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CHALLENGES OF TUBERCULOSIS CONTROL IN SOUTHWEST ETHIOPIA: TREATMENT DELAYS, COST, AND OUTCOMES

BY: ABYOT ASRES SHETANO

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List of Original papers

This dissertation is based on the following four papers, which will be referred to in the text by Roman numerals:

I. Asres A., Jerene D., Deressa W., Tuberculosis Treatment Outcomes of Six and Eight month Treatment Regimens in Districts of Southwestern Ethiopia: a comparative cross-sectional study. ***BMC Infectious Diseases (2016) 16:653***

II. Asres A., Jerene D., Deressa W., Pathways to Anti-tuberculosis Treatment Initiation among Cases on Directly Observed Treatment Short course in districts of Southwestern Ethiopia. A cross-sectional study (INFD-D-17-01386, ***BMC infectious diseases ,under review***)

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IV. Asres A., Jerene D., Deressa W. Delays to treatment initiation is associated with tuberculosis treatment outcomes among patients on Directly Observed Treatment Short course in southwest Ethiopia: a follow-up study (**BMC Pulmonary Medicine (2018) 18:64**

Acronyms and abbreviations

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AAU	Addis Ababa University
BCG	Bacille Calmette-Gue´rin
CDR	Case Detection Rate
CI	Confidence Interval
COPD	Chronic Obstructive Lung Disease
CPT	Cotrimoxazole Prophylactic Therapy
DOTS	Directly Observed Treatment Short Course
DST	Drug Susceptibility Test
6EH	Six months treatment with Ethambutol (E) and Isoniazid (H) combination
Epinfo	Epidemiological Information
EPTB	Extra Pulmonary Tuberculosis
ETB	Ethiopian Birr
FDC	Fixed Drug Combination
HBC	High Burden Countries
HIV	Human Immunodeficiency Virus
HCF	Healthcare Facility
HCP	Healthcare Provider
IPT	Isoniazid Preventive Therapy
IQR	Inter-quartile range
IRB	Institutional Review Board
MDG	Millennium Development Goal
MDR TB	Multi Drug Resistant Tuberculosis
MTB	Mycobacterium Tuberculosis
NGO	Nongovernmental Organization
NTLCP	National Tuberculosis and Leprosy Control Program
NTP	National Tuberculosis Control Program
OR	Odds Ratio
PAS	Para-Amino salt of Salicylic acid
PHCU	Primary Healthcare Unit

PPD	Purified Protein Derivative
PPM	Public-Private Mix
PTB	Pulmonary Tuberculosis
4RH	Four months treatment with Rifampicin(R) and Isoniazid (H) combination
RR	Relative Risk
SD	Standard Deviation
SDG	Sustainable Development Goal
SNNPR	Southern Nation Nationalities and Peoples Region
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TSR	Treatment Success Rate
US$	United States Dollar
VIF	Variance Inflation Factor
WHA	World Health Assembly
WHO	World Health Organization
XDR TB	Extensively Drug Resistant Tuberculosis

Summary

Background: Tuberculosis (TB) is among the major public health problems over the world. Thus, global efforts have been designed to combat three distinct, but overlapping humanitarian, public health, and economic burdens posed by the TB illness. Timely case detection and treatment of cases have been a focus and priority in the prevention and control of TB. However, long delays to initiate anti-TB treatment have been reported for which evidences on predictors of the delay and impact of the delayed treatment on outcomes are limited. Elimination of catastrophic costs posed by TB illness to patients and households has taken attention in the latest end TB strategy. On the other hand, evidences on magnitude and drivers of patient cost across continuum of TB care are scarce in Ethiopian setting. Treatment regimens play a vital role in reducing time delays to treatment and cost spent across continuum of TB care, and improving outcomes. Nonetheless, evidences on the interdependence among delays, patient cost of care and outcomes in the era of shortened treatment regimen is scanty in Ethiopian setting.

Objectives: The aims of the dissertation were 1) to compare outcomes of six and eight-month TB treatment regimen, 2) to determine time delays to initiate anti-TB treatment and its predictors, 3) to assess pre-and post-diagnosis patient costs for TB care and 4) to examine association between delayed anti-TB treatment initiation and treatment outcome.

Methods: A blend of cross-sectional and longitudinal studies were conducted among 735 TB cases on treatment and 790 patient records from 14 public health facilities of Bench Maji, Kaffa and Sheka zones in Southwest Ethiopia. The cases were selected using multistage cluster sampling technique. Both primary and secondary data were gathered and/or extracted using structured questionnaire from January 2015 through June 2016. For comparison of outcomes across the six and eight month regimen, patient clinical profiles and outcomes were extracted from unit TB register of cases registered during 2008 through 2014. Data for the cases on treatment were collected at two points; 1) at enrollment when patients' sociodemographics, care-seeking practices, direct and indirect costs of TB care seeking were collected and 2) at the end of treatment when treatment practices, patient cost of TB treatment and outcomes were inquired. The data were entered in to Epi-Data and processed on SPSS version 21 and STATA version 13. Since the cost data were right skewed, analysis was made on natural logarithm and reported in corresponding antilog. Bivariate and multiple logistic, linear, and log-binomial regression models were fitted to identify predictors of delays, cost, and outcome. In all the statistical tests, necessary assumptions were checked and significance judged at $p<0.05$.

Results: The overall treatment success among cases registered during 2008 through 2014 was 88 % (85.3% vs 90.6%, p=0.02 among those treated for eight months with 2ERHZ/6HE and six months with 2ERHZ/4RH regimens, respectively). Thus, 4RH continuation phase treatment adjusted Odds Ratio [aOR=0.55,95% CI;(0.34,0.89)], weight gain at the end of second month treatment [aOR=0.28, 95% CI; (0.11, 0.72)] predicted lower odds of unsuccessful outcome. On the other hand, age [aOR=1.02,95%CI; **(**1.001,1.022**)]**, rural residence [aOR=2.1,95%CI;(1.18,3.75**)]** and HIV co-infection [aOR=2.39,95%CI;(1.12,5.07**)**] independently predicted higher odds of unsuccessful outcome.

TB patients had spent a median [inter-quartile range (IQR)] of 55(32-100) days to initiate anti-TB treatment since onset of illness (total delay). Similarly a median (IQR) of 25(15-36) and 22(9-48) days had been elapsed respectively to initiate care seeking (patient delay) and anti-TB treatment since first consultation (provider delay). Thus 54.6% of the total delay was attributed to provider (health system) and the rest to the patient. Prior self-treatment (aOR: 1.72, 95% confidence interval [CI]:1.07-2.75), HIV co-infection (aOR: 1.80, 95% CI: 1.05-3.10) and extra pulmonary TB (aOR: 1.54, 95% CI: 1.03-2.29) independently predicted higher odds of patient delay. On the other hand, initial visits to health posts or private clinics (aOR: 1.42, 95% CI: 1.01, 2.0) and delayed to seek care (aOR: 1.81, 95% CI: 1.33-2.50) significantly predicted higher odds of provider delay.

Since onset of illness, TB patients totally incurred mean [(standard deviation (±SD)] of US$244.71(±0.1) for care seeking and treatment. Thus mean (±SD) US$108.0(±0.1) and US$117.0(±0.1) were respectively incurred during pre-diagnosis and post-diagnosis periods. Mean (±SD) out of pocket patient expenditures during pre-and post-diagnosis were US$21.46(0.16) and US$43.80(±0.1) respectively. Total indirect and pre-diagnosis costs constitute 70.6% and 53.6% of the total cost respectively. Patient delay (adjusted coefficient (β_{adj})= 0.004, p<0.001), provider delay (β_{adj} =0.004,p<0.001), number of visited healthcare facilities (β_{adj} =0.17,p<0.001) and diagnosis at private facilities (β_{adj}=0.16,p=0.02) independently predicted increased pre-diagnosis cost. Similarly, rural residence (β_{adj}=0.27,p<0.001), hospitalization (β_{adj}=0.91,p<0.001), patient delay (β_{adj}=0.002,p<0.001) and provider delay (β_{adj} =0.002,p<0.001) predicted increased post-diagnosis costs.

The overall treatment success among the prospectively enrolled cases was 89.7% (86.7% vs. 92.6%, p=0.01) respectively among those initiated anti-TB treatment beyond and within 55days

of onset of illness). Accordingly, treatment initiation beyond 55days of onset [Adjusted Relative Risk (aRR)=1.92, 95%CI:1.30, 2.81),treatment center being hospital (aRR=3.73, 95%CI:2.23, 6.25), and HIV co-infection (aRR=2.18, 95%CI: 1.47, 3.25) independently predicted higher risk of unsuccessful treatment outcome. In contrast, weight gain at the end of second month treatment (aRR=0.40, 95%CI: 0.19, 0.83) predicted lower risk of unsuccessful outcome.

Conclusions:

The switch of continuation phase TB treatment regimen from 6EH to 4RH has brought significantly higher treatment success that verified applicability of the regimen change in resource constrained and high burden countries. TB cases in the study area elapsed too long time to initiate care seeking and treatment. The delays are attributed to the patient, disease and health system related factors. Throughout the care seeking and treatment pathways, TB cases incurred substantial direct and indirect cost for TB care despite the "free TB service". The delay to initiate anti-TB treatment was significantly associated with increased patient costs and risk of unsuccessful outcome. Patient and health system attributes predicted both costs incurred across continuum of TB care and treatment outcome.

Recommendations

Promotion of early care seeking for TB through community level awareness creation; involving both formal and informal providers can minimize patient delays. Moreover, improving diagnostic and case-holding efficiencies of both private and public healthcare facilities can reduce delays to treatment and risk of unfavorable outcomes. On the other hand, adoption of patient centered TB care, reimbursement mechanisms of costs and scale up of the national community and social insurance schemes to the study area can reduce the financial burden on patients. Finally, further studies are required to explore reasons for patient and provider delays using qualitative designs, costs of TB care, and its impacts on household and health system.

Keywords: TB, Patient delay, provider delay, direct cost, indirect cost, pre-diagnosis cost, post-diagnosis cost, treatment outcome, longitudinal, Ethiopia

1. Introduction

1.1. Background of the study

Tuberculosis (TB) is a chronic infectious disease mainly caused by mycobacterium tuberculosis (MTB). It typically affects the lungs often called pulmonary tuberculosis (PTB) but can affect almost all body organs. The main sources of infection are those untreated smear-positive PTB from whom the bacilli transmits via airborne route during coughing or sneezing [1-3]. Globally, two billion people are infected with TB of whom about 10–15% develop active disease at some stage later in life. The progression from infection to active TB disease is governed by exogenous and endogenous risk factors [4-6]. In Human Immunodeficiency Virus (HIV) infected people, the rate of progression is much higher at about 10-15% per year [7, 8]. First-line drugs that can cure around 90% of TB cases have been available since 1950s [9]. Unless TB cases are treated in the earliest five years, 50% die, 25% cure and 25% remain sick and infectious [10].

Tuberculosis has been recognized as a global problem and declared a public health emergency by the World Health Organization (WHO) in 1993 at a time when an estimated 7-8 million cases and 1.3-1.6 million deaths occur each year [11]. Since then, different global strategies including, Directly Observed Treatment Short course (DOTS) [12, 13], collaborative TB/HIV interventions [14], stop TB strategy [15] and end TB strategy [16] have been designed and implemented . The global efforts to control TB have three distinct, but overlapping humanitarian, public health, and economic dimensions [12]. The humanitarian concern relates to alleviation of illness and death among patients through patient-centered approach and timely treatment. Thus effective treatments of patients decrease disease transmission within communities that respond to public concern. The economic dimension relates to the reduction of direct and indirect costs to the individuals and society. Implementations of the strategies have been expanded across the globe and brought decline in death rates [17]. Thus an estimated 49 million lives were saved between 2000 and 2015 [18].

Despite implementations of the strategies for decades, TB remained to be among the major public health problems over the world. Globally, in 2015, 10.4 million incident cases and 1.4 million deaths were estimated to occur. Thus TB became among the top 10 causes of death ranking above HIV/AIDS [18]. Since 1990s TB mortality rates have been falling in all WHO regions, but the fall is relatively little in Sub-Saharan Africa where about 20% case fatality was

reported [18]. The high rates of mortality in the sub-Saharan Africa is because of the sharp HIV-related increase in TB incidence [19]. The global TB morbidity and mortality pose an enormous economic burden. On average, a TB patient loses 3 to 4 months of work which corresponds to up to 30% annual household earnings and 0.52% loss of the world's gross national income [20].

Tuberculosis has been recognized as a major public health problem in Ethiopia and efforts to control it began since early 1960s [21]. Accordingly, the country has been adopting different strategies and targets recommended for TB control [22, 23].The first 2011 national TB prevalence survey revealed smear positive PTB prevalence of 108/100,000 of which 55% were not detected till the date of survey [24]. In 2015, about 205,463 new cases [25] and 29,000 deaths were estimated to occur in the country [18] when only 125,801 (61%) were notified to National TB control Program (NTP) [25]. TB has been the 4th and 6thcause of death in females and males, respectively [26]. Ethiopia is among the 14 TB, TB/HIV and Multi-Drug Resistance (MDR) TB High Burden Countries (HBC) [18].

1.2. Statement of the problem

Effective treatment of TB cases has been one of the pillars in TB prevention and control across different global strategies designed to date. Accordingly, different treatment regimens have been recommended for adoption among countries. The latest treatment guidelines [27] recommended six months treatment with rifampicin combination throughout both the intensive and continuation phases of the treatment periods. However, regimens without rifampicin had been considered safer in developing countries owing to irregular treatments and high absentee rates [9, 28]. Ethiopia has adopted a regimen replacing six months of Ethambutol and Isoniazid (6EH) with four months of rifampicin and Isoniazid (4RH) continuation phase treatment as end of 2011 for all new adult cases of TB [23]. Patients are required to visit weekly with the 4RH [23] unlike monthly visit during the 6EH continuation regimen [22]. Frequent visits to collect drugs are reported to adversely affect treatment adherence among patients [29] that ultimately lead to worse outcomes. A continuation phase treatment with 4RH elsewhere has demonstrated lower rates of unsuccessful outcomes and costs [30, 31]. A continuation phase treatment with 4RH and 6EH among HIV negatives, respectively, predicted 8.8% Vs 13.3% mortality, 5.2% Vs 10.4% failure/relapse and $23.64 and $26.07 average costs per patient [30]. Given the challenges of frequent patient visit with the new regimen, effect of the change on treatment outcomes in Ethiopia setting is not documented.

Timely case detection and treatment of cases under proper case management conditions have been a focus and priority in the prevention and control of TB [16, 32, 33]. When diagnosis of TB is delayed, patients go without treatment for longer period and transmit the infection. Thus, each infectious case will result in as many as 20 to 28 secondary infections that ultimately increase the infectious pool [34-37]. The delays to treatment could be due to delayed initiation of care seeking that constitutes patient delay or delayed diagnosis after seeking care that constitute provider delay. Consequently, analysis of TB transmission dynamics has stressed that delays to diagnosis present a major obstacle to the control of TB [34].

Delays to TB treatment have been studied in different parts of the world including Ethiopia. A review of studies reported median patient delay of 30days and provider delay of 7-28days [34, 38]. Studies from different parts of Ethiopia also reported longer delays to initiate treatment for TB with median patient delay of 20-90 days [39-41] and provider delay of 6-34days [39, 41-43]. The long delays are attributed to female gender, older age, low awareness about TB, repeated visits to health facilities, visiting lower level health care facilities and traditional healer [44, 45]. Subsequent to the prevailing long delays in Ethiopia, identification of barriers for diagnoses and treatment delays have been set as a national priority research agenda [46]. However, available studies in the country are limited to only few parts of the country (northern) [40, 47, 48], smear positive PTB cases [43], focused on cases presenting to either health centers [42] or hospitals [48] but not both. In addition, the studies were conducted before the introduction of six-month treatment in 2011. Shorter treatment regimens motivate TB suspects to seek care and treatment early [49]. However, complete picture of the patterns of delay at different health care setups in the era of reduced treatment duration is scanty in Ethiopia.

Delayed detection and treatment of TB result in more serious illness by the time of diagnosis, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance [50-54]. It is also reported that the high mortality rate among people living with HIV is also partly explained by delays in TB treatment [34, 35]. In contrast, a study in Tel Aviv reported no association between treatment success and delay [55]. Despite the prevailing long delays and controversial evidences on association between delay in seeking treatment and outcomes, evidences on the effect of treatment delays on outcomes are very limited in Ethiopia.

Delays to treatment represent a time span in which additional costs are incurred [56]. The high perceived or actual cost of TB care seeking and treatment result in delays for diagnoses [52, 57-

59] and poor treatment adherence [60]. Both the delays and poor adherence in turn leads to the development of MDR TB and extensively drug resistant TB (XDR TB) [61] those require much higher cost of care [62].Though TB care services are said to be provided for free, patient and household incur potentially catastrophic direct and indirect costs for TB care. Studies in Nigeria and Yemen, respectively, reported that seeking care and treatment of TB totally costs a median of US$592 per household [63] and mean cost of US$ 108.4 [64]. A study in Ethiopia also reported median costs of care seeking per patient incurred by patient, companion and the public health system were US$16 , US$3 and US$3, respectively [65]. In Ethiopia, household out-of-pocket expenditures are the major sources of funding for prevention and control of TB amounting to 63% of the total resources spent in 2008 [66].

In Ethiopia, only few studies exist on cost of TB to patients. The few studies exclusively dealt on cost of care seeking and diagnoses [65] and cost effectiveness of treatment observation modalities [67]. In addition the studies were conducted when the TB treatment regimen required less frequent patients visits to health facilities unlike the current regimen that requires patients visits as frequent as daily to weekly to the health facilities throughout the treatment period [23]. Hence, evidences on the patient financial burden posed by TB care seeking, diagnoses and treatment is lacking particularly in the era of reduced treatment regimen.

2. Literature Review

2.1. Epidemiology of tuberculosis

2.1.1. Etiology and mode of transmission

Tuberculosis is one of the oldest chronic infectious diseases known to affect humans. It usually affects the lungs often called PTB but other organs are also involved. TB is caused by bacteria belonging to the *MTB* complex (*M. bovis,M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti and M. mungi*) of which the most frequent and important agents of human disease are *MTB* and *M. bovis*. It is a rod - shaped bacterium which was discovered by Robert Koch in 1882 [1, 3, 68]. Mycobacteria are often neutral on Gram's staining but once stained, it cannot be decolorized by acid alcohol that dictates their classification as acid-fast bacilli (AFB). MTB had several characteristic proteins include those in purified protein derivative (PPD) tuberculin, a precipitate of non-species-specific molecules obtained from filtrates of heat-sterilized, concentrated broth cultures [1-3].

Tuberculosis is a communicable disease that usually transmits from infectious patients (smear positive PTB) via airborne droplet. The droplet nucleus produced from an infectious case is 1– 5 microns in diameter and aerosolized during coughing, sneezing, speaking, laughing or singing. An episode of cough may produce as many as 3000 infectious droplet nuclei equivalent to as many as 105 AFB/mL. The droplet then may remain suspended in the air for several hours and may gain access to the terminal air passages when inhaled [1-3, 68]. Studies revealed that culture positive sputum smear-negative PTB patients can also transmit infection attributing about 13% of transmission [69].

2.1.2. Risk factors of transmission and disease

Development of active TB is a two-stage process comprised of exposure to infection and infection to active disease. The processes are governed by both exogenous and endogenous risk factors. The risk of transmission and infection are both mainly governed by external factors. The risk of transmission increased by overcrowding, bad coughing hygiene, smear status of source and other conditions that prolong the length of exposure including delayed diagnoses [1]. Whereas the progression from exposure to infection is determined mainly by bacillary load in the sputum, duration of contact, the proximity of an individual to an index case, local air circulation, indoor air pollution, social and behavioral risk factors including smoking and alcohol [5, 6]. After infection, disease can develop at any time through reactivation of a previously acquired

(latent) infection or through exogenous re-infection. The risk of disease development after infection is governed by endogenous host factors. The risk of disease is much greater in the 5 years following infection and decline as the time interval increases [4, 70, 71].

Approximately 10-15% of those infected with MTB will develop TB disease at some point in their lives. In about 5% of infected cases, the progression occurs within the first two years of infection and the remainder over their lifetime [68, 70]. So far studies have well demonstrated that HIV infection, malnutrition, young/old age, diabetes mellitus, indoor air pollution, alcohol consumption, use of immunosuppressive drugs, and tobacco smoke significantly increase the risk of active disease development [5, 6]. In HIV infected and other immunocompromized individuals, the risk of progression to disease is higher at about 10% per year [7, 68, 72]. Further studies have also reported the risk of active disease is associated with male sex, family history of TB, history of asthma [73] being illiterate and possessing few goods [74].

2.1.3. Clinical manifestation and diagnosis

The clinical manifestations of tuberculosis are quite variable and depend on a number of factors including host (age, immunity, and concomitant diseases), severity, site of infection (PTB, EPTB) and microbial (virulence) factors. Before the advent of HIV, approximately 85% of reported tuberculosis cases were limited to the lungs. For PTB cough is the most common symptom which becomes sputum productive and subsequently with haemoptysis as the diseases progress. Other symptoms including fever, loss of appetite, weight loss, weakness, night sweats, and malaise are also common, but are more difficult to quantify since they may relate to coexisting diseases. Thus, patients presenting with these symptoms represent TB suspect [3, 75].

Definite diagnosis of TB requires bacteriologic examination through microscopy and/or culture of sputum or other clinical specimen. Accordingly, bacteriologic examination through sputum smear microscopy and then culture and drug susceptibility testing (DST) have been recommended method of TB diagnosis across the different TB control strategies [3, 15, 75]. A case of TB is bacteriologicaly confirmed (definite) or one in which a health worker diagnosed TB (clinically diagnosed) and has decided to treat the patient with a full course of anti-TB treatment. A definite case of TB is a patient with *MTB* complex identified from a sputum or clinical specimen, by sputum smear microscopy, culture or by a newer method such as molecular line probe assay [27, 76].

TB cases have been categorized in to different forms based on anatomical site involved, bacteriologic result, history of anti-TB treatment and HIV co-infection [27]. Thus, new cases are those never taken anti TB treatment or taken for less than one month. Cases that have taken anti TB treatments for at least one month are classified as previously treated cases including return after default, relapse, or return after treatment failure. Based on the anatomical sites involved, TB case can be pulmonary when lungs and/or other sites are involved and extra pulmonary when only organs other than lungs are involved. Pulmonary TB cases can further be classified as smear positive when one or more sputum smear specimens are positive for AFB and smear negative when sputum smear is negative but culture-positive for MTB or clinician decisions to treat with full course of anti-TB, radiographic abnormalities suggestive of active TB [27].

2.1.4. Treatment regimens

Before the advent of chemotherapy, 30-40% of TB cases used to die within a year and 50-70% within five to seven years after the onset of TB illness [9]. The first chemotherapy for TB, streptomycin was discovered in the mid-1940s, which led to cure and reduction of mortality for majority of cases [1, 77, 78]. However, shortly after the introduction of streptomycin therapy, resistance to the drug and poor adherence of patients were reported [79]. Thus, cure of TB required concomitant use of at least two agents to which the organism was susceptible. This became evident with the discovery of para-aminosalicylic acid (PAS) and Isoniazid [1, 80] at which time the therapy lasted for18-24months. Subsquent to discovery of Ethambutol that substituted PAS, treatment duration shortened to 18months [1]. In 1960's administration of 12 month treatments composed of Thiacetazone, Isoniazid and streptomycin for the first 2 months followed by Thiacetazone and Isoniazid for 10 months were taken as standard treatment [3, 9]. A standardized treatment means that all patients in a defined group receive the same treatment regimen regardless of where they are treated. Following the introduction of rifampicin in the early 1970s, effective short-course chemotherapy that lasted for less than 12 months was heralded. In 1982 with the augmented potency of isoniazid/rifampicin with pyrazinamide, treatments regimens became reduced to 6-month course of triple-drug regimen as standard therapy [1].

The Short-course regimens comprised of an initial, or bactericidal, phase called intensive that is aimed to kill bacilli and make patients non infectious and a continuation, or sterilizing, phase which eliminate persisting mycobacteria to prevent relapse [1, 3, 9]. To ensure patient adherence to treatment and ultimately cure among patients, direct observation of treatment and provision of

fixed-drug-combination (FDC) products have been recommended that have led to launch of the DOTS strategy [13]. Since then, WHO has been recommending treatment guideline for adoption across countries. Accordingly, the latest WHO guideline recommends 2-month initial phase of [Isoniazid(H), Rifampin (R), Pyrazinamide(Z) and Ethambutol(E) (2RHZE)] followed by a 4-month continuation phase of RH(4RH) for the treatment of virtually all forms of new TB patients in both adults and children [27].

Response to TB therapy should be monitored in order to facilitate cure, treatment completion, identify, and manage adverse drug reactions. Hence, monitoring of clinical and/or bacteriologic responses including weight monitoring, clinical symptoms, and bacteriologic responses through sputum microscopy/culture has been recommended [1, 3, 27]. Finally, treatment outcomes has been ascertained as per standard definitions issued by WHO that comprises of cure, treatment complete, lost to follow-up, treatment failure, and death. The sum of those completed treatment and cured constitute treatment success and the rest constitute poor or unsuccessful treatment outcomes [27].

2.1.5. Distribution of tuberculosis cases and deaths

Tuberculosis has been recognized as a global problem and declared a global public health emergency by WHO in 1993 at which time 7-8 million cases and 1.3-1.6 million deaths had been reported each year [11, 81]. To date, TB still causes ill health and death among millions of people each year. Globally, in 2015 10.4 million incident cases were estimated of TB of which 61% and 26% respectively occurred in Asia and African Region. The 30 high TB burden countries accounted for 87% of all estimated incident cases worldwide. The estimated incident cases corresponded to global average of 142 cases per 100 000 population that varied from under 10 per 100 000 population in most high-income countries to 150–300 in most of the 30 high TB burden countries. In the same year, 6.4 million cases of TB were notified to national TB programmes. Of those notified cases, 6.1million were incident cases (new and relapse). Similarly, among the notified cases, 62% were males and 90% were adults [18].

Though short-course regimens of first-line drugs that can cure around 90% of TB cases have been available for decades, TB is one of the top 10 causes of death worldwide, and caused more deaths than HIV/AIDS. Globally, in 2015, about 1.4 million TB deaths were estimated between

HIV negative and an additional 0.39million deaths among HIV infected. About 84% of TB deaths among HIV-negative people occurred in the African and South-East Asia those comprised 86% of the global deaths. The deaths among HIV negatives corresponded to 62% of deaths being in men, 25% in women, and 13% in children. Globally, in 2015 the estimated number of TB deaths among HIV-negative people was equivalent to 19 per 100 000 population, and 24 when TB deaths among HIV-positive people were included. The death rate varied from less than one TB death per 100 000 population in many high-income countries to more than 40 deaths per 100 000 population in most of the African Region and in five high TB burden countries in Asia [18].

In 2015, 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally had had Drug Susceptibility Test (DST) for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients. Thus an estimated 340 000 cases among notified TB patients were MDR/RR-TB that constitute 3.9% of new and 21% of previously treated cases. China, India, and the Russian constitute 45% of the global total cases of MDR/RR-TB. There were about 250 000 deaths from MDR/RR-TB in 2015 [18].

Of the incident TB cases notified in 2015, 55% had a documented HIV test result of whom 11% had HIV. TB patients with documented HIV test result were highest (81%) in the African Region where the burden of HIV-associated TB is highest. Similarly, the proportion of TB cases co infected with HIV was highest in countries of the African Region that exceeded 50% in parts of southern Africa. Globally in 2015, 78% of those TB cases co infected with HIV were on antiretroviral therapy (ART) [18].

2.2. Global strategies for the control of tuberculosis

Interventions for the control of TB date back to the pre-chemotherapy era where patients had been segregated and provided with fresh air, surgical and nutritional interventions [1]. Since the late 1940s that demarked the chemotherapy era, chemotherapies were discovered and brought dramatic effects towards the control of the disease. Apparently, the first public health act for the prevention of TB was the decree of Lucca, Italy in 1699 that required notification of cases of TB by physicians [9]. Since then different localized efforts had been implemented in different localities despite the widespread distribution of the disease. As a result, control of the disease had seemed to be achieved in industrialized countries and attention for TB had ceased for decades. Global efforts to control TB were initiated in 1991, when a World Health Assembly

(WHA) resolution recognized TB as a major global public health problem. Subsequently, in 1994, a global strategy, DOTS was launched to respond to the resurgence of TB in all areas of the world [11, 13, 82].

2.2.1. Directly Observed Treatment Short course (DOTS)

The DOTS strategy was an internationally recommended strategy composed of five key components namely government commitment; case detection by predominantly passive case-finding; standardized short-course chemotherapy under direct observation of health workers, regular drug supply; and monitoring and evaluation [13]. As part of the strategy, targets of detecting 70% of new smear positive cases, and curing 85% of them by the year 2000 were established and endorsed by the WHA resolution [11]. In the absence of HIV, achieving these targets would have reduced the incidence rate by 11% and the death rate by 12% per year. But without greater effort to control, the annual incidence of TB was expected to increase by 41% per year between 1998 and 2020 [83]. Later in view of the slow progress in many high burden countries, the targets were postponed to 2005. To alleviate impediments for the attainment of the targets, the control framework was expanded through reinforcing the five elements of DOTS which applies for HIV associated and drug resistant TB [12].

2.2.2. TB/HIV collaborative activities

Tuberculosis is the leading causes of HIV-related morbidity and mortality that accounts for about a third of Acquired Immunodeficiency syndrome (AIDS) deaths worldwide. HIV is also the most powerful known risk factor for the development of active and recurrent TB with annual risk ranging from 5-15% [84, 85]. In response to the recognition of the influences of the two diseases on one another, a need for unified health sector strategy was emphasized. Accordingly, the Stop TB department and the department of HIV/AIDS of the WHO published an interim policy on collaborative TB/HIV activities [84]. Later based on evidences from different studies and best practices of programmatic implementation, policy on collaborative activities was designed [85]. The recommended activities were establishment and strengthening of mechanisms for delivering integrated TB and HIV services; reduce the burden of TB on HIV and vice versa. To reduce burden of TB on people infected with HIV, Intensified TB case-finding and high quality anti-tuberculosis treatment, Isoniazid preventive therapy (IPT), early antiretroviral therapy (ART) and TB Infection control in health-care facilities and congregate settings were recommended [85]. On the other hand, to reduce the burden of HIV in patients with presumptive and diagnosed TB,

provision of HIV testing and counseling, HIV prevention interventions, co-trimoxazole preventive therapy (CPT) and ART were recommended [85]. Thus, between 2000 and 2015, TB treatment alone averted an estimated 39 million deaths among HIV-negative people. Similarly, TB treatment supported by ART averted an additional 9.6 million deaths among HIV-positive people [18].

2.2.3. Stop TB strategy

The stop TB strategy was designed in 2005 [15] to realize the target of dramatic reduction of global burden of TB by 2015 consistent with the Millennium Development Goals (MDGs) [86]. The strategy was designed to attain four major objectives namely to achieve universal access to high-quality diagnosis and treatment by people with TB, to reduce the suffering and socioeconomic burden associated with TB, to protect poor and vulnerable populations from TB, TB/HIV and MDR-TB, to support the development of new tools and enable their timely and effective use. The strategy both builds and expands the DOTS strategy to address remaining constraints and challenges for the control of TB. The strategy had six principal components namely pursue high-quality DOTS expansion and enhancement, address TB/HIV and MDR-TB and other special challenges, contribute to health system strengthening, engage all care providers, empower people with TB and communities and enable and promote research. The strategy adopted MDG targets of halting TB incidence and death by 2015 compared to the 1990 levels [15].

2.2.4. Impacts of the TB control strategies

Cognizant with the implementation of the global strategies, progress have been made with control of TB. The number of treatment cohorts treated with DOTS increased from one million in 1995 to 2.6 million in 2011. Since 1995, 56 million were successfully treated that raised treatment success rate from 57% in 1995 to 87% in 2011 [87]. Though the DOTS technical package has improved overall treatment success, it had no effect on case detection [81]. In addition, direct observation of treatment stipulated as pillar of the DOTS strategy, had not shown significance difference in cure rates compared to self-administered treatment. On the other hand, multiple visits to health care facility for the DOTS service pose tremendous burden including financial and social stigma. Thus, adoption of patient centered TB care is worthwhile for proper control of TB [88]. The proportion of TB patients who knew their HIV status improved from 40% in 2011 to 55% in 2015 globally but proportions as high as 81% was achieved in the

African region. On the other hand, coverage of ART among TB/HIV co infected patients improved from 49% in 2011 to 78% in 2015 [18].

Assessment of MDG targets of TB control indicated that the target was achieved on a worldwide basis, and in 16 of the 22 HBC. Globally, the TB mortality rate fell by 47% between 1990 and 2015. The target of a 50% reduction in TB mortality was met in four WHO regions; the Americas, the Eastern Mediterranean, the South-East Asia, and the Western Pacific Region and in 11 HBC. Similarly, TB prevalence fell by 42% between 1990 and 2015.The target of halting the prevalence was achieved in three WHO regions – the Region of the Americas, the South-East Asia Region and the Western Pacific Region and in nine TB HBC [18].

2.2.5. The End TB strategy

The 65th WHA held in May 2012 called upon WHO to develop a new post-2015 TB strategy and targets [89]. Thus strategy named end TB [16] consistent with the Sustainable Development Goals (SDG) was designed and endorsed by member states at the 67th WHA. The strategy has ten components organized under three pillars and four underlying principles. The principles of the strategy include government stewardship and accountability, strong coalition with civil societies, protection, and promotion of human right, ethics, and equity, and adaptation of the strategy and target at country level. The pillars of the strategy include integrated patient center care and prevention, bold policies and supportive systems and intensified research and innovation [16].

The integrated patient centered care and prevention pillar is composed of four components 1) early diagnosis and universal drug susceptibility testing, systematic screening of contacts and high risk groups,2) treat all people with TB including drug resistant with patient support,3) TB/HIV collaborative activities and management of co-morbidities and 4) preventive treatment of persons at high risk and vaccination against TB. Furthermore, the strategy comprised of targets to be attained by 2035 categorized in to three milestones five years apart to each other (2020, 2025 and 2030). Accordingly 95% in TB deaths, 90% in TB incidence equivalent to less than 10cases per 100,000 population) reductions compared to levels in 2015 and no affected families facing catastrophic costs due to TB by 2035 were set [16]. In line with the strategy, a five years (2016-2020) global plan to end TB was set by stop TB partnership [90]. Thus, three people-centered targets called the 90-(90)-90: reach 90% of all people who need TB treatment,

including 90% of people in key populations, and achieve at least 90% treatment success were set. The plan further emphasized the need for paradigm shift: a change in the way we fight TB at every level, in every community, in every health facility and in every country to end TB [90].

2.3. Tuberculosis control in Ethiopia

2.3.1. Ethiopia: the country

Ethiopia is located in Northeast Africa, commonly referred to as Horn of Africa, and is situated east of Sudan, north of Kenya, south of Eritrea, west of Djibouti, and northeast of Somalia. The country covers about 1.1 million Km^2 area of land endowed with diversified topography, climate, and more than ethnic groups' belonging to diverse religions. As per the projection of the 2007 census, total population of the country has reached 101.7 million in 2016 constituting second populous in Africa. The male to female ratio is 1.01 and 55% of the population is above the age of 15 years. The country is organized in to nine regional states and two city administrations those comprised of many zones and woredas [91].

2.3.2. Healthcare delivery in Ethiopia

The current healthcare delivery in Ethiopia is organized in to three levels those comprised of different healthcare facilities (Annex 2). The tiers of care include primary healthcare units, secondary level, and tertiary level of care. The primary health care unit (PHCU) is expected to provide basic preventive, promotive, curative, and rehabilitative healthcare for about 60000 to 100000 peoples in the catchment. The PHCU comprised of health posts, health centers, and a primary hospital. The secondary level health care unit, general hospital is expected to render healthcare services to about 1.5million peoples in the catchment. The tertiary hospitals or tertiary level of care is expected to provide advanced curative services to about five million peoples in the catchment. There were about 3564 health centers, 16480 health posts, and 241 hospitals operating throughout the country. In 2016, there were 1.4 per 1000 population different types of health workers operating across different health care facilities [26]. TB diagnosis and treatment services are provided across all the tires of care. However, all health posts and few newly built health centers provide mere observation of treatments of those patients diagnosed at hospitals and health centers. Many preventive and few curative healthcare services including child immunization, family planning, maternity, TB, malaria and HIV/AIDS treatments are provided for free [25] .

Healthcare delivery in Ethiopia is financed from variety of sources including the government treasury, bilateral and multilateral donors, household out-of-pocket expenditures, international

and local nongovernmental organizations (NGOs), private employers, and insurance schemes [92]. Cognizant of the under financing of healthcare in the country, government of Ethiopia endorsed a health care financing strategy in 1998 [66]. The strategy envisioned a wide range of reform initiatives including revenue retention and systematizing a fee-waiver system for the poor, standardizing exemption services, setting and revising user fees, introducing a private wing in public hospitals, outsourcing nonclinical services, and health insurance schemes. Thus in 2016, 10.4% of households were enrolled in community based health insurance [26]. Following the different healthcare financing initiatives, overall healthcare expenditure in 2010/11 has reached Birr 26.5 billion (US$1.6 billion) of which 34% were from household out of pocket expenditure. Similarly, per-capita healthcare expenditure has reached Birr 334.81 (US$20.77) in 2010/11 which was far below the US$60 recommended by the WHO [92].

2.3.3. National tuberculosis control program

Tuberculosis had been recognized as a major public health problem in Ethiopia long ago. Efforts to control TB began in the early 1960s with the establishment of TB centers and sanatoriums in three major urban areas. Subsequently Central Office (CO) of the National Tuberculosis Control Programme (NTCP) was established in 1976. In 1994, the National Tuberculosis and Leprosy Control programmes (NTLCP) became integrated and organized under the co-ordination and technical leadership of the CO. Later in June 2000, the NTLCP was accommodated under Disease Prevention and Control Department, which was previously named Epidemiology /AIDS Department. The former CO was then named Tuberculosis and Leprosy Control Team (TLCT) and became fully integrated into the general health services by the end of 2001 [22, 93]. In 1999 a global standardized TB prevention and control strategy, DOTS, was piloted in Arsi and Bale zones of the Oromia Region that subsequently scaled up throughout the country [22]. Later, the country has been adopting different strategies and targets recommended by WHO, including TB/HIV collaborative activities [85] and stop TB strategies [15] for which respective implementation guidelines have been adopted [23].

Subsequent to the adoption of different global control strategies, progress has been made with the control of TB. Accordingly case detection rate rose from 11% in 1995 to 64% in 2012 and treatment success among new smear positive from 61% in 1995 to 89% in 2015. Treatment cohorts registered have also shown improvement and rose from 5.1 thousand in 1995 to 91 thousand in 2011. Between 1995 and 2011, a total of 879 thousand new cases were treated [87]. As per the reports of the Ministry of Health, nearly 92% of hospitals and 95% of health centers

had been implementing DOTS in 2011. In addition, TB treatment follow-up had been started in 2100 health posts giving overall of 4577 public and 317 public–private mix DOTS facilities [94].

Despite achievements in global targets of TB control, TB remained among the major public health problem in the country. TB accounts for 4th and 6th causes of death among females and males respectively [26]. The first national TB prevalence survey in 2011 revealed smear positive PTB prevalence of 108/100,000 of which 55% were detected at the time of survey [24]. In 2015, about 205,463 new cases [25] and 29,000 were estimated to occur in the country [18] when 125,801 (61%) were notified to National TB control Program equivalent to 191 per 100,000people [25]. Of the notified TB cases in 2015, 77% had documented HIV test result of whom 8% were positive for HIV. In the same year, of those HIV co infected TB cases, 79% were on ART. In the same year a total of 25,000 deaths equivalent to 26 per 100,000 people were reported among HIV negatives and 3900 deaths equivalent to four per 100, 0000 among HIV positives were reported in Ethiopia. Thus, Ethiopia had been listed among the 22 and lately among 14 TB, TB/HIV, and MDR TB HBC. In 2015, a total of US$ 81million was required for prevention and control of TB in Ethiopia of which 11% was from domestic source, 51% international aid and 38% unfunded [18].

2.3.4. Tuberculosis control in Southern Nation Nationalities and Peoples Region

The Southern Nation Nationalities Region (SNNPR) is one of the nine regions in Ethiopia constituting 118,000sq.km and 20% of the national population. In the Region, TB is 4th cause of total admission and 3rd cause of inpatient deaths [95]. The nationally adopted TB control strategy, DOTS, was piloted in four health facilities in four zones as a vertical program in 1995. Later, the program became integrated into the general health service and scaled up to all zones and health facilities. Thus in 2011 about 601 health facilities were providing DOTS equivalent to DOTS coverage of 96% (hospitals and health centers). The number of TB cases registered for treatment has increased from 8,339 in 1997 to 24,772 in 2012 of which about 62% are smear positive [95, 96].

A retrospective trend analysis of the DOTS implementation in pilot zone of the region reported increased proportion of patients treated with short course chemotherapy (7% to 97%), reduced default rate (38% to 18%) and increased treatment success (38% to 73%) [97]. Similarly, analyses of ten years experiences of TB control showed, 136,572 cases were registered for treatment between 1995 and 2004, of which 47% were smear-positive, 25% were smear-negative

and 28% were extra-pulmonary tuberculosis (EPTB). As a result, the smear-positive case notification rate has increased from 45 to 143 per 100,000 populations between 1995 and 2004. In same time, the treatment success rate rose from 53% to 85% whereas the default and failure rates decreased from (26% to 6%) and (7% to 1%) respectively [98].

2.4. Challenges of tuberculosis control

2.4.1. Delays to seek care and treatment

Delays to initiate care seeking and treatment for TB can happen at home where patients are unable or do not want to seek care for their TB illness or at the health facility where longer time is spent for diagnoses and treatment initiation. The delay at home constitutes patient delay and that spent at health facilities represent health system or provider delays. The sum of the patient and provider delays or time elapsed since onset of illness to treatment initiation constitutes total delay. So far, an optimum cutoff for the delays at home and health system has not yet established. Thus, most studies across the globe describe the delays using median time spent between onsets of illness to first consultation of formal healthcare [48], diagnoses, and treatment initiation. There were also studies described the delays using time cutoff defined by the authors. Accordingly, time spans ranging from 1 to 4 weeks for patient delay [34, 39, 99], and 3-28 days [41, 99, 100] for provider delay were used to dichotomize the delays.

The different forms of delays prevail across the globe. A systematic review in high and low income countries reported median total delay, patient delay and health system delay of 25–185 days, 4.9–162 days and 2–87 days respectively [101]. Another review also indicated a total diagnostic delay of 60–90 days [44]. The level of delays vary across different settings with median total delays of 8 (0-45), 18 (0-191), 35 (21-56), 35(21-56), 21 (7-49) days at referral hospital, district hospital, health center, health post/clinic and community respectively [102, 103]. A multicountry study in the Eastern Mediterranean Region showed patient delay ranged from a mean of 9.9 days in Pakistan to 69 days in Somalia and system delay ranged from 5 days in Iraq to 90.7 days in Pakistan [104]. A cross-sectional study in an intermediate TB incidence setting also showed average patient's and total delays of 44 and 103 days respectively [105]. Studies reported 25% of the patents had delayed for longer than 42 days in China [106] and 30 days in Nepal [107] where 67.4% of the patients delayed the consultation beyond 30days.

Cross-sectional studies in African countries revealed median patient delay of 30 days in Angola [34] and 4 weeks in Kamapla, Uganda [38]. Similarly provider delays of 7days in Angola [34] 4weeks in Uganda [38] were reported. The study in Uganda further reported 24.1% of the patients had long total delay of >14 weeks and 29.3% had long health system delay of >6 weeks [38]. Another study in Uganda reported that patients present to drug shops or pharmacies (39.4%) and private clinics (36.8%) more commonly than government health units (14%) [35].

Findings from different parts of Ethiopia have also reported longer delays to initiate treatment for TB with median patient delay of 20- 90 days. Median patient delay of 30 and 90 days in Tigrai, and Amhara respectively, where 53 % of the patients had delayed for ≥30 days [39-41], 60 days in Addis Ababa [42], 20-63days in Afar, where 96% of the patients delayed for more than 21 days [43, 108] were reported. On the other hand, health service median delays of 6-34days were also reported ; 6days in Addis Ababa [42], 9days in Tigrai region [39], 21days in Amhara where only 9% of the patients were put on treatment within one month of the onset of their illness [41], and 34 days in Afar [43].

2.4.1.1. Factors associated with delays in seeking care and treatment

Studies have indicated that factors associated with patient delays are attributed to the patients' demographic and socioeconomic characteristics. A systematic review reported low income, rural life, unemployment, old age and female sex were consistently associated with patient delay [59]. Studies in Ethiopia and elsewhere have also reported rural residence [40, 48], illiteracy [40], subsistence farming [35], older age [99] as risk factors for patient delay. A study in Amazon showed that male gender and education less than secondary were associated with a 48% and 44% higher risks of longer patient delay respectively [50]. Similarly, a study in Malawi revealed social role construction for men hinder males from seeking cares early [109]. However, studies in Uganda [38] and Nigeria [99] respectively demonstrated female and male genders were independent predictors of system delay. In contrast, a study in Addis Ababa reported no significant difference in delay among socio-demographic factors [42].

Patient delays are also associated with the characteristics of the illness and other co-morbid conditions. Accordingly, coexistence of other lung diseases, negative sputum smear, extra pulmonary TB[48, 110], extensive radiologic abnormalities, absence of haemoptysis [106, 111] being smear positive [40, 111] and severity of illness at first presentation [43] are associated with patient delay. Studies also demonstrated that absence of cough, weight loss [112], fever, night

sweats and auscultation findings, presence of diabetes mellitus and cough as the only presenting symptom were significantly associated with patient's delay [105, 111].

HIV co infection had been reported to delay care seeking and retention in care. A systematic review reported contradicting reports on the association between HIV and delays. Patients with HIV sought a diagnosis for TB earlier than HIV-negative or unknown status [52]. In contrary, high awareness of AIDS, fear of learning their HIV status and a positive HIV test result or the stigma of being perceived to be HIV positive were reported to have longer delay [52, 113].

Patient perceptions towards the TB illness and their life styles were also reported to be associated with longer delays to seek care for TB. Studies have demonstrated that low awareness of TB [114], self or prescribed medication [112, 115, 116], lack of knowledge and mistrust of the TB control programme and stigma as risk factors of patient delay [44, 114, 117]. It was also reported that significantly longer delay of TB diagnosis among smokers [118] and those perceive smoking as a cause of TB [35, 38]. Furthermore patients who believe and knew TB is curable [35, 50] consume alcohol daily [35, 38] and perceive that tuberculosis was common [50] had longer delays. Studies in Ethiopia have also showed lack of awareness/misperceptions of causes of TB [40] and seeking care at out of DOTS facilities (holy water, traditional healer, private practitioners and drug vendors or non formal providers [40, 43], self treatment [41] were risk factors for the delay.

Studies have also reported that health system characteristics contribute to the patient delay. Accordingly, initial visit to government low-level healthcare facilities, private practitioner [112], or traditional healer [39] and longer walking distance/time to public facilities, service fee for TB care[43, 104], and profit-seeking behavior of providers[114] were reported as independent risk factors for patient delay. Studies in China [119] and Uganda [38] respectively showed 17-30% and 91% patients made more than 6 and median of 4 visits before diagnosis. Thus study in Zimbabwe [116] indicated having more than four visits to healthcare facilities before diagnosis predict longer provider delay.

Provider or system delays for diagnoses and initiation of treatment are also attributed to patient, disease and provider related factors. Systematic reviews showed low health care coverage, patient expenditures and entry into the health system by consulting a traditional healer or a non-skilled professional, long travel time for the return visit and longer waiting time to be

consistently associated with system delay [52, 59]. Studies in China indicated differences in districts, lack of knowledge and mistrust of the TB control programme, service fee for tests and treatments other than TB and profit seeking behavior of providers were independent predictors for provider delay [106, 114, 120]. Studies in Hong Kong and Taiwan attributed higher provider delay to patients and system characteristics including patient age older than 60 years, absence of initial sputum and chest X-ray examination, absence of haemoptysis and negative smear [111, 120]. On the other hand, diagnosis with Gene xpert predicted lower treatment delay among patients in Zimbabwe [116].

2.4.2. Cost of seeking care and treatment for TB

Economic burden of diseases can be ascertained by cost-of-illness (COI) studies that estimate the amount that could potentially be saved or gained if a disease were to be eradicated [121, 122]. It involves combining an epidemiological database with financial information to generate an amount valued in monetary terms about the costs of a particular disease [123]. Thus the aim of COI studies is to identify, measure, value, and sum the costs of a particular illness to reveal its economic burden across different bearers [124]. Illness-related costs incurred by patients constitute a severe economic burden for patients, households, the health system, and nation especially in low-income countries. High costs of illness lead to impoverishments that impair affordability and equitable access to health care [121, 122].

The costs of illness entail direct or explicit cost, indirect or implicit cost and intangible costs. The direct cost constitutes out of pocket expenditures for medical care (prevention, seeking care, diagnosis, treatment, and rehabilitation, etc) and nonmedical expenditures (transportation, household expenditures, relocating, property losses, and informal cares). The indirect or implicit cost refers to the forgone income due to productivity losses and subsequent income loss due to morbidity and mortality, borne by the individual, family, society, or the employer. The lost productivity or income could be due to inability to work because of the illness, loss of time due to visits to health facilities, or loss of job. Finally, the intangible costs are those cost of pain, grief, anxiety, and suffering which measures the psychological dimensions of illness. The different categories of the costs are usually further stratified in to time periods when the costs were incurred as those incurred prior to diagnosis, during diagnosis (prior to treatment) and costs incurred during treatment or rehabilitation (post diagnosis) [56, 125, 126].

In 2015, globally US$6.6billion budget were available for TB prevention, diagnosis and treatment in low and middle-income countries. Of the available budget globally in 2015, 84% were from domestic source with huge variation across countries. International donation accounted for 75% in 25HBC other than Brazil, Russia, India, China and South Africa (BRICS), 87% in low-income countries and 60% in lower middle-income countries [18]. An ecological study using mixed effects and generalized estimating equation models in the former 22 HBCs showed an increased in case detection, HIV testing, drug susceptibility testing, case notification and decrease in death of smear positive with increase in percent of NTP budget [127].

In Ethiopia, US$81million was available for TB prevention, diagnosis, and treatment of which 11% and 51% funded from domestic and international sources respectively. The rest 38% of the budget was unfunded [18]. The Ethiopian national health account (NHA) conducted in 2007/08 reported; a total of US$47.8 million was spent on TB prevention, diagnosis, and treatment. Households out of pocket expenditure were the major sources accounted for 63% of the total expenses. International donors and government respectively funded the rest 22% and 14% expenses. Of the resources spent, private for-profit hospitals, received 35% followed by providers and mangers of public health programs (22%). About 62% of TB funds were used for TB outpatient care, followed by other TB prevention services (17%) [66].

Although governments have been implementing ‘free TB service policy', TB care is posing tremendous financial burden in terms of time and productivity loss to both patients and their households [128, 129]. A systematic review in European Union countries revealed total average cost per-TB case of €10,282 for drug-susceptible TB, €57 213 for MDR-TB and €170,744 for XDR-TB. A total of 103,104 disability-adjusted life years were caused by 71,964 cases notified in 2012 in the European union equivalent to €5 361, 408 000 [130]. Similarly, a review from sub-Saharan Africa revealed costs per TB case varied from less than I$1 to almost I$600 or from a small fraction of mean monthly income for average annual income earners to over 10 times average annual income for low income earners [131]. A systematic review from middle and low-income countries also showed mean total costs ranged from U$55 to U$8198 for all types of TB, with a weighted average of US$847. On average, 20% of the total cost was due to direct medical costs, 20% to direct non-medical costs, and 60% to income loss. Half of the total cost was incurred before TB treatment. The total cost was equivalent to 58% of reported annual individual and 39% of reported household income [132].

Several studies have also reported high costs of TB across the different TB care pathways. A total average costs per episode of TB illness of US$1053 of which US$292, US$338 and US$422 were encountered before the start of treatment, during intensive phase and in continuation phase, respectively were reported in the former Soviet Union [133]. Median direct cost associated with TB of US$101 that represent 2.8 months of household income in Burkinafaso [134] and US$ 183 in Benin where 38% and 29% of the costs were spent during pre-diagnosis and intensive phase treatment respectively [135]. In Tigrai, northern Ethiopia, median cost of seeking care of US$27 per patient [65] were also reported.

Patients incur costs for TB care at the different stages of the diseases care pathway including, pre- diagnoses, diagnoses and treatment. A systematic review in Africa reported mean patient pre-diagnostic costs varied between US$36 and U$196, corresponding to 10.4% and 35% of their annual income respectively. The same review reported average patient treatment costs ranged between US$3 and US$662, corresponding to 0.2-30% of their annual income [136]. A synthesis of studies have also reported that low income patients, pay a total of US$ 149 to 724 for medical costs for the treatment course that represent 42% to 119% of the annual household income [60]. A cross-sectional study in Nigeria showed that median direct pre-diagnosis/diagnosis and indirect post-diagnostic/treatment costs of US$49 and US$416 per patient respectively. The indirect pre-diagnostic and treatment cost constitutes 79% of the total patient costs of US$528 [63]. A study in Burkinafaso also indicated that 72%, 95%, 68% and 50% patients respectively have incurred for pre-diagnosis, diagnosis, intensive phase and continuation phase treatments [134].

TB care also pose financial burden on households. A systematic review in Africa indicated total household treatment costs ranging between US$26 and US$662, accounting for 2.9-9.3% of annual household income [136]. Studies also reported that the median total cost of TB care per household was US$592; corresponding to 37% of median annual household income [63]. Further median costs for seeking care per patient incurred by escort of US$3 [65]. Following an episode of TB, household income reduced significantly and the proportion of households classified as poor increased from 54% to 79% [63]. On the other hand, communities perceived as high as two to five times higher costs than actually incurred cost for TB care [58].

Studies have also reported that health systems also incur cost for TB care that differs across the type of TB cases with mean cost per patient of US$ 34.0 and US$ 38.8 for pulmonary and extra

pulmonary TB treatment respectively. Of the costs, drug treatment for pulmonary and extra pulmonary TB represented 59.3% and 77.9% of total health service cost respectively [64]. A study in Ethiopia reported median costs of US$3 per patient was incurred by the public health system [65].

