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Therapeutic drug monitoring and virological response at week 48 in a cohort of HIV-1 infected-patients switching to dolutegravir/rilpivirine dual maintenance therapy (ANRS-MIE-BIRIDER Study)

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What is already known about this subject:

- Dolutegravir (DTG) and rilpivirine (RPV) dual therapy is recommended as a switch option in virologically suppressed HIV patients
- Virological failure with dual therapy could possibly relate to low concentrations of DTG and/or RPV
- Pharmacokinetic-pharmacodynamic associations have not yet been evaluated for dual therapy

What this study adds:

- Virological replication was more frequent in people living with HIV/AIDS with subtherapeutic plasma concentrations
- Trough concentrations of 640 ng/mL for DTG and 50 ng/mL for RPV can be used as threshold for efficacy in virologically suppressed HIV patients

Principal investigator: FL

Abbreviations:

AIDS: Acquired ImmunoDeficiency Syndrome

ARV: Antiretroviral

BICc: Bayesian Information Criterion Corrected

BMI: Body Mass Index

CKD-epi: Chronic Kidney Disease EPIdemiology

CL: Clearance

Cmin: Trough concentration

DTG: Dolutegravir

eGFR: estimation of Glomerular Filtration Rate

HIV: Human Immunodeficiency Virus

IOV: InterOccasion Variability

MDRD: Modified of Diet in Renal Disease

PK: Pharmacokinetics

PLWHA: People Living With HIV/AIDS

QD: Once daily

RPV: Rilpivirine

RSE: Residual Standard Error

V: Volume of distribution

VL: Viral Load

Acknowledgement: None

Ethics statement: All the PLWHA enrolled in this study gave their written informed consent to having their medical records stored in the Nadis® electronic medical record system, or local databases, which was designed for medical follow-up of PLWHA, including the use of their biological data for research studies (www.dataids.org Fedialis Medica, Marly Le Roi, France, CNIL number: 1171457 May 24th 2006).

Authors contribution: FL designed and supervised the study, provided data, performed the analysis and wrote the manuscript. JLR, MCG, FP, NV, MG, SB, RG, MPL, PM provided and analysis data and proofread the manuscript. EM modeled the data and proofread the manuscript. CS and GP designed and supervised the study, provided data, wrote the manuscript and gave their final approval. Collaborators from the study group included patients in the study, provided data and proofread the manuscript.

Data availability statement: Data available upon reasonable request

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All other authors have no conflict of interest to declare.

Abstract:

Aim: Dolutegravir (DTG) and rilpivirine (RPV) dual therapy is now recommended as a switch option in virologically suppressed HIV patients. Literature suggests that virological failure with dual therapy could possibly relate to sub-therapeutic drug concentrations. In this study, we aimed at describing the DTG and RPV trough plasma concentrations (C_{min}) and plasma HIV-1 RNA (VL) during maintenance dual therapy.

Methods: We performed a retrospective analysis of DTG and RPV Therapeutic Drug Monitoring in people living with HIV/AIDS (PLWHA) with dual therapy in 9 French centers. DTG and RPV trough plasma concentrations were estimated using a Bayesian approach to predict C_{min}. The relationship between the pharmacokinetics of DTG and RPV and VL>50cp/mL was explored using joint non-linear mixed models. The frequency of subtherapeutic threshold (DTG C_{min} below 640 ng/mL and RPV C_{min} below 50 ng/mL) were compared between PLWHA presenting VL>50 cp/mL or not during the study.

Results: At baseline, 209 PLWHA were enrolled in the study. At week 48, 19 people living with HIV/AIDS (9.1%) discontinued their treatment and 15 PLWHA (7.1%) exhibited VL>50 cp/mL. Six PLWHA out of 15 (40.0%) with VL>50 cp/mL during the follow-up had at least one C_{min} below the respective thresholds while only 26 / 194 patients (13.4%) without virological replication had at least one concentration below the threshold (p=0.015).

Conclusion: A majority of PLWHA receiving DTG/RPV maintenance dual therapy demonstrated VL<50 cp/mL but virological replication was more frequent in people living with HIV/AIDS with subtherapeutic C_{min}.

