Research Article

Rifampicin-Versus Ethambutol-Based Continuation Phase Anti Tuberculosis Treatment Regimen is among Factors Associated with Treatment Outcomes in Patients Treated at Six Health Facilities in Southern Ethiopia

Ozian Z Wubshet
Population Service International (PSI), Addis Ababa, Ethiopia

Meaza Demissie
Addis Continental institute of Public Health, Addis Ababa, Ethiopia

Eskezyiaw Agedew
Arba Minch University, Department of Public Health, Ethiopia

Direslgne Misker
Arba Minch University, Department of Public Health, Ethiopia

ABSTRACT

Background: The World Health Organization (WHO) states that treatment outcome is an important indicator to monitor tuberculosis (TB) prevention and control program. This study analyzed TB treatment outcome taking regimen change in continuation phase from EH (Ethambutol-Isoniazid) to RH (Rifampicin-Isoniazid) into account in Ethiopia as a factor.

Objective: to assess tuberculosis treatment success rate and associated factors in Gamo Gofa zone, Ethiopia.

Methods: We did a register based, retrospective cross-sectional study among TB patients who received treatment in five health facilities with high tuberculosis case load in Gamo Gofa zone. The study was conducted from October 2013 to May 2014. All eligible patients were studied. Binary and multiple logistic regression analysis were carried out to identify factors associated with successful treatment outcome.

Results: Among 2,019 TB patients registered for treatment, treatment outcome was evaluated for 1,667 (82.6%). Among these, 86.6% were successfully treated. Rural residence [AOR=0.62 (95% CI: 0.46-0.83)], being HIV Positive [AOR= 0.56 (95% CI: 0.39-0.81)], having smear positive pulmonary tuberculosis [AOR=0.59 (0.35-0.99)] and being on EH based anti-TB continuation phase treatment regimen [AOR= 0.72 (95% CI: 0.54-0.96)] were associated with lesser odds of having treatment success.

Conclusion: Treatment success in this study was very good. The level of treatment success in this study was encouraging at 86.6%. Transitioning continuation phase anti-TB treatment regimen to RH contributed to the improvement of tuberculosis treatment outcome.

Keywords: Tuberculosis; Anti-tuberculosis treatment; Treatment success; Continuation phase; Rifampicin-isoniazide; Ethambutol-isoniazide

Introduction

Tuberculosis (TB) remains a major global health problem. It causes ill-health among millions of people each year and ranks in the top ten leading causes of mortality. About a third of the world's population is estimated to be infected with TB bacilli and hence at risk of developing active disease. The latest estimates indicate almost 9 million new cases and 12 million prevalent cases of TB globally, of which 1.1 million (13%) were among people living with HIV in 2013, and 1.5 million TB deaths (360 000 were HIV-associated). About 26% of the incident TB cases occurred in Africa. The proportion of TB cases co-infected with HIV is highest in African country; overall, the African region accounted for 79% of TB cases among people living with HIV [1].

Ethiopia is one of the 22 High Burden Countries (HBCs) that have been given highest priority at the global level since 2000 and HBCs accounted for 80% of all estimated cases worldwide. According to the 2014 quarterly health bulletin of the Federal Ministry of Health (FMOH), tuberculosis was in the top ten causes of in-hospital deaths in Ethiopia [2,3].

For effective TB control program it is very important to detect the disease as early as possible and put patients on treatment and take those to completion in order to get cure [4]. According to the WHO, treatment outcome is an important indicator to monitor the TB prevention and control program [5]. A number of factors may affect treatment outcomes.The efficacy of treatment regimens is assumed to be the same but Refampicin-based continuation phase regimens are preferred

for various reasons including low treatment failure and relapse rate, higher cure rate, and shorter duration of treatment [6].

Since 2009, Ethiopia, in complaince with the global recommendations has changed the continuation phased regimen from Ethambutol-Isonized (EH) to Refampicin-Isoniazid (RH [6]. However, no study has compared treatment outcomes among patients treated with the two regimens after the change in treatment regimen. In addition, data source for a good number of studies that evaluated treatment outcome in Ethiopia were routine facility reports which might have low quality [7-12]. Therefore, in this study, we assessed treatment success rates and its predictors using the unit TB register as data source and included continuation phase treatment regimen as one of the independent variables in the analysis.

