A prospective comparison of the two main indications of efavirenz in 2001 highly active antiretroviral therapy (HAART) regimens: first-line versus salvage use

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Objective: To determine the efficacy of efavirenz introduction in first-line HAART compared with salvage multidrug regimens.

Patients and methods: Prospective 15 month comparison of 107 consecutive HIV-infected patients starting efavirenz, according to laboratory and clinical outcome of first-line versus rescue drug use, therapeutic history and association of selected antimicrobial agents: naive patients were compared with nucleoside reverse transcriptase inhibitor (NRTI)-experienced patients in the first group, and patients in the second group who had one or more NRTI changed when starting a rescue treatment containing one or more novel protease inhibitors (PIs) were compared with those who did not.

Results: Efavirenz was administered with one or more novel NRTIs to 55 patients (27 antiretroviral-naive and 28 patients experienced with NRTIs only), compared with 52 patients who needed a multidrug salvage regimen after two or more failures of a 15–40 month PI-containing regimen. In an intention-to-treat analysis, considering early interruption or an unsatisfactory virological course as a failure, only one patient on salvage therapy completed a favourable 15 month follow-up, compared with 31 patients experiencing first-line efavirenz-based HAART (P < 0.0001). The immunological response was less affected in both intensity and duration in patients undergoing rescue therapy. While no significant outcome difference was detected in the first group between naive and NRTI-experienced patients, among the salvage subjects the change of one or more NRTIs seemed to significantly improve virological and immunological outcome. Viral genotyping detected at least the K103N mutation in 41% of the 78 evaluable patients, despite lack of exposure to efavirenz and related compounds. Salvage patients had a significantly greater frequency of non-nucleoside RTI (NNRTI) resistance compared with the first-line group (P < 0.0001), in proportion to the extent of mutations affecting other drug classes (P < 0.0001).

Conclusion: An efavirenz-based initial triple drug HAART proved significantly more effective than efavirenz adjunct to a rescue treatment performed after repeated failures of PI-based regimens. The unsatisfactory response of the salvage group was probably due to diffuse cross-resistance descending from previous therapy, even when NNRTIs were never administered.

Keywords: antiretroviral resistance, efavirenz, efficacy, first-line treatment, highly active antiretroviral therapy, salvage regimen

Introduction

Non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz, nevirapine and delavirdine) are presently recommended as part of an initial combined antiretroviral therapy (as demonstrated in a number of controlled, randomized studies), but are also suggested as a switch therapy in patients failing to tolerate protease inhibitor-containing associations due to short- or long-term toxicity, as a replacement for protease inhibitors in attempts at treatment simplification or de-
intensification, and especially as an adjunct to a salvage multidrug regimen to be carried out in patients with previous (usually repeated) failure of highly active antiretroviral therapy (HAART) based on protease inhibitors or other combined compounds. However, as far as we know no controlled data are available comparing the two most frequent modes of efavirenz administration (i.e. first-line versus salvage HAART).

The aim of our study was to make a prospective intention-to-treat comparison of a mid-term (15 month) laboratory and clinical outcome of efavirenz introduced as part of first-line triple antiretroviral therapy versus efavirenz added to a salvage anti-HIV regimen following failure of at least two protease inhibitor-based HAART combinations.

Patients and methods

The virological, immunological and clinical response of patients who started for the first time a triple antiretroviral treatment based on efavirenz and two nucleoside analogues (group A) was prospectively compared with that of subjects who received efavirenz plus at least one novel protease inhibitor and two nucleoside analogues in a salvage antiretroviral therapy following failure of an at least second-line protease inhibitor-based drug regimen (group B). After informed consent was obtained from each patient involved in the study, treatment initiation or modification was conducted according to the updated international recommendations for antiretroviral therapy, and standard dosages of study drugs were administered.

Taking into account the entire cohort of subjects followed at our reference centre (c. 1000 patients per year), the present intention-to-treat study included all consecutive HIV-infected subjects starting efavirenz since 1999. Laboratory and clinical data were reported for patients who completed at least a 15 month follow-up. Early treatment failures, which were therefore excluded from the 15 month analysis, included: patients who abandoned treatment before the end of the study owing to voluntary withdrawal, intolerance or toxicity; patients who were lost to follow-up; patients who had a <90% adherence to all scheduled treatments and clinical and laboratory controls throughout the study period (as declared by patients and checked by monthly visits and drug accountability performed at our outpatient centre); and patients for whom therapeutic changes had to be made due to evident clinical worsening, severe virological failure (increase of plasma viral load ≥1 log10 within the first 6 months) or rapid immunological deterioration (a≥20% drop in CD4+ lymphocyte count versus baseline within the first 6 months).

