

Addis Ababa University
College of medicine and health sciences

Prevalence of hyperglycemia and associated factors among people living with HIV on dolutegravir based antiretroviral therapy regimen in Tikure Anbessa Specialized Hospital: A Hospital-based cross-sectional study

Mamaru Sintayehu (MD)

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Principal investigator: Mamaru Sintayehu (MD)

Advisor: Dr. Wondwossen Amogne (MD, PhD, Consultant Internist, Infectious Disease specialist)

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Principal investigator: Mamaru Sintayehu (MD)
✉mamarusintie@gmail.com
0912291743

Advisor: Dr.Wondwossen Amogne (MD, PhD, Consultant Internist, ID specialist): sign_____

Department head: Dr Abdurezak Ahmed (MD, Consultant internist, Enocrinologist): sign_____

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Abbreviations

3TC- Lamivudine

ABC- Abacavir

ART- Anti- Retroviral Treatment

AZT-Zidovudine

BB- Beta blocker

BMI- Body Mass Index

cART- Combination Anti-retroviral Treatment

CCB- Calcium Channel blocker

CVD- Cardio-vascular disease

DC- Data collector

DKA- Diabetic Ketoacidosis

D.M.- Diabetes Mellitus

DNA- Deoxyribonucleic Acid

DTG- Dolutegravir

D4T-Stavudine

ED- Emergency Department

EFV-Efavirenz

EPHI- Ethiopian public health institute

ETB- Ethiopian Birr

FBS- Fasting blood sugar

FMOH- Federal Ministry of Health- Ethiopia

FTC-Emtricitabine

HgA1C- Hemoglobin A1C

Hgb- Hemoglobin

HHS- Hyperosmolar Hyperglycemic state

HIV- Human Immunodeficiency Virus

HTN- Hypertension

IFG- Impaired Fasting glucose

IGT- Impaired Glucose Tolerance

INSTIs- Integrase strand transfer inhibitors

NNRTI- Non-nucleoside Reverse Transcriptase Inhibitors

NRTI- Nucleoside Reverse Transcriptase Inhibitors

NVP-Nevirapine

OGTT- Oral Glucose Tolerance Test

PI- principal investigator

PIs- Proteus Inhibitors

PLWH- People Living With HIV

RBS- Random blood sugar

RVI- Retroviral infection

SPSS-Statistical Package for Social Science

TASH- Tikure Anbessa Specialized Hospital

TDF- Tenofovir disoproxil fumarate

WHO- World Health Organization

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There were approximately 36.7 million people living with HIV (PLWH) at the end of 2015 with 2.1 million people becoming newly infected with HIV. Sub-Saharan Africa is the most affected region, with 25.6 million PLWH and accounts for two-thirds of the global total of new HIV infections.(1) 3

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Abstract

Background

The introduction of dolutegravir based Antiretroviral Therapy (ART) regimen has provided a potent treatment option for people living with HIV/AIDS. However, clinical settings showed growing evidence that dolutegravir could result in significant hyperglycemia. The prevalence of hyperglycemia in HIV patients taking dolutegravir is unknown. Knowledge of dolutegravir associated hyperglycemia is important for early interventions to reduce morbidity and mortality related to uncontrolled plasma glucose among HIV patients on DTG containing ART drugs.

Objective

The objective of this study was to assess the prevalence of hyperglycemia among People living with HIV taking dolutegravir based ART regimen and associated factors.

Methods

A cross-sectional study design was used. Study participants who met eligibility criteria were continuously selected and recorded clinical and laboratory data. Fasting blood glucose (FBS) was done using a point of care glucometer(prodigy™). Maximum data quality was ensured, entered into epi info and analyzed with SPSS version 26 software. The study was conducted from June 2021 to November 2021.

Results

The population studied were predominantly females (70%). The mean age was 46.2 years (SD=10.2 years). The majority were in the age group 41-65 years (66.5%). Hyperglycemia was observed in 38 (19%) of the study participants. Bivariable and multivariable logistic regression showed no significant association of hyperglycemia with the independent variables.

Conclusion

The study showed a consistent hyperglycemic risk for patients on dolutegravir and pointed out the usefulness of a glucose monitoring plan for such patients. The study also highlighted the importance of routine body weight monitoring in patients taking dolutegravir.

Keywords: Hyperglycemia, dolutegravir, prevalence, Tikure Anbessa specialized hospital ART clinic, Ethiopia.

Chapter one: Introduction

1.1 Background

The human immunodeficiency virus (HIV), a retroviral infection, is a global burden continuing to take a toll on human health. It has claimed more than 35 million lives globally so far. Approximately 36.7 million people lived with HIV (PLWH) at the end of 2015, with 2.1 million people becoming newly infected with HIV. Sub-Saharan Africa is the most affected region, with 25.6 million PLWH and accounts for two-thirds of the global total of new HIV infections (1).

