Initial therapy with nucleoside reverse transcriptase inhibitor-containing regimens is more effective than with regimens that spare them with no difference in short-term fat distribution: Hippocampe-ANRS 121 Trial

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Objectives: The aim of this study was to evaluate the impact on body fat of nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens compared with NRTI-containing therapy in HIV-1-infected antiretroviral (ARV)-naive patients.

Methods: A randomized, multicentre, open-label trial in ARV-naive patients. Subjects were randomized (2:1:1) to receive: (i) an NRTI-sparing regimen consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus a boosted protease inhibitor (PI/r); or (ii) an NRTI-containing regimen of (a) a PI/r plus two NRTIs or (b) an NNRTI plus two NRTIs. The primary endpoint was the change in subcutaneous limb fat measured by dual-energy X-ray absorptiometry at week (W) 96. Secondary endpoints included the proportion of patients with treatment failure, plasma HIV-RNA (pVL) <50 copies/mL and safety.

Results: One hundred and seventeen patients were enrolled between November 2003 and May 2004: 26% female; 42% from sub-Saharan Africa; median plasma HIV-RNA (pVL) 5.1 log10 copies/mL; median CD4 count 207 cells/mm3. A planned interim analysis demonstrated significantly lower treatment and virological responses with the NRTI-sparing strategy, resulting in premature study termination on 19 July 2005. The proportion of patients who remained on their assigned treatment strategy and had pVL <50 copies/mL on the NRTI-sparing regimen was 60.0%, compared with 82.5% on the NRTI-containing regimen at W24 (P = 0.009) and 66.7% and 82.5%, respectively, at W48 (P = 0.059). Treatment failure was associated with the NRTI-sparing strategy in patients with suboptimal adherence and with being from sub-Saharan Africa. No differences in fat distribution were noted.

Conclusions: An initial NRTI-sparing regimen is less successful and virologically less potent than standard NRTI-containing regimen and should not therefore be used as the first line of treatment.

Keywords: HIV-1, NRTI-sparing regimen, antiretroviral efficacy, lipoatrophy syndrome, tolerance

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Introduction

The use of effective antiretroviral therapy (ART) has resulted in a significant improvement in morbidity and mortality for HIV-infected individuals.1,2 The inability of any current antiviral regimen to actually eradicate HIV, coupled with the deleterious effects of any strategy involving treatment interruption,3 means that ART will have to be administered lifelong. Key factors for designing an optimal treatment strategy will therefore have to focus on the durability of antiviral efficacy and long-term tolerability.

Nucleoside analogues that inhibit reverse transcriptase (NRTIs) were the first ART drugs developed and they remain the classic backbone of today’s ART regimens. Although proven to be effective, they have known long-term safety problems including mitochondrial toxicity caused by their inhibition of mitochondrial polymerase-γ. One of the most disconcerting clinical consequences of this type of toxicity is lipoatrophy, which has been most directly associated with the thymidine analogues stavudine and zidovudine.4–7 The reversion of lipoatrophic changes has been observed after discontinuation of NRTIs; however, the process is slow and may be incomplete.8–11 The avoidance of lipoatrophy and other NRTI-related mitochondrial toxicities has led to an interest in investigating NRTI class-sparing regimens.12–16

The use of NRTI-sparing regimens in treatment-experienced patients has been shown to reduce mitochondrial toxicity and improve protease inhibitor (PI)-associated lipid abnormalities.14,16 Because of the slow reversibility of these changes in body composition, prevention of such complications is a treatment priority. To date, the most thoroughly investigated has been treatment with a combination of a ritonavir-boosted protease inhibitor (PI/r) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI). In light of these data, we designed this trial that compares a PI/r plus an NNRTI with standard regimens that include NRTIs in a group of patients initiating ART.