Each treatment group (A and B) that remained evaluable up to 15 months underwent further subanalysis, comparing patients naïve to antiretrovirals (group A1) with those already treated with nucleoside analogues (group A2), and patients who changed at least one nucleoside analogue at the time of efavirenz salvage therapy (group B1) with those in whom it was not possible to introduce one novel nucleoside analogue when switching to rescue treatment, because of demonstrated genotypic resistance to, or previous use of, all available compounds of this class (group B2). The primary study end-points were virological and immunological success compared with baseline features (according to international recommendations), tolerability index to the administered compounds and occurrence of novel or relapsing AIDS-defining diseases; the secondary end-points were related to the role of eventual, previous or concomitant antiretroviral therapy, and the underlying pattern of viral genotypic resistance.

Plasma HIV RNA levels were determined by a commercial ultrasensitive branched-DNA assay (Quantiplex HIV-RNA 3.0; Chiron, Emeryville, CA, USA) with a minimum detectable level of 50 copies/mL. Viral genotyping was carried out concurrently with efavirenz introduction whenever possible (78 out of 107 cases, 72.9%), using the standardized commercial kit Trugene HIV-1 (Visible Genetics, Toronto, Canada). All other resistance assays (genotypic and/or phenotypic) obtained or repeated after study initiation were not considered in this study, due to lack of reliable temporal comparison and relation with ongoing administered drugs.

Clinical assessment was performed according to the 1993 Centers for Disease Control staging: a new AIDS-related event or a relapse of a previously diagnosed disease represented the end-point of early clinical failure. Criteria for clinical and laboratory drug tolerability took into account the updated international guidelines for the management of antiretroviral therapy and the WHO drug toxicity grading.

Statistical analysis was carried out using Student’s t-test, Mantel–Haenszel χ2 test or Fisher’s exact test where appropriate, with the significance level set at P < 0.05.

Results

In group A (55 consecutive patients), efavirenz was started in combination with two nucleoside analogues in 27 patients naïve to antiretroviral compounds (group A1), whereas in the remaining 28 cases (treated with different nucleoside analogues for 13.1 ± 6.1 months, range 10–21 months) efavirenz was added to a combination including at least one novel nucleoside analogue (group A2). In group B (52 consecutive individuals), efavirenz was introduced together with the protease inhibitor nelfinavir in 27 patients, indinavir in nine and ritonavir-based dual protease inhibitor regimens in the remaining 16 subjects, after 39.3 ± 6.1 months of previous antiretroviral therapy, including 15–40 months (mean 23.1 ± 5.1 months) of administration of protease inhibitors different from those introduced as a salvage regimen. In group B, at the time of efavirenz adjunct, 27 patients did have at least one concurrent...
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Table 1. Clinical, therapeutic and laboratory features of study patients

<table>
<thead>
<tr>
<th>Patients’ features</th>
<th>Group A (n = 55)</th>
<th>Group B (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group A1 (n = 27)</td>
<td>group A2 (n = 28)</td>
</tr>
<tr>
<td>No. patients with early interruption (due to intolerance/failure/clinical deterioration)</td>
<td>2 (2/0/0)</td>
<td>4 (4/0/0)</td>
</tr>
<tr>
<td>No. patients still evaluable after 15 months</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Mean log$_{10}$ HIV RNA copies/mL (± S.D.) at baseline</td>
<td>4.2 ± 0.3</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Mean CD4$^+$ lymphocyte count/µL (± S.D.) at baseline</td>
<td>387.2 ± 34.3</td>
<td>365.8 ± 51.3</td>
</tr>
<tr>
<td>No. patients with a prior diagnosis of AIDS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No. patients with K103N mutation with or without other related mutations regarding non-nucleoside reverse transcriptase inhibitors (no. patients tested)</td>
<td>0 (14)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>No. patients with ≥2 mutations regarding nucleoside analogues/protease inhibitors (no. patients tested)</td>
<td>3/1 (14)</td>
<td>17/6 (19)</td>
</tr>
<tr>
<td>No. patients developing a novel or relapsing AIDS-defining disease throughout the study period</td>
<td>0</td>
<td>0</td>
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See text for definitions of groups A and B, and A1, A2, B1 and B2.

nucleoside analogue modified (group B1), whereas 25 patients were forced to maintain the same nucleoside analogues or attempted a rechallenge with a previously used compound of this class, regardless of its eventual in vitro resistance (group B2).

