Pharmacokinetics of Dolutegravir and Rilpivirine After Switching to the Two-Drug Regimen From an Efavirenz- or Nevirapine-Based Antiretroviral Regimen: SWORD-1 & -2 Pooled PK Analysis

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The requirement for lifelong ART for HIV infection has highlighted a need to minimize cumulative drug exposure.

The potency, safety, and resistance barrier of DTG make it an ideal core agent for a 2-drug regimen.

The safety, tolerability, and efficacy of RPV make it an optimal partner.

The SWORD-1 and SWORD-2 studies evaluated whether a 2-drug regimen of DTG + RPV once daily was as effective as a 3- or 4-drug regimen for the maintenance of virologic suppression.

- HIV-1 infected adults randomized to remain on current antiretroviral regimen (CAR) or switch from INI-, NNRTI-, or predominantly boosted PI-based regimen.
- DTG 50 mg + RPV 25 mg single entities co-administered once daily with a meal.

ART, antiretroviral therapy; DTG, dolutegravir; RPV, rilpivirine.


Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.
Background

• DTG is metabolized primarily by UGT1A1 and is a minor substrate for CYP3A4
  – Once-daily co-administration of DTG with EFV, a CYP3A4 and UGT1A1 inducer, decreased DTG AUC and C\(\tau\), necessitating DTG twice-daily dosing when co-administered with EFV¹

• The STRIIIVING PK sub-study evaluated the duration of EFV induction in patients switched from an EFV-based regimen to DTG/ABC/3TC QD
  – DTG concentration >PA-IC\(90\) at all sample times and maintenance of virologic suppression supported the switch to DTG/ABC/3TC from an EFV-containing regimen without need for DTG dosage adjustment²

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Background (cont)

- RPV is metabolized primarily by CYP3A4
  - A DDI study was performed to evaluate RPV PK immediately after a switch from the CYP3A inducer EFV and then over time
  - In the first weeks, the RPV exposure was lower after stopping EFV; but by 4 weeks after stopping EFV, the RPV exposure was similar to reference

- PK and virology data from 2 clinical trials supported the switch from an EFV- or NVP-containing 3-drug regimen to RPV/FTC/TDF without need for RPV dosage adjustment

CYP3A4, cytochrome P450 3A4; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation; TDF, tenofovir disoproxil fumarate.


Mean (95% CI) rilpivirine (C\text{\text{trough}}) or EFV concentrations (anytime). Black squares indicate EFV concentration. Gray circles indicate RPV C\text{\text{trough}}. Gray shaded area indicates RPV mean C\text{\text{trough}} ±1 SD.

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies

**Inclusion criteria**
- On stable CAR ≥6 months before screening
- First or second ART with no change in prior regimen due to virologic failure
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV negative

**VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs**

**Week 52**
Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)\(^a\)

**Week 148**

**Countries**
- Argentina
- Australia
- Belgium
- Canada
- France
- Germany
- Italy
- Netherlands
- Russia
- Spain
- Taiwan
- United Kingdom
- United States

**Screening**
1:1
VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs

**Early-switch phase**
DTG + RPV (N=513)
CAR (N=511)

**Late-switch phase**
DTG + RPV

**Continuation phase**
DTG + RPV

\(^a\) Non-inferiority margin of −8\% for pooled data. Non-inferiority margin of −10\% for individual studies.

ART, antiretroviral therapy; CAR, current antiretroviral regimen; DTG, dolutegravir; HBV, hepatitis B virus; INI, integrase inhibitor; ITT-E, intent-to-treat exposed; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PK, pharmacokinetic; RPV, rilpivirine; VL, viral load.