In Ethiopia, a 2018 report of federal ministry of health (FMOH) has showed that 722,248 people are living with HIV according to 2017 Ethiopian Public health institute (EPHI) HIV related estimation and projection. Furthermore, there were 22,827 new HIV infections according to the report. (1)

The first Antiretroviral therapy (ART) in Ethiopia began in 2003 and was launched for free in 2005. Currently 436,000 PLHIV are on ART according to 2018 FMOH report.(2)

Treatment of HIV has evolved a lot in using more efficacious and less toxic drugs.(3) The goal of HIV drug treatment is to achieve sustained viral suppression using combination of ART drugs that have less toxicity.(3)

People living with HIV have various metabolic derangements, insulin resistance (IR) being among the common ones. Factors associated with IR were chronic immune activation and inflammation due to HIV infection, obesity, abnormal fat distribution, low physical activity, Anti-Retroviral Treatment (ART) drugs and statin uses; as determined by homeostasis models assessment for insulin resistance (HOMA-IR).(4)

The advent and use of effective combination Antiretroviral therapy (cART) has shifted the pattern of morbidity and mortality of PLWH from AIDS related opportunistic infections towards age related comorbidities like dyslipidemia, Hypertension and Diabetes mellitus (DM).(5)

Over the last five years, preferred initial ART regimens for most people with HIV in US treatment guidelines have shifted from primarily non-nucleoside reverse transcriptase

inhibitors (NNRTI) and Proteose inhibitor (PI) based to integrase strand transfer inhibitor (INSTI)-based regimens. This is due to an excellent profile of potency and tolerability for INSTI, including few serious adverse effects observed in clinical trials of treatment-naïve persons.(4)

In low-income and middle-income countries, dolutegravir is replacing older antiretroviral therapies (ART) with less efficacy and greater toxicity. World health organization (WHO) indicates first-line and second-line regimens containing dolutegravir as preferred regimens.(6)

In August 2018, the Ethiopian National comprehensive HIV prevention, care and treatment guideline recommended initiating dolutegravir (DTG) based regimen as one of preferred first line regimen for adolescents living with HIV.(7)

Dolutegravir is a tricyclic carbamoyl pyridone integrase inhibitor that exerts its mechanism of action through inhibition of the strand transfer of retroviral deoxy ribonucleic acid (DNA) into the host cell genome. It is considered a second-generation INSTI because of its efficacy in the presence of raltegravir- and elvitegravir-associated mutations. It exhibits potent activity against wild-type HIV. (3)

Diabetes is defined by the WHO as a fasting plasma glucose equal to 126 mg/dL or more, or a 2-hour glucose 200 mg/dL or more during a 75 g oral glucose tolerance test (OGTT). Impaired glucose tolerance (IGT) is defined as a 2h plasma glucose 140 mg/dL or above during a 75 g OGTT and impaired fasting glucose (IFG) is defined more recently as a fasting plasma glucose 100 mg/dL or more. Both diabetes and IGT are associated with increased cardiovascular risk.(8)

Several case series and observational studies have shown the possible associations of hyperglycemia with integrase strand transfer inhibitors (INSTIs). But the exact prevalence of hyperglycemia, true association is not well established.(6,9–16)

The mechanism of hyperglycemia in INSTs is related to their mechanism of antiretroviral activity in that they chelate magnesium ion, which important cation for viral integration to host DNA. Magnesium also serves as a coenzyme in insulin action. Magnesium ion can also trigger autophosphorylation of insulin after binding with insulin receptor. Thus INSTI

induced decrease in magnesium ion level may be the probable mechanism for insulin resistance.(13)

1.2 Statement of the problem

Approximately 36.7 million people lived with HIV (PLWH) at the end of 2015, with 2.1 million people becoming newly infected with HIV. Sub-Saharan Africa is the most affected region, with 25.6 million PLWH and accounts for two-thirds of the global total of new HIV infections (1).

In Ethiopia, a 2018 report of the federal ministry of health (FMOH) has shown that 722,248 people live with HIV according to 2017 Ethiopian Public health institute (EPHI) HIV related estimation and projection. Furthermore, there were 22,827 new HIV infections, according to the report. (1)

The cumulative incidence of Overt DM in PLWH was 4.9% as seen from meta-analyses of 44-high quality studies worldwide (5). But the prevalence of DM in HIV infection treated with ART is higher in Africa and specifically Ethiopia(16.04%). These studies were done on PLWH treated with non- ISTI ART.(5,17)

In PLWH taking DTG containing ART, several cases reports from different centers show people recently started on DTG containing ART presented with severe symptomatic hyperglycemia and diabetic ketoacidosis requiring hospitalization. The prevalence of DM was 0.47% in PLWH taking DTG from the Ugandan cohort, but hyperglycemia was 55.9% from a Kenyan cross-sectional study.(6,9,10,14,15)

People living with HIV and DM have a significantly higher risk of cardiovascular disease, chronic kidney disease, and mortality than non-diabetics. Early diagnosis and management initiation is essential to prevent or at least delay the long term complications of hyperglycemia (18).

1.3 Significance of the study

As far as my knowledge, there are no studies conducted in our country assessing the prevalence of hyperglycemia in PLWH taking DTG based regimens since its introduction in the national ART guideline in 2018.

Knowledge of the prevalence of hyperglycemia in this group of patients will alert the caregivers to incorporate glycemic patterns and other metabolic panels in the routine ART follow up investigation. Furthermore, the study results will serve as a ground for larger nationwide studies that will impact the care of PLWH.

1.4 Objective

1.4.1 General objective:

- To assess the prevalence of hyperglycemia and its associated factors among PLWH on DTG based ART regimen.

1.4.2 Specific objectives:

- To determine the prevalence of hyperglycemia among PLWH on DTG based HAART.
- To identify factors associated with hyperglycemia.
- To assess weight changes after starting DTG based regimen.

Chapter Two: Literature review

2.1 Prevalence of hyperglycemia in PLWH taking Dolutegravir

No adequate data showed the prevalence of hyperglycemia in PLWH taking dolutegravir containing ART regimen. However, case reports are coming out from different centers worldwide, and there was a cohort study done in Uganda and a cross-sectional study in Kenya.

