Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 10: 1–4

DOI: 10.1177/2050313X221079444
journals.sagepub.com/home/sco
SAGE

Experience of dolutegravir-based antiretroviral treatment and risks of diabetes mellitus

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Abstract

HIV-infected people have started to live longer since the introduction of antiretroviral therapy, however various co-morbid illnesses have emerged. Three HIV-infected individuals, all at least 43 years old, reported with a new onset of type 2 diabetes after switching to dolutegravir-combined antiretroviral therapy regimen. These three people were switched to integrase strand transfer inhibitor (dolutegravir)-based first-line antiretroviral treatment after receiving non-nucleoside reverse transcriptase inhibitor-combined first-line antiretroviral treatment for at least 6 years, as recommended by the World Health Organization for Sub-Saharan African countries, including Ethiopia.All of the given cases had normal plasma fasting sugar (fasting blood sugar <100 mg/dL) at the time of switching. Polyuria, polydipsia, considerable weight loss, and fatigue were all classified as signs of diabetes mellitus in the two male cases. In addition, their laboratory results demonstrated hyperglycemia (plasma fasting blood sugar >200 mg/dL and urine glucose level $\geqslant 2+$) with no ketonuria after switching to dolutegravir for 4–10 months. A glycemic control was achieved, and metformin medication was continued. After 6 months of dolutegravir treatment, the third female case developed diabetic ketoacidosis and severe hyperglycemia (fasting blood glucose level 600 mg/dL, urine glucose level 3+, and ketonuria 3+). To recover from diabetic ketoacidosis, the patient was given intravenous normal saline and regular insulin. Her glycemic control was then restored, and she was switched to NPH insulin. For all of the cases presented, the dolutegravir-based regimen was maintained. Antiretroviral regimens using dolutegravir have the potential to cause hyperglycemia and other side effects. As a result, blood glucose monitoring is required throughout treatment initiation and regularly throughout treatment follow-up, particularly for those on dolutegravir-combined antiretroviral therapy regimens.

Keywords

Dolutegravir, hyperglycemia, diabetes mellitus, HIV, antiretroviral treatment

Date received: 1 October 2021; accepted: 21 January 2022

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.[1,2] 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).[3,4]

Meanwhile, with the introduction of ART, HIV-infected patients have started to live longer; however, some

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co-morbid conditions have emerged. Some of them are lipid derangement, metabolic syndrome, insulin resistance, hyperglycemia/diabetes, and obesity.[5] Myocardial infarction rates have increased by 26% per year in developed countries,[6] 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,[7,8] due to its improved virological suppression and pharmacological efficacy when compared with PI and NNRTI.[3] 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.[7,8] 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.[9] Principally, DTG inhibits the activity of integrase enzyme through binding with magnesium on its active site and prevents viral replication.[10] 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.[11] Low Mg^{2+} levels also decrease tyrosine kinase activity, impair post-receptor insulin action, alter cellular glucose transport, and decrease cellular glucose utilization, which lowers insulin sensitivity.[12]

Furthermore, a few reports demonstrated that INSTI-based regimens resulted in considerable body weight gains in both naive and switched individuals,[13,14] insulin-resistant diabetes,[15] and accelerated hyperglycemia in fewer cases.[16] 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/mm^3 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/mm^3), white blood cells (8700–14,100/mm^3), 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 bodyweight 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 undetected 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/mm^3 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 500 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/mm^3. 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/mm^3. 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 (10 IU intravenous + 10 IU intramuscular). After fully recovering from DKA and FBS achieving a manageable range (<130 mg/dL in repeated measurements), NPH insulin (24 IU and 14 IU 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.[7,8] The DTG-combined ART treatment was officially started due to its great effectiveness, tolerability, negligible pharmacological interaction, and least side effects according to several trial reports. However, some recent researchs suggest that initiating or switching to INSTI-based ART treatment can result in considerable weight gain or obesity[17,18] as well as hyperglycemia or type 2 diabetes mellitus.[19–22]

The specific mechanism of DTG-induced hyperglycemia or diabetes is unknown, although it is assumed that DTG chelates 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.[19,20] It inhibits/lowers the catalytic function of glycolytic enzymes and impairs insulin modulation, which consequences the disorders of glucose metabolism or hyperglycemia.[19,20,23] 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.[24] In addition, several clinical trials have proven that the virological suppression and therapeutic efficiency of DTG;[3] however, hyperglycemia was reported in several DTG trial studies such as SPRING-2, SAILING, SINGLE, and VIKING-3.[22,25–27] 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.[21]

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.

