.002**
Male	130 (75.1%)	83 (71.6%)	35 (52.2%)	248 (69.7%)	
Marital Status					
Married	82 (47.4%)	46 (39.7%)	24 (35.8%)	152 (42.7%)	
Single	68 (39.3%)	62 (53.4%)	38 (56.7%)	168 (47.2%)	**0.044**
Divorced/Widowed	23 (13.3%)	8 (6.9%)	5 (7.5%)	36 (10.1%)	
Educational level					
No education/Primary	54 (31.2%)	38 (32.8%)	19 (28.4%)	111 (31.2%)	
Secondary	85 (49.1%)	52 (44.8%)	33 (49.3%)	170 (47.8%)	0.926
Tertiary/Vocational	34 (19.7%)	26 (22.4%)	15 (22.4%)	75 (21.1%)	
Employment					
No	109 (63.0%)	70 (60.3%)	44 (65.7%)	223 (62.6%)	0.766
Yes	64 (37.0%)	46 (39.7%)	23 (34.3%)	133 (37.4%)	
Smoking					
No smoking experience	66 (38.2%)	63 (54.3%)	33 (49.3%)	162 (45.5%)	
Current smoker	48 (27.7%)	26 (22.4%)	9 (13.4%)	83 (23.3%)	**0.016**
Ex-Smoker	59 (34.1%)	27 (23.3%)	25 (37.3%)	111 (31.2%)	
Alcohol consumption					
Daily	44 (25.4%)	17 (14.7%)	14 (20.9%)	75 (21.1%)	
Weekly	22 (12.7%)	9 (7.8%)	11 (16.4%)	42 (11.8%)	0.113
Monthly	8 (4.6%)	8 (6.9%)	2 (3.0%)	18 (5.1%)	
Rarely/Never	99 (57.2%)	82 (70.7%)	40 (59.7%)	221 (62.1%)	
TB Treatment type					
Drug Sensitive	130 (75.1%)	99 (85.3%)	63 (94.0%)	292 (82.0%)	**0.002**
Drug Resistant	43 (24.9%)	17 (14.7%)	4 (6.0%)	64 (18.0%)	
Outcome					
New	102 (59.0%)	85 (73.3%)	47 (70.1%)	234 (65.7%)	
Relapse	58 (33.5%)	27 (23.3%)	15 (22.4%)	100 (28.1%)	
Treatment after loss to follow up [TALF]	11 (6.4%)	0 (0.0%)	3 (4.5%)	14 (3.9%)	**0.017**
Treatment after failure	2 (1.2%)	2 (1.7%)	0 (0.0%)	4 (1.1%)	
Previous treatment outcome unknown [PTOU]	0 (0.0%)	2 (1.7%)	2 (3.0%)	4 (1.1%)	

* The p-value for continuous variables were obtain through Anova test while for categorical using Chi-square test

Table 5: The demographic characteristics of the total study participants (356 participants)

3.2. Overview on the number of participants at different timepoints

Table 6 illustrates the number of participants with data for this study at the different treatment phase time points and the final treatment outcome as determined by the St-ATT study. Out of 356 of total participants included in these analyses 282 had study-specific data available at baseline. There were 149 participants with data for all treatment phases. Forty-one did not continue in the study after recruiting them at baseline due to different reasons. For example, two patients refused to continue participating in the main cohort study, 6 died (Deaths occurred within the period before the next visit was due), 20 patients Lost to Follow Up (LTFU), 1 patient moved away, and 12 were default (defined as a patient whose treatment was interrupted for 2 consecutive months or more) (**Table 6**). In total. There were 74 participants without baseline data on depression due to paused data collection to re-validate the translations after concerns were raised by the research nurses and local investigator. After resuming the data collection, those 74 participants were in different treatment timepoint and they were included in the study to achieve the planned sample size.

Phase	# of patients	Status							
		Refused	Tx Completed	Tx Failure	Died	Moved away	Default	LTFU	Cured
Baseline|EIP|MCP|ECP (All)	149	0	149	0	0	0	0	0	0
ECP	52	0	51	0	0	0	0	0	1
Baseline	41	2	0	0	6	1	12	20	0
Baseline|EIP|MCP	28	5	15	1	0	1	4	2	0
Baseline|MCP|ECP	21	0	21	0	0	0	0	0	0
Baseline|EIP|ECP	17	0	16	0	0	0	1	0	0
Baseline|EIP	15	2	5	0	0	3	2	3	0
EIP|MCP|ECP	10	0	10	0	0	0	0	0	0
Baseline|ECP	7	0	7	0	0	0	0	0	0
MCP|ECP	5	0	5	0	0	0	0	0	0
MCP	3	1	0	0	0	0	1	1	0
Baseline|MCP	4	2	1	0	0	1	0	0	0
EIP	1	1	0	0	0	0	0	0	0
EIP|ECP	3	0	3	0	0	0	0	0	0
Total	**356**	**13**	**283**	**1**	**6**	**6**	**20**	**26**	**1**
		356							

*__EIP__: End of Intensive Phase, __MCP__: Middle of Continuation Phase, __ECP__: End of Continuation Phase

Table 6: The number of participants at different time points with their final outcome

3.3. TB treatment adherence status, outcome, and adherence pattern at each follow-up timepoint and TB treatment outcome categorization

For adherence as main outcome, participants were categorized as adherent and nonadherent following the pre-defined cut-off point using the Morisky scale. When participants had missing study data for a visit, they were classified as non-adherent if they were classified as LTFU or Tx default by the main St-ATT study from the last available data time point. Data for TB medication adherence was obtained from 315 participants as adherence was not assessed at baseline, but only risk factors were assessed which include depression, anxiety, SFS, stigma and body mass index. Out of 315 participants, 11 refused to continue the study, 5 moved away from study sites, 8 were default, 6 were LTFU (**Table 6**).

Table 7 shows the pattern of study participants adherence behavior and the data available at each phase. The mark (**X**) was added for participants who were not interviewed to get their adherence status at a certain timepoint. The most common pattern among all participants was being adherent at all timepoints in 94 Participants, followed by being non-adherent of 33 participants who were interviewed only at end of the continuation phase (**Table 7**).

Table 8 shows the adherence outcome among 156 participants who missed at least one visits based on their final treatment outcome in the St-ATT study. For example, there were two people adherent until they became LTFU/default at end of continuation phase, 3 were unknown (including participants who refused to continue in the study or moved away). Only one participant died after became adherent at middle of continuation phase (**Table 8**).

Figure 12 shows the proportion of participants who reported adherence data using Morisky adherence scale among 315 participants. Out of 315, there were 159 who completed Morisky adherence scale at three time points (end of intensive phase, middle & end of continuation phase). Out of 156 participants who missed at least one visit (not include baseline visit as adherence was not measured), 17 had missing adherence data which was not possible to be replaced from the St-ATT outcome (Include participants who could not categorized their adherence due to the change in their adherence behavior with missing middle visits), 16 participants were not known (include participants who refused to continue in the study or moved away or died before end of intensive phase visits), and 123 participants who could fill their missing adherence data from their outcome (include participants who were LTFU, default, treatment completed).

Adherence pattern for all patients						
#	EIP	MCP	ECP	Baseline data availbility	Freq.	%
1	Adherent	Adherent	Adherent	Yes	94	30%
2	Adherent	Adherent	Non-adherent		13	4%
3	Non-adherent	Adherent	Adherent		12	4%
4	Non-adherent	Non-adherent	Adherent		10	3%
5	Adherent	Non-adherent	Adherent		8	3%
6	Non-adherent	Non-adherent	Non-adherent		5	2%
7	Non-adherent	Adherent	Non-adherent		4	1%
8	Adherent	Non-adherent	Non-adherent		3	1%
9	Adherent	Adherent	x	Yes	15	5%
10	Non-adherent	Non-adherent	x		6	2%
11	Non-adherent	Adherent	x		5	2%
12	Adherent	Non-adherent	x		2	0.6%
13	Adherent	x	Adherent	Yes	8	2.5%
14	Non-adherent	x	Adherent		7	2.2%
15	Adherent	x	Non-adherent		2	0.6%
16	x	Adherent	Adherent	Yes	14	4.4%
17	x	Non-adherent	Non-adherent		3	1.0%
18	x	Adherent	Non-adherent		3	1.0%
19	x	Non-adherent	Adherent		1	0.3%
20	Non-adherent	x	x	Yes	8	2.5%
21	Adherent	x	x		7	2.2%
22	x	Adherent	x	Yes	3	1.0%
23	x	Non-adherent	x		1	0.3%
24	x	x	Non-adherent	Yes	4	1.3%
25	x	x	Adherent		3	1.0%
26	Adherent	Adherent	Adherent	No	5	1.6%
27	Non-adherent	Non-adherent	Non-adherent		2	0.6%
28	Adherent	Adherent	Non-adherent		2	0.6%
29	Non-adherent	Adherent	Adherent		1	0.3%
30	Non-adherent	x	Non-adherent	No	2	0.6%
31	Adherent	x	Adherent		1	0.3%
32	x	Adherent	Non-adherent	No	3	1.0%
33	x	Non-adherent	Adherent		1	0.3%
34	x	Adherent	Adherent		1	0.3%
35	x	x	Non-adherent	No	33	10.5%
36	x	x	Adherent		19	6.0%
37	Adherent	x	x	No	1	0.3%
38	x	Adherent	x	No	3	1.0%
Total					**315**	
Total +41 participants had only baseline data					**356**	

*X represents that adherence data not available, **EIP**: End of Intensive Phase, **MCP**: Middle of the Continuation Phase, **ECP**: End of Continuation Phase

Table 7: Adherence patterns at different treatment phases

EIP	MCP	ECP	Freq.	%	Nonadherent	Treatment completed	Not known	Died
Adherent	Adherent	x	15	10%	2	10	3	0
Non-adherent	Non-adherent	x	6	4%	1	4	1	0
Non-adherent	Adherent	x	5	3%	1	1	2	1
Adherent	Non-adherent	x	2	1%	0	2	0	0
Adherent	x	Adherent	8	5%	0	8	0	0
Non-adherent	x	Adherent	7	4%	0	7	0	0
Adherent	x	Non-adherent	2	1%	0	2	0	0
x	Adherent	Adherent	14	9%	0	14	0	0
x	Non-adherent	Non-adherent	3	2%	0	3	0	0
x	Adherent	Non-adherent	3	2%	0	3	0	0
x	Non-adherent	Adherent	1	1%	0	1	0	0
Non-adherent	x	x	8	5%	2	3	3	0
Adherent	x	x	7	4%	3	2	2	0
x	Adherent	x	3	2%	0	1	2	0
x	Non-adherent	x	1	1%	0	0	1	0
x	x	Non-adherent	4	3%	0	4	0	0
x	x	Adherent	3	2%	0	3	0	0
Non-adherent	x	Non-adherent	2	1%	0	2	0	0
Adherent	x	Adherent	1	1%	0	1	0	0
x	Adherent	Non-adherent	3	2%	0	3	0	0
x	Non-adherent	Adherent	1	1%	0	1	0	0
x	Adherent	Adherent	1	1%	0	1	0	0
x	x	Non-adherent	33	21%	0	33	0	0
x	x	Adherent	19	12%	0	19	0	0
Adherent	x	x	1	1%	0	1	0	0
x	Adherent	x	3	2%	1	1	1	0

*__EIP__: End of Intensive Phase, __MCP__: Middle of Continuation Phase, __ECP__: End of Continuation Phase. Among 130 participants who completed treatment, 2 had treatment failure and one was cured. Not known include participants who refused or moved away. __X__ represents that adherence data not available.

Table 8: The adherence outcome of 156 participants with missing data based on their final treatment outcome

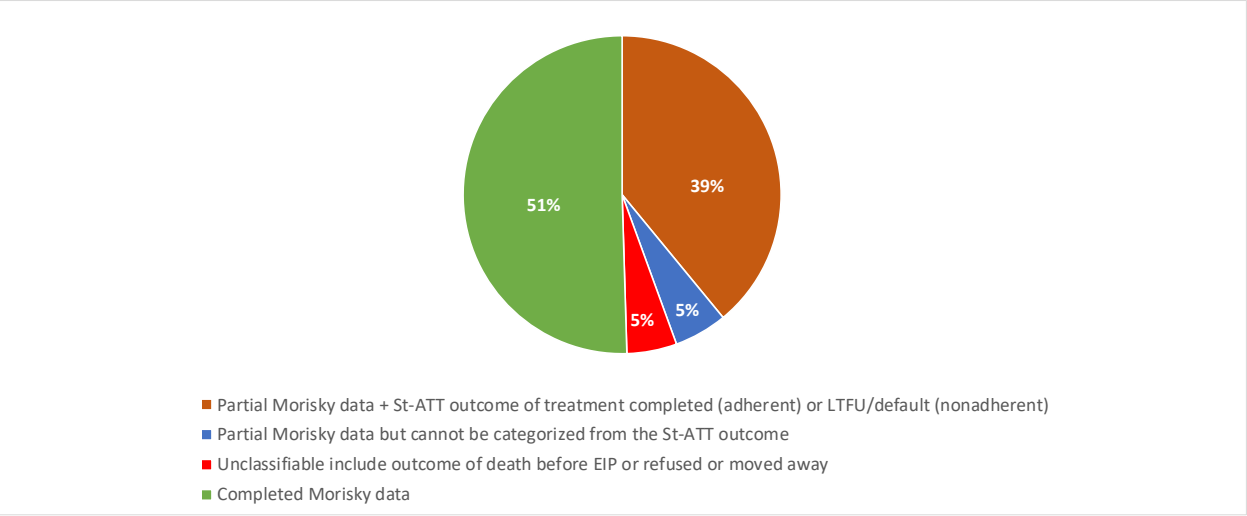


Figure 12: **Proportions by data sources to categorize adherence vs. nonadherence for all 315 participants**

3.4. Timepoints and range of days of actual treatment phases and collecting data

Table 9 shows the range of days difference between the planned visit date for each treatment phase and the actual interview date at each time point. At the end of intensive treatment phase visit, participants were interviewed before the expected date to end their treatment while at end of continuation phase, the interview conducted after finishing treatment due to the situation of COVID-19. At end of intensive treatment phase, 2 patients at DS-TB treatment extend their treatment while for DR-TB, 2 patients extend their EIP to 153 days (6 months). At middle of continuation phase, only 2 patients at DR-TB regimen extended their treatments to reach 213 days (7 months) and no one extend for DS-TB. At end of continuation phase, five patients at DS-TB treatment regime extended their treatments to 246 days (8 months) while 1 patient at DR-TB treatment regimen extended to 374 days (12.5 months) (**Table 9**).

	EIP	MCP	ECP
DS-TB			
Total participants	190	183	229
Median (IQR) of the difference between actual and planned visit	3 (-23 to +13)	7 (-20 to +17)	9 (-27 to +23)
Median (IQR) of actual visit	60 (51-88)	120 (110-155)	180 (175-231)
DR-TB			
Total participants	33	37	35
Median (IQR) of the difference between actual and planned visit	5 (-11 to +17)	7 (-5 to +12)	8 (-17 to +10)
Median (IQR) of actual visit	120 (117-153)	181 (178-213)	290 (269-365)
Total	**223**	**220**	**264**

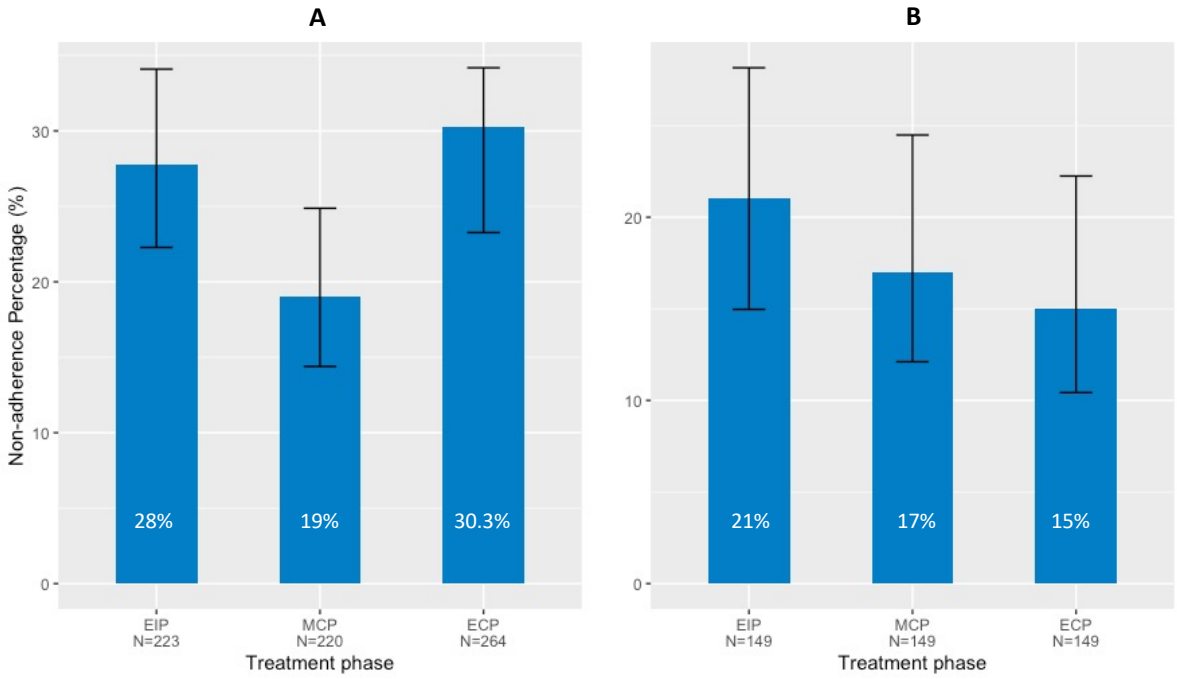
Table 9: The difference of days between the planned and actual interview date for each timepoint

3.5. The prevalence of adherence at each timepoints

Figure 13A shows the prevalence of nonadherence at different time points among all interviewed participants at each timepoints. The prevalence of nonadherence was decreasing until middle of continuation phase after that it was dramatically increased up to 30% at end of continuation phase.

Figure 13B shows the prevalence of nonadherence among 149 participants who completed all time points visits. The prevalence of nonadherence was gradually decreased toward the end of treatment. The prevalence. The vary between the prevalence of nonadherence at end of continuation phase between 264 participant and 149 participants might be due to the different of participants characteristics. Among 264 participants there were 30 MDR-TB patients, 58 were from NCR, 179 were male, 114 unemployed, 55 not educated, and 86 were single while

among 149 participants, there were 20 MDR-TB patients, 11 from NCR, 104 male, 89 unemployed, 44 not educated, 63 singles.



*__EIP__: End of Intensive Phase, __MCP__: Middle of Continuation Phase, __ECP__: End of Continuation Phase

Figure 13: The Prevalence of nonadherence for all participants vs. participants who completed all timepoints visits

3.6. The prevalence of exposures at different timepoints

Figure 14A shows the prevalence of exposures at the 4 different time points among all interviewed participants. There were 356 participants were interviewed in total, the prevalence of depression (defined as HADS score ≥8) at end of intensive phase was higher than other timepoints while anxiety (defined as HADS score ≥8), poor SFS (defined as MSPSS <49), and moderate/severe malnutrition (defined as BMI<17 kg/m^2), the prevalence was highest at baseline.

Figure 14B illustrated the prevalence of exposures among 149 participants who completed all timepoints visits. The prevalence of depression at baseline was quite similar to end of intensive phase while the prevalence of anxiety, less support and moderate/severe malnutrition was higher at baseline compared to other timepoints. less support was more common than depression among 149 participants compared to participants who did not complete all compared all timepoint visits.

The most striking feature that depression was more among all participants who did not attend all visits (**Figure 14A**) compared to participants who complete all timepoint visits (**Figure 14B**). This might be because of participants who LTFU or default were more likely to be depressed compared to participants who completed all visits.