A Randomized controlled, double-blind non-inferiority trial (SPRING-2) was conducted in 2010 in 100 centers in Canada, the USA, Europe and Australia involving 822 participants, which compared the efficacy of dolutegravir and raltegravir combined with an NRTI backbone in ART treatment naïve individuals. In this study, there was no reported hyperglycemia as a safety endpoint.(19)

In a randomized multicenter, double-blind phase-3 study comparing the efficacy of DTG+ABC+3TC and EFV+TDF+FTC (SINGLE trial), conducted in North America, Europe and Australia (April 2011-May 2012) involving 833 patients taking at least a single dose of DTG, there was no reported hyperglycemia as the safety endpoint. In this study, the median age of participants was 35 years, 16% of them were women, and 24% of them were blacks (20).

A cohort study was done in US and Canada from January 2007 to December 2017(NA-ACCORD study) involving 22,884 ART naïve PLWH comparing the risk of clinical occurrence of DM in PLWH taking PI or INSTIs Versus NRTIs based regimen. In this study, 722 PLWH (3%) developed DM, defined as: HgA1C>6.5%, initiation of DM specific medication. In addition, INSTIs were associated with a 17% increased risk of Clinical DM compared to NRTIs whereas PIs were associated with 27% increased risk DM compared with NRTIs (18).

A case-control study conducted in Uganda between March 2018 and March 2019 involving 6648 PLWH showed that among 3417 PLWH started on DTG, 16(0.47%) developed hyperglycemia. In this study majority (15 of 16) had severe hyperglycemia and required antidiabetic medication. The median time from initiation of DTG to the onset of hyperglycemia was four months(6).

A case report from Chicago showed an African-American male living with HIV who switched to abacavir/lamivudine and dolutegravir after 16 years of treatment with abacavir/lamivudine and efavirenz due to neuropsychiatric effects attributed to efavirenz, presented to the emergency department (ED) with symptomatic hyperglycemia, three weeks after the switch from efavirenz to dolutegravir. In this case report, the baseline FBS was 65 mg/dl and HgA1C was less than 6.2%, after which the patient presented with RBS of 949 mg/dl and HgA1C of 14.9% as early as three weeks of starting DTG (14).

A case series from Italy in 2020 showed that PLWH recently switched to DTG developed symptomatic DM, which improved with discontinuation of the drug and metformin treatment. In this case series, serologies for islet cells were negative for all cases. (12)

A cross-sectional study done in Nairobi, Kenya, from June-September 2020 involving 358 PLWH on DTG based ART showed that the prevalence of hyperglycemia was 55.9%. In this study, 60% of the study participants were females, and the mean age was 43.7 years (SD=10.6 years). Glycated hemoglobin and/or capillary glucose determination using a glucometer define hyperglycemia (10).

A case series from the University of Gondar Hospital, Northern Ethiopia, showed that 3 RVI patients on HAART recently shifted in the past year to DTG based HAART presented with severe hyperglycemia with DTG. In this case series, the cases were a 48-year-old male, a 49-year-old female, and a 46-year-old female diagnosed with HIV infection and were on ART for ten years, ten years and 11 years, respectively and recently switched to DTG based ART regimen. These patients developed severe hyperglycemia seven months, 12 months, and one month after starting DTG based ART regimen (9).

A systematic review and meta-analysis of 17 in Ethiopia from 5 regions (Addis Ababa, Amhara, Oromia, SNNPR and Harari) involving 6052 people living with HIV showed that the pooled prevalence of diabetes mellitus was 16.04%. This systematic review and metanalysis; fasting plasma glucose >126 mg/dl, random blood sugar >200 mg/dl, and oral glucose tolerance test >200 mg/dl to define diabetes mellitus (17).

2.2 Factors associated with hyperglycemia in PLWH taking DTG based regimen

Traditional risk factors for the development of PLWH are the same as the general population. These factors include older age, increasing BMI, central obesity, family history of DM and American or Hispanic origin (18).

In a systematic review and meta-analysis of 44 high-quality articles published all over the world from January 2000 to April 30, 2017, assessing the incidence of prediabetes and diabetes in PLHW, the major risk factors identified were:

- Older age
- Family history of DM.

- Increasing BMI
- Central obesity
- Lipodystrophy
- Dyslipidemia
- Metabolic syndrome
- Increased baseline FBS
- ART medications

ART medications found to increase the risk of prediabetes and diabetes were Proteus inhibitors, zidovudine, didanosine, lamivudine, stavudine and nevirapine. (5)

In the NA-ACCORD cohort, weight gain over 12 months was the mediator of development of DM on both cohorts on PI and INSTI based HAART. In this study, the participants were HAART naïve adults>18 years. The effect of INSTIs on the risk of development of DM was attenuated when accounting for 12 months weight gain. (5)

In the Ugandan case-control study, 8 of 16 (50%) cases with hyperglycemia diagnoses were older than 50 years. Most of these cases were taking ART medication for more than five years. Furthermore, 80% of cases had weight loss at diagnosis of hyperglycemia, while 20% had weight gain (6).

In the Italian case series involving a 46-year-old male Caucasian, a 39-year-old female African and a 57-year-old male Caucasian, all cases had optimal viro-immunological parameters. Hypertension and dyslipidemia were the common comorbidities in all 3 cases. Two of the three cases took protease inhibitor-based regimens (PI) before switching to DTG based regimen. In addition, the cases developed hyperglycemia four months, eight months and nine months after switching to DTG. Two of the three cases had weight loss during the diagnosis of DM(12).

