Intensive Phase Treatment Outcome and Associated Factors among Patients Treated for Multi Drug Resistant Tuberculosis in Ethiopia: A retrospective cohort study

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Abstract

Background Multi-drug resistant Tuberculosis (MDRTB) is a strain of Mycobacterium tuberculosis that is resistant to at least Rifampicin and Isoniazid drugs. The treatment success rate for MDRTB cases is lower than for drug susceptible TB. Monitoring the early treatment outcome and better understanding the specific reasons for early unfavorable treatment outcome are important to evaluate the effectiveness of tuberculosis control and preventing the emergence of extremely drug resistant tuberculosis. However, this information is scarce in Ethiopia. Therefore, this study aimed to determine the intensive phase treatment outcome and factors contributing among patients treated for MDRTB in Ethiopia. Methods A 6 year (2009 to 2014) retrospective cohort record review was conducted in fourteen treatment initiating centers in Ethiopia. The records of 751 MDRTB patients were randomly selected using simple random sampling. Data were collected using a pre-tested and structured checklist. Multivariable multinomial logistic regression model was undertaken to identify the contributing factors. Results At the end of the intensive phase, 17.3% of MDRTB patients had an unfavorable treatment outcome while 16.8% had an unknown outcome with the rest having a favorable outcome. The median duration of the intensive phase was 9.0 months (IQR 8.04-10.54). Having an unfavorable intensive phase treatment outcome was found to be more common among older aged [ARRR= 1.047, 95% CI (1.024, 1.072)] and those without a history of hypokalemia [ARRR=0.512, 95% CI (0.280, 0.939)]. Having an unknown intensive phase treatment outcome was found to be more common among those treated under the ambulatory care model [ARRR=3.2, 95% CI (1.6, 6.2)], rural dwellers [ARRR= 0.370, 95% CI (0.199, 0.66)], those without a treatment supporter [ARRR=0.022, 95% CI (0.002, 0.231)], and those with resistance to a limited number of drugs. Conclusion We observed a higher than anticipated rate of unfavorable and unknown treatment outcomes in this study. To improve favorable treatment outcome more emphasis should be given to conducting all scheduled laboratory monitoring tests, assignment of trained treatment supporters and ensuring complete recording and reporting which could be enhanced by quarterly cohort review. Older aged and rural patients need special attention. Furthermore, the sample referral network should be strengthened.

Background

Multi-Drug Resistance Tuberculosis (MDR-TB) is a strain of Mycobacterium tuberculosis that is resistant to at least rifampicin and isoniazid drugs. MDR-TB occurs either when a person is infected with a resistant strain of Mycobacterium tuberculosis (called primary MDR-TB) or when improper or inadequate treatment leads to drug selection of the resistant strain (called acquired MDR-TB)(WHO, 2013). The possible causes of inadequate treatment include provider and program related factors like inadequate regimens, lack of DST and poor access to health care (FMOH-E,2013), drug related factors like unavailability of certain drugs and poor storage conditions (FMOH-E,2013) and patient related factors, like poor adherence and lack of inadequate information(FMOH-E,2013). Primary MDR-TB, like drug susceptible TB, is transmitted through inhalation of droplet nuclei of the bacilli. The clinical manifestations of MDR-TB are similar to drug susceptible TB.
Increasing prevalence of Multi-Drug Resistance or Rifampicin Resistance Tuberculosis (MDR/RR-TB) represents a global public health emergency (WHO, 2017). With the emergence of Extensively Drug-Resistant TB (XDR-TB) further increasing the complexity for TB control programs, especially in low income countries (WHO, 2013). In 2017, an estimated 558,000 people developed MDR/RR-TB worldwide with 8.5% of estimated XDRTB (WHO, 2018). Ethiopia is among the 30 high MDR-TB burden countries with an estimated 2700 (1700-3700) MDR/RR TB cases among annually notified TB cases (WHO, 2018), the country reported 07 pre-XDRTB cases up to 2018. Its first Drug Resistance TB Survey (DRS) from 2003-2005, showed 1.6% of new cases and 11.8 % of retreatment cases were resistance to Isoniazid and Rifampicin (RH). While the second DRS (2011-2013), carried out as sentinel survey, indicated 2.3% among new and 17.8% among previously treated cases had MDR/RR-TB (FMOH-E, 2014). In line with this, the 2018 global TB report estimated 2.7% of new TB cases and 14% of previously treated cases had MDR/RR-TB in 2017. In Ethiopia, 2051 MDR/RR-TB cases were enrolled to SLD between 2009 and 2015 (FMOH-E, 2015), lower numbers than estimated.

