

Bictegravir-Based Antiretroviral Therapy-Associated Accelerated Hyperglycemia and Diabetes Mellitus

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Integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) is first line for treatment of people with human immunodeficiency virus (PWH). Emerging data suggest the possibility of adverse metabolic effects of these medications. We describe 3 cases in which PWH developed hyperglycemia and ketoacidosis within months of being switched to bictegravir-based ART.

Keywords: bictegravir; diabetes; HIV; hyperglycemia; integrase strand transfer inhibitors.

People with human immunodeficiency virus (PWH) have increased risk for developing type 2 diabetes mellitus (T2DM), regardless of exposure to antiretroviral therapy (ART) [1]. Although early ART regimens were associated with dyslipidemia and other metabolic derangements, contemporary ART, including the integrase strand transfer inhibitor (INSTI) class, are thought to have a better safety profile. Recent data has suggested that INSTI use may be associated with weight gain and the development of insulin-resistant diabetes [2, 3] and, in rarer cases, accelerated hyperglycemia [4–6]. Bictegravir (BIC) is a second-generation INSTI, available in coformulation with emtricitabine (FTC) and tenofovir alafenamide (TAF), and is currently recommended as a first-line ART regimen for newly diagnosed PWH [7, 8]. To our knowledge, there are no case reports of BIC-related accelerated hyperglycemia.

METHODS

We identified 3 PWH with new or acutely worsening hyperglycemia with ketoacidosis after initiation of BIC-based ART regimens.

Patient Consent Statement

The Washington University Institutional Review board evaluated this project and deemed it nonhuman subject research.

Case 1

A 50-year-old Filipino male with a 25-year history of human immunodeficiency virus (HIV), chronic hepatitis B, and schizoaffective disorder presented off medications for 2 months. His ART was transitioned from rilpivirine (RPV)/tenofovir disoproxil fumarate (TDF)/FTC to BIC/TAF/FTC. His other medications included stable doses of sertraline, prazosin, and paliperidone palmitate; the latter he had received by intramuscular injection for the past 3 years. His HbA1c at the time of medication transition was 6.6% and he had a fasting glucose of 85 mg/dL. Approximately 3 weeks after the ART switch, he had a random glucose of 223 mg/dL. Four months after the switch, he presented to the emergency department (ED) with abdominal pain. He was found to have a blood glucose concentration greater than 400 mg/dL and an elevated blood ketone level of 4.5 mmol/L. His C-peptide level was 1.2 ng/mL (normal limit 1.1–4.4 ng/mL). Upon presentation to the hospital his HbA1c was >17%. He was discharged receiving 1.4 units of insulin/kg per day and his ART was transitioned back to RPV/TDF/FTC. Within 2 months of discharge, he had a 70% reduction in insulin requirements with well controlled blood glucose concentrations and an HbA1c of 6.5%.

Case 2

A 56-year-old Black male with hypertension and well controlled HIV had his ART transitioned from efavirenz (EFV)/TDF/FTC to BIC/TAF/FTC based on insurance formulary. His other medication was a vitamin D supplement. Three weeks after the transition, he developed polyuria, polydipsia, and unintentional 15-kg weight loss. Laboratory evaluation in the ED revealed hyperglycemia (>500 mg/dL) and elevated blood ketones (4.4 mmol/L). His HbA1c on admission was 12.6%, which was increased from 6.0% 2 months prior. His insulin level on admission was 5 mIU/mL (normal limit 2.6 to 25 mIU/mL) and C-peptide level was 2.2 ng/mL (normal limit 1.1–4.4 ng/mL). He required subcutaneous insulin at 0.6 units/kg per day. Four months after discharge, his insulin requirements decreased; however, his glycemic control worsened, prompting an ART switch to RPV/TAF/FTC. Eight months later his HbA1c was 7.2% on metformin only.

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Case 3

A 41-year-old Black male with well controlled HIV and chronic hepatitis B on abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) and entecavir was transitioned to BIC/TAF/FTC and entecavir with plans to eventually be managed on BIC/TAF/FTC only. His only other medications included valacyclovir and recently initiated methocarbamol and pregabalin, given for chronic pain. At the time of transition he had a fasting glucose of 78 mg/dL. One month after transition he had a random glucose value of 157 mg/dL. Two months after the transition, he presented to the ED for nausea, vomiting, polyuria, and polydipsia. His blood glucose concentration was >600 mg/dL and blood ketones were 4.2 mmol/L. His C-peptide level was 1.4 ng/mL (normal limit 1.1–4.4 ng/mL). His HbA1c had increased to 12.4% compared with 5.6% from 3 months earlier. Insulin was initiated at a dose of 0.6 units/kg per day and ART was transitioned to FTC/TDF plus DTG. Two months after discharge, his blood glucose levels improved and his insulin requirement declined to 0.2 units/kg per day. Eight months after discharge his HbA1c was 5.0% and his insulin was being down-titrated.

DISCUSSION

We report 3 cases of individuals who transitioned ART to BIC/FTC/TAF and developed diabetic ketoacidosis (DKA) within weeks to months after transition. Characteristics about the patients can be found in Table 1. To our knowledge, this is the

first report of accelerated hyperglycemia associated with BIC-based ART. None of the patients were receiving medications for diabetes previously and HbA1c values before starting BIC-based ART were only modestly elevated (5.6%–6.6%). HbA1c at the time of presentation with hyperglycemia and ketoacidosis ranged from 12.4% to 17%. The short time period to development of DKA and rapid worsening of HbA1c strongly implicates the BIC as an associated factor. It is notable that no other medications affecting glycemia were changed or added before onset of dysglycemia. In addition, discontinuation of BIC-based ART resulted in significant decreases in insulin requirements at follow up.

