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Rilpivirine and cabotegravir trough concentrations in people with HIV on long-term treatment with long-acting injectable antiretrovirals

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Objective: Large inter-individual variability in the pharmacokinetics of rilpivirine and cabotegravir has been reported in the first weeks after starting long-acting injectable (LAI) therapy. Here, we assessed the distribution of rilpivirine and cabotegravir trough concentrations in people with HIV (PWH) on long-term LAI treatment.

Methods: Adult PWH treated with LAI for at least 32 weeks with an assessment of drug plasma trough concentrations were considered. The proportion of rilpivirine and cabotegravir plasma trough concentrations below four-times the protein-adjusted concentrations required for 90% inhibition of viral replication (4×PA-IC_{90}) was estimated.

Results: Sixty-seven PWH were identified. LAI treatment duration was 216 ± 80 weeks (range 32–320 weeks). Cabotegravir concentrations were associated with lower inter-individual variability compared with rilpivirine (45% versus 84%; $P<0.05$). No differences were found in rilpivirine (160 ± 118 versus 189 ± 81 ng/mL; $P=0.430$) and cabotegravir (1758 ± 807 versus 1969 ± 802 ng/mL; $P=0.416$) trough concentrations in males ($n=55$) versus females ($n=12$). A non-significant trend for lower cabotegravir concentrations was found in PWH with a body mass index >30 kg/m^2 ($n=9$) versus non-obese participants (1916 ± 905 versus 1606 ± 576 ng/mL; $P=0.131$). Three out of the 67 PWH had at least one drug concentration <4×PA-IC_{90}: 100% of PWH had undetectable HIV viral load.

Conclusions: At steady state, optimal systemic exposure of cabotegravir and rilpivirine was found in most PWH; cabotegravir trough concentrations were associated with lower inter-individual variability compared with rilpivirine. The study was not powered to assess the contribution of sex and/or body weight on LAI exposure due to the small number of females and obese PWH included.

Introduction

Rilpivirine, a known NNRTI, and cabotegravir, a new integrase inhibitor (INI) structurally related to dolutegravir, have been recently approved as a long-acting injectable (LAI) antiretroviral dual regimen for the treatment of HIV infection.[1–4] According to the international guidelines for HIV treatment, LAI rilpivirine and cabotegravir are now considered as a maintenance strategy for adult people with HIV (PWH) with sustained viral suppression, no history of virological failure or documented/suspected resistance to NNRTI or INI classes, and no active or occult hepatitis B virus infection.[5,6] LAI rilpivirine and cabotegravir can be administered after an optional oral lead-in period (rilpivirine 25 mg plus cabotegravir 30 mg once daily), or started immediately with intramuscular injections given at 4- or 8-week intervals, based on the optimal efficacy and tolerability results from Phase III clinical trials.[7–10]

Large inter-individual variability in the pharmacokinetics of rilpivirine and cabotegravir has been reported in the first weeks

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after starting LAI treatment and, most importantly, low rilpivirine and/or cabotegravir plasma trough concentrations combined with other risk factors (i.e. resistance-associated mutations, HIV subtype A6/A1 and BMI ≥ 30 kg/m^2) have been associated with increased risk of virologic failure.[11] Recent experiences with the therapeutic drug monitoring (TDM) of rilpivirine and cabotegravir plasma trough concentrations confirmed the high inter-individual variability and the potential risk of drug underexposure, mainly to rilpivirine, in the first weeks after starting LAI therapy.[12,13]

Here, we aimed to assess the distribution of rilpivirine and cabotegravir trough concentrations in PWH on long-term treatment with LAI antiretrovirals (i.e. up to 320 weeks) and, eventually, identify clinical variables associated with systemic drug exposure in a real-life setting.

