Adverse Drug Events Reported to EFDA from TICs through aDSM: Preliminary Report

Executive Summary

Treatment of tuberculosis need multidrug combinations, which is associated with increased incidence of adverse drug reactions that would be a barrier to the introduction of new drugs and novel regimens. The introduction and/or utilization of new anti-TB drugs can be slowed down or prevented due to lack of capacity in implementing active TB-drugs safety monitoring and management. As part of the global recommendation, the national TB program and Ethiopian Food and Drug Authority have set active TB-drugs safety monitoring and management as an essential requirement for the implementation of active monitoring, proper management, recording and reporting of AEs when introducing new anti-TB drugs and regimens. Hence, proper implementation of active TB-drugs safety monitoring and management is evaluated by the presence of effective monitoring, detection, management, recording, and reporting of adverse drug events of MDR-TB drugs.

GHSC-PSM is tasked by USAID to support the government in the management of TB commodities and its technical assistance including pharmacovigilance support to Ethiopian Food and Drug Authority. Since then, GHSC-PSM has been supporting the authority in implementing joint plan on safety monitoring and reporting of TB drugs including MDR-TB drugs. Since, March or April 2020, GHSC-PSM have been supporting EFDA, RHBs, TICs, TFCs and MOH-NTP to better detect, manage, report and prevent ADEs through supporting face to face discussions, site level supports to TICs and TFCs with ROSS, targeted supportive supervisions, printing and distribution of ADE reporting tools, development and provision of PV training to Healthcare professionals, and supporting TICs and TFCs to better detect and report ADEs to EFDA.

Since the implementation of aDSM, ADE reports experienced by MDR-TB patients have been received by EFDA from TICs throughout the country. However, these national ADE data is not yet comprehensively aggregated and analyzed to generate information for decision-making. Hence, it is important to analyze the ADE reports received by EFDA so far to identify the common ADEs and Serious adverse events (SAEs) regimens/drugs suspected to cause the ADEs and factors contributing to the occurrence of ADEs. This report therefore presents the description of the national ADEs data received by EFDA between 2017 to 2020.

Acknowledgement

List of Abbreviations/Acronyms

ADRs	Adverse Drug Reactions
ADEs	Adverse Drug Events
PV	Pharmacovigilance
MDR-TB	Multidrug-Resistant Tuberculosis
NTP	National TB Programs
TICs	TB Treatment Initiation Centers
EFDA	Ethiopian Food and Drug Authority
TLD	Tenofovir, Dolutegravir, Lamivudine
TFCs	
ARV	Antiretroviral
aDSM	Active Drug Safety Monitoring
DTG	Doultegarvir
Am	Amikacin
Bdq	Bedaquiline
Cm	Capreomycin
Cfz	Clofazimine
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol

H	Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
Lnz	Linezolid
Mfx	Moxifloxacin
PAS	Paminosalicylic acid
Pto	Prothionamide
Z	Pyrazinamide
R	Rifampicin
STR	Short Term Regimen
LTR	Long Term Regimen
SAE	Serious Adverse Event
TMP/SMX	Trimethoprim and Sulfamethoxazole
3TC	Lamivudine
TDF	Tenofovir
NVP	Nevirapine
HAART	Highly Active Antiretroviral Treatment
LPVr	Lopinavir

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1. Background

Multidrug-resistant tuberculosis (MDR-TB) has become a major public health problem, especially in developing countries, where the MDR-TB burden is the highest. Management of MDR-TB is a significant challenge to the global healthcare system due to the complexity and long duration of the MDR-TB treatment. Health programs that systematically monitor patient safety are in a better position to prevent and manage Adverse Drug Reaction (ADR) improve health-related quality of life, and improve treatment outcomes. Likewise, national TB programs (NTP) that actively pursue drug-safety monitoring and management are better prepared to introduce and implement new tuberculosis (TB) drugs and novel regimens.

Ethiopia has been implementing different regimens for treatment of RR/MDR-TB and introduced new MDR-TB drugs (Bedaquiline (Bdq) and delamanid (Dlm) and repurposed drugs (clofazimine and linezolid) for treatment of MDR-TB following WHO recommendations supported by in-country multi-site observational studies. The safety profiles of new drugs are not well established as these drugs did not complete their 3rdphase of clinical trial and the safety profiles of repurposed drugs are not yet fully understood when used in the MDR-TB regimen for a longer period.

The WHO recommends that countries introducing new drugs and novel treatment regimens for MDR-TB should develop and implement a system for active pharmacovigilance (PV) as one of the five conditions to be met when these drugs are used to treat MDR-TB patients allowing for detection, management, and reporting of ADRs.

