Monotherapy with lopinavir/ritonavir versus standard of care in HIV-infected patients virologically suppressed while on treatment with protease inhibitor-based regimens: results from the MoLo Study

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SUMMARY

This study compared the cost-efficacy ratios of lopinavir/ritonavir monotherapy (LPV/r-MT) and of standard of care in virologically suppressed HIV-infected patients. The results of the efficacy and safety analyses are presented.
We conducted a multicentre, randomised, open-label trial of HIV-infected adults on stable treatment, with HIV-RNA <50 copies/mL, randomised to continue the ongoing regimen (cART-arm) or to switch to LPV/r (400/100 mg BID) MT (MT-arm). Time to virological rebound (VR = confirmed HIV-RNA ≥50 copies/mL) was estimated by Kaplan-Meier method and changes in laboratory values during follow-up were evaluated by univariate mixed-linear models.
Ninety-four patients were randomised and analysed (43 in the MT-arm and 51 in the cART-arm). Five (four in the MT and 1 in the cART-arm; p=0.175) had VR, but time to VR did not statistically differ between the two arms (p=0.143). Major PI mutations were not detected at VR. Patients on MT had significant increases in total cholesterol [difference in mean change between MT and cART arm: 0.77 (±0.30) mg/dL per month; p=0.012] and eGFR [difference in mean change between MT and cART arm: 0.24 (±0.11) mL/min/1.73 m^2 per month; p=0.029].
LPV/r-MT seems safe in most patients and should be considered in patients who have developed kidney toxicity from tenofovir.

KEY WORDS: HIV, Monotherapy, Lopinavir/ritonavir, Protease inhibitor, Randomized clinical trial, eGFR.

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INTRODUCTION

Strategies to simplify HIV treatment were conceived when the initial enthusiasm over highly active antiretroviral therapy (cART) was tem-

pered by concerns about adverse effects such as lipodystrophy and cardiovascular complications, the challenge of lifelong adherence, and HIV multidrug resistance. Mitochondrial toxicity is the main cause of body changes (lipodystrophy) occurring in HIV-infected patients chronically treated with some NRTIs (thymidine analogues, in particular) (Moyle *et al.,* 2006; Podzamczer *et al.,* 2007; Cameron *et al.,* 2008; Riddler *et al.,* 2008; Fisher *et al.,* 2009). In the past years, this led to a progressive switch from thymidine analogues to nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir (ABC) and tenofovir (TDF) deemed to cause less mitochondrial toxicity (Moyle *et al.,* 2006; Podzamczer *et al.,* 2007; Fisher *et al.,* 2009). However, exposure to ABC was then associated with a higher risk of cardiovascular events (D:A:D Study Group *et al.,* 2008; Strategies for Management of Anti-Retroviral Therapy/INSIGHT, DAD Study Groups, 2008; Lang *et al.,* 2010; Durand *et al.,* 2011). On the other hand, the use of TDF was associated with kidney damage (Mocroft *et al.,* 2007; Labarga *et al.,* 2009; Post *et al.,* 2010; Horberg *et al.,* 2010) and a reduction in bone mass density (Lang *et al.,* 2010; Gallant *et al.,* 2004; Stellbrink *et al.,* 2010; McComsey *et al.,* 2011; Tordato *et al.,* 2011), both potentially irreversible (McComsey *et al.,* 2011; Wever *et al.,* 2010; Sax *et al.,* 2011; Scherzer *et al.,* 2012). Maintenance strategies with boosted-protease inhibitors (PIs/r) monotherapy (MT) might have the advantage of sparing NRTIs toxicity.

A PI/r MT strategy with lopinavir/ritonavir (LPV/r) or darunavir/ritonavir (DRV/r) has been investigated previously in randomized clinical trials (Pulido *et al.,* 2008; Gutmann *et al.,* 2010; Katlama *et al.,* 2010; Clumeck *et al.,* 2011). Altogether, the results of these trials showed that

1) MT expose patients to a small additional risk of virological failure with low-level viraemia;
2) at virological rebound (VR), HIV variants resistant to PIs are usually not selected;
3) once NRTIs are reintroduced in the regimen, virological suppression below 50 HIV-RNA copies/mL can be easily obtained in most cases in a few weeks.

