



Report on Cohort Event Monitoring (CEM) of Dolutegravir Containing ART Regimens in Selected Health Facilities of Addis Ababa, Ethiopia

**By the Ethiopian Food and Drug Authority (EFDA) in collaboration
with the Global Fund (GF) and the USAID Global Health Supply Chain
Program-Procurement and Supply Management (GHSC-PSM) project.**

**December 2023
Addis Ababa, Ethiopia**

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Acknowledgement

The Ethiopian Food and Drug Authority would like to express its heart felt appreciations to the experts and their respective institutions who were involved in the design, implementation, follow-up, supervision of this active surveillance, cohort-event monitoring, on DTG containing regimens in ART sites of Addis Baba. In addition, we have a great acknowledgement to those AAU and hospital experts who involved in the data entry, cleaning, analysis and report-write-up of this study. Accordingly, our gratitude is extended to the following individuals and organizations whose role was critical in the successful conduction of this study.

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Finally, we would like to thank the USAID Global Health Supply Chain Program- Procurement and Supply Management (GHSC-PSM) project, World health Organization (WHO), and the Global Fund (GF) for their financial and technical support and the Ohio State University (OSU) and Tony Blair Institute (TBI) for the technical support.

Abbreviations and acronyms

3TC	Lamivudine
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ART	Anti-retroviral Therapy
ARV	Antiretrovirals
CEM	Cohort Event Monitoring
DTG	Dolutegravir
EFV	Efavirenz
FTC	Emtricitabine
HIV	Human Immunodeficiency virus
INSTIs	Integrase Strand Transfer Inhibitors
LMICs	Low- and Middle-Income Countries
LPV/r	Lopinavir/ritonavir
NNRTIs	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside/nucleotide Reverse Transcriptase Inhibitors
PIs	Protease Inhibitors
RAL	Raltegravir
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Executive summary

Background

Even though the introduction of DTG based ART has provided a potent treatment option for persons living with HIV, there is growing evidence from clinical settings that use of DTG can result in hyperglycemia, serious neurologic and neuropsychiatric side effects. Moreover, there is currently insufficient information regarding the safety of DTG-based combination regimen, including the types and frequency of suspected adverse drug events (ADEs) experienced and reported in Ethiopian population. Hence, the Ethiopian Food and Drug Authority (EFDA) conducted a Cohort Event Monitoring (CEM) on DTG based regimen in collaboration with stakeholders and partners among patients receiving ART service in selected health facilities of Addis Ababa.

Objective:

To assess the real-life safety experiences following the intake of DTG based regimens in Addis Ababa selected ART sites.

Methodology:

The study was conducted in 20 selected public health facilities (4 hospitals and 16 health centers) of Addis Ababa City. A facility based prospective observational cohort study was employed in the current study. All individuals with a confirmed diagnosis of HIV, commencing treatment with DTG based regimen, either as treatment naïve or switched from another ARV regimen at the selected sites that fulfill the inclusion/exclusion criteria and having a follow-up during the study period. The study period was three years starting from April 2022 and each participant in the cohort was followed for a period of 1 year starting from the enrolment using phone call and during routine care visits. During follow-up, presence or absence of ADRs, improvement of previously occurred ADRs, severity and seriousness and adherence were checked and documented. The intended size of the cohort was 3000 patients to be followed for 12 months. This sample size provides a 95% chance of identifying AEs having an incidence of 1:1000. In this interim data analysis and preliminary report, only 1294 patients are included.

Data collection tool (Annex 2) was developed using the national comprehensive HIV prevention, care and treatment guidelines and pharmacovigilance guidelines; and it was modified based on data collectors' feedback during orientation session. The data collection tool contains information regarding socio-demographic characteristics, clinical characteristics, laboratory values and components related to medication use. Data was collected by recruited and trained health professionals from study sentinel sites under supervision of pharmacovigilance experts from EFDA and GHSC-PSM project. Participants were followed on day 1, 3, 7, 15 and then monthly for one year through phone call. As per the regular visit to sentinel sites, participants were contacted physically by data collectors.

The data was entered using MS excel version 22, exported to, and analyzed using statistical package for social science (SPSS) version 25. Mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variable were computed using descriptive statistics. Univariate and Multivariate analysis were conducted to determine association between dependent and independent variables. P-value ≤ 0.05 is considered statistically significant.

Result:

The research included 1294 participants who were on a DTG-based ART regimen for the interim data analysis and preliminary report. Over two-thirds (837; 64.7%) of them were females and the largest proportion of participants fell within the 36-49 years age range. Until the interim data analysis, only 22.5% of them have completed the follow-up and 56.8% of them are on follow-up. At baseline, two-third (65.7%) of patients were on WHO category stage I and three fourth (75.7%) of them were working functional status. Only 5.9% and 18.2% of participants had comorbid conditions and opportunity infections, respectively. Only 11.4% of the participants had previous regimen and 1E (TDF/3TC/EFV) was the most prescribed ART regimen. About current regimen, most (98.8%) of the patients were on 1J ((TDF/3TC/DTG). Close to two-third (63%) of participants received at least one prophylactic medication and 3HP was the most used prophylactic medications. Besides the ART regimen, only 5.3% of the participants were on concomitant medications.

In this study, 141 (10.9 %) of them reported to have one or more ADRs. Of the reported ADRs, the most frequently reported ADRs were headache, (16.5%) and fatigue (14.6). Among the reported ADRs, 47.2% were classified as mild. The highest percentage (75%) of participants who developed ADR encountered ADR on the first 15 days of initiation of the DTG-based therapy. Of the total, 20 (1.5%) of the participants changed regimen due to the ADRs and 6 (0.5%) of the total died while on treatment.

Conclusion and recommendations:

In our study, the overall prevalence of ADR was 10.9%. meaning nearly eleven percent of the patients who were taking DTG based ART regimen developed at least one ADR during their follow-up period. The most common ADR reported was headache, followed by fatigue, nausea, vomiting, hypersensitivity reaction, GI related ADRs, insomnia, and anorexia. Of the ADRs reported, nearly half were mild in severity. Of those who developed ADR, three-fourth of the participants encountered the ADR on the first two weeks of initiation of the DTG-based therapy.

Based on the findings of the interim data analysis and preliminary results, the following recommendations are forwarded:

- The follow-up study should be continued until the planned sample size reached in order to better detect and document ADRs and associated factors.
- Data quality, mainly data accuracy and data completeness, should be improved by data collectors through close follow-up, supervision, and feedback mechanism.
- The data collection tool should be revised based on the gaps identified during this interim data analysis but without creating discrepancy with the original one.
- ADR investigation for some of the serious ADRs such as death should be conducted as early as possible.
- Provide sensitization training to data collectors to create uniform understanding among them about the study, data collection and issues of data quality.

