Rilpivirine exposure in plasma and sanctuary site compartments after switching from nevirapine-containing combined antiretroviral therapy

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Objectives: Pharmacokinetic parameters following modifications to antiretroviral therapy and sanctuary site exposure are often unknown for recently licensed antiretrovirals. We assessed plasma, CSF and seminal plasma (SP) exposure of rilpivirine after switching from nevirapine.

Methods: HIV-infected male subjects receiving tenofovir/emtricitabine/nevirapine (245/200/400 mg) once daily switched to tenofovir/emtricitabine/rilpivirine (245/200/25 mg) once daily for 60 days when CSF and semen samples were collected. Mean and individual plasma concentrations of nevirapine and rilpivirine were compared with the proposed plasma target concentration for nevirapine (3000 ng/mL) and the protein binding-adjusted EC90 for rilpivirine (12.1 ng/mL). Mean rilpivirine CSF and SP concentrations were calculated and individual values compared with the EC50 and EC90 for wild-type virus (0.27 and 0.66 ng/mL, respectively).

Results: Of 13 subjects completing study procedures including CSF examination, 8 provided seminal samples. By day 3, the mean plasma rilpivirine trough concentration was 29.7 ng/mL (95% CI: 23.8–37). No patient presented rilpivirine plasma concentrations under the proposed threshold. The mean rilpivirine concentration in CSF was 0.8 ng/mL (95% CI: 0.7–1.0), representing a CSF:plasma ratio of 1.4%, with concentrations above the EC90 in 85% (11/13) of patients. In SP, the mean rilpivirine concentration was 4.9 ng/mL (95% CI: 3.3–7.2), representing an SP:plasma ratio of 9.5%, with all concentrations above the EC90.

Conclusions: Switching from nevirapine- to rilpivirine-containing antiretroviral therapy was safe and well tolerated, with plasma rilpivirine concentrations above the protein binding-adjusted EC90 in all subjects. Rilpivirine concentrations were always above the EC50 in the CSF and the EC90 in SP.

Keywords: CSF, seminal plasma, nevirapine, switch

Introduction

Rilpivirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) recently licensed for the treatment of therapy-naïve HIV-1-infected patients, offering a further treatment option within combination antiretroviral therapy (cART) regimens.1,2 Pharmacokinetic parameters such as drug concentrations after switching antiretroviral therapy and anatomical sanctuary site exposure are often unknown for recently licensed antiretroviral agents. To date, no studies have described the CSF or seminal exposure of rilpivirine and no pharmacokinetic switch data are available after modification of cART from nevirapine-containing regimens.

Regarding antiretroviral switch pharmacokinetics, when switching from the NNRTI efavirenz to rilpivirine an initial reduction in rilpivirine drug concentrations has been described.3 As nevirapine has a lesser effect on the induction of CYP3A enzymes as compared with efavirenz, a reduced effect on potentially decreased concentrations of rilpivirine would be expected on switching therapy from nevirapine to rilpivirine.

With regard to sanctuary site penetration, greater CNS exposure of antiretroviral agents may assist in preventing the evolution of HIV-associated brain disease by suppressing HIV replication in this compartment.4–6 Controversy exists in this area, e.g. neuronal toxicities of antiretroviral drugs may also play an important role in the pathogenesis of HIV-associated brain disorders and therefore
antiretroviral agents with greater CNS penetration could potentially result in increased CNS toxicity. However, CNS exposure is of clinical interest and antiretroviral drug concentration in CSF is frequently utilized as a surrogate to estimate CNS exposure. The CSF concentrations of several other NNRTIs have been reported, with CSF:plasma ratios of 63% observed for nevirapine, 0.5% for efavirenz, and 1% for etravirine. Interpretation of antiretroviral CSF exposure is often limited by the cohorts in which data on such pharmacokinetic parameters are obtained; in particular, CNS comorbidities may affect the CSF exposure of drugs in subjects who are often included in such studies.

Regarding genital tract penetration, the concentration of drug(s) in seminal plasma (SP) is often used as a surrogate marker in male subjects. Current data on the SP penetration of antiretrovirals suggest that higher concentrations in the genital tract may correlate with suppressed HIV replication in this compartment. This may have implications for a reduction in the sexual transmission of HIV. In addition, a greater understanding of antiretroviral pharmacokinetics in SP could influence drug selection in serodiscordant couples wishing to conceive.

