

Immunovirological outcomes in 70 HIV-1-infected patients who switched to lopinavir/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study

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The immunovirological outcome of lopinavir/ritonavir was evaluated in 70 antiretroviral-experienced HIV patients; at baseline, median CD4+ cell count was 218 cells/mm³ and median plasma viraemia 4.58 log₁₀ copies/mL. After 12 months, we observed an increase in CD4+ cell count to 322 cells/mm³ ($P = 0.0001$) and a decrease in plasma viraemia to 2.35 log₁₀ copies/mL ($P = 0.0001$). Four patients discontinued lopinavir/ritonavir during observation. Among metabolic parameters, only triglyceride concentrations increased during treatment ($P = 0.02$). Twenty-six patients had a genotypic resistance test at baseline; four had ≥ 6 mutations known to reduce susceptibility to lopinavir/ritonavir. Undetectable plasma viraemia was obtained only in patients with ≤ 5 mutations (61.9%).

Introduction

Antiretroviral therapy containing protease inhibitors (PIs) for HIV-1-infected patients is often associated with a dramatic decline in plasma viraemia as well as an improvement in immunological status; in patients previously treated with several other antiretroviral drugs, this outcome is rarely obtained. Lopinavir/ritonavir (LPV/RTV, Kaletra), a second generation PI with a favourable resistance profile, is an attractive therapeutic option in patients with multiple failures to other agents. However, at the moment only few data are available on its use in field practice, as most data are taken from clinical trials.^{1,2}

The aim of our retrospective study is to describe the immunological and virological outcome of a switch to an LPV/RTV-containing regimen in PI-experienced patients, to relate it to the resistance profile at baseline and to assess the tolerability of the new regimen.

Materials and methods

The study population was retrospectively selected from among the patients who started an LPV/RTV-containing regimen

at our Institute from September 2000 to March 2002; those who showed a viral load (VL) > 3 log₁₀ copies/mL while on highly active antiretroviral therapy (HAART) and with a follow-up of at least 3 months were included. HIV-RNA levels were measured using the branched chain DNA (b-DNA) technique (Chiron, Inc.; detection limit 50 copies/mL).

Primary endpoints were virological failure (a decrease in HIV-RNA of < 0.5 log₁₀ copies/mL) and immunological failure (a return of CD4+ cell count to baseline values) after at least 3 months of treatment. Whenever possible, a genotypic resistance test (Visible Genetics, Trugene, Toronto, Ontario, Canada) was carried out at baseline. The virological outcome was also analysed in relation to the presence or absence of LPV-related mutations at baseline (L10I, K20R, L24I, M46I, F53L, I54V, L63P, A71V, V82A, I84V and L90M).^{3,4} The course of HIV-RNA and CD4+ cell count as well as of glucose (normal range 80–110 mg/dL), triglycerides (normal value < 180 mg/dL) and total serum cholesterol (normal value < 190 mg/dL) in fasting conditions were also evaluated. Finally, any change in the salvage regimen and its reasons were also recorded.

We carried out a statistical analysis using the Friedman non-parametric test to evaluate the course of viral load and

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CD4 count at different times. A Cox regression model in an intention-to-treat multivariate analysis was carried out to identify any predictor of virological failure in our cohort. The variables included in the model were: gender, age, risk factors for HIV infection, CDC stage, CD4 counts and HIV-RNA at baseline, presence of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the LPV-containing regimen, and number of PIs, nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) previously failed. For all the analyses, SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows was used.

Results

Patients were mostly men ($n = 52, 74.3\%$), with a median age of 40 years (range 29–67); 24 (34.3%) were classified as CDC stage C. All patients were on HAART when switching to LPV/RTV. Most of the patients ($n = 39, 55.7\%$) had already experienced six or more regimens; only three patients (4.3%)

were at their first failure. The median period of the last regimen was 368 days (range 23–1359). In the majority of cases, their last regimen included two NRTIs plus 1–2 PIs ($n = 38, 54.3\%$); 19 patients (27.1%) switched from a regimen containing one NNRTI plus 1–2 PIs, and 13 patients (18.6%) switched from an NNRTI-containing HAART. All the patients had previously failed a PI-containing regimen. Eight patients (11.4%) switched to LPV/RTV both because of virological failure and because of toxicity to the previous regimen (two for renal failure, two for gastrointestinal intolerance, one for cutaneous rash, one for hepatic failure, one for lypodystrophy and one for paraesthesia). LPV/RTV was used in combination with two NRTIs in 47 patients (67.1%), with one NRTI and one NNRTI in 13 patients (18.6%), with three NRTIs in five patients (7.1%) and with two NRTIs and one NNRTI in five patients (7.1%). Moreover, seven patients (10%) added two new (never used) drugs to the LPV/RTV-containing regimen (four added two new NRTIs, and three added one new NRTI and one new NNRTI), 19 patients (27.1%) added one new NRTI and 12 (17.1%) added one new NNRTI to the regimen.