Keywords: Antiretrovirals; Non-nucleoside reverse transcriptase inhibitors; Integrase strand transfer inhibitors; Pharmacokinetics; Pharmacodynamics

Introduction:

Human Immunodeficiency Virus (HIV-1) treatment with dolutegravir (DTG) and rilpivirine (RPV) dual therapy is now recommended as a switch option in virologically suppressed patients¹⁻³. Indeed, the SWORD-1 and SWORD-2 studies have shown the non-inferiority of a once-daily regimen of DTG 50 mg plus RPV 25 mg versus the current 3-drug antiretroviral (ARV) treatment of people living with HIV/AIDS (PLWHA) at week 48 (W48) and W100^{4,5}. This dual therapy is a single tablet, pill burden reducing strategy which avoids the use of nucleos(t)ide reverse transcriptase inhibitors and boosted protease inhibitors in non-HBV coinfecting patients⁶. The aims are to limit cumulative lifetime drug exposure along with associated adverse events related to these drugs while limiting the risk of drug-drug interaction⁷⁻⁹. Despite these advantages, a small percentage of PLWHA on dual therapy experience virological failure¹⁰⁻¹². We can hypothesize that these poor outcomes might be partly associated with inadequate drug exposure and therapeutic drug monitoring is then an additional tool in management of PLWHA, which can clarify patients' drug exposures, enabling rational adjustment of their medications or adherence interventions. Therapeutic drug monitoring is recognized and used in many clinical settings, particularly in patients on immunosuppressants, but has not yet become routine practice in the field of HIV. In the context of dual therapy during maintenance treatment, little is known about the DTG and/or RPV exposure - effect relationship. One of the limitations frequently encountered with ARV pharmacokinetic evaluations is the inability to collect "real life" trough plasma concentrations in an outpatient setting. Indeed, the variability in daytime intake of treatment by patients makes it difficult to ensure that ARV concentration measurements conducted during the consultation visit will match with the exact trough concentration time. To that end, population pharmacokinetic (PK) modeling based on measured plasma concentrations performed at any time of the day can be used to arrive at a Bayesian estimation of C_{min} ^{13,14}. It is also likely that two drug-regimens may be a more suitable model to a two-drug regimen appears as a more suitable model to study the weight of each drug exposure on efficacy and safety than the usual triple drug therapy including nucleos(t)ide reverse transcriptase inhibitors.

The main aim of the present study was therefore to describe the DTG and RPV C_{min} and VL<50 copies/milliliter (cp/mL) during maintenance dual therapy. The other objectives were to assess and describe the treatment response at Week 48 (W48) including therapeutic failure and adverse events and to explore the impact of subtherapeutic concentrations on virological suppression.

Methods:

Patients:

From October 2014 to December 2019, consecutive PLWHA switched to a dual fixed dose combination DTG/RPV 50/25mg once daily (QD) therapy and with a VL below 50 cp/mL were included in this retrospective, multicenter (n=9 centers in France) study. To obtain at least 15 PLWHA with a VL>50 cp/mL, planned inclusion into the study was set at 177 HIV-1 infected patients considering a 8.5% rate for this event^{4,5}. PLWHA characteristics and laboratory evaluations were collected at Day 0, including age, gender, body weight, body mass index (BMI), previous ARV regimen, switch indication, relevant co-medications, hepatitis B and C co-infection status, CD4 cells nadir, Zenith VL, CD4/CD8 ratio, creatinine, estimation of glomerular filtration rate (eGFR) through the Modified of Diet in Renal Disease (MDRD) and Chronic Kidney Disease EPIdemiology collaboration formulas (CKD-epi) were collected at day-0^{15,16}. Variables collected at W4, W12, W24 and W48 included VL, DTG and RPV plasma concentrations, DTG and RPV sampling time and interval between last drug intake and sampling, CD4 cells, creatinine, MDRD eGFR, delta MDRD eGFR from day-0 to W4, W12, W24 and W48, CKD-epi eGFR, delta CKD-epi from day-0 to W4, W12, W24 and W48. Virological replication was defined as the occurrence of a VL > 50 cp/mL at any observation time during the 48 weeks of follow-up.

