Efficacy and safety of ritonavir-boosted dual protease inhibitor therapy in antiretroviral-naive HIV-1-infected patients: the 2IP ANRS 127 study

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Objectives: We evaluate the efficacy and tolerability of ritonavir-boosted dual protease inhibitor as a nucleoside reverse transcriptase inhibitor-sparing regimen in a prospective open-label randomized pilot trial in antiretroviral-naive patients.

Methods: Thirty patients received fosamprenavir/atazanavir/ritonavir (Group 1) and 31 patients received saquinavir/atazanavir/ritonavir (Group 2). The primary endpoint for efficacy was the rate of early virological success, defined as plasma viral load < 50 copies/mL at week 16. The study is registered with ClinicalTrials.gov (NCT00122603).

Results: At baseline, median (range) viral load was 4.8 log10 copies/mL (4.0–5.7) and the median CD4 cell count was 271/mm3 (197–740). Viral load was < 50 copies/mL in 12/30 patients (40%, 95% confidence interval (CI) 23%–58%) and 13/31 patients (42%, 95% CI 25%–59%) at week 16 in Groups 1 and 2, respectively. Patients with failing regimens (viral load ≥ 400 copies/mL at week 16 or ≥ 50 copies/mL at week 24) were switched to a standard antiretroviral regimen. At week 48, by an intention-to-treat analysis, 23/30 patients (77%) and 26/31 patients (84%) had plasma HIV-1 RNA < 50 copies/mL in Groups 1 and 2, respectively. Four patients discontinued treatment for adverse events, all before week 4. No major changes in the protease gene were detected at treatment failure relative to baseline. Baseline viral load < 50000 copies/mL was the only predictor of virological success at week 16.

Conclusions: Ritonavir-boosted dual protease inhibitor regimens targeting only one step of viral replication were insufficient to rapidly suppress plasma HIV RNA to < 50 copies/mL in antiretroviral-naive patients with high viral load at baseline.

Keywords: atazanavir, saquinavir, fosamprenavir

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Dual boosted protease inhibitor regimens

Introduction

A combination of three antiretroviral drugs is recommended for initial treatment of HIV infection and is usually based on two nucleoside reverse transcriptase inhibitors (NRTIs) plus either one ritonavir-boosted protease inhibitor (PI/r) or one nonnucleoside reverse transcriptase inhibitor (NNRTI).\(^7\)\(^-\)\(^9\) NRTIs are a mainstay of highly active antiretroviral therapy (HAART) but can cause troublesome mitochondrial toxicity and lipodystrophy.\(^2\) Different strategies were discussed to build a NRTI-sparing regimen, including the use of NNRTI + PI/r,\(^3\) PI/r monotherapy\(^4\) and dual PI/r regimens. Dual PI/r regimens, such as lopinavir/ritonavir + saquinavir, have been used as salvage or maintenance therapy for patients with reverse transcriptase (RT) mutations or NRTI intolerance.\(^5\)\(^-\)\(^6\) Nevertheless, at the time our study was designed, the intrinsic viral potency and tolerability of dual PI/r regimens in induction therapy in naive patients was not known. The objective of our study was to assess the possible value of dual PI/r regimens as first-line regimens. We chose to study atazanavir/ritonavir plus fosamprenavir and atazanavir/ritonavir plus saquinavir regimens based on their favourable pharmacokinetics and low risk of drug–drug interactions.\(^7\)\(^-\)\(^9\)

Methods

Patients and study design

An early endpoint at week 16 was selected in our trial as likely to be the most sensitive and discriminative of a potent regimen and limited the consequences of treatment modifications and missing data. Based on published data, specifically those of the ACTG 5095 trial, which provided precise estimates of response rates to three different triple combination regimens in a large population of untreated HIV-positive patients,\(^10\) we considered that a minimum of 50% efficacy at week 16 was required while rates >70% could be expected from the most potent regimens.

