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Lopinavir/ritonavir vs. indinavir/ritonavir in antiretroviral naive HIV-infected patients: immunovirological outcome and side effects

Marco Bongiovanni [a,*], Teresa Bini [a], Elisabetta Chiesa [a], Paola Cicconi [a], Fulvio Adorni [b], Antonella d'Arminio Monforte [a]

[a] *Institute of Infectious Diseases and Tropical Medicine, Luigi Sacco Hospital, University of Milan, Via G.B. Grassi 74, 20157 Milano, Italy*
[b] *National Research Council, Milan, Italy*

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Abstract

We compared immunovirological outcomes and toxicities of HAART regimens including LPV/r and IDV/r in antiretroviral naïve HIV-1 patients. We retrospectively selected 55 patients starting LPV/r and 52 starting IDV/r as first-line HAART. Immunovirological and metabolic parameters were recorded at baseline and every 3 months as were side effects, AIDS-defining events and deaths. Demographic characteristics and NRTIs included in the regimens were comparable. Both groups reached undetectable HIV-RNA plasma viremia from third month and maintained during follow-up. However, patients receiving IDV/r had a lower probability to obtain virological success (RH: 0.46). Patients receiving IDV/r patients showed a greater increase of total cholesterol ($P = 0.01$). Three patients on LPV/r and 21 on IDV/r discontinued the drug for toxicity, leading to a 8.40 higher risk of discontinuation in the latter group. In our clinical setting IDV/r showed to be less effective and more toxic than LPV/RTV as first-line HAART.

Keywords: HAART; LPV/RTV; IDV/RTV

The use of boostered protease inhibitors (PI) is a valid option as part of an highly active antiretroviral regimen (HAART) in both naïve and experienced patients (Yeni et al., 2002; Flexner, 2000; Walmsley et al., 2002; Young et al., 2002). Among the currently available PIs, indinavir (IDV) and lopinavir (LPV) can be boostered when combined with a low dose of ritonavir (IDV/r and LPV/r) (Hsu et al., 1998; Van Heeswijk et al., 1999; Sham et al., 1998). Furthermore, boostered PIs have proved to be more effective than their non-boostered counterparts because of their better pharmacokinetics; however, the higher drug exposure is related to an higher risk of adverse events (Arnaiz et al., 2003; Barreiro et al., 2000; Rockstroh et al., 2000).

The aim of our observational study was to compare immunovirological outcomes in antiretroviral naïve HIV-infected patients starting IDV/r or LPV/r as their first PI-based HAART. We also compared the toxicities of the two drugs in order to identify the risk of discontinuation.

In our study, we included all the HIV-infected patients starting LPV/r or IDV/r as first-line PI-based HAART in our Clinic from February 2001 and February 2003. Their demographic characteristics, HIV-RNA serum levels, CD4+ cell counts, serum tryglicerides, total serum cholesterol and fasting serum glucose levels were recorded at baseline and every 3 months. Drug-related side effects, AIDS-defining events and deaths were also recorded.

HIV-RNA measurements were performed using the branched chain DNA (b-DNA) technique (Chiron®, Inc., detection limit 50 copies/ml) and CD4+ cell counts using Elite flow cytometer technique (Coulter Corporation, Miami, FL, USA).

Primary study end-point was to compare the probability of reaching virological success, defined as achieving HIV-RNA <50 copies/ml in two consecutive determinations. The secondary end-point was to evaluate the probability of HAART discontinuation due to toxicity.

ANOVA analysis, Mann–Whitney and Friedman non-parametric tests were used to evaluate any differences during follow-up within and between the two groups, as well as to evaluate their immunological, virological and metabolic outcomes. The baseline characteristics of the pa-

* Corresponding author. Tel.: +39-0239042677; fax: +39-023560805.
E-mail address: marco.bongiovanni@unimi.it (M. Bongiovanni).