A virological, immunological and clinical evaluation was carried out for the 85 patients who remained evaluable for at least 15 months, according to the scheduled monthly clinical and pharmacological assessment, and an at least quarterly complete laboratory work-up. Six patients in group A versus 25 in group B did not reach the final 15 month evaluation, because of one or more of the above-mentioned criteria for early termination, and were deemed as treatment failures, according to the defined intention-to-treat analysis. These early treatment terminations or changes (assimilated to failures) occurred in two and four patients in groups A1 and A2, respectively (not significant), whereas in group B early withdrawals proved significantly more frequent than in group A (P < 0.02), as well as in group B2 compared with group B1 (P < 0.02) (Table 1). The 22 patients out of 107 (20.6%) who abandoned the trial did so after 4.6 ± 4.1 months (range 0.5–10 months), most frequently because of early efavirenz intolerance (13 cases, 59.1%), followed by virological and/or immunological and/or clinical failure prompting treatment suspension or change (seven patients), and nelfinavir-related side effects (two cases). A significant difference was also found when considering time to treatment switch because of drug intolerance (3.2 ± 0.6 months) compared with time to treatment failure (7.2 ± 3.1 months) (P < 0.0001). The 22 above-mentioned patients had their treatment modified according to international antiretroviral therapy guidelines,8,9 but their overall laboratory outcome did not show significant differences in group B patients, regardless of the antimicrobial combination subsequently administered (usually including recycled, previously used drugs).

Group B patients had a greater mean viraemia and a lower mean CD4$^+$ cell count at baseline (as expected) (P < 0.0001) (without differences between groups A1 and A2, or B1 and B2) (Table 1), and a prior diagnosis of AIDS was more frequent in group B than group A (one versus nine cases; P < 0.007); as a consequence, the laboratory and clinical course of HIV disease proved significantly different in the subsequent 15 month follow-up period.

In fact, when compared with patients in group B, those followed in group A showed a significantly elevated mean viral load reduction throughout the study period (starting at the third month of assessment) (P < 0.0001), and persisting until 15 months: −2.4 ± 0.9 log$_{10}$ HIV RNA copies/mL at the end of the study. Thirty-nine patients of 49 in group A (79.6%) achieved complete viral suppression at any time during the follow-up, compared with a mean drop of 0.8 ± 0.6 HIV RNA copies/mL achieved by group B at 15 months (P < 0.0001), with only 16.7% of patients reaching undetectable viraemia after 6–9 months, and only one of them (2.8%) maintaining viral suppression after 15 months (P < 0.0001).

The virological trend is summarized in Figure 1: while no difference was found among A1 and A2 groups throughout the study period (without appreciable differences according to the selected nucleoside analogues; data not shown), patients who had at least one nucleoside analogue changed
while introducing efavirenz and one or more protease inhibitors (group B1) had an appreciable virological advantage over those belonging to group B2 at 6, 9 and 15 months ($P < 0.02$, $P = 0.01$ and $P = 0.02$, respectively). On the other hand, no significant difference was found when comparing patients who added nelfinavir, compared with indinavir or dual protease inhibitor regimens, in group B2 (data not shown).

From an immunological point of view (Figure 2), a rise in mean CD4+ lymphocyte count compared with baseline was also observed in group A compared with group B, starting from the third month ($P < 0.0001$), and continuing throughout the examined period until 15 months ($+72.2 \pm 23.1\%$ compared with $+32.4 \pm 17.9\%; P < 0.0001$). Again, no significant difference was found between the CD4+ lymphocyte count response of antiretroviral therapy-naive and -experienced patients in group A (regardless of administered nucleoside analogues), or between subjects treated with nelfinavir and those receiving other protease inhibitors in group B (data not shown). However, overall in group B the concurrent change of at least one nucleoside analogue led to a better immunological result in the period ranging from 3 months to 12 months ($P = 0.02–0.004$), although this result was not maintained up to the end of follow-up.