This open-label trial with two parallel groups was performed in 19 centres in France. The treatments were randomly allocated in order to ensure that the groups were comparable at baseline. Randomization was performed by a centralized procedure. Permuted blocks were used and no stratification was performed.

Patients were eligible if they were aged 18 years or more, had never received antiretroviral therapy, were infected with a virus with no resistance mutations in the RT and no major resistance mutations in the protease genes, and had a CD4 cell count >200/mm\(^3\) and a plasma HIV RNA level between 10000 and 750000 copies/mL. Patients with an active hepatitis B infection were excluded. Patients with hepatitis C with no major liver dysfunction were allowed to participate in our study.

The study protocol was approved by an institutional ethics review board (Saint-Germain en Laye, France), and all the patients provided their written informed consent. The study is registered with ClinicalTrials.gov (NCT00122603). An ongoing safety monitoring performed and controlled by a Data and Safety Monitoring Board.

The patients were randomly assigned at a ratio of 1:1 to receive either fosamprenavir (700 mg twice daily)+atazanavir (300 mg once daily)/ritonavir (100 mg twice daily) (Group 1) or saquinavir (1500 mg once daily)+atazanavir (300 mg once daily)/ritonavir (100 mg once daily) (Group 2).

The patients were assessed at baseline, and at weeks 4, 8, 12, 16, 24 and 48, with a physical examination, CD4 cell count, plasma HIV-1 RNA assay, haematological analyses, plasma chemistry and fasting lipid levels.

Primary efficacy endpoint

The primary efficacy endpoint was the rate of early virological responses, defined as plasma HIV RNA level <50 copies/mL at week 16. To replace conventional HAART, we considered that each dual PI/r combination should provide at least a 50% early success rate, using the lower boundary of the one-sided 95% confidence interval (CI) of the observed success rate at week 16.

Samples used to assess the primary endpoint were centralized for HIV RNA assay.

Statistical analysis

Primary efficacy analysis was planned as a test for a single proportion (binomial distribution) performed in each of the two groups. Based on a virological success rate of at least 50% at week 16 (see previous text), 30 subjects per group were required, with a type I error of 5% and 80% power, to test the null hypothesis of <50% efficacy against the alternative hypothesis of at least 72% efficacy. In each of the two groups, the one-sided 95% CI of the observed proportion of patients reaching the efficacy endpoint was calculated and the lower boundary was compared with 50%. Primary efficacy analysis was performed on an intention-to-treat (ITT) basis, and

Plasma HIV-1 RNA was determined at each study visit in a local laboratory to monitor response to therapy. All laboratories participated in a quality control programme. Virological failure was defined as a plasma viral load ≥400 copies/mL at week 16 or ≥50 copies/mL from weeks 24 to 48 on a single measurement. Patients with failing regimens were switched to a standard antiretroviral regimen chosen with their clinician based on genotypic results.

A virological substudy evaluating the kinetics of early virus decay in plasma was performed on 19 patients who agreed to participate (11 in Group 1 and 8 in Group 2), based on virological success rates obtained on days 0, 3, 6 and 9.

HIV-1 RNA measures for the study of both the efficacy outcome (weeks 0 and 16) and virus decay were performed centrally in batches on stored plasma samples.

Plasma samples were collected for genotypic resistance testing at baseline and in case of virological failure. Sequencing was performed in each centre belonging to ANRS resistance group Quality Control and all the sequences were then analysed in a central virology laboratory. The RT and protease gene sequences were determined by population sequencing, using the consensus method of the Agence nationale de recherches sur le sida et les hépatites virales (http://www.hivfrenchresistance.org).

Plasma concentrations of amprenavir, saquinavir and atazanavir were determined at weeks 4, 8, 16, 24 and 48 by using HPLC with fluorimetric or UV detection. The lowest limits of quantification were 5 ng/mL (amprenavir), 20 mg/mL (saquinavir), 30 ng/mL (atazanavir) and 30 mg/mL (ritonavir).