Patients and methods

Study design

The Hippocampe ANRS-121 study was a randomized, multicentre, open-label, clinical trial comparing two first-line treatment NRTI-sparing (NNRTI + PI/r) strategies: and two NRTI-containing (PI/r + NRTIs and NNRTI + NRTIs) strategies. The primary endpoint of the study was the change from baseline in limb fat as measured by dual-energy X-ray absorptiometry (DEXA) at week (W) 96. Randomization was stratified by sex to take into account the differences in fat distribution according to gender. Subjects were centrally randomized 2:1:1, respectively. The two randomization lists (one per stratum) were drawn with a block of size 6, using the SAS PLAN procedure. The Institutional Review Board of Pitie´-Salpeˆtrie`re Hospital approved the study protocol. All patients provided written informed consent. The ClinicalTrials.gov identifier was NCT00122668.

Patients

HIV-1-infected patients at least 18 years of age and ARV treatment-naive patients were eligible if they had a CD4 count <350 cells/mm³ and a plasma HIV-RNA (pVL) >5000 or >100 000 copies/mL regardless of the CD4 count.

Study treatment

Prior to randomization, investigators had to select two NRTIs among the currently available licensed ARV drugs, except stavudine and zalcitabine. They also selected which PI/r and which NNRTI they would prescribe depending on randomization. Ritonavir-boosted indinavir 400/100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily were the only PIs allowed, and nevirapine and efavirenz were the only NNRTIs allowed. To account for the drug–drug interaction between co-administered NNRTIs and PIs, ritonavir-boosted indinavir and lopinavir/ritonavir were given at higher doses (ritonavir-boosted indinavir 600/100 mg twice daily and lopinavir/ritonavir 533/133 mg twice daily)17 in NRTI-sparing regimens. In the event of drug intolerance, investigators were allowed to modify the treatment but to remain within the same ARV strategy—a change in strategy was considered a treatment failure.

Study follow-up

Patients were seen at screening, baseline (D0), W2, W4 and W12 and then every 12 weeks until W96. At each visit, subjects had routine safety monitoring, CD4+ cell counts and pVL (Amplicor® ultrasensitive). HIV-DNA in peripheral blood mononuclear cells (PBMCs) was quantified at D0, W48 and W96 according to published techniques.18 Genotype resistance testing was performed at each time point after W24 when pVL was >50 copies/mL and retrospectively for the baseline sample. No genotype resistance test was performed systematically at enrolment, because this was introduced in the French guidelines only in 2006. Mutations associated with reduced ARV drug susceptibility were based on the International AIDS Society-USA Panel Guidelines.19 Fasting lipids including triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured at D0, W12, W24, W48, W72 and W96, and glucose and lactates were measured at D0, W48 and W96. DEXA was used to quantify total and regional body fat (limb) at D0, W48 and W96 with centralized analysis. Lunar® and Hologic® DEXA devices were used, the same device being always used for a given patient. Quality controls were performed centrally on DEXA to verify the validity of imaging procedures. Only images that satisfied the quality control were considered as available. The adherence was measured at W4, W24, W48, W72 and W96 using the ANRS self-reported questionnaires based on 4 day recall.20,21 Using this technique, the level of adherence is classified in three levels: <80%, 80% to 99% and >99%. Lopinavir, indinavir, efavirenz and nevirapine plasma trough concentrations (Cmin) were determined by high-performance liquid chromatography at W4, W12, W24 and W96 and whenever virological failure or adverse events were observed. Adjusting of the PI dosage was recommended if the Cmin was subtherapeutic. The Cmin (12 h) was defined as adequate if the concentration was ≥3000 ng/mL for lopinavir,22,23 ≥150 ng/mL for indinavir,24–26 ≥3400 ng/mL for nevirapine27–29 and ≥1100 ng/mL for efavirenz.30

Exclusion criteria included any active AIDS-defining illness in the last 30 days, acute viral hepatitis, chronic hepatitis B or C requiring specific therapy, any cytotoxic chemotherapy, aspartate aminotransferase and/or alanine aminotransferase value or serum creatinine concentration more than two times the upper limit of normal, haemoglobin level <8 g/dL, platelet count <20 000/mm³ or an absolute neutrophil count <750 cells/mm³, pregnancy or breastfeeding.