Genotypic resistance assays carried out before efavirenz introduction detected mutations at codon 103 (with or without those involving codons 181, 190, 188 and 100), responsible for resistance or cross-resistance to all non-nucleoside reverse transcriptase inhibitors (including efavirenz), in 32 cases out of the 78 evaluated (41%), with a greater frequency among group B patients (64.4%) compared with group A (9.1%) ($P < 0.0001$), although a mixed viral population including ‘wild-type’ organisms was noted in nine strains among those expressing the K103N mutation. Notably, none of these subjects was previously exposed to a non-nucleoside reverse transcriptase inhibitor, and the result of this laboratory assay usually became available 5–10 weeks after study initiation. Concurrent, multiple genotypic mutations involving nucleoside analogues and protease inhibitors were detected with a progressive, highly significant ($P < 0.0001$) increase from group A1 towards group B2, with B2 patients suffering from two or more mutations against nucleoside analogues and protease inhibitors in 86.9% and 95.6% of cases, respectively (Table 1). Both frequency and extent of overall genotypic mutation appeared to be related to frequency and duration of previous use of assessed antimicrobial compounds ($P < 0.0001$ for both nucleoside analogues and protease inhibitors), except for non-nucleoside reverse transcriptase inhibitors.

From a clinical point of view, only nine patients developed a newly diagnosed or relapse of an AIDS-defining disease throughout the 15 month study period, and all nine belonged to group B ($P < 0.002$ compared with group A); seven in group B2 and two in group B1 ($P < 0.004$) (Table 1).

**Discussion**

Owing to their elevated potency and substantially different resistance and toxicity profiles compared with those of nucleoside analogues and protease inhibitors, non-nucleoside reverse transcriptase inhibitors are increasing in proposed use in patients who initiate, fail or cannot tolerate other HAART regimens. Unfortunately, even a single HIV genome mutation (that involving the K103N codon, associated or not with minor ones) is expected to impair the activity of the entire drug class and the sequential use of these compounds, as demonstrated by both *in vivo* studies and *in vitro* experiences conducted in different clinical situations.16,18–21

Most literature studies have been carried out in patients naive to all non-nucleoside reverse transcriptase inhibitors,
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and often to all antiretrovirals. In a recently published controlled, randomized study conducted in 165 patients previously exposed to nucleoside analogues only, the adjunct of efavirenz plus nelfinavir and at least one novel nucleoside analogue had a greater virological success rate as measured by obtaining a viraemia of <500 copies/mL at 48 weeks, compared with that of regimens based on efavirenz or nelfinavir alone, plus nucleoside analogues.

Other surveys examined the laboratory outcome of patients who started non-nucleoside reverse transcriptase inhibitors after repeated failure or intolerance of previous protease inhibitor-containing HAART. In these cases, genotypic and phenotypic viral resistance profiles acted as the strongest predictors of success, particularly when previous virological failure was of concern.

The introduction of a non-nucleoside reverse transcriptase inhibitor is expected to add significantly to both initial triple antiretroviral regimens, as well as rescue treatment of patients who failed two or more protease inhibitor-containing combinations but remained naive to non-nucleoside reverse transcriptase inhibitors, as a result of their different mechanisms of action, and resistance and safety profiles. Therefore, our observational single-centre prospective study compared all consecutive subjects who initiated or switched to an efavirenz-based HAART, as these two HIV-infected patient populations represent the most common candidates since 1999 for receiving a non-nucleoside reverse transcriptase inhibitor.

In our study, although limited by its single-centre origin and affected by proportionally limited and non-comparable patient samples, 107 patients starting efavirenz were prospectively compared, according to first-line drug introduction (55 patients, including 27 antiretroviral-naive subjects compared with 28 antiretroviral-experienced patients), or efavirenz adjunct to a multidrug salvage regimen including at least one novel protease inhibitor (52 patients who had experienced at least two failures of 15–40 month protease inhibitor-based regimens, including 25 subjects who introduced at least one novel nucleoside analogue compared with the 27 individuals who did not).

On the whole, in our intention-to-treat analysis, early interruption of scheduled regimens mostly involved patients on rescue therapy, and was due to early efavirenz intolerance in nearly 60% of cases (P < 0.0001). Unfortunately, the initial neuropsychiatric side effects of efavirenz were responsible for this appreciable number of early drop-outs, and the consequent reduction of patients who completed the 15 month prospective survey. No significant difference was found regarding efavirenz intolerance among group A and B subjects and related subgroups (data not shown).

Among patients who completed the 15 month study, subjects on rescue therapy experienced significantly more unfavourable virological and immunological results throughout the entire period (P < 0.0001), and were also affected by the only nine observed cases of clinical progression (P < 0.002 compared with group A subjects).

