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# Adverse Drug Reactions of Primary Anti-tuberculosis Drugs Among Tuberculosis Patients Treated in Chest Clinic

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## Abstract

Tuberculosis is a communicable infectious disease caused by *Mycobacterium tuberculosis*, recently become second leading infectious diseases that cause death after HIV-AIDS. Adverse drug reactions related to anti-tuberculosis also become important as longer use of these drugs. This study aimed to explore and to observe adverse reactions occurrence of anti-tuberculosis drugs among tuberculosis patients and its management. An observational retrospective cohort study was used in this study. Patients taken for this study that treated for tuberculosis in Chest Clinic Department of General Hospital Penang, Malaysia that in our inclusion criteria. Data was descriptively analyzed by using statistical package for social sciences (SPSS 15). There are 653 tuberculosis patients included to this study after inclusion and exclusion criteria. Out of 653 patients 103 (15.8%) patients had an experience on adverse drug reactions. The majority case of adverse drug reactions is skin reaction happened in 51 (7.8%) patients followed by hepatotoxicity in 17 (2.6%) patients, then gastrointestinal reactions in 16 (2.5%) patients. Adverse drug reactions management mostly by add on medication in 56 (8.6%), stop (withhold) treatment regimens on 40 (6.1%), continue medication without any changes 6 (0.9%) and only 1 (0.2%) of patient need regimens changes from total adverse drug reactions occurrence. Several adverse drug reactions related to primary anti-tuberculosis drugs, common adverse drug reactions is skin reactions. There are some risk factor that may affect on adverse drug reactions occurrence.

**Key-Words:** Adverse Drug Reactions, Anti-tuberculosis drugs, Chest Clinic, toxicity

## Introduction

Tuberculosis an infectious disease caused by *Mycobacterium tuberculosis*, now become the second leading infectious cause of death in the world [1]. Active pulmonary TB incidence estimated around 8 million new cases per year worldwide and approximately cause death 2 million per year [2]. In 2009, there were an estimated 9.4 million incident cases of TB globally that is equivalent to 137 cases per 100 000 population. Most of the estimated number of cases in 2009 occurred in Asia (55%) and Africa (30%);3 smaller proportions of cases occurred in the Eastern Mediterranean Region (7%), the European Region (4%) and the Region of the Americas (3%) [3]. Malaysia according to statistic data WHO in 2009 has total populations 27,468,000. In Malaysia, ranked 46th in total number of tuberculosis cases worldwide for the year 1999, 14908 new cases of tuberculosis were reported. Majoring of the cases was in the 15-50 years age group Malaysia.

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There were 603 cases of HIV and TB co-infection notified for the same year. The total number of death due to TB reported was 853. This makes TB the single most important killer among other infectious disease in Malaysia (MOH, 2002). Incidence rate in Malaysia is 47 per 100,000 population per year with prevalence 136 cases and mortality rate related with tuberculosis is estimated 17 cases per year [4].

Tuberculosis treatment mostly need more than one drug combination to eradicate tuberculosis bacteria. First line anti-tuberculosis drugs recommended by WHO are combination between isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin [5]. The necessity use of multidrug regimens has been associated with increased incidence of adverse drug reactions of anti-tuberculosis drugs. This adverse drug reactions may be mild as well as fatal [2]. Anti-tuberculosis agent that commonly use such as, isoniazid, rifampicin and pirazinamide are highly effective but also can cause hepatotoxicity [6]. Treatment on people with tuberculosis require treatment for at least six months, it may find difficulty to complete

treatment and this serves as a major constraint to eradicating the disease [7].

## Methodology

The study was conducted as a 30 months retrospective cross-sectional study by conducting observation on tuberculosis patient treated on Respiratory Department, General Hospital Pulau Pinang, Malaysia. This study was carried out by collecting patient's medical record from year January 2008 to June 2010. Research subject are patient that treated as tuberculosis patient (an outpatient) in Chest Clinic, Respiratory Department, General Hospital Pulau Pinang, Malaysia. This study aimed to identify incidence of anti-tuberculosis adverse drug reactions tuberculosis in respiratory department of General Hospital Pulau Pinang, Malaysia.

