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Complete List of Authors:	Ambaw, Fentie; Addis Ababa University, psychiatry Mayston, Rosie; King's College, London, Centre for Global Mental Health, Institute of Psychiatry Hanlon, Charlotte; Addis Ababa University, psychiatry; King's College, London, Centre for Global Mental Health, Institute of Psychiatry Alem, Atalay; Addis Ababa University, psychiatry
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Depression among tuberculosis patients: determinants, course and impact on pathways to care and treatment outcomes in a primary care setting in southern Ethiopia-a study protocol

Fentie Ambaw, [1 3] Dr. Rosie Mayston,[2] Dr. Charlotte Hanlon,[2 3] Prof. Atalay Alem[3]

1=School of Public Health, Bahir Dar University; 2=Centre for Global Mental Health, Institute of Psychiatry, King's College, London ; 3=Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University.

Abstract

Introduction: Depression is commonly co-morbid with chronic physical illnesses and is associated with a range of adverse clinical outcomes. The role of depression in the course and outcome of tuberculosis (TB) (a chronic, treatable but stigmatized disease) is currently unknown.

Aim: Our aim is to examine the relationship between depression and TB among people newly diagnosed and accessing care for TB in a rural Ethiopian setting. Our objectives are to investigate: the prevalence and determinants of probable depression, the role of depression in influencing pathways to treatment of TB, the incidence of depression during treatment, the impact of anti-TB treatment on the prognosis of depression, and the impact of depression upon the outcomes of TB treatment.

Methods and Analysis: We will use a prospective cohort design. Seven hundred and three newly diagnosed cases of TB (469 without depression and 234 with depression) will be consecutively recruited from primary care health centres. Data collection will take place at baseline, two months and six months after treatment initiation. The primary exposure variable is probable depression measured using the Patient Health Questionnaire-9. Outcome variables include: pathways to treatment, classical outcomes for anti-TB treatment quality of life, and disability. Descriptive statistics, logistic regression, and multilevel mixed effect analysis will be used to test the study hypotheses.

Ethics and dissemination: Ethical approval has been obtained from the Institutional Review Board (IRB) of the College of Health Sciences, Addis Ababa University. Findings will be disseminated through scientific publications, conference presentations, community meetings and policy briefs.

Anticipated impact: Findings will contribute to a sparse evidence base about co-morbidity of depression and TB. We hope the dissemination of findings will raise awareness of co-morbidity among clinicians and service-providers and contribute to ongoing debates regarding the delivery of mental health care in primary care in Ethiopia.

INTRODUCTION

The relationship between depression and chronic physical illnesses is bi-directional. Co-morbidity is associated with a range of adverse outcomes, including functional impairment, increased medical costs, poor adherence to medication and self-care regimens, increased medical symptom burden and increased mortality.[1 2] Individually, depression[3 4] and tuberculosis [4 5] are recognized as important public health concerns, contributing to 2.5% and 2.0% of Disability Adjusted Life Years (DALYs) worldwide in 2010, respectively.[6] In Ethiopia, the prevalence of depression was found to be 9.1% in a nationally representative sample;[7] and in a population based survey carried out in southern Ethiopia, depression was found to be the seventh leading cause of disease burden contributing to 6.5% of the DALYs in 1998.[8] TB is a key public health concern in Ethiopia: in 2009/10, it was the second most important cause of death.[9] Ethiopia is ranked seventh among the 22 high burden countries that account for 81% of all cases of TB and 80% of all TB deaths worldwide. Ethiopia is also one of 27 countries identified as having a high prevalence of multi-drug resistant TB (MDR-TB). The burden of MDR-TB in these countries accounts for 86% of cases worldwide.[9 10]

Evidence from cross-sectional studies (some of which were carried out in hospital settings in African countries) indicate a very high prevalence of co-morbid depression (ranging from 10-52%) among patients with TB.[11-18] However, because longitudinal research on TB and depression is scarce, the nature of the relationship and trajectory of co-morbidity is little understood. Most high quality studies examining the prevalence and impact of co-morbid depression in the context of chronic physical diseases were conducted among people with diabetes mellitus, ischaemic heart diseases, cancer and chronic obstructive pulmonary diseases.[1 2 19] The extent to which the impact of co-morbid depression in the context of TB is comparable to depression co-morbid with other non-communicable chronic conditions is unclear. TB is a curable condition with relatively shorter treatment duration and therefore has the potential for more favorable outcomes than many non-communicable chronic diseases.[16] On the other hand, TB remains a debilitating, stigmatized communicable disease requiring complex and aggressive treatment. Similarly to depression in the context of HIV/AIDS, the potential for depression to impair adherence to complex TB medication regimens is not only

problematic in terms of individual patient outcomes but also poses a threat to public health through the potential for the development of multi-drug resistance. For now, the role of depression in classical TB outcomes (treatment default, interruption, completion, failure, death) is unclear. We did not find any studies where authors included depression in their analyses of determinants of TB treatment outcomes and treatment pathways (routes of help seeking for TB treatment withinmodern or traditional care systems).

POSSIBLE MECHANISMS FOR THE ASSOCIATION BETWEEN TB AND DEPRESSION

It is likely that pathways for associations between TB and depression are complex and multidirectional. Biological and psychosocial pathways may be responsible for observed associations. The extent to which different pathways contribute to the burden of co-morbidity is currently unclear. For example, some researchers have suggested that TB patients may develop depression as a result of chronic infection or related psycho-socio-economic stressors[20] or due to the effects of treatment such as isoniazid.[21] An alternative pathway may be that TB is contracted as a result of compromised immunity and neglected self-care associated with depression.[22] Finally, there is evidence to suggest that TB and depression may share risk factors.[2 22 23]

Immunological responses have been implicated in the association between chronic disease and depression. Chronic infectious conditions may lead to overproduction of pro-inflammatory cytokines such as interleukin-6 which facilitate cascades of endocrine reactions that are suggested to result in depressive symptoms.[23] On the other hand, there is growing evidence that depression itself enhances the production of pro-inflammatory cytokines and directly minimizes the immunological competence of patients by down-regulating cellular and humoral responses.[1 2 22 23] In addition, in chronic pulmonary conditions with hypoxia, the hypoxic condition can act directly to make patients anxious and depressed. Likewise, general factors associated with chronic disease such as weight loss, fatigue, psychological and social losses may trigger depressive reactions. [20]

There is a consensus among experts that people who have chronic diseases and co-morbid depression can benefit from treatments for depression, including treatment with

antidepressants.[1 14 19 24 25] If depression in the context of TB is associated with a biological pathway or is a response to the burden of chronic infection, it might be expected that treatment of TB may lead to reduced symptoms of depression, perhaps without the need for further intervention. As intervention for depression among TB patients is likely to incur additional costs, pill burden, and potential stress, it is important to understand to what extent TB treatment alone may be an effective intervention for depressive symptoms. In addition, anti-TB medications, especially isoniazid, a core drug in anti-TB treatment,[26] may have significant interactions with selective serotonin reuptake inhibitors (SSRIs),[27] a WHO- recommended drug for the treatment of depression in the mental health gap intervention programme (mhGAP) guideline.[28] The integration of mental health care into primary care settings is currently being scaled up in Ethiopia,[28 29] with depression as one of the priority disorders. The results of the proposed study will help to inform the targeting and delivery of mental health services in the context of TB in Ethiopia.

AIMS & OBJECTIVES

Our overall aim is to carry out a longitudinal study of depression in the context of TB, in order to determine the impact of co-morbid depression upon TB outcomes. In this way, we hope to contribute to a sparse evidence-base that lacks high quality evidence from African countries, where the highest rates of cases and deaths relative to population size occur.[30] Our study has five objectives:

1. To determine the prevalence of depression in people with TB at the time of anti-TB treatment initiation
2. To assess whether socio-demographic characteristics of the patient, severity of physical symptoms of TB, perceived social support, disability, and substance use (alcohol, khat, tobacco) are independently associated with baseline depression
3. To determine the incidence (risk) of depression in TB patients at two and six months after starting anti- TB treatment
4. To assess the impact of depression on anti-TB treatment outcomes (classical treatment outcomes: treatment default, interruption, completion, failure, death, disability score,

and health-related quality of life) at 2 and 6 months and to explore the moderating effect of mhGAP depression interventions delivered in routine settings

5. To assess whether depression is associated independently with longer pathways to anti-TB treatment (after adjusting for socio-demographic variables).