Previously presented by Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.
Secondary PK Objectives

- To evaluate DTG and RPV steady-state PK in all patients switching to the 2-drug regimen
  - C0 at Weeks 4, 24, 48

- To evaluate DTG and RPV PK in a subset of patients who switched from an EFV- or NVP-based regimen to the 2-drug regimen
  - NNRTI Subset
  - NNRTI Subset with Extra Sampling (~20 subjects per study)
    - DTG and RPV C0 at Weeks 2, 4, 8, 24, 48
    - EFV or NVP residual concentrations at Weeks 2 and 4

- Plasma concentrations were measured with validated LC/MS/MS methods
  - DTG and RPV LOQ of 20 ng/mL and 1 ng/mL, respectively
  - EFV and NVP LOQ was 4 ng/mL for both
  - Samples collected 20 to 28 hours post dose were included in C0 summary analyses

C0, pre-dose plasma concentration; DTG, dolutegravir; EFV, efavirenz; LC/MS/MS, liquid chromatography with tandem mass spectrometry; LOQ, limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PK, pharmacokinetic; RPV, rilpivirine.
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV (n=513)</th>
<th>CAR (n=511)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>43 (11.1)</td>
<td>43 (10.2)</td>
</tr>
<tr>
<td></td>
<td>147 (29)</td>
<td>142 (28)</td>
</tr>
<tr>
<td>Female</td>
<td>120 (23)</td>
<td>108 (21)</td>
</tr>
<tr>
<td>Race, non-white</td>
<td>92 (18)</td>
<td>111 (22)</td>
</tr>
<tr>
<td><strong>CD4+ cell count, median, cells/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>611</td>
<td>638</td>
</tr>
<tr>
<td></td>
<td>165 (32)</td>
<td>149 (29)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>348 (68)</td>
<td>362 (71)</td>
</tr>
<tr>
<td><strong>Baseline third-agent class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>133 (26)</td>
<td>136 (27)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>275 (54)</td>
<td>278 (54)</td>
</tr>
<tr>
<td>INI</td>
<td>105 (20)</td>
<td>97 (19)</td>
</tr>
<tr>
<td><strong>Baseline TDF use</strong></td>
<td>374 (73)</td>
<td>359 (70)</td>
</tr>
<tr>
<td><strong>Duration of ART prior to Day 1, median, months</strong></td>
<td>51</td>
<td>53</td>
</tr>
</tbody>
</table>


Previously presented by Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.
Snapshot Outcomes at Week 48 (Pooled)

**Virologic outcomes**

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV (n=513)</th>
<th>CAR (n=511)</th>
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<tbody>
<tr>
<td>Virologic success</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>No virologic data</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48.

Previously presented by Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

ART, antiretroviral therapy; CAR, current antiretroviral regimen; CI, confidence interval; DTG, dolutegravir; ITT-E, intent-to-treat exposed; RPV, rilpivirine. "Adjusted for age and baseline third agent."
PK Results: Overall Population

Pooled study results

- All patients who switched to 2-drug regimen
- C0 at Week 4 to 48 comparable to previously observed DTG and RPV
  - DTG C0=1.11 (46) µg/mL (geometric mean; CV, %)\(^1\)
  - RPV C0=79 ± 35 ng/mL (mean ± SD; N=679)\(^2\)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre-dose concentration, geometric mean (95% CI) [CVb, %](^a)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Week 4</td>
<td>306</td>
</tr>
<tr>
<td>Week 24</td>
<td>417</td>
</tr>
<tr>
<td>Week 48</td>
<td>430</td>
</tr>
<tr>
<td>C0avg</td>
<td>481</td>
</tr>
</tbody>
</table>

\(^a\)Pre-dose defined as sample taken within 20 to 28 hours after the last dose and documented administration of last 3 doses.

C0, pre-dose plasma concentration; C0avg, average pre-dose plasma concentration across Weeks 4, 24, and 48; CI, confidence interval; CV, coefficient of variation; CVb, between subject coefficient of variation; DTG, dolutegravir; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation.