Ethiopia has introduced Active Drug safety monitoring and management (aDSM) as part of the introduction of new TB drugs and novel MDR-TB regimens and different activities including trainings, sensitization workshops, and supportive supervisions have been conducted to strengthen the system. All NTP sites (TB treatment initiation centres (TICS) treating eligible patients with new and repurposed medicines, and novel MDR-TB regimens require to implement aDSM and hence monitor, manage, record and report ADEs experienced by patients treated with MDR-TB drugs. The recording and reporting activities of aDSM primarily target the serious adverse events (SAEs) as a priority requirement. MDR-TB treatment sites may also monitor other ADEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

Starting from July 2019, GHSC-PSM have been supporting Ethiopian Food and Drug Authority (EFDA) in safety monitoring and reporting of medicines mainly PV of new Antiretroviral (ARVs)

including doultegravir (DTG) and DTG containing regimens such as tenofovir, dolutegravir, lamivudine (TLD). Since then, the project has been supporting EFDA, regional health bureaus (RHBs), and health facilities to conduct different health system interventions including orientation trainings, face-to-face discussions, supportive supervisions, drug use evaluations and printing and distribution of Adverse drug event(ADE) reporting forms. As a result of this and other stakeholders support, the total number of ADE reports received by EFDA has increased from an average of 700 ADE reports per year to 1400 ADE reports per year for two subsequent years.

Again, starting from April 2020, GHSC-PSM is tasked by USAID to support the government in the management of TB commodities and its technical assistance including PV support to EFDA. Since March/April 2020, GHSC-PSM have been supporting EFDA, RHBs, TICs, TFCs and MOH-NTP to better detect, manage, report and prevent ADEs. Since the introduction of aDSM, different activities were conducted by ministry of health (MOH) & EFDA in collaboration with GHSC-SPM including Program sensitization workshops, face to face discussions, site level supports to TICs and TFCs with ROSS, targeted supportive supervisions, drug use evaluations, printing and distribution of ADE reporting tools, development and provision of PV training to HCP. In addition, PSM is supporting TICs and TFCs to detect and report ADEs to EFDA.

Since the implementation of aDSM, ADE reports experienced by MDR-TB patients have been received by EFDA from TICs throughout the country. However, these national ADE data is not yet comprehensively aggregated and analyzed to generate information for decision-making. Hence, it is important to analyze the ADE reports received by EFDA so far so to identify the common AEs and SAEs, regimens/drugs suspected to cause the ADEs and factors contributing to the occurrence of ADEs. This report therefore presents the description of the national ADE data received by EFDA between 2017-2020.

2. Objectives

2.1 General Objective

- To present the national adverse drug events data experienced by patients taking MDR-TB drugs in TB-treatment initiation centers of Ethiopia from 2017-2020.

2.2 Specific Objectives

- To describe the sociodemographic characteristics of patients experienced ADEs

- To identify the common ADE reporter TICs and professionals
- To determine the extent of ADEs reported on patients with MDR-TB drugs
- To discuss the trend of ADE reports to EFDA
- To describe the common types of ADEs reported
- To identify the common regimens and suspected drugs related with ADEs reported
- To identify the extent of serious and severe ADEs reported on patients with MDR-TB drugs
- To identify common concomitant medications and medical histories of patients experiencing ADEs
- To describe outcomes/sequel of ADEs reported

3. Methodology

An excel data aggregation form was prepared using the monthly AE line listing form. ADE reports received by EFDA through the monthly AE line listing form, yellow form, and e - reporting from 2017 to May 2020 were entered to the data aggregation tool. After thorough data cleaning, data analysis was performed using Excel and SPSS and simple descriptive statistics was used to present the data including frequency, percentage, and mean. Tables and figures were used to present the data.

4. Results

According to the MOH-NTP, 708, 720, 658 and 579 patients received MDR-TB treatment in 2017[1], 2018, 2019 and 2020, respectively. Since 2017, EFDA received a total of 392 valid[2] ADE reports from MDR-TB treatment initiation centers (TICs) throughout the country. The aggregate results of the analysis presented as follows.

4.1. Sociodemographic Characteristcs of ADE Reports

Out of the total 392 ADE reports, 170 (43.4%) were males and 209 (53.3%) were females and the rest 13 (3.3%) were with missing data. Regarding age of patients, the mean age of patients who

[1] Even though MDR-TB treatment is started before, ADE data recording, reporting and documentation through the implementation of active TB-drugs safety monitoring and management (aDSM) is formally started since 2017.
[2] Valid ADE report means in this report, an ADE report that at least contains the adverse event description or name or code regardless of other data completeness.

experienced ADR was 34 years (range 7-80 years); the most common age range who experienced ADE was 18-35 years, which accounts 59.7% of the total cases reported.

Table 1: Sociodemographic characteristcs of ADE reports

Characteristics	Category	Frequency (%)
Age	7-18	15 (3.8%)
	18-35	234 (59.7%)
	36-59	111 (28.3%)
	60-80	28 (7.2%)
	Missing	4 (1.0%)
Sex	Female	209 (53.3%)
	Male	170 (43.4%)
	Missing	13 (3.3%)

4.2. Common ADE reporters, TICs and professionals: Reporters information

So far, EFDA received ADEs from only 13 health facilities (TICs) out of the total 67 TICs throughout the country. This makes the percentage of reporter TICs only 19.4%. Of these TICs, two hospitals, namely ALERT Hospital and St.Peter Hospital, contributed to 305 (77.8%) ADE reports (Figure 1). Regarding reporters profession, Nurses were the top ADE reporters which accounts 152 (34%) and pharamcists are among the least reporters of ADEs in this program (Figure 2).