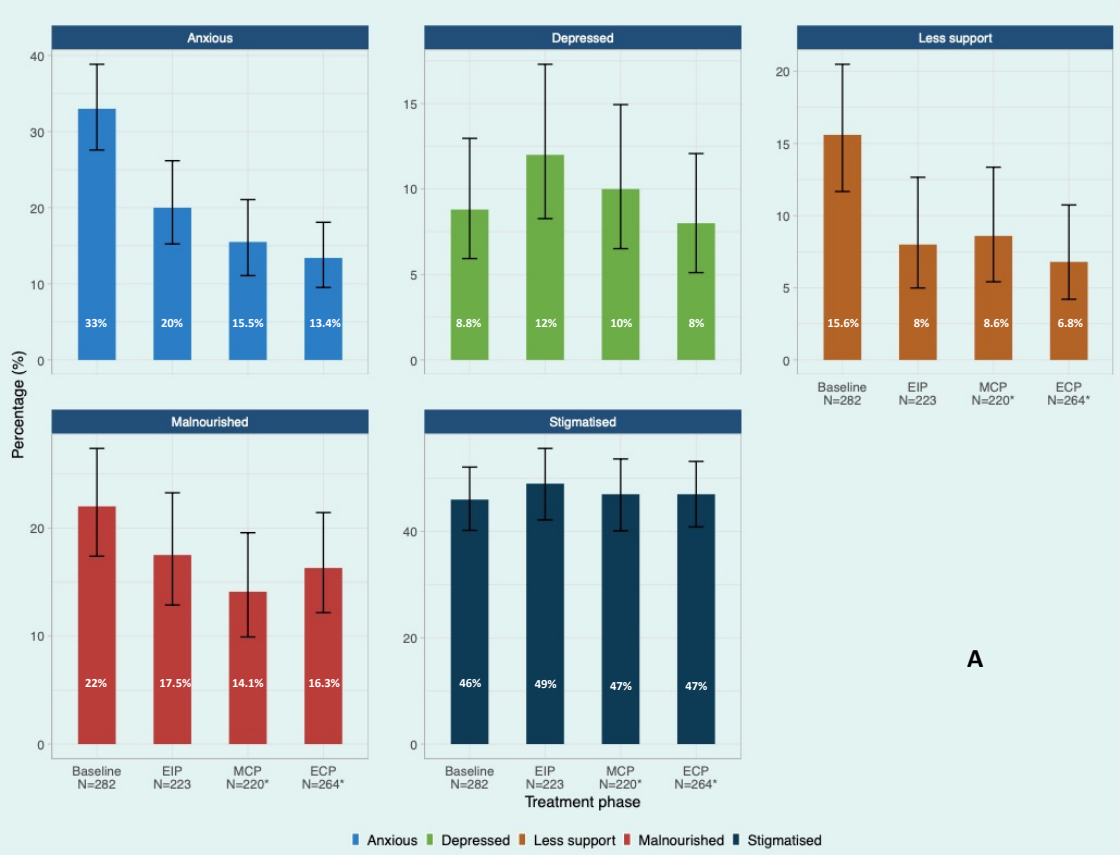
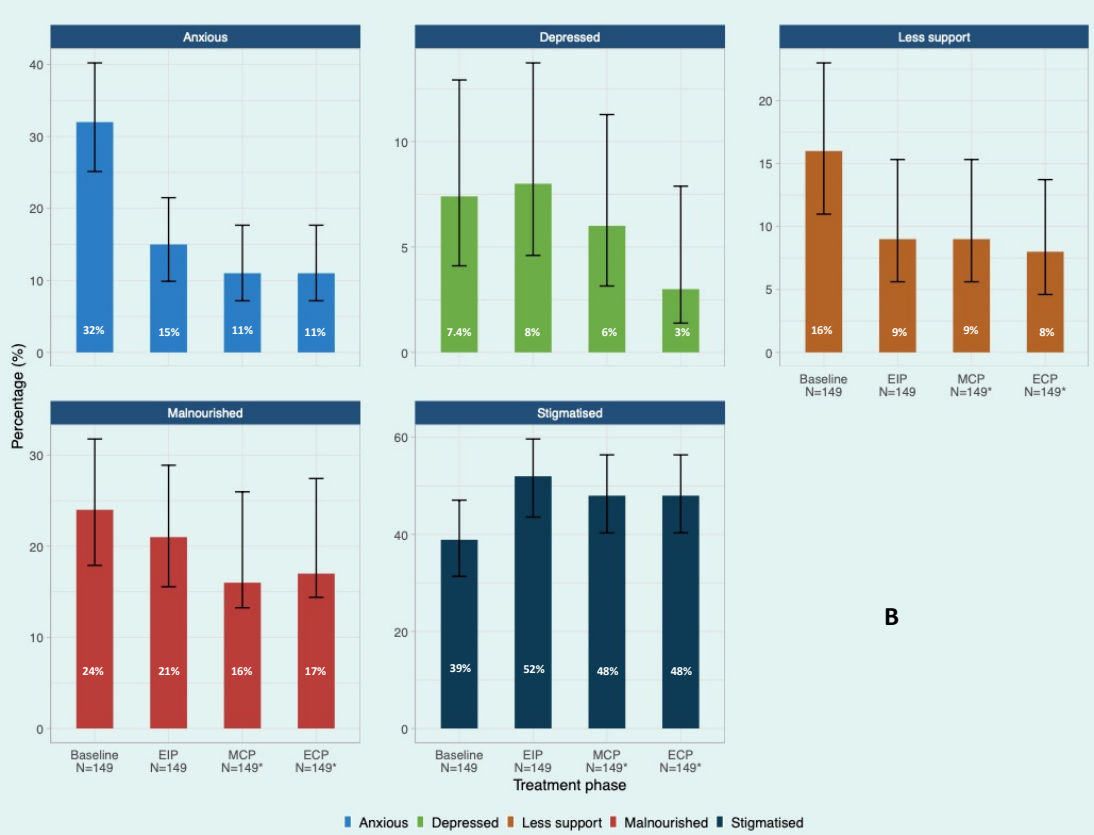


Figure 14: The prevalence of exposures for all participants vs. completed all visits



*EIP: End of Intensive Phase, MCP: Middle of Continuation Phase, ECP: End of Continuation Phase. There were 6 participants who did not report BMI at both middle and end of continuation phase

3.7. Association between main exposures at baseline

Table 10 reports associations between the main exposure variables of interest at baseline (e.g., anxiety, SFS, stigma, BMI, MUAC, and depression. There was a positive correlation between depression and anxiety, stigma, BMI, MUAC, age while negative correlation was observed between depression and social/family support. This linear regression analysis was conducted to see which exposures associated with one to another and to see if it requires a separate model to avoid collinearity between exposures. Based on this result, depression and anxiety needed to be in a separate model which was done in the next section (**Figure 15**).

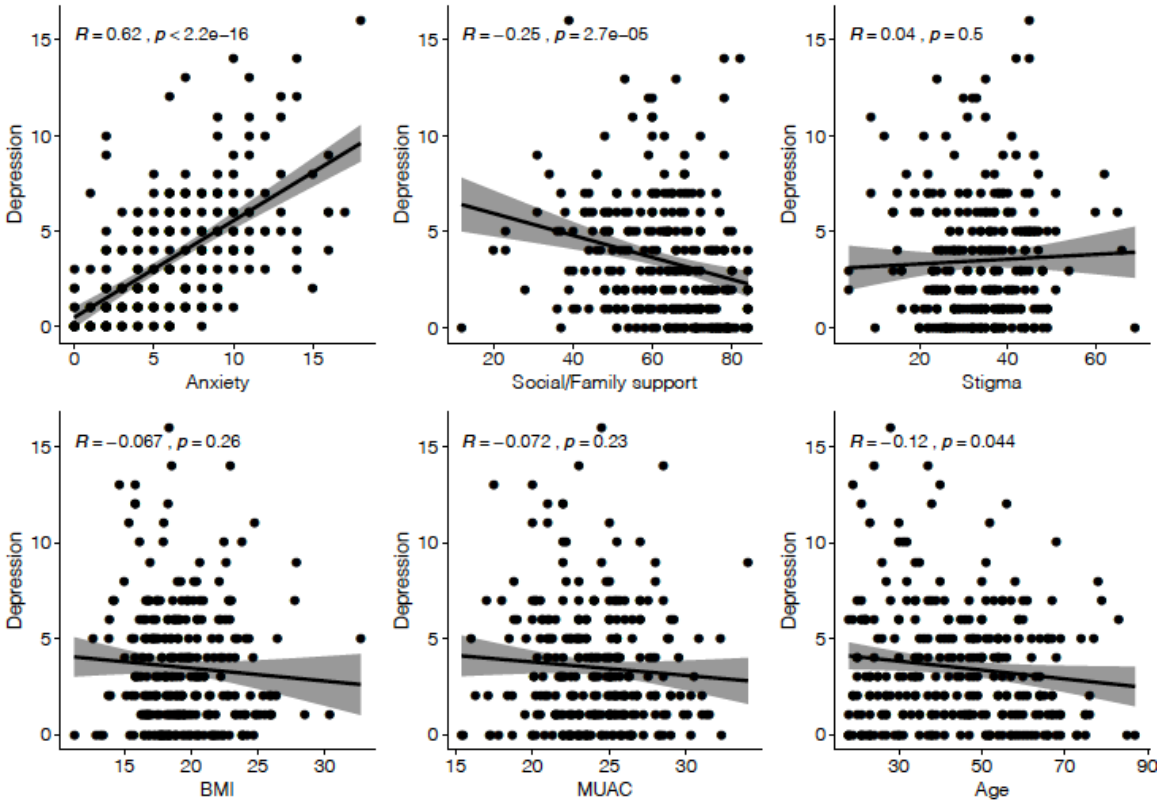


Figure 15 Association between co-variates and depression as the main exposure of interest

Variables	Age	Depression score	Anxiety score	SFS score	Stigma score	BMI	MUAC
Age	-	-0.12 (-0.233 -0.003)	0.083 (-0.198 - 0.034)	0.037 (-0.12 - 0.113)	0.081 (-0.036 - 0.196)	0.072 (-0.046 - 0.187)	0.012 (-0.129 -0.105)
Depression score	**-0.12 (-0.233 -0.003)**	-	**0.62 (0.544 - 0.688)**	**0.25 (-0.354 -0.134)**	0.04 (-0.077- 0.156)	0.067 (-0.183 - 0.049)	0.072 (-0.187 - 0.046)
Anxiety score	0.083 (-0.198 - 0.034)	0.62 (0.544 - 0.688)	-	0.14 (-0.254 -0.025)	**0.21 (0.101 -0.323)**	0.06 (-0.184 - 0.049)	0.084 (-0.199 - 0.033)
SFS score	0.037 (-0.12 - 0.113)	-0.25 (-0.354 - 0.134)	**0.14 (-0.254 -0.025)**	-	0.11 (-0.224 - 0.007)	0.11 (-0.011 - 0.219)	0.036 (-0.080 - 0.152)
Stigma score	0.081 (-0.036 - 0.196)	0.04 (-0.077 - 0.156)	**0.21 (0.101 - 0.323)**	0.11 (-0.224 - 0.007)	-	0.028 (-0.144 - 0.089)	0.057 (-0.059 - 0.173)
BMI (kg/m2)	0.072 (-0.046 - 0.187)	-0.067 (-0.183 -0.050)	0.07 (-0.184 - 0.049)	0.11 (-0.011 - 0.219)	0.028 (-0.144 - 0.089)	-	**0.075 (0.692 - 0.796)**
MUAC	0.012 (-0.129 -0.105)	-0.072 (-0.187 -0.046)	0.084 (-0.199 - 0.033)	0.036 (-0.081 - 0.152)	0.057 (-0.059 - 0.173)	**0.75 (0.692 - 0.796)**	-

Table 10: Beta coefficients (95% CI) of the linear relationship between continuous measures of the main exposures of interest

3.8. The effect of risk factors on nonadherence at End of Intensive Phase (EIP), and change in status of exposures during treatment period

The prevalence of nonadherence and exposures which include depression, anxiety, stigma, SFS, and BMI in this subset was similar to the full data set for each timepoints (**Figure 14**).

For analysis of risk of nonadherence, patterns of exposures at both timepoints were conducted. The most common pattern for all the main exposures of interest was being non-depressed, non-anxious, non-stigmatized, high SFS, and non-malnourished (BMI≥17) at both timepoints (**Table 11**).

3.8.1. Effects of psychological, social and nutrition factors on nonadherence at end of intensive phase:

Table 11 shows results of unadjusted and adjusted logistic regression among 209 participants for the modifiable and non-modifiable risk factors to adherence. No associations between age, sex, region or demographic variables with adherence were observed. In the crude analysis, MDR-TB participants were more likely to be nonadherent to the TB treatments compared to DS-TB (OR=3.92; 95%CI:1.83-8.49). Participants who were depressed at both timepoints were more likely to be nonadherent (OR=9.95; 95%CI:1.24-204.15) compared to patients who were non-depressed at both timepoints. The same pattern was observed for anxiety, participants who were anxious at both timepoints were more likely to be nonadherent compared to those who were non-anxious at both timepoints (OR=6.08; 95%CI:2.62-14.53). Participants who were stigmatized at both timepoints were less likely to be nonadherent compared to those non-stigmatized group at both timepoints (OR= 0.30; 95%CI:0.13-0.66).

1. Multivariable Model 1 (Depression as main exposure)

After adjustment for potential confounding by TB-treatment regimen, both depression and stigma remained significantly associated with nonadherence. Participants who were depressed at both timepoints had increased risk of being nonadherent compared to participants who did not experience depression (AOR=10.65; 95%CI: 1.07-257.00). Participants who were stigmatized at both timepoints were less likely to be nonadherent to TB-treatments (AOR=0.38, 95%CI:0.14-0.93). Also, participants whose stigma status changed from being non-stigmatized at baseline to stigmatised at end of intensive phase were less likely to be nonadherent to their TB medication. DR-TB patients were more likely to be nonadherent compared to DS-TB (AOR= 3.48, 95%CI:1.49-8.27). (**Table 10**).

2. Multivariable Model 2 (Anxiety as main exposure)

After adjustment for potential confounding by TB-treatment regimen, both anxiety and stigma remained significantly associated with nonadherence. Participants who were anxious at both timepoints were more likely to be nonadherent to TB-treatment (AOR=4.33, 95%CI: 1.72-11.08).

Participants who were stigmatized at both timepoints were less likely to be nonadherent to TB-treatments (AOR= 0.41; 95%CI: 0.15-1.03). DR-TB patients were more likely to be nonadherent compared to DS-TB (AOR= 2.71; 95%CI 1.13-6.52) (**Table 10**).

Variable		N	Non-adherent	OR (univariable)	Depression OR (multivariable)	LRT p-value	Anxiety OR (multivariable)	LRT p-value
Age	Mean (SD)	43.6 (15.9)	41.6 (16.0)	0.99 (0.97-1.01)	1.00 (0.97-1.02)	0.802	1.00 (0.98-1.02)	0.968
Sex	Female	57 (27%)	17 (29.8)	-	-	0.425	-	0.551
	Male	152 (73%)	40 (26.3)	0.84 (0.43-1.67)	0.73 (0.34-1.61)		0.79 (0.36-1.74)	
Region	Region VI (Western Visayas)	125 (60%)	35 (28.0)	-	-	0.417	-	0.996
	Region VII (Central Visayas)	68 (33%)	18 (26.5)	0.93 (0.47-1.79)	0.85 (0.37-1.93)		0.98 (0.43-2.22)	
	National Capital Region (NCR)	16 (8%)	4 (25.0)	0.86 (0.23-2.65)	0.38 (0.07-1.54)		0.95 (0.23-3.30)	
Marital status	Married	97 (46%)	24 (24.7)	-	-	-	-	
	Single	90 (43%)	26 (28.9)	1.24 (0.65-2.37)	-		-	
	Divorced/Widowed	22 (11%)	7 (31.8)	1.42 (0.49-3.80)	-		-	
Educational level	Tertiary/Vocational	50 (24%)	17 (34.0)	-	-	-	-	
	Secondary	105 (50%)	26 (24.8)	0.64 (0.31-1.34)	-		-	
	No education/Primary	54 (26%)	14 (25.9)	0.68 (0.29-1.58)	-		-	
Employment	Yes	83 (40%)	20 (24.1)	-	-	-	-	
	No	126 (60%)	37 (29.4)	1.31 (0.70-2.50)	-		-	
smoking behavior	No smoking experience	87 (42%)	25 (28.7)	-	-	-	-	
	Current smoker	60 (29%)	18 (30.0)	1.06 (0.51-2.18)	-		-	
	Ex-Smoker	62 (30%)	14 (22.6)	0.72 (0.33-1.52)	-		-	
Alcohol behavior	Rarely/Never	131 (63%)	36 (27.5)	-	-	-	-	
	Monthly	9 (4%)	2 (22.2)	0.75 (0.11-3.30)	-		-	
	Weekly	28 (13%)	8 (28.6)	1.06 (0.41-2.54)	-		-	
	Daily	41 (20%)	11 (26.8)	0.97 (0.43-2.09)	-		-	
TB treatment type	Drug Sensitive	175 (48%)	39 (22.3)	-	-	**0.004**	-	**0.025**
	Drug Resistant	34 (16%)	18 (52.9)	3.92 (1.83-8.49)	3.48 (1.49-8.27)		2.71 (1.13-6.52)	
Change in depression (Depressed ≥ 8, Non-depressed <8)	Nondepressed /Nondepressed	177 (85%)	41 (23.2)	-	-	**0.025**	-	-
	Depressed / Nondepressed	11 (5%)	6 (54.5)	3.98 (1.14-14.46)	4.74 (1.16-20.61)		-	
	Nondepressed / Depressed	17 (8%)	7 (41.2)	2.32 (0.80-6.44)	2.50 (0.77-7.92)		-	
	Depressed / Depressed	4 (2%)	3 (75.0)	9.95 (1.24-204.15)	10.65 (1.07-257.00		-	
Change in anxiety Anxious ≥8, Not anxious <8	Non-anxious / Non-anxious	130 (62%)	23 (17.7)	-	-	-	-	**0.010**
	Anxious / Non-anxious	38 (18%)	12 (31.6)	2.15 (0.93-4.83)	-		1.69 (0.68-4.02)	
	Non-anxious / Anxious	11 (5%)	5 (45.5)	3.88 (1.04-13.97)	-		3.83 (0.91-15.58)	
	Anxious / Anxious	30 (14%)	17 (56.7)	6.08 (2.62-14.53)	-		4.33 (1.72-11.08)	
Change in social & Family support (High SFS score ≥48, Low SFS <48=Low SFS)	High SFS / High SFS	167 (80%)	42 (25.1)	-	-	-	-	
	Low SFS/ High SFS	24 (11%)	8 (33.3)	1.49 (0.57-3.64)	-		-	
	High SFS / Low SFS	8 (4%)	4 (50.0)	2.98 (0.68-13.09)	-		-	
	Low SFS / Low SFS	10 (5%)	3 (30.0)	1.28 (0.27-4.82)	-		-	
Change in stigma (Stigmatized score <33, Non-stigmatized ≥33)	No stigma / No stigma	73 (35%)	28 (38.4)	-	-	**0.046**	-	**0.049**
	Stigma / No stigma	28 (13%)	10 (35.7)	0.89 (0.35-2.18)	1.25 (0.43-3.52)		1.37 (0.48-3.82)	
	No stigma / Stigma	44 (21%)	9 (20.5)	0.41 (0.17-0.96)	0.45 (0.17-1.11)		0.42 (0.16-1.08)	
	Stigma / Stigma	64 (31%)	10 (15.6)	0.30 (0.13-0.66)	0.38 (0.14-0.93)		0.41 (0.15-1.03)	
Change in Nutritional Status (Nourished BMI≥18.5, Malnourished BMI≤17)	Non-undernourished	151 (72%)	38 (25.2)	-	-	-	-	
	Improved malnourished	19 (9%)	7 (36.8)	1.73 (0.61-4.64)	-		-	
	Worsen malnourished	12 (6%)	4 (33.3)	1.49 (0.38-5.01)	-		-	
	Malnourished	27 (13%)	8 (29.6)	1.25 (0.48-3.01)	-		-	

Table 11: associations between depression and other risk factors and adherence at End of Intensive Phase

3.9. Risk factors for nonadherence at Middle of Continuation Phase (MCP), and change in status of exposures during treatment period

The prevalence of nonadherence in this subset was similar to that in the full dataset for each timepoints (19.4% (38/196) vs. 19% (42/220)) at middle of continuation phase. The prevalence of depression in this subset was close to the full dataset (7% (14/196) vs. 10% (22/220)). Same was observed for anxiety 16.8% (33/196) vs. 15.5% (34/220), Less-SFS 9.7% (19/196) vs. 8.6% (19/220), Stigma 50.5% (99/196) vs. 47% (103/220), and malnutrition 15.8% (31/196) and 14% (31/220).

For analysis of risk of nonadherence, patterns of exposures at both timepoints were conducted. The most common pattern for all the main exposures of interest was being non-depressed, non-anxious, non-stigmatized, high SFS, and non-malnourished (BMI≥17) at both timepoints (**Table 12**).

