# Adverse Drug Reactions Among Patients Being Treated For Multi-Drug Resistant Tuberculosis In Nairobi City County Health Facilities

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## Abstract

### Background

Increased incidence of Multidrug-resistant tuberculosis (MDR-TB) is eroding the gains made in controlling the disease. The drugs used to treat MDR-TB have several side effects which enhance morbidity and mortality associated with the disease.

### Objective

To determine the prevalence of adverse drug events among patients on MDR-TB therapy in Nairobi City County.

### Methods

A longitudinal study was carried out in four health facilities within Nairobi City County. It involved twenty- three participants who were on MDR-TB treatment selected through universal sampling. Eligible respondents were taken through a consenting process and those who concurred were included in the study. Data was collected using a researcher-administered questionnaire. The participants were interviewed and their responses entered accordingly. Analysis of the data was done using STATA version 13 and both inferential and descriptive analyses were used to generate the report.

### Results

Among the patients who were on therapy for drug-resistant tuberculosis, the main adverse drug events involved disturbances of the nervous system (91.3%), gastrointestinal (87%), musculoskeletal (73.9%), cardiovascular (43.5%) and endocrine (43.5%) systems. The other less common but serious adverse drug events were nephrotoxicity (6, 21.6%), hepatotoxicity (5, 21.7%) and rash (5, 21.6%). All the participants suffered from many adverse events and 12(52.2%) had experienced ten and below while 11(47.8%) had more than ten adverse events.

### Conclusion

MDR –TB therapy causes several adverse events involving most body systems.

**Key words:** *MDR-tuberculosis, Adverse drug reactions.*

## Introduction

Multi-drug resistant tuberculosis (MDR-TB) describes the disease caused by Mycobacterium tuberculosis strains that are resistant to at least isoniazid and rifampicin (1). Globally, MDR-TB is a threat to the gains made in the control of tuberculosis. According to the World Health Organization (WHO), there were an estimated 480 000 new cases of multidrug-resistant TB in 2015 (2). Drug resistance surveillance data show that 3.9% of new and 21% of previously treated TB cases were estimated to have had rifampicin-or multidrug-resistant tuberculosis. The incidence of MDR-TB was 4.4% among new cases in 2015 in Kenya (3). Drugs used for MDR-TB treatment, are grouped into 5 categories according to efficacy, the experience of use and drug class as shown in table 1. Treatment mainly involves the use of drugs from group 1-4.

**Table 1.** Drugs used in the treatment of MDR-TB

| Group | Drug |
|---|---|
| 1 | Pyrazinamide, Ethambutol, Rifabutin, and Isoniazid |
| 2 | Aminoglycosides – Kanamycin or Amikacin, Capreomycin |
| 3 | Fluoroquinolones-Levofloxacin, Moxifloxacin |
| 4 | Ethionamide (or protionamide), cycloserine Terizidone |
| 5 | Clofazimine, Linezolid, Amoxicillin/clavulanate, Thiacetazone, Imipenem/cilastatin, high-dose isoniazid, and Clarithromycin |

Occasionally depending on the response, group 5 agents can be added. Group 1 drugs are the most potent and best tolerated. Group 2 which consists of aminoglycosides is the first choice of an injectable agent. Patients who cannot tolerate aminoglycosides are given capreomycin. All

patients receive a group 3 medication and a group 4 agents because of their effectiveness and low cost. When two agents are needed, cycloserine can be added.

Terizidone can be used instead of cycloserine and is assumed to be equally efficacious. In Kenya, MDR-TB treatment is accomplished in two phases (4). The intensive phase and continuation phase lasts for 8 and 12 months respectively. Five drugs are used during the intensive phase and these are; Kanamycin or capreomycin, Protionamide, levofloxacin, cycloserine, and pyrazinamide. Drugs used in the continuation phase are; levofloxacin, protionamide, cycloserine, and pyrazinamide. Extensively drug-resistant tuberculosis (X-MDR- TB) is treated for a longer period. The intensive phase takes 12 months and drugs used are; capreomycin, moxifloxacin, para-aminosalicylate, clofazamine, and amoxicillin/ clavulanate. The continuation phase lasts for 18 months and drugs used are moxifloxacin, PAS, clofazimine and amoxicillin/ clavulanate. A shorter treatment regimen is being initiated among newly diagnosed MDR-TB cases which lasts for nine months.