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Study endpoints

The primary endpoint was the change in limb fat between baseline and W96, as evaluated by DEXA. Secondary endpoints included: the proportion of patients with treatment failure as defined by pVL >50 copies/mL at W48 or any change in treatment strategy, the proportion of patients with pVL <50 copies/mL at W48 and W96, the evolution of the viral load, the PBMC HIV-DNA, characterization of the resistance profile in case of virological failure, change in the CD4 count, the number of serious adverse events (SAEs), the change in limb fat between baseline and W48, and adherence and the change in fasting lipids, glucose and lactate levels.

Statistical considerations

There were two primary comparisons: change in limb fat between baseline and W96 in the NRTI-sparing group compared with each of the arms of the NRTI-containing strategy: the PI/r + NRTIs arm and the NNRTI + NRTIs arm. Assuming an SD of 650 g as in the Mitox study, by including 50 patients in the NRTI-sparing group and 25 patients in each of the two NRTI-containing arms, the study had 95% power to detect a difference of 650 g in the change of limb fat up to W96 between the NRTI-sparing group and each of the NRTI-containing arms, with a type-I error of 2.5% for each comparison and a two-sided non-parametric test. To account for the dilution effect associated with non-assessable patients, 112 patients were planned to be enrolled. With this sample size, the power to test non-inferiority on the percentage of patients with a pVL <50 copies/mL in the NRTI-sparing group compared with the two NRTI-containing arms combined was 69% with a non-inferiority limit of 15%.

To ensure the virological safety of the new strategy, an interim analysis comparing the proportion of patients with pVL <400 copies/mL between the two treatment strategies (NRTI-sparing and NRTI-containing regimens) had been planned after half of the randomized patients had reached W24. Following this interim analysis on 6 October 2004, the Data and Safety Monitoring Board (DSMB) requested a second interim analysis using <50 copies/mL for pVL. Based on this analysis, on 6 July 2005 the DSMB recommended that the study be stopped because of more treatment and virological failures with the NRTI-sparing strategy. The discontinuation of the study was effective from 19 July 2005. For patients with an NRTI-sparing regimen, a change of treatment was advised if the viral load was above the limit of detection, after performing a genotype to choose the new treatment according to the French guidelines, while no change was advised for those with an undetectable viral load. We report here the results at W48, as all patients had completed W48 evaluation at the time of the study discontinuation.

Ninety-five percent confidence intervals were calculated to assess non-inferiority for virological failure endpoints, with a non-inferiority limit of 15% in a per-protocol analysis (ignoring missing data and modification of ARV strategy), and for treatment failure endpoints in an intent-to-treat (ITT) analysis (with missing data and modification of ARV strategy equaling failure). Fisher’s exact test was used to compare the proportion of patients with pVL <50 copies/mL and no change in strategy between the NRTI-sparing group and the two NRTI-containing arms combined, with an ITT approach (missing = failure). Additionally, we compared each NRTI-containing arm with the NRTI-sparing group. With regard to the other endpoints, the analyses were performed with an ITT approach on available data and any two arms or strategy were compared. Continuous variables were expressed as the mean and SD or the median and range, at baseline and at W48. Changes between baseline and W48 were compared between the groups by using the non-parametric Mann–Whitney test.

For change in viral load, the censoring of viral load measurements due to lower limits of the assay was accounted for by use of a program designed for parametric survival analysis models (e.g. PROC LIFERING in SAS, using the IDST = Normal option).

Univariate and multivariable logistic regressions were used to assess the factors associated with treatment failure, defined as pVL >50 copies/mL at W48 or change in treatment strategy. The following variables were assessed: age, sex, ethnic origin, transmission group, baseline CD4, baseline pVL, baseline HIV-DNA in PBMCs, virus subtype, prior AIDS event, known duration of HIV infection, adherence at W4 and W24 and Cmin above the threshold in at least two of three evaluations at W2, W12 and W24. Variables with a P value <0.20 in the univariate analysis were retained for the multivariable analysis. Interactions between treatment strategies and these variables were systematically looked for and retained when P < 0.10. Following this, a backward multivariable model was built to determine the independent predictors of treatment failure. All reported P values were two-tailed, with a significance level of 0.05. Analyses were performed with the SPSS software package version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient disposition

Between November 2003 and May 2004, 118 patients were enrolled from 23 centres in France. Patient disposition is presented in Figure 1. One patient never received study treatment and was excluded from the analysis, hence 117 patients were analysed: 60 in the NRTI-sparing group and 57 in the NRTI-containing group, with 29 in the PI/r + NRTIs arm and 28 in the NNRTI + NRTIs arm.