3.9.1. Effects of psychological, social and nutrition factors on nonadherence at middle of continuation phase:

Table 12 shows results of unadjusted and adjusted logistic regression among 196 participants for the modifiable and non-modifiable risk factors to adherence. No associations between age, sex, region, or demographic variables with adherence were observed. In the crude analysis, MDR-TB participants were more likely to be nonadherent to the TB treatments compared to DS-TB (OR=3.83; 95%CI:1.73-8.42). Participants who were anxious only at mid continuation phase and those who were anxious at both time points were more likely to be non-adherent

compared to participants who were not anxious at both time points (OR=5.05, 95%CI:1.35-17.95 & OR=9.42, 95%CI: 3.45-26.97) respectively (**Table 12**).

1. Multivariable Model 1 (Depression as main exposure)

After adjustment for potential confounding by TB-treatment regimen, depression was not significantly associated with nonadherence. The DR-TB participants were more likely to be nonadherent compared to DS-TB (AOR= 3.77, 95%CI: 1.64-8.68).

2. Multivariable Model 2 (Anxiety as main exposure)

After adjustment for potential confounding by TB-treatment regimen, anxiety remained significantly associated with nonadherence. Participants who were anxious at both timepoints were more likely to be nonadherent to TB-treatment (AOR= 7.65, 95%CI: 2.51-24.42). Also, participants whose anxiety status changed from being non-anxious at baseline to anxious at middle of continuation phase were more likely to be nonadherent compared to participants who did not experience anxiety (AOR= 5.13; 95%CI: 1.30-19.31). The DR-TB patients were more likely to be nonadherent compared to DS-TB (AOR= 3.17; 95%CI: 1.29-7.77) (**Table 12**).

Variable		N	Non-adherent	OR (univariable)	Depression OR (multivariable)	LRT p-value	Anxiety OR (multivariable)	LRT p-value
Age	Mean (SD)	44.1 (16.1)	40.2 (12.7)	0.98 (0.96-1.00)	0.98 (0.96-1.01)	0.140	0.99 (0.97-1.02)	0.595
Sex	Female	54 (28%)	9 (16.7)	-	-	0.662	-	0.379
	Male	142 (72%)	29 (20.4)	1.28 (0.58-3.07)	1.22 (0.52-3.10)		1.53 (0.60-4.25)	
Region	Region VI (Western Visayas)	127 (65%)	24 (18.9)	-	-	0.878	-	0.653
	Region VII (Central Visayas)	60 (31%)	12 (20.0)	1.07 (0.48-2.29)	1.01 (0.39-2.45)		0.96 (0.38-2.34)	
	National Capital Region (NCR)	9 (5%)	2 (22.2)	1.23 (0.18-5.46)	1.58 (0.21-8.25)		2.34 (0.30-12.69)	
Marital status	Married	90 (46%)	20 (22.2)	-	-	-	-	-
	Single	85 (43%)	16 (18.8)	0.81 (0.38-1.69)	-		-	
	Divorced/Widowed	21 (11%)	2 (9.5)	0.37 (0.06-1.42)	-		-	
Educational level	Tertiary/Vocational	46 (23%)	13 (28.3)	-	-	-	-	-
	Secondary	97 (49%)	14 (14.4)	0.43 (0.18-1.01)	-		-	
	No education/Primary	53 (27%)	11 (20.8)	0.66 (0.26-1.67)	-		-	
Employment	Yes	79 (40%)	16 (20.3)	-	-	-	-	-
	No	117 (60%)	22 (18.8)	0.91 (0.45-1.89)	-		-	
smoking behavior	No smoking experience	87 (44%)	17 (19.5)	-	-	-	-	-
	Current smoker	49 (25%)	12 (24.5)	1.34 (0.57-3.08)	-		-	
	Ex-Smoker	60 (31%)	9 (15.0)	0.73 (0.29-1.73)	-		-	
Alcohol behavior	Rarely/Never	121 (62%)	17 (14.0)	-	-	-	-	-
	Monthly	11 (6%)	4 (36.4)	3.50 (0.84-12.93)	-		-	
	Weekly	26 (13%)	7 (26.9)	2.25 (0.78-6.03)	-		-	
	Daily	38 (19%)	10 (26.3)	2.18 (0.88-5.25)	-		-	
TB treatment type	Drug Sensitive	158 (81%)	23 (14.6)	-	-	**0.002**	-	**0.013**
	Drug Resistant	38 (19%)	15 (39.5)	3.83 (1.73-8.42)	3.77 (1.64-8.68)		3.17 (1.29-7.77)	
Change in depression (Depressed ≥ 8, Non-depressed <8)	Nondepressed /Nondepressed	173 (88%)	32 (18.5)	-	-	**0.928**	-	-
	Depressed / Nondepressed	9 (5%)	2 (22.2)	1.26 (0.18-5.50)	0.85 (0.11-4.18)		-	
	Nondepressed / Depressed	9 (5%)	3 (33.3)	2.20 (0.45-8.83)	1.71 (0.29-8.40)		-	
	Depressed / Depressed	5 (3%)	1 (20.0)	1.10 (0.06-7.76)	1.13 (0.05-8.99)		-	
Change in anxiety Anxious ≥8, Not anxious <8	Non-anxious / Non-anxious	121 (62%)	15 (12.4)	-	-	-	-	**0.001**
	Anxious / Non-anxious	42 (21%)	6 (14.3)	1.18 (0.40-3.14)	-		1.02 (0.33-2.85)	
	Non-anxious / Anxious	12 (6%)	5 (41.7)	5.05 (1.35-17.95)	-		5.13 (1.30-19.31)	
	Anxious / Anxious	21 (11%)	12 (57.1)	9.42 (3.45-26.97)	-		7.65 (2.51-24.42)	
Change in social & Family support (High SFS score ≥48, Low SFS <48=Low SFS)	High SFS / High SFS	153 (78%)	28 (18.3)	-	-	-	-	-
	Low SFS/ High SFS	24 (12%)	6 (25.0)	1.49 (0.50-3.92)	-		-	
	High SFS / Low SFS	11 (6%)	2 (18.2)	0.99 (0.15-4.12)	-		-	
	Low SFS / Low SFS	8 (4%)	2 (25.0)	1.49 (0.21-6.86)	-		-	
Change in stigma (Stigmatized score <33, Non-stigmatized ≥33)	No stigma / No stigma	67 (34%)	20 (29.9)	-	-	-	-	-
	Stigma / No stigma	30 (15%)	3 (10.0)	0.26 (0.06-0.85)	-		-	
	No stigma / Stigma	42 (21%)	7 (16.7)	0.47 (0.17-1.19)	-		-	
	Stigma / Stigma	57 (29%)	8 (14.0)	0.38 (0.15-0.93)	-		-	
Change in Nutritional Status (Nourished BMI≥18.5, Malnourished BMI≤17)	Non-undernourished	142 (72%)	30 (21.1)	-	-	-	-	-
	Improved malnourished	23 (12%)	5 (21.7)	1.04 (0.32-2.85)	-		-	
	Worsen malnourished	10 (5%)	1 (10.0)	0.41 (0.02-2.34)	-		-	
	Malnourished	21 (11%)	2 (9.5)	0.39 (0.06-1.46)	-		-	

Table 12: Prevalence and associations between risk factors and adherence from recruiting to Middle of Continuation Phase (MCP)

3.10. The prevalence of adherence and risk factors at End of Continuation Phase (ECP)

The prevalence of nonadherence in this subset was different than the full dataset for each timepoints 16% (30/188) vs. 30.3% (80/264). The prevalence of this subset was different compared to the full dataset in depression (2.7% (5/188) vs. 8% (21/264)), and anxiety (11.2% (21/188) vs. 13.3% (35/264)). However, the prevalence of this subset was slightly close to the full dataset for Less-SFS (6.4% (12/188) vs. 6.8% (18/264)), Stigma (50.6% (97/188) vs. 47% (124/264)), and malnutrition was 19.7% (37/188) and 16.3% (43/264).

For analysis of risk of nonadherence, patterns of exposures at both timepoints were conducted. The most notable thing that no one experienced depression at both baseline and end of continuation phase while 5 participants who were nondepressed at baseline then became depressed only at end of continuation phase. The most common pattern for all the main exposures of interest was being non-depressed, non-anxious, non-stigmatised, high SF, and non-malnourished (BMI≥17) at both timepoints (**Table 13**).

3.10.1. Effects of psychological, social and nutrition factors on nonadherence at end of continuation phase:

Table 13 shows results of unadjusted and adjusted logistic regression among 188 participants for the modifiable and non-modifiable risk factors to adherence. There were association between age, region, and alcohol behaviour with adherence. A one unit increase of age was associated with a 4% increase of the odds of being adherent. Participants in National Capital

Region were more likely to be nonadherent compared to other regions (OR=15.84; 95%CI: 5.06-56.48). Participants who drink alcohol on weekly base were more at risk for being nonadherent (OR= 4.98; 95%CI: 1.84-13.49). In the crude analysis, participants whose anxiety status changed from non-anxious at baseline to anxious at end of continuation phase were more likely to be nonadherent compared to participants who did not experience anxiety (OR= 8.69; 95%CI: 1.48-51.45). Participants who were stigmatized at both timepoints were less likely to be nonadherent to TB-treatments (AOR= 0.22; 95%CI: 0.05-0.68, p=0.018).

1. Model 1 (Depression as main exposure)

After adjustment for potential confounding, age, region, and alcohol behaviour remained significantly associated with nonadherence. A one unit increase of age was associated with a 5% increase of the odds of being adherent. Being in National Capital region were increasing the risk of being nonadherent (AOR=31.83; 95%CI: 6.53-209.79), and drinking alcohol weekly increased the risk of being nonadherent compared to participants who did not drink alcohol (AOR= 6.45; 95%CI:1.53-30.69) (**Table 13**).

2. Model 2 (Anxiety as main exposure)

After adjustment for potential confounding, age, region, alcohol behavior, anxiety and stigma remained associated with nonadherence at end of continuation phase. Age (AOR= 0.95; 95%CI: 0.91-0.9), Participants from National Capital region were more likely to be nonadherent (AOR= 66.49; 95%CI: 11.75-551.46). Participants who drinking alcohol monthly were more at risk of being nonadherent to TB-treatment (AOR= 11.55; 95%CI: 1.48-90.97). Also, participants whose anxiety status change from being anxious at baseline to non-

anxious at end of continuation phase were more at risk of being nonadherent (AOR= 5.95; 95%CI: 1.70-22.76) compared to non-anxious participants. Participants who were non-stigmatized at baseline and became stigmatised at end of continuation phase were less likely to be nonadherent to TB treatments compared to participants who did not experience stigma (AOR= 0.24; 95%CI: 0.06-0.84) (**Table 13**).

Variable		N	Non-adherent	OR (univariable)	Depression OR (multivariable)	LRT p-value	Anxiety OR (multivariable)	LRT p-value
Age	Mean (SD)	44.8 (16.1)	37.5 (13.7)	0.96 (0.94-0.99)	0.95 (0.91-0.98)	**0.004**	0.95 (0.91-0.99)	0.112
Sex	Female	54 (29%)	7 (13.0)	-	-	0.753	-	0.207
	Male	134 (71%)	23 (17.2)	1.39 (0.58-3.71)	1.29 (0.26-6.80)		1.54 (0.30-8.80)	
Region	Region VI (Western Visayas)	123 (65%)	15 (12.2)	-	-		-	
	Region VII (Central Visayas)	49 (26%)	4 (8.2)	0.64 (0.18-1.88)	0.56 (0.13-2.07)	**0.014**	0.89 (0.19-3.77)	**>0.001**
	National Capital Region (NCR)	16 (9%)	11 (68.8)	15.84 (5.06-56.48)	31.83 (6.53-209.79)		66.49 (11.75-551.46)	
Marital status	Married	83 (44%)	10 (12.0)	-	-		-	
	Single	83 (44%)	18 (21.7)	2.02 (0.89-4.85)	-	-	-	-
	Divorced/Widowed	22 (12%)	2 (9.1)	0.73 (0.11-3.06)	-		-	
Educational level	Tertiary/Vocational	38 (20%)	11 (28.9)	-	-		-	
	Secondary	96 (51%)	15 (15.6)	0.45 (0.19-1.13)	-	0.3671	-	0.4203
	No education/Primary	54 (29%)	4 (7.4)	0.20 (0.05-0.63)	-		-	
Employment	Yes	77 (41%)	14 (18.2)	-	-	-	-	-
	No	111 (59%)	16 (14.4)	0.76 (0.35-1.68)	-		-	
smoking behavior	No smoking experience	78 (41%)	12 (15.4)	-	-		-	
	Current smoker	51 (27%)	10 (19.6)	1.34 (0.52-3.39)	-	-	-	-
	Ex-Smoker	59 (31%)	8 (13.6)	0.86 (0.32-2.24)	-		-	
Alcohol behavior	Rarely/Never	115 (61%)	11 (9.6)	-	-		-	
	Monthly	11 (6%)	3 (27.3)	3.55 (0.70-14.44)	9.05 (1.35-58.84)	**0.007576**	11.55 (1.48-90.97)	**0.01404**
	Weekly	29 (15%)	10 (34.5)	4.98 (1.84-13.49)	6.45 (1.53-30.69)		4.80 (1.02-25.64)	
	Daily	33 (18%)	6 (18.2)	2.10 (0.67-6.06)	3.72 (0.78-19.82)		5.38 (1.03-33.74)	
TB treatment type	Drug Sensitive	158 (84%)	22 (13.9)	-	-	-	-	-
	Drug Resistant	30 (16%)	8 (26.7)	2.25 (0.85-5.54)	-		-	
Change in depression (Depressed ≥ 8, Non-depressed <8)	Nondepressed /Nondepressed	171 (91%)	24 (14.0)	-	-	0.340		-
	Depressed / Nondepressed	12 (6%)	4 (33.3)	3.06 (0.77-10.55)	1.78 (0.18-12.78)			
	Nondepressed / Depressed	5 (3%)	2 (40.0)	4.08 (0.52-25.89)	5.77 (0.47-58.24)			
	Depressed / Depressed	0 (0%)	0	-	-			
Change in anxiety Anxious ≥8, Not anxious <8	Non-anxious / Non-anxious	126 (67%)	13 (10.3)	-	-	-	-	**0.028**
	Anxious / Non-anxious	41 (22%)	10 (24.4)	2.80 (1.10-7.00)	-		5.95 (1.70-22.76)	
	Non-anxious / Anxious	6 (3%)	3 (50.0)	8.69 (1.48-51.45)	-		8.59 (0.48-179.16)	
	Anxious / Anxious	15 (8%)	4 (26.7)	3.16 (0.79-10.85)	-		3.24 (0.53-17.57)	
Change in social & Family support (High SFS score ≥48, Low SFS <48=Low SFS)	High SFS / High SFS	148 (79%)	23 (15.5)	-	-	-		-
	Low SFS/ High SFS	28 (15%)	3 (10.7)	0.65 (0.15-2.06)	-			
	High SFS / Low SFS	8 (4%)	3 (37.5)	3.26 (0.63-14.25)	-			
	Low SFS / Low SFS	4 (2%)	1 (25.0)	1.81 (0.09-14.86)	-			
Change in stigma (Stigmatized score <33, Non-stigmatized ≥33)	No stigma / No stigma	91 (48%)	21 (23.1)	-	-	**0.038**	-	**0.034**
	Stigma / No stigma	0 (0%)	0	-	-		-	
	No stigma / Stigma	48 (26%)	6 (12.5)	0.48 (0.16-1.21)	0.29 (0.08-0.96)		0.24 (0.06-0.84)	
	Stigma / Stigma	49 (26%)	3 (6.1)	0.22 (0.05-0.68)	0.23 (0.04-0.96)		0.27 (0.04-1.15)	
Change in Nutritional Status (Nourished BMI≥18.5, Malnourished BMI≤17)	Non-undernourished	128 (68%)	19 (14.8)	-	-	-	-	-
	Improved malnourished	23 (12%)	4 (17.4)	1.21 (0.32-3.66)	-		-	
	Worsen malnourished	15 (8%)	5 (33.3)	2.87 (0.82-9.07)	-		-	
	Malnourished	22 (12%)	2 (9.1)	0.57 (0.09-2.19)	-		-	

Table 13: Prevalence and associations between risk factors and adherence from recruiting to End of continuation Phase (ECP)

3.11. Relationship between Morisky score of adherence and risk factors among all participants using repeated measures (Mixed effects model)

Table 14 presents the result of repeated measures using mixed effects model to see the association between Morisky score of adherence and risk factors. On average at any given time points the Morisky adherence score decreased in NCP and Central Visayas region compared to western Visayas. Also, at mid and end of continuation phase, the Morisky adherence score increased compared to end of intensive phase. On average, the Morisky adherence score at any time points decreased for participants who are drinking alcohol daily compared to participants who are not or rarely drinking. For MDR-TB, the Morisky adherence score decreased compared to DS-TB. Finally, the Morisky adherence score decreased on average at any given time points per unit increase of HADS depression score, HADS anxiety score, and TB-Stigma score. (**Table 14**).

1. **Model 1 (Depression as main exposure)**

On average at any given timepoint, participants from NCP had a lower Morisky adherence score (β coefficient=-0.22) compared to participants from Western Visayas region. On average at any given timepoint, participants on MDR-TB treatment had a lower Morisky adherence compared to DS-TB treatment participants (β coefficient=-0.68). Finally, Morisky adherence score was decreased by -0.05 per unit increase in HADS depression score at any given timepoint.

2. Model 2 (Anxiety as main exposure)

On average at any given timepoint, participants from NCP had a lower Morisky adherence score (β coefficient=-0.34) compared to participants from Western Visayas. On average at any given timepoint, participants on MDR-TB treatment and participants who daily drink alcohol had a lower Morisky adherence (β coefficient=-0.52 and -0.19 respectively) compared to DS-TB and participants and participants who rarely or never drinking alcohol respectively. Finally, Morisky adherence score was decreasing by -0.07 per unit increase in HADS anxiety score at any giving timepoint.

Variable		N	β coefficients (95% CI)	Depression Model β coefficients	LRT p-value	Anxiety Model β coefficients	LRT p-value
Age	Mean (SD)	44.60 (16.15)	0.003 (-0.003 0.0002)	0.003 (-0.0009 0.006)	0.149	0.002 (-0.0001 0.006)	0.167
Time of starting treatment (Days)	Mean (SD)	96.59 (78.48)	-0.0008 (-0.002 0.0001)	0.005 (-0.0012 0.011)	0.070	.004 (-0.002 0.010)	1.86
Phase	End of intensive phase	223 (23%)	-	-	-	-	-
	Mid of continuation phase	220 (22%)	0.299 (0.116 0.482)	-0.312 (-0.7135 0.089)		-0.241 (-0.632 0.150)	
	End of continuiation phase	264 (27%)	0.477 (0.204 0.751)	-0.739 (-1.542 0.064)		-0.574 (-1.355 0.208)	
Sex	Male	696 (70%)	-	-	0.86	-	0.203
	Female	293 (30%)	0.030 (-0.095 0.155)	0.012 (-0.12 0.14)		.084 (-0.045 0.2136)	
Region	Region VI (Western Visayas)	552 (56%)	-	-	**0.012**	-	**<0.001**
	Region VII (Central Visayas)	294 (30%)	-0.144 (-0.275 -0.014)	**-0.150 (-0.293 -0.021)**		**-0.197 (-0.321 -0.072)**	
	National Capital Region (NCR)	143 (14%)	-0.349 (-0.508 -0.190)	**-0.219 (-0.392 -0.060)**		**-0.336 (-0.491 -0.182)**	
Marital status	Married	441 (45%)	-	-	-	-	-
	Single	445 (45%)	-0.112 (-0.232 0.009)	-		-	
	Divorced/Widowed	103 (10%)	0.017 (-0.178 0.212)	-		-	
Educational level	No education/Primary	288 (29%)	-	-	-	-	-
	Secondary	485 (49%)	0.074 (-0.058 0.205)	-		-	
	Tertiary/Vocational	216 (22%)	-0.090 (-0.251 0.072)	-		-	
Employment	No	607 (61%)	-	-	-	-	-
	Yes	382 (39%)	-0.051 (-0.168 0.067)	-		-	
smoking behaviour	No smoking experience	439 (44%)	-	-	-	-	-
	Current smoker	247 (25%)	-0.01 (-0.152 0.133)	-		-	
	Ex-Smoker	303 (31%)	0.099 (-0.035 0.233)	-		-	
Alcohol behaviour	Rarely/Never	611 (62%)	-	-	0.204		0.078
	Monthly	51 (5%)	-0.037 (-0.299 0.226)	-0.050 (-0.291 0.191)		-0.034 (-0.275 0.206)	
	Weekly	126 (13%)	-0.082 (-0.259 0.095)	-0.064 (-0.229 0.100)		-0.086 (-0.250 0.079)	
	Daily	201 (20%)	-0.161 (-0.304 -0.019)	**-0.178 (-0.311 -0.044)**		-0.188 (-0.320 -0.055)	
TB treatment type	Drug Sensitive	862 (87%)	-	-	**0.007**		**0.034**
	Drug Resistant	163 (16%)	-0.305 (-0.483 -0.127)	**-0.679 (-1.17 -0.186)**		**-0.522 (-1.004 -0.041)**	
HADS depression score	Mean (SD)	3.03 (3.015)	-0.067 (-0.086 -0.048)	**-048 (-0.068 -0.002)**	**<0.001**	-	-
HADS Anxiety score	Mean (SD)	4.69 (3.53)	-0.075 (-0.092 -0.059)	-	-	**-0.066 (-0.0801 -0.047)**	**<0.001**
MSPSS Social & Family support score	Mean (SD)	64.43 (11.72)	0.004 (-0.001 0.010)	-	-	-	-
TB-Stigma score	Mean (SD)	33.15 (9.88)	-0.01 (-0.016 -0.004)	0.004 (-0.010 0.002)	0.170	**-0.004 (-0.009 0.002)**	0.174
BMI	Mean (SD)	20.19 (3.28)	-0.007 (-0.025 0.012)	-		-	-

* Time of starting treatment is the number of days between outcome measurements and baseline starting treatment

Table 14: The mixed effects model analysis between Morisky adherence score and risk factors

Chapter 4

4. Understanding reasons for being nonadherent to TB treatments: qualitative findings

4.1. Study participants recruitment procedure and timing of interview

In total, 61 participants were identified based on the quantitative characteristic selected to be included in this qualitative analysis (**Figure 9**). Since research nurses had established a good rapport with the participants and they were fully aware of their characteristics and their ability to talk about their experience without affecting them mentally and emotionally, 2 participants were excluded from the opinion of suitability. Among those 2 excluded participants, one had a suicide history and were excluded to avoid triggering the participant with any sensitive questions especially it would be difficult to manage the situation while the interview was conducted through phone and not face to face. The other participant was excluded due to the disability of communicating effectively. There were fifty-nine participants approached. Out of 59 participants, 11 could not be reached (LTFU), 9 did not have phone, 7 were difficult to access (either location or phone signal), 5 moved away from the study site, 4 were so sick to talk, 3 had HIV, 3 died, and 2 refused to join the study. Due to Covid-19 situation, Philippines's government-imposed community quarantine which started from 1st March 2020 to cover all region and provinces. Therefore, the interviews were conducted by phone in the period 6th to 20th August 2020 (in the 6th months of lockdown) (**Figure 16**).

