Switch from Enfuvirtide to Raltegravir Lowers Plasma Concentrations of Darunavir and Tipranavir: a pharmacokinetic sub-study of the EASIER-ANRS 138 trial

Lauriane Goldwirt1, Joséphine Braun2, Nathalie de Castro3, Isabelle Charreau2, Aurélie Barrail-Tran1, Constance Delaugerre4, François Raffi5, Caroline Lascoux-Combe6, Jean-Pierre Aboulker2, Anne-Marie Taburet1* and Jean-Michel Molina3

1 Department of Clinical Pharmacy, Bicêtre Hospital, Assistance Publique Hôpitaux de Paris, and University Paris 11, 2INSERM SC10, Villejuif, 3Department of Infectious Diseases Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris, and University Paris Diderot-Paris 7 4 Virology Department Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris, 5 CISIH, CHU Hotel Dieu, Nantes, 6Department of Internal Medicine Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris.

Text: 1000 words/1000 Abstract: 75 words/75 1 table and 1 figure

Running title: darunavir or tipranavir and enfuvirtide or raltegravir

*Correspondent footnote:

Dr Anne-Marie Taburet
Clinical Pharmacy department
78 rue du Général Leclerc,
94275 Le Kremlin Bicêtre, France
anne-marie.taburet@bct.aphp.fr
Abstract

We compared tipranavir and darunavir concentrations measured at steady state in 20 HIV-infected patients enrolled in the ANRS 138-EASIER clinical trial who switched from enfuvirtide to raltegravir while maintaining the same background regimen. Geometric mean ratio of C\textsubscript{trough}, C\textsubscript{max} and AUC before (day 0) and after (week 24) the switch were 0.49, 0.76, 0.67 and 0.82, 0.68, 0.64 for tipranavir and darunavir, respectively. The virologic consequences of these drug interactions are yet to be determined.
Among patients with multidrug-resistant human immunodeficiency virus type 1 (HIV-1) infection, salvage antiretroviral regimens including enfuvirtide have demonstrated sustained efficacy. Nowadays, reluctance to subcutaneous injections supports replacement of enfuvirtide with newly available antiretrovirals, such as raltegravir an integrase inhibitor administered orally. The ANRS 138-EASIER clinical trial demonstrated that a switch to raltegravir was safe, well tolerated, and virologically non-inferior to the maintenance of enfuvirtide in patients infected with multidrug-resistant HIV-1 infection who were receiving suppressive antiretroviral therapy (4). Although enfuvirtide is a peptide, with no \textit{in vitro} effect on drug metabolizing enzymes or transporters, increases in saquinavir, lopinavir or tipranavir concentrations have been reported when these protease inhibitors were combined with enfuvirtide (5, 11). Raltegravir is biotransformed mainly via glucuronidation and has been reported not to alter pharmacokinetics of co-administered antiretrovirals (3). A pharmacokinetic sub-study was designed in the ANRS 138 trial, in order to assess a potential decrease in two protease inhibitors exposure, tipranavir and darunavir following the switch from enfuvirtide to raltegravir.

EASIER-ANRS 138 was an open-label, multi-center, randomized clinical trial that demonstrated the non-inferior antiviral efficacy at 24 weeks of a switch from enfuvirtide to raltegravir among treatment-experienced patients with suppression of plasma HIV-1 RNA below 400 copies/mL under enfuvirtide-based regimen (4). Twenty patients enrolled in this trial gave their written informed consent to participate in the pharmacokinetic study. Nine patients were receiving ritonavir-boosted tipranavir (500/200mg bid), and 11 patients were receiving ritonavir-boosted darunavir (600/100 mg bid) as part of their optimized background regimen.
Blood samples were drawn prior to the morning drug intake with a light continental breakfast and 1h, 3h, 5h and 9h post dosing when darunavir or tipranavir were combined to enfuvirtide (period 1) and 24 weeks after the switch from enfuvirtide to raltegravir (period 2).

Tipranavir, darunavir and ritonavir were assayed by validated high performance liquid chromatography methods with ultraviolet detection according to a previously described method modified (8). The lower limit of quantification of tipranavir, darunavir and ritonavir were 400, 40 and 25 ng/mL respectively. Coefficient of variation of quality control samples included in each analytical run was below 8%.