PK Results: Concentrations Over Time

NNRTI subset with extra sampling

- **DTG**
  - Concentration over time graph showing increasing concentration from week 2 to week 48.
  - **DTG PA-IC$_{90}$ = 0.064 µg/mL**

- **RPV**
  - Concentration over time graph showing decreasing concentration from week 2 to week 48.
  - **RPV PA-IC$_{90}$ = 12 ng/mL**

**Legend**:
- DTG: Dolutegravir
- RPV: Rilpivirine

**Additional Notes**:
- BQL: below quantifiable limit
- DTG, dolutegravir
- CI: confidence interval
- EFV: efavirenz
- NNRTI: non-nucleoside reverse transcriptase inhibitor
- NVP: nevirapine
- PK: pharmacokinetic
- RPV, rilpivirine
- SD: standard deviation
- NVP: 4/8 and 7/8 BQL at Weeks 2 and 4; EFV: 8/31 BQL at Week 4.

**Data**:
- Data presented as geometric mean and 95% CI (N=54).
- Data presented as mean (SD).

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PK Results: Concentrations Over Time (cont)

NNRTI subset with extra sampling

DTG concentration, µg/mL

RPV concentration, ng/mL

Time, weeks

Data presented as geometric mean and 95% CI (N=54).

DTG PA IC₉₀ = 0.064 µg/mL

RPV PA IC₉₀ = 12 ng/mL

BQL, below quantifiable limit; DTG, dolutegravir; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation. *Data presented as geometric mean and 95% CI (N=54). †Data presented as mean (SD). NVP: 4/8 and 7/8 BQL at Weeks 2 and 4; EFV: 8/31 BQL at Week 4.

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PK Results: Comparison Across PK Populations

Pre-dose concentration over Weeks 4 to 48

- DTG and RPV C0 in the NNRTI subset with extra sampling were above PA-IC\textsubscript{90} and comparable to those observed in

**Note:**
- Data presented as geometric mean and 95% CI.

**Abbreviations:**
- DTG, dolutegravir; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PA-IC\textsubscript{90}, protein-adjusted 90% inhibitory concentration; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation.

**Graph Details:**
- DTG concentration, µg/mL
- RPV concentration, ng/mL
- Time, weeks

- PPV PA-IC\textsubscript{90}=12ng/mL
- DTG PA-IC\textsubscript{90}=0.064µg/mL

**NNRTI subset with extra sampling (N=54)**
PK Results: Comparison Across PK Populations (cont)

Pre-dose concentration over Weeks 4 to 48

- DTG and RPV C0 in the NNRTI subset with extra sampling were above PA-IC90 and comparable to those observed in
  - The larger NNRTI subset of patients who switched from EFV or NVP to the 2-drug regimen

DTG, dolutegravir; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PA-IC90, protein-adjusted 90% inhibitory concentration; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation. *Data presented as geometric mean and 95% CI.

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PK Results: Comparison Across PK Populations (cont)

Pre-dose concentration over Weeks 4 to 48

- DTG and RPV C0 in the NNRTI subset with extra sampling were above PA-IC_{90} and comparable to those observed in:
  - The larger NNRTI subset of patients who switched from EFV or NVP to the 2-drug regimen
  - All patients who switched to the 2-drug regimen

![Graph showing pre-dose concentration over weeks 4 to 48 for DTG and RPV](image)

**DTG**
- **RPV**

DTG, dolutegravir; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PA-IC{90}, protein-adjusted 90% inhibitory concentration; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation. ^Data presented as geometric mean and 95% CI.

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Conclusions

• After switching to DTG + RPV, residual NVP and EFV plasma concentrations decreased to negligible levels by Week 2 and Week 4, respectively.

• In the NNRTI subset with extra sampling, DTG and RPV C0 increased between Week 2 and 4, and by Week 4 C0 were comparable to those observed for the overall SWORD study population and to previously observed steady-state trough concentrations.

• DTG and RPV C0 were above their respective PA-IC_{90} values, as was expected based on PK results from prior EFV- and NVP-switch studies.

• The efficacy and virology results demonstrate that the DTG and RPV exposures during the post-NNRTI switch stage were sufficient to maintain virologic suppression.

C0, pre-dose plasma concentration; DTG, dolutegravir; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; PK, pharmacokinetic; RPV, rilpivirine.

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  – Clinical investigators and their staffs
  – GlaxoSmithKline and ViiV Healthcare study teams
  – PPD and PRA bioanalytical labs