Acknowledgements

The authors acknowledge our clients who gave us written informed consent to publish their medical conditions.

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.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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References

1. Barbaro G. Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection. *Curr HIV Res* 2006; 4(1): 79–85.
2. Palella Jr FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338(13): 853–860.
3. Panel on Antiretroviral Guidelines for Adults Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. *Department of Health and Human Services*, http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf (accessed 4 August 2021).
4. European AIDS Clinical Society. Guidelines. Clinical Management and Treatment of HIV Infected Adults in Europe. 7.1. November 2014, http://www.eacsociety.org/Portals/0/GUIDELINES/English%20PDF%20-%20Version%207.1.pdf (accessed 4 August 2021).
5. Cohan GR. HIV-associated metabolic and morphologic abnormality syndrome: welcome therapy may have unwelcome effects. *Postgrad Med* 2000; 107(4): 141–146.
6. Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349(21): 1993–2003.
7. World Health Organization. *Updated recommendations on first-line and second-line 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: World Health Organization, 2018.
8. Ethiopia national consolidated guidelines for comprehensive HIV prevention, care and treatment, 2018, http://www.afro.who.int (accessed 4 August 2021).
9. Mesplède T, Quashie PK, Zanichelli V, et al. Integrase strand transfer inhibitors in the management of HIV-positive individuals. *Ann Med* 2014; 46(3): 123–129.
10. Song I, Borland J, Arya N, et al. Pharmacokinetics of dolutegravir when administered with mineral supplements in healthy adult subjects. *J Clin Pharmacol* 2015; 55(5): 490–496.
11. Barbagallo M, Dominguez LJ, Galioto A, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol Aspects Med* 2003; 24(1–3): 39–52.
12. Kostov K. Effects of magnesium deficiency on mechanisms of insulin resistance in type 2 diabetes: focusing on the processes of insulin secretion and signaling. *Int J Mol Sci* 2019; 20(6): 1351.
13. Bernardino JI, Mocroft A, Wallet C, et al. NEAT001/ ANRS143 Trial Study GroupBody composition and adipokines changes after initial treatment with darunavir-ritonavir plus either raltegravir or tenofovir disoproxil fumarate-emtricitabine: a substudy of the NEAT001/ANRS143 randomized trial. *PLoS ONE* 2019; 14: e0209911.
14. Menard A, Meddeb L, Tissot-Dupont H, et al. Dolutegravir and weight gain. *AIDS* 2017; 31: 1499–1500.
15. Rebeiro PF, Jenkins CA, Bian A, et al. Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor–based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. *Clin Infect Dis* 2021; 73: e2234–e2242.
16. Lamorde M, Atwiine M, Owarwo NC, et al. Dolutegravir-associated hyperglycaemia in patients with HIV. *Lancet HIV* 2020; 7(7): e461–e462.
17. Hsu R, Brunet L, Mounzer K, et al. Characterizations of weight gain following antiretroviral regimen initiation in treatment-naïve individuals living with HIV. *Inhiv Med* 2019; 20: 69–69.
18. Caniglia EC, Shapiro R, Diseko M, et al. Weight gain during pregnancy among women initiating dolutegravir in Botswana. *Eclinicalmedicine* 2020; 29–30: 100615.
19. McLaughlin M, Walsh S and Galvin S. Dolutegravir-induced hyperglycaemia in a patient living with HIV. *J Antimicrob Chemother* 2017; 73(1): 258–260.
20. Kamal P and Sharma S. SUN-187 Dolutegravir Causing Diabetes. *J Endocr Soc* 2019; 3, https://academic.oup.com/jes/article/3/Supplement_1/SUN-187/5483934
21. Hailu W, Tesfaye T and Tadesse A. Hyperglycemia after dolutegravir-based antiretroviral therapy. *Int Med Case Rep J* 2021; 14: 503–507.
22. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet* 2013; 382(9893): 700–708.
23. Barbagallo M, Dominguez LJ, Galioto A, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol Aspects Med* 2003; 24(1–3): 39–52.
24. ViiV Healthcare. Tivicay (dolutegravir tablets). Full Prescribing Information. Viiv Healthcare, Research Triangle Park, NC 27709, 2018, https://www.gsksource.com/pharma/content/.dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF (accessed 3 August 2021).
25. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir-and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis* 2014; 210(3): 354–362.
26. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet* 2013; 381(9868): 735–743.
27. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369(19): 1807–1818.