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Switch to Efavirenz (EFV) after Protease-inhibitor (PI) - Failure: Explorative Analysis of Outcome by Baseline Viral VS Tolerability Failure

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Abstract
The aim of this database analysis was to investigate the efficacy and safety of efavirenz (EFV)-based highly active antiretroviral therapy (HAART) after switching from failed protease inhibitor (PI)- and boosted PI (PI/r)-based regimens.

Data were analyzed from 17 adult patients previously treated with a PI-based HAART with substitution of PI with EFV because of virologic failure and from 14 patients previously treated with a PI-based HAART, with substitution of PI due to tolerability issues.

Of 17 patients who switched therapy because of virologic failure, 5 patients maintained EFV-therapy for more than 1 year. In 11/17 patients, EFV-based HAART was discontinued during follow-up and one patient was lost to follow-up. Reasons for discontinuation were: virologic failure in 4, adverse events in 6 (5 CNS-adverse events and 1 rash) and non-compliance in 1 of 17 patients.

Of 14 patients who stopped PI-therapy and switched to EFV due to tolerability issues, 6 patients maintained EFV-therapy for more than 1 year. In 8/14 patients EFV-based HAART was discontinued during follow-up. Reasons for discontinuation were: virologic failure in 3, adverse events in 3 (2 CNS-adverse events and 1 patient had rash) and non-compliance in 2 of 14 patients.

Instable switch to an EFV-based regimen due to virologic failure or toxicity reasons with a boosted or unboosted PI does not show significant differences but outcome was worse than had been described previously for stable switch settings, likely due to multiple prior virologic failures in many patients.
Key words: Efavirenz, protease inhibitor, therapy switch

Background

The use of highly active antiretroviral therapy (HAART) consisting of two Nucleoside Reverse Transcriptase Inhibitors (NRTI) plus either a Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI) or a Ritonavir-boosted Protease Inhibitor (PI/r) decreases morbidity and mortality associated with human immunodeficiency virus type-1 (HIV-1) infection [1, 2]. The NNRTI Efavirenz (EFV) is a widely investigated and proven component of initial standard-of-care treatment and is a preferred part of recommended regimens in HIV treatment guidelines [3, 4]. EFV plus 2 NRTI used as first-line regimen showed virologic efficacy equal [5] or superior [6-11] to Ritonavir-unboosted [5-7] or -boosted [8-11] PI-based HAART.

Switching patients with a HIV-1-RNA level below the limit of detection from a PI- to an EFV-based regimen to prevent PI-associated side effects and to improve adherence and eventually long-term efficacy of HAART has been shown to be safe and efficacious [12-16]. However, switching to EFV-based HAART after PI-treatment failure in later therapy lines - due to virologic failure or treatment-limiting toxicity - has not been fully explored.

We therefore already investigated in a pilot study the efficacy and safety of an EFV-based HAART regimen after PI-failure ("instable" switch) [17]. In this second step, we now devided the cohort into two patient groups: (a) pts. who switched their PI-Regimen because of virologic failure and (b) pts. who switched because of suspected PI-associated toxicity.

Objectives

The objectives of this study were to investigate efficacy and safety of EFV-based HAART after instable switch from PI-based regimen subsequent to virologic failure or treatment-limiting toxicity (incl. subjective reasons). To describe potential differences between these differing causes for PI-regimen termination.

Methods

Exploratory analyses of data were performed based on both patient files and electronic database of the Frankfurt HIV Cohort.

Respective analysis was performed for (a) patients with PI-virological failure and (b) patients with PI-treatment-limiting toxicity. The results of each are presented separately. At weeks 4, 8, 12, 24 and 48 changes in viral load and CD4 count were evaluated, and the proportion of patients with a viral load <400 copies/ml was recorded using an Intent-to-Treat exposed (ITTe: analyzed were all patients who at least took one dose of the medication) and an On-treatment (OT) analysis.

The primary end point was the proportion of patients with an HIV-RNA level of less than 400 copies/ml.

Secondary end points were CD4 cell count increase and incidence and type of side effects. Data were analyzed using Chi-square (χ^2) Fisher´s exact test for significance of the relationship between categorical variables.

