<table>
<thead>
<tr>
<th>P050</th>
<th>Cerebrospinal-fluid exposure of efavirenz and its major metabolites when dosed at 400 and 600mg once daily; a randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winston, A*; Puls, R; CSF Sub-study Group (London, UK)</td>
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</tr>
</tbody>
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<table>
<thead>
<tr>
<th>P051</th>
<th>Should the dose of tenofovir be reduced to 200-250mg/day, when combined with protease inhibitors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill, A*; Khoo, S; Back, D; Pozniak, A; Boffito, M (Liverpool, UK)</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>P053</th>
<th>Low isoniazid and rifampicin concentrations in TB/HIV co-infected patients in Uganda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sekaggya Wiltshire, C*; Lamorde, M; Scherrer, A; Musaazi, J; Corti, N; Allan, B; Nakijjoba, R; Nalwanga, O; Henning, L; Von Braun, A; Okware, S; Castelnuovo, B; Kambugu, A; Fehr, J (Kampala, Uganda)</td>
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<table>
<thead>
<tr>
<th>P054</th>
<th>Simulation of the impact of rifampicin on darunavir/ritonavir PK and dose adjustment strategies in HIV-Infected patients: a population PK approach</th>
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</thead>
<tbody>
<tr>
<td>Dickinson, L*; Winston, A; Boffito, M; Khoo, S; Back, D; Siccardi, M (Liverpool, UK)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>P055</th>
<th>CSF LPV concentrations and viral load in viral suppressed patients on LPV/r monotherapy given once daily</th>
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</thead>
<tbody>
<tr>
<td>Tiraboschi, J*; Imaz, A; Ferrer, E; Saumoy, M; Rozas, N; Maso, M; Vila, A; Niubo, J; Podzamczer, D (Barcelona, Spain)</td>
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<table>
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<tr>
<th>P057</th>
<th>Potential implications of CYP3A4, CYP3A5 and MDR-1 genetic variants on the efficacy of Lopinavir/Ritonavir (LPV/r) monotherapy in HIV-1 patients</th>
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</thead>
<tbody>
<tr>
<td>Berno, G; Zaccarelli, M; Gori, C; Tempestilli, M; Pucci, L; Antinori, A; Perno, C; Pucillo, L; D’Arrigo, R* (Rome, Italy)</td>
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</table>

<table>
<thead>
<tr>
<th>P058</th>
<th>Efficacy, safety, and lack of interactions with the use of raltegravir in HIV-infected patients undergoing antineoplastic chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahinol, S*; Machuca, I; Araujo, S; Moreno, A; Perez-Elias, M; Moreno, S; Casado, J (Madrid, Spain)</td>
<td></td>
</tr>
</tbody>
</table>

*Indicates presenting author.
Cerebrospinal-fluid exposure of efavirenz and its major metabolites when dosed at 400 and 600mg once daily; a randomised controlled trial.

Alan Winston1, Janaki Amin2, Amanda Clarke3, Laura Else4, Alieu Amara4, Tristan Barber3, Heiko Jessen6, Anchalee Avinghsanon3, Ploenchit Chetchotisakd7, Sae Khoo6, David A Cooper8, Sean Emery9 and Rebekah Pul5 for the ENCORE CSF sub-study team. 1. Section of Infectious Diseases, Imperial College London, London, UK; 2. Kirby Institute, University of New South Wales, Sydney, Australia; 3. Thai Red Cross AIDS Research Centre, Bangkok, Thailand; 4. Department of Pharmacology, University of Liverpool, Liverpool, UK; 5. Chelsea and Westminster NHS Foundation Trust, London, UK; 6. Medical Group Practice, Berlin, Germany; 7. Srinagarind Hospital, Khon Kaen University, Thailand.

Background: metabolism of efavirenz

- Efavirenz is metabolised into 3 major metabolites.
- None of these metabolites are thought to have significant virological activity.
- However the BOH-efavirenz metabolite has been associated with CNS toxicities in laboratory models.

Results (1): baseline characteristics

- OF 15 subjects screened, 18 subjects completed all study procedures.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median/n</th>
<th>IQR/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td>Male</td>
<td>28</td>
</tr>
<tr>
<td>Ethnicity (n, %)</td>
<td>African</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>9</td>
</tr>
<tr>
<td>Baseline CD4+ T cell count (cells/µl)</td>
<td>266</td>
<td>132</td>
</tr>
<tr>
<td>Baseline plasma HIV RNA (log10 copies/ml)</td>
<td>4.8</td>
<td>1</td>
</tr>
<tr>
<td>Randomised efavirenz dose (n, %)</td>
<td>400 mg</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
<td>16</td>
</tr>
<tr>
<td>Successful CSF examination (n, %)</td>
<td>600 mg</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>14</td>
</tr>
<tr>
<td>CSF protein (g/dl)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>CSF HIV RNA (copies/ml)</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

Results (2): pharmacokinetic results

- CSF efavirenz exposure was above 0.51 ng/ml in all subjects (both treatment groups).
- CSF BOH-efavirenz exposure was above 3.3 ng/ml in 11/14 (400mg) and 3/14 (600mg) subjects.