Methods

Study design and enrolment

This retrospective, observational study was aimed to describe the distribution of rilpivirine and cabotegravir trough concentrations in steady-state conditions. To address this issue, we included consecutive PWH from our hospital treated with LAI rilpivirine and cabotegravir as antiretroviral regimen for at least 32 weeks with an assessment of drug plasma trough concentrations collected from March to June 2023. We considered eligible for the study all adults starting cabotegravir and rilpivirine following the approval of the long-acting combined antiretroviral therapy (April 2022 in Italy), as well as those previously enrolled in the pivotal phase II and III studies (in these patients, the blood samples for the TDM were collected after the end of the study), regardless to lead-in phase and timing of drug injection (i.e. starting every 4 or 8 weeks), with no exclusion criteria. Demographic, clinical and pharmacologic information were extracted from the hospital database. As the primary study outcome, we estimated the proportion of rilpivirine and cabotegravir plasma trough concentrations below 4-fold the protein-adjusted concentrations required for 90% inhibition of viral replication (4×PA-IC$_{90}$) set, at 50 and 664 ng/mL for rilpivirine and cabotegravir, respectively.[12,13] As secondary analyses, we attempted to identify demographic and/or clinical variables eventually associated with rilpivirine and cabotegravir trough concentrations.

The study was approved by local Ethical Committee (IRB approval no. 11903). All data used in the study were previously anonymized, according to the requirements of the Italian Data Protection Code (leg. decree 196/2003) and by the general authorizations issued by the Data Protection Authority. All patients signed a written informed consent for medical procedures/interventions performed for routine treatment purposes, according to the Ethics Committee (Comitato Etico Interaziendale Area 1, Milan, Italy).

Assessment of drug plasma trough concentrations

Each blood trough sample for the assessment of rilpivirine and cabotegravir trough concentration was drawn just before the scheduled injection (every 8 weeks) and collected in lithium heparin vacutainer. After drawing, whole blood samples were kept at room temperature for a maximum of 4 hours, then centrifuged (1400**g**, 10 min at 4°C), inactivated for HIV (35 min at 58°C), and the separated plasma was frozen at −80°C until analysis. Plasma quantification of rilpivirine and cabotegravir was performed using an ultrahigh-performance liquid chromatography with tandem mass spectrometry method, modified from the one previously published as described next.[14] Fifty microlitres of plasma samples (from patients, calibrators or quality controls) were added to 100 µL of internal standard solution and 600 µL of precipitant solution (acetonitrile:methanol 50:50). After vortex mixing, the samples were centrifuged at 14 000 rpm for 10 min at 4°C and 300 µL of the supernatant were added to 600 µL of diluent solution (water 100%). Five microlitres were injected in the Acquity® UPLC HSS T3 column, (2.1 × 150 mm, 1.8 µm, Waters, Milan, Italy) and analysed with the chromatographic system Perkin Elmer LX-50® UHPLC system coupled with a Triple Quadrupole QSight 220® at 50°C using a column thermostat, at a flowrate of 0.4 mL/min with a gradient of two mobile phases: phase A (formic acid 0.05%) and phase B (acetonitrile + formic acid 0.05%). The instrument was settled in positive electrospray ionization mode for both drugs, a source temperature of 350°C, a desolvation temperature of 280°C and the chromatographic run lasted 15.0 minutes for each injection. Linearity ranged from 10 to 2500 ng/mL and from 40 to 10 000 ng/mL for rilpivirine and cabotegravir, respectively. All samples collected in the present study were processed in a single analytical run.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation and compared using an unpaired *t*-test; categorical variables were expressed as an absolute number or as a percentage, and their frequency was compared using the chi-squared test. Inter-individual variability in the rilpivirine and cabotegravir plasma trough concentrations was calculated as the percentage of coefficient of variation (CV%). Univariate and multivariate linear regression analyses were carried out considering either rilpivirine or cabotegravir plasma trough concentrations as the dependent variable and clinical characteristics (age, sex, ethnicity, BMI, duration of LAI therapy, serum creatinine and transaminases) as independent variables. Only dependent variables resulting in statistical association with drug concentrations in the univariate analyses were included in the multivariable model.