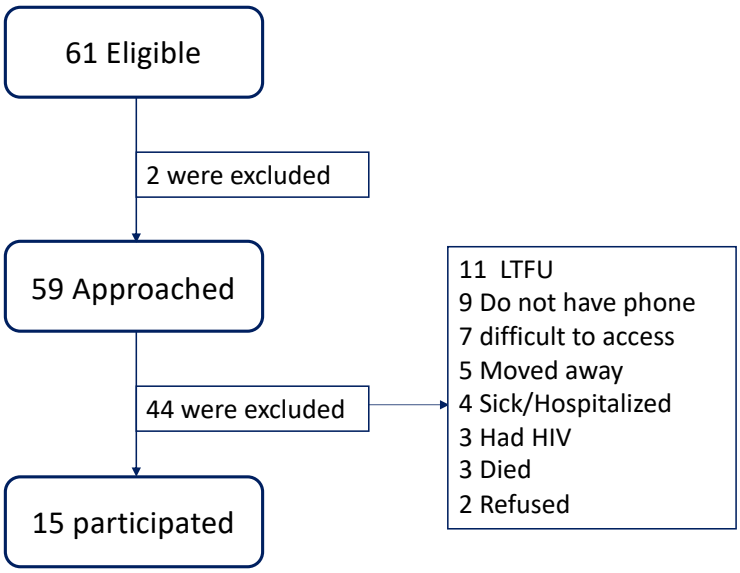


Figure 16: The qualitative study recruitment procedure

4.2. Participant background profile

Out of the total 15 TB patients, 10 were male and 5 females. Nine patients were single while 5 were married and 1 widowed. Three participants had no education/ primary, 5 had secondary education, and the rest were tertiary/ vocational. Only 4 were employed. Ten participants had DS-TB. Six participants were interviewed at 1-2 months of starting their treatments (**Table 15**).

Characteristics	Freq.	%
Sex		
Male	10	67%
Female	5	33%
Age group		
18–24	2	13%
24–34	5	33%
35–44	2	13%
45–54	4	27%
55-64	1	7%
≥65	1	7%
Marital Status		
Single	9	60%
Married	5	33%
Widowed	1	7%
Educational level		
No education/Primary	3	20%
Secondary	6	40%
Tertiary/Vocational	6	40%
Employment status		
Employed	4	27%
Unemployed	11	73%
Location		
Bago CHO	5	33%
Valladolid RHU	3	20%
La Carlota CHO	3	20%
Riverside PMDT	2	13%
Bacolod CHO	2	13%
TB category		
Drug Sensitive	10	67%
Drug Resistant	5	33%
Treatment type		
standard Cat I	10	67%
WHO shorter regimen	5	33%
Household income		
Less than 5,000 PHP	6	40%
5000 - 9999 PHP	6	40%
10,000 - 14,999 PHP	3	20%

Table 15: Background profile of TB patient study participants in Negros, (n = 15)

Theme	Code
Pre-diagnosis & patient pathway	• Recognition of symptoms • Initial seeking care • Diagnosis place - Private clinic - Public health center
Quality of care	• Communication with HCP & medication instructions • Available treatment • Covid-19 effect
Social & family support	• Reason to share diagnosis • Nature of family/ friend's reactions • People who support
Reason to be nonadherent	• Psychological reasons • Patient behaviors reasons • Medication reasons • Health system reasons • Financial reasons
Emotional and personal experience	• Stigma & discrimination • Reason to be depressed or anxious
Patient's TB knowledge	• Reason to get TB • Quack doctors (Tradition healer), culture concept & believes

Table 16: Thematic analysis

4.3. Result

4.3.1. Pre-diagnosis & patient pathway

The most common initial symptom reported by the participants was cough (12/15), accompanied by other symptoms such as back aches, chest pain, sleeping trouble, cough with blood, and loss of appetite.

"I feel weak, then back aches, I also cough, and felt cold. I always want to sleep. I have profuse coughing. I don't have an appetite to eat" (53 years-old, Male, DS-TB, 4th months of starting treatment).

*"I had a severe cough and got exhausted quickly. I cannot sleep or breath normally" (*22 years-old, Female, DS-TB, 3rd months of starting treatment).

A private clinic was the first health care provider contacted by most of the patients (10/15). This pattern of care provider preference was the most common. After the start of TB symptoms, 9 patients went to health check-up within one month while 6 patients took 3 months to seek care (**Figure 17**). The most common pathways involved taking time to visit health centre immediately after the onset of symptoms, which the patient justified as illustrate in the quote below,

"*The symptoms got on and off; that is why I thought of not going to the doctor right away. only decided to seek consultation when I had my bleeding*" (36 years-old, Male, MDR-TB, 4th month of starting treatment).

Other patient mentioned the reason not to seek care immediately was because of not having any symptoms. Patient knew through the health check-up before travel overseas for work.

"*I did not feel anything. I was about to pass my requirements abroad in Manila. I had my medical examination as a requirement for those going abroad. It turned out that I had tuberculosis based on the doctor's findings*" (32 years-old, Male, MDR-TB, 5thcmonths of starting treatment).

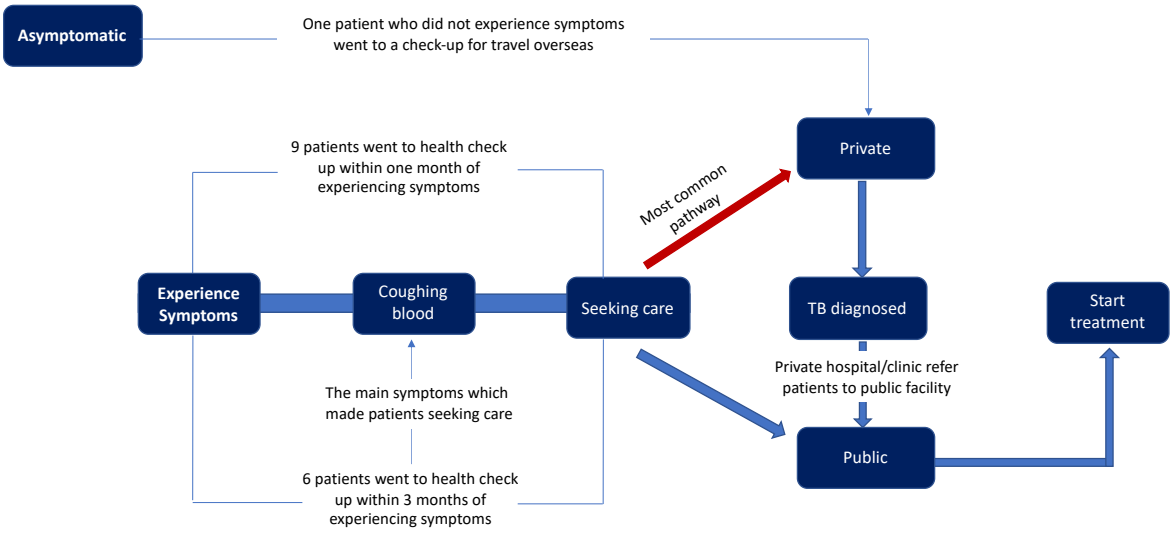


Figure 17: The patient's pathway to seek care

4.3.2. Quality of care

- **Communication with HCP & medication instructions**

When we asked the patients about HCP's way of communication, eleven patients had a good experience with a clear explanation of medication instruction as shown in below quotes,

"*The health workers were all kind. They took care and accommodated us. Their behaviour did not affect us since they were good and even lessens our anxiety and worries*" (50 years-old, Female, MDR-TB, 5th months of starting treatment).

"*They explained medication instructions well and cleared, sir. I understood everything that they told us. Also, if I said to them that I am not feeling well, they told me to stop for a while my medication and then check me up for a bit. They also remind me to take my medications daily not to skip any day. Based on my experience, their service is excellent*" (33 years-old, Male, MDR-TB, 4th months of starting treatment).

Four patients had bad experience with HCP. When we asked them to explain more about their experience, we found 3 main reasons behind this attitude. First, long waiting time. One patient reported that he needed to wait for long time to get his medication. However, if he knows someone inside, that could fasten the medication processor.

"*I can't deny that we have several ill-mannered health workers in the health centre. They would not entertain you immediately if you do not connect with anyone in the health centre*" (45 years-old, Male, DS-TB, 2nd months of starting treatment).

Second, unpleasant and aggressive communication. Two patients reported unpleasant way of communication with HCP which make one of patient hesitated to go back to health center to avoid the conflict with staff which might affect his adherence behavior.

"*They told me aggressively that if I don't take medication, then it means goodbye world, meaning I would die. Their words hurtled me a lot. I felt they do not care about my feeling. I did not want to go back"* (22 years-old, Female, DS-TB, 3rd months of starting treatment).

"*I encountered one BHW who is unpleasant. She talked to me badly and was giving me medication in rude way. There are times I am tempted not to go back just to avoid conflict"* (36 years-old, Male, MDR-TB, 4th month of starting treatment).

Third, stigmatized by HCP. One patient was stigmatized as the staff did not allow him to come close to them.

"*HCP will not allow you to go near them. They asked me to be away. I feel sad about their behaviors as if I am very sick and contagious. I could not ask any questions to them or sharing my concerns. I also want to move outside the house, but I decided not anymore because if HCP won't understand my situation, I cannot expect others to understand*" (66-year-old, female, DS-TB, 2nd month of starting treatment).

- **<u>Available treatment</u>**

Twelve patients reported that medication was available most of the time whilst 3 patients only in Bago city struggled to get their medication. Patients reported that the medication supply sometimes delayed being delivered to Bago health center. which make HCP asked patients to buy their medication from their own money, as illustrated in the quote bellow:

"*Medication was for free, but sometimes I had to buy my medications since the health center did not have it in stock. I just bought 27 or 28 medicines earlier this week since they were not available in the health center but most of the time, I just wait the medication until it come back"* (28-year-old, Male, DS-TB, 2nd month of starting treatment).

"*Most of the time, the health center does not have available medicines for us, so we still have to buy it with our own money, which is expensive. You have to purchase several of your medications because it will take several days or weeks before the health center replenish their supplies. Sometimes I borrow money from my mother since I do not have enough to buy my medications, especially at the lockdown time"* (45 years-old, Male, DS-TB, 2nd months of starting treatment).

This had a negative effect on patient's adherence as some of them could not afford buying the treatments and this lead to skip some dosages until the stock of medication become available.

- **Covid-19 effect**

Three patients (2 from Bago, and one participant on MDR-TB treatment from La Carlota) were affected by the lockdown due to covid-19.

Participant reported that due to the curfew, there was difficulty to go to the health center and get the medication. Moreover, there was delay in the medication supply to Bago health center due to the emergency which stopped all the transportation. Of equal note, patient need prescription to purchase the medication from pharmacy which was difficult to be obtained plus the financial constrain.

"*It was challenging to obtain the medicines because of the lockdown, no transportation available to go to different center, and it is expensive to buy from privet pharmacy*" (28 years-old, Male, DS-TB, 2nd months of starting treatment).

"At times, there are no medicines, Sir. To go out is prohibited. The supply is running out. I need a prescription from the doctor, and you have to be the one to buy the medicines that are out of stock in the Centre" (20 years-old, Female, DS-TB, 3rd months of starting treatment).

This situation makes patients skipped their medication for several days.

"I was greatly affected during the first three months of my treatment because of the lockdown, I missed taking my medications for 2 weeks" (33 years-old, Male, DR-TB, 4th months of starting treatment).

4.3.3. Social & family support

- **Reason to share diagnosis**

Almost all participants disclosed the diagnosis with their family. When we asked them about the reason behind sharing, some said to get emotional support which helped them during their treatment journey such as

"*I was afraid. I needed someone to tell me everything will be ok. I was worried about my health, and I was scared to die*" (53 years-old, Male, DS-TB, 4th months of starting treatment). Some others instead, shared the information to get financial aid from their family epically, as they could not work anymore.

"*It was hard for me since there were many things that I could not do. I could not go out, I could not work, and I could not mingle with my neighbors and friends. I wanted my family to help me financially"* (50 years-old, Female, MDR-TB, 5th months of starting treatment).

Only one patient did not share his diagnosis with his sibling as he wanted to avoid judgement which would stress him.

"*I was afraid if they learned that I have TB, they would surely blame me and that will stress me*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

Regarding sharing diagnosis with friends, there were four patients avoided telling their friends. The main reason to hide their diagnosis was that they were ashamed of getting TB which reflect negatively on their self-esteem. For example, one patient reported that he wanted to die once he knew that he had TB.

"*I did not want to tell my friends as my reaction to myself is that I feel dirty; if I just wanted not to live anymore since I got TB. I do not think they will understand my situation*" (45 years-old, Male, DS-TB, 2nd months of starting treatment)

Also, patients were afraid of being avoided and isolated from their friends after they knew their situation to avoid being infected which may hurt patient's feeling.

"*I find my condition embarrassing. I do not want them to distance themselves from me because of fear of getting infected. I am also afraid of gossiping. It kills me*" (20 years-old, Female, DS-TB, 3rd months of starting treatment)

"*I did not tell my friends because I am afraid if they learned that I have TB, they would surely avoid me. I cannot bear that feeling*" (22 years-old, Female, DS-TB, 3rd months of starting treatment)

- **Nature of family/friend reactions**

The common reactions from patient's family after sharing diagnosis was positive and supportive. Some patient expressed how their family supported them emotionally by showing their sympathy, talking and contain their feelings which gave them hope to be treated.

"*When my family learned about it, it was OK for them; they sympathized with me. I didn't feel any form of discrimination by them. I was released after telling them*" (53 years-old, Male, DS-TB, 4th months of starting treatment).

"*My family was there to talk to me, including my in-laws, nieces, and nephews*" (59 years-old, Female, DS-TB, 5th months of starting treatment).

Others expressed how their family accepted their disease and encouraged them, as shown in the quote below:

"*My family did not badly react since they were not scared of my disease. They did not mind my illness because it was my illness and theirs. They told me that they will always support me*" (45 years-old, Male, DS-TB, 2nd months of starting treatment).

Other patients mentioned that their family did not change their way of communication after they knew diagnosis:

"*They treated me the same as before. They did not say anything wrong about me after I openly told them that I was TB positive. I think they were matured enough to accept my condition.*

They were willing to listen to anything and avoided things that could offend me" (31 years-old, Male, DS-TB, 2nd months of starting treatment).

Also, the most reported advice from patient's family was asking patients to separate their stuff such as dining utilities not to infect other family members. For example

"*My family didn't treat me differently, but they told me to separate the things I use. They treat me as same as before because I'm their mother. If I am another person, they probably could have treated me and reacted differently*" (66 years-old, Female, DS-TB, 2nd months of starting treatment).

Despite positive attitudes observed overall, four patients reported having experienced negative feedback from their family. The main reported reaction was being avoided from their family which hurt them emotionally.

"*My family took a distance and avoid me after I shared my diagnosis. I am crying once I remember their attitude*" *(*22 years-old, Female, DS-TB, 3rd months of starting treatment)

"*Before, my siblings and friends were always at my house, and they would always talk to me whenever we would see each other. Now, when they learned that I had TB, they avoided me*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

"*My close friends and family don't interact with me anymore. They do not even talk to me*" (32 years-old, Male, MDR-TB, 5th months of starting treatment).

"*My sister-in-law avoided me, and she asked me always to be away from her. This hurts a lot*" (41 years-old, Male, DS-TB, 2nd months of starting treatment).

- **People who support and how**

Most of the patients reported having the required support from their family members. Five patients got the emotional supports from their family such as preparing medication, food, and doing household work which reflected positively on patient's psychological status, improve their adherence behaviors, and make them able to get enough rest and recovered quickly.

"*My wife prepared my medications every day. She always reminds me when I forgot my medication. She supported me a lot and that make me feel good. She gave me hope to be cured soon"* (45 years-old, Male, DS-TB, 2nd months of starting treatment).

"*My family took care of preparing foods for me; they do the household chores and other work so I could rest and recover faster. I could not do any work because I felt dizzy or wanted to vomit as I moved around. What I did was to rest and sleep*" (50 years-old, Female, MDR-TB, 5th months of starting treatment).

Six patients reported receiving financial support from their family which helped them to cover the transportation cost.

"*My aunt and uncle, sir. They gave me a travel allowance of 2, 500 pesos for my travel expenses going to the health center. Also, my young sibling, When I went for a check-up, I was given two prescriptions. my young sibling was the one who bought and provided all my medications when it is not available in the health center*" (32 years-old, Male, MDR-TB, 5th months of starting treatment).

Twelve patients had emotional, financial, and medication support from their family and/or friends.

"*My neighbors donated food for my consumption and my auntie was the one who accompanied me every time I had to go to the health canter. She is the one who helped me get better*" (28 years-old, Male, DS-TB, 2nd months of starting treatment, DS-TB, 2nd months of starting treatment).

"*My female friend. Her concern and affection, as well as financial help. She takes care of me, especially when I am not feeling well"* (22 years-old, Female, DS-TB, 3rd months of starting treatment).

"*My wife helped me a lot. My siblings would occasionally help me, maybe once, because I'm also hesitant to ask help from my siblings. My wife worked as a laundrywoman so we could*

buy our food and pay for other expenses" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

On the other hand, three patients had no support from anyone. They were relying on themselves to get better.

"*No one helped me at all, only the health center by giving me medication and allowance*" (41 years-old, Male, DS-TB, 2nd months of starting treatment).

4.3.4. Reasons to be non-adherent

Participants identified several factors that were considered to affect their adherence behaviour to TB treatment. I categorized the reasons following the WHO categories of reasons for nonadherence (**Figure 2**).

- **Psychological reasons**

Two patients reported that the reason of nonadherence was psychological. One was due to depression, one patient reported that he did not take his medication as he wanted to die after knowing his diagnosis.

"*I think at first my depression had effect on taking medication. I was so sad and wanted to die, I did not want to get well* "(54 years-old, Male, MDR-TB, 4th months of starting treatment).

The other one was due to stigma. He was afraid to be isolated if people saw him taking medication and going to the health center.

"*At first, I was hesitated to take my medication as people avoided me if they saw me taking my medication or going to the health center "(*32 years-old, Male, MDR-TB, 5th months of starting treatment).