Results (3): associations [CSF BOH]

Associations between CYP2B6 516G→T genotype and pharmacokinetic results:


Conclusions

The CSF exposure of efavirenz was above 0.51 ng/ml (proposed IC50) in all subjects with both dosing schedules. The CSF exposure of BOH-efavirenz was above 3.3 ng/ml (a proposed toxicity threshold) in 11/14 (400mg) and 7/14 (600mg) subjects.

CSF efavirenz concentration was associated with dose of efavirenz, plasma efavirenz concentration and host genotype.

CSF BOH-efavirenz concentration was not associated with these parameters.

Possible underlying mechanisms may include i) auto-induction of efavirenz and ii) satured pharmacokinetic effects.
Should the dose of tenofovir be reduced to 200-250mg/day, when combined with protease inhibitors or elvitegravir?

Andrew Hill, Saye Khoo, David Back, Department of Molecular and Clinical Pharmacology, Liverpool University, UK
Anton Pozniak, Marta Boffito, SSAT, St Stephens Centre, Chelsea and Westminster Hospital, London, UK

HIV Drug Therapy Conference, Glasgow, Scotland, November 2014 [poster P051]

Effects of protease inhibitors or cobicistat on tenofovir PK

The original dose-ranging studies of tenofovir showed no increased efficacy above 300mg OD [1-3]. The pivotal trials of tenofovir were conducted mainly with efavirenz [4-6], which does not affect tenofovir concentrations. Co-administration of three ritonavir-boosted lopinavir, darunavir and atazanavir, or elvitegravir/cobicistat - raises the Cmax, AUC and Cmin of plasma tenofovir [7-10] (Table 1). The mechanism behind these increases in tenofovir plasma concentrations is either by modulating intestinal absorption and consequently increasing bioavailability [12,13] or by inhibiting its renal elimination [13] (Table 1). The coefficient of variation in lopinavir and darunavir concentrations was not affected by co-administration with tenofovir [7, 8].

Renal toxicity of tenofovir

Patients are routinely treated with TDF at the standard 300mg once daily dose in combination with the three protease inhibitors and elvitegravir/cobicistat, despite these drug interactions. However, results from randomised trials and cohort studies have shown an increased risk of renal adverse events when tenofovir is used in combination with a protease inhibitor or elvitegravir, and if tenofovir plasma concentrations are high [14-17].

Dose-adjustment of tenofovir with PIs – predicted effects

Tenofovir tablets have recently been approved at doses of 150, 200 and 250mg, for use in paediatrics [1]. Results from the original dose-ranging study showed linear dose-proportional rises in tenofovir plasma concentrations with increasing dose [2]. Therefore we would expect that the 250mg tablet would achieve plasma concentrations 17% lower than the 300mg dose, and the 200mg tablet to achieve plasma concentrations 33% lower.

Tables 2 and 3 show the predicted tenofovir Cmax, AUC and Cmin which would be achieved by using either the 250 or 200mg tablets of tenofovir with a protease inhibitor or elvitegravir/cobicistat, compared to using the 300mg tablet of tenofovir in non-nucleoside based treatment. Using a 250mg dose of tenofovir in combination with atazanavir, darunavir or lopinavir or ELV/c (Table 2), the Cmax and AUC would all remain slightly higher than for tenofovir treatment with a non-nucleoside. The Cmin would be 4-20% higher than during treatment with efavirenz. However, using the 200mg dose of tenofovir with the three protease inhibitors, the tenofovir Cmin would be bioequivalent to tenofovir 300mg used with efavirenz (90% confidence intervals predicted to be within limits of 0.80 to 1.25). Using the 200mg dose of tenofovir with these protease inhibitors, the Cmax of tenofovir would be 2% higher for lopinavir, 14% lower for atazanavir, 8% lower for darunavir, and 16% lower for elvitegravir, compared to using tenofovir 300mg with efavirenz.

