Short communication

Durability of lopinavir/ritonavir monotherapy in individuals with viral load ≤50 copies/ml in an observational setting

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Background: The main objective is to evaluate the efficacy and durability of lopinavir-ritonavir monotherapy (LPV/r-MT) in virologically controlled HIV-positive individuals switching from combination antiretroviral therapy (cART).

Methods: Criteria to be included in this observational study were to have initiated for the first time LPV/r-MT after ≥2 consecutive HIV RNA≤50 copies/ml achieved on a ≥3-drug-including regimen. The main end points were time to virological rebound (VR; defined in two ways: time of first of two consecutive viral load [VL]>50 and >200 copies/ml), time to discontinuation/intensification and time to experience either a single VL>200 copies/ml or discontinuation/intensification (treatment failure [TF]). Individuals' follow-up accrued from the date of starting LPV/r-MT to event or last available VL. Kaplan–Meier curves and Cox regression analyses were used.

Results: A total of 228 individuals were included: median age 46 years (IQR 40–50), 36% females, 36% intravenous drug users and 25% HCV-coinfected. Median CD4$^+$ T-cell count at nadir was 215 cell/mm^3 (IQR 116–336) and at baseline was 615 cell/mm^3 (IQR 436–768). By 36 months after switching to LPV/r-MT, the proportion of individuals with VR (confirmed VL>200 copies/ml) was 11% and with TF was 35%. In the multivariable Cox model the factors associated with a lower risk of TF was the duration of viral suppression <50 copies/ml prior to baseline (ARH=0.92; 95% CI 0.85, 0.99; *P*=0.024, per 6 months longer) and having LPV/r as part of last cART (ARH=0.45; 95% CI 0.21, 0.95; *P*=0.037).

Conclusions: In daily clinical practice, we confirm a relatively safe approach of treatment simplification to LPV-MT in a selected population with long-lasting virological control.

Introduction

Simplification of three-drug combination antiretroviral therapy (cART) to boosted protease inhibitors (PI/r) monotherapy (MT) may be a useful strategy to reduce the number of drugs and related toxicities as well as of therapy costs.

Lopinavir/ritonavir MT (LPV/r-MT) has been demonstrated in randomized clinical trials to be a safe simplification approach, able to maintain viral suppression in individuals with long-lasting undetectable HIV RNA copy levels and no history of failure to PIs. It has been evaluated in a number of clinical trials including also HCV-coinfected individuals [1–4], but currently there are still no conclusive data on the efficacy and toxicity of such a regimen in daily clinical practice.

Although in Italy PI/r-MT regimens were not officially recommended for use by licensing authority until June 2013, an increasing number of clinicians chose this strategy for their patients for a number of reasons, including reduction or prevention of nucleoside toxicities, sparing of antiretroviral therapy classes and, recently, costs containment. Therefore, we constructed a clinical database to evaluate the durability of LPV/r-MT among HIV-infected individuals with long-lasting HIV control on cART who were followed-up in a number of clinical sites in Italy.

Methods

This is a retrospective analysis of prospectively collected data on selected individuals recruited from sites participating in the Icona cohort. Details of the Icona study have been previously published [5]. The Icona cohort study was approved by each ethics committee to which the individual participating centres refer. All of the individuals enrolled in the Icona cohort study provided written informed consent at enrolment. Criteria of individuals' selection for this analysis were to have initiated for the first time LPV/r-MT as a simplification strategy after >2 consecutive HIV RNA≤50 copies/ml achieved on a three or more drugs regimen. This newly created clinical database includes both individuals from Icona and individuals recruited by the same centres, even if not part of Icona but who satisfied the inclusion criteria for this project. These latter patients have also given their written informed consent to participate in the study. The date of starting LPV/r-MT was defined as baseline. Virological failure to PI prior to baseline was defined as a single viral load (VL)>500 copies/ml at least 4 months after starting a PI-including regimen and while still receiving a PI. Drug resistance mutations were defined according to the IAS classification [6].

The main outcomes were to obtain estimates of the time to virological rebound (VR), time to discontinuation/intensification and time to experience a composite end point of either failure or discontinuation/intensification (defined as treatment failure [TF]). Individuals' follow-up accrued from the date of starting LPV/r-MT to the event of interest. The date of VR was defined at the time of the first of two consecutive VL above a threshold of 50 and 200 copies/ml. In alternative analyses we used a single value of VL above these thresholds, without the confirmatory value. Follow-up of participants not experiencing VR was censored at the date of their last available VL measurement. The composite end point of TF was defined after recording a single VR>200 copies/ml or discontinuation/intensification of LPV/r-MT, whichever occurred first. Follow-up of participants not experiencing TF was censored at the date of their last available visit or VL measurement.