Concentrations determined 24 ± 4 h (atazanavir and saquinavir) or 12 ± 2 h after the last drug intake (amprenavir) were interpreted according to the respective efficacy cut-offs for wild-type HIV-1, i.e. 150 ng/mL (atazanavir), 100 ng/mL (saquinavir) and 228 ng/mL (amprenavir).

Adherence to treatment was assessed by self-administered questions on missed doses.

Quality of life was assessed by a self-administered questionnaire (WHOQOL-HIV 31-BREF) that explores six domains.\(^15\) For each of these domains, a score ranging from 4 to 20 was calculated with higher values denoting better quality of life.
patients who modified the allocated treatment including dosage or were missing were analysed as failures. After week 16, virological evaluations were analysed by ITT analyses whether the subjects had discontinued study treatments or not, missing data being considered as failures. On-treatment analyses (data were censored at the stop of the study treatment or after virological failure) were also performed. Baseline characteristics including gender, CD4, HIV-1 RNA, HIV-1 subtype (B versus non-B) and averaged plasma concentrations at weeks 4, 8 and 16 of each study drug (atazanavir, saquinavir and amprenavir) were investigated as potential predictive factors for virological success at week 16. Univariate analysis (Wilcoxon rank sum test or $\chi^2$ test) was performed on the basis of on-treatment analysis. Quantitative data were described with median and interquartile range (IQR).

Viral load reduction from baseline to week 16 was estimated using the Kaplan–Meier method to take account of the values censored by the lower limit of detection of the assay.16

The safety analyses were performed on all subjects through the follow-up on an ITT approach ignoring the changes in the allocated treatment. Subsidiary on-treatment analyses (data were censored 30 days after the stop of the study treatment) were also performed. Kinetics of viral decay using $\log_{10}$-transformed HIV-1 RNA measures at days 3, 6 and 9 was estimated by a mixed linear model to determine the mean slope after day 3 and half-life, e.g. time to reduce by 50% the number of HIV RNA copies per mL of plasma.17

Results

Baseline characteristics and patient disposition

Recruitment took place between January and September 2006. Eighty-nine patients were screened for inclusion in the study, and 61 were randomized, 30 to Group 1 and 31 to Group 2 (Figure 1). Fifty-five patients (90%) completed the study. Baseline characteristics were similar in the two groups (Table 1). The median baseline HIV-1 RNA value was $4.9 \log_{10}$ copies/mL in Group 1 and $4.6 \log_{10}$ copies/mL in Group 2 ($4.8 \log_{10}$ copies/mL overall). Nineteen patients (31%) had HIV-1 RNA $\geq 100000$ copies/mL. The median CD4 cell count was $271/mm^3$ (265 in Group 1 and 274 in Group 2). Thirty-seven patients (61%) were infected by HIV-1 subtype B [18 (60%) in Group 1 and 19 (61%) in Group 2].

Primary efficacy endpoint at week 16

At week 16, 12/30 patients in Group 1 (40%, 95% CI 23%–58%) and 13/31 patients in Group 2 (42%, 95% CI 25%–59%) had an HIV RNA level $< 50$ copies/mL (Table 2). The estimated falls in viral load in Groups 1 and 2 were 3.1 and $2.9 \log_{10}$ copies/mL, respectively. Neither of the two dual PI/r regimens thus reached the specified threshold of early efficacy.

Therapy was modified before week 16 in eight patients, owing to adverse events (two patients in each group), to poor compliance (one patient in Group 1) or physician decision (one patient in Group 1 and two patients in Group 2). Eight patients with viral load $\geq 400$ copies/mL at week 16 were switched based on genotypic results and physician decision to a standard triple antiretroviral treatment, as required by the study protocol.