1. Introduction

1.1. Background

Approximately 39 million (33.1-45.7) individuals worldwide were living with HIV by the end of 2022, with over two thirds of them (25.6 million) residing in the WHO African Region, and 1.5 million being children under 15 years of age. In 2022, there were 1.3 million new HIV infections and 630,000 AIDS-related deaths (1). As of 30 June 2021, around 28.2 million people living with HIV were receiving antiretroviral therapy (ART). In Ethiopia, the estimates and projections for 2022–2023 suggested that approximately 603,537 individuals were living with HIV, including 33,026 children under the age of 15. The same data indicated 7194 new infections and 9984 deaths due to AIDS. The report further indicated that in Addis Ababa a total of 110,289 people are estimated to be living with HIV in the same year, including 2,793 children (2).

In Ethiopia, Antiretroviral treatment (ART) was first initiated in 2003, and after two years, in early 2005, Ethiopia launched a free ART program. Since then, ART has not only saved the lives of millions of individuals but has also provided those living with HIV/AIDS the opportunity to lead long and fulfilling lives, as a result of the collaborative efforts of the government and development partners (3). The fundamental approach to HIV treatment has involved using a combination of at least two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) such as tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and emtricitabine (FTC), along with a third drug from one of the following medication categories: non-nucleoside reverse transcriptase inhibitors (NNRTIs) like nevirapine and efavirenz (EFV); protease inhibitors (PIs) including lopinavir/ritonavir (LPV/r), atazanavir, and integrase strand transfer inhibitors (INSTIs) such as dolutegravir (DTG) and raltegravir (RAL) (4).

Based on WHO's recommendation, Ethiopia has adopted DTG based regimen into the 2018 edition of the national comprehensive HIV prevention, care, and treatment guideline for all adult, pregnant and breast-feeding clients (5). This regimen with two nucleoside reverse transcriptase inhibitors paired with DTG, an integrase inhibitor, is reported to be more effective, with higher viral suppression and CD₄cell count recovery rates and lower risk of treatment discontinuation compared with efavirenz (EFV)-based regimens among treatment-naive adults. DTG has other advantages over EFV, including a lower potential for drug–drug interactions, more rapid viral

suppression and a higher protectiveness with respect to drug-resistance. The high barrier to drug-resistance is important given the growing proportion of PLWH with pre-treatment drug resistance to NNRTIs (6).

DTG is also active against HIV-2 infection, which is naturally resistant to EFV. DTG is available in the generic fixed dose formulation at a price comparable with current regimens in most low-and-middle-income countries (LMICs), making it a favorable option for initiating ART (7-10).

Clinical trial data showed that DTG was a very well tolerated drug in addition to the already established high certainty with respect to viral suppression, discontinuations and incidence of adverse effect (<5%) as compared with EFV. The frequently reported adverse effects of DTG were gastrointestinal symptoms (nausea, vomiting), hypersensitivity skin reactions and central nervous system effects (insomnia, dizziness) which were often mild and self-limiting (11).

In spite of the fact that the introduction of DTG based ART has provided a potent treatment option for persons living with HIV, there is growing evidence from clinical settings that use of DTG can result in hyperglycemia, serious neurologic and neuropsychiatric side effects (11, 12). Moreover, there is currently insufficient information regarding the safety of DTG-based combination regimen, including the types and frequency of suspected adverse drug events (ADEs) experienced and reported in Ethiopian population. Hence, the Ethiopian Food and Drug Authority (EFDA) aimed to carry out Cohort Event Monitoring (CEM) on DTG based regimen in collaboration with stakeholders and partners among patients receiving ART service in selected health facilities of Addis Ababa.

1.2. Rationale of the Study

Despite the optimal safety profile demonstrated in clinical trials, recent data from observational studies have questioned the tolerability of DTG, reporting a paradoxical high incidence of discontinuations due to toxicity, mainly related to adverse events (AEs). Severe neuropsychiatric AEs including headache, dizziness, sleep disturbances, mood disturbances, suicidal ideation and cognitive problems were reported (13). A study conducted in Kenya further reported a consistent hyperglycemic risk for patients on DTG and highlighted the importance of routine body weight monitoring for all patients on DTG (12). Moreover, case series report from Ethiopia revealed that hyperglycemia is a potential and noticed side effect of the DTG-based ART regimen (14).

In US, European and Australian cohort studies, AEs have led to DTG discontinuation in 1.6% to 13.7% of the patients. This is superior to a previously reported EFV discontinuation rate of 4.3% in a Thai ART-naive cohort (15). Treatment discontinuation and other forms of medication non-adherence associated with ADRs are significant risk factors for virologic failure. Furthermore, failure of first-line ART regimens resulting from ADRs creates the need for more expensive and difficult-to-implement second-line regimens that are often unaffordable in most resource-constrained countries, which are largely donor dependent for their ART programs (16).

Determination of patient safety plays a pivotal role in curbing the problems of treatment failure, improving patient's survival, clinical outcome, and quality of life. It is also important to preserve the long term efficacy of available drugs. However, currently, there is a paucity of data regarding the safety of DTG-based combination regimen, including the types and frequency of suspected adverse drug events (ADEs) experienced and reported, in Ethiopian population. Therefore, the aim of this study was to determine the safety profile of DTG in people living with HIV. This study further aimed to provide baseline information to conduct other similar studies on HIV treatment. Moreover, data derived from within the country or region may have greater relevance and may encourage national regulatory decision-making.

1.3. Significance of the Study

Drug safety monitoring has the potential to inspire confidence and trust among patients and health professionals in medicines and contributes to raising standards of medical practice. The findings of this CEM helps to:

- Identify types and incidences of AEs in Ethiopian population on DTG based regimen
- Understand the risk factors for the occurrence of AEs in persons on DTG based regimen
- Generate evidence-based safety information for regulatory decision-making and in improving the process of care and treatment outcomes for people living with HIV
- This study reports only presents the preliminary findings of the cohort. This will enable EFDA, MOH, partners and other stakeholders get preliminary results to better guide next actions in the study as well as HIV program.

2. Objectives

2.1 General objective

- The general objective of this study was to assess the real-life safety experiences following the intake of DTG based regimens in Addis Ababa selected ART sites.

2.2 Specific objectives

- To identify the types of AEs associated with the use of DTG based regimen
- To determine the incidence of AEs of DTG based regimen
- To categorise the outcome of AEs of DTG based regimen
- To assess factors associated with the occurrence of AEs of DTG based regimen
- To identify potential signals of DTG based regimen
- To identify AEs of DTG based regimen in special population (pregnant, lactating, geriatrics, and pediatrics)

3. Methodology

3.1 Study Site

The study was conducted in 20 selected public health facilities (4 hospitals and 16 health centers) of Addis Ababa City. These facilities were selected based on their high patient load, with sites having over 1000 patients were included. Data of these facilities was obtained from the most recent monthly patient uptake report accessed from archives of Addis Ababa city administration Health Bureau. The list of selected facilities for this CEM is annexed (Annex 1):

3.2 Study Design and Follow-up

A facility based prospective observational cohort study was employed in the current study. The study period was three years starting from April 2022 and each participant in the cohort was followed for a period of 1 year starting from the enrolment using phone call and during routine care visits. During follow-up, presence or absence of ADRs, improvement of previously occurred ADRs, severity and adherence were checked and documented.

3.3 Source and Study Population

3.3.1 Source Population

All individuals with a confirmed diagnosis of HIV, commencing treatment with DTG based regimen, either as treatment naïve or switched from another ARV regimen at the selected site served as a source population.

