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BRIEF REPORT

Gynoid Fat Distribution and Adipocyte Trapping May Explain Virological Failure With Intramuscular Long-Acting Cabotegravir and Rilpivirine

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Intramuscular long-acting antiretroviral drugs can improve adherence to lifelong antiretroviral treatment. Nevertheless, adipose tissue thickness and distribution play a critical role with injectable drugs. We describe a virological failure with cabotegravir and rilpivirine in a Black African woman with human immunodeficiency virus type 1 with gynoid fat distribution (ie, adipose tissue prevailing in the pelvis and hip area) and body mass index <30 kg/m^2.

Keywords. adipocyte trapping; gynecoid fat distribution; HIV infection; intramuscular long-acting antiretroviral drugs; virological failure.

The discovery and widespread use of combination antiretroviral therapies changed the paradigm of human immunodeficiency virus (HIV) infection, increasing the lifespan of patients with HIV [1]. Nevertheless, adherence to a lifelong daily oral regimen is critical for long-term immunovirological response.

Adherence to antiretroviral therapy (ART) has been enhanced by injectable long-acting cabotegravir (CAB) and rilpivirine (RPV), commercialized since 2020 as maintenance therapy in patients with virological control on standard oral ART. Both drugs are currently administered by intramuscular injection in the gluteal muscle every 2 months.

Received 01 February 2023; editorial decision 17 April 2023; accepted 17 April 2023; published online 2 May 2023

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https://doi.org/10.1093/ofid/ofad217

Two phase 3 trials (First Long-Acting Injectable Regimen [FLAIR] [2] and Antiretroviral Therapy As Long Acting Suppression [ATLAS] [3]) proved the safety and the noninferiority of long-acting formulations of CAB and RPV versus standard oral combination ART. Both trials emphasize the importance of deep intramuscular injection technique to ensure that drugs are not injected in the subcutaneous tissue. Indeed, the use of injectable long-acting drugs in obese patients with a body mass index (BMI) >30 kg/m^2 could modify the bioavailability of these drugs [4]. For obese patients, the use of longer needles (2 inches if BMI >30 kg/m^2 vs 1.5 inches if BMI ≤30 kg/m^2) is recommended to obtain intramuscular administration of CAB and RPV.

However, our recent clinical findings, as described in the following clinical case, suggest that the cutoff BMI value of <30 kg/m^2 may be insufficient for a correct intramuscular distribution of both drugs, particularly in patients with a gynoid distribution of adipose tissue.

A 46-year-old Black African woman, diagnosed with HIV-1 in 2008, was hospitalized in March 2022 for uncontrolled HIV-1 infection and Kaposi sarcoma, with a plasma HIV-1 RNA of 1417 copies/mL and CD4$^+$ T-cell count of 68 cells/μL. She had a history of antiretroviral (ARV) treatment failure, related to poor adherence, on both emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF)/lopinavir (LPV)/ritonavir (RTV) and FTC/TDF/darunavir/RTV. She tested negative for hepatitis B virus infection. ARV resistance genotyping was performed and did not find any resistance mutation. The HIV-1 subtype was CRF02-AG. ART with combined oral bictegravir (BIC)/tenofovir alafenamide (TAF)/FTC was then started on March 2022. HIV replication was rapidly controlled, with an undetectable plasma viral load (pVL) on May 2022 and a CD4$^+$ T-cell count of 93 cells/μL.

To improve treatment adherence, a switch to maintenance injectable ART was started, without oral leading phase, in June 2022, with CAB (600 mg/3 mL, injected in the left gluteal muscle) and RPV (900 mg/3 mL, injected in the right gluteal muscle). The injections were performed by a nurse previously trained to CAB and RPV intramuscular injections, with a 1.5-inch-long needle, as recommended by the US Food and Drug Administration for patients with a BMI <30 kg/m^2 (patient's BMI: 27 kg/m^2) [5]. At the 1-month follow-up visit (M1) on 5 July 2022, the second intramuscular injection was performed for both drugs (at the same dose as for the first injection), with a 1.5-inch-long needle (Table 1).

At M1, virological failure was documented, with a HIV pVL of 54 827 copies/mL (4.7 log copies/mL). According to Cutrell et al [6], the most common factors associated with virological

Table 1. Monitoring of Drug Plasma Concentrations and Viral Load Under Antiretroviral Therapy

Date of HIV RNA	HIV RNA	Date IM	CAB IM	RPV IM	Date of OT	BIC/FTC/TAF	Plasma Concentration	Interval	CAB C_{min}, ng/mL	RPV C_{min}, ng/mL	Interval, h	FTC, ng/mL	TAF, ng/mL	BIC, ng/mL
5 Jun 2022	< 50 c/mL	06/05/2022	600 mg Q4W	900 mg Q4W	…	…	…	…	…	…	…	…	…	…
	…	…	…	…	…	…	5 Jul 2022	M1	422	<5	…	…	…	…
8 Jul 2022	50 000 c/mL	07/08/2022	600 mg Q8W	900 mg Q8W	…	…	…	…	…	…	…	…	…	…
	…	…	…	…	13 Jul 2022	50/200/25 mg QD	13 Jul 2022	D5	1461	40	…	…	…	…
	…	…	…	…	…	…	20 Jul 2022	D12	1347	20	20:00	96	<5	1915
	…	…	…	…	…	…	22 Jul 2022	D14	643	23	21:45	92	8	585
	…	…	…	…	…	…	29 Jul 2022	D21	191	<5	22:00	96	10	1162
	…	…	…	…	…	…	3 Aug 2022	D25	669	22	?	162	9	3002
12 Aug 2022	<50 c/mL	…	…	…	…	…	12 Aug 2022	D34	371	12	23:00	45	12	344
	…	…	…	…	…	…	19 Aug 2022	D42	700	8	21:30	103	10	1126
	…	…	…	…	…	…	2 Sep 2022	D55	521	11	21:30	111	6	1554
	…	…	…	…	…	…	21 Sep 2022	D75	593	19	12:00	705	20	2739

Abbreviations: BIC, bictegravir; CAB, cabotegravir; Cmin, trough plasma concetration; c/mL; copies per milliliter; D, day; FTC, emtricitabine; HIV RNA, plasma human immunodeficiency virus load; IM, intramuscular injection; M, month; OT, introduction of oral treatment; Q4W, every 4 week; Q8W, every 8 week; QD, day-to-day administration; RPV, rilpivirine; TAF, tenofovir alafenamide.