Statistical significances were set at $P < 0.05$ (a significant difference) and $P < 0.01$ (a highly significant difference).

Results

Demographic and clinical characteristics

Data on rilpivirine and cabotegravir trough concentrations were available for 67 PWH. They were mostly men (82%), with a mean age of 45 ± 13 years, a duration of viral suppression of 10 ± 5 years and had been previously treated with 1.9 ± 0.3 oral antiretroviral regimens before starting LAI therapy. No major differences in the clinical characteristics were observed between females and males (Table 1). Fourteen percent of the enrolled PWH (8% females versus 15% of males; $P = 0.567$) had BMI >30 kg/m^2. All PWH had preserved kidney and liver function and optimal immune-virologic control (100% of PWH had undetectable HIV viral load, 3% had CD4 cell count <350 cells/mm^3). No viral blips were observed during the treatment period with LAI.

Rilpivirine and cabotegravir dosing schemes

All the patients received two injections (cabotegravir and rilpivirine), one into the muscle of each side of buttocks, and none of them were concomitantly treated with moderate/strong drug inducers or inhibitors. All injections were given within the ±7-day window. We used a 23G needle (0.60 × 25 mm) and a 21G (0.80 × 40 mm) in PWH with BMI < 30 and >30 kg/m^2, respectively. Fifty-nine out of the 67 PWH (88%) had previously been enrolled in pivotal LAI studies, namely ATLAS ($n = 35$), FLAIR ($n = 12$) and SOLAR ($n = 12$).[7–10] Sixty-one of them were treated with an oral, lead-in phase (Table 2). Forty-nine (73%)

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Table 1. Demographic and clinical characteristics of the 67 PWH on long-term maintenance therapy with LAI antiretrovirals (continuous variables were expressed as mean ± standard deviation; categorical variables were expressed as absolute number or as percentage)

Variable	Overall	Females	Males
Patients, *n*	67	12	55
Age, years	45 ± 13	47 ± 13	45 ± 14
Body weight, kg	78 ± 13	68 ± 11	80 ± 13*
BMI, kg × h/m^2	25.7 ± 3.9	24.4 ± 3.4	25.4 ± 3.8
Patients with BMI >30 kg × h/m^2, %	14	8	15
Duration of viral suppression, years	10 ± 5	11 ± 9	10 ± 4
Previous antiretroviral regimens, *n*	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3
Previous antiretroviral regimens			
- bictegravir/TAF/FTC	15	5	10
- elvitegravir/c/TAF/FTC	10	2	8
- rilpivirine/TAF/FTC	12	1	11
- rilpivirine/TDF/FTC	5	1	4
- raltegravir/TDF/FTC	5	2	3
- dolutegravir/3TC	4	1	3
- others	16	0	16
Nationality, %			
- Italian	69	50	72
- Peruvian	14	17	13
- Brazilian	6	8	9
- Others	11	25	6
CD4, cells/mm^3	707 ± 285	783 ± 357	690 ± 268
HIV RNA < 50 copies/mL, %	100	100	100
Serum creatinine, mg/dL	0.9 ± 0.2	0.8 ± 0.2	1.0 ± 0.2**
Alanine aminotransferase, unit/L	23 ± 16	19 ± 8	24 ± 17

*P < 0.05 and **P < 0.01 versus females.

of the PWH were initially treated with a LAI injection every 4 weeks for an average of 108 ± 56 weeks and then shifted to the 8-week frequency; the remaining (n = 18) started and maintained LAI injections every 8 weeks (with the first two injections administered 4 weeks apart). At the time of the assessment of drug concentrations, all the PWH were on maintenance rilpivirine plus cabotegravir LAI regimens given every 8 weeks (treatment duration 216 ± 80 weeks, ranging from a minimum of 32 to a maximum of 320 weeks after starting LAI therapy).