In this study, we aimed to assess rilpivirine drug concentrations after an antiretroviral switch from nevirapine and also examine rilpivirine exposure in two sanctuary sites, CSF and SP.

Methods
Subject selection
Neuro-asymptomatic HIV-1–infected male adult subjects receiving antiretroviral therapy comprising tenofovir/emtricitabine/nevirapine (245/200/400 mg), all once daily, were eligible to participate. Additional inclusion criteria included the following: plasma HIV RNA <50 copies/mL (Quantiplex assay; Bayer, Emeryville, CA, USA) at screening and on at least one other occasion in the preceding 3 months, screening laboratory testing parameters within reference ranges and a body mass index between 18 and 32 kg/m².

Exclusion criteria included: previous exposure to rilpivirine; presence of clinically significant HIV drug-associated resistance documented on any prior HIV-1 genotypic resistance testing; contraindication to magnetic resonance imaging (MRI) examination or lumbar puncture (LP) examination; recent head injury or chronic ongoing neurological diseases; current alcohol abuse, drug dependence or positive urine for drug of abuse at screening; pregnancy; current breast feeding; positive urine or saliva screen for drug of abuse taken within the preceding 3 months; screening laboratory testing parameters outside reference ranges; abnormal full blood count and clotting profile; abnormal liver, kidney or lipid screen; active infection with hepatitis B or C; and/or significant concomitant medication with a potential known drug–drug interaction, such as proton pump inhibitors; or active opportunistic infection and/or significant comorbidities, such as viral hepatitis B or C coinfection.

Study design and procedures
This prospective pharmacokinetic switch study was conducted at Imperial College Healthcare NHS Trust (St Mary’s Hospital, London, UK) between March and December 2012. Nevirapine was switched to 25 mg of rilpivirine daily for 60 days, maintaining a tenofovir/emtricitabine backbone. Participants abstained from drinking alcohol for 72 h before study visits, which took place on days 0, 3, 7, 14, 28, 42, 59 and 60. For safety monitoring, plasma HIV-1 RNA (Quantiplex assay), CD4+ lymphocyte count, urine screen for drugs of abuse, haematology (full blood count and clotting) and chemistry (liver function tests, renal function tests, electrolytes, amylase and lipids) panels were undertaken throughout the study period. On day 59, a seminal fluid sample was collected in order to assess SP rilpivirine concentration and HIV RNA. MRI of the brain was performed at screening, plasma HIV-1 RNA (Quantiplex assay), CD4 lymphocyte count, and HIV RNA load using a nested real-time PCR using the Qiagen Probe PCR method. A standard curve was generated from dilutions of the international working reagent WR1 (NIBSC, Potters Bar, UK).

Concentrations of nevirapine in plasma and of rilpivirine in plasma, CSF and SP were analysed by HPLC–tandem mass spectrometry as previously described. Pharmacokinetic assessments for the decay nevirapine plasma concentration and the pre-dose trough rilpivirine plasma concentration (defined as the concentration at 24 h after the observed dose, Cτrough) were assessed on days 0, 3, 7, 14, 28, 42, 59 and 60 after switch. The rilpivirine concentration was also assessed pre-dose in SP on day 59 and at 4, 6 or 8 h post-dose in CSF on day 60, with subjects sequentially allocated to each time. Dosing took place after a standardized breakfast. The lower limits of quantification for plasma rilpivirine, CSF rilpivirine, SP rilpivirine and plasma nevirapine were 5, 0.49, 0.5 and 10 ng/mL, respectively. Inter- and intra-assay precision did not exceed 10% for any compound. CSF and SP were additionally tested for HIV RNA load using a high-sensitivity in-house assay with a detection limit of 5 RNA copies/mL, assuming an available volume of 2 mL. When <2 mL of sample was available, the cut-off was adjusted proportionately. Briefly, virus was pellet centrifugation and RNA extracted by the Qiagen MinElute method (Qiagen, Crawley, UK). The eluate was reverse transcribed and amplified for 20 cycles using the Invitrogen One-Step method (Invitrogen, Paisley, UK) and PCR products quantified in a nested real-time PCR using the Qiagen Probe PCR method. A standard curve was generated from dilutions of the international working reagent WR1 (NIBSC, Potters Bar, UK).