As a consequence, the risk of losing future treatment options with PI/r MT seems minimal. In one small study, however, patients with low nadir CD4+ cell counts treated with LPV/r MT showed a higher risk of symptomatic viral escape at central nervous system, which reversed after the reintroduction of NRTIs (Gutmann *et al.,* 2010). We compared the efficacy and safety of a LPV/r MT with that of the cART in HIV-infected patients virologically suppressed while receiving LPV/r with two NRTIs.

METHODS

The Monotherapy in Lombardy (MoLo) Study was designed as a 144-week, multicentre, randomized, phase 3b, open-label trial.

Patients were recruited in 11 Italian centres; the study protocol was approved by each local Ethical Committee and patients gave their written informed consent. The study was promoted by the Lombardy section of the Italian Society of Infectious and Tropical Diseases (SIMIT) and by the Health Service of the Lombardy Region. The Lombardy Region (the Institution paying for antiretroviral drugs prescribed and delivered throughout the whole Region) supported the study by reimbursing LPV/r MT (which, being an off-label regimen, should have been not reimbursable according to the Italian law).

HIV-infected patients were enrolled if they were at least 18 years old, on stable treatment with a PI and two NRTIs for at least six months, had plasma HIV-RNA <50 copies/mL for at least six months, and CD4+ count of >350 cells/μL. Exclusion criteria were pregnancy or breast-feeding, a positive HBsAg, a nadir CD4+ count of <100 cells/μL, previous failure(s) of PI-including regimens (defined HIV-RNA >50 copies/mL in two consecutive samples drawn at least two weeks apart), presence in the historical genotypic resistance test(s) of one or more of the following mutations: 32I, 33F, 46I/L, 47A/V, 50V, 54A/L/M/S/T/V, 76V, 82A/F/S/T, 84V, 90M.

At baseline, patients were randomised to continue the ongoing PI-based regimen (cART arm) or to switch to LPV/r, 400/100 mg BID (soft-gel capsules until July 2011 and in the Meltrex® formulation thereafter), MT (MT arm); visits and blood samples were then scheduled at week 4, week 12, and every 12 weeks thereafter.

Drug-resistance testing had to be performed in case of confirmed VR. Also, in case of confirmed VR two NRTIs had to be reintroduced in the regimen.
All laboratory tests, including viral load, were performed at the reference laboratory of each participating centre; all these laboratories measured viral load through an assay with a detection limit of at least 50 HIV-RNA copies/mL. Genotypic resistance testing was also performed at each centre, according to local procedures.
Glomerular filtration rate was estimated (eGFR) by the CKD-EPI formula (Levey *et al.*, 2009).

STATISTICAL ANALYSIS

Descriptive data are expressed as median (interquatile range) of frequency (%), as appropriate. Characteristics of patients were compared and tested for statistical significance using the Wilcoxon rank-sum test for continuous and the chi-square or Fisher's exact test for categorical variables.
Viral blips were defined as unconfirmed HIV-RNA measurements ≥50 copies/mL. VR was defined as two consecutive measurements of HIV-RNA ≥50 copies/mL. Treatment failure was defined by a VR or reintroduction of NRTIs (in the MT arm) for any reason, or discontinuation of the study treatment for any reason.
The crude incidence rates of clinical adverse events (overall and drug-related) are expressed per person year of follow-up (PYFU) and were calculated as the total number of episodes divided by cumulative follow-up contributed by all subjects. The incidence rate between the two arms was compared using Poisson regression.
Time to VR and to treatment failure were estimated by Kaplan-Meier curves and compared by the log-rank test.
Univariate mixed-linear models on change of CD4+ cells-count, ALT transaminases, serum triglycerides, eGFR and total and LDL serum cholesterol from BL were applied to identify differences over time and between the MT- and cART arms. Model-based unadjusted mean changes from BL per month were reported with the corresponding standard error (±SE).
All of the statistical tests were two-sided at 5% level, and were performed using SAS Software (release 9.2; SAS Institute).