Secondary objectives were to identify factors associated with faster progression to TF, to evaluate changes from baseline in $CD4^+$ T-cell count over follow-up, to evaluate changes from baseline in plasma lipids (cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides) and estimated glomerular filtration rate (eGFR) after follow-up. Standard survival analysis employing Kaplan–Meier curves and Cox regression analysis were used.

Mean and standard deviation of the change from baseline in $CD4^+$ T-cell count, eGFR (calculated using the MDRD formula), alanine aminotransferase (ALT), aspartate aminotransferase (AST), HDL, total cholesterol and triglycerides were also estimated at 3-monthly intervals and up to 2 years after baseline. All values of these markers were included in a main analysis regardless of whether the individuals were still receiving LPV/r-MT. In an alternative analysis, follow-up was censored at the time of discontinuation/intensification of LPV/r-MT. Beside the descriptive analysis we also performed a mixed-model to estimate the slope of change per month in these parameters.

Results

A total of 228 individuals fulfilling the criteria of inclusion were analysed: median age was 46 (IQR 40–50) years, 36% were females, 36% were intravenous drug users (IDUs), 25% were HCV-coinfected and none were positive for hepatitis B surface antigen. Median $CD4^+$ T-cell count at nadir was 215 cell/mm^3 (IQR 116–336). In 50 participants (22%), $CD4^+$ T-cell count at nadir was ≤100 cells/mm^3, in 52 (23%) was 101–200 cells/mm^3, in 71 (31%) 201–350 cells/mm^3, in 29 (13%) 351–500 cells/mm^3 and in 26 (11%) >500 cells/mm^3. At baseline, median $CD4^+$ T-cell count was of 615 cells/mm^3 (IQR 436–768), in 28 (12%) individuals $CD4^+$ T-cell count was ≤350 cells/mm^3; duration of viral suppression <50 copies/ml before switch

was of 47 months (IQR 20–73). A total of 52 (23%) individuals previously failed virologically to a PI-based regimen (Table 1). At most recent time before baseline, nearly half of the individuals (*n*=104, 47%) received the combination of tenofovir/emtricitabine/LPV/r. Other frequently received combinations were zidovudine/lamivudine/LPV/r (*n*=34, 18%), tenofovir/lamivudine/LPV/r (*n*=17, 8%) and lamivudine/abacavir/LPV/r (*n*=12, 5%). In terms of cART regimen received at the time of switching to LPV/r-MT, the distribution was 5% 2 NRTI+NNRTI, 1% 2 NRTI+unboosted PI, 87% 2 NRTI+PI/r, 3% 3 NRTI and 4% other >3 drugs combinations. Overall, only 37 (16%) individuals did not receive LPV/r at time of switch to monotherapy.

Table 1. Baseline characteristics of patients included in the analysis

Characteristic	Value[a]
Female gender, *n* (%)	81 (36)
Median age, years (IQR)	46 (40–50)
Mode of HIV transmission	
IDU, *n* (%)	82 (36)
Homosexual contacts, *n* (%)	45 (20)
Heterosexual contacts, *n* (%)	72 (32)
Other/unknown, *n* (%)	29 (13)
Hepatitis coinfection[b]	
No, *n* (%)	120 (53)
Yes, *n* (%)	56 (25)
Not tested	52 (23)
Median nadir CD4$^+$ T-cell count, cells/mm^3 (IQR)	215 (116–336)
CD4$^+$ T-cell count at starting LPV/r-MT, cells/mm^3 (IQR)	615 (436–768)
CD8$^+$ T-cell count at starting LPV/r-MT, cells/mm^3 (IQR)	884 (651–1,263)
Median time from ART initiation to start of LPV/r-MT, years (IQR)	8 (4–13)
Median time with VL≤50 before switch to LPV/r-MT, months (IQR)	47 (20–73)
Previously virologically failed a PI	
Yes, *n* (%)	52 (23)
Median calendar year of starting LPV/r-MT (IQR)	2010 (2009–2011)
Type of cART prior to switch to LPV/r-MT	
2 NRTI+PI, *n* (%)	2 (1)
2 NRTI+PI/r, *n* (%)	198 (87)
2 NRTI+NNRTI, *n* (%)	12 (5)
3 NRTI, *n* (%)	7 (3)
Other, *n* (%)	9 (4)
Median ALT at starting LPV/r-MT, UI/l (IQR)	24 (18–35)
Median AST at starting LPV/r-MT, UI/l (IQR)	27 (8–553)
Median eGFR at starting LPV/r-MT, ml/min/1.73 m^2 (IQR)	94 (78–13)
Median cholesterol at starting LPV/r-MT, mg/dl (IQR)	195 (173–222)
Median HDL at starting LPV/r-MT, mg/dl (IQR)	45 (38–56)
Median triglycerides at starting LPV/r-MT, mg/dl (IQR)	147 (110–215)
Median follow-up for composite outcome, months (IQR)	14 (7–23)