Distribution of rilpivirine and cabotegravir trough concentrations

The single assessment of rilpivirine and cabotegravir trough concentrations was performed at 216 ± 80 weeks after starting LAI treatment (range 32–320 weeks), with 88% of samples collected after a minimum of 100 weeks. Overall, rilpivirine and cabotegravir trough concentrations ranged from 81 to 877 ng/mL (177 ± 149 ng/mL) and from 577 to 5740 ng/mL (1792 ± 799 ng/mL), respectively (Table 2). As visualized in Figure 1, cabotegravir plasma trough concentrations were associated with a lower inter-individual variability over time compared with rilpivirine (CV%: 45% versus 84%; P < 0.05). A non-significant trend for lower rilpivirine (160 ± 118 versus 189 ± 81 ng/mL, −15%; P = 0.430) and cabotegravir (1758 ± 807 versus 1969 ± 802 ng/mL, −11%; P = 0.416) trough concentrations was observed in males versus females (Figure 2). Similarly, no statistical differences were found when stratifying drug trough concentrations according to BMI (Figure 3). None of the clinical variables resulted significantly associated with rilpivirine or cabotegravir trough concentrations in the univariate analysis, preventing the possibility to perform multivariate models. No significant effect was found for rilpivirine [156 ± 64 (CV% 41%) versus 153 ± 64 (CV% 42%) ng/mL, P = 0.854] and cabotegravir [1913 ± 1009 (CV% 52%) versus 1710 ± 654 (CV% 38%) ng/mL, P = 0.342] concentrations when dosing was started a 4- versus 8-week interval.

None of the samples produced a result below the PA-IC$_{90}$ for each drug; three rilpivirine (41, 43 and 49 ng/mL corresponding to 4.5% of all assessments) and one cabotegravir (577 ng/mL, 1.5%) trough concentrations produced a result below the target of 4×PA-IC$_{90}$. The only patient with both drugs below this target was a 43-year-old Caucasian man on treatment with LAI for 132 weeks and with a BMI of 33.1 kg/m^2; the other two patients with rilpivirine <50 ng/mL were both Caucasian men with BMI of 23.8 and 25.4 kg/m^2, being treated with LAI, respectively, for 116 and 240 weeks. All injections were administered at the scheduled day. Two out of the 67 PWH had rilpivirine concentrations >500 ng/mL. The first was a 32-year-old man with a BMI of 21.2 kg/m^2 and the second was a 62-year-old man with a BMI of 34.6 kg/m^2. Neither of them was receiving enzyme inhibitor therapy; both had an ECG that showed no evidence of QT prolongation.

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Table 2. Pharmacologic data of rilpivirine and cabotegravir in the 67 PWH on long-term maintenance therapy with LAI antiretrovirals (continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as an absolute number or as a percentage)

Variable	Data
Patients with available TDM data, *n*	67
Patients treated with a lead-in phase, *n*	61
Patients starting LAI every 4 weeks, *n*	49
Treatment duration at 4 weeks, weeks	108 ± 96
Patients starting LAI every 8 weeks, *n*	18
Treatment duration at 8 weeks, weeks	108 ± 96
Patients given LAI every 8 weeks at TDM, *n*	67
LAI treatment duration at TDM, weeks	216 ± 80
Rilpivirine trough, ng/mL (range)	177 ± 149 (41–983)
Rilpivirine inter-individual CV, %	84
Rilpivirine TDM < Pa-IC_{90}, *n* (%)	0
Rilpivirine TDM <4×Pa-IC_{90}, *n* (%)	3 (4.5)
Cabotegravir trough, ng/mL (range)	1792 ± 799 (577–5740)
Cabotegravir inter-individual CV, %	45
Cabotegravir TDM < Pa-IC_{90}, *n* (%)	0
Cabotegravir TDM <4×Pa-IC_{90}, *n* (%)	1 (1.5)

PA-IC_{90}, protein-adjusted 90% inhibitory concentrations (rilpivirine: 12 ng/mL, cabotegravir: 166 ng/mL).