RESULTS

Ninety-seven patients were randomised (46 in the MT arm and 51 in the cART arm); there were three protocol violations in the MT arm: 94 patients (43 in the MT arm and 51 in the cART arm) were thus eligible for the present analysis; their baseline characteristics are illustrated in table 1.
The median follow-up was 96 (72-144) weeks [96 (72-144) vs. 96 (60-132) weeks in the MT vs. the cART arm; p=0.690] and 24/94 (26%) completed 144 weeks of follow-up at the time of study interruption. Treatment discontinuations occurred in 12 (13%) patients, 8 (19%) in the MT arm and 4 (8%) in the cART arm (p=0.135).
The proportion of patients with VR or treatment failure at each time-point is reported in table 2.
Viral blips (Figure 1, panel A) were not observed with a statistically different frequency in the two arms: 13 (30%) patients in the MT arm vs 8 (16%) patients in the cART arm had at least one viral blip (p=0.135). Five patients (four in the MT arm and 1 in the cART arm) had VR. Viral load at VR was 7047 copies/mL in one case and below 1000 copies/mL in the other four cases; resistance testing was available in only one case (on MT) and showed the 54A and the 184V mutations; this patient first reintroduced NRTI with a transient reduction of viral load to below 50 copies/mL, but then had to change all drugs because of a new VR. In another patient with VR while receiving MT the reintroduction of NRTI was followed by persistent undetectable viral load; in this case, resistance testing at VR was not available due to a very low viral load. The other three patients did not change the ongoing treatment regimen because VR was ascribed to non-compliance and followed by undetectable viraemia.
No statistically significant difference in the probability of VR or of treatment failure was detected between arms (Figure 1, panel B and panel C). Also, we did not observe any significant difference between arms in the change of CD4+ cell counts during follow-up (MT arm

TABLE 1 - *Patients' characteristics at baseline.*

Characteristic	*Overall (n=94)*	*LPV/r-MT (n=43)*	*cART (n=51)*	*p-value*
Age, years, median (IQR)	45 (38-49)	45 (37-50)	45 (38-49)	0.760
Male, n (%)	69 (73%)	33 (77%)	36 (71%)	0.640
HIV risk factor, n (%)				0.719
Drug addiction	15 (16%)	6 (14%)	9 (18%)	
Male who have sex with males	27 (29%)	13 (30%)	14 (27%)	
Heterosexual	34 (36%)	14 (33%)	20 (39%)	
Other	1 (1%)	1 (2%)	0	
Unknown	17 (18%)	9 (21%)	8 (16%)	
Years since HIV infection, median (IQR)	10 (6-17)	11 (6-15)	10 (5-18.5)	0.671
Nadir CD4+ count, cells/μL, median (IQR)	247 (162-310)	248 (169-292)	234 (154-315)	0.733
C CDC stage, n (%)	9 (11%)	3 (9%)	6 (12%)	0.501
Co-infection with HCV, n (%)	32 (34%)	13 (30%)	19 (37%)	0.479
Ongoing regimen, n (%)				0.416
LPV/r + TDF + FTC	60 (64%)	28 (65%)	32 (63%)	
LPV/r + 3TC + ABC	12 (13%)	7 (16%)	5 (10%)	
LPV/r + 3TC + AZT	6 (7%)	2 (5%)	4 (8%)	
FPV/r + 3TC + ABC	3 (3%)	1 (2%)	2 (4%)	
FPV/r + TDF + FTC	3 (3%)	2 (5%)	1 (2%)	
LPV/r + 3TC + ddI	2 (2%)	2 (5%)	0	
LPV/r + TDF + 3TC	2 (2%)	0	2 (4%)	
DRV/r + TDF + FTC	2 (2%)	0	2 (4%)	
Other (used by no more than one patient)	4 (4%)	1 (2%)	3 (6%)	
CD4+ count, cells/μL, median (IQR)	660 (536-874)	653 (561-854)	689 (536-926)	0.747
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2, median (IQR)	103 (90-111)	102 (90-111)	103 (90-110)	0.903
Total cholesterol, mg/dL, median (IQR)	198 (174-222)	201 (183-222)	195 (170-224)	0.557
Low density lipoprotein (LDL)-cholesterol, mg/dL, median (IQR)	120 (99-136)	122 (105-136)	115 (95-135)	0.540
Triglycerides, mg/dL, median (IQR)	154 (100-208)	157 (101-192)	147 (100-210)	0.858
Alanine amino transferase (ALT), U/L, median (IQR)	25 (18-37)	24 (19-33)	28 (18-43)	0.252