[a]*n*=228. [b]Number of cases with HCV antibody positivity. ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; IDU, intravenous drug user; LPV/r-MT, lopinavir/ritonavir monotherapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

The median (IQR) VL monitoring after initiation of LPV/r-MT was 3.3 (2.7–4.6) measures per year in our study population.

The number of people experiencing an event by 12 and 36 months are reported in Table 2, and cumulative incidence estimated by Kaplan–Meier in Figure 1. By 36 months after switching to LPV/r-MT, the proportion of individuals no longer with a suppressed VL while still receiving LPV/r-MT was 11% (confirmed VR>200 copies/ml), whereas the proportion on TF was of 35%.

Of the 26 individuals with a determination >200 copies/ml, in 12 individuals the following determination was below 200 copies/ml (range 20–193 copies/ml), in 12 individuals it was followed by another value also >200 copies/ml (range 220–14,520 copies/ml) and for the remaining 2 individuals it was the last available VL.

A total of 28 (12%) individuals interrupted LPV/r-MT due to intensifications. Of these, 22 (79%) had a VL suppressed below 50 copies/ml, a median (range) of 2 (1–6) months after the date of intensification. Of note, of the 47 individuals experiencing TF, 21 were single HIV RNA>200 copies/ml, 21 were intensifications and 5 individuals stopped LPV-MT (reason unknown).

Table 3 shows HIV resistance data for individuals who had a confirmed VR with >200 HIV RNA copies/ml.

In the multivariable Cox regression model, the factors significantly associated with a lower risk of TF were the duration of viral suppression <50 copies/ml prior to baseline and receiving a LPV/r-based regimen before switch (Table 4).

The estimated slope/month from the mixed-model were the following: CD4$^+$ T-cell count (+1.33, *P*=0.61), triglycerides (-0.29, *P*=0.61), HDL (+0.16, *P*=0.07), eGFR (-0.11, *P*=0.36), total cholesterol (+0.83, *P*=0.0001), ALT (-0.10, *P*=0.69) and AST (+0.06, *P*=0.79).

Discussion

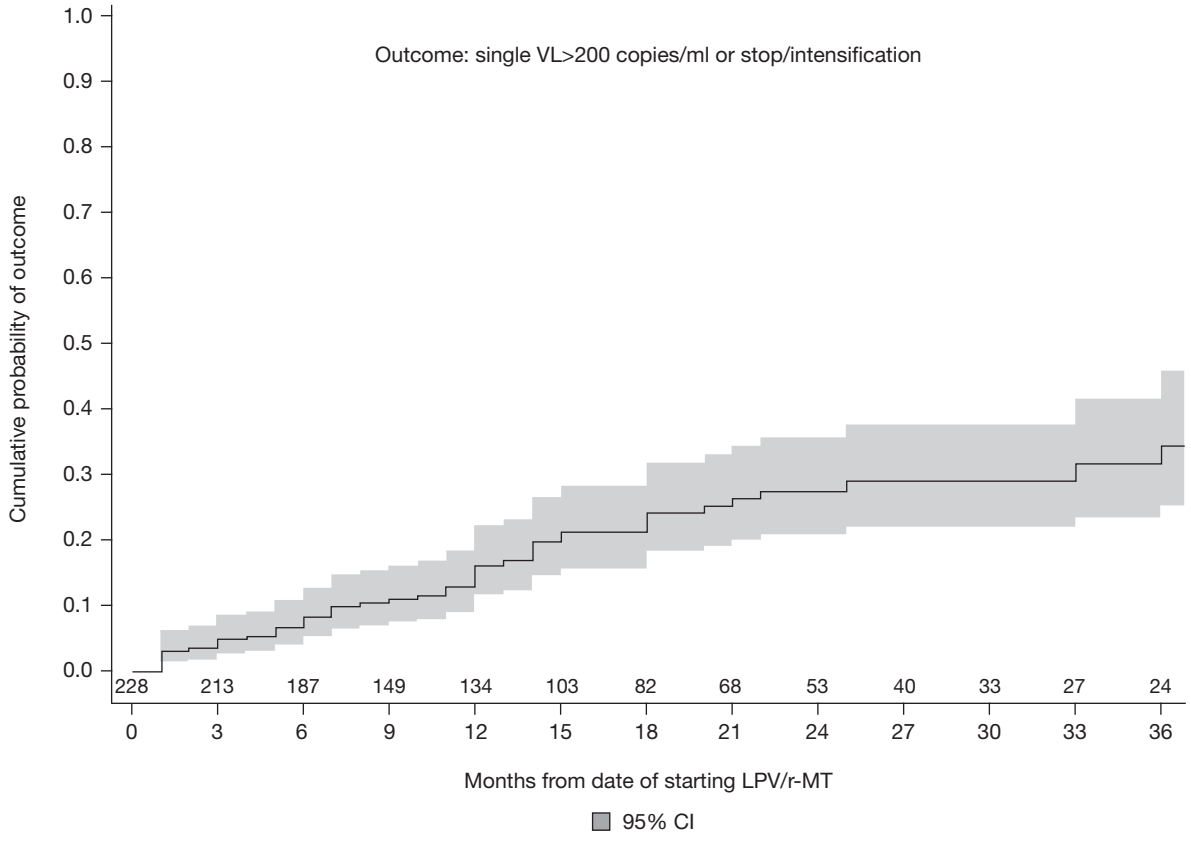
When looking at a range of possible pure virological failure end points in our cohort of over 200 individuals who switched to an LPV/r-MT from a three-drug-based cART, the probability of turning to uncontrolled viral replication ranged between the most conservative

