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SHORT COMMUNICATION

Monotherapy with darunavir/ritonavir or lopinavir/ritonavir versus standard antiretroviral therapy: a randomized clinical trial (2pm Study)

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SUMMARY

In a multicentre, open-label, clinical trial, 43 patients virologically suppressed while receiving a standard triple antiretroviral therapy were randomized (1:1:1) to switch to monotherapy with darunavir/ritonavir (DRV/r-MT arm), monotherapy with lopinavir/ritonavir (LPV/r-MT arm) or to continue on the ongoing regimen (cART arm). The proportion (95% CI) of patients with virological success (Snapshot analysis) at week 48 was 73% (48%-90%) in the DRV/r-MT arm, 69% (42%-88%) in the LPV/r-MT arm and 87% (61%-98%) in the cART arm. Virological failure was detected in only one patient receiving LPV/r-MT. The LPV/r-MT arm showed a modest worsening in lipid profile.

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Italian guidelines consider boosted-protease inhibitor-based monotherapy (PI/r-MT) with darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r) a possible alternative to standard combination antiretroviral therapy (cART) in case of drug toxicity due to nucleoside reverse transcriptase inhibitors (NRTIs) in patients with a nadir CD4+ T-lymphocyte count of >200 cells/μL, already in treatment with PIs, with no clinical history of virological failure during PI treatment, no evidence of mutation conferring resistance to PIs and plasma HIV-RNA <50 copies/mL for at least 12 months (Antinori *et al.,* 2016).

PI/r-MT has been tested in different randomized studies showing that the switch is safe in subjects with undetectable viral load in the large majority of cases. These studies have also demonstrated that in case of failure there were no PI drug-resistance mutations and re-introduction of triple therapy was successful (Cameron *et al.,* 2008; Arribas *et al.,* 2009, Katlama *et al.,* 2010, Arribas *et al.,* 2012, Gianotti *et al.,* 2014, Castagna *et al.,* 2014, Paton *et al.,* 2015, Santos *et al.,* 2015, Arribas *et al.,* 2015, Antinori *et al.,* 2016). The largest study conducted on PI/r-MT (PIVOT Study) confirmed that this strategy, with regular viral load monitoring and prompt reintroduction of combination treatment for rebound, preserved future treatment options and did not change overall clinical outcomes (Paton *et al.,* 2015).

However, no published clinical trial randomized patients to an MT with DRV/r or LPV/r and no randomized clinical trial compared DRV/r-MT with LPV/r-MT.

The primary objective of the present study (2pm Study) was to demonstrate the virological non-inferiority of two different PI/r-MT regimens (DRV/r-MT and LPV/r-MT) versus continuing ongoing cART in virologically suppressed (HIV-RNA <50 copies/mL) HIV-infected patients.

Due to the slow recruitment rate, enrolment was interrupted after two years. For this reason the non-inferiority of the two MT regimens versus standard antiretroviral therapy could not be assessed. Here we describe the virological and safety outcomes of the patients enrolled in the study.

The 2pm Study was a multi-centre, open label, non-inferiority, randomized clinical trial. Patients were recruited from 10 Italian centers. The study protocol was approved by each local Ethical Committee and all patients gave their written informed consent. The study was supported in part by a grant from the Italian National Health Ministry (RF-2009-1526102).

Key words:
Antiretroviral therapy, HIV PI/r monotherapy, Darunavir/ritonavir; Lopinavir/ritonavir, Randomized clinical trial

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HIV-infected adults receiving cART, virologically suppressed (HIV-RNA <50 copies/mL since at least 48 weeks), with current CD4+ T-lymphocyte count of >200 cells/μL and a nadir CD4+ T-lymphocyte count of >100 cells/μL were included in the study.

Main exclusion criteria were the detection at any time of any DRV-resistance mutations (11I, 32I, 33F, 47V, 50V, 54L/M, 74P, 76V, 84V, 89V) or any LPV-resistance mutations (according to IAS classification: 32I, 33F, 46I/L, 47A/V, 50V, 54A/L/M/S/T/V, 76V, 82A/F/S/T, 84V, 90M), previous virological failure (at least 2 consecutive HIV RNA >50 copies/mL) while receiving a PI, Child-Pugh B or C liver cirrhosis, ongoing acute hepatitis, evidence of active HBV infection (HBsAg positive), pregnancy (ongoing or planned in the next 48 weeks) and breast-feeding women, ongoing AIDS defining events and malignancies requiring chemotherapy or radiotherapy.