Statistical analysis
Subject characteristics and laboratory parameters were analysed descriptively. Geometric means (GMs) and 95% CIs were calculated for plasma concentrations of nevirapine and rilpivirine as well as for rilpivirine concentrations in the CSF and SP. GMs and 95% CIs for rilpivirine CSF:plasma ratios were calculated and expressed as percentages. The CIs were determined using logarithms of the individual GM values; the calculated values were then expressed as linear values. Interpatient variability in the pharmacokinetic parameters was expressed as a coefficient of variation [(standard deviation/mean) × 100]. The number of subjects with plasma rilpivirine CTrough <12.1 ng/mL (EC90 for wild-type virus adjusted by protein binding in the presence of whole human serum where the anti-viral activity of rilpivirine is decreased by a factor of 18.5) and nevirapine concentrations <3000 ng/mL (clinical target concentration associated with maximal efficacy) were assessed. Individual rilpivirine CSF concentrations were compared with the EC90 and EC50 rilpivirine concentrations for wild-type virus (0.27 and 0.66 ng/mL, respectively). Associations between

Ethical and patient safety considerations
This study was registered in the European Clinical Trials Database (EudraCT number 2011-004026-98) and local human ethics committee approval was granted prior to recruiting participants. All patients were required to sign an informed consent prior to entering screening.

As no previous study has assessed the efficacy of switching cART from nevirapine-based regimens to rilpivirine-based regimens, subjects were enrolled in groups of three subjects, with results from each group reviewed by the Trial Steering Committee (TSC; A. W., D. B. and N. E. M.) prior to further subjects being enrolled. The TSC reviewed plasma HIV RNA and key pharmacokinetic parameters for each completed group.
total rilpivirine CSF exposure (log_{10} transformed) and both patient characteristics and rilpivirine C_\text{trough} at day 60 were investigated using linear regression modelling. The CIs were then expressed as linear values. All statistical calculations were performed using SPSS (version 20.0; SPSS Inc., Chicago, IL, USA).

Results

**Patient characteristics and drug tolerability**

Of 17 subjects screened, 14 patients were enrolled, 13 underwent LP and 8 provided a seminal fluid sample. Three patients were excluded at screening due to contraindication for MRI (prosthetic metal implant), unstable compliance to cART and positive urine drug screen test. Another patient discontinued on day 59 due to a positive urine drug screen test. The patients' baseline characteristics are described in Table 1. The study medications were well tolerated and no safety or laboratory concerns were observed. All patients reported 100% adherence to the therapy, as confirmed by pill counts. During the study period, plasma HIV RNA remained undetectable in all patients. However, at follow-up, in two patients HIV RNA was detected (53 and 63 copies/mL), which became undetectable (<50 copies/mL) without treatment changes at a subsequent follow-up visit within 2 months.

**Plasma pharmacokinetic parameters over the switch period**

GMs for nevirapine concentrations declined rapidly from 4561 ng/mL (95% CI: 4069–5114) on day 0 to 591 ng/mL (95% CI: 365–957) on day 3 after switching therapy, whereas GMs for rilpivirine C_\text{trough} increased from 29.7 ng/mL (95% CI: 23.8–37) on day 3 to 36.9 ng/mL (95% CI: 29.4–44) on day 7 and achieved a plateau rilpivirine C_\text{trough} between days 14 and 28 (see Table 2 and Figure 1). All individual plasma rilpivirine C_\text{trough} were above the protein binding-adjusted EC_{50} from day 3 throughout the study period. On one isolated occasion in two subjects and on two occasions in a third individual, rilpivirine C_\text{trough} was <20 ng/mL (on day 3 rilpivirine C_\text{trough} was 14 and 19 ng/mL, on day 7 rilpivirine C_\text{trough} was 17 ng/mL and on day 14 rilpivirine C_\text{trough} was 18 ng/mL; Table 3).

**Rilpivirine exposure in CSF**

The overall GM rilpivirine CSF concentration was 0.8 ng/mL (95% CI: 0.7–1.0), representing a mean CSF:plasma percentage ratio of 1.4% (95% CI: 1.2%–1.6%). The mean CSF:plasma percentage ratio varied from 1.2% (95% CI: 1.0%–1.6%) at 4 h post-dose to 1.5% (95% CI: 0.8%–2.8%) at 8 h post-dose. However, these small differences were not statistically significant (P=0.08, Table 3). Individual rilpivirine CSF concentrations were above the EC_{50} in all subjects and above the EC_{90} in 85% (11/13) of the subjects (the remaining 2 patients presented with a rilpivirine CSF concentration of 0.5 and 0.6 ng/mL, respectively) (Figure 2). HIV-1 RNA in CSF, measured by a highly sensitive in-house technique, was undetectable (<5 copies/mL) in all patients. Higher concentrations of rilpivirine in the CSF were weakly associated with higher plasma rilpivirine C_\text{trough}, at day 60 (P=0.072), without significant associations with any other patient characteristic or pharmacokinetic parameter.