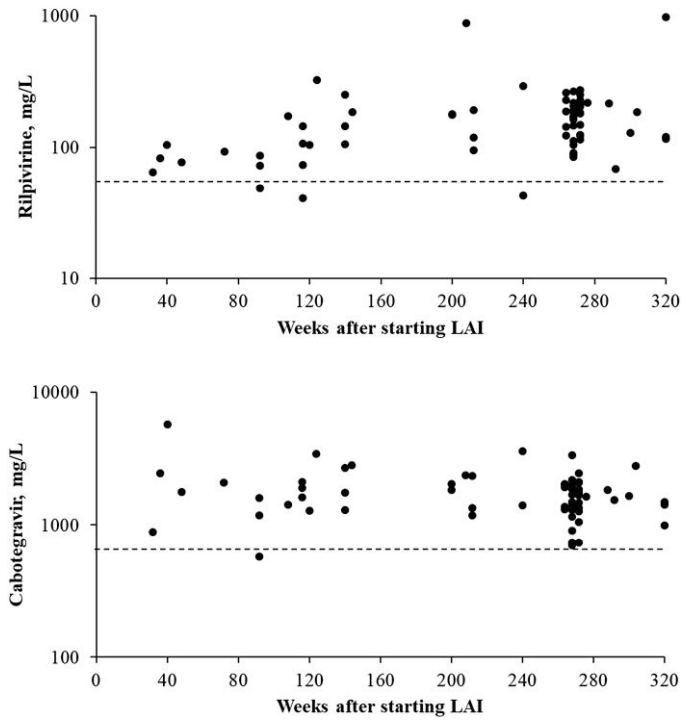


Figure 1. Time course of rilpivirine (upper panel) and cabotegravir (lower panel) plasma trough concentrations. Dashed lines represented the 4×PA-IC_{90} (50 ng/mL for rilpivirine and 664 ng/mL for cabotegravir).

Discussion

In this study following up PWH on long-term LAI (up to 320 weeks), we observed a lower inter-individual variability in cabotegravir plasma trough concentrations and a lower proportion of individuals with cabotegravir and rilpivirine concentrations below the 4×PA-IC_{90} threshold compared to previous cohort studies with TDM data in the early period after LAI initiation.[12,13]

To the best of our knowledge, this is the first report of real-life data on the assessment of plasma trough concentrations of LAI rilpivirine and cabotegravir with an observational period largely exceeding 200 weeks. Indeed, by analysing 91 blood samples from 46 PWH, in 2022 Thoueille *et al.* had confirmed the considerable inter-individual pharmacokinetic variability previously observed in phase II–III trials, with rilpivirine trough concentrations that, in some instances, did not exceed twice the PA-IC_{90}.[12] However, in that study, patients were treated with LAI until the maximum of 60 weeks, and most samples were collected during the first 20 weeks: therefore, the TDM were not performed at the steady state. Both drugs are in fact characterized by a very long half-life, namely 13–28 weeks for rilpivirine and 6–12 weeks for cabotegravir, with the steady state expected to be achieved after 65–140 and 30–60 weeks, respectively (estimated as five times the half-life).[4,15] More recently, the same authors published an update of the study, presenting results based on 725 TDM obtained from 186 PWH treated for up to 196 weeks.[13] They confirmed the significant pharmacokinetic variability of rilpivirine and cabotegravir, with a higher risk of having some drug trough concentrations below 4×PA-IC_{90} in the first 40–50 weeks compared with the second year of treatment. However, most TDM samples were collected in the first year of treatment, not at steady state. Conversely, nearly 90% of our samples were collected after at least 2 years of LAI treatment, with a high probability of reaching the steady state. This may explain the reduced inter-individual variability observed compared with the Swiss study.[13]

As an additional finding, Thoueille *et al.* reported significantly lower cabotegravir trough concentrations (−30%) in males compared with females.[13] This is only partly in agreement with our findings: thus, we observed that male PWH had, respectively, 15% and 10% lower rilpivirine and cabotegravir levels than those measured in female PWH. The different findings might reflect great differences in the population characteristics. Indeed, in the Swiss study only 24% of females were white (52% were black), whereas in our study there were 50% of white females (less than 10% were black). Therefore, the possibility that rilpivirine and/or cabotegravir concentrations may be differently affected by sex and ethnicity remains ill defined.