Malaysia has a tuberculosis control program which is called TB Negara. Under this program, patients that suspected have tuberculosis should do some test series to develop a diagnosis, those test such as tuberculin test, sputum AFB test, culture test, chest x-ray and any other test that necessary for diagnosed. Patients who were diagnosed with tuberculosis before taking treatment they have to do some more test series such as baseline liver function test, renal function test and hematology test including HIV screening test. In some certain case, reactivation tuberculosis patient have to undergo sensitivity test also for high risk tuberculosis patient. All tuberculosis patients were reviewed at first two week after started treatment and thereafter every month, except if they have an experience of adverse drug reactions, they were informed to visit the doctor immediately.

Sampling techniques used in this study was the universal sampling technique by collecting patient's medical record that available in medical record office. There was no information gathered directly from patients in ward. Patient's medical records were sorted and selected according to the inclusion and exclusion criteria. Inclusion criteria for this study are: patient that diagnosed tuberculosis, adult patient (18 years of age and above), and normal liver function test before start taking anti-TB drugs regimen. Exclusion criteria of this study are: patient with abnormal liver function test before start taking anti-TB drugs regimen, pediatric patient (below than 18 years of age), serological evidence of an acute infection with hepatitis B or C and was diagnosed hepatitis, and inadequate medical record to allow complete analysis.

Collected data analyzed using Statistical Package for Social Sciences version 15.0. Categorical variables such as patient's gender, race, type of tuberculosis, treatment regimen, treatment duration, and others expressed in frequencies and percentage. Numerical categories such as age expressed in mean. Socio-demographic, lifestyle and habits patients that may related to adverse drug reactions occurrence was analyzed with chi-square, p-value >0.05 considered statistically significant.

## Results and Discussion

### Patient's Socio-Demographic

The result show, among 653 patients, 402 (61.6%) patients age between 18-54 years of age while the other 251 (38.4%) patients age 54 years old above with 464 (71.1%) patients male and 189 (28.9%) female. According to race, majority race included to this study is Chinese 342 (52.4%), followed by Malay 218 (33.4%), Indian 59 (9.0%) and other race 34 (5.2%). It seems that patient demographic characteristics mostly are age between 18-54 years old, male and Chinese. According to habit and lifestyle, there are 313 (47.9%) smoker, small number on alcohol use 79 (12.1%), and only 60 (12.1%) patients drug abuser patients. There are 53 (8%) patients determined with HIV, 457 (70%) not determined with HIV and 143 (22%) data regarding HIV was not found. Tuberculosis patients with diabetes mellitus as co-morbidity are in 170 (26%) patients with diabetes mellitus as co-morbidity and 483 (74%) patients determined without diabetes mellitus as co-morbidity. Patient's socio-demographic characteristic can be seen on table 1.

Type of tuberculosis majority is pulmonary tuberculosis on 549 (84.1%) patients. 79 (12.1%) patients suffer from extra-pulmonary tuberculosis and other 25 (3.8%) suffer of both pulmonary and extra-pulmonary tuberculosis. Tuberculosis treatment divided into two phase of treatment: intensive phase with commonly 4 drugs combination then followed by maintenance phase with 2 drugs combination. Drug combination used on intensive phase among tuberculosis patient included in this study can be seen on table 2. The table showed that combination of isoniazid, rifampicin, ethambutol, and pyrazinamide are mostly used on patient as much as 530 (81.2%) of total patients. Maintenance phase drug combinations can be seen on table 2, this table showed that 283 (43.3%) patients of total patients on combination isoniazid and rifampicin daily use, followed by combination isoniazid and rifampicin on biweekly use. Treatment duration of anti-tuberculosis drugs among tuberculosis patients included to this study showed on table 2. There are 190 (29.1%) patients of total patient need 9 months on therapy and 157 (24.0%) need 6 months treatment.

Adverse drug reactions define as a harmful reaction of medicine that occurred in normal use of medication.