Biological analysis

All the PLWHA enrolled in this study gave their written informed consent to having their medical records stored in the Nadis[®] electronic medical record system, or local databases, which was designed

for medical follow-up of PLWHA, including the use of their biological data for research studies (www.dataids.org Fedialis Medica, Marly Le Roi, France, CNIL number: 1171457 May 24th 2006). DTG and RPV plasma concentrations were measured locally in each center using a validated liquid-chromatography tandem-mass spectrometry method. Blood collection time and time of the last administration were recorded according to the nurse's recording and the statement of people living with HIV/AIDS, respectively. All pharmacology laboratory contributing to therapeutic drug monitoring data in this study is registered to the same external quality control program. All results of these external quality controls were in agreement between laboratories.

HIV-1 RNA quantification in plasma was locally performed using the commercial assay routinely used in each center. The defined threshold for a detectable viral load was 50 cp/mL. Genotyping tests and mutation resistance detection were performed using a sequencing method.

Statistical analysis / Joint model of PK and viral loads

DTG and RPV C_{min} were estimated using a Bayesian approach: the plasma concentrations measured during the study for each PLWHA were combined with existing population PK models as prior information to estimate individual parameters, considering each occasion as a separate subject to allow for interoccasion variability (IOV), and the individual parameters estimated for each occasion were then used to predict the corresponding C_{min}. For DTG, we used the 1-compartment model with first-order absorption and a lag time developed by Parant and colleagues¹⁷. The interindividual variabilities for clearance (CL) and volume (V) were set to the sum of the interindividual (IIV) and IOV variabilities estimated in the population PK analysis to reflect the total variability. Among covariates, only body weight was included in the modeling. Smoking status of PLWHA was not available and none of the co-medications influencing the model (i.e rifampicin as other inducers, atazanavir and darunavir boosted ritonavir) was given to PLWHA. For RPV, individual parameters were estimated using the model developed by Néant and colleagues¹⁸, with the same method. We used the saemix package in R¹⁹ to estimate individual parameters by fixing the population parameters for each drug separately to

obtain the conditional distributions of the individual parameters for each subject at each occasion. R was then used to compute the trough concentrations as well as their confidence interval, which can be obtained from the standard deviation of the conditional distributions on each parameter. The predicted C_{min} were then used to test for an association between low C_{min} and the probability of VL>50 cp/mL. For each subject, we defined an indicator variable (1 if the subject presented a virological replication at any given time, and 0 if not), and we compared the lowest predicted C_{min} achieved before the failure occurred (or over the entire study for subjects who remained under the threshold during the whole study period) using a Wilcoxon signed rank test, for both RPV and DTG. Because these analyses depend on the prediction of C_{min}, we also repeated them using the observed concentrations when they were within a window around the nominal residual time of 24h (between 20 and 28h post-dose).

The relationship between the PK of DTG and RPV and virological replication was explored using joint non-linear mixed models using Monolix (Monolix suite 2020, Lixoft), combining the PK data with a variable indicating whether VL>50 cp/mL had occurred for each occasion. For this analysis, we built a joint model using the same PK models as above for DTG and RPV. The probability of VL>50 cp/mL was modelled using logistic regression according to the following equation linking P_{ij} (CV > 50 cp/mL), the probability for subject i to experiment virological replication at week j (W_{ij}), to the corresponding C_{min} of RPV and DTG (C_{min,ij}(RPV) and C_{min,ij}(DTG)):

$$\text{logit}(P_{ij} (\text{VL} > 50 \text{ cp/mL})) = \alpha + \beta_{\text{RPV}} \ln (C_{\text{min},ij}(\text{RPV})/0.08) + \beta_{\text{DTG}} \ln (C_{\text{min},ij}(\text{DTG})/1.6) + \beta_{\text{time}} (W_{ij}-4) \quad (1)$$

Concentrations were centered to the estimated median and the effect of the visit was centered on week 4, the first measurement after baseline. The parameters for the PK models were fixed again to their population values from the previous analysis, but this time the estimated IIV and IOV were included as separate components of the model. An explicit equation was used to compute the C_{min} as a function of the individual parameters, and the parameters of the logistic model in equation (1)

were estimated via the SAEM algorithm. We used log-likelihood ratio tests (for nested models) and the corrected Bayesian information criterion (BICc, for non-nested models) to select the model. In addition, the final model was to have relative standard errors of estimation lower than 50% for all the parameters in the model. This combined criterion was used to test whether there was a relationship between the probability of virological replication, Cmin of DTG and RPV, and time in follow up.