Methods

Study setting

We conducted this study in Gamo Gofa zone is one of the 15 administrative zones of Southern Nations Nationalities and Peoples (SNNP) region in Ethiopia. Administratively, it is subdivided in to 15 woreda or district and two town administrations. The total population of the zone was 1,793,255 in 2011 which account for 10.7% of the regional population. Based on the high TB case load, we selected Arba Minch general hospital, Arba Minch health center, Sawla hospital, Sawla health center and Chencha Hospital for this study. In 1992 a standardized TB prevention and control programme, incorporating Directly Observed Treatment, Short Course (DOTS), was started in the country as a pilot, at Arsi zone in Oromia. According to the Ministry of Health 2011 report, the DOTS geographic coverage reaches 100%, whereas hospital and health centre coverage is 92% and 95%, respectively. TB treatment regimen change in the continuation phase from Ethambutol Isoniazid (EH) to Rifampicin Isoniazid (RH) has been already started on Sep 11, 2009. This change reduced TB treatment period from 8 month to 6 month.

Study design

A register based, four year retrospective cross sectional study of TB patients under DOTS in Gamo Gofa Zone was carried out from October 2013 to May 2014.

Study population

We included all TB Patients who took anti TB as new treatment category for more than one month in the selected facilities and in the time period between June 2009 and July 2013. We excluded those TB patients who were diagnosed and started TB treatment in the selected facilities but transferred out to other facilities for continuation of treatment, retreatment cases (relapse, treatment after failure, or return after lost to follow-up) and TB Patients who had incomplete documentation on important variable such as Age, Sex and outcome variable.

Data management and analysis

We used data abstraction tool to collect the age, sex, address, type of TB, HIV status, continuation phase anti-TB treatment regimen, and treatment success (either cure or treatment completion). Data collection was supervised and 5% of random sample of records were rechecked for completeness and accuracy against registration books. The data was entered into SPSS version 20 and cleaned for further analysis. Predictors of treatment success were analyzed using logistic regression. All variables significant at 0.25 levels on the binary logistic analysis were included in to multi variable logistic regression model. After model selection Hosmer and Lemeshow Goodness of fit test was carried out. P value of less than 5% was considered statistically significant.

Operational definition

Treatment outcome defined as treatment success if patient who was cured or who completed treatment whereas unsuccessful treatment is a patient, whose treatment was interrupted, failed on treatment or died [6].

Ethical consideration

The study protocol was reviewed and approved by Addis Continental Institute of Public Health and Arba Minch University Institutional Review Board, and permission was also obtained from the study facilities. Consent was not required as patients were not contacted. In addition, any identifier data was removed from the final dataset after completion of data collection.

Results

Demographic and clinical characteristics of study participants

Among 2,019 TB patients registered for treatment in the selected health facilities between July 2009 and June 2013, treatment outcome was evaluated for 1,667 (82.6%) patients. From all patient 87 (4.3%) were excluded because they were retreatment cases (relapse, treatment after failure, or return after lost to follow-up). Additional 265 patients were excluded because they were transferred-out to other facilities and their treatment outcome was not known. Of the final study sample 1,052 (63.1%) were male. The median age of the study participants was 26 years. From all considered patient for analysis 540 (32.4 %) were smear pulmonary positive cases, 888 (53.3%) were smear pulmonary negative TB cases and 239 (14.3%) were extra-pulmonary TB patients. The majority of the patients 1,454 (87.2 %) were between ages 15 and 64 years. About 56 % (n=927) of the patients were urban residents. HIV status for 1,603 (96.2%) patients was known and 14.2% (n=237) of them were HIV positive.

Tuberculosis treatment outcome

Fifty seven percent (n=951) of the patients took Rifampicin-Isoniazid (RH) during continuation phase of anti-tuberculosis treatment as shown in and 43 % were on EH (Table 1).

Of the smear positive TB patients, sputum smear microscopy was done for 455 (84.3%) at the end of the second month of treatment and 22 (4.1%) were documented to have smear positive microscopy findings at that stage. but only, 2 (0.2%) were still smear positive at the end of the treatment, which indicates failure to respond to the first line anti TB drugs.

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3

Table 1: Baseline characteristics of study sample for TB patients in selected facilities in Gamo Gofa Zone, Ethiopia, 2014.