Treatment outcomes for MDR-TB cases are poorer compared to drug-susceptible TB cases. This is due to medications used in the treatment of MDR-TB are less effective and associated with a greater number of side effects, also, treatment duration is at least 20 months which can compromise adherence (WHO, 2008; FMOH-E, 2014). Ethiopia is one of the five high MDR-TB burden countries that achieved a treatment success rate of above 70% (WHO, 2018). However, globally only 55% of patients with MDR/RR-TB in the 2015 cohort were successfully treated, as a result of high mortality and loss to follow-up (WHO, 2018).

Early sputum culture conversion, to end the intensive phase, is very important to prevent transmission of MDR-TB, reduce hospitalization time, and reduce cost for both patients and health system. Evidence has shown that delayed sputum conversion is associated with amplifications of drug resistance including XDR-TB (Temple et al., 2008). The few published studies that examined sputum conversion at two months among MDR-TB patients showed diversity with the proportion of MDRTB patients who converted to culture negative after a median time of 2 months of treatment initiation ranged from 77% to 88% (Holtz et al., 2006; Qazi et al., 2011).

Some studies indicate factors associated with failing to culture converted and unfavorable treatment outcome were older age, being male, unemployment, prisoner, alcoholism, baseline AFB smear positive and lung cavitation at baseline chest X-ray, resistance to ofloxacin and streptomycin, any history of the previous TB treatment and poor outcome of previous anti-tuberculosis treatment, smoker, drug user, HIV coinfection, lower body mass index and lower CD4 count (Kurbatova et al., 2012; Brust et al., 2011; Gandhi et al., 2012; Holtz et al., 2006; Qazi et al., 2011).

Few studies have been conducted on intensive phase treatment outcome and contributing factors among MDR-TB patients though no study has been conducted in Ethiopia despite it being one of high MDR-TB burden countries. Gaining insight in the early treatment outcome could assist the Ethiopian National TB Program to further improve the treatment success rate for MDR-TB patients in the country. At the same time, this study would also serve as a baseline for future measurement.
Therefore, this study was conducted to determine intensive phase treatment outcome and associated factors among patients treated for MDR-TB in Ethiopia.

**Methods And Materials**

**Study Setting**

This study was conducted in a random set of patients from all MDRTB treatment initiation sites in Ethiopia. The country population was estimated at 102 million in 2017, with 84% being rural [Federal Democratic Republic of Ethiopia, Population Census Commission (FDRE-PCC), 2007]. In 2018, there were 281 public hospitals, 3,622 health centers, and 16,660 health posts in the country. All the hospitals and health centers provided TB diagnosis and treatment services while 65% of health posts provided DOTs service for drug susceptible TB (FMOH-E, 2018). The MDRTB control program in Ethiopia commenced in 2009 and is an integrated part of the national TB control program. In 2015, there were 37 MDR-TB treatment initiating centers (TIC) and 477 MDR-TB treatments follow up centers (TFC) (FMOH-E, 2015). At the beginning of MDR-TB services, the programmatic approach was a hospitalized (inpatient) model of care. This shifted to a clinic based ambulatory model of care since 2013/14 (FMOH-E, 2014). In the current ambulatory model of care, temporary inpatient care is reserved for patients who develop severe adverse events during the course of treatment. In addition, patients with either serious medical condition or socio-economic reasons may also be admitted by decision of a MDRTB panel team at the TIC. At present, in the country, the duration of the intensive phase treatment is 4 months after culture conversion with a minimum of 8 months. Total duration of MDR-TB treatment should continue for a minimum of 20 months and at least 18 months after the patient becomes culture-negative—whichever is longer.

From 2009 to 2014, a total of 1559 MDR-TB patients were enrolled on second line treatment; the treatment success rate of the 2014/15 cohort was 71% (FMOH-E, 2016/17). The study was conducted on a random subset of the patients who started MDR-TB treatment between 2009 and 2014 (Figure 1).