Table 1: Effects of PIs and Elvitegravir on tenofovir

<table>
<thead>
<tr>
<th>PI/ELV</th>
<th>Effect on Tenofovir (GMR; 90%CI)</th>
<th>Cmax</th>
<th>AUC</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (0.72-0.82)</td>
<td>Cmax (0.84-0.93)</td>
<td>Cmax (0.92-1.11)</td>
<td></td>
</tr>
</tbody>
</table>

It is likely that the efficacy of tenofovir treatment is most closely associated with Cmin, while the toxicity profile is linked with Cmax and AUC. Using a 200-250mg dose of tenofovir with one of these three protease inhibitors or elvitegravir could therefore potentially lower the risk of renal adverse events, while maintaining the efficacy of tenofovir at the same levels as seen in the pivotal trials.

Design of tenofovir low-dose study

The pharmacokinetics of lower dose tenofovir predicted from this analysis could be validated by a three-stage cross-over study (shown in Figure 1). Patients currently on tenofovir 300mg OD in combination with raltegravir (which does not affect PI concentrations) could be switched to tenofovir 300mg plus one of the three protease inhibitors or elvitegravir, and then to tenofovir 200mg OD plus the same PI or ELV/c. The pharmacokinetics of tenofovir and importantly the active intracellular diphosphate could then be compared between the three combinations. Demonstration of bioequivalence between TDF 300mg without a protease inhibitor and a lower TDF dose with a protease inhibitor (PK1 versus PK3 in Figure 1), could justify a change in dosing in the future.

Conclusions

The approved dose of tenofovir disoproxil fumarate, 300mg once daily, was established in clinical trials in combination with efavirenz, which does not significantly affect tenofovir concentrations [1].

Combining tenofovir with elvitegravir/cobicistat, lopinavir/ritonavir, darunavir or atazanavir increases tenofovir Cmax by 15-55% and AUC by 22%-37%, which raises the risk of renal adverse events, but is unlikely to improve efficacy.

Use of paediatric doses of tenofovir (200-250mg once daily) with these protease inhibitors could compensate for the drug interaction, providing a safer but equally effective dose of tenofovir.

These predicted TDF concentrations need to be validated in a prospective PK study.

References

3. Schooley RT, AIDS 2002;16:1257
15. Scherzer R et al. AIDS 2012, 26: 380

Table 2: Predicted effects of switching to 250mg TDF tablets (17% reduction in tenofovir levels)

<table>
<thead>
<tr>
<th>PI/ELV</th>
<th>Effect on Tenofovir (GMR; 90%CI)</th>
<th>Cmax</th>
<th>AUC</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (0.89-1.02)</td>
<td>Cmax (1.04-1.15)</td>
<td>Cmax (1.14-1.38)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Predicted effects of switching to 200mg TDF tablets (33% reduction in tenofovir levels)

<table>
<thead>
<tr>
<th>PI/ELV</th>
<th>Effect on Tenofovir (GMR; 90%CI)</th>
<th>Cmax</th>
<th>AUC</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (0.78-0.93)</td>
<td>Cmax (0.82-0.94)</td>
<td>Cmax (0.78-0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Design of validation study to evaluate lower doses of tenofovir with PIs or ELV/c

TDF PK1
TDF 300mg + FTC + RAL
TDF PK2
TDF 300mg + FTC + PI/r
TDF PK3
TDF 200mg + FTC + PI/r

TDF PK1
TDF PK2
TDF PK3

Figure 1: Design of validation study to evaluate lower doses of tenofovir with PIs or ELV/c
Low isoniazid and rifampicin concentrations in TB/HIV co-infected patients in Uganda

Sekaggya C1, Lamorde M1, Scherrer A.U1, Musaazi J2, Corti N, Buzibye A1, Muller D2, Nakijoba R1, Gutierrez U1, Nalwanga D1, Henning L2, von Braun A1, Okware S1, Castelnuovo B1, Kambugu A1, *Fehr J2

1 Infectious Diseases Institute, Makerere University, Uganda, 2 University Hospital Zurich, University of Zurich, Zurich, Switzerland

Background

- HIV-infection is a major risk factor for development of active tuberculosis (TB) and has been associated with poor outcome and high relapse rates.1–3
- There is limited data on exposure to anti-TB drugs in the HIV/TB co-infected population in Sub-Saharan Africa.
- The proposed reference ranges for anti-TB drugs indicated below were derived from HIV negative patients without TB4 and some studies have demonstrated that patients who do not achieve concentrations in these reference ranges have good clinical outcomes.
- The reference ranges currently used for the maximum concentration (Cmax) are: isoniazid 3-6µg/mL, rifampicin 8-24µg/mL, pyrazinamide 20-60µg/mL and ethambutol 2-6µg/mL.
- The objective of this study is to describe the serum levels of anti-TB drugs in a well characterized prospective cohort of adult HIV/TB co-infected patients commencing treatment for pulmonary TB.