Median and interquartile range [IQR25-75%] were presented. Whatever the sampling time, DTG concentrations below 640 ng/mL (i.e 10-fold the protein-adjusted 90% inhibitory concentration of 64 ng/ml) and RPV concentrations below 50 ng/ml were considered as subtherapeutic concentrations²⁰⁻²³. Another threshold for DTG (i.e 300 ng/mL) was also tested as it was suggested to be a cut-off in a pharmacokinetic-pharmacodynamic study and close to the value reported in a dolutegravir monotherapy study^{22,24}. The frequency of subtherapeutic threshold were compared between the group of PLWHA observed to have a virological replication at any time during the study and PLWHA without any virological replication using a Fisher exact test^{21,25}. Finally, the protein-adjusted 90% inhibitory concentration of 64 ng/ml has not been tested given the fact that most quantification methods of the participating centers had a higher limit of quantification than this threshold.

Results:

Patients and treatment:

Two-hundred and twenty-five PLWHA were screened and 209 PLWHA were finally enrolled in the study. Among the 16 non-included PLWHA, 7 PLWHA had a VL at baseline above 50 cp/mL, 6 PLWHA had no DTG and RPV plasma concentration measurement and 3 PLWHA were not on dual therapy. Baseline characteristics of PLWHA are presented in **Table 1**. PLWHA had a median nadir CD4 of 197 cells/mm³ and zenith VL of 90,518 cp/mL. A majority of included PLWHA (73%) were male with a median age of 56 years and a median BMI of 24 kg/m². Before switching, PLWHA were mainly treated with triple drug therapy (n=148). Forty-two PLWHA were already treated with DTG and 34 PLWHA

were already treated with RPV. At W48, 19 PLWHA (9.1%) discontinued their treatment: 3 PLWHA for confirmed virological failure, 6 PLWHA for adverse events and 10 PLWHA for other reasons including 1 decision of PLWHA, 1 PLWHA for ongoing viral replication without resistance onset, 2 PLWHA with discontinuation due to the presence of baseline RPV resistance/reduced susceptibility, 3 PLWHA for drug-drug interaction prevention and 3 PLWHA who were lost to follow-up. Virological failures and adverse events leading to treatment discontinuation are summarized in **Table 2**. During the 48-week follow-up, 307 DTG and 308 RPV plasma concentrations were measured in the 209 PLWHA, respectively. Median [IQR25%-75%] DTG and RPV concentrations were 2,167 ng/mL [1,325-3,149 ng/mL] and 112 ng/mL [77-176 ng/mL], respectively. Median sampling time was 20.25 hours [14.75-24.25 hours] in the group of PLWHA with therapeutic concentrations and 17.13 hours [13.69-23.04 hours] in the group of PLWHA with concentrations below the therapeutic threshold. Sampling times were not statistically different ($p=0.109$, Wilcoxon rank sum test).

Relationship between C_{min} and the occurrence of virological replication

Predicted C_{min}

During the 48-week follow-up, 15 PLWHA (7.1%) exhibited a VL>50 cp/mL. Due to a lack of PK and virological contemporary data (the same day) for one PLWHA, 14 PLWHA were finally included in the joint model analysis. Fixing the population parameters using the previously published models, we could estimate individual parameters for the two drugs received by PLWHA. There was a good agreement between predicted and measured concentrations for DTG, with a tendency to underpredict high concentrations, while there was more variability and a more pronounced underprediction for RPV (**Figure 1**). Reflecting the larger IIV and IOV for RPV, we also estimated larger confidence intervals for C_{min} for this drug, while the predictions for DTG were much narrower. Considering each visit separately, we found no difference in mean concentrations for either DTG or

RPV between subjects with virological replication or not according to a Wilcoxon test with a Bonferroni correction for the 4 tests (**Figure 2**). Pooling the data by defining an indicator of virological replication, we found no difference in the lowest Cmin of RPV or DTG when comparing subjects who experienced virological replication during the study to subjects who remained controlled throughout. Similar results were found when we considered the observed concentrations instead of the predicted ones (data not shown).