Although the incidence of MDR-TB cases is on the rise, no previous study has been done to assess the effects of the drugs among patients in Nairobi City County. The objective of this study was to evaluate the adverse drug events of MDR-TB therapy.

# Methods

A retrospective longitudinal design was used. All the participants suffering from drug-resistant tuberculosis and attending health facilities in Nairobi City County for treatment were eligible to participate in the study. The participants were; on drug-resistant TB drugs for at least one month, aged 18 years and above, able to communicate effectively and consented to participate in the study.

Approval to carry out the study was given by Kenyatta National Hospital- University of Nairobi Ethical and Research Committee. Permission was also granted by the department of health of Nairobi City County. The managers for the respective health facilities where data were collected also gave a nod.

All the twenty-three participants who were accessible and eligible during the study period were assessed. A researcher administered questionnaire was used to collect data. The participants were individually invited for a face to face interview and responses entered into the questionnaire. This was done in a place within the health facility where only the researcher and participant were present to ensure confidentiality. These facilities were Kenyatta National Hospital and several health centers including; Dandora phase I and II, Westlands, Bahati, and Langata. Some of the data that could not be obtained directly from the participant were abstracted from the clinic records and entered into the questionnaire. This included the serum levels of potassium, creatinine, hemoglobin, liver enzymes and thyroid hormones. Hepatotoxicity was diagnosed if the serum level of alanine aminotransferase was elevated. Nephrotoxicity was detected if the serum creatinine was elevated. Low or high serum potassium levels were interpreted as hypokalemia and hyperkalemia respectively. Anemia was characterized by low level of hemoglobin.

# Results

## Sociodemographic characteristics

Twenty-three participants were recruited in the study and 17(73.9%) were males (Table 2). The the majority (13, 56.5%) of the respondents were married. The mean age was 37.1(SD+/- 11.4) years and the range was 20 to 50 years. Fifteen (65.2%) respondents were below forty years of age Eleven (47.8%) participants had normal body mass index but 9(39.1%) had lower than required. All the participants were literate, 6(26.1%) had a primary education while 12(52.2%) had attained the secondary level of education. Previous lifestyle habits before diagnosis and initiation of treatment of the disease were smoking and alcoholism which were associated with 10(43.5%) respondents. Eleven (47.8%) participants had previous episode of tuberculosis infection. The comorbidities present were human immuno-deficiency virus infection (10, 43.5%), malnutrition (9, 39.1%) and diabetes mellitus (1, 4.4%) respectively.

**Table 2.** Socio demographic characteristics (N=23)

| Variable | Frequency | Percent |
|---|---|---|
| ***Sex*** | | |
| Male | 17 | 73.9 |
| Female | 6 | 26.1 |
| ***Marital status*** | | |
| Married | 13 | 56.5 |
| Single | 10 | 43.5 |
| ***Age category (years)*** | | |
| 18-30 | 8 | 34.8 |
| 31-40 | 7 | 30.4 |
| Above 41 | 8 | 34.8 |
| ***Body mass index*** | | |
| Below 18.5 | 9 | 39.1 |
| 18.6-25 | 11 | 47.8 |
| 25.1-30 | 2 | 8.7 |
| Above 30 | 1 | 4.4 |
| ***Level of education*** | | |
| Primary | 6 | 26.1 |
| Secondary | 12 | 52.2 |
| Tertiary | 5 | 21.7 |
| ***Comorbidities*** | | |
| HIV infection | 10 | 43.5 |
| Malnutrition | 9 | 39.1 |
| Diabetes mellitus | 1 | 4.4 |
| | | |
| Alcoholism | 10 | 43.5 |
| Tobacco smoking | 10 | 43.5 |
| Previous hospitalization | 3 | 13.0 |
| Previous TB infection | 11 | 47.0 |

## Prevalence of adverse drug events

Several drugs were used depending on the phase of therapy (Figure 1). Six (26%) respondents were in the intensive phase of treatment where five drugs were used including; kanamycin (kn) or capreomycin (Cm), levofloxacin, protionamide(PTO), cycloserine (CS), and pyrazinamide. Another six (26%) patients were on high

dose isoniazid (H), ethambutol (E), pyrazinamide (Z), kanamycin (kn), moxifloxacin (Mfx), protionamide, and clofazamine (Cfx). The continuation phase was accomplished with four drugs including; levofloxacin (Lev), protionamide, cycloserine, and pyrazinamide. (Figure Next page)