Predictors of virological efficacy

In the on-treatment analysis, the following parameters were not associated with the virological response at week 16: gender
(P = 0.71), the CD4 cell count at baseline (P = 0.87), the HIV subtype (B versus non-B, P = 0.61), the treatment group (P = 0.88) and the averaged plasma concentrations of atazanavir (n = 41, P = 0.47), amprenavir (n = 23, P = 1.0) and saquinavir (n = 19, P = 0.9). The only factor predictive of virological success was baseline viral load (median 4.3 log_{10} copies/mL in responders, 4.8 log_{10} copies/mL in non-responders; P = 0.0003). In a post hoc analysis, using a plasma viral load cut-off of 50000 copies/mL, virological response was obtained at week 16 in 21/33 patients (64%, CI 95% 47%–80%) with baseline viral load <50000 copies/mL and in only 3/19 patients (16%) with baseline viral load ≥50000 copies/mL (P = 0.0009). This figure becomes 23/44 (52%) in patients with a baseline HIV-1 RNA <100000 copies/mL compared with 1/8 (13%) in patients with baseline HIV-1 RNA ≥100000 copies/mL.

Early viral kinetics

For the 19 patients participating in the kinetics of virus decay substudy, the median change in viral load from day 0 to day 3 was −0.1 log_{10} copies/mL and from day 0 to day 9

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**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ATV + FPV/r, n = 30</th>
<th>ATV + SQV/r, n = 31</th>
<th>Total, n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>4 (13%)</td>
<td>7 (23%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0 (34.4–46.0)</td>
<td>36.4 (30.5–42.4)</td>
<td>39.2 (32.8–44.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.5 (61.0–77.0)</td>
<td>67.2 (60.0–74.7)</td>
<td>68.0 (61.0–75.0)</td>
</tr>
<tr>
<td>CDC class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>23 (77%)</td>
<td>24 (77%)</td>
<td>47 (77%)</td>
</tr>
<tr>
<td>B</td>
<td>7 (23%)</td>
<td>7 (23%)</td>
<td>14 (23%)</td>
</tr>
<tr>
<td>HIV-1 risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>homosexual</td>
<td>17 (57%)</td>
<td>12 (39%)</td>
<td>29 (48%)</td>
</tr>
<tr>
<td>heterosexual</td>
<td>11 (37%)</td>
<td>15 (48%)</td>
<td>26 (43%)</td>
</tr>
<tr>
<td>injection drug use</td>
<td>1 (3%)</td>
<td>3 (10%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>not known</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} copies/mL)</td>
<td>4.9 (4.6–5.1)</td>
<td>4.6 (4.3–5.0)</td>
<td>4.8 (4.4–5.1)</td>
</tr>
<tr>
<td>min–max</td>
<td>4.1–5.7</td>
<td>4.0–5.7</td>
<td>4.0–5.7</td>
</tr>
<tr>
<td>&lt;50000 copies/mL</td>
<td>10 (33%)</td>
<td>17 (55%)</td>
<td>27 (44%)</td>
</tr>
<tr>
<td>≥100000 copies/mL</td>
<td>11 (37%)</td>
<td>8 (26%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Subtype B</td>
<td>18 (60%)</td>
<td>19 (61%)</td>
<td>37 (61%)</td>
</tr>
<tr>
<td>CD4 (/mm3)</td>
<td>265 (223–320)</td>
<td>274 (255–312)</td>
<td>271 (243–312)</td>
</tr>
</tbody>
</table>

ATV, atazanavir; FPV, fosamprenavir; SQV, saquinavir; r, ritonavir.
Data are numbers of patients (%) unless otherwise stated.

*Median (IQR).

**Table 2. Primary efficacy endpoint at week 16 (HIV-1 RNA <50 copies/mL)**

<table>
<thead>
<tr>
<th></th>
<th>ATV + FPV/r, n = 30</th>
<th>ATV + SQV/r, n = 31</th>
<th>Total, n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint (HIV-1 RNA &lt;50 copies/mL at week 16), 95% CI</td>
<td>12 (40%), 23%–58%</td>
<td>13 (42%), 25%–59%</td>
<td>25 (41%), 29%–53%</td>
</tr>
<tr>
<td>Reasons for failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug modification before week 16</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>adverse event, n</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>investigator decision, n</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>non-compliance, n</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 copies/mL and &lt;400 copies/mL</td>
<td>11 (37%)</td>
<td>10 (32%)</td>
<td>21 (34%)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥400 copies/mL</td>
<td>3 (10%)</td>
<td>4 (13%)</td>
<td>7 (11%)</td>
</tr>
</tbody>
</table>