LPV/r-MT= monotherapy with lopinavir/ritonavir; cART = combination antiretroviral therapy; r = ritonavir at boosting dose; LPV = lopinavir; TDF = tenofovir; FTC = emtricitabine; 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; FPV = fosamprenavir; ddI = didanosine; DRV = darunavir.

TABLE 2 - *Proportion of patients with viral rebound and treatment failure by week 48, 96 and 144.*

Characteristic	*LPV/r-MT (n=43)*	*cART (n=51)*	*p-value*
Viral rebound by week 48	2.3 (0.1-4.5)	2.0 (0.1-3.8)	0.999
Viral rebound by week 96	4.7 (0.9-6.9)	2.0 (0.1-5.1)	0.510
Viral rebound by week 144	9.3 (3.6-11.5)	2.0 (0.1-6.8)	0.175
Treatment failure by week 48	11.6 (4.9-17.6)	7.8 (2.8-13.5)	0.728
Treatment failure by week 96	20.9 (12.3-27.0)	7.8 (2.7-15.2)	0.079
Treatment failure by week 144	23.3 (14.1-30.2)	9.8 (4.0-17.5)	0.094

LPV/r-MT= monotherapy with lopinavir/ritonavir; cART = combination antiretroviral therapy. Results are reported as % (95% confidence interval).