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Table 1
Demographic characteristics of the patients included in the study

	Total (%)	LPV/r (%)	IDV/r (%)	*P*
Males	81 (75.7)	38 (70.4)	43 (82.7)	
Females	26 (24.3)	17 (29.6)	9 (17.3)	0.14
Age				
<39 years	57 (53.3)	33 (60.0)	24 (46.2)	
>39 years	50 (46.7)	22 (40.0)	28 (53.8)	0.26
Exposure				
IVDU	21 (19.6)	12 (21.8)	9 (17.3)	
Homosexual	27 (25.2)	17 (30.9)	10 (19.2)	
Heterosexual	55 (51.4)	25 (45.4)	30 (57.7)	0.33
Other	4 (3.7)	1 (1.8)	3 (5.8)	
CDC stage				
A	42 (39.2)	19 (34.5)	23 (44.2)	
B	33 (30.8)	19 (34.5)	14 (26.9)	
C	32 (30.0)	17 (31.0)	15 (28.9)	0.27
Baseline CD4+ count				
<100 cell/mm^3	65 (60.7)	35 (63.6)	30 (57.7)	
100–250 cell/mm^3	29 (27.1)	15 (27.3)	14 (26.9)	
250 cell/mm^3	13 (12.2)	5 (9.1)	8 (15.4)	0.56
Median (range)	87 (4–406)	74 (8–292)	97 (4–406)	
Baseline HIV-RNA				
<4 $\log_{10}$ copies/ml	18 (16.8)	8 (14.5)	10 (19.2)	
4–5 $\log_{10}$ copies/ml	55 (51.4)	29 (52.7)	26 (50.0)	
5 $\log_{10}$ copies/ml	34 (31.8)	18 (32.8)	16 (30.8)	0.82
Median (range)	4.80 (2.93–5.70)	4.73 (2.98–5.70)	4.86 (2.93–5.70)	

IVDU, intravenous drug abusers.

tients were compared by using the Chi-square and *t*-tests. A Kaplan–Meyer analysis was performed in order to evaluate the probability of developing virological success or HAART discontinuation for toxicity. Moreover, a multivariate survival analysis using Cox's proportional hazards model according to an intention to treat (ITT) and to an on treatment (OT) approach was performed to identify any independent predictive factor of virological success or HAART discontinuation. The variables included in the analyses were gender, age, risk factor for HIV, CDC stage, CD4+ cell count and HIV-RNA plasma viremia at baseline, and the PI-included in the HAART regimen.

One hundred and seven patients were included in the study: 52 received IDV/r (800/100 mg twice daily) and 55 LPV/r (400/100 mg twice daily). The demographic characteristics of the two groups were comparable (Table 1). All the patients started a regimen containing two nucleoside reverse trascriptase inhibitors (NRTIs) plus LPV/r or IDV/r. Nucleosides included in the combinations were similar in the two groups, the most frequent combination being zidovudine plus lamivudine, used by 45 patients receiving IDV/r and by 44 receiving LPV/r. Other combinations were less prescribed. At baseline, median CD4+ cell count was 74 cell/mm^3 (range 8–292) in the LPV/r group and 97 cell/mm^3 (range 4–406) in the IDV/r group ($P = 0.56$), and median HIV-RNA plasma viremia was 4.73 $\log_{10}$/ml (range 2.98–5.70) versus 4.86 (range 2.93–5.70) ($P = 0.82$), respectively. At the same time, both groups had normal total cholesterol (164 mg/dl, range 98–243 versus 167 mg/dl, range 86–241), triglycerides (144 mg/dl, range 46–281 versus 159 mg/dl, range 72–362) and glucose serum levels (90 mg/dl, range 71–230 versus 90 mg/dl, range 66–132).

Over a median follow-up of 504 days (range 284–904) in the LPV/r and 555 days (range 276–918) in the IDV/r group, median CD4+ cell counts rapidly increased in both groups when compared to baseline: 174 cell/mm^3 (range 2–607) versus 233 cell/mm^3 (range 19–532) at third month ($P = 0.001$) and 231 cell/mm^3 (range 39–717) versus 253 cell/mm^3 (range 69–718) at 12th month ($P = 0.001$) in the LPV/r and IDV/r group, respectively. No significant differences were found between the groups.

Median HIV-RNA plasma viremia rapidly decreased from baseline, becoming undetectable in both groups starting by the third month ($P = 0.001$); furthermore, median HIV-RNA plasma viremia remained persistently undetectable during all the observation.