Patient and households use different coping mechanisms for the financial burden posed by the TB illness and care. A systematic review in Africa showed that 18-61% of patients received financial assistance from outside their household to cope with the cost of TB care [136]. A study in Nigeria reported that 47%, 9% and 32% of patients and households borrowed money, sold asset and both borrowed and sold asset to cope with cost of care [63]. In Ethiopia, illness costs coping strategies among rural households included waiver privileges, selling household assets, using savings and division of labor among household members to compensate for the loss of working time due to sickness. Thus, the study indicated financial and time costs of illness seemed to significantly contribute to the impoverishment of rural households [137]. A reduction of US$1.95 to US$0.9 and US$4.28 to US$3.24 median patients' income and household expenditure respectively compared to the pre illness time were also reported [138].

Different factors are reported to increase the amount of cost incurred by patients, households, and health systems. A study in Yemen reported differences in mean costs for pulmonary (US$108.4) and extra pulmonary (US$ 328) TB treatments where laboratory and X-ray costs account about (55.5%) of the EPTB treatment [64]. Moreover significantly higher median out-of-pocket costs for hospitalized (US$166.1) and ambulatory (US$94.16) cares, before (US$35.23), during (US$27.12) and after diagnosis (US$23.43) were reported [139]. A study in Ethiopia have showed that the total cost of diagnoses per patient was higher for women, rural residents; those who received government food for work support, patients with smear negative pulmonary tuberculosis patients and being diagnosed in places other than public diagnostic centers [65]. Being female and patient delays in seeking care in Zambia [57] and consulting private doctor in Bolivian city of Cochabamba [140] revealed as significant predictors of total patient cost. A study in Nigeria also reported no statistical significance association between total out-of-pocket spending and HIV status [139].

Health facility based treatment has been reported to incur higher costs compared to community-based treatments. A prospective cohort study in Sidama, southern Ethiopia showed community-based treatment reduced the total cost of care and successful treatment of a smear-positive

patient costs (US$61.7) which is 39% lower compared to the treatment at health facility (U$158.9) [67]. A study in Zambia also showed treatment costs incurred by patients on the clinic-based DOTS were more than three times greater than those incurred on the self-administered treatment strategy [57].

Cost of additional drugs and tests for adjunctive therapies during diagnoses and treatment of TB were reported to increase out-of-pocket expenditures. Studies in China revealed that patients charge per visit which amounts on average about 40 US dollars and additional drugs and tests expenditure [141] and repeated outpatient visits before diagnosis, over-prescription of drugs and prolonged treatments cost China [58] were reasons for high cost. Studies also indicated that high out-of-pocket costs and productivity losses are associated with hospitalization, adverse drug reactions, cost of drugs to 'protect' the liver, cost of diagnostic delay [128], MDR and XDR TBs those incur [62]. A study in South Africa revealed that per patient cost of care for XDR-TB per patient US$26,392, four times higher than MDR-TB (US$6772), and 103 times greater than drug-sensitive TB (US$257). As a result drug resistant TB consume about 32% of the total estimated national TB budget despite the fact that they constitute only 2.2% of the case burden [62]. Studies have shown that financial interventions including financing TB programs improved TB controls programs.

2.4.3. Unsuccessful treatment outcomes

The ultimate goal of any TB control programs is to reduce morbidity and mortality among patients and stop transmission through curing the infectious cases [9]. As a result, treatment of TB is not only treating an individual patient, rather it is a public health intervention. To this end, a treatment outcome of patient is crucial in ensuring reduced patient morbidity and transmission to others. TB treatment outcomes have been ascertained based on standard definitions issued by WHO. Thus outcomes of TB patients fall in to either cure, treatment complete, failure, death and lost to follow-up [23, 27, 89]. The cure and treatment completion rates constitute treatment success that has been taken among indicators of TB control programs. The other outcomes; death, lost to follow-up and treatment failure constitute unsuccessful or poor or unfavorable outcome. The treatment outcomes are associated with variety of patient, disease and health system related factors.

2.4.3.1. Treatment regimen and outcomes

Treatment outcomes of TB patients are dependent on adherence of health care provider to the standard treatment and patient to the prescribed anti TB therapy. Standardized anti-TB treatment regimens comprise of combinations of different drugs across the phases of treatment (intensive and continuation) [27]. The level of adherence to the standardized therapy is affected by variety of factors including, demographic, economic, patient-related factors, therapy-related factors, health care team and system-related factors [142]. Throughout the history of TB treatment, introduction of rifampicin has impacted in shortening of treatment duration and better outcomes [143]. Introduction of rifampicin for the continuation phase treatment among adults reduced treatment length from eight to six month [27].

A systematic review with meta analyses showed regimens utilizing rifampicin for only the first 1-2 months had significantly higher rates of failure, relapse, and acquired drug resistance, as compared to regimens that used for 6 months [31]. A study in Nigeria, reported significantly higher treatment success (85.2% vs. 77.8%) among patients treated with 4RH and 6EH continuation phase respectively. Thus, defaulting was significantly more frequent in patients who received 6EH (14.3%) vs. 4RH (5.5%). However proportion of treatment failure was not significantly different among the 6EH and 4RH continuation phase treatments [144]. In contrast a study from Uganda reported significantly lower failure/relapse among 4RH (5.2%) compared to 6EH (10.4%) continuation phase treatment for those HIV negatives [30]. The study further reported (12.4% vs 13.7%) relapse/failure among HIV positive respectively among patients treated with 4RH and 6EH during the continuation phase. Furthermore, significantly lower mortality 8.8% among 4RH and 13.3% among 6EH was predicted. Lastly an average treatment cost per patient was predicted at $26.07 for 6HE and $23.64 for 4RH [30].

2.4.3.2. Delayed TB treatment and patient outcome

Delays to diagnosis and treatment of TB result in more serious illness, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance [34, 53, 54]. A cohort study in Amhara region, northern Ethiopia showed patients with total delay of > 60 days were more likely to have unfavorable TB treatment outcome compared to those with total delay of<=60 days [145]. A case control study in public hospital in Johannesburg, South Africa attributed high mortality among TB patients in the first weeks of admission to late presentation of cases [146]. Similarly a study in China showed patient delay of more than 30days was risk

factor for non cure among TB patients on treatment [54]. In contrast, a study in Tel Aviv reported no association between treatment success and delay in treatment initiation [55].

2.4.3.3. HIV/AIDS and other co-morbidities as predictors of outcome

HIV has been reported to be a major risk factor for occurrence and poor treatment outcomes of TB [147-150]. Studies have reported that HIV co infection independent predict unsuccessful TB outcomes [151] including low cure, higher death [152] and lost to follow-up [153]. Compared to HIV negative, HIV positive TB patients had more than 13 times higher 10 year case fatality [8]. A prospective cohort study in Nigeria, reported significantly lower cure and higher mortality in HIV infected compared with non-HIV infected TB patients. However, there was no significance difference with lost to follow-up from treatment and treatment failures across the HIV status [154]. A retrospective cohort study in Hawassa, Southern Ethiopia [155] reported lower survival among TB HIV co infected patients.

The risk of death among HIV co-infected TB patients had been reduced by use of ART and prophylactic therapies for other opportunistic infections. An observational study among HIV infected TB patients in Thailand showed lower risk of death among those treated with ART CPT and fluconazole therapy [156]. However, a study from Thailand reported no association between CPT and death among TB/HIV co infected patients [157]. On the other hand ,the risk of death among HIV co infected TB cases increased with hospitalization at enrollment and low CD4 cell count [157] and the longer that ART was delayed during TB treatment [156].

2.4.3.4. Patient Clinical conditions and sociodemographic factors

Unsuccessful TB treatment outcomes are also associated with patient clinical condition, and the type of TB. Studies conducted in different settings reported that advanced chest X-ray findings [151] and lack of appetite as an initial symptom of TB disease [158] as independent predictors of unsuccessful treatment outcomes. Studies also revealed sputum smear positivity at enrollment [159] and being on retreatment patient category [24] were significantly associated with death during treatment. Moreover, remaining severely underweight or moving to a lower Body Mass Index(BMI) category while on treatment [160] or body weight <35Kg at initiation of treatment [24] predicted death among TB patients on treatment. On the other hand, Patients gained weight after 2 months of treatment had a significantly smaller risk of an unsuccessful treatment outcome compared to those lost their pretreatment weight [161, 162].

Patient demographic and economic conditions contribute for the occurrence of poor TB treatment outcomes. Studies on new TB cases have reported that older age [151, 152, 163], being male [159, 164, 165], low education level [158], having family size above 5 and unemployment [163] as an independent predictor of poor treatment outcomes. On the other hand, a study among re treatment cases in India, reported that default rate of 21.4% which was significantly higher among employed and illiterate [166].

2.4.3.5. Perceptions about TB, treatment setting and outcome

Patients' perception and knowledge also affect treatment outcome of TB treatment. A case control study among new TB patients in South Africa showed feeling ashamed to have TB, feeling better, drinking any alcohol and seeing a traditional healer during TB treatment, and not receiving adequate counseling about their treatment were significantly associated with default [167]. A Study among sputum smear-positive PTB patients in Nigeria showed patients with poor knowledge of tuberculosis had a higher risk of poor treatment outcomes [164]. Similarly a study in Pakistan reported those patients satisfied with their health care workers attitude were more likely to achieve cure [168].

Treatment observation, treatment setting, and person observing the treatment has also been reported to predict treatment outcomes of TB patients. A cohort study in urban Pakistan revealed that patients on clinic DOT observed by health care providers more likely achieved cure than those observed by family at home [168]. On the other hand, a case-control study among smear positive TB in Shaanxi Province, China reported that not having a treatment observer as independent risk factor for non cure [158]. Findings from studies in Ethiopia showed that treatment center were independent predictors for death [24] and treatment success in Addis Ababa[169] and higher treatment success rates were observed where treatment took place at peripheral centers in Hadiya Zone [97] or regional capital health center [165]. Studies also indicated that diagnoses of TB outside of the government TB control centers [158] and treatment centers were risk factors for non cure [164].

2.5. Rationale and significance of the dissertation

Though global strategies are relevant, investigation of local operational challenges is highly required in order to adapt to the local settings. Hence, local operational studies have been recommended and taken as a pillar for the different TB control strategies designed to date [89, 170]. Ethiopia has adopted treatment regimen change that recommended use of rifampcin throughout the six months treatment period. However, effect of the regimen change on treatment outcomes has not yet been well studied.

Delays to TB treatment prolong disease transmission, worsen illness, and increase cost of care those result in poor outcome among patients. Enabling achievement of high cure rates help to reduce transmission and attract the great majority of existing cases. Hence, it is imperative to have evidences on the patterns of delay and the consequences on cost of care and outcomes of among patients. The existing studies are limited to only few of the dimensions, despite the multifaceted and interlinked dimensions of the TB burden (humanitarian, public and economic). Specifically studies linking delay, cost, and subsequent outcomes among patients are limited in Ethiopian setting. Consequently comprehensive evidences on humanitarian, public and economic burdens those pose tremendous challenges on the control of the disease are limited in Ethiopia.

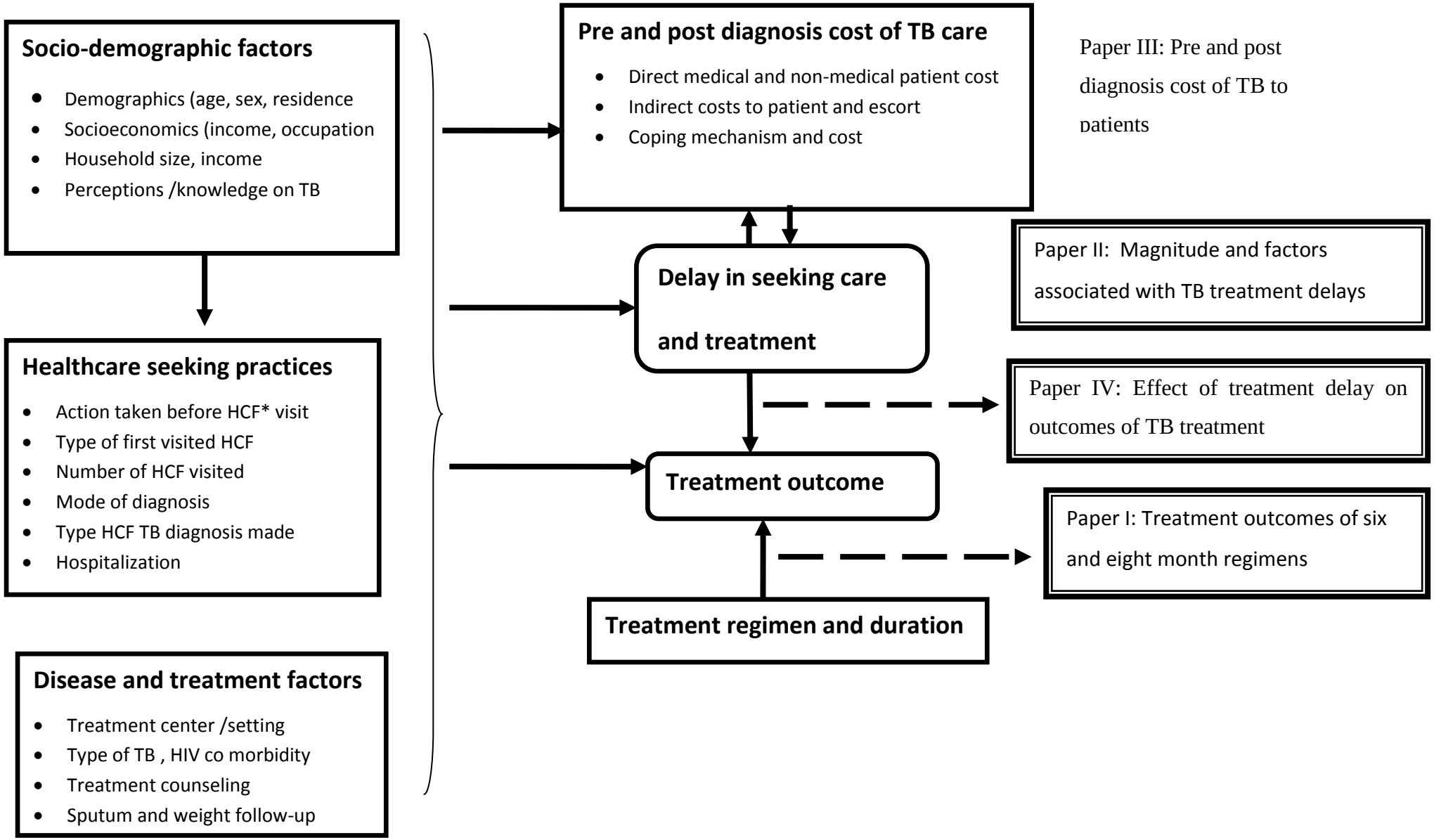
The study generated evidences on magnitude and predictors of treatment delays along with the association between delay and outcomes. Moreover, predictors of cost incurred by patients across the treatment pathways were assessed. Overall, the dissertation generated comprehensive evidences on the humanitarian, public and economic aspects of TB disease. So, the evidences support design of multidimensional interventions required to realize the targets of ending TB.

The evidences generated are important inputs to policy, program, practice, and future research. The unacceptable prolonged patient and provider delays imply for wide spread transmission of the TB illness to community at large and undesired outcomes to the patients. The delay potentially hampers an ambitious target of reducing 50% incidence and 75% mortality of TB by 2025. Hence, the evidence on magnitude of delays and their predictors are important inputs for policy and program actions targeting reduction of the delay involving patients, informal care providers, community, and healthcare providers (health system). Similarly, an ambitious target of no TB affected families to face catastrophic costs by 2025 has been set globally and adopted by the country. Evidences on amount of patient costs and their predictors will be inputs for designing financial protection mechanisms that ultimately supports the national and local programs targeted to elimination of costs posed by TB illness to the patient and households.

Moreover, the dissertation will be a baseline for future research needs on patient and provider delays, effective and efficient strategies to reduce delays to treatment and implications of the patient cost to the household impoverishment.

2.6. Conceptual framework of the study

To better understand the problem under study and guide the analyses of findings, a conceptual framework (Figure 1) was devised based on findings of literatures. The framework portrays factors underlying time delays to anti-TB treatment initiation, patient cost of care and treatment outcomes. Thus, it explains the interdependence of the time delays to initiate treatment, cost of care and ultimate treatment outcome. The delay to anti-TB treatment commencement was affected by patient, health system and disease attributes those ultimately predict the cost of care and outcomes. On the other hand, treatment outcomes of TB patients were also predicted by treatment regimen and duration. Finally, the conceptual framework indicated how each papers of the dissertation were linked to the aspects of the framework.



Healthcare facility

Figure 1: Conceptual framework for the analyses of predictors and interrelationships between delays, cost and treatment outcomes of TB treatment

3. Research questions

1. Is there a difference in treatment success among new TB cases treated with six compared with eight-month treatment regimens?
2. How long do TB patients elapse to initiate care seeking and treatment for TB?
3. What factors are associated with time delays to initiate care seeking and treatment?
4. How much do seeking care, diagnosis, and treatment of TB cost to patients?
5. What is the effect of treatment delays on treatment outcomes of TB patients?

4. Objectives of the dissertation

4.1. General objective

The general aim of the study was to assess treatment delays, cost, and outcomes of TB in districts of Southwestern Ethiopia.

4.2. Specific objectives

1. To compare outcomes of six and eight month treatment regimens of new TB cases (Paper I)
2. To assess magnitude and associated factors with TB treatment delay (Paper II)
3. To determine pre and post diagnosis cost of TB to patients (Paper III)
4. To evaluate effects of treatment delay on treatment outcomes of TB patients (Paper IV)

5. Methods

5.1. Study area and setting

The study was conducted in three zones of Southern Nation Nationalities and Peoples Region (SNNPR) one of the nine regions in Ethiopia. As per the projections by Central Statistical Agency (CSA) for 2014 [91], the region has a total population of 17,837,005 and it constitutes the third populous Region among nine Regions and two city administrations in Ethiopia. The Region is a home for more than 56 ethnic groups and located in the southern and southwestern part of the country. The Region is organized in to 15 zones and four special *woredas*. The potential health service coverage of the Region in 2011 was estimated to be 93%, but actual utilization, doesn't exceed 50% [96]. In the same year, 96% of the health facilities (22 hospitals and 632 health centres) were providing TB DOTS [96].

The three study Zones, Bench Maji, Kaffa, and Sheka are located at the southwestern border of the Ethiopia (Figure 2) bordering South Sudan to the west. As per the projection by CSA for the year 2014 [91] the zones harbor 2,064,102 inhabitants composed of almost all ethnic groups in the country. The zones are known for their coffee and tea plantations and gold mining those deploy peoples from almost all parts of the country. The zones are organized in to four town administrations and more than 26 *woredas* comprised of many kebeles. During the study period, the zones had one hospital each and more than 65 functional health centers in all the three zones. All of the three hospitals and health centers are providing DOTS of which the three hospitals and 27 health centers were providing TB/HIV collaborative activities [96].

Diagnosis and treatment of TB across the country is being provided based on an adopted national guideline that describe diagnostic and treatment standards [23]. Thus, diagnosis of TB is made using sputum smear microscopy and clinical signs. Treatment regimens on the other hand depend on type of TB, age, and other conditions. Accordingly, all new adult cases of TB had been treated for eight months with combination of Ethambutol(E), Rifampicin(R),Isoniazid(H) and pyrazinamide(Z) for first two months (2ERHZ) followed by Ethambutol and Isoniazid combinations for six months (6HE). However, as of 2011, the continuation phase regimen for new adult cases has been changed to four months (4RH) reducing total duration to six months.

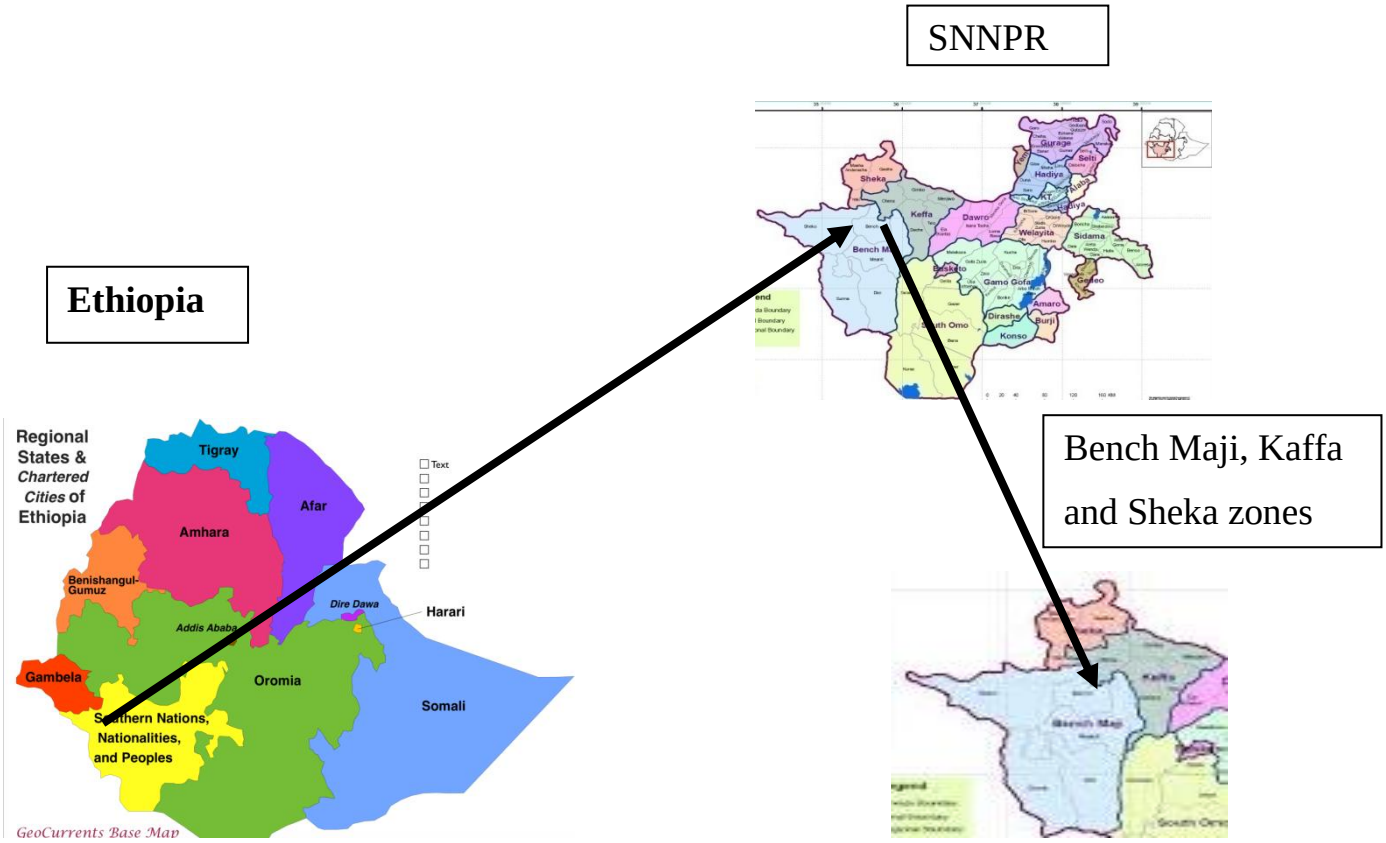


Figure 2: Map of the study area showing region and zones where the study was conducted

5.2. Study designs and period

Both cross-sectional and longitudinal study designs were employed to answer the research questions. Thus for paper I, comparative cross-sectional study design was used to compare outcomes of TB cases treated with the eight and six months regimen (before and after introduction of six months regimen). For paper II, pathways to anti-TB treatment initiation were described using cross sectional design so that magnitude of delays to treatment initiation was determined. For paper III, a longitudinal design was used to determine pre-and post-TB diagnosis costs incurred by patients from onset of illness through treatment. Finally, for paper IV, a follow-up study among those patients surveyed for determination of time delays was employed to ascertain effect of treatment delays on outcomes (Figure 3). Hence, patients were followed until earliest treatment outcome was observed.

The whole study project was conducted from January 2015 through June 2016.

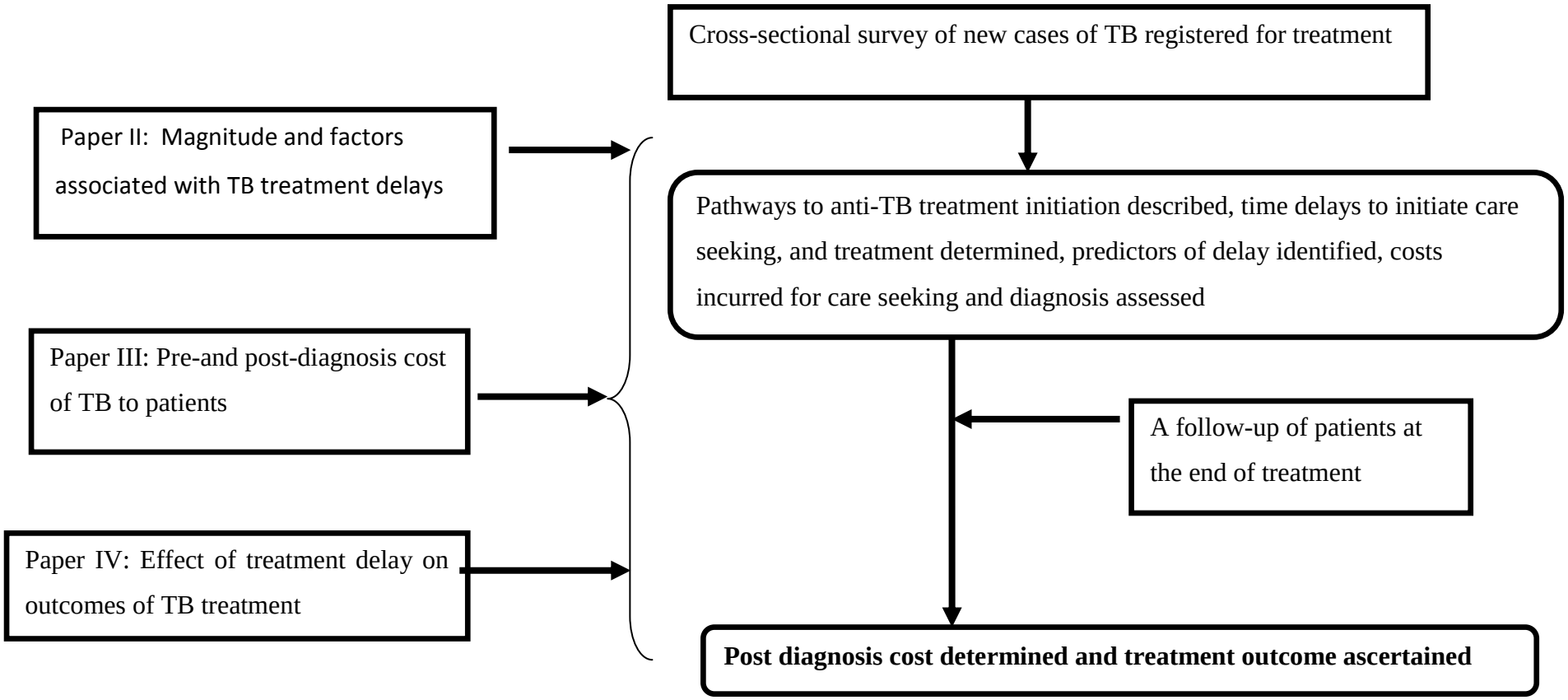


Figure 3: Schematic description of study designs used for the dissertation

5.3. Study population and sampling

5.3.1. Source and study population

For paper I, that compared outcomes of patients treated with the older eight months (2ERHZ/6HE) and current six months (2ERHZ/4RH) treatment regimens, the source population was all new cases of TB aged above 15 years who were registered during 2008 through 2014 at public healthcare facilities (HCFs). The years 2008 through 2014 were purposefully selected to accommodate cases treated before and after the introduction of new regimen in 2011. The age cutoff of 15 years was chosen since the regimen change introduced in 2011 was only for cases older than 15years. Thus, the study population was those patients older than 15years and registered at the selected healthcare facilities of the study zones during 2008 through 2014.

For papers (II-IV), the source population was all new adult TB cases aged above 18 years who were registered at all public HCF of three zones. Thus, the study population was those patients registered at selected HCFs in the three study zones.

5.3.2. Sample size determination

Sample size computation for the studies considered objectives and study designs. Accordingly, the calculations were made using StatCalc program of Epinfo and/or STATA version 13 at confidence level of 95%, power of 80% and ratio of comparable groups (r=1) .

Sample size calculation formula for single population

$$n = \frac{(Z_{\alpha/2})^2\, P(1-p)}{d^2} \qquad\qquad n = \frac{(Z_{\alpha/2})^2 \delta^2}{d^2}$$

where;

P is the estimated proportion of delay >30days

δ is the expected standard deviation

$Z_{\alpha/2}$ corresponding z score for significance level of (1- α)%

d is the desired precision (margin of error 5% for proportion and 5unit for mean)

For the two-population formula either of the following formula were used

$$n_1 = \frac{\left[Z_{\frac{\alpha}{2}} \sqrt{(1+\frac{1}{r})P(1-p)} + Z_{\beta} \sqrt{P_1(1-P_1) + \frac{P_2(1-P_2)}{r}} \right]^2}{(P_1 - P_2)^2}$$

$$n_1 = \frac{\left[Z_{\frac{\alpha}{2}} \sqrt{(1+\frac{1}{r})\frac{1}{P(1-P)}} + Z_{\beta} \sqrt{\frac{1}{P_1(1-P_1)} + \frac{1}{rP_2(1-P_2)}} \right]^2}{(\ln OR)^2}$$

p is pooled proportion $P = \frac{P_1 + rP_2}{1+r}$

r is ratio of unexposed to exposed or with outcome to without outcome of interest groups

Z_{β} Corresponding z score for power (1-β)

$Z_{\alpha/2}$ corresponding z score for significance level of (1- α)

p_1 is proportion of exposure/outcome among population 1

p_2 is proportion of exposure/outcome among population 2

n_1 sample size required from population 1 and $n_2 = rn_1$,

OR- is odds ratio

For paper I, the sample required from those treated with 2ERHZ/6HE and 2ERHZ/4RH was computed using proportion of death between the groups (Table 1).

For papers (II-IV) since the same population was studied, sample sizes calculated for each objective (papers) were compared and the largest of all was used. Thus, either single or two population formulas (as appropriate to objectives) were used. For the determination of proportion of patients delayed to initiate anti-TB treatment, a single population proportion formula was used with inputs of estimated proportion of those delayed for greater than 30 days of 53% [40], confidence level of 95% and margin of error of 5% gave 353 patients. Inputs used for calculation for the sample size for patient cost, identification of predictors of delay and its effect on outcome were presented in (Table 1) below.

Table 1: Sample sizes calculated for different objectives of the study

1. For comparison of 4RH and 6EH continuation phase TB treatment outcome					
Exposure variable	% Expected outcome in unexposed(6EH)	Odds ratio	Group treated with (4RH)	Group treated with (6EH)	Total
4RH	Death(13.3) [30]	0.416	256	256	512

2. For the assessment of factors associated with delay					
Exposure variable	% expected exposure in control(delay<=30days*	Odds ratio	Required Sample size		
			Delayed	Not delayed	Total
Illiteracy	37.8 delay [40]	1.7	228	228	456
Rural residence	40.4 delay [40]	1.9	155	155	310
Non formal treatment	33.9 delay [40]	2.61	71	71	142

3. For the assessment of effect of treatment delay on treatment outcomes					
Exposure variable	% Expected outcome in unexposed(delay<=30days)	% difference to detect	Required sample size		
			Delayed	Not delayed	Total
Delay >=30days*	3 [54]	7	194	194	388

4. For the determination of total patient cost and predictors of the cost				
Variable	Mean (US$)	Mean difference to detect (US$)	SD(US$)	Total sample required
Patient cost of care seeking among female	29.5[65]	5	14	250
TB treatment cost to patients at health facility	24.4[67]	5	12.2	190

*= median patient delay

As shown in the above table (Table1), the largest sample size among those computed for estimation of patient cost, magnitude of delay, factors associated with the delay and its effect on treatment outcomes was 456. Since cases recruited for the assessment of time delays to treatment were followed for both patients cost of care and outcomes, the largest sample size, 456 suffice for the rest of the objectives. Hence, considering design effect of 1.5 and non-response or loss to follow up of 10%, the final required sample for papers (II-IV) was 456*1.5+10%=752 cases.

For the comparison of 4RH and 6EH continuation phase treatment, the estimated sample was 512. Considering design effect of 1.5 and 10% incomplete records, 846 cases (423 each treated with 6EH and 4RH continuation phase) were required.

5.3.3. Sampling procedure

Three zones (Kaffa, Bench-Maji and Sheka) from SNNPR were purposefully selected. Then 10 *woredas* were selected from the zones based on proportional allocation and probability proportional to size (PPS). Selection of the *woredas* was based on probability proportional to size of the total TB cases notified during 2008 throgh 2014 for paper I and the preceding fiscal year for papers I-IV. After selection of *woredas*, all the health facilities providing TB diagnosis and treatment service were included. The samples for each HCF were determined based on proportional allocation referring to the TB case notification (Figure 4).

For (paper I), that compared 4RH and 6EH continuation phase TB treatment outcomes, treatment records of cases from the selected HCFs were categorized in to two groups. Those treated between 2008 and 2011 constitute continuation phase treatment with 6EH and 2012 to 2014 constitute continuation phase treatment with 4RH. Finally, unit TB number of all the cases registered in the two categories were extracted and entered into SPSS spreadsheet. So that the required samples from the two categories were drawn randomly.

For papers I-IV, after selecting HCF and determining cases required from each HCFs, all consecutive patients registered at the selected facilities during the study period were recruited until required samples were reached. Thus, the recruited cases were assessed for time delays to seek care and initiate treatment (paper II). Then, similar cases were followed to asses for post-diagnosis costs and final treatment outcomes.

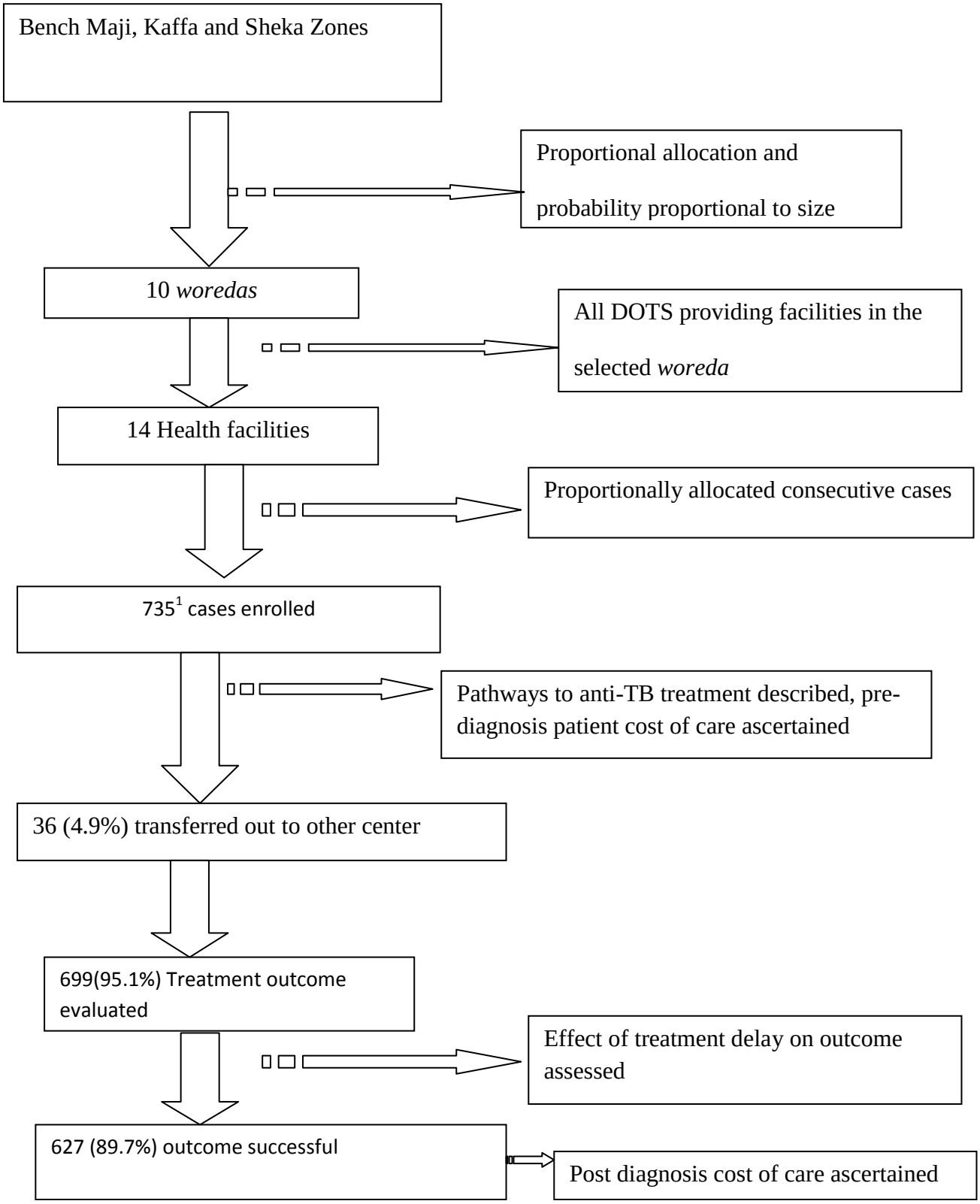


Figure 4: Schematic presentation of the sampling procedure and sample size analyzed

5.3.4. Inclusion and exclusion criteria

For the assessment of delay, cost and effect of delay on outcomes those new TB cases, older than 18years and on intensive phase of treatment at time of enrollment were included. Whereas cases unable to respond, died or lost to follow up or transferred out to other center before and after enrollment were excluded from baseline and end line surveys respectively. For the comparison of treatment, outcomes across six and eight month regimens, new cases and those older than 15years were included and those with missing treatment records were excluded from the study.

5.4. Study variables

5.4.1. Dependent variables

- Delays to anti-TB treatment
- Costs of TB illness to patients
- Treatment success

5.4.2. Some of the independent/explanatory variables

- **Socio-demographics**(age, residence, literacy, occupation, income etc),
- **Care seeking practices:** first action to illness, type of health facility visited, number of visits, Type of HCF where TB diagnosed, etc
- **Clinical factors**: encountered symptoms, HIV co morbidity,
- **Perception/ knowledge** about TB, information provision during treatment etc
- **Disease related**: type of TB, treatment regimen, sputum and weight monitoring etc

5.5. Data collection tools and procedure

Data for the study variables were gathered using varieties of methods and sources. Accordingly, structured questionnaire was adapted from tools recommended and used elsewhere for the cost [56, 171, 172]. The structured questionnaire composed of sociodemographic, socioeconomic, perceptions, knowledge, clinical, household variables, and health care seeking practices. The questionnaire was translated into national language (*Amharic*) spoken by almost all residents in the study area. Moreover structured data extraction checklist was also adopted from unit TB register and clinical charts.

Training manual comprised of aim and implementation of the study, basics of TB control, TB case definitions, components of questionnaire and interviewing techniques was prepared. Ten diploma graduate nurse data collectors and three public health specialist (MPH) supervisors were recruited and trained for three days. The training included description of questionnaire details,

interviewing techniques, role play and pretest among TB cases on DOTS at nearby health facilities not selected for the study. So that, the questionnaire was customized to local expressions and wordings found during the pretest. Finally, new cases of TB on intensive phase treatment (the first two months of treatment) were traced from the unit TB register of the health facility and interviewed. The interview was held face to face at TB clinic after the necessary cares were provided to the patients. Upon completion of the baseline interview, the patients were appointed for further interview at the end of treatment. Then a follow-up interview was held at the end of treatment when costs incurred after treatment initiation and outcome of treatment were ascertained. Besides, data abstraction checklist was prepared to draw clinical, bacteriologic and treatment outcomes of the patients from TB register.

5.5.1. Ascertainment of delays to treatment

Delays to treatment measured by days elapsed between onsets of illness to initiation of anti-TB treatment (total delay). The total delay comprises both patient and provider delays. Patient delay was assessed by asking patients to recall and estimate date or number of days elapsed between onset of TB constitutional symptoms such as cough, fever, night sweats, chest pain, weight loss, and loss of appetite until formal care seeking. Similarly, provider delay was estimated by asking date or number of days elapsed between first formal health care facility visits to anti-TB treatment initiation. Finally, total delay was computed as a sum of patient and provider delay or number of days elapsed between onsets of illness to initiation of anti-TB treatment. The median total delay of the cases enrolled was 55days. Therefore, cases with total delay above 55 days were categorized as exposed and those with 55days and lower were grouped as non-exposed.

5.5.2. Patient cost ascertainment

Cost data were ascertained from patient perspective employing prevalent cases approach [122]. Both direct out of pocket expenditure (for medical and non-medical) and indirect costs were measured. Direct costs consisted of out of pocket expenditures for medical (consultation, drugs, laboratory tests, x-ray, and hospitalization) and non-medical (transportation, meal, and accommodation). Pre-diagnosis direct cost (incurred from onset of illness to treatment initiation), was determined by asking patient expense at each visit for consultation, laboratory tests, drugs, transportation, meals and lodging. Post diagnosis direct costs (incurred from treatment initiation to completion) were measured by inquiring patients' expense for treatment. The number of visits for the pre diagnosis period was solicited from patients and post diagnosis visits were taken from

attendance records on unit register. Thus, transportation cost was calculated as the numbers of visits multiplied by single trip fee as reported by the patients.

The indirect costs were estimated using human capital approach. Patients were requested to estimate time lost due to sickness and visits for consultation, hospitalization, drug collection, and trip journey. Then the time in any units (second, minute or hours) were all converted to hours and then to days at an average of 8 working hours in a day (8hours = 1day). Finally, the number of days were multiplied by an average daily wage rate of (US$2.43=50Ethiopian Birr) for unemployed and daily rate calculated from their gross monthly salary for employed. For all the cost items if no cost was incurred it was recorded as zero. All the costs were inquired in local currency, Ethiopian Birr (ETB) and then converted in to US dollars (US$) using average exchange rate of (1US$= 20.56ETB) during the study period [173].

5.5.3. Treatment outcome ascertainment

Treatment outcome was ascertained based on standard definitions recommended by the WHO and adopted by the country [23, 174]. Accordingly, treatment outcomes of TB fall in to cured or treatment completed or lost to follow up or death or treatment failure or transferred out. The outcomes were retrieved from unit TB register of respective HCFs. Finally the outcomes were categorized into successful when the TB patient completed treatment with or without evidence of cure and unsuccessful when died or lost to follow-up or treatment failure. So that, coding was made as unsuccessful outcomes=1 and successful=0. Details of the outcome definitions are presented in definition terms section.

5.6. Data management and analysis

At the field, data were checked for consistency and completeness every day by supervisors and/or principal investigator (PI). Then, data entry template was created on Epidata V3.5 based on coded responses. Two experienced clerks entered the data of which 10% was randomly double-checked by the PI. The data were then exported to SPSS version 21 and STATA version 13 where further recoding and cleaning was done to check for inconsistencies, outliers, and missing values. Finally, the cleaned data were processed and analyzed using SPSS or STATA.

Before further processing of the data, numeric data were checked for normality using normality plots (Q-Q plots and/or histograms) or normality tests (Kolmogorov-Smirnov test). Thus distribution of number of days elapsed across pathways to anti-TB treatment initiation were not normal so that median days elapsed between the time points were used describe delays. Patient, provider and total delays were defined based on median days elapsed between onset of illness to first visit, first visit to treatment initiation and onset of illness to treatment initiation respectively. The cost data distribution was right skewed so that log-transformation was made and data became lognormal. Hence, all the statistical tests pertaining to the cost were done with the log-transformed data and reported by back transforming the log data.

Knowledge about TB was assessed using eight items with "yes" or "no" questions including cause of TB (microbe,bacteria,germ), TB is hereditary, TB is contagious, mode of TB transmission [(breathing, sneezing, coughing, raw milk intake), symptoms of TB, TB is curable, length of treatment (6 month=yes, otherwise no) and TB treatment modalities as free=yes or for charge=no. The responses were coded as 0=no and 1=yes). The items internal consistency was checked (Cronbach's Alpha (α)=0.75) before computing an index. Finaly an index was computed from the scores and dichotomized in to good for those scored above median or poor otherwise.
Information provision adequacy during treatment initiation was assessed based on 15 items constructed from TB treatment guidelines. The internal consistency of the items was checked by Cronbach's Alpha (α) =0.87). A score of one is given for proper information and zero otherwise. So that information adequacy index was computed and labeled adequate when above median and inadequate when below median scores.

5.6.1. Data description and analysis

The data were described using frequency, proportions, mean, median, standard deviation, inter-quartile range, tables, and graphs. Comparisons of proportions among categorical variables were made using Chi-squared test. Similarly, associations between numeric variables were tested using simple correlation analysis. For distributions those exhibited normality, comparison of mean among different categories was made using independent t-test, paired t-test, and one-way Analyis of variance (ANOVA). For non-normal distributions median across categories were compared using Manwhitney U and Kruskual Walis tests. In all the tests statistical significance was judged at $p<0.05$.

5.6.2. Logistic regression

Bivariate and multiple binary logistic regression models were fitted to control potential confounders and to identify independent predictors of delays to initiate care seeking and treatment. Furthermore, the logistic regression model was also fitted to control for confounding factors while comparing the outcomes among the six and eight treatment regimens. For the identification of predictors of delay (dependent variable) at home and health system, median time elapsed were used to dichotomize the delays. The dependent variable was coded as 1=delayed beyond median and 0= delayed for median and below days. The other dependent variable, treatment outcome was coded as 1=unsuccessful and 0=successful. The unsuccessful outcome constitute death, lost to follow-up or treatment failure whereas successful constitute those cured or treatment completed.

Variables for the multiple regression model was fitted using "enter" method. Variables entered into the multivariate model were those having p<=0.25 with the biviarate regression. While fitting the model, fitness of the model was assessed using Hosmer-Lemeshow statistic. Finally, the outputs of bivariate and multiple logistic models were presented respectively as Crude Odds Ratio (COR) and Adjusted Odds Ratio (AOR) along with their 95% Confidence interval (CI).

5.6.3. Linear regression

Simple and multiple linear regression models were fitted to control for potential confounders and to identify predictors of patient pre-diagnosis and post-diagnosis costs. Thus, the outcome variable was log pre-diagnosis and post-diagnosis costs incurred by patients. Those variables having p<=0.25 with the biviarate regression were entered in to the multiple regression model. While fitting the model, major assumptions including normality, homoscedasticity and independence, linearity, and absence of multicollinearity were checked to be satisfied. Normality of error terms was checked using probability plots. Multicollinearity was considered to be absent when Variance Inflation Factor (VIF) is below 10. Assumptions of linearity, homoscedasticity and independence of error terms were visually evaluated using residual plots. The fitness of the models were assessed using adjusted R-squared and F test statistic. The outputs of the simple and multiple models were presented in crude and adjusted coefficients respectively with their 95%CI.

5.6.4. Log-binomial regression

For the assessment of effect of delayed treatment outcomes, log-binomial regression model was fitted. The model was preferred as it directly estimates Relative Risk (RR), which is a suitable estimate for follow-up studies. In addition, as the proportion of unsuccessful outcome is above 10%, use of OR as a measure of association can potentially result in overestimation of risk. The outcome variable was treatment outcome coded as 1=unsuccessful and 0=successful. Alike other models, both simple and multiple log-binomial models were fitted. Thus variables for the multiple regression was selected based on p<=0.25 with the bivariate analysis. The goodness-of-fit of the model was assessed using Pearson chi-square and Deviance tests. Finally, the outputs were presented in crude and adjusted relative risk (RR) with their 95%CIs. Summary of the methods used for each paper is presented in table (Table 2).

Table 2 :Summary of dissertation work by major components of study methods and objective

Objective	Study design	Study population	Sample size and sampling	Data collection tools	Data analyses
To compare treatment outcomes of 6EH and 4RH continuation phase treatment of TB (Paper I)	Comparative cross sectional	Treatment cohorts treated for with 4RH and 6EH continuation phase treatment	790, simple random sampling	Structured data abstraction checklist	Descriptive measures, Logistic regression,
To determine magnitude and associated factors of delays to anti-TB treatment (Paper II)	Cross-sectional	Adult new cases of TB registered for treatment at health facilities	735, multistage sampling	Interviewer administered questionnaire	Descriptive measures, binary logistic regression
To determine pre and post diagnosis costs of TB to patients (paper III)	Follow-up	Adult new cases of TB registered for treatment at health facilities	735,multistage sampling	Interviewer administered questionnaire	Descriptive measures, linear regression
To asses effect of treatment delay on outcomes of TB patients (Paper IV)	Follow-up	Adult new cases of TB on treatment at health facilities	735,multistage sampling	Interviewer administered structured questionnaire	Descriptive measures, Log-binomial regression

5.7. Data quality assurance

To ensure quality of the data, various actions were taken starting from designing the tool to data analysis and interpretations. The questionnaires were adapted from standard instruments those had been used in Ethiopia [172] and elsewhere [56, 171]. To avoid different forms of measurement bias, questions were customized to local expressions following a pre-test of the tools. Experienced diploma holder nurse data collectors and master holder supervisors were recruited and trained intensively. Both the data collectors and supervisors were accustomed to the local languages, cultures, and events. During the data collection, supervisors and PI conducted close supportive supervision to data collectors so that immediate feedback had been provided.

To minimize errors during data entry, the templates were programmed using check codes. Data entry was handled by experienced clerks on user-friendly software, Epidata. Then sample of the entered data were rechecked against the questionnaire for correctness of entry so that necessary corrections were made before the analysis. During analysis and interpretation, appropriate models and statistical tests were applied. Thus, important assumptions underlying the tests and models fitness were checked with standard procedures.

5.8. Ethical considerations

The study was conducted in compliance with the international [175] and national [176] ethical principles and standards for biomedical research involving human subjects. Thus, the Institutional Review Board (IRB) of College of Health Science, Addis Ababa University (AAU) ethically approved the study protocol with reference number SPH/14. Moreover, purpose of the study was communicated and permission sought from SNNPR health bureau, Kaffa, Bench-Maji and Sheka zones health department, respective *woreda* health offices and Health facilities.

Participation of the study subjects was entirely on voluntary basis. Hence, informed consent was taken from the study subjects using the annexed consent and information sheet (Annex 3-4). The information included purposes of the study, the rights of participants, potential benefits, and harms of the study. The study did not involve any undue financial or non-financial inducement for participation. In addition, the subjects were not persuaded or influenced in anyway by anybody to take part in the study. To ensure confidentiality of the information provided by the

participants, personal identifiers were not gathered. The questionnaires were kept in a locked cabinet and data in password-protected computer accessible to the PI.

The study did not introduce any harm to the participant. Hence, utmost effort was made to maximize the benefit to the participants. During the data collection participants were provided with information on cause, mode of transmission, manifestation, need for adhering to treatment and avoidance of transmission of TB to others.

5.9. Definition of terms

The following operational definitions adopted from WHO and national TB control guidelines [23, 27] and similar literatures were used.

- **Smear positive PTB** is a patient with at least two smear examinations positive for AFB **Or** with one smear examination positive for AFB by direct microscopy and culture positive, **Or** with one initial smear examination positive for AFB and radiographic abnormalities consistent with active TB as determined by a clinician.
- **Smear negative pulmonary TB** is a patient having symptoms suggestive of TB with at least three initial smear examinations negative for AFB by direct microscopy, **and** no response to a course of broad-spectrum antibiotics, **and** again three negative smear examinations by direct microscopy **and** radiological abnormalities consistent with pulmonary tuberculosis, **and** decision by a clinician to treat with a full course of anti- tuberculosis **Or** a patient whose diagnosis is based on culture positive for M. tuberculosis but three initial smear examinations are negative by direct microscopy
- **Extra pulmonary TB is** TB in organs other than the lungs, proven by one culture-positive specimen from an extra-pulmonary site or histo-pathological evidence from a biopsy, **Or** TB based on strong clinical evidence consistent with active EPTB and the decision by a physician to treat with a full course of anti-TB therapy.
- **New case of TB** is a patient who never had treatment for TB, or has been on anti-TB treatment for less than four weeks in the past.
- **HIV-positive TB patient** refers to any case of TB who has a positive result from HIV testing at the time of TB diagnosis or other documented evidence of enrolment in HIV care
- **HIV-negative TB patient-** any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis.

- **Cured:** a patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear or culture-negative in the last month of treatment and on at least one previous occasion.
- **Treatment completed:** completed treatment but does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
- **Treatment failure:** a patient whose sputum smear or culture is positive at five months or later during treatment or patients found to harbor MDR TB strain at any point of time during the treatment, whether they are smear-negative or positive.
- **Died:** a patient who dies for any reason during the course of TB treatment.
- **Lost to follow-up:** a patient who has been on treatment for at least four weeks and interrupted treatment for eight or more consecutive weeks.
- **Transfer out:** a patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
- **Treatment success:** TB cases who either completed the treatment or cured of it.
- **Patient delay- days** elapsed between onsets of illness to first formal healthcare seeking
- **Health system /provider delay** is days spent between first consultation to initiation of treatments
- **Total delay:** number of days elapsed since onset of illness to anti-TB treatment initiation
- **Direct cost:** out of pocket expenditure for TB care seeking, diagnoses and treatment by patient, household and health system for medical or non medical conditions
- **Indirect cost:** lost income due to TB illness, care seeking, and treatment.
- **Pre-diagnosis cost:** cost incurred since onset of illness to treatment initiation
- **Post-diagnosis cost:** cost incurred since commencement to completion of treatment
- **Total cost** is the sum of both direct and indirect costs incurred for care seeking, diagnoses and treatment of TB.

6. Results

6.1. Summary of key findings from papers (I-IV)

A total of 790 TB patient records (paper I) and 735 new TB cases on treatment (papers II-IV) were studied from 14 public health facilities (three hospitals and 11 health centers) of the selected 10 *woredas*. Of the 790 treatment records retrieved, 395 (50%) of the cases received eight month (2ERHZE/6HE) and the rest 50% received six month (2ERHZ/4RH) anti-TB treatment. Thus, significantly better outcome (treatment success) was observed among those received the six-month regimen compared with the eight-month treatment regimen (Table 3).