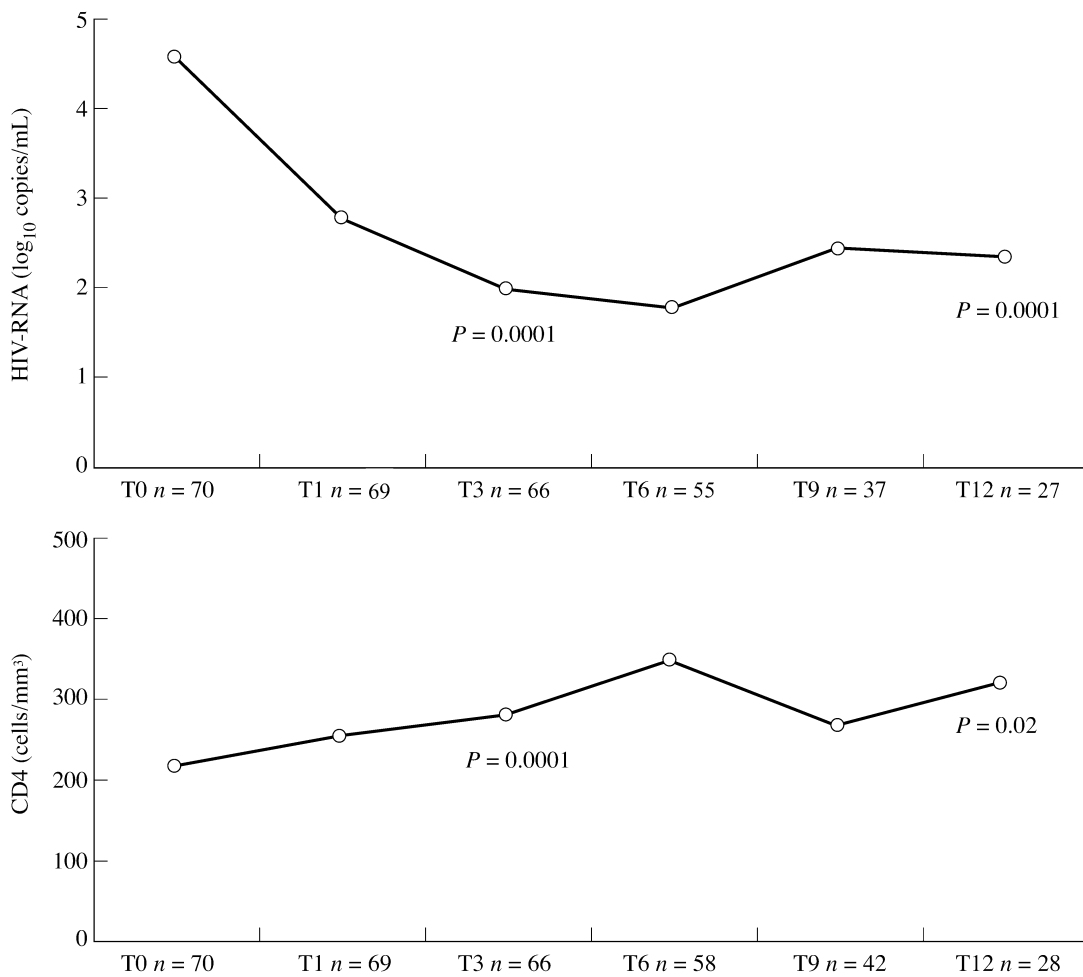


Figure 1. Virological (top panel) and immunological (bottom panel) outcomes during follow-up.