3.3.2 Study Population

All individuals with a confirmed diagnosis of HIV, commencing treatment with DTG based regimen, either as treatment naïve or switched from another ARV regimen at the selected sites that fulfill the inclusion/exclusion criteria and having a follow-up during the study period.

3.4 Sampling and Sample Size Determination

Healthcare providers at the selected sentinel sites are requested to enroll eligible patients into the cohort during treatment DTG containing regimens initiation visits. The intended size of the cohort was 3000 patients to be followed for 12 months. This sample size provides a 95% chance of identifying AEs having an incidence of 1:1000. In the current preliminary report, only 1294 patients are included in the analysis.

3.5 Study variables

3.5.1 Dependent variable

- Occurrence of AEs

3.5.2 Independent variable

- Socio-demographic characteristics (age, sex, BMI, etc).
- Clinical characteristics (WHO stage, T-stage, baseline viral load, baseline CD4 count, comorbidity, concomitant drug use, OIs, functional status, taking prophylaxis).

3.6 Inclusion and exclusion criteria

3.6.1 Inclusion criteria

Willingness to participate in the study; and age greater than or equal to 4 weeks and weight greater than or equal to 3 kg.

3.6.2 Exclusion criteria

Unable to give consent (mental illness) and unreachable individuals for study follow-up.

3.7 Data Collection and Management

3.7.1 Data Collection Procedure

Data was collected by recruited and trained health professionals from study sentinel sites under supervision of pharmacovigilance experts from EFDA and GHSC-PSM project. Participants were followed on day 1, 3, 7, 15 and then monthly for one year through phone call. As per the regular visit to sentinel sites, participants were contacted physically by data collectors.

3.7.2 Data Collection Instrument

Data collection tool (Annex 2) was developed using the national comprehensive HIV prevention, care and treatment guidelines and pharmacovigilance guidelines; and it was modified based on data collectors' feedback during orientation session. The data collection tool contains information regarding socio-demographic characteristics, clinical characteristics, laboratory values and components related to medication use etc.

3.8 Data Quality Assurance

The developed tool was pre-tested, data collectors were trained and supervisors from EFDA regularly followed and monitored the data collection process. Monitoring was also carried out during supportive supervision visits using a checklist (Annex 3) and discussions were carried out with the data collectors and coordinator (s) at each site. Additional need-based site level supports

were provided when there were staff turnover and to increase the engagement of higher officials, such as medical directors in the study. Meetings and discussions were also conducted with supervisors at EFDA and partners to evaluate progress of data collection process. Besides tool distribution, remote support via telephone and weekly tracking and report collection via telegram page were conducted.

3.9 Data Analysis and Interpretation

The data was entered using MS excel version 22, exported to, and analyzed using statistical package for social science (SPSS) version 25. Mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variable were computed using descriptive statistics. Univariate and Multivariate analysis were conducted to determine association between dependent and independent variables. P-value ≤ 0.05 is considered statistically significant. To get preliminary reports, the interim data analysis and preliminary report was aimed to be conducted using a sample size of 1000. However, a total of 1294 samples were collected and included in this preliminary data analysis.

3.10 Ethical Considerations

Ethical clearance was obtained from Addis Ababa University, College of Health Sciences, School of Pharmacy, Ethical Review Committee (ERC). Informed consent (Annex 4) and assent were obtained from each participant/guardian/parent who agrees to participate on the study. Participants were allowed to withdraw from the study anytime.

3.11 Operational Definitions

- **Adverse drug event** means any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.
- **Adverse Drug Reaction** means a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
- **Onset of ADR:** The time gap in days between being put on DTG-based ART to the development of the first episode of ART adverse drug reactions.

- **Cohort event monitoring** is an active surveillance method that is used to monitor and document ADRs experienced by patients who have been enrolled to investigate the effects of the prescribed medication. It is a prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period.

4. Results

4.1. Sociodemographic characteristics of the study participants

The research included 1294 participants who were on a DTG-based ART regimen for the preliminary report and interim data analysis. Out of these participants, over two-thirds (837; 64.7%) of them were females. Among the female participants, 3.6% of them were pregnant, and only 9(0.7%) were breastfeeding. Additionally, the largest proportion of participants fell within the 36-49 years age range. The majority, 607(46.9%) of participants had normal BMI during the initiation of the DTG-based regimen (Table 1).

Table 1: Sociodemographic characteristics of the study participants, Addis Ababa, April 2022- November 2023, N=1294.

Variable	Category	N (%)
Sex	Male	451 (34.9)
	Female	837 (64.7)
	Missing	6 (0.5)
Age (Years)	>=5	14 (1.1.)
	6-18	30 (2.3)
	19-34	506 (39.1)
	35-49	557 (43.0)
	50-64	143 (11.1.)
	>=65	14 (1.1)
	Missing	30 (2.3)
Pregnancy status	Yes	47 (3.6)
	No	790 (61.1)
	Not applicable	452 (34.9)
	Missing	5 (0.4)
Breast feeding	Yes	9 (0.7)
	No	826 (63.8)
	Not applicable	454 (35.1)
	Missing	5 (0.4)
Wight	Mean	56.8 (SD ±12.9)
Height	Mean	161.6 (±SD 12.9)
BMI (Kg/M²)	Underweight (<18.5)	223 (17.2)
	Normal (18.5-24.9)	607 (46.9)
	Overweight (25-29.9)	153 (11.8)
	Obese (>=30)	52 (4.0)
	Not available	259 (20.0)

4.2. Follow up status of the study participants

Among the total number of participants followed, 330 (22.5%) of them have completed the follow-up and 735 (56.8%) of them are on follow-up (Figure 2).

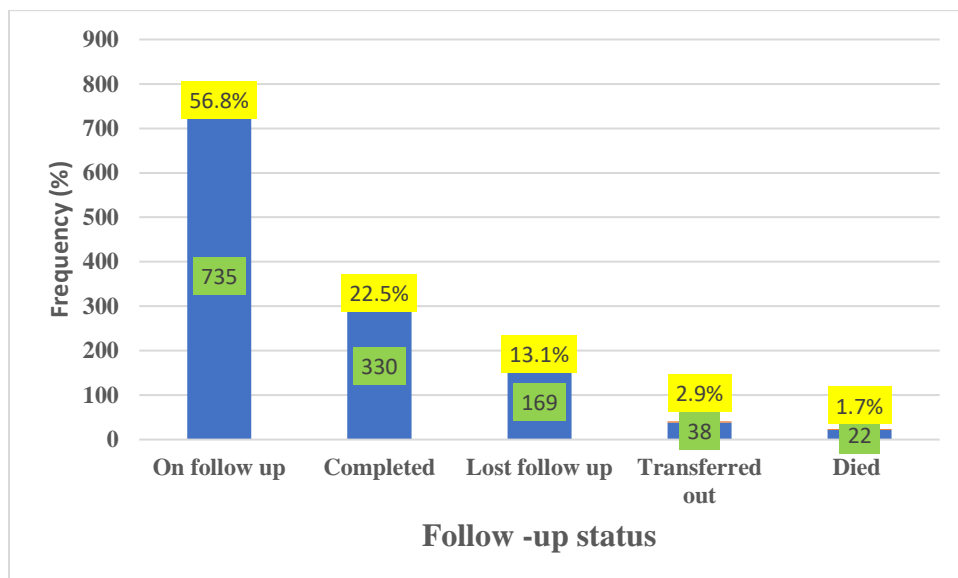


Figure 2: Follow-up status of the study participants, Addis Ababa, April 2022-November 2023, N=212

4.3. Clinical and laboratory characteristics of the study participants

4.3.1. Clinical characteristics

More than half, 850 (65.7%) of patients were on WHO category stage I. Moreover, more than 36% (36.4%) and near to three fourth, 980 (75.7) of the patients were on T1 stage and working respectively (Table 2).