Research result showed that among 653 patients included to the study 103 (15.8%) patients had an experience on adverse drug reactions. The majority case of adverse drug reactions is skin reaction such as itchiness, rashes and any other skin reactions due to anti-tuberculosis drugs, it happened in 51 (7.8%) patients followed by hepatotoxicity in 17 (2.6%) patients, then gastrointestinal reactions such as nausea, vomiting or gastrointestinal upset in 16 (2.5%) patient. All adverse drug reactions that occurred among tuberculosis patients can be seen in table 2. We also noted about adverse drug reactions management. Add on medication in 56 (8.6%) patients, is the most common step to manage adverse drug reactions especially in skin reaction, the clinicians add on anti histamine for relieving patient from itchiness or rashes. Then in some cases the clinicians stop the drugs (withhold) when severe reactions appeared, this in 40 (6.1%) patients. Detail of adverse drug reaction taken by the clinicians can be seen on table 2 as well.

Among 103 patients that had an experience on adverse drug reactions (ADRs) 64 (9.8%) male and 39 (6.0%) female, with age between 18-54 years old 57 (8.7%) and 54 years of age above 46 (7.1%). Dominant race is Chinese 59 (9.0%), followed by Malay 37 (5.7%), Indian 5 (0.8%) and others race 2 (0.3%) patients. Chi-square test result for gender and ADRs occurrence showed p-value 0.30 (>0.05), means that patients gender affected to ADRs occurrence and male patients is most affected than on female patients. Related to ages, chi-square test result showed p-value above than 0.05 (0.157), it means that age also related to ADRs occurrence, also in races, chi-square test result showed p-value beyond 0.05 (0.129) means that patient's race also affected in occurrence of ADRs. Patient's distribution according to patient's socio-demographic characteristics and adverse drug reactions (ADRs) occurrence can be seen in table 4.

Correlation between patient's lifestyle-habits and ADRs occurrence can be seen on table 5. The chi square results showed that smoking status may be affected on ADRs occurrence with p value beyond 0.05 while other lifestyle and habit such as alcohol use and drug abuse may not affected to ADR occurrence (p-value <0.05). ADRs occurrence related to smoking status, alcohol use and drug abuse can be seen in table 5. Table 5 shown that 43 (6.6%) smoker patients had an experience on ADRs and it seem statistically significant affected on ADRs occurrence. While on drug alcoholic patients and drug abuser patient only few number of patients that had an experience on ADRs, only 5 (0.8%) for alcoholic patients and 4 (0.6%) for drug abuser. Chi-square result test on ADRs occurrence related to alcoholic and drug abuse habits showed that those two habits statistically not significant affected on ADRs (p-value <0.05).

Adverse drug reactions occurrence related to anti tuberculosis drugs can be seen on table 6. The results showed that there is a correlation between ADRs occurrence with intensive phase treatment and treatment duration, chi-square test result showed significant p value beyond 0.05. Table 6 shown that intensive phase with combination of ethambutol, isoniazid, rifampicin and pyrazinamide is with highly incidence on ADRs occurrence. Maintenance phase with daily isoniazid and rifampicin is has highly number of ADRs occurrence but statistically anti-tuberculosis drugs on maintenance phase not significantly affected on ASRs occurrence (with p-value <0.05).

Tuberculosis until now still become worldwide health problem not only on developing country but also in developed country even the number of tuberculosis patients most large in developing country, like in Malaysia where the study was conducted. Tuberculosis treatment required combination more than 2 drugs and long term use of drugs. These tuberculosis treatments furthermore lead to the potential adverse drug reactions occurrence due to anti-tuberculosis drugs use. Aim of study is to give picture on adverse drug reactions happened in patients with anti-tuberculosis treatment in Chest Clinic, General Hospital Pulau Penang, Malaysia. We analyzed total 653 tuberculosis patients that meet our inclusion and exclusion criteria. The result showed that tuberculosis mainly happened in male patients in this study 71.1% patients are male and the others are female patients. Other study also showed the same results that male is a high risk gender on getting tuberculosis while female have less risk [4, 8-10]. Age related to tuberculosis between 18-54 years of age which is productive age with mean age on 48 years of age. Other studies also have same result that productive age highly related on tuberculosis disease[6, 8, 10]. Race that related to tuberculosis is Chinese, it might be happened because of most of Pulau Pinang citizens are Chinese. If the study conducted in other part of Malaysia maybe there are different number of tuberculosis patient related to race, such as when the research conducted in Kuala Lumpur Malaysia the large number tuberculosis patient happened in Malay race[4].

