Adverse Drug Events Reported on DTG-Containing Regimens: Preliminary Analysis Report

October 2021

Addis Ababa, Ethiopia

Executive Summary

Although antiretroviral therapy (ART) has changed the natural history of HIV infection, the presences of adverse events have limited its efficacy. Almost all ARV drugs have some adverse effects which can be specific to a single drug or shared by class of drug or could be shared by all ARV drugs. Drug toxicity is the main reason for treatment change and also reported as one of the main difficulties for patients using ART.

Starting from July 2019,EFDA in safety monitoring and reporting of medicines mainly pharmacovigilance of new ARVs including DTG and DTG containing regimens such as TLD.Since then, the project has been supporting EFDA, 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 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.

Based on available clinical information to date, DTG has relatively few side effects and is well tolerated compared with most other available antiretrovirals, but post marketing data is limited. Since the introduction of DTG, ADE reports experienced by HIV patients have been received by EFDA from health facilities 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 and ADE reported from health facilities of Addis Ababa received by EFDA between 2017-2020.

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LIST OF ABBREVIATIONS/ACRONYMS

3TC	Lamivudine
AEs	Adverse Effects
ART	Antiretroviral therapy
ADE	Adverse Drug Events
ADR	Adverse Drug Reaction
DTG	Dolutegravir
EFDA	Ethiopian Food and Drug Authority
EFV	Efavirenz
GHSC-PSM	Global Health Supply Chain Programme-Procurement and Supply Management
HIV	Human Immuno-deficiency Virus
TB	Tuberculosis
TDF	Tenofovir
TLD	TDF/3TC/DTG
WHO	World Health Organization
USAID	United States Agency for International Development

1. BACKGROUND

The Ethiopian MOH has recommended the use of TDF+3TC+DTG (TLD) as first-line regimen for adults, adolescents and pregnant women which is simplified, less toxic and more effective and convenient regimens as fixed-dose combinations (FDC) for ART since 2019. The efficacy of dolutegravir (DTG) has been demonstrated in several randomized control trialsconducted among antiretroviral therapy(ART) naïve andexperienced patients.

Although antiretroviral therapy (ART) has changed the natural history of HIV infection, the presences of adverse events have limited its efficacy. Almost all ARV drugs have some adverse effects which can be specific to a single drug or shared by class of drug or could be shared by all ARV drugs. Drug toxicity is the main reason for treatment change and also reported as one of the main difficulties for patients using ART. Moreover, ADRs are one of the leading causes of morbidity & mortality in the health care. Recent systematic reviews and meta-analysis conducted by WHO have showed that DTG-based regimens are better tolerated and tend to be protective against treatment discontinuation due to adverse events (AEs), when compared with EFV600. The most common reported AEs associated with DTG are gastrointestinal symptoms(nausea, vomiting), hypersensitivity skin reactions, and central nervous system effects (insomnia, dizziness) which are most often mild and self-limited. Discontinuation rates observed in clinical trials and in programme data are low.

Starting from July 2019, EFDA in safety monitoring and reporting of medicines mainly pharmacovigilance of new ARVs including DTG and DTG containing regimens such as TLD. Since then, the project has been supporting EFDA, 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 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.

Since the introduction of aDSM, different activities were conducted by MOH & EFDA 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, EFDA is supporting TICs and TFCs to detect and report ADEs.

Based on available clinical information to date, DTG has relatively few side effects and is well tolerated compared with mostother available antiretrovirals, but postmarketing data is limited.Health programs that systematically monitor patient safety are in a better position to prevent and manage adverse drug reactions (ADRs), improve health-related quality of life, and improve treatment outcomes. Since the introduction of DTG, ADE reports experienced by HIV 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 and ADE reported from health facilities of Addis Ababa received by EFDA between 2017-2020.

2. OBJECTIVES

2.1. General Objective

- To present adverse effects reported from Addis Ababa and the national adverse drug events (ADEs) experienced by patients taking DTG based antiretroviral therapyfrom 2018-2020.