On the other hand, out of the 735 TB cases enrolled, 469(63.8%) and 266(37.2%) of the cases were registered at health centers and hospitals respectively. Until anti-TB treatment commencement, a median of 55days had been elapsed since onset of their illness. During the pathways to treatment, TB patients totally incurred a median of US$ 201.48 and US$93.75 until TB diagnosis and after the diagnosis respectively. Of the total cases enrolled, 36(4.9%) were transferred out to other treatment center so that treatment outcome was evaluated for the rest 699 (95.1%). Thus, significantly lower treatment success was observed among those initiated anti-TB treatments beyond a median 55days compared to those initiated within 55days of the onset of illness (Table 3).

Table 3; Summary of key findings of the dissertation by objectives

Objective	Key findings
To compare treatment outcomes of 6EH and 4RH continuation phase treatment of TB (Paper I)	• Overall treatment success was 88% with significantly higher (90.6% vs 85.3%) among those treated with 4RH and continuation phase treatment respectively • 4RH continuation phase predicted lower odds of unsuccessful outcome whereas, HIV co infection and rural residence predicted higher odds of unsuccessful outcome
To determine magnitude and associated factors of delays to treatment among TB patients on DOTS (Paper II)	• TB patients initiated formal healthcare seeking after median(IQR) 25(15-36) days since onset of illness • Commencement of treatment since first formal healthcare seeking spent median(IQR) 22(9-48)days • Patients elapsed median (IQR) of 55(32-100) days since onset of illness to anti-TB treatment where 54.6% of the delay was attributed to the provider (health system). • Patient and provider delays are positively correlated • Self treatment, HIV co infection, having extra pulmonary TB predict higher patient delay • First visitation to lower public and private facilities, delayed care seeking predict higher provider delay
To determine pre and post diagnosis costs of TB to patients (Paper III)	• TB patients incurred median(IQR) US$201.48(136.70-318.94) from illness onset to completion of treatment • Direct out-of-pocket patient expenditure during pre-diagnosis and post diagnosis respectively amounted to median(IQR) US$21.64(10.23-48.31) and US$35.02(0-70.40) • Indirect and Pre-diagnosis cost respectively constituted 70.6% and 53.6% of the total patient cost • Delays to treatment, visiting more than one HCF, care seeking at private HCF predicted increased pre-diagnosis cost • Delays to treatment, rural residence and hospitalization predicted increased post diagnosis cost
To asses effect of treatment delay on outcomes of TB patients (Paper IV)	• Over all treatment success was 89.6% (86.7% and 92.6%) respectively among those initiated treatment beyond and within 55days of onset of illness • Treatment initiation >55days of onset, HIV co infection and treatment center being hospital predicted higher risk of unsuccessful outcome • Weight gain and having sputum checkup after diagnosis predicted lower risk of unsuccessful outcome

6.2. TB treatment outcomes of eight and six months regimens (paper I)

6.2.1. Demographic and clinical characteristics of cases

A comparative study among 790 [395 each treated with 2RHZE/6HE for eight months and 2RHZE/4RH for six months regimens) was carried out. The mean age of the patients was 30.8(31.1 vs 30.9 years, p=0. 5) respectively, among those treated with 6HE and 4RH continuation phase treatment. More than half, 56.6%, and 55.7% were, respectively male and reside in rural areas. Of the cases, 86.8% and 51.8% were respectively registered at health center and from Bench Maji Zone. Six hundred and seventy five (85.4%) of the cases had undergone sputum smear microscopy test of whom 359(45.4%) became smear positive. Thus 608 (77.0%) of the cases had pulmonary TB. Among the total cases, 765 (96.8%) were new (378 treated with 6EH vs 387 with 4RH continuation phase regimen) and the rest [25(3.2%) (17 from 6EH vs 8 from 4RH) were transferred in and other cases treated with new case regimen. HIV test result was available for 612 (77.5%) with statistically significant difference among the two groups [283(71.6%) from 6EH and 329 (83.3%) from 4RH,p<0.001]. Among those tested HIV positives, 44(57.1%) received either (CPT) or ART with no statistically significant difference among the regimens 24(64.9%) from 6EH and 20(50%) from RH, p=0.2 (Table 4).

Table 4: Demographic and clinical characteristics of the patients, 2008-2014, Southwest Ethiopia

Variable		Continuation phase treatment regimen		Total N=790	P value
		6EH (n=395) n (%)	4RH (n=395) n(%)		
Age (years)	Mean ±SD[a]	31.1±12.9	30.5±11.9	30.8±12.4	0.5
Gender	Male	221(55.9)	226(57.2)	447(56.6)	0.7
	Female	174(44.1)	169(42.8)	343(43.4)	
Residence	Urban	175(44.3)	175(44.3)	350(44.3)	1
	Rural	220(55.7)	220(55.7)	440(55.7)	
Zone	Kaffa	106(26.8)	104(26.3)	210(26.6)	0.9
	Bench Maji	206(52.2)	203(26.3)	409(51.8)	
	Sheka	83(21.0)	88(22.3)	171(21.6)	
Treatment center	Hospital	55(13.9)	49(12.4)	104(13.2)	0.5
	Health center	340(86.1)	346(87.6)	686(86.8)	
Baseline weight	Mean ±SD	47.6 ±8.6	48.4 ±8.5	48± 8.5	0.2
Baseline sputum smear	Positive	186 (47.1)	173(43.8)	359(45.4)	0.6
	Negative	151 (38.2)	165(41.8)	316(40)	
	Unknown	58 (14.7)	57(14.4)	115(14.6)	
Type of TB	Pulmonary	303 (76.7	305 (77.2)	608 (77.0)	0.9
	Positive	186 (47.1)	173 (43.8)	359 (45.4)	
	Negative	117 (30.4)	132 (33.4)	252 (31.9)	
	Extra pulmonary	92 (23.3)	90 (22.8)	179 (23)	
HIV status	Positive	37 (9.4)	40 (10.1)	77 (9.7)	<0.001
	Negative	246 (62.3)	289 (73.2)	535 (67.7)	
	Unknown	112 (28.4)	66 (16.7)	178 (22.5)	
Received CPT[b] (n=77)	Yes	18(48.6)	17(42.5)	35(45.5)	0.6
Both CPT or ART[c] (n=77)	Yes	6(16.2)	6(15.0)	12(15.6)	0.8
Received ART (n=77)	Yes	12(32.4)	9(22.5)	21(27.3)	0.3

[a]Standard deviation, [b] Cotrimoxazole prophylactic therapy, [c]Antiretroviral therapy

6.2.2. Patient follow-up and outcomes

Measurements of patient weight at the end of second, fifth and sixth/seventh months of treatment were available for 504 (63.8%), 145 (18.4%) and 141 (17.8%) respectively. Thus, 368 (46.6%) or (48.4% from 6EH and 44.8% from 4RH, p=0.4) have gained some amount of weight at the

end of second month of treatment. On the other hand, of those initially smear positive pulmonary TB cases, 78.6% had undergone sputum follow up examination at least once after the diagnosis (76.3% among 6HE and 80.9% among 4RH,p=0.3). Accordingly sputum smear results at the end of second, fifth and sixth/seventh months of treatment were available for 274 (76.3%), 184(51.3%) and 179(49.9%) cases respectively with no statistically significant differences among those received 6EH and 4RH regimens. The majority of the smear positives (69.9% vs 79.8% respectively from the 6EH and 4RH regimens, p=0.09) converted to negative at the end of second month treatment (Table 5).

A total of 695(88%)[95% CI;85.5%,90.1%] of the patients had successful treatment outcomes with significantly higher treatment success (90.6% vs 85.3%,p=0.02) among those received 6HE and 4RH continuation phase treatment , respectively (Table 5). Similarly, 324 (90.3%), 208 (85.4%) and 163 (91.1%) of pulmonary positive, pulmonary negative and extra pulmonary TB cases respectively had successful outcomes, P=0.03. Besides, statistically significant differences (P=0.01) treatment success was observed among HIV co-infected 64 (83.1%), HIV negative 482 (90.1%) and cases with unknown HIV status 149(83.7%.

Table 5; Follow-up characteristics and outcomes of TB cases, 2008 to 2014, Southwest Ethiopia

Variables		Continuation phase treatment regimen		Total (N=790)	
		6EH(n=395) n(%)	4RH(n=395) n (%)	N(%)	P value
Weight at 2nd month	Mean ±SD	49.9 ±8.9	50.8 ±8.2	50.4±8.6	0.2
Weight at 5th month	Mean ±SD	51.4 ± 8.6	51.3 ±7.3	51.3± 7.9	0.9
Weight at 6/7th month	Mean ±SD	51.1 ±8.9	52.5 ±6.5	51.7 ±7.9	0.3
Change in weight end of 2nd month	Not increased	49(12.4)	61(15.4)	110(13.9)	0.4
	Increased	191(48.4)	177(44.8)	368(46.6)	
	Unknown	155(39.2)	157(39.7)	312(39.5)	
Sputum smear end of 2nd month (n=359)	Positive	4(2.2)	2(1.2)	6(1.7)	0.09
	Negative	130(69.9)	138(79.8)	268(74.7)	
	Unknown	52(28)	33(19.1)	85(23.7)	
Sputum smear end of 5th month(n=359)	Positive	1(0.5)	0(0)	1(0.3)	0.03
	Negative	83(44.6)	100(57.8)	183(51)	
	Unknown	102(54.8)	73(42.2)	175(48.7)	
Sputum smear end of 6/7th month (n=359)	Positive	0(0)	0(0)	0(0)	0.8
	Negative	94(50.5)	85(49.1)	179(49.9)	
	Unknown	92(49.5)	88(50.9)	180(50.1)	
Sputum smear during treatment (n=359)	No	44(23.7)	33(19.1)	77(21.4)	0.3
	At least once	142(76.3)	140(80.9)	282(78.6)	
Treatment outcome	Successful	337(85.3)	358(90.6)	695(88)	0.02

Cured	77(19.5)	85(21.5)	162(20.5)
Completed	260(65.8)	273(69.1)	533(67)
Unsuccessful	58(14.7)	37(9.4)	95(12)
Died	28(7.1)	18(4.6)	46(5.8)
Defaulted	29(7.3)	19(4.8)	48(6.1)
Failure	1(0.3)	0(0)	1(0.1)

6.2.3. Association between treatment regimen and outcomes

In multivariate analysis 4RH continuation phase treatment regimen [AOR (95% CI) 0.55(0.34,0.89)], treatment center being health center [AOR (95% CI) 0.37(0.14,0.97)] and gained weight at the end of the second month [AOR (95% CI) 0.28(0.11,0.72)] predicted lower odds of unsuccessful outcome. Patient age [AOR (95% CI) 1.02(1.001,1.022)], rural residence [AOR (95% CI) 2.1(1.18,3.75)] and HIV co-infection [AOR (95% CI 2.38(1.12,5.07)], independently predicted higher odds of unsuccessful treatment outcome (Table 6). Treatment with 4RH continuation phase predicted lower odds of unsuccessful outcome compared to those treated with 6EH regimen. Thus, cases treated with 4RH continuation phase regimen are 45% less likely to have unsuccessful outcome compared to those treated with the 6EH regimen. On the other hand, higher chance of unsuccessful outcome was observed among the elders, rural residents and HIV co-infected cases compared to respectively younger, urban residents and HIV negative cases. The likelihood of having unsuccessful outcome increase by 2% for every one year increase in age (AOR=1.02). Patients followed anti-TB treatment at health center had about 63% lower odds of unsuccessful outcome compared to those followed at hospital (AOR=0.37). HIV co infected TB patients are more than twice as likely to have unsuccessful outcomes compared to HIV negatives (AOR=2.39). Those patients gained weight at the end of the second month of treatment have 72% lower odds of unsuccessful outcomes compared to those with reduced or unchanged weight (AOR=0.28).

Table 6; Predictors of unsuccessful TB treatment outcomes, 2008-2014, Southwestern Ethiopia

Variables		Treatment outcomes		Odds ratio (OR)	
		Unsuccessful n (%)	Successful n (%)	Crude OR 95% CI	Adjusted OR 95% CI
Age (years)	Mean(SD)	33.5(14)	30.4(12.0)	1.02(1.002,1.03)	1.02(1.001,1.022)*
Gender	Male	60(13.4)	387(86.6)	1.00	1.00
	Female	35(10.2)	308(89.8)	0.73(0.47.1.14)	0.63(0.38,1.03)
Residence	Urban	32(9.1)	318(90.9)	1.00	1
	Rural	63(14.3)	377(85.7)	1.66(1.06,2.61)	2.1(1.18,3.75)*
Zone	Kaffa	34(16.2)	176(83.8)	1.00	1
	Bench Maji	50(12.2)	359(87.8)	0.72(0.45,1.14)	1.41(0.73,2.75)
	Sheka	11(6.4)	160(93.6)	0.36(0.17,0.73)	1.2(0.44,3.32)
Treatment center	HC**	78(11.4)	608(88.6)	0.66(0.37,1.16)	0.37(0.14,0.97)*
	Hospital	17(16.3)	87(83.7)	1.00	1.00
Type of TB	Pulmonary	78(12.8)	530(87.2)	1	1
	EPTB**	17(9.3)	165(90.7)	0.70(0.40,1.22)	0.57(0.32,1.04)
HIV status	Negative	53(9.9)	482(90.1)	1.00	1.00
	Positive	13(16.9)	64(83.1)	1.85(0.95,3.57)	2.39(1.12,5.07)*
	Unknown	29(16.3)	178(83.7)	1.77(1.08,2.88)	2.26(1.23,4.11)*
Weight change end of 2nd month	No increase	11(8.2)	357(91.8)	1.00	1
	Increased	9(3)	101(97)	0.35(0.14,0.86)	0.28(0.11,0.72)*
	Unknown	75(24)	237(76)	3.55(1.71,7.37)	3.48(1.60,7.54)*
Continuation phase regimen	6EH	58(14.7)	337(85.3)	1.00	1.00
	4RH	37(9.4)	358(90.6)	0.60(0.39,0.93)	0.55(0.34,0.89)*

*statistically significant at p<0.05,*HC=Health center***=Extra pulmonary Tuberculosis,

A subgroup analysis among smear positive pulmonary cases showed having a sputum checkup at least once during treatment independently predicted 96% lower odds of unsuccessful outcomes compared to those unchecked (AOR= 0.04,95% CI, 0.01-0.12),P<0.001).

6.3. Pathways to anti-TB treatment initiation (Paper II)

6.3.1. Sociodemogaphic characteristics of the cases

A total of 735 (97.7%) of the required new TB cases on anti-TB treatment from 14 public health facilities (three hospitals and 11 health centers) were enrolled for the study. Accordingly, 469(63.8%) of the cases were registered at health centers and 39.3% were females. The median (inter-quartile range (IQR)) age of the cases was 27(20-37) years. Majority of the cases, 71.2%, and 55% of the cases respectively have completed at least primary school and currently married. Three hundred (40.8%) of the cases were followers of orthodox Christian and 50.2% of the enrolled cases resided in urban (Table 7).

Table 7;Sociodemographic characteristics of TB cases in southwest Ethiopia, January to December 2015 (n=735)

Variable		Frequency (%)
Treatment center	Health center	469(63.8)
	Hospital	266(37.2)
Gender	Male	446(60.7)
Age(years)	18-34	503(68.4)
	35-65	216 (29.4)
	>65	16(2.2)
Marital status	Never married	275(37.4)
	Currently married	404(55)
	Widowed/divorced	56(7.6)
Educational status	No formal education	212(28.8)
	Completed elementary	389(53.0)
	Secondary and above	134(18.2)
Occupation	Employed	172(23.4)
	Farming	216(29.4)
	Unskilled work [b]	51(6.9)
	Dependants [c]	296(40.3)
Religion	Orthodox	300(40.8)
	Muslim	104(14.1)
	Catholic	4(0.5)
	Protestant	314(42.7)
	Traditional	13(1.8)
Residence	Urban	369(50.2)
	Rural	366(49.8)
Household size	Mean/SD	4.3/2.1

[a] Standard deviation [b] housemaid, daily laborer, [c] students, house wife, [d] father/ mother /husband/

wife/brother/sister/employer

6.3.2. Healthcare seeking practices and patient delay

At the onset of illness, 563(76.6%) and 345(46.9%) of the cases had respectively encountered cough and night sweating. Subsequent to the symptoms, 139(18.9%) took actions including self-treatment and consulting traditional healer prior to healthcare facility (HCF) visit. Ultimate decision to visit health facility was made upon referral and/or advice from relatives (38.6%), Health Extension Worker (HEW) (4.5%) and TB patients on treatment (4.2%). Two hundred and seventy six (37.6%) first visited to HCFs not providing TB DOTS service including private clinics and health posts. Since onset of the illness, a median 25(15-36) days had been elapsed to initiate formal healthcare seeking. Nearly a third, 240(32.6%) of the cases had made first consultation within 15 days of the onset of illness. Of the cases, 317(43.1%) perceived their first visit was delayed for which 256(80.8%) and 109(26.1%) reasoned expecting the illness to limit by itself and lack of money respectively. Among the cases, 545(74.1%) had relatively good knowledge about TB illness and its treatment (Table 8).

Table 8; Healthcare seeking practices among TB cases, Southwestern Ethiopia, January to December 2015 (n=735)

Variable		Frequency (%)
First symptoms encountered *	Cough	563(76.6)
	Night sweat	345(46.9)
	Fever	300(40.8)
	Loss of appetite	279(38)
	Chest pain	267(36.3)
	Weight loss	236(32.1)
	Haemoptysis	144(19.6)
	Others[a]	62(8.4)
First action to illness	Visit HCF	596(81.1)
	Self-treatment	98(13.3)
	Visit holy water	26(3.5)
	Consult traditional healer	15(2.0)
Perceived reason for not visiting HCF first (n=149)*	Thought illness limit by itself	97(65.1)
	Perceived long waiting time at HCF	37(24.8)
	Perceived expensive service fee	37(24.8)
	HCF too far	29(19.5)
	Other [b]	22(14.8)
First HCF visited	Private clinic	260(35.4)
	Health center	238(32.4)

	Hospital	221(30.1)
	Health post	16(2.2)
Source of advice/referral to visit first HCF	Self	472(64.2)
	Parent/relative	280(38.1)
	HEW [c]	32(4.4)
	TB patient	30(4.1)
	HIV care clinic	16(2.2)
	Other[d]	31(4.2)
Travel time to treatment center	<=1hour	582(79.2)
	>1hour	153(20.8)
Knowledge towards TB	Good	545(74.1)
	Poor	190(25.9)
Patient delay (days)	Median(IQR)	25(15-36)
	Median (95%CI)	25(22,28)

[*]percentage total beyond 100% due to multiple response [a] neck swelling, head ache, joint pain, back pain, wound ,[b]HCF closed, mistrust health care provider, bad previous experience at HCF, fear of HIV test and fear of TB diagnosis, [c]HEW= Health Extension worker(trained females those provide household package of health care to household), [d]drug shop(13),holy water(14),traditional healer(4)

6.3.3. Health system delays and clinical characteristics of the cases

After the first formal healthcare consultation, diagnosis and initiation of anti-TB treatment took a median (IQR) 22(8-48) days (provider or health system delay). The provider delay is significantly correlated with patient delay (r=0.2, P<0.001). Patients made a median (IQR) of 3(2-4) visits to median (IQR) 2(1-3) healthcare facilities until TB diagnosis. Diagnosis of 61.0% of the cases was made at hospital (Table 9) and in 373(50.7%), diagnosis was bacteriologically confirmed with sputum smear microscopy. Thus 586(79.7%) of the cases had pulmonary TB of whom 373(63.2%) were smear positive. Before commencement of treatment, all of the cases were offered HIV screening test of whom 68 (9.3%) tested positive [95% CI (7.2%-11.3%)].

Following the diagnosis of TB, 613(83.4%) of the cases were put on anti-TB treatment immediately and the rest after a median (range) 2(1-7) days. Of the total cases, 162(22%) started anti-TB treatment within 30days of the onset of illness. Since onset of the illness, a median (IQR) of 55(32-100) days had undergone until anti-TB treatment initiation (total delay). More than half (54.6%) of the total delay was attributed to provider and the rest to the patient.

Table 9: Clinical characteristics and delays to treatment among TB patients, January to December 2015, Southwest Ethiopia

Variable		Frequency (%)
Place TB diagnosis made	Hospital	448(61.0)
	Health center	188(25.6)
	Private clinic	99(13.5)
Type of TB	Smear positive Pulmonary	373(50.3)
	Smear negative Pulmonary	213(29.0)
	Extra pulmonary	149(20.3)
Mode of diagnosis	Bacteriological	373(50.7)
	Clinical	362(49.3)
HIV status	Positive	68(9.3)
	Negative	667(90.7)
Number of HCF visited [a]	Median (IQR)	2(1-3)
Number of visits made [b]	Median (IQR)	3(2-4)
Provider delay (days)	Median (IQR)	22(8-48)
	Median(95%CI)	22(19,25)
Total delay (days)	Median (IQR)	55(32-100)
	Median (95%CI)	55(49,61)
Hospitalized during treatment	Yes	19(2.6)

[a] number of HCF visited until diagnosis of TB is made, [b] number of total visits made to different HCF until TB diagnosis

6.3.4. Predictors of patient delay

In a multiple logistic regression, extra pulmonary TB [AOR=1.60,95%CI; (1.07,2.33)], HIV co-infection [AOR=2.17,95%CI; (1.25,3.73)] , self treatment before HCF visit [AOR=1.64,95% CI;(1.02,2.63)], informal care before HCF visit (AOR=2.54,95%CI;1.25,5.17) traveled more than an hour to HCF [AOR=1.37,95% CI;(1.01,1.88) independently predicted higher odds of patient delay beyond median of 25days. On the other hand having good knowledge about TB [AOR=0.67,95% CI; (0.46,0.95)] independently predicted lower odds of patient delay beyond the median of 25days (Table 10). Those cases having good knowledge about TB were 33% less likely (AOR=0.67) to delay care seeking compared to those with poor knowledge. Patients diagnosed to have extra pulmonary TB cases are 60% more likely (AOR=1.60) to delay care seeking compared to smear positive pulmonary cases. TB cases co infected with HIV are more than twice as likely to delay care seeking than HIV negative cases. Similarly those cases who took informal care including traditional or holy water care before visiting HCF are more than twice as likely (AOR=1.72) to delay formal healthcare seeking beyond 25 days (Table 10).

Table 10: Predictors of patient delay, southwest Ethiopia, January to December 2015

Variable		Patient delay(days)		Crude Odds ratio (COR) 95% CI	Adjusted Odds ratio (AOR) 95%CI
		>25 n(%)	<=25 n(%)		
Age (years)	18-34	250(49.7)	253(50.3)	1.00	1.00
	35-64	112(51.9)	104(48.1)	1.20(0.79,1.50)	1.07(0.75,1.52)
	>65	8(50.0)	8(50.0)	1.01(0.37,2.74)	1.32(0.47,3.72)
Education status	Illiterate	89(42.0)	123(58.0)	1.00	1.00
	Completed primary	215(55.3)	174(44.7)	1.71)1.21,2.4)	1.17(0.80,1.71)
	Above Secondary	63(47.0)	71(53.0	1.22(0.80,1.90)	1.19(0.71,2.0)
Residence	Urban	177(48.1)	191(51.9)	1.00	1.00
	Rural	193(52.6)	174(47.6)	1.20(0.90,1.60)	1.04(0.74,1.48)
Type of TB	Pulmonary positive	175(47.9)	190(52.1)	1.00	1.00
	Pulmonary negative	104(47.7)	114(52.3)	0.95(0.68,1.32)	1.03(0.72,1.46)
	EPTB	91(59.9)	61(40.1)	1.51(1.03,2.21)	1.60(1.07,2.35)*
HIV status	Positive	41(60.3)	27(39.7)	1.52(0.92,2.52)	2.17(1.26,3.73)
	Negative	329(50.7)	338(49.3)	1.00	1.00

First action to illness	Self treatment	60(61.2)	38(38.8)	1.84(1.17,2.85)	1.64(1.02,2.63)*
	Informal care**	29(70.7)	12(29.3)	2.70(1.35,5.40)	2.54(1.25,5.17)*
	Consult HCP	281(47.1)	315(52.9)	1.00	1.00
First visited HCF	Health post	13(81.3)	3(18.8)	1.00	1.00
	Health center	130(54.6)	108(45.4)	0.26(0.07,0.95)	0.28(0.10,1.05)
	Hospital	98(44.3)	123(55.7)	0.18(0.0,0.64)	0.19(0.05,0.71)*
	Private clinic	129(49.6)	131(50.4)	0.22(0.06,0.79)	0.24(0.06,0.87)*
Travel time to HCF	<=1hour	205(46.9)	232(53.1)	1.00	1.00
	>1hour	165(55.4)	133(44.6)	1.37(1.02,1.84)	1.37(1.01,1.88)*
Knowledge towards TB	Good	264(48.4)	281(51.6)	0.77(0.55,1.07)	0.67(0.46,0.98)*
	Poor	106(55.8)	84(44.2)	1.00	1.00

*statistically significant at p<0.05,** Traditional care or Holy water

6.3.5. Predictors of provider delay

First visiting non DOTS HCF [AOR=1.42,95% CI;(1.01, 2.0)], visited more than one HCF AOR=2.34, 95% CI;(1.69, 3.24) and sought care after 25days from onset of illness AOR=1.81,95% CI;(1.33, 2.5) independently predicted higher odds of provider delays exceeding 22 days (Table 11). Those cases first visited non-DOTS center including health post or private clinics are 42% more likely to have delayed diagnosis and treatment compared to those visited DOTS providing facilities. Cases who delayed beyond 25days are 81% more likely to have provider delay beyond the median of 22days. Cases who visited more than one HCF until diagnosis are more than twice as likely to have diagnosis and treatment delay beyond 22 days.

Table 11: Predictors of provider delay among TB cases, southwest Ethiopia, January to December 2015

Variable		Provider delay(days)		COR(95% CI)	AOR(95%CI)
		>22 n(%)	<=22 n(%)		
TB type	PPos[a]	182(49.9)	183(50.1)	1.00	1.00
	PNeg[b]	10347.2)	115(52.8)	0.9(0.64,1.26)	0.87(0.60,1.25)
	Extra pulmonary	82(53.9)	70(46.1)	1.18(0.81,1.72)	1.08(0.72,1.62)
HIV status	Positive	39(57.4)	29(42.6)	1.38(0.84,2.30)	1.33(0.78,2.27)
	Negative	328(49.2)	339(50.8)	1.00	1.00
First action to illness	Self treatment	44 (44.9)	54(55.1)	0.81(0.53,1.25)	0.75(0.47,1.19)
	Traditional care	9(60.0)	6(40.0)	1.5(0.53,4.27)	1.19(0.47,3.51)
	Holy water	16(61.5)	10(38.5)	1.6(0.71,3.58)	1.28(0.55,2.99)
	Consult HCP[c]	298(50.0)	298(50.0)	1.00	1.00
First	DOTS center	203(44.2)	256(55.8)	1.00	1.00

visited HCF	Non DOTS	164(59.4)	112(40.6)	1.85(1.36,2.50)	**1.42(1.01,2.00)***
HCF visited	1	69(28.3)	175(71.7)	1.00	1.00
	>1	298(60.7)	193(39.3)	3.92(2.81,5.46)	**2.34(1.69,3.24)***
Patient delay days	>25	213(57.6)	157(42.4)	1.80(1.36,2.50)	**1.81(1.33,2.50)***
	<25	154(42.2)	211(57.8)	1.00	1.00

*statistically significant at p<0.05, [a] Pulmonary positive, [b] pulmonary negative, [c] Health Care Provider

6.4. Pre-and post TB diagnosis costs to patients (Paper III)

6.4.1. Demographic and clinical characteristics of cases at base line and end line

Costs incurred by patients while seeking care and treatment were assessed during the enrollment (baseline survey) and end of treatment (end line survey). Thus, costs incurred until diagnosis (pre-diagnosis) and after diagnosis (post-diagnosis) were determined. A total of 735 TB cases were enrolled (baseline) of which 627(85.3%) completed the follow-up (end line). Those lost cases, 108(14.7%), were 29(26.9)%) death, 36(33.3)%) transferred to other treatment centers, 5(4.6%) treatment failure and 38(35.2%) lost to follow-up. Nonetheless, there were no statistical significant differences with the proportions of the patient sociodemographic and clinical attributes across the baseline and end line surveys (Table 12). Female patients constituted 39.2% vs 38.9%,p=0.9 in the baseline and end line surveys respectively. Similarly, 314(85.8%) rural residents, 176(82.6%) smear negative pulmonary and 219(82.3%) registered at hospital had completed the follow-up.

Table 12: Sociodemographic and clinical characteristics of TB cases in southwest Ethiopia, January to December 2015

Variable		Baseline (n=735) n (%)	End line (n=627) n (%)	P value
Gender	Female	288(39.2)	244(38.9)	0.9
Age(years)	18-34	503(68.4)	431(68.7)	0.9
	35-65	216 (29.4)	183(29.1)	0.8
	>65	16(2.2)	13(2.1)	0.89
Educational status	No formal education	212(28.8)	176(28.1)	0.77
	Completed elementary	389(53)	340(54.2)	0.66
	Secondary and above	134(18.2)	111(17.7)	0.8
Residence	Urban	369(50.2)	313(49.9)	0.94
	Rural	366(49.8)	314(50.1)	0.74
Action before	None	586(79.7)	497(79.3)	0.85

visiting HCF	Took action [a]	149(20.3)	130(20.7)	0.85
First visited HCF	DOTS center	459(62.5)	387(61.7)	0.85
	Non DOTS	276 (37.5)	240(38.3)	0.76
Type of TB	Pulmonary positive	373(50.7)	320(51.0))	0.90
	Pulmonary negative	213(29.0)	176(28.1)	0.70
	Extra pulmonary	149(20.3)	131(20.9)	0.70
Mode of diagnosis	Bacteriological	373(50.7)	319(50.9)	0.90
	Clinical	362(49.3)	308(49.1)	0.90
Treatment center	Health center	469(36.2)	408(65.1)	0.70
	Hospital	266(63.8)	219(34.9)	0.70
Travel time to treatment HCF	=<1hour	437(59.5)	373(59.5)	1.00
	>1hour	298(40.5)	254(40.5)	1.00
Hospitalized for treatment	Yes	19(2.6)	15(2.4)	0.40
HIV status	Positive	68(9.3)	46(7.3)	0.10
Patient delay	Median (IQR)days	25(15-36)	23(14-34)	0.20
Provider delay	Median (IQR)days	22(9-48)	20(8-48)	0.40
Total delay	Median (IQR)days	55(32-100)	52(31-93)	0.50

[a] self treatment, consult traditional healer, used holy water

6.4.2. Total cost of care seeking and treatment to patients

Total costs incurred by patients for care seeking, diagnosis and treatment amounted to mean (±SD) of US$244.0(±0.10). From the total cost, direct out of pocket expenditure (direct cost) during the pre-diagnosis and post-diagnosis periods amounted to mean (±SD) of US$84.8(±0.15). During the care seeking and treatment visits, patients had totally lost a median (IQR) 51.7 (32.0-80.8) workdays that corresponded to mean (±SD) US$140.31(±0.1)) income loss (indirect cost) (Table 13).

Table 13: Distribution of TB patient costs across cost categories and periods in south west Ethiopia, January to December 2015

Cost category		**Cost period**		
		Pre-diagnosis (US$)	Post diagnosis (US$)	Total (US$)
Medical	Mean (SD)	8.56(0.2)	4.4(0.13)	8.75(0.21)
	Mean(95%CI)	8.56(7.68,9.54)	4.4(3.23,6.0)	8.75(7.85,9.75)
	Median (IQR)	10.72(4.58-23.76)	0(0-0)	11.19(4.73-24.08)
Non medical	Mean (SD)	10.08(0.21)	43.27(0.10)	64.1(019)
	Mean(95%CI)	10.08(8.99,11.30)	43.27(38.32,48.23)	64.1(58.34,69.9)
	Median(IQR)	8.27(1.61-24.32)	35.02(0-70.04)	37.11(14.35-85.12)

Total direct	Mean (SD)	21.46(0.16)	43.80(0.12)	84.82(0.15)
	Mean(95%CI)	21.46(19.65,23.43)	43.8(38.82,48.78)	87.82(77.92,91.72)
	Median(IQR)	21.64(10.23-48.31)	35.02(0-70.04)	59.58(29.43-113.81)
Indirect	Mean (SD)	75.62(0.12)	75.20(3.06)	140.31(0.1)
	Mean(95%CI)	75.62(70.68,80.9)	75.2(69.14,81.26)	140.31(132.35,148.74)
	Median(IQR)	64.45(39.82-128.8)	51.07(34.65-93.02)	127.68(78.43-201.85)
Total	Mean (SD)	108.0(0.1)	117.0(0.10)	244.71(0.10)
	Mean(95%CI)	108.0(101.31,115.11)	117.0(110.47,123.87)	244.71(229.45,260.98)
	Median(IQR)	97.62(56.43-184.22)	93.75(56.91-141.54)	201.48(136.7-318.94)

Pre-diagnosis and post diagnosis costs respectively constituted 57.6% and 42.3% of the total cost. Total direct and indirect costs constituted 29.4% and 70.6% respectively of the total cost similarly, total medical costs amount to mean (±SD) US$8.75(±0.21) and constitute 6.4% of the total cost (Figure5). More than half (50.4%), 44.6% and 5% of the total medical cost were incurred for drugs other than anti-TB, diagnostic laboratory/imaging test and consultation respectively. Similarly, majority (73.9%), 14.4% and 11.7% of the total non-medical costs were spent respectively for transportation, lodging, and meal while visiting healthcare facilities.

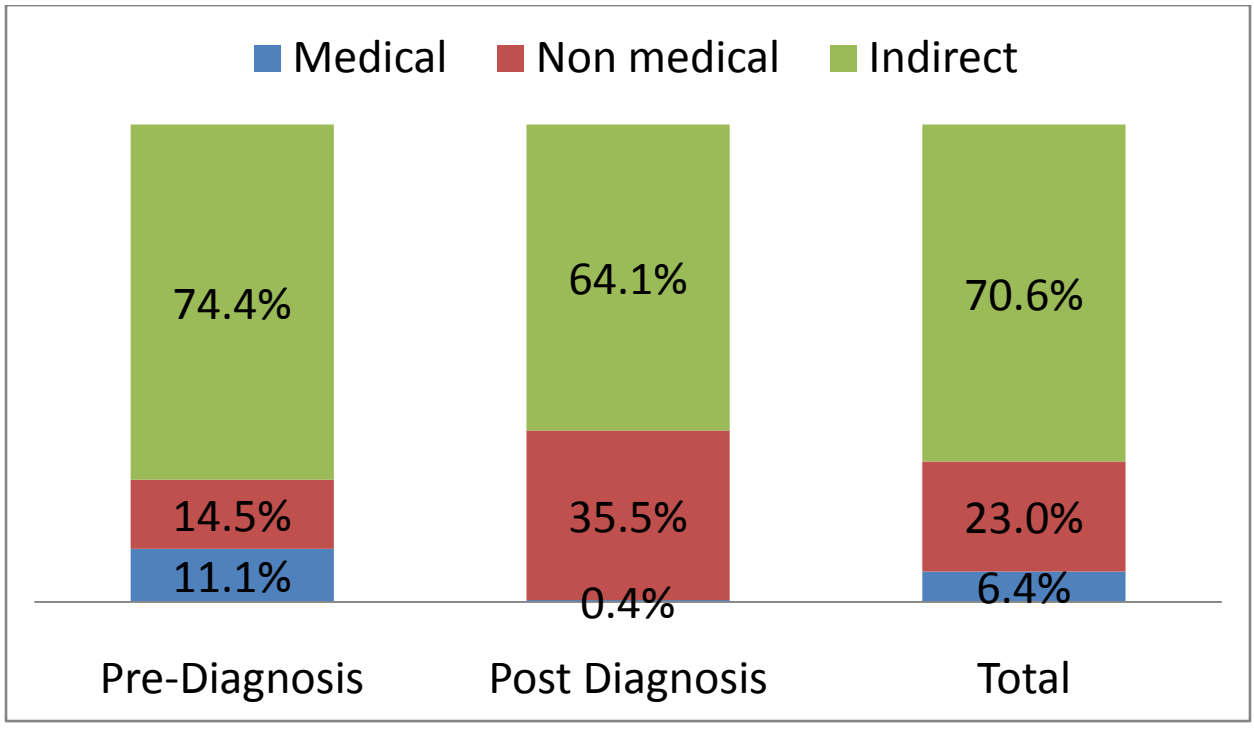


Figure 5; Distribution of patient costs across pre and post diagnosis periods among TB cases on treatment in districts of southwest Ethiopia January to December 2015

6.4.3. Pre-diagnosis patient cost and its predictors

Variable	Total pre diagnosis cost(US$)	Total post diagnosis cost(US$)	Total cost(US$)

Until diagnosis of TB (pre-diagnosis), patients incurred a mean (±SD) US$108.0 (±0.1) for care seeking and diagnosis (Table 13). Of the total pre-diagnosis cost, direct out-of-pocket expenditures (direct cost) amounted to mean (±SD) US$21.46(±0.16) and constituted 25.6% of the total pre diagnosis costs (Figure 5). Patients had lost median (IQR) of 24.7(15.1-48.4) workdays until diagnosis that corresponded to mean (±SD) US$75.62(±0.12) income loss. Out of the total pre-diagnosis medical costs, more than half (52.5%), 41.3% and 6.2% were incurred for drugs other than anti-TB, diagnostic laboratory/imaging tests, and consultation fee respectively. Similarly, 38.9%, 36.3% and 24.8% were respectively spent for transportation, meal and lodging while visiting healthcare facilities. The pre-diagnosis cost is significantly correlated with patient (γ=0.32,p<0.001), provider (γ =0.64,p<0.001) and total delays (γ =0.68,p<0.001) and number of HCF visited until diagnosis (γ=0.42,p<0.001). The mean pre-diagnosis cost is significantly different across type of TB (F=10.03,p<0.00), type of first visited HCF(p=0.002), type of HCF where diagnosis made (p<0.001) and mode of diagnosis (p=0.001) (Table 14).

Table 14; Differences in pre and post TB diagnosis patient cost across different attributes, January to December 2015, Southwest Ethiopia

		Mean(SD)	P value	Mean(SD)	P value	Mean(SD)	P value
Gender	Male	112.62(0.12)	0.3	119.73(0.1)	0.09	254.61(0.1)	0.1
	Female	101.25(0.11)		112.51(0.1)		229.12(0.09)	
HIV result	Reactive	131.2(0.13)	0.7	123.52(0.1)	0.2	287.2(0.11)	0.4
	Non reactive	106.02(0.11)		116.2(0.1)		240.22(0.1)	
Mode of diagnosis	Bacteriological	97.0(0.11)		118.25(0.1)		234.25(0.1)	
	Clinical	121.08(0.12)	0.03	115.82(0.1)	0.1	255.16(0.1)	0.06
Type of TB	Pulmonary pos.	97.62(0.14)	F=10.03	118.78(0.1)	F=0.52	236.16(0.1)	F=3.68
	Pulmonary neg.	106.9(0.1)	P<0.001	111.85(0.1)	P=0.5	230.25(0.1)	P=0.03
	Extrapulmonary	142.75(0.13)		120.20(0.1)		290.11(0.10)	
Treatment center	Hospital	121.77(0.13)	0.1	103.05(0.1)	0.01	239.3(0.1)	0.1
	Health center	100.86(0.11)		131.43(0.1)		249.8(0.1)	
Residence	Urban	114.61(0.12)	0.7	94.02(0.1)	<0.001	216.83(0.1)	0.003
	Rural	102.13(0.12)		154.7(0.08)		282.4(0.1)	
Total delay	<=55days	66.33(0.1)	<0.001	102.53(0.1)	<0.001	182.19(0.08)	<0.001
	>55days	177.33(0.11)		134.85(0.1)		337.06(0.09)	
Patient delay	<=25days	80.86(0.1)	<0.001	103.92(0.1)	<0.001	200.46(0.1)	<0.001
	>25days	144.72(0.12)		132.31(0.1)		302.61(0.1)	
Provider delay	<=22days	69.25(0.1)	<0.001	110.08(0.1)	0.03	193.9(0.09)	<0.001
	>22days	167.11(0.11)		125.28(0.1)		317.39(0.1)	
Action before HCF visit	None	106.72(0.12)	0.8	111.85(0.11)	0.005	235.89(0.1)	0.006
	Took action*	113.41(0.11)		137.34(0.11)		282.12(0.08)	
First visited HCF	DOTS center	99.97(0.12)	<0.001	118.2(0.1)	0.3	241.61(0.1)	0.04
	Non DOTS	122.57(0.11)		114.87(0.1)		250.25(0.1)	
Travel time to HCF	<=1hr	105.8(0.12)	0.1	105.70(0.08)	<0.001	227.27(0.09)	0.08
	>1hr	111.20(0.11)		145.14(0.09)		285.25(0.09)	
TB diagnosed HCF	Public	101.78(0.11)	<0.001	116.37(0.1)	0.3	237.9(0.1)	<0.001
	Private	153.88(0.13)		121.27(0.11)		292.16(0.1)	
Hospitalized for treatment	Yes	186.96(0.17)	0.01	240.8(0.09)	<0.001	477.85(0.12)	<0.001
	No	106.49(0.12)		113.3(0.11)		237.81(0.1)	

6.4.4. Predictors of pre-diagnosis cost

In multiple linear regression patient delay ($\beta_{adjusted(adj.)}$=0.004,p<0.001) and provider delay ($\beta_{adj.}$= 0.004,p<0.001), being diagnosed at private facilities ($\beta_{adj.}$= 0.16,p= 0.02), and number of visited healthcare facilities ($\beta_{adj.}$= 0.17,p<0.001) independently predicted increased mean pre-diagnosis costs (Table 15). Every patient and provider delays each increase the mean pre-diagnosis cost to patients by US$0.004 or 0.4%. Those patients diagnosed clinically increase mean pre-diagnosis cost to patient by US$0.10 or 10% compared to those diagnosed bacteriologicaly. Similarly, TB

diagnosis at private facilities increase mean total pre-diagnosis cost to patient by US$0.18 or 18% compared to diagnosis at public healthcare facilities.

Table 15: Predictors of pre-diagnosis cost among TB cases southwest Ethiopia January to December 2015

Variable		Mean (SD) (US$)[a]	Unadjusted [b] coefficient (β) (95% CI)	Adjusted coefficient[b] (β)(95% CI)	e^{β} (95%CI)
Gender	Male	112.62(0.12)	Ref.	Ref.	Ref.
	Female	101.25(0.11)	-0.05(-0.10,0.01)	-0.065(-0.16,0.026)	0.94(0.86,1.03)
HIV result	Positive	131.2(0.13)	0.93(-0.01,0.19)	0.16(0.003,0.32)*	1.17(1.00,1.38)
	Negative	106.02(0.11)	Ref.	Ref.	Ref.
Mode of diagnosis	Bacteriological	97.00(0.11)	Ref.	Ref.	
	Clinical	121.08(0.12)	0.97(0.04,0.15)*	0.08(0.011,0.17)	1.1(1.01,1.18)
Residence	Urban	114.61(0.12)	Ref.	Ref.	Ref.
	Rural	102.13(0.1)	-0.05(-0.1,0.004)	-0.014(-0.13,0.10)	0.96(0.88,1.06)
Patient delay [c](days)			0.003(0.002,0.003)*	0.004(0.004,0.005)*	1.004(1.004,1.005)*
Provider delay [c](days)			0.003(0.002,0.003)*	0.004(0.004,0.005)*	1.004(1.004,1.005)*
Action before HCF visit	None	106.72(0.12)	Ref.	Ref.	Ref.
	Took action [d]	113.41(0.11)	0.1(0.03,0.14)*	0.14(0.03,0.25)*	1.1(1.0,1.18)
First visited HCF	DOTS center	99.97(0.11)	Ref.	Ref.	Ref.
	Non DOTS center	122.57(0.11)	0.1(0.03,0.14)*	0.013(-0.087,0.112)	1.01(0.92,1.12)
TB diagnosed HCF	Public	101.78(0.11)	Ref.	Ref.	Ref.
	Private	153.88(0.13)	0.18(0.1,0.26)*	0.16 (0.032,0.293)*	1.18(1.03,1.34)*
Number of HCF visited until Diagnosis [b]			0.15(0.13,0.17)*	0.17(0.13,0.32)*	1.18(1.13,1.23)*
Constant (95%CI)				3.04(2.97,3.10)	

*Statistically significant at p<0.05, [a] mean total pre-diagnosis cost [b] outcome variable is logpre-diagnosis cost in US$ [c] variable treated as continuous, [d] self treatment, used holy water, consult traditional healer

6.4.5. Post-diagnosis cost and its predictors

After the diagnosis of TB, patients totally incurred a mean (±SD) US$117.0(±0.09) until completion of treatment (Table 13). During the post diagnosis period patients incurred total of mean (±SD) 43.8(±0.12) for direct medical and non-medical expenses (direct cost). Thus, direct out of pocket expenditure during the post diagnosis period constitutes 35.9% (Fig 5) of the total post diagnosis cost. During the treatment, TB patients had lost median (IQR) of 21(13-35.3) workdays that corresponded to mean (+SD) US$75.2(3.06) income loss (indirect cost). An

alarming majority (94.6%) of the total non-medical cost was incurred for transportation and the rest (5.4%) for meal and lodging while visiting healthcare facilities.

During the post diagnosis period, patients incurred significantly lower mean medical (US$3.89 vs16.9,P<0.001) costs compared to the pre-diagnosis period. In contrary, significantly higher mean non-medical cost (US$60.77 vs 9.74) was incurred during the post diagnosis period compared with the pre-diagnosis. The post diagnosis cost is significantly correlated with patient (γ=0.20, p<0.001 and provider (γ =0.23,p<0.001) delays. The mean total post diagnosis cost is significantly different with treatment center (p=0.01), residence (p<0.001), travel time to treatment center (p<0.001) and hospitalization for treatment (p<0.001) (Table 14).

6.4.6. Predictors of post-diagnosis cost

In the multiple linear regression analysis being rural resident ($\beta_{adj.}$= 0.27,p<0.001), travel time beyond one hour to treatment center ($\beta_{adj.}$=0.1, p=0.03), hospitalized for anti-TB treatment ($\beta_{adj.}$= 0.91,p<0.001), patient delay days ($\beta_{adj.}$= 0.002,p<0.001) and provider delay days ($\beta_{adj.}$= 0.002,p<0.001) independently predicted higher mean post diagnosis cost. On the other hand, following anti-TB treatment at hospital ($\beta_{adj.}$= -0.13,p<0.001) predicted lower mean post diagnosis costs (Table 16). Thus being rural resident increase mean post diagnosis cost to patient by US$1.32 or 32% compared to those urban residents. Every patient and provider delays increase mean post diagnosis cost to patients by 0.002US$ or 0.2%. Those patients hospitalized for anti-TB treatment increased mean post diagnosis cost to patient by US$2.49compared to those not hospitalized. Following anti-TB treatment at hospitals, reduce post-diagnosis cost to patient by US$ 0.13 or 13% compared to following the treatment at health center.

Table 16: Predictors of post diagnosis cost among TB cases on treatment in southwest Ethiopia, January to December 2015

Variable		Mean(SD)US$[a]	Unadjusted [b] coefficient(β) (95% CI)	Adjusted [b] coefficient(β) (95% CI)	e^{β} (95%CI)
Gender	Male	119.73(0.1)	Ref.	Ref.	Ref.
	Female	112.51(0.1)	-0.03(-0.08,0.25)	0.12(-0.23,0.018)	0.92(0.87,1.02)
Residence	Urban	94.02(0.11)	Ref.	Ref.	
	Rural	154.7(0.08)	0.21(0.17,0.26)*	0.27(0.16,0.39)	1.32(1.18,1.48)*
Educational status	Illiterate	137.15(0.09)	Ref	Ref	Ref.
	Primary	117.35(0.09)	-0.06(-0.13,-0.01)*	0.87(0.77,0.97)	0.91(0.81,1.03)
	Secondary	97.79(0.08)	-0.15(-0.22,-0.1)*	0.83(0.72,0.95)	0.89(0.76,1.04)
HIV result	Positive	123.52(0.1)	0.02(-0.05,0.11)	0.08(-0.11,0.27)	1.08(0.90,1.31)
	Negative	116.20(0.1)	Ref.	Ref.	Ref.
Mode of diagnosis	Bacteriological	118.25(0.1)	Ref.	Ref.	Ref.
	Clinical	115.82(0.1)	-0.01(-0.06,0.04)	0.59(-0.04,0.16)	1.07(0.96,1.17)
Treatment center	Hospital	103.05(0.1)	-0.11(-0.15,-0.1)*	-0.13(-0.22,-0.02)	0.88(0.80,0.98)*
	Health center	131.43(0.1)	Ref.	Ref.	
Travel time to treatment	>1hour	105.7(0.08)	0.14(0.1,0.19)*	0.1(0.03,0.25)	1.11(1.03,1.28)*
	<=1hour	145.14(0.09)	Ref.	Ref.	
Patient delay [c]			0.001(0.001,0.002*	0.002(0.002,0.003)	1.002(1.001,1.003*
Provider delay [c]			0.001(0.001,0.002*	0.002(0.002,0.003)	1.002(1.001,1.003*
Action before HCF visit	None	111.85(0.11)	Ref.	Ref.	
	Took action [d]	137.34(0.1)	0.1(0.03,0.15)*	0.14(0.021,0.27)	1.15(1.02,1.30)
TB diagnosed HCF	Public	116.37(0.1)	Ref.		Ref.
	Private	121.27(0.1)	0.02(-0.06,0.09)	0.04(-0.01,0.19)	1.04(0.90,1.20)
Hospitalized for treatment	Yes	240.82(0.1)	0.33(0.21,0.45)*	0.91(0.59,1.24)	2.49(1.79,3.45)*
	No	113.3(0.1)	Ref.	Ref.	Ref.
Constant (95%CI)			7.22(7.01,7.40)		

*statistically significant at p<0.05, [a] mean total post-diagnosis cost, [b] outcome variable is logpost-diagnosis cost in US$[c] variable

treated as continuous, [c] self treatment, used holy water, consult traditional healer

6.5. Delayed anti-TB treatment and patient outcomes (Paper IV)

A median (IQR) of 55 days had been elapsed since onset of illness to TB treatment initiation. Thus 370 (50.3%) and 365(49.7%) had respectively initiated anti-TB treatment within and above the median of 55days. The two groups, those initiated treatments above 55 days (exposed) and within 55 days of onset (non-exposed) were followed for their treatment outcomes. As shown in (Table 17), there were no statistically significant difference with gender (p=0.6), residence (p=0.7), educational status (0=0.2) and HIV status (p=0.4) across the two groups (exposed and non-exposed). In contrary, there were statistical significant difference in proportions of type of TB (p=0.02), age group (p=0.04), and action before formal healthcare visit (p=0.04). At the start of treatment, 723 (98.4%) of the cases were offered with information about the TB disease and its treatment. Nonetheless, adequate information were provided for 357 (48.6%) of the cases were offered adequate information.

Table 17 Characteristics of TB cases across time spent to initiate treatment in southwest Ethiopia January to December 2015

		Total delay(days)		
		>55 (Exposed)	<=55 (Non exposed)	
Variable		n(%) (n=365)	N(%) (n=370)	P value
Gender	Male	219(60)	228(61.6)	0.6
	Female	146(40)	142((30.4)	
Age group (years)	18-34	255(69.8)	248(67.0)	0.04
	35-65	107(29.3)	109(29.5)	
	>65	3(0.9)	13(3.5)	
Residence	Urban	180(49.3)	188(50.8)	0.7
	Rural	185(50.7)	182(49.2)	
Educational status	Illiterate	96(26.3)	116(31.4)	0.2
	Completed primary	206(56.4)	183(49.5)	
	Above secondary	63(17.3)	71(19.1)	
Type of TB	Pulmonary positive	172(47.1)	201(54.3)	0.02
	Pulmonary negative	104(28.5)	109(29.5)	
	Extra pulmonary	89(24.4)	60(16.2)	

HIV status	Positive	37(10.1)	31(8.4)	0.4
	Negative	328(89.9)	339(91.6)	
Treatment center	Hospital	148(40.5)	118(31.9)	0.3
	Health center	217(59.5)	252(68.1)	
Action before HCF[1] visit	None	280(76.7)	306(82.7)	0.04
	Took actions[2]	85(23.3)	64(17.3)	
Treatment information	Adequate	163(44.7)	194(52.4)	0.2
Initial weight	Mean(±SD) Kg	48.7(±8.4)	48.7(±8.9)	0.9

[a] housemaid, daily laborer, [b] students, housewife

During treatment, patients had undergone weight and sputum smear monitoring as per the recommended schedules at end of second, fifth and six months of treatment. Accordingly, 501(68.2%), 266(36.2%) and 239(32.5%) of the cases had documented weight at end of second, fifth and sixth months of treatment respectively. A statistically significant difference in mean weights were observed between baseline and end of second month ($t_{df=500}$=13.94, p<0.001), between sixth month and baseline weight (t_{238}=11.81,P<0.001). At the end of second month 378(51.5%) of the total cases had gained some amount of weight with no statistical significance difference between those initiated treatments within and beyond median of 55days (p=0.2) (Table 18).

On the other hand, among bacteriologicaly confirmed cases (373(50.7%)) eligible for monitoring of sputum smear, 231(61.9%), 200(53.6%) and 178(47.5%) had documented sputum smear result at end of second, fifth and sixth months of treatment respectively. Thus 231 (61.9%) had had at least one sputum check up after during the anti-TB treatment. So, among those with documented follow-up sputum result, (97.4% from both groups converted to negatives at the end of second month treatment, p=0.5).