Table 2: Clinical characteristics of the study participants, Addis Ababa, April 2022-November 2023, N=1294.

Variable	Category	N (%)
Time since HIV confirmed		
WHO clinical stage	Stage 1	850 (65.7)
	Stage 2	109 (8.4)
	Stage 3	128 (9.9)
	Stage 4	41 (3.2)
	Not available	166 (12.8)
T-Stage	T1	471 (36.4)
	T2	21 (1.6)
	T3	25 (1.9)
	T4	6 (0.5)
	Not available	771 (59.6)

Functional status	Working	980 (75.7)
	Ambulatory	97 (7.5)
	Bedridden	12 (0.9)
	Not available	205 (15.8)

4.3.2. Types of comorbid conditions and opportunity infections

Below 10% (5.9%) and close to 18% (18.2%) of participants were comorbid conditions and opportunity infections respectively. Of those having comorbid conditions and opportunity infections, hypertension (1%) and tuberculosis (8.3%) have the highest percentage (Table 3).

Table 3: Types of comorbid conditions and opportunity infections of the study participants, Addis Ababa, April 2022-November 2023, N=1294.

Characteristics	Category	n (%)
Comorbid conditions	Yes	76 (5.9)
	No	1218 (94.1)
Opportunistic Infections	Yes	236 (18.2)
	No	1058 (81.8)
Comorbid conditions	Hypertension	13 (1.0)
	Diabetes mellitus	10 (0.8)
	Mental illness	3 (0.2)
	Anemia	6 (0.5)
	Liver diseases	9 (0.7)
	Cancer†	10 (0.8)
	Neurological disorder‡	6 (0.5)
	Others*	21 (1.6)
Opportunity infections	Respiratory infections#	18 (1.4)
	Toxoplasmosis	8 (0.6)
	Tuberculosis	107 (8.3)
	Cryptococcus meningitis	3 (0.2)
	Candidiasis	25 (1.9)
	Skin related OIs£	46 (3.6)
	Diarrhea	9 (0.7)

*Chronic bronchitis, Brain injury, Hyper/hypothyroidism, Epigastric pain, Hypercholesterolemia, Second stage ulcer, CHF, **abdominal lymphadenopathy**, Sub-clinical hypothyroidism, Hemangioma, cortical renal cyst, uterine myoma, hemorrhoid, DVT, psoriasis, mild pericardial effusion, perianal abscess.

†Bilateral salpingo carcinoma, Ovarian cancer, Acinar cell carcinoma (pancreatic cell malignancy), Nasopharyngeal carcinoma, Cervical mass (cervical cancer), Bladder cancer, brain tumor

‡Neurological disorders (Lumbar spine degenerative spondylosis, Paralysis, Bell's palsy, Hemiparalysis, Epilepsy.)

#Respiratory infection (Pneumonia, URTI, PCP)

£Skin related OIs (Genital wart, Warts in the face, Herpes zoster, fungal nail infection, Molluscum Contagiosum, Seborrheic dermatitis, minor mucocutaneous manifestation, fungal nail infection)

4.3.3. Laboratory findings

Figure 4: Laboratory tests reported, Addis Ababa, April 2022-November 2023, N=1294.

Description		Day 0	Day 15	1 month	2 month	3 month	4 month	5 month	6 month	12 month
Lab test reported	Yes	766 (59.2)	27 (2.1)	27 (2.1)	13 (1)	20 (1.5)	5 (0.4)	6 (0.5)	92 (7.1)	12 (0.9)
	No	528 (40.8)	1267(97.9)	1267 (97.9)	1281 (99)	1274 (98.5)	1289 (99.6)	1288 (99.5)	1202 (92.9)	1282 (99.1)
CD4 (Cells/mm ³)	Mean	353.8	306.6	237.8	333.4	293.8	619.3		362.3	2456
Viral load (Copis/ml),	≤50	38 (67.8)	2 (100)	1 (50)	1 (100)	6 (100)	1 (100)	4 (100)	71 (91.0)	7 (77.8)
	51-1000	8 (14.3)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	6 (7.7)	2 (22.2)
	>1000	10 (17.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)	0 (0)
ALT (ULNx)	<1.25	236 (90.1)	2 (66.7)	6 (75)	3 (100)	3 (100)	2(100)	0 (0)	15 (93.8)	0 (0)
	1.25-2.5	24 (9.1)	1 (33.3)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.2)	0 (0)
	2.6-5	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	6-10	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	>10	0	0	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SCr. (mg/dl)	Normal	265 (91.7)	1 (100)	5 (83.3)	3 (100)	5 (83.3)	2 (100)	0 (0)	13 (100)	0 (0)
	Above normal	24 (8.3)	0 (0)	1(16.7)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)
Hgb (mg/dl)	Normal	356 (69.9)	2 (33.3)	9 (81.8)	5 (100)	6 (85.7)	3 (100)	0 (0)	20 (86.9)	1 (100)
	Below normal	153 (30.1)	4 (66.7)	2 (18.2)	0 (0)	1 (14.3)	0 (0)	0 (0)	3 (13.1)	0 (0)
RBS (mg/dl)	<200	121 (98.4)	12 (100)	5 (100.0)	1 (100)	3 (100)	0 (0)	0 (0)	2 (100)	1 (100)
	≥200	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FBS (mg/dl)	<100	108 (71.5)	1 (33.3)	3 (75)	2 (66.7)	1 (100)	1 (100)	1 (100)	12 (100)	0 (0)
	100-125	34 (22.5)	2 (66.7)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥126	9 (6.0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- SCr≤1.3 is normal for male and SCr≤1.1 is normal for female
- Hgb≥ 14 is normal for male and Hgb≥ 12 is normal for female

4.4. Medication Information

4.4.1. Previous and current regimens

The ART regimen of the patients before and during the follow up period is depicted in table 5. Of the total 1294 patients followed in the study, 147 (11.4%) of them have previous regimen. Among the previous regimens, 1E (TDF/3TC/EFV) was the most commonly prescribed ART regimen. From the current regimens, 1278 (98.8%) of the patients were on 1J ((TDF/3TC/DTG) (Table 5)

Table 5: Previous and current regimen information of the study participants, Addis Ababa, April 2022-November 2023, N=1294.