2.2. Specific Objectives

- To present the socio-demographic characteristics of clients who have experienced adverse effects
- To describe the prevalence of ADEs reported nationally on patients with HIV patients taking DTG based ART regimen
- To assess the common types of adverse effects reported in Health facilities of Addis Ababa in HIV patients taking DTG based ART regimen
- To identify the suspected drugs related with ADEs reported
- To describe the onset of the adverse effects reported after the initiation of DTG based ART
- To identify common concomitant medications & medical histories of patients experiencing ADEs
- To identify the common ADE reporter health facilities and professionals
- To describe outcomes/sequel of ADEs reported

3. METHODOLOGY

The national data regarding adverse effects were collected using spontaneous reporting whereby case reports of adverse drug events are voluntarily submitted by health professionals to EFDA. In addition, adverse effects in health facilities of Addis Ababa were obtained by routine service data through program support.An excel data aggregation form was then prepared using the monthly AE line listing form. Adverse drug evets (ADE) reports received by EFDA through the monthly AE line listing form, yellow form, and e-reporting from 2017 to 2021 were entered to the data aggregation tool. After thorough data cleaning, data analysis was performed using SPSS version 25 and simple descriptive statistics was used to present the data including frequency, percentage, and mean and presented usingtables and figures.

4. RESULTS

Socio-Demographic Characteristics

As depicted in table 1, 67 HIV patients taking DTG based ART have reported adverse effects. Almost half (50.7%) of the patients are females and most of the clients 32 (47.8%) and 27 (40.3%) are in the age group from 31-45 and 46-65 respectively.

Table 1: Socio-demographic characteristics of clients who have experienced DTG adverse effects, National DTG Report, 2017-2021.

Characteristics	Category	Frequency	Percentage (%)
Sex	Female	34	50.7
	Male	32	47.8
	Missing	1	1.5
	Total	67	100
Age	18-30	4	6.0
	31-45	32	47.8
	46-65	27	40.3
	>=65	3	4.5
	Missing	1	1.5
	Total	67	100

Concomitant drugs and clinical conditions

All of the 67 patients who have reported adverse effects are taking the first line ART regimen TDF/3TC/DTG. However, 13 (19.4%) of the patients have also reported the use of other concomitant drugs like Cotrimoxazole 3 (4.5%), metronidazole 2 (3%) and others as described in table 2. Moreover, other clinical conditionlike toxoplasmosis and type II diabetes were reported in 4 (6%) of the patients who experienced ADEs.

Table 2: Concomitant drugs use and clinical conditions in patients with reported adverse events, National DTG Report, 2017-2021.

Type of drug		Frequency	Percent
Concomitant Drugs	Cotrimoxazole	3	4.5
	Phenytoin	1	1.5
	Ceftriaxone	1	1.5
	Doxycycline	1	1.5
	Metronidazle	2	3.0
	Clortrimazole	1	1.5
	Pyridoxine	1	1.5
	Furosemide	1	1.5
	Anti-TB	1	1.5
	Metformin	1	1.5
	Missing		
	Total	13	19.5

other Clinical Conditions/comorbidities	CNS toxoplasmosis	1	1.5
	Disseminated TB	1	1.5
	Allergy	1	1.5
	TypeII DM	1	1.5
	Missing	63	94
	Total	67	100

Reported Adverse drug events

The occurrence of the different ADEs reported is shown in Table 3. Among the total 67 patients a total of 127 ADEs were reported. The predominant adverse effectsreported were hyperglycemia accounting for 28.4% (n = 19) followed by hypersensitivity skin reaction (25.4%), CNS side effects most commonly insomnia (20.9%), gastrointestinal side effects (19.4%) and muscloskeletal (16.4%). Other ADRs which are reported include were weight loss, loss of appetite, nausea and vomiting, diarrhea, neurological side effects and others as illustrated in Table 2.

From the total 127 cases of adverse effects reported equal cases (50%) were observed in males and females. Hypersensitivity skin reactions (15%), muscloskeletal (12%), GI related side effects (10.5%%) were experienced by females whereas hyperglycemia (18%), CNS side effects (13.5%) and weight loss (9%) were common in males. Moreover, most of the patients who have reported ADEs are from 31-45 years (57.1%) and with BMI <18 (53 cases).