Methods

The SOUTH study (Study on outcomes related to tuberculosis and HIV drug concentrations in Uganda) is an ongoing study within the TB/HIV integrated clinic at the Infectious Diseases Institute of Makerere University in Kampala, Uganda focusing on correlating the pharmacokinetics of anti-TB drugs with the outcome of TB treatment.

- Inclusion criteria: HIV positive patients with first episode of pulmonary TB. Exclusion criteria: TB of any organ requiring treatment for more than 6 months, previous treatment for mycobacteria other than TB (MOT), pregnancy, decompensated liver and renal disease. Patients with resistance to any first line anti-TB drug were withdrawn from the study.
- TB diagnosis and outcomes follow up: sputum microscopy and culture were done at baseline, week 2, week 8, week 24.
- Serum concentrations of anti-TB drugs were measured: at 1 hour, 2 hours, and 4 hours post TB drug dose at 2 weeks, 8 weeks, 24 weeks after initiation of anti-TB treatment, using locally implemented and validated high performance liquid chromatography with ultraviolet detection (HPLC-UV).

Analysis

- We describe the maximum concentration (Cmax) of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) and compare them with the reference ranges as indicated above.

Results

From April 2013 till April 2014, we started 113 HIV-infected adults on a fixed dose combination of HREZ.

Baseline characteristics are described in Table 1.

- The boxplot graph (Figure 1) shows the median Cmax and IQR of H and R.
- Levels of H were found to be below the reference ranges: in 54/77 (70.1%), 38/59 (64.4%) and 15/24 (62.5%) participants at weeks 2, 8, and 24, respectively.
- Levels were below the reference ranges: in 41/66 (62.1%), 26/48 (54.2%) and 8/10 (80%) participants at weeks 2, 8, and 24, respectively.
- The mean Cmax of E and Z were within the reference range at week 2 and 8; mean Cmax of 3.2±SD2.1µg/mL and 4.0±SD3.1µg/mL for E and Z, respectively.
- The mean Cmax of E and Z were within the reference range at week 2 and 8; mean Cmax of 3.2±SD2.1µg/mL and 4.0±SD3.1µg/mL for E and Z, respectively.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males)</td>
<td>59 (52.1%)</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>33 (IQR: 26, 38)</td>
</tr>
<tr>
<td>BMI (median, kg/m²)</td>
<td>19.0 (IQR: 17.5, 21.8)</td>
</tr>
<tr>
<td>Time since HIV diagnosis (median, months)</td>
<td>5 (IQR: 0, 23)</td>
</tr>
<tr>
<td>WHO stage II</td>
<td>95 (84.1%)</td>
</tr>
<tr>
<td>WHO stage IV</td>
<td>18 (15.9%)</td>
</tr>
<tr>
<td>CD4 count &gt;200 cells/µL</td>
<td>142 (IQR: 94, 249)</td>
</tr>
<tr>
<td>CD4 count &lt;200 cells/µL</td>
<td>57 (60.0%)</td>
</tr>
<tr>
<td>First line ART at baseline</td>
<td>26 (23.0%)</td>
</tr>
<tr>
<td>Second line ART at baseline</td>
<td>3 (11.5%)</td>
</tr>
</tbody>
</table>

Conclusions

- We observed lower concentrations of isoniazid and rifampicin in our study population of HIV/TB co-infected patients compared to the reference ranges previously described.
- The clinical implications of these findings are not yet clear.
- We plan to correlate these findings with the response to TB treatment (resolution of clinical symptoms, sputum smear and culture conversion rates, and resolution of chest x-ray findings).

References


Acknowledgements

The first author received a travel grant to attend this conference from Gilead sciences.

All sponsors and partners: Gilead, Abbvie, BMS, Janssen Pharmaceuticals, MSD, Roche-Diagnostics, Shimadzu, ViV-Healthcare, Verein Lunge Zurich.
Simulation of the Impact of Rifampicin on Darunavir/Ritonavir PK and Dose Adjustment Strategies in HIV-Infected Patients: A Population PK Approach

Laura Dickinson1, Alan Winston2,3, Marta Boffito4, Saye Khoo1, David Back1, Marco Siccardi1

1 Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK
2 Faculty of Medicine, Imperial College, London, UK
3 Department of HIV & GU Medicine, Imperial College Healthcare NHS Trust, St Mary’s Hospital, London, UK
4 St Stephen’s Centre, Chelsea & Westminster Foundation Trust, London, UK

INTRODUCTION

• Treatment of HIV-tuberculosis (TB) co-infection is challenging due to high propensity for drug-drug interactions (DDI) between antiretrovirals and rifamycins, such as rifampicin (RIF).

• The PK interaction between once daily darunavir/ritonavir (DRV/RTV) and RIF has not been studied.

• Utilising DDI data from another protease inhibitor previously evaluated in the presence of RIF, population PK modelling and simulation can be used to assess the impact of RIF on DRV/RTV PK.