- **<u>Patient behaviour reasons</u>**

The most reported reason in this section was being busy and forgot. Five patients reported that they forgot to take their medication. For example,

"*I was busy. I remembered that I still have medicine to take. I usually take it in the morning, but there were times that I forgot to take them*" (31 years-old, Male, DS-TB, 2nd months of starting treatment).

"*I sometimes forget to take it on the prescribed time. So, I sometimes get delayed by 2 days"* (22 years-old, Female, DS-TB, 3rd months of starting treatment).

The second most reported reason was the duration of treatment which mainly reported by MDR-TB patients. Three patients reported that the long treatment course duration was making them tired, such that they became impatient to complete their course.

"*I get tired of taking the medication, get impatient with the daily routine, and its duration*" (36 years-old, Male, MDR-TB, 4th months of starting treatment).

Two patients reported that once they don't experience symptoms, they stopped their medication.

"*I thought I was already okay. I do not cough or feel pain. So, I stopped my medication* "(66 years-old, Female, DS-TB, 2nd months of starting treatment).

One patient reported that because of TB symptoms, he felt too sick to take the medication.

"*Sometimes I did not take my medication because I felt ill. I cannot even move. I just want to sleep and have rest"* (33 years-old, Male, MDR-TB, 4th months of starting treatment).

Several other reasons were identified, such as the far distance to the health center, and being hospitalized. One patient in Bago reported that the far distance to health center from his accommodation made him skip some dosages for 1 week.

"I am leaving away from the health center, sometimes I don't have my medication for 1 week" (41 years-old, Male, DS-TB, 2nd months of starting treatment).

Another patient reported that because she went to hospital because of her kidney damage, she stopped taking her TB medication for 5 days.

"*When I was admitted to the hospital, I stopped taking medication for five days. It was difficult to take a lot of medications at that time. After that, I went back to retake the treatment*" (50 years-old, Female, MDR-TB, 5th months of starting treatment).

- **Medication reasons**

The side effect of medication was the most reported reasons of being nonadherent. Nine patients were nonadherent because they experience medication side effect such as dizziness (3/15), vomiting (2/15) lost hearing (2/15), allergy (2/15), difficult to breath (1/15), Stomach-ache (1/15), and Kidney disfunction (1/15).

"I sometimes experienced vomiting after I took my medicines" (32 years-old, Male, MDR-TB, 5th months of starting treatment).

"*I took my medicine for one month. my kidney was damaged because of medication, so I stopped taking TB medication. I had to treat my kidney first. It felt like I was about to die*" (59 years-old, Female, DS-TB, 5th months of starting treatment).

"*I stopped taking the medication since I lost my hearing through injectable drugs*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

"*I stopped taking my medication when I experience many red spots all over my body as if like burned skin as I am allergic to Rifampicin, Levofloxacin. Also, medication affected my hearing*" (22 years-old, Female, DS-TB, 3rd months of starting treatment).

"*I felt pain in my stomach, and I could not bear to take my medication because it gets worse*" (33 years-old, Male, MDR-TB, 4th months of starting treatment).

Moreover, 6 patients reported that the big size of pills make them nonadherent as they faced difficulty to swallow.

"*Sometimes I did not take my medication because it was big, and I found it disgusting. Besides, it was a hassle since I had to take three tablets very early in the morning without eating anything. I found it difficult to swallow. It was disgusting, Sir"* (20 years-old, Female, DS-TB, 3rd months).

- **Health system reasons**

Two patients reported that they stopped taking the medication for 2 weeks as it was not available at Bago health center.

"*There was a time when I stopped taking my medication for 2 weeks because it was not available in the health center. So, we had to buy it with our own money from the hospital or pharmacy*" (45 years-old, Male, DS-TB, 2nd months of starting treatment).

- **Financial reasons**

There are 4 patients stopped their treatment due to financial reasons. Travelling cost to the health center, buying food, and buying the medication when it was not available was the main reported reasons to stop taking medication.

"*We lack financial resources, and I am a breadwinner in the family. After I finished taking the TB medication from the health canter for six months, I stopped without consulting doctors. After some time, I had chills again, but I thought it was nothing*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

"*I have many primary needs in life that I can't afford, I have many problems, I don't have money to buy nutritious food, I have family concerns, especially on disciplining my children*" (36 years-old, Male, MDR-TB, 4th months of starting treatment).

4.3.5. Emotions and personal experience

- **Stigma & discrimination**

Most of the stigma related behaviors that faced patients were related to the perceived risk of infection by being contaminated by person with TB. Eight patients reported being stigmatized. The examples of stigma reactions faced by patients in this study were keeping distance and avoiding communication with patients which led some patients avoided to go to health center.

"*I feel bad and it is painful because people were running away from me. They seem to look at me with disdain. Sometimes I avoided going to the center because I was afraid of*

discrimination, but I was trying to go discretely not to be seen by others "(22 years-old, Female, DS-TB, 3rd months of starting treatment).

"*I noticed that My friends are hesitant to come near me, so what I do, I am the one who walks towards them. I don't stop. I only say "hello" and leave* "(66 years-old, Female, DS-TB, 2nd months of starting treatment).

"*I felt rejected, sir. When my co-workers and my aunt found out I was TB positive, they no longer come near me. They told me not to come near them. I felt that they wanted to isolate me*" (31 years-old, Male, DS-TB, 2nd months of starting treatment).

Also, some patients reported that they heard others talking badly since getting TB considered a shame. This made some patients felt ashamed and that affect their self-esteem which may lead to be depressed.

"*I heard them uttered hurtful words about me and my illness. That happened when they learned about my condition the first time. I am ashamed of myself"* (41 years-old, Male, DS-TB, 2nd months of starting treatment)

"*Until now, sometimes I just sit outside my house alone, wanting to talk to anyone. But none would approach me. I noticed that when I tried to talk, they were always in a hurry and left me alone. Some time I hear them gossiping about me. It was tough, I experienced*

discrimination from my friends and neighbours because of my TB" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

- **Reason to be depressed or anxious**

All the patients experienced depression and/or anxiety for many reasons. Seven patients reported financial reasons such as being a load to their family and cannot work. Also, due to their appearance as some patients lost a lot of weight. For example,

"*I felt like a burden to my family. I should be working to support them, but here I am, sick, and a liability to them. Also, I was ashamed to go out before because I lost so much weight. My weight back was 60 kgs; then, it went down to 45kgs when I got sick*" (28 years-old, Male, DS-TB, 2nd months of starting treatment).

"*I worried about my children. I worried about the difficult financial situation I have in the family. I have a lot of expenses. I cannot buy my vitamins and medicines. That is why I feel depressed, but what can we do since we are in this situation*" (66 years-old, Female, DS-TB, 2nd months of starting treatment).

"*I was depressed as I experienced a hard life, not knowing where to get the money for daily use; and I can't work having this illness. My children are still very young*" (36 years-old, Male, MDR-TB, 4th months of starting treatment).

Six patients were worried about their health condition especially after taking the medication and experience the side effects. For example,

"*I was depressed. I had begun asking the question, why me? Why I acquired this illness especially after I took the medication, I felt dizzy, and I lost my appetite. I always vomit, and I felt exhausted always. I didn't want to move, I just wanted to rest, and my body was weak*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

Two patients reported stigma and feeling ashamed were the main reason behind their anxiety and depression.

"*I was so depressed and ashamed because I heard many unpleasant words from other people who did not understand my situation*" (33 years-old, Male, MDR-TB, 4th months of starting treatment).

"*I feel anxious and worried because I thought I am good for nothing. I can't do anything because I am sick, weak, have the difficulty of breathing. I would think that it would have been better if I die because even if I get well, I will still live at others' mercy*" (22 years-old, Female, DS-TB, 3rd months of starting treatment).

Two patients reported that they were worried to contaminate their family.

"*What I am afraid of is that my family would get sick, too, Sir. Then, I got scared because I lost weight and became thin* "(20 years-old, Female, DS-TB, 3rd months of starting treatment).

4.3.6. TB knowledge

- **Reason to get TB**

In this study, the patient's statements reflected a poor knowledge about TB. Most of the patients had no or an ambiguous idea as to what caused the disease, the mode of transmission or length of treatment duration.

"*I believe I got this illness from excessive drinking of alcohol, smoking, and lack of sleep. I got infected with TB twice. I did not finish my treatment the first time - I stopped my therapy after only two months as I felt better. Then I developed the symptoms, and again I was treated*" (36 years-old, Male, MDR-TB, 4th months of starting treatment).

"*The real cause could be my work, I'd would stay longer under the heat of the sun, and also too much alcohol drinking*" (53 years-old, Male, DS-TB, 4th months of starting treatment).

- **Tradition healer, cultural concepts, and beliefs**

Only one patient reported going to traditional healer before seeking care from health centre while the others consulted only medical doctors. The patient believed once he had massage with herps, the cough will stop.

"*Only once I went to quack doctor when I coughed up blood. The usual ritual of a quack doctor was massaging parts of the body and applied medicinal herbs*" (54 years-old, Male, MDR-TB, 4th months of starting treatment).

Another patient had a belief that eggs and alpine milk in the morning will help to be cured before start going to health canter to get medication.

"*Before I went to health canter, I bought eggs and alpine milk because people said eggs and alpine milk could treat pneumonia. I drink the milk with an egg every morning*" (31 years-old, Male, DS-TB, 2nd months of starting treatment).

4.4. Summary of the results

Figure 18 showed the summary of the quantitative and qualitative results. In the quantitative analysis, I found that depression, anxiety, MDR-TB treatment, and region are independently associated with nonadherence. In qualitative analysis, participants explained how those risk factors affected their adherence behavior.

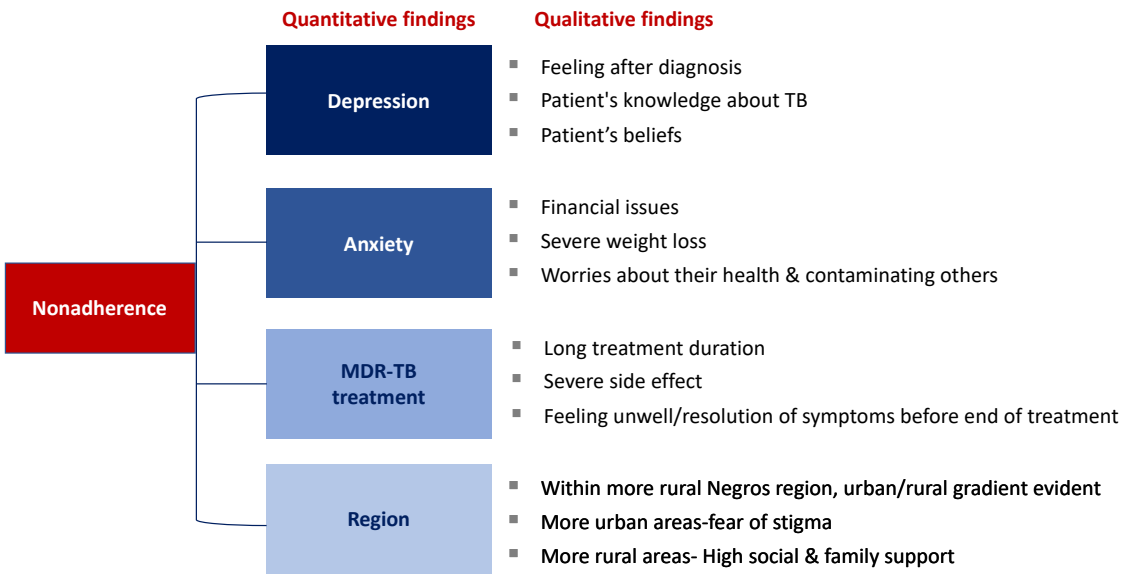


Figure 18: Summary of the study findings

Chapter 5

5. Discussion and Conclusion

Adherence to TB treatment is complicated as it is affected by multiple factors. To my knowledge, this study is the first longitudinal study assessing the association between depression/anxiety with nonadherence among Filipino persons with TB during the course of treatment. I chose a mixed methods study design to explore risk factors affecting adherence, and to understand the result and the contradiction between quantitative results and qualitative findings to ensure that the study findings are based on participant's experiences. This final chapter presents a discussion of the quantitative and qualitative findings. Also, the strengths and weaknesses of the study. Finally, I make recommendation to the TB program and for future research.

5.1. Adherence in other diseases

Nonadherence is one of the common problems which negatively affect the clinical outcome for any disease. One study that analyzed 17,000 patients' dosing histories who were diagnosed with different diseases which include osteoporosis, diabetes, hypertension, asthma, depression, and HIV found that 4% never initiated their treatment, nearly 40% discontinued, and only 55% took their treatment as prescribed[127]. The negative consequences of nonadherence have been widely reported in the literature especially for chronic diseases. The magnitude of nonadherence in chronic diseases in previous literature was ranged from 40-65%[128]. A recent systematic review found the economic impact of non-adherence, including the healthcare costs, ranged from $949 to $44,190 per patient annually across 14 chronic diseases[129].

Adherence is more critical in infectious diseases. Being nonadherent with the communicable disease has a negative impact on both individuals and the community by increasing the risk of transmission of disease to healthy people. There is a large amount of literature addressing the factors influencing adherence to medication in patients suffering from chronic disease which might be slightly different from infectious disease. For example, stigma is considered one of the main barriers to adherence in infectious diseases since people were afraid to be infected once they knew someone had an infectious disease such as TB. However, adopting a new lifestyle, having comorbidities with other diseases, and lack of motivation were the most reported barriers in chronic diseases[130,131]. In the last 10 years, there has been a lot of evidence that demonstrating the impact of diverse interventions on medication adherence and how it can improve clinical outcomes[132]. There are different interventions were applied to improve adherence. For example, In a longitudinal study done by Morisky et al. among hypertensive patients suggested three adherence promoting interventions: physician counseling, family support for monitoring pill-taking, group sessions with a social worker. The 5-year analysis showed a continuing positive effect on appointment-keeping, weight control, and blood-pressure control in the intervention groups. Also, this study found that the mortality rate was 57.3% less for the intervention group than for the control group. This result provided evidence to support the use of adherence-enhancing interventions in patients with hypertension[133]. Another intervention recommended by different studies among patients with asthma or diabetes was training patients in self-management which involves self-monitoring of symptoms in addition to providing a written action plan that appeared to improve health outcomes for adults with asthma or diabetes. Also, self-management education proved that it can reduce hospitalizations, visits by the doctor, unscheduled visits to the doctor, and days off work[134,135]. Treatment adherence is affected by several factors. These factors are

divided into five different categories which include socio-economic, health care system, condition, therapy and patient factors[9]. Although several studies about adherence in other diseases than TB showed that interventions targeting these factors can significantly improve adherence rates such as telephone counseling, SMS reminder combined with motivational messages, coaching adherence, and self-esteem counselling[136–138], a better understanding of the effects of possible interventions among people with TB is needed.

5.2. Discussion of quantitative findings

5.2.1. Prevalence of nonadherence

Tuberculosis nonadherence is the major challenge in TB treatment which may lead to multidrug resistance and extended treatment duration[139]. Although it is recommended that TB person should follow properly their anti-TB treatment regimen through following DOT strategy [140], the findings of this study showed that the prevalence of nonadherence at end of the intensive phase was 28%. This result was different from other studies. In a prospective cohort study done in Tanzania, the prevalence of nonadherence among 331 DS-TB participants was 16.9% at end of intensive phase[141] while a prospective cohort study in India found that the prevalence of nonadherence among 156 participants at end of the intensive phase was 50%[142]. In a cross-sectional study in Thailand among 225, the prevalence of nonadherence was 15.5%[143]. Also, in a cross-section study in south Ethiopia among 261, the prevalence of nonadherence was 24.5%[91], and 30.5% in other a cross-sectional study done among 390 at north-west Nigeria[144]. This variance might be due to the difference in TB medication adherence's perception and the definitions of nonadherence. There is no standard

role definition of adherence towards anti-TB treatment. TB medication adherence depends on the amount and the timing of dosages missed[144]. It is recommended to use a standardized adherence scales tool that could explain medication adherence behavior and improve treatment outcomes. In this study, a standardized measure of TB medication adherence was used. So, TB participants were classified into adherents vs. nonadherent according to their Morsiky scores while other studies such as the Tanzanian study measured nonadherence using TB adherence chart from the clinic which classified patients who missed less than 5 doses as adherent and patients who missed 5 or more doses as nonadherent[141]. This way is measuring adherence according to patient's visits, not according to the actual mediation taking behavior which might not give an accurate prevalence of nonadherence[9,144]. In a Thai study, adherence was measured using visual analogue. This method relies on patient assumptions which might be affected by person's concern to satisfy health care providers with their answers. This might lead to overestimate prevalence of adherence[145,146]. In a Nigerian study, adherence measure using a standardized scale "Tuberculosis Medication Adherence Questionnaire" (TBMAQ) which use a low cut-off point (≤4 nonadherent). Using a low cut-off point might give an overestimate the prevalence of nonadherence[144]. On other hand, some studies considered participants as nonadherent if they stop their medication for 6 days which might lower the estimated nonadherence rate[147,148].

Previous studies reported that the nonadherence rate is the highest in low-and-middle-income countries (LMICs) at end of the continuation phase compared to other phases[149–151]. The prevalence of nonadherence at end of the continuation phase in this study was 30%. This proportion was similar to a cohort study in Morocco with 1039 TB participants[150], a cross-sectional study in Zambia among 382 was 29%, and a retrospective study in Nigeria among

671 was 28.6%[152]. This might be explained because of the long treatment duration or participants do not feel any more symptoms and they felt cured. Interventions should be considered to improve adherence among TB patients during the continuation phase. Such interventions could include health counseling, drug education, and increasing patient's TB knowledge about the importance of completing treatment course though no symptoms were experienced.

5.2.2. The prevalence of depression

Depression playing an important role in changing patient's behavior and consequently their adherence to the medication due to several reasons: anxiety, hopelessness, low self-esteem, loss of interest in living, social stigma, and discrimination[131]. Depression is a common comorbidity among patients with TB which is associated with poor adherence to anti-TB medications[63,153]. Depression may affect as many as half of individuals with tuberculosis[154]. This shows a significant challenge to manage this comorbidity to ensure a better outcome. When a person with TB suffers from depression, there is a greater risk for other comorbidities to occurs such as neglect self-care[131], cost increase[155], anxiety[153], and increased susceptibility to TB reactivation by compromising immunity[131]. The prevalence of depression in this study was the highest at end of the intensive phase (12%). This was slightly higher than a cross-sectional study done among 250 participants which showed that the prevalence of depression was 10%. This Nepalese study used Patient Health Questionnaire (PHQ-9) to measure depression using 10 as cut-off point (≥10 depressed, <10 non-depressed). Using such a high cut-off point in PHQ-9 is too high to screen depression compared to cut-off point 8 in HADS which might underestimate the prevalence of depression[156]. In a cohort study in Ethiopia

among 648 newly diagnosed TB participants, the prevalence of depression after 2 months of starting treatment was 7.8% using PHQ-9 to screen depression. This result lower than my study which might be explained as using a high cut-off point (≥10) which lowers estimate depression. Also, the Ethiopian study did not include MDR-TB participants which had a high probability to be depressed compared to DS-TB due to their long and complex treatment. A cross-sectional study done among 60 hospitalized TB persons in Pakistan found the prevalence of depression was 80% which might be due to being hospitalized, severe symptoms, high healthcare costs, and stigma which might affect adherence behavior and worse the outcome[157] (This was matching with our findings in qualitative part). In Brazil, a cross-sectional study among 86 MDR-TB persons showed the prevalence of depression was 31.4% using HADS scales[158]. This was higher than my study even though the same scale was used. One reason might be that in the Brazilian study, all participants were following MDR-TB treatment which is longer and had severe side effects compared to DS-TB treatment. This is matched with the findings of my study that people who following MDR-TB treatment are more likely to be depressed compared to DS-TB.

In general, the prevalence of depression among TB patients in previous studies was ranged from 11.3% to 80.2%. This differs depending on several factors such as the tools used to measure depression, the characteristics of the population, the type of TB-treatment, and the gap between TB symptoms and depression especially the physical symptoms (e.g., appetite changes, sleep disorder, and energy level)[159]. Also, using different cut-off point scores for each scale might either overestimate or underestimate the prevalence of depression and the difference of scale validation on people with TB compared to a healthy population. For

example, individuals with a high scores on self-reported scales for depression who met the criteria of having depressive symptoms (True positive) are different from participants who had a similar high scores on the same measurement scale and do not meet the depressive criteria (False positive)[159,160]. In this stud, HADS scale was used to assess depression which is one of the most widely scales used to screen depression among people with TB. However, the prevalence of depression in my study was lower than other studies using the HADS among TB people (**Table 2**). Compared to other studies, the prevalence of depression in this study was lower than in Pakistan (64.3%)[161], Turkey (60.5%)[162], India (55%)[163], and Ethiopia (43.4%)[153]. Other studies that used PHQ-9 found a similar high prevalence of depression such as Cameroon (61.1%)[64], Nigeria (27.7%)[164], Ethiopia (51.9%)[66], Botswana (47.2%)[165], and China (17.7%)[166]. Moreover, some studies used Hamilton Depression Rating Scale (HDRS) such as Pakistan (49.4%)[167], India (39.5%)[168], and Nigeria (45.5%)[169].