The result determined that 84.1% tuberculosis cases are pulmonary tuberculosis, this result is consistent with other research results[4, 11]. Tuberculosis treatment regimens 81.2% require 4 combinations of anti-tuberculosis drugs (ethambutol, isoniazid, rifampicin

and pyrazinamide) for the initial phase and 43.3% patients with 2 anti-tuberculosis drugs combination (isoniazid and rifampicin) on daily use for maintenance or continuous phase treatment while 37.4% patients also with 2 anti-tuberculosis drugs combination but on biweekly use. This regimens same with recommendation from World Health Organization and National Institute for Health and Clinical Excellence (United Kingdom)[5, 12]. Treatments duration mostly required 6-9 months on 69.1% patients. Patients with treatment duration less than 6 months considered as defaulted regimens.

ADRs occurrence happened in 103 patients or 15.8% from total number of patients. Type of ADRs are skin reaction 51 (7.8%), gastrointestinal reactions 16 (2.5%), hepatotoxicity 17 (2.6%), central nervous system reactions 2 (0.3%), skin along with gastrointestinal reactions 5 (0.8%), skin along with central nervous system reactions 6 (0.9%), gastrointestinal along with central nervous system reactions 4 (0.6%), gastrointestinal along with skin reaction and muscle ache 1 (0.2%), and the last is skin reaction along with flu like syndrome 1 (0.2%) from all total patients. Most common adverse reaction is skin reaction such as itchiness, rashes and any other kind of skin reactions. Common causes of skin reactions due to anti-tuberculosis drugs are isoniazid and rifampicin, rarely in use of pyrazinamide and ethambutol. Hepatotoxicity adverse reaction due to anti-tuberculosis is already widely noticed and there are many researches about these[4, 6, 9, 13-14]. American Thoracic Society (ATS) also issued an official ATS statement about Hepatotoxicity of Antituberculosis Therapy in 2006[15]. Common causes of hepatotoxicity are isoniazid, pyrazinamide and rifampicin, mostly in pyrazinamide use in regimens[16]. The result suggested that there are correlation between ADRs occurrence and patient's socio-demographics characteristics such as gender, age and race. We also recorded all risk factor that related to tuberculosis disease to know whether all these risk factor also related to ADRs occurrence, risk factor that we recorded include smoking status, alcohol use and drug abuse. These three risk factors are closely related on tuberculosis, but only smoking status that also related to ADRs occurrence while others two risk factors were not related to ADRs occurrence.

Management to ADRs occurrence mostly with add on medication, then followed by withhold the medication regimens, continue without changes and the last is change patient's treatment regimens. Add on medication such as antiemetic for relieving patient from minor gastrointestinal reactions (nausea or vomiting) and add a antihistamine agent for reducing minor skin reactions. On severe cases the clinicians stopped the medications and did a close evaluation of patient's medications. Philadelphia tuberculosis control program suggested if skin reaction appeared due to antimicrobial use first step we have to take is to discontinue of the drugs until the reaction resolved after that identify the causative agents by re-challenging (restarting) each drug[17]. Management for hepatotoxicity cases, depend on the liver function test elevated value and symptoms. Asymptomatic patients with LFT elevation <3-5xnormal, continue the medication with closely monitoring but if the LFT value elevation >3-5xnormal, then the medication should be stopped until return to baseline level. Symptomatic patient, when the symptom appeared we immediately have to stop the medication and do the LFTs test, then it depends on the LFTs result[17]. Philadelphia tuberculosis control program not mention about adding other medication to relieve patients from adverse reactions.

Among 653 patients there are 103 (15.8%) patients had an experience on adverse drug reactions, that's a quite large number and potentially interrupted patient's treatment and medication outcome. Management on adverse drug reactions mostly with add on medication which is potentially also add a new adverse reactions due to add on medication that at first to relieving patients from adverse reaction due to anti-tuberculosis drugs.