OBJECTIVES

• Simulate the change in DRV/RTV exposure co-administered with RIF.

• Generate alternative dosing strategies to mitigate the interaction and aid clinical trial design.

METHODS

• Patients & PK model: A previously developed model in HIV patients (n=51, 7 female) describing DRV/RTV PK including data from 3 studies was used.

• All patients were stable on DRV/RTV 800/100 mg (n=32) or 900/100 mg (n=19) once daily (qd) and 1 PK profile per patient was included.

• Median (range) age, weight and baseline CD4 cell count were: 39 yr (21-63), 74 kg (57-105) and 500 cells/mm³ (227-1129), respectively; 49/51 were virologically suppressed at time of PK sampling.

• Interaction with RIF: The interaction between DRV/RTV and RIF was assumed to mimic that observed for lopinavir (LPV)/RTV administered to HIV-infected, TB negative patients (n=21). LPV and RTV apparent oral clearance (CL/F) were shown to increase by 71% and 36%, respectively whilst relative bioavailability (F) decreased by 20% (LPV) and 45% (RTV) in the presence of RIF.

• Simulations of DRV/RTV 800/100 mg (n=1000) were performed (-RIF) using NONMEM (v.7.2).

• The DRV/RTV model was adapted to alter typical values of CL/F and F by the magnitudes reported for LPV/RTV (Table 1) and DRV/RTV profiles simulated for 800/100 mg qd (n=1000; +RIF).

• Dose Adjustments: Alternative doses were based on increments of theoretical DRV/RTV 400/50 mg or 600/100 mg combination tablets.

• Dose adjustments of DRV/RTV in the presence of RIF to 1200/200 mg and 1600/200 mg qd and 800/100 mg and 1200/150 mg twice daily (bid) were simulated.

• Changes in simulated DRV trough concentration (C(y)) after 12 h or 24 h post-dose for a twice and once daily regimen, respectively) and area under the curve over 24 h (AUC(y)) were determined by geometric mean ratio and 90% CI, using DRV/RTV 800/100 mg qd without RIF as a reference.

RESULTS

• PK model: A 2 and 1-compartment model with first order absorption and lag-time best described DRV and RTV PK, respectively.

• Inhibition of DRV apparent oral clearance (CL/F) by RTV followed a maximum effect function (Figure 1).

• DRV CL/F (L/h) decreased by 20% (LPV) and 45% (RTV) in the presence of RIF.

• A DRV CL/F of 0.32 ml/min was associated with 50% maximum inhibition of DRV CL/F (maximum inhibitory effect fixed to 1).

• For the simulation study, weight was included on all clearance and volume of distribution parameters for DRV and RTV by allometric scaling.

• Interaction with RIF & Dose Adjustments: Median DRV and RTV concentrations of simulated regimens without and with RIF are shown (Figure 2).

• Compared to the reference regimen (800/100 mg qd;-RIF), simulated DRV CL/F and AUC were decreased by 70% and 57%, respectively (Table 2).

• Following dose adjustments, simulated DRV CL/F and AUC were 46% and 26%, 28% and 1%, 20% and 16% lower for 1200/200 mg qd, 1600/200 mg qd and 800/100 mg bid, respectively. DRV exposure was increased by 39% for 1200/150 mg bid (Table 2).

CONCLUSIONS

• Modelling and simulation was used to evaluate the theoretical impact of RIF on DRV/RTV PK.

• Based on simulations, 800/100 mg and 1200/150 mg both bid and 1600/200 mg qd could largely overcome the impact of the interaction.

• The risk of increased RTV-related side effects and higher pill burden should be considered and the effect on virological outcome would require investigation.

• In vitro work is ongoing to develop a physiologically based model characterising the interaction and informing simulations.

REFERENCES

1. Dickinson L et al. 12th International Congress on Drug Therapy in HIV, Glasgow, UK, 02-06 November 2014


This work was undertaken with the support of Janssen Pharmaceutica N.V.

Table 1. Typical values of DRV/RTV apparent oral clearance (CL/F) and relative bioavailability (F) without and with RIF.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV CL/F (L/h)</th>
<th>RTV CL/F (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without RIF</td>
<td>14.8</td>
<td>23.0</td>
</tr>
<tr>
<td>With RIF</td>
<td>14.8 ± 5.3</td>
<td>23.0 ± 3.1</td>
</tr>
</tbody>
</table>

• DRV F 1.00 Decreased 20%

• RTV F 1.00 Decreased 45%

• ↑ clearance

• ↓ bioavailability

• Diagram illustrating the DRV/RTV model and potential interaction with RIF.