**Study Design and Population**

A health facility-based retrospective cohort study design was used. The study population was all pulmonary MDR-TB patients who started treatment between January 1, 2009 and December 31, 2014 in all MDR-TB TICs in Ethiopia. Confirmed pulmonary MDR-TB patients based on culture and DST or Genexpert or Line Probe Assay and with positive base line culture were included in the study. Patients who transferred in were excluded from the sample.

**Sample Size and Sampling Techniques**

The sample size was calculated considering 95% Confidence level (Za/2) at 1.96; 31.6% unfavorable treatment outcome (p) [Seung et al., 2009]; 2.5% degree of precision (d); Total study population (N)=1559 and finite population correction (Daniel, 1999). Based on this, the calculated sample size was 751.

**Sampling Technique**
All the 14 MDRTB treatment initiating centers (TICs) found in Ethiopia from 2009 to till the end of 2014 were included in the study. These TICs were dispersed over the country with one found in Tigrai, 3 in Amhara, 5 in Oromia, 2 in Southern Nations and Nationality peoples’ Regional States (SNNPR), 2 in Addis Ababa and 1 in Dire Dawa City Administrations. The patient load of the Regional States and City Administrations was 83 (5.3%) in Tigrai, 272 (17.5%) in Amhara, 134 (8.5%) in Oromia, 66 (4.2%) in SNNPR, 942 (60.5%) in Addis Ababa and 62 (4%) in Dire Dawa city administrations. The sample size was proportionally distributed to each treatment initiating center based on their patient load. These TICs also hosted patients from the other five regions in the country that did not have TICs. A sampling frame for each TIC was prepared from the MDR-TB register to select the 751 patients using the simple random sampling method. The sampling procedure is pictured in Figure 2.

Measurements

The main outcome variable of this study was treatment outcome (categorized as favorable, unknown or unfavorable). The independent variables included were socio-demographic characteristics (age, sex and place of residence) and clinical conditions [type or forms of TB (smear positive or smear negative TB), HIV/AIDS status, category of TB patients (new, return after lost to follow up, treatment failure, relapse and other), weight, presence of a TB treatment supporter, treatment regimen (new versus retreatment), having co-morbidities other than HIV/AIDS, BMI, bacilli load, degree of drug resistant and X-ray findings].

Operational Definitions /definition of terms

**MDR-TB**: a strain resistant to at least Rifampicin or both Rifampicin and Isoniazid;

**Intensive phase treatment outcome**: The outcome at which injectable agent was discontinued and the patient put on an oral continuation regimen;

**Favorable treatment outcome**: The outcome at which the patient was culture converted and alive at the end of the intensive phase.

**Unknown treatment outcome**: The outcome at which sputum culture not done or sputum culture sample sent but no feedback or no result or information to assign culture converted or not;

**Unfavorable treatment outcome**: included lost to follow up, died, not evaluated, treatment terminated and culture not converted at the end of the intensive phase;

**Sputum conversion**: defined as two consecutive negative smears or cultures from samples collected at least 30 days apart.

Data collection

A pretested and structured record review checklist was used to collect the data from the MDR-TB register and treatment card. Where needed, the ART register was reviewed to complete missing information from the MDR-TB register for those HIV positive patients enrolled to chronic HIV/ART care. Data were collected
by two teams each consisting of one supervisor and two data collectors. The data collectors were trained nurses and the supervisors were trained BSc public health graduates. To enhance quality, the collected data were submitted daily to the supervisors for verification with feedback provided the following morning.

Statistical Analysis

Data were entered into and cleaned using Epidata software version 3.02 and analyzed using SPSS (Statistical Package for Social Sciences) version 20.0. Exploratory data analysis was carried out to check the level of missing values and presence of influential outliers. Multi-co linearity, normality was also checked for continuous variables. The normality of the data was checked using a histogram. For continuous and normally distributed data mean and standard deviation were reported and otherwise median and inter quartile range were reported. For categorical variables, frequencies and percentage were reported. The median duration of the intensive phase treatment and the median time of sputum culture and smear conversion were computed.

The association between the independents and dependent variables was performed first with bivariate multinomial logistic regression analysis with relative risk ratio (RRR) at 95% confidence interval and favorable, unknown and unfavorable treatment outcomes were reported.