HYPOTHESES

1. People with TB who have depression at the time of treatment initiation (baseline) will have worse treatment outcomes of TB (classical treatment outcomes, disability score, and health related quality of life) at the end of two and six months follow-up when compared to those without depression at baseline.
2. Anti-TB treatment will progressively reduce depressive symptoms so that those with depression at baseline will have reduced severity of depression (PHQ-9 scores) or no depression after two and six months treatment for TB.

METHODS AND ANALYSIS

Study setting: The study will be conducted from December 2014 to December 2015 in nine primary care facilities in Butajira town, Meskan district, Sodo district and Silti district of the Southern, Nations, Nationalities and Peoples' Region (SNNPR) of Ethiopia. Farming is the main economic activity in the area. In 2012/2013, there were 2,742 people with TB in the zone. Directly Observed Treatment (DOTS) for TB is being implemented in all health facilities.[9] In 2011, the anti-TB treatment defaulter rate, death rate and treatment success rate were 2.5%, 2.0% and 82.3%, respectively, in SNNPR.[31]

Delivery of anti-TB treatment & care in rural Ethiopia: The Directly Observed Treatment (DOT) for new TB patients lasts for six months, and consists of two phases: intensive and continuation. The intensive phase consists of treatment with a combination of four medications (Rifampicin, Ethambutol, Isoniazid and Pyrazinamide) for the first two months, and the continuation phase consists of a combination of two medications (Rifampicin and Isoniazid), to be taken for four months immediately after the intensive phase. A health worker or community-based anti-TB treatment supporter has to observe the patient swallow the medications once a day. Currently,

anti-TB treatment is being delivered in health centers, hospitals (by health workers) or at health posts (by trained community-based "health extension workers").[9] Health posts are the lowest level of health care in Ethiopia serving 5000 people. The flow of TB patients in each of the health facilities selected for this study is above 5/month.

Study design: The study is a prospective cohort in which adults with newly diagnosed TB will be recruited at the time of initiating treatment and followed up to the end of treatment (six months after initiation). Data collection will occur at three time-points: baseline (before anti-TB treatment), at two months (end of intensive phase) and at six months (end of continuation phase) (table 1). Figure 1 shows the approach to investigation of the effect of TB on depression and Figure 2 shows the approach to investigation of the effect of depression on TB.

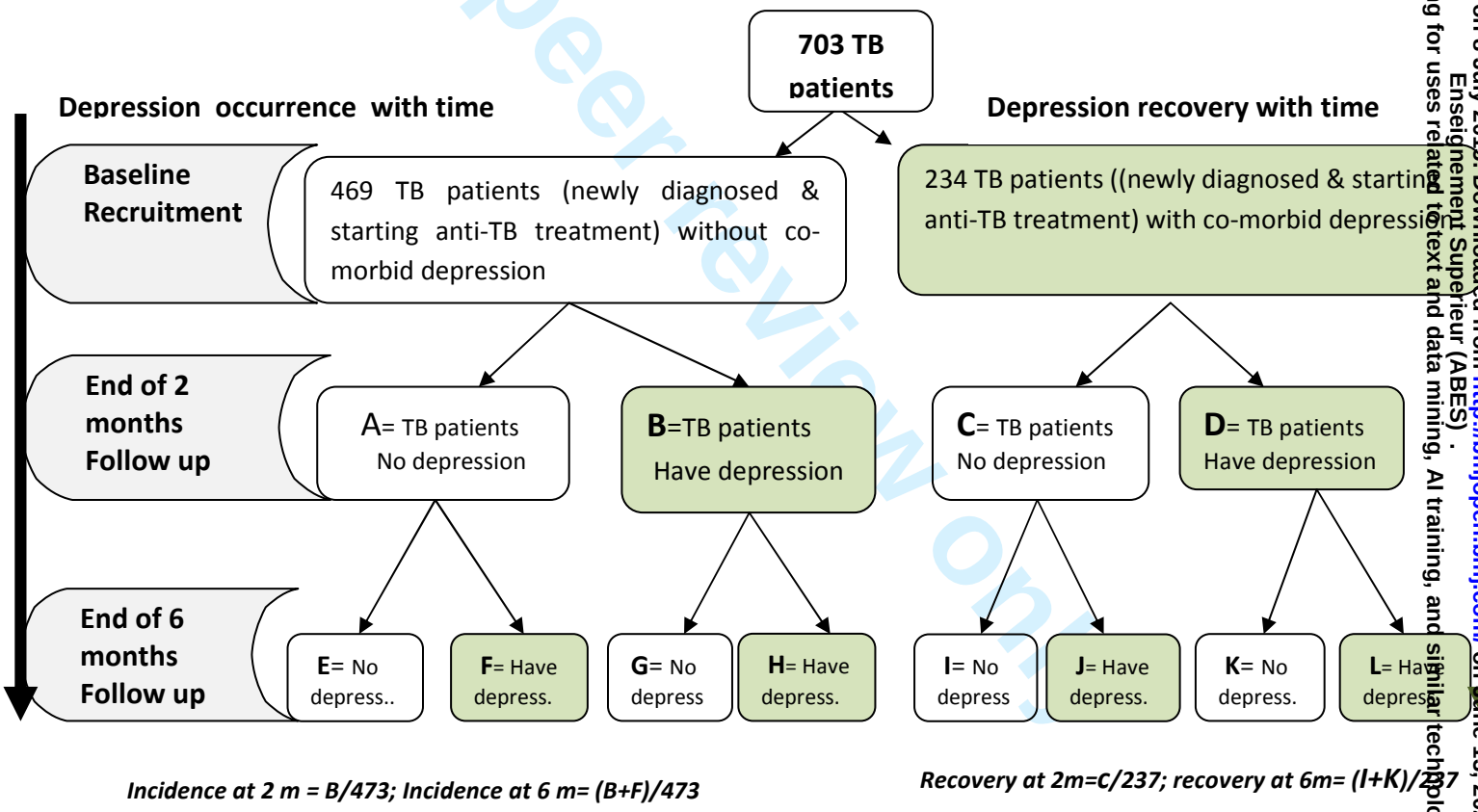

Figure 1: Schematic illustration for analyzing effect of tuberculosis on depression