Table 2. DRV C(y) and AUC(y) simulated by the model for each dosing regimen without and with RIF. Changes in parameters, compared to the reference regimen (800/100 mg qd;-RIF).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>C90% of COC (90% CI)</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800/100 mg qd;-(RIF)</td>
<td>1.64 (1.59-1.70)</td>
<td>0.996 (0.994-1.00)</td>
</tr>
<tr>
<td>800/100 mg qd;(+RIF)</td>
<td>0.49 (0.47-0.51)</td>
<td>1.04 (1.03-1.06)</td>
</tr>
<tr>
<td>1200/200 mg qd;-(RIF)</td>
<td>0.88 (0.85-0.92)</td>
<td>1.11 (1.08-1.13)</td>
</tr>
<tr>
<td>1600/200 mg qd;-(RIF)</td>
<td>1.18 (1.13-1.23)</td>
<td>1.25 (1.21-1.29)</td>
</tr>
<tr>
<td>800/100 mg bid;(+RIF)</td>
<td>1.31 (1.27-1.36)</td>
<td>1.22 (1.19-1.25)</td>
</tr>
<tr>
<td>1200/150 mg bid;-(RIF)</td>
<td>0.88 (0.85-0.92)</td>
<td>1.11 (1.08-1.13)</td>
</tr>
<tr>
<td>1600/200 mg bid;-(RIF)</td>
<td>0.79 (0.76-0.81)</td>
<td>1.26 (1.23-1.29)</td>
</tr>
<tr>
<td>1200/150 mg bid;(+RIF)</td>
<td>1.64 (1.60-1.68)</td>
<td>0.996 (0.994-1.00)</td>
</tr>
</tbody>
</table>

* C12: concentration 12 h post-dose for twice daily regimen; C24: concentration 24 h post-dose for once daily regimen

** COC: DRV CL/F (maximum inhibitory effect fixed to 1)

** GMR: DRV CL/F (maximum inhibitory effect fixed to 1)
CSF LPV Concentrations and Viral Load in Virologically Suppressed Patients on LPV/r Monotherapy Given Once Daily

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BACKGROUND
Plasma trough concentrations of lopinavir (LPV) given as LPV/r 800/200 mg once daily (OD) are reduced in comparison with 400/100 mg twice daily (BID). While OD dosage of LPV/r is sufficient to achieve viral suppression in plasma, data about drug penetration and viral suppression in central nervous system (CNS) is needed, mainly if LPVr is used as maintenance monotherapy strategy in selected pts.

OBJECTIVE
The objective of this study was to evaluate CSF HIV-1 RNA and CSF LPV concentrations in pts receiving LPV/r monotherapy OD (LPV/Mod).

PATIENTS AND METHODS
This is a cross-sectional sub-study within a prospective, open-label pilot simulation study to evaluate the efficacy and safety of LPV/rMOD in virologically suppressed pts previously receiving a BID LPV/r monotherapy regimen (LPV/r/MBID), the “Kmon study” (NCT01581853).

To assess LPV concentrations and HIV-1 RNA in CSF, a lumbar puncture (LP) was performed in a subgroup of patients after at least one month of LPV/Mod treatment. CSF and Blood Plasma paired samples of all participants were obtained 24 hrs (11-28) after the last LPV/r dose. HIV-1 RNA was determined by real-time PCR (limit of detection 40 copies/ml). Liquid chromatography-tandem mass spectrometry (Tandem labs, NJ) was used to determine CSF and blood plasma LPV concentrations.

RESULTS

| BASELINE CHARACTERISTICS | N (%) | Age, median(range) | Gender, n (%) | Risk practice, n (%) | Hepatitis C, n (%) | CD4 count (cells/µl), median (range) | Nadir CD4 T cells/µl | AIDS, n (%) | Median time on a LPV/r-containing regimen (before starting LPV/r MOD) years | Median time on LPV/rMBID (before starting LPV/r MOD) years | Median time with undetectable VL (before starting LPV/r MOD) years | At least 1 bilp before LPV/r MOD, n (%) |
|-------------------------|-------|-------------------|---------------|---------------------|------------------|--------------------------------------|----------------------|-------------|---------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------|-----------------------------|
| N (%)                   | 9 (100%) | 48.3 (35.4-57.3) | Male          | 7 (77.8)            | 2 (22.2)         | 672 (252-1468)                      | 125 (37-537)         | Yes         | 9.0 (3.9-10.6)                             | 1.6 (0.7-4.5)                                | 7.6 (3.6-11.9)                              | 2 (22.2)                               | 7 (77.8)                                   |
| Gender, n (%)           |        |                   | Female        | 2 (22.2)            |                  |                                      |                      | No          |                                             |                                               |                                              |                                           |                                           |
| Risk practice, n (%)    |        |                   | Drug users    | 3 (33.3)            |                  |                                      |                      | No          |                                             |                                               |                                              |                                           |                                           |
|                         |        |                   | Homosexuals   | 3 (33.3)            |                  |                                      |                      | Yes         |                                             |                                               |                                              |                                           |                                           |
|                         |        |                   | Others        | 0 (0.0)             |                  |                                      |                      | No          |                                             |                                               |                                              |                                           |                                           |
| Hepatitis C, n (%)      |        |                   | Yes           | 4 (44.4)            |                  |                                      |                      | No          |                                             |                                               |                                              |                                           |                                           |
|                         |        |                   | No            | 5 (55.6)            |                  |                                      |                      | No          |                                             |                                               |                                              |                                           |                                           |
| CD4 count (cells/µl), median (range) | 672 (252-1468) | 125 (37-537) | Yes | 3 (33.3) | 6 (66.7) | 9.0 (3.9-10.6) | 1.6 (0.7-4.5) | 7.6 (3.6-11.9) | 2 (22.2) | 7 (77.8) |