Joint modelling

Using a joint model, we could account for repeated measurements within each subject and test for relationships between the probability of virological replication at a given time and the Cmin over the same period. We tested different models as shown in **Table 3** starting from a model with a constant probability of experiencing a detectable VL over time (base model). Introducing a time effect or an effect of the concentrations improved the model in terms of likelihood. When both RPV and DTG concentrations are introduced in the model, the estimates were exactly opposite, due to the strong correlation between the two variables, and the RSE of some parameters were much higher. The model with DTG and time of follow-up had a better BICc than the model with RPV and time of follow up, which also had higher estimation errors. The lowest BICc was obtained for a model with both DTG and time, however the time effect was poorly estimated (RSE=66%) and there was a much larger variability for α_1 in that model ($\omega=2.13$ instead of 1.42), so our final model included only an effect of DTG. This model estimated a probability of VL>50 cp/mL around 0.3% ($p=1/(1+\exp(-\alpha))=0.003$ [0.001-0.01]) for a median DTG Cmin of 1,600 ng/mL. Note that the model predicts an increase of the probability of VL>50 cp/mL when DTG increases suggesting erratic adherence to treatment and probable alternation of low and high exposure in these non-adherent PLWHA.

Impact of subtherapeutic concentrations on plasma VL

Irrespective of the sample time measurement, 18 (5.9%) and 26 (8.4%) of measured concentrations were below clinical thresholds of 640 and 50 ng/mL for DTG and RPV, respectively. During the follow-up period (W4-W48), 32 PLWHA (15.2%) had at least one concentration below the clinical threshold. In PLWHA who had a detectable viral load (> 50 cp/mL) during the follow-up, 6 PLWHA out of 15 (40.0%) had at least one concentration below the threshold while 26 out of 194 PLWHA (13.4%) without any detectable viral load had at least one concentration of DTG or RPV below the threshold ($p=0.015$, Fisher exact test). Considering a 300 ng/mL threshold for subtherapeutic DTG concentrations only 5 (1.6%) of measured concentrations were below this threshold and the frequency of patients with a subtherapeutic concentrations drops to 25 (11.9%). Of these, 5 PLWHA out of 15 (33.3%) had at least one concentration below the threshold while 20 out of 194 PLWHA (10.3%) without any detectable viral load had at least one concentration of DTG or RPV below the threshold ($p=0.021$, Fisher exact test).

Discussion:

This “real-life” study was the first of its kind aiming at combining the evaluation of ARV dual therapy exposure and HIV virological replication. Regarding therapeutic exposure, a Cmin below 640 ng/mL for DTG and below 50 ng/mL for RPV were associated with a higher rate of virological replication and can be used as alert threshold prompting an intervention to decrease this risk. These results are consistent with plasma concentration thresholds proposed in clinical practice. The choice of subtherapeutic threshold can be debated but is based on literature (640 ng/mL for DTG is 10 times the protein-adjusted 90% inhibitory concentration and 50 ng/mL for RPV, the limit recommended in the French national guidelines on HIV, which has been proposed as trough concentration thresholds for these drugs)^{21–23,25}. A DTG plasma concentration of 300 ng/mL can also be proposed as a threshold for loss of treatment efficacy as ‘subtherapeutic concentrations’ using DTG<300 ng/mL or RPV<50 ng/mL is also associated with a higher rate of virological replication^{22,24}. Of note, these results were

largely driven by patients with RPV below 50 ng/mL. However, using modeling, we did not show a relationship between drug exposure and viral replication at any time of the study. This result can be explained by the low number of events (14 out of more than 200 subjects). The retrospective nature of the study may explain missing data, which decrease the ability of the model to detect any difference. Other sources of potential biases in the modeling approach comprise: differences in monitoring of PLWHA (e.g PLWHA who have a VL > 50 cp/mL can be monitored differently or have treatment changes); inability of the models to account for the delay between drug concentrations dropping and the VL increase and potential discrepancies between C_{min} used in the models and real drug exposure. It also shows the difficulty of establishing an exposure-response relationship in a switch option strategy in virologically suppressed patients. A prospective design with systematic assessment of both DTG and RPV C_{min} may finally be more appropriate to capture the dynamic nature of the mechanism of viral replication after a period of low drug exposure.