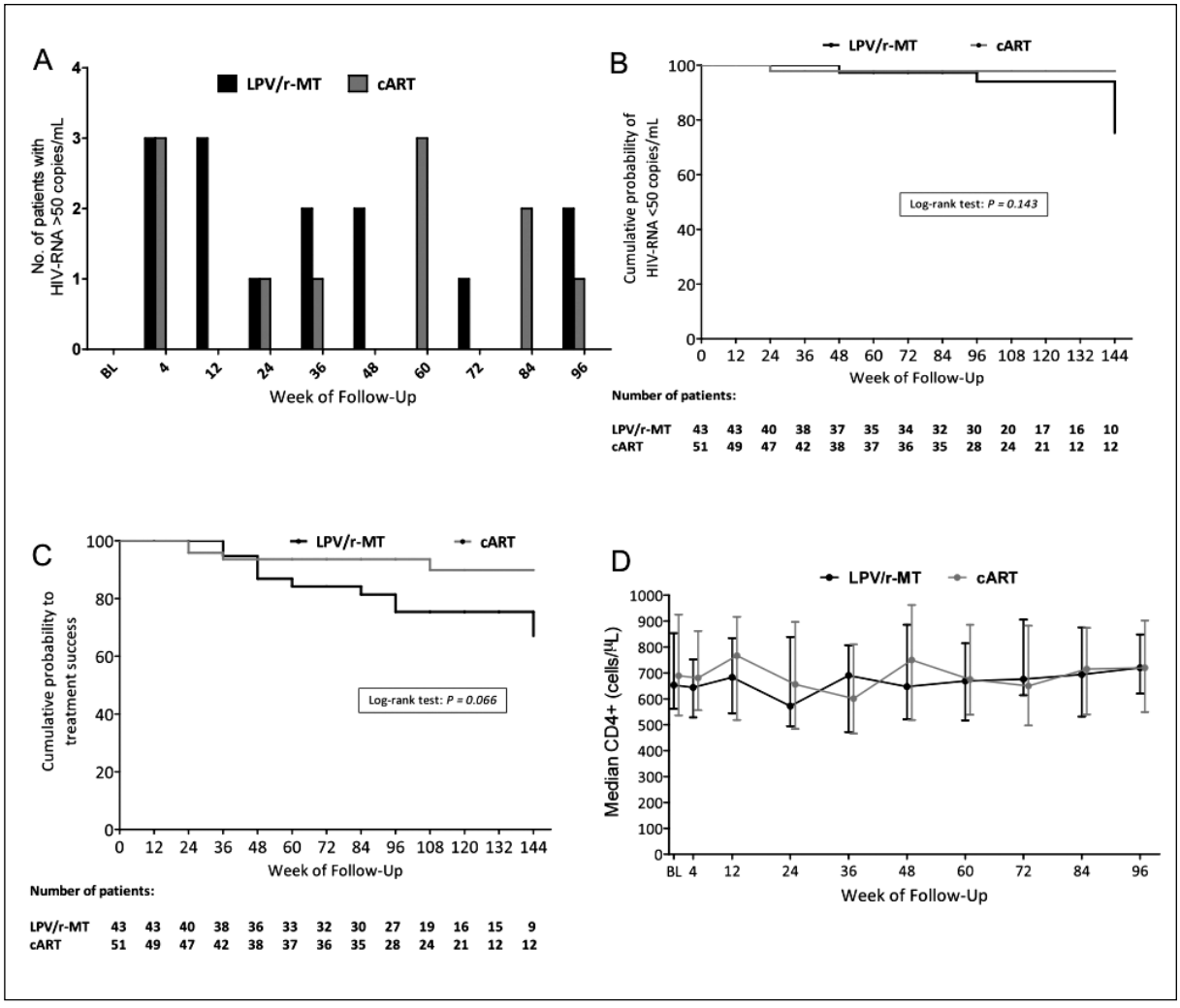

FIGURE 1 - *Virological and immunological outcome; panel A: viral blips; panel B: time to virological rebound; panel C: time to treatment failure; panel D: CD4+ cell counts changes. Monotherapy with lopinavir/ritonavir (LPV/r-MT): black lines; combination antiretroviral therapy (cART): grey lines.*

TABLE 3 - *Patients' disposition at premature study closure and clinical adverse events during follow-up.*

	Overall (n=94)	*LPV/r-MT (n=43)*	*cART (n=51)*	*p-value*
Discontinued for any reason, n (%)	12 (13%)	8 (19%)	4 (8%)	0. 135
Virological rebound, n (%)	5 (5%)	4 (9%)	1 (2%)	0.175
AIDS-defining event, n (%)	1 (1%)	1(2%)	0	0.457
Serious adverse event, n (%)	6 (6%)	3 (7%)	3 (6%)	0.999
IR clinical adverse events (any grade, including serious adverse events)/PYFU, median (IQR)	1.35 (1.18-1.52)	1.48 (1.22-1.75)	1.23 (1.00-1.45)	0.789
IR treatment-related clinical adverse events (any grade)/PYFU, median (IQR)	0.26 (0.19-0.34)	0.24 (0.14-0.35)	0.28 (0.18-0.39)	0.421
Grade 3 total cholesterol, n (%)	5 (5%)	2 (5%)	3 (6%)	0.999
Grade 3 low density lipoprotein (LDL)-cholesterol, n (%)	9 (10%)	5 (12%)	4 (8%)	0.728
Grade 3 triglycerides, n (%)	0	0	0	
Grade 3 creatinine, n (%)	1 (1%)	1 (2%)	0	0.457
Grade 3 alanine amino transferase (ALT), n (%)	3 (3%)	1 (2%)	2 (4%)	0.999

LPV/r-MT= monotherapy with lopinavir/ritonavir; cART = combination antiretroviral therapy; IR = incidence rate.

vs cART arm =0.64 (±1.83) cells/μL per month; p=0.729; figure 1 panel D). However, we observed a significant mean CD4+ change (±SE) per month of 2.19 (±0.29) cells/μL (p=0.013) in the MT arm, but not in the cART arm (1.55 (±0.69) cells/μL; p=0.713).