The Kenyan cross-sectional study on the prevalence of hyperglycemia in DTG reported that the development of hyperglycemia was associated with advanced age, being female, being overweight and obesity (10).

Hypertension was seen in two of the three case series reported from Gondar. The time from initiation of DTG based ART regimen to development of symptomatic hyperglycemia

ranged from 1 month to 12 months in this case series. Additionally, all three cases were on other ART regimens for more than ten years (9).

In the metanalysis of 17 studies from Ethiopia, the associated factors for being diabetic were the duration of HAART, hypertension, overweight, obesity, age and educational status (17).

Methodology

3.1 Study setting and period

The study was conducted in the ART clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Tikur Anbessa Specialized Hospital is the largest tertiary referral hospital in Ethiopia. It is also the primary teaching hospital for the College of Health Sciences, Addis Ababa University. The hospital launched a digital record system since 2018 where the clinical data and other pertinent profiles of the patients are stored and retrieved when needed. It has different clinics that provide services for patients from all country regions. The ART clinic is one of the clinics which provides care and follow-up for PLWH. Most patients are followed by nurses and refill the medications on a paper-based patient profile chart. Patients who have medical complaints will see a doctor with a digital medical record number to store patient profiles. The ART Clinic provides service for these patients on all working days of the week and weekends, with a daily average of 30-35 cases attending the clinic, most of whom are taking DTG based ART regimens. The study was conducted in the ART clinic of the hospital.

3.2 Study time

The study was conducted from June 2021 to November 2021.

3.3 Study design

A hospital-based cross-sectional study design was used for this study.

3.4 Source and study population

The source population comprised all patients (PLWH) attending the ART clinic.

The study population were adult PLWH initiated on dolutegravir based ART regimen.

3.5 Eligibility criteria

3.5.1 Inclusion Criteria

- All adult PLWH on DTG- based regimen
- Those who took this regimen for at least one month
- Those who are willing to participate in the study
- Those who came after overnight fasting

3.5.2 Exclusion criteria

- PLWH on ART regimen without DTG
- Known DM patients
- Patients taking corticosteroids treatment for any reason
- Patients taking chemotherapeutic agents

3.6 Sample size Determination

The sample size was determined using the following formula for a cross-sectional study.

$$n = \frac{Z_{\frac{\alpha}{2}}^{2} P (1 - P)}{d^{2}}$$

Where;

n = required sample size

$\mathbf{Z_{\alpha/2}}$ = critical value for normal distribution at 95% confidence interval= 1.96 ($\alpha = 0.05$).

P = Proportion = 16.04%, from metanalysis of 17 studies across Ethiopia, since there is no similar local study in the same topic. It is assumed that the prevalence of hyperglycemia is at least 16.04%

d = margin of error= 5%

Substituting the variables into the equation

$n=1.96^2 \times 0.16(1-0.16)/ (0.05)^2$ $n=207.05$ $n\approx207$

3.7 Sampling Techniques

A convenient sampling technique was used. Patients started on DTG based regimen were continuously sampled until the required sample size was reached. Those who fulfilled the eligibility criteria were included in the study.

3.8 Study variables

3.8.1 Outcome variable

- Prevalence of hyperglycemia

3.8.2 Explanatory variables

- Sociodemographic variables (age, sex, place of residence, marital status, educational status)
- Behavioral variables (smoking, alcoholism, khat chewing, physical exercise)
- HIV related variables
    - Duration of HIV infection
    - CD4 count and viral load
    - Type of ART regimen used before DTG was started
    - Duration of ART treatment
    - Duration of DTG treatment
- Comorbid medical conditions (HTN, CVD, Dyslipidemia, others)
- Anthropometric variables (BMI, weight, waist circumference)
- The medication participant was taking (statin, beta-blockers, diuretics, antidiabetic agents)
- laboratory measurements (Hgb, Cr, Lipid panel)

3.8.3 Operational definitions

For this study, the American diabetic association 2021 standards of medical care guideline definition were used (Ref…..).

DM: was defined as a case meeting in either of the following.

- FBS>=126 mg /dl after at least 8 hours of fasting
- HgA1C>6.5%
- RBS >200 mg/dl determined at any time of the day

Prediabetes: was defined as a case meeting either of (ADA 2021)

- FBS: 100-125 mg/dl
- HgA1C: 5.7-6.4%
- 2 Hour Plasma glucose after 75 gm OGTT 140-199

Hyperglycemia: was defined as a case meeting either of the DM or prediabetes criteria (FBS>=100)

Overweight: BMI of 25-29.9 kg/m2

Obesity: A BMI>= 30 kg/m2

Central obesity: a waist circumference measurement > 88 cm for females and 102 cm for males.

Adults: for this study, adult is defined as PLWH having followed up at adult ART clinic age ≥ 18 years.

FBS: a blood sugar measured after at least 8 hours of fasting.

3.9 Data collection

Data was collected using a semi-structured questionnaire by data collectors. Eligible participants were interviewed in a separate room, and clinical, and laboratory parameters were measured and recorded. For study participants who had no results of plasma glucose determination, capillary glucose was determined using Prodigy™ glucometer (S.N.:PA00053763, Strip Lot No: D6201123-1 Expiry date: 2022-11, and control solution Lot No:GL200713-1 Expiry date :2022-01).