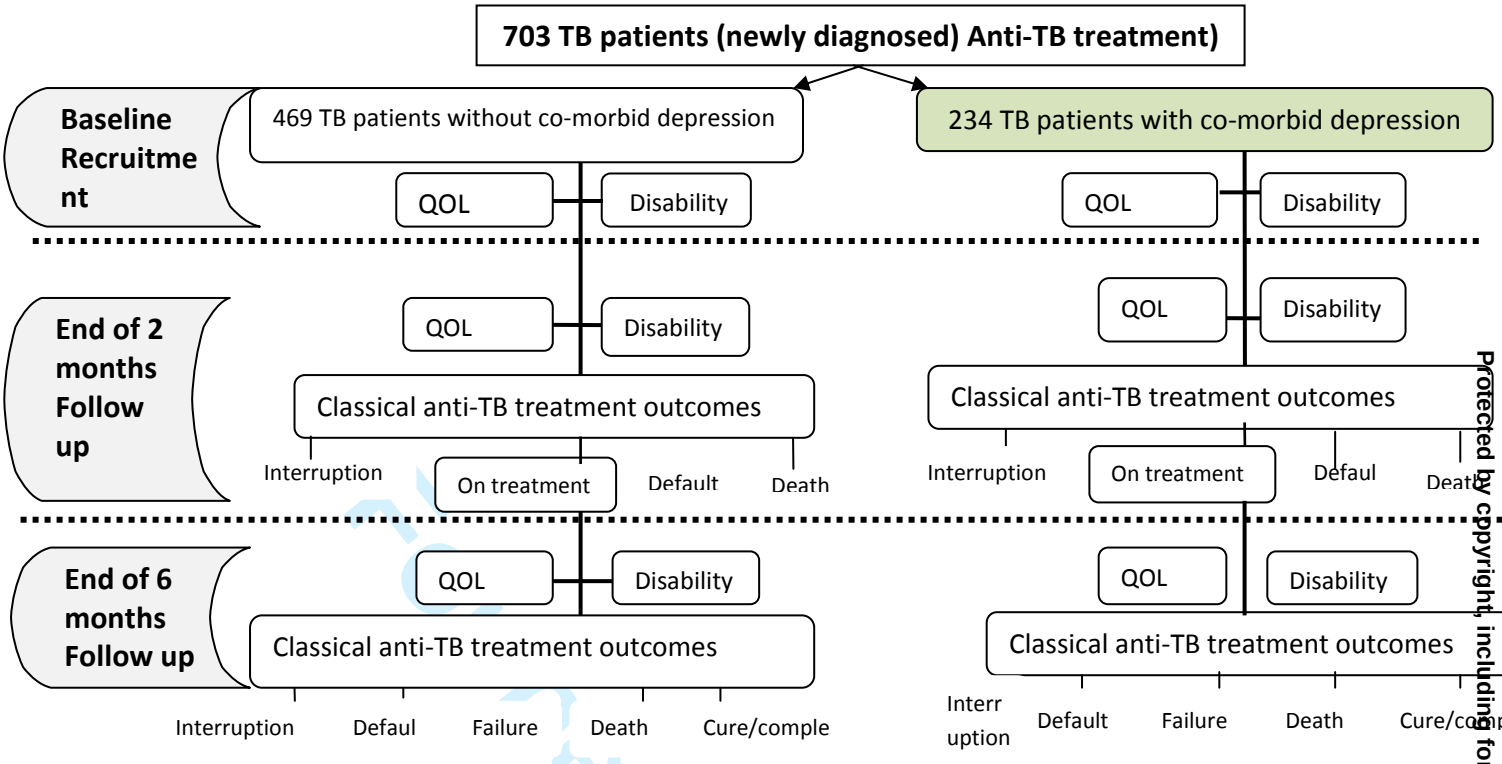

Figure 2: Schematic illustration for analyzing effect of depression on tuberculosis

INCLUSION CRITERIA

- Patients attending the selected health centres who have started their anti-TB treatment within the last one month
- Those aged over 17 years

EXCLUSION CRITERIA

- Patients with a known plan to be transferred out of the study sites
- Those too ill to be interviewed at baseline as perceived by the interviewer or the patient
- Those patients admitted to the in-patient unit for more than five days in the last one month

SAMPLE SIZE DETERMINATION

The sample size was calculated using STATA 12.0.[32] We used the following parameters: 80% power, 95% confidence (one-sided). We estimated that the prevalence of treatment default among TB patients without depression will be 2.5% (estimate for the SNNPR).[31] We used an estimate of a 5% increase in prevalence of defaulting among co-morbid patients (i.e. a prevalence of treatment default of 7.5% among people with TB and co-morbid depression).

Given the risk of death and drug resistance among treatment defaulters, a 5% difference could be a clinically important effect.[33] We estimate that we will find a ratio of 2:1 of non-exposed (not depressed) to exposed (depressed) participants. With these assumptions, the required sample size is 639. After adding 10% contingency to account for potential loss to follow up, the total sample size is 703 of which 234 will be exposed (with depression) and 469 will be non-exposed (without baseline depression). In a recent cross-sectional study carried out in outpatient healthcare settings in northern Ethiopia, the ratio of non-exposed (TB patients without depression) to exposed (TB patients with depression) was approximately 2:1. In the same study 31% of the TB patients had depression, as measured using both SRQ-20 (cut off seven or above) and HADS (cut off eight or above).[34]

RECRUITMENT & DATA COLLECTION

The health professional (usually BSc nurses and health officers) running the TB Clinic at each site will identify the study participants that meet the inclusion criteria consecutively until a total of 703 participants is reached and link to experienced and trained diploma holder nurse research assistants employed to collect data full time. The health professionals in the TB clinics will also have a role of helping the research assistants in reviewing the patients' charts for TB treatment outcomes, co-morbid illness, and drug side effects. The research assistants will provide information about the study to the patient and seek informed written consent. She/he will enroll patients that consent and arrange appointment dates for the next interviews, and carry out interviews at the health institutes. When patients do not consent to participate in the study, the research assistant will request permission to record sex, age, level of education, and occupation of the patient. The list of variables and timing of data collection is described Table 1.

Table 1: Variables of the study and their plan of measurement

No.	Variables	Measurement time			Variable category
		Baseline	End of 2nd month	End of 6th month	
1	Depression	√	√	√	Exposure
2	Treatment outcomes of TB (complete, cure, failure, default, death, interruption)		√*	√	Outcome
3	Quality of Life	√	√	√	Outcome
4	Disability	√	√	√	Outcome
5	Pathways to TB health care	√			Outcome
6	Severity of signs and symptoms of TB	√	√	√	Predictor
7	Socio-demographic variables	√			Predictor
8	Substance use	√	√	√	Predictor
9	Co-morbid illness /negative life event	√	√	√	Predictor
10	perceived social support	√	√	√	Predictor
11	Perceptions of patient about TB		√		Predictor
12	medication side effects		√	√	Predictor
13	Tuberculosis related stigma		√	√	Predictor

MEASUREMENT

The primary exposure variable

Depression will be measured using Patient Health Questionnaire-9 (PHQ-9).[35 36] The PHQ-9 has been validated and used in Ethiopia.[37] Symptoms will be categorised using established cut-points five, ten, fifteen, and twenty (mild, moderate, moderately severe and severe depression respectively).[35 36] The aim of this categorisation is to enable assessment of different levels of exposure and to facilitate the computation of interval level scoring to allow us to examine

changes in intensity of depression when the co-morbid TB is treated. Patients scoring ten or more will be classified as having high depressive symptoms (exposed) as the items in PHQ-9 related to appetite and fatigue overlap with symptoms of TB.

Outcome variables

Primary outcome variable: Classical TB outcomes as defined by WHO[26] and Federal Ministry of Health of Ethiopia:[9] treatment defaulted, interrupted, failure, completed, cured or death. Data on the patients' status on the primary outcome variable will be extracted from the TB register.

Secondary Outcome Variables:

Quality of life (QOL): measured using a single-item "How would you rate your quality of life?" with a continuous numerical scale with values ranging from zero (worst possible quality of life) to ten (highest possible quality of life) as recommended by de Boer et al.[38] and WHO.[39]

Disability: will be measured using the interviewer administered version of the 12-item WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)[40] with scores ranging from 12-60, where higher scores will represent worse levels of disability. WHODAS 2.0 has been used previously in Ethiopia and found to have convergent validity.[41 42]

Pathways to health care: We are interested in what other care providers (i.e. traditional healers, other modern medicine providers) TB patients have visited in relation to symptoms related to the present illness before attending the TB clinic. This will be measured at baseline using a modified version of the WHO encounter form for mental disorders.[43]

Independent variables

Signs and symptoms of tuberculosis: Body Mass Index (BMI) (weight in kg/height in meters squared), fever, night sweats, cough, pain perceived weakness, and anorexia will be measured using single-item numerical indicator with scores ranging from zero to ten where zero means absence of a symptom. The items will be as follows: "How is your cough this week", "how is your fever this week", "how is your night sweat this week", "how is your pain this week", "how weak do you feel this week", and "how is your appetite this week?"

Socio-demographic variables: will include age, sex, marital status, level of education, religion, ethnicity, average household monthly income, perceived access to the household income for

the purpose of health care (no access, only some access, adequate access), household size, occupation, place of residence (urban versus rural), distance of the residence from health institute (estimates in kilometeres) and presence of dependent children. Data on socio-demographic variables will be collected at baseline using a structured questionnaire administered by interviewers.

Substance use: The use of alcohol, tobacco and khat among the study participants will be measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (version 3.1)[44] at the three time points. ASSIST is a valid and reliable scale in primary care settings in low and middle income countries.[44-47]

Co-morbid illness and major life events: Data on the presence of co-morbid illnesses such as HIV co-infection, cardiovascular diseases, chronic obstructive pulmonary diseases, diabetes mellitus, and mental illnesses including previously diagnosed depression will be collected by asking the patient "Do you have other (other than TB) diagnosed health problem(s)? Please specify" at all three time points. If reported, the type of co-morbid illness, time of diagnosis and treatment being taken (if any) will be specified. Similarly major life events of clients over the last 2 months will be captured by asking the question "Did you have an event (events) that you think has negatively affected your life over the last 2 months (e.g. death of a family member, divorce, loss of property?"

