

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Pharmacokinetics of 400 mg of raltegravir once daily in combination with atazanavir/ritonavir plus two nucleoside/nucleotide reverse transcriptase inhibitors.**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/124546> since

*Published version:*

DOI:10.1093/jac/dks413

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

A. Calcagno;M. C. Tettoni;M. Simiele;L. Trentini;C. Montrucchio;A. D'Avolio;G. D. Perri;S. Bonora. Pharmacokinetics of 400 mg of raltegravir once daily in combination with atazanavir/ritonavir plus two nucleoside/nucleotide reverse transcriptase inhibitors.. JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY. 68 (2) pp: 482-484.  
DOI: 10.1093/jac/dks413

The publisher's version is available at:

<http://www.jac.oxfordjournals.org/cgi/doi/10.1093/jac/dks413>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/124546>

**Pharmacokinetics of 400 mg of raltegravir once daily in combination with atazanavir/ritonavir plus two nucleoside/nucleotide reverse transcriptase inhibitors**

A. Calcagno<sup>1,\*</sup>, M. C. Tettoni<sup>1</sup>, M. Simiele<sup>2</sup>, L. Trentini<sup>1</sup>, C. Montrucchio<sup>1</sup>, A. D'Avolio<sup>2</sup>, G. Di Perri<sup>1</sup> and S. Bonora<sup>1</sup>

<sup>1</sup>Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

<sup>2</sup>Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Torino, Torino, Italy

\*Corresponding author. Tel: +390114393884; Fax: +390114393818;

E-mail: [andrea.calcagno@unito.it](mailto:andrea.calcagno@unito.it)

Sir,

Long-term side effects and medication costs are driving research on antiretroviral therapy towards dose-optimization and dose-reduction strategies. Two main factors are supporting this trend: the knowledge that doses lower than those adopted for clinical use are equally effective (as seen in Phase II studies of most antiretrovirals),<sup>1</sup> and the increasing evidence of immunovirological efficacy of simplified regimens consisting of fewer than three drugs, particularly in induction–maintenance strategies. One of the major interests in this setting is to validate regimens devoid of nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs), and several small-sized clinical studies are investigating the efficacy of different N/NtRTI-sparing combinations. The raltegravir and atazanavir dual combination was found to be effective in a comparative study in treatment-naïve patients, but the trial was prematurely stopped following the excess of resistance to raltegravir in those who experienced virological failure.<sup>2</sup> In this study, however, a non-conventional twice-daily unboosted atazanavir dosage was employed (300 mg), possibly resulting in raltegravir monotherapy in case of suboptimal adherence. Based on the results of the dose-finding Phase II study of raltegravir (in which twice-daily doses ranging from 100 to 600 mg were found to be immunovirologically equivalent at 48 weeks),<sup>3</sup> on two small reports of once-daily dosing of 400 mg of raltegravir<sup>4,5</sup> and on the property of atazanavir to increase raltegravir exposure (by UGT1A1 inhibition),<sup>6</sup> we carried out a pilot clinical investigation to evaluate the raltegravir pharmacokinetic profile when administered at 400 mg once daily with boosted atazanavir-based regimens.

Adult HIV-infected patients without severe clinical comorbidities and on successful treatment with atazanavir/ritonavir plus two N/NtRTIs had their regimens intensified for 10 days with 400 mg of raltegravir once daily. The protocol was approved by our local ethics board and each participant gave written informed consent. Serial plasma samples for pharmacokinetic analysis were collected

on day 10 at pre-dose (0 h) and 1.5, 3, 4.5, 6, 8, 12 and 24 h after the morning dose. Plasma concentrations were measured by a validated HPLC-PDA (where PDA is photo diode array) method [limit of detection (LOD) 11 ng/mL].<sup>7</sup> Steady-state pharmacokinetic parameters were derived by non-compartmental analysis using the validated computer program Kinetica and are expressed as medians and interquartile ranges.