5.2.3. Factors associated with nonadherence

A. <u>Depression</u>

This study found that depression was an independently risk factor of nonadherence. A one unit increase in HADS depression score was associated with a -0.05 decrease in Morisky adherence score at any given timepoints. Also, the ranges of OR between depression and nonadherence were ranged from 1.13 to 10.6 at different treatment phases. This was less than a cross-sectional study in South Africa among 3107 which found that depression was associated with nonadherence (OR:1.31, 95%CI:1.09–1.57) within the first three weeks of treatment[170]. A cross-sectional study in China among 1342 participants found that severe depression had a greater risk of being nonadherent (OR:3.67)[171]. A prospective cohort study

in Ethiopia among 648 showed that depressed participants had a 9.09 greater risk of LTFU[172]. A prospective cohort study in South Africa among 159 people found that a higher depression score was associated with nonadherence to TB- treatment within the end of the intensive phase (Mean: 7.14; 95%CI 6.28–8.0 vs 2.55)[173]. Another prospective study in Peru among 325 found the depression was associated with a 3.46 risk of LTFU. A recent meta-analysis study published in 2020 was assessing the association between depression and negative outcomes (defined as death, loss to follow-up, or nonadherence) among people with DS-TB, found that depression had a strong association with negative TB-treatment outcomes (OR=4.26, 95%CI: 2.33-7.79). Moreover, depression was associated with LTFU, and death (OR=8.7, 95%CI: 6.50-11.64) (OR=2.85, CI95%:1.52–5.36) respectively while there was no association between depression and nonadherence (OR = 1.34, CI95%:0.70–2.72)[174]. These variations might be due to differences in socio-demographic characteristics, sample size, study designs, treatment settings, and measurement tools. Both the cross-sectional study and prospective cohort study in South Africa with cohort study in Ethiopia included TB/HIV co-infected which might increase the risk of being depressed and nonadherent. Participants who had co-infection need to take two sets of drugs, which could be quite burdensome. Moreover, the use of a multiple-drug regimen may cause drug reactions which may lead to uncontrolled side-effects leading to treatment default and increase the risk of nonadherence[131,175,176]. Though the cross-sectional study in China used the Morisky adherence scale to measure adherence, the risk of being nonadherent due to depression was higher than my findings. This might be explained as the Chinese study used the Center for Epidemiological Studies Depression(CES-D) which was designed and validated in different populations to detect mainly severe forms of depression[177,178]. Comparing HADS and CES-D, HADS with cut-off point 8 showed more

accuracy to screen depression compared to diagnosis by a psychiatrist[178]. In the previous studies, adherence and depression were assessed from starting treatment until end of the intensive phase (6months) which may show a high probability of being more depressed and/or nonadherent compared to other phases[153,176,179,180].

B. <u>Anxiety</u>

This study found that anxiety was an independently risk factor of nonadherence. A one unit increase in HADS anxiety score was associated with a -0.07 decrease in Morisky adherence score at any given timepoints. Also, the ranges of OR between anxiety and nonadherence were 3.17 to 4.3 at different treatment phases. This was different than what was found in a clinical trial done among 1502 in 4 Sothern African countries (included South Africa, Zimbabwe, Zambia, and Tanzania) which found a one unit increase in Kessler psychological distress scale score, 8% increase in the odds of nonadherence[181]. This might be because participants were classified as nonadherent if they missed one visit during 6 months of treatment assessed at two months and six months after initial treatment according to their DOTS treatment cards. This way only recorded if patients visited the DOTS clinic or not and did not report the actual number of missed doses during a specific period. This might lead to classify participants who missed a few doses same as participants who were completely nonadherent or default which might overestimate the rate of nonadherence. Also, measuring adherence only according to the DOTS clinic attendance may not be accurate compared to the validated scales which measured the actual medication-taking behavior. For example, if nurses forgot to record patient attendance on the treatment card, that person would be considered as nonadherent. Moreover, participants who visited the clinic but did not take their medication were considered

adherent. In comparison with the Morisky adherence scale, participants can report how many doses they missed in the last week which enables to classify participants as adherent or not according to their missed doses. Another explanation could be that study measured psychological distress (include anxiety) only once following a cross-sectional basis when ideally should be measured longitudinally over the treatment course. Also, that study was conducted among the African population which might have different characteristics than Filipinos. A cross-sectional study in Pakistan that included 108 participants showed a negative outcome was more among participants who suffered from anxiety, a positive correlation was observed between anxiety and controlling illness ($r = 0.271$, $p = 0.005$) by using the HADS scale which may affect patent's adherence behavior[161]. A qualitative findings in a cross-section study done in Japan among 125 found that anxiety and was one of the main barriers to treatment adherence[182]. Limited studies were assessing the association between depression, anxiety, and adherence among the TB population. Most of the available studies were conducted among people with HIV. To the best of my knowledge, this study is the first to report the association between depression, anxiety, and nonadherence among TB patients in the Philippines.

C. <u>TB-treatment type</u>

This study found that participants who were taking MDR-TB treatment are more likely to be nonadherent compared to DS-TB treatment. This was matching with a retrospective study in Uganda among 227 participants, which found MDR-TB patients were 3.5 times more likely to be nonadherent[183]. A prospective cohort study in South Africa found that missing one visit to DOTS was 1.5 times more likely to get unsuccessful outcomes among MDR-TB patients[184].

A case-control study among 124 in Serbia found people who are taking MDR-TB treatment were 3.3 times more likely to be default[185]. Previous studies reported that the reasons for making MDR-TB more like to be nonadherent were the severe adverse drug reactions associated with MDR-TB drugs especially in the intensive phase, long duration of treatment, Perception that nonadherence is unnecessary, lack of TB symptoms, and feeling better at end of continuation phase[186–188]. All of these were also reported by participants in in-depth interviews especially those on MDR-TB treatment. The MDR-TB regimen included second-line drugs which have more toxicity, worse side effects, a high number of pills, and less individual efficacy compared to first-line drugs[189–191]. A successful method to improved adherence among patients following MDR-TB is the community-based care strategy proposed by WHO. This technique allows patients to receive their treatments at home through well-trained community health workers and community volunteers[192]. Applying this strategy allow patients and health care workers to develop a strong relationship and give patients a full understanding of their disease and the importance of finishing treatment cours[192–194]. This strategy was effective for controlling MDR-TB and increase the adherence rate[191,195,196].

D. <u>Region</u>

Most of the studies showed that people in rural areas are more likely to be nonadherent to their medication compared to urban areas. This might be because of urban areas have more infrastructure, are well equipped with diagnosis tools, medication stock, and have staff to monitor patients more than rural areas. Also, some studies have shown that patient care could be commonly ignored in rural areas compared to urban[197,198]. In contrast, this study found that patients from NCR are more nonadherent to their medication compared to patients from

Western Visayas. This difference could be due to the limited number of participants in NCR compared to Western Visayas (143 vs. 552 Participants). Another explanation could be due to the difference in population characteristics between urban and rural areas. In the NCR, most of the participants included in this study are living in slum urban areas which may affect their access to public services. This could be either due to a lack of TB knowledge and its treatment-related knowledge or the long travel time to the nearest DOTS clinic due to traffic jams. Another reason could be financial, participants needed to work and save money for their family to get their essential needs. In my qualitative findings, some participants explained that they could not go to the DOTS center due to the travel cost. So, rather than spending money for transportation to go to the health center, they prefer to buy food and go to work to earn money especially most of them are the breadwinner for their family. Several studies showed that internal migrants who living in slum urban areas are more likely to be nonadherent and default compared to people living in rural areas because of several barriers such as stigma, financial, SFS, and TB knowledge[199–203]. In my study, stigma and SFS did not show association with nonadherence. Therefore, those factors might not mediate the path between region and nonadherence.

5.2.4. Summary of the studies differences

The potential reasons of differences between studies for depression and nonadherence may be considered within the following headings:

I. <u>Tools</u>

The tools used to measure depression and adherence play important role in that difference. For adherence, studies used validated tools to measure adherence that could be more accurate

than the studies used self-reported questions such as adherence chart and visual adherence analogue or asking patients what the proportion of taking doses was. This method depends on patient assumptions which might be affected by a person's concern [145,146]. Some participants would over-report their adherence to avoid any criticism from health care providers. The social desirability and memory biases can lead to overestimating adherence through reporting a perfect adherence behavior by respondent [179]. For depression, some studies used scales designed to mainly measure severe depression such as CES-D. This might underestimate the prevalence of depression as such a tool was designed and validated to screen severe depression and participants who have mild or moderate depression will be missed. Also, different cut-off points can affect classifying participants as depressed vs. nondepressed. For example, some studies reported that the cut-off point of PHQ-9 more than 9 was too high to screen depression. Such high cut-off points were validated in different populations to screen major depression only which may lead to underestimating adherenceprevalence[145,146,204].

II. Study design and sample size

Most of the available studies which assessed the association between depression/anxiety with adherence among the TB population are cross-sectional. A cross-sectional study gives a rapid assessment of adherence. However, it can only measure it at one-time point which does not allow assessing the variation of adherence over the full length of treatment compared to the use of a prospective cohort study[205]. Also, due to the exclusion criteria of cross-sectional study (e.g. hospitalized, default, and LTFU), This may overestimate of the adherence rate. This is because adherence is usually assessed among patients who had come to the DOTS center to

collect their medication. This may cause an overestimation of the adherence because treatment adherence is likely to be better in the days surrounding clinical appointment[180]. Cross-sectional studies cannot determine the systematic differences and pattern of both exposures and outcome compared to cohort studies, to identify the adherence and depression pattern throughout the treatment course. This will help to know the best time to apply intervention (e.g. during an intensive phase or continuation phase) to improve patients outcomes. In addition to study design, the sample size may affect the result. Some studies were conduction among 60-80 participants. This increase the chance of false-positive which overestimate the association between depression/anxiety with nonadherence[206].

III. Population

Different population characteristics might be the cause of different results from one study to another. Studies that included people with HIV showed a higher prevalence of both depression and nonadherence. This mainly because taking two different sets of medication might lead to more side effects, and drug interactions. This may negatively affect depression and adherence status. Also, the disease symptoms that occur due to HIV/TB might cause more depression compared to patients with TB[131,175,176]. Studies that excluded MDR-TB patients showed a lower prevalence of depression and/or nonadherence. Due to the long duration of MDR-TB treatment and more severity, participants could have a higher prevalence of depression which consequently affects adherence[169–170]. Studies that assessed adherence in urban areas showed that respondents were more likely to have high adherence compared to rural areas. This might be because of the well-equipped diagnosis tools and available medication stocks in urban areas

compared to rural [174,178]. In addition, education level was higher in urban areas which showed an association with high adherence in the previous studies[174,178,183].

5.3. Discussion of qualitative findings

Adherence to TB treatment has been influenced by several factors. In a quantitative study, I identified the factors that showed significance association with nonadherence. This qualitative study helped to explain more in detail how these factors affecting adherence. Moreover, it helped to identify other critical social drivers of nonadherence. This study found four major factors that most nonadherent patients mentioned in this study. These factors were 1) psychological factors, 2) personal & behavioral factors, 3) medication-related factors, 4) financial factors. These factors represented the opinions of 15 nonadherent TB patients.

5.3.1. Psychological factors

In this study, some participants reported that being depressed was the reason for nonadherence. This was mainly due to the patient's beliefs, lack of TB knowledge, and stigma. Some participants reported that they got TB due to their bad behavior. They used words such as "dirty or shame or worthless or die" to describe their feeling after diagnosed with TB as they felt discouraged to face their disease alone, especially with TB symptoms and adverse effects treatment. Previous studies showed that the fear and denial of the TB diagnosis were common factors affecting adherence. Some studies showed that patients struggled to accept their diagnosis and to take treatment as they preferred to hide their disease[207–209]. However, other studies showed that TB diagnosis was a motive for adherence to be cured[210–212]. Also, the fear of negative consequences was the encouragement of being adherent[210,213]. In this

study, participants living in rural areas were open to sharing their diagnosis with their family and neighbors. Some reported that they got food and financial support from neighbors. However, participants living in urban areas were hesitant to go to the health center to avoid being identified. They tried to isolate themselves to avoid gossip, potential discrimination, and comments about their severe weight loss. Previous studies showed that stigma can affect adherence as patients tried to isolate themselves from their family, society, and friends due to their fear of stigma[16,214–216].

5.3.2. Personal & behavioural factors

In this study, patients mentioned that they forgot to take their medication when they are busy with their work. Previous studies showed that after the diagnosis of TB, patients could not adopt to changes in their life. It was difficult for them to balance between taking their medication and their normal life rhythm[87,217]. Also, when the patient did not experience symptoms, they stopped taking their medication as they thought they cured. Some studies explained that this was because of the lack of TB knowledge. Those patients did not know the duration of treatment is at least 6 months or longer. Some of the participants were unaware of the complication of stop taking medication. Therefore, they stopped taking their medication at any time they felt better[5,91,217,218]. In contrast, some participants stopped taking medication due to the severe side effects. Most of the studies reported that side effects such as nausea, vomiting, fatigue, dizziness, rashes, and itching were the main reasons for stopping treatment. Patients were feeling uncomfortable and sicker after taking their medication which affects their daily lives[219–221]. Therefore, it is important to teach patients the possible side effects they might face and how to deal with it. One of the unique finding of the adherence barrier in this

study was poor self-management (included physically and emotionally). I found that some participants might be incapable of taking medication due to severe TB symptoms. They felt so weak to pick their medication and care for themselves. Moreover, some participants felt worthless and no motive for taking medications. This leads them to isolate themselves and avoid going to health facilities. Most of the literatures had barely reported poor self-management as a barrier to taking medication. Only a recently published qualitative study conducted in Tibet found that poor self-management capability led to medication nonadherence[222].

5.3.3. Medication-related factors

The long duration of TB treatment was the most reported reason for nonadherence among patients taking MDR-TB treatment. This is mainly because of the challenges facing patients and their family which affect their daily routine activities. Some studies found that the long treatment duration of TB treatment course challenges patients financially, physically, and psychologically[5,223]. Especially MDR-TB regimen which includes second-line drugs that have more toxicity, worse side effects, a high number of pills, and less individual efficacy compared to first-line drugs[189–191]. Another reported reason for nonadherence was the big size of the pills which is the unique finding of this study. Patients complained that it is difficult to swallow the pills. No previous studies found that size of the pills was barrier to adherence. The commonly reported reason in literature was the having many numbers of pills[89,148,217].

5.3.4. Financial factors

Despite TB treatment is provided free of charge in the Philippines, this study found that financial burden is one of the main barriers to nonadherence. Similar findings were found in other studies[13,224–227]. The main aspects of financial burden mentioned by many participants included: travel cost to DOTS clinic, food expenses, and medication cost when the treatment is not available at the clinic. A systematic review conducted in developing countries reported that financial burden is the main reason for nonadherence and LTFU[228]. Patients prefer to save money used for commuting or buying medication to buy food for their family. Moreover, financial constraints limit the patient's ability to have adequate nutritious food which negatively influences adherence. In this study, some participants showed that they prioritise their family's need over going to the clinic, especially if they are the family breadwinner. Also, some patients lost their work after their diagnosis of TB and cannot do many activities due to the symptoms of TB and treatment side effects. Some participants avoid going to the clinic not to be a burden on their family especially after they lost their job.

5.4. Quantitative & qualitative integration conclusion

In this study, the qualitative and quantitative findings were used to address the study objectives by complemented each other and produced a richer understanding of the reasons for nonadherence among Filipino people with TB. I found that depression was one of the barriers associated with nonadherence. As known from the qualitative findings, patient's beliefs, knowledge, and interpretations of getting TB lead to develop depression which affects negatively on adherence. This emphasizes the importance of raising patient awareness regarding TB. Many studies addressed the influence of patient's understanding of treatment

including causes of TB, how it transmits, the treatment duration, and the consequences of defaulting on adherence to the treatment[203]. Also, the fear and denial of diagnosis were common reasons addressed by other studies which lead to depression. Some participants had difficulties accepting their diagnosis and tend to hide their disease. That makes them avoid going to the health center and seeking care[225–228].

Anxiety was another barrier to adherence. In this study, the main reason behind being anxious was financial constrain. Most of the key informants in this study reported that they are the breadwinner for their families. Getting TB had consequences for losing their work. In addition to increasing their financial burden due to TB. In other studies, some patients hide their diagnosis as they were afraid from their employer to discover that they have TB which consequently affect their adherence[230,233,234]. Other studies found different reasons for being anxious such as difficulty to get sick leave for treatment, fear of asking money to buy food and treatment, and fear of losing their work[230,235]. In this study, another reason for being anxious explained by qualitative findings was the severe weight loss and the change in appearance. The severe weight loss affects physically and mentally persons with TB. Previous studies showed that losing weight and change in appearance involved body dissatisfaction which lead to poor self-esteem and poor quality of life[236,237]. Providing financial and food incentives is one of the powerful interventions to improve adherence as it showed evidence to increase the cure rate by 18%[238].

Taking MDR-TB treatment regimen was associated with nonadherence. It's known that the MDR-TB regimen includes second-line drugs that have more toxicity, worse side effects, a

high number of pills, and less individual efficacy compared to first-line drugs [189–191]. In this study, participants who were following the MDR-TB regimen reported that they stop their medication due to the severe side effects and the long treatment duration. Some studies reported that participants were not informed about the side effects and how to handle them [231,239,240]. Also, some studies found that patients did not report their side effects to their doctors[234] while other studies found that health care providers did not give attention to the reported side effects[210,229]. The finding of this study was matching with other studies which reported that some patients abandon their treatment due to the severe side effects which were difficult for them to continue[241]. It is important for health care providers to ensure patient's understanding of the MDR-TB regimen and the importance of completing the treatment course. Also, training health care providers to ensure a patient-centered approach is an important intervention to ensure there compliance.

5.5. Study strengths and limitations

A strength of this study is the design as a prospective cohort study allowing estimates of adherence behavior and association with time-varying risk factors to be assessed, not subjected to recall bias over time compared to cross-sectional studies or retrospective studies. In addition, the study allowed identification of the most critical phase to apply future intervention to improve adherence. Also, using objective tools to measure adherence and risk factors is more accurate compared to self-reported measurements or relying on medical records. Including the qualitative study helped to get the possible explanatory factors of nonadherence among Filipino TB persons. This study had several limitations. Selection bias could have occurred due to LTFU as these could not be included in risk factor analyses and

we do not know if those who were LTFU from the cohort, were also LTFU from the TB treatment program, but this seems likely. The Covid-19 pandemic occurred in the middle of my study which might affect the quality of data collection and resulted in missing data for variables such as BMI that could not be collected during telephone interviews. The proportions of participants compared to the St-ATT study were approximately similar between sites except for NCR. The NCR was slightly lower due to the delay in obtaining the ethics to start data collection from San Lazaro Hospital. Also in this study, there was no choice about the number of participants available to recruit from sites as it was affected by St-ATT. The impacts of Covid-19 on the usual practices of TB-DOTS treatment, with changes and disruptions to clinic visits also make it difficult to generalize the study results to "normal" times, whilst the extra pressures of the pandemic were difficult to disentangle from that of TB treatment on symptoms of depression and anxiety. Another limitation was using repeated measurements which might make participants adapt their answers in the follow-up visits to satisfy what they perceive as the "correct" or responses desired by their health care provider. I tried to reduce the potential of that by using standardized tools which ask the same questions in different ways to try getting participant's real answers without adaptation and use of independent study research nurses to conduct the questionnaires.

5.6. Conclusions

In conclusion, this study found an association between depression/ anxiety and nonadherence to TB medication in Filipino persons undergoing routine treatment at government facilities, especially within the intensive phase. Also, Patients who are taking MDR-TB treatment are more at risk of being non-adherent compared to DS-TB. These findings indicate that mental

health evaluation and treatment adherence should be regularly incorporated in the management of TB patients, providing adequate tools to the clinician to identify and manage these patients at clinics especially, at the first six months of starting treatment. It is important to ensure adherence among all TB patients, with more focus on patients who are taking MDR-TB treatment. This can be done through 1)comprehensive educational health campaigns to raise patient's awareness about the nature of the disease, duration of treatment, possible side effects and how to deal with them and consequences of not completing TB treatment, 2) providing further information to MDR-TB patients about the need to complete treatment and that they should expect to feel better before the disease is "gone", 3) Create a peer support group with supervision from health care providers can help on improving adherence especially at the beginning of the patient's diagnosis as depression and anxiety are the highest. persons with TB might prefer to share their experiences with others who were undergoing similar obstacles compared to reporting their difficulties to their health care providers. 4) sending SMS to remind patients to take their medication could help patients to adapt their life after the diagnosis of TB, 5) Train some community members to visit the patient's house and ensure their adherence especially, for patients who are so sick to come to the DOTS or who cannot afford travel costs. Providing financial allowance and food vouchers might improve adherence behavior among Filipino TB people.