ATV, atazanavir; FPV, fosamprenavir; SQV, saquinavir; r, ritonavir.
Data are numbers of patients (%) unless otherwise stated.
Missing data and treatment modifications equal failure.
HIV-1 RNA on-treatment analysis, 19/21 (90%) and 19/19 (100%) had at weeks 24 and 48, respectively (ITT analysis). Using non-B strains [CRF02_AG (n=4), CRF06_cpx (n=2), G (n=1), J (n=1), CRF11_cpx (n=1), CRF18_cpx (n=1) and unknown (n=1)]. No major mutations associated with resistance to PIs (IAS-USA expert list of mutations, http://www.iasusa.org) were detected at baseline. The median (IQR) number of minor PI mutations was 3 (2–4), and was similar in the two groups.

The virus was genotyped at the time of virological failure in 21 of the 22 patients concerned (one sample was not amplifiable). Compared with baseline, no major PI resistance mutations were detected. Nine patients had viruses with minor PI resistance mutations (IAS-USA 2008) and other substitutions with an unknown influence on PI efficacy (L10I, V11I, K21E, L21F, K14R, L19I). The six remaining patients had substitutions not listed in IAS-USA 2008 (K57R, V11I, M36I, K43R, A71V and I93L). All the PI mutations were distributed in the protease domain, and were similar in the two groups. The six remaining patients had no changes in the protease gene between baseline and virological failure.

Follow-up from weeks 16 to 48

Virological responses by ITT and on-treatment analyses at weeks 24 and 48 are reported in Table 3. At week 48, 23/30 patients (77%) and 26/31 patients (84%) achieved plasma HIV-1 RNA <50 copies/mL in Groups 1 and 2, respectively.

For patients with baseline viral load <50 000 copies/mL, 5/6 (83%) had HIV-1 RNA <50 copies/mL at weeks 24 and 48, respectively (ITT analysis). Using on-treatment analysis, 19/21 (90%) and 19/19 (100%) had HIV-1 RNA <50 copies/mL at weeks 24 and 48, respectively.

Among the 61 patients, 29 discontinued their initial dual PI/r therapy; 13 changed for two NRTIs and a PI/r and 9 for two NRTIs and efavirenz. 4 had increased dose of saquinavir, 1 had lost to follow-up, 1 had withdrawn his consent and 1 had stopped treatment.

At week 48, 32 patients remained on their initial dual PI/r therapy. Patients who reached HIV-1 RNA <50 copies/mL at week 16 (26 patients) kept viral load <50 copies/mL until week 48 except for two patients (one had 69 copies/mL and another had discontinued the study treatments).

Genotyping results

At baseline, 24 (39%) patients were infected by HIV-1 subtype non-B strains [CRF02_AG (n=10), CRF01_AE (n=3), A1 (n=4), CRF06_cpx (n=2), G (n=1), J (n=1), CRF11_cpx (n=1), CRF18_cpx (n=1) and unknown (n=1)]. No major mutations associated with resistance to PIs (IAS-USA expert list of mutations, http://www.iasusa.org) were detected at baseline. The median (IQR) number of minor PI mutations was 3 (2–4), and was similar in the two groups.

The virus was genotyped at the time of virological failure in 21 of the 22 patients concerned (one sample was not amplifiable). Compared with baseline, no major PI resistance mutations were detected. Nine patients had viruses with minor PI resistance mutations (IAS-USA 2008) and other substitutions with an unknown influence on PI efficacy (L10I, V11I, K21E, L21F, K14R, L19I). The six remaining patients had substitutions not listed in IAS-USA 2008 (K57R, V11I, M36I, K43R, A71V and I93L). All the PI mutations were distributed in the protease domain, and were similar in the two groups. The six remaining patients had no changes in the protease gene between baseline and virological failure.