Randomized patients were followed-up with standard clinical and laboratory monitoring (HIV viral load, CD4+ and CD8+ T-lymphocytes counts, full blood cells counts, liver function tests, creatinine and estimated glomerular filtration rate [eGFR], calcium and phosphate, fasting glucose and lipid profile) at the following time-points: baseline, weeks 4, 12, 24, 36, and 48.

All laboratory tests, including HIV viral load, were performed at the reference laboratory of each participating centre according to local procedures. All these laboratories measured HIV viral load through an assay with a detection limit of at least 50 HIV-RNA copies/mL. Glomerular filtration rate was estimated by the CKD-EPI formula (Levey *et al.,* 2009).

The description of the enrolled subjects' characteristics is provided by use of the median and quartiles (Q1; Q3) or frequency (%). Kruskal-Wallis test or Chi-square or Fisher exact test, as appropriate, were applied to compare patients' characteristics.

Virological outcome was assessed by the Snapshot algorithm: an HIV-RNA <50 copies/mL at week 48 in a patient still taking the randomized treatment was defined as virological success; an HIV-RNA >50 copies/mL at week 48 or a missing HIV-RNA value at week 48 or discontinuation of the randomized treatment before or at week 48 was defined as failure (a week 44-54 window was used to determine the 48-week outcome).

A confirmed virological rebound was defined as the occurrence of two consecutive HIV-RNA values >50 copies/mL.

The analyses on the laboratory changes at week 48 from baseline were performed following the intention-to-treat (ITT) principle and used the LOCF technique (last observation carried forward). The ITT population consisted of all the randomized subjects who received at least one day of the study treatment.

The 48-week changes from baseline in CD4+ cell count, CD4+/CD8+ ratio and the other laboratory parameters were evaluated and assessed for significance using the Wilcoxon signed rank test.

All analyses were conducted using SAS statistical software version 9.2 (Statistical Analyses System Inc, Cary, NC, USA).

Forty-five patients were screened between June 2013 and July 2014; two patients did not meet eligibility criteria and were not randomized; 43 were randomized, 15 to simplify therapy with an MT of DRV/r 800 mg/100 mg once daily (DRV/r-MT arm), 13 patients to simplify therapy with a MT with LPV/r 400mg/100mg twice daily (LPV/r-MT arm) and 15 patients to continue on the ongoing cART regimen (cART arm).

The 43 randomized patients (77% males) were 46 (41; 53) years old and had a nadir and current CD4+ T-lymphocyte count of 277 (170; 327) and 688 (507; 826) cells/μL, respectively. Other baseline characteristics are shown in *Table 1*. No significant differences in demographic and clinical characteristics were observed among the three groups.

In the DRV/r-MT arm, two (13%) patients discontinued (one for pregnancy at week 4 and one withdrew consent at week 36); none had confirmed virological rebound. In the LPV/r-MT arm, three (23%) patients discontinued (all discontinuations because of patient's will, two at week 0 and one at week 24); one (8%) patient showed virological failure (HIV-RNA=362 copies/mL at week 48, but an HIV-RNA value of 2480 copies/mL was already detected at week 24 and it was followed by an undetectable viral load at week 36; no HIV-resistance testing was available). In the cART arm, two (13%) patients discontinued (one for an adverse event [dyslipidemia] and one at week 36 for patient's will); none had confirmed virological rebound.

The proportion of patients with virological success (95% CI by modified Wald method) was 73% (95% CI: 48% to 90%) in the DRV/r-MT arm, 69% (95% CI: 42% to 88%) in the LPV/r-MT arm and 87% (95% CI: 61% to 98%) in the cART arm. *Figure 1* shows the virological outcome at 48 weeks in the three study arms according to the Snapshot algorithm.

During 48-weeks of follow-up, seven clinical drug-related adverse events occurred in six patients: hypercholesterolemia in five cases (one in the DRV/r-MT arm, one in the LPV/r-MT arm and three in the cART arm), nausea in one patient in the LPV/r-MT arm and diarrhea in one patient in the cART arm. The only serious adverse event which occurred during the study period was a case of pregnancy in the DRV/r-MT arm.

In the DRV/r-MT arm, one (6.7%) patient had a grade 3 total bilirubin elevation. In the LPV/r-MT arm, one (7.7%) patient had a grade 3 total cholesterol plus a grade 3 low-density lipoprotein (LDL)-cholesterol elevation and one (7.7%) patient had a grade 3 LDL-cholesterol elevation. In the cART arm, one (6.7%) patient had a grade 3 LDL-cholesterol elevation subsequently treated with a statin.

