

# A nucleoside-sparing regimen of dolutegravir plus ritonavir-boosted atazanavir in HIV-1-infected patients with virological failure: the DOLATAV study

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## Introduction

The increased exposure of dolutegravir (DTG) when given with atazanavir/ritonavir (ATV/r), as well as the acceptable safety profile, may suggest the use of this combination as a two-drug regimen both in virologically suppressed and treatment-failing subjects.<sup>1-5</sup>

This nucleoside reverse transcriptase inhibitors (NRTIs)-sparing regimen, characterized by a high genetic barrier, may represent an option in patients who have failed previous regimens and developed pharmacoresistance mutations to NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

However, no data on DTG plus boosted ATV in patients with virological failure are currently available.

Therefore, the aim of the DOLATAV study was to investigate the efficacy, safety, and pharmacokinetics of ATV/r 300/100 mg once-daily plus DTG 50 mg once-daily in treatment-failing HIV-1-infected patients.

## Methods

DOLATAV is a prospective, single-arm, monocentric, open label, pilot study (NCT02542852). It was approved by the Ethics Committee of the San Raffaele Scientific Institute, conducted in accordance with the Declaration of Helsinki, and all participants in it signed the study's informed consent at screening. The study was conducted on HIV-infected subjects with virological failure, defined as two consecutive viral loads  $\geq 200$  copies/mL, without a history of ATV failure and ATV resistance and without any exposure to integrase strand transfer inhibitors.

Patients were assessed at screening, baseline (ATV/r plus DTG initiation), day 8, weeks 4, 8, 12, 16, and 24 (or study discontinuation).

Treatment failure was defined as virological failure (confirmed rebound in plasma HIV-RNA levels  $\geq 50$  copies/mL after prior confirmed suppression to  $< 50$  copies/mL or a plasma HIV-1 RNA level  $\geq 50$  copies/mL at week 24) or study discontinuation for any reason.  $C_{\text{trough}}$  of ATV and DTG were evaluated at each time-point after baseline by sensitive liquid chromatography tandem mass spectrometry.

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Results were described as median (IQR) or frequency (%). The ANOVA for repeated measures was used to evaluate differences in laboratory parameters over time. Significant changes at each time-point were assessed by the Wilcoxon signed-rank test; the Bonferroni correction was applied.

## Results

We screened 16 subjects (5 screening failures for HIV-RNA <200 copies/mL, 1 withdrawal of consent) and enrolled 10 participants with a median age of 47 (42–50) years. Patients had a known HIV infection of 14.4 (11.7–28.9) years and 10.7 (5.1–18.0) years of antiretroviral therapy exposure. Sixty percent of patients were on a failing boosted protease inhibitor (PI)-based regimen and 40% on a NNRTIs-based treatment; HIV-RNA was 2.77 (2.09–2.98) log<sub>10</sub> copies/mL at baseline. In addition, 80% of the patients had NRTIs or NNRTIs mutations and one subject showed archived PIs mutations at HIV genotype screening (Table 1).

At week 24, the proportion of virological efficacy (HIV-RNA <50 copies/mL) was 100% and the corresponding 95%CI extended from 68% to 100%, in both the intention-to-treat and on-treatment analyses. None of the enrolled participants discontinued the treatment regimen.

Six clinical adverse events (AEs) occurred in five participants: three subjects experienced a drug-related clinical event (scleral jaundice) of grade 2 (one participant) or grade 1 (two participants); three participants had non-drug related AEs (a grade-1 pharyngitis, a grade-2 subcutaneous abscess and a grade-2 accidental nasal fracture). No clinical event was serious and no neuropsychiatric events were reported.

A significant increase of total bilirubin (+1.97 mg/dL [+0.77; +3.44];  $P=0.004$ ) and a marginally significant decline in eGFR (–9.5 mL/min/1.73 m<sup>2</sup> [–16; –2];  $P=0.084$ ) were observed during the treatment with DTG plus ATV/r.

No significant variations during follow-up were found in immunological, hepatic and hematological parameters or lipid and glucose levels.

ATV and DTG plasma concentrations were stable during follow-up as shown in Table 2.