Immunological response

The median (IQR) increase in the CD4 cell count at week 16 relative to baseline was 122/mm³ (27–190) in the ITT analysis and 120/mm³ (52–187) in the on-treatment analysis. At week 48, the median (IQR) increase from baseline was 203 cells/mm³ (112–254) in the ITT analysis and 224 cells/mm³ (160–255) in the on-treatment analysis.

Adverse events

The most frequent adverse events (grade ≥2) were gastrointestinal disorders (23% of patients, 30% in Group 1 and 16% in Group 2), including diarrhoea (13%), abdominal pain (5%),
nausea (5%) and vomiting (3%). Eight patients (13%) had a skin rash, mainly in Group 1 (7/8).

Eighteen patients (30%) experienced at least a grade 3 or 4 adverse event, most of which were hyperbilirubinaemia [10 patients (16%); 3 (10%) in Group 1 and 7 (23%) in Group 2]. Two patients experienced hepatic cytolysis (Group 2). One patient (Group 1) developed acute cholecystitis after 4 weeks of treatment and underwent cholecystectomy. This patient continued on the same treatment and had plasma HIV-1 RNA <50 copies/mL at week 48.

Four patients (two in each group) discontinued treatment for adverse effects: two for grade 3 skin rash, one for dizziness and tachycardia, and one for grade 3 hepatic cytolysis. All adverse events leading to study drug discontinuation occurred before week 4.

At week 16, bilirubin was higher in Group 2 than in Group 1 (42 versus 26 mM, \(P=0.007\)), and triglyceride and LDL cholesterol in Group 1 than in Group 2 (1.4 versus 1.1 mM, \(P=0.036\) and 3.7 versus 2.8 mM, \(P=0.026\)).

At week 48, the lipid changes between groups remained statistically different. For bilirubin, the difference in change between groups was not significant (0.9 versus 1.3, \(P=0.23\)).

**Pharmacokinetics**

Plasma samples taken within 24 ± 4 h (atazanavir and saquinavir) or 12 ± 2 h (amprenavir) after the last drug intake were available for at least one visit in 46 patients. No deleterious pharmacokinetic interactions were observed between atazanavir and amprenavir/ritonavir or between atazanavir and saquinavir/ritonavir. Potentially effective trough plasma concentrations were obtained with boosted atazanavir, amprenavir and saquinavir (Figure 2). The median (IQR) of averaged atazanavir plasma concentrations was 616 (367–899) ng/mL in Group 1 and 742 (528–1042) in Group 2. The medians (IQRs) of averaged plasma saquinavir and amprenavir concentrations, respectively, were 164 (112–365) and 1568 (1210–2079) ng/mL. The intra-individual coefficients of variation of these concentrations were 16% for atazanavir, 22% for saquinavir and 5% for amprenavir.

No relationship was observed between PI trough plasma concentrations at week 4 and the virological response at week 16.

**Adherence**

In the on-treatment analysis at weeks 4, 8 and 16, 51/55 (93%), 47/51 (90%) and 49/49 (100%) patients reported no missed doses during the previous 4 days and 52/57 (91%), 52/53 (98%) and 49/49 (100%) patients reported no missed doses during the previous 4 weeks, respectively.

**Quality of life**

At baseline, median scores in the WHOQOL-HIV 31-BREF questionnaire were high in each domain: a median of 16 for physical, 15 for psychological, 17 for level of independence, 14 for social relationships, 14 for environment and 12 for spirituality.

At weeks 16 and 48, by on-treatment analysis, the median changes in scores from baseline were low, ranging from 0 to 1 for each domain. Results were similar between treatment groups, and there were no differences in changes according to the virological response at week 16.