The participants experienced several adverse drug events as shown in figure 2 and table 3 respectively. Twenty-one (91.3%) participants exhibited nervous system (NS) disturbances which included; drowsiness, tingling sensation, headache, dizziness, insomnia, depression, and nightmares. Gastrointestinal tract (GIT) disturbances were the second most prevalent where 20 (87%) participants were affected and complained of nausea, vomiting, abdominal pain, flatulence,

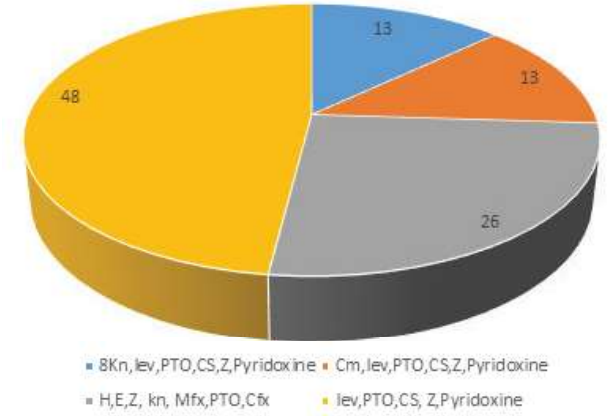


**Figure 1.** Types of drug regimens

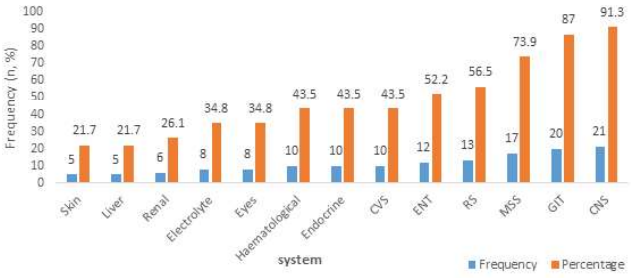


**Figure 2.** Systemic categorization of adverse drug events due to MDR-TB drugs.

excessive salivation, diarrhea, constipation, abdominal cramps, loss of appetite, black tarry stool, dry mouth and mouth ulcers. Seventeen (73.9%) respondents suffered from the musculoskeletal system (MSS) adverse effects including joint pains, backache, muscle spasms and pain in the big toe. Respiratory system was affected in 13(56.5%) participants who presented with a cough, chest pain and dyspnea. Twelve (52.2%) respondents had ear, nose, and throat (ENT) problems and the most common was a loss of hearing. Cardiovascular system (CVS) was affected in 10(43.5%) cases who had palpitations. Among the 10(43.5%) who had endocrine disturbances, 7(30.4%) had hypothyroidism and 5(21.7%) experienced sexual dysfunction. Eight (34.8%) participants complained of visual disturbances while 5(21.7%) and 3(13%) were victims of hyperkalemia and hypokalemia respectively. Among the 10(43.4%) participants with hematological problems,