Variable	Subcategory	Frequency (n)	Percentage (%)
Age in years	<15	149	8.94
	15-39	1,112	66.71
	40-64	342	20.52
	>64	64	3.84
Gender	Male	1,052	63.11
	Female	615	36.89
Address	Urban	927	55.61
	Rural	740	44.39
HIV status	Negative	1,366	81.94
	Positive	237	14.22
	Unknown	64	3.84
Type of Tuberculosis	Smear positive pulmonary	540	32.39
	Smear negative pulmonary	888	53.27
	Extra pulmonary	239	14.34
Continuation phase treatment regimen	Rifampicin-Isoniazid	951	57.05
	Ethambutol-Isoniazid	716	42.95
Treatment center	Arba Minch Hospital	603	36.17
	Arba Minch HC	254	15.24
	Sawla Hospital	182	10.92
	Sawla HC	65	3.9
	Chencha Hospital	563	33.77
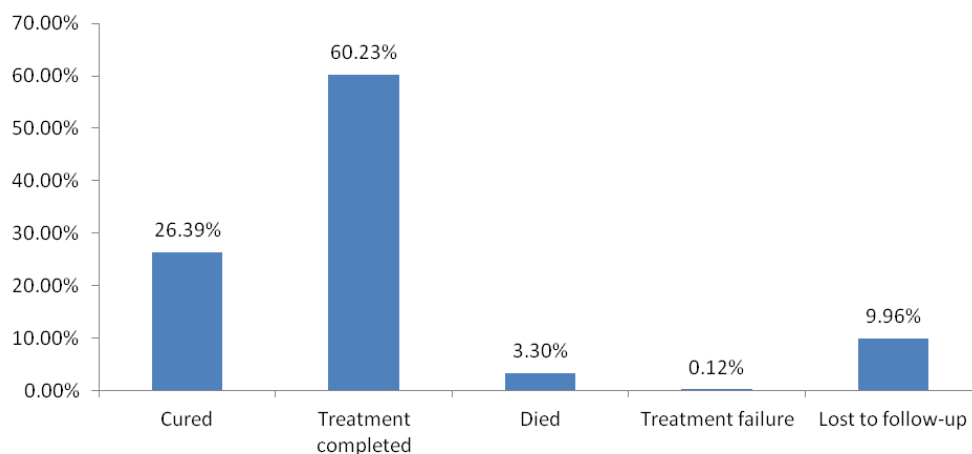
Figure 1: Treatment outcome detail for TB patients in selected facilities in Gamo Gofa zone, Ethiopia, 2014.

As for treatment outcome, 1,004 (60.2%) completed treatment out of which 440 patients were cured (26.4%) this adds up to a total of 1,444 (86.6%) patients with treatment success or favorable treatment outcome. Of the remaining patients 55 (3.3%) had died, 2 (0.1%) had treatment failure and 166(10%) were lost to follow-up as shown in Figure 1.

There is a trend of increasing treatment success from year 2009/10 to 2012/13 as shown in Figure 2 reaching 90% in the final follow-up interval. Proportion of patients who were lost to follow-up from treatment steadily dropped from 14.6% to 6.2% over the study period. The proportion of TB patients with unknown HIV status also showed a reduction from 7.4% in 2009/10 to 2.2 % in 2012/13. Although treatment success of 86.3% was high overall in the study there were variations across treatment centers from as low as 80.1% in Chencha hospital to as high as 91.7% in Arba Minch health center (p<0.001).

Factors affecting treatment success

Result from multivariable logistic regression analysis reveals that place of residence, type of TB, anti-TB regimen during continuation phase, and HIV status were found to be significantly associated with treatment success. Patients from rural areas had significantly lower treatment success [AOR=0.62 (95% CI 0.46-0.83)] than those from urban areas. HIV positivity on the TB patients who [AOR=0.56 (95% CI 0.39-0.81)] was independently associated with higher proportion of unfavorable treatment outcome. Ethambutol-Isoniazid Regimen during continuation phase [AOR=0.72 (0.54-0.96)] was associated with unfavorable treatment outcome. Similarly,