Perceived social support: the individual's evaluation of whether and to what extent relationships are helpful[48] and the expectation of whether support will be provided within one's social network.[49] These two domains will be measured using the three-item Oslo Scale of Perceived Social Support[50] with scores ranging from three to fourteen, with higher scores indicating better perceived social support.

Perceptions of patients about TB: perceived causes, severity, benefits of anti-TB treatment and barriers to anti-TB treatment will be measured using open ended semi-structured interviews that will be coded thematically, categorized, and quantified so that responses may be included in the quantitative analysis as categorical variables. The guiding questions will be 'what do you think causes TB?' 'How severe do you think TB can be?' 'How helpful do you think the

treatments of TB would be?' 'What do you think your barriers may be to completing your treatment?'

Medication side effect: Information about medication side effects will be extracted from patient's chart.

Tuberculosis related stigma: will be measured using a ten-item TB stigma scale adopted from Macq et al.[51] in Nicaragua. This instrument has been piloted on 68 TB patients who will be excluded from the main study and was found to be understandable (except one of the items which has been modified after the pilot), acceptable to the respondents and data collectors, and to have an internal consistency coefficient (alpha value) of 0.78. The translation of the instrument into the local language was done using the mixed methods translation and consensus generation approach.[52]

Treatment for depression: For patients with diagnosed depression, the appropriateness of their treatments (for the depression) will be coded as appropriate if they are in accordance with mhGAP interventions guidelines[28] and inappropriate if they do not follow the recommended treatment approaches.

Data management

Data will be checked for consistency and completeness by supervisors, double-checked by the principal investigator and double-entered to EpiData 3.1 by experienced data entry clerks. Then, it will be exported to SPSS version 20 for cleaning and analysis. Hard copies of the data will be stored in a locked cabinet and consent forms will be separated from the data.

Data analysis

Data will be analyzed using SPSS version 20. Descriptive statistics will be computed to describe the socio-demographic characteristics of participants and to summarize the distribution of each of the dependent (outcome) and independent variables. We will check to see whether refusal or losses to follow up is associated with socio-demographic characteristics by testing the statistical significance of differences between refusals and consenters and those lost to follow-up versus those retained at 6 months in terms of age, sex, and level of education.

The prevalence of probable depression among TB patients at baseline will be determined by computing the proportion of patients scoring ten and above on the PHQ-9 scale. The same

analysis will be carried out at endline and the magnitude of the difference between the two measurements (baseline and endline) will be calculated and the statistical significance tested using McNemar test for repeated measures. Determinants of depression at baseline will be examined using logistic regression with depression as a dependent variable and socio-demographic characteristics, symptoms of TB, perceived social support, and substance included as predictors. The proportion of TB patients that scored below ten on PHQ-9 at baseline but who had scores of ten and above at the end of the second month will be computed to determine incidence (risk) of depression at two months. This will be repeated at six months.

The change in depressive symptoms (PHQ-9 scores) over the three data collection points will be analyzed using multilevel mixed effect model by setting measurement occasions as level-1 and individual TB patients as level-2 of the analysis. Level of disability, substance use, presence of additional chronic illnesses, level of perceived social support, perceptions of patients about TB, and appropriateness of depression treatment will be predictors at level-1; socio-demographic characteristics of the individual will be predictors at level-2. We have selected this analysis approach as it does not require complete data over measurement occasions, equal interval of measurement for each case, or sphericity assumptions.[53-56]

The effect of depression on the treatment pathways of TB patients will be analyzed using binary logistic regression. The pathways followed by participants to access care will be entered as separate dependent variables after coding each of the different pathways as zero (if specific pathway not followed) or one (if specific pathway followed), depression will be included as an independent variable. We will adjust for socio-demographic characteristics.

To determine the effect of depression on the classical outcomes of anti-TB treatment, logistic regression will be carried out at the end of sixth months with the treatment outcomes (interrupted, defaulted, completed) as dependent variables and depression as an independent variable. We will adjust for substance use, stigma, co-morbid illnesses, socio-demographic factors, drug side effects, perceived social support, and perceptions of the patient about TB. Although multinomial logistic regression could handle the mutually exclusive treatment outcomes as values of one dependent variable with more than two categories, we have elected to use logistic regression in order to simplify the interpretation of our results.

The change in quality of life and disability levels over time will be modeled by setting measurement occasions as level-1 and individual patients as level-2. In this analysis, PHQ-9 scores, substance use, presence of additional chronic illnesses, level of perceived social support, appropriateness of depression treatment, level of TB-stigma, medication side effects, and perceptions of patient about TB will be modeled as level-1 predictors and socio-demographic characteristics of the individual will be predictors at level-2.

All the necessary assumptions will be tested and the findings will be reported before inferential statistics are calculated. Statistical tests will be considered significant when p-values are less than 0.05 and 95% confidence intervals will be presented throughout.

Ethical considerations

The proposal has been ethically cleared by the Institutional review board (IRB) of College of Health Sciences, Addis Ababa University on 23/07/2014, number 027/14/Psy. Informed written consent will be obtained from every participant. Finger prints will be taken from consenting illiterate participants. Patients identified as having PHQ-9 scores ten or above or endorsing the suicide item of PHQ-9 will be referred to nurses trained in mental health interventions.

Dissemination plan

Findings will be disseminated through publications in peer reviewed journals and conference presentations. Summary reports will be submitted to health institutions concerned and policy makers. Community meetings will be held to disseminate findings to the local community, including study participants.

Limitations of the study

Currently, health institutes are actively strengthening tracing mechanisms in order to decrease treatment default and treatment interruption. This work may mean that those who are otherwise more likely to default or interrupt treatment may complete their treatment, which may, in turn, weaken any association between the exposure and these outcome variables. There may also conceivably be a “treatment effect” of study participation in terms of improving depressive symptoms and encouraging people to adhere to treatment. Quality of life will be

measured using a single item and we will therefore not obtain detailed information on the various dimensions that make up this construct.

Strengths of the study

The study will provide much-needed evidence about the impact of co-morbid depression upon the course and outcome of TB. The longitudinal study design will allow us to estimate the incidence of depression among people engaged with TB treatment. The observation of depression-tuberculosis co-morbid patients from treatment initiation to completion date will allow us to investigate whether TB treatment alone may be sufficient to reduce depressive symptoms. The study will enable us to investigate the impact of depression in determining the course and outcome of TB, independent of the effects of other factors such as socio-demographic variables, stigma, perceived social support, substance use, and co-morbid illnesses such as HIV. So far as we are aware, this study will be the first in Ethiopia, or any African setting, to examine the potentially important role of depression in determining pathways to TB care.

Expected benefits of the findings

Our findings will contribute to a sparse evidence base about mental health, TB and other chronic diseases in low and middle income countries. We hope that other researchers will be encouraged to investigate important questions in this area. We anticipate that study findings will contribute to awareness raising among Ethiopian clinicians and service providers about the potential impact of co-morbid depression upon the course and management of chronic disease, as well as informing future plans and policies related to the delivery of mental health care in primary care and other healthcare settings in Ethiopia.

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COMPETING INTERESTS: None

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Depression among tuberculosis patients: determinants, course and impact on pathways to care and treatment outcomes in a primary care setting in southern Ethiopia-a study protocol

Fentie Ambaw, [1 3] **Dr. Rosie Mayston,**[2] **Dr. Charlotte Hanlon,**[2 3] **Prof. Atalay Alem**[3]

1=School of Public Health, Bahir Dar University; 2=Centre for Global Mental Health, Institute of Psychiatry, King's College, London ; 3=Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University.

Corresponding Author: Fentie Ambaw

fentambaw@yahoo.com

Abstract

Introduction: Depression is commonly co-morbid with chronic physical illnesses and is associated with a range of adverse clinical outcomes. Currently, the literature on the role of depression in determining the course and outcome of tuberculosis (TB) is very limited.