Patient characteristics

Baseline characteristics were well balanced between the two strategies (Table 1). Overall, 74% were male and 40% were from sub-Saharan Africa. HIV infection was diagnosed at a median of 6 months prior to study entry. The baseline median CD4 count was 207 cells/mm³ and median pVL was 5.1 log10 copies/mL. In the 60 patients in the NRTI-sparing group, 33 received efavirenz plus lopinavir/ritonavir, 14 received nevirapine plus lopinavir/ritonavir, 8 received nevirapine plus ritonavir-boosted indinavir and 5 patients received efavirenz plus ritonavir-boosted indinavir. In the 57 patients from the two NRTI-containing arms, the NRTI backbone was zidovudine plus lamivudine in 51, didanosine plus lamivudine in 4 and tenofovir plus lamivudine in 2 patients; these nucleoside combinations were administered with lopinavir/ritonavir in 15, ritonavir-boosted indinavir in 14, efavirenz in 22 and with nevirapine in 6 patients.

Subtype determination of viruses showed that 44% of the patients harboured a B subtype, 32% a CRF02-AG subtype. At baseline, retrospective genotype testing showed that four patients (3.4%) had RT mutations (L210W T215D; T215S; M41L T215S; L210W); three of the four patients were in the NRTI-sparing group; none experienced virological failure.

Evolution of subcutaneous fat tissue

At baseline, the mean subcutaneous limb fat measured by DEXA was 6.7 kg (SD 3.8) with no difference between the groups.
Because of premature study discontinuation, the primary endpoint could not be measured at W96; however, the W48 results (a planned secondary endpoint) were available and analysed in 98 subjects, with no difference noted between the groups and an overall mean limb fat increase of 0.7 kg (SD 1.7) (Table 2).

**Virological and immunological responses**

In the interim analysis, designed to ensure that the two strategies had similar treatment and virological efficacy, an assessment at each time point was made comparing pVL in the NRTI-sparing group with the two NRTI-containing arms combined. At each time point, less than four patients had missing pVL values. Since the upper limits of the 95% confidence interval (CI) of the difference between the two groups were above the non-inferiority margin (15%) at all time points, non-inferiority was rejected in the per-protocol analysis (Figure 2a) and in the ITT analysis (Figure 2b). Moreover, the proportion of patients with treatment success was significantly lower at each time point in the NRTI-sparing group compared with the two NRTI-containing arms combined (Figure 2b). By ITT analysis (missing ARV strategy or modifying it equalled failure), the proportion of patients with treatment success at W24 was 60.0% in the NRTI-sparing group compared with 82.5% for the NRTI-containing strategy ($P = 0.009$), the corresponding figures were 66.7% and 82.5% at W48 ($P = 0.059$). Because the NRTI-sparing group had significantly less treatment and virological efficacy, the DSMB recommended that the study be terminated.

The proportion of patients who achieved a pVL $< 50$ copies/mL and no change of the allocated strategy was 60% in the NRTI-sparing group compared with 76% in the PI/r + NRTIs arm and 89.3% in the NNRTI + NRTIs arm at W24. By W48, these proportions were 66.7%, 83% and 82.1%, respectively (Figure 2c). Similar results were observed in the per-protocol analysis (data not
NRTI-sparing regimen suboptimal as initial therapy