Table 18: Treatment follow-up characteristics of TB patients across time spent to intiate treatment January 2015 to june 2016

		Total delay(days)		Total (N=735) N(%)	
Variable		>55 n(%)	<=55 n(%)		P value
Sputum smear end of	Positive	3(50)	3(50)	6(1.6)	0.5

2nd month(n=373)	Negative	111(49.3)	114(50.7)	225(60.3)	
	Not available	61(43.0)	81(57.0)	142(38.1)	
Sputum smear end of 5th month(n=373)	Positive	4(80.0)	1(20.0)	5(1.3)	
	Negative	93(47.7)	102(52.3)	195(52.3)	0.4
	Not available	78(45.1)	95(54.9)	173(46.4)	
Sputum smear end of 6th month(n=373)	Negative	89(50.0)	89(50.0)	178(47.7)	0.3
	Not available	83(42.9)	112(57.1)	195(52.3)	
Sputum check up during treatment (n=373)	None	61(43.0)	81(57.0)	142(38.1)	0.3
	At least once	111(48.1)	120(51.9)	231(61.9)	
Weight end of 2nd month	Mean(SD)	51.3(8.3)	51.4(8.9)	51.3(8.6)	0.9
Weight change end of 2nd month	Unchanged/lost	58(47.2)	65(52.8)	123(16.7)	0.2
	Gained	200(52.9)	178(47.1)	378(51.5)	
	Unknown	107(45.7)	127(54.9)	234(31.8)	
Weight end of 5th month	Mean(SD)	54.1(8.4)	53.3(9.5)	53.6(8.9)	0.5
Weight end of 6th month	Mean(SD)	55.0(8.7)	52.8(10.9)	53.9(9.9)	0.1

*cases transferred out to other treatment centers

Six hundred ninety nine (95.1%) of the cases had documented treatment outcome of whom 627(89.7%), 95%CI (87.2%, 91.7%) had successfully completed their treatment. The treatment success was significantly different among cases initiated treatment beyond and within 55 days of onset of illness (86.7% vs 92.6%, P= 0.01) respectively. Thus significant difference in proportions of death (5.5% Vs 2.8%), treatment failure(1.1% Vs 0.3%) and loss to follow-up (6.6% Vs 4.2%) respectively among those delayed treatment beyond and within 55days of onset p=0.04. The treatment success across HIV positive and negatives respectively was 75.8% vs 91.1%, p<0.001. Disaggregation of the treatment success among bacteriologicaly confirmed and clinically diagnosed cases respectively revealed 90.1% vs 89.3%, p=0.7. Among those bacteriologicaly confirmed cases, only 177(47.5%) were declared cured. Furthermore, we found no statistically significant differences in treatment success among pulmonary positive (90.1%), pulmonary negative (88.0%) and extra pulmonary cases (91.1%) p=0.6.

Treatment outcome of patients varied significantly across time elapsed for initiation of treatment. Thus patients delayed to initiate treatment (>55days) had 92% higher risk of having unsuccessful outcome, Adjusted relative risk (ARR)=1.92, 95%CI;(1.30, 2.81). Moreover HIV co infection ARR=2.18,95% CI;(1.47, 3.25) and treatment center being hospital ARR=3.73,95% CI;(2.23, 6.25) independently predicted higher risk of unsuccessful outcomes. In contrast, weight gain at the end of second month treatment, ARR=0.40,95% CI;(0.19, 0.83) predicted lower risk of unsuccessful outcome. Those patients gained weight at the end of two-month treatment compared to the baseline had about 60% lower risk of having unsuccessful outcome (Table 19).

Table 19: Predictors of unsuccessful treatment outcome among TB cases in southwest Ethiopia January 2015 to June 2016 (N=699)

		Unsuccessful n(%)	Successful n(%)	CRR(95%CI)	ARR(95%CI)
Gender	Male	44(10.3)	382(89.7)	Ref.	Ref.
	Female	28(10.3)	245(89.7)	0.9(0.63,1.56)	0.78(0.53,1.16)
Age group(years	18-34	48(10.0)	433(90.0)	Ref.	Ref.
	35-65	20(9.9)	183(90.1)	0.9(0.60,.62)	0.83(0.59,1.16)
	>65	4(26.7)	11(73.3)	2.67(1.11,6.45)	4.17(2.63,6.60)*
Educational status	Illiterate	25(12.3)	178(87.7)	Ref.	Ref.
	Primary	37(9.9)	338(90.1)	0.8(0.50,1.29)	0.81(0.49,1.31)
	Secondary+	10(8.3)	111(91.7	0.67(0.33,1.35)	0.90(0.48,1.69)
Treatment center	Hospital	31(12.6)	215(87.4)	1.39(0.9,2.16)	3.73(2.23,6.25)*
	HC	41(9.1)	412(90.9)	Ref.	Ref.
Action before HCF	None	57(10.3)	498(89.7)	Ref.	Ref.
	Took action	15(10.4)	129(89.6)	1.01(0.59,1.74)	0.84(0.59,1.21)

Mode of TB diagnosis	Bacteriological	35(9.9)	320(90.1)	Ref.	Ref.
	Clinical	37(10.7)	308(89.3)	1.09(0.7,1.7)	0.91(0.69,1.21)
HIV status	Positive	15(24.2)	47(75.8)	2.7(1.63,4.5)	2.18(1.47,3.25)*
	Negative	57(8.9)	580(91.1)	Ref.	Ref.
Weight change end of 2nd month	No change/lost	13(11.2)	103(88.8)	Ref.	Ref.
	Gained	15(4.1)	354(95.9)	0.36(0.18,0.74)	0.40(0.19,0.83)
	Unknown	44(20.6)	170(79.4)	1.83(1.03,3.26)	4.20(2.37.56)*
Total delay(days)	<=55	26(7.4)	327(92.6)	Ref.	Ref.
	>55	46(13.3)	300(86.7)	1.81(1.14,2.85)	1.92(1.30,2.81)*
Treatment information	Inadequate	39(11.0)	314(89.0)	0.86(0.56,1.34)	1.09(0.71,1.68)
	Adequate	33(9.5)	313(90.5)	Ref.	Ref.

*statistically significant at p<0.05 ** Healthcare facility, + secondary and above schooling

7. Discussion

The dissertation investigated time delays to initiate care-seeking, costs incurred by patient and treatment outcomes in the era of reduced treatment regimen in Ethiopia. Thus, the study showed introduction of six-month treatment was associated with better outcomes compared to the eight-month treatment. Furthermore, TB patients in the study area elapsed too long time to initiate care seeking and treatment. The prolonged pathway to treatment is associated with substantial cost to patients and ultimate unsuccessful treatment outcomes.

7.1. TB Treatment outcomes of eight and six month regimens (Paper I)

Treatment of new TB cases in Ethiopia had been for eight-months with combinations of four drugs (2ERHZ) in the intensive phase and two drugs (6HE) during the continuation phase. Following WHO recommendation of switching treatment regimen, the country introduced the six-month treatment regimen as end of 2011. The change was on continuation phase treatment where six months therapy (6HE) replaced with four months (4RH). Thus, comparison of new TB patients treated with 6EH and 4RH during continuation phase revealed no statistically significant difference with respect to socio-demographic, baseline clinical, sputum smear conversion at end of intensive phase treatment. The indifference between the two groups of cases depicts comparability of the groups. However, there was significant difference with treatment success (90.6% vs. 85.3%) respectively among those received the 4RH and 6EH continuation phase treatment. The finding portrays adoption of the continuation phase treatment regimen change [23] in high prevalent and resource constrained settings is working well.

The 4RH continuation phase treatment predicted lower likelihood of unsuccessful treatment outcome compared to 6EH regimen. Similarly, a study from Nigeria [144] reported higher odds of unsuccessful outcome among those treated with 6EH. The explanation could be differences in length and type of drugs used during the continuation phase treatment those influence adherence and ultimate outcome. Studies reported that reduced continuation phase (from 6EH to 4HR) treatment was associated with lower cost and expected mortality [30]. On the other hand, use of rifampcin (R) for longer period for treatment of TB had been associated with better outcomes [31] that might be related with efficacy of the drug. Though rifampicin works better for TB treatment, it had not been recommended in developing countries owing to irregular treatments and high absentee rates in the region [142, 177].To maintain the better outcome with rifampicin throughout the TB treatment period, strong patient and provider relationship should be built for optimum adherence. Optimum adherence is not only for sustaining better outcome to the patients but also for avoidance resistance to this most potent anti-TB drug. Hence, there should be continuous monitoring of adverse effect including drug resistance and adherence among both the healthcare providers and patients.

7.2. Pathways to anti-TB treatment initiation (Paper II)

Prompt detection and treatment of cases has been a priority in the prevention and control of TB. This depends on timely seeking care by patients and reaching at diagnosis within a reasonable time by the health system. Nonetheless, patients in the study area had waited for a median of 25 days (patient delay) and 55 days (total delay) respectively to initiate seeking care and anti-TB treatment. The patients and health system delays contributed nearly equally to the total delay which is consistent with other studies from Ethiopia [42] and elsewhere [38]. The longer time elapsed since onset of illness to treatment initiation implies increased risk of morbidity and mortality among the cases and diseases transmission in the community [36, 53, 178, 179]. This an unacceptably long delays to initiate care seeking and provider delays implies for the need for multifaceted actions towards achieving ambitious targets of reducing TB 90% incidence and mortality by 2035 [16].

Before visits to formal health care facility, patients had taken variety of actions those influenced timing of care seeking. Consistent with other studies, patients who took self-treatment before the formal care seeking were more likely to delay seeking care at the formal care units compared to those first consulted health care providers [112, 116]. This could be due to use of some home remedies or over the counter antibiotics or analgesics those might lessen the manifestation of the illness for the time being [109]. Moreover, those patients first visited traditional healer and holy water are more likely to have higher total delay. This could be due to the beliefs attached to the traditional care and holy water those might inhibit timely presentation and diagnosis [45].

Patients had waited for a median of 25 days until seeking help at formal health care providers which is consistent with 30 days in northern part of Ethiopia [41, 108], 28 days in Uganda [38] and 30 days in Angola [34]. The relatively lower delay could be due to better access to HCF where nearly 80% of the cases traveled less than an hour to reach the first HCF. However, only less than a third (32%) of the cases had made first visit to formal health care within 15 days of onset that is recommended optimum timeline for consultation [23]. Besides, more than half (57%) of the cases did not perceive their care seeking was delayed which implies the symptoms were taken as common and less severe to urge consultation of health care provider.

The first consultation at HCF was made primarily (69.9%) at lower level public health care units

(health posts and health centers) and private clinics. This is consistent with a study in Mediterranean countries that reported two thirds of patients first visited private sectors [104]. Nonetheless, diagnosis of TB was made primarily at hospital (61%) despite only few had made first visit to the hospitals. As a result, majority of the cases had made more than one visit to different HCFs until diagnosis. Similarly, studies from Uganda [38] and China [119] reported significant number of patients had visited more than one HCF until diagnosis. Subsequent to the missed opportunities during the repeated visits, diagnosis of TB had been made after a median of 22 days from the first visit to HCF. This is consistent with 21 days in a study from Amhara Region in Ethiopia [41] but higher than 6 days in Addis Ababa [42] and 9 days in Tigray, northern Ethiopia [39]. The discrepancies could be due to the differences in accessibility to well-equipped HCFs and skilled providers usually situated in cities like Addis Ababa. The longer provider delays due to the repeated visits portray high level of missed opportunities of early diagnosis that could have increased infectious period of the cases and costs incurred by the patients and households. In addition, the longer provider delay shows TB diagnostic inefficiency of lower level public and private healthcare facilities.

Longer provider delays had been reported among patients who first visited HCFs not providing DOTS services including health posts and private clinics. This is consistent with a study from Uzbekistan [112] and India [180].The higher provider delay at lower care units and private clinic could be due to lack of supplies, guidelines and skilled providers that enhance adherence to the national TB control program. In the current study, diagnosis of TB was mainly made at hospitals despite many patients had made first visits at the lower public and private clinics. This depict patients are being provided with unnecessary drugs and treatments at series of HCFs visits. Besides, the medications at the repeated visits themselves lead to delays to diagnosis and serious outcomes including drug resistance [181]. On the other hand, the lower health care units and private clinics might lack proper logistics and skilled providers to timely diagnose the cases. Hence, equipping the HCFs with cost effective and efficient rapid diagnostic tests along with expansions of the DOTS package at the reach of community is required to curb the long delays.
Patients co-infected with HIV are more likely to delay care seeking compared to those non-infected. This could be due to the alteration of classical clinical manifestations and signs of TB among HIV co infected patients [182]. On the other hand, patients suspected or tested HIV

positive delay to present themselves to HCF due to fear of stigma attached to the co-occurrence of TB and HIV [52, 113, 117] . As a result, the high mortality among HIV co infected TB patients had been partly explained by the delays to TB treatment [34, 35]. Those extra pulmonary cases patients are more likely to delay seeking care compared to the pulmonary cases. Similarly, a study from northwest Ethiopia reported higher odds of delayed care seeking among EPTB [48]. This could be due to the fact that EPTB cases manifest with less severe and non-specific symptoms so that patients consider their illness to be non-serious and do not deserve medical attention [180].

Patient's perception and knowledge towards the TB disease and control activities do have impact on the care seeking practices. The study revealed that patients with good knowledge towards the TB disease and program are less likely to delay seeking care. Similarly, other studies have reported lack of knowledge and mistrust of the TB program as a reason for delayed care seeking [44, 104, 114]. In contrast, awareness and belief about TB's curability is associated with longer patients delay [38, 50]. These imply need for awareness creation towards the TB illness and its control program to clear the paradox between the belief and longer delay.

We found that patients delayed to seek care are also more likely to have delayed diagnosis and treatment after they initiated care seeking. In contrast a study in Georgia [115] reported those patients with increased patient delay are less likely to have prolonged diagnostic delay. The discrepancy could be due to differences in measurement of the two delays. The higher odds of provider delay among those delayed to seek care can be explained by patients use of different forms of self-treatment and homemade remedies those might alter the manifestations of the TB illness that pose difficulties in timely diagnosis [109, 115]. Those patients delayed to seek care might have been ill for such long duration at which time productivity is compromised. Hence, the patients might be unable to cope with the costs required to have timely diagnosis even after initiating the care seeking. In addition, the long ill days are also associated with more severe disease at presentation [53] which hinders timely diagnosis [43].

7.3. Pre –and post TB diagnosis costs to patients (Paper III)

The dissertation revealed that TB cases on DOTS incurred substantial cost across pathways to TB treatment. Thus median out of pocket expenditure for the episode of TB illness amounted US$59.58 that constitutes more than a quarter (29.4%) of the total cost. More than half (53.6%) of total cost were incurred before diagnosis of TB and majority (70.6%) of the total cost were attributed to nearly 52 lost workdays per patient. Compared to the post diagnosis, significantly higher medical and indirect costs and lower non-medical costs were incurred during the pre-diagnosis period. Patient and provider delays, taking informal treatment before HCF visit, diagnosis at private facilities, clinical diagnosis, and number of visited health facilities predicted increased pre-diagnosis cost. On the other hand, rural residence, hospitalization for treatment and treated at health center predicted higher post diagnosis cost.

The substantial amount of money spent by patient despite the "free TB service" indicates the difficulty of attaining global target of avoiding no families to face catastrophic cost due to TB [16] by 2025. This is because only sputum smear test and anti-TB drugs are waived for patients. However, an alarming majority (95%) of the medical costs was incurred for drugs other than anti-TB and diagnostic tests showing patients are being administered with unnecessary drugs and tests. Hence, there is a need to capacitate healthcare providers to early suspect TB and prescribe standard diagnostic tests. Similarly, majority of non-medical costs were spent for transportation depicting poor accessibility of HCF providing efficient TB diagnosis.

The total cost incurred across the care seeking and treatment pathways are significantly correlated with both patient and provider delays. The increased pre-diagnosis cost with patient delay could be due to increased risk of severe manifestation [53] that lead to hospitalization and companion during care seeking and treatment. Furthermore, the patient delay is associated with informal care including self-treatment and traditional cares [112, 135] incurring cost. The patient delay is associated with longer lost workdays that might have reduced patient income. On the other hand, delay at health system (provider delay) is associated with repeated visits to different HCF incurring both medical and non-medical costs. Few patient in this study suggested lack of money as a hindrance and delay care seeking in turn leads to increased cost for subsequent care. This indicates interdependence between delay to care seeking and cost of care.

Those patients diagnosed clinically incur significantly higher pre diagnosis cost. This could be due to national diagnostic algorithm that requires 2-8weeks follow-up for the clinical diagnosis of TB [23]. The clinical diagnosis requires experienced clinician decisions guided with better diagnostic facilities. Such facilities exist at few healthcare facilities situated in cities for which patients need to travel repeatedly. The relatively lower cost of bacteriologicaly confirmed diagnosis could be due to exemption of sputum smear microscopy and culture by the national TB control program. Hence, ensuring efficient diagnostic algorithms and quality bacteriological tests can reduce the financial burden of TB patients.

Consistent with other studies [140, 183] patients diagnosed at private facilities incur significantly higher pre diagnosis cost compared to those at public. The different cost items and rates at the private facilities can explain this, where every service including sputum microscopy is charged. Since there were no PPM-DOTS in the study area at the time of study, the private HCF might not implement the proper diagnostic algorithm that might lead to delay and extra cost. Furthermore, public health facilities requirement of retesting positive sputum result from private facilities for treatment initiation lead to delay and extra cost [184].

We found patients followed their ant-TB treatment at hospital had significantly lower post diagnosis cost compared to those followed at health center. This could be due to full time staffs that exclusively provide TB patient care at hospitals. However, at health centers, DOTS providers carryout multiple duties other than TB DOTS that might have increased patient waiting time and respective costs. In addition, health centers are situated in rural areas where there is no transport access within villages in contrast to hospitals in urban areas easily accessible to patients within the town. Thus statistically significant difference in mean total time (71.17minutes Vs 106.79minutes, $p<0.001$) had been respectively spent per each patient visit to hospitals and health centers. Consistent with other studies [183, 185] we found significantly higher post diagnosis cost incurred by patients from rural areas compared to those from urban. The reason could be due to significantly higher mean time spent per each visits among patients from rural and urban residents (119.51minute Vs. 68.35minutes,$p<0.001$) respectively.

7.4. Delayed anti-TB treatment and patient outcomes (Paper IV)

The study revealed patients elapsed too long time (median of 55 days) to initiate anti-TB treatment since onset of the illness. Accordingly, the treatment success was significantly different (92.6% vs 86.7%) respectively among those initiated treatment within and beyond 55days of onset. Those patients initiated anti-TB treatment beyond 55days of onset had higher risk of unsuccessful outcomes including death, lost to follow up and treatment failure. Patients initiated treatment within and beyond 55 days of onset had undergone significantly diverse healthcare seeking practices, patient and provider delays. However, both groups of patients had no significant differences in sputum smear conversion and weight changes at end of second month treatment. The longer delays to initiate treatment accompanied by higher risk of unsuccessful outcomes depict increased morbidity and mortality to patients and prolonged period of transmission to the community. The finding suggests need for prompt detection and treatment of cases to ensure better outcomes among patients and reduce burden in community.

The higher risk of unsuccessful outcome among those patients delayed to initiate anti-TB treatment had been consistently reported in studies from Ethiopia [145] and elsewhere [54]. The increased risk of unsuccessful outcome among patients delayed treatment initiation could be due to various factors. First, delayed initiation of treatment had been reported to be associated with severe clinical presentation [36, 53] which predict unsuccessful outcomes [146]. In this study, patients delayed to initiate treatment had relatively higher rate of hospitalization (3% vs 2.1%) that would be proxy measure of severe presentation. Second, a delay to treatment is associated with both prescribed and self-treatment those lead to poor treatment outcome [115, 181, 186]. In the current study, the majority (84.7%) of the cases had visited an average of 2.2 HCFs until diagnosis of TB when patients were taking both self and prescribed medicines. Third, delays to treatment often accompanied by higher direct and indirect costs that impoverish households [65, 187] and ultimately lead to poor treatment compliance and outcome [187]. In this study, we observed significantly higher median pre-diagnosis (US$171.7 vs. 61.5,p=0.001) and post-diagnosis (US$108.70 vs.75.2,p<0.001) costs respectively among those initiated treatment which beyond and within 55 days of onset.

7.4.1. Other predictors of treatment outcome

In response to influences of HIV and TB on each other, TB/HIV collaborative interventions had been recommended [85]. Thus systematic review in African context reported better outcomes among concurrently screened and managed TB and HIV infected patients [188]. In the current dissertation, 77.5% of those TB cases retrieved retrospectively (2008-2014) and 100% (for 2015) of the cases enrolled prospectively had documented HIV status. Thus, TB/HIV co infection ranged from 9.3% to 9.7% comparable to the national average of 8% for the year 2015. The proportion of HIV screening among TB cases showed progress over the years and higher than a national average of 77% for the year 2015[18]. Nonetheless, only few (39.7%) of those HIV co infected TB cases had documented ART service provision which is far lower than the national average of 79% for 2015 [18].

Consistent with studies in Ethiopia [145, 154, 155] and elsewhere [149, 150, 152, 153], HIV co-morbidity increased risk of unsuccessful outcome among TB cases. Thus, treatment success (75.8% vs 91.1%, $p<0.001$) was significantly lower among HIV co infected and negatives respectively. The observed lower treatment success among HIV co infected is far below the targeted 90% success to be met by 2020 [16]. The increased risk of unsuccessful outcome among the HIV co infected could be due to longer median time to initiate care-seeking among HIV co infected (29days) compared to 24 days among negatives. Studies reported that HIV co morbidity delay anti-TB treatment initiation [52, 148] that explained the high mortality among HIV co infected TB patients [34, 35]. In addition, HIV co infection independently increases risk of unsuccessful outcome due the complex and overlapping drug interactions and toxicities and TB-associated immune reconstitution inflammatory syndrome [189]. Furthermore the low uptake of ART and CPT those predicted worse outcome elsewhere [149] can also explain the lower treatment success among HIV co infected cases.

Socio-demographic attributes of TB cases play an important role of predicting outcome among patients. Age of TB cases had an inverse relation with unsuccessful outcome where the odds of unsuccessful outcome increase with age. The finding is consistent with reports from studies in Ethiopia [165, 190] and elsewhere [152, 191, 192]. Similarly, several studies also reported that

older patients were more likely to have unsuccessful outcomes than those younger cases [163, 165, 190, 193]. The increased risk of unsuccessful outcome among the older could be due to higher occurrence of age related co morbidities [191] those increase risk of unsuccessful outcomes.

In this dissertation, patients took anti-TB treatment at hospital had higher risk of unsuccessful outcome compared to those treated at health center. Similarly, Studies from Ethiopia [169] and Nigeria [164] reported treatment centers predicted treatment outcomes. The higher unsuccessful outcomes among those treated at hospitals could be due to significantly higher proportion of delays to initiate anti-TB treatment (55.6% Vs46.3%,p=0.02), HIV co infection (14.3% Vs 6.4%,p<0.001) and hospitalization (5.3% Vs 1.1%,p=0.001) at hospitals than health centers. Studies reported HIV co infection [149, 150], hospitalization [146] and delays to treatment[54, 145] to predict higher risk of unsuccessful outcomes. Moreover, patients treated at hospitals were more of pulmonary negative (36.5% vs 24.7%,p<0.001) and extra pulmonary (21.8% vs 19.4%,p<0.001) those predict unsuccessful outcome [165].

Regular monitoring of TB patients during treatment is vital to assess response to therapy and facilitates treatment completion. Accordingly regular sputum and weight monitoring have been recommended TB patients on treatment [27]. Despite, low sensitivity and modest specificity of sputum results at the end of intensive phase to predict failure and relapse [194], sputum conversion to negative had been among the indicators of TB program [27]. Consistent to findings from African settings [195] majority of those patients undergone sputum checkup during treatment converted to negative. In the current study there was no significant in sputum smear conversion at end of second month treatment differences among patients initiated treatment within and beyond 55days of onset. Studies from Ethiopia [165] and elsewhere [196] reported, negative sputum smear conversion at the end of intensive phase treatment predicted lower risk of unsuccessful outcome. In this study, 3/6(50%) of those treatment failure cases had positive smear at the end of second month treatment. On the other hand, detection of sputum positive during treatment trigger further patient assessment that influence treatment regimens and ultimate outcome. The higher risk among those positives could be due to possible poor quality of initial therapy and co morbid conditions that interfere with adherence or response [27].

Patients gained some amount of weight at the end of second month treatment had lower risk of unsuccessful outcomes which is consistent with other studies [161, 162]. This could be due to positive association between weight gain and level of improvement from the TB illness. Changes in weight while on treatment might be an indication of appropriateness of the anti-TB drug dose that affects the outcome. On the other hand, those with unknown weight change at the end of first two months treatment had higher odds of unsuccessful outcomes compared to those gained weight. The weight change might be unknown due to patients' treatment interruption subsequent to treatment default or death those constitute unsuccessful outcome.

7.5. Validity and Generalizability

The validity (internal or external) of any study is dependent on study designs employed, tools for data collection, appropriate methods to handle random and non random errors. Thus, various designs including cross-sectional and longitudinal study designs were used to answer the research questions. Besides, the dissertation employed different methods to control possible influences of bias, chance, and confounding factors on the validity of the dissertation.

To minimize the role of selection bias, adequate and representative samples of TB cases were enrolled consecutively from representative health facilities. In addition, the dropout rate for the prospective cohort study was 9.7% that was nearly the same as stipulated rate of 10% during sample size calculation. On the other hand, use of standard data collection instruments, interviewing patients as soon as possible, recruitment of qualified data collectors (Nurses) and supervisors (Public health specialists), thorough training, supervision and proper data management minimized measurement bias.

To control for the effect of confounding factors; first the dissertation captured as much predictor and confounding variables as possible guided by the literature review and conceptual framework. Then eligible variables for multivariate analysis were selected based on strength of association on bivariate analysis, clinical and practical importance. Finally different multiple regression models including linear, logistic, and log-binomial were fitted for the selected variables to identify independent predictors. In all the analysis, the role of chance was checked using proper statistical significance tests at 5% significance level.

The dissertation was carried out among new TB cases registered at public health centers and hospitals. The health facilities represented ten districts of three zones (Bench-Maji, Kaffa and Sheka) in SNNPR. TB cases registered at public health facilities across the SNNPR in particular and the country in general do exhibit similar characteristics. Hence, the findings of this dissertation (healthcare seeking practices, costs incurred by patient and treatment outcomes) can reasonably be generalizable to new TB cases registered at public healthcare facilities across the SNNPR and Ethiopia with similar settings.

7.6. Strengths and limitations

The dissertation has some limitations. First assessment of healthcare seeking practices was carried out on those cases ultimately sought care and on treatment at the time of the study. Therefore, the finding might not reflect experiences of those did not seek care and initiate treatment. Second assessment of time delays to treatment and costs incurred relied on patient self-report, which was liable to recall bias. We minimized the bias by interviewing patients soon after diagnosis and helping them to recall using local events. Third, there was no set optimum time for delayed treatment; median time elapsed since onset of illness was used to ascertain delayed treatment. Lastly, cost ascertainment employed patient perspective and prevalent approach so that costs incurred by health system, households and community were not determined.

For the comparison of treatment outcomes among six and eight month regimens, the study was limited to control for possible changes in medical resources, polices and quality of care across the study periods those could influence the treatment outcomes. However, the patients did not

have significant differences with socio-demographic and clinical factors. The other limitation was lack of drug susceptibility pattern across the treatment regimens.

The study had several strengths. First, the study employed relatively large sample those were consecutively enrolled that minimized selection bias. Second, patient costs were ascertained longitudinally since onset of illness to treatment completion. Thus, predictors of costs incurred before and after diagnosis of TB were assessed. Third, prospective assessment of effect of delayed treatment on patient clinical outcome and direct estimation of risk were also strengths of the study. Lastly, use of standard outcome definition and abstraction of clinical data from standard registers were strengths of the dissertation.

8. Conclusion

The dissertation revealed that the switch of continuation phase TB treatment regimen from 6EH to 4RH has brought significantly lower unsuccessful outcome. The findings verified applicability of the WHO recommendation and national adoption of the regimen change to high prevalent and resource constrained settings.

TB cases in the study area elapsed too long time to initiate care seeking and treatment in the era of shortened regimen. The delays are at home (patient) and provider (health system) those are positively correlated and contributed nearly equally to the total delay. The unacceptably long delay at home is accompanied by high level of missed opportunities of early diagnosis at health system. Both delays imply longer period of morbidity to the patients and transmission within the

community. The patient, provider and total delays are attributed to the patient, disease and health system related factors reflecting need for multifaceted intervention.

Throughout the care seeking and treatment pathways, TB cases on DOTS incurred substantial direct and indirect cost. Despite the "free service", TB patients expended significant amount of money for care seeking and following anti-TB treatment. The patients incurred significantly higher cost during the pre-diagnosis period compared to the post diagnosis. Increased pre-diagnosis costs are attributed to patient and provider delays, prior informal care, seeking care at private healthcare facilities and clinical TB diagnosis. On the other hand, higher post diagnosis costs were attributed to patient and provider delays and rural residence.

The delayed treatment initiation is associated with higher risk of unsuccessful outcome including death, treatment failure and lost to follow-up. Apart from the delayed treatment, HIV co infection, treatment center, weight change and sputum conversion at the end of second month treatment independently predicted unsuccessful outcomes.

9. Recommendations

Policy and practical implications

- Raise community level awareness about TB and promote early care seeking involving health extension program and other related health programs
- Intensify TB case finding involving the community, formal and informal providers
- Engage traditional healers and priests at holy water in TB case finding
- Decentralize efficient TB diagnostic and therapeutic services to lower level public and private healthcare facilities
- Revise the prolonged diagnostic algorithms for smear negative and extra pulmonary TBs
- Scale up and decentralize rapid diagnostic technologies like GeneXpert MTB/RIF

- Scale up of national community and social insurance schemes to the study area
- Introduction of cost reimbursement mechanisims
- Adopt and implement patient centered TB care to reduce the frequent patient visits
- Strengthen the TB/HIV collaborative interventions

Further research directions

- Design of effective and efficient early TB case finding strategies
- Conduct active case finding through community based TB prevalence surveys
- In-depth understanding of reasons for patient and provider delays using qualitative designs
- Costs of TB care to health system and household employing societal perspective costing
- Implications of the costs of TB care to patients and household impoverishment
- Evaluation of sensitivity and specificity of Genexpert test in local settings
- Readiness of private and public healthcare facilities to introduce rapid diagnostic tests
- Level of patient and healthcare provider adherence to the six month treatment regimen
- Instate drug resistance surveillance for the six month anti-TB treatment with rifampicin combination throughout the course of treatment

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RESEARCH ARTICLE Open Access

Tuberculosis treatment outcomes of six and eight month treatment regimens in districts of Southwestern Ethiopia: a comparative cross-sectional study

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Abstract

Background: A switch of continuation phase tuberculosis (TB) treatment regimen from Ethambutol (E) and Isoniazid (H) combination for 6 months (6EH) to Rifampicin (R) and Isoniazid (H) combination for 4 months (4RH) was recommended. However, the effect of the regimen switch in Ethiopian setting is not known.

Methods: A comparative cross-sectional study among 790 randomly selected new cases of TB (395 each treated with 4RH and 6EH during the continuation phase) was conducted in nine health centers and one hospital in three zones in southwestern Ethiopia. Data were abstracted from the standard unit TB register composed of standard case and treatment outcome definitions. Data were analyzed using STATA version 13 where binary logistic regression was fitted to identify independent predictors of unsuccessful treatment outcomes at 5 % significance level.

Results: Over all, 695 (88 %) of the patients had a successful treatment outcome with statistically significant difference (85.3 % vs 90.6 %, $p = 0.02$) among the 6HE and 4RH regimens, respectively. After adjusting for confounders, 4RH continuation phase treatment regimen adjusted odds ratio (AOR) [(95 % confidence interval (CI)) 0.55 (0.34,0.89)], age [AOR (95 % CI 1.02 (1.001,1.022)], rural residence [AOR (95 % CI) 2.1 (1.18,3.75)] Human Immunodeficiency virus (HIV) positives [AOR (95 % CI) 2.39 (1.12,5.07)] and increased weight at the end of the second month [AOR (95 % CI 0.28 (0.11,0.72)] independently predicted treatment outcome.

Conclusion: The switch of continuation phase TB treatment regimen from 6EH to 4RH has brought better treatment outcomes which imply applicability of the recommendation in high prevalent and resource constrained settings. Therefore, it should be maintained and augmented through further studies on its impact among the older, rural residents and HIV positives.

Keywords: Tuberculosis, Continuation phase, treatment regimen, Treatment outcome, Ethiopia

Background

In the history of tuberculosis (TB) control, discovery of chemotherapy [1] brought about dramatic changes in patient survival. Before the advent of chemotherapy, 30–40 % of TB cases used to die within a year and 50–70 % within 5–7 years after the onset of TB illness [2]. Introduction of chemotherapy resulted in cure and reduction of mortality for majority of TB cases [1, 3]. However, shortly after the therapy, resistance to drug and poor adherence by patients were reported [4]. Consequently, the first standard combination therapy for 12 months comprised of Thiacetazone (T), Isoniazid(H) and streptomycin(S) for the first 2 months (2STH) followed by T and H for 10 months(10TH) was issued [2]. Subsequent to the introduction of rifampicin (R), effective short-course chemotherapy regimens for less than 12 months became standard therapy [2, 5–7]. The short-course regimens comprised of an initial, or bactericidal, phase called intensive that aimed to kill bacilli and make patients non infectious and a continuation or sterilizing

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phase which eliminates persisting mycobacteria to prevent relapse [1, 8]. Thus evidence based combinations of drugs for different categories of cases have been recommended for the two phases across the different regimens [5–7].

Introduction of Rifampicin has shortened TB treatment duration [1, 9]. In 1991, an eight months treatment regimen composed of 2 months intensive with Isoniazid(H), Rifampicin (R), Pyrazinamide(Z) and Ethambutol(E) (2RHZE/S) and 6 months continuation (6HE) phases were recommended for all new cases of TB across the world [6]. To avoid resistance to the most potent drugs, isoniazid and rifampcin and ensure patient adherence, directly observed treatment short course (DOTS) strategy was launched in 1994 [10]. Later in 2003, a directly observed intensive phase treatment followed by two continuation phase regimens, 6 months of isoniazid plus ethambutol (6HE) or 4 months of isoniazid plus rifampicin (4HR) were recommended. The 4HR continuation phase treatment regimen needed to be observed throughout the treatment period whereas the 6EH regimen relied on self administered treatment [5]. As a result, regimens without rifampicin had been considered safer in developing countries owing to irregular treatments and high absentee rates [1, 5]. However, the latest World Health Organization (WHO) guideline recommends 2-month initial phase of (2RHZE) and a 4-month continuation phase (4RH) for the treatment of virtually all forms of new TB cases across the globe [7].

The government of Ethiopia has adopted the switch of 4HR continuation phase TB treatment for all new cases and accommodated in the latest TB treatment guideline [11]. Though global strategies are relevant, investigation of the applicability to the local settings is highly required. A continuation phase treatment with 4HR regimen elsewhere has demonstrated lower unsuccessful treatment outcomes and costs as compared to 6EH continuation phase [12–15]. But well designed studies evaluating effects of the introduction of 4RH for the continuation phase TB treatment in high TB burden and resource limited settings like Ethiopia are limited. Thus, we compared treatment outcomes of TB cases who received 4RH and 6EH continuation phase regimens under routine program condition in high burden and resource limited setting. Our objective was to compare baseline patients' bacteriologic, socio-demographics, clinical characteristics and treatment outcomes among those TB patients treated with the 4RH and 6EH continuation phase treatment regimens.

Methods

Study setting

We conducted this study in ten health facilities (one hospital and nine health centres) in three remote *zones* of Southern Nation Nationalities and Peoples Region (SNNPR), one of the nine regions in Ethiopia with about 18million population [16]. Ethiopia is among the 22 TB High Burden Countries (HBC) where 230,000 incident cases of which 147,592 (64 %) were notified. In the same year, 16100 deaths and 90 % treatment success among the smear positives cases registered in 2011 were reported [17, 18]. The country has adopted and implemented the DOTS strategy for the treatment of all forms of TB. Accordingly new cases of TB had been treated with directly observed RHZE combinations for the first 2 months (2RHZE) followed by self administered EH combinations for six months (6EH) [19]. As of the end of 2011, the continuation phase treatment was switched from 6EH to 4RH. Thus the regimen became directly observed 2RHZE/4RH combinations for all forms of new TB cases throughout the 6 months treatment period [11].

The three study *Zones*, Bench Maji, Kaffa and Sheka are located at the southwestern border of the SNNPR where about 2,064,102 peoples reside [16]. The *zones* (an administrative unit that liaison *weredas* with the region) are organized in to four town administrations and 26 *weredas* (lowest administrative unit closer to the community) those have three hospitals and 65 health centers those provide TB DOTS services for free. However, the three hospitals and only 27 health centers were providing TB/Human Immunodeficeincy Virus (HIV) collaborative activities [20].

Study design and sampling

A comparative cross-sectional study among TB cases treated with 2RHZE/6EH and 2RHZE/4RH regimens was carried out. New cases registered between 2008 and 2014 were eligible of which those aged above 15 years were studied. Sample size was estimated using the Stat Calc program of Epi Info version 7 [21] with 95 % confidence level, 80 % power and ratio of 6EH to 4RH ($r = 1$). Accordingly, 512 cases (256 from each group) was required to detect 7 % difference [12] in the proportion of unsuccessful outcome among the 6EH and 4RH groups. Finally, considering the design effect of 1.5 and 10 % missing records, a total of 846 cases were required. The samples were selected through proportional allocation to the three zones followed by selection of *weredas* and health facilities from the zone using probability proportional to size. The allocation and selection was made based on total number of cases reported from the *weredas* and health facilities during 2008 through 2014. Lastly, cases from the selected health facilities were selected randomly using SPSS statistical software using TB unit number of the cases.

Data were extracted from a standard unit TB register recommended by the WHO [11, 19, 22] using extraction

format prepared for the study. Thus patients' baseline attributes (age, gender, residence, sputum smear, type of TB, HIV status) and follow-up measures (sputum smear, weight, drug regimen and treatment outcomes) were extracted. The following standard case and outcome definitions were adopted and used for the study [11, 19].

- New case of TB a patient who never had treatment for TB, or had been on anti-TB treatment for less than four weeks in the past
- Other cases are those patients who do not fulfill the criteria for new, relapse, and return after default or treatment after failure.
- Cured: a patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear or culture-negative in the last month of treatment and on at least one previous occasion.
- Treatment completed: completed treatment but does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
- Treatment failure: a patient whose sputum smear or culture is positive at 5 months or later during treatment or patients found to harbor Multidrug Resistant (MDR) TB strain at any point of time during the treatment, whether they are smear-negative or -positive.
- Died: a patient who dies for any reason during the course of TB treatment.
- Defaulter/loss to follow-up: a patient who has been on treatment for at least 4 weeks and interrupted treatment for eight or more consecutive weeks.
- Successful treatment: a treatment that ends up in cure or treatment completion
- Unsuccessful treatment: a treatment that end up in treatment default or loss to follow up, treatment failure or death.

The extracted data were checked for consistency and completeness and entered in to Epinfo version 7 that later exported to STATA 12 [23] for analysis. Data were described separately for the two groups (6EH and 4RH) using frequencies, mean, standard deviations and tables. Besides, crude comparisons of the baseline and follow up measures among the 6EH and 4RH groups were made using chi square (x^2) or t-tests as appropriate. Subsequently, bivariate and multiple binary logistic regression analysis were made to compute crude and adjusted odds ratios respectively between the explanatory and outcome variables. Multiple logistic regression model was fitted with those variables having $p \leq 0.2$ on bivariate analysis. Finally, statistical significance was judged at $p < 0.05$ and/or 95 % confidence interval (CI) of odds ratio (OR) excluding one.

Ethical considerations

We received ethical approval from the institutional review board of the College of Health Sciences at Addis Ababa University. Accordingly, anonymous patient data were extracted from routine service registry upon permission from the respective institutions.

Results

Demographic and baseline clinical characteristics

We retrieved 846 patient records of which 790 (93.4 %) with complete outcome records [395 each treated with 2RHZE/6HE and 2RHZE/4RHregimens respectively] were described and analyzed. The mean age of the patients was 30.8 (31.5 vs 30.9 years, $p = 0.5$) respectively, for those treated with 6HE and 4HR (Table 1). More than half, 56.6 % and 55.7 % of the patients were male and reside in rural areas, respectively, with no statistically significant difference among the two groups. With regard to the patient profile, 86.8 % and 77%were registered at health center and had pulmonary TB, respectively. Of the patients, 765 (96.8 %) were new cases (378 treated with 6EH vs387 with 4RH regimen) and the rest ((25 (3.2 %) (17 from 6EH vs 8 from 4RH) were transferred in and other cases treated with new case regimen. Human Immunodeficiency virus (HIV) test result was available for 612 (77.5 %) with statistically significant difference among the two groups [283 (71.6 %) from 6EH and 329 (83.3 %) from 4RH, $p < 0.001$]. Among those tested HIV positives, 44 (57.1 %) received either Cotrimoxazole Prophylactic Therapy (CPT) or Antiretroviral Therapy (ART) with no statistically significant difference among the regimens 24 (64.9 %) from 6EH and 20 (50 %), $p = 0.2$.

Patient follow-ups and treatment outcomes

A total of 695 (88 %) of the patients had successful treatment outcomes with statistically significant difference (85.3 % vs 90.6 %, $p = 0.02$) among the 6HE and 4RH groups, respectively (Table 2). A total of, 324 (90.3 %), 208 (85.4 %) and 163 (91.1 %) of pulmonary positive, pulmonary negative and extra pulmonary TB cases respectively had successful outcomes with statistically significant difference, $P = 0.03$. Besides, statistically significant differences in successful outcomes, 64 (83.1 %), 482 (90.1 %) and 149 (83.7 %, $p = 0.005$ were also found among HIV positive, HIV negatives and unknown HIV status TB cases, respectively.

Measurements of patient weight at the end of second, fifth and sixth/seventh months of treatment were available for 504 (63.8 %), 145 (18.4 %) and 141 (17.8 %) respectively. Thus, 368 (46.6 %) or (48.4 % from 6EH and 44.8 % from 4RH, $p = 0.4$) have gained some amount of weight at the end of second month of treatment. On the other hand, of those initially smear positive pulmonary

Table 1 Demographic and clinical characteristics of the tuberculosis patients registered between, 2008–2014, Southwest Ethiopia

Variable		Continuation phase treatment regimen		Total	*P* value
		6EH (*n* = 395) *n* (%)	4RH (*n* = 395) *n* (%)		
Age (years)	Mean ± SD[a]	31.1 ± 12.9	30.5 ± 11.9	30.8 ± 12.4	0.5
Gender	Male	221 (55.9)	226 (57.2)	447 (56.6)	0.7
	Female	174 (44.1)	169 (42.8)	343 (43.4)	
Residence	Urban	175 (44.3)	175 (44.3)	350 (44.3)	1
	Rural	220 (55.7)	220 (55.7)	440 (55.7)	
Zone	Kaffa	106 (26.8)	104 (26.3)	210 (26.6)	0.9
	Bench Maji	206 (52.2)	203 (26.3)	409 (51.8)	
	Sheka	83 (21.0)	88 (22.3)	171 (21.6)	
Treatment center	Hospital	55 (13.9)	49 (12.4)	104 (13.2)	0.5
	Health center	340 (86.1)	346 (87.6)	686 (86.8)	
Baseline weight	Mean ± SD[a]	47.6 ± 8.6	48.4 ± 8.5	48 ± 8.5	0.2
Baseline sputum smear	Positive	186 (47.1)	173 (43.8)	359 (45.4)	0.6
	Negative	151 (38.2)	165 (41.8)	316 (40)	
	Unknown	58 (14.7)	57 (14.4)	115 (14.6)	
Type of TB	Pulmonary	303 (76.7	305 (77.2)	608 (77.0)	0.9
	Positive	186 (47.1)	173 (43.8)	359 (45.4)	
	Negative	117 (30.4)	132 (33.4)	252 (31.9)	
	Extra pulmonary	92 (23.3)	90 (22.8)	179 (23)	
HIV status	Positive	37 (9.4)	40 (10.1)	77 (9.7)	<0.001
	Negative	246 (62.3)	289 (73.2)	535 (67.7)	
	Unknown	112 (28.4)	66 (16.7)	178 (22.5)	
Received CPT[b] (*n* = 77)	Yes	18 (48.6)	17 (42.5)	35 (45.5)	0.6
Received CPT or ART[c] (*n* = 77)	Yes	6 (16.2)	6 (15.0)	12 (15.6)	0.8
Received ART (*n* = 77)	Yes	12 (32.4)	9 (22.5)	21 (27.3)	0.3
Baseline sputum smear	Positive	186 (47.1)	173 (43.8)	359 (45.4)	0.6
	Negative	151 (38.2)	165 (41.8)	316 (40)	
	Unknown	58 (14.7)	57 (14.4)	115 (14.6)	

[a]Standard deviation,[b] *CPT* Cotrimoxazole prophylactic therapy, [c]*ART* antiretroviral therapy

TB cases, 78.6 % had undergone sputum follow up examination at least once after the diagnosis (76.3 % among 6HE and 80.9 % among 4HR, $p = 0.3$). Thus sputum smear results at the end of second, fifth and sixth/seventh months of treatment were available for274 (76.3 %), 184 (51.3 %) and 179 (49.9 %) cases respectively with no statistically significant differences among the 6EH and 4RH regimens. The majority of the smear positives (69.9 % vs 79.8 % respectively from the 6EH and 4RH regimens, $p = 0.4$) converted to negative at the end of second month treatment.

Factors associated with unsuccessful treatment outcomes

In bivariate analysis patient age, residence, zone, weight change at the end of the second month of treatment, sputum smear follow-up and continuation phase regimen are associated with treatment success at $p < 0.05$. But, in multivariate analysis 4RH continuation phase treatment regimen [AOR (95 % CI) 0.55 (0.34,0.89)], patient age [AOR (95 % CI) 1.02 (1.001,1.022)], rural residence [AOR (95 % CI) 2.1 (1.18,3.75)], treated at health center [AOR (95 % CI) 0.37 (0.14,0.97)], HIV positives [AOR (95 % CI 2.38 (1.12,5.07)], gained weight at the end of the second month [AOR (95 % CI) 0.28 (0.11,0.72)] independently predicted unsuccessful treatment outcome (Table 3). The odds of unsuccessful outcome was higher among the older, rural residents, HIV positives and unknown weight change at the end of second month treatment. The odds of having unsuccessful outcome increase by 2 % for every one year increase in age (AOR = 1.02).On the other hand, treated with 4RH continuation phase regimen, being treated at health center and weight gain at the end of

Table 2 Patient follow-up measures and treatment outcomes of TB patients registered during 2008–2014, Southwest Ethiopia

Variables		Continuation phase treatment regimen			
		6EH ($n = 395$) *n* (%)	4RH ($n = 395$) *n* (%)	Total *N* (%)	*P* value
Weight at 2nd month	Mean ± SD	49.9 ± 8.9	50.8 ± 8.2	50.4 ± 8.6	0.2
Weight at 5th month	Mean ± SD	51.4 ± 8.6	51.3 ± 7.3	51.3 ± 7.9	0.9
Weight at 6/7th month	Mean ± SD	51.1 ± 8.9	52.5 ± 6.5	51.7 ± 7.9	0.3
Change in weight at 2nd month	Not increased	49 (12.4)	61 (15.4)	110 (13.9)	0.4
	Increased	191 (48.4)	177 (44.8)	368 (46.6)	
	Unknown	155 (39.2)	157 (39.7)	312 (39.5)	
Sputum smear end of 2nd month ($n = 359$)	Positive	4 (2.2)	2 (1.2)	6 (1.7)	0.09
	Negative	130 (69.9)	138 (79.8)	268 (74.7)	
	Unknown	52 (28)	33 (19.1)	85 (23.7)	
Sputum smear end of 5th month ($n = 359$)	Positive	1 (0.5)	0 (0)	1 (0.3)	0.03
	Negative	83 (44.6)	100 (57.8)	183 (51)	
	Unknown	102 (54.8)	73 (42.2)	175 (48.7)	
Sputum smear end of 6/7th month ($n = 359$)	Positive	0	0	0	0.8
	Negative	94 (50.5)	85 (49.1)	179 (49.9)	
	Unknown	92 (49.5)	88 (50.9)	180 (50.1)	
Sputum smear done during treatment ($n = 359$)	No	44 (23.7)	33 (19.1)	77 (21.4)	0.3
	At least once	142 (76.3)	140 (80.9)	282 (78.6)	
Continuation phase visit	Mean ± SD	5.8 ± 1.1	5.4 ± 3.1		0.09
Treatment outcome	Successful	337 (85.3)	358 (90.6)	695 (88)	0.02
	Cured	77 (19.5)	85 (21.5)	162 (20.5)	
	Completed	260 (65.8)	273 (69.1)	533 (67)	
	Unsuccessful	58 (14.7)	37 (9.4)	95 (12)	
	Died	28 (7.1)	18 (4.6)	46 (5.8)	
	Defaulted	29 (7.3)	19 (4.8)	48 (6.1)	
	Failure	1 (0.3)	0	1 (0.1)	

second month have lower likelihood of unsuccessful outcome. Patients put on 4RH continuation phase of treatment regimen are 45 % less likely to have unsuccessful outcome compared to those put on 6EH regimen. Patients treated at health center have about 63 % lower odds of unsuccessful outcome as compared to those treated at hospitals. HIV co infected TB patients have more than two fold higher risk of unsuccessful outcomes compared to HIV negatives (AOR = 2.38). Those patients gained weight at the end of the second month of treatment have 72 % lower odds of unsuccessful outcomes compared to those with reduced or unchanged weight (AOR = 0.28). A subgroup analysis among smear positive pulmonary cases showed having a sputum checkup at least once during treatment independently predicted 96 % lower odds of unsuccessful outcomes compared to those unchecked (AOR 0.04 (95 % CI, 0.01–0.12), $P < 0.001$) (Additional file 1).

Discussion

Treatment outcomes among TB patients treated with RHZE for the first 2 months, followed by HE for 6 months (2RHZE/6EH) and RH for 4 months (2RHZE/4RH) was compared. Both groups of the cases had no statistically significant difference with respect to socio-demographic, baseline clinical, bacteriologic and follow up measures that depict comparability of the groups. The comparison was made between regimens used during the continuation phase treatment (4RH vs 6EH). Thus a lower rate of unsuccessful outcomes was reported among those treated with 4RH continuation phase regimen.

A statistically significant difference in treatment outcomes where lower unsuccessful treatment outcome (9.4 % vs 14.7 %) was observed among patients treated with 4RH and 6EH regimen respectively. Similarly, a study conducted in Nigeria [14] reported higher odds of unsuccessful outcome among those treated with 6EH.

Table 3 Factors associated with unsuccessful treatment outcomes among TB patients registered during 2008–2014, Southwestern Ethiopia

Variables		Treatment outcomes		Odds ratio (OR)	
		Unsuccessful *n* (%)	Successful *n* (%)	Crude OR 95 % CI[a]	Adjusted OR 95 % CI
Age (years)	Mean(SD)	33.5 (14)	30.4 (12.0)	1.02 (1.002,1.03)	**1.02 (1.001,1.022)**
Gender	Male	60 (13.4)	387 (86.6)	1	1
	Female	35 (10.2)	308 (89.8)	0.73 (0.47.1.14)	0.63 (0.38,1.03)
Residence	Urban	32 (9.1)	318 (90.9)	1	1
	Rural	63 (14.3)	377 (85.7)	1.66 (1.06,2.61)	**2.1 (1.18,3.75)**
Zone	Kaffa	34 (16.2)	176 (83.8)	1	1
	Bench Maji	50 (12.2)	359 (87.8)	0.72 (0.45,1.14)	1.41 (0.73,2.75)
	Sheka	11 (6.4)	160 (93.6)	0.36 (0.17,0.73)	1.2 (0.44,3.32)
Treatment center	Hospital	17 (16.3)	87 (83.7)	1	1
	HC	78 (11.4)	608 (88.6)	0.66 (0.37,1.16)	**0.37 (0.14,0.97)**
Type of TB	Pulmonary	78 (12.8)	530 (87.2)	1	1
	EPTB[b]	17 (9.3)	165 (90.7)	0.70 (0.40,1.22)	0.57 (0.32,1.04)
HIV status	Negative	53 (9.9)	482 (90.1)	1	1
	Positive	13 (16.9)	64 (83.1)	1.85 (0.95,3.57)	**2.39 (1.12,5.07)**
	Unknown	29 (16.3)	178 (83.7)	1.77 (1.08,2.88)	**2.26 (1.23,4.11)**
Weight change end of 2nd month	No increase	11 (8.2)	357 (91.8)	1	1
	Increased	9 (3)	101 (97)	0.35 (0.14,0.86)	**0.28 (0.11,0.72)**
	Unknown	75 (24)	237 (76)	3.55 (1.71,7.37)	**3.48 (1.60,7.54)**
Continuation phase regimen	6EH	58 (14.7)	337 (85.3)	1	1
	4RH	37 (9.4)	358 (90.6)	0.60 (0.39,0.93)	**0.55 (0.34,0.89)**

[a]Confidence interval, [b]Extra pulmonary Tuberculosis, bold figures indicate statisticaly significant at $p<0.05$

This could be due to the differences in length and type of drugs used during the continuation phase treatment those influence adherence and ultimate outcome. Studies reported that reduced continuation phase (from 6EH to 4HR) treatment is associated with lower cost and expected mortality [12] that enhance successful treatment outcome. On the other hand, use of rifampcin for longer period of time during the treatment of TB is associated with better outcomes [13] that might be related with efficacy of the drug. The finding implies the adoption [11] of the latest WHO recommendation [7] in high prevalent and resource constrained settings is working well.

Apart from the treatment regimens, patient attribute like age and residence independently predicted treatment outcomes. We found that age had an inverse relation with unsuccessful outcome where the odds of unsuccessful outcome increase with age. Several studies also reported that older patients were more likely to have unsuccessful outcomes than younger [24–27]. This could be due to higher risk of age related co morbid situations those lead to poor adherence and outcomes [28]. Patients residing in rural areas had higher risk of unsuccessful outcomes which could be attributed to the low access to TB care and unfavorable living conditions. The findings imply need for focused intervention targeted to those older age groups and rural dwellers besides the treatment regimen.

Monitoring of patient weight and sputum are among the recommended follow-up measures required for TB patients on treatment [7]. The results of both weight and sputum monitoring are used to adjust for drug dose and predict outcomes of the treatment. The proportion of smear positive patients converted to negative at the end of the intensive phase has been taken among indicators of TB programme performance [7]. However, only small proportion of patients had documented results of the weight and sputum follow-ups particularly at the later periods of treatment. Consistent to findings from African settings [29] majority of those patients undergone sputum checkup during treatment converted to negative.