**Rilpivirine penetration in SP**

The GM rilpivirine concentration in SP was 4.9 ng/mL (95% CI: 3.3–7.2), representing a GM ratio for SP:plasma of 9.5% (95% CI: 6.3%–14.3%, Table 3). All rilpivirine SP concentrations were above the EC_{50} rilpivirine concentration for wild-type virus. HIV-1 RNA in SP was undetectable in all eight patients, with a maximal assay cut-off of <50 copies/mL.

**Discussion**

We have made several important observations in our study. Firstly, adequate rilpivirine plasma exposure is achieved within a short

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**Table 1. Patient demographics and clinical characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>13</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>43.8 (9.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Baseline CD4+ count (cells/mm³), mean (SD)</td>
<td>534 (233)</td>
</tr>
<tr>
<td>Nadir CD4+ count (cells/mm³), mean (SD)</td>
<td>174 (96)</td>
</tr>
<tr>
<td>Duration of nevirapine therapy prior to study entry (months), median (IQR)</td>
<td>52 (25–128.5)</td>
</tr>
<tr>
<td>Time with virological suppression (months), median (IQR)</td>
<td>52 (21.5–140)</td>
</tr>
</tbody>
</table>

**Table 2. GMs for nevirapine (NVP) decay concentrations and trough plasma concentrations (C_\text{trough}) of rilpivirine (RPV) during the switch period**

<table>
<thead>
<tr>
<th>Day</th>
<th>NVP decay concentrations (ng/mL)</th>
<th>RPV C_\text{trough} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>value (95% CI) CV%</td>
<td>value (95% CI) CV%</td>
</tr>
<tr>
<td>0</td>
<td>4561 (4069–5114) 19.7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>591 (365–957) 65.6</td>
<td>29.7 (23.8–37) 33.3</td>
</tr>
<tr>
<td>7</td>
<td>102 (54–193) 98</td>
<td>36 (29.4–44) 29</td>
</tr>
<tr>
<td>14</td>
<td>19 (11–32) 96</td>
<td>44.9 (34.4–58.7) 41</td>
</tr>
<tr>
<td>28</td>
<td>&lt;LLQ NA</td>
<td>57.3 (48.8–67.2) 24.6</td>
</tr>
<tr>
<td>42</td>
<td>&lt;LLQ NA</td>
<td>57 (46.2–70.5) 35</td>
</tr>
<tr>
<td>59</td>
<td>&lt;LLQ NA</td>
<td>55.1 (44.9–67.7) 33.3</td>
</tr>
<tr>
<td>60</td>
<td>&lt;LLQ NA</td>
<td>58.2 (49.1–69.1) 27.4</td>
</tr>
</tbody>
</table>

CV, coefficient of variation [standard deviation/mean] × 100; C_\text{trough}, trough plasma concentration; LLQ, lower limit of quantification (10 ng/mL for nevirapine); NA, not applicable.

n=13.
time period when switching from nevirapine within this selected study cohort. Secondly, sanctuary site exposure of rilpivirine in the CNS and genital tract have been described for the first time and overall rilpivirine exposure exceeded the EC 50 in CSF and the EC 90 in SP.

Subsequent to the switch in antiretroviral therapy undertaken in our study, the mean nevirapine plasma concentration decayed to concentrations below the clinical target (3000 ng/mL) by day 3. Concurrently, mean rilpivirine plasma concentrations exceeded the protein binding-adjusted EC 90 concentration for rilpivirine (12.1 ng/mL) at that timepoint. Of note, on four individual occasions among three patients, the plasma rilpivirine C trough was observed to be 20 ng/mL while their time-coupled nevirapine plasma concentrations were well below the clinical target. Reassuringly, we did not observe detectable plasma HIV RNA during the study period. This finding may result from a number of factors, including the long-term prior plasma virological suppression, the concomitant presence of nevirapine at low concentrations up to day 14, the continued dosing with emtricitabine plus tenofovir and the attainment of a plasma rilpivirine C trough plateau, which exceeded the protein binding-adjusted EC 90 concentration by an average of 4.5-fold between days 14 and 28.