Finally, multivariable multinomial logistic regression analysis was done to identify independent factors associated with MDR-TB intensive phase treatment outcomes. For the purpose of selecting potential candidate variables, multivariable model was constructed for variables having a P value <0.25 in the bivariate analysis. Statistical significance was considered with two sided P-values of 0.05 and 95% Confidence Intervals (CI).

Results

Socio-demographic characteristics
A total of 751 MDR-TB patient's records were reviewed for intensive phase treatment outcome. The median age of the patients was 28 (IQR 23-38) years. Most of them were urban dwellers (67.6%) and males (57.7%). A total of 454 (60.5%) of patients were treated at TICs in Addis Ababa City Administration (AACA) of which 181 (40%) of the patients were came from other Regional States other than AACA. The majority of the patients were being treated at St. Peter Hospital TIC, 376 (50%) followed by Gonder University Hospital TIC, 93 (12.4%) (Table1).

Clinical/programmatic characteristics
From the 751 records reviewed, 563 (75%) patients were treated under the hospitalized model of care. About two-in-five, 293 (39.0%) had a history of at least one co-morbidity with 164 (21.8%) being HIV co-infected. Only 455 (60.6%) had recorded information to calculate the BMI. Among them, 314 (69%) had a BMI below 18.5kg/m2 while the median BMI was 16.65 (IQR14.80-19.20) kg/m2.
From the total sample, 542 (72.2%) patients were sputum smear positive at month zero. From these, sputum grading or bacilli load data were available only for 396 (73%). Almost all patients (97%) were previously treated for TB with nearly three quarters (73.9%) was after treatment failure registration group. All of the included patients were resistant to Rifampicin. Regarding potassium (K+) and x-ray findings, 45.1% had history of hypokalemia and 90.6% had abnormal x-ray findings (90.6%) (Table2).

Treatment outcomes

One hundred and thirty (17.3%) of the patients had an unfavorable, 126 (16.8%) had an unknown and 495 (65.9%) had a favorable treatment outcome. The trend of favorable treatment outcome declined from 2009 to 2011; but showed a slight increment from 2012 to 2013. The unfavorable treatment outcome increased during the year 2010 and became constant thereafter. The median time from diagnosis to treatment initiation of MDR-TB was 2.96 months (IQR=0.73-7.24). The median duration of intensive phase treatment was 9.01 months (IQR 8.04-10.54) (Figure3).

Sputum smear and culture conversion
At month Zero, 542 (72.2%) patients were known to be sputum smear positive of whom complete data to determine rate of sputum smear conversion was available for 466 (86%). From these (466), 255 (54.7%) of the patients converted to sputum smear negative at month one and 378 (81%) converted to negative at month two. From the 751 initial sputum cultures positive patients, complete data were available for 524 (69.8%) to determine rate of sputum culture conversion. Of these, 146 (27.9%) converted at month one and 293 (55.9%) converted at month two. The median duration of sputum smear conversion was 1 month (IQR =1-2) while for culture conversion this was 2 months (IQR= 1-3) (Figure 4).

Factors associated with intensive phase treatment outcome
In bivariate analysis, the co-variates with p-value less than or equal to 0.25 of level of significant for unknown treatment outcome were age, residence, model of care, TB treatment supporter, history of TB treatment interruption, history of medication changed, sputum smear positive, bacilli load, liver function test, number of abnormal X-rays findings, category of the patient, previous history of FLD and SLD TB treatment, degree of drug resistance, history of hypokalemia and year of treatment initiation.

Whereas age, comorbidity, BMI, treatment outcome of first line TB, category of the patient, history of treatment interruption, HIV status, type of TB treatment supporter, model of care, degree of drug resistance, history of hypokalemia, liver function test and year of treatment initiation were statistically significant at 0.25 level of significant for unfavorable treatment outcome.

In multivariable analysis, model of care, residence, TB treatment supporter and degree of drug resistance were statistically significant for unknown outcome at 0.05 level of significant. For unfavorable treatment outcome age and serum potassium level were statistically significant at 0.05 level of significant and included in the final model (Table 3 and 4).

Discussion
Our study showed that about two third, 495 (65.9%) of patients had a favorable outcome at the end of intensive phase, whereas 130 (17.3%) had an unfavorable; and 126 (16.8%) had an unknown treatment outcome. The median duration of intensive phase treatment was 9.0 months. Being older age and hypokalemic were associated with unfavorable intensive phase treatment outcome whereas, having been treated under the ambulatory model of care, being a rural dweller, not having a treatment supporter and lower degree of drug resistance were factors associated with unknown treatment outcome.