Table 5 shows the distribution of ADRs in relation to onset of adverse effects.Most of the ADE cases were observed early before 15 days (49 cases) after starting the DTG based ART therapy. The time gap between start and experience of ADR was different depending on the type of ADR. Hypersensetivity skin reactions (8 cases), CNS side effects (7 cases), muscloskeltal side effects (6 cases) and others before 15days. The other ADRS like weight loss occurred mostly from 15 days to 1 month and for hyperglycemia after 3 months.

Table 3: Type, frequency and percentage of adverse drug events reported in HIV patients, National DTG Report, 2017-2021.

S/N	Type of adverse effect	Frequency	Percentage
1	Hyperglycemia	19	28.4
2	Hypersensitivity skin reactions	17	25.4
3	CNS side effects (Insomnia, dizziness, anxiety)	14	20.9
4	Other GI related side effects (abdominal cramp/pain, abdominal distension, burning sensation, GI disturbance, heart burn, difficulty of swallowing)	13	19.4
5	Muscloskeletal side effects (Joint Pain, rehamatic pain, muscle weakness, malaise,back pain)	11	16.4
6	Weight loss	9	13.4
7	Anorexia (loss of appetite)	8	11.9
8	Neurological side effects (headache, unconsciousness, shivering)	8	11.9
9	Nausea and vomiting	6	9
10	Edema	4	6
11	Fatigue	4	6
12	Diarrhea	3	4.5
13	Respiratory side effects (Cough, shortness of breath)	2	3

14	Lipodystrophy	2	3
15	Hepatotoxicity	1	1.5
16	Others (Sweating, weight gain, hypertension, fever, high viral load)	6	9
	Total	127	

Table 4: Distribution of adverse drug events reported based on socio-demographic characteristics of the patients, National DTG Report, 2017-2021.

Characteristics		Hyperglycemia	Hypersensitivity skin reactions	CNS side effects	Weight loss	Musculoskeletal side effects	Nausea and vomiting	Diarrhea	Other GI related side effects	Anorexia	Edema	Neurological Side effects	Fatigue	Respiratory side effects	Lipodystrophy	Hepatotoxiicty	Others	Total
Sex	Female	7(10.4%)	10(15%)	5(7.4%)	3(4.5%)	8(12%)	3(6%)	1(1.5%)	7(10.5%)	4(6%)	2(3%)	3(4.5%)	2(3%)	0	1(1.5%)	1(1.5%)	6(9%)	63(50%)
	Male	12(18%)	7(10.5%)	9(13.4%)	6(9%)	3(4.5%)	3(4.5%)	2(3%)	6(9%)	4(6%)	2(3%)	5(7.5%	2(3%)	2(3%)	0	0	0	63(50%)
Age	18-30	0	3	0	0	0	0	0	0	0	1(1.5%	0	0	0	0	1(1.5%)	0	5(4%)

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	31-45	8(12%)	11	10(15%)	4(6%)	7(10.4%)	3(4.5%)	2(3%)	9(13.4%)	4(6%)	3(4.5%)	4(6%)	3(4.5%)	2(3%)	1(1.5%)	0	1(1.5%)	72(57.1%)
	46-65	10(15%)	3(4.5%)	4(6%)	5(7.5%)	4(6%)	2(3%)	0	3(4.5%)	4(6%)	0	3(4.5%)	1(1.5%)	0	0	0	5(7.5%)	44(34.9%)
	>=65	1	0	0	0	0	1	1	1	0	0	1	0	0	0	0	0	5(4%)
BMI	<18	2(3%)	7(10.5%)	10(15%)	6(9%)	8(12%)	2(3%)	2(3%)	5(7.5%)	6(9%)	1(1.5%)	5(7.5%)	1(1.5%)	1(1.5%)	0	0	2(3%)	58
	18-25	4(6%)	1(1.5%)	1(1.5%)	2(3%)	1(1.5%)	1(1.5%)	0	0	1(1.5%	0	1(1.5%	1(1.5%)	0	0	0	0	13

Table 5: Distribution of adverse drug events reported based on onset of adverse effects, National DTG Report, 2017-2021.