Trends of treatment outcome by year
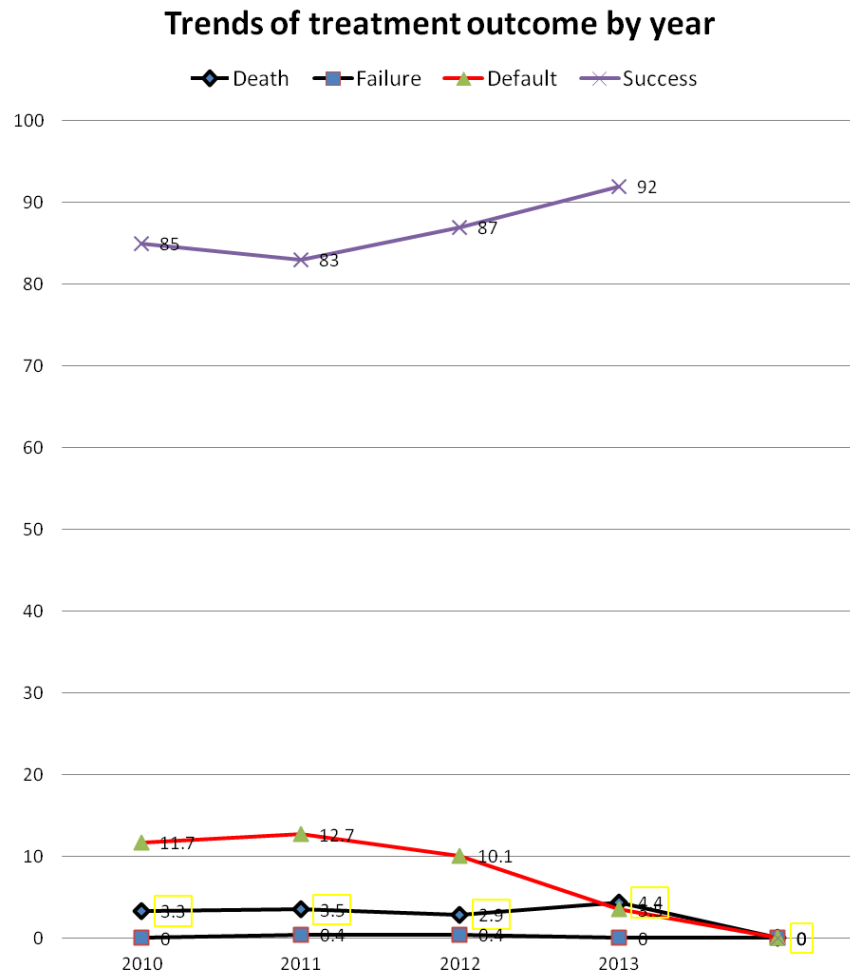
Figure 2: Trends of treatment success, mortality, failure and default across year of treatment among TB patients in selected health facilities in Gamo Gofa zone, Ethiopia, 2010-2013.

Table 2: Factors associated with TB treatment success among TB patients registered from 2009-2013 in Gamo Gofa Zone, South Ethiopia (1,444).

Variable	Subcategory	Treatment success, Number	Treatment success, Percent	Crude Odds ratio (95% CI)	adjusted Odds ratio (95% CI)	P value
Age, in years	<15	132	89%	1		
	15-39	975	88%	0.92 (0.54-1.6)		
	40-64	283	83%	0.62 (0.35-1.1)		
	>64	54	84%	0.70 (0.30-1.6)		
Gender	Male	917	87%	1		
	Female	527	86%	0.88 (0.66-1.2)		
Address	Urban	825	89%	1	1	
	Rural	619	84%	**0.63 (0.48-0.84)**	**0.62 (0.46-0.83)**	**0.001**
HIV status	Negative	1,197	88%	1	1	
	Positive	191	81%	**0.59 (0.41-0.84)**	**0.56 (0.39-0.81)**	**0.002**
	Unknown	56	88%	0.99 (0.46-2.1)	0.90 (0.42-1.9)	0.786
Type of Tuberculosis	Extra pulmonary	219	92%	1	1	
	Smear positive pulmonary	462	86%	**0.54 (0.32-0.91)**	**0.59 (0.35-0.99)**	**0.048**
	Smear negative pulmonary	763	86%	**0.56 (0.34-0.91)**	**0.63 (0.38-1.0)**	**0.070**
Continuation phase treatment regimen	Rifampicin-Isoniazid	839	88%	1	1	
	Ethambutol-Isoniazid	605	84%	0.73 (0.55-0.97)	0.72 (0.54-0.96)	0.023

patients with pulmonary TB - smear positive pulmonary TB patients [AOR=0.59 (95% CI=0.35-0.99)] and Smear negative pulmonary TB patients [AOR=0.63 (95% CI=0.38-1.00)] had significantly lower treatment success as compared to extra pulmonary TB patients (Table 2).

Discussion

Treatment success patients in this study is 86.6% (95% CI=85.0-88.3) was high and favorable treatment outcomes improved steadily over the last four years in six health facilities with high TB case load in Gamo Gofa Zone of southern Ethiopia. Being HIV negative, having extra-pulmonary TB and being on RH-based continuation phase regimen were associated with favorable treatment success.