Variable	Category	n(%)
History of previous regimen	Yes	147 (11.4)
	No*	1147 (88.6)
Previous regimen, n=147	1E	127 (86.4)
	1d	5 (3.4)
	4d	1 (0.7)
	1J	3 (2.0)
	1C	4 (2.7)
	4J	1 (0.7)
	4E	1 (0.7)
	2I	1 (0.7)
	2E	1 (0.7)
	Unspecified regimen	3 (2)
Current regimen	1J	1278 (98.8)
	4J	12 (0.9)
	1K	4 (0.3)

*No previous regimen or data not available

1C=ZDV/3TC/NVP; 1D =ZDV/3TC/EFV; 1E= TDF/3TC/EFV; 1J =TDF/3TC/DTG; 1K= ZDV/3TC/DTG; 2I=AB C/3TC/LPV/r; 4J =ABC/3TC/DTG; 4E =TDF/3TC/EFV; 2E =ZDV/3TC/LPV/r

Regarding reasons for regimen change, this study revealed that treatment protocol change was the most commonly reported reasons 128 (87.1%) (Table 6).

Table 6: Reasons for changing previous regimen of the study participants, Addis Ababa, April 2022- November 2023, n=147.

	Category	n (%)
Reason for change	Treatment protocol change	128 (87.1)
	Poor adherence	4 (2.7)
	Pregnancy	1 (0.7)
	Toxicity	1 (0.7)
	Patient decision	5 (3.4)
	Others	16 (10)

4.4.2. Prophylactic and concomitant medications

In this follow-up study, close to two-third (63%) of participants received at least one prophylactic medication and 3HP was the most commonly used prophylactic medication. Besides the ART regimen, only 5.3% of the participants were on concomitant medications (Table 6).

Table 6: Prophylactic and concomitant medications of the study participants, Addis Ababa, April 2022-November 2023, N=xxx.

Variable	Category	N
Prophylactic medications	Yes	815 (63.0)
	No	479 (37.0)
Types of prophylactic medications	CPT	275 (21.3)
	IPT	60 (4.6)
	3HP	573 (44.3)
	9RH	45 (3.5)
	FPT	1 (0.1)
Concomitant medications	Yes	69 (5.3)
	No	1225 (94.7)
Types of concomitant medications	Anti-TB	42 (3.2)
	Pyridoxine	15 (1.2)
	Iron	3 (0.2)
	Fluconazole	2 (0.2)
	Others*	8 (0.6)

* Ceftriaxone, TTC eye ointment, Doxycycline, Levothyroxine, Nifedipine, Acyclovir, Amlodipine, Azithromycin

4.5. Adverse drug reactions

4.5.1. Occurrence and types of adverse drug reactions

In this study, from the total 1294 patients, 141 (10.9 %) reported to have one or more ADRs.

Of the reported ADRs, the most frequently reported ADRs were headache, (16.5%) and fatigue (14.6%) (Table 7).

Table 7: Types of reported ARDs of the study participants, Addis Ababa, April 2022-November 2023, N=212.

Types of ADRs	n (%)
Hyperglycemia	2 (0.9)
Hypersensitivity reaction	17 (8.0)
Insomnia	10 (4.7)
GI related ADE	13 (6.1)
Musculoskeletal	4 (1.9)
Weight loss	13 (6.1)
Anorexia	10 (4.7)
Headache	35 (16.5)
Nausea	19 (9.0)
Vomiting	14 (6.6)
Diarrhea	4 (1.9)
Hepatotoxicity	2 (0.9)
Fatigue	31 (14.6)
Weight gain	9 (4.2)
Urine discoloration	9 (4.2)
Others*	20 (9.4)
Total	212 (100)

4.5.2. Severity of reported adverse drug reactions

Among the reported ADRs were classified as mild, 100 (47.2%), moderate 51(24%), severe 14 (6.6%) and life threatening, 5 (2.4%), respectively. The level of severity of the remaining ADRs, 42(19.8%) were not recorded (Table 8)

Table 8: Severity of ADRs of the study participants, Addis Ababa, April 2022-November 2023, N=212.

Type of ADRs	Severity of ADRs			
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Life threatening, n (%)
Hyperglycemia, n=2	0	1	1	0
Hypersensitivity reaction, n=17	8	6		
Insomnia, n=10	3	6	1	0
GI related ADE, n=13	7	2	1	
Musculoskeletal, n=4	3	1		
Weight loss, n=13	5			1
Anorexia, n=10	5	3		
Headache , n=35	22	8	3	
Nausea , 19	11	3	1	1
Vomiting, n=14	3	3	4	2
Diarrhea, 4	1		1	
Hepatotoxicity, n=2	2			
Fatigue, 31	16	9	2	
Weight gain, n=9	2	4		
Urine discoloration, 9=	5	1		
Others*, n=20	7	4	0	1
Total	100	51	14	5

* Back pain, Blurred vision, Burning sensation, Convulsion, Cough & Flu like symptoms, Dizziness, Fever, Generalized body weakness, Hospitalization, Lymphadenopathy, neuropathy, Night sweating/sweating, Renal problem, Shortness of breath

4.5.3. Onset of adverse drug reactions

As shown in the figure below (figure 1), the highest percentage (75%) of participants who developed ADR has encountered the ADR on the first 15 days of initiation of the DTG-based therapy. However, 11 (9%) and 9(7%) individuals has developed the ADR within 1 and 3 months and beyond 3 months, respectively.

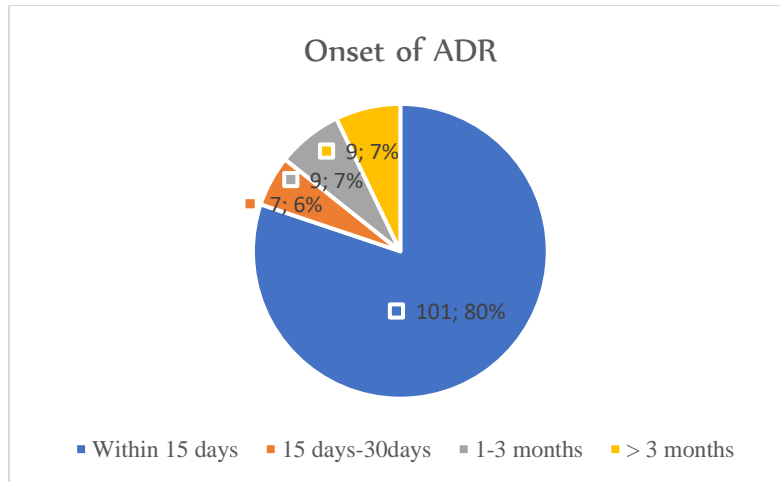


Figure 1: Onset of ADRs from initiation of DTG-based therapy, April 2022-November 2023.

4.5.4. Outcome and consequences of adverse drug reactions

Among the total 212 ADRs encountered, 69 (32.5%) participants' ADRs were resolved and 6 (2.8%) of them were died. On the other hand, 108 (50.9%) of the ADRs outcome were not recorded (Table 9).

