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Short Report

Severe hyperglycemia after initiation of long-acting cabotegravir in two antiretroviral treatment-controlled people with HIV

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ABSTRACT

We report two cases of normoglycemic people with HIV well-controlled by antiretroviral therapy who were switched to a dual long-acting therapy consisting of cabotegravir (CAB), an integrase strand transfer inhibitor, and rilpivirine (RIL), a non-nucleoside analog reverse transcriptase inhibitor, administred intramuscularly once a month then every two months. Both cases developed shortly acute severe hyperglycemia with ketoacidosis or insulinopenia requiring intravenous insulin therapy. Anti-pancreatic autoantibodies were absent. The hyperglycemic episode resumed after stopping CAB/RIL and/or initiating metformin. To our knowledge these are the first reported cases of severe CAB/RIL-induced hyperglycemia. Up to now, long-acting CAB/RIL has not been associated with metabolic outcomes. These cases serve as a warning to clinicians to monitor glycemia when initiating long-acting CAB/RIL therapy.

Introduction

Recent studies indicate that initiating or switching people with HIV (PWH) to integrase strand transfer inhibitor (INSTI)-based antiretroviral treatment (ART) can result in weight gain or obesity. INSTI initiation has also been associated with an increased risk of type 2 diabetes within the first year of INSTI treatment, which has been related, at least in part, to weight gain [1–5].

Additionally, some rare clinical cases of rapid severe hyperglycemia occurring shortly after initiating an orally given INSTI raltegravir (RAL), evitegravir (EVG), dolutegravir (DTG) or bictegravir (BIC) have been reported [6–13]. To our knowledge, no case of rapidly occurring severe hyperglycemia has been reported after long-acting (LA) cabotegravir (CAB) initiation administered monthly the first two months then every two months via intramuscular injection in association with the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (CAR-LA). We report here two cases of ART-controlled PWH, switched to CAR-LA for simplification, who developed severe hyperglycemia a few weeks after receiving the initial CAR-LA injection.

Cases

The main characteristics of PWH are presented in Table 1.

Case 1, a 62-year-old Caucasian man, was diagnosed with HIV in 1996. He received multiple lines of ART and achieved viral suppression with a regimen of two nucleoside analog reverse transcriptase inhibitors (NRTIs, lamivudine and tenofovir diproxil fumarate) and a NNRTI (nevirapine) with a CD4+ *T* lymphocytes level of 918 cells/mm^3 and an undetectable viral load. He was switched to oral CAB/RPV for one month, then injectable CAR-LA. His BMI was in the overweight range (27.9 kg/m^2) at CAR-LA initiation and his glycemic level was 101 mg/dl though he presented a glycemia value of 118 mg/dl in the previous year.

After 2 months of CAR-LA treatment, he presented with polyuria, polydipsia and lethargy as well as weight loss of 5 kg. He presented with

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Table 1
Characteristics of the two cases who developed acute hyperglycemia after starting CAB-LA.

	Case 1	Case 2
Age(years) / sex	62 / M	60 / M
Year of HIV seropositivity	1986	2004
Main medical history	High blood pressure Liver steatosis	High blood pressure Dyslipidemia
Comedications	amlodipine/ perindopril	amlodipine/valsartan rosuvastatin acetylsalicylic acid hydrochlorothiazide tamsulosin serenoa repens extract (saw palmetto)
CD4+*T* cell count at the time of the switch (cells/mm^3) (%CD4)	918 (31 %)	330 (21 %)
HIV RNA at the time of the switch (copies/ml)	<30	<30
Previous ART regimen	02/1996- 01/1997: ZDV/DDC 01/1997–05/1998: ZDV/3TC 05/1998–10/2002: 3TC/STV/NFV 10/2002–10/2010: 3TC/TDF/EFV 10/2010–11/2022: 3TC/TDF /NVP 11/2022–11/2022: CAB/RIL 12/2022–03/2023: CAB/RIL LA	08/2004–03/2007: 3TC/ ZDV/EFV 03/2007–09/2007: 3TC/ ZDV/LPV/r 09/2007–10/2015: 3TC/ TDF/LPV/r 10/2015–02/2025: 3TC/ TDF/RIL 02/2025-: CAB/RIL LA
Reasons for switching to CAR-LA	simplification	simplification
BMI at the time of the switch (kg/m^2)	27.9	34.6
Weight at the time of the switch (kg)	76	110
Glycemia at the time of the switch (mg/dl)	101	108
Maximal recorded glycemia before the switch (mg/dl)	118	112
Time to diagnosis of hyperglycemia after the switch	2 months	5 months
BMI at the time of hyperglycemia diagnosis (kg/m^2)	25.3	33.1
Weight at the time of hyperglycemia diagnosis (kg)	71	105
HbA1c at the time of hyperglycemia diagnosis	14.1 %	14.5 %
Diabetic ketoacidosis presence	Yes	No
Autoantibodies (Anti IA2, Anti GAD and Anti ZnT8)	No	No
Initial insulin requirement	IV then long and short acting insulin	IV then long and short acting insulin
Switch off CAB	Yes, TDF/FTC/ doravirine	No
HbA1c at follow-up (months)	6.6 % (3)	6.4 % (3)
Continued need for insulin at follow-up	No	No

Abbreviations : 3TC: lamivudine, BMI : body mass index, CAB: cabotegravir, DDC: zalcitabine, EFV: efavirenz, LPV/r: lopinavir/ritonavir, NFV: nelfinavir, NVP: nevirapine, RIL: rilpivirine, STV: stavudine, TDF: tenofovir, ZDV: zidovudine.

diabetic ketoacidosis (DKA) and severe hyperglycemia: glucose 391 mg/dl, HbA1c 14.1 %, metabolic acidosis (pH: 7.36, serum bicarbonate: 17.6 mEq/l), and urine ketones (4+). Pancreatic autoantibodies (anti-IA2, anti-GAD and anti-ZnT8) were negative. There was no documented preceding infection. He had no family history of diabetes.