Patients gained some amount of weight at the end of second month treatment had lower risk of unsuccessful outcomes which is consistent with other studies [30, 31]. This could be explained by the fact that weight gain marks some level of improvement from the TB illness including reduced appetite. In addition, changes in weight while on treatment might be an indication of appropriateness of the drug dose to treat the illness. On the other hand those with unknown weight change at the end of first two months treatment had higher odds

of unsuccessful outcomes. This might have occurred due to possible misclassification of cases with reduced or remains unchanged to unknown. The weight change might be unknown due to patients' treatment interruption subsequent to treatment default or death those constitute unsuccessful outcome. So that patient's status of weight during treatment might be left undetermined.

Having sputum checkup at least once during treatment among initially smear positives predicted lower risk of unsuccessful outcome. However, reviews showed low sensitivity and modest specificity of sputum results at the end of intensive phase to predict failure and relapse [32]. On the other hand, detection of sputum positive during treatment trigger further patient assessment that influence treatment regimens and ultimate outcome. Hence, the routine sputum monitoring adopted by the country [11] during treatment should be improved as it is an indicator of program performance and trigger for patient assessment.

Consistent with other studies [33, 34], HIV positive TB patients are more likely to have unsuccessful outcomes compared to those negatives. This could be due to multifaceted influences of HIV on TB diagnosis and response to TB treatment those negatively affect the outcomes of TB treatment [35]. Consequently, collaborative services have been recommended in order to curb the influence of HIV on TB and vice versa [36]. Evidences from systematic review in African context supported the recommendation and reported better outcomes among concurrently screened and managed TB and HIV infected patients [37]. Nonetheless, we found no statistically significant difference in treatment success among those infected TB patients provided with CPT and/or ART. The indifference could be explained by the low uptake of integrated TB/HIV collaborative services among the studied patients. In this study, more than three quarter of the patients were offered HIV test which is little higher than the national average of 65 % [18] and 9.7 % TB/HIV co infected patients which is almost similar to the national average of 10 %. However, only few HIV co infected patients (45 % on CPT and 27.3 % on ART) were found to have documented service provision. [18]. The discrepancies could be due to differences in reporting periods where the national average is a single year attainment but that of this study is over a period of six years including the nationally reported year. Over all, the targets set for the TB/HIV service collaboration has not yet met which calls for in depth understanding and focused intervention that suit local settings. On the other hand, unknown HIV status predicted higher odds of unsuccessful outcomes. This could be due to possible misclassification of HIV positive cases those predict worse outcome in to unknown. The study is limited to control for changes in medical resources, polices and quality of care across the study periods. Since only few variables were captured on the register, we could not control for possible confounding effect of socio-economic, lifestyle and co morbid illness. Furthermore resistance pattern of the treatment regimens could not be evaluated which is recommended for the assessment of impact of treatment regimens. On the other hand the random selection of relatively large sample from both groups minimized risk of selection bias. The groups treated with 4RH and 6EH had insignificant differences with regard to baseline and follow-up clinical and bacteriologic attributes that enhanced comparability of the groups. Besides, we extracted data from a standardized routine programme register that reflect operational reality. In general, our study is valid and can apply in similar settings given the limitations.

Conclusion

In conclusion, the switch of continuation phase TB treatment regimen for new cases from 6EH to 4RH has brought better treatment outcomes. The findings verified the applicability of latest WHO recommendation and national adoption to the high prevalent and resource constrained settings. However, the unsuccessful outcome among the older, rural dwellers and HIV positives is higher independent of the treatment regimen that need further investigation and focused intervention. Therefore, the recommended switch of treatment regimen should be maintained and progressively assessed for outcomes, including drug resistance survey or surveillance. Moreover, further studies should be carried out on the impact of treatment regimens among older, rural residents and HIV positives.

Additional file

Additional file 1: Table 4: Factors associated with unsuccessful treatment outcome among smear positive pulmonary TB cases registered during 2008-2014, southwestern Ethiopia (n=359). Table 5: Factors associated with unsuccessful outcome among clinically diagnosed (smear negative 10.1186/s12879-016-1917-0 pulmonary and extra pulmonary) TB cases registered during 2008-2014, Southwestern Ethiopia (n=431). (DOCX 17 kb)

Abbreviations

ART: Antiretroviral therapy; CI: Confidence interval; CPT: Cotrimoxazole prophylactic therapy; DOTS: Directly Observed Treatment Short course; EH: Ethambutol and Isoniazid combination; HIV: Human Immunodeficiency Virus; OR: Odds ratio; RH: Rifampicin and Isoniazid combination; RHZE: Rifampicin, Isoniazid, Pyrazinamide and Ethambutol combination; TB: Tuberculosis; WHO: World Health Organization

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Availability of data and materials
The datasets analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' contributions
AA conceived, designed the study, analyzed data and prepared manuscript. WD and DJ critically reviewed for intellectual content of the study protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study protocol was approved by the institutional review board of the college of health sciences at Addis Ababa University (protocol number 045/14/sph). Since we did not carry out patient interview or examination, consent of participation was not sought as the patients were not on treatment at the time of study. Accordingly an anonymous patient data from routine service registry (unit TB register) were abstracted upon formal permissions of the health facilities.

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Pathways to anti-tuberculosis treatment initiation among cases on Directly Observed Treatment Short course in districts of Southwestern Ethiopia. A cross-sectional study

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Abstract

Background: Delayed tuberculosis (TB) diagnosis and treatment increase morbidity, mortality, expenditure, and transmission in the community. The aim of this study was to assess time delays to initiate care seeking and treatment for TB and factors associated with the delays.

Methods: A cross-sectional study was conducted among 735 consecutive new adult TB cases registered between January to December 2015 in 10 *woredas* (districts) of southwestern Ethiopia. Data were collected through face-to-face interview of patients within the first two months of treatment initiation. Three forms of delay were assessed; as number of days elapsed between 1) onset of TB symptoms to first formal healthcare seeking (patient delay), 2) first consultation to treatment initiation (provider delay) and 3) onset of illness to treatment initiation (total delay). Days spent beyond median were used to define the delays.

Result: The median (inter-quartile range) of patient, provider and total delays were 25(15-36), 22(9-48) and 55(32-100) days, respectively. More than half (54.6%) of the total delay was attributed to health system and the rest to patient. Prior self-treatment [adjusted Odds Ratio(aOR)] : 1.72, 95% confidence interval [CI]:1.07-2.75), HIV co-infection (aOR:1.8, 95% CI :1.05-3.1) and extra-pulmonary TB (aOR: 1.54,95% CI:1.03-2.29)were independently associated with increased odds of patient delay. However, initial visits to health posts or private clinics (aOR: 1.42, 95% CI: 1.01, 2.0) and delayed to seek care (aOR: 1.81, 95% CI: 1.33-2.5) significantly predicted longer provider delay. Finally, having extra pulmonary TB (aOR: 1.6, 95% CI: 1.07-2.38), prior consultation of traditional healer (aOR: 3.72, 95% CI: 1.01-13.77) and use of holy water (aOR: 2.73, 95% CI: 1.11, 6.7) independently predicted longer total delay.

Conclusion: TB patients waited too long time to initiate care seeking and treatment reflecting longer periods of morbidity and disease transmission. The delays are attributed to the patient, disease and health system related factors. Hence, involving informal providers, improving diagnostic efficiencies of healthcare facilities, and community awareness can reduce the delays.

Key words: Tuberculosis, healthcare seeking, patient delay, provider delay, total delay, Ethiopia

Introduction

Tuberculosis (TB) has been recognized as a global public health problem since 1993 when an estimated 7-8 million cases and 1.3-1.6 million deaths occur each year [1] . Since then, different global strategies have been designed and implemented for the control of TB, including Directly Observed Treatment Short course (DOTS), "Stop TB" and "End TB" strategies[1-4]. Thus between 2000 and 2015effective diagnosis and treatment of TB saved an estimated 49 million lives[5]. Despite such achievement and the fact that nearly all cases can be cured, TB remained to be among the major global public health problems. Globally, 10.4 million incident cases were estimated to occur in2015, of which 6.1 million (58.6%) were notified to National TB programs (NTPs) [5].

Tuberculosis has been recognized as major public health problem in Ethiopia and efforts to control it has begun since early 1960s . Nonetheless, TB remained among the major public health problems in the country that account for third cause of hospital admission and second cause of death[6]. The first national TB prevalence survey in 2011 revealed smear positive pulmonary TB(PTB) prevalence of 108/100,000, of which 55% were not detected by the routine passive case finding [7]. In 2015, about 205,463 new cases and 29,000 deaths were estimated to occur in the country[5].Thus Ethiopia has been among the 22 TB High Burden Countries (HBC) and 27 multiple drug resistant TB (MDR TB) high priority countries. Of the estimated cases in 2015, 125,801 (61%) were notified to NTP and a treatment success of cases registered in the 2014 was 89% [8].

Early case detection and treatment of cases under proper case management conditions have been a priority in the prevention and control of TB [9].When diagnosis of TB is delayed, patients go without treatment for long and transmit the disease. Each infectious case can result in as many as 20 to 28 secondary infections [10, 11]. Moreover, delays to diagnosis and treatment of TB result in more serious illness by the time of diagnosis, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance [12-16]. On the other hand, delays represent a time span in which additional costs are incurred [17]. Consequently, analysis of TB transmission dynamics has emphasized that delays to diagnosis present a major obstacle to TB

control [10].The delay to TB treatment can be categorized into: 1) patient delay as time span between onset of TB symptoms to first time formal care seeking, 2) provider delay a time elapsed between first consultation to anti-TB treatment initiation and 3) total delay as time elapsed between onsets of TB symptoms to anti-TB treatment initiation.

Delays to TB treatment have been studied in different parts of the world and Ethiopia. Thus reviews of the studies reported median patient delay of 30days and provider delay of 7-28days [10, 18]. On the other hand, diagnostic delays ranging from a median of 8-191days at different levels of health care delivery systems [12, 13, 19-22] were reported. Studies from different parts of Ethiopia also reported longer delays to initiate treatment for TB with median patient delay of 20- 90 days[20, 21, 23] and provider delay of 6-34days [21, 23-25]. Moreover nationwide[7] and pocket [26] prevalence surveys in Ethiopia respectively reported 55% and about two-thirds of active TB cases were not detected timely. The long delays are attributed to female gender, older age, low awareness about TB, repeated visits to health facilities, visiting lower level health care facilities and traditional healer[27, 28].

The available studies in Ethiopia are limited to smear positive PTB cases [25], focused on cases presenting to either health centers [24] or hospitals [29] but not both. Thus complete picture of the patterns of delay at different health care setups is scanty in the country. As a result, identification of barriers for the different forms of delays to TB treatment have been set as a national priority research agenda [30]. Shorter treatment regimens could dramatically accelerate the reductions in TB incidence and mortality that can motivate those suspects to early seek care and treatment [31]. In Ethiopia, treatment regimen of six months was introduced in 2011 and studies describing patterns of delay in the era of reduced regimen is very scanty. In particular no studies have been conducted in southwestern parts of the country. Therefore this study investigated time delays to initiate care seeking, diagnosis and treatment along with factors associated with the delays among TB cases on DOTS in districts of southwestern Ethiopia.

Methods

Study setting

The study was conducted in 14 health facilities (3 hospitals and 11 health centers) in three *zones* of Southern Nation Nationalities and Peoples Region (SNNPR), one of the nine Regional States in Ethiopia with an estimated 18million inhabitants [32].The three study *Zones*, Bench Maji, Kaffa and Sheka are located at the southwestern border of the country where about 2,064,102 peoples reside[32]. The *zones* (an administrative unit that liaison weredas with the region) are organized in to four town administrations and 26 *weredas*(lowest administrative unit closer to the community). During the study there were 3 hospitals and 65 health centers providing TB DOTS services .

Diagnosis and treatment of all forms of TB across the country is based on the adopted national TB control guidelines [33, 34] that specifies case definitions, diagnostic and treatment standards. Previously, diagnosis and treatment of TB had been limited to public hospitals and health centers but in recent years public private mix (PPM) DOTS to private health care facilities and community DOTS to health posts have been introduced. Currently, diagnosis and treatment of TB are solely being provided at public and private hospitals, public health centers and higher level private clinics in an integrated manner. Thus in 2011, 92% of public hospitals and 95% of health centers, 2100 health posts and 317 PPM –DOTS centers were providing DOTS based diagnosis and/or treatment of TB cases [35]. .

Study design and sampling

A cross-sectional study among TB cases on DOTS registered from January to December 2015 in the 14 health facilities was carried out. The sample size required to identify factors associated with delays to seek care was computed using StatCalc program of EpiInfo using 95% significance level, 80% power, expected frequency of exposure (illiteracy)among controls (delayed for less than 30 days) of 38% and odds ratio (OR) 1.7[36]. The calculation provided 486 cases, considering design effect of 1.5 and non-response of 10% a total of 802 new cases were required. The samples were proportionally allocated to the zones, weredas and health facilities based on the caseloads reported during the preceding year. Finally, consecutive consenting cases from the respective health facilities were prospectively enrolled until the required sample was reached. Those new cases, older than 18 years of age, on intensive phase of

treatment were included in the study and those transferred out and died before the interview were excluded.

Data collection and analysis

A structured questionnaire adapted from tools used elsewhere [7, 17, 37]was used to gather the data. Besides, data abstraction checklist was prepared to draw clinical profiles of the patients from TB register and individual clinical chart. The questionnaire was translated into national language (*Amharic*) spoken by almost all residents in the study area. Training manual comprised of aim and implementation of the study, basics of TB control, TB case definitions, components of questionnaire and interviewing techniques was prepared. Ten diploma graduate nurse data collectors and three public health specialist (MPH) supervisors were recruited and trained for three days. The training included description of questionnaire details, interviewing techniques, role play and pretest among TB cases on DOTS at nearby health facilities not included in the study. Modifications on the questionnaire were made to suit local expressions and wordings those were found during the pretesting. Finally, new cases of TB on intensive phase treatment (the first two months of treatment) were traced from the unit TB register of the selected facility and interviewed for their sociodemographic, health care seeking practices and knowledge towards TB.

Patient delay was assessed by asking the participants to recall/estimate the date or number of days elapsed between onset of TB constitutional symptoms (cough, fever, night sweats, chest pain, weight loss, loss of appetite) until they seek care. Similarly, provider delay was estimated by asking date or number of days elapsed between first formal health care facility visit to final diagnosis and treatment initiation with anti-TB treatment. Finally, total delay was computed as a sum of patient and provider delay or number of days elapsed between onsets of illness to initiation of anti-TB treatment. The dates were recorded in Ethiopian calendar and later converted in to corresponding Gregorian calendar to be used by different statistical software.

Knowledge about TB was assessed using eight items with “yes” or “no” questions including cause of TB(microbe,bacteria,germ),TB is hereditary, TB is contagious, mode of TB

transmission [(breathing, sneezing, coughing, raw milk intake), symptoms of TB,TB is curable, length of treatment (6 month=yes, otherwise no) and TB treatment modalities as free=yes or for charge=no. The responses were coded as 0=no and 1=yes). The items internal consistency was checked (Cronbach's Alpha (α)=0.75) before computing an index.

Data were checked for consistency and completeness and entered into Epi data, and then exported to SPSS version 21for cleaning and analysis. Subsequently, the cleaned data were described using frequency, proportions, mean, median, standard deviation and inter-quartile range, tables and graphs. In addition, numeric variables were further explored for skeweness, kurtosis, normality plots (Q-Q plots and/or histograms) or Kolmogorov-Smirnov test to check for normality. The distribution of number of days elapsed across different time points were not normal and median days were used as a cutoff point to define delays. Thus patient, provider and total delays were defined based on median days elapsed between onset of illness to first visit, first visit to treatment initiation and onset of illness to treatment initiation respectively. For the assessment of knowledge towards TB, correct responses were summed up and distribution was explored for normality. The score did not show normality and median was used to dichotomize good and poor knowledge. Accordingly those scored above median are labeled as having good knowledge and below median as having poor knowledge.

Comparisons of proportions among categorical variables was made using Chi-squared and Manwhitney U and Kruskual Walis tests were used to compare medians across different groups for those variables did not exhibit normality. Finally, bivariate and multiple binary logistic regression models were fitted to compute crude and adjusted odds ratios that reflect strength of association and identify independent predictors of delays. Selection of the variables for multiple regression were made based on p value <=0.25 on crude analysis. The logistic models fitness was checked using Hosmer and Lemeshow test. In all the statistical tests, statistical significance was judged at $p<0.05$.

Ethical issues

The study was ethically approved by Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University. Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and unit register was retrieved upon permission from respective health care facilities.

Results

Sociodemographic characteristics of the patients

A total of 735 TB cases from 14 public health facilities (three hospitals and 11 health centers) of the selected 10 *weredas* in the three *zones* (Kaffa, Bench Maji and Sheka) participated in the study. Accordingly, 469(63.8%) and 266(37.2%) of the cases were registered at health centers and hospitals, respectively. Of the cases, 221(30.1%), 199(27.1%) and 140(19%) respectively were from Kafficho, Bench and Amhara ethnic groups. The median age (inter-quartile range (IQR)) and mean (±standard deviation/SD) of the cases was 27(20-37) and 30.8(12.9) years, respectively. Among the cases, 52.9% and 29.4% had completed elementary school and involved in subsistence farming respectively (Table1).

Health care seeking practices

As an onset of illness, 563(76.6%), 345(46.9%) and 300(40.8%) of the cases had respectively encountered cough, night sweating and fever (Table 2). Thus, 596(81.1%) cases visited healthcare facility (HCF) as first action to the illness but the rest 139(18.9%) took some informal care including self-treatment and consulting traditional healer before visiting HCF. Ultimate decision to visit health facility was made upon referral and/or advice from relatives (38.6%), Health Extension Worker (HEW) (4.5%) and TB patients on treatment (4.2%). Thus, 35.4% and 32.4% first visited private clinics and public health centers respectively. The first visit to HCFs among 276(37.6%) were made at HCFs not providing DOTS service. The type of first HCF visited as DOTS providing or not is statistically significantly associated with source of advice/referral received (p=0.009) before deciding to visit HCF. Among the cases 210(28.6%), suspected their illness to be TB.

TB diagnosis of 448(61%) and 99 (13.5%) cases were made at hospital and private clinics respectively. The diagnosis among 244(33.2%) was made at the first visited HCF and the rest

491(66.8%) of the cases were referred or went by themselves to other facilities. One hundred twelve (15.2%) cases were diagnosed at their first visit and the rest were diagnosed after an average (SD) of 3.6(2.4) visits to an average (±SD) of 2.2(1.2) healthcare facilities at which time the patients had been treated with different medicines. Proportion of cases diagnosed at their first visit significantly differ across the type of visited HCFs (58/206(28.2%), 44/224(19.6%) and 7/236(4.2%) at hospital, health center and private clinics respectively ($p<0.001$). Both the median number of visits and HCFs visited significantly differ across the first visited HCFs ($P<0.001$). After diagnosis, 529(72%) of the cases were put on anti-TB treatment immediately and the rest started treatment after an average of 0.48days (range 0-8 days).

Sputum smear result during commencement of treatment was available for 629(85.6%) cases of whom 373(50.7% tested positive (Table 3).Thus, diagnosis of 373(50.7%) cases were bacteriologically confirmed and the rest 362(49.3%) were clinically diagnosed. Generally, 586(79.7%) of the cases had pulmonary TB [373 (63.2%) smear positive and 213(36.8%)] and the rest, 149 (20.3%) were extra pulmonary (EPTB) cases. All of the cases were offered HIV screening test of whom 68 (9.3%) tested positive (95% CI (7.2%-11.3%)). The HIV status is significantly associated with marital status ((x^2=15.1,p=0.001) and educational status (x^2=10.6,p=0.01). Of those TB/HIV co infected cases, 27(39.7%) and 32(47.1%) were respectively receiving antiretroviral therapy (ART) and Cotrimoxazole prophylactic therapy (CPT).The types of TB cases as bacteriologically or clinically diagnosed is significantly associated with where the diagnosis of TB was made (x^2=20.7,p<0.001). However, there were no statistically significant difference across HIV status (x^2=1.2, p=0.3), age groups (x^2=3.2,p=0.2) and gender (x^2=1.5,p=0.2).The mean (SD) weight of the cases at the commencement of anti-TB treatment was 48.8(8.3) kg.

Knowledge towards tuberculosis

Almost all 721(98.1%) of the cases mentioned the illness they were being treated as TB. But only 539(73.3%) had ever heard about TB before they were diagnosed as TB case. Among those ever heard about TB, 253(48.3%), 200(38.1%), 191(36.4%) and 190(35.3%) had heard from mass media, health facilities, TB patients and relatives respectively. The aggregated knowledge score about TB revealed, 545(74.1%) had scored above a median of 4.5 out of the eight items

and labeled as having good knowledge.

Delays to seek care and treatment

Patient delay

The median (IQR) days elapsed between onset of illness to first health facility visit (patient delay) was 25 (15-36) and median (95% CI) 25(21, 28). Nearly a third, 240(32.6%) of the cases made first consultation within 15 days of the onset of illness. Of the cases, 317(43.1%) perceived their first visit was delayed for which 256(80.8%) and 109(26.1%) reasoned expecting the illness to limit by itself and lack of money respectively. The median patient delay is significantly different with type of TB (P=0.03), educational status (p=0.04), marital status (p=0.01) and knowledge towards TB (p=0.002). But, the median patient delay is not significantly different with HIV status, gender, residence and occupation (Table 3).

In a multiple logistic regression, those extra pulmonary TB AOR (95%CI) 1.54(1.03,2.29), HIV positives AOR(95%CI) 1.80(1.05,3.1) , took self treatment before HCF visit AOR(95% CI) 1.72(1.07,2.75), first visited other than health post, traveled more than an hour to nearby HCF AOR(95% CI) 1.37(1.01,1.88) and good knowledge about TB AOR(95% CI) 0.67 (0.46,0.95) cases were independently associated with patient delay beyond the median (Table 4). Those cases travelled more than an hour to reach the first visited HCF are 37% more likely to delay care seeking compared to their counter parts. Extra pulmonary TB cases are 54% more likely to delay seeking care compared to smear positive pulmonary cases. TB cases co infected with HIV are 80% more likely to delay care seeking than HIV negative TB cases.

Provider delay

After the first visit, diagnosis of TB spent a median (IQR) 22(8-48) and median (95% CI) 22(19, 24) days at the HCFs. Following the diagnosis of TB, 613(83.4%) of the cases were put on anti-TB treatment immediately and the rest delayed for a median (range) 2(1-7) days until treatment initiation. In general, median (IQR) days elapsed between first HCF visit to initiation of anti-TB treatment (provider delay) was 22(9-48) days. Provider delay is significantly correlated with patient delay (r=0.2, P<0.001). The median provider delay is significantly different with type of TB (p=0.02), type of first visited HCF (p<0.001) and HCF where final diagnosis was made

(p=0.01)(Table 3). However the median provider delay is not significantly different with HIV status, first action taken to the illness and knowledge towards TB. In multiple logistic regression analysis, first visiting non DOTS HCF AOR (95% CI) 1.42(1.01, 2.0), visited more than one HCF AOR (95% CI) 2.34(1.69, 3.24) and sought care after 25days from onset of illness AOR (95% CI) 1.81(1.33, 2.5) independently predicted provider delays exceeding 22 days(Table 5). Those cases first visited non DOTS center are 42% more likely to have delayed diagnosis compared to those visited DOTS providing facilities. Cases who delayed beyond 25days are 81% more likely to have provider delay beyond the median of 22days.

Total delay

The median (IQR) days undergone since onset of illness to TB treatment initiation (total delay) was 55(32-100) with median (95% CI) 55(49, 60) days. More than half (54.6%) of the total delay was attributed to provider (health system) and the rest to patient. Of the cases, 162(22%) were put on anti-TB treatment within 30days of the onset of illness. The median total delay is significantly different with type of TB (p<0.001), first action taken to illness (p=0.001) and first visited HCF (p=0.04)(Table 3).On the other hand, those extra pulmonary AOR (95% CI) 1.60(1.07, 2.38), consult traditional healer AOR (96%CI) 3.72(1.01, 13.77) or went to holy water AOR (95% CI) 2.73(1.11, 6.7) before visiting HCF and visited non DOTS center AOR (95% CI) 1.63(1.19, 2.24) independently predicted total delay beyond the median (55 days)(Table 6).

Discussion

Prompt detection and treatment of TB cases has been a priority in the prevention and control of the disease. This would be attained upon timely seeking care by patients and reaching at diagnosis within a reasonable time by the health system. We assessed the delay and associated factors with the diagnosis and treatment of TB in rural districts of southwestern Ethiopia. Thus this study revealed long delays to seek care, diagnosis and treatment initiation among cases on treatment. Patients in the study area had waited for a median of 25 days and 55 days respectively until seeking care and initiation of anti-TB treatment since the onset of illness. Both patients and health system delays contribute nearly equally to the total delay which is consistent with other studies from Ethiopia [24] and elsewhere [18].The longer time elapsed since onset of illness to treatment initiation implies increased risk of morbidity and mortality among the cases and diseases transmission in the community [11, 15, 38, 39].All forms of the delays are affected by

patient, disease and health system related factors. This implies the delays are multifaceted that calls for intensified TB case finding through health promotion activities and expansion of DOTS.

Patients had waited for a median of 25 days until seeking help at formal health care providers which is consistent with 30 days in northern part of Ethiopia [21, 36, 40], 28 days in Uganda [18]and 30 days in Angola [10].The relatively lower delay could be due to better access to HCF where nearly 80% of the cases traveled less than an hour to reach the first HCF. However, only less than a third (32%) of the cases had made visits to formal health care within 15 days of recommended timeline for TB suspects to visit HCF [33].Besides, more than half (57%) of the cases did not perceive their care seeking was delayed which implies the symptoms are taken as common and less severe to urge consultation of health care provider.

Before visits to formal health care facility, patients had taken variety of actions those influence timing of care seeking. Consistent with other studies, patients who took self-treatment before the formal care seeking were more likely to delay seeking care at the formal care units compared to those first consulted health care providers[41, 42]. This could be due to use of some home remedies or over the counter antibiotics or analgesics those might lessen the manifestation of the illness for the time being [43]. Moreover, those patients first visited traditional healer and holy water are more likely to have higher total delay. This could be due to the beliefs attached to the traditional care and holy water those might inhibit timely presentation and diagnosis [28].

Patients co infected with HIV are more likely to delay care seeking compared to those non-infected. This could be due to the alteration of classical clinical manifestations and signs of TB among HIV co infected patients [44]. On the other hand, patients suspected or tested HIV positive delay to present themselves to HCF due to fear of stigma attached to the co-occurrence of TB and HIV[14, 45, 46]. As a result the high mortality among HIV co infected TB patients is partly explained by the delays to TB treatment [10, 47]. Those extra pulmonary cases patients are more likely to delay seeking care compared to the pulmonary cases. A similar finding was also reported form a study in northwest Ethiopia [29]. This could be due to the fact that extra

pulmonary cases manifest with less severe and non-specific symptoms that urge patients to perceive the illness to be non-serious[48].

Patient's perception and knowledge towards the TB disease and control activities do have impact on the care seeking practices. The study revealed that patients with good knowledge towards the TB disease and program are less likely to delay seeking care. Similarly, other studies have reported lack of knowledge and mistrust of the TB program as a reason for delayed care seeking [27, 49, 50]. In contrast, awareness and belief about TB's curability is associated with longer patients delay [12, 18]. These imply need for awareness creation towards the TB illness and its control program to clear the paradox between the belief and longer delay.

The first consultation at HCF was made primarily (69.9%) at lower level public health care units (health posts and health centers) and private clinics. This is consistent with a study in Mediterranean countries that reported two thirds of patients first visited private sectors [50]. Nonetheless, diagnosis of TB was made primarily at hospital (61%) despite only few had made first visit to the hospitals. As a result, majority of the cases had made more than one visit to different HCFs until diagnosis. Similarly, studies from Uganda [18] and China [51]reported significant number of patients had visited more than one HCF until diagnosis. Subsequent to the missed opportunities during the repeated visits, diagnosis of TB had been made after a median of 22 days from the first visit to HCF. This is consistent with 21 days in a study from Amhara Region in Ethiopia [21] but higher than 6 in Addis Ababa [24] and 9 days in Tigray, northern Ethiopia [23]. The discrepancies could be due to the differences in accessibility to well equipped HCFs and skilled providers usually situated in cities like Addis Ababa. The longer provider delays due to the repeated visits portray high level of missed opportunities of early diagnosis that could have increased infectious period of the cases and costs incurred by the patients and households.

Longer provider delays had been reported among patients who first visited HCFs not providing DOTS services including health posts and private clinics. This is consistent with a study from Uzbekistan[42] and India [48].The higher provider delay at lower care units and private clinic could be due to lack of supplies, guidelines and skilled providers that enhance adherence to the

national TB control program. In the current study, diagnosis of TB was mainly made at hospitals despite many patients had made first visits at the lower public and private clinics. This depict patients are being provided with unnecessary drugs and treatments at series of HCFs incurring extra cost. Besides the cost incurred, medications at the repeated visits themselves lead to delays to diagnosis and serious outcomes including drug resistance [52].On the other hand, the lower health care units and private clinics might lack proper logistics and skilled providers to timely diagnose the cases. Hence expansions of the DOTS package to the lower and private clinic is required to curb the prevailing long delays.

We found that patients delayed to seek care are also more likely to have delayed diagnosis and treatment after they initiated care seeking. In contrast a study in Georgia [53] reported those patients with increased patient delay are less likely to have prolonged diagnostic delay. The discrepancy could be due to differences in measurement of the two delays. The higher odds of provider delay among those delayed to seek care can be explained by patients use of different forms of self-treatment and homemade remedies those might alter the manifestations of the TB illness that pose difficulties in timely diagnosis [43, 53]. Those patients delayed to seek care might have been ill for such long duration at which time productivity is compromised. Hence the patients might be unable to cope with the costs required to have timely diagnosis even after initiating the care seeking. In addition, the long ill days are also associated with more severe disease at presentation [15] which hinders timely diagnosis[25].

Our study has several limitations. First the study was carried out on those cases ultimately sought care and on treatment at the time of the study. Thus measurement of delays relied on patient self-report which is liable to recall bias. We minimized this bias through interviewing patients soon after diagnosis and helping them to recall using local events. Second, the assessment of patients' knowledge towards the TB diseases and its control program might be influenced by the information provided during treatment initiation. So this could have brought egg and chicken dilemma as the knowledge or care seeking preceded one to other. Third, we studied only new and adult cases so that the findings cannot be generalized to all forms of TB cases among all age groups. Lastly our study lacked qualitative assessment of patients and health system those would have supplemented the quantitative data. On the other hand, consecutive enrollment of cases that

minimized selection bias and triangulation of data sources from patient interview and chart reviews could be mentioned as strength of the study. Finally, our study is valid and genralizable to new adult cases in similar settings.

Conclusions

The study revealed that TB patients on DOTS in the study area have passed too long journey to initiate anti TB treatment. Thus majority of the patients waited too long time to initiate care seeking, diagnosis and commence the treatment. The patient and provider delays are positively correlated and contributed nearly equally to the total delay. On the other hand, the elapsed too long time until treatment initiation was accompanied by repeated visits to both formal and informal care units where costs were incurred. This portrays high level of missed opportunities of early diagnosis at different levels that would have reduced severity of illness among the cases, transmission to the community and household impoverishment. The study further revealed the patient, provider and total delays are attributed to the patient, disease and health system related factors reflecting need for intervention at all levels. Therefore, intensified TB case finding as early as possible involving the community, formal and informal providers is required to avert the prevailing long journeys to initiate TB treatment. To this end, engagement of informal providers, strengthening health care facilities capacity and community level awareness creation about the disease and its control strategies may reduce the delays.

Declarations

Ethics statement

The study was ethically approved by Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and unit register was retrieved upon permission from respective health care facilities.

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Competing interest

We declare that we do not have any competing interests.

Author's contributions

AA conceived and designed the study, collected and analyzed data, prepared manuscript:

WD and DJ critically reviewed for intellectual content of the study protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript.

Availability of data and materials

The data from which the paper was built will be available from corresponding author upon request.

Abbreviations

ART	Antiretroviral Therapy
CI	Confidence Interval
CPT	Cotrimoxazole Prophylactic Therapy
DOTS	Directly Observed Treatment Short course
EPTB	Extra pulmonary Tuberculosis
HBC	High Burden Countries
HCF	Healthcare Facility
HIV	Human Immunodeficiency Virus

IQR	Inter-quartile Range
OR	Odds Ratio
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
WHO	World Health Organization

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Table 1 Sociodemographic characteristics of TB cases on directly observed short course treatment (DOTS) in districts of southwestern Ethiopia, January to December 2015 (n=735)

Variable		Frequency (%)
Gender	Male	446(60.7)
Age(years)	18-34	503(68.4)
	35-65	216 (29.4)
	>65	16(2.2)
Marital status	Never married	275(37.4)
	Currently married	404(55)
	Widowed/divorced	56(7.6)
Educational status	No formal education	212(28.8)
	Completed elementary	389(53.0)
	Secondary and above	134(18.2)
Occupation	Employed	172(23.4)
	Farming	216(29.4)
	Unskilled work [b]	51(6.9)
	Dependants [c]	296(40.3)
Religion	Orthodox	300(40.8)
	Muslim	104(14.1)
	Catholic	4(0.5)
	Protestant	314(42.7)
	Traditional	13(1.8)
Residence	Urban	369(50.2)
	Rural	366(49.8)
Household size	Mean/SD	4.3/2.1

[a] Standard deviation [b]housemaid, daily laborer, [c] students, house wife, [d] father/ mother /husband/ wife/brother/sister/employer

Table 2: Health care seeking practices among new TB cases on directly observed short course therapy (DOTS), Southwestern Ethiopia, January to December 2015 (n=735)

Variable		Frequency (%)
Initial symptoms encountered	Cough	563(76.6)
	Night sweat	345(46.9)
	Fever	300(40.8)
	Loss of appetite	279(38)
	Chest pain	267(36.3)
	Weight loss	236(32.1)
	Haemoptysis	144(19.6)
	Others[a]	62(8.4)
First action to illness	Visit HCF	596(81.1)
	Self-treatment	98(13.3)
	Visit holy water	26(3.5)
	Consult traditional healer	15(2.0)
Perceived reason for not visiting HCF first (n=149)	Thought illness limit by itself	97(65.1)
	Perceived long waiting time at HCF	37(24.8)
	Perceived expensive service fee	37(24.8)
	HCF too far	29(19.5)
	Other [b]	22(14.8)
First HCF visited	Private clinic	260(35.4)
	Health center	238(32.4)
	Hospital	221(30.1)
	Health post	16(2.2)
Source of advice/referral to visit first HCF	Self	472(64.2)
	Parent/relative	280(38.1)
	HEW [c]	32(4.4)
	TB patient	30(4.1)
	HIV care clinic	16(2.2)
	Other[d]	31(4.2)
Travel time to first HCF visited	<=1hour	582(79.2)
	>1hour	153(20.8)
Place TB diagnosis made	Hospital	448(61.0)
	Health center	188(25.6)
	Private clinic	99(13.5)

[a] neck swelling, head ache, joint pain, back pain, wound ,[b]HCF closed, mistrust health care provider, bad previous experience at HCF, fear of HIV test and fear of TB diagnosis, [c]HEW= Health Extension worker(trained females those provide household package of health care to household), [d]drug shop(13),holy water(14),traditional healer(4)

Table 3: Differences in median patient, provider and total delays among TB cases on DOTS, Southwestern Ethiopia, January to December 2015

		Patient delay		Provider delay		Total delay	
Variable		Median	p value	Median	p value	Median	P value
Gender	Male	25	0.9	22	0.9	54	0.7
	Female	25		23		57	
Type of TB	Pulmonary positive	23	0.03	22	0.02	53	<0.001
	Pulmonary negative	23		19		51	
	Extra pulmonary	29		26		67	
HIV result	Reactive	29	0.3	32	0.14	63	0.4
	Non reactive	24		22		54	
Residence	Urban	23	0.3	22	0.6	52	0.9
	Rural	28		23		56	
Marital status	Single	21	0.01	22	0.4	53	0.1
	Married	27		22		55	
	Divorced/widowed	29		26		65	
Educational status	Illiterate	26	0.04	18	0.03	48	0.14
	Primary	26		26		59	
	>=Secondary	21		20		50	
First action taken	Visited HF	22	<0.001	23	0.4	53	0.001
	Other actions*	30		22		64	
Travel time to nearby HF	<=1Hr	21	0.001	22	0.9	53	0.2
	>1Hr	29		23		58	
Knowledge on TB	Poor	29	0.002	22	0.8	57	0.1
	Good	22		22		54	
Occupation	Employed	25	0.24	24	0.07	61	0.01
	Farming	22		22		53	
	Unskilled work	31		35		91	
	Dependents	25		21		50	
First visited HCF	Health Post	52	0.003	13	<0.001	78	0.04
	Hospital	22		17		42	
	Health center	29		19		55	
	Private clinic	23		30		62	
Visited >1HCF	Yes	27	0.87	31	<0.001	63	<0.001
	NO	23		14		41	
Place TB diagnosis made	HC	30	0.002	18	0.005	54	0.3
	Hospital	21		23		52	
	Private clinic	26		29		61	

*self treatment, consult traditional healer, used holy water

Table 4 Factors associated with patient delay among TB patients on DOTS, southwestern Ethiopia January to December 2015

Variable		Patient delay		Crude Odds ratio (COR) 95% CI	Adjusted Odds ratio (AOR) 95%CI
		Yes n(%)	No n(%)		
Age				1.01(0.99,1.02)	**1.01(1.001,1.03)***
Educational status	Illiterate	89(42.0)	123(58.0)	1.00	1.00
	Completed primary	215(55.3)	174(44.7)	1.05(0.75,1.47)	1.23(0.85,1.78)
	Secondary and above	63(47.0)	71(53.0	0.92(0.59,1.42)	1.27(0.77,2.1)
Type of TB	Pulmonary positive	175(47.9)	190(52.1)	1.00	1.00
	Pulmonary negative	104(47.7)	114(52.3)	0.95(0.68,1.32)	0.93(0.65,1.33)
	EPTB	91(59.9)	61(40.1)	1.51(1.03,2.21)	**1.54(1.03,2.29)***
HIV status	Positive	41(60.3)	27(39.7)	1.52(0.92,2.52)	**1.80(1.05,3.1)**
	Negative	329(50.7)	338(49.3)	1.00	1.00
First action to illness	Self treatment	60(61.2)	38(38.8)	1.84(1.19,2.85)	**1.72(1.07,2.75)***
	Traditional care	11(73.3)	4(26.7)	3.21(1.01,10.2)	2.98(0.91,9.72)
	Holy water	18(69.2)	8(30.8)	2.2(0.96,5.03)	2.01(0.86,4.67)
	Consult HCP	281	315	1.00	1.00
First visited HCF	Health post	13(81.3)	3(18.8)	1.00	1.00
	Health center	130(54.6)	108(45.4)	0.26(0.07,0.95)	**0.25(0.07,0.94)***
	Hospital	98(44.3)	123(55.7)	0.18(0.0,0.64)	**0.17(0.05,0.64)***
	Private clinic	129(49.6)	131(50.4)	0.22(0.06,0.79)	**0.22(0.06,0.81)***
Travel time to first HCF	<=1hour	205(46.9)	232(53.1)	1.00	1.00
	>1hour	165(55.4)	133(44.6)	1.37(1.02,1.84)	**1.37(1.01,1.88)***
Knowledge towards TB	Good	264(48.4)	281(51.6)	0.77(0.55,1.07)	**0.67(0.46,0.98)***
	Poor	106(55.8)	84(44.2)	1.00	1.00

*statistically significant at $p<0.05$

Table 5 Factors associated with provider delay among TB patients on DOTS southwest Ethiopia, January to December 2015

Variable		Provider delay		COR(95% CI)	AOR(95%CI)
		Yes n(%)	No n(%)		
Type of TB	Pulmonary positive	182(49.9)	183(50.1)	1.00	1.00
	Pulmonary negative	10347.2)	115(52.8)	0.9(0.64,1.26)	0.87(0.60,1.25)
	Extra pulmonary	82(53.9)	70(46.1)	1.18(0.81,1.72)	1.08(0.72,1.62)
HIV status	Positive	39(57.4)	29(42.6)	1.38(0.84,2.30)	1.33(0.78,2.27)
	Negative	328(49.2)	339(50.8)	1.00	1.00
First action to illness	Self treatment	44 (44.9)	54(55.1)	0.81(0.53,1.25)	0.75(0.47,1.19)
	Traditional care	9(60.0)	6(40.0)	1.5(0.53,4.27)	1.19(0.47,3.51)
	Holy water	16(61.5)	10(38.5)	1.6(0.71,3.58)	1.28(0.55,2.99)
	Consult HCP	298(50.0)	298(50.0)	1.00	1.00
First visited HCF	DOTS center	203(44.2)	256(55.8)	1.00	1.00
	Non DOTS	164(59.4)	112(40.6)	1.85(1.36,2.50)	**1.42(1.01,2.00)***
Number of visited HCF	1	233(62.0)	143(38.0)	2.77(2.05,3.73)	**2.34(1.69,3.24)***
	>1	133(37.2)	225(62.8)	1.00	1.00
Patient delay	Yes	213(57.6)	157(42.4)	1.80(1.36,2.50)	**1.81(1.33,2.50)***
	No	154(42.2)	211(57.8)	1.00	1.00

HCP=Health Care Provider, *statistically significant at p<0.05

Table 6 Factors associated with total delay among TB patients on DOTS, southwest Ethiopia January to December 2015

Variable		Total delay		Crude Odds ratio (COR) 95% CI	Adjusted Odds ratio (AOR) 95%CI
		Yes	No		
Residence	Urban	180(48.9)	188(51.1)	1.00	1.00
	Rural	185(50.4)	182(49.6)	1.06(0.80,1.42)	1.26(0.90,1.77)
Educational status	Illiterate	96(45.3)	116(54.7)	1.00	1.00
	Completed primary	206(53.0)	183(47.0)	1.36(0.97,1.90)	1.41(0.95,2.10)
	Secondary and above	63(47.0)	71(53.0)	1.07(0.69,1.65)	1.27(0.74,2.17)
Type of TB	Pulmonary positive	175(47.9)	190(52.1)	1.00	1.00
	Pulmonary negative	101(46.3)	117(53.7)	0.94(0.67,1.31)	0.95(0.67,1.36)
	Extra pulmonary	89(58.6)	63(41.4)	1.55(1.05,2.25)	**1.60(1.07,2.38)***
HIV status	Positive	38(55.9)	30(44.1)	1.32(0.80,2.18)	1.36(0.79,2.35)
	Negative	327(49.0)	340(51.0)	1.00	1.00
First action to illness	Self treatment	49(50.0)	49(50.0)	1.09(0.71,1.67)	0.91(0.58,1.43)
	Traditional care	12(80.0)	3(20.0)	4.36(1.22,15.63)	**3.72(1.01,13.77)***
	Holy water	19(73.1)	7(26.9)	2.96(1.23,7.15)	**2.73(1.11,6.7)***
	Consult HCP	285	311	1.00	1.00
Travel time to nearby HCF	<=1hour	210(48.1)	227(51.9)	1.00	1.00
	>1hour	155(52.0)	143(48.0)	1.17(0.87,1.57)	1.27(0.93,1.74)
Type of first visited HCF	DOTS center	208(45.3)	251(54.7)	1.00	1.00
	Non DOTS	157(56.9)	119(43.1)	1.59(1.18,2.15)	**1.63(1.19,2.24)***
Knowledge towards TB	Good	269(49.4)	276(50.6)	0.95(0.68,1.33)	0.89(0.6,1.29)
	Poor	96(50.5)	94(49.5)	1	1
Visited more than one HCF	Yes	224(59.6)	152(40.4)	2.25(1.68,3.03)	**2.12(1.53,2.95)***
	No	141(39.4)	217(60.6)	1.00	1.00
Marital status	Married	201(49.8)	203(50.2)	1.00	1.00
	Single	131(47.6)	144(52.4)	0.92(0.67,1.25)	0.80(0.55,1.15)
	Divorced/widowed	33(58.9)	23(41.1)	1.45(0.82,2.55)	1.32(0.72,2.41)
Occupation	Employed	89(51.7)	83(48.3)	1.00	1.00
	Farming	103(47.7)	113(52.3)	0.85(0.57,1.27)	0.83(0.51,1.34)
	Unskilled work	36(70.6)	15(29.4)	2.24(1.14,4.38)	**2.31(1.15,4.6)***
	Dependents	137(46.3)	159(53.7)	0.80(0.55,1.17)	0.87(0.57,1.33)

*statistically significant at $p<0.05$

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Pre- and post-diagnosis costs of tuberculosis to patients on Directly Observed Treatment Short course in districts of southwestern Ethiopia: a longitudinal study

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Abstract

Background: Financial burden on tuberculosis (TB) patients results in delayed treatment and poor compliance. We assessed pre- and post-diagnosis costs to TB patients.

Methods: A longitudinal study among 735 new TB cases was conducted from January 2015 through June 2016 in 10 woredas (districts) of southwestern Ethiopia. Direct out-of-pocket, payments, and lost income (indirect cost) were solicited from patients during the first 2 months and at the end of treatment. Thus, we ascertained direct medical, nonmedical, and indirect costs incurred by patients during pre- and post-diagnosis periods. We categorized costs incurred from onset of illness until TB diagnosis as pre-diagnosis and that incurred after diagnosis through treatment completion as post-diagnosis. Pre- and post-diagnosis costs constitute total cost incurred by the patients. We fitted linear regression model to identify predictors of cost.

Results: Between onset of illness and anti-TB treatment course, patients incurred a median (inter-quartile range (IQR)) of US$201.48 (136.7–318.94). Of the total cost, the indirect and direct costs respectively constituted 70.6 and 29.4%. TB patients incurred a median (IQR) of US$97.62 (6.43–184.22) and US$93.75 (56.91–141.54) during the pre- and post-diagnosis periods, respectively. Thus, patients incurred 53.6% of the total cost during the pre-diagnosis period. Direct out-of-pocket expenses during the pre- and post-diagnosis periods respectively amount to median (IQR) of US$21.64 (10.23–48.31) and US$35.02 (0–70.04). Patient delay days ($p < 0.001$), provider delay days ($p < 0.001$), number of healthcare facilities visited until TB diagnosis ($p < 0.001$), and TB diagnosis at private facilities ($p = 0.02$) independently predicted increased pre-diagnosis cost. Similarly, rural residence ($p < 0.001$), hospitalization during anti-TB treatment ($p < 0.001$), patient delay days ($p < 0.001$), and provider delay days ($p < 0.001$) predicted increased post-diagnosis costs.

Conclusion: TB patients incur substantial cost for care seeking and treatment despite "free service" for TB. Therefore, promoting early care seeking, decentralizing efficient diagnosis, and treatment services within reach of peoples, and introducing reimbursement system for direct costs can help minimize financial burden to the patient.

Keywords: TB, Direct cost, Indirect cost, Longitudinal, Pre-diagnosis, Post-diagnosis, Ethiopia

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Background

Tuberculosis (TB) remained among the major global public health problems. In 2015, an estimated 10.4 million cases and 1.4 million deaths occurred globally. The African Region constitutes 28% of the global cases and the most severe burden relative to population (281 cases per 100,000 people) [1]. TB morbidity and mortality pose an enormous economic burden to patients, household, and society. Each year, a TB patient loses on average 3 to 4 months of work and up to 30% of household earnings [2].

Efforts to control TB have three distinct, but overlapping humanitarian, public health, and economic dimensions. The efforts imply timely diagnosis and treatment of patients and reduction of costs due to TB [3]. The latest TB control strategy, End TB, underlined the need for universal access to health services without financial hardship, social protection for income replacement, and support in the event of illness [4]. Accordingly, a global target has been set to have no TB-affected family facing catastrophic costs due to TB by 2020 [4, 5]. Costs incurred by a TB patient include either direct or indirect costs. The direct costs comprise out-of-pocket expenses for medical and nonmedical services whereas the indirect costs constitute foregone income because of lost workdays [6].

Despite the free TB diagnosis and treatment, TB patients and families incur high direct and indirect costs due to TB illness [5]. Systematic reviews across low- and middle-income countries showed mean total costs of TB ranging from fewer than I$1 to I$8198 [5, 7]. The review further reported indirect and direct costs incurred for TB care respectively constituted 60 and 40% of the total cost [5]. Studies also reported that seeking care and treatment of TB costs a median of United States of America Dollar (US$) 592 in Nigeria [8] and mean cost of US$108.4 in Yemen [9] per household. The high cost of TB care seeking and treatment result in delays to diagnoses [10, 11] and poor outcome [12, 13]. The poor outcome lead to development of drug resistant TB [14] that require much higher cost of care [15].

Implementation of global TB control strategies in Ethiopia have led to improvements in access to TB care, decline in TB morbidity, and mortality [16]. Nonetheless, Ethiopia belongs to the 14 TB, TB/human immunodeficiency virus (HIV), and multi-drug resistant (MDR) TB high-burden countries [1]. Out of a total US$47.8 million spent for TB control in 2008, household out-of-pocket expenses constituted 62% [17]. A cost and epidemiological modelling in Ethiopia, showed out-of-pocket medical cost for TB amounted to US$49 per patient that led households to fall below poverty line [18]. A study in Tigray, Northern Ethiopia from patient perspective reported median cost incurred for care seeking to be US$16 [19]. A community randomized trial using societal perspective in southern Ethiopia revealed a successful treatment of a smear-positive patient costs US$158.9 at a health facility compared to that within the community (US$61.7) [20].

It is important to understand the financial burden of TB patients to adapt and realize a global target of having no households incurring catastrophic costs because of TB [1]. However, only few studies exist in Ethiopia, those dealt on the financial burden of TB patients. The few studies dealt on cost of care seeking and diagnosis [19] or cost of treatment [20] but not both. The studies were conducted during the 8 months of treatment regimen. However, the current 6-month regimen requires frequent visits (daily to weekly) to health facilities throughout the course of treatment [21]. Furthermore, none of the studies analyzed cost predictors across the continuum of care. Generally, evidences on financial burden posed to TB patients across the pathways to treatment are limited in Ethiopia. Therefore, we studied costs incurred by TB patients across the pre- and post-diagnosis periods including cost drivers in districts of southwestern Ethiopia.

Methods

Study setting and design

A longitudinal study among new TB cases on Directly Observed Treatment Short course (DOTS) was carried out from January 2015 through June 2016. We included 14 public healthcare facilities (three hospitals and 11 health centers) from 10 *woredas* (an administrative unit equivalent to district) in three zones (an administrative structure that oversees woredas and report to regional states). The zones, Bench Maji, Kaffa, and Sheka, are among the 15 zones in Southern Nations Nationalities and Peoples Region (SNNPR). The zones are located at the southwestern border of the region where an estimated 2,064,102 people reside [22]. The zones are organized into four town administrations and 26 woredas. During the study, three hospitals and 65 health centers were providing TB DOTS [23].

Diagnosis and treatment for all forms of TB in Ethiopia is according to a national guidelines [21, 24] that specify case definitions, diagnostic, and treatment standards. Diagnosis based on sputum microscopy, sputum follow-up test, and anti-TB drugs are free of charge in all public and selected private facilities. Since the end of 2011, all forms of new TB cases are treated for 6 months with combination of rifampicin (R), isoniazid (H), pyramidal (Z), and ethambutol (E) for the first 2 months (intensive phase) (2RHZE) followed by rifampicin (R) and isoniazid (H) for 4 months (4RH). Thus, patients need to visit a DOTS center daily and weekly during intensive and continuation phase treatments, respectively.

Sample size and sampling

The sample size needed for the study was calculated using STATA V13 considering a mean (SD) patient cost of care seeking of US$29(14) [19] to detect a US$5 difference which revealed 250 cases. This study is part of a doctoral dissertation aimed at assessing time delays, cost, and outcomes of TB patients on DOTS. Thus, among the sample sizes calculated for each objective of the dissertation, which required for assessing predictors of delay, 802 cases was the largest. Since similar cases were studied for all the objectives, the largest sample, 802 cases was used for this study.

We selected the region (SNNPR) and zones (Bench Maji, Kaffa, and Sheka) conveniently. Considering the available resources and representativeness, we decided to study 10 woredas of the three zones. Thus, through proportional allocation, we determined the number of woredas from each zone. Considering the number of TB cases notified in the preceding year to the study time, we selected the woredas from each zones. Then, all public health facilities providing diagnosis and treatment of TB in the selected woredas were included for the study. We included 14 health facilities (three hospitals and 11 health centers). Therefore, we allocated the 802 cases proportionally to the zones, woredas, and health facilities based on their preceding year TB case notification. Finally, successive consenting cases were enrolled until the required sample reaches. Those new cases, older than 18 years and on intensive phase treatment, were included and those on continuation phase, transferred to other treatment center, lost to follow-up, and died before the enrollment were excluded from study.

Data collection

Data were collected using structured questionnaire (Additional file 1) adapted from the tool to estimate TB patients' cost developed by the WHO and other partners [6]. Similarly, data abstraction checklist was prepared to extract data from the standard unit TB register. The questionnaire was translated in to the national language (Amharic) to ease the understanding among both the data collectors and participants. Then, 10 diploma graduate nurse data collectors and three master holder supervisors were recruited and trained for 3 days. The training included the basics of TB control, details of questionnaire, data abstraction, interviewing techniques, and pretest of the tool at health facilities not included in the study. Finally, eligible cases were traced from the unit TB register, and face-to-face interview was held within the intensive phase and end of treatment. The first interview-included patients' sociodemographic, healthcare-seeking practices, and costs incurred until TB diagnosis (pre-diagnosis cost). The follow-up interview inquired costs incurred after the diagnosis of TB through completion of the treatment (post-diagnosis cost).

Cost ascertainment

Cost data were ascertained from patient perspective using prevalent approach that estimate financial burden of an illness to patients at specified period of time [25]. So costs incurred by patients for care seeking and treatment of TB were collected at two-time points, during the first 2 months of treatment and at the end of the treatment. Both direct out-of-pocket expenses (for medical and nonmedical services) and indirect costs were measured. Direct costs consisted of out-of-pocket charges for medical services (consultation, drugs, laboratory tests, X-ray, and hospitalization) and nonmedical services (transportation, meal, and accommodation) while visiting healthcare facilities.

Direct out-of-pocket patient expenses during the pre-diagnosis period (incurred from onset of illness to treatment initiation) were determined by asking patient expense at each visit for consultation, laboratory tests, drugs, transportation, meals, and lodging. In the same way, post-diagnosis direct costs (incurred from initiation to completion of the prescribed treatment) were measured by inquiring patients' medical and nonmedical expenses during visits for anti-TB treatment. The number of visits for the pre-diagnosis period was solicited from patients, and post-diagnosis visits were taken from attendance records on a unit register. Thus, transportation cost was calculated by multiplying the number of visits with the fee per trip.