Another clinical variable potentially associated with the pharmacokinetics of LAI and, possibly, with the response to therapy, is the body weight.[11] Recently, Van Welzen *et al.*, presented five cases with virologic failure on LAI rilpivirine and cabotegravir collected in different centres in the Netherlands.[16] All cases displayed low drug levels of either cabotegravir, rilpivirine or both during the treatment course that were attributed to technical problems (i.e. needle length not adjusted for increased body weight, erroneous injection during the loading phase, needle length not adjusted in an obese PWH because the body fat was

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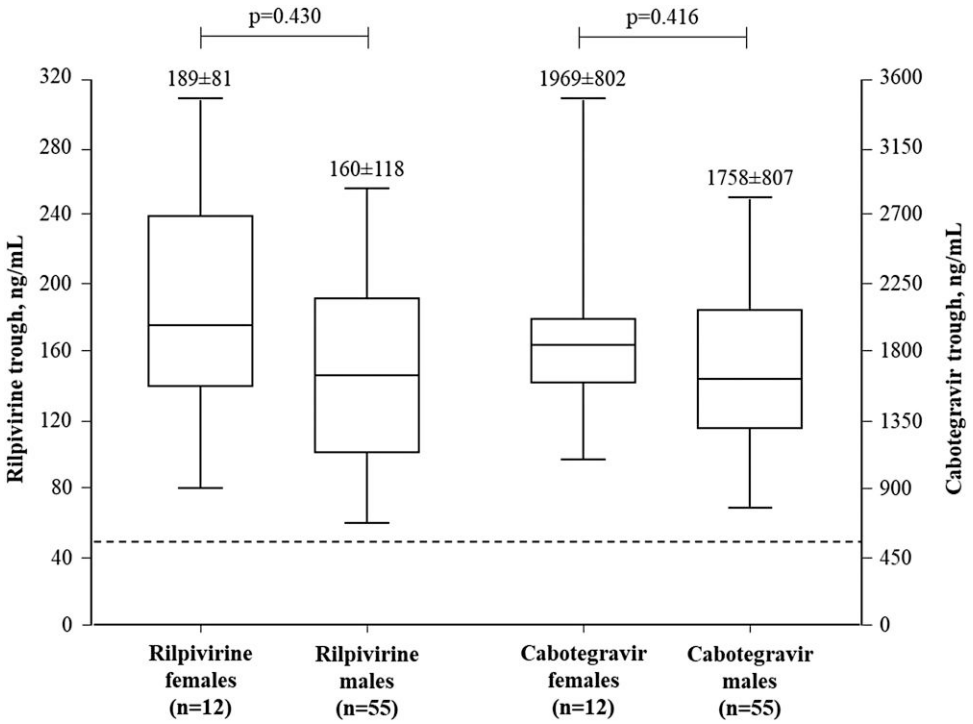


Figure 2. Box-plot of rilpivirine and cabotegravir plasma trough concentrations in female and male people with HIV. Dashed lines represented the 4×PA-IC_{90} (50 ng/mL for rilpivirine and 664 ng/mL for cabotegravir).

localized in the abdominal area, prolonged dosing interval) with single injections occurring mainly in PHW with BMI >30 kg/m^2. Remarkably, genotypic resistance testing revealed extensive selection of NNRTI-associated mutations in all and INI mutations in four cases at the time of virological failure. These cases, together with pooled analyses from Phase III trials, suggest that obesity may represent an important key factor potentially associated with suboptimal exposure of rilpivirine or cabotegravir and eventually a high risk of virological failure.[11,16]