Serious adverse events (SAEs) occurred in three patients in both arms. All SAEs were hospital admissions; neither was considered treatment-related by the investigators. In the MT arm, causes of admissions were: hepatitis due to isoniazid (started for a recrudescence of lymph nodal tuberculosis), pulmonary embolism (this patient eventually died because of this event), acute respiratory insufficiency; in the cART arm, causes of admission were: removal of cutaneous squamous cell carcinoma, removal of dermal fibro-sarcoma, acute psychosis.

As shown in table 3, the incidence rate of clinical adverse events was 1.48 (1.22-1.75)/PYFU in the MT arm and 1.23 (1.00-1.45)/PYFU in the cART arm (p=0.789); no significant difference between arms was detected with regard to treatment-related adverse events: 0.24 (0.14-0.35)/PYFU in the MT arm vs. 0.28 (0.18-0.39)/PYFU in the cART arm (p=0.421).

Grade 3 laboratory toxicities (none drug-related) were observed in a minority of patients and are also detailed in table 2. Grade 4 laboratory toxicities were never detected during-follow-up. Figure 2 shows total and LDL cholesterol, triglycerides and eGFR values recorded during follow-up. Total cholesterol significantly increased in the MT arm (p=0.001), but not in the cART arm (p=0.597); mean changes between arms were also significantly different (p=0.012). Similarly, LDL-cholesterol significantly increased in the MT arm (p=0.046), but not in the cART arm (p=0.857); in this case, however, mean changes between arms were not significantly different (p=0.347). We did not observe significant differences between arms with regard to mean changes in triglycerides (p=0.263) or in ALT (p=0.722). By contrast, eGFR significantly increased in the MT arm (p=0.026) and mean changes between arms in eGFR were also significantly different (p=0.029). Changes in these laboratory parameters are detailed further in table 4.