The indirect costs were estimated using the human capital approach. Patients were requested to estimate time lost due to sickness and visits for consultation, hospitalization, drug collection, and trip journey. The time spent second or minute were converted to hours and then to days at an average of eight working hours in a day (8 h = 1 day). Finally, the number of days was multiplied by an average daily wage rate of US$2.43 = 50 Ethiopian Birr for those unemployed and daily rate calculated from their gross monthly salary for those formally employed. Monthly income of formally employed cases was inquired from patients by asking their monthly salary. For self-employed, self-estimated average monthly earning was used to calculate daily rate. An average wage rate estimated by the social affair offices was used for unemployed cases.

For cost items with no charge, it was recorded as zero. All the costs were inquired in local currency, Ethiopian Birr (ETB), and then converted into US dollars (US$) using the average exchange rate of (US$1 = 20.56 ETB) during January through December 2015 [26].

Data management

Data were entered into EpiData v3.1 then exported to SPSS version 21 for cleaning and then to STATA 13 for analysis. The data were described using frequency, proportions, mean (standard deviation), and median (inter-quartile range), and normality of the cost data were checked using plots (Q-Q plots and/or histograms) or Kolmogorov-Smirnov test. The cost data were right skewed and became log normal upon log transformation to base 10. Hence, all the statistical tests were done with the lognormal data and reported by back transforming to its anti-log.

Proportion and mean differences across categorical variables were tested using chi-square and independent *t* tests respectively. Associations between continuous variables were tested with simple correlation. Mean difference between pre- and post-diagnosis costs were tested with paired *t* test. Finally, simple and multiple linear regression models were fitted to identify predictors of pre- and post-TB diagnosis costs. Assumptions and fitness for the linear regression model were assessed and ensured. In all the statistical tests, significance was judged at $p < 0.05$.

Ethical issues

The Institutional Review Board of the College of Health Sciences at Addis Ababa University approved the study protocol. Therefore, patients consented in written for the interview and clinical records of patients were retrieved upon permission from the respective health facilities.

Operational definitions

Patient delay is days elapsed between onsets of illness to the first formal healthcare seeking.

Health system/provider delay is the number of days spent between the first consultations to initiation of treatments.

Total delay is the number of days elapsed since onset of illness to anti-TB treatment initiation.

Medical cost is costs incurred for medical services including consultation, laboratory tests, drugs other than anti-TB, X-ray, and related services.

Nonmedical cost is costs incurred for transportation, accommodation, meal, and related services while seeking care for TB and visiting to collect anti-TB drugs.

Direct cost is out-of-pocket patient expenses for medical or nonmedical services while seeking care, diagnosis, and treatment for TB.

Indirect cost is lost earning because of inability to work or lost workdays while traveling to seek care, diagnosis, and treatment for TB.

Pre-diagnosis cost is the cost incurred since onset of illness until anti-TB treatment initiation.

Post-diagnosis cost is the cost incurred since the beginning up to the completion of anti-TB treatment.

Total cost is both direct and indirect costs incurred for care seeking, diagnosis, and treatment of TB.

Results

A total of 735 TB cases were enrolled of which 627(85.3%) completed the follow-up. Those lost included 29(3.9%) deaths, 36(4.9%) transferred to other treatment centers, 5(0.7%) treatment failure, and 38(5.2%) lost to follow-up. Nonetheless, there were no statistical significant differences with the proportions of the attributes across the baseline and end line surveys (Table 1). The median age (inter-quartile range (IQR)) of the cases during enrollment (baseline) was 27(20–37) years. Of the cases enrolled, 53 and 29.4% completed elementary school and are involved in farming, respectively. The mean (+ SD) of size and median annual income of the households were 4.3(+ 2.1) and US$466.93, respectively.

Care-seeking pathways

TB patients first visited a healthcare facility after a median of 25 days from onset of illness (patient delay). Thus, 35.4 and 32.4% of the cases first visited private clinics and public health centers, respectively (Table 2). The rest of the cases first visited hospitals (30.1%) and health posts (2.1%). TB diagnosis of 448(61%) cases was made at a hospital, and for 244(33.2%), the diagnosis was made at the first visited health facility. Diagnosis of 491(66.8%) were reached after an average (+SD) of 3.6(+ 2.4) visits to an average (+SD) of 2.2(+ 1.2) healthcare facilities (HCF). Since the first consultation, a median of 22 days had been elapsed to initiate anti-TB treatment. Among the cases, 586(79.7%) had pulmonary TB and 362(49.3%) were diagnosed clinically. All of the cases were offered HIV screening test of whom 68 (9.3%) tested positive, 95% CI (7.2–11.3%).

Pre-diagnosis cost

Until diagnosis of TB, patients incurred a median (IQR) cost of US$97.6 (56.4–184.2) (Table 3). Direct cost amount to median (IQR) US$21.64 (10.23–48.31) and constitute 25.6% (Fig. 1) of the total pre-diagnosis costs. Patients had lost median (IQR) of 24.7(15.1–48.4) workdays until diagnosis of TB that corresponded to median (IQR) US$64.45 (39.8–128.8) income loss.

The pre-diagnosis cost was positively correlated with patient ($\gamma = 0.32$, $p < 0.001$), provider ($\gamma = 0.64$, $p < 0.001$) and total delays ($\gamma = 0.68$, $p < 0.001$), and the number of HCF visited until diagnosis ($\gamma = 0.42$, $p < 0.001$). The mean pre-diagnosis cost was significantly different across the types of TB ($F = 10.03$, $p < 0.00$), type of first visited HCF ($p = 0.002$), HCF where diagnosis was made ($p < 0.001$), and mode of diagnosis ($p = 0.001$) (Additional file 2: Table S1).

Table 1 Sociodemographic characteristics of TB cases in districts of southwestern Ethiopia, January to December 2015

Variable		Baseline ($n = 735$) n(%)	End line ($n = 627$) n(%)	P value
Gender	Female	288(39.2)	244(38.9)	0.9
Age(years)	18–34	503(68.4)	431(68.7)	0.9
	35–65	216 (29.4)	183(29.1)	0.8
	> 65	16(2.2)	13(2.1)	0.89
Marital status	Never married	275(37.4)	235(37.5)	0.97
	Currently married	404(55)	342(54.5)	0.85
	Widowed/divorced	56(7.6)	50(8)	0.78
Educational status	No formal education	212(28.8)	176(28.1)	0.77
	Completed elementary	389(53)	340(54.2)	0.66
	Secondary and above	134(18.2)	111(17.7)	0.8
Occupation	Employed	172(23.4)	147(23.4)	1.00
	Farming	216(29.4)	188(30.0)	0.81
	Unskilled work[a]	51(6.9)	43(6.9)	1.00
	Dependents[b]	296(40.3)	249(39.7)	0.82
Residence	Urban	369(50.2)	313(49.9)	0.94
	Rural	367(49.9)	314(50.1)	0.74
Household main income earner	Self	370(50.3)	310(49.4)	0.74
	Other[c]	365(49.7)	317(50.6)	0.8
Household income	≤ US$466.93	288(50.6)	242(50.3)	0.9
	> US$466.93	281(49.4)	239(49.7)	0.9

[a]Housemaid, daily laborer
[b]Students, housewife
[c]Father/mother/husband/wife/brother/sister/employer

In a multiple regression patient and provider delays, being clinically diagnosed, TB diagnosis at private facilities and the number of visited healthcare facilities independently predicted higher mean pre-diagnosis costs (Table 4). Every single patient and provider delay days each increased the mean pre-diagnosis cost by 0.5%. Those patients' diagnosed clinically incurred 11% higher mean pre-diagnosis costs compared to those diagnosed bacteriologically. Similarly, patients diagnosed at private HCFs incurred 18% higher mean pre-diagnosis cost compared to those diagnosed at public HCFs.

Post-diagnosis cost

After the diagnosis of TB, patients incurred a total median (IQR) of US$93.75 (56.9–141.54) until the completion of the treatment (Table 3). The direct cost amounted to a median (IQR) of US$35.02 (0–70.04) and constitutes 35.9% (Fig. 1) of the total post-diagnosis cost. During the treatment, TB patients had lost a median (IQR) of 21(13–35.3) workdays that corresponded to a median (IQR) of US$51.0 (34.6–97.0) income loss (indirect cost). Thus, significantly lower medical and indirect costs and higher nonmedical costs were incurred during the post-diagnosis period compared to the pre-diagnosis. The post-diagnosis cost was positively correlated with patient ($\gamma = 0.20$, $p < 0.001$) and provider ($\gamma = 0.23$, $p < 0.001$) delays.

In the multiple regression analysis, being a rural resident, having a travel time beyond 1 h to the treatment center, being admitted for anti-TB treatment, patient and provider delays independently predicted higher mean post-diagnosis cost. On the other hand, completing primary and higher educational status and being treated at a hospital predicted lower mean post-diagnosis costs (Table 5). Thus, being a rural resident was associated with an increase in mean post-diagnosis cost by 48% compared to those being urban residents. Every patient and provider delay days increases the mean post-diagnosis cost by 0.3 and 0.2%, respectively. Those patients hospitalized for anti-TB treatment had more than twofold higher mean post-diagnosis cost compared to those patients never hospitalized for anti-TB treatment. Patients who followed their course of anti-TB treatment at hospitals had about 18% lower mean post-diagnosis cost compared to those who received the anti-TB treatment at health centers.

Table 2 Care-seeking pathways and clinical characteristics of TB cases on treatment in districts of southwestern Ethiopia, January to December 2015

Variable		Baseline ($n = 735$)	End line ($n = 627$)	*P* value
		n(%)	*n*(%)	
Action to illness before visiting HCF	None	586(79.7)	497(79.3)	0.85
	Took action[a]	149(20.3)	130(20.7)	0.85
First visited HCF	DOTS center	459(62.5)	387(61.7)	0.85
	Non-DOTS	276 (37.5)	240(38.3)	0.76
Diagnosis made HCF	Public	636(86.5)	537(85.6)	0.76
	Private	99(13.5)	90(14.4)	0.70
Type of TB	Pulmonary positive	373(50.7)	320(51.0))	0.90
	Pulmonary negative	213(29.0)	176(28.1)	0.70
	Extra pulmonary	149(20.3)	131(20.9)	0.70
Mode of diagnosis	Bacteriological	373(50.7)	319(50.9)	0.90
	Clinical	362(49.3)	308(49.1)	0.90
Treatment center	Health center	469(36.2)	408(65.1)	0.70
	Hospital	266(63.8)	219(34.9)	0.70
Travel time to treatment center	≤ 1 h	437(59.5)	373(59.5)	1.00
	> 1 h	298(40.5)	254(40.5)	1.00
Hospitalized for treatment	Yes	19(2.6)	15(2.4)	0.40
HIV co-infection	Yes	68(9.3)	46(7.3)	0.10
Patient delay	Median (IQR) days	25((15–36)	23(14–34)	0.20
Provider delay	Median (IQR) days	22(9–48)	20(8–48)	0.40
Total delay	Median (IQR) days	55(32–100)	52(31–93)	0.50

[a]Self-treatment, consult traditional healer, used holy water

Total cost of TB care seeking and treatment

Total costs incurred by patients for care seeking, diagnosis, and treatment amount to a median (IQR) of US$201.48 (136.70–318.94) (Table 3). Pre- and post-diagnosis costs respectively constituted 53.6 and 46.4% of the total cost. Total direct cost constituted 29.4% (Fig. 1) of the total cost and amounted to a median (IQR) of US$59.58 (29.43–113.81). Drugs other than anti-TB and diagnostic tests (laboratory or imaging tests) corresponded to 49.7 and 44.6% of the total medical costs, respectively. During the care seeking and treatment visits, patients had totally lost a median (IQR) 51.7 (32.0–80.8) workdays that corresponded to a median (IQR) of US$127.68 (78.43–201.85) income loss (indirect cost). Out of the total forgone income due to the TB illness, the loss due to lost workdays following care-seeking visits amounted to a median (IQR) of US$18.02

Table 3 Distribution of TB patient costs across cost categories and periods in districts of southwestern Ethiopia, January to December 2015

Cost category		Cost period		
		Pre-diagnosis (US$)	Post-diagnosis (US$)	Total (US$)
Medical	Mean (95% CI)	8.56 (7.68, 9.54)	4.4 (3.23, 6.0)	8.75 (7.85, 9.75)
	Median (IQR)	10.72 (4.58, 23.76)	0 (0)	11.19 (4.73–24.08)
Nonmedical	Mean (95% CI)	10.08 (8.99, 11.30)	43.27 (38.32, 48.23))	64.1 (58.34, 69.9)
	Median (IQR)	8.27 (1.61, 24.32)	35.02 (0–70.04)	37.11 (14.35, 85.12)
Total direct	Mean (95% CI)	21.46 (19.65, 23.43)	43.80 (38.82, 48.78)	84.82 (77.92, 91.72)
	Median (IQR)	21.64 (10.23, 48.31)	35.02 (0–70.04)	59.58 (29.43, 113.81)
Indirect	Mean (95% CI)	75.62 (70.68, 80.90)	75.20 (69.14, 81.26))	140.31 (132.35, 148.74)
	Median (IQR)	64.45 (39.82, 128.80)	51.07 (34.65, 93.02)	127.68 (78.43, 201.85)
Total	Mean (95% CI)	108.0 (101.31, 115.11)	117.0 (110.47, 123.87)	244.71 (229.45, 260.98)
	Median (IQR)	97.62 (56.43, 184.22)	93.75 (56.91, 141.54)	201.48 (136.7, 318.94)

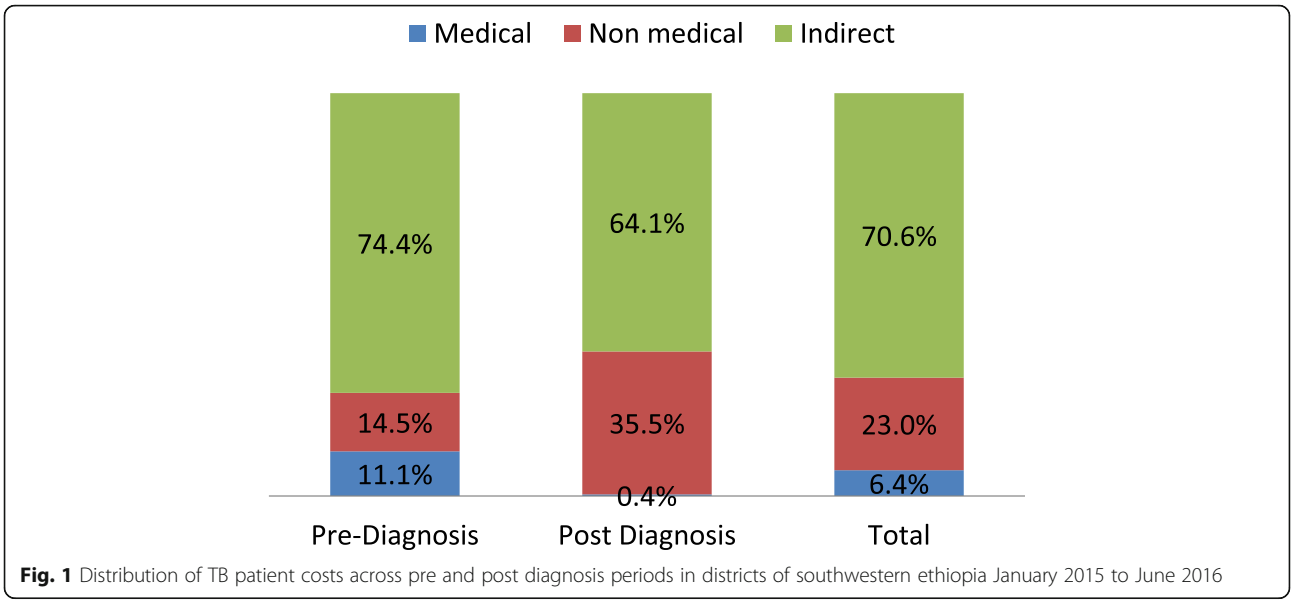

Fig. 1 Distribution of TB patient costs across pre and post diagnosis periods in districts of southwestern ethiopia January 2015 to June 2016

(11.35–30.85) that constitutes 28.4% of the total indirect cost. For 471/569 (82.8%) of the cases, the total cost represents more than 10% of their estimated household annual income.

The mean total cost is significantly different across the types of TB (F = 3.68, $p = 0.03$), action taken before HCF visit ($p = 0.01$), travel time to treatment center ($p = 0.001$), and hospitalization for anti-TB treatment ($p = 0.005$) (Additional file 2: Table S1). In multiple regression, rural residence, travel time to treatment center beyond 1 h, action taken before HCF visit, hospitalized for anti-TB treatment, number of visited HCF, and patient and

Table 4 Predictors of pre-diagnosis cost among TB cases on treatment in districts of southwestern Ethiopia January to December 2015

Variable		Mean(SD) (US$)	Unadjusted exp.[a] coefficient (95% CI)	*P* value	Adjusted exp.[b] coefficient (95% CI)	*P* value
Gender	Male	112.62(0.12)	Ref.		Ref.	
	Female	101.25(0.11)	0.90(0.79, 1.02)	0.1	0.94(0.86, 1.03)	0.20
HIV result	Positive	131.2(0.13)	1.24(0.98, 1.55)	0.07	1.16(0.99, 1.36)	0.06
	Negative	106.02(0.11)	Ref.		Ref.	
Mode of diagnosis	Bacteriological	97.00(0.11)	Ref.		Ref.	
	Clinical	121.08(0.12)	1.25(1.10, 1.42)	0.001	1.08(0.99, 1.18)	0.09
Residence	Urban	114.61(0.12)	Ref.		Ref.	
	Rural	102.13(0.1)	0.89(0.78, 1.01)	0.07		
Patient delay[c](days)			1.006(1.005, 1.006)	< 0.001	1.005(1.004, 1.01)	< 0.001*
Provider delay[c](days)			1.006(1.005, 1.01)	< 0.001	1.005(1.004, 1.01)	< 0.001*
Action before HCF visit	None	106.72(0.12)	Ref.		Ref.	
	Took action[d]	113.41(0.11)	1.23(1.07, 1.41)	0.03	1.15(1.03, 1.28)	0.01
First visited HCF	DOTS center	99.97(0.11)	Ref.		Ref.	
	Non-DOTS center	122.57(0.11)	1.23(1.07, 1.40)	0.002	1.01(0.91, 1.11)	0.8
TB diagnosed HCF	Public	101.78(0.11)	Ref.		Ref.	
	Private	153.88(0.13)	1.5(1.26, 1.81)	< 0.001	1.18(1.03, 1.34)	0.02*
Number of HCF visited until diagnosis[b]			1.40(1.34, 1.47)	< 0.001	1.18(1.13, 1.23)	< 0.001*

*Statistically significant at $p < 0.05$
[a]Exponent to the power of 10
[b]Adjusted for all the variables listed in the table
[c]Variable treated as continuous
[d]Self-treatment, used holy water, consult traditional healer

Table 5 Predictors of post-diagnosis cost among TB cases on treatment in districts of southwestern Ethiopia January to December 2015

Variable		Mean(SD)	Unadjusted exp[a] coefficient (95% CI)	*P* value	Adjusted exp[b] coefficient (95% CI)	*P* value
Gender	Male	119.73(0.1)	Ref.		Ref.	
	Female	112.51(0.1)	0.94(0.83, 1.06)	0.3	0.92(0.83, 1.02)	0.07
Residence	Urban	94.02(0.11)				
	Rural	154.7(0.08)	1.64(1.48, 1.83)	< 0.001	1.48(1.34, 1.64)	< 0.001*
Educational status	Illiterate	137.15(0.09)	Ref		Ref	
	Primary	117.35(0.09)	0.86(0.74, 0.98)	0.03	0.87(0.77, 0.97)	0.02*
	Secondary and above	97.79(0.08)	0.71(0.60, 0.84)	< 0.001	0.83(0.72, 0.95)	0.01*
HIV result	Positive	123.52(0.1)	1.06(0.88, 1.28)	0.5	1.13(0.97, 1.30)	0.1
	Negative	116.20(0.1)	Ref.		Ref.	
Mode of diagnosis	Bacteriological	118.25(0.1)	Ref.		Ref.	
	Clinical	115.82(0.1)	0.98(0.87, 1.10)	0.7	0.96(0.87, 1.05)	0.3
Treatment center	Hospital	103.05(0.1)	0.78(0.70, 0.88)	< 0.001	0.82(0.74, 0.90)	< 0.001*
	Health center	131.43(0.1)				
Travel time to treatment center	> 1 h	105.7(0.08)	1.37(1.22, 1.55)	< 0.001	1.09(1.02, 1.21)	0.03*
	≤ 1 h	145.14(0.09)	Ref.		Ref.	
Patient delay[c]			1.003(1.002, 1.004)	< 0.001	1.003(1.001, 1.003)	< 0.001*
Provider delay[c]			1.002(1.001, 1.003)	< 0.001	1.002(1.001, 1.002)	< 0.001*
Action before HCF visit	None	111.85(0.11)	Ref.		Ref.	
	Took action[d]	137.34(0.1)	1.23(1.07, 1.41)	0.003	1.08(0.98, 1.28)	0.1
TB diagnosed HCF	Public	116.37(0.1)	Ref.			
	Private	121.27(0.1)	1.04(0.87, 1.24)	0.5	0.95(0.83, 1.09)	0.5
Hospitalized for treatment	Yes	240.82(0.1)	2.13(1.61, 2.80)	< 0.001	2.3(1.84, 2.88)	< 0.001*
	No	113.3(0.1)	Ref.		Ref.	

*Statistically significant at $p < 0.05$
[a]Exponent to the power of 10
[b]Adjusted for variables in the table
[c]Variable treated as continuous
[d]Self-treatment, used holy water, consult traditional healer

provider delays all independently predicted increased mean total patient cost of TB care (Additional file 2: Table S2). The mean total cost incurred by patients who are rural residents is about 24% higher than that by urban residents, adjusted exp. coefficient (AeC) (95% CI) 1.24 (1.13, 1.4). Similarly, every patient and provider delay day predicts about 0.3% each AeC (95% CI) 1.003(1.002–1.004) increment in mean total patient cost. Those patients who took action before initiating HCF visits had incurred 17% higher mean total cost compared to those who did not took action. Hospitalization during anti-TB treatment increase the total mean patient cost by 97% compared to those not hospitalized.

Discussion

This follow-up study of new TB cases on DOTS revealed patients incurred substantial cost across pathways to TB treatment. Thus, the median out-of-pocket payment for an episode of TB illness amounted to US$59.58 that constitutes more than a quarter (29.4%) of the total cost. More than half (53.6%) of the total cost were incurred before diagnosis of TB, and majority (70.6%) of the total cost were attributed to nearly 52 lost workdays per patient. Compared to the post-diagnosis, patients incurred significantly higher medical and indirect costs and lower nonmedical costs during the pre-diagnosis period. Increased pre-diagnosis costs were attributed to patient and provider delays, taking informal treatment before HCF visit, diagnosis at private facilities, being clinically diagnosed, and the number of visited health facilities. On the other hand, rural residence, hospitalization for anti-TB treatment, and following anti-TB treatment at a health center predicted increased post-diagnosis patient costs.

The total cost incurred across the care-seeking and treatment pathways are significantly correlated with both patient and provider delays. The increased pre-diagnosis

cost with patient delay could be due to increased risks of severe manifestation [27] that lead to hospitalization and companion during care seeking and treatment. Besides, the patient delay is associated with informal care including self-treatment and traditional cares [28, 29] that pose costs to patients. The patient delays are accompanied by longer lost workdays that reduced patient income. On the other hand, the delay at health system (provider delay) is associated with repeated visits to different HCF when patients incur for both medical and nonmedical services.

Those patients diagnosed clinically incur significantly higher pre-diagnosis cost. This could be due to national diagnostic algorithm that respectively requires 2–4 and 4–8 weeks follow-up for the clinical diagnosis of smear negative and extra pulmonary TB [21]. The higher costs for the clinical diagnosis could be due to the requirement of experienced clinician decisions guided by better diagnostic facilities. Such experts and facilities exist at only few healthcare facilities situated in cities very far from the majority of the people that lead to higher transportation and lodging costs to patients. The repeated consultations and diagnostic tests until diagnosis of TB all incur cost to the patients. The relatively lower cost of bacteriologically confirmed diagnosis could be due to exemption of sputum smear microscopy and culture by the national TB control program. Hence, ensuring efficient diagnostic algorithms and quality bacteriological tests can reduce the financial burden of TB patients.

Consistent with other studies [8, 30] patients diagnosed at private facilities incur significantly higher pre-diagnosis cost compared to those diagnosed at public facilities. The different cost items and rates at the private facilities where every services including sputum microscopy is charged can explain the relatively higher cost at the private. Since there were no public-private mix (PPM)-DOTS in the study area at the time of study, the private HCF might not implement the proper diagnostic algorithm that might lead to delay and extra cost. Furthermore, public health facilities requirement of retesting a positive sputum result from private facilities for treatment initiation leads to delay and extra cost [31].

We found patients treated at hospitals had significantly lower post-diagnosis cost compared to those treated at health center. This could be due to the presence of full-time staff that exclusively provides TB patient care at hospitals. However, at health centers, providers are given multiple duties other than TB DOTS that increase patient waiting time and costs. In addition, health centers are situated in rural areas where there is no transport access within villages in contrast to hospitals in urban areas easily accessible to patients within the town. Thus, statistically significant difference in mean total time (71.17 vs 106. 79 min, $p < 0.001$) had been respectively spent per each patient visit to hospitals and health centers. Consistent with other studies [8, 32], we found significantly higher post-diagnosis cost incurred by patients from rural areas compared to those from urban areas. The reason could be due to significantly higher mean time spent per each visit among patients that are rural and urban residents (119.51 vs. 68.35 min, $p < 0.001$), respectively.

Our study had some limitations. First, cost measurements relied on patient recall, which was liable to recall bias. However, we did the baseline interview within the first 2 months of treatment when patients are highly likely to recall about the costs they incurred. Second, the study employed only patient perspective so that we were not able to determine costs incurred by health systems, households, and communities. Lastly, we determined the cost based on a prevalent approach that measure costs for an episode of illness so that we could not determine lifetime cost of TB illness. On the other hand, our study employed a longitudinal design involving a relatively large sample recruited consecutively. As a result, selection bias was minimized and patient costs from care seeking through treatment completion were determined. The findings in the paper are valid but need to be interpreted cautiously considering the limitations. Given the internal validity, the findings can be applied to patients in similar settings since the characteristics of patients and the health systems in similar settings might not differ significantly.

Conclusion

The study revealed TB patients on DOTS incur substantial cost across the pathways to anti-TB treatment despite the "free service." Significantly, higher cost was incurred during the pre-diagnosis period compared to the post-diagnosis period showing longer pathways of care seeking. Increased pre-diagnosis costs are attributed to patient and provider delays, informal care before consultation, seeking care at private healthcare facilities, and clinical diagnosis. Higher post-diagnosis costs are attributed to patient and provider delays, rural residence, and being treated at health center. Thus, implementation of patient-centered TB care introducing reimbursement mechanisms and scaling up of national community and social insurance initiatives to the study area are vital to reduce patients' out-of-pocket expenditures. In addition, introducing reimbursement of direct costs, promoting early care seeking, equipping healthcare facilities with the necessary equipments, and staffing with qualified health work force, and decentralizing efficient diagnosis and treatment within reach of patients can minimize the patient costs.

Additional files

Additional file 1: Consent form and questionnaire. (DOCX 112 kb)

Additional file 2: Table S1. Mean differences of pre, post, and total costs to patients among TB cases on treatment in districts of southwestern Ethiopia January to December 2015. Table S2. Predictors of total cost to patients among TB cases on treatment in districts of southwestern Ethiopia January to December 2015. (DOCX 25 kb)

Abbreviations

CI: Confidence interval; DOTS: Directly Observed Treatment Short course; ETB: Ethiopian Birr; HCF: Healthcare facility; HIV: Human immunodeficiency virus; IQR: Inter-quartile range; PPM: Public-private mix; SD: Standard deviation; TB: Tuberculosis; US$: United States of America Dollar

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Availability of data and materials

The data from which conclusion of this study was made can be available upon request from the corresponding author.

Authors' contributions

AA conceived and designed the study, collected and analyzed the data, and prepared the manuscript. WD and DJ critically reviewed the study protocol and manuscript for intellectual content as primary and co-supervisor, respectively. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was ethically approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and a unit register was retrieved upon permission from respective health care facilities.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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RESEARCH ARTICLE Open Access

Delays to treatment initiation is associated with tuberculosis treatment outcomes among patients on directly observed treatment short course in Southwest Ethiopia: a follow-up study

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Abstract

Background: Despite reported long delays to initiate anti-TB treatment and poor outcomes in different parts of Ethiopia and elsewhere, evidences on association between the delay and treatment outcomes are scanty.

Methods: A follow up study among 735 new TB cases registered at health facilities in districts of southwest Ethiopia was conducted from January 2015 to June 2016. Patients reported days elapsed between onset of illness and treatment commencement of 30 days cutoff was considered to ascertain exposure. Thus, those elapsed beyond 30 days to initiate anti-TB treatment since onset of illness were exposed and otherwise non-exposed. The cases were followed until earliest outcome was observed. Treatment outcomes was ascertained as per the World Health Organization standard definitions and dichotomized into 'successful' when cured or treatment completed and 'unsuccessful' when lost to follow-up or died or treatment failure. Bivariate and multiple log-binomial models were fitted to identify predictors of unsuccessful outcomes.

Results: The overall treatment success among the treatment cohort was 89.7% (88.4% vs. 94.2%, $p = 0.01$ respectively among those initiated treatment beyond and within of 30 days of onset of illness. Higher risk of unsuccessful outcome was predicted by treatment initiation beyond 30 days of onset [Adjusted Relative Risk (ARR) = 1.92, 95%CI:1.30, 2.81], HIV co-infection (ARR = 2.18, 95%CI:1.47, 3.25) and received treatment at hospital (ARR = 3.73, 95%CI:2.23, 6.25). On the other hand, lower risk of unsuccessful outcome was predicted by weight gain (ARR = 0.40, 95%CI:0.19, 0.83) and sputum smear negative conversion (ARR = 0.17,95% CI:0.09, 0.33) at the end of second month treatment.

Conclusion: Higher risk of unsuccessful outcome is associated with prolonged days elapsed between onset of illness and treatment commencement. Hence, promotion of early care seeking, improving diagnostic and case holding efficiencies of health facilities and TB/HIV collaborative interventions can reduce risk of unsuccessful outcome.

Keywords: TB, Delay, Follow-up, Log-binomial, Ethiopia

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Background

Despite the fact that nearly all cases can be cured, tuberculosis (TB) remained to be among the major global public health problems. Globally, 10.4 million incident cases, of whom 6.1million notified and 1.4 million deaths were estimated to occur in 2015 [1]. Thus, the latest strategy, "End TB" has been designed in line with the sustainable development goals (SDG). The strategy aimed at reaching 90% case detection and treatment success by 2025 [2].

Tuberculosis has been recognized as a major public health problem in Ethiopia and efforts to control the disease has begun since early 1960s [3]. Nonetheless, TB has remained among the major public health problems in the country [4]. Accordingly, Ethiopia has been listed among the 14 TB, TB/HIV (Human Immunodeficiency Virus) and Multi-Drug Resistant TB (MDR TB) High Burden Countries (HBC) [1]. The first national TB prevalence survey conducted in 2011 revealed smear positive pulmonary TB(PTB) prevalence of 108/100,000; of which 55% were not detected before the survey [5] . In 2015, about 205,463 new cases [6] and 29,000 deaths were estimated to occur in the country [1] when only 125,801 (61%) were notified to National TB control Program (NTP) [6].

The ultimate goal of any TB control program is reduction of morbidity and mortality among patients and stop transmission through curing infectious cases [7]. Hence early detection and treatment of cases have been a pillar for the end TB strategy [2]. Nonetheless, studies from different parts of Ethiopia reported patients elapse too long time to initiate care seeking and treatment. TB patients elapse median of 30 [8, 9] in Northern Ethiopia and 63 days in Bale [10] to initiate care seeking and median of six in Addis Ababa [11] and 34 days in Bale [10] to commence treatment.

Delays to diagnosis and treatment of TB result in more serious illness, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance [12–16]. It is also reported that the high mortality rate among people living with HIV is also partly explained by delays to TB treatment [16, 17]. In contrast, a study in Tel Aviv reported no association between treatment success and delay in treatment initiation [18].

Achieving high cure rates help to reduce transmission of TB and attract the great majority of existing cases to seek treatment [19]. As a result, treatment of TB is beyond treating an individual patient, rather it is considered as a public health intervention. Globally, 83% of cases successfully completed their treatment in 2015,and effective diagnosis and treatment of TB saved an estimated 49 million lives between 2000 through 2015 [1]. In Ethiopia, 89% (range: 69%–95%)of treatment cohort in different regions attained successful TB treatment [6]. However, cure rates of 81% (range: 38% to 92%) [4] across regions of the country have been reported.

Studies uncovered that patient demographics, clinical, bacteriologic and HIV co morbidity were associated with unsuccessful TB treatment outcomes [20–23]. Despite the prevailing long delays to initiate anti-TB treatment and poor outcomes in different parts of Ethiopia and elsewhere, evidences on effect of the delay on treatment outcomes are scanty. Hence, this study assessed effect of delayed treatment initiation on outcomes of TB. Evidences on the association between treatment delay and outcome is crucial to realize the targets of ending TB epidemic [2].

Methods

Study setting

The study was conducted in 14 health facilities (three hospitals and 11 health centers) in three zones of Southern Nation, Nationalities, and Peoples Region (SNNPR) of Ethiopia. The SNNPR is one of the nine Regional States in the country with an estimated 15.7million population in 2017 [24]. The three study Zones (Bench Maji, Kaffa and Sheka) are located at the southwestern part of Ethiopia bordering South Sudan and harbor an estimated 1.8million peoples [24]. The zones (an administrative unit that liaison *woredas* with the region) are organized into four town administrations and 26 *woredas*(administrative unit equivalent to districts). At the time of the study, three hospitals and 65 health centers were providing TB Directly Observed Treatment Short course (DOTS) services. However, all the hospitals and only 25 health centers were providing TB/HIV collaborative interventions [25].

Diagnosis and treatment of all forms of TB across Ethiopia has been based on national TB control guidelines that specify case definitions, diagnostic and treatment standards [26]. Thus all TB cases enrolled for this study were diagnosed using either sputum smear microcopy or clinical signs aided with x-ray. Those cases with sputum smear positive were labeled as smear positive pulmonary TB and negatives were smear negative pulmonary TB. Diagnosis of smear negative and extrapulmonary TB were made using diagnostic algorithm recommended by the national guideline [26]. Detail definitions for each cases presented in definition of terms section. Previously, TB diagnosis and treatment had been limited to public hospitals and health centers, but public private mix (PPM) DOTS and community DOTS to public health posts have been recently introduced. Thus, in 2011, 92% of public hospitals and 95% of health centers, 2100 health posts and 317 PPM–DOTS centers were providing DOTS based diagnosis and/or treatment of TB in the country [27].

Study design and sampling

A prospective cohort study among new TB cases was carried out from January 2015 through June 2016. The treatment cohorts were recruited from baseline survey designed to determine delays to initiate treatment. Since no standard cutoff point for delay to treatment, a clinical sound cutoff of 30 days was used to ascertain exposure. Thus TB cases who elapsed beyond 30 days to initiate treatment since onset of illness were labeled as exposed and those started treatment within 30 days of onset of illness were non exposed. Then the cases were followed until earliest treatment outcome. The sample size was computed using StatCalc program of EpiInfo at 95% significance level, 80% power, expected outcome (unsuccessful of 3% [15] among those delayed beyond 30 days) to detect a difference of 7% with those initiated treatment earlier and considering design effect of 1.5 and 10% lost to follow up a total of 640 cases were required., However, the sample size for assessing predictors of delaycomputed using the same procedure provided a total of 802 new cases . Hence, the same cases were followed for the outcome; the larger sample of 802 was taken the final sample size.

The sample was proportionally allocated to the zones, *woredas* and health facilities based on TB cases reported during the year preceding the study. Finally, consecutive consenting cases from were prospectively enrolled until the required sample was reached and followed until completion of the six-month treatment or earliest outcome. During the enrollment those new cases, older than 18 years of age, on intensive phase treatment were included and those transferred out and died before the interview were excluded from the study.

Data collection

A structured questionnaire adapted from tools used elsewhere [5, 28] and standard TB register book [26] was used to gather the data. Besides, data abstraction checklist was prepared to draw clinical, bacteriologic and treatment outcomes of the patients from TB register. The questionnaire was translated into national language (*Amharic*) spoken by almost all residents in the study area. Ten diploma graduate nurse data collectors and three public health specialist supervisors were recruited and trained for 3 days. The training included description of questionnaire, interviewing techniques and pretest among TB cases on DOTS at nearby health facilities not included in the study. Finally, eligible cases were traced from the unit TB register and interviewed for sociodemographic, health care seeking, and treatment practices.

Exposure ascertainment

The main exposure variable was delays to treatment measured by days elapsed between onsets of illness to initiation of anti-TB treatment (total delay). The total delay comprises both patient and provider delays. Patient delay was assessed by asking patients to recall and estimate date or number of days elapsed between onset of TB constitutional symptoms such as cough, fever, night sweats, chest pain, weight loss and loss of appetite until formal care seeking. Similarly, provider delay was estimated by asking date or number of days elapsed between first formal health care facility visits to anti-TB treatment initiation. Finally, total delay was computed as a sum of patient and provider delay or number of days elapsed between onsets of illness to initiation of anti-TB treatment. Since no standard cut off for delay, a clinically sound cut off of 30 days delay was taken to define exposure status. Therefore, cases who delayed beyond 30 days were categorized as exposed and those initiated within 30 days were grouped as non-exposed.

Outcome ascertainment

The main outcome variable was treatment outcome which was ascertained based on standard definitions [26, 29]. Accordingly, outcomes were categorized into successful when the TB patient completed treatment with or without evidence of cure and unsuccessful when died or lost to follow-up or treatment failure. So that, coding was made as unsuccessful outcomes = 1 and successful = 0.

Data processing

Data were entered in to Epi-Data V 3.5 and processed on SPSS version 21 and/or STATA version 13. The data were described using frequencies, proportions, mean, median, inter-quartile range and standard deviation as appropriate. Both the baseline and follow-up data were described and compared across the exposed and non-exposed groups. Categorical variables were compared using chi square test and numeric variables using independent and paired t tests as appropriate.

Information provision adequacy during treatment initiation was assessed based on 15 items constructed from TB treatment guidelines. The internal consistency of the items was checked by Cronbach's Alpha (α) =0.87). A score of one is given for proper information and zero otherwise. So that information adequacy index was computed and labeled adequate when above median and inadequate when below median scores.

Association between the exposure (exposed vs, non-exposed) and outcome (unsuccessful vs. successful) was determined by log-binomial regression. Accordingly, bivariate and multiple log-binomial regression models were fitted to estimate crude and adjusted relative risk (RR) of unsuccessful outcome. In all the statistical tests, significance was judged at p value < 0.05.

Ethical issues

The study was ethically approved by the Institutional Review Board (IRB) of college of Health Sciences at Addis Ababa University. Informed written consent was sought from patients before the two interviews, during the intensive phase and end of treatment.

Definition of terms

- New case those never been treated for TB or have taken anti-TB drugs for less than 1 month.
- Smear positive PTB is a patient with at least two sputum smear examinations positive for Acid Fast Bacilli (AFB) by direct microscopy.
- Smear negative pulmonary TB is a patient having symptoms suggestive of TB with at least three initial smear examinations negative for AFB by direct microscopy, and no response to a course of broad-spectrum antibiotics, and again three negative smear examinations by direct microscopy and radiological abnormalities consistent with pulmonary tuberculosis, and decision by a clinician to treat with a full course of anti- tuberculosis
- Extra pulmonary TB is TB in organs other than the lungs, proven by histo-pathological evidence from a biopsy, Or based on strong clinical evidence consistent with active EPTB and the decision by a physician to treat with a full course of anti-TB therapy.
- Cured: A bacteriologically confirmed pulmonary TB case at the beginning of treatment who was smear or culture-negative at last month of treatment and on at least one previous occasion.
- Treatment completed: A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative
- Treatment failure: TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
- Died: TB patient who dies for any reason during the course of treatment.
- Lost to follow up: TB patient interrupted treatment for 2 or more consecutive months.
- Treatment outcome not evaluated TB patient for whom no treatment outcome is assigned including cases “transferred out” to another treatment unit.

Results

Profile of study participants

A total of 735 (91.6%) of TB cases required were enrolled from 11 health centers and 3 hospitals. The rest of cases 67(8.4%) were not retrieved due to refusals (9), inability to respond (3) and end of the survey time (55). Of the cases 574 (78.4%) and 161(21.9%) had initiated anti-TB treatment within and above 30 days of onset of illness, respectively. Of the cases enrolled, 699 (95.1%) had documented treatment outcome and analyzed (Fig. 1).

Baseline sociodemographic characteristics of study participants

The median age [inter-quartile range (IQR)] and of the cases was 27(20–37) years. Among the cases, 52.9% and 29.4% had completed elementary school and involved in subsistence farming respectively (Table 1).

Care seeking and treatment practices

Patients initially presented to healthcare facility after a median (IQR) 25(15–36) days (patient delay) since the onset of illness. Diagnosis of 623(84.7%) of the cases were made after an average (±SD) of 3.6(±2.4) visits to an average (±SD) of 2.2(±1.2) healthcare facilities at which time the patients had been treated with different medicines. The rest of the cases, 112(15.3%) were diagnosed at their first visit to the first health facilities. Thus diagnosis and initiation of anti-TB treatment took a median (IQR) of 22(9–48) days (provider delay) since the first visit to health care facilities. Generally, a median (IQR) 55(32–100) days (total delay) had been elapsed to initiate treatment since the onset of illness. Of the total cases, 373(50.7% were smear positive pulmonary in whom diagnosis was bacteriologicaly confirmed using sputum smear microscopy. All of the cases were offered HIV screening test, of whom 68 (9.3%) tested positive (95% CI: 7.2%–11.3%)). Of those TB/HIV co infected cases, 27(39.7%) and 32(47.1%) were respectively receiving antiretroviral therapy (ART) and Cotrimoxazole Prophylactic Therapy (CPT)(Table 2).

Follow-up and treatment outcomes

After initiation of treatment, patients had undergone weight and sputum smear monitoring as per the recommended schedules. Accordingly, 501(68.2%), 266(36.2%) and 239(32.5%) of the cases had documented weight at end of second, fifth and sixth months of treatment respectively. Thus, a statistically significant difference in mean weights were observed between baseline and end of second month ($t_{df=500} = 13.94$, $p < 0.001$), between sixth month and baseline weight ($t_{238} = 11.81$, $P < 0.001$). On the other hand, among those smear positive pulmonary TB cases (373(50.7%)) eligible for monitoring of sputum smear, 231(61.9%), 200(53.6%) and 178(47.5%) had documented sputum smear result at end of second, fifth and sixth months of treatment respectively. So, among those with documented follow-up sputum result, 225 (97.4%) from both groups converted to negatives at the end of second month treatment $p = 0.5$) (Table 3).

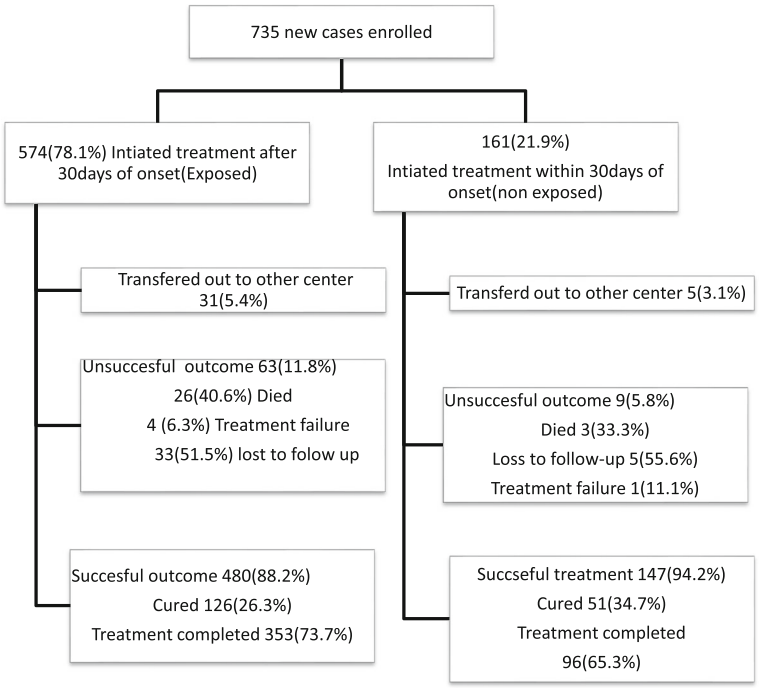

Fig. 1 Flow chart of exposure and outcome ascertainment of TB cases Southwest Ethiopia,January 2015 to June 2016

Table 1 Socidemographic characteristics and delays to treatment in southwest Ethiopia January to December 2015

Variable		Total delay(days)		*P* value	Total N(%)
		> 30 (Exposed) *N* = 574 n(%)	<=30 (Non exposed) *N* = 161 n(%)		
Gender	Male	345(60.1)	102(63.4)	0.6	447(60.8)
	Female	229(39.9)	59(36.6)		288(39.2)
Age group (years)	18–34	389(67.8)	114(70.8)	0.04	503(68.4)
	35–65	173(30.1)	43(26.7)		216(29.4)
	> 65	12(2.1)	4(2.5)		16(2.2)
Residence	Urban	280(48.9)	88(54.7)	0.7	368(50.1)
	Rural	294(51.1)	73(45.3)		367(49.9)
Marital status	Never married	208(36.2)	67(41.6)	0.3	275(37.4)
	Currently married	315(54.8)	89(55.3)		404(55.0)
	Divorced/widowed	51(9)	5(3.1)		56(7.6)
Educational status	Illiterate	168(29.3)	44(27.3)	0.2	212(28.8)
	Completed primary	309(53.8)	80(49.7)		389(52.9)
	Secondary & above	97(16.9)	37(23.0)		134(18.2)
Occupation	Employed	134(23.3)	38(23.6)	0.01	172(23.4)
	Farming	163(28.4)	53(32.9)		216(29.4)
	Unskilled work [a]	42(7.3)	9(5.6)		51(6.9)
	Dependents [b]	235(40.9)	61(37.9)		296(40.3)

[a]housemaid, daily laborer, [b]students, housewife

Table 2 Patient characteristics and time delays to treatment southwest Ethiopia January to December 2015

Variable		Total delay(days)			Total
		> 30 (Exposed) *N* = 574	<=30(non exposed) *N* = 161		
		n(%)	n(%)	*P* value	n(%)
Type of TB	Pulmonary positive	277(48.3)	96(59.6)	0.02	373(50.7)
	Pulmonary negative	167(29.1)	46(28.6)		213(29.0)
	Extra pulmonary	130(22.6)	19(11.8)		149(20.3)
HIV status	Positive	57(9.9)	11(6.8)	0.4	68(9.3)
	Negative	517(90.1)	150(93.2)		667(90.7)
Mode of TB diagnosis	Bacteriological	277(48.3)	96(59.6)	0.04	373(50.6)
	Clinical	297(51.7)	65(40.4)		363(49.4)
Treatment center	Hospital	206(35.9)	60(37.3)	0.02	266(36.2)
	Health center	368(64.1)	101(62.7)		469(63.8)
Action before HCF[a] visit	None	440(76.7)	146(90.7)	0.04	586(79.7)
	Took actions[b]	134(23.3)	15(9.3)		149(20.3)
Place TB diagnosis made	Public	493(85.9)	143(88.8)	0.09	636(86.5)
	Private	81(14.1)	18(11.2)		99(13.5)
Hospitalized for TB illness	Yes	15(2.6)	4(2.5)	0.5	19(2.6)
Knowledge about TB	Poor	159(27.7)	31(19.3)	0.8	190(25.8)
	Good	415(72.3)	130(80.7)		545(74.2)
Patient delay	Median(IQR)days	30(16–57)	14(10–17)	< 0.001	25(15–36)
Provider delay	Median (IQR)days	31(16–64)	7(3–10)	< 0.001	22(9–48)
Pre-diagnosis cost	Median(IQR) US$[c]	119.1(74.0–221.6)	48.2(36.3–66.8)	< 0.001	
Post-diagnosis cost	Median(IQR) US$[c]	93.7(56.9–141.3)	78.8(41.5–113.7)	< 0.001	
Treatment information adequate	Yes	279(48.6)	78(48.4)	0.04	357(48.6)
	No	295(51.4)	83(51.6)		378(51.4)
Initial weight	Mean(±SD) Kg	49.0(8.6)	47.7(8.5)	0.9	48.7(± 8.6)

[a]Healthcare Facility, [b]self treatment, traditional healer, holy water, [c](1US$ = 20.56Birr)

At the end of follow-up, 699(95.1%) TB patients had documented treatment outcome of whom 627(89.7%, 95%CI:87.2–91.7%) had successfully completed their treatment. However, among those smear positive TB cases, only 177(47.5%) were declared cured. The treatment success is significantly different among cases initiated treatment beyond and within 30 days of onset of illness (88.4% vs 94.2%, $P = 0.01$), respectively. Thus, significant difference in proportions of death (4.8% Vs 1. 9%), treatment failure (0.7% Vs 0.6%) and loss to follow-up (6.1% vs. 3.2%), respectively, among those initiated treatments beyond and within 30 days of onset $p = 0.04$. The treatment success across HIV positive and negatives respectively was 75.8% vs 91.1%, $p < 0.001$. Disaggregation of the treatment success among bacteriologicaly confirmed (smear positive pulmonary) and clinically diagnosed cases respectively revealed 90.1% vs 89.3%, $p = 0.7$. Furthermore, we found no statistically significant differences in treatment success among smear positive pulmonary (90.1%), smear negative pulmonary (88.0%) and extra pulmonary cases (91.1%) ($p = 0.6$).

Predictors of unsuccessful treatment outcomes

Treatment outcome of the study patients varied significantly across time elapsed for initiation of treatment. Patients delayed for > 30 days to initiate treatment had more than twice higher risk of having unsuccessful outcome Adjusted relative risk [(ARR) = 2.02, 95% confidence interval (CI); 1.03,3.95). Moreover, being older than 65 years, (ARR = 3.83,95% CI; 2.04,6.1), HIV co infection (ARR = 1.93,95% CI; 1.23,3.01) and treatment center being hospital (ARR = 3.78, 95% CI;2.25,6.36) independently predicted higher risk of unsuccessful outcomes. On the other hand, weight gain at the end of second month treatment (ARR = 0.45,95% CI;0.22,0.91) predicted lower risk of unsuccessful outcome. Those patients gained weight at the end of two-month treatment compared to the baseline had about 60% lower risk of having unsuccessful outcome (Table 4).

Subgroup analysis among smear positive pulmonary cases revealed delays to initiate treatment (ARR = 1. 56,95%CI;1.46,1.65), HIV co infection (ARR = 3.73,95%CI: 1.68,5.97), treatment center being hospital (ARR = 1.

Table 3 Follow-up characteristics and outcomes across delays to treatment southwest Ethiopia January 2015 to june 2016

Variable		Total delay(days)			
		> 30(exposed) *N* = 574	<=30 (non exposed) *N* = 161		Total
		n(%)	n(%)	*P* value	n(%)
Sputum smear end of 2nd month(*n* = 373)	Positive	3(1.1)	3(3.0)	0.5	6(1.6)
	Negative	158(57.9)	67(67.0)		225(60.3)
	Not available	112(41.0)	30(30.0)		142(38.1)
Sputum smear end of 5th month(*n* = 373)	Positive	4(1.5)	1(1.0)	0.4	5(1.3)
	Negative	137(50.1)	58(58.0)		195(52.3)
	Not available	132(48.4)	41(41.0)		173(46.4)
Sputum smear end of 6th month(*n* = 373)	Negative	127(46.5)	51(51.0)	0.3	178(47.7)
	Not available	146(53.5)	49(49)		195(52.3)
Sputum check up after diagnosis(*n* = 373)	None	112 (41.0)	30(30.0)	0.3	142(38.1)
	At least once	161(59.0)	70(70.0)		231(61.9)
Weight end of 2ndmonth	Mean(SD)	51.2(8.6)	50.2(8.6)	0.9	51.3(8.6)
Weight change end of 2nd month	Unchanged/lost	93(16.2)	30(18.6)	0.2	123(16.7)
	Gained	298(52.0)	80(49.7)		378(51.5)
	Unknown	183(31.8)	51(31.7)		234(31.8)
Weight end of 5thmonth	Mean(SD)	54.2(8.7)	51.8(9.5)	0.5	53.6(8.9)
Weight end of 6th month	Mean(SD)	54.2(10.3)	52.9(9.0)	0.1	53.9(9.9)
Treatment out come	Cured	126(21.9)	51(31.7)	0.04	177(24.2)
	Treatment complete	354(61.5)	96(59.6)		450(61.1)
	Loss to follow-up	33(5.7)	5(3.1)		38(5.2)
	Died	26(4.5)	3(1.9)		29(3.9)
	Treatment failure	4(0.7)	1(0.6)		5(0.7)
	Not evaluated[a]	31(5.4)	5(3.1)		36(4.9)
Treatment success (*n* = 699)	Unsuccessful	63(11.6)	9(5.8)	0.01	72(10.3)
	Successful	480(88.4)	147(94.2)		627(89.7)

[a]cases transferred out to other treatment centers

89,95%CI:1.04,3.45) and age older than 65 years (ARR = 6.49,95%CI:3.60,11.70) as independent predictors of unsuccessful outcomes. Similarly analysis among clinically diagnosed cases showed delayed treatment, HIV co-infection, treatment center being hospital and older than 65 years independently predicted higher risk of unsuccessful outcome. Weight gain at the end of second month (ARR = 0.16,95%CI: 0.05, 0.53) predicted higher risk of unsuccessful outcome among clinically diagnosed cases and having at least one sputum checkup after diagnosis (ARR = 0.17, 95%CI:0.09, 0.33) predicted higher risk of unsuccessful outcomes among smear positive cases. Analysis of treatment outcomes among HIV negatives showed initiated treatment after 30 days of onset (ARR = 2.52,95%CI:1. 55, 4.10), weight gain at the end of second month treatment (ARR = 0.27,95%CI:0.12, 0.64) and treatment center being hospital (ARR = 2.33,95%CI:1.33, 4.09) independently predicted unsuccessful treatment outcome (Additional file 1: Tables S1-S3).