There have been growing concerns of weight gain and long-term cardiometabolic effects associated with INSTI-based ART [9–11]. Recent case reports have also documented the development of accelerated hyperglycemia and DKA after initiation of these therapies. In One case series, 3 patients developed DKA while on DTG- or elvitegravir-based regimens [12]. However, 2 of the 3 reported patients developed diabetes more than 1 year after starting an INSTI-based regimen, making the association with ART therapy less clear. Two other individual case reports have suggested a temporal association between initiation of the first-generation INSTI raltegravir and the development of DKA [5, 13]. Another reported case of DTG-associated hyperglycemia occurred after approximately 3 weeks of treatment in a patient who had prior history of well controlled type II diabetes [6]. More recently, DTG has been implicated in hyperglycemic

Table 1. Characteristics of Patients who Developed Acute Hyperglycemia while on Bictegravir

	Case 1	Case 2	Case 3
Age/Sex	50/Male	56/Male	41/Male
CD4 ⁺ T Cell count	345	792	114
HIV RNA at switch	17900 copies/mL	Undetectable	<20 copies/mL
Previous ART regimen	FTC/RPV/TDF	EFV/FTC/TDF	ABC/DTG/3TC
Reason for switch to B/F/TAF	Represented after being off meds	Insurance formulary change	Goal of monotherapy for HIV and HBV
Weight (kg) at time of switch	63.3 kg	100.9 kg	104.6 kg
BMI at time of switch (kg/m ²)	21.2	32.8	31.3
HbA1c at time of switch	6.6%	6%	5.6%
Time to onset of hyperglycemia presentation	4 months	3 weeks	2 months
Weight at presentation (kg)	54.4 kg	84.4 kg	88.9 kg
BMI at presentation (kg/m ²)	18.3	28.3	26.6
HbA1c post ART switch	17%	12.6%	12.4%
Diabetic ketoacidosis present	Yes	Yes	Yes
Initiating TAF	Yes	Yes	Yes
C-peptide [NL 1.1–4.4]	1.2	2.2	1.4
GAD-65 or Insulin antibodies?	No	No	No
Initial insulin requirement	2.5 units per kg daily	0.6 units per kg daily	0.6 units per kg daily
Regimen switched post hyperglycemic episode	Yes	Initially no, switched 6 months later	Yes
Regimen switched to post episode	FTC/RPV/TDF	RPV/TAF/FTC	TDF/FTC + DTG
HbA1c at follow up (months)	6.5% (7)	7.2% (8)	5.0% (7)
Continued need for insulin at follow up?	Yes; 0.4 units/kg	No	Yes; 0.2 units/kg

Abbreviations: ABC, abacavir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; DTG, dolutegravir; ART, antiretroviral therapy; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; NL, normal limit; RNA, ribonucleic acid; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

events in Uganda, at a rate of 0.47% [4]. An analysis of FDA Adverse Event Reporting Systems data has demonstrated reported events of hyperglycemia related to BIC; however, the temporality and presence of DKA are unclear [14].

It is worth noting that in addition to BIC, all 3 cases initiated TAF. In patient 3, DTG was transitioned to BIC, which is a transition of one INSTI to another. This case could provide evidence of an association of hyperglycemia and TAF. Although cases of acute hyperglycemia have not been reported with TAF in other settings, it is possible that the observations presented may relate to the drug combination rather than an individual component of the regimen. However, in the Ugandan cohort, patients given DTG were not transitioned to TAF [4].

The mechanism leading to rapid acceleration of hyperglycemia in patients after initiation of INSTI-based ART is not clear. Although weight gain may play a role in development of T2DM, all of our patients lost weight between initiation of BIC and hospital presentation. All 3 PWH had modestly elevated HbA1c values at baseline; however, they had rapid development of severe hyperglycemia and ketoacidosis, suggesting that INSTI use may be associated with rapid acceleration of dysglycemia and that these agents may contribute to beta-cell dysfunction and/or insulin resistance independent of weight gain. The presence of ketoacidosis supports the possibility of impaired beta-cell function in addition to increased insulin resistance. Although insulin requirements declined after a switch in ART, this can be seen after resolution of glucose toxicity and does not demonstrate that INSTIs directly impair beta-cell function. It is also not clear whether impaired glycemic control completely resolves with discontinuation of the offending INSTI. Future prospective studies will be necessary to clarify these mechanism(s).

The Department of Health and Human Services guidelines recommend close monitoring in the first 3 months after an ART switch. Patients should have a visit or phone call in the first couple weeks to assess possible side effects, and laboratories should be obtained in the first 2 months to assess for viral rebound [8]. It is unclear whether increased screening for diabetes after initiation of INSTI therapies is likely to improve outcomes, particularly given the rarity of these events. Educating patients, particularly those who have other risk factors for, or history of, diabetes, on signs of symptoms associated with new onset diabetes may be beneficial in early identification of postswitch metabolic changes.

CONCLUSIONS

These cases document the development of hyperglycemia and DKA shortly after BIC initiation. This may be an early signal of adverse metabolic effects of BIC because long-term studies

are lacking. Bictegravir-containing ART is now first line for treatment of HIV in PWH and is likely to be prescribed with increasing frequency. Although it is not clear that routine screening for dysglycemia in patients after initiation of BIC is indicated, those with risk factors or history of diabetes should be alerted to signs and symptoms of hyperglycemia. Large population-level studies are needed to determine the overall risk and outcomes related to BIC use and its possible effect on metabolic conditions.

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