He was immediately treated with intravenous insulin. Slow-acting insulin (26 UI) and rapid-acting insulin (6/8/7 UI) were initiated and later changed to metformin 500 mg twice a day, then three times a day, 4 days after admission. The CAR-LA regimen was switched to TDF/FTC/doravirine. After 3 months, he achieved good glycemic control (HbA1c: 6.6 %) on metformin alone.

Case 2, a 60-year-old Sub-Saharan African man was diagnosed with HIV in 2004. He was well controlled for his HIV infection by two NRTIs (lamivudine and tenofovir diproxil fumarate) and a NNRTI (RIL) with a CD4+ lymphocyte level of 330 cells/mm^3 and an undetectable viral load. His BMI was in the obese range at 34.6 kg/m^2. His glycemia was at 108 mg/dl at initiation with a value at 112 mg/dl in the previous year. Five months after initiating CAR-LA, he presented with polyuria, polydipsia and fatigue. Glycemic value was 343 mg/dl, HbA1c 14.5 %, and urine glucose 3+ with no ketone bodies. He had lost 5 kg since switching to CAR-LA. There was no infection. He had a family history of type 2 diabetes mellitus (his sister). Serum C-peptide level was low 0.29 nmol/L (N 0.4–1.7 nmol/l). Pancreatic autoantibodies (anti-IA2, anti-GAD and anti-ZnT8) were negative. He was treated with intravenous insulin. Slow-acting (25UI) and rapid-acting insulins were initiated, later changed to metformin 1000 mg twice a day and diamicron 120 mg, 4 days after admission. Good glycemic control (glycemia: 81 mg/dl, HbA1c: 6.4 %) was obtained 3 months later with metformin while the INSTI-based ART regimen was continued.

Discussion

We report here two cases of PWH who transitioned ART to injectable CAR-LA and developed severe hyperglycemia within weeks to months after the transition. Both patients had normal glycemic values before starting CAR-LA-based ART but both presented in the preceding year with mildly increased glycemic values suggesting a prediabetic condition. Initial type 1 diabetes was ruled out as pancreatic autoantibodies were negative. The hyperglycemia occurred alongside weight loss of 5 kg, ruling out diabetes associated with INSTI-related weight gain. Hyperglycemia was diagnosed 2 and 5 months after the switch, when it became clinically evident, though it likely occurred earlier. The clinical presentation resembles ketosis-prone diabetes [14] but it differs due to its iatrogenic onset early after INSTI initiation.

In the literature, no increased incidence of diabetes has been reported in CAB-treated PWH. In the global pharmacovigilance database, we found 5 reported cases of diabetes associated with cabotegravir, with no associated pharmacovigilance signals. There are no reported cases of rilpivirine-induced diabetes in the literature nor were any cases reported in the global pharmacovigilance database with rilpivirine alone (cabotegravir is always used in combination). Furthermore, Case 2 was treated with rilpivirine for 10 years prior to initiating CAR-LA and did not develop diabetes. Neither diabetes nor hyperglycemia is listed as an adverse event in the cabotegravir and rilpivirine summary of product characteristics.

Importantly, CAR-LA has been reported to have a safe metabolic profile in clinical trials and in real-life studies [15]. However, it is important to acknowledge that most CAR-LA-treated PWH in clinical trials were already controlled by an INSTI-based regimen before being switched to CAR-LA (all PWH in the SOLAR and FLAIR trials and the majority in the ATLAS trial) which precludes the revelation of any INSTI-related weight gain and associated metabolic alterations.

A few cases of INSTI-induced acute severe hyperglycemia have already been reported in PWH treated with orally administered INSTIs such as RAL, EVG, DTG and BIC [6–13]. One possible mechanism for INSTI-induced hyperglycemia is the chelation of magnesium, which could inhibit insulin secretion. These are the first reported cases for PWH initiating CAB. Even though CAB is administered intramuscularly, it is likely that the CAB molecule is responsible for hyperglycemia rather than the route of administration.

Our PWH were probably prediabetic (previous mildly elevated glycemia) with limited insulin production capacity. Even mild inhibition of

insulin secretion by CAB could result in insulinopenia and consequently hyperglycemia. Indeed, the level of peptide-C was low in Case 2 and the presence of ketoacidosis in case 1 is in line with severe insulinopenia. Both PWH benefited from a treatment with intravenous insulin which reversed hyperglycemia. Interestingly, in case 2, after the acute episode, glycemia was controlled by metformin while CAR-LA was pursued.

Our case reports serve as a warning regarding glycemia after CAB use. Clinicians should closely monitor blood glucose in cabotegravir-treated patients throughout treatment initiation and follow-up, especially PWH with metabolic syndrome features, mildly increased glycemia or with a high BMI.

CRediT authorship contribution statement

Nadia Valin: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Pauline Campa:** Investigation, Methodology. **Thibault Chiarabini:** Investigation. **Joëlle Michot:** Investigation. **Carole Collet-Gaudillat:** Validation. **Stéphanie Kury Paulin:** Validation. **Jacqueline Capeau:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Karine Lacombe:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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