Characterstics		Hyperglycemia	Hypersensitivity skin reactions	CNS side effects	Weight loss	Musculoskeletal side effects	Nausea and vomiting	Diarrhea	Other GI related side effects	Anorexia	Edema	Neurological Side effects	Fatigue	Respiratory side effects	Lipodystrophy	Hepatotoxiicty	Others	Total
Onset of Adverse effect	<= 15 days	5(7.5%)	8(12%)	7(10.5%)	1(1.5%)	6(9%)	2(3%)	1(1.5%)	4(6%)	4(6%)	1(1.5%)	4(6%)	2(3%)	0	1(1.5%)	0	3(4.5%)	49
	15 day	3(4.5%)	2(3%)	0	3(4.5%	0	0	0	0	0	0	0	1(1.5%	0	0	0	1(1.5%	10

	s upto 1 month				)							)				)	
	1 month upto 3 months	2(3%)	3(4.5%)	0	2(3%)	0	0	0	0	0	1(1.5%)	0	1(1.5%)	0	0	0	1(1.5%)	9
	>3 months	7(10.5%)	0	0	2(3%)	1(1.5%)	1(1.5)%	1(1.5%)	3(4.5%)	0	1(1.5%)	2(3%)	0	2(3%)	0	0	0	20

Suspected Drug and measures taken

For most (62 cases from the total 67 patients) of the adverse effects observed, DTG based antiretroviral drug was suspected to be responsible for the occurrence of the reported adverse effects (Figure 1). Only 2 cases of hypersensitivity skin reaction were related to the use of Cotrimoxazole and hepatotoxicity was suspected by the use of anti-TB drug (RHZE). As it is shown in Table 6 different measures were taken after the occurrence of adverse effects. Although the ART regimen was continued with reassurance for most of the patients, the regimen TDF/3TC/DTG was changed to TDF/3TC/EFV based regimen in 13 (19.5%) and the suspected drug was discontinued in 4 (6%) patients. Symptomatic management using antihistamine (5 cases), analgesic, antiemetic and antidiarrheal was also used as a management strategy for the adverse effects.

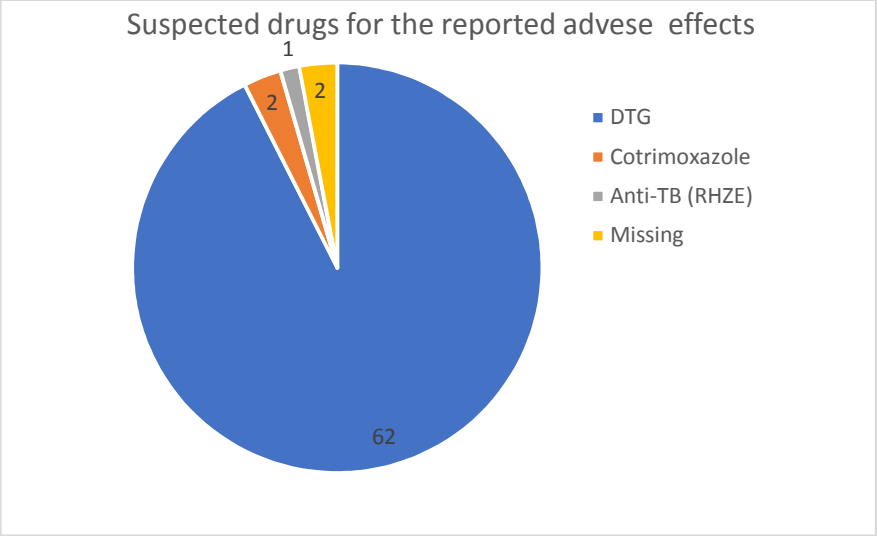

Figure1: Frequency of suspected drugs for the reported adverse effects, National DTG Report, 2017-2021.

Table 6: Measures taken after the occurrence of adverse effect, National DTG Report, 2017-2021.