Discussion

This follow-up study revealed patients elapse too long time (median of 55 days) to initiate anti-TB treatment since onset of the illness. Subsequently, we found statistically significant differences in treatment success (94.2% vs 88.4%) respectively among those who initiated treatment within and beyond 55 days of onset. Those patients initiated anti-TB treatment beyond 30 days of onset had higher risk of unsuccessful outcomes including death, lost to follow up and treatment failure. Patients initiated treatment within and beyond 30 days of onset had undergone significantly diverse healthcare seeking practices, patient and provider delays. However, both groups of patients had no significant differences in sputum smear conversion and weight changes at end of second month treatment. The longer delays to initiate treatment accompanied by higher risk of unsuccessful outcomes depict increased morbidity and mortality to patients and prolonged period of transmission to the community. The finding suggests need for prompt

Table 4 Predictors of TB treatment outcome in districts of southwest Ethiopia January 2015 to June 2016

Variable		Treatment success		Crude Relative Risk (CRR) (95%CI)	Adjusted relative risk (ARR) (95% CI)
		Unsuccessful n(%)	Successful n(%)		
Gender	Male	44(10.3)	382(89.7)	Ref.	Ref.
	Female	28(10.3)	245(89.7)	0.9(0.63,1.56)	0.87(0.61,1.25)
Age group(years)	18–34	48(10.0)	433(90.0)	Ref.	Ref.
	35–65	20(9.9)	183(90.1)	0.9(0.60,.62)	0.88(0.68,1.12)
	> 65	4(26.7)	11(73.3)	2.67(1.11,6.45)	3.82(2.4,6.10)*
Educational status	Illiterate	25(12.3)	178(87.7)	Ref.	Ref.
	Completed primary	37(9.9)	338(90.1)	0.8(0.50,1.29)	0.93(0.61,1.41)
	Secondary & above	10(8.3)	111(91.7	0.67(0.33,1.35)	1.00(0.64,1.56)
Treatment center	Hospital	31(12.6)	215(87.4)	1.39(0.9,2.16)	3.78(2.4,6.35)*
	Health center	41(9.1)	412(90.9)	Ref.	Ref.
Action before HCF [a]visit	None	57(10.3)	498(89.7)	Ref.	Ref.
	Took action	15(10.4)	129(89.6)	1.01(0.59,1.74)	0.81(0.50,1.30)
Mode of TB diagnosis	Bacteriological	35(9.9)	320(90.1)	Ref.	Ref.
	Clinical	37(10.7)	308(89.3)	1.09(0.7,1.7)	0.86(0.67,1.10)
HIV status	Positive	15(24.2)	47(75.8)	2.7(1.63,4.5)	1.93(1.23,3.01)*
	Negative	57(8.9)	580(91.1)	Ref.	Ref.
Weight change end of 2nd month	No change/lost	13(11.2)	103(88.8)	Ref.	Ref.
	Gained	15(4.1)	354(95.9)	0.36(0.18,0.74)	0.45(0.22,0.91)
	Unknown	44(20.6)	170(79.4)	1.83(1.03,3.26)	4.34(2.47.7.65)*
Total delay(days)	<=30	9(5.8)	147(94.2)	Ref.	Ref.
	> 30	63(11.6)	480(88.4)	2.01(1.02,3.95)	2.02(1.03,3.95)*
Treatment information provided	Inadequate	39(11.0)	314(89.0)	0.86(0.56,1.34)	1.06(0.70,1.63)
	Adequate	33(9.5)	313(90.5)	Ref.	Ref.

*statistically significant at $p < 0.05$ [a] Healthcare facility

detection and treatment of cases to ensure better outcomes among patients and reduce burden in community.

The higher risk of unsuccessful outcome among those patients delayed to initiate anti-TB treatment had been consistently reported in studies from Ethiopia [30] and elsewhere [15]. The increased risk of unsuccessful outcome among patients delayed treatment initiation could be explained by various factors. First, delayed initiation of treatment had been reported to be associated with severe clinical presentation [14, 31] which predict unsuccessful outcomes [32]. In this study, patients delayed to initiate treatment had relatively higher rate of hospitalization (3% vs 2.1%) that would be proxy measure of severe presentation. Second, a delay to treatment is associated with both prescribed and self-treatment those lead to poor treatment outcome [33–35]. In the current study, the majority (84.7%) of the cases had visited an average of 2.2 HCFs until diagnosis of TB at which time both self and prescribed medicines had been used. Third, delays to treatment often accompanied by higher direct and indirect costs that impoverish households [36, 37] and ultimately lead to poor treatment compliance and outcome [36]. In our study we observed significantly higher median pre diagnosis (US$119.1 vs 48.2, $p = 0.001$)and post diagnosis (US$93.7vs.98.8, $p < 0.001$) costs among those delayed to initiate treatment which could explain the increased risk of unsuccessful outcome.

Consistent with studies in Ethiopia [30, 38] and elsewhere [39–42], the current study revealed that HIV comorbidity increase risk of unsuccessful outcome. Hence, significantly lower (75.8% vs 91.1%, $p < 0.001$) treatment success with higher deaths (12.9% vs. 3.3%, $p = 0.002$) were observed among HIV co infected compared to negatives. The observed lower treatment success among HIV co infected is far below the targeted 90% success to be met by 2020 [2]. The increased risk of unsuccessful outcome among the HIV co infected could be due to significantly prolonged time to initiate care seeking (median of 29 vs.

24 days, $P = 0.04$) among HIV co infected patients. Thus HIV co morbidity had been reported to delay anti-TB treatment initiation [13, 43]that explain the high mortality among HIV co infected TB patients [16, 17]. In addition, HIV co infection independently increases risk of unsuccessful outcome due the complex and overlapping drug interactions and toxicities and TB-associated immune reconstitution inflammatory syndrome [44]. Furthermore the increased risk could also be explained by the low uptake of TB/HIV collaborative interventions (39.7% and 47.1% on ART and CPT, respectively) those proved to bring better outcome [45]and predict worse outcome in their absence [40].

We found patients took anti-TB treatment at hospital had higher risk of unsuccessful outcome compared to those treated at health center. This could be due to significantly higher proportion of delays to initiate anti-TB treatment (55.6% Vs46.3%, $p = 0.02$), HIV co infection (14.3% Vs 6.4%, $p < 0.001$) and hospitalization (5.3% Vs 1.1%, $p = 0.001$) among patients treated at hospitals. Studies reported HIV co infection [39, 40], hospitalization [32] and delays to treatment [15, 30] to predict higher risk of unsuccessful outcomes. Moreover, patients treated at hospitals were more of pulmonary negative (36.5% vs 24.7%, $p < 0.001$) and extra pulmonary (21.8% vs 19.4%, $p < 0.001$) those had been reported to predict unsuccessful outcome [46].

Regular monitoring of TB patients during treatment is among standard of TB care, which is used to assess response to therapy and facilitates treatment completion. Accordingly regular sputum and weight monitoring have been recommended TB patients on treatment [47]. Despite low sensitivity and modest specificity of sputum results at the end of intensive phase to predict failure and relapse [48], sputum conversion to negative among those positive at initiation of treatment had been taken as one of the indicator TB control program performance [47]. In the current study no significant differences was observed in sputum smear conversion at end of second month treatment in both patients initiated treatment within and beyond 30 days of onset. Consistent with studies in Ethiopia [46]and elsewhere [49] smear conversion to negative at the end of second month treatment had lower risk of unsuccessful outcome. In this study, 3/6(50%) of those treatment failure cases had positive smear at the end of second month treatment. The higher risk among those positives could be due to possible poor quality of initial therapy and co morbid conditions that interfere with adherence or response [47]. Similarly, weight gain at the end of second month treatment predicted lower risk of unsuccessful outcomes which is in line with reports from Vietnam [50].

This study has some limitations. First, exposure assessment relied upon patient recall of the onset of illness that might be subjected to recall bias and ultimate misclassification bias. But efforts had been made to minimize the bias through use of local and national event listing. The second limitation was inability to measure treatment adherence that could have effect on treatment outcome. Third, we did not test for drug susceptibility so that we could not associate delay with resistance. Lastly, we studied only new adult TB cases so that the findings will not apply to all TB cases. On the other hand, relatively large sample and geographic coverage, reduced selection bias through consecutive enrolment, being prospective design, direct estimation of risk and use of standard outcome ascertainment could be mentioned as strength of the study. Therefore, the study is valid and applies to new TB cases in similar settings.

Conclusion

TB patients in the study area elapse too long time to initiate anti-TB treatment. The delayed treatment initiation was associated with higher risk of unsuccessful outcome including death, treatment failure and lost to follow-up. Apart from the delayed treatment, HIV co infection, treatment center being hospital, weight change and sputum conversion at the end of second month treatment independently predicted unsuccessful outcomes. Therefore, promotion of early care seeking within community, improving diagnostic, and case holding efficiencies of HCF and TB/HIV collaborative interventions could enhance the TB treatment success. Time delays to TB diagnosis can be reduced by raising community level awareness on TB suggestive symptoms, involving traditional healer, religious and private healthcare institutions in TB case finding, equipping healthcare facilities with rapid diagnostic tests and building capacities of healthcare providers to suspect and diagnose TB.

Additional file

Additional file 1: Table S1. Predictors of unsuccessful outcomes among new smear positive pulmonary TB cases in districts southwest Ethiopia January 2015 to June 2016 ($n = 355$). Table S2 Predictors of unsuccessful outcomes among new clinically diagnosed TB cases in districts southwest Ethiopia January 2015 to June 2016 ($n = 344$). Table S3 Predictors of unsuccessful outcomes among not HIV coinfected TB cases in districts of southwest Ethiopia January 2015 to June 2016. (DOCX 20 kb)

Abbreviations

ARR: Adjusted relative risk; ART: Antiretroviral therapy; CI: Confidence Interval; CPT: Cotrimoxazole prophylactic therapy; DOTS: Directly Observed Treatment Short course; HCF: Healthcare Facility; HIV: Human Immunodeficiency Virus; IQR: Inter-quartile Range; SD: Standard deviation; TB: Tuberculosis; US$: United States dollar

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
AA conceived and designed the study, collected and analyzed data, prepared manuscript:
WD and DJ critically reviewed for intellectual content of the study protocol and manuscript as primary and co-supervisors respectively. All authors approved the final version of the manuscript for submission.

Ethics approval and consent to participate
The study was ethically approved by Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University (protocol number: 045/14/sph). Written informed consent was sought from each study participant before the interview. Patient clinical profile from records and unit register was retrieved upon permission from respective health care facilities.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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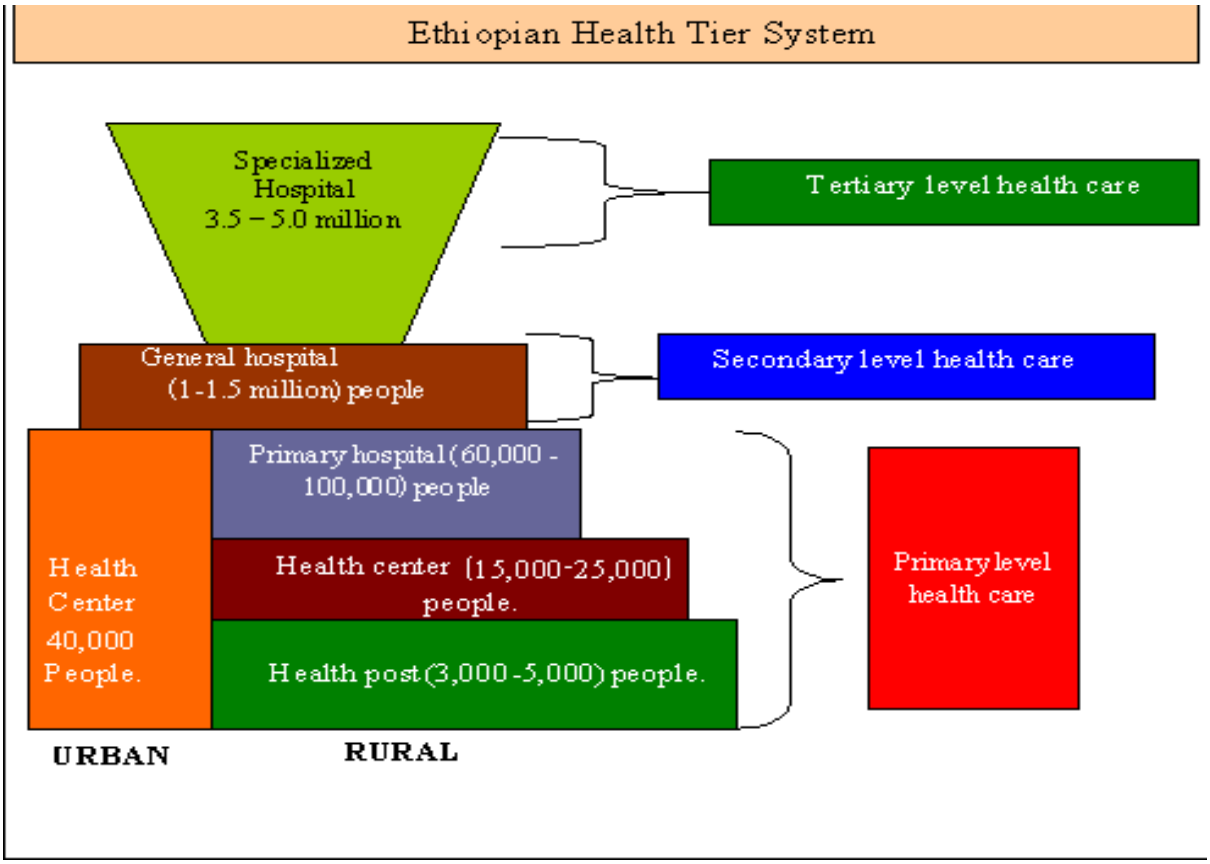
Annex 1 : Ethiopian healthcare delivery tier



Annex 2: English version information sheet, consent form and questionnaire

Title of the project: Tuberculosis treatment delays, cost and outcomes in districts of southwestern Ethiopia

Principal Investigator: Abyot Asres

Primary supervisor: Wakgari Deressa (PhD, Associate Professor)

Secondary supervisor: Degu Jerene (MD, PhD)

Coordinating office: Addis Ababa University, School of Public Health

Introduction: Tuberculosis (TB) is an infectious disease that poses varieties of burden on patients, public and the economy. Consequently, global efforts to alleviate the overlapping humanitarian, public health, and economic dimensions have been devised and adopted across the nations. Thus, prompt diagnosis and proper treatment that ultimately cure patients and reduce transmission in the community is the corner stone in the prevention and control of TB. However long delays in seeking care and diagnoses have been reported in Ethiopia and elsewhere for which comprehensive evidences on the barriers are lacking. Hence evidences on the barriers, economic burdens and subsequent effect on treatment outcomes of the delay is highly required to enable the current control strategies envisioned to eliminate TB.

Purpose: The aim of this study is to investigate the patient and health facility barriers of early care seeking for TB illness, the effects of longer delay on treatment outcomes, and the direct and indirect cost of TB care seeking and treatment. This research undertaking is a Doctoral degree in public health partial fulfillment dissertation.

Procedure and participation: The method of the research involves cross-sectional and prospective cohort studies so that you will be asked at four different times throughout your treatment period including this interview. Your particular participation is affirmed by probability sampling technique which was carried out on the basis of chance and the interview will take about 30minutes. You will be asked to participate in this research because the trustful information, which you will provide, is important for the understanding of the proposed subject matter. You will be asked about your socio-demographic, socioeconomic, income and expenditure, care-seeking practices about your current illness, current treatment, and cost you

incurred for seeking care and treatment and other related questions that are very important for the fulfillment of the research.

Confidentiality: The information you provide will be kept confidential so that any of your personal identifications including name or phone numbers will not be recorded. Rather codes will be assigned to your data for processing. Moreover, the original data will be locked in cabinets until processing and no person other than the principal investigator and supervisors' access. The use of information for any purpose other than that to which participants consented is unethical so that your income and expenditure data will not be disclosed to tax administrator or anyone else for tax purpose. The information you provide will not be disclosed in a way it identified your personal characteristics and privacy rather aggregate findings will be reported. Particularly, s and Finally all the data you provide will be incinerated in secure manner upon finalizing the research work and public defense that will be due when approved by the school of public health academic commission and university senate.

Benefit: The research does not have a short term financial, health care and capacity building benefit to the research participant as an individual or as a group. However in the long run, different stakeholders will use the evidence for designing strategies that alleviate burden posed by TB on TB patients, household and health system. Subsequently, control and ultimate elimination of the TB disease will be realized that will benefit all peoples across world. On the other hand, information related to the TB disease and its treatment will be provided for the participants while gathering the data.

Risk: The proposed research does not have any inhumane treatment of research participants and any physical harm, social discrimination, psychological trauma and economic loss. Your participation or not in the study will not interrupt or affect in any way the treatment you are currently receiving.

Inducement, incentive and Compensation: This study process has not any form of inducement, coercion and the study does not bring any risks that incur compensation.

Results dissemination: The researcher is responsible for dissemination of findings and fully accountable to provide feedback to the concerned health departments and districts in the area. Besides, presentations at national and international scientific conferences and publication in reputable scientific journal of the findings will be attempted.

Freedom to withdraw: If you don't want to participate in the study, you have full right to with draw from the study any time you wish. This would have no effect at all on your health benefit or other administrative effect that you get from the health facilities and nobody will enforce you to explain the reason of withdrawal.

Person to Contact: The participant has the right to ask information that is not clear about the research context and content before and/or during the research work. You can contact the principal investigator and supervisors via the addresses provided below. Since this research has undergone ethical review and approval by Addis Ababa University College of Health Sciences IRB that is responsible for ensuring adherence of ethical principles to avoid harm on participants, you can also contact the board.

If you want more information about the project, you can contact the following;

Addis Ababa University College of Health Sciences IRB Secretary

Office Tel. 0115512876

Principal Investigator:

Abyot Asres , Mizan Tepi University ,*Mob: +251 911905554* ,E-mail: abyotas@yahoo.com

Supervisors: Wakgari Deressa (PhD, Associate prof.)

Cell phone: +251 911483714

School of Public Health, College of Health Science, Addis Ababa University

Degu Jerene (MD, PhD), Cell phone: +251 911546407

Annex 1: Consent Form

My name is _____. I am working with a research team from Addis Ababa University. The purpose of the study is to assess delays in care seeking and treatment for TB, the cost incurred for the care seeking that is helpful to design interventions for the delays and financial burden posed by TB. We are interviewing systematically selected TB patients on treatment about their care seeking practices, treatment practices, and cost incurred for care seeking and treatment. I am going to ask you some questions regarding your sociodemographics, care seeking practices, and cost incurred for the care seeking and treatment that are crucial for the proposed research. Thus, your honest responses will enable design and implementation of interventions that enhance control of the TB disease. Your responses will be completely confidential which will be ensured by avoiding your name or other identifications in connection with any of the information you tell me. You do not have to answer any question that you do not want to answer, and you may end this interview at any time you wish. We would greatly appreciate your help in responding to this survey.

Person to contact:

Principal Investigator:

Abyot Asres (Mizan Tepi University, *Mob: +251911905554* E-mail: abyotas@yahoo.com)

Supervisors: Dr. Wakgari Deressa (School of Public Health, College of Health Science, Addis Ababa University, Cell phone: +251 911483714) and;

Dr. Degu Jerene (Cell phone: +251 911546407)

A. Are the information/ objectives clear?

1. Yes 2. No ⟶ explain again

B. Would you be willing to participate?

1. Yes ⟶ continue the interview
2. No ⟶ Stop and go to the next patient

Thank him/her

C. Interviewer's signature certifying that, the informed consent has been given by the respondent

Name_____ Signature _____ Date_____

Baseline Engilish version questionnaire

1.1. General information about questionnaire

Questionnaire ID						
Name of Zone/	1. Kaffa	2. Bench Maji			3. Sheka	
Name of wereda	1. Bonga town 2. Decha 3. Chena	4. Mizan Aman 5. Shey Bench 6. North Bench 7. Meinet Goldiya			8. Tepi town 9. Yeki 10. Masha	
Name of Health Facility						
Type of Health facility	1. Hospital	2. Health center	3. Health post	4. Other (specify)------		
Interviewee	1. Patient	2. Treatment supporter	3. Other specify------			
Date of interview		Follow-up visit schedule:				
Name and signature of interviewer		Name and signature of supervisor:				

1.2. Medical record review checklist

Medical record number	_____	Date of recent visit:_____	
		Duration of illness (dd,week,mm)	
Chief complaint	1. Cough		
	2. Fever		
	3. Chest pain		
	4. Night sweating		
	5. Swelling over neck		
	6. Other specify----------		
Key physical findings	1. HEENT		
	2. LGS		
	3. Chest		
	4. CVS		
	5. Abdomen		
	6. Other specify----------		
Investigations requested ,their results and unit cost	Investigation	Result	Unit cost of the investigation
	1. Sputum for AFB		
	2. Xpert MTB/RIF		
	3. CXR(chest x ray)		
	4. ESR		
	5. WBC		
	6. Other specify		
Diagnosis/Assessement	Diagnosis	Date of diagnosis	
	1. TB		
	2. Pneumonia		

	3. B.Asthma	
	4. Other specify----------	
	5. Not stated/written	
Treatments/plan prescribed and their unit cost		Unit cost of the treatment prescribed

1.3. Unit TB register review

TB unit number		**Wereda**		**kebele**	
Sex	1. Male 2. Female				
Age	_____years				
Smear result	1. Positive 2. Negative 3. Not done		**Lab number**:_____		
Baseline/intial weight (Kg)	_____				
Patient category	1. New 2. Transfer in 3. Other 4. Other specify_____				
Type of TB	1. PPos 2. Pneg 3. EPTB				
Intensive drugs	1. RHZE 2. SRHZE 3. Other -----		Dose (#of tabs):_____		
Treatment started date/dd/mm/yy	_____				
Xpert MTB/RIF result	1. Positive 2. Negative 3. Not done		Lab serial #:		
HIV test offered	1. Yes 2. No				
HIV test performed	1. Yes 2. No				
Place HIV test performed	1. OPD 2. Lab 3. TB clinic 4. Other ----				
HIV result	1. Reactive 2. Non reactive 3. NA				
CPT started date	1. Yes 2. No if yes when----------dd/mm/yy				
Date HIV care enrolled	Yes 2. No if yes when----------dd/mm/yy				
Date ART started	Yes 2. No if yes when----------dd/mm/yy				
ART unique number					

Part I; Patients' general background information (socidemographic and Socioeconomic characteristics)

Q no	Questions	Options/responses	Skip
101	Your usual residence	1. Urban 2. Rural (woreda-----kebele----	
102	Your current marital status	1. Never married 2. Married 3. Widowed 4. Divorced/Separated	
103	To which religion do you belong?	1. Orthodox Christian 2. Muslim 3. Catholic 4. Protestant Christian 5. Traditional 6. Other specify--------	
104	To which ethnic group do you belong?	1. Kafficho 2. Bench 3. Shekacho 4. Sheko 5. Amhara 6. Tigire 7. Oromo 8. Meinit 9. Other (specify	
105	What is your highest level of education completed?	1. Never attended formal school 2. 1-4 (First cycle primary 3. 5-8 (2^{nd} cycle primary) 4. 9-10/12 5. Graduate/certificate (10+1/2/3 or 12+1/2/3/4) 6. Other (specify--------	
106	What is your main occupation?	1. Government employee 2. Private employee 3. Self employed 4. Housemaid 5. House wife 6. Student 7. Farmer	

		8. Daily laborer 9. Merchant 10. Other (specify--	
Part II. Care seeking practices and costs incurred for the illness until diagnosis of TB			
201	When was the current illness you are being treated started?	1. -------/---------/-------dd/mm/yy 2. I donot know/remember	
202	What was/were your chief symptoms and date of onset of the current illness? **Note for interviwer: More than one response possible and check for that without reading options**	1. Cough (dd/mm/yy): [ ] [ ] [ ] 2. Fever (dd/mm/yy): [ ] [ ] [ ] 3. Loss of Weight:(dd/mm/yy): [ ] [ ] [ ] 4. Haemoptysis (dd/mm/yy): [ ] [ ] [ ] 5. Chest pain : (dd/mm/yy): [ ] [ ] [ ] 6. Others (specify) (dd/mm/yy): [ ] [ ] [ ]	
203	Which symptom(s) made you seek care? **Note for interviwer: More than one response possible and check for that without reading options**	1. Cough 2. Fever 3. Loss of Weight 4. Haemoptysis 5. Chest pain 6. Others (specify----------	
204	Where and when did you first seek care for the complaints?	**Action taken** / **Date of visit/action** 1. Self medication 2. Used traditional medicine 3. Used holly water 4. Consult HEW 5. Consult HCP at HF → 6. Other (specify----------)	206
205	Why did not you consult health facility first during the onset of symptoms? **Note for interviwer: Health facility is to mean private clinic or hospital, public health center, or hospital or health post** **More than one response possible and check for that without reading options**	1. Thought it was mild and relived by it self 2. Health facilities were too far 3. Facility do not provide the service 4. Too busy/long waiting time 5. Previous bad experiences 6. Fear of being diagnosed for TB 7. TB is common and cure by itself 8. Fear of HIV test 9. I don't know service is provided there 10. I thought the cost is too expensive 11. Mistrust of health services provision 12. My belief system don't allow 13. Other (specify)----------	

206	Which HCF did you first visit?	1. Health post 2. Public Hospita 3. Health center 4. Private (Hospital/Clinic) 5. Others (specify--------	
207	How far is the HCF you visited first from your ususal residence?	_____minute/hour walking distance/transport _____Km	
208	How did you come to visit the health care facility? **Note for interviwer: More than one response possible and check for that without reading options**	1. Referred from drug vendor/store/pharmacy 2. Referred /advised by HEW 3. Refred/advised from HIV clinic 4. Referred/advised from holly water 5. Adivised/refered by traditional healer 6. Advised by TB patient on treatment 7. Advised by relatives/families 8. Self intiated 9. Other specify----------	
209	When did you first visit the HCF?	---------/---------/----------dd/mm/yy	
210	In total how long time, did you spend from the onset of illness to the first HCF visit?	_____days/weeks/months	
211	Do you think that you delayed consultation of HCP for your illness?	1. Yes 2. No →	213
212	If felt delayed, Why did you delay consultation of HCP at health facilities?	1. Hoped symptoms would go away on their own 2. Fear of social isolation 3. Fear of being diagnosed for TB 4. Fear of routine HIV test at health faciliteis 5. Lack of money to cover consultation fees 6. Bad staff attitude to patients 7. Perceived poor qualities of health services 8. Others (mention----------)	
213	Why did you prefer to visit the first health facility to other facilities? **Note for interviwer: More than one response possible and check for that without reading options**	1. It is accessible/near to my residence 2. Services are available anytime 3. Services are provided for free 4. Confidence in getting cured at the HCF 5. Advised by somebody 6. Facility do maintain confidentiality 7. Facility staffed with skilled providers 8. Facility well equipped with diagnostic facilities 9. Others (specify----------	

214	What was the diagnosis of your illness during the first consultation at the facility?	1. Common cold 2. Pneumonia 3. B.Asthma 4. TB ⟶ 5. I was not told/I donot know 6. Other (specify----------	218
215	Were you referred or self referred to other facilities?	1. Yes 2. No ⟶	218
216	To which facility were you refered?	1. Health center 2. Hospital 3. Other specify------	
217	Why were you refered to other HCF?	1. Lack of laboratory 2. Lack of x ray 3. HCF donot provide TB diagnosis and treatment 4. HCP unable to diagnose my illness 5. Other specify----------	
218	When was your final diagnosis of TB made?	----------dd/mm/yyyy	
219	Did you suspect your illness be TB?	1. Yes 2. No	
220	What did yo feel when you were told to have TB?	1. So frightend 2. Guilty 3. Nothing 4. Hopless 5. Other --	
221	Where was the final diagnosis of TB made?	1. Health center 2. Hospital 3. Private clinic 4. Other	
222	Until the final diagnosis of TB, how many facilities did visit?	_____	
223	How many visits did you made to HCF until the final diagnosis of TB?	----------	
224	In total how long time did you spend from the onset of your illness to diagnoses of TB?	_____days/weeks/months	
225	How long time did you spend since you first visited HCF until TB diagnosis?	_____days/weeks/months	
226	Do you think that diagnosis of TB was	1. Yes	

	delayed after you made visits to HF?	2. No →	228
227	If felt delayed, what do you think is/are the reasons for the delay? **Note for interviewer: More than one response possible and check for that without reading options**	1. Failure of providers to reach at diagnosis 2. Lack of facilities/supplies for diagnoses 3. Prescription of unnecessary drugs 4. Repeated referrals to different facilities 5. Other specify----------	
228	In your family, does anyone have an illness like you?	1. Yes (how many---------- 2. No →	231
229	Did they seek care for it?	1. Yes → 2. No	231
230	Why they did not seek care? **Note for interviewer: More than one response possible and check for that without reading options**	1. Took from my medicine 2. Expensive healthcare fee 3. Refused 4. Other (specify----------	

Cost of seeking care and diagnosis

About how much did you spend in ETB for each of the visits before you were diagnosed with TB, including the visit when you actually received your diagnosis? *For all that do not apply, mark N/A; Fill one line per visit*

Visit	Name of Providers/ institution where treatment or advice sought	Total time spent (in hours, including travel)	Accompanies (Y/N) (# of accompanies	Consultation /card charge	All test costs (for sputum, blood, stool, urine or other specify----)	X ray/ US or other diagnostic costs	Total drug costs (all kinds	Travel Costs (round trip including accompany if any	Food costs (total	Accommodation costs if any	Any other costs(specify	Total costs per visit
Visit 1												
Visit 2												
Visit 3												
Visit 4												
Visit 5												
Visit 6												
Visit 7												
Visit 8												
Visit 9												
Total direct pre-diagnostic and diagnostic costs												

Note for interviewer: provider could be traditional healer, holy water, any healthcare facility.

Time elapsed is time in minute/hours spent for round trip travel and waiting time at the provider

Drug is any medication prescribed and taken at each visits to provider

Part III; Anti-TB treatment practices and patient cost of care			
Q no	Question	Options /response	Skip
301	When did you start antiTB treatment?	_____dd/mm/yy	
302	How long it takes you to start TB treatment since first HCP consultation?	----------days/weeks/months	
303	How long after the diagnosis of TB that you commenced anti-TB treatment?	1. Immediately ⟶ 2. ----------days/weeks	305
304	Why you did not start treatment immediately?	1. I was reluctant to initiate the treatment 2. Fear of long treatment 3. Lack of anti-TB drugs at the facility 4. TB clinic was closed 5. Absence of DOT provider 6. Failure to present treatment supporter 7. Inability to arrange accommodation at nearby 8. Too ill to initiate early 9. Other (specify----------	
305	At which health facility did you start the anti-TB treatment?	1. In this facility ⟶ 2. Other facility(specify------	308
306	If started elsewhere, why you did you start treatment there?	1. It was must to start at diagnosed HCF 2. I was too ill and told to be admitted there 3. Treatment was not available here at the time 4. I was near to that facility at the time 5. Other specify----------	
307	For how long did you take the treatment there?	_____days/weeks/months	
308	How were you taking the anti-TB drugs?	1. Hospitalized 2. Ambulatory ⟶	312
309	For how long did you stay at the hospital?	_____days/weeks/months	
310	Did someone accompany you during hospitalization?	1. Yes (for ----------days/weeks/months 2. No	
311	During the hospitalization, how much did you pay in total for the following items?	1. Food ---------- 2. Accommodation --------- 3. Laboratory tests---------- 4. Drugs ---------- 5. Service charge--------- 6. Other(specify------ 7. I did not pay	

		8. I donot remeber 9. Did not pay (its free or covered by specify-------	
312	How far is this facility from your residence?	----------minutes/hour walk/vehicle -------Km	
313	How long time did you spend for a single visit including round trip travel and waiting time?	Round trip travel-----minutes/hour walking/vehicle waiting time at facility____minute/hour total----------	
314	Were your family/ other accompanied you or gone in your place to pick anti-TB drugs?	1. Yes (in how many visits---------- 2. No →	316
315	Why did someone accompany or gone in place of you?	1. Too ill to travel alone or at all 2. Fear of security 3. Was required for treatment 4. Other (specify-----	
316	During the current treatment, were you told about the following **Note for interviewer: options should be read and circle those responded**	1. Opting for treatment center 2. Person to observe your treatment 3. Length of treatment 4. Type of the drug 5. Dose and frequency of the drugs 6. Drug adverse effects 7. Need for repeated examinations/sputum test 8. Measures avoid TB transmission to others 9. Need for adherence to treatment 10. Risk s of improper drug intake 11. Cause and manifestations of TB illness 12. Need for screening household contacts 13. TB curability 14. Cost of anti-TB drugs and treatment 15. Who else should be examined/screened 16. Other specify----------	

Part IV: **Indirect costs of care seeking and diagnosis before starting treatment**			
401	What is your formal work?	1. Government/private employed 2. Farmer 3. Daily laborer 4. Student 5. Merchant 6. No work 7. Other (specify)--	
402	Do you work additional works (partime, maintenance, trade etc)	1. Yes 2. No	
403	Do you regularly perform your works?	1. Yes →	406
		2. No	
404	Why did not you regularly work?	1. Due to the TB illness	
		2. Other reasons (specify---------- →	406
405	When was the last time you were working your regular work?	----------dd/mm/yy ----------days/weeks/months from now	
406	On average, how many hours did you work per day **BEFORE** you became ill with TB?		
407	On average, how many hours per day do you work after you became ill with TB?		
408	If work hour is different, is the change related to the TB illness?	1. Yes 2. No	
409	Have you ever stopped working/going to school/doing housework due to TB illness?	1. Yes 2. No →	413
410	If YES: for how long did you quit working?	----------days/weeks/months	
411	Who covers the work that you used to work?	1. Family member 2. Delegate office mate/co-worker 3. Hired person 4. Nobody 5. Other specify-------	
412	How much ETB did you estimate the loss of income due to lost workdays?	_____	
413	Did someone quit his or her regular work specifically to take care/accompany you?	1. Yes (how many---------- 2. No →	501
414	What was the main occupation of your accompanies/care giver?	1. Government/private employed (monthly salary--- 2. Farmer 3. Daily laborer (daily wage--------	

		4. Student 5. Merchant	
Part VI; Coping mechanisms for costs due to TB illness		6. No work	
		7. Other (specify)--	
415	For how long did they quit their work?	_____days/weeks/months	
416	How much ETB would you estimate have they lost while taking care of you?	_____ETB	
Part V: Household characteristics, assets, Income and Spending			
501	Who is the head of the household?	1. Patient 2. Husband/father 3. Wife/mother 4. Brother/sister 5. Other specify----------	
502	Who is the primary income earner in the household? *Circle most appropriate*	1. Patient 4. Wife/mother 2. Husband/father 5. Extended family 3. Son/daughter 6. Other (specify	
503	What is the highest level of education of Primary income earner?	1. Not attended/illiterate 4. Completed secondary 2. Completed primary 5. Graduate/certificate 3. Other specify----	
504	What is the highest level of education of head of household if different from primary income earner?	1. Not attended/illiterate 4. Completed secondary 2. Completed primary 5. Graduate/certificate 3. Other specify----	
505	How many people regularly sleep in your house?		
506	How many of the household members are paid for working? (including patient)	_____	
507	How much do you estimate was the average annual income of your household (for all persons in the house, including patient)	1. Income of patient: ---------- 2. Other household member---------- 3. Other income : ---------- TOTAL: ----------	
508	Do you think that your TB illness reduced the total household income?	1. Yes 2. No	
509	Besides yourself, does anyone else of your household receive treatment for TB?	1. Yes 2. No	

601	How much do you estimate that your household incurred your TB care seeking?	1. ----------ETB 2. I donot Know	
602	How would you describe the expenditure for your TB care?	1. Expensive 2. Fair 3. Cheap 4. Free	
603	How did you cover the costs incurred for TB illness and care seeking? **Note**: **more than one response is possible and put amount of money generated with each coping mechanisms**	1. Sold assets/products 2. Received financial assistance from outside---- 3. Withdrew saving---------- 4. Borrow money---------- 5. Changed jobs 6. Reduced food consumption 7. Drop out of school 8. Other specify----------	607
604	If you sold assets, what did you sell? *Circle most appropriate*	1. Land 5. Vehicle 2. Livestock 4. Farm produce 3. Household item 6. Other----	
605	What is the estimated market value of the property you sold?		
606	How much did you earn from the sale?	_____	
607	Has the TB illness affected your social or private life in any way?	1. Yes 2. No →	609
608	If Yes, what did it brought on you?	1. Divorce 2. Disruption of sexual life 3. Drop out of school 4. Loss of Job 5. Reduced income 6. Other------	
609	If the government could provide you with some service to ease the burden of TB on you and your household, what would you prefer to have? ***State options, choose one***	1. Transport vouchers 2. food vouchers 3. More efficient service 4. Other (specify):	

Part VII; Perceptions, Knowledge and attitudes about TB			
701	What kind of disease are you being treated currently?	1. TB 2. Pneumonia 3. Cold 4. I donot know 5. Other specify----	
702	Have you ever heard of TB illness before?	1. Yes 2. No →	704
703	Where did you hear about TB (source of information on TB) **Note for interviewer: More than one response possible and check for that without reading options**	1. Mass media (radio,TV,news letter etc) 2. MOH banners,brochers,pamphlet etc 3. HEW 4. Health facility 5. Friends/relatives 6. TB case treated/on treatment 7. Other (specify------	
704	What do you think is the causative agent of TB?	1. Bacteria 2. Smoking cigarette 3. Exposure to cold 4. Fungus 5. Virus 6. Curse 7. Other Specify---------- 8. I don't know	
705	Is TB contagious?	1. Yes 2. No →	707
706	If contagious, how can a person get tuberculosis? **Note for interviewer: More than one response possible and check for that without reading options**	1. Through the air when coughing or sneezing 2. Through sharing utensils 3. Through touching a person 4. Through food 5. Through sexual contact 6. Through mosquito bites 7. Through drinking unboiled milk 8. Other (specify)---------- 9. I Don't know	
707	What symptoms does a person with tuberculosis have?	1. Persistent cough (greater than 2weeks) 2. Coughing up blood	

	Note for interviwer: More than one response possible and check for that without reading options	3. Weight loss 4. Poor appetite 5. Night sweating 6. Chest pain 7. Fever 8. Other (specify---------- 9. Don't know	
708	Is TB hereditary?	1. Yes 2. No	
709	Do you know if there is a vaccine for TB?	1. Yes 2. No	
710	How is treatment of TB provided?	1. For free 2. For charge	
711	Do you know the approximated duration of TB treatment?	1. Yes (specify---------- 2. No	
712	Do you know the kind of TB drugs?	1. Yes 2. No	
713	Is tuberculosis curable?	1. Yes 2. No	

Annex 3: Amharic version information sheet, consent form, and questionnaires

አባሪ ፣፡ ለጥናት ተሳታፊዎች የሚሰጥ መረጃ

የጥናቱ ርዕስ፡ የቲቢ ህሙማን ህክምና መዘግየት፣ ወጪያቸዉና ህክምና ዉጤት

ዋና አጥኚ፤ አብዮት አስረስ(የህ/ሰብ ጤና አጠባበቅ እስፐሻልስት)

ዋና አማካሪ፤ ዶ/ር ዋቅጋሪ ዴሬሳ(ተባባሪ ፕሮፌሰር)

ሁለተኛ አማካሪ፤ ዶ/ር ደጉ ጀረኔ (ረዳት ፕሮፌሰር)

አስተባባሪ መ/ቤት፤ በአድስ አበባ ዩኒቨርሲቲ የህ/ሰብ ጤና አጠባበቅ ት/ቤት

<u>መግቢያ</u>፤ ቲቢ በተዋሲያን የሚመጣ በሽታ ሲሆን በታማሚዎች፣በማህበረሰቡና በኢኮኖሚ ላይ ከፍተኛ ጫና ያሳድራል፡፡ በመሆኑም ይህንን የተደራረቡ ሰባዊ፣ማህበረሰባዊና ኢኮኖሚያዊ ጉዳዮችን ለመቅረፍና ለመቆጣጠር አለም አቀፍ ጥረቶች በአገራት ስተገበሩ ቆይተዋል፡፡ ለዚሁም ህሙማንን በቶሎ መለየትና ተገቢዉን ህክምና ሰጥቶ ማዳን በማህበረሰቡ ዉስጥ የበሽታዉን መዛመት ስለሚቀንስ ዋነኛዉ የቲቢ በሽታ መከላከልና መቆጣጠር መንገድ ነዉ፡፡ ይሁን እንጂ ህሙማን ሳይመረመሩና ሳይታከሙ ለረጅም ጊዜ እንደሚቆዩ በኢትዬጵያና ሌሎች ሀገሮች የተሰሩ ጥናቶች አሳይተዋል፡፡ ይህ ሆኖ ሳለ ግን የታማሚዎች መዘግየት ምክንያቶችን የሚሳይ የተሟላ መረጃ በስፋት አይገኝም፡፡ የህሙማን በቶሎ አለመመርምርና መታከም መሰናክሎች፣በህክምና ዉጤት ላይ የሚስከትለዉን ችግርና የበሽታዉ ኢኮኖሚያዊ ጫና መረጃዎች አሁን እየተሰራበት ያሉትንና ቲቢን በእጅጉ ቀንሶ ለማጥፋት ያለሙት ስትራተጂዎችን በከፍተኛ ሁኔታ ይደግፋል፡፡

<u>የጥናቱ ዓላማ</u>፤ የዚህ ጥናት አላማ በታማሚዎች፣በጤና ተቋማትና በማ/ሰቡ ዘንድ ያሉትን የምርመራና ህክምና መዘግየት መሰናክሎች፤ መዘግየታቸዉ በህክምና ዉጤታቸዉ ላይ የሚያመጣዉን ችግርና ለቲቢ በሽታ ምርመራና ህክምና በቀጥታም ሆነ በተዘዋዋሪ የሚወጡ ወጪዎችን መለየት ነዉ፡፡

<u>የጥናቱ አፈጻጸምና ተሳትፎ</u>፤ ጥናቱ የመጀመሪያ ዳሰሳና ተከታታይነት ያለዉ መረጃ አሰባሰብ ዜደ ይጠቀማል፡፡ በመሆኑም እስከ ህክምናዉ ፍፃሜ ድረስ አራት በተለያዩ ጊዜያት መረጃዎች ይሰበሰባል፡፡ የዕርስዎ በጥናቱ መሳተፍ የተፈለገዉ የሚሰጡን ተአማኒ መረጃ እየተጠና ያለዉን ጉዳይ ለመረዳት እጅግ አስፈላጊ ስለሆነ ነዉ፡፡ ተሳትፎዎትም የተወሰነዉ በዕድል ላይ ተመስርቶ በተደረገዉ የመረጣ ስልት ሲሆን በየጊዜያቱ የሚደረጉ መጤይቆች በአማካይ 30ደቂቃዎችን ይፈጃሉ፡፡ በመጠይቁም ወቅት የዕርስዎ ማህበራዊ፣ኢኮኖሚያዊ፣ የግልና በተሰብ ገቢና ወጪዎችን፣ስለአሁኑ ህመምዎ ምርመራና ህክምና ህደቶችንና ወጪዎችን ይጠየቃሉ፡፡

<u>የምስጥር አጠባበቅ</u>፤ የሚሰጡን ማናቸዉም መረጃዎች ምስጥሩ የተጠበቀ ለማድረግ የግል መግለጫ የሆኑት ስምዎትና ስልክ ቁጥሮት ሳይመዘገቡ በሚሰጦት መለያ መሰረት ተተንትኖ ማንነቶን በማይገፅ መልኩ ብቻ ይሰራጫል፡፡ በተጨማሪም መረጃዉ ከአጥኝዎች ዉጭ ማንም በማይደርስበት ቦታ ተቆልፎ ይቀመጣል፡፡ የሚሰጡንን መረጃ ከጥናቱ አላማ ዉጪ ማዋል የጥናት ስነምግባር ስላልሆነ ለሌላ ጉዳይ አይዉልም፡፡ ስለሆነም የገቢዎትና ወጪዎች መረጃ ለግብር ሰብሳቢ መ/ቤት ተላልፎ አይሰጥም፡፡ በመጨረሻም የተሰበሰበዉ መረጃ ጥናቱ መጠናቀቁ በህ/ሰብ ጤና አጠባበቅ ት/ቤትና ዩኒቨርሲተዉ የት/ርት ጉባኤ ሲረጋገጥ ደህንነቱ በተረጋገጠ ቦታ ላይ ይቃጠላል፡፡

<u>የሚያገኙት ጥቅም</u>፤ ጥናቱ የአጭር ጊዜ የገንዘብ፣የጤና አገልግሎትም ሆኔ አቅም ግንባታ ጥቅማጥቅሞች ለተሳታፊዎች በግልም ሆኔ በቡድን አይኖርም፡፡ ይሁን እንጂ ወደፊት የሚመለከታቸዉ ክፍሎች መረጃዉን በመጠቀም የቲቢ በሽታ በበተሴብ እና ጤና አገልግሎት ላይ የሚያሳድረዉን ጫና የሚቀንሱ ስትራቴጅዎችን ይቀርፁበታል፡፡ በመሆኑም የቲቢ በሽታን በእጅጉ የመቆጣጠርና ማጥፋት ራዕይን በማሳካት መላዉ የዓለም ህዝቦች ከቲቢ በሽታ ጫና ነጻ እንዲሆኑ ያደርጋል፡፡ በሌላ መልኩ መረጃዉ በሚሰበሰብበት ወቅት ለተሳታፊዎች ስለ ቲቢ በሽታና ህክምና መረጃዎች ይሰጣቸዋል፡፡

<u>የሚያስከትለዉ አደጋ</u>፤ የታሰበዉ ጥናት በሚሳተፉ ሰዎች ላይ ምንም ዓይነት ኢሰባዊ ድርጊቶች፣አካላዊ ጉዳት፣ማህበራዊ፣ ኢኮኖሚያዊ እና ስነ ልቦናዊ ጉዳቶችን አያመጣም፡፡ በተጨማሪም በጥናቱ መሳተፎ ወይም አለመሳተፎ የሚያገኙት ህክምናን በምንም መልኩ አይጎዳም፡፡

<u>ስጦታዎች</u>፤ የጥናቱ ህደት ምንም ዓይነት መደለያ ወይም ማስገደጃ ድርጊት ወይም ስጦታ የለሌዉ ከመሆኑም በላይ ጥናቱ ካሳ የሚያስከፍል ህደትም የለዉም፡፡

<u>መረጃ ስለማሰራጨት</u>፤ አጥኚዎቹ የጥናቱን ዉጤቶች የማሰራጨት ሙሉ ኃላፊነት የሚኖራቸዉ ሲሆን ለሚመለከታቸዉ ጤና መምሪያዎችና ወረዳዎች ተገቢዉን ግብረ መልስ ይሰጣሉ፡፡ በተጨማሪም የጥናቱን ዉጤቶች በተለያዩ አገርዊና አለም አቀፋዊ ሳይንሳዊ ጉባኤያት ላይ በማቅረብ እንዲሁም በተዓማኒ የጥናት መፅሄቶች ላይ በማሳተምም ይሰራጨል፡፡

<u>ከጥናቱ ስለማቋረጥ</u>፤ በጥናቱ መሳተፍ ካልፈለጉ በማንኛዉም ጊዜ የማ**ቋ**ረጥ መብት አለዎት፡፡ ይህን በማድረጎም ምንም ዓይነት የጤና አገልግሎትና አሰተዳደራዊ ችግሮች አይደርስቦትም፤ የሚያ**ቋ**ርጡብትንም ምክንያት እንዲገልጹ ማንም አያስገድዶትም፡፡

<u>መረጃ ስለመጠየቅ</u>፤ የጥናቱ ተሳታፊዎች ማናቸዉንም ስለጥናቱ ያልገባቸዉንም ሆነ ጥናቱ የሚያካትታቸዉን ጉዳዮች የመጠየቅ መብት አላቸዉ፡፡ ስለሆነም መረጃ ከፈለጉ ከዚህ በታች በተዘረዘሩ የዋና አጥኚ፣ አማካሪዎች ወይም አድስ አበባ ዩኒቨርሲቲ ጤና ሣይንስ ኮለጅ የተ**ቋ**ሟዊ ጥናት ስነ ምግባር አጣሪ ቦርድ አድራሻዎች መጠየቅ ይችላሉ፡፡

1. አድስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮለጅ ተ**ቋ**ማዊ የጥናት ስነምግባር አጣሪ ቦርድ ጽ/ቤት

ስልክ ቁጥር፡ 01155512876

2. ዋና አጥኚ-አብዮት አስረስ (ሚዛን ቴፒ ዩኒቨርሲቲ፣ስልክ ቁጥር፡ 0911905554)
3. አማካሪዎች

- ✓ ዶ/ር ዋቅጋሪ ደሬሳ (አድስ አበባ ዩኒቨርሲቲ የህ/ሰብ ጤና አጠባበቅ ት/ቤት፣ ስልክ ቁጥር ፡0911483714)
- ✓ ዶ/ር ደጉ ጀረኔ ስልክ ቁጥር፡ 0911546

አዲስ አበባ ዩኒቨርሲቲ

ጤና ሳይንስ ኮሌጅ

ህ/ሰብ ጤና ት/ቤት

የቲቢ በሽታ ህክምና መዘግየት፣ ወጪዉና የህክምና ዉጤት የስድስት ወራት ህክምና ከመጀመሩ በፊትና በኋላ፤ ለፍልስፍና ዶክቴሬት ዲግሪ በህ/ሰብ ጤና ማሟያ ምርምር የጥናት ተሳታፊ ህሙማን መጠይቅ

<u>የጥናት ተሳታፊዎች ስምምነት መቀበያ</u>

ጤና ይስጥልኝ! ----------እባላለሁ፡፡ከአዲስ አበባ ዩኒቨርሲቲ የጥናት ቡድን ጋር የሚሰራ ሲሆን በሳይንሳዊ ዜዴ የተመረጡ ቲቢ ህሙማንን በበሽታዉ የምርመራና የህክምና ልምዶቻቸዉ እና ወጪያቸዉ ዙሪያ እንጠይቃለን፡፡ የጥናቱም ዓላማ ለቲቢ በሽታ ምርመራና ህክምና መዘግየት ምክንያቶችንና ተያያዥ ወጪዎችን በመለየት የመፍትሄ አቅጣጫዎችን መጠቆም ነዉ፡፡ ስለሆነም ለታሰበዉ ጥናት በጣም ጠቃሚ የሆኑ መረጃዎችን ስለምጠይቅዎት የሚሰጡኝ እዉነተኛ መረጃ ለሚታቀደዉ መፍትሄ ወሳኝ ሚና ይኖረዋል፡፡ በማናቸዉም ጉዳዮች ዙሪያ የሚሰጡኝ መረጃ ምስጥራዊነቱ የተጠበቀ ነዉ፤ ለዚሁም ማንነትዎን የሚገለጽ ማንኛዉም መረጃ የማይያያዝ ከመሆኑም ባሻገር መረጃዉ ከጥናቱ ዓላማ ዉጭ ለሌላ ወገን ወይም ጉዳይ የማይዉል መሆኑን እናረጋግጣለን፡፡ መጠይቁ 30 ደቂቃ የሚፈጅ ሲሆን መመለስ የማይፈልጉት ጥያቄ ካለ አለመመለስ ወይም በፈለጉበት ጊዜ ማቆም ይችላሉ፡፡ስለተሳትፎዎ እጅግ አድርገን እያመሰገንን ስለጥናቱ ማንኛዉንም መረጃ ከፈለጉ በሚከተሉት አድራሻዎች መጠየቅ ይችላሉ፡፡

1. አቶ አብዮት አስረስ ዋና አጥኚ ፡ ስልክ ቁጥር፡ 0911905554
2. ዶ/ር ዋቅጋሪ ዴረሳ የጥናቱ አማካሪ ፡ ስልክ ቁጥር 0911483714
3. ዶ/ር ደጉ ጀረኔ የጥናቱ አማካሪ ፡ ስልክ ቁጥር 0911546407
4. አድስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የጥናት ስነምግባር ገምጋሚ ቦርድ፡ ስልክ ቁጥር 01155512876

ሀ. መረጃዉና የጥናቱ ዓላማ ግልጽ ነዉ ? 1. አዎን 2. አይደለም----------በድጋሜ አብራራ/ሪ

ለ. በጥናቱ ለመሳተፍ ፈቃደኛ ነዎት?