PLASMA AND CSF LPV CONCENTRATION AND VIRAL LOAD CONCENTRATIONS

<table>
<thead>
<tr>
<th>Number</th>
<th>Hours since last dose to PL</th>
<th>CSF VL copies/ml</th>
<th>CSF LPV (ng/ml)</th>
<th>Plasma VL copies/ml</th>
<th>Plasma LPV (ng/ml)</th>
<th>CSF/Plasma Ratio</th>
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<td>1</td>
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<tr>
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<td>11</td>
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<td>&lt;40</td>
<td>16700*</td>
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</tr>
<tr>
<td>3</td>
<td>&lt;40</td>
<td>4.7</td>
<td>&lt;40</td>
<td>377</td>
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<tr>
<td>4</td>
<td>23</td>
<td>2.49</td>
<td>&lt;40</td>
<td>640</td>
<td>0.004</td>
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</tr>
<tr>
<td>5</td>
<td>24</td>
<td>28.7</td>
<td>&lt;40</td>
<td>154</td>
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</tr>
<tr>
<td>6</td>
<td>26</td>
<td>19.1</td>
<td>&lt;40</td>
<td>5000*</td>
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</tr>
<tr>
<td>7</td>
<td>26</td>
<td>9.78</td>
<td>&lt;40</td>
<td>7780*</td>
<td>0.001</td>
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<tr>
<td>8</td>
<td>26</td>
<td>1.93</td>
<td>&lt;40</td>
<td>1610</td>
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<tr>
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<td>6.75</td>
<td>&lt;40</td>
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</tr>
</tbody>
</table>

Median (range) 24 (11-28) <40 9.8 (1.9-78.3) <40 1970 (154-16700) 0.004 (0.001-0.018)

* >ULQ (Upper Limit of Quantification)

CONCLUSIONS
No CSF viral escape was detected, and LPV concentrations were above the IC50 for wtHIV-1 (1.9 ng/ml). However, as CSF LPV concentrations were close to IC50 in some pts, a careful clinical follow up of pts receiving this regimen would be advisable. Larger longitudinal studies will be helpful for a better understanding of the CNS antiviral activity of LPV/r monotherapy.
Potential implications of CYP3A4, CYP3A5 and MDR-1 genetic variants on the efficacy of Lopinavir/Ritonavir (LPV/r) monotherapy in HIV-1 patients

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Background

Several genetic single nucleotide polymorphisms (SNPs) in biotransformation enzymes (CYP3A4, CYP3A5) or transporter proteins (multidrug resistance MDR-1 gene product, P-gp) are involved in PI metabolism so that PI pharmacokinetics are characterized by a large inter-individual variability.

The aim of this study was:

- to develop an in-house PCR/direct sequencing, based on DNA purification of full-length CYP3A4 and CYP3A5 genes (SNPs) and MDR1 C3435T variant;
- to investigate association of CYP3A4 and CYP3A5 reported or unreported genetic polymorphisms and MDR1-C3435T (CC homozygote, CT heterozygote, TT homozygote) with clinical outcome of HIV-1 infected subjects treated with PI.

Methods

- Overall, 40 HIV-1 infected patients receiving boosted Lopinavir (LPV/r) monotherapy after virological suppression were genotyped and analyzed through PCR and direct sequencing of full-length CYP3A4 and CYP3A5 gene sequences and MDR1 gene (C3435T).[1]
- All patients were chosen if full adherent to therapy;
- Plasma viral load was analysed before and after LPV/r initiation; LPV/r therapeutic drug monitoring (TDM) was determined at 12-hours.
- The probability of virological failure was assessed with Kaplan-Meier survival analysis and differences in probability of failure between patients carrying or not carrying SNPs were calculated using log-rank test.