However, while no significant difference was detected in group A between naive and nucleoside analogue-experienced patients (group A1 compared with group A2), regardless of the selected nucleoside analogue combination, in the rescue patient group the adjunct of at least one novel nucleoside analogue when introducing the efavirenz salvage regimen led to a better (and proportionally more sustained) virological and immunological outcome.

When adding intolerance, failure or other causes prompting early study withdrawal to an insufficient virological and/or clinical response observed after 15 months in our intention-to-treat analysis, a favourable virological and clinical outcome (as defined by the capability to maintain all drugs introduced at baseline, the attainment of a complete viral suppression at the end of follow-up and the lack of AIDS-related events throughout the study period) occurred in 39 patients in group A (70.9%), compared with only one subject out of 52 in group B (1.9%) (P < 0.0001).

However, when considering patient course regardless of virological response, even those who experienced a low virological success, or rebound or failure, had a better and more sustained immunological result compared with the virological one. Although this confirms some recent reports, this intriguing phenomenon deserves further investigation regarding its frequency, pathogenetic mechanisms and consequences on long-term HIV-related immunodeficiency and the expected disease course.

Despite a lack of previous exposure to all non-nucleoside reverse transcriptase inhibitors, viral genotyping disclosed mutations involving at least codon 103 (and leading to cross-resistance to efavirenz and related compounds) in 41% of the 78 patients assessed at baseline. This appeared much more frequently in group B than group A, and seemed to be directly related to both frequency and number of genotypic mutations involving both nucleoside analogues and protease inhibitors, among the heavily pre-treated individuals characterizing group B (P < 0.03). However, in this area our study had some potential limitations: (i) genotypic assay was not carried out for the whole study population before efavirenz introduction; (ii) phenotypic assays were not available at the time of the start of our study; (iii) patients heavily treated for many years with suboptimal regimens were more prone to receive early genotyping, and in nine cases a mixed population including ‘wild-type’ viruses was detected together with organisms expressing the mutation at codon 103. Despite these limitations, our observations confirm some recent, worrying reports, and also a cross-sectional survey performed at our centre on 267 patients who underwent a genotyping assay upon failure of a prolonged (36–139 months) antiretroviral therapy, which disclosed a 17.2% overall rate of K103N codon mutation.
This was predominantly in patients with multiple concomitant protease inhibitor mutations, but also in 25 subjects who had undergone previous non-nucleoside reverse transcriptase therapy for ≤6 months, and even nine patients (19.6%) who had never been exposed to efavirenz, nevirapine or delavirdine. In this last survey, the in vitro resistance assay predicted an unfavourable subsequent laboratory outcome upon treatment modification. In fact, a broad spectrum of genotypic and/or phenotypic resistances is related to short-term virological response to antiretroviral treatment containing compounds with reduced in vitro activity, and is also predicted for non-nucleoside reverse transcriptase inhibitors, as indicated by our data and non-comparative literature reports. On the other hand, Shulman et al. recently demonstrated an increased phenotypic hypersensitivity to non-nucleoside reverse transcriptase inhibitors in patients heavily pre-treated with nucleoside analogues, who became resistant to multiple compounds of this class, so that efavirenz-containing regimens registered a favourable 24 week virological response in these non-nucleoside reverse transcriptase inhibitor-naive subjects.

In conclusion, in our 15 month prospective intention-to-treat comparative study, an efavirenz-based initial triple antiretroviral therapy led to a significantly more favourable virological, immunological and clinical outcome compared with efavirenz adjunct to different types of rescue anti-HIV regimen performed in patients with repeated (two or more) failures of protease inhibitor-containing HAART. This is probably due to the spread of viral resistance and cross-resistance accumulated over time, and is also expressed against never-taken drugs, such as non-nucleoside reverse transcriptase inhibitors. Extensive, controlled studies are warranted to compare the clinical role of efavirenz administration in different therapeutic situations with regard to prior treatment, genotypic and phenotypic resistance profiles, tolerability, and long-term laboratory and clinical outcomes. Class resistance to all available non-nucleoside reverse transcriptase inhibitors may be more frequent than expected, especially in patients who underwent and subsequently failed long-term HAART. As a consequence, patients who are candidates for including non-nucleoside reverse transcriptase inhibitors in their first-line and especially salvage regimens should undergo preliminary genotypic or phenotypic resistance testing (and continued resistance monitoring should be carried out, especially when signs of virological failure become apparent), until newer agents of this class (presently under development) are able to overcome this problem.

References


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