(a) EFV-Patients with previous PI-virologic failure
Data were analyzed from 23 adult patients previously treated with a PI-based HAART (backbone: 2 to 3 NRTI), with substitution of the boosted or unboosted PI with EFV because of virologic failure. Included were patients who started EFV-containing HAART as of 2002 and failed virologically an initial, 2nd or 3rd PI-based regimen after at least 3 months of therapy. Virologic failure was defined as: (1) single measurement of >1000 copies/ml or (2) confirmed viral rebound to >400 copies/ml after achieving an HIV-1 RNA level below the limit of detection. Six of 23 patients were not NNRTI-naïve and therefore excluded from analysis, leaving 17 patients to be included.

(b) EFV-Patients with previous PI-failure due to toxicity
Data were analyzed from 14 adult patients previously treated with a PI-based HAART (backbone: 2 to 3 NRTI), with substitution of the boosted or unboosted PI with EFV due to toxicity. Toxicity was defined by treating physicians in accordance with patients as intolerable symptoms, most likely PI-associated.

Results

After switch from a PI- to an EFV-containing regimen, the reasons for therapy discontinuation during 12 months of follow-up were analyzed for both groups.

(a) EFV-Patients with previous PI-virological failure
Of the 17 patients eligible for analysis, 14 patients were male. The median baseline CD4 count was 261 cells/µl, the median baseline HIV-1 viral load was 31,750 copies/ml (4.5 $\log_{10}$). All patients were treatment-experienced. Most frequently used PI were Saquinavir (SQV), Nelfinavir (NFV), Lopinavir (LPV) and Indinavir (IDV).

Of 17 patients who switched therapy because of virologic failure, 5 patients maintained EFV-therapy for more than 1 year. In 11/17 patients, EFV-based HAART was discontinued during follow-up and one patient was lost to follow-up.

Reasons for discontinuation were: virologic failure in 4, adverse events in 6 (5 CNS-adverse events and 1 rash) and non-compliance in 1 of 17 patients.

Table 1. Baseline characteristics (of switches due to virologic failure).

n	17
Males, no.	14 (82%)
Age, years median	41.0
CD4 cells median (/_l)	261
Viral load median (copies/ml)	31,750
PI withdrawn, no. (%, exceeding 100% =pts with double-boosted PI)	
NFV	4 (24%)
SQV	4 (24%)
LPV	5 (29%)
IDV	4 (24%)
APV/f-APV	2 (12%)
ATV	1 (6%)
Number of therapy regimens in past median (range)	2 (1-11)

(b) EFV-Patients with previous PI-failure due to toxicity
All 14 patients were eligible for analysis. 10 patients (71%) were male, median age was 39 years. The median baseline CD4 count was 188/µl, median viral load 40 copies/ml. Most frequently used PI were LPV, SQV and (fos)-Amprenavir.

Of 14 patients who stopped PI-therapy and switched to EFV, 10 had gastrointestinal adverse effects; further PI side effects were allergic reaction, lipodystrophy, pancreatitis and liver enzyme elevation. After the switch, 6 patients maintained EFV-therapy for more than 1 year. In 8/14 patients EFV-based HAART was discontinued during follow-up.

Reasons for discontinuation were: virologic failure in 3, adverse events in 3 (2 CNS-adverse events and 1 patient had rash) and non-compliance in 2 of 14 patients.

Efficacy

(a) EFV-Patients with previous PI-virologic failure
Proportions of patients with a HIV-1 RNA suppression to <400 copies/ml at week 24 were 6/17 (35.3%)

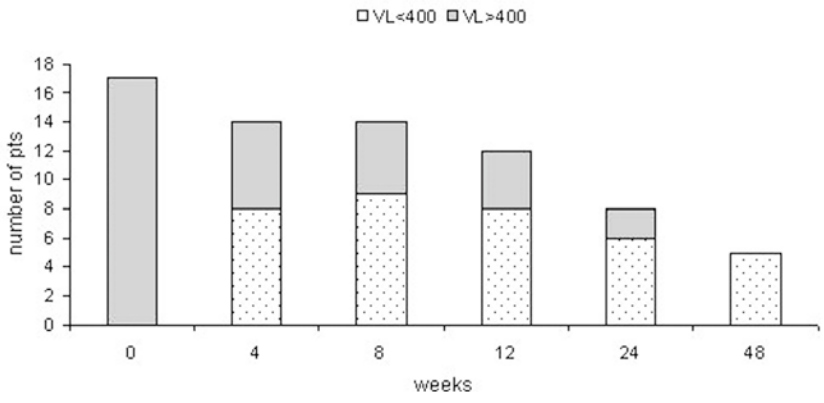

Fig. 1. Number of patients with VL <400 (OT-analysis).