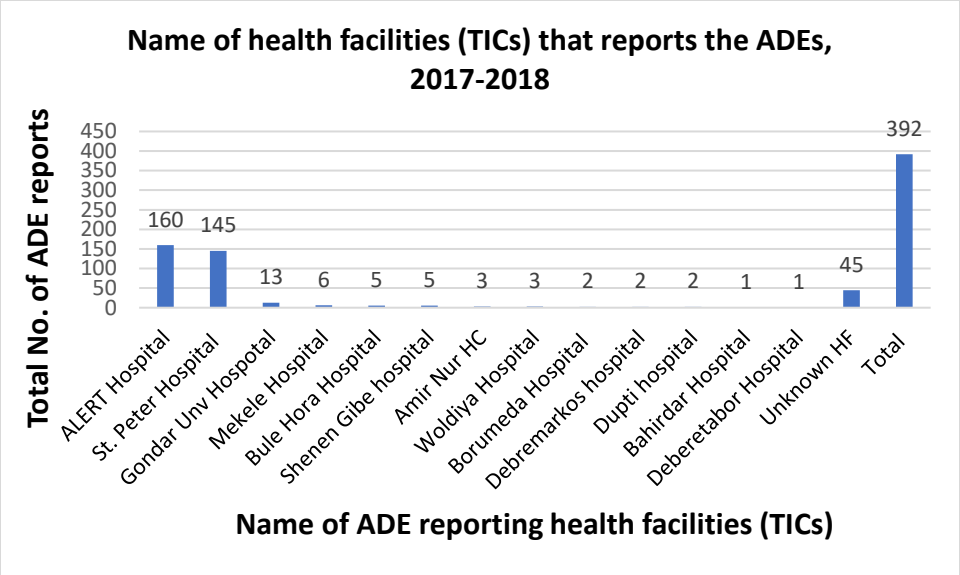

Figure 1: Name of health facilities (TICs) that reports the ADEs

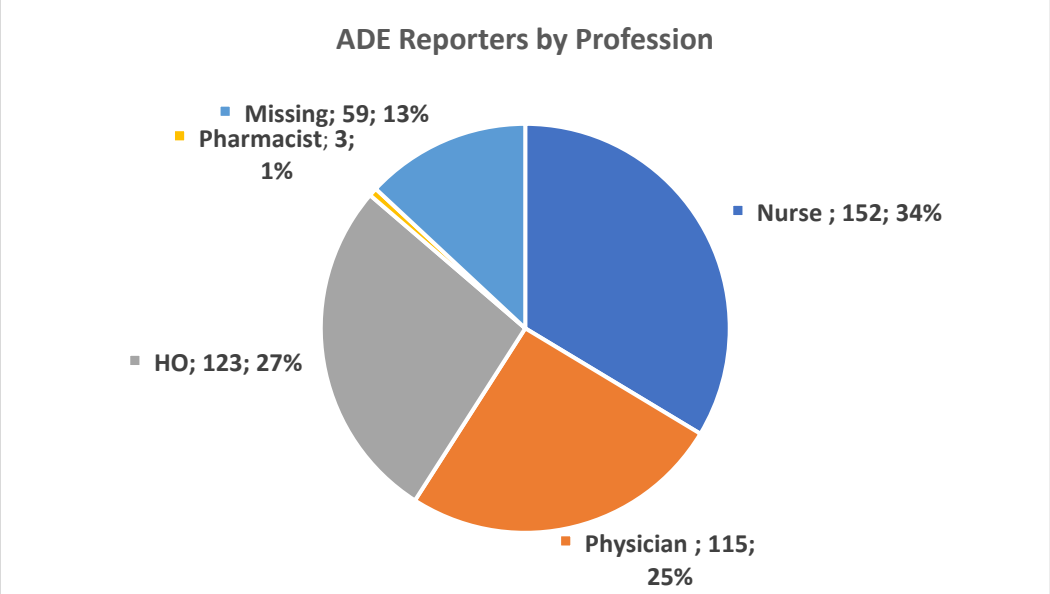

Figure 2: Profession of ADE reporters from TICs

4.3. Trends of MDR-TB Cases (2017-2020)

As depicted in figure 3 below, even though the number of MDR-TB cases showed a mild increase in the year 2018 compared to 2017, but the incidence of MDR-TB cases showed a decreasing pattern in the year 2019 and 2020.