Action Taken	Frequency	Percentage
ART Regimen changed	13	19.5
Antihistamine given	5	7.5

Analgesic given	4	6
Discontinued the drug	4	6.0
Anti-diabetic started/drug changed	3	4.5
Anti-emetic given	2	3
Antidiarheal drug given	1	1.5
Anti_Tb regimen changed	1	1.5
Time for ART adjusted, Sedative given	1	1.5
Missing	40	59.7
Total	67	100

Reporters information

The ADEs reported in this study come from 17 health facilities nationally. From this three health facilities namely Mekelle hospital, Alert hospital and Bole 17 health center contibuted 31 (46.3%) ADEs reports (Table 7).With regard to the region, more than half (52.2%) of the reports come from Addis Ababa (figure 3) and Pharmacist were the top ADE reporters (45%) compared to other health professionals (Figure 4).

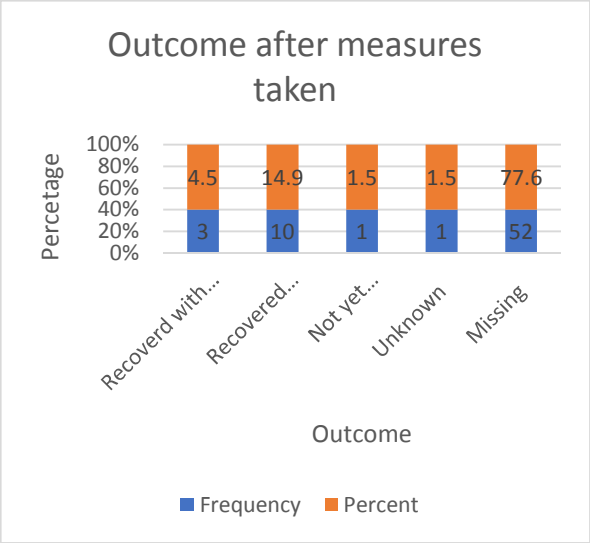

Figure 2: Outcome after measures taken for the reported adverse effects

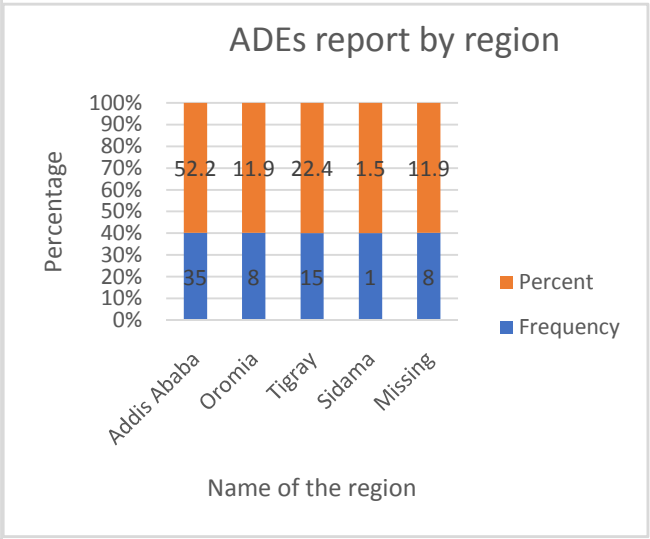

Figure 3. Adverse effect report by region

Table 7: The health facilities who have reported the adverse effects, National DTG Report, 2017-2021.

Name of the Health facility	Frequency	Percent
Mikelle Hospital	15	22.4
Bole 17 health center	8	11.9
Alert Hospital	8	11.9
Bole Arabsa HC	5	7.5
Jimma specialized Hospital	4	6.0
RasDesta Hospital	3	4.5
Tekelhaimanot Health Center	3	4.5
Black Lion Hospital	2	3.0

Tulu dimtu Health center	2	3.0
Adama Hospital Medical center	2	3.0
KuasMeda Health Center	1	1.5
Shegole Health Center	1	1.5
Meshaleki'a Health center	1	1.5
Modjo Health center	1	1.5
Kolobo Health Center	1	1.5
Adare General Hospital	1	1.5
Akakikaliti HC	1	1.5
Total	59	88.1
Missing	8	11.9
Total	67	100