## Discussion and conclusion

To our knowledge, our study investigated for the first time the association of DTG plus ATV/r as rescue therapy in patients with virological failure. However, our trial has several limitations, such as the monocentric and single arm design of the study. In addition, given the small number of participants, mainly due to the low number of observed virological failures in our cohort during the enrollment period, another clear limitation of this study is the low statistical power.

In conclusion, this pilot study showed that in HIV-infected subjects with virological failure, a long antiretroviral therapy exposure and resistance to NRTIs and NNRTIs, a dual regimen with DTG plus ATV/r may represent a novel and well-tolerated therapeutic option with excellent efficacy and a high genetic barrier.

## Data sharing statement

Individual participant data that underlie the results reported in this article, after de-identification (text and tables) will be shared with researchers who provide a proposal, beginning

**Table 1** Patients' HIV drug resistance profile at the start of the ATV/r + DTG treatment

Patient	HIV subtype	PIs resistance mutations	NRTIs resistance mutations	NNRTIs resistance mutation	INSTIs resistance mutations
001	B	None	M184MV	K103KN	None
002	B	None	None	None	None
003	B	None	L210W, T215D	Y181C	None
004	B	I54V, V82A	M41L, M184V, T215Y	None	None
005	B	None	None	None	None
006	B	None	L74V, M184V	K103N, V108I, E138A, P225H	None
007	B	None	K70R	E138G	None
008	B	None	M184IV	K103N, Y181C	None
009	B	None	None	E138A	None
010	B	None	M184I	E138K	None

**Abbreviations:** ATV/r, atazanavir/ritonavir; DTG, dolutegravir; PIs, protease inhibitors; NRTIs, nucleotide reverse transcriptase inhibitors; NNRTIs, non-nucleotide reverse transcriptase inhibitors; INSTIs, integrase strand transfer inhibitors.

**Table 2** Atazanavir and dolutegravir C<sub>trough</sub> during follow-up

	Day 8	Week 4	Week 8	Week 12	Week 16	Week 24	P-value <sup>a</sup>
DTG (ng/mL)	2,989 (2,059–5,451)	4,156 (3,135–6,138)	3,971 (3,577–5,259)	3,915 (3,435–4,823)	3,379 (2,882–6,074)	3,721 (3,279–4,929)	0.706
Change <sup>b</sup> in DTG C <sub>trough</sub> (ng/mL)	–	–	922 (–291; 1,117)	–36 (–333; 1,833)	–21 (–576; 219)	–183 (–922; 73)	0.969
ATV (ng/mL)	467 (299–752)	753 (188–1,360)	584 (419–667)	443 (399–1,541)	798 (424–1,112)	802 (307–1,060)	0.174
Change <sup>b</sup> in ATV C <sub>trough</sub> (ng/mL)	–	–	–184 (–488; 154)	–188 (–369; 76)	–12 (–187; 255)	51 (–273; 192)	0.334

**Notes:** Results are reported as median (quartiles). <sup>a</sup>By univariate mixed-linear regression model. <sup>b</sup>Changes were calculated since week 4 and subsequent time-points.

**Abbreviations:** ATV, atazanavir; DTG, dolutegravir.

3 months and ending 5 years after article publication. Proposals may include individual participant data meta-analysis and should be directed to [spagnuolo.vincenzo@hsr.it](mailto:spagnuolo.vincenzo@hsr.it) to get access to the data. The study protocol and the statistical analysis plan are available at <https://clinicaltrials.gov/ct2/show/NCT02542852>.

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## Author contributions

VS conceived the study, followed the patients and wrote the first draft of the manuscript; AC conceived the study and reviewed and edited the manuscript; LG and AP performed statistical analyses and reviewed and edited the manuscript; DF and ML performed pharmacokinetic analyses and reviewed and edited the manuscript; AB, NG, SN, LF, and AL followed the patients and reviewed and edited the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

AC, AL, SN, and NG have received consultancy payments and speaking fee from Bristol–Myers Squibb, Gilead, ViiV Healthcare, Merck Sharp Dohme, Janssen. VS has received consultancy payments and speaking fee from Gilead, ViiV Healthcare and Janssen-Cilag. The authors report no other conflicts of interest in this work.

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