In the CNS compartment, CSF rilpivirine concentrations were all above the EC 50 for wild-type virus, with 85% (11/13) of the patients presenting concentrations above the EC 90. These concentrations represented a CSF:plasma ratio of 1.4% and were weakly associated with the rilpivirine plasma trough concentration (P = 0.072). This association suggesting that rilpivirine concentrations in the CNS are correlated with plasma concentrations requires cautious interpretation due to the small sample size within this pharmacokinetic study. Pre-dose CSF concentrations may be lower than the concentration observed at 4–8 h post-

Table 3. Rilpivirine (RPV) concentrations in sanctuary sites and their ratios with respect to plasma trough rilpivirine concentrations

<table>
<thead>
<tr>
<th>Time elapsed from RPV dosing to LP</th>
<th>Total, n=13</th>
<th>4 h, n=6</th>
<th>6 h, n=3</th>
<th>8 h, n=4</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV concentration in CSF (ng/mL)</td>
<td>0.8 (0.7–1.0)</td>
<td>0.8 (0.6–1.0)</td>
<td>0.8 (0.4–1.8)</td>
<td>0.8 (0.4–1.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>RPV CSF:plasma ratio (%)</td>
<td>1.4 (1.2–1.6)</td>
<td>1.2 (1.0–1.6)</td>
<td>1.5 (0.8–2.7)</td>
<td>1.5 (0.8–2.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>RPV concentration in SP (ng/mL)</td>
<td>4.9 (3.3–7.2)</td>
<td>————</td>
<td>————</td>
<td>————</td>
<td>————</td>
</tr>
<tr>
<td>RPV SP:plasma ratio (%)</td>
<td>9.5 (6.3–14.3)</td>
<td>————</td>
<td>————</td>
<td>————</td>
<td>————</td>
</tr>
</tbody>
</table>

Values are presented as GM (95% CI).

*Kruskal–Wallis test for the difference between time groups from RPV dosing to LP.

*SP available only from eight subjects.

Figure 1. GMs for nevirapine (NVP) decay concentrations and trough plasma concentrations (C trough) of rilpivirine (RPV) during the study. [NVP] = 3000 ng/mL: proposed plasma target concentration for nevirapine. [RPV] = 12.1 ng/mL: protein binding-adjusted EC 90 for rilpivirine.
In the male genital compartment, the mean total rilpivirine concentration in SP was ~7.5-fold higher than the EC90 free rilpivirine concentration for wild-type virus, representing a GM ratio for SP:plasma of 9.5%. Rilpivirine is ~99.7% bound to plasma proteins in vitro, primarily to albumin. However, rilpivirine binding to SP proteins is unknown. The interpretation of the observed rilpivirine concentration in SP critically relies on the fraction of free active compound unbound to SP proteins. In this study, all participants who provided seminal fluid had undetectable HIV RNA in SP (<50 copies/mL). Nonetheless, due to the small sample size and relatively short duration of the study, it is difficult to draw any clinical conclusions from these SP concentrations.

When comparing these results with the penetration of the other second-generation NNRTI etravirine, rilpivirine shows a comparable mean CSF:plasma ratio (1% vs 0.8%, respectively), with a similar nearly 3-fold increase in CSF concentrations above their respective in vitro IC50 and EC50 for wild-type virus. These similarities also apply for the SP:plasma ratio, which has been reported as high as 16% for etravirine versus 9.5% for rilpivirine observed in our study.

Unlike for nevirapine, a minimum effective plasma concentration in vivo has not yet been defined for rilpivirine. The thresholds proposed for the concentration of rilpivirine we have utilized in this article arise from in vitro studies and have not been validated as an assessment of in vivo antiviral efficacy. Clinical validation of these values within further studies is required.

In summary, we observed that switching therapy from nevirapine-containing cART to rilpivirine-containing cART was safe and well tolerated, with plasma concentrations above the protein binding-adjusted EC90 in the majority of subjects throughout the study period. Importantly, the plasma HIV-1 RNA of all patients remained undetectable. Rilpivirine penetration is different for each anatomical sanctuary site. The mean total rilpivirine concentration is above the EC50 for wild-type virus in the CSF and above the EC90 for wild-type virus in SP. However, the effectiveness of rilpivirine in the CNS and SP at the detected concentrations is not well understood and further studies are required to elucidate the clinical implications of these findings.

Acknowledgements

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Transparency declarations

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References