Immunovirological outcomes in HIV-1-infected patients

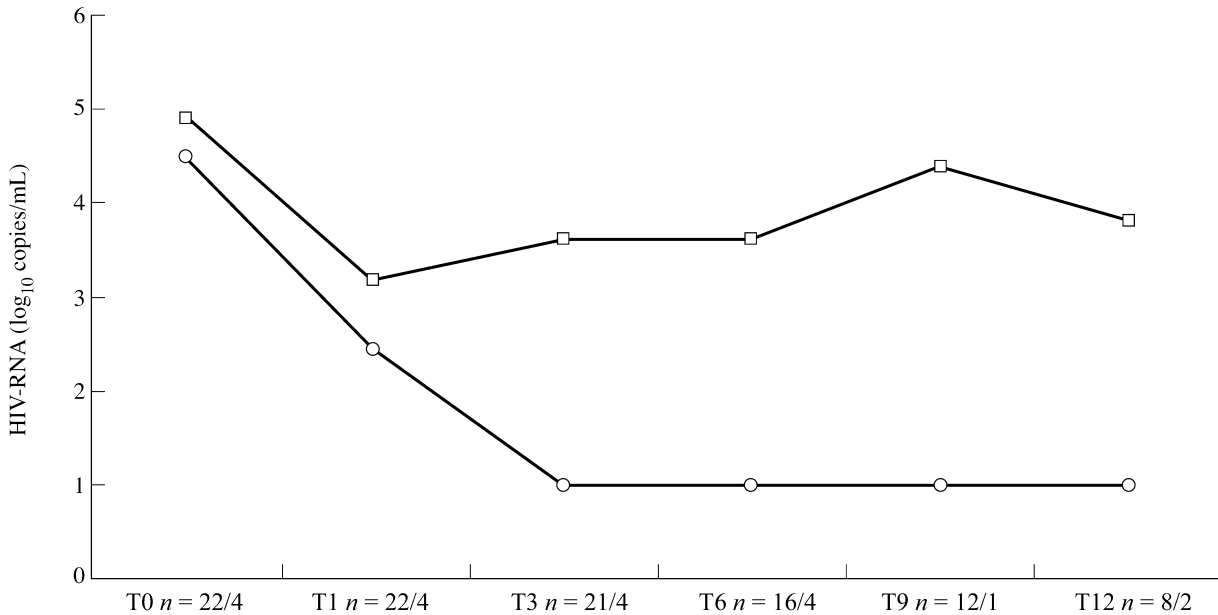


Figure 2. Virological outcome in relation to the number of mutations at baseline. Open squares indicate patients with ≥ 6 mutations at baseline ($n = 1-4$); open circles indicate patients with < 6 mutations at baseline ($n = 8-22$).

At baseline, median CD4+ cell count was 218 cells/mm³ (range 3–581) and median plasma viraemia was 4.58 log₁₀ copies/mL (range 3.51–5.77). Overall, the median CD4+ cell count increased steadily during the follow-up, with a statistically significant increase (baseline versus month 3: $P = 0.0001$; baseline versus month 12: $P = 0.02$) (Figure 1, bottom panel). Concomitantly, we observed a progressive median statistically significant decrease in plasma viraemia (baseline versus month 3: $P = 0.0001$; baseline versus month 12: $P = 0.0001$) (Figure 1, top panel). The percentage of undetectable plasma viraemia was 14.5% (10/69), 39.4% (26/66), 47.3% (26/55) and 51.8% (14/27) at months 1, 3, 6 and 12, respectively.

During a median follow-up of 329 days (range 95–587), eight (11.4%) patients developed virological, seven (10%) immunological and five (7.1%) immunovirological failure; median time to failure was 196 days (range 95–328).

For metabolic parameters, we observed an increase in the median triglyceride serum levels starting from the first month (baseline 208 mg/dL, 1st month 332 mg/dL, 12th month 289 mg/dL; $P = 0.02$); the other parameters (serum cholesterol and glycaemia) did not show any significant changes.

None of the variables included in the Cox regression model were found to be independently associated with virological failure (data not shown).

Four patients (5.7%) stopped LPV/RTV during the observation period; three for hepatotoxicity and one for immunovirological failure. Two of the three patients who stopped LPV/RTV because of hepatic toxicity died with cirrhosis 28 and 264 days after stopping; both patients had hepatitis C

virus/hepatitis B virus co-infection. No other patients died or developed an AIDS-defining illness during follow-up.

We then analysed the outcome of the 26 patients (37.1%) who had a genotypic resistance test at baseline. Twenty-two (84.6%) carried < 6 mutations and four (15.4%) ≥ 6 mutations known to be associated with a reduced susceptibility to LPV/RTV.

Figure 2 shows the course of HIV-RNA in relation to the presence or absence of at least six LPV/RTV-related mutations. In the group with < 6 mutations, median plasma viraemia showed a dramatic decline during the first 3 months of follow-up; 13/21 (61.9%) patients reached undetectable plasma viraemia from the third month, whereas in the group of patients with ≥ 6 mutations, median plasma viraemia declined during the first month, but it slowly increased thereafter. None of the patients in this last group experienced an undetectable plasma viraemia during the follow-up.

Conclusions

The small number of patients and the 1 year long follow-up are obviously a limit when drawing definite conclusions. Despite these limitations some points need to be discussed. First of all, our results confirm^{5,6} in a clinical setting that the use of LPV/RTV as part of a salvage therapy in patients previously treated with several antiretroviral drugs allows a substantial increase in CD4+ cell count and a sustained decline in plasma viraemia. LPV/RTV-containing regimens were usually well tolerated: only 5.7% of patients stopped because of toxicity; hypertriglyceridaemia was the most

important metabolic modification observed; nevertheless, a longer follow-up is required to improve evaluation of other possible metabolic modifications. In those patients who harboured multiply resistant viruses we observed only a transient virological response: the number of mutations before using LPV/RTV seems to be related to virological response in the medium to long term.

Acknowledgements

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