3.10 Data Quality control

Maximum effort was made to ensure data quality. Data collectors (Nurses working at the ART clinic) gave training training. The collected data were checked for completeness and

consistency on each day of data collection. Supervision and monitoring were made daily by the principal investigator.

3.11 Data processing and analysis

After data collection, it was entered to Epi info version 7.2 software; then, it was exported to IBM SPSS version 26 software for analysis. Statistical parameters were described using tables, charts. Proportions were calculated from case/non-case, the case being the participants meeting the definition for hyperglycemia.

Correlation between dependent and independent variables was tested using bivariable binary logistic regression models for categorical variables. Crude odds ratio (COR) with two-sided 95% confidence interval (CI) was used to assess correlation, and p-value <0.1 was used as cut off for significance for each categorical variable binary logistic regression analysis to be taken into multivariable binary logistic analysis.

Multivariable binary logistic regression analysis was used for variables that had significant correlation with the dependent variable to test for actual correlation. The Adjusted odds ratio (AOR), two-sided 95% CI and p-value <0.05 were used to define significant correlation.

3.12 Ethical considerations

The study was done in conformity with the ethical guidelines. Ethical clearance for the study was obtained from Addis Ababa University, College of health sciences, school of medicine Institutional Review Board (IRB). This study holds no possible risk for the participants except for the intended parameters and a single finger prick for capillary blood glucose determination.

Informed verbal and written consent was taken from participants. All participants' rights, privacy and autonomy were respected. Participation was voluntary.

Results

4.1. Baseline characteristics

From the expected 207 study participants on dolutegravir based antiretroviral treatment, 200 participated, making the response rate 96.6%. As shown in Table 1, 140 (70%) were females among the participants. The mean age of participants was 46.2±10.2 years, the majority (66.5%) of the participants being in the age range of 41-65 years, while 30.5% of the participants were in the age range 18-40 years. Almost all (94.5%) of the participants were from Addis Ababa. The majority of them (42.5%) were married, followed by widowed (24.5%) and single and divorced accounting equally (16.5%). Among all participants, 89 (44.5%) had private businesses while 77(38.5%) were unemployed and 31(15.5%) were government employees. Forty-three (43%) of them attended secondary school, followed by an elementary school (25%, diploma and above (21%), and did not participate in formal education at all (10.5%). While 44 (22%) of the participants had the habit of physical exercise, only 2 (1%), 12 (6%) and 7 (3.5%) of them had a current or past history of smoking, alcohol drinking and khat chewing, respectively.

Among all study participants, only 34(17%) had comorbidities: hypertension being the most common (8.5%) followed by other comorbidities (6.5%) and cardiovascular disease and dyslipidemia, each accounting for one (1%) them.

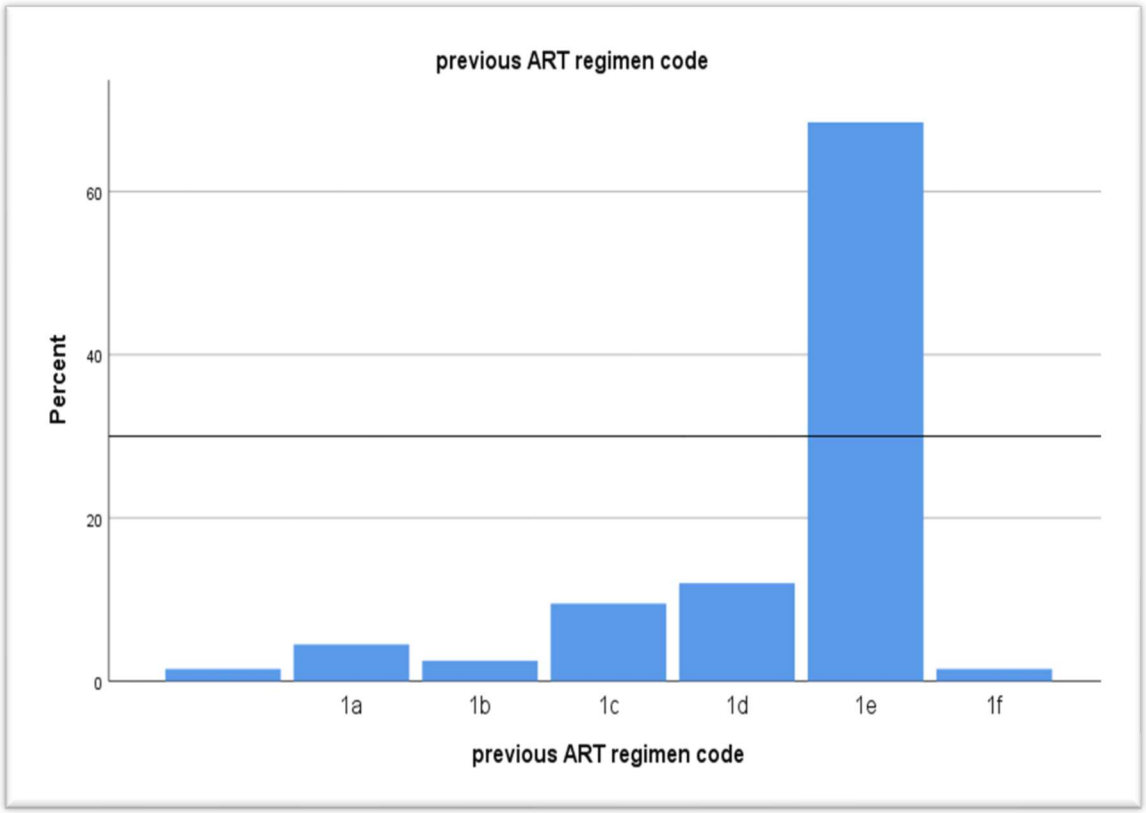
One hundred and ninety-seven (98.5%) of participants had a previous Antiretroviral treatment regimen before currently starting on dolutegravir. Majority (68.5%) were taking 1e (TDF,3TC, EFV) regimen followed by 1d (12%), 1c (9.5%) and 1a (4.5%) regimens. Figure 4.1 shows the summary of previous ART regimens.