Interval between the first injection and plasma concentration dosing.

Interval between the last intake and plasma concentration dosing.

failure on injectable CAB and RPV are (1) a BMI >30 kg/m^2, (2) the presence of major integrase strand transfer inhibitor (INSTI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance–associated mutations, or (3) HIV-1 subtype A1/A6. A second HIV drug resistance genotype was then performed and did not find any emerging resistance mutation to INSTIs or NNRTIs. In addition, the patient harbored a HIV-1 subtype CRF02-AG, and her BMI was <30 kg/m^2.

Drug interactions were checked among the following comedications: liposomal doxorubicin (20 mg/m^2 every 15 days), sulfamethoxazole-trimethoprim (400/80 mg daily), levofloxacin (750 mg daily), extended-release oxycodone (60 mg twice per day), and amitriptyline (10 mg daily). None of these drugs were reported to interact with injectable CAB and RPV [4, 7].

At M1 (ie, 4 weeks after the first injection) together with pVL, trough plasma concentrations were determined using ultra-high-performance liquid chromatography–tandem mass spectrometry and were, respectively, 422 ng/mL for CAB (only 2.5-fold the in vitro protein-adjusted concentration for 90% of the maximum inhibition of viral growth [166 ng/mL] and 4 times lower than the median trough plasma concentration [1610 ng/mL; Q1, Q3: 1120, 2100]) and <5 ng/mL for rilpivirine (approximately 8 times lower than the median trough plasma concentration of 41.5 ng/mL [Q1, Q3: 32.1, 54.30]) [6]). However, it must be considered that these trough plasma concentrations reported by Cutrell et al were performed at 8 weeks (ie, 4 weeks after the first injection but in the context of an additional 4-week oral lead-in), whereas for this patient they were measured only 4 weeks after the first injection in the absence of an oral lead-in. To be noted, recent data [8] suggest the lack of an oral lead-in as a potential risk factor for low trough concentrations, but further studies are needed to confirm this preliminary result.

The patient was switched back to the initial oral triple-drug regimen (BIC/TAF/FTC), and 2 months later plasma HIV-1 pVL was undetectable.

Intramuscular injections were correctly performed by the nurse with the recommended standard 1.5-inch needles. Given the low plasma concentrations of CAB and RPV, we measured the thickness of the subcutaneous tissue of the injection site on an axial computed tomographic section (Supplementary Appendix). The patient presented a gynoid adipose tissue distribution, particularly in the gluteal area, with a thickness of >2 inches, more than the 1.5-inch length of standard needles.

We suspected that insufficient length of standard needles used in this patient with a BMI <30 kg/m^2 let the 2 drugs diffuse in the subcutaneous gluteal adipose tissue, with subsequent adipocyte trapping of the 2 drugs, in particular RPV, and trough plasma concentration below the limit of quantification. As previously described for efavirenz, liposoluble drug as CAB or RPV may accumulate in subcutaneous adipose tissue according to treatment duration [9]. This could explain why trough plasma concentrations for CAB and RPV were still detectable and had some fluctuations at 1 and 4 months after the stop of injectable drugs (Table 1).

Moreover, the SSAT040 trial, although evaluating different dosages of RPV than those of this report, showed that sex

(but not BMI) was associated with variations of overall RPV plasma exposure post–single long-acting intramuscular injection in multivariate analysis (−28.1% effect, $P = .032$) [10].

Major phase 3 trials (FLAIR [2] and ATLAS [3]) were performed in a predominantly male population (only 33% of the participants were women in ATLAS, and 22% in FLAIR), with a median BMI <30 kg/m^2 (26 kg/m^2 in the ATLAS trial, 24 kg/m^2 in the FLAIR trial), raising the question of how to transpose results to the global population of people living with HIV, in particular female patients. Indeed, this case describes a female patient living with HIV, with a high BMI but under the proposed cutoff 30 kg/m^2 and a gynoid adipose tissue distribution, possibly explaining virological failure. Of note, detectable trough plasma concentrations for CAB and RPV 1 month and 4 months after injectable drugs were stopped (Table 1) were probably linked to a secondary leakage by adipocytes. This raises the concern of the long-term persistence of detectable plasma concentrations for both drugs, increasing the risk of resistance mutation emergence.

Adipose tissue thickness assessment before starting injectable long-acting CAB and RPV seems imperative. Measuring the thickness of subcutaneous fat at the injection site with nonradiating imaging as ultrasounds could be useful for patients with a BMI of 25–30 kg/m^2 and a gynoid fat distribution, to avoid unintentional subcutaneous injections (occurring in about 68% of patients, and up to 92% in female patients, as suggested by Chan et al [11]). When the thickness of subcutaneous fat is relevant, it would be better to inject the drugs in the vastus lateralis muscle [12] or to use longer needles, as recommended for BMI ≥30 kg/m^2, to prevent unexpected virological failure.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. We obtained the patient's consent for collecting computerized and anonymized data as part of her medical care during her hospitalization and the different follow-up visits.

Potential conflicts of interest. All authors: No potential conflicts.

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