Aim: Our aim is to examine the relationship between depression and TB among people newly diagnosed and accessing care for TB in a rural Ethiopian setting. Our objectives are to investigate: the prevalence and determinants of probable depression, the role of depression in influencing pathways to treatment of TB, the incidence of depression during treatment, the impact of anti-TB treatment on the prognosis of depression, and the impact of depression upon the outcomes of TB treatment.

Methods and Analysis: We will use a prospective cohort design. Seven hundred and three newly diagnosed cases of TB (469 without depression and 234 with depression) will be consecutively recruited from primary care health centres. Data collection will take place at baseline, two months and six months after treatment initiation. The primary exposure variable is probable depression measured using the Patient Health Questionnaire-9. Outcome variables include: pathways to treatment, classical outcomes for anti-TB treatment quality of life, and disability. Descriptive statistics, logistic regression, and multilevel mixed effect analysis will be used to test the study hypotheses.

Ethics and dissemination: Ethical approval has been obtained from the Institutional Review Board (IRB) of the College of Health Sciences, Addis Ababa University. Findings will be disseminated through scientific publications, conference presentations, community meetings and policy briefs.

Anticipated impact: Findings will contribute to a sparse evidence base about co-morbidity of depression and TB. We hope the dissemination of findings will raise awareness of co-morbidity among clinicians and service-providers and contribute to ongoing debates regarding the delivery of mental health care in primary care in Ethiopia.

INTRODUCTION

The relationship between depression and chronic physical illnesses is bi-directional. Co-morbidity is associated with a range of adverse outcomes, including functional impairment, increased medical costs, poor adherence to medication and self-care regimens, increased medical symptom burden and increased mortality.[1 2] Individually, depression[3 4] and tuberculosis [4 5] are recognized as important public health concerns, contributing to 2.5% and 2.0% of Disability Adjusted Life Years (DALYs) worldwide in 2010, respectively.[6] In Ethiopia, the prevalence of depression was found to be 9.1% in a nationally representative sample;[7] and in a population based survey carried out in southern Ethiopia, depression was found to be the seventh leading cause of disease burden contributing to 6.5% of the DALYs in 1998.[8] TB is a key public health concern in Ethiopia: in 2009/10, it was the second most important cause of death.[9] Ethiopia is ranked seventh among the 22 high burden countries that account for 81% of all cases of TB and 80% of all TB deaths worldwide. Ethiopia is also one of 27 countries identified as having a high prevalence of multi-drug resistant TB (MDR-TB). The burden of MDR-TB in these countries accounts for 86% of cases worldwide.[9 10]

Evidence from cross-sectional studies (some of which were carried out in hospital settings in African countries) indicate a very high prevalence of co-morbid depression (ranging from 10-52%) among patients with TB.[11-18] However, because longitudinal research on TB and depression is scarce, the nature of the relationship and trajectory of co-morbidity is little understood. Most high quality studies examining the prevalence and impact of co-morbid depression in the context of chronic physical diseases were conducted among people with diabetes mellitus, ischaemic heart diseases, cancer and chronic obstructive pulmonary diseases.[1 2 19] The extent to which the impact of co-morbid depression in the context of TB is comparable to depression co-morbid with other non-communicable chronic conditions is unclear. TB is a curable condition with relatively shorter treatment duration and therefore has the potential for more favorable outcomes than many non-communicable chronic diseases.[16] On the other hand, TB remains a debilitating, stigmatized communicable disease requiring complex and aggressive treatment. Similar to depression in the context of HIV/AIDS, the potential for depression to impair adherence to complex TB medication regimens is not only

problematic in terms of individual patient outcomes but also poses a threat to public health through the potential for the development of multi-drug resistance.[20] For now, the literature on the role of depression in determining TB treatment outcomes (treatment default, interruption, completion, failure, death) and treatment pathways (routes of help seeking for TB treatment within modern or traditional care systems) is very limited.

POSSIBLE MECHANISMS FOR THE ASSOCIATION BETWEEN TB AND DEPRESSION

It is likely that pathways for associations between TB and depression are complex and multidirectional. Biological and psychosocial pathways may be responsible for observed associations. The extent to which different pathways contribute to the burden of co-morbidity is currently unclear. For example, some researchers have suggested that TB patients may develop depression as a result of chronic infection or related psycho-socio-economic stressors[21] or due to the effects of treatment such as isoniazid.[22] An alternative pathway may be that TB is contracted as a result of compromised immunity and neglected self-care associated with depression.[23] Finally, there is evidence to suggest that TB and depression may share risk factors.[2 23 24]

Immunological responses have been implicated in the association between chronic disease and depression. Chronic infectious conditions may lead to overproduction of pro-inflammatory cytokines such as interleukin-6 which facilitate cascades of endocrine reactions that are suggested to result in depressive symptoms.[24] On the other hand, there is growing evidence that depression itself enhances the production of pro-inflammatory cytokines and directly minimizes the immunological competence of patients by down-regulating cellular and humoral responses.[1 2 23 24] In addition, in chronic pulmonary conditions with hypoxia, the hypoxic condition can act directly to make patients anxious and depressed. Likewise, general factors associated with chronic disease such as weight loss, fatigue, psychological and social losses may trigger depressive reactions. [21]

There is a consensus among experts that people who have chronic diseases and co-morbid depression can benefit from treatments for depression, including treatment with antidepressants.[1 14 19 25 26] If depression in the context of TB is associated with a biological

pathway or is a response to the burden of chronic infection, it might be expected that treatment of TB may lead to reduced symptoms of depression, perhaps without the need for further intervention. As intervention for depression among TB patients is likely to incur additional costs, pill burden, and potential stress, it is important to understand to what extent TB treatment alone may be an effective intervention for depressive symptoms. In addition, anti-TB medications, especially isoniazid, the first of the monoamine oxidase inhibitors to be considered for the treatment of mental disorders in the 1950s,[27] and now a core drug in anti-TB treatment,[28] may have significant interactions with selective serotonin reuptake inhibitors (SSRIs),[27] a WHO- recommended drug for the treatment of depression in the mental health gap intervention programme (mhGAP) guideline.[29] The integration of mental health care into primary care settings is currently being scaled up in Ethiopia,[29 30] with depression as one of the priority disorders. The results of the proposed study will help to inform the targeting and delivery of mental health services in the context of TB in Ethiopia.

Figure 1: Conceptual framework of the study

AIMS & OBJECTIVES

Our overall aim is to carry out a longitudinal study of depression in the context of TB, in order to determine the impact of co-morbid depression upon TB outcomes. In this way, we hope to contribute to a sparse evidence-base that lacks high quality evidence from African countries, where the highest rates of cases and deaths relative to population size occur.[31] Our study has five objectives:

1. To determine the prevalence of depression in people with TB at the time of anti-TB treatment initiation
2. To assess factors associated with baseline depression
3. To determine the incidence (risk) of depression in TB patients at two and six months after starting anti- TB treatment
4. To assess the impact of depression on anti-TB treatment outcomes (classical treatment outcomes: treatment default, interruption, completion, failure, death, disability score, and health-related quality of life) at 2 and 6 months and to explore the moderating effect of mhGAP depression interventions delivered in routine settings
5. To assess whether depression is associated independently with longer pathways to anti-TB treatment (after adjusting for socio-demographic variables).

HYPOTHESES

1. People with TB who have depression at the time of treatment initiation (baseline) will have worse treatment outcomes of TB (classical treatment outcomes, disability score, and health related quality of life) at the end of two and six months follow-up when compared to those without depression at baseline.
2. Anti-TB treatment will progressively reduce depressive symptoms so that those with depression at baseline will have reduced severity of depression (PHQ-9 scores) or no depression after two and six months treatment for TB.