The favorable treatment outcome trend sharply declined from 86% in 2009 to 67.2% in 2011 and increased again slightly to 74% in 2013 but showed again a sharp decline to 52% in 2014. The trend is largely affected by those with an unknown outcome. A possible explanation for the fluctuation could be the shift to the ambulatory (decentralized) model of care since 2013/14 and lack of access to culture result due to limited number of culture facilities in the peripheral part of the country.

The proportion of patients with an unfavorable treatment outcome in this study was 17.3%. This was similar to studies conducted in Nigeria (15%) (Oladimeji et al., 2014) and Botswana (16%,15% and 17% among overall, HIV positive and HIV negative MDRTB patients respectively) (Hafkin et al., 2013). This was higher than study conducted in Tanzania (11%) (Mpagama et al., 2013), but lower than studies reported in South Africa (31.6%) (Seung et al., 2009), China (26.6%) (He et al., 2010) and India (38%) (Isaakidis et al, 2011). The observed differences might be due to expansion of the ambulatory model of care in Ethiopia, also the other studies did not consider unknown treatment outcome or to other differences i.e., in sample, study period and study setting. For instance, the studies in Tanzania and Nigeria (Mpagama et al., 2013; Oladimeji et al., 2014) were conducted over shorter periods of 3 years (2011-2012 and 2009–2011, respectively) while this study included 6 years data, twice as long. The Tanzanian study was hospitalized model of care. However, our study was conducted for longer period of time (2009 to 2014) including both the hospitalized and ambulatory model of care.

The median duration of the intensive phase treatment in this study was 9 months (IQR= 8.0-10.5). This duration is longer than the 7 months (IQR= 6-8) reported from Tanzania [Mpagama et al., 2013].This could be due to differences in the case definition of the duration of the intensive phase. For example, in Tanzania it was defined as 8 months OR 4 months after culture conversion. However, in Ethiopia, it is defined as at least 8 months AND 4 months after culture conversion, whichever is longer. Inadequate access to culture facilities at the peripheral part of the country could also contribute as often the duration of the intensive phase is decided by panel team clinically as culture results are not available which might result in long durations of the intensive phase.

As age increases by one year (older age), the likelihood of experiencing unfavorable treatment outcome increased by 1.047(ARRR=1.047:1.024, 1.072). Similar findings from Lima, Peru, Latvia, Estonia, Tomsk, Russia and Manila, the Philippines reported that older age was associated with less likelihood of culture conversion (kurbatova et al, 2012).

Serum potassium level was factors significantly associated with unfavorable treatment outcome; having a history of hypokalemia decreased the risk of unfavorable treatment outcome by 49 %(p value 0.031)
compared with those who did not have a history of hypokalemia. This is an unexpected finding and needs further exploration.

The proportion of patients with an unknown treatment outcome in this study was 16.8% which fluctuated over the study period showing an overall increase over time. Other studies did not include those with unknown outcome. If we take these out of the analysis the proportion with favorable outcome is 79.2% and those with unfavorable is 20.8%.

Those patients who had been treated under the ambulatory model of care were 3.2 times more likely (ARRR=3.2:1.612, 6.185) to have an unknown treatment outcome. This might be due to the fact that this is relatively decentralized and there are a limited number of culture facilities in the peripheral part of the county. This may result in delayed feedback of culture result or not sending a sample for culture resulting in unknown outcome. This needs further exploration as it is important that as per guideline all patients have all required specimen taken and analyzed to allow for proper outcome monitoring and correct treatment.

Place of residence was also associated with unknown treatment outcome. For urban dweller the likelihood of having unknown treatment outcome decreased by 63 % (p-value<0.01) when compared to rural dwellers. This may be due to the distance which may lead to non-adherence to scheduled laboratory monitoring. Or the urban TICs may have better recording practice.

Patients resistant to two or three drugs were less likely to have unknown treatment outcome compared to those resistant to a single drug. This finding was unexpected and need further exploration. It may be that those patients with multiple drug resistant were given closer follow up and patients diagnosed by Genexpert had information only about rifampicin resistant even though the patients might be resistant to other drugs besides rifampicin which might mask the true findings.