Table 2. Kaplan–Meier estimates of the risk of failure of LPV/r-MT[a]

End point	12 Months			36 Months		
	Events, *n*	Point estimate, %	95% CI	Events, *n*	Point estimate, %	95% CI
Stop/intensification	22	11.3	6.5, 15.5	36	28.0	18.0, 38.0
Single VL>50 copies/ml	39	19.9	13.3, 24.7	54	35.1	26.3, 43.8
Confirmed VL>50 copies/ml	18	9.5	4.7, 13.3	25	17.1	10.1, 23.9
Single VL>200 copies/ml	17	8.9	4.9, 13.1	26	19.7	12.0, 28.0
Confirmed VL>200 copies/ml	6	3.3	0.5, 5.5	12	11.2	4.3, 17.7
Single VL>200 copies/ml or stop/intensification	31	16.2	10.7, 21.3	47	34.5	21.1, 48.9
Confirmed VL>200 copies/ml or stop/intensification	22	12.1	7.2, 16.8	36	30.0	19.4, 40.6

[a]All individuals. LPV/r-MT, lopinavir/ritonavir monotherapy; VL, viral load.

Figure 1. Kaplan–Meier curve for the treatment failure end point



Numbers above the *x*-axis denote the number of patients at risk. LPV/r-MT, monotherapy with lopinavir/ritonavir; VL, viral load.

estimate of 3% (confirmed rebounds >200 copies/ml) to the least conservative estimate of 20% (single VL>50 copies/ml) by 1 year; from a virological stand point, this confirms the retained efficacy of this approach in most individuals. The same figures by the more clinical relevant time point of 36 months were 11% and 35%, respectively. Our findings are consistent with those of the OK4 trial showing a rate of virological success (defined as maintaining a HIV load ≤50 copies/ml at 48 weeks according to TLOVR algorithm) of 83% [1].

When we used the more stringent definition of TF, we estimated that 16% experienced failure by 1 year

Table 3. Drug resistance mutations in the protease coding gene detected before and at failure[a] of lopinavir/ritonavir monotherapy

Patient ID	DRMs detected up to initiation of LPV/r-MT (historic)	Tested at failure of LPV/r-MT	Reason for not testing at failure	DRMs detected at failure of LPV/r-MT
7	Not done	No	No adherence	–
13	Not done	No	No adherence	–
71	Not done	No	No adherence	–
85	63P, 77I, 93L	Yes	–	No DRMs
126	36I, 62V, 63P, 64V	No	No adherence	–
137	Not done	Yes	–	10I
190	Not done	Yes	–	36L, 63P, 93L
192	Not done	Yes	–	10V, 36I, 89M
200	Not available	Yes	–	No DRM
202	63P, 77I	Yes	–	63P, 77I
206	20R, 62V, 64V	Yes	–	20R, 62V, 64V
211	Not done	Yes	–	77I

[a]Confirmed >200 HIV RNA copies/ml. DRMs, drug resistance mutations; LPV/r-MT, lopinavir/ritonavir monotherapy.