Table 9: Outcome and consequences of ADRs of the study participants, Addis Ababa, April 2022-November 2023, n=212

Type of ADRs	Outcomes of ADR					Consequence of ADR	
	Resolved, n (%)	Resolving, n (%)	Resolved with sequel, n (%)	Not resolved, n (%)	Died, n (%)	Regimen switch	Others
Hyperglycemia, n=2	1	0	0	1	0	2	0
Hypersensitivity reaction, n=17	6		1	1		4	0
Insomnia, n=10	2		2	2		3	0
GI related ADE, n=13	5	2					0
Musculoskeletal, n=4	1	1				1	0
Weight loss, n=13				1			0
Anorexia, n=10							0
Headache, n=35	13	2		2	1	2	2
Nausea, n=19	11	1		1		1	0
Vomiting, n=14	4	1		4	1	1	2
Diarrhea, n=4	2						0
Hepatotoxicity, n=2	1	1					0
Fatigue, n=31	17	3				3	0
Weight gain, n=9						1	0
Urine discoloration, n=9	1	1				1	0
Others*, n=20	5	1	1	0	4	1	0
Total	69 (32.5)	13 (6.1)	4 (18.9)	12 (5.6)	6 (2.8)	20	4

* Back pain, Blurred vision, Burning sensation, Convulsion, Cough & Flu like symptoms, Dizziness, Fever, Generalized body weakness, Hospitalization, Lymphadenopathy, neuropathy, Night sweating/sweating, Renal problem, Shortness of breath

4.5.5. Factors associated with the occurrence of ADR on DTG regimen

Univariate analysis showed that WHO Clinical Stage, co-morbidity, Opportunistic infection, Concomitant medication, and previous regimen have been revealed p-value which was less than 0.25 (Table 1) and they were incorporated for multivariate binary logistic regressions. According to the multivariate analysis, three variables were significantly associated with the ADR of DTG. Statistically significant correlations with the ADR were found in opportunistic infection, the WHO Clinical Stage, and concomitant medication.

A significant association was found between ADR developed HIV patients with DTG regimen with OI (AOR = 1.627; 95% CI: 1.005– 3.739, P = 0.040). Following that, the WHO Clinical Stage II (AOR = 1.851; 95% CI: 0.418– 2.633, P = 0.041) HIV patients 1.8 times higher risk to develop ADR as compared to WHO Stage I. Moreover, these HIV patients who were having OI infection one and half -times higher risk to develop ADR than who didn't have. Participants who were having a concomitant medication had a significant association with occurrence of ADR (AOR = 3.165; 95% CI: 1.674-5.982) P = 0.001). This indicates, those HIV patients who were taking concomitant medications have three- times higher risk to develop ADR as compared to who didn't took those medication.

Table 10: Univariate and multivariate logistic regression analysis of factors associated with adverse drug reactions of DTG containing ARV regimens among HIV patients, Ethiopia from (n = 1294).

Outcome variables	Occurrence of ADRs, n(%)		Univariate analysis		Multivariate analysis	
	ARD, n (%)	Non-ADR, n (%)	COR (95% CI)	P-value	AOR (95% CI)	P-value
WHO clinical stage						
Stage I	83(9.8)	797(90.)	1.000		1.000	
Stage II	15(12.2)	94(86.2)	0.779(.298-2.040)	0.258	0.866(.327-2.299)	0.712
Stage III	20(15.6)	108(84.4)	1.149(0.389-3.392)	0.030	1.851(0.418-3.739)	0.040*
Stage IV	5(12.2)	36(87.8)	1.333(0.467-3.810)	2.88	2.37(0.391-3.312)	0.081
Comorbidity						
No	127(10.4)	1091(89.6)	1.000		1.000	
Yes	14(18.4)	62(81.6)	1.940(1.056-3.3564)	0.003	1.656(.886-3.094)	0.144
Opportunistic infection						
No	98(9.3)	960(90.7)	1.000		1.000	
Yes	43(18.2)	193(81.8)	2.183(1.447-3.225)	0.000	1.627(1.005-2.033)	0.041*
Concomitant medications						
No	122(10)	1103(90)	1.000		1.000	
Yes	19(29.5)	50(72.5)	3.436(1.962-6.017)	0.000	3.165(1.674-5.982)	0.001*
Previous regimen						
No	120(10.5)	1027(89.5)	1.000		1.000	
Yes	21(14.3)	1261(85.7)	1.426(.866-2.350)	0.016	1.648(.988-2.750)	0.56

COR = crude odds ratio, AOR = adjusted odds ratio, CI = confidence interval, ADRs = Adverse Drug Reactions,

* = significant association (p < 0.05)

5. Conclusion and Recommendation

5.1. Conclusion

A total of 1294 participants who were on a DTG-based ART regimen were included for the interim data analysis and preliminary report of this follow-up CEM study. However, a quarter of the study participants completed their follow-up. In our study, the overall prevalence of ADR was 10.9% meaning nearly eleven percent of the patients who were taking DTG based ART regimen developed at least one ADR during their follow-up period. The most common ADR reported was headache, followed by fatigue, nausea, vomiting, hypersensitivity reaction, GI related ADRs, insomnia, and anorexia. Of the ADRs reported, nearly half were mild in severity. Of those who developed ADR, three-fourth of the participants encountered the ADR on the first two weeks of initiation of the DTG-based therapy.

5.2. Recommendations

Based on the findings of the interim data analysis and preliminary results, the following recommendations are forwarded:

- The follow-up study should be continued until the planned sample size reached in order to better detect and document ADRs and associated factors.
- Data quality, mainly data accuracy and data completeness, should be improved by data collectors through close follow-up, supervision, and feedback mechanism.
- The data collection tool should be revised based on the gaps identified during this interim data analysis but without creating discrepancy with the original one.
- ADR investigation for some of the serious ADRs such as death should be conducted as early as possible.
- Provide sensitization training to data collectors to create uniform understanding among them about the study, data collection and issues of data quality.

References

- 1) World Health Organization. Epidemiological fact sheet. HIV statistics, globally and by WHO region, 2023. <http://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes>
- 2) The ethiopian public health institute. 2023. HIV Related Estimates and Projections in Ethiopia for the Year 2022- 2023
- 3) Federal ministry of Health.2017.NATIONAL GUIDELINES FOR COMPREHENSIVE HIV PREVENTION, CARE AND TREATMENT
- 4) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf>. Accessed [29 March 2022].
- 5) Mehari EA, Muche EA, Gonete KA (2021). Virological Suppression and Its Associated Factors of Dolutegravir Based Regimen in a Resource-Limited Setting: An Observational Retrospective Study in Ethiopia. HIV/AIDS - Research and Palliative Care 13 709–17.
- 6) Kanters S, Vitoria M, Zoratti M, Doherty M, Penazzato M, Rangaraj A, Ford N, Thorlund K, Anis PAH, Karim ME, Mofenson L, Zash R, Calmy A, Kredo T, Bansback N. Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: A systematic literature review and network meta-analysis. EClinicalMedicine. 2020 Oct 16;28:100573. doi: 10.1016/j.eclinm.2020.100573. PMID: 33294805; PMCID: PMC7700905.
- 7) WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - Second edition. 2nd ed. Geneva: World Health Organization, 2018. <http://www.who.int/hiv/pub/arv/arv-2016/en/>.
- 8) WHO. Updated recommendations on first-line and secondline antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: WHO, 2018. <https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf>.