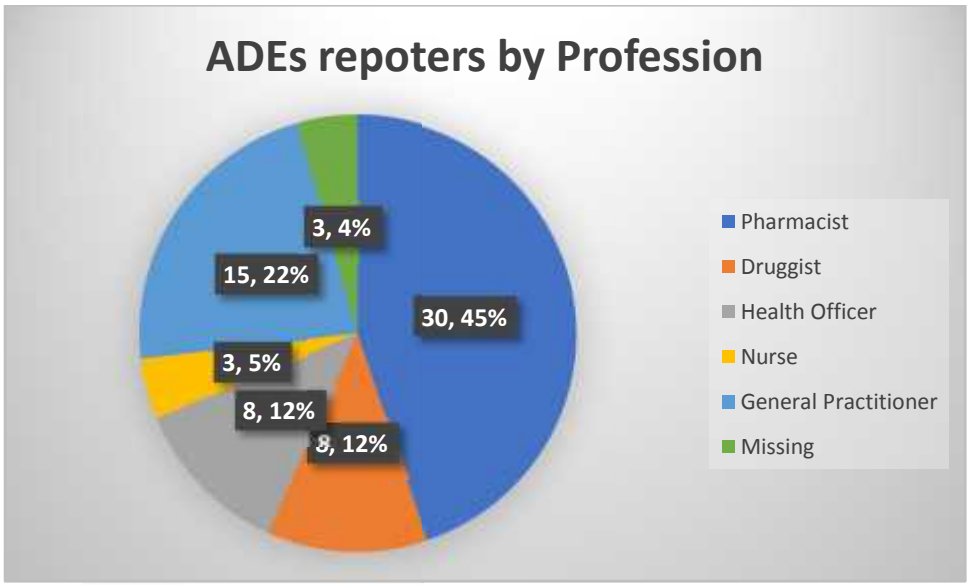

Figure 4: Adverse effect report by profession, National DTG Report, 2017-2021.

Adverse effect report from Addis Ababa

In addition to the above-mentioned adverse effect reports from different regions of the country, 290 cases of adverse effects were also reported from different health facilities of Addis Ababa. All of the patients who have experienced the adverse effects were taking DTG based ART. Insomnia (42.4%), hyperglycemia (23.4%), peripheral neuropathy (13.8%) and weight gain (12.8%) were the most common adverse effects reported as shown in Table 7.

Table 8: Type, frequency and percentage of adverse drug events reported in health Facilities of Addis Ababa, 2018-2021.

S/N	Type of Adverse effect	Frequency	Percentage
1	Insomnia	123	42.4
2	Hyperglycemia	68	23.4
3	Peripheral neuropathy	40	13.8
4	Weight gain	37	12.8
5	Weight Loss	10	3.4

6	Skin rash/stephenson Johnson reaction	5	1.7
7	Poor Lipido	1	0.3
8	Polyphagia	1	0.3
9	Hypersominia/Somlocense	1	0.3
10	Edema	1	0.3
11	Gastritis	1	0.3
12	Renal Dysfunction	1	0.3
13	Fetal diffuse subcutaneus edema	1	0.3
	Total	290	100.0

5. CHALLENGES/LIMITATIONS

- Incomplete fields on some of the variables contributing for high number of missing data
- Inconsistency in the filled data like the case of different ways of writing the same adverse effects
- Data sources are different and brings complex data structures and increases the difficulty of data integration.
- 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.
- 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
- Poor culture and absence of system in place to share ADE data and reports by EFDA to relevant stakeholders
- Repetition of reports in two or more months
- Invalid reports (ADE reports without at least the ADE description)

6. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

In conclusion, 127 cases of ADEs were reported from 67 HIV patientsreceiving DTG based ART and 17 health facilities nationally. From this Hyper glycemia and hypersensitivity skin reaction were the most common adverse effects reported and most of the adverse effects were observed from 31-45 years and those having BMI <18. Moreover, most of the ADEs were observed within 15 days after starting the ART. Inaddition, 290 ADEs were also reported from health facilities of Addis Ababa where insomnia, hyperglycemia and peripheral neuropathy were the most common ADEs reported.