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**Table 1: Patients Distribution According to Socio-Demographic and BCG Vaccine History**

| Socio-Demographic Characteristic | | N (%) |
|---|---|---|
| Age | 18 – 54 years of age | 402 (61.6) |
| | >54 years of age | 251 (38.4) |
| | Minimum age | 18 |
| | Maximum age | 91 |
| | Median age | 48 |
| Gender | Male | 464 (71.1) |
| | Female | 189(28.9) |
| Race | Chinese | 342 (52.4) |
| | Malay | 218 (33.4) |
| | Indian | 59 (9.0) |
| | Others | 34 (5.2) |
| Smoking | Smoker | 313 (47.9) |
| | Non smoker | 340 (52.1) |
| Alcohol use | Alcoholic | 79 (12.1) |
| | Non alcoholic | 574 (87.9) |
| Drug abuse | Drug abuser | 60 (9.2) |
| | Non drug abuser | 593 (90.8) |
| HIV | Positive | 53 (8.0) |
| | Negative | 457 (70.0) |
| | Data not available | 143 (22.0) |
| Diabetes Mellitus | Yes | 170 (26.0) |
| | No | 483 (74.0) |

**Table 2: Type of Tuberculosis, Treatment and Treatment Duration of Anti-Tuberculosis Drugs**

| Type of Tuberculosis and Tuberculosis Treatment | | Number (n) | Percentage (%) |
|---|---|---|---|
| **Type of Tuberculosis** | Pulmonary Tuberculosis | 549 | 84.1 |
| | Extra-pulmonary tuberculosis | 79 | 12.1 |
| | Pulmonary and Extra-pulmonary tuberculosis | 25 | 3.8 |
| **TB treatment** | | | |
| **Intensive phase** | EHRZ | 530 | 81.2 |
| | HRZ | 86 | 13.2 |
| | SEHRZ | 10 | 1.1 |
| | HER | 7 | 1.5 |
| **Maintenance phase** | Others | 20 | 3.1 |
| | HR (daily) | 283 | 43.3 |
| | H2R2 (biweekly) | 244 | 37.4 |
| | Others | 31 | 4.7 |
| | Not on maintenance phase | 95 | 14.5 |
| **Duration of treatment** | 6 months | 157 | 24.0 |
| | 7 months | 46 | 7.0 |
| | 8 months | 58 | 8.9 |
| | 9 months | 190 | 29.1 |
| | 10 months | 12 | 1.8 |
| | 11 months | 14 | 2.1 |
| | 12 months | 34 | 5.2 |
| | Less than 6 months | 133 | 20.4 |
| | More than 12 months | 5 | 0.8 |
| | Not known | 4 | 0.6 |
| **Treatment Duration categories** | <6 months | 133 | 20.3 |
| | 6-9 months | 451 | 69.1 |
| | >9-12 months | 60 | 9.2 |
| | >12 months | 5 | 0.8 |
| | unknown | 4 | 0.6 |

**Table 3: Adverse Drug Reactions Type and Management**

| Type of ADRs and ADRs Management | | Number (n) | Percentage (%) |
|---|---|---|---|
| **Adverse Drug Reactions** | **Yes** | **103** | **15.8** |
| | **No** | **550** | **84.2** |
| **Type of Adverse Drug Reactions** | Skin reaction | 51 | 7.8 |
| | Gastrointestinal disturbance (nausea, vomiting, GI upset) | 16 | 2.5 |
| | Hepatotoxicity (hepatitis) | 17 | 2.6 |
| | CNS adverse reactions (dizziness, headache) | 2 | 0.3 |
| | | 5 | 0.8 |
| | Skin reaction and GI disturbance | 6 | 0.9 |

| | | | |
|---|---|---|---|
| | Skin reaction and CNS adverse reactions | 4 | 0.6 |
| | GI disturbance and CNS adverse reactions | 1 | 0.2 |
| | GI disturbance, skin reaction and muscleache | 1 | 0.2 |
| | Skin reaction and flu like syndrome | | |
| **Management** | Add on medication | 56 | 8.6 |
| | Withhold treatment | 40 | 6.1 |
| | Continue medication without change | 6 | 0.9 |
| | Change regimen | 1 | 0.2 |

