Effect of LPV trough level on the biological markers of cardiovascular risk in LPV/r treated HIV infected patients

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Background

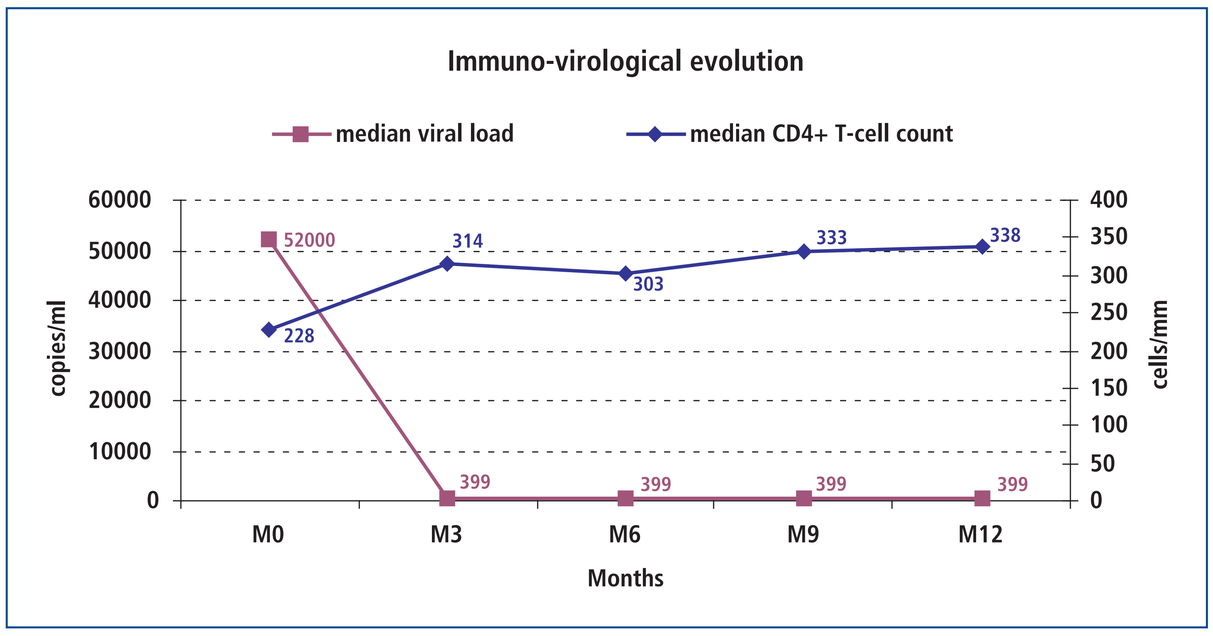
Adverse events related to anti-retroviral treatment are now well documented and are a major concern for physicians. Among patients receiving protease inhibitors (PI), dyslipidemia is very frequent and may lead to cardiovascular complications.
Kaletra® is a recent PI combination of lopinavir and 100mg ritonavir. Trials investigating the impact of Kaletra® on patient lipid profile have mainly revealed a significant increase in total cholesterol (TC) and triglycerides (TG). To our knowledge, no data are available regarding HDL cholesterol (HDL-c) and TC/HDL-c ratio, both known to be predictors of cardiovascular risk.
The Nice HIV cohort provided an opportunity to assess the impact of Kaletra® (LPV/r) on these variables in "real life" conditions.