No significant change at week 48 from BL in CD4+ T-lymphocyte counts was observed in any study arm (DRV/r-MT arm: -31 [-117; +51] cells/μL; p=0.542; LPV/r-MT arm: +10 [-11; +63] cells/μL; p=0.320; cART arm: -4 [-61; +172] cells/μL; p=0.639). At week 48, patients randomized to DRV/r-MT had a significant median [Q1; Q3] reduction from BL in CD8+ T-lymphocytes (-60 [-119; +14] cells/μL; p=0.031) and in alkaline phosphatase (ALP; -13 [-25; -3] U/L; p=0.010), patients randomized to LPV/r-MT had a significant increase from BL in total cholesterol (+18 [+16; +33] mg/dL; p=0.004) and LDL-cholesterol (+23 [0; +28] mg/dL; p=0.014), while those randomized to continue ongoing cART had a significant reduction from BL in direct bilirubin (-0.08 [-0.12; -0.02] mg/dL; p=0.029).

Significant differences among study arms were observed in the 48-week change of ALP (DRV/r-MT arm: -13 [-25; -3] U/L; LPV/r-MT arm: -2 [-12; +2] U/L; cART arm: 0 [-6; +10] U/L; p=0.021 by Kruskal-Wallis test). No statistically significant differences among study arms with respect to the 48-week changes of any laboratory parameters.

The results from the present study are generally in line

Table 1 - *Baseline characteristics of the randomized patients, according to study arm.*

	Overall (N=43)	*DRV/r-MT (N=15)*	*LPV/r-MT (N=13)*	*cART (N=15)*	*P-value*
Median age, years (IQR)	46 (41-53)	45 (41-49)	43 (36-51)	48 (43-56)	0.269[b]
Male gender, n (%)	33 (77%)	9 (60%)	11 (85%)	13 (87%)	0.162[a]
Race, n (%)					0.803[a]
Caucasian	37 (86%)	13 (87%)	11 (85%)	13 (87%)	
Other	6 (14%)	2 (13%)	2 (15%)	2 (13%)	
Median BMI, kg/m^2 (IQR)	24.0 (22.3-26.7)	23.0 (21.6-26.6)	24.0 (23.4-25.3)	24.5 (21.5-26.8)	0.895[b]
Median years since HIV diagnosis, (IQR)	11 (7-16)	13 (5-21)	8 (6-15)	9 (7-16)	0.729[b]
HIV risk factor, n (%)					0.714[a]
MSM	13 (30%)	3 (20%)	4 (31%)	6 (40%)	
Heterosexual	19 (44%)	8 (53%)	5 (38%)	6 (40%)	
Other/unknown	11 (26%)	4 (27%)	4 (31%)	3 (20%)	
CDC Stage, n (%)					0.474[a]
A	32 (74%)	12 (80%)	8 (80%)	12 (80%)	
B	4 (9%)	1 (7%)	2 (7%)	1 (7%)	
C	6 (14%)	2 (13%)	2 (13%)	2 (13%)	
PI/r-based cART, n (%)	36 (84%)	13 (87%)	10 (77%)	13 (87%)	0.133[a]
NNRTI-based cART, n (%)	7 (16%)	2 (13%)	3 (23%)	2 (13%)	0.867[a]
TDF-based cART, n (%)	26 (60%)	11 (73%)	8 (62%)	7 (47%)	0.267[a]
Median CD4+ nadir, cells/µL (IQR)	277 (170-327)	251 (169-316)	283 (179-432)	256 (194-300)	0.586[b]