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>NRTI-sparing regimen</th>
<th>NRTI-containing regimen (n = 57)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NNRTI + PI/r (n = 60)</td>
<td>PI/r + NRTIs (n = 29)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>Transmission groups, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>men having sex with men</td>
<td>30</td>
<td>52</td>
</tr>
<tr>
<td>heterosexual</td>
<td>63</td>
<td>41</td>
</tr>
<tr>
<td>unknown/other</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Ethnic origins, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasians</td>
<td>22 (37)</td>
<td>17 (59)</td>
</tr>
<tr>
<td>sub-Saharan Africans</td>
<td>29 (49)</td>
<td>10 (35)</td>
</tr>
<tr>
<td>others</td>
<td>8 (14)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>HIV subtype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>19 (33)</td>
<td>16 (55)</td>
</tr>
<tr>
<td>CRF02-AG</td>
<td>20 (35)</td>
<td>10 (35)</td>
</tr>
<tr>
<td>others</td>
<td>18 (32)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Median [IQR] HIV DNA in PBMCs, log_{10} copies/10⁶ PBMCs</td>
<td>3.06 [2.79–3.35]</td>
<td>3.04 [2.82–3.43]</td>
</tr>
</tbody>
</table>

As shown). Of note, in the NRTI-sparing group, results were not significantly different for patients receiving efavirenz plus lopinavir/ritonavir, the most frequent regimen (33/60), and in patients receiving other NRTI-sparing combinations (on treatment analysis: 63% versus 70% at W24, \( P = 0.773 \) and 76% versus 88% at W48, \( P = 0.463 \); ITT analysis: 52% versus 70% at W24, \( P = 0.188 \) and 58% versus 78% at W48, \( P = 0.168 \). At W4, the early kinetics of decrease in pVL was different between the groups, with \(-2.20 \log_{10} \text{ copies/mL}\) in the NRTI-sparing group, \(-2.35 \log_{10} \text{ copies/mL}\) in the PI/r + NRTIs arm (\( P = 0.212 \)) and \(-2.69 \log_{10} \text{ copies/mL}\) in the NNRTI + NRTIs arm (\( P = 0.0001 \)) (Figure 3a).

The mean baseline PBMC HIV-DNA was 2.98 (SD 0.50) \log_{10} \text{ copies/10}^6 \text{ PBMCs}\) with no difference between the treatment arms. Overall, the mean change in PBMC HIV-DNA over the 48 week period was similar in each arm with a decrease of \(-0.47 \log_{10} \text{ copies/10}^6 \text{ PBMCs}\) (SD 0.42; \( P = 0.47 \)) between baseline and W48.

There was no significant difference in the median increase in CD4 cell counts at W48 between the groups (+149, +198 and +137 CD4 cells/mm³, respectively; \( P = 0.73 \)) (Figure 3b). Three quarters of the patients reported high adherence to therapy (>99% intake) with no difference between arms (71%, 79% and 77% in the NRTI-sparing group, the PI/r + NRTIs arm and the NNRTI + NRTIs arm, respectively; \( P = 0.687 \)). As only five patients reported an adherence lower than 80% (4%) and 24% (21%) a level between 80% and 99%, in the following analyses, a high level of adherence was defined as >99% intake.

Genotypic resistance
Overall, 24 (20.5%) patients experienced treatment failure defined by pVL >50 copies/mL at W48 or change in treatment strategy, 17/60 (28.3%) in the NRTI-sparing group, 4/29 (13.8%) in the PI/r + NRTIs arm and 3/28 (10.7%) in the NNRTI + NRTIs arm. In the NRTI-sparing group, nine failures were early (failure to become undetectable), which led to a change in strategy in six; six were late (rebound of detectable viraemia after having become undetectable) and there were two changes of strategy for adverse events. In the PI/r + NRTI arm, there were two early and two late failures and one early and two late failures in the NNRTI + NRTIs arm. Genotypic resistance testing was available for 14, 3 and 3, respectively. In the NRTI-sparing group, mutations conferring resistance to NNRTI were detected in 6/14 samples (K103N in 3, V106M in 3, Y188H in 1 and Y181C in 1) compared with 1/3 (K103N) in the NNRTI + NRTIs arm. A primary PI mutation (V82A) was detected in one sample from the NRTI-sparing group and none in the PI/r + NRTIs arm. No NRTI mutation was detected. Overall, wild-type viruses were detected in 7/14 in the NRTI-sparing group, 3/3 in the PI/r + NRTI arm and 2/3 in the NNRTI + NRTI arm.