The high unfavorable and unknown treatment outcomes have impacts on quality of life and transmission MDR-TB in community. This might also prone an individual towards extensive drug resistance TB.

The study has strengths and limitations. Having a national representative data and a large sample size are clear strengths. In addition, including unknown outcome as done in this study is important to fully understand the picture of early treatment outcome and does provide important insight for TB prevention and control program. Limitations are that we did not consider multilevel modeling to understand the regional Variation in terms of different factors.

Conclusion

The intensive phase favourable treatment outcome continues to decline in the study area with an increase unfavorable and unknown treatment outcomes most likely after the implementation of the ambulatory model of care which requires attention. Ambulatory model of care, rural dwellers, not having treatment supporter and limited number of drug resistance were associated with unknown treatment outcome. While age and serum potassium levels were associated with unfavourable treatment outcome.
In order to minimize the unknown and unfavorable outcomes and have complete data for in-depth analysis, health care providers working in the different treatment initiating centers should adhere to the scheduled laboratory monitoring test especially culture, drug susceptibility test and serum potassium level and track the culture result feedback as early as possible. Health care providers should also closely monitor older aged patients, do regular death audit, trace lost to follow up and ensure that treatment supporters were trained and assigned for every patient.

The Federal Ministry of Health and Regional Health Bureau should strengthen sample referral system to increase access to culture and drug susceptibility testing facilities and feedback system especially for the ambulatory model and rural residents. Further, a study by including primary data and multilevel modeling in order to explore additional contributing factors to the intensive phase treatment outcome at all levels of the treatment initiating centers. Moreover, study should be conducted on the final treatment outcome for the same study subjects to see whether similar outcomes will be achieved or not.

**Abbreviation And Acronyms**

AFB Acid Fast Bacilli

AIDS Acquired Immune Deficiency Syndrome

ARRR Adjusted Relative Risk Ratio

ART Antiretroviral Therapy

BMI Body Mass Index

CPT Cotrimoxazole Preventive Therapy

CSA Central Statistical Authority

DR-TB Drug Resistant Tuberculosis

FDRE-PCC Federal Democratic Republic of Ethiopia- Population Census Commission

FMOH-E Federal Ministry of Health of Ethiopia

HBCs High Burden Countries

HC Health Center

HIV Human Immuno Deficiency Virus

HRS Isoniazid, Rifampicin and Streptomycin

HR Isoniazid and rifampicin
Declaration

Ethical approval and consent to participate

The study was approved by Haramaya University, Collage of Health and Medical Sciences Ethics Review Committee and National Review Board of the Ministry of Science and Technology of Ethiopia. Support letter was also written from the Federal Ministry of Health of Ethiopia to the respective Regional Health Bureaus to get permission to access health facilities or MDR-TB treatment initiating centers.

Consent for publication
Written consent was obtained from each treatment initiating centers where data were collected for publication.

Availability of data and materials

All the necessary data supporting our findings are contained within the manuscript.

Competing interest

The authors have no competing interests for this study.

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Author’s contribution

1. Teklu Molie Tao: involved in the study from the inception to write-up of this manuscript.
2. Dr. Berhanu Seyoum, Mr. Zelalaem Teklemariam, Dr. Eveline Klinkenberg, Dr. Yadeta Dessie and Dr. Andargachew Kumsa were involved in the study from proposal writing to write-up of this manuscript.
3. Hussen Mohammed, Adisalem Debebe, Dr. Dawit Assefa, Dr. Abebe Habte, Dr. Ahmed Bedru and Dr. Daniel Fiseha were involved in the study from result writing to write up of this manuscript.

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Author’s information

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### Tables

The tables can be found in the supplemental files section in the Figures and tables document.

### Figures
Figure 1

Map of Ethiopia with the location of MDRTB treatment initiation centres included in the study. Source: Federal Democratic Republic of Ethiopia Population Census Commission Bureau
Figure 2

Schematic diagram of sampling technique for MDRTB patients treated in Ethiopia, 2009-2014.

Figure 3

Trends of intensive phase treatment outcome among patients treated for MDRTB in Ethiopia from 2009-2014
Figure 4

Rate of sputum smear and culture conversion among patients treated for MDR-TB in Ethiopia, 2009 – 2014.

Supplementary Files

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