We explored the impact of BMI on cabotegravir and rilpivirine concentrations by stratifying data on rilpivirine and cabotegravir plasma trough concentrations according to BMI (<25 versus 25–30 versus >30 Kg/m^2) failing, however, to document statistically significant difference for both drugs in the three groups. Our results agree with new findings from Elliott *et al.* that, by pooling together data from the FLAIR, ATLAS and ATLAS-2M trials (1245 participants, of whom 17% had a baseline BMI ≥30 kg/m^2), reported that pharmacokinetic profiles of both rilpivirine and cabotegravir were comparable across BMI categories.[17] The discordant results on the potential association (or lack of) between obesity and the risk of suboptimal exposure to rilpivirine and cabotegravir can be related to different factors. First, the definition of obesity as BMI >30 kg/m^2 is too limited. Indeed, Berton *et al.* have shown that the pharmacokinetics of different antiretrovirals can also change within individual defined as obese but stratified further according to BMI sub-categories (i.e. 30–35 versus 35–40 versus 40–50 versus 50–60 kg/m^2).[18] Interestingly, the same authors, by performing physiologically based pharmacokinetic modelling, have recently shown that obesity may have a greater effect on cabotegravir than rilpivirine, with a decrease in cabotegravir AUC >35% for BMI >35 kg/m^2 and in rilpivirine AUC >18% for BMI >40 kg/m^2 at steady state.[19] Second, no standardized procedures are available yet for the selection of the length of the needle according to the distribution of the body fat. For instance, in one of the cases described by Van Welzen *et al.*, the virological failure to LAI has been attributed to the underestimation of the presence of abdominal fat localization in the needle selection.[16] Accordingly, it cannot be excluded that centres across the globe may adopt different procedures for LAI administration in obese versus non-obese patients, eventually contributing to pharmacokinetic variability and discrepant TDM findings.

Only three out of the 67 PWH enrolled in the present study had rilpivirine and/or cabotegravir trough concentrations below the target of 4×PA-IC_{90}. None of them experienced virologic failure (overall, 100% of PWH at undetectable viral load both before starting LAI and at the time of TDM). We were, therefore, unable to correlate drug underexposure with clinical efficacy outcome. It must be pointed out, however, that the definition of optimal exposure to LAI rilpivirine and cabotegravir is presently ill defined. Indeed, some authors considered the target to be the PA-IC_{90} or 4×PA-IC_{90} (as we did), whereas others considered the cut-off to be the first quartile of the pooled trough concentrations from Phase III trials (Q1: 32 ng/mL for rilpivirine and 1120 ng/mL for cabotegravir).[12,13,16] The resulting confusion makes it hard to interpret TDM results and generalize the findings. For instance, in the case series published by Van Welzen *et al.*, one patient was considered as having an adequate concentration of rilpivirine with a trough of 38 ng/mL (because it was higher than the Q1) and a sub-therapeutic concentration of cabotegravir with a trough