METHODS AND ANALYSIS

Study setting: The study will be conducted from December 2014 to December 2015 in nine primary care facilities in Butajira town, Mareko district, Meskan district, Sodo district and Silte district of the Southern Nations, Nationalities and Peoples' Region (SNNPR) of Ethiopia. Farming is the main economic activity in the area. In 2012/2013, there were 2,742 people with TB in the zone. Directly Observed Treatment (DOTS) for TB is being implemented in all health facilities.[9] In 2011, the anti-TB treatment defaulter rate, death rate and treatment success rate were 2.5%, 2.0% and 82.3%, respectively, in SNNPR.[32]

Figure 2: Map of the study area

Delivery of anti-TB treatment & care in rural Ethiopia: The Directly Observed Treatment (DOT) for new TB patients lasts for six months, and consists of two phases: intensive and continuation. The intensive phase consists of treatment with a combination of four medications (Rifampicin, Ethambutol, Isoniazid and Pyrazinamide) for the first two months, and the continuation phase consists of a combination of two medications (Rifampicin and Isoniazid), to be taken for four months immediately after the intensive phase. A health worker or community-based anti-TB treatment supporter has to observe the patient swallow the medications once a day. Currently,

anti-TB treatment is being delivered in health centers, hospitals (by health workers) or at health posts (by trained community-based "health extension workers").[9] Health posts are the lowest level of health care in Ethiopia serving 5000 people. The flow of TB patients in each of the health facilities selected for this study is above 5/month.

Study design: The study is a prospective cohort in which adults with newly diagnosed TB will be recruited at the time of initiating treatment and followed up to the end of treatment (six months after initiation). Data collection will occur at three time-points: baseline (before anti-TB treatment), at two months (end of intensive phase) and at six months (end of continuation phase) (table 1). Figure 3 shows the approach to investigation of the effect of TB on depression and Figure 4 shows the approach to investigation of the effect of depression on TB.

Figure 3: Schematic illustration for analyzing effect of tuberculosis on depression

Figure 4: Schematic illustration for analyzing effect of depression on tuberculosis

INCLUSION CRITERIA

- Patients attending the selected health centres who have started their anti-TB treatment within the last one month
- Those aged over 17 years

EXCLUSION CRITERIA

- Patients with a known plan to be transferred out of the study sites
- Those too ill to be interviewed at baseline as perceived by the interviewer or the patient
- Those patients admitted to the in-patient unit for more than five days in the last one month
- Patients with MDR-TB constitute a different population because their treatment is different (more toxic medications for a much longer duration). MDR-TB is a much more feared and stigmatized condition with patients probably told that no further treatment is available. In addition to that, only one of the study health institutions has recently started the service for MDR-TB patients.
- Patients on retreatment have experiences of previous failures and usually have MDR-TB. When we try to see "what happens to the depression at baseline when the TB is treated?"

we are assuming that the treatment for the TB works well. Therefore, this group of patients will be excluded.

SAMPLE SIZE DETERMINATION

The sample size was calculated using STATA 12.0.[33] We used the following parameters: 80% power, 95% confidence (one-sided). We estimated that the prevalence of treatment default among TB patients without depression will be 2.5% (estimate for the SNNPR).[32] We used an estimate of a 5% increase in prevalence of defaulting among co-morbid patients (i.e. a prevalence of treatment default of 7.5% among people with TB and co-morbid depression). Given the risk of death and drug resistance among treatment defaulters, a 5% difference could be a clinically important effect.[34] We estimate that we will find a ratio of 2:1 of non-exposed (not depressed) to exposed (depressed) participants. With these assumptions, the required sample size is 639. After adding 10% contingency to account for potential loss to follow up, the total sample size is 703 of which 234 will be exposed (with depression) and 469 will be non-exposed (without baseline depression). In a recent cross-sectional study carried out in outpatient healthcare settings in northern Ethiopia, the ratio of non-exposed (TB patients without depression) to exposed (TB patients with depression) was approximately 2:1. In the same study 31% of the TB patients had depression, as measured using both SRQ-20 (cut off seven or above) and HADS (cut off eight or above).[35]

RECRUITMENT AND DATA COLLECTION

The health professional (usually BSc nurses and health officers) running the TB Clinic at each site will identify the study participants that meet the inclusion criteria consecutively until a total of 703 participants is reached and link to experienced and trained diploma holder nurse research assistants employed to collect data full time. The health professionals in the TB clinics will also have a role of helping the research assistants in reviewing the patients' charts for TB treatment outcomes, co-morbid illness, and drug side effects. The research assistants will provide information about the study to the patient and seek informed written consent. She/he will enroll patients that consent and arrange appointment dates for the next interviews, and carry out interviews at the health institutes. When patients do not consent to participate in the study, the research assistant will request permission to record sex, age, level of education, and

occupation of the patient. The list of variables and timing of data collection is described in table 1.

Table 1: Variables of the study and their plan of measurement

No.	Variables	Measurement time			Variable category
		Baseline	End of 2nd month	End of 6th month	
1	Depression	√	√	√	Exposure
2	Treatment outcomes of TB (complete, cure, failure, default, death, interruption)		√*	√	Outcome
3	Quality of Life	√	√	√	Outcome
4	Disability	√	√	√	Outcome
5	Pathways to TB health care	√			Outcome
6	Severity of signs and symptoms of TB	√	√	√	Predictor
7	Socio-demographic variables	√			Predictor
8	Substance use	√	√	√	Predictor
9	Co-morbid illness /negative life event	√	√	√	Predictor
10	perceived social support	√	√	√	Predictor
11	Perceptions of patient about TB		√		Predictor
12	medication side effects		√	√	Predictor
13	Tuberculosis related stigma		√	√	Predictor

√* = only the presence/absence of treatment interruption, death, and default will be measured.

MEASUREMENT

The primary exposure variable

Depression will be measured using Patient Health Questionnaire-9 (PHQ-9).[36 37] The PHQ-9 has been validated and used in Ethiopia.[38] Patients scoring ten or more will be classified as having high depressive symptoms (exposed). Symptoms will be categorised using established cut-points five, ten, fifteen, and twenty (mild, moderate, moderately severe and severe depression

respectively)[36 37] to determine the different severities of exposure and interval level scoring will be computed to examine changes in intensity of depression when the co-morbid TB is treated.

Outcome variables

Primary outcome variable: Classical TB outcomes as defined by WHO[28] and Federal Ministry of Health of Ethiopia: [9] treatment defaulted, interrupted, failure, completed, cured or death. Data on the patients' status on the primary outcome variable will be extracted from the TB register.

Secondary Outcome Variables:

Quality of life (QOL): measured using a single-item "How would you rate your quality of life?" with a continuous numerical scale with values ranging from zero (worst possible quality of life) to ten (highest possible quality of life) as recommended by de Boer et al.[39] and WHO.[40]

Disability: will be measured using the interviewer administered version of the 12-item WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)[41] with scores ranging from 12-60, where higher scores will represent worse levels of disability. WHODAS 2.0 has been used previously in Ethiopia and found to have convergent validity.[42 43]

Pathways to health care: We are interested in what other care providers (i.e. traditional healers, other modern medicine providers) TB patients have visited in relation to symptoms related to the present illness before attending the TB clinic. This will be measured at baseline using a modified version of the WHO encounter form for mental disorders.[44]

Independent variables

Signs and symptoms of tuberculosis: Body Mass Index (BMI) (weight in kg/height in meters squared), fever, night sweats, cough, pain, perceived weakness, and anorexia will be measured using single-item numerical indicator with scores ranging from zero to ten where zero means absence of a symptom. The items will be as follows: "How is your cough this week", "how is your fever this week", "how is your night sweat this week", "how is your pain this week", "how weak do you feel this week", and "how is your appetite this week?"

Socio-demographic variables: will include age, sex, marital status, level of education, religion, ethnicity, average household monthly income, perceived access to the household income for the purpose of health care (no access, only some access, adequate access), household size,

occupation, place of residence (urban versus rural), distance of the residence from health institute (estimates in kilometeres) and presence of dependent children. Data on socio-demographic variables will be collected at baseline using a structured questionnaire administered by interviewers.

Substance use: The use of alcohol, tobacco and khat among the study participants will be measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (version 3.1)[45] at the three time points. ASSIST consists of eight items for each of alcohol and khat use and seven items for tobacco products. It is a valid and reliable scale in primary care settings in low and middle income countries.[45-48]

Co-morbid illness and major life events: Data on the presence of co-morbid illnesses such as HIV co-infection, cardiovascular diseases, chronic obstructive pulmonary diseases, diabetes mellitus, and mental illnesses including previously diagnosed depression will be collected by asking the patient "Do you have other (other than TB) diagnosed health problem(s)? Please specify" at all three time points. If reported, the type of co-morbid illness, time of diagnosis and treatment being taken (if any) will be specified by reviewing the participants' medical records. Similarly major life events of clients over the last 2 months will be captured by asking the question "Did you have an event (events) that you think has negatively affected your life over the last 2 months (e.g. death of a family member, divorce, loss of property?"