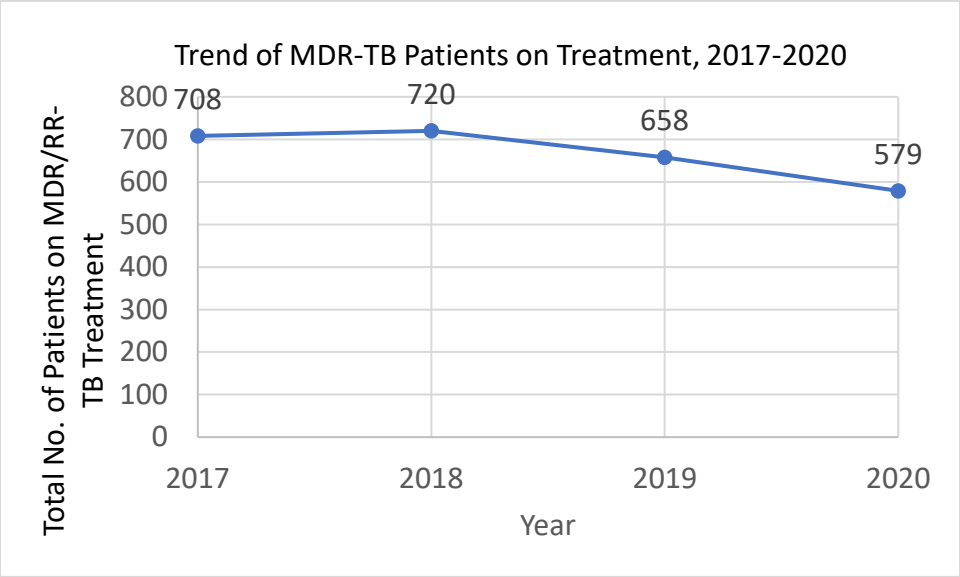

Figure 3: Trend of MDR-TB Patients on Treatment, 2017-2020

4.4. Common Types of ADEs Reported

Among the top 10 reported ADEs, majority were vomiting (13%) and epigastric pain (11.2% followed by nausea (10.2), Peripheral neuropathy (8.7%), joint pain (14.38%), and respiratory (7.8%). The remaining top 10 ADEs reported depicted in figure 2 below. The list of all reported ADEs associated with MDR-TB treatment annexed for reference (Annex 1).

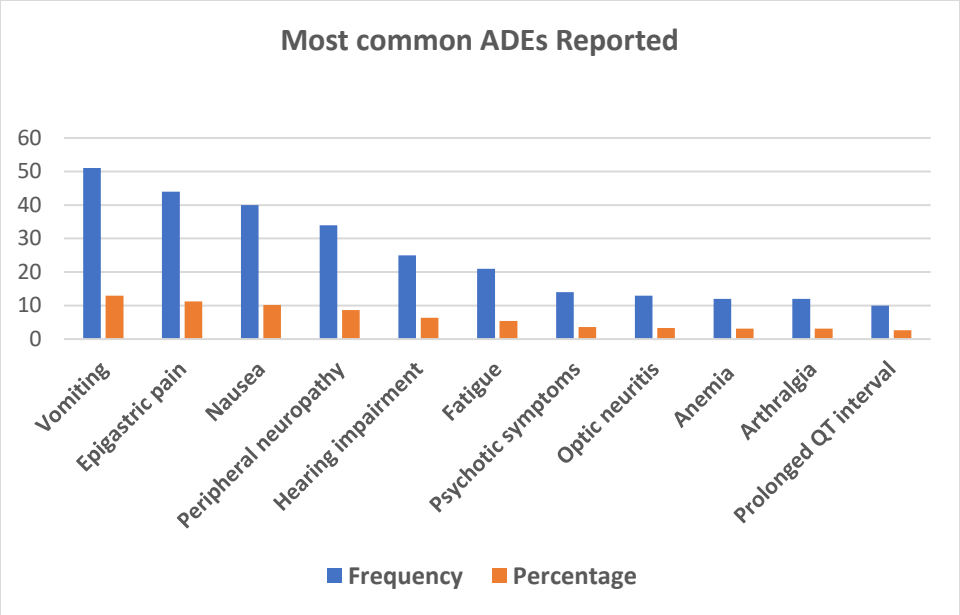

Figure 3: Common Reported ADEs (top 10) with MDR-TB treatment

Table 2: Categorization of ADEs Reported (Based on national Classification)

S.N	ADEs category	Frequency	Percentage
1	Nausea & Vomiting	91	23.2
2	Gastritis	44	11.2
3	Peripheral neuropathy	34	8.7
4	Seizure	4	1
5	Hearing impairment	28	7.2
6	Depression & Anxiety	2	0.6
7	Psychiatric symptoms	22	5.3
8	Hypothyroidism	1	0.3
9	Drug induced hepatic impairment	2	0.5
10	Renal toxicity	4	1
11	Electrolyte disturbance	1	0.3
12	Optic neuritis	13	3.3
13	Arthralgia, Arthritis	12	3.1
14	Prolonged QT interval	10	2.6
15	Others (PCP, Pregnancy, tooth ache, tendinitis, SOB, Photophobia, shoulder pain , death, syncope,	124	31.6

Among the total ADEs reports with MDR-TB treatments, the majority 138 (35.2%) of ADEs reported were associated with GI problems such as nausea, vomiting and Epigastric pain followed by neurological, Ophthalmologic, psychiatric and dermatologic problems (table 3).