Pharmacokinetic parameters were calculated by noncompartmental method (WinNonlin; Pharsight Corporation, Mountain View, Calif.). The area under the plasma concentration-time curve from 0 to the last sampling time (9 hours post-dosing) [AUC_{0-9}] were determined at steady state and calculated according to the linear up/log down trapezoidal rule (WinNonLin, Pharsight, CA). The maximum concentration observed in plasma (C_{max}), the observed predose concentration (C_{trough} or C_{0}) and the time of C_{max} (T_{max}) were obtained from the plasma concentration-time curves. For each drug, a 90% confidence interval [90% CI] was constructed for the geometric mean ratio (GMR) (with enfuvirtide/with raltegravir) of C_{0}, C_{max} and AUC_{0,9} and analysed using a bioequivalence approach after log transformation (Statgraphics, version 5.1 Manugistics, Inc. Rockville, Maryland, USA).

Twenty patients were included in this pharmacokinetic study. Baseline characteristics of the 9 patients (8 males) on tipranavir and the 11 patients (9 males) on darunavir, were respectively median age: 47 and 49 years, median CD4: 475 and 252 cells/µL, median duration of antiretroviral therapy: 13 and 13 years, viral load below 50
copies/mL: 89% and 91%, median weight: 60 and 79 kg. All but one patient also received N(t)RTIs in combination with PIs. A single patient in each PI group was on proton pump inhibitors.

The pharmacokinetic parameters calculated for darunavir, tipranavir and ritonavir at periods 1 with enfuvirtide (day 0) and 2 after 24 weeks of raltegravir, are compared in table1. Both tipranavir and darunavir concentrations decreased when enfuvirtide was switched to raltegravir. 90% CI of GMR was lower than the bioequivalence range (0.80-1.25) for most parameters. Ritonavir concentrations were also higher when combined to enfuvirtide, although the decrease observed after the switch to raltegravir was modest with a wide range of the 90% CI.

Darunavir and tipranavir exposure and inter-individual variability were in agreement with previous pharmacokinetic data performed in HIV infected patients (1, 2, 12, 14). After switching from enfuvirtide to raltegravir, concentrations of both protease inhibitors were significantly reduced. Such drug-drug interaction, although unexpected has been observed previously for tipranavir/ritonavir, lopinavir/ritonavir and saquinavir/ritonavir (5, 11). In the RESIST study, it has been reported that patients who were on enfuvirtide-based regimen had higher tipranavir concentrations than those who were not (11). Reasons for observed decrease are presently unknown. An inhibitory effect of enfuvirtide or an inductive effect of raltegravir on CYP3A are unlikely as on one hand, protease inhibitors were co-administered with ritonavir, a very potent CYP3A inhibitor and on the other hand, no inductive effect has ever been reported for raltegravir (7). Effect of enfuvirtide or raltegravir on transporters cannot be ruled out, as there is increasing evidence that protease inhibitors are substrate of ABC or SLC transporters (9, 10, 13). Garvey and collaborators reported that adding
raltegravir to a darunavir/ritonavir/tenofovir/emtricitabine regimen did not affect
darunavir concentration (6) which suggests that enfuvirtide increases protease
inhibitors concentrations. Further studies should be conducted to assess whether
enfuvirtide or raltegravir can affect the activity of such transporters especially those
expressed in enterocytes or hepatocytes. Unfortunately, slow and variable rates of
absorption do not allow comparison of terminal half lives during a 12-h dosing
interval and therefore there is no evidence whether bioavailability, clearance or
possibly volume of distribution of protease inhibitors are impaired by enfuvirtide
and/or raltegravir. Food effect is unlikely since protease inhibitors were taken with a
light meal as a continental breakfast the day of the sampling for pharmacokinetic
study.

Despite this decrease in PIs concentrations following the switch from enfuvirtide to
raltegravir, no virological failure was observed in these patients up to 48 weeks after
the switch, but the study was not powered to really assess the long term virologic
outcomes of this drug interaction (4).