Median CD4+, cells/µL (IQR)	688 (507-826)	587 (482-897)	760 (669-789)	658 (500-826)	0.720[b]
Median CD4+% (IQR)	32.7 (29.5)37.4)	33.4 (26.8-36.0)	33.0 (30.8-39.0)	31.7 (26.3-38.1)	0.330[b]
Median CD8+, cells/µL (IQR)	828 (627-1071)	741 (572-1001)	819 (475-932)	939 (757-1210)	0.403[b]
Median CD8+% (IQR)	42.9 (34.0-47.9)	40.3 (32-49.3)	41.9 (35.0-47.0)	44.2 (34.0-47.9)	0.921[b]
Median CD4+/CD8+ ratio, (IQR)	0.84 (0.62-1.06)	0.83 (0.55-1.06)	0.86 (0.70-1.07)	0.70 (0.54-0.92)	0.338[b]
Median haemoglobin, g/dL (IQR)	14.5 (13.1-15.7)	15.0 (13.1-15.7)	13.8 (13.4-15.9)	14.2 (12.6-15.2)	0.643[b]
Median white blood cells, 10^9 cells/L (IQR)	5.78 (4.76-7.12)	5.78 (4.38-7.68)	5.76 (5.46-7.30)	5.89 (4.76-6.68)	0.904 [b]
Median total lymphocytes, 10^9 cells/L (IQR)	2.18 (1.60-2.38)	2.05 (1.50-2.30)	2.14 (1.60-2.29)	2.21 (1.74-2.50)	0.484[b]
Median neutrophils, 10^9 cells/µL (IQR)	2.95 (2.4-4.1)	2.88 (2.21-4.10)	2.97 (2.58-4.50)	2.94 (2.40-3.69)	0.887[b]
Median Platelets, 10^9 cells/L (IQR)	203 (180-244)	202 (173-247)	214 (180-244)	199 (180-241)	0.827 [b]
Median AST, U/L (IQR)	21 (18-32)	21 (20-40)	25 (18-32)	19 (13-24)	0.142[b]
Median ALT, U/L (IQR)	25 (17-34)	25 (13-33)	25 (19-35)	25 (15-34)	0.770[b]
Median ALP, U/L (IQR)	75 (60-89)	79 (64-94)	69 (54-96)	70 (61-84)	0.559[b]
Median phosphate, mmol/L (IQR)	0.86 (0.75-1.02)	0.84 (0.83-1.05)	0.97 (0.81-1.19)	0.80 (0.74-0.93)	0.322[b]
Median calcium, mmol/L (IQR)	2.34 (2.15-2.45)	2.32 (2.16-2.45)	2.38 (2.21-2.43)	2.32 (2.14-2.50)	0.965[b]
Median creatinine, mg/dL (IQR)	0.85 (0.69-1.00)	0.74 (0.63-0.96)	0.89 (0.76-1.06)	0.89 (0.77-1.00)	0.175[b]
Median total cholesterol, mg/dL (IQR)	197 (178-218)	181 (172-208)	202 (183-218)	198 (191-223)	0.410[b]
Median LDL-cholesterol, mg/dL (IQR)	114 (97-131)	102 (97-123)	110 (96-128)	123 (114-148)	0.402[b]
Median HDL-cholesterol, mg/dL (IQR)	47 (39-54)	48 (41-61)	45 (40-48)	44 (35-55)	0.672[b]
Median triglycerides, mg/dL (IQR)	132 (110-194)	129 (118-152)	128 (83-198)	141 (99-194)	0.796[b]
Median glucose, mg/dL (IQR)	86 (79-95)	86 (77-98)	85 (73-93)	88 (84-96)	0.547 [b]
Median total bilirubin, mg/dL (IQR)	0.70 (0.50-1.17)	0.71 (0.53-1.00)	0.70 (0.30-1.16)	0.63 (0.53-1.75)	0.545[b]
Median direct bilirubin, mg/dL (IQR)	0.20 (0.16-0.35)	0.25 (0.16-0.30)	0.25 (0.11-0.40)	0.20 (0.15-0.35)	0.997[b]