Table 4. 1. Baseline characteristics of PLWH currently taking DTG based ART, TASH 2021

Variable	Category	Frequency	Percent
Age (years)	mean/SD	46.2±10.2	
	18-40	61	30.5
	41-65	133	66.5
	>65	6	3.0
Sex	Male	60	30.0
	Female	140	70.0
Marital status	Single	33	16.5
	Married	85	42.5
	Divorced	33	16.5
	Widowed	49	24.5
Educational level	Illiterate	21	10.5
	Elementary school	51	25.5
	Secondary school	86	43.0
	Diploma and above	42	21.0
Current Employment status	Unemployed	77	38.5
	Civil servant	31	15.5
	Private business	89	44.5
	Health care worker	3	1.5
Smoking history	no	198	99.0
	yes	2	1.0
Alcohol Drinking history	no	188	94.0
	yes	12	6.0
Khat chewing history	no	193	96.5
	yes	7	3.5
Physical exercise	no	156	78.0
	yes	44	22.0
Comorbidities	HTN	17	8.5
	CVD	2	1.0
	dyslipidemia	2	1.0
	Others	13	6.5
Total duration of ART (years	>10	161	80.5
	5-10	31	15.5
	<5	8	4
Duration of DTG based ART (years)	>2	48	24
	1-2	145	72.5
	<1	7	3.5
BMI (kg/m2)	>=30	27	13.5
	25.29.9	56	28
	18.5-24.9	104	52
	<18.5	13	6.5
Waist circumference (cm)	>120	6	3
	100-120	62	31
	89-99	81	40.5
	<88	51	25.5

HTN=hypertension, CVD=cardiovascular disease, BMI=body mass index, DTG=dolutegravir, ART=anti-retroviral treatment, cm=centimeter

Figure 4. 1 Previous ART regimen for PLWH currently on DTG, TASH 2021



1a=d4T+3TC+NVP, 1b=d4T+3TC+EFV, 1c=AZT+3TC+NVP, 1d=AZT+3TC+EFV, 1e=TDF+3TC+EFV, 1f=TDF+3TC+NVP

Figure 4. 2 Previous ART regimen for PLWH currently on DTG, TASH 2021

4.2 Anthropometric and laboratory results

Two hundred (100%) of the participants had documented weight, Body mass index (BMI), waist circumference and recorded fasting blood sugar (FBS) as summarized in Table 4.2. Participants' mean body mass index was 24.5±4.3 kg/m2 ranging from 15.8-35 kg/m2. The mean waist circumference of participants was 94.9 cm±12.5 cm (64-165 cm). Sixty-nine (34.5%) of the participants had weight changes after they were started on dolutegravir of which 52 (26%) was weight gain, and 17 (8.5%) was weight loss. The subgroups' median weight gain and loss were 5 kilograms (range 2-17 kilograms) and 3 kilograms (range 2-19 kilograms), respectively. The mean fasting blood sugar was 94.5±19.4. Lipid panel, hemoglobin and serum creatinine were determined only for 52(26%), 53 (26.5%) and 32

(16%) of the participants, respectively. Figure 4.2 shows clustered bar mean of patients' total cholesterol, mean FBS by waist circumference category.

Table 4. 2 Anthropometric and Laboratory parameters of patients of DTG at TASH,2021

variable	Frequency	Mean	SD	Median	Minimum	Maximum
Age	200	46.2	10.2	46	18	75
Weight	200	65.9	12.6	65	37	116
BMI	200	24.5	4.3	24	15.8	35
Waist circumference	200	94.9	12.51	94	64	165
Creatinine	32	0.9	0.2	1.0	0.7	1.0
Total cholesterol	52	204.2	63.5	201.5	91	450
Triglyceride	52	144.9	100.3	110	54	519
HDL	52	57.4	24	54	26	133
LDL	52	52	38	111.5	63	218
Hgb	53	14.3	1.7	14.6	6.8	17
FBS	200	94.5	19.4	91	63	179
Weight changes after starting DTG	N(%)					
Weight loss	17(8.5)	4.3	4	3	2	19
Weight gain	52(26)	6.1	3.4	5	2	17
No change	131(65.5)					

SD=standard deviation, DTG=dolutegravir, FBS=fasting blood sugar, BMI= body mass index