The choice of models used can also be criticized but these were the most recently published models at the time of the study and were based on a similar number of subjects and populations. Finally, other models published in the literature show similar estimates.

In this study, with respect to virological response, DTG/RPV maintenance dual therapy has demonstrated a VL < 50 c/mL in a majority of PLWHA. Treatment discontinuation at week 48 was 9.1% but only 1.4% of PLWHA had confirmed virological failure which is consistent with previously studies published^{12,26,27}. This might be explained by the relatively high drug exposure in the study population for both DTG and RPV and the long dissociation half-life of DTG from the integrase enzyme (96 hours, compared with raltegravir, 10 hours, or elvitegravir, 3.3 hours.) This may explain greater forgiveness despite suboptimal adherence or lower DTG concentrations in people with HIV/AIDS²⁸. This dual therapy was well tolerated with only 2.9% (6 PLWHA) discontinuing their treatment at week 48. Dual therapy appears as an interesting model to decipher the impact of drug exposure on treatment

efficacy while monotherapy, which is, obviously, the ideal situation to capture the exposure – effect relationship of a drug cannot be used in real-life HIV patients. Indeed, monotherapy had shown immuno-virological effect vulnerability and dual therapy should be optimized to avoid treatment failure and resistance onset ²⁹. TDM should also be a marker of drug adherence which is a crucial parameter in HIV treatment success, particularly in the case of drug-reducing strategies ^{30,31}. In that respect, TDM appears as an useful tool to optimize dual therapy during maintenance therapy, particularly to intervene upon periods of adherence lapses. A systematic TDM may help preventing virological failure that could happen several days after a period of low exposure and repeated measure of plasma concentrations should be required to prevent virological replication. Lowering viral load detection threshold, even up to a positive/negative PCR signal level, may also help detecting differences between PLWHA in a virologically-suppressed cohort of PLWHA ³².

Conclusion:

A majority of PLWHA receiving DTG/RPV maintenance dual therapy demonstrated virological success at W48 suggesting treatment efficacy of this one pill QD regimen. Using modeling, drug exposure was not associated with VL>50 cp/mL during the 48-week study period possibly due to a low power/low number of events and a relatively high drug exposure for both drugs. However, virological replication was more frequent in PLWHA with subtherapeutic plasma concentrations, when using concentration thresholds of 640 ng/mL for DTG and 50 ng/mL for RPV. In that respect, TDM appears as a useful tool to optimize dual therapy during maintenance therapy, particularly to intervene upon periods of adherence lapses.

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Table 1: Baseline demographics, biological and treatment parameters of people living with HIV/AIDS (IQR: interquartile range; F: female; M: men; BMI: Body Mass Index; CD4: CD4 T-Cells; VL: Viral Load; CD8: CD8 T-cells; DTG: Dolutegravir; RPV: Rilpivirine)

	Median	IQR25%-75%
Age (years)	56.0	51.0-63.0
Gender ratio (F/M)	0.37	
Weight (kg)	73.0	63.0-82.0
BMI (kg/m²)	24.0	21.8-26.9
Nadir CD4 (cell/mm³)	197	96-335
Zenith VL (cp/mL)	90,518	27,042-296,500
CD4/CD8 ratio	0.92	0.64-1.34
Reason for DTG/RPV dual therapy (n)		
<i>Simplification</i>	145	
<i>Toxicity prevention</i>	19	
<i>Lipodystrophy</i>	11	
<i>Renal toxicity</i>	12	
<i>Other toxicity</i>	16	
<i>Treatment failure</i>	6	

Table 2: summary of the virological failure and adverse events leading to treatment discontinuation