Abbreviations. DRV/r-MT: monotherapy with darunavir/ritonavir; LPV/r-MT: monotherapy with lopinavir/ritonavir; cART: combination antiretroviral therapy; IQR: interquartile range; BMI: body max index; MSM: man who have sex with men; CDC: Centers for Disease Control; PI/r: ritonavir-boosted protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; CD: cluster differentiation; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alcaline phosphatase; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

[a]by Chi-square or Fisher exact test, as appropriate.

[b]by Kruskal-Wallis test.

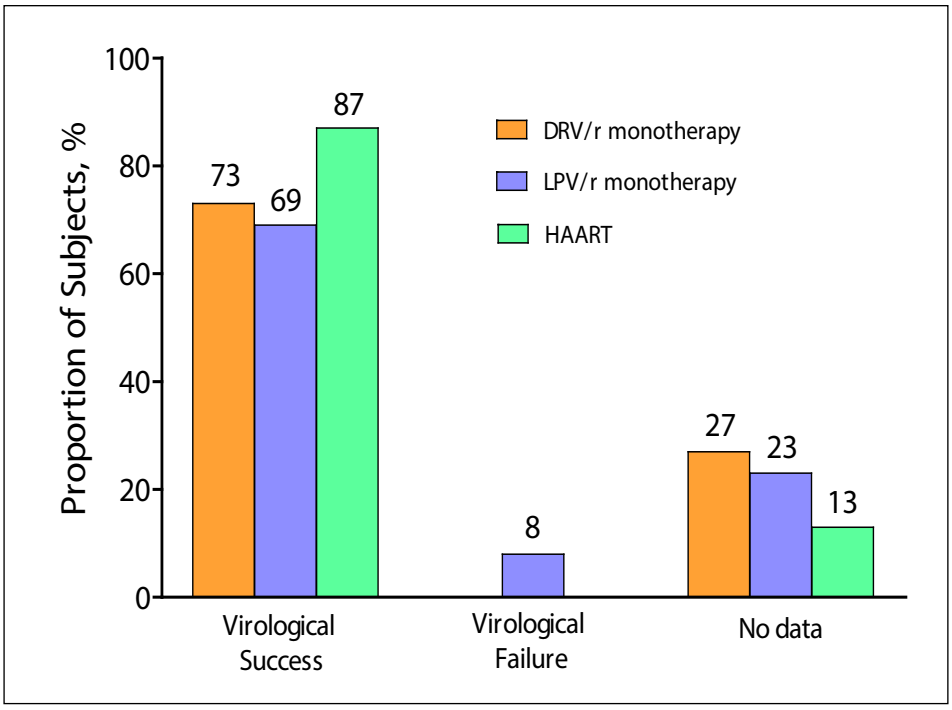

Figure 1 - *Virological outcome at 48 weeks, according to the Snapshot algorithm in the three study arms.*

with those from other larger randomized clinical trials. It is worth noting that only one patient showed virological failure through 48 weeks of observation. This is a reassuring result compared to those from the PIVOT trial (Paton *et al.,* 2015) in which the virological failure rate was 24 per 100 person-years in the first year and, cumulatively, 35% of patients receiving PI/r-MT failed through three years. Furthermore, in the present study most discontinuations were due to patients' will and not caused by drug toxicity or adverse clinical events.

In the PROTEA study, most virological failures and CNS escape occurred in patients with nadir CD4+ T-lymphocyte counts of <200 cells/μL (Antinori *et al.,* 2016); the CD4+ T-lymphocyte nadir was a major determinant of virological failure and CNS escape in patients receiving LPV/r-MT (Gutmann *et al.,* 2010; Pulido *et al.,* 2009). Patients with nadir CD4+ T-lymphocyte counts of <100 cells/μL were excluded from our study. This decision was thus wise and the absence of CNS events in the present study suggests that the recommendations in current Italian guidelines should not be modified.

We had previously studied MT regimens with LPV/r (Hasson *et al.,* 2012; Gianotti *et al.,* 2014) or atazanavir/ritonavir (Castagna *et al.,* 2014): in patients enrolled in these studies we observed an improvement in eGFR, which was ascribed to the removal of tenofovir disoproxil fumarate (TDF) from the ongoing regimen. Similar findings were reported in the PIVOT Study (Paton *et al.,* 2015), but not confirmed in the present study, consistently with results from other clinical trials of DRV/r-MT (Arribas *et al.,* 2012, Antinori *et al.,* 2015b). Altogether, these finding suggest that the impact on eGFR of switching from a TDF-including cART to a PI/r-MT is variable and limited in most patients (Clumeck *et al.,* 2014).

We found a worsening in lipid profile with MT regimens, consistently with what was observed in other studies where TDF was removed from the regimen (Gianotti *et al.,* 2014; Castagna *et al.,* 2014; Mills *et al.,* 2015). It is thought that this phenomenon is the consequence of a "statin-like" effect of TDF (Clumeck *et al.,* 2011).

An unprecedented finding from the present study is the reduction in ALP values in patients treated with DRV/r-MT: this reduction was already observed in patients switched from cART to ATV/r-MT (Castagna *et al.,* 2014) and may suggest a reduction in bone turnover, driven by the removal of TDF. Indeed, discontinuing nucleoside analogues and switching to DRV/r-MT was associated with a small but statistically significant recovery of bone mineral density (Guaraldi *et al.,* 2014; Galli *et al.,* 2016).

Finally, we observed a reduction in CD8+ T-lymphocytes in patients who received an MT regimen with DRV/r, as previously reported in one study of patients receiving MT with boosted or unboosted atazanavir (Cossarini *et al.,* 2012), but not in another (Torres *et al.,* 2014). The clinical impact of this observation, which may suggest a reduction in the patients' inflammatory status, remains to be defined by further investigations.

The major limitation of the present study is the small sample size. However, this was the first clinical trial in which patients were randomized to two PI/r-based MT regimens: these findings are a further contribution to the existing knowledge on efficacy and safety of DRV/r-MT and LPV/r-MT, which was obtained until now only from studies in which these two PI/r-MT regimens were never compared simultaneously to cART.

In conclusion, in this randomized clinical trial of DRV/r-MT or LPV/r-MT versus continuing ongoing cART, virological failure was observed in only one patient receiving LPV/r-MT, suggesting that a strategy of PI/r-MT can be suitable for patients suffering from NRTI toxicity.

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