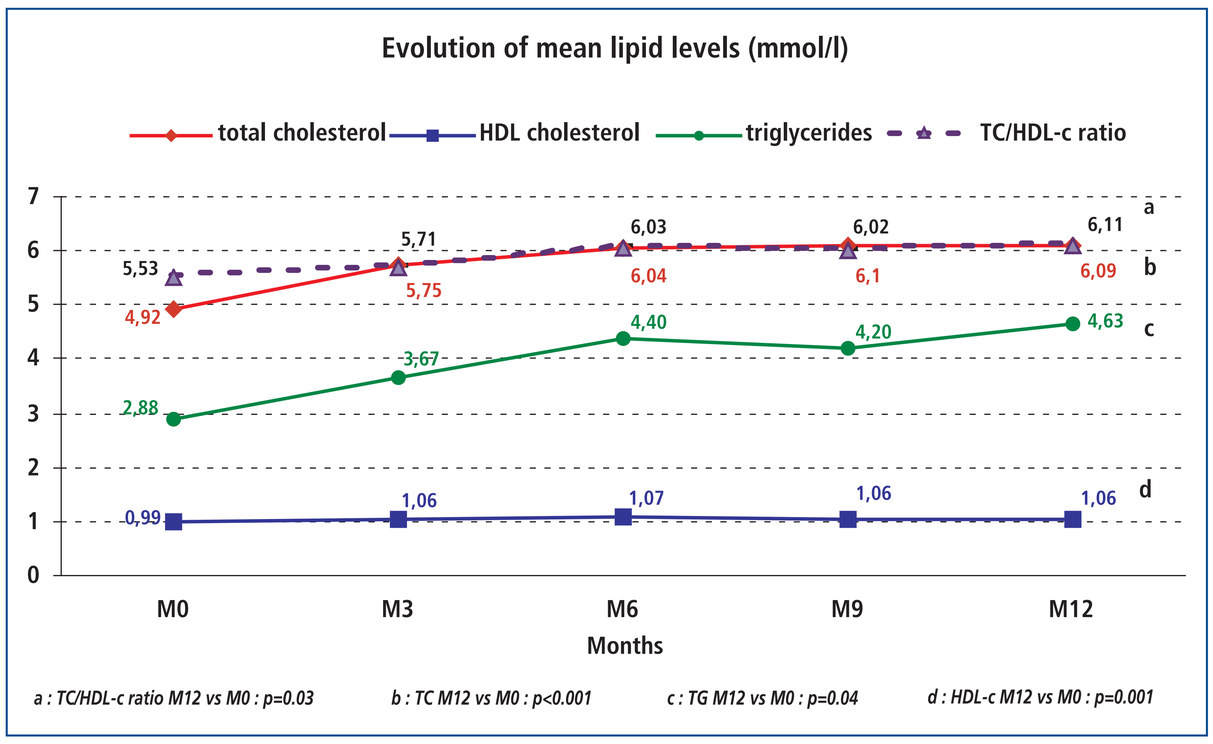
Method

Data: the Nice HIV cohort includes 4,500 patients, with 49,500 regular day-hospital visits between 1995 and 2002 at the Infectious Diseases Department of Nice University Hospital.
Design: This is a retrospective observational cohort study of HIV-infected patients. Patients over 15-years-old who had received LPV/r and for whom serum lipid measurements were available upon treatment initiation were included. Inclusion date coincided with the first LPV/r prescription. Patients treated for less than one month and those whose last serum lipid measurements exceeded 3 months prior to LPV/r initiation were excluded.
Variables of interest comprised total cholesterol, HDL-c, triglycerides, TC/HDL-c ratio. Dyslipidemia was defined according to the thresholds established by the US National Cholesterol Education Program (TC ≥ 6.2mmol/l, HDL-c ≤ 1mmol/l, TG ≥ 2.3 mmol/l), and ≥ 6.5 for the TC/HDL-c ratio. LPV and RTV plasma levels at M3 and M6, when available, were analyzed.
The statistical analysis was conducted using SPSS software package 11.0.

Results

142 patients treated with LPV/r were included (characteristics Table 1). Mean follow-up duration was 14 months. These patients had previously received multiple treatments (8 treatment regimens on average). Mean viral load (VL) was 4.5 $\log_{10}$ copies/ml; 42% of patients had >100,000 copies; mean CD4 T-cell count was 247 ± 199.106/l and was < 200.106/l in 45% of patients. Trends in CD4 T-cell count, VL and serum lipid concentrations are shown in figures below. Among the patients with available LPV and RTV plasma determinations at M3 (n=30), a higher LPV trough concentration was observed in those with high TG; at M6 (n=15), the elevated ratio group had also a higher LPV trough value (Table 2).