Treatment success in this study was very good as it exceeded the earlier WHO target of 85% and is close to the Millennium Development Goal target of 87% [13]. The reason for progressive improvement of treatment outcome may be the use of DOTS treatment supporters to closely monitor and trace patients who default from treatment. The presence of health extension workers may also have contributed for this as there is well documented evidence from studies conducted in other parts of Ethiopia [14,15] that reported higher treatment success as a result of the use of community health extension workers to follow-up patients. The finding of treatment success in this study is lower than what was reported in Dabat district in Amhara region, in Tigray region and in southern Ethiopia with 87.8%, 89.2% and 89.3% respectively [14-16]. At the same time it is higher as compared to previous reports from in SNNP region [8], Bahir Dar [17], Gondar [10] and Brazil [18] which reported treatment outcomes of 74.8%, 26%, 29.5% and 75.9% respectively. These lower or under estimated achievement in the other studies could be due to the fact that large numbers of transferred-out TB patients are categorized as having unfavorable treatment outcome.

Rifampicin-Isoniazid based anti-TB Regimen in continuation phase was associated with higher rate of treatment success. This might be due to the effectiveness of RH regimen in treating TB or improvement of adherence associated with shortening treatment period from eight to six months. It might also be due to co-interventions like availability of treatment supporters associated with treatment with RH which was not present in the period EH was dispensed during continuation phase [6].

The TB/HIV co-infection in this study was 14.2%. There are lower, 10.9% [19] as well as higher reports of TB/HIV co-infection, 52.1% [20] reported from Ethiopia which may depend on the local epidemiology of HIV. Treatment success was 81%among HIV positive and 88%among HIV negative patients, and the difference in treatment outcome was statistically significant. This is in agreement with previous studies conducted in Kolla Diba [19], Azezo [21] and Addis Ababa [22] and in Malawi [23]. This might be due to increased prevalence of toxicity, high pill burden and high death rate among HIV positive [24].

The lower treatment success among pulmonary TB patients, as compared to extra-pulmonary TB patients, observed in this study were demonstrated in one other study as well [21] but was inconsistent with other studies done in Ethiopia [10,19]. The reason for higher treatment success for patients with extra-pulmonary TB may be because the commonest form of extra-pulmonary TB, which is lymph node accounting for 60% of all extra-pulmonary TB cases, is a less severe disease associated higher proportion of treatment success [25]. In addition, treatment outcome is determined clinically for extra-pulmonary patients in Ethiopia for which reason they are unlikely to be classified as having treatment failure by bacteriological criteria as compared to smear positive pulmonary patients. However, the contribution of this factor may not be that much as treatment failure is generally low at around 1%.

Urban residence was associated with better treatment success. This might be due to better access to health facilities or better access to information in people living in urban areas.

One of the most important lessons to take from this study is the wide variation of treatment outcome across treatment centers. This might be due to geographic accessibility of facilities or cultural factors and provider factors. It is important to find out what worked for those with higher treatment success and replicate it in those places where it was lower. The establishment and maintenance of functional tracing mechanism at community level is very important to be able to locate patients lost to follow-up and address barriers to treatment completion there-by reducing risk of disease transmission, drug resistance or even death. Clinicians and health extension workers should also pay particular attention to HIV positive TB patients who are prone to develop other opportunistic infections which may affect their TB treatment outcome [26].

The study has strengths and limitations. We included continuation phase drug regimen as key predictor variable in our analysis. We also used data from multiple treatment sites. However, important social and clinical variables were missing from the data source which restricted our ability to do more analysis. The fact that this was a retrospective review made it impossible to get treatment outcome for patients transferred-out to other facilities. This is because of the lack of feedback mechanism between facilities on final status of patients. This was handled by excluding these patients.

Conclusion

The level of treatment success in this study was encouraging at 86.6%. Transitioning continuation phase anti-TB treatment regimen from EH to RH contributed to the improvement of treatment outcome. However, more effort is needed to further improve treatment success rates among patients from rural areas, those co-infected with HIV, and patients with pulmonary TB. Factors contributing to variations in treatment outcomes among the different health facilities should be studied further.

AUTHORS' CONTRIBUTION

OZ: Initiated the research, wrote the research proposal, conducted the research, did data analysis and wrote the manuscript, EA: Involved in the write up of methodology of proposal and research work.

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ADDRESS FOR CORRESPONDENCE:

Eskezyiaw Getahun Adedew, Mater in Public Health, Arba Minch University, Arba Minch, Southern Ethiopia, Ethiopia, Tel:+251-934624484; E-mail: esk1agid@gmail.com