Table 3: System Based ADEs Classification

S.N	ADEs category	Frequency	Percentage
1	GI problems (Nausea & Vomiting, Diarrhea, Epigastric pain, Abdominal pain and cramp)	138	35.2
2	Neurological problems (Seizure, peripheral neuropathy, numbness, paresthesia, headache & burning sensation)	57	14.5
3	Dermatologic problems (skin rash, itching, allergic reaction, skin discoloration, skin dryness, injection site reaction)	19	4.9
	Psychiatric problems (Depression, anxiety, insomnia, mood disturbance, sleep disturbance, confusion & delusion)	26	6.6
4	Ophthalmologic problems (Vision problem, blurred vision, optic neuritis, conjunctivitis, photophobia)	51	13
5	Musculoskeletal (Arthralgia , Myalgia, joint and limb swelling, tendinitis, joint pain, shoulder pain)	27	6.9
6	Ototoxicity (hearing loss, tinnitus)	28	7.1
7	Renal problems and electrolyte disturbance (decreased urine output, hypokalemia, Flank pain)	9	2.3
8	Respiratory problems (SOB, Cough, hemoptysis, chest pain & PCP)	9	2.3
9	Myelosuppression (Anemia, Pancytopenia)	15	3.8
10	Others (Fever, hypothyroidism, toothache, hypoglycemia & syncope, pregnancy, liver enzyme elevation, death, QT prolongation, loss of appetite, xerostomia, back pain, fatigue)	13	3.3

Based on ADEs of special interest, Peripheral neuropathy was found the leading ADES reported 41 (10.5) followed by ototoxicity, 28 (7.2%) and psychiatric, 26 (6.6%). The details of the rest of ADEs described in (Annex 2).

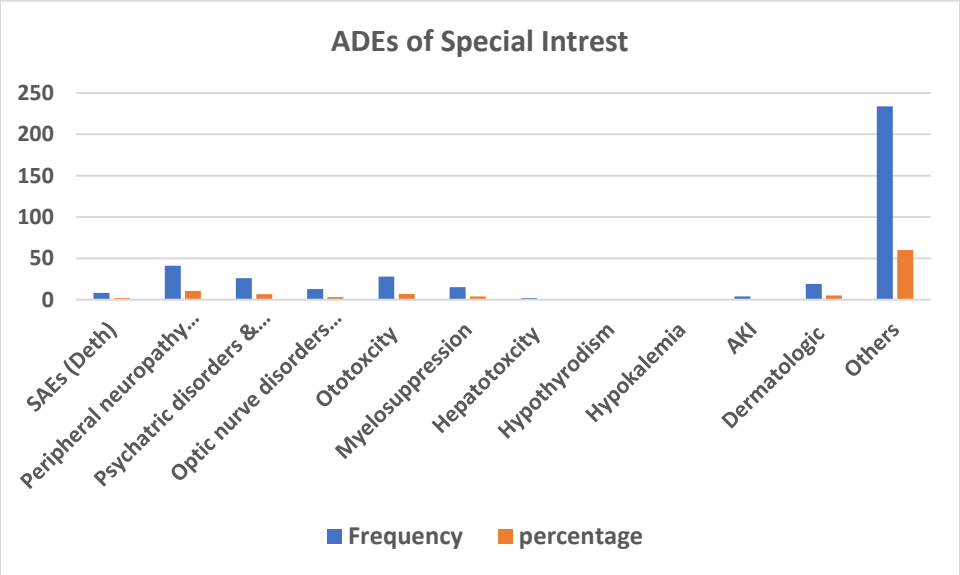

Figure 4: List of ADEs of special interest

4.5. Medical Histories of Patients Experiencing ADEs and Concomitant Medications

4.5.1. Comorbid Conditions

As indicated in table 5 below, from the total 392-repoted cases, 92 patients reported as having other comorbidities whereas the remaining 300 cases did not show any descriptions for the presence of comorbidities. Of these identified comorbidities, RVI found as most frequently reported comorbid condition following severe acute malnutrition (SAM), Diabetes Mellitus (DM), Chronic Kidney Disease (CKD), Hypothyroidism, epilepsy and heart diseases. Comorbid conditions with less frequency reported as others.

Table 4: Co-morbidities among the reported cases

S.N	Co-Morbidity	Frequency	Percentage
1	RVI	49	12.5
2	DM	8	2
3	CKD	7	1.8
4	SAM	10	2.6
5	Epilepsy	4	1
6	Hypothyroidism	5	1.3
7	Heart diseases (HTN, HF)	4	1
8	Others *	5	1.3
9	ADEs without comorbidity description	300	76.5

***:** Liver diseases, vaginal candidiasis, Cancers, Psychosis, DVT, Anemia, and Asthma

4.5.2. Concomitant Medications Reported

Among the prescribed concomitant medications (individual and combined regimen) for other comorbid conditions in patients with MDR-TB treatment, TDF/3TC/DTG with TMP/SMX (4.6%) was the dominant regimen following TDF/3TC/DTG and HAART (3.6%) .The remaining concomitant medications described in table 7.

Table 5: Concomitant medications reported in patients with MDR-TB treatment

S.N	Concomitant Medication	Frequency	Percentage	S.N	Concomitant medication	Frequency	Percentage
1	TDF/3TC/DTG, TMP/SMX	18	4.6	11	Thyroxin	3	0.8
2	TDF/3TC/DTG	14	3.6	12	Risperidone	2	0.6
3	HAART (Unspecified regimen)	14	3.6	13	Fluoxetine	2	0.6
4	Plumpynut	13	3.3	14	Bromazepam, Na Valproate	4	1
5	TDF/3TC/NVP	7	1.8	15	Amitriptyline	2	0.6
6	Potassium Chloride	6	1.6	16	Cefatzidime, Vancomycin, Metronidazole	5	1.3
7	TDF/3TC/NVP, TMP/SMX	4	1	17	Insulin (NPH)	4	1
8	TDF/3TC/EFV,TMP/SMX	3	0.8	18	ATZ, 3TC, NVP	4	1
9	TDF/3TC/LPVr	4	1	19	Others	32	8.2
10	TDF/3TC/ATZr, TMP/SMX	2	0.6				

4.6. Common Regimens Described in ADEs reporting in Patients with MDR-TB Treatment

As described in table 6 below, from a total 392 reported ADEs, more than half (55.6%) of the cases were received LTR (Fully Oral Longer RR/MDR-TB) regimens and about (18.4%) of the reported cases were had received STR (shorter all oral MDR-TB) regimes while the remaining MDR-TB treatment were accounts lest percentage.