6.2. Recommendations

- Support EFDA and TICs to increase the reporting rate through site level support, close-follow-up from the center through telephone call and improving the feedback mechanism of EFDA.
- Strengthen the data management system at EFDA (data handling, data entry, and aggregation) for the ADE reports at EFDA through revising the data aggregation excel, timely data entry, and performing regular data aggregation and report writing at national level.
- Generate information for decision making using the ADE reports collected through proper data analysis and report writing disaggregated by type of ADR (AEs and SAEs), reporter TIC, the type of regimen the patient was taking at the time of experiencing ADR, the type of specific MDR-TB drug suspected for the ADR, trend of reporting rate by TIC and year, and type of ADRs reported by frequency, age sex, regimen, duration of treatment, concomitant illness and concomitant drug…

REFERENCES

Bratt G, Koppel K, Sandstorm E. The development of laboratory cardiovascular risk factors in patients on HAART during 24 months followup. Inter Medic press, 2001; 6(14): 52.

Fauci AS, Lane CH. (2005) Human Immunodeficiency virus disease AIDS and related disorders. In Harison's principle of medicine Kasper Dennis L., Longo DL., Braunwald E., Hauser SL., Jomson LD. (eds), 16th ed. Mc Grraw Hill, Newyork 1071-1139.

Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, Balakrishnan P, Saghayam S, *et al*. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. J Acquir Immune DeficSyndr, 2006; 41:53-8.

WHO (2018) Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir /lamivudine /dolutegravir (TLD) April 30 2018 Briefing note.

ANNEX I

Detailed Adverse drug events reported

Type, frequency and percentage of adverse drug events reported by HIV patients

S/N	Type of Adverse effects	Frequency	Percentage
1	Hyperglycemia	19	28.4
2	Insomnia	11	16.4
3	Skin rash	9	13.4
4	Weight loss	9	13.4
5	Loss of appetite	8	11.9
6	Nausea and vomiting	6	9
7	Joint Pain	4	6
8	Headache	4	6
9	Abdominal cramp/pain	4	6
10	Fatigue	4	6
11	Itching	3	4.5
12	Diarrhea	3	4.5
13	Abdominal distension	3	4.5
14	Back Pain	2	3
15	Rheumatic pain	2	3

16	Shivering	2	3
17	Fever	2	3
18	Burning sensation	2	3
19	Difficulty of swallowing	2	3
20	Unconsciousness	2	3
21	Mucosal Swelling	2	3
22	Discoloration of skin	2	3
23	Edema	2	3
24	Anxiety	2	3
25	Lipodystrophy	2	3
26	Dizziness	1	1.5
27	Spot appearance on tigh	1	1.5
28	Muscle weakness	1	1.5
29	Cough	1	1.5
30	Hepatotoxicity	1	1.5
31	Shortness of breath	1	1.5
32	Hypersensitivity reaction	1	1.5
33	Sweating	1	1.5

34	Allergic reaction	1	1.5
35	Weight gain	1	1.5
36	Pain	1	1.5
37	Hypertension	1	1.5
38	GI disturbance	1	1.5
39	Malaise	1	1.5
40	Heart Burn	1	1.5
41	High viral load	1	1.5
	Total	127	

ANNEX II

Detailedmeasures taken after the occurrence of adverse effect for each case

Type of ADEs	**Action taken**	**Suspected drug**	**Other remark**	
Feeling sleepy, itchy and spot appearance on her thighs and lower limbis	continue ART medications	DTG	Recovered with sequalene	
Itching (G-II cotrimoxazole toxicity)	Loratidine 10 PO/day	Cotrimoxazole	Recovered without sequalene	Hospitalization prolonged
Cough, persistent headache	Paracetamol 1gm PO PRN		Recovered without sequalene	
Drug induced hepatotoxicity (ALP=163, AST=188, ALT=33)	Anti-TB restarted by omitting Pyrazinamide and supportive care	Anti-TB	Recovered without sequalene	
Joint pain, Burning sensation	Diclophenac 50mg PO PRN		Recovered without sequalene	
Insomnia for month	take the medication at morning and Amitriptylin		Recovered without sequalene	