1. አዎን----------ጥያቄዉን ቀጥል/ይ
2. አይደለም----------አቁም/ሚና ወደ ቀጣይ ታማሚ ሂድ/ጅ

ሐ. ስምምነቱ በጥናቱ ተሳታፊ ስለመሰጠቱ የጠያቂዉ ማረጋገጫ

የጠያቂዉ ስም----------ፊርማ----------ቀን----------

1.2.የመጠይቁ አጠቃላይ መግለጫ						
የመጠይቅ መለያ						
ዞን	ነ. ካፋ		2. በንች ማጂ		3. ሸካ	
ወረዳ	ነ. ቦንጋ ከተማ 2. ደቻ 3. ጨና		4. ሚዛን አማን 5. ሰሜን በንች 6. ሸይ በንች 7. ሜኢኒትነልድያ		8. ቴፒ ከተማ 9. የኪ ነ0. ማሻ	
የጤና ተቋሙ ስም						
የጤና ተቋሙ ዓይነት	ነ. ሆስፒታል	2. ጤና ጣቢያ	3. ጤና ኬላ	4. ሌላ ይጠቀስ----------		
ተጠያቂዉ	ነ. ታማሚዉ	2. የታማሚዉ ቤተሰብ	3. የህክምና አጋዥ/ረዳት	4. ሌላ-------		
መጠይቁ የተሞላበት ቀን			የቀጣይ ቀጠሮ ቀን፡_____			
የጠያቂዉ/መረጃ ሰብሳቢ ስምና ፊርማ			የተቆጣጣሪዉ ስምና ፊርማ፡ _____			

1.1. Medical record review checklist			
Medical record number	_____	Date of recent visit:_____	
		Duration of illness (dd,week,mm)	
Chief complaint	1. Cough		
	2. Fever		
	3. Chest pain		
	4. Night sweating		
	5. Swelling over neck		
	6. Other specify----------		
Key physical findings	1. HEENT		
	2. LGS		
	3. Chest		
	4. CVS		
	5. Abdomen		
	6. Other specify----------		
Investigations requested ,their results and unit cost	Investigation	Result	Unit cost of the investigation
	1. Sputum for AFB		
	2. GeneXpert MTB/RIF		
	3. CXR(chest x ray)		
	4. ESR		
	5. WBC		
	6. Other specify		
Diagnosis/Assessement	Diagnosis	Date of diagnosis	
	1. TB		

	2. Pneumonia	
	3. B.Asthma	
	4. Other specify----------	
	5. Not stated/written	
Treatments/plan prescribed and their unit cost		Unit cost of the treatment precribed

1.2. Unit TB register review

TB unit number		**Wereda**		**kebele**	
Sex	1. Male 2. Female				
Age	_____years				
Smear result	1. Positive 2. Negative 3. Not done		**Lab number**:_____		
Baseline/intial weight (Kg)	_____				
Patient category	1. New 2. Transfer in 3. Other 4. Other specify_____				
Type of TB	1. PPos 2. Pneg 3. EPTB				
Intensive drugs	1. RHZE 2. SRHZE 3. Other -----		Dose (#of tabs):_____		
Treatment started date/dd/mm/yy	_____				
Xpert MTB/RIF result	1. Positive 2. Negative 3. Not done		Lab serial #:		
HIV test offered	1. Yes 2. No				
HIV test performed	1. Yes 2. No				
Place HIV test performed	1. OPD 2. Lab 3. TB clinic 4. Other ----				
HIV result	1. Reactive 2. Non reactive 3. NA				
CPT started date	1. Yes 2. No if yes when----------dd/mm/yy				
Date HIV care enrolled	Yes 2. No if yes when----------dd/mm/yy				
Date ART started	Yes 2. No if yes when----------dd/mm/yy				
ART unique number					

ክፍል አንድ፡ የታማሚዉ አጠቃላይ ማህበራዊ እና ኢኮኖሚያዊ መረጃዎች

ተቁ	ጥያቄ	ምላሽ/አማራጭ	ወደ
101	ቋሚ የመኖሪያ አድራሻዎ የት ነዉ?	1. ከተማ 2. ገጠር (ወረዳ_____ ቀበሌ_____	
102	የትዳር ሁኔታ እንዴት ነዉ?	1. ፈፅሞ ያላገባ/ች 3 ባል/ሚስት የሞተበት/ባት 2. ያገባ/ች 4. የተፋታ/ች/የተለያዩ	
103	ሃይማኖትዎ ምንድን ነዉ?	1. ኦርቶዶክስ ክርስቲያን 4. ፕሮቴስታንት 2. ሙስሊም 5. ባህላዊ 3. ካቶሊክ 6. ሌላ----------	
104	የትኛዉ ብሄረሰብ አባል ነዎት?	1. ካፍኞ 4. ሸኮ 7. ኦሮሞ 2. ቤንች 5. አማራ 8. ሜኒት 3. ሸካኞ 6. ትግሬ 9. ሌላ----------	
105	የጨረሱት ከፍተኛ የት/ርት ደረጃ ?	1. ምንም ያልተማረ 4. ሁለተኛ ደረጃ ያጠናቀቀ(9-12) 2. የመጀመሪያ ሳይክል ያጠናቀቀ/ች (1-4) 5. የተመረቀ /ሰርትፍኬት/ዲፕሎማ/ዲግሪ 3. ሁለተኛ ሳይክል ያጠናቀቀ/ች (5-8)	
106	ዋና/መደበኛ ስራዎ ምንድነዉ?	1. የመንግስት ተቀጣሪ 6. የቤት እመቤት 10. ነጋዴ 2. የግል ተቀጣሪ 7. ተማሪ 11. ሌላ---------- 3. በግል ስራ የሚተዳደር 8. አርሶ አደር 4. የቤት ሰራተኛ 9. የቀን ሰራተኛ	

ክፍል ሁለት፡ የህመም እጅግመር፣ ህክምና ዕርዳታ አፈላለግ ልምድና ወጪያቸዉ

201	አሁን እየታከሙ ያሉት የቲቢ ህመም መቼ ነበር የጀመርዎት?	1. _____ቀን/ወር/ዓም/ 2. _____በፊት 3. አላስታዉስም		
202	መጀመሪያ የታየብዎት ዋና ምልክት/ቶች ምን/ምን ምን ነበር/ሩ? መቼ ነበር ምልክቶቹ የታዩት? ***ከአንድ በላይ ምላሽ ልናረዉ ይችላል/ ምርጫ አይነበብም ሌላሰ በማለት ተጨማሪ ይጠየቅ***	የታዩ ምልክቶች	የጀመረበት ጊዜ/ቀን/ወር/ዓም	
		1. ሳል		
		2. ትኩሳት:		
		3. የምግብ ፍላጎት መቀነስ		
		4. ደም የቀላቀለ ሳል		
		5. ክብደት መቀነስ		
		6. የደረት ህመም/ዉጋት		
		7. ማታ ማታ ማላብ		
		8. ሌላ ይጠቀስ----------		
203	የትኛዉ ምልክት ነበር መፍትሄ/ የህክምና እርዳታ እንዲፈለጉ ያደረግዎት? ***ከአንድ በላይ ምላሽ ልናረዉ ይችላል፤ የ202 ምላሽ አስታዉስ/ሽ ወይም ከ202 ምላሽ ዉስጥ አስመርጥ/ጪ***	1. ሳል 5. ትኩሳት 2. ክብደት መቀነስ 6. የደረት ህመም. 3. ደም የቀላቀለ ሳል 7. ማታ ማታ ማላብ 4. የምግብ ፍላጎት መቀነስ 8. ሌላ----------		
204	ህመሙ እንደጀመርዎት <u>መጀመሪያ</u> ምንድነዉ ያደረጉት ወይም ምን እርምጃ ነዉ የወሰዱት? መፍትሄዉን ወይም እርምጃዉን መቼ ነበር የወሰዱት?	**የተወሰደ መፍትሄ**	**የተወሰደበት ጊዜ/ቀን/ወር/ዓም**	
		1. በራሴ መድሃኒት ገዝቼ ዋጥኩ		
		2. የባህል ህክምና ቦታ ሄድኩ		

	ምርጫ አይነበብም፤ አንድ ምላሽ ብቻ ይናረዋል።።	3. ጸበል ቦታ ሄድኩ/ጠጣሁ		
		4. የጤና ኤክስቴንሽን አማከርኩ		
		5. ጤና ተቋም /የግል ክልኒክ፣ የመንግስት ጤና ክላ፣ጤና ጣቢያ፣ ሆስፒታል ሄድኩ/	→	206
		6. ሌላ----------		
205	ህመሙ እንደጀመርዎት መጀመሪያ ወደ ጤና ተቋም ያልሄዱት ለምንድን ነዉ? ***ጤና ተቋም ማለት የግል ክልኒክ ወይም ጤና ኬላ ወይም ጤና ጣቢያ ወይም ሆስፒታልን ያካትታል።።*** ***ከአንድ በላይ ምላሽ ሊኖረዉ ይችላል፤ምርጫ አይነበብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	1. ህመሙ በራሱ ይተዋል ብዬ 2. ጤና ተቋማቱ ስለራቁኝ 3. ጤና ተቋማቱ አገልግሎት ስለማይሰጡ 4. በተቋማቱ አገልግሎቱን ለማግኘት ረጅም ጊዜ ስለሚፈጅ 5. በተቋማቱ መጥፎ ገጠመኝ ስለነበረኝ 6. የምርመራ ዉጤቱ ቲቢ እንዳይሆን ፈርቼ 7. ቲቢ የተለመደና በራሱ የሚድን በሽታ ስለሆነ 8. የኤች አይ ቪ ምርመራ ፈርቼ 9. የህክምና ወጪ ዉድ ስለሆነ 10. የጤና ባለሙያዎችን ስለማላምንባቸዉ 11. ሌላ ይጠቀስ----------		
206	የትኛዉ ጤና ተቋም ነበር መጀመሪያ የሄዱት? ***ጤና ተቋም የግል ክሊኒክ ወይም ጤና ኬላ ወይም ጤና ጣቢያ ወይም ሆስፒታልን ያካትታል።።***	1. ጤና ኬላ 2. መንግስት ሆስፒታል 3. ጤና ጣቢያ 4. የግል ሆስፒታል/ክሊኒክ 5. ሌላ --------		
207	ይህ የሄዱበት ጤና ተቋም ከቤትዎ ምን ያህል ይርቃል?	_____ሰዓት የእግር መንገድ/ኪሜ/		
208	ወደ ጤና ተቋሙ ማለትም /የግል ክሊኒክ፣ የመንግስት ጤና ኬላ፣ጤና ጣቢያ፣ ሆስፒታል/ ለመሄድ እንዴት ተነሳሱ ወይም ምን ገፋፍትዎት ነዉ ሊሄዱ የቻሉት? ***ከአንድ በላይ ምላሽ ልናረዉ ይችላል፤ምርጫ አይነበብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	1. ከመድሃኒት ቤት/መደብር ተልኬ 2. የጤና ኤክስቴንሽን ባለሙያ ልካኝ 3. ከኤች አይ ቪ ክፍል ተልኬ/ሪፈር ተደርጌ 4. ከጸበል ቦታ ተልኬ/ተመክሬ 5. በህክምና ላይ ባለ/ች ቲቢ ታማሚ ተመክሬ 6. ዘመዶቼ/ቤተሰቦቼ መክረዉኝ 7. በራሴ ተነሳስቼ 8. በባህል ሃኪም ተመክሬ 9. ሌላ----------	
209	ለህመሙ በመጀመሪያ ጊዜ ወደ ጤና ተቋሙ የሄዱት መቼ ነዉ?	_____ቀን/ወር/ዓም		
210	ህመሙ ከጀምርዎት ከምን ያህል ጊዜ በኋላ ነዉ መጀመሪያ ወደ ጤና ተቋም የሄዱት?	----------ቀናት/ሳምንት/ወራት		
211	ህመሙ እንደጀመርዎ ወደ ጤና ተቋም ለመሄድ የዘገዩ ይመስልዎታል?	1. አዎን 2. አይደለም →		213
212	የዘገዩ ከሆነ ወደ ጤና ተቋም ለመሄድ የዘገዩበት ምክንያትዎ ምንድነዉ? ***ምርጫ አይነበብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	1. ህመሙ በራሱ ይተዋል ብዬ ተስፋ በማድረግ 2. ከማህበረሰቡ መገለል እንዳይደርስብኝ ፈርቼ 3. በሽታዉ ቲቢ እንዳይሆን ፈርቼ 4. በጤና ተቋም የሚደረግ ኤች አይ ቪ ምርመራ ፈርቼ		

		5. የገንዘብ ችግር ስለገጠመኝ 6. በጤና ተቋም ያሉ ባለሙያዎች አመለካከት ጥሩ ስላልሆነ 7. በጤና ተቋም የሚሰጡ አገልግሎት ጥራት ስለሌላቸዉ 8. ሌላ ይጠቀስ----------	
213	**<u>መጀመሪያ የሄዱበትን</u>** ጤና ተቋም ለምን መረጡ? ***የ2006 ምላሽ አሰታዉሰ/ሽ ከአንድ በላይ ምላሽ ሊኖረዉ ይችላል/ ምርጫ አይነበብም፣ ሌላሰ በማለት ተጨማሪ ይጠየቅ***	1. ቅርብ ስለሆነ 2. አገልግሎቱ ሁል ጊዜ/በማንኛዉም ጊዜ ስለሚገኝ 3. አገልግሎቱ በነጻ ስለሚሰጥ 4. በተቋሙ እንደምድን ስለተማመንኩ 5. በሌላ ሰዉ ተመከሬ 6. በተቋሙ ሚስጥር ስለሚጠበቅ 7. ብቁ ባለሙያዎች በተቋሙ ስለሚገኙ 8. የተሟላ የምርመራ መሳሪያዎች በተቋሙ ስለሚገኙ 9. ሌላ ይጠቀስ----------	
214	መጀመሪያ ጤና ተቋም በሄዱበት ወቅት የህመምዎ የምርመራ ዉጤት ምን ነበር?	1. ጉንፋን 4. ቲቢ ⟶ 2. ሳንባ ምች 5. አልተነገረኝም/አላዉቅም 3. አስም 6. ሌላ----------	218
215	ወደ ሌላ ተቋም ሪፈር ተደርገዉ ወይም በራስዎ ሄደዉ ነበር?	1. አዎን 2. አይደለም ⟶	218
216	ወደ የትኛዉ ተቋም ነበር የተላኩትወይም በራስዎ የሄዱት?	1. ጤና ጣቢያ 2. ሆስፒታል 3. ሌላ ይጠቀስ------	
217	ለምን ነበር ሪፈር የተደረጉት ወይም በራስዎ የሄዱት?	1. ላቦራቶሪ ስላልነበር 4. በሽታዬን ማወቅ ስላልቻሉ 2. ኤክስሬይ ስላልነበር 5. ሌላ ይጠቀስ---------- 3. ተቋሙ የቲቢ ምርምራና ህክምና ስለማይሰጥ	
218	ህመምዎ ቲቢ መሆኑ የተረጋገጠዉ መቼ ነበር?	_____ቀን/ወር/ዓም / ----------ቀናት/ሳምንት/ወር በፊት	
219	ህመምዎ ቲቢ አንደሚሆን ጠርጥረዉ ነበር?	1. አዎን 2. አይደለም	
220	ህመምዎ ቲቢ ነዉ ሲባሉ ምን ተሰማዎ?	1. ፍርሃት 4. ተስፋ መቁረጥ 2. ሃፍረት 5. ሌላ---------- 3. ምንም አልተሰማኝም	
221	ህመምዎ ቲቢ መሆኑ የተረጋገጠዉ የት ነበር?	1. ጤና ጣቢያ 3. የግል ክሊኒክ/ሆስፒታል 2. ሆስፒታል 4. ሌላ-------	
222	ቲቢ እስኪረጋገጥ ድረስ በአጠቃላይ **<u>ወደ ስንት ጤና ተቋማት</u>** ሄዱ?	_____ ***የሄዱባቸዉን ተቋማት ብዛት ያስታዉሱ***	
223	ቲቢ እስኪረጋገጥ ድረስ በአጠቃላይ ወደ ጤና ተቋም **<u>ስንት ጊዜ</u>** ተመላለሱ? **/የሄዱባቸዉን ተቋማት በማስታወስ እርዳ/ጂ**	---------- ***በየተቋማቱ ያደረጉትን ምልልስ ብዛት ይጠይቁ***	
224	በአጠቃላይ **<u>ህመሙ ከጀመርዎ አንስቶ ቲቢ እስኪረጋገጥ</u>** ድረስ ምን ያህል ጊዜ ፈጅቦዎ?	_____ቀናት/ሳምንት/ወራት	
225	ለህመሙ **<u>የጤና ተቋም መጀመሪያ ከሄዱ ጊዜ አንስቶ ቲቢ</u>**	_____ቀናት/ሳምንት/ወራት	

	<u>እስኪረጋጥ</u> ምን ያህል ጊዜ ፈጅብዎ?		
226	ወደ **<u>ጤና ተቋም ከሄዱ በኋላ ቲቢ እስኪረጋጥ</u>**የዘገዩ ይመስሎታል?	1. አዎን 2. አይደለም ⟶	228
227	የዘገዩ ወይም ረጅም ጊዜ የወሰደ ከመሰልዎት የዘገየበት ወይም ቶሎ ያልተረጋገጠበት ምክንያት ምንድነዉ ይላሉ? ***ምርጫ አይነበብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	1. ባለሙያዎች በሽታዉን መለየት ስላልቻሉ 2. ለምርመራ የሚያስፈልጉ ግብዐቶች እጥረት 3. አላስፈላጊ መድሃኒቶች መስጠታቸዉ 4. ወደ ተለያዩ ጤና ተቋማት ሪፈር ሲደረግ ቆይቼ 5. ሌላ ይጠቀስ----------	
228	በቤተሰብዎ ዉስጥ የእርስዎን ዓይነት ህመም የሚያመዉ ሰዉ አለ?	ነ. አዎን/ስንት ናቸዉ---------- 2. አይደለም ⟶	231
229	የታመመ ካለ ወደ ህክምና ተቋም ሄደዋል/ተመርምረዋል?	ነ. አዎን ⟶ 2. አይደለም	231
230	ወደህክምና ያልሄዱት ለምንድነዉ? ***ምርጫ አይነበብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	ነ. ከእኔ መድሃኒት ስለወሰዱ 2. የህክምና ወጪዉ ዉድ ስለሆነ 3. ታማሚዎቹ እምቢ ብለዉ 4. ሌላ----------	

231. የቲቢ በሽታ እስኪረጋገጠልዎ ድረስ ወደ ተለያዩ ቦታዎች ወይም ጤና ተቋም በተመላለሱበት ወቅት ቲቢ የተረጋገጠበትን ዕለት ጨምሮ ምን ያህል ከፈሉ፡፡

ምልልስ	ምርመራ/ህክምና የተሰጠበት ቦታ	የፈጀብዎት ጊዜ(ቆይታ ጉዞን ጨምሮ)	አብሮዎት ሌላ ሰው ነበር(ስንት ሰዎች)	ለካርድ የከፈሉት ብር	ለተለያዩ ላቦራቶሪ ምርመራዎች (ደም፣አክታ፣ሽንት) ተ□ምሮ □ሞላ	ለራጅ ምርመራ	ለመድሃኒት	ለደርሶ መልስ ትራንስፖርት አብሮዎት ከነበሩት ሰዉ ጭምር	ለምግብና መጠጥ መንገድ ላይና ዉጤት ሲጠብቁ	ለአልጋ	ለሌሎች ወጪዎች	አጠቃላይ የአንድ ምልልስ ወጪ
ነ												
2												
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6												
7												
9												
አጠቃላይ ወጪዎች ድምር በብር												

መግለጫ፤ ***ህክምና የተሰጠበት*** ቦታ ማለት ባህል ህክምና፣ጸበል፣ ጤና ተቋም ወይም ሌላ ቦታ ማለት ነዉ፡፡ ***የፈጀዉ ጊዜ*** ማለት መንገድ ላይና በቦታዉ

የተቆየበት ማለት ነዉ፡፡ መድሃኒት ማለት በየምልልሱ የታዘዙ መድሃኒቶች ነዉ፡፡

ክፍል ሶስት፤ የቲቢ ህክምና ልምዶችና ወጪያቸዉ			
301	የቲቢ መድሃኒትዎን መዉሰድ የጀመሩት መቼ ነዉ?	_____ቀን/ወር/ዓም	
302	**ለህመሙ ጤና ተቋም ከሄዱ ጊዜ** አንስቶ የቲቢ መድሃኒቱን መዉሰድ እስኪጀምሩ ድረስ ምን ያህል ጊዜ ፈጅቦዎ?	----------ቀናት/ሳምንት/ወራት	
303	**ቲቢ ከተረጋገጠ ከምን ያህል ጊዜ በኋላ** ነበር የቲቢ መድሃኒት መዉሰድ የጀመሩት?	1. ወድያዉኑ ነዉ የጀመርኩት ⟶ 2. ----------ቀናት/ሳምንት/ወር በኋላ	305
304	የቲቢ መድሃኒቱን ወድያዉኑ ያልጀመሩት ለምንድነዉ? ***ምርጫ ኣይነብብም፣ ሌላስ በማለት ተጨማሪ ይጠየቅ***	1. መድሃኒቱን ለመጀመር ሳመነታ ቆይቼ 2. የህክምናዉን ርዝማኔ ፈርቼ 3. በጤና ተቋሙ መድሃኒት ስላልነበር 4. ጤና ተቋሙ ዝግ ስለነበር 5. መድሃኒቱን የሚሰጠኝ ባለሙያ ስላልነብር 6. የህክምና ረዳት/ዋስ ማቅረብ ስላልቻልኩ 7. ህክምናዉን ለመከታተል ቤት መከራየት ስላልቻለኩ 8. በጣም ስላመመኝ 9. ሌላ----------	
305	የቲቢ መድሃኒት መዉሰድ የጀመሩት የት ነበር?	1. በዚሁ ተቋም/ጣቢያ ⟶ 2. ሌላ (ይጠቀስ----------	308
306	የቲቢ መድሃኒቱን ለምንድነዉ ሌላ ቦታ የጀመሩት?	1. ቲቢዉ የተረጋገጠበት ቦታ መዉሰድ ግድ ስለሆነ 2. በወቅቱ በጣም ስላመመኝና ተኝቼ መዉሰድ ስለነበረብኝ 3. መድሃኒቱ በወቅቱ እዚህ ስላልነበረ 4. በወቅቱ እዝያ አካባቢ ስለነበርኩ 5. ሌላ----------	
307	ለምን ያህል ጊዜ ነበር በዚያ ጣቢያ መድሃኒቱን የተከታተሉት?	_____ቀናት/ሳምንት/ወራት	
308	የቲቢ መድሃኒቱን እንዴት ነበር/ነዉ የወሰዱት/እየወሰዱ የነበር?	1. ሆስፒታል ተኝቼ 2. ተመላልሼ ⟶	312
309	ለምን ያህል ጊዜ ነበር የተኙት?	----------ቀናት/ሳምንት/ወራት	
310	በሆስፒታሉ ሌላ ሰዉ/ አስታማሚ/ ከእርስዎ ጋር ቆይቶ ነበር/ሩ?	1. አዎን (ስንት? ----------ለ-----ቀናት 2. አልነበረም	
311	የቲቢ መድሃኒት ለመዉሰድ **<u>ሆስፒታል በተኙበት ጊዜ</u>** በአጠቃላይ ለእርስዎና አስታማሚዎ ለሚከተሉት ጉዳዮች ምን ያህል ብር ከፈሉ?	1. ለምግብ---------- 2. ለመኝታ ---------- 3. ለላብራቶሪ ምርመራዎች------- 4. ለመድሃኒት---------- 5. ለሆስፒታል አገልግሎት--------- 6. ሌላ---------- 7. ምንም አልከፈልኩም 8. አላስታዉስም	
312	አሁን መድሃኒት የሚወስዱበት ይህ ጣቢያ ከቤትዎ ምን ያህል ይርቃል?	_____ሰዓት/ደቂቃ በእግር /በትራንስፖርት----------/ኪሜ/	

313	የቲቢ መድሃኒት ለመዉሰድ ሲመጡ በአጠቃላይ ለአንድ ምልልስ ምን ያህል ጊዜ ይፈጃሉ?/ ***ደርሶ መልሰ ጉዞን በማሰላት ይምላ***	ደርሶ መልስ ጉዞ------ደቂቃ/ሰዓት እግር ጉዞ/በመኪና በህክምና ጣቢያ የቆዩበት _____ደቂቃ፤ በድምሩ---------ሰዓት	
314	መድሃኒት ለመዉሰድ ሲመላለሱ የቤተሰብ አባል/ህክምና ረዳት/ሌላ አብርዎት/በምትክዎ መድሃኒት አምጥተዉ ያዉቃሉ?	1. አዎን **/ከሆነ ለምን ያህል ጊዜ ነዉ** ---------- 2. አይደለም → 316	
315	ተጨማሪ ሰዉ አብርዎት/ተክትዎት የሄዱት ለምንድን ነዉ ?	1. ብቻዬን /ሙሉ በሙሉ መሄድ ስላልቻልኩ 2. ለደህንነቱ ስለምፈራ 3. ለህክምና አሰጣጥ የግድ ስለሆነ 4. ሌላ-----	
316	የቲቢ መድሃኒት በጀመሩበት ወይም መድሃኒቱን እየወሰዱ ባሉበት ወቅት የሚከተሉት ጉዳዮች ተነግርዎት ነበር? ***(እያንዳንዱን ጠይቅ/ቂና የተመለሱት ይከበቡ)***	1. ህክምና መከታተል የሚፈልጉበት ቦታ 2. መድሃኒት ሲወስዱ የሚከታተልልዎ/የሚያይዎ ሰዉ ምርጫ 3. የህክምናዉ እርዝማኔ 4. የሚወስዱት መድሃኒት ዓይነትና ብዛት 5. የመድሀኒቶቹ አወሳሰድ መጠን 6. መድሃኒቶቹ ስለሚያስከትሉት ጎንዮሽ ጉዳት 7. መድሃኒቱን በሌላ ሰዉ/ባለሙያ ፊት መዉሰድ እንዳለብዎ 8. ተደጋጋሚ የአክታና ሌሎች ምርመራ አስፈላጊነት 9. ቲቢን ለሌላ ሰዉ ላለማስተላለፍ የሚደረግ ጥንቃቄ 10. መድሃኒቱን በአግባቡና ሳያቋርጡ የመዉሰድ አስፈላጊነት 11. መደሃኒቱን በአግባቡ ያለመዉሰድ የሚያመጣቸዉ ጉዳቶች 12. ስለቲቢ ምንነት/መነሻዉና ምልክቶቹ 13. ሌሎች መመርመር ስላለባቸዉ ቤተሰብ አባላት 14. ቲቢ የሚድን በሽታ መሆኑን 15. ስለቲቢ መድሃኒትና ህክምና ወጪ 16. ሌላ----------	

ክፍል አራት፤ ቀጥተኛ ያልሆኑ የቲቢ ህክምና አገልግሎት ፍለጋ፤ ምርመራና ህክምና ወጪዎች			
401	መደበኛ ስራዎ ምንድነዉ?	ነ. የመንግስት/ግል ተቀጣሪ 7. ተማሪ 7. ሌላ---------- 2. አርሶ አደር 5. ነጋዴ 3. የቀን ሰራተኛ 6. የለኝም	
402	ከመደበኛ ስራ ዉጭ ሌላ **ተጨማሪ /የትርፍ ሰዓት ስራ፣ ስልጠና፣ጥገናዎች፣ ንግድ ሌላ /** ስራ ይሰራሉ?	ነ. አዎን 2. አልሰራም	
403	መደበኛም ሆነ ተጨማሪ ስራዎን ሁል ጊዜ ይሰራሉ?	1. አዎን ⟶ 2. አይደለም	406
404	መደበኛ/ተጨማሪ ስራዎን ሁልጊዜ ያልሰሩት ለምንድነዉ?	1. በቲቢ ህመም ምክንያት 2. ሌላ----------	
405	መደበኛ ስራዎን ሙሉ በሙሉ ሲሰሩ የነበሩት መቼ ነዉ ?	1. ----------ቀን/ወር/ዓም 2. ---------ቀናት/ሳምንት/ወር በፊት	
406	ቲቢ **ከመታመምዎ በፊት** በቀን ምን ያህል ሰዓት ይሰራሉ?	----------ሰዓት በቀን	
407	ቲቢ **ከታመሙ በኋላስ** በቀን ምን ያህል ሰዓት ይሰራሉ?	----------ሰዓት በቀን	
408	**የስራ ሰዓቱ ልዩነት ካለዉ፤** ልዩነቱ በቲቢ ምክንያት ነዉ?	ነ. አዎን 2. አይደለም	
409	በቲቢ ህመምና ህክምና ምክንያት ስራ አቁመዉ ነበር?	3. አዎን 2. አይደለም ⟶	413
410	አቁመዉ ከሆነ፤ ለምን ያህል ጊዜ ነበር ያቆሙት?	----------ቀን/ሳምንት/ወራት	
411	በእርስዎ ይሸፈን የነበረዉን የቤት ወይም ሌላ ስራ ማን ነበር የሚሰራልዎ?	ነ. የቤተሰብ አባል 3. የተቀጠረ ቅጥረኛ 5. ሌላ 2. ተወካይ 4. ማንም አልሰራልኝም	
412	ስራዎትን በማቆምዎ ምን ያህል ገቢ ያጡ ይመስልዎታል?	ነ. ከመደበኛ ስራ---------- ብር በቀን/ወር/ ዓመት 2. ከተጨማሪ ስራ----------ብር በቀን/ወር/ ዓመት	
413	ከቤተሰብ አባልዎ በእርስዎ ቲቢ ህመም ምክንያት መደበኛ ስራቸዉን አቁመዉ ነበር?	ነ. አዎን /ስንት ናቸዉ---------- 2. አይደለም ⟶	501
414	ስራቸዉን ያቆሙት ዋና ስራቸዉ ምንድነዉ?	ነ. የመንግስት/ግል ተቀጣሪ 7. ተማሪ 7. ሌላ---------- 2. አርሶ አደር 5. ነጋዴ 3. የቀን ሰራተኛ 6. የለኝም	
415	ለምን ያህል ጊዜ ነበር ስራቸዉን ያቆሙት?	----------ቀናት/ሳምንት/ወራት	
416	የቤተሰብ አባልዎ ስራቸዉን ባለመስራታቸዉ ምን ያህል ገቢ ያጡ ይመስሎታል?/ ***አባላቱን በመዘርዘር ይጠየቅ***	1. _____ብር 2. አላዉቅም	
ክፍል 5፡ የቤተሰብ ገቢ፣ ወጪና አጠቃላይ ሁኔታዎች			
501	የቤታችሁ አባወራ ማን ነዉ?	ነ. እኔ/ታማሚዉ 3. አባቴ 5. ወንድሜ/እህቴ 2. ባለቤቴ 4. እናቴ 6. ሌላ----------	
502	የቤተሰቡ ዋና ገቢ ምንጭ/ዋና ገቢ የሚያገኝ ማን ነዉ?	ነ. እኔ/ታማሚዉ 3. አባቴ 5. ወንድሜ/እህቴ 2. ባለቤቴ 4. እናቴ 6. ሌላ----------	
503	የቤቱ ዋና ገቢ ምንጭ ከፍተኛ የት/ርት ደረጃዉ ምንድነዉ?	ነ. ምንም ያልተማረ 2. የመጀመሪያ ሳይክል ያጠናቀቀ/ች (ነ-4) 3. ሁለተኛ ሳይክል ያጠናቀቀ/ች (5-8) 4. ሁለተኛ ደረጃ ያጠናቀቀ(9-ነ2) 5. የተመረቀ /ሰርትፍኬት/ዲፕሎማ/ዲግሪ	
504	የቤቱ አባወራ ከፍተኛ የት/ርት ደረጃ	ነ. ምንም ያልተማረ	

	ከዋና ገቢ ምንጩ የተለየ ከሆነ?	2. የመጀመሪያ ሳይክል ያጠናቀቀ/ች (1-4) 3. ሁለተኛ ሳይክል ያጠናቀቀ/ች (5-8) 4. ሁለተኛ ደረጃ ያጠናቀቀ(9-12) 5. የተመረቀ /ሰርትፍከት/ዲፕሎማ/ዲግሪ	
505	በቤታችሁ በመደበኛነት ስንት ሰዎች ይተኛሉ/ይኖራሉ?	_____	
506	ከቤታችሁ ሰርተዉ የሚከፈላቸዉ አባላት ስንት ናቸዉ/ታማሚዉን ጨምሮ	_____	
507	እርስዎና በተሰብዎ በአጠቃላይ ከመደበኛና ተጨማሪ ስራዎች በዓመት ምን ያህል ገቢ ታገኛላችሁ? የቤተሰብ አባላት በማሰታወስ ገቢያቸዉ ይሞላ።። ***ገቢ ለማይታወቁት የዓመቱን ሽያጭ ገቢዎች በመጠየቅ ይሞላ***	1. የታማሚዉ ገቢ ---------- ሌላ ገቢ---------- 2. የሌሎች አባላት ገቢ---------- ድምር----------	
508	የቲቢ በሽታ የበተሰባችሁን ገቢ የቀነሰ ይመስልዎታል?	1. አዎን 2. አይደለም	
509	ከእርስዎ በተጨማሪ ሌላ ለቲቢ የሚታከም ሰዉ በቤቱ አለ?	1. አዎን/ስንት ናቸዉ---------- 2. የለም	
ክፍል 6፡ በቲቢ ምክንያት ለተከሰቱ ወጪዎች የተሰጠ ምላሽና ህመሙ ያስከተላቸዉ ቀዉሶች			
601	የቲቢ ህመምና ህክምና በእርስዎና ቤተሰብዎ ላይ በአጠቃላይ ምን ያህል ወጪ አስከተለብዎ?	ነ. ----------ብር 2. አላዉቅም	
602	የቲቢ ህመምና ህክምና ወጪዎችን እንዴት ይገልፀታል ? ***በቀጥታ ከክሰ የወጣና በለመሰራታቸዉ ያጡትን ገቢ ጭምር***	ነ. በጣም ዉድ 3. እርካሽ 2. መጠነኛ 4. ነፃ	
603	የቲቢ ህመምና ህክምና ያስከተለቦትን ወጪዎችን ለመሸፈን እርስዎ/ቤተሰብዎ ምን ምን እርምጃ ወሰዱ? ***ከአንድ በላይ ምላሽ ሊኖረዉ ይችላል*** ***ለተመለሱት የብር መጠኑ ይሞላ***	1. ንብረቶችን/ምርት መሸጥ 2. የገንዘብ እርዳታ ወሰድኩ /ስንት?----------ብር 3. የተቆጠበ ገንዘብ መጠቀም/----------ብር 4. ገንዘብ መበደር/----------ብር 5. ስራ መቀየር/ተጨማሪ ገቢ ለማግኘት 6. የምግብ ፍጆታ ወጪ መቀነስ 7. ከትምህርት ማቋረጥ 8. ሌላ----------	607
604	***ንብረት/ምርት የተሸጠ ከሆነ፤*** ምን ነበር የሸጡት? ***/ከአንድ በላይ ንብረት ሊሆን ስለሚችል ሌላስ በማለት ጠየቅ/ቂ***	ነ. መሬት 5. መኪና/ተሽከሪካሪ 2. ከብቶች/ብዛት-------- 6. ምርት 3. የቤት ዕቃ/ይጠቀስ---------- 7. ሌላ	
605	የተሸጡ ንብረቶች/ምርት የዋጋ ግምት ምን ያህል ነበር?	_____	
606	ንብረቶቹ በምን ያህል ብር ተሸጡ? ***የተሸጡትን ደምር/ሪ***	_____	
607	የቲቢ በሽታ የግል/ማህበራዊ ህይወትዎን ጎድቶታል ይላሉ?	ነ. አዎን 2. አይደለም →	609
608	ጎድቶት ከሆነ፤ ምን ምን ችግሮን አስከትሏል ይላሉ?	ነ. ከትዳር መፋታት/መለያየት 4. የስራ መፈናቀል/ማጣት 2. የወሲብ ህይወት መዛባት 5. የገቢ መቀነስ 3. ከት/ርት ማቋረጥ 6. ሌላ----------	
609	መንግስት/ረጂ ድርጅት በቲቢ ምክንያት የሚከሰተዉን ወጪ ለመደገፍ ቢፈልግ ምን ድጋፍ ለእርስዎ/ቤተሰብዎ ቢደረግ	ነ. ትራንስፖርት 5. የት/ርት	

	ይመርጣሉ? ***አማራጮቹ ይነበባሉ***/ከአንድ በላይ ምላሽ ሊኖር ይችላል፡፡	2. ምግብ 6. ከቲቢ ዉጭ ሌሎች መድሃኒቶች 3. የተቀላጠፈ አገልግሎት 4. ሌላ----------	
ክፍል 7፡ የቲቢ በሽታ ግንዛቤ፣ ዕዉቀትና አመለካከት			
701	እየታከሙ ያሉት በሽታ ምንድነዉ?	1. ቲቢ 4. አላዉቅም 2. የሳንባ ምች 5. ሌላ---- 3. ብርድ	
702	ስለ ቲቢ በሽታ ሰምተዉ ያዉቃሉ?	1. አዎን 2. አላዉቅም ⟶	704
703	ከየት ነዉ ስለ ቲቢ የሰሙት? ***ከአንድ በላይ ምላሽ ሊኖረዉ ይችላል***	1. ከመገናኛ ብዙሃን(ሬድዮ፣ቲቪ፣ጋዜጣ ወዘተ) 2. የጤና ጥበቃ ብሮሸሮች፣ በራሪ ወረቀት ወዘተ 3. የጤና ኤክስቴንሽን 7. ሌላ---------- 4. ከጤና ተቋማት 5. ጓደኛ/ዘመድ 6. ቲቢ ታማሚ ጓደኛ/ዘመድ	
704	ቲቢ በምን የሚመጣ ይመስሎታል?	1. በባክቴሪያ 4. በፋንገስ 5. በቫይረስ 2. ስጋራ በማጨስ 6. በእርግማን 3. ለብርድ በመጋለጥ 7. አላዉቅም 8. ሌላ-------	
705	የቲቢ በሽታ ይተላለፋል?	1. አዎን 2. አይደለም ⟶	707
706	የሚተላለፍ ከሆነ እንዴት ነዉ የሚተላለፈዉ? ***ምርጫ አይነበብም ግን ከአንድ በላይ ምላሽ ሊኖረዉ ስለሚችል ሌላስ በማለት ይጠየቅ***	ı. በትንፋሽ 6. ዕቃዎችን በጋራ በመጠቀም 2. በመነካካት 7. በምግብ 3. በግብሬ ስጋ ግኑኝነት 8. በወባ ትንኝ ንክሻ 4. ያልተፈላ ወተት በመጠጣት 5. አላዉቅም 9. ሌላ----------	
707	የቲቢ በሽታ ያለበት ሰዉ ምን ምን ምልክቶች ያሳያል? ***ከአንድ በላይ ምላሽ ሊኖረዉ ስለሚችል ሌላስ በማለት ጠይቅ/ቂ፡ምርጫ አይነበብም***	1. ከ2ሳምንት በላይ የቆዬ ሳል 7. ትኩሳት 2. ደም የቀላቀለ አክታ ያለዉ ሳል 8. አላዉቅም 3. የክብደት መቀነስ 9. ሌላ---------- 4. የምግብ ፍላጎት መቀነስ 5. ማታ ማታ ማላብ 6. የደረት ህመም/ዉጋት	
708	የቲቢ በሽታ በዘር ይወረሳል?	1. አዎን 2. አይደለም	
709	የቲቢ መከላከያ ክትባት አለዉ?	1. አዎን 2. አላዉቅም	
710	የቲቢ ህክምና አሰጣጥ እንዴት ነዉ/በክፍያ/ነጻ?	2. በነጻ 2. በክፍያ	
711	የቲቢ ህክምና የሚሰጠዉ ለምን ያህል ጊዜ ነዉ?	---------- 2. አላዉቅም	
712	የቲቢ መድሃኒት ዓይነቶችን ያዉቃሉ?	1. አዎን 2. አላዉቅም	
713	ቲቢ የሚድን በሽታ ነዉ?	ı. አዎን 2. አላዉቅም	

Patient followup questionnaire

No	Questionnaire ID						
001	Zone	1. Kaffa	Bench-Maji	Sheka			
002	Woreda	1. Bonga town 2. Decha 3. Chena	4. Mizan Aman 5. North Bench 6. Shey Bench 7. Meint Goldiya	8. Tepi town 9. Yeki 10. Masha			
003	Name of health facility	1. Hospital 2. Health center 3. Health post 4. Other(specify--------					
004	Date of interview (dd/mm/yy)						
005	Name and signature of data collector						
006	Name and signature of supervisor						

Unit TB register review (fill what has been documented after the treatment intiation)

007	TB unit number		Date anti-TB started_____dd/mm/yy		
008	Sputum Smear result	Test time	Result	Lab number	
		End of 2nd month	1. Positive 2. Negative 3. Not available		
		End of 5th month	1. Positive 2. Negative 3. Not available		
		End of treatment	1. Positive 2. Negative 3. Not available		
009	Weight (Kg)	Time of measurement	Weight (Kg)		
		End of 2nd month			
		End of 5th month			
		End of treatment			
010	HIV test result	2. Reactive 2. Non-reactive 3. Not available			
011	HIV care enrolled	1. Yes 2. No 3. NA if Yes when_____dd/mm/yy			
012	CPT started	1. Yes 2. No 3. NA if Yes when_____dd/mm/yy			
013	ART started	1. Yes 2. No 3. NA if Yes when_____dd/mm/yy		ART no	
014	Recorded number of attendance	Intensive phase	Continuation phase		
015	Treatment outcome	1. Cured 2. Completed 3. Lost to follow-up 4. Transferred out	5. Treatment Failure 6. Died 7. Other specify----		
016	Date outcome ascertained (dd/mm/yy)				

Medical record number (MRN)	

Number of Visits after TB DX			
Date of Visit (dd/mm/yy)	Reason for visit /diagnosis	Investigations/ Treatment prescribed	Unit cost

Patient follow-up interview questionnaire

801	Date of follow up (dd/mm/yy)			
802	Place follow up made	1. Home 2. Health facility		
803	Outcome of follow up	1. Patient traced and interviewed 2. Patient transferred to other treatment center 3. Patient lost to follow-up 4. Treatment failed and regimen changed 5. Patient died		Stop
804	Person interviewed	1. Patient 2. Parents/care giver 3. Treatment supporter 4. Other (specify----------		
805	From where were you getting the required drugs?	During intensive phase	Continuation phase	
		1. This center 2. Health post 3. Other (--------	1. This center 2. Health post 3. Other (--------	
806	How frequent were you picking the anti-TB drugs	During intensive phase	Continuation phase	
		1. Daily 2. Every three days 3. Weekly 4. Other ----------	1. Daily 2. Every three days 3. Weekly 4. Monthly	
807	Were you ever been observed by someone while you took the anti-TB drugs	1. Yes 2. No →		810
808	While you were taking your medicines,	During intensive phase	Continuation phase	

	In how many occasions did someone observe you?	1. All occasions 2. Occasionally 3. None of the occasions 4. Other ----------	1. All occasions 2. Occasionally 3. None of the occasions 4. Other ----------	
809	Who were observing you while you took the anti-TB drugs?	During intensive phase	Continuation phase	
		1. Health care provider 2. HEW 3. Treatment supporter 4. Family member 5. No one 6. Other ----------	1. Health care provider 2. HEW 3. Treatment supporter 4. Family member 5. No one 6. Other ----------	
810	While you visit HCF for collecting anti-TB drugs, how long time you elapse for a single visit	During intensive phase	Continuation phase	
		Round trip travel-------min Waiting time--------min	Round trip travel-------min Waiting time--------min	
811	During your visits for anti-TB drug collection, how much ETB did pay in total for the following? **Note: transport, food , accommodation includes those incurred for accompanies if any**	During intensive phase	Continuation phase	
		1. Service fee---- 2. TB drug-------- 3. Sputum test------ 4. Other lab tests--- 5. Other drugs------ 6. Lodging-------- 7. Food---------- 8. Transport (round trip)- 9. Other ------	1. Service fee---- 2. TB drug-------- 3. Sputum test------ 4. Other lab tests--- 5. Other drugs------ 6. Lodging-------- 7. Food---------- 8. Transport (round trip)- 9. Other ------	
812	After you initiated anti-TB treatment, have encountered any other illness?	1. Yes 2. No →		815
813	Have you sought care for the illness?	1. Yes 2. No		
814	How much did you pay for the investigations and drugs during the care seeking and treatment?	Consultation------- transport------lodging----- Laboratory tests------- food ------ other------- Drugs ----- Total----------		
815	Have you commenced your regular work?	1. Yes 2. No →		Finish
816	When did you start the work?	1. _____dd/mm/yy 2. After ----------days/weeks/months treatment		

በቲቢ ህክምና ላይ ያሉ ታማሚዎች መከታተያ መጠይቅ							
ተቁ	የመጠይቅ መለያ						
001	ዞን	2. ካፋ	2. በንች ማጂ	3. ሸካ			
002	ወረዳ	4. ቦንጋ ከተማ 5. ደቻ 6. ጨና	4. ሚዛን አማን 5. ሰሜን በንች 6. ሽይ በንች 7. ሜኢኒት ጎልድያ	8. ቴፒ ከተማ 9. የኪ 10. ማሻ			
003	የጤና ተቋሙ ስም						
004	የጤና ተቋሙ ዓይነት	2. ሆስፒታል	2. ጤና ጣቢያ	3. ጤና ኬላ	4. ሌላ ይጠቀስ----------		
005	መጠይቁ የተሞላበት ቀን			የተቆጣጣሪዉ ስም_____			
006	መረጃ ሰብሳቢ ስምና ፊርማ			ፊርማ፡ _____			
Unit TB register review (fill what has been documented after the treatment intiation)							
007	TB unit number		Date anti-TB started_____dd/mm/yy				
008	Sputum Smear result	Test time	Result			Lab number	
		End of 2nd month	2. Positive 2. Negative 3. Not available				
		End of 5th month	2. Positive 2. Negative 3. Not available				
		End of treatment	2. Positive 2. Negative 3. Not available				
009	Weight (Kg)	Time of measurement	Weight (Kg)				
		End of 2nd month					
		End of 5th month					
		End of treatment					
010	HIV test result	3. Reactive	2. Non-reactive	3. Not available			
011	HIV care enrolled	2. Yes 2. No 3. NA if Yes when_____dd/mm/yy					
012	CPT started	2. Yes 2. No 3. NA if Yes when_____dd/mm/yy					
013	ART started	2. Yes 2. No 3. NA if Yes when_____dd/mm/yy			ART no		
014	Recorded number of attendance	Intensive phase	Continuation phase				
015	Treatment outcome	5. Cured 6. Completed 7. Lost to follow-up 8. Transferred out	5. Treatment Failure 6. Died 7. Other specify----				
016	Date outcome ascertained (dd/mm/yy)						

Medical record number (MRN)	

Number of Visits after TB DX			
Date of Visit (dd/mm/yy)	Reason for visit /diagnosis	Investigations/ Treatment prescribed	Unit cost

የታማሚ ወይም አስታማሚዎች ክትትል መጠይቅ

801	ክትትሉ የተደረገበት ጊዜ/ቀን/ወር/ዓም/			
802	ክትትሉ የተደረገበት ቦታ	2. የታማሚ ቤት 2. በጤና ተቀም 3. ሌላ ካለ ይገለፅ----		
803	የክትትሉ ዉጤት	6. ታማሚዉ ተሻሽቶ ተጠይቋል 7. ታማሚዉ ወደ ሌላ ህክምና ጣቢያ ተዛዉሯል /ይጠቀስ---------- 8. ታማሚዉ ህክምናዉን አቋርጧል 9. ታማሚዉ ህክምናዉን ቀይሯል 10. ታማሚዉ ሞቷል		አቁም
804	ቃለ መጠየቁ የተደረገለት ሰዉ	5. ታማሚዉ 3. የህክምና ረዳት 6. የቤተሰብ አባል/ይጠቀስ---------- 4. ሌላ ይገለፅ----------		
805	የሚያስፈልጎትን መድሃኒት መጠን ከየት ነበር የሚያገኙት ?	በመጀመሪያ ሁለት ወራት	ቀጣይ አራት ወራት	
		4. እዝሁ ጣቢያ 5. ጤና ከላ 6. ሌላ ----------	1. እዝሁ ጣቢያ 2. ጤና ከላ 3. ሌላ ----------	
806	የሚያስፈልጎትን መድሃኒት መጠን በምን ያህል ጊዜ ነበር የሚያገኙት ?	በመጀመሪያ ሁለት ወራት	ቀጣይ አራት ወራት	
		5. በየቀኑ 6. በየሶስት ቀን 7. በየሳምንቱ 8. ሌላ ይጠቀስ.....	5. በየቀኑ 6. በየሶስት ቀን 7. በየሳምንቱ 8. በየወሩ	
807	መድሃኒት በሚዉጡበት ጊዜ ሌላ ሰዉ አይቶት ያዉቃል?	1. አዎን 2. አይደለም →		810
808	ባለፉት የመድሃኒት አወሳሰድ ወቅት መድሃኒትዎን ሲዉጡ ሌላ ሰዉ ለምን ያህል ጊዜ ነበር ያየዎት?	በመጀመሪያ ሁለት ወራት	ቀጣይ አራት ወራት	
		5. ሁሉም ጊዜ 6. አልፎ አልፎ 7. አንድም ቀን አልታየሁም 8. ሌላ----------	1. ሁሉም ጊዜ 2. አልፎ አልፎ 3. አንድም ቀን አልታየሁም → 4. ሌላ----------	
809	መድሃኒትዎን ሲዉጡ አብዛኛዉን ጊዜ የሚከታተልዎ/	በመጀመሪያ ሁለት ወራት	ቀጣይ አራት ወራት	

	የሚያይዎ ማን ነበር?	7. የጤና ባለሙያ 8. ጤና ኤክስቴንሽን ሰራተኛ 9. የህክምና ረዳት 10. ቤተሰብ/ዘመድ 11. ማንም አላየኝም 12. ሌላ----------	1. የጤና ባለሙያ 2. ጤና ኤክስቴንሽን ሰራተኛ 3. የህክምና ረዳት 4. ቤተሰብ/ዘመድ 5. ማንም አላየኝም 6. ሌላ----------	
810	መድሃኒት ለመዉሰድ ሲመላለሱ በአንድ ምልልስ ለጉዞ በመንገድ ላይና መድሃኒት ለመዉሰድ በአጠቃለይ ምን ያህል ጊዜ ይወስድበዎት ነበር?	በመጀመሪያ ሁለት ወራት ደርሶ መልስ ጉዞ----------ደቂቃ በጣቢያዉ----------ደቂቃ	ቀጣይ አራት ወራት ደርሶ መልስ ጉዞ----------ደቂቃ በጣቢያዉ----------ደቂቃ	
811	**ቲቢ መድሃኒት መዉሰድ ከጀመሩ በኋላ መድሃኒት ለመዉሰድ** ሲመላለሱ እስካሁን ለሚከተሉት ጉዳዮች ምን ያህል ብር ከፈሉ? **/ትራንስፖርት፣ ምግብ፣ መኝታ ሌላ ተጨማሪ ሰዉ አብረዉ ከነበሩ የእነሱን ጭምር ይሞላ**	በመጀመሪያ ሁለት ወራት 10. አገልግሎት ክፍያ---------- 11. ለቲቢ መድሃኒት--------- 12. ለአክታ ምርመራ--------- 13. ሌላ ላብራቶሪ ምርመራ------ 14. ከቲቢ ዉጭ መድሃኒት ----- 15. ለመኝታ/ማደሪያ---------- 16. ምግብ በመንገድ ላይ-------- 17. ለትራንስፖርት **/አንድ ደርሶ መልስ** /---------- 18. ሌላ----------	ቀጣይ አራት ወራት 1. አገልግሎት ክፍያ---------- 2. ለቲቢ መድሃኒት--------- 3. ለአክታ ምርመራ--------- 4. ሌላ ላብራቶሪ ምርመራ------ 5. ከቲቢ ዉጭ መድሃኒት ----- 6. ለመኝታ/ማደሪያ---------- 7. ምግብ በመንገድ ላይ-------- 8. ለትራንስፖርት **/አንድ ደርሶ መልስ** /---------- 9. ሌላ----------	
812	የቲቢ መድሃኒት መዉሰድ ከጀመሩ በኋላ ሌላ ህመም አመዎት ያዉቃል?	3. አዎን 4. አይደለም ⟶		815
813	ለህመሙ ህክምና እርዳታ አግኝተዉ ነበር?	1. አዎን 2. አይደለም		
814	ለህመሙ ህክምና፣ ምርመራና መድሃኒት ምን ያህል ብር ከፈሉ?	ለካርድ-------- ለትራንስፖርት--------- ሌሎች ወጪዎች--------- ላብራቶሪ-------- ለምግብና መጠጥ------- ድምር---------- መድሃኒት-------- ለማደሪያ----------		
815	የቲቢ መድሃኒት ከጀመሩ በኋላ የዘወትር ተግባርዎን/ስራዎን ይሰራሉ?	2. አዎን 3. አይደለም ⟶		ጨርስ
816	መቼ ነዉ የዘወትር ተግባርዎን/ስራዎን የጀመሩት?	----------ቀን/ወር----------ቀናት/ሳምንታት/ ወራት በኋላ		

Patient record review/data extraction checklist											
Name of data collector						**Name of supervisor**					
Name of the facility					**Type of facility**			1. Hospital 2. Health center 3. Health post 4. Other-----)			
Zone		1. Kaffa 2. Bench Maji 3. Sheka			**Wereda**	1. Bonga Town 2. Decha 3. Ginbo 4. Chena	5. Mizan Aman 6. Debub Bench 7. Sheybench 8. Sheko	9. Semen Bench 10. Tepi town 11. Yeki			
Patient serial number		01	02	03	04	05	06	07	08	09	10
Date of extraction (dd/mm/yy)											
Patient Unit TB registration number											
Sex (1. Male 2. Female)	1										
Age	2										
Wereda of patient	3										
Kebele of patient	4										
Smear result (1. Pos 2. Neg. 3.not available (NA)	5										
Baseline weight	6										
Treatment category 1. New 2. Transfer in 3. Other	7										
Type of TB 1. PTB+ 2. PTBN 3. EP	8										
Drugs 1. ERHZ 2. Other ---	9										
Dose (# of tabs)	10										
Date treatment started	11										
# of attendance counts (intensive)	12										
Date intensive ended (dd/mm/yy)	13										
HIV test offered (1. Yes 2. No)	14										

HIV test result 1. R 2. NR → **22**	15										
Enrolled for HIV care 1. Yes 2. No	16										
CPT started 1. Yes 2. No	17										
Date CPT started	18										
ART started (1. Yes 2. No)	19										
ART unique number	20										
Date ART started	21										
Weight 2nd month	22										
Weight 5th month	23										
Weight 6th /7th month	24										
Sputum result end of 2nd month 1. Positive 2. Negative 3.NA	25										
Sputum result end of 5th month 1. Positive 2. Negative 3.NA	26										
Sputum result end of 6th /7th month 1. Positive 2. Negative 3.NA	28										
Date continuation started	29										
Drugs (continuation) 1. HE 2. RH	30										
Dose/#of tabs	31										
# of visits recorded	32										
Treatment outcome 1. Cure 2.Complete 3.Default 5. Death 6. TO 7. Failure	33										
Date outcome ascertained (dd/mm/yy)	34										

Annex 4: Assurance of principal investigator

I, the undersigned, declare that this is my original work, has never been presented in this or any other University for fulfillment of any degree, and that all the resources and materials used for the thesis, have been fully acknowledged.

Name of the PhD student: Abyot Asres

Signature: _____

Date: _____

Approval of the primary Supervisor

Name of the primary Supervisor: **Wakgari Deressa (PhD, Associate professor)**

Signature: _____

Date: _____