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8. Appendixes

8.1. The St-ATT study information sheet

Starting anti-TB Treatment Study (St-ATT): Participant Informed Consent Form for TB patients

Introduction

Tuberculosis (TB) disease can cause poor appetite and increases the risk of poor nutritional states, or "malnutrition". There is scientific evidence to suggest that malnutrition plays a role in the risk of becoming infected with TB, the risk of progressing to active TB disease, and an increased risk of TB treatment failure.

Diabetes is a condition where a person's blood sugar becomes too high. Around 5% or more of Filipinos have diabetes and probably more TB patients may have diabetes, as we now know that having diabetes can increase a person's risk of developing active TB disease. Many people with diabetes may not know that they have diabetes until symptoms become severe, which can include kidney problems, nerve damage and poor blood flow, particularly in the feet. TB may worsen control of blood sugars among diabetics and diabetes may increase the risk of TB treatment failure.

As of 2018, there continues to be a high rate of TB infections in the Philippines while diabetes prevalence is increasing.

Purpose

"The purpose of this study is to find out if malnutrition and diabetes in TB patients will affect TB treatment success and if total TB patient costs are increased by malnutrition and diabetes. This information will help scientists plan what kind of interventions and services are helpful and practical for TB patients to address malnutrition and diabetes.

This study is voluntary and is external to the health center. Participating or refusing to take part in this study will not alter the TB treatment you receive in any way.

I am_____and I work for Nagasaki University and Nutrition Center of the Philippines as a Research Nurse. You are invited to participate in the study entitled "Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino patients starting anti-TB treatment" under the supervision of

Professor Sharon Cox (Nagasaki University and London School of Hygiene and Tropical Medicine), Dr. Celina Garfin (National TB Programme) and Dr. Juan Antonio Solon (Nutrition Center of the Philippines).

We would like to explain to you the following before you sign the informed consent:

Duration of participation:

The duration of your participation in the study is expected to be for 6-12 months, depending on the duration of the planned TB treatment period.

Procedures

If you agree to take part in the research, we will request the following from you:

(A) At the baseline visit, after TB diagnosis and before or within 5 days of starting anti-TB treatment and after signing the consent form we will request the following from you:

a. information about your general health, age and background and to provide a contact number and area of residence.

b. We will measure your height and weight; handgrip strength; and your mid-upper arm circumference to assess wasting (malnutrition) and your blood pressure. If you are attending TB-DOTS in San Lazaro Hospital (SLH), we will also measure your body fat and muscle using a simple electronic device (2-3 minutes, painless process requiring you to stand on a special weighing scale and hold the handgrips while it calculates your body fat and muscle.

c. We will collect a 0.2ml (spot of blood) from a finger prick sample and provide results in 20 minutes. We will use this for the following:

   i. Screen for diabetes by measuring a random blood sugar from a finger-prick sample. If it is high, we will also measure HbA1C. If you are already known to have diabetes, HbA1C only will be measured and this is used to assess your disease severity and, if applicable, how well your treatment is controlling it.

   ii. Measure your blood level to test for anemia (low level of blood) from a finger-prick sample.

d. We may request a chest x-ray if you don't have one already.

e. If you give additional consent, we will collect a 5ml (1 teaspoon) venous blood sample. We will use this to

measure your immune responses to TB antigens as we want to know if this is affected by malnutrition or diabetes. In this case, a finger prick sample (c.) for screen for diabetes and anaemia will not be collected.

f. If you give additional consent, we will test for HIV, in case you have not already been tested at the start of your TB-DOTS treatment. In many areas of the Philippines and in the rest of the world this is standard practice as HIV increases the risk of TB treatment failure, and effective HIV treatment is available sponsored through the government and Philhealth. You will be provided with the standard pre- and post-test counselling by a DOH registered counsellor and the results will be treated as confidential but will be included in your medical records.

g. We will collect a study-specific sputum sample from you. This will be stored for future additional testing to try to learn more about the nature of TB infections.

h. We will ask that you encourage all your household members to come for free, voluntary TB-testing at your local health centre. We would also like to enrol 1 adult member of your household, who has been screened and not found to have TB for assessment. If the member of your household gives additional consent, we will measure and follow up of their nutrition and anemia status at 3 monthly visits (using finger-prick blood samples).

(B) At monthly follow-up visits when you attend either your TB-DOTS health centre or Barangay health post, we will:

a. conduct a short interview and ask about your medication history and if you have experienced any side effects.

b. Measure your weight, handgrip, mid-upper arm circumference and blood pressure, plus body fat and muscle (if at SLH).

c. If you have diabetes or pre-diabetes (possible early-stage diabetes), every 3 months, we will also measure your HbA1C (finger prick sample).

(C) At the end of your intensive treatment phase and mid and end of continuation treatment phase, as well as at baseline, we will ask you questions designed to assess the impact of TB and diabetes (if applicable) on your quality of life and asses your household food security. These interviews will be combined with the normal monthly interview so will not require an additional study visit.

(D) If you provide additional consent, we will conduct detailed TB patient-cost assessment interviews during a home visit organized at your convenience at the following intervals: start of treatment, end of intensive treatment

phase, in the middle of the continuation phase and at the end of treatment. These interviews will comprise:

a. Questions about costs you incurred relating to your TB and diabetes diagnosis/treatments (as applicable) in the previous month, including direct medical cost (e.g.consultation fees, laboratory tests, drugs), direct non-medical costs (e.g. transportation and special foods/drinks you buy for TB/diabetes) and indirect costs (e.g. loss of income).
b. Questions about what kinds of financial sources you utilized to pay for these costs (e.g.using cash/mobilizing savings, sales of assets, taking loans or support from relatives or community).

(E) If you provide additional consent, we will conduct interview to ask about depression, social and family support, and stigma

Collection of Samples:

If you are selected and agree, a 5 mL of venous blood (equivalent to 1 teaspoon) will be collected by the study research nurse for testing immune responses to TB. This blood sample will also be used to test if you might have diabetes and to test for anemia. Otherwise, a finger-prick blood spot (0.2ml) will be collected by the study research nurse for diabetes and anemia testing.

The results of the diabetes screening and anemia testing will be shared with you immediately. The HIV screening will be done at an approved laboratory and will take time until the result is available. It will be shared with you by the appropriate health facility staff in charge at each health center. The results of the immune responses test will not be shared with you since it is measured only for the research purpose.

Sputum samples and any remaining blood (for those that participate in the immune sub-study) will be stored in a study freezer archive at -80□C and used for further TB-related tests during this study or by other researchers for ethically approved research – please see confidentiality section below.

All clinical and experimental data will be carefully handled as confidential information.

Benefits

We will assess your nutritional status. The results (weight and body mass index (BMI)) will be shared with you. The BMI will help you know whether your weight is appropriate for your height. The blood sample will be used to screen you for possible diabetes, anemia, and HIV if additional consent is given. If the sugar in your blood is high, you will be referred for further confirmatory tests for diabetes. A certain degree of anemia is expected in TB patients but if it is severe, you will be referred for further follow-up. There will be no other benefit from you taking part in the study, but you will also not incur any costs. This research will help to improve the delivery of TB treatment program for future patients.

Risks and discomfort

The risks involved in this study are minimal and include: the discomfort when drawing blood, and very rarely infection at the site of the needle stick. The procedure will be done using a clean technique and will be performed by a trained staff, so the risk of infection is minimized. A new sterile needle will be used for each patient so there is no risk for transmitting diseases.

Compensation

You will receive some small compensation in the form of phone credit compensation for your time at each study visit. At the baseline visit you will receive the equivalent of PHP 150 and then PHP 50 at each monthly follow-up visit completed. If you agree to participate in the TB patient cost study, you will receive an additional PHP 250 for each home visit (4 in total) as phone credit or cash. This larger amount is to reflect the increased time required for these interviews. You will not incur any cost for taking part in this study.

Confidentiality

All information that you provide will be considered confidential. Information will be digitally collected using a tablet, but all the information will be sent to and kept in a password protected database after each participant is interviewed. Only members of the research team will have access to the information you provide until the data is anonymized. Anonymized data (with your name, address, phone number removed) will be stored in a database

and then kept in a university research data repository for 10 years after completion of the project. Any sputum or blood remaining after this project is finished will be stored in the Philippines for up to 10 years and linked only to your anonymized data. This anonymized data and any remaining sputum/blood samples will be available for use by other health researchers for ethically approved projects related to TB after the end of this project to maximize benefit from your contribution to research on the health and wellbeing of Filipinos. After the 10-year period, unless data/samples are still being used, they will be deleted/destroyed.

Right to Refuse or Withdraw

You may choose not to participate in this study, and you may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which you would otherwise be entitled. You do not have to explain why you do not wish to participate or why you want to withdraw. Refusing to take part in this study will not alter the treatment you are receiving in any way. This study is external to the health center and the staff conducting the research are not hired by where you are receiving care. This study is completely voluntary.

Contact information:

Dr. Mary Christine R. Castro, Executive Director of Nutrition Centre of the Philippines

Tel No: +632-807-4982 or Mobile: +63-922-801-39-56

8.2. Patient's informed consent of St-ATT study

St-ATT CERTIFICATE OF CONSENT – TB Patients

I have been invited to participate in a research project of "Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino patients starting anti-TB treatment". I agree to participate in this research study where I will be asked to answer some questions about my health and recent treatments. I have read the foregoing information, (or it has been read and explained to me). I have had the opportunity to ask questions about it and any questions I have asked, have been answered to my satisfaction. I consent voluntarily to participate in this study.

☐ I agree to participate in this study, including TB patient cost study - OR

☐ I agree to participate in this study, but NOT the TB patient cost study

☐ I agree to participate in this study, including depression study - OR

☐ I agree to participate in this study, but NOT the depression study

☐ I understand that the data, sputum samples and any remaining blood collected from me may be used to support other future research and may be shared anonymously with other researchers, for their projects.

For Immune assessment

I agree to provide a 5ml venous blood sample ☐ NOT applicable

Print Full Name of Participant _____

Signature of Participant _____

Date (DD/MMM/YY) _____

If illiterate (Statement of witness): I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely and voluntarily.

Thumb print of participant

Print name of witness_____

Signature of witness _____

Date (DD/MMM/YY) _____

Statement by the researcher/person taking consent

I have accurately read and explained to the best of my ability, the informed consent sheet to the potential participant. I ensured that he/she understands what is involved in participation and their right to withdraw at any time without giving a reason and that this would not affect their treatment. I confirm that the potential participant was given an opportunity to ask questions about the study, and all questions asked to have been answered correctly to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this Informed Consent Form has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date (DD/MMM/YY) _____

8.3. In-depth interview guide

Individual interviews with TB patients

A. Using this topic guide

Note to Moderator: In advance, make sure you are fully familiar with the interview questions. Questions should be added where a participant mentions something of interest or touches on something that needs further clarification. Questions can be skipped where a participant answers the question in a previous response. It is not normally necessary to go through all questions.

Thank you for agreeing to take part in this interview. My name is ..... and I am part of a team conducting research on adherence barriers among Filipino TB patients. I am now going to ask you some questions regarding your adherence behavior to TB medications. Whether or not you decide to take part in the interview, your care will not be affected in any way. You are free to withdraw from the study at any time if you feel you are not in a private or safe enough location to speak over the phone, you can stop it at any point if you want. Now, I would like to take your consent verbally over the phone to participate in this study.

This interview will be audio-recorded and will take approximately 60 minutes. Thank you for your time.

B. General information

Location of the interview	
Name of the interviewer	
Date of the interview	
People present during the interview	
patient gender	
Start time	
End time	

C. Introduction

1. What is your name?
2. How old are you?
3. What is your occupation?
4. What is the highest level of education you have completed?
5. What is your civil status?
6. What is your monthly household income?

D. Overview of the patient pathway

1. Could you take me through your journey, since you started experiencing symptom such as coughing, chest pain, fever, back pain, etc. (pre-diagnosis) until now? the health-seeking practices in chronological order

⇒ When did you come to suspect that you had TB?

⇒ Where did you go for diagnosis and treatment (public or private or informal)?

⇒ How long did you take to go to the health facility?

⇒ When did you start taking TB treatment? (if patients is **Not** newly diagnosed)

⇒ How many times did you stop taking your medication? Why? (if patients is **Not** newly diagnosed)

E. TB patients' experiences and reflections when receiving the TB diagnosis

1. In your own words, tell me what happened and what you did when you were diagnosed with TB?

⇒ How did you feel about it?

⇒ Who did you tell?

⇒ Was there anyone you didn't want to know about your diagnosis? Why?

⇒ How did your close friends, family, and coworkers treat you when they found out you were infected with TB?

⇒ Did you ask anyone for advice about what to do? (friends or family)

⇒ Did you go to someone besides the health center for treatment? advice? (healer, family, friend)

2. What was the worst thing when you were diagnosed with TB?

3. How do you deal with these problems in your life?

4. In your opinion, why did you get TB?

F. TB patients' adherence behavior:

5. Could you tell me how you start taking your TB medication (The story of your TB treatment)?

   ⇒ Did you start treatment immediately after diagnosis?

   ⇒ If no, what made you delay started taking your medication directly after diagnosis?

6. How is your treatment process? What was easy? what was difficult?

7. What is you're feeling about taking medicines to treat TB infection?

8. What did you feel about taking your TB medicine when you are not feeling sick?

9. What do you think about the length (duration) of TB treatment?

10. In your opinion, what are the common reasons make people would not take their TB medicines? (General reasons)

   ⇒ What are the difficulties personally you face during taking your medication?

   ⇒ What is the main reason made you stop taking your medication? (Top 5 reasons)

   ⇒ Does COVID-19 affect your medication and adherence behaviour? If yes, how?

11. Have you ever stopped taking your medication without consultation?

   ⇒ How many times?

   ⇒What are the reasons made you stopped?

   ⇒What makes you retake the medication again after stopping? (explain)

12. In your opinion, why patients may stop taking their medication? (Your experience or friend)

13. Did you stop taking your medication due to psychological reasons such as being depressed or anxious? Why?

   ⇒ What makes you feel depressed/ anxious?

   ⇒ What is you biggest fear?

14. Do you feel overwhelmed to take your medication?

   ⇒ Can you explain your feeling?

   ⇒ How many times did you felt so?

⇒ In your opinion, why do you feel so?

15. Have you ever stopped taking medication to avoid being stigmatized or identified by anyone? Why?

⇒ Why did you feel so?

⇒ From whom you were afraid to be judged or stigmatizes/discriminate? Why?

⇒ Did you avoid going to health centre for those reasons?

G. Patient's experience with healthcare providers:

16. How did the TB clinic staff support you before, during and after your treatment?

17. How did the observer (or treatment partner) support you during your treatment?

18. What are your thoughts about having someone watch you take your medicine in the clinic (health center)? In your home? In another location?

19. Who helped you to manage your medicine regularly? How?

20. How do you feel when you are taking medicine?

21. Who has been helpful to you during your treatment?

22. Who has given the most support to you during your treatment?

23. From your experience, does the attitude of the healthcare worker determine your health-seeking behaviour? How?

24. What can you say about the information that you got from the healthcare worker? (Regarding your diagnosis and treatment)

⇒ Was that information accessible? did it help you?

25. From your experience, are healthcare workers fully armed with knowledge on tuberculosis?

⇒ How was the explanation about the instructions of taking medications from them?

⇒ Were the instructions clear for you?

⇒ Did they give you time to ask?

⇒ How did the TB healthcare providers support you before, during, and after your treatment?

H. TB patients' Knowledge

26. What do you think caused your TB?

⇒ Knowledge of tuberculosis

⇒ Ways of transmission

⇒ Ways of prevention

⇒ Do you think tuberculosis is curable?

27. Where do you get information about tuberculosis?

⇒ Channels of communication

⇒ Frequency of information, accessibility of information

⇒ Usefulness of information

28. Patient's experience with Stigma and discrimination

29. How do people around you react to the fact that you have TB?

30. (From family, friends, community, neighbours, and health workers/facilities sides)

31. Tell me about any form of discrimination/stigma you may have experienced before, during, and after treatment?

⇒ Have you ever faced any discrimination from healthcare providers, community, college, family? If yes, how? (With an example)

⇒ Have you ever avoid going to the health centres not to be stigmatized?

⇒If yes, could you tell me an example?

8.4. Qualitative study information sheet

Patient study information Sheet for BARRIER study

A study looking at barriers to medication adherence: Understanding barriers and factors influencing adherence to tuberculosis treatment in The Philippines, Negros Occidental: A qualitative study.

This information sheet aims to help you understand why the research is being done and what taking part would involve for you. We hope it will help you decide whether or not you would like to take part.

What the study is about, and why it is important?

This study is about the barriers which may prevent persons with TB from adhering to their TB medication as intended. We will investigate these from several points of view (patients, treatment partners, and health care providers). There may be lots of reasons for this, but we don't know which ones are the most important among Filipino TB patients.

Finding out what you think about this topic will be very useful, so that we can tell health care providers and decision makers to be aware of those reasons to help you to adhere to your medication and provide future interventions.

After doing the interviews and comparing the different answers, we shall be looking for patterns in what people say, to try to characterize the most common reasons contributing to Filipino TB patients not being able or having difficulty in fully adhering to their TB treatment.

Who is doing the study?

My name is Hend Elsayed, and I am doing this research as part of my PhD with support from the World Health Organization (WPRO); Nagasaki University; and London School of Tropical Medicine (LSHTM), and Nutrition Center Philippines (NCP).

What this study will involve for you, if you decide to take part?

A. Agreeing to take part

1- Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do wish to take part, we will ask you to sign a consent form before the interview commences or taking verbally consent over the phone Whether or not you decide to take part in the interview, your care will not be affected in any way.

2- What if I change my mind?

You are free to withdraw from the study at any time. You do not have to give a reason for withdrawing. Even if you start an interview, or if you feel you are not in a private or safe enough location to speak over the phone, you can stop it at any point if you want to

Any information you provide will be withdrawn if you request this.

B. Interviews

The interviews will take place at a time and place that suits you. You will be receive a small reimbursement to thank you for your time of 250 PHP.

When community quarantine has ended and local travel is allowed, we will arrange for the St-ATT research nurses to provide this payment or will arrange a local cash pick-up.

We will issue you phone minutes to pay for the entire duration of all phone calls related to this interview.

In the interview, a researcher will ask you as part of a small group of other similar TB patients to discuss and rank the relative importance of the reasons or difficulties that you think TB patients face in managing to take their TB medication. This will involve discussion and some structured activities (that we hope will be fun!) within the group and with the researcher. This will take about 40-60 minutes. We may request to have short one-to one private discussions after the group activities with some participants and you will be free to agree or not to this.

We would like to use a tape recorder during the activities and if you are interviewed, but if you prefer, we could just make written notes instead (up to your decision).

c. Mental support services:

For your information, we would like to tell you about the 24 hrs. free service provided by the Philippines Mental Health Association "PMHA Bacolod Chapter".

If as a result of the interview you experience any distress and wish to discontinue the interview, please inform the researcher/interviewer. We will stop the interview. If you need any psychological help, please, don't hesitate to ask the interviewer about appropriate mental health services to be

referred. Moreover, we can coordinate with the Medical Health Officer (MHO)/ municipal health center for referral or with the PMHA Bacolod chapter.

D. Confidentiality

We hope to end up with some interesting answers to my questions, and will want to discuss them with colleagues and perhaps to write something about them, but in writing or discussion we will never refer to you by name: nobody will be able to tell who gave which answer. All records with personally identifiable information will be kept confidential and will not be made publicly available, Your identity will remain confidential in the event the study results are published. Your name and other personally identifiable information will NOT be included in the research database, which will use only a research ID number. The data, records, and informed consent forms from participants will be stored in an encrypted server and written paper forms will be in a locked cabinet room. The data can be accessed only by the research team members. Your personal information will not be mentioned in any reports or publications. Anonymized data (with your name, address, phone number removed) will be stored in a database and then kept in a university research data repository for 10 years after completion of the project. After this period, it will be deleted. The researchers will abide by the Data Privacy Law of the Philippines.