Predictive factors of virological failure or changing strategy
The results of the multivariable analysis of predictive factors of virological failure or changing strategy are shown in Table 3. An interaction between strategy and adherence was seen, and the patient’s origin was also associated with the risk of failure. Patients originating from sub-Saharan Africa had a 2.8-fold increased risk of failure when compared with patients from other origins (\( P = 0.053 \)). When compared with patients receiving an NRTI-containing regimen with a high level of adherence, the risk of failure was not significantly different in patients receiving an NRTI-containing regimen with a low level of adherence, or in patients receiving an NRTI-sparing regimen with a high level...
of adherence. The risk was increased 6.9-fold in patients receiving an NRTI-sparing regimen with a low level of adherence ($P = 0.006$), suggesting that NRTI-sparing regimens are less forgiving compared with NRTI-containing regimens.

**Safety assessment and lipid parameters**

Thirty-two SAEs occurred in 28 patients in the NRTI-sparing group, compared with 9 SAEs in 9 patients in the PI/r + NRTIs arm and 16 SAEs in 13 patients in the NNRTI + NRTIs arm; there was no significant difference between the three groups ($P = 0.340$) (Table 4). The changes in metabolic parameters between baseline and W48 are shown in Table 2. The increase in total cholesterol, LDL cholesterol and triglycerides were significantly higher in the NRTI-sparing group compared with the NNRTI + NRTIs arm between baseline and W48, with only one patient experiencing a grade 4 SAE.

**Discussion**

The study was originally designed to evaluate the effect on body fat composition of an NRTI-sparing treatment strategy compared with standard NRTI-containing triple combinations, which included either a boosted PI or NNRTI. Our hypothesis was that the NRTI-sparing strategy would have fewer adverse effects on body fat composition during the first 2 years of treatment and that this strategy would have the same treatment and virological efficacy as standard therapy—an essential goal of any first-line therapy—as suggested by switch studies and other comparative trials. While the evolution of subcutaneous limb fat was similar among the three groups with a mean increase of 0.7 kg (SD 1.7) at W48, a finding observed in previously reported studies in the first year following antiretroviral treatment initiation,9,31–36 we were not able to assess the long-term impact of the tested strategies on body fat because of the interruption of the study. We also found that an NRTI-sparing regimen had a worse impact on the lipid profile than an NNRTI + NRTIs-containing regimen, as observed previously.36

Unexpectedly, our study showed that the NRTI-sparing strategy was less effective than the NRTI-containing strategy. By ITT analysis, the proportion of patients successfully treated at W24 was smaller in the NRTI-sparing strategy (60.0%) than in the NRTI-containing strategy (82.5%). At W48, these proportions were 66.7% and 82.5%, respectively.

In trials studying ART-naive populations, the percentage of patients achieving plasma pVL levels <50 copies/mL at 48 weeks increased over time.37 In more recent trials, >80% of the patients may reach this threshold.33,34,38–41 The best responses are achieved in patients receiving either NNRTI- or boosted PI-containing regimens in combination with two NRTIs.37 Drug resistance appears to be less commonly reported among patients receiving boosted PI-containing regimens than NNRTI-containing regimens.32

In the open-label BIKS trial,13 21 treatment-experienced and 65 ARV-naive patients received a combination of lopinavir/ritonavir + efavirenz; the proportion of patients with a pVL <50 copies/mL at W48 was 69%. More recently, another NRTI-sparing study assessing efavirenz + atazanavir/ritonavir at

