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BRIEF REPORT

Therapeutic Drug Monitoring of Long-Acting Rilpivirine and Cabotegravir for Treatment of HIV-1 Infection—A Case Series of Five Patients With One Virologic Failure After Development of Two-Class Resistance

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Virologic failure of long-acting rilpivirine/cabotegravir is rare but may result in severely limited treatment options. Known risk factors cannot predict all cases. Therapeutic drug monitoring (TDM) may help identify patients at risk, but reliable thresholds are missing. We report retrospective TDM in a cohort of 5 patients, including 1 virological failure.

Keywords. cabotegravir; rilpivirine; TDM; two-class resistance; virologic failure.

Long-acting (LA) dual antiretroviral therapy (ART) using the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) and the second-generation integrase strand transfer inhibitor (INSTI) cabotegravir (CAB) is the first and so far the only licensed injectable complete maintenance treatment option for people with HIV (PWH). LA RPV/CAB is recommended for PWH who are on oral ART, with no resistance to any INSTI or NNRTI class drugs and no previous episodes of virological failure (VF) [1]. Phase III trials have shown good virological efficacy of LA ART, with incidence rates of VF of 1.2% (n = 19/1651) and 1.4% (n = 23/1651) after 48 and 152 weeks, respectively [2]. Data from real-world cohorts have confirmed these findings with similar risk of VF (1.8%, 2.0%, and 1.9%, respectively) [3–5]. Recent reports have shown growing concerns about potentially rapid acquisition of resistance against either or both INSTIs and NNRTIs following VF [6].

Therapeutic drug monitoring (TDM) during the early phase after switch to LA ART has been discussed to help identify additional patients at risk for VF. A multivariable analysis of possible risk factors identified CAB and RPV trough levels 4 weeks and 44 weeks postinitiation to be associated with VF. However, addition of TDM to previously identified risk factors only slightly improved model-based prediction of VF, and the authors themselves questioned its clinical utility given the complexity of TDM [2]. Another issue concerning the use of TDM as a prognostic tool for VF is the lack of well-defined cutoff values, as both drugs show relatively high intra- and inter-individual variability in drug levels, as recently shown in real-world TDM by Thoueille et al. [5].

Different thresholds have been proposed, including the protein-adjusted concentration for 90% viral replication ($PAIC_{90}$) and 2 and 4 times this respective value [7]. Others have suggested the lower quartile of trough levels, derived from pooled data of the phase III trials ($Q1_{Ctrough}$) [8]. The data from Thoueille et al. include 3 participants with VF, of whom 2 had repeatedly low trough levels. On the other hand, a vast proportion of participants had low trough levels without any signs of VF. Low trough levels of CAB and/or RPV at the moment of VF were also shown in 4 participants among a case series of 5, reported by van Welzen et al. [6]. However, this report did not include any control group. Thus, there remains an ongoing debate regarding if and when to implement routine TDM in at-risk patients to prevent VF [9, 10]. As TDM data of patients with VF in real-world settings are still scarce, we aim to contribute to this knowledge gap with the presentation of TDM data from a case series of 5 patients on LA RPV/CAB including 1 experiencing VF.

METHODS

At the outpatient HIV treatment center in Jena, 5 PWH on oral daily regimens were switched to LA RPV/CAB treatment between August 2021 and January 2022. Leftover plasma samples from viral load monitoring are routinely stored at −20°C for at least 24 months in our institution. To retrospectively

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investigate drug levels, all stored samples available from the 5 patients since their switch to LA RPV/CAB, collected directly before the injection of LA RPV/CAB, were taken to measure drug trough levels using a validated high-performance liquid chromatography coupled with ultraviolet detection (HPLC-UV) method modified from Charbe et al. [11]. Resistance testing was performed from stored patient plasma samples with detectable viral loads and interpreted using the HIV-Grade algorithm [12]. A written declaration of consent for the publication of the anonymized data was given by every patient.

RESULTS

The series comprised 5 males aged 45–61 years with a diagnosis of HIV between 2008 and 2021. One patient each had subtype A1 and A2, whereas all the others had subtype B. Initial resistance testing showed an NNRTI and INSTI RAM for 1 patient. All other patients had no apparent risk factors for VF at baseline. None had a known episode of previous VF. The clinical characteristics of each participant at the time of treatment switch are summarized in Table 1.