- 9) Pujari S, Patel A, Gaikwad S, et al (2020). Effectiveness of dolutegravir based antiretroviral treatment for HIV-2 infection: retrospective observational study from Western India. *J Antimicrob Chemother* 75:1950–4.
- 10) Treviño A, Cabezas T, Lozano AB, et al (2015). Dolutegravir for the treatment of HIV-2 infection. *J Clin Virol* 64:12–5
- 11) Chilambe M, Kalungia A, Mangani A, Munkombwe Z (2019). An Analysis of Pharmacovigilance Case Reports of Adverse Drug Events Attributable to Dolutegravir based Antiretroviral Treatment for HIV in Zambia. *Medical Journal of Zambia* 46 (4): 305-13. (2019).
- 12) Odenyo JA (2020). Prevalence of dolutegravir associated hyperglycemia and its covariates among persons living with HIV on treatment at kenyatta national hospital. MSc Thesis. <http://erepository.uonbi.ac.ke/handle/11295/154331>.
- 13) Kandel CE, Walmsley SL (2015). Dolutegravir—a review of the pharmacology, efficacy, and safety in the treatment of HIV. *Drug design, development and therapy* 9:3547.
- 14) Hailu W, Tesfaye T, Tadesse A (2021). Hyperglycemia After Dolutegravir-Based Antiretroviral Therapy. *International Medical Case Reports Journal* 14 503–07.
- 15) Goh OQ, Colby DJ, Pinyakorn S, et al., (2019). Switch to dolutegravir is well tolerated in Thais with HIV infection. *Journal of the International AIDS Society* 1;22(7).
- 16) Abah IO, Ncube N, Bradley HA, Agbaji OO, Kanki P (2018). Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure-A Retrospective Cohort Study in Nigeria. *Current HIV research*. 16(6):436-46.

6. Annexes

Annex 1: List of health facilities included in the study

a. Hospitals

- ALERT Hospital
- Betiel Hospital
- Ras Desta Hospital
- St. Paul's Millennium Medical College Hospital

b. Health Centers

- Akaki Health Center
- Beletshachew Health Center
- Betel Hospital
- Bole 17 Health Center
- Bole 17/20 Health Center
- Kality Health Center
- Kolfe Health Center
- Kotebe Health Center
- Kuas Meda HC
- Lideta Health Center
- Saris Health Center
- Selam Health Center
- Semen Health Center
- Teklehaymanot HC
- N/S/L Woreda 9 HC
- Yeka Health Center
- Jagemkelo Health Center

Annexes 2: Data collection form for CEM study on Dolutegravir (DTG)

I. Socio-Demographic Characteristics

Participant ID _____

Name of Health Facility _____

Name and phone no. of data collector _____

A. Participant details: Age: _____ Sex Male Female

If female; Pregnant Lactating Non pregnant/non-lactating

Height: _____ meter Weight: _____ Kg

II. Clinical Characteristics

a. Date Of confirmed HIV _____ E.C (DD/MM/YYYY)

b. WHO stage of HIV: Stage I Stage II Stage III Stage IV

c. T-Stage T1 T2 T3 T4

d. Functional Status of the participant: Working Ambulatory Bed Ridden

e. Co-morbid conditions: Yes No If yes, please specify

f. Opportunistic Infections: Yes No If yes, please specify

III. Laboratory Values

Table 1. Laboratory Values

Test	CD ₄	Viral Load	LFT					RFT		CBC				
Specific Tests			AST	ALT	ALP	Bilirubin	Albumin	Serum Creatinine	BUN	WBC	Hbg	Ptl	Lymphocyte	Neutrophils
Day: _____														
Date: dd/mm/yy _____														
Test: _____														
Day: _____														
Date: dd/mm/yy _____														
Test: _____														
Day: _____														
Date: dd/mm/yy _____														
Test: _____														
Day: _____														
Date: dd/mm/yy _____														
Test: _____														

Note: Day: 1, 3, 7, 15, 30 (1st month), 60 (2nd month), 90 (3rd month), 120 (4th month), 150 (5th month), 180 (6th month).....

Date: DD/MM/YYYY E.C

Test: 1, 2, 3, 4.....

Table 2. Laboratory values

Test	Lipid Profile				Blood Glucose Test			Coagulation Profile			Serum Electrolyte			
Specific Tests	Cholesterol	HDL	LDL	Triglyceride	RBS	FBS	HA1c	Pt	Ptt	INR	Na ⁺	K ⁺	Ca ⁺	Cl ⁻
Day: _____														
Date: dd/mm/yy														
Test: _____														
Day: _____														
Date: dd/mm/yy														
Test: _____														
Day: _____														
Date: dd/mm/yy														
Test: _____														
Day: _____														
Date: dd/mm/yy														
Test: _____														

Note: Day: 1, 3, 7, 15, 30 (1st month), 60 (2nd month), 90 (3rd month), 120 (4th month), 150 (5th month), 180 (6th month).....

Date: DD/MM/YYYY E.C

Test: 1, 2, 3, 4.....

Table 3. Laboratory values

Test	Urine Analysis						Other, Specify
Specific Tests	Specific Gravity	Protein	Glucose	Ketone	WBC	RBC	
Day: _____ Date: dd/mm/yy _____ Test: _____							
Day: _____ Date: dd/mm/yy _____ Test: _____							
Day: _____ Date: dd/mm/yy _____ Test: _____							

Note: Day: 1, 3, 7, 15, 30 (1st month), 60 (2nd month), 90 (3rd month), 120 (4th month), 150 (5th month), 180 (6th month).....

Date: DD/MM/YYYY E.C

Test: 1, 2, 3, 4.....

IV. Medication history

Medication Regimen	Daily dose	Date started DD/MM/YYYY E.C	Date Stopped DD/MM/YYYY E.C	Reason (s)* for Stopping	Restart Date if any DD/MM/YYYY E.C
Previous Regimen					
If there is history of medication change, mention the reason					
Response to restart ^C if any					
Current Regimen					
Prophylactic Medication (CPT, TPT (3HP, 6H, 9HR), FPT, Vit B-6)					
Concomitant Medication,					

***Reason(s) for stopping:** (insert code). Codes: 1. Toxicity; 2. Pregnancy; 3. Treatment Failure; 4. Poor adherence.
 5. Illness, Hospitalization; 6. Drug out of stock; 7. Cost; 8. Other Patient Decision; 9. Planned Interruption.
 10. Drug Interaction 11. Treatment Protocol Change 12. Other

C. Response to restart codes: “No” if no re-challenge; ‘+ve’ if recurrence of event; ‘-ve’ if no recurrence ‘uk’ if response is unknown

V. Adverse Events:

Day: _____ **Date:** _____ DD/MM/YYYY E.C

Were there any adverse events encountered or worsening problems over the period since last seen? Yes No

Adverse Events (including any medicine Quality issue)	Severity ^A	Seriousness ^B	Date Started	End Date	Outcome ^B	ADR resulted in ^C

Day: _____ **Date:** _____ DD/MM/YYYY E.C

Were there any adverse events encountered or worsening problems over the period since last seen? Yes No