Patients on IDV/r had an higher increase of total serum cholesterol at third (224 mg/dl, range 132–276 versus 168 mg/dl, range 101–286, $P = 0.01$) and 12th month (226 mg/dl, range 107–336 versus 195 mg/dl, range 103–329, $P = 0.01$) compared to LPV/r patients.

Median triglycerides similarly increased in both groups; at third month: 209 mg/dl (range 82–698) versus 199 mg/dl

(range 56–416); at 12th month: 237 mg/dl (range 87–628) versus 218 mg/dl (range 82–868), P = ns at both times in IDV/r and LPV/r group, respectively. Median fasting serum glucose levels remained stable in the two groups throughout the follow-up.

Fifty-one patients (92.7%) receiving LPV/r and 46 (88.5%) receiving IDV/r reached virological success during the observation by using the ITT analysis. Kaplan–Meyer analysis established a significant difference between the two groups: the probability to obtain virological success at 12th month was 88.2% (95% CI: 79.6–96.9) of patients in LPV/r and 73.1% (range 65.1–85.1) in IDV/r, $P = 0.001$ (Fig. 1A). These data were also confirmed by the OT analysis (88.1%, range 79.2–97.0 versus 68.7%, range 54.0–83.4, $P = 0.001$).

The Cox proportional multivariate model showed that the use of IDV/r was significant associated with a lower probability of success in the ITT (RH: 0.46, 95% CI: 0.29–0.72, $P = 0.001$) (Table 2, left). This result was confirmed by the OT analysis (RH: 0.46, 95% CI: 0.28–0.74, $P = 0.002$).

Toxicity led to drug discontinuation in three patients receiving LPV/r (one case of severe alopecia, disappeared when LPV/r was replaced by nelfinavir, one case of diarrhea and one case of increase of liver enzymes), and in 21 receiving IDV/r. Renal toxicity (nine cases, defined as increase of creatinine serum levels or symptomatic renal colics) and nausea or diarrhea (seven cases) were the more often observed adverse events; moreover, three patients developed alopecia, one onychomycosis and one had an increase of liver enzymes. Kaplan–Meyer analysis revealed a significant difference of the probability of HAART discontinuation due to toxicity at 12th month (5.5%, 95% CI: 0–11.4 versus 28.9%, 95% CI: 16.6–41.2, $P = 0.0001$ for LPV/r and IDV/r group, respectively). Predictive factors of discontinuation were the presence of IDV/r in the regimen (RH: 8.40, 95% CI: 2.35–30.03, $P = 0.001$) and an higher level of CD4 cells at baseline (RH: 1.68, 95% CI: 1.12–2.52, $P = 0.01$ for each 100 cell/mm^3 more) (Table 2, right).

None of the patients developed an AIDS-defining event or died during follow-up.

In our observational study, the use of both LPV/r and IDV/r as first-line HAART was associated with a significant immunological and virological improvement, thus confirming the potency of these boostered PIs previously demonstrated in clinical trials (Walmsley et al., 2002; Young et al., 2002). However, the combinations containing IDV/r seem to be significantly less effective in obtaining virological success (RH: 0.46).

A greater increase of serum total cholesterol was observed among the patients receiving IDV/r ($P = 0.01$), whereas the increase in triglycerides was similar in both groups.

Furthermore patients receiving IDV/r had a 8.40 times higher risk of discontinuing HAART for toxicity when compared with those receiving LPV/r.

Obviously, the results of our study do not allow any definite conclusions to be drawn because of the small number of patients and of its observational nature. Moreover, some biases about the selection of IDV/r or LPV/r as first HAART cannot be excluded. However, we observed a significant higher virological efficacy of LPV/r when compared with IDV/r in HIV-infected naive patients, and a higher probability of toxicity-induced discontinuation in patients receiving IDV/r.

To the best of our knowledge, no randomized trials comparing these two boostered PIs have yet been performed, but they are needed in order to confirm our results.Work supported by a grant from the Italian Institute of Health AIDS Project (No. 50D.06).