Case Descriptions

Case 1: A 42-year-old man who has sex with men (MSM) with a body mass index (BMI) of 19.8 kg/m^2 presented in March 2021 after first diagnosis with HIV-1 infection with an initial HIV-RNA of 1.39×10^5 cp/mL and a CD4 cell count of 153/µL. The current clinical category according to the Centers of Disease Control and Prevention (CDC) classification (1993) was B3 due to previously treated oral candidiasis and suspected bacillary angiomatosis. Baseline resistance testing found no evidence for resistance-associated mutations (RAMs), and ART was started with bictegravir/emtricitabine/tenofovir-alafenamide. Five weeks later, the patient's HIV-RNA had declined to 51 cp/mL, and his CD4 cell count had increased to 288/µL. Concomitant neurosyphilis, confirmed after lumbar puncture, was treated with intravenous ceftriaxone. Rectal chlamydia trachomatis infection was treated with oral doxycycline. In January 2022, the patient was switched from his oral regimen to LA RPV/CAB after sustained virological suppression (<50 cp/mL) for 9 months. After a 4-week oral lead-in, the first intragluteal injections (900 mg RPV and 600 mg CAB) were administered in February 2022. Second doses were given after 4 weeks, followed by injections every 8 weeks thereafter. At week 30 postswitch, quarterly routine determination of viral load revealed 2530 cp/mL just before the fifth injection. Follow-up measurement at week 32 revealed resuppression of HIV-1 (<50 cp/mL). This 1-time viremia coincided with an acute mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

A second increase in viral load to 667 cp/mL was detected at week 64. Due to suspected syphilis re-infection, the patient and his partner were treated with intramuscular benzylpenicillin-benzathine. Follow-up at weeks 68 and 69 revealed an increasing viral load of 10 200 cp/mL and 22 200 cp/mL, respectively. Retrospective TDM derived from the blood sample at week 64 showed trough levels of 778 ng/mL and 51 ng/mL for CAB and RPV, respectively, and resistance testing revealed emerging 2-class resistance for both INSTI (138 K and 148R mutations) and NNRTI (101P mutation). Treatment was therefore changed to an oral regimen (darunavir/cobicistat/emtricitabine/tenofovir-alafenamide) starting June 2023, and HIV-RNA was resuppressed (<50 cp/mL).

Case 2: A 44-year-old MSM, the life partner of patient 1, presented in March 2021 with neurosyphilis and rectal chlamydia, which was treated with intravenous ceftriaxone and oral doxycycline. HIV was diagnosed with an initial viral load of 0.76×10^5 cp/mL, a CD4 cell count of 147/µL, and a CDC classification of B3. He had a history of tobacco smoking (16 pack-years), previous oral candidiasis, a positive serology for bacillary angiomatosis and status post–hepatitis B infection with HBs and HBc seroconversion. Oral ART was initiated with bictegravir/emtricitabine/tenofoviralafenamide (BIC/FTC/TAF) and after confirmed viral suppression switched to LA RPV/CAB in January 2022. At week 30 postswitch, he showed an increase of viral load up to 3460 cp/mL during quarterly routine viral load determination. This "blip" coincided with the same acute mild SARS-CoV-2 infection and blip as his life partner (patient 1). Follow-up measurement at week 32 post-treatment showed viral loads <50 cp/mL. He had an episode of gonorrhea at week 40 post-treatment that was treated with ceftriaxone and azithromycin. At week 63 post-treatment, he was again treated for a suspected syphilis re-infection with 2×1.2 million (4 mL) intramuscular benzylpenicillin-benzathine, which was administered intragluteally. Routine monitoring of viral load showed no signs of VF. However, due to the recurrent "blip" his life partner had on LA RPV/CAB, the patient decided to switch back to his previous oral ART at week 91 post-treatment.

Case 3: A 60-year-old man presented in January 2020 with clinical signs of Lues and was afterwards first diagnosed with HIV-1 infection with an initial HIV-RNA level of 3.38×10^5 cp/mL, a CD4 cell count of 180/µL, and a CDC classification of A3. Initial resistance testing showed both an NNRTI and INSTI RAM: F227V mutation (RPV susceptible) and M50I mutation (limited sensitivity to BIC; other INSTIs susceptible; CAB no information available). An oral ART with BIC/FTC/TAF was started and switched to LA RPV/CAB in October 2021. Since this time point, the patient's viral load has repeatedly measured <50 cp/mL.