E. Information & Publication

The study team is responsible for the dissemination of finding to stakeholders locally and internationally. As applicable, the study team will publish findings in academic journals in the field or present findings at regional or international conferences. The collected data will be used to answer the identified research topic.

Any questions?

If you think of any more questions in the meantime, we will be happy to answer them before we begin, or If you have any further questions, clarification or if any problems arise, you may contact the local Investigator: Dr. Mary (Ina) Christine R. Castro, Executive Director of Nutrition Center of the Philippines: Tel No: +632-807-4982 or Mobile: +63-922-801-39-56 or Dr. Emerson M. Cruz, chair of SCMC-AEI Tel No: 632 8982020 loc. 865.

Thank you for taking the time to read this.

8.5. Qualitative study informed consent

Informed Consent sheet from patients for BARRIER study

I have received and been explained the enclosed Information Sheet of the study, which I fully understand. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I am aware that in case of any questions or need of additional information, I can contact. Dr. Mary (Ina) Christine R. Castro, Executive Director of Nutrition Center of the Philippines: Tel No: +632-807-4982 or Mobile: +63-922-801-39-56.

You are selected as a potential participant because you have been diagnosed with active TB disease and your thoughts and beliefs are important to support and enhance our understanding of the difficulties persons with TB disease face in take anti-TB medications.

I am aware that:

- My participation in this study is completely voluntary and I am free to change my mind at any time; ☐
- I agree to record my interview either by audio or paper transcript ☐
- I understand that the collected information such as audio records and transcripts will be stored in secure storage for a minimum of ten years; ☐
- I understand that only the investigators and Research Assistants will have access to my personal information; ☐
- I understand that the results of the study may be published but my name and other information that could reveal my identity will be protected by strict adherence to anonymity, confidentiality and use of pseudonym; ☐
- I have been given contact information for the study and I understand that I may contact her at any point in case I need to discuss any issues related to my participation in this study. ☐
- I would like to participate in this study ☐

Name of Participant: _____

Signature: _____

Date:_____

If participant illiterate (Statement of witness):

Participant's thumb print

Name of witness: _____

Signature: _____

Date:_____

Statement by the researcher/person taking consent

I have accurately read and explained to the best of my ability, the informed consent sheet to the potential participant. I ensured that he/she understands what is involved in participation and their right to withdraw at any time without giving a reason and that this would not affect their treatment. I confirm that the potential participant was given an opportunity to ask questions about the study, and all questions asked to have been answered correctly to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this Informed Consent Form has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date (DD/MMM/YY) _____

8.6. The ethical approval of St-ATT study

8.6.1. Asian eye institute (local ethical committee)

ST. CABRINI MEDICAL CENTER
ASIAN EYE INSTITUTE

01 October 2018

Sharon Cox, PhD
Primary Investigator
Nagasaki School of Tropical Medicine and Global Health

ERC # 2018-008

Protocol Code: St-ATT[1]

RE: Protocol Title: Effects of Malnutrition and Diabetes on Treatment Outcome and Total Patient Costs in Filipino Drug Resistant and Drug Sensitive Patients Starting Anti-TB Treatment: A Cohort Study

Dear Dr. Cox,

In response to the documents submitted dated 21 September 2018 regarding the above-mentioned study, the SCMC-AEI ERC approves the following documents:

1. *Protocol D6.5*
2. *Informed Consent in English and Filipino*

However, the *Summary of Changes* was reviewed as reference.

It is hereby confirmed that neither you nor any member of the study team has participated in the review, decision making and voting procedures of the above study protocol/document.

This approval shall be valid for **1 year** from the date above. The investigator is required to submit progress report 1 month prior to the expiration date. During the duration of the study, the investigator is required to submit the following reports at a schedule set in the SCMC-AEI ERC SOP: SAE/SUSAR, protocol deviations, close-out report, early study termination, final report and any modifications or amendments in the study.

This SCMC-AEI ERC is organized and operates in compliance with ICH-GCP, 21 CFR Parts 50&56, NEGHR 2011 and according to the applicable laws and regulations.

Yours sincerely,

Emerson M. Cruz, MD
SCMC-AEI ERC Chairperson

8.6.2. London School and Tropical Medicine (LSHTM)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Doctor Sharon Cox
Associate Professor
Department of Population Health (DPH)
Epidemiology and Population Health (EPH)
LSHTM

10 May 2018

Dear Sharon

Study Title: Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino drug resistant and non-resistant patients starting anti-TB treatment: A cohort study.

LSHTM Ethics Ref: 14894

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Information Sheet	St-ATT ENGLISH_ICsheet_HIV_D1	24/01/2018	D1
Investigator CV	Cox_CV_full_Jan2018_short	31/01/2018	Jan2018_short
Investigator CV	Edwards_CV_2017_MRC-Newton_2pages	01/02/2018	MRC
Investigator CV	juansoloncv_2017_Nov 2017	01/02/2018	LSHTM
Protocol / Proposal	St-ATT_Protocol_NEC_D6.2_7Feb2018	07/02/2018	D6.2
Information Sheet	St-ATT ENGLISH_ICsheet_HHCs_D3_LSHTM_clean	11/02/2018	D3
Information Sheet	St-ATT ENGLISH_IC sheet_D5_LSHTM_clean	11/02/2018	D5
Local Approval	St-ATT TMGH Ethical approval_1stMarch2018	01/03/2018	1
Information Sheet	St-ATT ENGLISH_IC sheet_D5.1_AEI_re-submit_18April2018 (1)	17/04/2018	5.1
Information Sheet	St-ATT ENGLISH_ICsheet_HHCs_D3.1_AEI_re-submit_18April2018 (1)	17/04/2018	3.1
Information Sheet	St-ATT ENGLISH_ICsheet_HIV_D1.1_AEI_re-submit_18Apil2018 (1)	17/04/2018	1.1
Covering Letter	Cover_letter_LSHTM_responses_23Apr2018_submitted	23/04/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

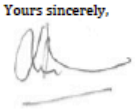
An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,



Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

8.6.3. School of Tropical Medicine and Global Health, Nagasaki University (TMGH)

Ethical Committee
Graduate School of Tropical Medicine and Global Health
Nagasaki University

APPROVAL FORM

November 20, 2018

Project Title:	Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino drug resistant and non-resistant patients starting anti-TB treatment: A cohort study.		
Principle Investigator:	Sharon Cox		
Date Submitted:	October 30, 2018	**Ref. No.**	50

Dear Sir / Madam,

We are pleased to inform you that the above project has been approved.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the Ethical Committee.

Sincerely,

Kiyoshi Kita

Kiyoshi Kita
Dean, School of Tropical Medicine and Global Health
Nagasaki University, Japan

8.7. Qualitative study ethical approval

8.7.1. Asian eye institute (local ethical committee)

ST. CABRINI MEDICAL CENTER

ASIAN EYE INSTITUTE

12 September 2019

Sharon Cox, PhD
Principal Investigator

ERC #2019-017

RE: Title: BARRIER TB Treatment: Barrier to Adherence and Related Risk Factors for TB Treatment

Dear Dr. Cox:

The SCMC-AEI ERC had an expedited review on the above-mentioned protocol and has given their approval on the following documents:

1. *Protocol v.1.1_7 July 2019*
2. *Informed Consent Form (English/Filipino) v.1.1_7th July 2019*
   - *Informed Consent Form (English) v.1.1_7th July 2019*
   - *Informed Consent Form (Hiligaynon) v.1.1_7th July 2019*
3. *Study information sheet V.1.1_7July2019 (English/Filipino)*
   - *Study information sheet V.1.1_7July2019 (English)*
   - *Study information sheet V.1.1_7July2019 (Hiligaynon)*
4. *Data Collection Tools*
   - *Interview Guide with TB patients v1.1 7th July 2019*
   - *Interview Guide with Treatment partner v1.1 7th July 2019*
   - *Interview Guide with Health Care Providers v1.1 7th July 2019*
   - *Indibiduwal nga Interbyu sa Pasyente nga may TB*

The following documents *were* reviewed as reference:

1. *Cover Letter*
2. *Summary of Changes*
3. *Up-to-date CVs for the principal investigator (Sharon Cox) and co-investigators.*
4. *One-page summary of the study*

It is hereby confirmed that neither you nor any member of the study team has participated in the review, decision making and voting procedures of the above study protocol/document.

This approval shall be valid for **1 year** from the date above. The investigator is required to submit progress report 1 month prior to the expiration date. During the duration of the study, the investigator is required to submit the following reports at a schedule set in the SCMC-AEI ERC SOP: SAE/SUSAR, protocol deviations, close-out report, early study termination, final report and any modifications or amendments in the study.

ST. CABRINI MEDICAL CENTER
ASIAN EYE INSTITUTE

SCMC-AEI ERC is organized and operates in compliance with ICH-GCP, 21 CFR Parts 50&56 and according to the applicable laws and regulations.

Yours sincerely,

Dr. Emerson M. Cruz
SCMC-AEI ERC Chairperson

8.7.2. London School and Tropical Medicine (LSHTM)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Sharon Cox
LSHTM

26 July 2019

Dear Sharon

Study Title: Understanding barriers to and factors influencing adherence to anti-tuberculosis treatment in The Philippines, Negros Occidental: A qualitative study.

LSHTM Ethics Ref: 17416

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Information Sheet	Informed Consent_v.1.0_30 April 2019	30/04/2019	1.0
Investigator CV	juansoloncv_pubs_2019_May	30/04/2019	1.0
Investigator CV	Papachristou_CV	30/04/2019	1.0
Investigator CV	Matsuyama CV_04172019.docx	30/04/2019	1.0
Investigator CV	CV Hend Saad Elsayed	30/04/2019	1.0
Protocol / Proposal	topic guides_V1.0 30April2019	30/04/2019	1.0
Investigator CV	Cox_CV_April2019	08/05/2019	1.0
Protocol / Proposal	BARRIER_st_v.1.1_7 July 19	07/07/2019	1.1
Information Sheet	Information sheet_V.1.1_7July2019	07/07/2019	1.1
Covering Letter	Cover letter of changes LSHTM_v_1.0_7July19	07/07/2019	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

8.7.3. School of Tropical Medicine and Global Health, Nagasaki University (TMGH)

Ethical Committee
Graduate School of Tropical Medicine and Global Health
Nagasaki University

APPROVAL FORM

Approval No.NU_TMGH_2019-073-0

OCT. 19, 2019

Project Title:	BARRIER TB Treatment: Barrier to Adherence and Related Risk factoRs to TB treatment.	
Principle Investigator:	Hend Saad Elsayed Elsayed	
Date Submitted:	7th July2019(Revised:15th Oct.2019)	Ref.73
Protocol version:	Ver.1.1 7th July2019	

Dear Sir / Madam,

We are pleased to inform you that the above project has been approved.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the Ethical Committee.

Sincerely,

Kiyoshi Kita

Kiyoshi Kita
Dean, School of Tropical Medicine and Global Health
Nagasaki University, Japan

8.8. St-ATT Covid-19 amendment ethical approval

8.8.1. Asian eye institute (local ethical committee)

ST. CABRINI MEDICAL CENTER

ASIAN EYE INSTITUTE

24 May 2019

Sharon Cox, PhD
Primary Investigator
Nagasaki School of Tropical Medicine and Global Health

ERC No. 2018-008

Protocol No.: St-ATT[1]

Re: Protocol Title: Effects of Malnutrition and Diabetes on Treatment Outcome and Total Patient Costs in Filipino Drug Resistant and Drug Sensitive Patients Starting Anti-TB Treatment: A Cohort Study

Dear Dr. Cox:

The SCMC-AEI ERC had an expedited review on the above-mentioned protocol and has given their approval on the following documents:

1. *Protocol (V2.0, 3rd May 2019)*
2. *Informed Consent Forms:*
   - A. *Informed Consent Form for newly enrolled patients (English) – V2.0, 3rd May 2019*
   - B. *Informed Consent Form for newly enrolled patients (Tagalog) – V2.0, 3rd May 2019*
   - C. *Informed Consent Form for post-treatment follow-up (English) – V1.0, 3rd May 2019*
   - D. *Informed Consent Form for post-treatment follow-up (Tagalog) – V1.0, 3rd May 2019*

However, the *Summary of Changes* was reviewed as reference.

It is hereby confirmed that neither you nor any member of the study team has participated in the review, decision making and voting procedures of the above study protocol/document.

This approval shall be valid for **1 year** from the date above. The investigator is required to submit progress report 1 month prior to the expiration date. During the duration of the study, the investigator is required to submit the following reports at a schedule set in the SCMC-AEI ERC SOP: SAE/SUSAR, protocol deviations, close-out report, early study termination, final report and any modifications or amendments in the study.

ST. CABRINI MEDICAL CENTER

ASIAN EYE INSTITUTE

SCMC-AEI ERC is organized and operates in compliance with ICH-GCP, 21 CFR Parts 50&56 and according to the applicable laws and regulations.

Yours sincerely,

Dr. Emerson M. Cruz
SCMC-AEI ERC Chairperson

8.8.2. London School and Tropical Medicine (LSHTM)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Research Ethics Committee

Doctor Sharon Cox

LSHTM
London
WC1E7HT

16 April 2020

Dear Sharon,

Study Title: Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino drug resistant and non-resistant patients starting anti-TB treatment: A cohort study.

LSHTM Ethics ref: 14894 - 3

Thank you for submitting your amendment for the above research project.

Your amendment has been assessed by the Research Governance & Integrity Office and has been approved as a non-substantial change. The amendment does not require further ethical approval from the observational ethics committee.

List of documents reviewed:

Document Type	File Name	Date	Version
Other	Current_St-ATT ENGLISH_IC sheet_V1.0_20190503_enrolled	03/05/2019	1.0
Other	PostTx FU Script_PrevEnrolled patients	15/04/2020	1.0

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website: http://leo.lshtm.ac.uk .

Best of luck with your project.

Yours sincerely,

Rebecca Carter

Research Governance Coordinator

Ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

8.8.3. School of Tropical Medicine and Global Health, Nagasaki University (TMGH)

Ethical Committee
Graduate School of Tropical Medicine and Global Health
Nagasaki University

APPROVAL FORM

Apr. 30, 2020

Project Title:	Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino drug resistant and non-resistant patients starting anti-TB treatment: A cohort study.	
Principle Investigator:	Sharon Cox	
Date Submitted:	April 21st, 2020	Ref.No.50
Approval Number:	NU_TMGH_2020_050_5	
Protocol version:	St-ATT study: V2.0_03052019	

Dear Sir / Madam,

We are pleased to inform you that the above project has been approved.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the Ethical Committee.

Sincerely,

Kiyoshi Kita

Kiyoshi Kita
Dean, School of Tropical Medicine and Global Health
Nagasaki University, Japan

8.9. Qualitative study Covid-19 amendment ethical approval

8.9.1. Asian eye institute (local ethical committee)

ST. CABRINI MEDICAL CENTER
ASIAN EYE INSTITUTE

02 June 2020

Sharon Cox, PhD
Principal Investigator

ERC #2019-017

RE: Title: BARRIER TB Treatment: Barrier to Adherence and Related Risk Factors for TB Treatment

Dear Dr. Cox:

The SCMC-AEI ERC had an expedited review on the above-mentioned protocol and has given their approval on the following documents:

1. *Revised protocol Version 2.0. dated 07 May 2020*
2. *Study information sheet for telephone informed consent process for interview participants. (English/ Hiligaynon) dated 20 May 2020, v2.0*

The following documents *were* reviewed as reference:

1. *Cover Letter*
2. *Summary of Changes*

It is hereby confirmed that neither you nor any member of the study team has participated in the review, decision making and voting procedures of the above study protocol/document.

This approval shall be valid for 1 year from the date above. The investigator is required to submit progress report 1 month prior to the expiration date. During the duration of the study, the investigator is required to submit the following reports at a schedule set in the SCMC-AEI ERC SOP: SAE/SUSAR, protocol deviations, close-out report, early study termination, final report and any modifications or amendments in the study.

SCMC-AEI ERC is organized and operates in compliance with ICH-GCP, 21 CFR Parts 50&56 and according to the applicable laws and regulations.

Yours sincerely,

Dr. Emerson M. Cruz
SCMC-AEI ERC Chairperson

8.9.2. London School and Tropical Medicine (LSHTM)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Research Ethics Committee

Dr Sharon Cox

LSHTM
London
WC1E 7HT

11 June 2020

Dear Sharon,

Study Title: Understanding barriers to and factors influencing adherence to anti-tuberculosis treatment in The Philippines, Negros Occidental: A qualitative study.

LSHTM Ethics ref: 17416 - 1

Thank you for submitting your amendment for the above research project.

Your amendment has been assessed by the Research Governance & Integrity Office and has been approved as a non-substantial change. The amendment does not require further ethical approval from the observational ethics committee.

List of documents reviewed:

Document Type	File Name	Date	Version
Other	BARRIER_st_v.2.0_7 June 20	07/06/2020	2
Other	Information sheet_V.2_7June2020	07/06/2020	2

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website: http://leo.lshtm.ac.uk .

Best of luck with your project.

Yours sincerely,

Rebecca Carter

Research Governance Coordinator

Ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

8.9.3. School of Tropical Medicine and Global Health, Nagasaki University (TMGH)

Ethical Committee
Graduate School of Tropical Medicine and Global Health
Nagasaki University

APPROVAL FORM

June. 12, 2020

Project Title:	BARRIER TB Testament: Barrier to Adherence and Related RIsk factoRs to TB treatment.	
Principle Investigator:	Hend Saad Elsayed	
Date Submitted:	June 5th, 2020	Ref.No.073
Approval Number:	NU_TMGH_2020_073_2	
Protocol version:	V2.0	

Dear Sir / Madam,

We are pleased to inform you that the above project has been approved.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the Ethical Committee.

Sincerely,

Kiyoshi Kita

Kiyoshi Kita
Dean, School of Tropical Medicine and Global Health
Nagasaki University, Japan

8.10. Questionaries used in quantitative study

8.10.1. Depression & anxiety

HADS questionnaire	
Anxiety	I feel tense or 'wound up'
Depression	I still enjoying the things I used to enjoy
Anxiety	I get a sort of frightened feeling like something awful is about to happen
Depression	I can laugh and see the funny side of things
Anxiety	Worrying thoughts go through my mind
Depression	I feel cheerful
Anxiety	I can sit at ease and feel relaxed
Depression	I feel as if I am slowed down
Anxiety	I get a sort of frightened feeling like 'butterflies in the stomach'
Depression	I have lost interest in my appearance
Anxiety	I feel restless as if I have to be on the move
Depression	I look forward with enjoyment to things
Anxiety	I get sudden feelings of panic
Depression	I can enjoy a good book or radio or TV programme

8.10.2. Social & family support

MSPSS questionnaire
There is a special person who is around when I am in need.
There is a special person with whom I can share my joys and sorrows.
My family really tries to help me.
I get the emotional help and support I need from my family.
I have a special person who is a real source of comfort to me.
My friends really try to help me.
I can count on my friends when things go wrong.
I can talk about my problems with my family.
I have friends with whom I can share my joys and sorrows.
There is a special person in my life who cares about my feelings.
My family is willing to help me make decisions.
I can talk about my problems with my friends.

8.10.3. Stigma

TB related stigma scale
A. Community perspectives toward tuberculosis
Some people may not want to eat or drink with friends who have TB
Some people feel uncomfortable about being near those with TB
If a person has TB, some community members will behave differently towards that person for the rest of his/her life
Some people do not want those with TB playing with their children
Some people keep their distance from people with TB
Some people think that those with TB are disgusting
Some people do not want to talk to others with TB
Some people are afraid of those with TB
Some people try not to touch others with TB
Some people may not want to eat or drink with relatives who have TB
Some people prefer not to have those with TB living in their community
B. Patient perspectives toward tuberculosis
Some people who have TB feel hurt of how others react to knowing they have TB
Some people who have TB lose friends when they share with them, they have TB
Some people who have TB feel alone
Some people who have TB keep their distance from others to avoid spreading TB germs
Some people who have TB are afraid to tell those outside their family that they have TB
Some people who have TB are afraid of going to TB clinics because other people may see them there

Some people who have TB are afraid to tell others that they have TB because others may think that they also have AIDS?
Some people who have TB feel guilty because their family has the burden of caring for them
Some people who have TB will choose carefully who they tell about having TB
Some people who have TB feel guilty for getting TB because of their smoking, drinking, or other careless behaviors
Some people who have TB are worried about having AIDS
Some people who have TB are afraid to tell their family that they have TB

8.10.4. Adherence

Morisky adherence scale
Do you sometimes forget to take your pills?
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
When you travel or leave home, do you sometimes forget to bring along your medication?
Did you take your medicine yesterday?
When you feel like your illness is under control, do you sometimes stop taking your medicine?
Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your TB treatment plan?
How often do you have difficulty remembering to take all your medications?