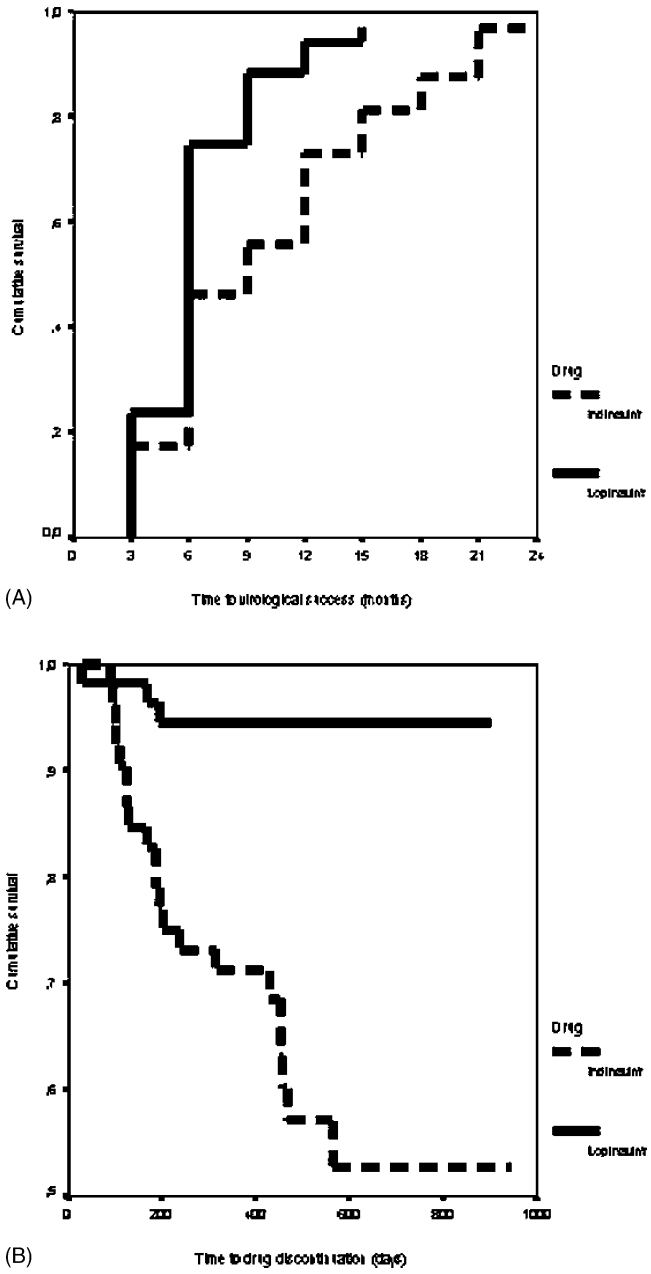

Fig. 1. (A) Kaplan–Meyer analysis on virological success. (B) Kaplan–Meyer survival analysis on drug discontinuation.

Table 2
Predictive factors of virological success (ITT analysis) and of discontinuation of HAART for toxicity in the study population: results from a multivariate Cox proportional hazards model

	Virological success			Discontinuation of HAART for toxicity		
	RH	95% CI	*P*	RH	95% CI	*P*
Females vs. males	0.85	0.46–1.55	0.59	2.13	0.47–9.56	0.33
Age >39 years vs. age <39 years	1.03	1.00–1.06	0.05	0.99	0.93–1.06	0.83
Homosexual exposure vs. IVDU exposure	0.61	0.33–1.13	0.12	1.50	0.35–6.36	0.58
Heterosexual exposure vs. IVDU exposure	0.53	0.27–1.03	0.06	0.99	0.21–4.68	0.99
Other exposure vs. IVDU exposure	0.61	0.17–2.26	0.46	3.05	0.24–39.56	0.39
CDC stage C vs. CDC stage A	0.97	0.57–1.65	0.90	2.86	0.93–8.78	0.07
CDC stage C vs. CDC stage B	1.33	0.77–2.30	0.31	0.76	0.23–2.47	0.64
CD4+ count at baseline (each additional 100 cell/mm^3)	1.22	0.96–1.54	0.10	1.68	1.12–2.52	0.01
HIV-RNA at baseline (each additional $\log_{10}$ copies/ml)	0.83	0.62–1.11	0.22	0.85	0.47–1.54	0.59
IDV/RTV-containing HAART vs. LPV/RTV-containing HAART	0.46	0.29–0.72	0.01	8.40	2.35–30.03	0.001

RH, relative hazards; CI, confidence interval.

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