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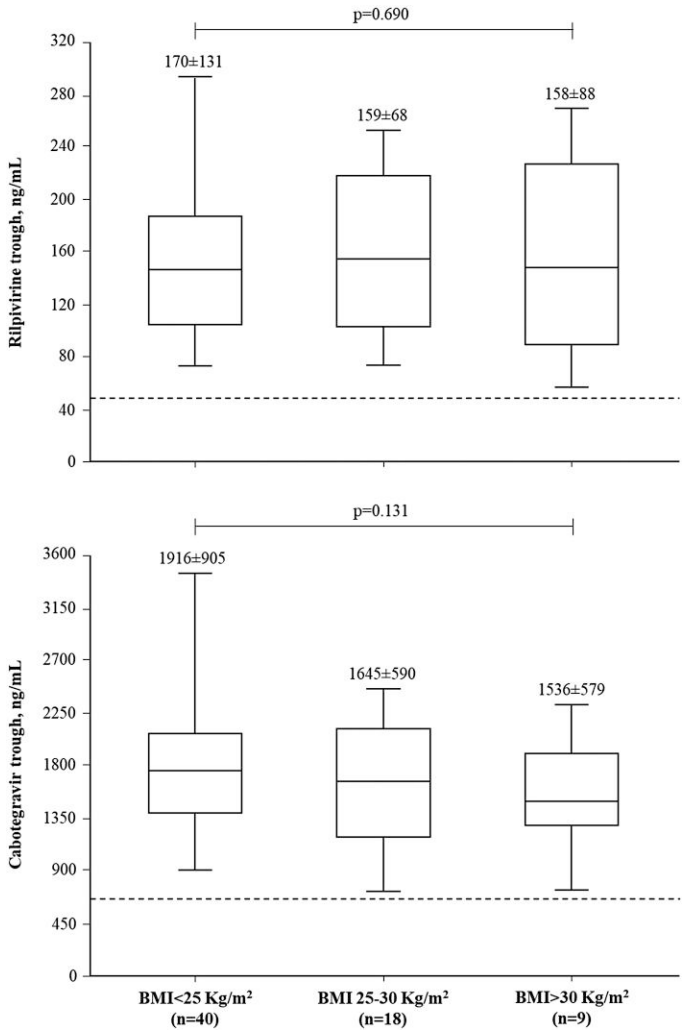


Figure 3. Box-plot of rilpivirine (upper panel) and cabotegravir (lower panel) plasma trough concentrations clustered according to BMI. Dashed lines represented the 4×PA-IC_{90} (50 ng/mL for rilpivirine and 664 ng/mL for cabotegravir).

of 890 ng/mL (because it was lower than Q1).[16] The scenario is exactly the opposite when considering as target 4×PA-IC_{90} (sub-therapeutic for rilpivirine and therapeutic for cabotegravir). In this regard, the correct interpretation of TDM data of LAI rilpivirine and cabotegravir concentrations may be facilitated by the guidance recently provided by Thoueille *et al.*[20]

Potential limitations of our study are represented in the retrospective design and the small sample size that limits generalizability of findings. Indeed, it cannot be excluded that the reduced inter-individual variability of rilpivirine and cabotegravir concentrations observed in our single-centre experience compared with other multicentre studies may be related, at least in part, to the practice accumulated in more than 5 years of LAI injections (most of the patients were enrolled in the phase II–III trials) by the same nursing staff with limited turnover. Furthermore, in our study we did not assess the intra-individual variability of rilpivirine and cabotegravir concentrations. Therefore, the contribution of this additional factor to differences in trough drug concentrations cannot be ruled out. Similarly, we cannot exclude the possibility that differences in the clinical/demographic characteristics of PWH may be associated with inter-individual variability in LAI pharmacokinetics. Indeed, the lack of PWH with BMI >35 kg/m^2 did not allow us to investigate in depth the contribution of morbid obesity to rilpivirine and cabotegravir pharmacokinetic variability, and the study was not powered to assess the contribution of sex and/or body weight to LAI exposure given the low number of females (18%) and obese PWH (13%) included.

Despite these limitations, we are confident that our study could provide preliminary evidence that, at steady state, cabotegravir and rilpivirine are associated with optimal systemic exposure in most PWH, with cabotegravir trough concentrations being associated with lower inter-individual variability compared to rilpivirine.

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This study was carried out as part of our routine work.

Transparency declarations

The authors declare no conflict of interest.

Author contributions

D.C. and C.G. supervised all the stages of the study and wrote the first draft of the manuscript. S.S. and A.D.A. performed laboratory analyses and revised the draft manuscript. M.V.C., D.M. and A.G. took care of the patients and revised the draft manuscript. S.A., A.G. and G.R. supervised the study, contributed to the interpretation of the data and revised the draft version of the manuscript.

Data availability

Data are available from the corresponding author upon reasonable request.

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