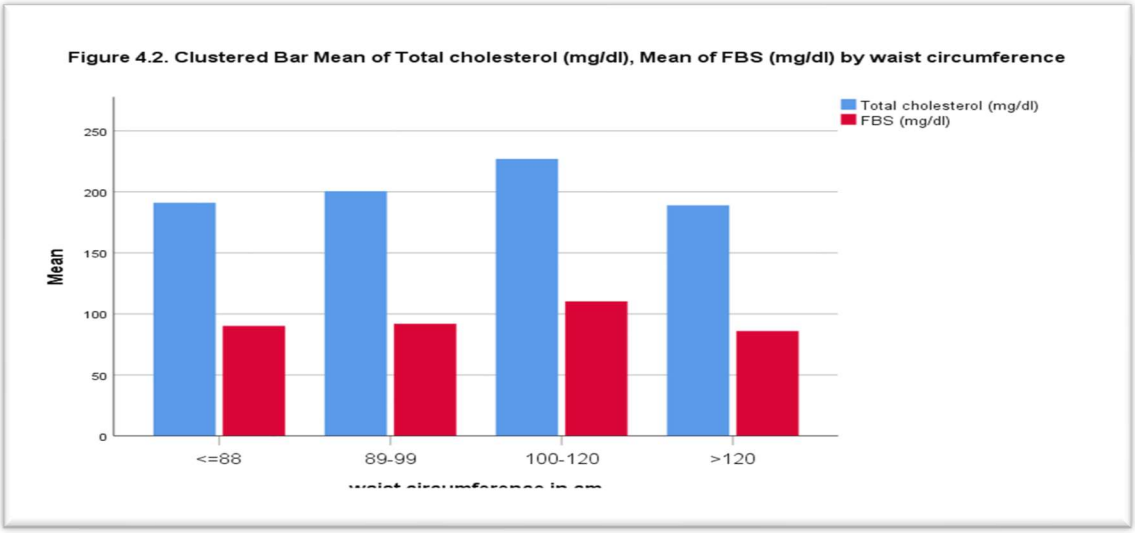


Figure 4. 3 cluster bar means of total cholesterol and FBS by WC of PLWH on DTG,TASH-2021

4.3 Proportion of hyperglycemia and covariates

Hyperglycemia was observed in 38(19%) of the study population. The proportion of males who developed hyperglycemia was higher 16 (26.6%) than females 22(15.7%), p-value????. On bivariable binary logistic regression analysis, comorbidity (hypertension), habit of physical exercise, Body mass index and waist circumference correlated with hyperglycemia. But when multivariable binary logistic regression analysis was done for these variables, there was no significant correlation. Table 4.3 shows the results of bivariable and multivariable binary logistic regression analysis.

Table 4. 3 Hyperglycemia and covariates in PLWH taking DTG based ART at TASH,2021

Variable	Category	hyperglycemia		Bivariate analysis		Multivariate analysis	
		yes	no	COR (95% CI)	p-value	AOR (95% CI)	p-value
HTN	yes	6	11	0.389(0.134-1.127)	**0.082***	0.423(0.134-1.339)	0.143
	No	32	151	1			
Physical exercise	No	14	132	0.390(0.181-0.841)	**0.016***	0.421(0.189-0.941)	0.035*
	Yes	30	24	1			
BMI (kg/m2)	>=30	8	19	2.658(0.997-7.082)	**0.051***	2.069(0.527-8.126)	0.298
	25-29.9	14	42	4.00(0.476-33.585)	**0.069***	1.473().575-3.775)	0.420
	<25	16	101	1		1	
Waist circumference (cm)	>=102	14	32	3.57(1.16-11.005)	**0.026***	1.678(0.377-7.466)	0.479
	88-102	19	89	1.751(0.661-5.014)	0.297	1.381(0.452-4.224)	0.571
	<88	5	41	1			

COR= crude odds ratio, AOR= adjusted odds ratio, CI= confidence interval, DTG=dolutegravir, BMI=body mass index, cm= centimeter, N=number, *= significant correlation,

Chapter five: Discussion conclusion and recommendation

5.1 Discussion

The study was a hospital-based descriptive cross-sectional study where 200 patients on dolutegravir containing ART regimen for at least one month were assessed for the prevalence of Dolutegravir associated hyperglycemia. Thirty-eight patients (19%) were hyperglycemic the blood sugar being determined by capillary fasting state blood capillary glucose using a glucometer. There were no associations between sociodemographic and behavioral factors and the development of hyperglycemia.

The finding suggests that hyperglycemia is relatively prevalent among patients taking dolutegravir containing regimens at Tikur Anbessa specialized Hospital. So far there are no published studies on the prevalence of DTG associated hyperglycemia in our country

except for a few cases and incidence reports.(9) This is the first prevalence study done in Ethiopia, given that the drug is relatively new for HIV treatment in Ethiopia and Sub-Saharan Africa.

The prevalence of hyperglycemia (19%) in this study was higher than that observed in the previous metanalysis from Ethiopian studies (16.04%), Ugandan cohort (0.47%) but much lower than the Kenyan study (55.9%). The method of glucose determination used in this study was capillary blood glucose which is liable for many confounders. The previous studies on RVI patients in Ethiopia, not on dolutegravir used plasma blood glucose from venous blood analyzed in a chemistry machine. The Kenyan study used a combination of capillary blood glucose and venous blood glucose as well as glycated hemoglobin level to define hyperglycemia and the Ugandan cohort used a combination of plasma glucose and glycated hemoglobin level.(6,10,17)

Weight changes after starting DTG were contradicting in different studies. In the Ugandan cohort, more patients lost weight before the development of hyperglycemia. However, this was not true in the Kenyan study where more patients had weight gain. Comparatively, more patients had weight gain than weight loss in our study.(6,10) However, demographic and behavioral variables did not show a correlation with hyperglycemia as compared to a study in Kenya.(6,10)

The mean age of our study population was higher than previous studies on the prevalence of DM in HIV pts not on dolutegravir, a cohort study in Uganda and a cross-sectional study in Kenya, but was comparable with the age of case reports from northern Ethiopia.(6,9,10,17)

Due to the lack of previous prevalence study, p-value was taken from the pooled prevalence of meta-analysis of 17 studies across Ethiopia on HIV patients in calculating sample size, assuming the prevalence of dolutegravir associated hyperglycemia is at least the same as that observed in metanalysis. This might underestimate the prevalence and hence the sample size because the definition for diabetes mellitus (FBS>126 mg/dl) was used in all studies of the metanalysis as compared to hyperglycemia (FBS>=100 mg/dl) in our study (17).