**Discussion**

This clinical randomized pilot study showed that dual PI/r alone with atazanavir/ritonavir plus saquinavir or fosamprenavir are...
insufficient to provide a high rate of early virological success in antiretroviral-naive HIV-1-infected patients. Neither of these two regimens reached a success rate of at least 50% that would have qualified them as potent antiretroviral regimens for initial therapy according to our pre-specified criterion. These results were confirmed by two other studies evaluating dual PI/r in naive patients. The first reported a slow viral decline with a different dosing of saquinavir plus lopinavir/ritonavir; the second was terminated prematurely because the treatment lacked the potency of atazanavir plus lopinavir/ritonavir compared with a lopinavir/ritonavir-containing triple-drug regimen.

An early efficacy endpoint was selected in our trial as likely to be the most sensitive and discriminative of a potent regimen. We considered that a minimum of 50% efficacy at week 16 was required while rates >70% could be expected from the most potent regimens. Recent data from ACTG 5142 on two NRTIs plus efavirenz or lopinavir/ritonavir, as well as other studies with NRTIs plus atazanavir/ritonavir, fosamprenavir/ritonavir or darunavir/ritonavir, confirmed a virological efficacy of at least 55%–60% at week 16. Indeed, in our study, all patients with an early response at week 16 (<50 copies/mL), except one, maintained plasma HIV RNA <50 copies/mL throughout week 48.

Obviously, limitations of our study include the lack of a triple-drug group and the small number of patients included. Significant predictors of virological efficacy of dual PI/r regimens were previously described during salvage therapy and included the CD4 cell count and viral load at baseline, past antiretroviral exposure and previous PI resistance.

The poor virological results obtained in this study with naive patients were not due to problems of tolerability or compliance. Only four patients discontinued therapy because of clinical or biological adverse events, and adherence to both regimens was good. Trough plasma concentrations of boosted atazanavir, amprenavir and saquinavir were adequate, and PI trough plasma concentrations at week 4 did not influence the virological response at week 16. Antagonism has been observed in vitro between saquinavir and other PI on wild-type HIV and on saquinavir-resistant variants. We cannot exclude a molecular antagonism with atazanavir or fosamprenavir as this has not been described so far. The low penetration of these PIs in sanctuaries where production of viruses can occur might also explain some of the failures observed.

HIV-1 subtype (B or non-B) could not explain the poor virological efficacy at week 16. PIs are designed to fit the active site of the HIV-1 protease and are thus sensitive to structural changes in the viral protein. It was recently reported that the virological response to tipranavir/ritonavir- or lopinavir/ritonavir-containing regimens might be compromised in patients with HIV-1 non-clade B infection. As stated above, however, subtype non-B infection was not associated with poorer virological outcome at week 16 in our patients.

We found no link between the predicted individual mean slopes of early viral load and the subsequent virological response at week 16. Decline in viral load on day 9 (−1.4 log10 copies/mL) was similar to that obtained with two NRTIs + efavirenz on day 7 (−1.49 log10 copies/mL) in a sub-study of the ACTG 5142 trial. In our setting of first-line therapy, we demonstrated that a low baseline viral load was the only significant predictor for the early virological response. Indeed, in a post hoc analysis, patients with a baseline plasma HIV-1 RNA <50000 copies/mL achieved a 64% rate of virological responses at week 16 much closer to the expected value.

This difference in antiretroviral power notably affects the response rate in patients with higher levels of HIV RNA. The most probable reason for the limited efficacy observed in our trial is that dual PI/r regimens target only one step of viral replication, in the same way as triple NRTI and single PI regimens, which has consistently been insufficient to rapidly suppress plasma HIV RNA to <50 copies/mL in antiretroviral-naive patients with high viral load at baseline.

Furthermore, although direct comparisons with single PI regimens are lacking in our study, our data do not suggest that dual boosted PI combinations are more potent than single PI regimens.

Finally, the recent availability of new drugs, such as integrase inhibitors, second-generation NNRTIs, new PIs or CCR5 inhibitors, which bring more options to build nucleoside analogue-free combinations, further undermines the potential value of dual PI/r regimens.

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Transparency declarations

None to declare.
Dual boosted protease inhibitor regimens


References