Perceived social support: the individual's evaluation of whether and to what extent relationships are helpful[49] and the expectation of whether support will be provided within one's social network.[50] These two domains will be measured using the three-item Oslo Scale of Perceived Social Support[51] with scores ranging from three to fourteen, with higher scores indicating better perceived social support.

Perceptions of patients about TB: perceived causes, severity, benefits of anti-TB treatment and barriers to anti-TB treatment will be measured using open ended semi-structured interviews that will be coded thematically, categorized, and quantified so that responses may be included in the quantitative analysis as categorical variables. The guiding questions will be 'what do you think causes TB?' 'How severe do you think TB can be?' 'How helpful do you think the treatments of TB would be?' 'What do you think your barriers may be to completing your

treatment?' Measurement will be done at the second month to minimize the burden of items at baseline when patients may be most ill.

Medication side effect: Information about medication side effects will be extracted from patient's chart.

Tuberculosis related stigma: will be measured using a ten-item TB stigma scale adopted from Macq et al.[52] in Nicaragua. This instrument has been piloted on 68 TB patients who will be excluded from the main study and was found to be understandable (except one of the items which has been modified after the pilot), acceptable to the respondents and data collectors, and to have an internal consistency coefficient (alpha value) of 0.78. The translation of the instrument into the local language was done using the mixed methods translation and consensus generation approach. This is a three-step process. In step-one, panelists independently translate all items and then independently rate every translation so that the translations are categorized in to inappropriate, modifiable and appropriate. In step-two, modifiable translations are modified, rated independently and categorized in to inappropriate or appropriate translation. In step-three, a consensus discussion is made on items categorized as appropriately translated in step-one and step-two, and ranked to get the best translations .[53] TB-related stigma will be measured at the end of the second month and at the end of the sixth month to provide time for social interaction after diagnosis and to distinguish between stigmatizing attitudes or behaviors from appropriate precautions to prevent TB transmission. A patient with smear positive pulmonary TB becomes non-infectious usually within 2-3 weeks except in the case of drug resistance.[9]

Treatment for depression: For patients with diagnosed depression by the health system, the appropriateness of their treatments (for the depression) will be coded as appropriate if they are in accordance with mhGAP interventions guidelines and inappropriate if they do not follow the recommended treatment approaches. According to this guideline, an adult endorsing at least two of the three core depression symptoms (depressed mood, loss of interest in activities, and decreased energy), three other features of depression (reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic view of the future, ideas or acts of self-harm or suicide, disturbed sleep, diminished appetite)

and having difficulties carrying out usual work, school, domestic, or social activities over the same last two weeks period in the absence of bereavement or other major loss in prior two months is identified as likely to have moderate-severe depression.[29]

The recommended treatment is providing psychoeducation, addressing existing psychosocial stressors, reactivating social networks, structured physical activity programme, offering regular follow-up, and considering antidepressants (fluoxetine and amitriptyline (as well as other tricyclic antidepressants).[29] The nurses and health officers of the health facilities who are the main care providers have been trained by the health system and the drugs are given to patients free of charge.

Data management

Data will be checked for consistency and completeness by supervisors, double-checked by the principal investigator and double-entered to EpiData 3.1 by experienced data entry clerks. Then, it will be exported to SPSS version 20 for cleaning and analysis. Hard copies of the data will be stored in a locked cabinet and consent forms will be separated from the data.

Data analysis

Data will be analyzed using SPSS version 20. Descriptive statistics will be computed to describe the socio-demographic characteristics of participants and to summarize the distribution of each of the dependent (outcome) and independent variables. We will check to see whether refusal or losses to follow up is associated with socio-demographic characteristics by testing the statistical significance of differences between refusals and consenters and those lost to follow-up versus those retained at 6 months in terms of age, sex, and level of education.

The prevalence of probable depression among TB patients at baseline will be determined by computing the proportion of patients scoring ten and above on the PHQ-9 scale. The same analysis will be carried out at endline and the magnitude of the difference between the two measurements (baseline and endline) will be calculated and the statistical significance tested using McNemar test for repeated measures. Determinants of depression at baseline will be examined using logistic regression with depression as a dependent variable and socio-demographic characteristics, symptoms of TB, perceived social support, and substance use

included as predictors. The proportion of TB patients that scored below ten on PHQ-9 at baseline but who had scores of ten and above at the end of the second month will be computed to determine incidence (risk) of depression at two months. This will be repeated at six months.

The change in depressive symptoms (PHQ-9 scores) over the three data collection points will be analyzed using multilevel mixed effect model by setting measurement occasions as level-1 and individual TB patients as level-2 of the analysis. Level of disability, substance use, presence of additional chronic illnesses, level of perceived social support, perceptions of patients about TB, and appropriateness of depression treatment will be predictors at level-1; socio-demographic characteristics of the individual will be predictors at level-2. We have selected this analysis approach as it does not require complete data over measurement occasions, equal interval of measurement for each case, or sphericity assumptions.[54-57]

The effect of depression on the treatment pathways of TB patients will be analyzed using binary logistic regression. The pathways followed by participants to access care will be entered as separate dependent variables after coding each of the different pathways as zero (if specific pathway not followed) or one (if specific pathway followed), depression will be included as an independent variable. We will adjust for socio-demographic characteristics.

To determine the effect of depression on the classical outcomes of anti-TB treatment, logistic regression will be carried out at the end of sixth months with the treatment outcomes (interrupted, defaulted, completed) as dependent variables and depression as an independent variable. We will adjust for substance use, stigma, co-morbid illnesses, socio-demographic factors, medication side effects, perceived social support, and perceptions of the patient about TB. Although multinomial logistic regression could handle the mutually exclusive treatment outcomes as values of one dependent variable with more than two categories, we have elected to use logistic regression in order to simplify the interpretation of our results.

The change in quality of life and disability levels over time will be modeled by setting measurement occasions as level-1 and individual patients as level-2. In this analysis, PHQ-9 scores, substance use, presence of additional chronic illnesses, level of perceived social support,

appropriateness of depression treatment, level of TB-stigma, medication side effects, and perceptions of patient about TB will be modeled as level-1 predictors and socio-demographic characteristics of the individual will be predictors at level-2.

All the necessary assumptions will be tested and the findings will be reported before inferential statistics are calculated. Statistical tests will be considered significant when p-values are less than 0.05 and 95% confidence intervals will be presented throughout.

Ethical considerations

The proposal has been ethically cleared by the Institutional review board (IRB) of College of Health Sciences, Addis Ababa University on 23/07/2014, number 027/14/Psy. Informed written consent will be obtained from every participant. Finger prints will be taken from consenting illiterate participants. Patients identified as having PHQ-9 scores ten or above or endorsing the suicide item of PHQ-9 will be referred to nurses trained in mental health interventions by another project working in collaboration with the Ministry of Health of Ethiopia. We will give each participant 30.00 Birr ($1.50) to compensate them for the time they spend with us. This amount of money is enough to cover a bottle of soft drink and some breakfast. We will not give any other incentives.

Dissemination plan

Findings will be disseminated through publications in peer reviewed journals and conference presentations. Summary reports will be submitted to health institutions concerned and policy makers. Community meetings will be held to disseminate findings to the local community, including study participants.

Limitations of the study

We have used PHQ-9 (a screening tool) to measure depression which may lead to error of categorizing patients in to exposed and not exposed at baseline. However, this will not compromise the work of capturing the change in depression scores overtime.

Currently, health institutes are actively strengthening tracing mechanisms in order to decrease treatment default and treatment interruption. This work may mean that those who are otherwise more likely to default or interrupt treatment may complete their treatment, which

may, in turn, weaken any association between the exposure and these outcome variables. There may also conceivably be a "treatment effect" of study participation in terms of improving depressive symptoms and encouraging people to adhere to treatment. In this low income setting, people may have undiagnosed co-morbid illnesses and our method of capturing co-morbid illnesses may not be strong. Quality of life will be measured using a single item and we will therefore not obtain detailed information on the various dimensions that make up this construct. In addition to that, our conclusions cannot be applied to MDR-TB patients and patients on retreatment for TB.