People living with HIV/AIDS"	Cause for treatment discontinuation	VL at failure in cp/mL (time of failure in weeks, W)	Resistance mutation selected
#2	Virological failure	152 (W6)	None
#7	Virological failure	5600 (W27)	None
#31	Hepatitis B replication		
#96	Digestive disorders, fatigue, muscle pain, joint pain		
#99	Digestive disorders		
#178	Digestive disorders		
#179	Virological failure	176 (W7)	None
#211	Neuropsychiatric disorders		
#216	Osteoarticular disorders		

Table 3: joint models tested using Monolix

Model description	BICc
Base model with only α_1	550.35
Model with a linear time effect	-143.96
Model with an effect of DTG and time	-839.38
Model with DTG, no time effect	-155.44
Model with an effect of RPV and time	-156.92
Model with DTG, RPV and time	559.75

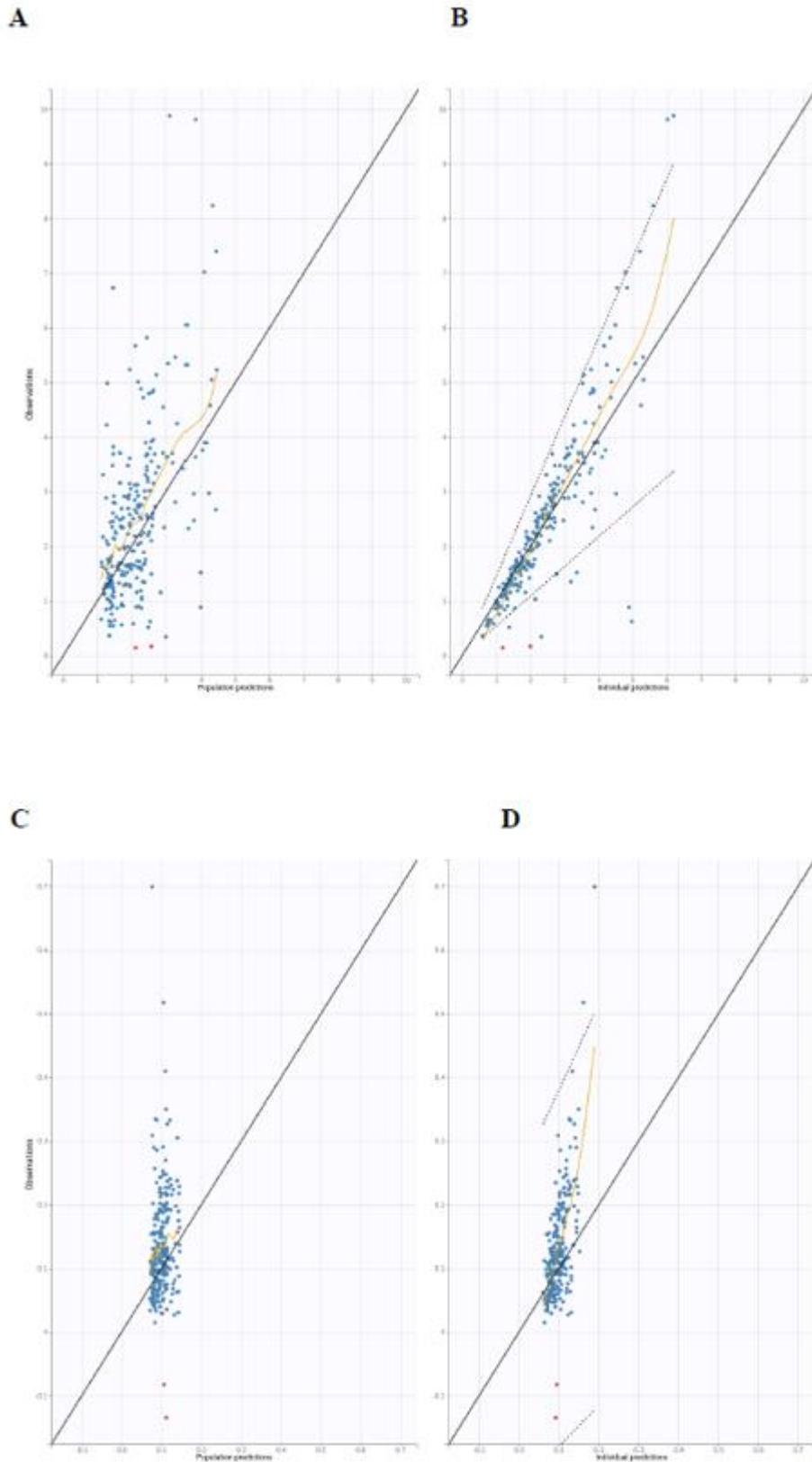