**Table 3.** Prevalence of adverse drug events of MDR-TB therapy (N=23)

| Adverse event | n | % | Adverse event | n | % |
|---|---|---|---|---|---|
| Nephrotoxicity | 6 | 26.1 | Mental depression | 8 | 34.8 |
| Hypothyroidism | 7 | 30.4 | Agitation | 6 | 26.1 |
| Hyperkalemia | 5 | 21.7 | Cough | 6 | 26.1 |
| Hypokalemia | 3 | 13 | Chest pain | 5 | 21.7 |
| Anemia | 9 | 39.1 | Dyspnea | 4 | 17.4 |
| Hepatotoxicity | 6 | 26.1 | Painful urination | 3 | 13 |
| Nausea | 20 | 87 | Frequent urination | 5 | 21.7 |
| Vomiting | 15 | 65.2 | Reduced urine | 3 | 13 |
| Abdominal pain | 12 | 52.2 | Joint pains | 15 | 65.2 |
| Flatulence | 17 | 73.9 | Backache | 9 | 39.1 |
| Excessive salivation | 15 | 65.2 | Pain in the big toe | 3 | 13 |
| Diarrhea | 1 | 4.4 | Muscle spasms | 3 | 13 |
| Constipation | 3 | 13 | Fullness in the ears | 2 | 8.7 |
| Abdominal cramps | 12 | 52.2 | Deafness | 10 | 43.5 |
| Loss of appetite | 11 | 47.8 | Vertigo | 1 | 4.4 |
| Black tarry stool | 2 | 8.7 | Sore throat | 1 | 4.4 |
| Dry mouth | 5 | 21.7 | Sexual dysfunction | 5 | 21.7 |
| Mouth ulcers | 1 | 4.4 | Bleeding | 2 | 8.7 |
| Palpitations | 7 | 30.4 | Malaise | 14 | 60.9 |
| Headache | 9 | 39.1 | Jaundice | 1 | 4.4 |
| Dizziness | 9 | 39.1 | Visual impairment | 7 | 30.4 |
| Confusion | 4 | 17.4 | Weight gain | 3 | 13 |
| Irritability | 8 | 34.8 | Fever | 1 | 4.4 |
| Nightmares | 6 | 26.1 | Paleness of the skin | 1 | 4.4 |
| Drowsiness | 11 | 47.8 | Tremor | 2 | 8.7 |
| Speech problems | 2 | 8.7 | Rash | 5 | 21.7 |
| Suicide thoughts | 5 | 21.7 | | | |
| Tingling sensation | 10 | 43.4 | | | |
| Insomnia | 9 | 39.1 | | | |

anemia was the most common. The other less common but serious adverse drug events were nephrotoxicity (6, 21.6%), hepatotoxicity (5, 21.7%) and rash (5, 21.6%). All the participants suffered from many adverse events and 12(52.2%) experienced ten and below while 11(47.8%) had more than ten.

## Bivariate analysis of adverse drug events and MDR-TB regimens

A bivariate analysis was conducted using Fischer's exact test between the type of MDR-TB regimen used and adverse drug events and the results are shown in table 4.

**Table 4.** Association between adverse drug events and MDR-TB regimens (N=23)

| System/Organ | Type of regimen | | | | P value |
|---|---|---|---|---|---|
| | R1 (n, %) | R2 (n, %) | R3 (n, %) | R4 (n, %) | |
| Renal | 0 | 2(8.7) | 4(17.4) | 0 | 0.097 |
| Endocrine | 0 | 1(4.3) | 7 (30.4) | 2(8.7) | 0.267 |
| Electrolyte | 0 | 2 (8.7) | 3 (13) | 3 (13) | 0.408 |
| GIT | 3 (13) | 3 (13) | 8 (34.8) | 6 (26.1) | 0.590 |
| CVS | 1(4.3) | 1(4.3) | 6 (26.1) | 2(8.7) | 0.927 |
| CNS | 3 (13) | 3 (13) | 10 (43.5) | 5 (21.7) | 1 |
| RS | 2 (8.7) | 2 (8.7) | 5 (21.7) | 5 (21.7) | 0.927 |
| MSS | 2 (8.7) | 3 (13) | 8 (34.8) | 4 (17.4) | 0.912 |
| ENT | 2 (8.7) | 2 (8.7) | 7 (30.4) | 1(4.3) | 0.261 |
| Eyes | 1(4.3) | 1(4.3) | 6 (26.1) | 0 | 0.138 |
| Skin | 1(4.3) | 0 | 1(4.3) | 3 (13) | 0.217 |
| Haematological | 0 | 1(4.3) | 4 (17.4) | 2(8.7) | 0.836 |
| Liver | 0 | 0 | 4 (17.4) | 1(4.3) | 0.515 |

***R1-8kn, lev, PTO, CS, Z, Pyridoxine R2- Cm, lev, PTO, CS, Z, Pyridoxine***

***R3- lev, PTO, CS, Z, Pyridoxine R4- H, E, Z, Kn, Mfx, PTO, Cfx***

Generally, more adverse events were experienced by the participants who were using the R3 and R4. Despite this observation, there was no statistical relationship between the type of MDR-TB regimen used and adverse events that were experienced by the participants.

## Bivariate analysis of adverse drug events and phase of MDR-TB therapy

Additional analysis was done using Fischer's exact test between the phase of therapy and adverse drug events and the results are shown in table 5.