Strengths of the study

The study will provide much-needed evidence about the impact of co-morbid depression upon the course and outcome of TB. The longitudinal study design will allow us to estimate the incidence of depression among people engaged with TB treatment. The observation of depression-tuberculosis co-morbid patients from treatment initiation to completion date will allow us to investigate whether TB treatment alone may be sufficient to reduce depressive symptoms. The study will enable us to investigate the impact of depression in determining the course and outcome of TB, independent of the effects of other factors such as socio-demographic variables, stigma, perceived social support, substance use, and co-morbid illnesses such as HIV. So far as we are aware, this study will be the first in Ethiopia, or any African setting, to examine the potentially important role of depression in determining pathways to TB care.

Expected benefits of the findings

Our findings will contribute to a sparse evidence base about mental health, TB and other chronic diseases in low and middle income countries. We hope that other researchers will be encouraged to investigate important questions in this area. We anticipate that study findings will contribute to awareness raising among Ethiopian clinicians and service providers about the potential impact of co-morbid depression upon the course and management of chronic disease, as well as informing future plans and policies related to the delivery of mental health care in primary care and other healthcare settings in Ethiopia.

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COMPETING INTERESTS: None

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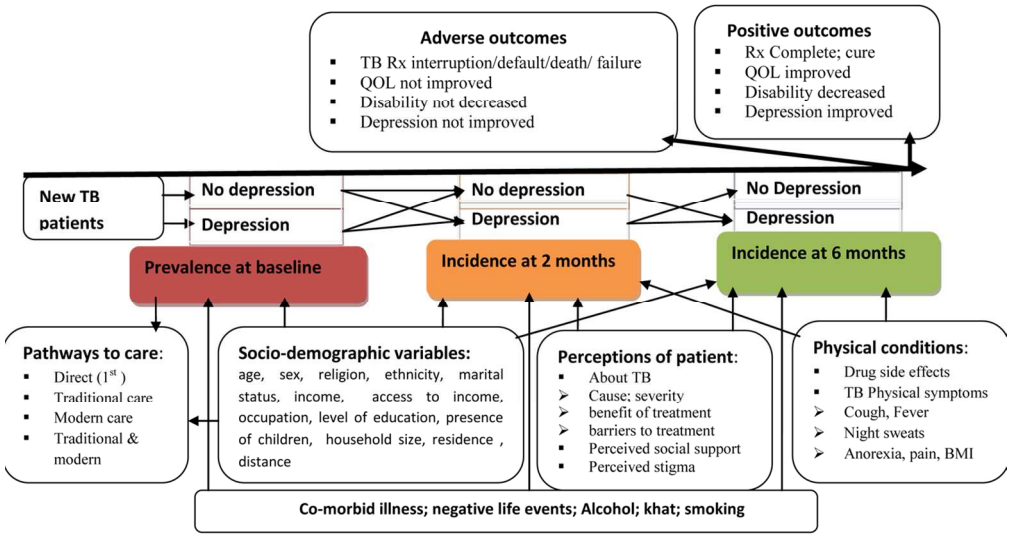

Figure 1: Conceptual framework of the study
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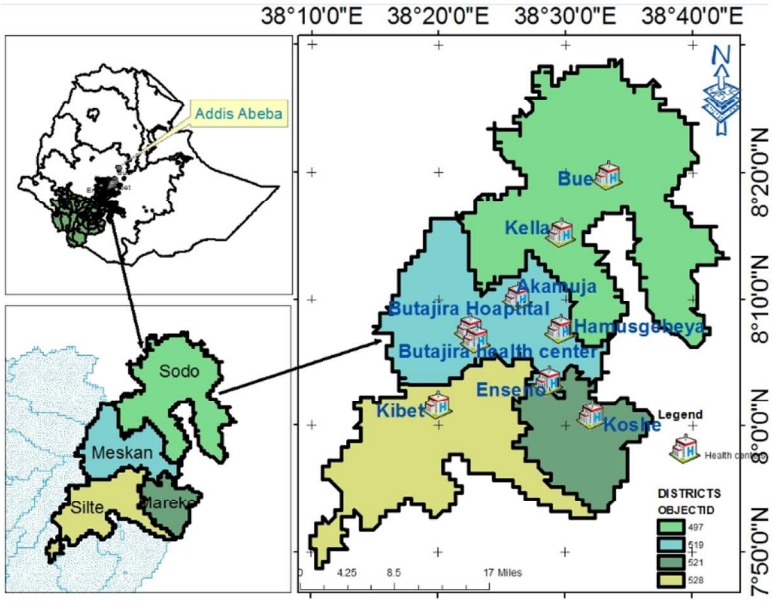

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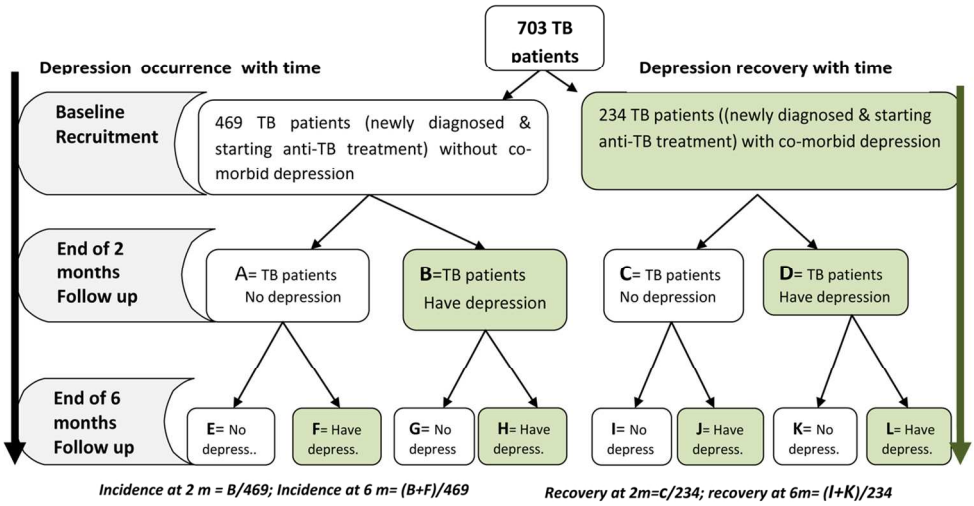

Figure 3: Schematic illustration for analyzing effect of tuberculosis on depression
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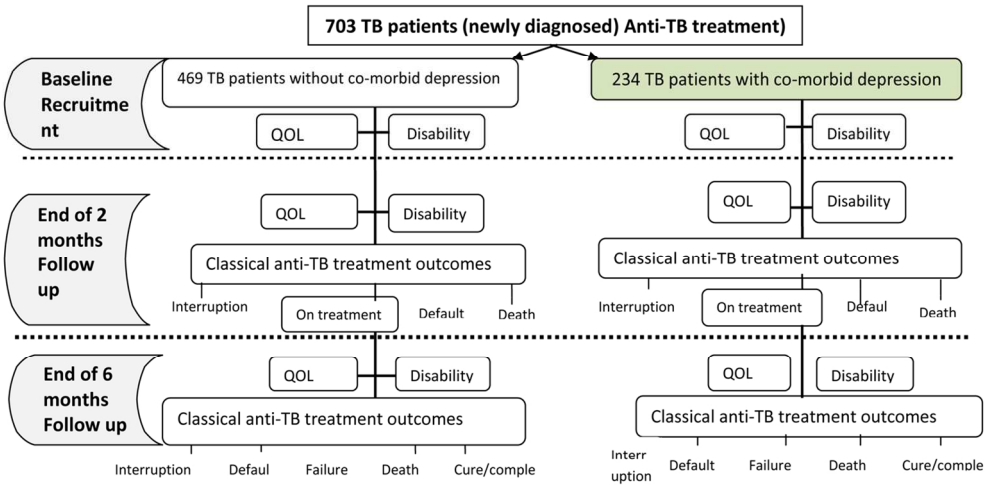

Figure 4: Schematic illustration for analyzing effect of depression on tuberculosis
127x76mm (300 x 300 DPI)