Table 6: Common MDR-TB treatment regimens prescribed for reported cases

S.N	MDR-TB Regimens	Frequency	Percentage
1	LTR	218	55.6
2	STR	72	18.4
3	BPaL	60	15.3
4	Individualized	35	8.9
5	Hr-TB	1	.3
6	Missing	6	1.5

4.7. Suspected drugs related with ADEs reported

Linezolid was the most common, 65 (16.3%) suspected medicines causing ADEs followed by Cycloserine and all drugs in the regimen, 36 (9.2%), 32 (8.1%) respectively.

Table 8: Suspected drugs implicated in ADE (Adverse Reactions)

S.N	Suspected drug	Number	Percentage (%)
1	Linezolid	65	16.3
2	Cycloserine	36	9.2
3	All regimens	32	8.1
4	Cycloseine, Linezolid	22	5.6
5	Kanamycin	21	5.1
6	Clofazimine	21	5.1
7	Prothionamide	21	5.1

8	Bedaquinine	19	4.8
9	Levofloxacin	11	2.8
10	Bedaquinine, Clofazimine	7	1.8
11	Pyrazinamide	7	1.8
12	Amikacin	5	1.3
13	Amikacin, Protlonamide	5	1.3
14	Linezolid, Clofazimine	5	1.3
15	Others *	58	14.8
16	Missing Value	57	14.5

***:** *Cm , AmZE, BdqCfzDlm, BdqDlm, BdqLfx, BqdLzd, BdqLzdCFfz, BdqMfxCfz, BdqCfz, LfxCfz, CfzLzd, CsCfz, TMP/SMX, CsH, CsLzdLfx, CsLzdBdq, Dlm,DlmLzd,E, CsE, H, KmDlm, KmHZPto, LfxCs, LfxLzd, LfxLzdCfz, Mfx, PAS, MfxPtoPAS, KmPto, AmPtoMfxE, PtoCfzH, PtoE, PtoHZ, PtoZ, Pto, bdqZCfz, & ZE.*

4.8. ADEs Grading by Severity and Seriousness

4.8.1. ADEs grading by Severity

Regarding the severity of ADEs reported, majority of the reported cases were mild, 188 (48%) and 3.8% of the cases were reported as life threatening. The details of ADEs grading indicate in figure 4.

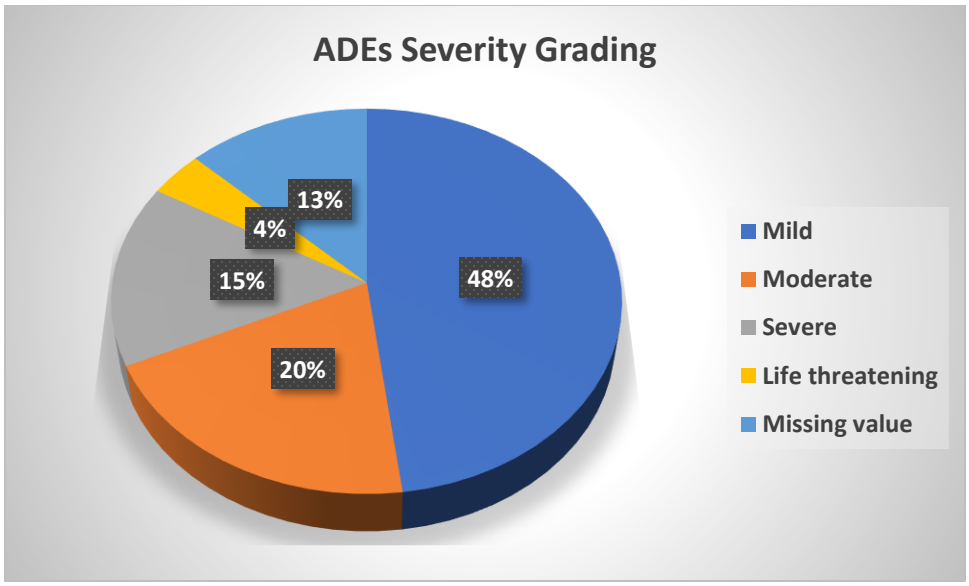

Figure 4: Extent of serious ADEs reported on patients with MDR-TB Drugs

4.8.2. Seriousness of ADEs on Reported cases

From 392 reported cases, majority of the cases (93.9%) were not describe the seriousness of the ADEs. But about 24(6.1%) of ADEs reported as SAE with MDR-TB treatment, of which 16 reported cases (67.7 %) had experienced with pronged hospitalization and unfavorable (death) outcomes were reported for 8 patients (Figure 5).