**Table 5.** Association between adverse drug events and phase of therapy (N=23)

| System/ Organ affected | Phase of therapy | | P value |
|---|---|---|---|
| | Intensive phase (n, %) | Continuation phase (n, %) | |
| Kidney | 3 (13) | 3 (13) | 1 |
| Endocrine | 2 (8.7) | 8 (34.8) | **0.012*** |
| Electrolytes | 4 (17.4) | 4 (17.4) | 1 |
| Gastrointestinal tract | 12 (52.2) | 8 (34.8) | 0.093 |
| Cardiovascular | 4 (17.4) | 6 (26.1) | 0.414 |
| Nervous | 11 (47.8) | 10 (43.5) | 1 |
| Respiratory | 8 (34.8) | 5 (21.7) | 0.414 |
| Musculoskeletal | 9 (39.1) | 8 (34.8) | 1 |
| Ear | 5 (21.7) | 7 (30.4) | 0.414 |
| Eyes | 2 (8.7) | 6 (26.1) | 0.089 |
| Skin | 4 (17.4) | 1 (4.3) | 0.317 |
| Blood | 4 (17.4) | 3 (13) | 1 |
| Liver | 1 (4.3) | 4 (17.4) | 0.155 |

****- Statistically significant p-value***

Endocrine disturbances were more common in the continuation phase than an intensive phase and the difference was statistically significant (p=0.012). The other adverse drug events were present in both phases and the differences in their occurrence were not statistically significant between the two phases.

# Discussion

Male predominance was observed in the study which has been observed elsewhere (5). Both genetic and behavioral characteristics are predisposition factors. Males are known to be more outgoing than women and androgens are known to suppress the immune system of the body. About a third of the participants were undernourished which was lower than that from an Indian study (5). Tuberculosis is a catabolic disease and also cause anorexia leading to loss of body mass. HIV coinfection had a prevalence of 43.5% which was quite high. The disease destroys the body immune system especially the cell-mediated one which protects the body against intracellular microorganisms. Tobacco smoking and alcoholism are also known to be immunosuppressant in different ways. Forty-seven percent of the respondents had relapsed tuberculosis suggesting that the resistance was acquired against first-line drugs due to different reasons such as non-adherence or poor quality drugs.

The most common side effects were central nervous disturbances (91.3%) which were most likely due to cycloserine, isoniazid, levofloxacin, and moxifloxacin. The prevalence of these adverse drug events was higher than what was noted in a study from South Korea (6). The most common symptoms were drowsiness, depression, and insomnia which were more prevalent than what was found in an Ethiopian study (7). Peripheral neuropathy which presented as tingling and burning sensations in the extremities was mainly due to isoniazid, ethambutol, and prothionamide. Isoniazid is a competitive inhibitor of pyridoxine in the nerves. Gastrointestinal disturbances such as nausea, vomiting, and abdominal pain had a prevalence of 87% which was higher than a similar study done in Namibia (8) and drugs that were are implicated included prothionamide, quinolones, isoniazid, and pyrazinamide. Musculoskeletal side effects such as muscle spasms, backache, and joint pains were probably due to the accumulation of uric acid triggered by pyrazinamide which reduces its excretion. Ototoxicity manifesting as hearing loss, dizziness and vertigo were due to Kanamycin and capreomycin which damages the auditory nerve and the prevalence was higher than from a Korean study (6). Visual impairment was reported by 30.4% of the respondents which was higher than that from an Ethiopian study (8). Ethambutol was probably the culprit since it damages the optic nerve. Hepatotoxicity occurred in 26.1% of the respondents which was higher than that from a Korean study (6) and drugs responsible were protionamide, isoniazid, and pyrazinamide which are known to damage the hepatocytes. Nephrotoxicity occurred in 26.1% of the respondents which was higher than that observed in Ethiopia (8) and the drugs responsible were kanamycin and capreomycin. The damage to the kidneys was the main cause of hyperkalemia, hypokalemia, and changes in the frequency of urination. Anemia that occurred in 39.1% of the cases and was likely due poor feeding habits and

myelosuppression which usually occurs in chronic illnesses.

## Conclusion

Drug-resistant tuberculosis was more common in males than females. Many participants suffered from the adverse events of drugs which became less severe as the treatment progressed from intensive to the continuous phase. These adverse events manifested in all body systems with the nervous and gastrointestinal tract being most affected.

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