Adverse Events (including any medicine Quality issue)	Severity ^A	Seriousness ^B	Date Started	End Date	Outcome ^B	ADR resulted in ^C

Day: _____ **Date:** _____ DD/MM/YYYY E.C

Were there any adverse events encountered or worsening problems over the period since last seen? Yes No

Adverse Events (including any medicine Quality issue)	Severity ^A	Seriousness ^B	Date Started	End Date	Outcome ^B	ADR resulted in ^C

- A. Severity code:** I. Mild; 2. Moderate; 3. Severe; 4. Life threatening
B. Seriousness code: 1. Death 2. Life threatening 3. Hospitalization/prolonged hospitalization 3. Significant disability 4. Congenital anomaly/birth defect
B. Outcome code: A. Resolved; B. Resolving; C. Resolved with sequelae; D. Not resolved; E. Worse; F. Death; G. Unknown.
C. ADR resulted in 1. Non-adherence 2. Switch to regimen 3. Other, specify _____

Note: Day: 1, 3, 7, 15, 30 (1st month), 60 (2nd month), 90 (3rd month), 120 (4th month), 150 (5th month), 180 (6th month).....

Date: DD/MM/YYYY E.C

Annex II: Supportive Supervision Checklist for the ‘Cohort Event Monitoring (CEM) on Dolutegravir Containing Regimens at ART Sites in Addis Ababa, Ethiopia’.

(Please fill this checklist in both ART clinic and ART pharmacy separately. Please ask all trained CEM data collectors in the facility)

A. General

1. Name of health facility..... Sub city.....Tel.....
2. Name of CEM data collector..... Mobile..... Department: ART clinic, ART pharmacy)
3. How many total professionals are available in this unit?_____
4. How many trained/assigned CEM data collectors are available in the facility? _____
5. Is there any trained/assigned CEM data collector who left the facility/change department?
6. Do you receive orientation for the DTG CEM data collection? yes No

B. Study Details

- 1) When did you start enrolling clients to the CEM (start date of enrolment)
- 2) Total number of patients currently on ART?.....
- 3) How many new patients started ART in the past one year (FY2014)?.....
- 4) How many new patients started DTG containing regimens in the past one year (FY2014)?.....
- 5) Total no of participants enrolled to CEM so far?.....; M.....F.....; Adult....Pedi.....
- 6) Presence of data collection checklist Yes No
- 7) Presence of consent form Yes No
- 8) Presence of trained data collectors during supervision Yes No
- 9) Total no follow up call conducted to the participant
- 9.1 Total no of respondents.....
- 9.2 Total no of non-respondent switched off.....No response.....
- 10) Are you enrolling all new patients in to the CEM? yes No
- 11) If no, why?
 - 11.1 Non willingness of clients
 - 12.2 Shortage of trained/assigned personnel for the CEM
 - 13.3 Limited number of new clients starting treatment
 - 14.4 Other, specify.....
- 12) Out of the total enrolled clients, how many patients experience at least one ADR so far?.....
- 13) How many ADRs are detected/identified/documentated so far from all clients enrolled?_____(Please write the ADR types and number below in the table by looking at the data collection tools)
- 14) Have you identified serious ADR so far? yes No
- 15) If yes, did you report to EFDA? yes No
- 16) If you didn't report to EFDA, why?.....

C. Data Quality Assurance

- 1) Please pick all filled CEM data and check their completeness. Total CEM data checked?.....
- 2) For how many CEM data do they filled all components of the form appropriately? Yes No
- 3) Did they document all follow-up calls expected (3rd, 7th, 15th, 30th days and then monthly)? Yes No
- 4) Please rate the overall completeness and quality of filled data? Poor Good Very good Excellent

D) What are the challenges raised by data collectors so far?

- 1.
- 2.
- 3.

E) Recommendation of the data collectors to improve the CEM?

- 1.
- 2.
- 3.

F) Supervisors comment/feedback to improve the program

- 1.
- 2.
- 3.

G) Supervisors Details

Name Signature..... Date.....
 Name Signature..... Date.....
 Name Signature..... Date.....

Type of ADRs and its frequency identified/documented so far *(use separate paper if needed)*

S. No.	Regimen	Type of ADR	Number of patients with this ADR	No. of Serious ADR	Remark
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					

Annex III: Participant consent form

Participant enrolment number: _____

Title: Active Surveillance of Dolutegravir (DTG)

The Ethiopian Food and Drug Administration (EFDA) is mandated to conduct safety monitoring on medicines marketed in Ethiopia. EFDA has been doing safety surveillance on Dolutegravir (DTG) since Ethiopia adopted a DTG-containing regimen for National Comprehensive Policies on HIV Prevention, Care and Treatment and all eligible existing first-line patients were shifted to DTG-containing regime. Currently EFDA has planned to conduct cohort event monitoring on DTG-containing regimen to detect any adverse events after administration of the drug in healthcare facilities that have been selected as a sentinel site for this safety monitoring program. Thus, you are invited to participate in the follow-up/study to monitor adverse events associated with dolutegravir administration. This information will help you to decide your participation in this surveillance.

Purpose of the surveillance

The purpose of this follow-up is to evaluate any adverse events following administration of the drug Dolutegravir as part of the National HIV Prevention, Care and Treatment Program at selected hospitals and health centers.

Procedure of the surveillance

You will be contacted by phone call on the 1st, 3rd, 7th, 15th day and then monthly for a year after starting the drug dolutegravir and followed-up and asked if you experience any adverse events after administration. You will also be physically contacted on your regular follow up.

Do I have to be in the surveillance?

The choice is yours. Your participation in this follow up is completely voluntarily. You can even change your mind anytime if you decide not to participate any more.

What are the benefits to me?

Taking part in this follow up will help you to early identify AEs after drug administration and help to get treatment immediately. In addition to this the community at large may benefit from this follow up outcome through provision of information that may help the HIV prevention, care and treatment national program.

Are there any risks to me if I decided to be involved in this surveillance?

There is no foreseeable risk of participating in the follow-up activity; the most likely cost is the time you spent during the 16 follow-up calls.

How will my information be protected?

Your responses will be kept strictly confidential, and confidentiality will be maintained by entering data into a password-protected computer. Only authorized personnel or government officials have access to this information. Your personal identifiers will not be disclosed in the final report and publication

What if I have questions?

If you have questions about the surveillance programme, you can ask the following person/s anytime during the follow up. Contact person name, telephone number and email address: **Asnakech Alemu** (Product Safety Directorate Director); **09 13 24 95 22; aalemu@efda.gov.et**

You can also contact the following EFDA staffs if there are concerns:

1. Habtamu Gashaw 09 13 44 70 81 ghabtamu@efda.gov
2. Meron Kifle 09 13 06 48 42 mkifle@efda.gov.et
3. Mehret Maru 09 10 00 79 42 mmaru@efda.gov.et
4. Demeke Amare 0960412512 damare@efda.gov.et
5. Merkeb Ayitenfsu 0911834156 maytenfsu@efda.gov.et

I have been well informed about the surveillance and agreed to participate in it.

Name.....Phone no.....

Signature.....

Data collector: Name..... Phone no.....

Signature.....