Results - Probability of Failure

- LPV/r TDM (ng/ml) did not show significant differences among CYP3A4 or CYP3A5 SNPs, although a mean lower level of LPV/r was associated with detection of several SNPs: CYP3A5*3 rs776746; CYP3A5 rs28365088, CYP3A5 rs15524, CYP3A4 rs2687116, and CYP3A4 rs2242480.
- In follow-up analysis, <90% adherence was the main factor associated with virological failure of LPV/r monotherapy (83.3% of failure vs. 34.4%, p<0.001 at log-rank test).
- Adjusting for adherence two single CYP3A5 SNPs were associated with significant high probability of virological failure: CYP3A5 rs776746 and CYP3A5 rs15524 (Figure 1 and Figure 2). In general, the detection of CYP3A5 SNPs seems to show a better association with virological failure than the detection of CYP3A4 SNPs, although the detection of at least one CYP3A5 SNP was only marginally associated with virological failure (Figure 3).
- The polymorphisms of MDR1-C3435T gene results in our sample to be protective for virological failure if TT phenotype was detected (Figure 4). Indeed no patient carrying the TT homozygote gene failed LPV/r monotherapy.

Conclusion

Efficacy of PI monotherapy is strongly dependent from patient adherence, but, in adherent patients, genetic factors, such as CYP3A5 and MDR1-C3435T gene variants, may affect the response to treatment, though their role, as well of other genetic variants, need further investigation.

Reference


Acknowledgment

L. Spallanzani Hospital, Rome, Italy
Efficacy, safety, and lack of interactions with the use of raltegravir in HIV-infected patients undergoing antineoplastic chemotherapy.

Bañón, Sara; Machuca, Isabel; Araujo, Susana; Moreno, Ana; Perez-Elías, María J; Moreno, Santiago; Casado, José Luis
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BACKGROUND
• Concomitant use of combination antiretroviral regimen (cART) and cancer chemotherapy is difficult due to complex interactions and increased toxicity. Raltegravir could be an adequate option through its favorable drug-drug interaction profile

OBJECTIVES
• To evaluate efficacy and safety of the concomitant use of RAL plus cancer chemotherapy in HIV patients, and to assess pharmacokinetic interactions

METHODS
• Prospective longitudinal study of HIV patients with cancer; AIDS related or not, undergoing chemotherapy. Patients without resistance or previous failure were switched or initiated raltegravir plus two nucleoside analogues.
• Plasma trough levels of RAL were measured by HPLC with fluorescence detector (HPLC-MD, Waters, MA, USA).

RESULTS
• Overall, 28 patients receiving a raltegravir-based regimen (4 naive) with tenofovir-emtricitabine (18 cases) or abacavir-lamivudine (10 cases) were included.
• Mean age was 46.2 years (IQR, 39-52.7), and 79% were male.
• Median time of HIV was 201.7 months, CD4+ nadir was 268 cells/mm3, and 75% had previous AIDS.
• At the diagnosis of neoplasia, 17 were on protease inhibitors and 4 with efavirenz.
• Ten patients had a non HIV related cancer (3 breast, 2 pancreatic, 1 Ewing Sarcoma, 1 myeloblastic leukemia, 1 melanoma, 1 parotid adenocarcinoma, 1 lung), and 18 had an HIV-related cancer (9 non Hodgkin lymphoma, 7 Hodgkin disease, 2 anal cancer).
• Overall, 43% of patients received more than 1 line of chemotherapy, including antimetabolites in 12 patients (5-FU, capecitabine, methotrexate, gemcitabine), alkylating agents in 12 cases (ciclophosphamide, iphosphamide), vinca alkaloids in 20 patients (vincristine, vinblastine, vindesine), antitumor antibiotics in 16 cases (adriamycin), cisplatin or carboplatin in 6, and monoclonal antibodies in 6 patients (rituximab, trastuzumab, cetuximab).
• Six patients modified the doses of antineoplastic agents due to toxicity (4 neutropenia), not related to raltegravir.
• Plasma concentrations of raltegravir in 8 patients showed a median concentration of 143 ng/ml (79-455).
• During a median follow up of 12.7 patients-year in concomitant therapy there was only 1 case of virological failure and no patient discontinued raltegravir.
• Four patients (14%) died during the study, not related to AIDS progression.
• Raltegravir was continued after chemotherapy in all the cases.

CONCLUSIONS
• A raltegravir-based therapy is safe and effective in HIV patients undergoing antineoplastic chemotherapy, regardless of the type of tumor, and type and duration of chemotherapy.
• Pharmacokinetic data show adequate raltegravir levels.