Case 4: A 42-year-old MSM was diagnosed in April 2016 with HIV during an occupational health check. Initial viral load was

Table 1. Baseline Characteristics of Patients Before Switching to LA RPV/CAB

	Patient 1 (VF)	Patient 2	Patient 3	Patient 4	Patient 5
Sex	M	M	M	M	M
Age, y	43	45	61	47	56
Weight, kg	63	65	100	82	74
BMI, kg/m^2	19.8	20	28.5	20.5	23.9
HIV subtype	B	B	B	A1	A2
NNRTI resistance	None	None	F227V	None	None
INSTI resistance	None	None	M50I	None	None
HIV diagnosis	03/2021	03/2021	01/2020	04/2016	2008
Reason for HIV testing	Oral candidiasis + Lues	Oral candidiasis + Lues	Lues	Occupational health check	NA
CD4 cells at diagnosis	153	147	180	484	410 (05/03/09)
Viral load at diagnosis, cp/mL	139 000	76 900	338 000	119 000	45 100
ART history	BIC/FTC/TAF (04/21–10/21)	BIC/FTC/TAF (03/21–10/21)	BIC/FTC/TAF (02/20–10/21)	FTC/TAF + DTG (06/16–06/19)	ABC/3TC + EFV (06/09–unknown)
	Oral lead-in (01/22–02/22)	Oral lead-in (01/22–02/22)	Oral lead-in (10/21–11/21)	3TC + DTG (06/19)	FTC/TAF/RPV (04/19–12/21)
	LA CAB/RPV (02/22–06/23)	LA CAB/RPV (02/22–11/23)	LA CAB/RPV (since 11/21)	DTG/3TC (07/20–10/21)	Oral lead-in (12/21–01/22)
	FTC/TAF/DRV/c (since 06/23)	BIC/FTC/TAF (since 11/23)		Oral lead-in (10/21–11/21)	LA CAB/RPV (since 12/21)
				LA CAB/RPV (since 11/21)	
Previous VF	None	None	None	None	None

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitor; LA RPV/CAB, long-acting rilpivirine/cabotegravir; BIC, bictegravir; FTC, emtricitabine; TAF, tenofoviralafenamide; DRV, darunavir; DTG, dolutegravir; 3TC, lamivudine; ABC, abacavir; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; VF, virological failure.