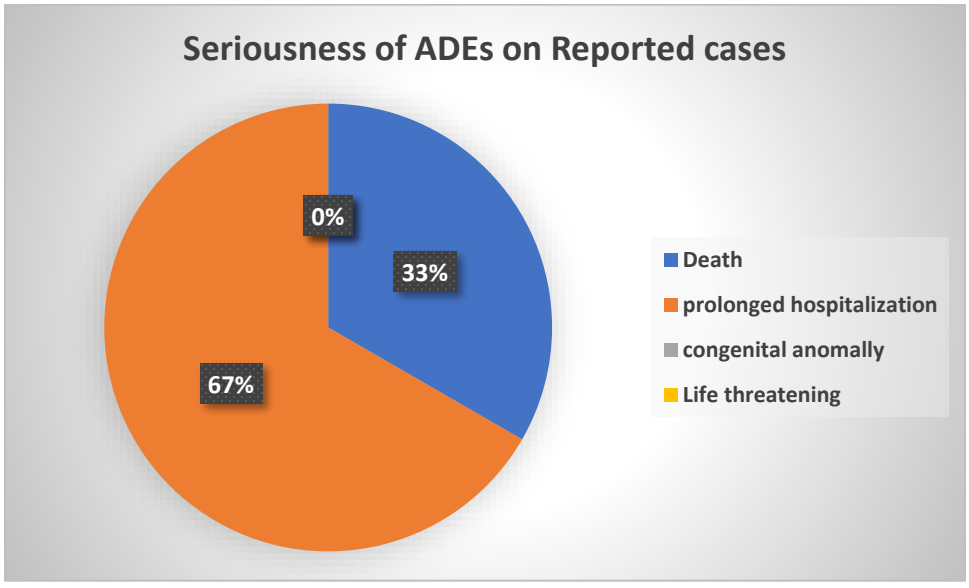

Figure 5: Consequences of the ADEs and follow up outcomes of MDR-TB treatment

As illustrated in Figure 6 below, that shows the outcomes of reported ADEs cases, majority (36.5%) of the reported cases were resolved and about 9.2% cases reported as ongoing progress and 3.8% reported as fatal.

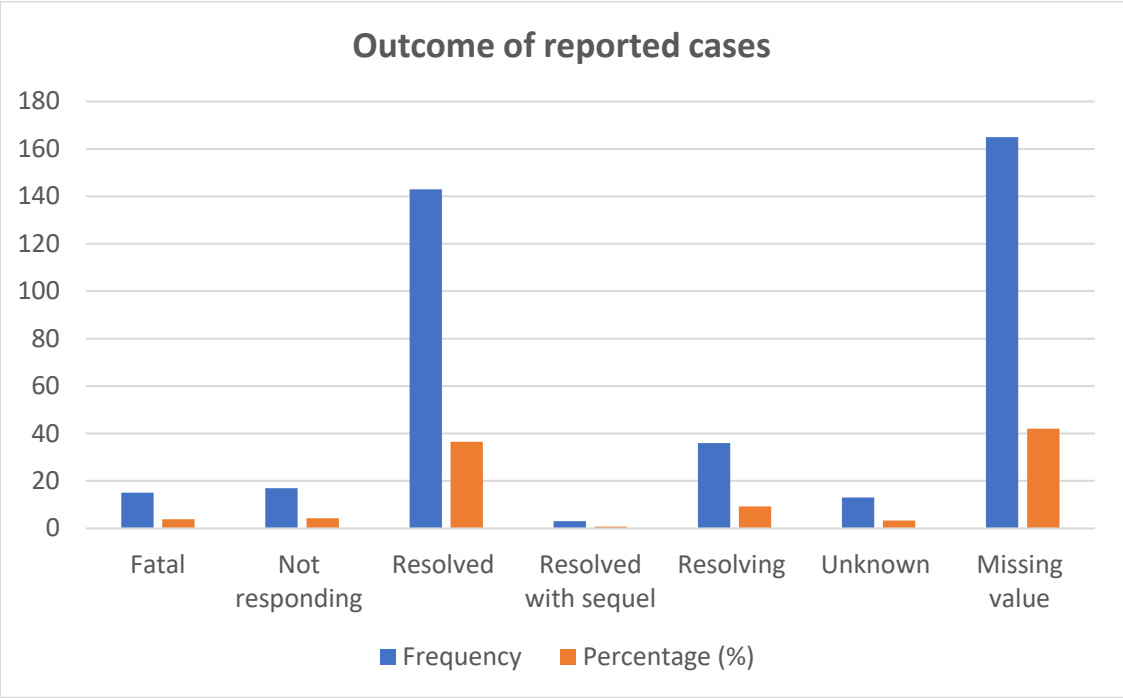

Figure 6: Outcome of reported ADE cases in patients with MDR-TB treatment

5. Challenges/Limitations

During the preparation of this preliminary report, the following main challenges were encountered.