Higher body mass index, advanced age and being male were associated with risk of hyperglycemia in the Kenyan cross-sectional study and metanalysis of Ethiopian studies, but this was not seen in our study. This may be due to the relatively small sample size of this study.(6,10,17)

5.2 limitation of the study

The study's cross-sectional nature makes it difficult to conclude the causation of hyperglycemia. The method used to screen for hyperglycemia was capillary glucose with a glucometer, which may not be consistent with plasma glucose determined from venous blood.

5.3 Conclusion

Hyperglycemia is prevalent in RVI patients dolutegravir containing regimen and the drug is associated with weight changes. Hence routine plasma glucose and body weight monitoring is important in the care of RVI patients on dolutegravir.

5.4 Recommendations

5.4.1 Recommendations for practice

1. Hyperglycemia screening and monitoring should be done for patients taking dolutegravir.
2. Patients on dolutegravir should be alerted to watch for weight changes and symptoms of hyperglycemia to early recognize and seek treatment for hyperglycemia and other metabolic derangements.

5.4.2 Recommendations for further research

1. Better to conduct a prospective cohort study involving larger population from different ART centers for a better understanding of contributing factors for abnormal glucose homeostasis in patients taking Dolutegravir.
2. Better to conduct a comparative analysis of DTG containing and non DTG containing regimen to ascertain causality.

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Annex 2: information and consent sheet

Information sheet

Dear participant,

The purpose of this study is to know the prevalence of hyperglycemia and associated factors in patients taking DTG. Since the findings of this study is very important in determining future decisions in improving care of PLWH taking DTG, I kindly request your genuine participation.

You have full right to participate or never participate in the study.

The information you give will be used only for the purpose of this study confidentially.

Thank you for your valuable time.

Consent form

I, the undersigned, have heard the information in the information sheet and understood the purpose and significance of the study.

I agree to participate in the research voluntarily with the hope of contributing to the effort to assess hyperglycemia and DTG based regime.

Name ----------

Signature---------- date----------

MRN----------

Annex 3: Questionnaire- English version

100. Sociodemographic characteristics		
101	Age	-------years
102	Sex	1/Male 2/Female
103	Residence?	1/ Addis Ababa 2/ out of Addis Ababa
104	Marital status	1/ single 2/ married 3/divorced 4/ widowed
105	Educational status	1/ did not attend formal education 2/ Elementary school 3/ secondary school 4/ Diploma 5/ degree and above
106	Current Employment status?	1/ Unemployed 2/ Civil servant 3/ Private business 4/ health care worker
200. Behavioural characterstics		
201	Do you have history of Cigarette Smoking?	1/Yes 2/ No
202	Do you have history of Alcohol drinking? (if yes state the type and amount of alcohol per day	1/ yes 2/ No Type--- Amount---
203	Do you have history of KHAT chewing?	1/ yes 2/ No
204	Do you have habit of Physical exercise? (if yes state the type and duration of exercise per week)	1/ yes 2/ no Type ---- Duration----
300 HIV and ART related factors		
301	CD4 count (baseline) in cells/ml	
302	Viral load (baseline)in copies/ml	
303	Duration of HIV infection	----------(years)
304	Total duration since starting of ART drugs	----------years

305	Did you have Previous ART regimen? (if yes, state the regimen code)	1/ Yes 2/ No 3/ regimen code--------
306	Duration of Current DTG based regimen	----------years
400. comorbidities		
401	Other Medical conditions	1/ HTN 2/ Dyslipidemia 3/ CVD 4/ other (describe)
500.Weight changes after starting DTG based regimen		
501	Do you have Weight changes after starting of current DTG based regimen?	1/ weight gain 2/ weight loss 3/ no change
502	If your answer for question 501 is yes, what weight changes did you notice?	□ Weight gain----------kgs □ Weight loss----------kgs
600.Family history		
601	Do you have Family history of type 2 DM?	1/ Yes 2/ No
700. Symptoms of hyperglycemia		
701	Patient reported symptoms of hyperglycemia	1/ Polyuria 2/ polydipsia 3/ polyphagia 4/ fatigue 5/ no symptoms
800.Anthropometric measurements (to be measured and recorded by data collector)		
801	Weight (in Kg)	----------kgs
802	BMI (kg/m2)	----------Kgs/m2
803	Waist Circumference (in cm)	----------cm
900. Medications the individual is taking other than ART regimen		
901	What medications are you taking other than ART regimen?	1/ Statin 2/ BB 3/ Diuretics 4/CCB 5/ others(list)

1000. laboratory parameters at baseline and follow up time				
	Baseline Date		Follow up/recent Date	
1001	Hemoglobin			
1002	FBS			
1003	HgA1C			
1004	Total cholesterol			
1005	Triglyceride			
1006	HDL			
1007	LDL			
1008	Serum creatinine			
1009	HBSAg			
1010	HCV Ab			