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**Table 2.** DEXA measurements and metabolic parameters (ITT analysis on available data); comparator = NNRTI + PI/r group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NNRTI + PI/r (n = 49)</th>
<th>PI/r + NRTIs (n = 28)</th>
<th>NNRTI + NRTIs (n = 21)</th>
<th>PI/r + NRTIs (n = 28)</th>
<th>NNRTI + NRTIs (n = 21)</th>
<th>PI/r + NRTIs (n = 28)</th>
<th>W48 baseline mean (SD)</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limb fat (kg)</strong></td>
<td>7.06 (4.04)</td>
<td>6.26 (2.47)</td>
<td>6.47 (4.72)</td>
<td>32.2 (3.26)</td>
<td>22.8 (2.43)</td>
<td>9.97 (1.98)</td>
<td>0.79 (1.63)</td>
<td>—</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.3 (4.34)</td>
<td>3.53 (1.75)</td>
<td>0.90 (1.79)</td>
<td>0.39 (1.37)</td>
<td>0.92 (1.96)</td>
<td>0.135</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Triglyceride level (mmol/L)</strong></td>
<td>0.71 (0.73)</td>
<td>1.22 (0.85)</td>
<td>0.43 (0.74)</td>
<td>0.05 (0.51)</td>
<td>0.589</td>
<td>0.019</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/L)</strong></td>
<td>4.41 (0.97)</td>
<td>4.34 (0.96)</td>
<td>1.02 (0.95)</td>
<td>1.11 (0.49)</td>
<td>0.589</td>
<td>0.055</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.06 (0.30)</td>
<td>1.09 (0.29)</td>
<td>0.14 (0.30)</td>
<td>1.13 (0.26)</td>
<td>0.31 (0.25)</td>
<td>0.328</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/L)</strong></td>
<td>2.84 (0.79)</td>
<td>2.70 (0.77)</td>
<td>0.65 (0.70)</td>
<td>2.90 (0.92)</td>
<td>0.22 (0.69)</td>
<td>0.007</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Glycaemia (mmol/L)</strong></td>
<td>5.11 (1.40)</td>
<td>5.08 (0.64)</td>
<td>0.06 (0.45)</td>
<td>4.94 (0.88)</td>
<td>0.47 (0.64)</td>
<td>0.090</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Lactate level (mmol/L)</strong></td>
<td>1.41 (0.73)</td>
<td>1.03 (0.30)</td>
<td>0.20 (0.83)</td>
<td>1.46 (0.70)</td>
<td>0.20 (0.50)</td>
<td>0.082</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$Comparison versus NNRTI + PI/r.
NRTI-sparing regimen suboptimal as initial therapy

Figure 2. Proportion of patients with plasma HIV-RNA <50 copies/mL between W4 and W48. (a) Comparison between the NRTI-sparing group and the two NRTI-containing arms combined in the per-protocol analysis (ignoring missing and modification of ARV strategy). The 95% CIs of the difference in the proportion of patients with plasma HIV-RNA <50 copies/mL are reported in parentheses. (b) Comparison between the NRTI-sparing group and the two NRTI-containing arms combined in the ITT analysis (missing and modification of ARV strategy equal failure). The 95% CIs of the difference in the proportion of patients with treatment success are reported in parentheses. The $P$ value of the $\chi^2$ tests are also reported. (c) Comparison between the NNRTI + PI/r arm, the PI/r + NRTIs arm and the NNRTI + NRTIs arm in the ITT analysis (missing and modification of ARV strategy equal failure). The two reported $P$ values correspond to the comparison of the NNRTI + PI/r arm with the PI/r + NRTIs arm and with the NNRTI + NRTIs arm.
two dosages in naive patients reported that 63% and 61% with atazanavir/ritonavir 300/100 and 400/100 mg, respectively, had pVL <50 copies/mL at W48. The results in these studies are very similar to our own where 66.7% in the NRTI-sparing arm had <50 copies/mL at W48 in the ITT analysis. But this success rate is much smaller that the one we observed in the NRTI-containing strategy (82.5%).

In contrast to our study, the results of ACTG 5142 study did not demonstrate a difference in virological outcomes between NRTI-sparing and NRTI-containing groups. In that trial, treatment-naïve patients were randomized to receive an NRTI-sparing regimen consisting of lopinavir/ritonavir + efavirenz or an NNRTI-sparing regimen of lopinavir/ritonavir + 2 NRTIs or a PI-sparing regimen of efavirenz + 2 NRTIs. By ITT analysis...
At W96, the proportion of patients with pVL \(<50\,\text{copies/mL}\) were 83%, 77% and 89% for the NRTI-sparing regimen, the NNRTI-sparing and the PI-sparing arms, respectively. A possible explanation for these conflicting virological results between our study and ACTG 5142 might be that we counted any change in strategy as a treatment failure. There were eight such ‘failures’ occurring in our NRTI-sparing group versus none in the other two arms, which might have influenced the ITT analysis. As no difference was evident between patients receiving efavirenz plus lopinavir/ritonavir and patients receiving other NRTI-sparing combinations, the differences in regimen are unlikely to explain the difference between our study and ACTG 5142 study.