- Poor data incompleteness and cleanliness
- Use of different versions of monthly AE line listing forms (e.g. some versions have weight others do not).
- Poor documentation or filing of ADE reports
- Lack of dedicated government expert at EFDA to properly receive, acknowledge, enter the data, manage, analyze and prepare regular reports on ADEs of MDR TB drugs.
- Lack of clear accountability if ADE reports are not properly managed at EFDA
- Lack of regular follow-up and report request by team leader/managers/directors on ADEs of MDR-TB drugs
- Poor culture and absence of system in place to share ADE data and reports by EFDA to relevant stakeholders
- Use of non-uniform format to write date, month and year (DDD/MM/YYYY and MM/DDD/YYYY)
- Reporting similar ADEs by two different providers
- Repetition of reports in two or more months
- Invalid reports (ADE reports without at least the ADE description)
- Reporting of ADEs with incomplete information

5. Conclusion and Recommendation

5.1. Conclusion

The preliminary analysis report indicated that ALERT hospital and St. Peter TB specialized hospitals were found highest contributors in reporting of ADEs cases from the available TICs. A GI related problem (nausea and vomiting) was found most common ADE reported in MDR-TB treated patients. Majority of the reported cases were mild in severity and prolonged hospitalization was recorded as leading among the SAE reported followed by death. HIV was the common comorbid medical condition and HAART was the most frequently prescribed concomitant medication (regimen). In addition, Linezolid and Cycloserine were found common suspected drugs causing the reported ADEs and majority of patients experienced ADEs reported as resolved.

5.2. Recommendations

Based on the finding of this preliminary report, the following recommendations were forwarded.

- Special attention and close monitoring should be given for patients on MDR-TB treatments

- Continuous active monitoring (aDSM) program should be implemented at TICs throughout the country
- Continuous training and supervision of TICs should be conducted to increase reporting rate and quality of reports
- There should be consistent use reporting forms (AE line listing) and formats for reporting of MDR-TB treatment related ADEs
- Data handling system should be strengthened at reporting facilities (TICS) and EFDA

Annex 1: List of Adverse Drug Events Experienced by patients with MDR-TB Treatment

S.N	Name of Adverse event	Frequency	Percentage (%)	S.N	Name of Adverse event	Frequency	Percentage (%)
1	Nausea	40	10.2	32	Death	8	2
2	Vomiting	51	13	33	Syncope	3	0.8
3	Headache	3	0.8	34	Depression	1	0.3
4	Peripheral neuropathy	34	8.7	35	Anxiety	1	0.3
5	Skin discoloration	7	1.8	36	Injection site pain	1	0.3
6	Fatigue	21	5.4	37	Prolonged QT interval	10	2.6
7	Anemia	12	3.1	38	Allergic reaction	1	0.3
8	Decrease urine output	4	1	39	Insomnia	6	1.5
9	Hearing problem	25	6.4	40	Hypokalemia	1	0.3
10	Vision problem	6	1.5	41	Seizure	4	1
11	Blurred vision	25	6.4	42	Liver enzyme elevation	2	0.5
12	Joint pain	6	1.5	43	Pregnancy	2	0.5
13	Back pain	2	0.5	44	Hearing loss	3	0.8
14	Chest pain	2	0.5	45	Hypoglycemia	3	0.8
15	Flank pain	4	1	46	Abdominal cramp	1	0.3
16	Epigastric pain	44	11.2	47	Itching	3	0.8
17	Abdominal pain	1	0.3	48	Joint swelling	1	0.3
18	Numbness	5	1.3	49	Limb swelling	1	0.3
19	Xerostomia	1	0.3	50	Optic neuritis	13	3.3
20	Psychotic symptoms	14	3.6	51	Shoulder pain	1	0.3
21	Arthralgia	12	3.1	52	Myalgia	1	0.3
22	Dryness of skin	2	0.5	53	Hemoptysis	1	0.3
23	Paresthesia	7	1.8	54	Diarrhea	1	0.3
24	Skin rash	5	1.3	55	Pancytopenia	3	0.8
25	Cough	2	0.5	56	Hypothyroidism	1	0.3
26	Confusion	1	0.3	57	Tendinitis	5	1.3
27	Mood disturbance	3	0.8	58	Tooth ache	1	0.3
28	Burning sensation	4	1	59	Shortness of breath (SOB)	3	0.8
29	Fever	3	0.8	60	Photophobia	1	0.3
30	Loss of appetite	2	0.5	61	PCP	1	0.3
31	Sleep disturbance	1	0.3	62	Conjunctivitis	6	1.5

Annex 2: List of ADEs of special interest

S.N	ADEs of Special Interest	Frequency	Percentage
1	SAE (Death)	8	2
2	Peripheral neuropathy (paresthesia)	41	10.5
3	Psychiatric disorders & CNs toxicity	26	6.6
4	Optic nerve disorders (Optic neuritis) or Retinopathy*	13	3.3
5	Ototoxicity	28	7.2
6	Myelosupprssion	15	3.9
7	Hepatotoxicity	2	0.6
8	Hypothyroidism	1	0.3
9	Hypokalemia	1	0.3
10	Acute Kidney injury (ARF)	4	1
11	Dermatologic	19	4.9
12	Others	234	60

*****Blurred Vission 25(6.2%), Vission problems 6(1.5%), conjuctivitis 6(1.5%), Photophobia 1(0.3%) were not classified in AEs of special interest category (considered as limitation).

References

Annexes