	25mg PO Nonct			
Burnig sensation and itching for 7 days	Loratidine 10mg PO/day		Recovered without sequalene	
Mucosal swelling and redness, discoloration of skin	Regimen changed		Recovered without sequalene	
Skin rash	Promethazine 25mg PO/day for 5 days			
DTG Toxicity (severe headache	Paracetamol 1gm PO PRN			
Hypersensetive reaction	Shifted to TDT+3TC+EFV regimen		Recovered without sequalene	
Sweating, diarrhea, loss of appetite, vomitting	Shifted to TDT+3TC+EFV regimen(ORS, Metoclopromide and multivitamine was given)			
Severe allergic reaction	discontinued the drug			
multitude vesicular lesions on	discontinued the		Recovered without	

the face	drug		sequalene	
Nausea, sleep disturbance, tirerdness, weight loss	Regimen changed			
Mucopapular Rash, periorbital edema	discontinued the drug		Recovered without sequalene	
severe joint pain	Regimen changed			
Hyperglycemia (RBC=439mg/dl, ketone= +3), significant weight loss (from 82 to 67kg within 3 months)	Regimen changed and DKA managed		Recovered without sequalene	
Insomnia, Rheumatic pain, poor appetite, shivering, Abdominal cramp, fever	Regimen changed			
Hyperglycemia and BGL didn't decrease even though she is taking metformin It rather increased	Drug was changed to Insulin			
Hyperglycemia	Drug changed to TDF 3TC EFV			
Diabetusmileitus; FBS increased	Drug changed to TDF			
Hyperglycemia	Started			

	metformin 500mg,Daonil 5mg po day. Changed to TDF			
Abdominal ditension,vomiting,right upper quadrant severe pain,general body rash,anorexia,insomnia,anxiety with discomfort	Drug switched to TDF/3TC/EFV	Hospitalization Prolonged		
Rash for 15 days	Loratidine was prescribed and drug changed to TDF/3TC/EFV			
Skin rash, hypertension to DTG	Loratidine was given and drug changed to TDF/3TC/EFV			
headache, nausea, diarrhea and abdominal pain	Plasil,paracetamol was given			
Diabetusmellitis	Discontinued the drug			

ANNEX III

Measures Taken after the occurrence of adverse effect

Action Taken	Frequency	Percentage	Description of adverse effects
Antihistamine was given	3	4.5	Hypersensitive skin reaction (itching, skin rash and burning sensation)
Analgesic given	3	4.5	Cough and persistent headache (1), Joint pain and burning sensation (1), severe headache (1)
ART Regimen changed	8	11.9	Mucosal swelling and redness and skin discoloration (1), hypersensitivity reaction (1), nausea, insomnia, fatigue and weight loss (1),Severe joint pain (1), Insomnia, rheumatic pain, loss of appetite, fever, shvering and abdominal cramp (1), Hyperglycemia (2), abdominal distension, vomiting, pain, rash, anorexia, insomnia and anxiety (1)
Discontinued the drug	4	6.0	Severe allergic reaction (1), multitude vesicular lesion on face (1), maculopapular rash and pretibial edema (1), Hyperglycemia (1)
ART Regimen changed, DKA managed	1	1.5	Hyperglycemia (RBC=439mg/dl, ketone= +3), significant weight loss (from 82 to 67kg within 3 months)
Metformin changed to insulin	1	1.5	Hyperglycemia and BGL didn't decrease even though she is taking metformin It rather increased
Regimen changed, Metformin started	1	1.5	Hyperglycemia
Regimen changed,	2	3.0	Skin rash and hypertension

antihistamine given			
Regimen changed, antiemetic and anti-diarrheal given	1	1.5	Sweating, diarrhea, loss of appetite, vomiting
Antiemetic given, analgesic given	1	1.5	Headache, nausea, diarrhea and abdominal pain
Anti_Tb regimen changed	1	1.5	Drug induced hepatotoxicity (ALP=163, AST=188, ALT=33)
Time for ART adjusted, Sedative given	1	1.5	Insomnia for month
Missing	40	59.7	
Total	67	100	