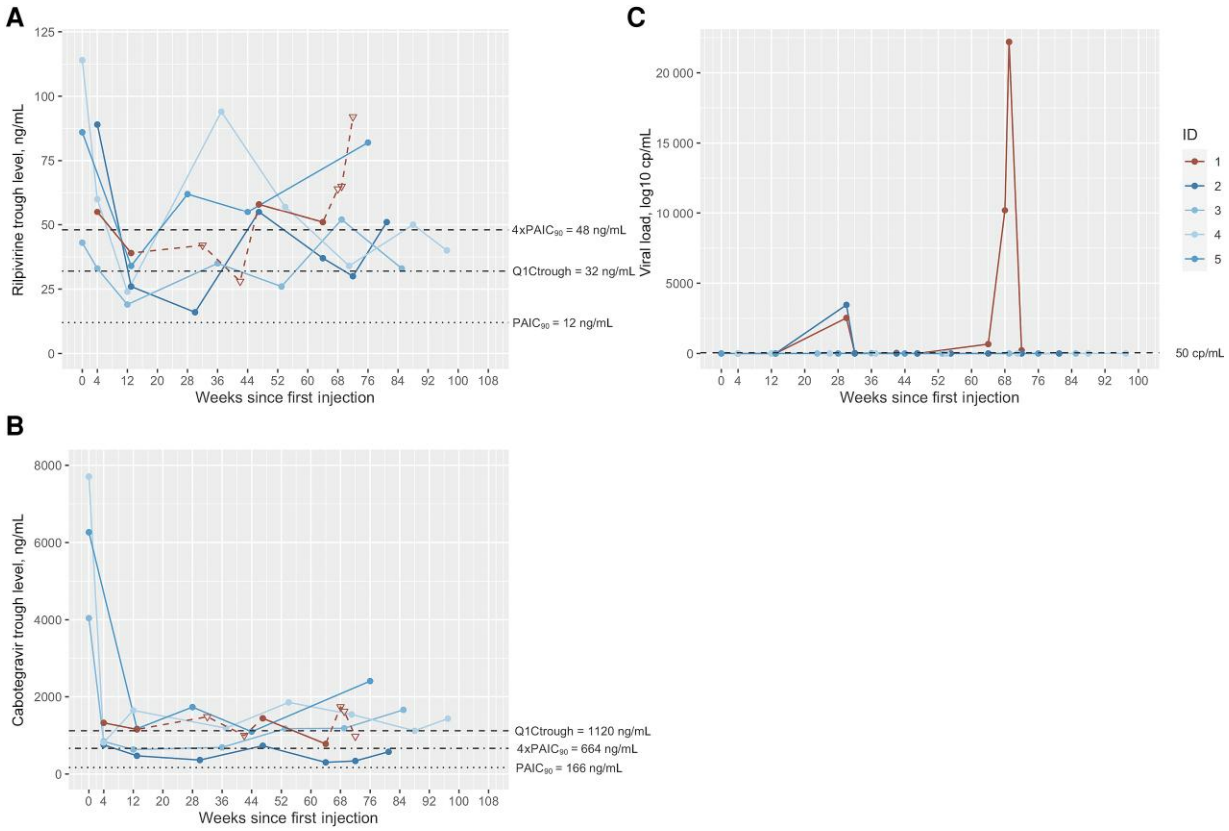

Figure 1. A, Rilpivirine plasma trough concentrations of patients. B, Cabotegravir plasma trough concentrations. C, Viral loads of patients. Red lines correspond to the patient with VF; blue lines correspond to other patients from the cohort. Down-pointing triangles and the dashed red line indicate TDM values that do not meet criteria for trough levels. Horizontal lines indicate different proposed thresholds of TDM as indicated on the right side. $Q1_{Ctrough}$ = 1st quartile of the pooled data analysis from the phase 3 trials (Flair/Atlas/Atlas-2M). Abbreviations: $PAIC_{90}$, protein binding–adjusted inhibitory concentration of 90%; TDM, therapeutic drug monitoring; VF, virologic failure.

1.19×10^5 cp/mL; CD4 cell count was 484/μL, resulting in a CDC category of A2. Oral ART with emtricitabine/tenofovirala-fenamide and dolutegravir (FTC/TAF + DTG) was initiated. In October 2021, ART was switched to LA RPV/CAB. Ever since, his viral load has measured <50 cp/mL.

Case 5: A 43-year-old MSM first presented in April 2019 to our treatment center. An HIV infection had been diagnosed 2008, as well as a concomitant hepatitis C virus infection. The CDC category at the time of diagnosis was unknown. Previous oral ART was given with abacavir/lamivudine and efa-virenz (ABC/3TC + EFV) but was discontinued later. We initi-ated oral ART with emtricitabine/tenofoviralafenamide/ rilpivirine (FTC/TAF/RPV) and switched to LA RPV/CAP in December 2021. Viral load repeatedly measured <50 cp/mL.

Therapeutic Drug Monitoring

Retrospective TDM for RPV/CAB was derived from all avail-able samples. All injections were on time. Individual trough levels of RPV and CAB and viral load from routine visits are shown for each patient in Figure 1. Figure 1C shows the simultaneous rebound of viral load from patients 1 and 2 at week 30 post–treatment initiation that appeared throughout the above-mentioned SARS-CoV-2 infection. Retrospective TDM of patient 2 showed worrisomely low drug levels at week 30 (CAB: 361 ng/mL; RPV: 16 ng/mL). Unfortunately, patient 1's week 30 plasma sample volume did not allow for ret-rospective TDM. However, when patient 1 developed con-firmed VF at week 64, retrospective TDM showed values above the $4\times PAIC_{90}$ threshold for both RPV and CAB. Meanwhile, retrospective TDM of other cohort patients showed trough levels below $4\times PAIC_{90}$ for both RPV (patient 3) and CAB (patient 2) without any signs of VF.