In conclusion, this pharmacokinetic study has shown a small but significant decrease
in tipranavir and darunavir concentrations following a switch from enfuvirtide to
raltegravir. Further studies are needed to explain such interaction and to assess the
long term virologic consequences of this observation.

Acknowledgements

We thank the patients who participated in this sub-study. We thank the departments of
hematology, Emile Muller Hospital, Mulhouse; of Infectious Diseases and
Hematology, Font Pré Hospital, Toulon; of Infectious and Tropical Diseases, Cote de
Nacre Hospital, Caen; of Infectious Diseases, Hotel Dieu Hospital, Nantes; of Internal
1 Medicine, Bicêtre Hospital, Le Kremlin Bicêtre; of Infectious and Tropical Diseases,
2 Saint-Antoine Hospital, Paris and of Internal Medicine, of Infectious Diseases, Saint-
3 Louis Hospital, Paris; France, for inclusion of patients in this study.
References


Panel A

Figure 1

Mean plasma concentrations (and standard deviation) of tipranavir (n=9) (panel A) or darunavir (n=11) (panel B) when combined to enfuvirtide (open diamonds and solid lines) or raltegravir (closed squares and dotted lines).
Table 1: Pharmacokinetics parameters, median and (range) of tipranavir (n=9), darunavir (n=11) and co-administered ritonavir during period 1, when combined to enfuvirtide and period 2, when combined to raltegravir. Parameters were compared by geometric mean ratio (GMR) and 90% confidence interval [90%CI].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1</th>
<th>Period 2</th>
<th>GMR (90% CI)</th>
<th>GMR (90% CI)</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Week 0</td>
<td>Week 0</td>
<td>Week 24</td>
<td>Week 24</td>
<td>Week 24</td>
</tr>
<tr>
<td>C₀ (ng/mL)</td>
<td>42201 (17417 – 109792)</td>
<td>15321 (10740 – 49991)</td>
<td>Tipranavir</td>
<td>0.49 [0.42 – 0.56]</td>
<td>0.76 [0.63 – 0.92]</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>71329 (35837 – 138808)</td>
<td>50501 (30516 – 102642)</td>
<td>0.76 [0.40 – 1.44]</td>
<td>0.73 [0.40 – 1.34]</td>
<td>0.76 [0.44 – 1.34]</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.0 (1.0 - 5.0)</td>
<td>3.0 (2.5 - 5.0)</td>
<td>6728 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
<tr>
<td>AUC₀⁻⁹ (ng.h/mL)</td>
<td>437014 (212973 – 1165190)</td>
<td>330315 (171030 – 706218)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
<tr>
<td>Ritonavir (combined with tipranavir)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₀ (ng/mL)</td>
<td>514 (98 – 2031)</td>
<td>291 (176 – 542)</td>
<td>Ritonavir</td>
<td>0.76 [0.40 – 1.44]</td>
<td>0.73 [0.40 – 1.34]</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1431 (342 – 3234)</td>
<td>1093 (356 – 2033)</td>
<td>0.76 [0.40 – 1.44]</td>
<td>0.73 [0.40 – 1.34]</td>
<td>0.76 [0.44 – 1.34]</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.2 (0.0 – 6.0)</td>
<td>4.5 (0.0 – 5.0)</td>
<td>6728 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
<tr>
<td>AUC₀⁻⁹ (ng.h/mL)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₀ (ng/mL)</td>
<td>7033 (1737 – 15237)</td>
<td>4641 (1905 – 13351)</td>
<td>Darunavir</td>
<td>0.82 [0.61 – 1.10]</td>
<td>0.68 [0.59 – 0.79]</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10699 (8412 – 16995)</td>
<td>7369 (4629 – 13351)</td>
<td>0.82 [0.61 – 1.10]</td>
<td>0.68 [0.59 – 0.79]</td>
<td>0.64 [0.53 – 0.77]</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.0 (1.0 – 5.1)</td>
<td>1.4 (0.0 – 8.3)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
<tr>
<td>AUC₀⁻⁹ (ng.h/mL)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>62094 (1708 – 14412)</td>
<td>4687 (1580 – 11070)</td>
<td>0.78 [0.59 – 1.02]</td>
</tr>
</tbody>
</table>