In the multivariable analysis, patients from sub-Saharan Africa had a 2.8-fold increase in the risk of failure compared with patients from other regions. Three cohort studies have shown a poorer virological response in African versus European patients, which has been attributed by the authors to a possible lack of adherence, even though this was not formally or thoroughly assessed.\(^43\)–\(^45\) More recently, ACTG A5095\(^46\) reported a greater effect of non-adherence on virological failure in blacks given efavirenz-containing regimens than in whites. Some studies pointed out differences in efavirenz pharmacokinetics in African patients compared with patients from other origins, explained by specific mutations in the CYP2B6 gene leading to higher concentrations of efavirenz in African patients.\(^47\)–\(^48\) Conversely, several studies have shown that adherence to ART and response to ART did not appear to differ according to birthplace.\(^49\)–\(^51\) Several reports indicate that individuals living in poverty in industrialized settings have suboptimal adherence whatever the ethnic origin.\(^52\) In our study, being from sub-Saharan Africa is a predictive factor for virological failure independent of adherence. Additionally, there was no difference in self-reported adherence (W24) according to country of origin with 69% adherence in sub-Saharan patients and 77% in others (\(P = 0.381\)). The reasons why origin is associated with virological outcome independent of adherence in the Hippocampe study are therefore not clearly understood. The slight imbalance on origin seen at baseline between the NRTI-sparing group and the NRTI-containing group did not explain the difference in virological failure, as the treatment group was still a significant predictor of treatment failure after adjusting for origin.

Our study also showed that the level of adherence necessary for complete viral suppression is much higher when using an NRTI-sparing regimen than an NRTI-containing regimen, suggesting that NRTI-sparing regimens are less forgiving compared with NRTI-containing regimens. This difference is not explained by drug–drug interactions (data not shown), but may be due to the discordant half-lives of the NNRTI and PI/r, with the NNRTI half-lives being much longer than the PI/r half-lives.

Table 4. Number of serious adverse events and number of patients with serious adverse events (in brackets) reported within the study follow-up

<table>
<thead>
<tr>
<th></th>
<th>NRTI-sparing NNRTI + PI/r</th>
<th>NRTI-containing PI/r + NRTIs</th>
<th>NRTI-containing NNRTI + NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT &gt;5 UNL</td>
<td>7 (7)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>(including hypersensitivity syndrome)</td>
<td>2 (2)</td>
<td>0</td>
<td>(1) (1)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Elevated triglyceride level</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections (including OI)</td>
<td>9 (1) [8 (1)]</td>
<td>3 (1) [3 (1)]</td>
<td>3 (1) [2 (1)]</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1 (1)</td>
<td>0</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (7)</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total events</td>
<td>32 (28)</td>
<td>9 (9)</td>
<td>16 (13)</td>
</tr>
</tbody>
</table>

\(^{43\)–\(^45\) A high level of adherence was defined by >99% intake.
Patients with suboptimal adherence could functionally have periods of NNRTI-monotherapy and therefore would be more likely to select for resistance mutations. As NRTI-sparing regimens have shown that they can maintain full viral suppression in pre-treated patients who switched from a classic NRTI-containing regimen while pVL is already <50 copies/mL, this strategy should not be discarded entirely, but is insufficiently reliable in the population of ARV-naive patients with relatively advanced disease, as it demands a very high level of adherence.

In conclusion, our results show that in ARV-naive patients, an NRTI-sparing strategy was virologically less potent and less well tolerated than standard NRTI-containing ART regimens and therefore should not be recommended as first-line therapy.

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Presented at the XVle IAS, Toronto, Canada, 2006 (Abstract THPE0112).

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Members of the Hippocampe study team:


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Transparency declarations

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