Table 4. Relative hazards of experiencing treatment failure from fitting a Cox regression

	Crude and adjusted RH of single VL>200 copies/ml or stop/intensification			
	Crude RH (95% CI)	*P*-value	Adjusted RH (95% CI)	*P*-value
Gender				
Female versus male	0.63 (0.33, 1.21)	0.166	0.50 (0.22, 1.15)	0.102
Mode of HIV transmission				
Homosexual contacts versus IDU	1.22 (0.59, 2.53)	0.593	0.98 (0.39, 2.50)	0.973
Heterosexual contacts versus IDU	0.77 (0.36, 1.67)	0.510	0.71 (0.26, 1.93)	0.502
Other/unknown versus IDU	1.26 (0.55, 2.88)	0.591	0.78 (0.29, 2.06)	0.610
Hepatitis coinfection[a]				
Yes versus no	0.80 (0.39, 1.64)	0.548	0.60 (0.24, 1.52)	0.282
Not tested versus no	1.46 (0.75, 2.84)	0.263	1.64 (0.78, 3.46)	0.194
Calendar year of starting LPV/r-MT				
Per more recent	0.90 (0.77, 1.05)	0.194	1.02 (0.84, 1.25)	0.832
Age				
Per 10 years older	0.99 (0.74, 1.32)	0.951	0.96 (0.69, 1.32)	0.781
$CD4^+$ T-cell count at starting LPV/r-MT				
≤300 versus >300 cells/mm^3	2.01 (0.94, 4.29)	0.073	1.66 (0.63, 4.33)	0.302
$CD4^+$ T-cell count nadir				
Per 100 cells higher	0.89 (0.76, 1.04)	0.131	0.89 (0.75, 1.07)	0.220
Time with VL≤50 copies/ml				
Per 6 months longer	0.95 (0.89, 1.00)	0.066	0.92 (0.85, 1.00)	0.042
Dropped NRTI coming from two NRTI+LPV/r				
Yes versus no	0.65 (0.33, 1.28)	0.210	0.45 (0.21, 0.96)	0.039
Previously failed a PI				
Yes versus no	1.45 (0.78, 2.71)	0.243	1.95 (0.65, 5.89)	0.234

[a]Positive for HCV antibodies. IDU, intravenous drug user; LPV/r-MT, monotherapy with lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RH, relative hazard; VL, viral load.

and 35% by 3 years, very close to the 85% proportion reported in the randomized trial, when missing HIV RNA level values or changes in the randomized therapy were both considered as failure [1]. People who were receiving an LPV-based three-drug cART regimen prior to baseline were at 55% reduced risk to experience TF than those who were switched from regimens not including LPV/r; possible explanations of this finding are related to the selection of participants who were already on an LPV-based drug and had a good tolerability to LPV/r and, vice versa, possible complains due to double ritonavir tablets in those individuals

who were taking LPV/r for the first time. Moreover, a reduced risk of failure during PI/r-MT was observed according to prolonged duration of previous viral suppression below 50 copies/ml. These data are consistent with the independent predictive value of longer time on viral suppression even from adherence level [7], and confirm that duration of previous viral suppression is a main predictor also for long-term success of PI/r-MT strategy [8]. There was no association with nadir $CD4^+$ T-cell count, contrary to findings from prospective clinical trials [9,10], despite almost half of our individuals being severely immunosuppressed (that is, had a nadir $CD4^+$ T-cell count of <200 cells/mm^3).

Our results are relevant as they document the prognosis of individuals treated with a strategy commonly used in clinical practice but with a limited support from available data. In addition, as estimates of failure are calculated using data from a group of unselected individuals treated in everyday clinical practice, these estimates reflect more faithfully than those obtained from clinical trials the trends in the average HIV-infected individual in care in Italy.

Moreover, it is important to note that simplification to LPV/r-MT did not result in a decrease of $CD4^+$ T-cell count over time and, in regard to plasma lipids on LPV/r-MT, it seems that there are no major changes as compared with levels during cART.

A limitation of this analysis is the observational context as we cannot exclude the selection of individuals undergoing LPV-MT who would have a better immune-virological response and a good tolerability to cART.

In conclusion, in this daily clinical practice context we can confirm a good virological and clinical outcome of simplification with LPV-MT up to a median of 14 months of follow-up. The long-term outcome of such a simplification strategy has still to be ascertained.

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Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: A list of the Icona Foundation Study Group members and further acknowledgements can be found at http://www.intmedpress.com/uploads/documents/2994_Monforte_Additionalfile1.pdf

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