The eight patients enrolled were mainly male (7, 87.5%) and middle-aged [48.5 years (48–62)] and their body mass index was 21.8 kg/m<sup>2</sup> (19.3–24.4). HIV RNA was <20 copies/mL in all patients and the CD4 count was 190 cells/ $\mu$ L (86–288); two patients (25%) presented a chronic infection with HCV. Concomitant N/NtRTIs included tenofovir/emtricitabine (five patients) and abacavir/lamivudine (three patients). Plasma creatinine and estimated glomerular filtration rate were 1.01 mg/dL (0.97–1.32) and 69.3 mL/min/24 h (67.7–72.8), respectively. Raltegravir AUC, C<sub>max</sub>, C<sub>24</sub>, half-life and clearance were, respectively, 17 547 ng · h/mL (14 212–33 132), 4200 ng/mL (3885–6655), 51 ng/mL (28–58), 3.4 h (2.8–4.5) and 23.2 L/h (12.1–28.1) (Figure 1). Raltegravir pre-dose and C<sub>24</sub> were below the LOD in one patient. Atazanavir AUC, C<sub>max</sub>, C<sub>24</sub>, half-life and clearance were, respectively, 26 414 ng · h/mL (23 679–46 799), 2625 ng/mL (1920–3904), 526 ng/mL (355–908), 10.6 h (9.0–13.0) and 11.3 L/h (7.3–12.7). Ritonavir AUC, C<sub>max</sub>, C<sub>24</sub>, half-life and clearance were, respectively, 11 873 ng · h/mL (8373–20 727), 1205 ng/mL (1053–1910), 99 ng/mL (54–166), 5.6 h (4.8–6.3) and 8.7 L/h (4.8–11.9).

With the limitation of a single-arm protocol, this pilot study shows that half-dose raltegravir exposure, when combined with atazanavir/ritonavir, seems to be adequate in the majority of patients, with just one trough concentration (out of 16 measurements considering both C<sub>0</sub> and C<sub>24</sub>) reported to be below the 95% inhibitory concentration for the wild-type virus. Although C<sub>max</sub> appeared to be slightly higher and C<sub>24</sub> slightly lower than the historical data with the twice-daily dosing (2170 versus 4200 ng/mL and 68.6 versus 51 ng/mL, respectively), plasma exposure of

400 mg of raltegravir once daily in our study was equivalent to 800 mg once-daily dosing without atazanavir or standard 400 mg twice-daily dosing. Specifically, the raltegravir AUC<sub>0–24</sub> of our patients was similar to the AUC<sub>0–24</sub> of the 800 mg once-daily dosage in the QDMARK study (14 895 ng·h/mL) and 2-fold higher than the reported AUC<sub>0–12</sub> values with standard 400 mg twice-daily dosage (6340–6910 ng · h/mL).<sup>8,9</sup> It must be noted that in the QDMARK study the difference in the virological response between the two arms (raltegravir once daily versus twice daily) was seen only in those who started with a baseline viraemia >100 000 copies/mL, in association with a C<sub>trough</sub> <33 nM (15 ng/mL).<sup>2</sup> Neely et al.<sup>10</sup> previously described lower raltegravir exposure when associated with atazanavir as compared with our results, but different dosing (unboosted versus boosted atazanavir) and study design (healthy volunteers versus patients) could explain these differences. Atazanavir concentrations were comparable to historical data and C<sub>trough</sub> values were above the target level (150 ng/mL) in all patients. On a presumptive basis, the pharmacokinetic exposure of the raltegravir dose of 400 mg once daily seen in our patients in association with atazanavir/ritonavir might be sufficient to provide adequate antiretroviral coverage in an induction–maintenance strategy; should this drug combination prove to be successful in a clinical study, it would enable a reduction in both N/NtRTI-related toxicity and drug expenditure.

## Funding

This work was funded by internal funding.

## Transparency declarations

A. C. has received travel grants or speaker's honoraria from Abbott, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD) and Janssen-Cilag. G. D. P. has received grants, travel grants and consultancy fees from Abbott, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, MSD, Pfizer, Roche and Tibotec (Johnson & Johnson). S. B. has received grants, travel grants and consultancy fees from Abbott, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, MSD, Pfizer and Janssen-Cilag.

All other authors: none to declare.

## Acknowledgements

The data in this manuscript were presented at the Thirteenth International Workshop on Clinical Pharmacology of HIV Treatment (IWCPHT), Barcelona, Spain, 2012 (Poster P\_05).