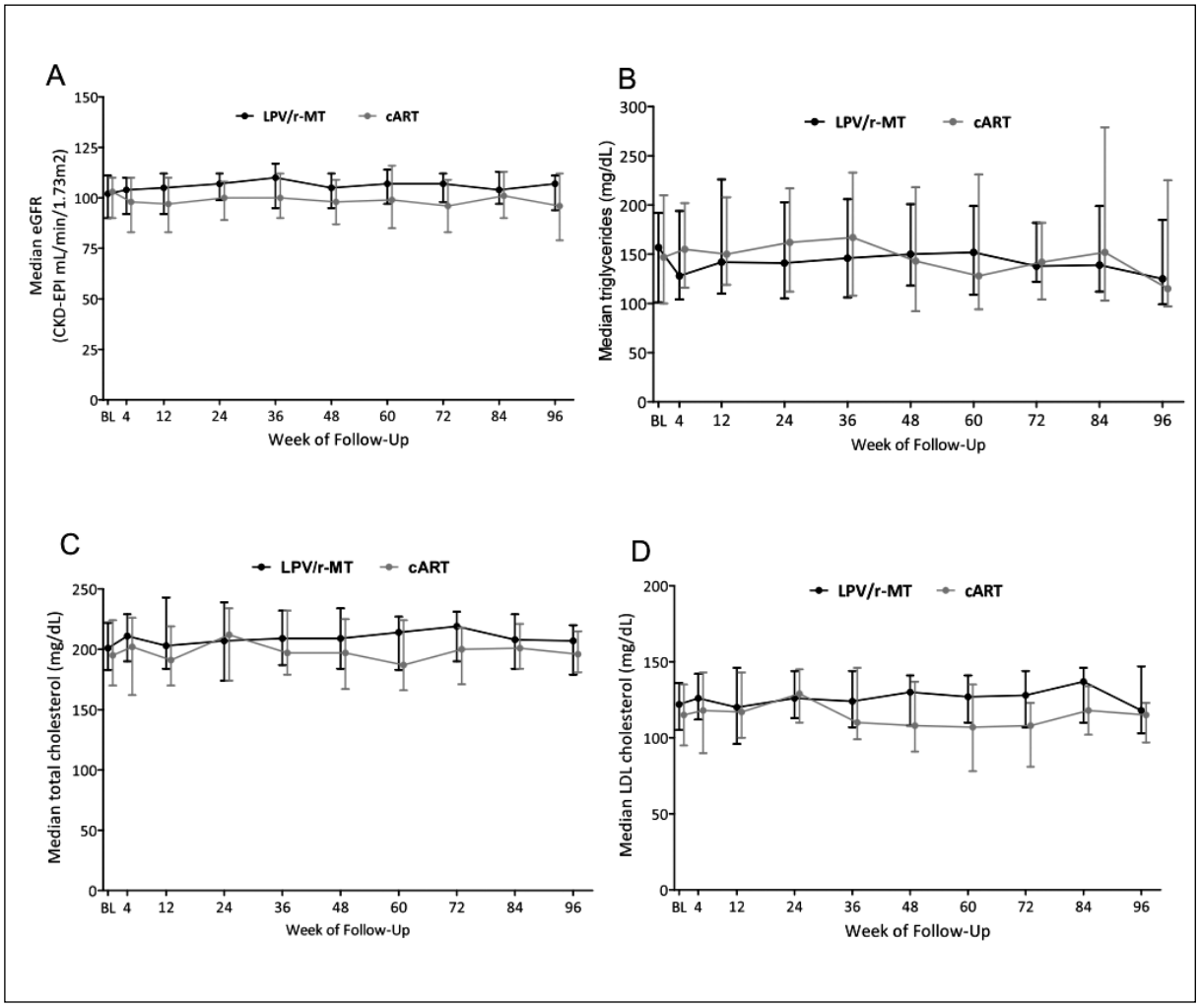

FIGURE 2 - *eGFR (panel A), triglycerides (panel B), total cholesterol (panel C) and LDL-cholesterol (panel D) values during follow-up. Monotherapy with lopinavir/ritonavir (LPV/r-MT): black lines; combination antiretroviral therapy (cART): grey lines.*

TABLE 4 - *Mean changes from BL per month (± standard error) in main laboratory parameters.*

	MT arm	*p-value*	*cART arm*	*p-value*	*MT arm vs cART arm*	*p-value*
Total cholesterol, mg/dL	0.90 (±0.04)	0.001	0.13 (±0.11)	0.597	0.77 (±0.30)	0.012
Low density lipoprotein (LDL)-cholesterol, mg/dL	0.18 (±0.10)	0.046	-0.23 (±0.12)	0.857	0.41 (±0.44)	0.347
Triglycerides, mg/dL	0.84 (±0.10)	0.568	-0.05 (±0.27)	0.723	0.89 (±0.79)	0.263
Alanine amino transferase (ALT), UI/L	0.33 (±0.08)	0.372	0.26 (±0.28)	0.825	0.07 (±0.21)	0.722
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2	0.26 (±0.01)	0.026	0.01 (±0.04)	0.077	0.24 (±0.11)	0.029

LPV/r-MT= monotherapy with lopinavir/ritonavir; cART = combination antiretroviral therapy.

