Introduction

The introduction of antiretroviral therapy (ART) has led to a dramatic declining in acquired immunodeficiency syndrome (AIDS)-associated diseases and fatality, and the condition directly changed from killer to a chronic, controllable infectious disease. Nowadays, the standard and recommended treatments for HIV are a combinations of three-drugs that comprise a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs), typically abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/lamivudine (TDF/3TC). Meanwhile, with the introduction of ART, HIV-infected patients have started to live longer; however, some...
co-morbid conditions have emerged. Some of them are lipid derangement, metabolic syndrome, insulin resistance, hyperglycemia/diabetes, and obesity. Myocardial infarction rates have increased by 26% per year in developed countries, which could be due to complications associated with long-term use of combination ART.

The dolutegravir (DTG) is an INSTI and indicated by World Health Organization (WHO) to be incorporated into ART regimens for Sub-Saharan Africa, due to its improved virological suppression and pharmacological efficacy when compared with PI and NNRTI. The drug is included in the first-line and second-line regimens by substituting the previous therapeutic regimen that has lesser efficacy and increased toxicities. In addition, the action of DTG is inhibiting HIV integrase enzyme catalytic activity, which is essential for the insertion of viral genomic material into the deoxyribonucleic acid (DNA) of the host cell for viral replication. Principally, DTG inhibits the activity of integrase enzyme through binding with magnesium on its active site and prevents viral replication. Moreover, the enzymes for glucose metabolism require magnesium as an important cofactor and magnesium also acts as a second messenger in insulin action. Low levels of magnesium can therefore hinder reactions of several enzymes that are linked with glucose metabolism as well as insulin receptor function through increased microviscosity of the plasma membrane and thus upsurges insulin resistance. Low Mg²⁺ levels also decrease tyrosine kinase activity, impair post-receptor insulin action, alter cellular glucose transport, and decrease cellular glucose utilization, which lowers insulin sensitivity.

Furthermore, a few reports demonstrated that INSTI-based regimens resulted in considerable body weight gains in both naive and switched individuals, insulin-resistant diabetes, and accelerated hyperglycemia in fewer cases. This case series from Ethiopia is to report on the emergence of metabolic side effects in HIV patients after switching to an ART regimen that includes DTG.

**Case presentation**

**Case A**
A 50-year-old HIV-positive male, diagnosed with WHO stage IV infection at the age of 35, was transferred from another hospital before 15 years. And his baseline CD4+ cells count and body weight was 194 cells/mm³ and 64 kg, respectively. He was initiated to stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP) ART regimen (40 mg + 150 mg + 200 mg) BID with cotrimoxazole preventive therapy as per treatment and management guidelines. In addition, he had good adherence and his minimum and maximum blood parameters during d4T treatment were CD4+ count (412–1025/mm³), white blood cells (8700–14,100/mm³), hemoglobin (14.8–17.2 g%), alkaline phosphatase (313–415 U/L), aspartate transaminase (34–42 U/L), alanine transaminase (28–49 U/L), urea (7–38 mg/dL), and creatinine (0.5–1.2 mg/dL). In addition, the minimum and maximum body weight of the case during d4T treatment was 64–76 kg. After 8 years latter, d4T was shifted to AZT/3TC/NVP (300 mg + 150 mg + 200 mg) BID as per the recommendation of national HIV care guidelines and he had received AZT for 7 years and 5 months and the case attained an undetectable viral load. On 29 October 2019, however, the regimen was again shifted to TDF/3TC/DTG (300 mg + 300 mg + 50 mg) daily as indicated by national guidelines. When the case was transferred to this regimen, his plasma fasting blood sugar (FBS) was normal (99 mg/dL) and he had no classic symptoms.

He was diagnosed with type 2 diabetes mellitus four months later (on February 28, 2020), with clinical symptoms including polyuria, polydipsia, lethargy, and significant weight loss (from 74 to 64 kg). The case’s test values further confirmed the diagnosis of diabetes (FBS = 334 mg/dL and urine glucose 3+ with no ketone bodies). Then the case was treated with metformin by 750 mg PO and continued the DTG-combined ART regimen. The glycemic status of the case returned to controllable range (<130 mg/dL) with metformin, and counseling regarding dietary and physical exercise was given.

**Case B**
A 47-year-old male HIV-infected patient 7 years back (when he was 40 years old) presented with an abnormal musculoskeletal system, chronic diarrhea with more than 1 month, and WHO stage III infection. The case baseline CD4+ count and body weights were 298 cells/mm³ and 60 kg, respectively. On 16 July 2014, the case was initiated to TDF + 3TC + efavirenz (EFV) (300 mg + 300 mg + 600 mg) daily including with cotrimoxazole prophylaxis, and the case attained undetectable viral load after a year of treatment. The case had been on TDF + EFV for about 6 years, and then the regimen was shifted to TDF + 3TC + DTG (300 mg + 300 mg + 50 mg) and his FBS become 97 mg/dL.