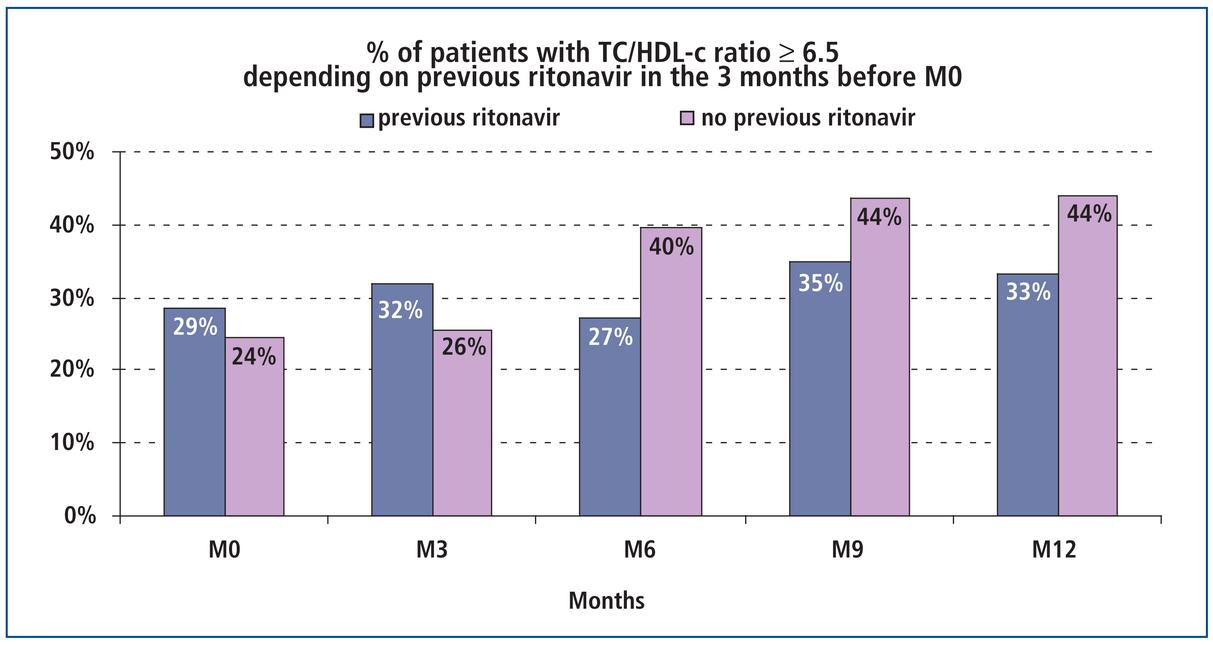


Table 1: Baseline characteristics of the study population
Values are n, % or Median (IQR) as appropriate

	n	%
Number of patients	142	100 %
Male	112	79 %
Age	142	39.5 (36 - 45)
BMI (Kg/m^2)	142	22 (20 - 23)
Lipodystrophy (atrophy or hypertrophy)	103	73 %
Transmission mode		
Homo/bisexual	46	32 %
Heterosexual	38	27 %
Intravenous drug user	43	30 %
Other / unknown	15	11 %
AIDS stage	50	35 %
CD4 count (cells/mm^3)	141	228 (81 - 373)
Viral load (copies/ml)	142	52 000 (8 350 - 230 000)
Dyslipidemia		
Total cholesterol ≥ 6.2 mmol.l^{-1}	23	17 %
HDL-c ≤ 1 mmol.l^{-1}	72	63 %
Triglycerides ≥ 2.3 mmol.l^{-1}	69	49 %
TC/HDL-c ratio ≥ 6.5	29	25 %
Previous antiretroviral treatment		
Naïve	6	4 %
Previous ritonavir	91	64 %
Previous PI	126	89 %
Previous NNRTI	101	71 %
Treatments associated with LPV/r		
PI	10	7 %
NNRTI	33	23 %

Table 2: Pharmacokinetic analysis (µg/ml) and dyslipidemia.
Values are median (IQR).

M3	TG < 2.3 mmol.l^{-1}	TG ≥ 2.3 mmol.l^{-1}	p
LPV C_{min}	3.02 (1.89-8.10)	6.78 (4.90-8.17)	**0.051**
RTV C_{min}	0.14 (0.08-0.24)	0.21 (0.04-0.32)	1

M6	TC/HDL-c ratio < 6.5	TC/HDL-c ratio ≥ 6.5	p
LPV C_{min}	0.96 (0.11-4.93)	9.19 (5.25-10.00)	**0.016**
RTV C_{min}	0.04 (0.04-0.29)	0.16 (0.06-0.34)	0.133

Conclusions

For 50% of patients, VL was undetectable up until M12.
Mean increase in CD4 T-cell count was 168.10^6/l (p<0.001).
Regarding dyslipidemia, our study :

- ❑ Confirms the increase in TC and TG in patients treated with LPV/r
- ❑ Shows a significant rise in the TC/HDL-c ratio among the overall study population, as well as an increase in HDL-c levels between M0 to M12.

However, the number of patients with a TC/HDL-c ratio ≥ 6.5 increased significantly during the study period only among those patients who had not received ritonavir during the three months before LPV/r treatment initiation.
Elevated levels of TG and TC/HDL-c ratio were significantly associated with high trough concentrations of LPV, which argues for systematic drug monitoring.