DISCUSSION

In this randomised clinical trial of a MT with LPV/r in HIV-infected patients virologically suppressed while receiving LPV/r with two NRTIs, the number of VRs was higher in the MT arm; all the events occurred at low levels of viral load and none was associated with neurological symptoms. Due to the very low levels of viraemia at rebound, we were not able to assess drug resistance in all cases; in one of those tested one minor PI resistance mutation was detected, but the patient only temporarily responded to the reintroduction of NRTIs. In addition, we were not able to test fully the efficacy of reintroducing NRTIs because this was not done in all cases. Although we cannot exclude that this might be due to the small sample size, the probability of VR or treatment failure was not significantly higher in the MT arm than in the cART arm. However, it must be emphasized that the proportion of patients with VR in the MT arm was consistent with larger randomized clinical trials (Pulido *et al.,* 2008; Gutmann *et al.,* 2010; Katlama *et al.*, 2010; Clumeck *et al.,* 2011).

Clinical events were also remarkably similar across study arms. On the one hand, this suggests that the LPV/r MT does not pose patients at risk of avoidable events. On the other, this suggest that in the short term the LPV/r MT does not avoid relevant NRTI toxicity. Even if the proportion of clinical events did not statistically differ between arms, we observed some differences in the changes in some laboratory parameters: CD4+ cell counts, eGFR, total and LDL-cholesterol significantly increased during MT. All these phenomena were likely due to NRTI removal; the increase in cholesterol values was likely due to a "statin-like" effect of TDF, also detected in other studies of TDF-sparing regimens (Clumeck *et al.,* 2011; Reynes *et al.,* 2013; Di Giambenedetto *et al.,* 2013; d'Arminio Monforte *et al.,* 2013). The increase in CD4+ cell count was not reported in previous MT studies, but was also observed with other NRTI-sparing regimens (Pulido *et al.,* 2009; Kozal *et al.,* 2012; SECOND-LINE Study Group *et al.,* 2013) and suggests that NRTIs may hamper CD4+ recovery in some patients. However, both CD4+ and lipid increases can be considered clinically negligible.

Although the primary kidney toxicity of TDF is tubular, the use of this drug was also associated with a reduction in eGFR (Mocroft *et al.,* 2007; Horberg *et al.,* 2010; Wever *et al.,* 2010; Sax *et al.,* 2011; Scherzer *et al.,* 2012). Indeed, the improvement in eGFR observed in the MT arm might be considered lower than expected, but kidney toxicity from TDF may not always be fully reversible (Wever *et al.,* 2010; Sax *et al.*, 2011; Scherzer *et al.,* 2012) and we cannot exclude that in the long term this improvement can become clinically relevant. Furthermore, this is the first study showing an improvement in kidney function with PI/ MT.

By sparing further NRTI toxicity, PI/r MT could have potential advantages also in patients co-infected with HCV receiving treatment with interferon and ribavirin (Hasson, *et al.,* 2012).

It could be also argued that in terms of costs MT seems to have a favourable trade-off: in the MT arm four "avoidable" drug-resistance tests in 43 patients were performed, but there was no increase in the number of clinical events or hospital admissions. Cost savings due to sparing of NRTIs clearly overcome costs of drug-resistance testing.

This study has several limitations. Viral load was not measured in a single laboratory; however, all centres used a validated method with a lower detection limit of at least 50 copies/mL and so we are confident that the number of VRs was not underestimated. We were unable to evaluate adequately the efficacy of reintroducing NRTIs because of the low number of VRs and because NRTIs were not reintroduced in all cases. In addition, we were not able to assess fully the risk of losing treatment options with LPV/r-MT because, due to the very low viral load at VR in most patients, resistance testing was not always available; major PI mutations were not detected at VR when resistance testing was available. Finally, the follow-up might have been too short to show some clinical benefit that may became evident only after many years of MT and we did not assess whether the removal of TDF could improve bone mass density, as suggested by other studies (Reynes *et al.,* 2013; Di Giambenedetto *et al.,* 2013).

In conclusion, LPV/r MT seems safe in most patients: this strategy should be considered in patients who have developed kidney toxicity from

TDF if they do not have resistance to LPV/r, did not have failures of PIs and have been virologically suppressed for at least six months. However, the potential benefits of this regimen in the context of proactive switches (to prevent the occurrence of toxicities due to NRTIs) should likely be assessed on a longer time frame and in a larger number of patients.

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