Figure 1. Goodness of fit obtained with the models of Parant et al. for dolutegravir (A and B) and of Néant et al. for rilpivirine (C and D), representing for (A/C) observations versus population predictions

and for (B/D) observations versus individual predictions. In each plot, the observations are shown with blue dots, while red dots indicate observed values below the limit of quantification, which are imputed to the individual predictions. The identity line is shown in black and indicates perfect match between observations and predictions, and the yellow line is a spline adjusted to the data to help visualize departures from the identity line. Finally, the dotted line represents the 90% prediction interval.

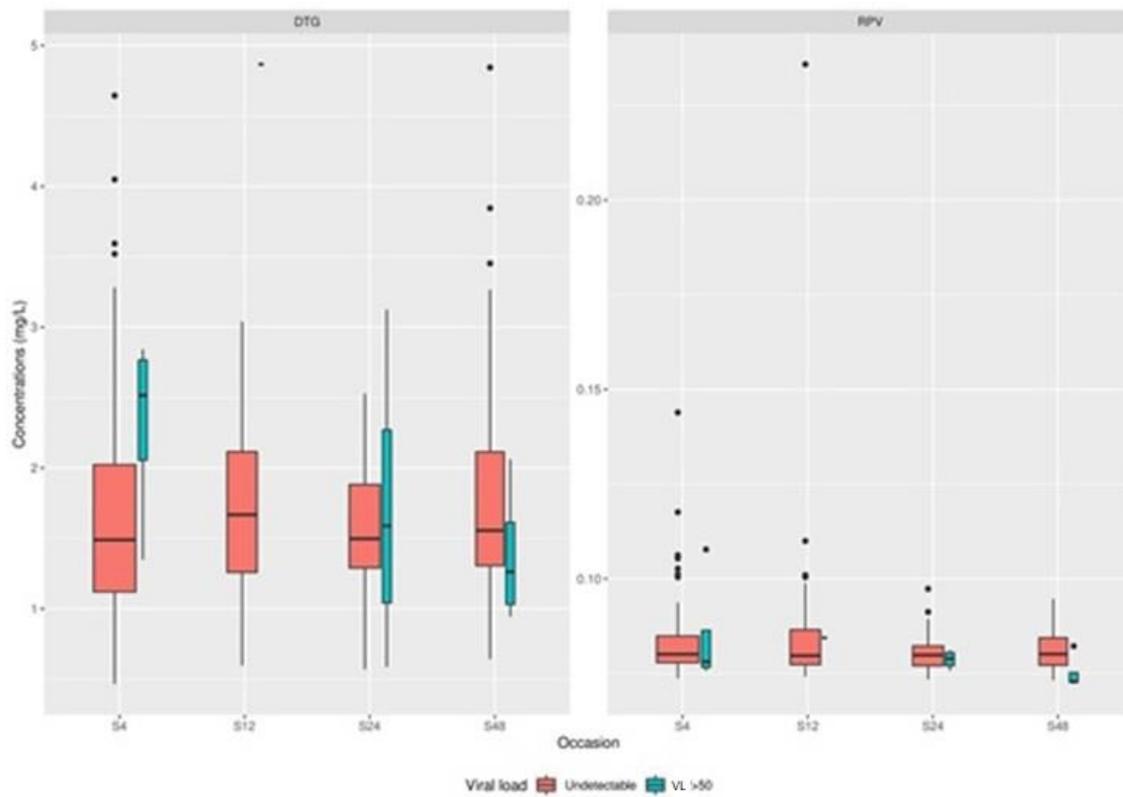


Figure 2. Relationship between predicted dolutegravir (DTG) and rilpivirine (RPV) trough concentrations and the occurrence of viral replication (VL: viral load)