DISCUSSION

Although LA RPV/CAB has been successfully introduced as a new option for maintenance treatment for PWH with prior vi-rologic suppression, there is serious concern about develop-ment of 2-class antiretroviral resistance in the context of VF [6]. The post hoc multivariable analysis of pooled data from respective phase III trials (FLAIR, ATLAS, and ATLAS-2M)

has identified predictive risk factors for VF, including BMI >30 kg/m^2, HIV subtype A1/A6, and the presence of RPV RAMs. Although the number of failures was relatively large for subtype A6 (11), it was very small for subtype A1 (only 2), making it hard to determine if this was chance or indeed an increased risk for subtype A1 [2]. Recent data presented from the CARES study with far larger numbers suggested that A1 is not a risk factor for failure [13]. The role of baseline polymorphisms at integrase position 74 remains to be determined (J. M. Schapiro, personal communication, April 7, 2024). The benefit of TDM as an additional tool to predict VF remains questionable, and there is a lack of reliable cutoffs regarding drug trough levels. As mentioned above, there is a high intra- and interindividual variability of drug concentrations. Although previous publications have reported several cases of VF accompanied by low drug levels [5, 6], a significant proportion of patients without VF have similarly low drug levels without compromise of therapy [5]. This is similar in our presented case series. Therefore, outside the given risk categories, the role of TDM in the management of virological response is not yet fully determined and should not be overestimated.

New recommendations for interpreting threshold values have recently been published, using $PAIC_{90}$ and 4 and 2 times the respective value as a guide for clinical decision-making [7]. To date, however, TDM is neither recommended nor implemented in clinical routine. Overall, VF has been rare in clinical trials, implementation trials, and real-world data, with an approximate incidence of 1%–2% after up to 188 weeks of follow-up. However, as VF is infrequent in patients on oral ART with good adherence, even a few cases of VF after switching to LA ART from prior reliable virologic suppression may challenge this new treatment modality. Although second-generation INSTIs are believed to have a higher genetic resistance barrier [14], the emergence of 2-class resistance in the context of VF causes profound worry to clinicians as treatment options are then highly restricted.

Emerging resistance in the participant with VF was found unexpectedly and affected both INSTI and NNRTI, significantly limiting further treatment options. Retrospective TDM of stored plasma samples from routine viral monitoring revealed no clear relation between VF and low trough levels of either RPV or CAB. However, one limitation of our study remains, that TDM was not investigated systematically before each injection of RPV/CAB. Even if the one-time "blip" in viral load in patient 2 during his mild coronavirus disease 2019 episode occurred simultaneously with an RPV trough level <2-fold $PAIC_{90}$, no increase in viral load was observed among others with similar trough levels. One possible explanation for the repeatedly low drug levels in patient 2 could be the concomitant intramuscular administration of benzylpenicillin-benzathine. Although no pharmacological interactions between these drugs are known [15], the placement of the penicillin depot in the gluteal muscle, in close proximity to the injected LA-ART, could potentially represent a chemical–pharmacokinetic obstacle to the release of the antiretroviral drugs from the muscle. Meanwhile, patient 1 with confirmed VF had trough levels >4-fold $PAIC_{90}$ for both RPV and CAB at the time of VF. It is possible that blips have a different relevance for LA RPV/CAB than for conventional daily oral ART. Notably, blips were unusually high at week 30 in both patients with >2000 cp/mL. We also took into consideration a rebound in the context of resistant superinfection, as recently described for the first time with LA RPV/CAB [16], but further phylogenetic analysis did not reveal any evidence for this. However, targeted investigations of such blips in patients on RPV/CAB should be conducted to better elucidate the genetic component.

CONCLUSIONS

Even if the frequency of VF during ART using LA RPV/CAB appears to be low, the risk of emerging 2-class resistance should not be underestimated, as treatment options are severely limited thereafter. Careful selection of patients to switch to LA ART is therefore of absolute clinical importance. Currently known predictive risk factors for VF help to identify patients at risk but do not provide absolute security even when used together with TDM. It appears that some cases of VF occur that cannot be prevented by strict avoidance of risk factors or explained through drug monitoring accompanying therapy. If "blips" are observed in patients on LA ART, we recommend close monitoring of the HIV viral load, for example, within a time frame of 2–4 weeks, and collection of samples for TDM if possible. If the viral load exceeds 1000 copies/mL, which is atypical for a blip and should instead be interpreted as a rebound, therapy should be switched back preventively to oral ART to avoid treatment failure with 2-class resistance. This is even more important if TDM values are <4×$PAIC_{90}$.

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Data access. The genome sequence data from this case series have been submitted to GenBank (https://www.ncbi.nlm.nih.gov/genbank/), accession numbers PQ035021 and PQ095886-PQ095890 for patients 1 and 2.

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