Ten months later (on 31 May 2021), the case was diagnosed to have type 2 diabetes mellitus with clinical symptoms of diabetes. Laboratory findings indicate raised FBS (204 mg/dL) with a urine glucose level of 2+. The case was treated with metformin 300 mg PO daily, and the glycemic status become under control (less than 130 mg/dL) with repeated measures and continued DTG-combined ART. Moreover, all required advices were given to him including adherence to diabetic self-care.

**Case C**
A 43-year-old female patient presented with lymphadenopathy and WHO stage III infection 12 years and 11 months ago (when she was 30 years old). Besides, her body weight was 70 kg and she had FNAC-confirmed TB lymphadenopathy
with a baseline CD4+ count of 70 cells/mm³. The case was initiated to d4T + 3TC + NVP (40 mg + 150 mg + 200 mg) BID including with anti-TB drugs and cotrimoxazole preventive therapy. The treatment adherence of the case was good and gained 10 kg weight during d4T treatment. After 2 years and 3 months of treatment, the ART regimen was shifted to TDF + 3TC + NVP and she took this regimen for 8 years and 8 months. Her bodyweight become 91 kg with gaining of 11 kg and her minimum and maximum CD4+ cells count become 316–611 cells/mm³. The viral load test was done when the patient was on TDF + 3TC + NVP (300 mg + 150 mg + 200 mg) daily and attained viral suppression level or undetected viral load. The case was diagnosed with hypertension and receiving antihypertensive agents (enalapril and nifedipine). Her serum electrolytes were K⁺ 3.25 mmol/L (RR = 3.5–4.5), Na⁺ 114 mmol/L (RR = 135–145), and Cl⁻ 81.2 mmol/L (RR = 96–106). Moreover, the case had cholelithiasis and severe fatty liver, which were confirmed by ultrasound and treated several times for epigastric pain. After 8 years and 10 months of treatment, the case again switched to TDF + 3TC + DTG (300 mg + 300 mg + 50 mg) treatment daily on 1 October 2019. Her plasma FBS concentration was normal (89 mg/dL) during treatment initiation and she had no classical symptoms of diabetes. Furthermore, on 6 February 2020, cholecystectomy was done and the case improved well.

Six months and 19 days later (on 20 May 2020), the case was diagnosed to have type 2 diabetes mellitus with diabetic ketoacidosis (DKA) and having clinical symptoms such as polyuria, polydipsia, and fatigue. In addition, the case had lost a significant amount of weight (from 94 to 73 kg), and laboratory results revealed severe hyperglycemia (FBS = 600 mg/dL), as well as urine glucose 3+ and ketone bodies 3+. The case was admitted and treated with normal saline plus insulin regular (101U intravenous + 101U intramuscular). After fully recovering from DKA and FBS achieving a manageable range (<130 mg/dL in repeated measurements), NPH insulin (241U and 141U daily) was started. The case was advised for dietary modification, diabetic self-care, and regular follow-up of the diabetic clinic along with the continuation of DTG-based ART.

Discussion

In low- and middle-income countries, including Ethiopia, INSTI-based ART regimens are replacing older ART regimens, particularly those with lower therapeutic efficacy and higher adverse effects (toxicities), and the initiation or transition to DTG-combined treatment is being done in accordance with the WHO recommendations. The specific mechanism of DTG-induced hyperglycemia or diabetes is unknown, although it is assumed that DTG increases triglycerides and decreases magnesium levels, which could alter glucose transport via the glucose transport-4 (GLUT-4) receptor, resulting in increased glucose synthesis by the liver. It inhibits/lowers the catalytic function of glycolytic enzymes and impairs insulin modulation, which consequences the disorders of glucose metabolism or hyperglycemia.

Similarly, the pivotal DTG trials suggest that extended exposure to DTG combination treatment increases the risk of hyperglycemia, and that the risk increases with treatment duration. The presented switched cases developed DTG-induced hyperglycemia with clinical features of type 2 diabetes. In addition, several clinical trials have proven that the virological suppression and therapeutic efficiency of DTG; however, hyperglycemia was reported in several DTG trial studies such as SPRING-2, SAILING, SINGLE, and VIKING-3. Furthermore, after being treated to TDF + 3TC + DTG, one of the patients developed severe hyperglycemia (FBS = 600 mg/dL) and DKA, which is consistent with a case report from another region of Ethiopia.

Conclusion

Finally, the findings suggest that DTG-combined antiviral regimens may increase the risk of hyperglycemia and accompanying adverse effects. As a result, blood glucose monitoring is required during treatment commencement and on a regular basis during treatment follow-up, especially for individuals on DTG-combined ART regimens.

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Author contributions

A.T.H., W.K., and S.G. had initial contact with the patients. S.G. took care of follow-up of the cases. W.K. did the diagnosis of their medical conditions and therapeutic consultancy for cases management. A.E. supported during cases assessment. A.T.H. drafted the report, did correction for article text, and evaluation of the manuscript. In addition, all authors critically revised and approved the final version of the manuscript.

Availability of data and materials

All data generated or investigated throughout this study are included in the manuscript.

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