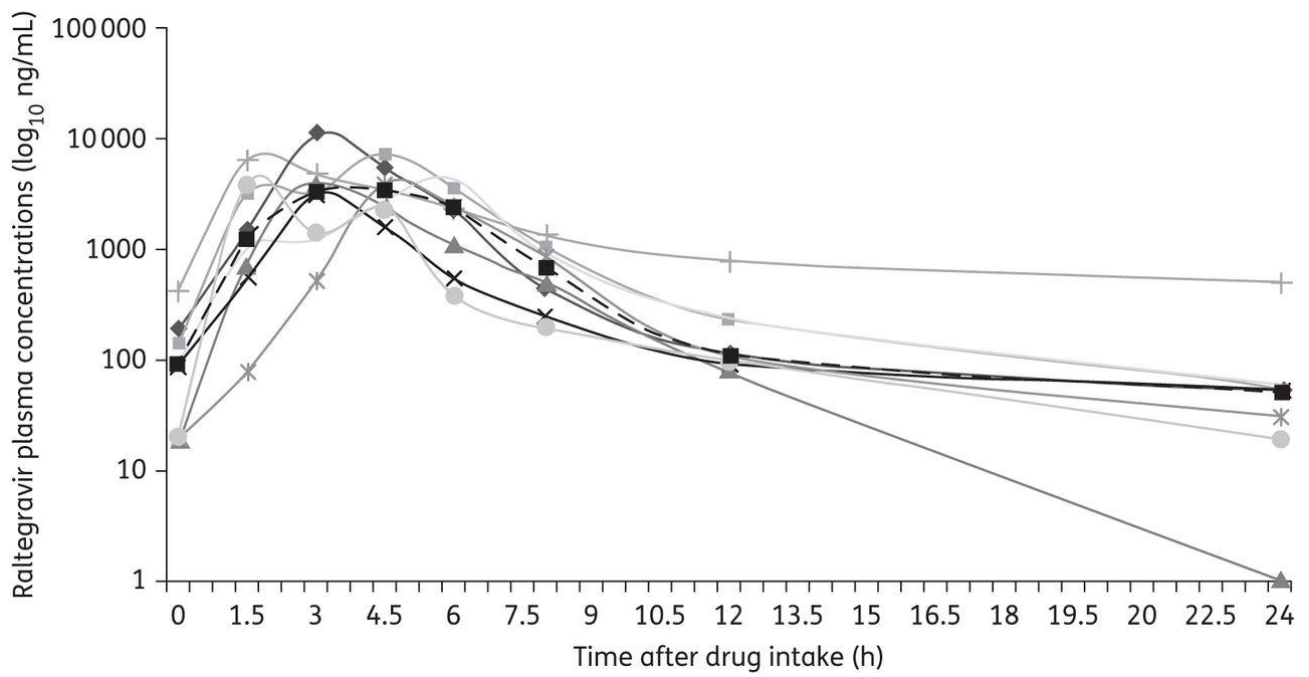
We would like to thank the study participants and to acknowledge the great help by the nurses that allowed sample collection and processing.

## References

1. Gorowara M, Burger D, Hill A, et al. Pharmacokinetics of low-dose protease inhibitors and efavirenz in low- and middle-income countries. *Curr Opin HIV AIDS* 2010;5:90-6.
2. Kozal MJ, Lupo S, DeJesus E, et al. A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naïve HIV-infected patients: SPARTAN study results. *HIV Clin Trials* 2012;13:119-30.
3. Markowitz M, Nguyen B, Gotuzzo E, et al. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007;46:125-33.
4. Lanzafame M, Hill A, Lattuada E, et al. Raltegravir: is a 400 mg once-daily dose enough? *J Antimicrob Chemother* 2010;65:595-7.
5. Ananworanich J, Gorowara M, Avihingsanon A, et al. Pharmacokinetics of and short-term virologic response to low-dose 400-milligram once-daily raltegravir maintenance therapy. *Antimicrob Agents Chemother* 2012;56:1892-8.
6. Cattaneo D, Ripamonti D, Baldelli S, et al. Exposure-related effects of atazanavir on the pharmacokinetics of raltegravir in HIV-1-infected patients. *Ther Drug Monit* 2010;32:782-6.
7. D'Avolio A, Baietto L, Siccardi M, et al. An HPLC-PDA method for the simultaneous quantification of the HIV integrase inhibitor raltegravir, the new non nucleoside reverse transcriptase inhibitor etravirine, and 11 other antiretroviral agents in the plasma of HIV-infected patients. *Ther Drug Monit* 2008;30:662-9.
8. Rizk ML, Hang Y, Luo WL, et al. Pharmacokinetics and pharmacodynamics of once-daily versus twice-daily raltegravir in treatment-naive HIV-infected patients. *Antimicrob Agents Chemother* 2012;56:3101-6.



9. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naïve HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2006;43:509-15.
10. Neely M, Decosterd L, Fayet A, et al. Pharmacokinetics and pharmacogenomics of once-daily raltegravir and atazanavir in healthy volunteers. *Antimicrob Agents Chemother* 2010;54:4619-25.



**Figure 1.**

Raltegravir log<sub>10</sub>-transformed concentrations (log<sub>10</sub> ng/mL) according to time post-dose (h) when administered as 400 mg once daily in association with atazanavir/ritonavir/two N/NtRTIs. Every continuous line represents a single patient profile while the broken line is the median of the studied population.