**Table 4: Distribution of Patients According to Socio-Demographic and ADRs Occurrence**

| Demographic Characteristics | | ADRs Occurrence | | Total | p-value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| **Gender** | **Male** | 64 (9.8%) | 400 (61.2%) | 464 (71%) | 0.30 |
| | **Female** | 39 (6.0%) | 150 (23%) | 189 (29%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |
| **Age** | **18-54 years old** | 57 (8.7%) | 345 (52.8%) | 402 (61.5%) | 0.157 |
| | **>54 years old** | 46 (7.1%) | 205 (31.4%) | 251 (38.5%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |
| **Race** | **Malay** | 37 (5.7 %) | 181 (27.7%) | 218 (33.4%) | 0.129 |
| | **Chinese** | 59 (9.0%) | 283 (43.3%) | 342 (52.3%) | |
| | **Indian** | 5 (0.8%) | 54 (8.3%) | 59 (9.1%) | |
| | **Others** | 2 (0.3%) | 32 (4.9%) | 34 (5.2%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |

**Table 5: Patients Distribution According to Patients Lifestyle-Habits, and ADRs Occurrence**

| Lifestyle and Habits | | ADRs Occurrence | | Total | p-value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| **Smoking status** | **Yes** | 43 (6.6%) | 270 (41.3%) | 313 (47.9%) | 0.171 |
| | **No** | 60 (9.2%) | 280 (42.9%) | 340 (52.1%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |
| **Alcohol use** | **Yes** | 5 (0.8%) | 74 (11.3%) | 79 (12.1%) | 0.014 |
| | **No** | 98 (15%) | 476 (72.9%) | 574 (87.9%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |
| **Drug abuse** | **Yes** | 4 (0.6%) | 56 (8.6%) | 60 (9.2%) | 0.042 |
| | **No** | 99 (15.2%) | 494 (75.6%) | 593 (90.8%) | |
| | **Total** | 103 (15.8%) | 550 (84.2%) | 653 (100%) | |

**Table 6: Treatment and Treatment Duration Related to ADRs Occurrence**

| Treatment and Duration | | ADRs Occurrence | | Total (%) | p-value |
|---|---|---|---|---|---|
| | | Yes (%) | No (%) | | |
| **Intensive Phase** | **EHRZ** | 75 (11.5) | 455 (69.7) | 530 (81.2) | 0.169 |
| | **HRZ** | 18 (2.8) | 68 (10.4) | 86 (13.2) | |
| | **SEHRZ** | 3 (0.4) | 7 (1.1) | 10 (1.5) | |
| | **HER** | 2 (0.3) | 5 (0.8) | 7 (1.1) | |

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| | | | | | |
|---|---|---|---|---|---|
| | **Others** | 5 (0.8) | 15 (2.3) | 20 (3.1) | |
| | **Total** | 103 (15.8) | 550 (84.2) | 653 (100) | |
| **Maintenance Phase** | **HR (daily)** | 40 (6.1) | 243 (37.2) | 283 (43.3) | 0.000 |
| | **H2R2** | 39 (6) | 205 (31.4) | 244 (37.4) | |
| | **Others** | 18 (2.8) | 13 (2.0) | 31 (4.7) | |
| | **Not on maintenance** | 6 (0.9) | 89 (13.6) | 95 (14.5) | |
| | **Total** | 103 (15.8) | 550 (84.2) | 653 (100) | |
| **Treatment Duration** | **<6 months** | 21 (3.2) | 112 (17.1) | 133 (20.3) | 0.632 |
| | **6-9 months** | 75 (11.5) | 376 (5.7) | 451 (69.1 | |
| | **>9-12 months** | 6 (0.9) | 54 (8.3) | 60 (9.2) | |
| | **>12 months** | 1 (0.2) | 4 (0.6) | 5 (0.8) | |
| | **Not known** | 0 | 4 (0.6) | 4 (0.6) | |
| | **Total** | 103 (15.8) | 550 (84.2) | 653 (100) | |

Note :
E (Ethambutol), H (Isoniazid), R (Rifampicin), Z (Pyrazinamide), S (Streptomycin), HR (combination Isoniazid and Rifampicin daily), and H2R2 (combination isoniazid and rifampicin biweekly use)