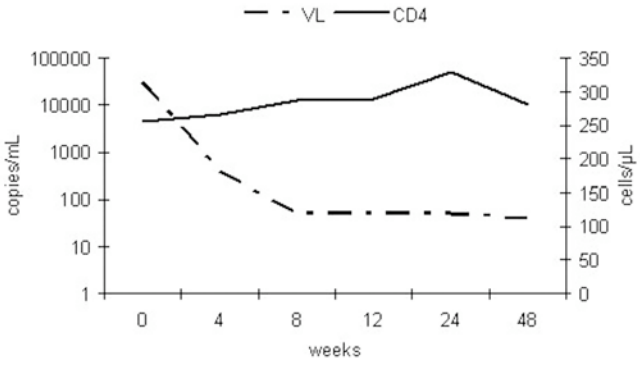

Fig. 2. VL and CD4 responses for pts on treatment.

in the ITTe (χ^2 = 7.286; p = 0.009 compared to baseline) and 6/8 (75.0%) in the OT analysis, and 5/17 (29.4%) in the ITTe (χ^2 = 5.862; p = 0.022 compared to baseline) and 5/5 (100%) in the OT analysis, respectively, at week 48. The changes over time of patients with viral load less than 400 copies/ml relative to patients on therapy is shown in Figure 1 (OT-analysis).

At week 4 the change in viral load was -1,89 log10 copies/ml and CD4 count increased from baseline to 272 (+11) cells/µl. At week 8 the change in viral load was -2,80 log10 copies/ml and CD4 count increased to 295 (+34) cells/µl; at week 12 -2,80 log10 copies/ml and 306 (+45) cells/µl;, at week 24 -2,80 log10 copies/ml and 335 (+74) cells/µl and at week 48 -2,89 log10 copies/ml and 288 (+27) cells/µl (all median).

The median virologic and immunologic treatment responses are shown in Figure 2.

After switch to EFV-containing HAART, 4/17 (23.5%) patients experienced virologic failure. All patients were ART-experienced with several different therapy regimens.

(b) EFV-Patients with previous PI-failure due to toxicity

Proportions of patients with a HIV-1 RNA suppression to <400 copies/ml at week four was 12/14 (85.7%) in ITTe and OT (χ^2 = 2.154; p = 0.241 compared to baseline), median CD4 count was 223 cells/µl. At week eight 12/14 (85.7%) and 12/13 (92.3%) patients had HIV-1 RNA <400 copies/ml in the ITTe and OT analysis (χ^2 = 2.154; p = 0.241 compare to baseline for ITTe), respectively, with median CD4 count of 260 cells/µl. At week 12 these proportions were 10/14 (71.4%) in the ITTe (χ^2 = 4.667; p = 0.5 compare to baseline) and 10/11 (90.9%) in OT analysis, median CD4 count was 255 cells/µl.

Proportions of patients with a HIV-1 RNA suppression to <400 copies/ml at week 24 as well as at week 48 were 6/14 (42.8%) in the ITTe (χ^2 = 11.2; p = 0.001 compared to baseline) and 6/6 (100.0%) in OT analysis. The median CD4 count was 253 and 247 cells/µl, respectively.

Discussion

In this small pilot study we retrospectively analyzed efficacy and safety of utilizing Efavirenz as a second or later line third agent after a switch from a failing PI-based regimen for (a) virological reasons or (b) treatment-limiting PI-associated toxicity. Interpretation of these exploratory analyses is limited as study was not powered to draw confirmative conclusions.

Of 17 patients who switched therapy because of virologic failure, 5 patients maintained EFV-therapy for more than 1 year. In 11/17 patients, EFV-based HAART was discontinued during follow-up and one patient was lost to follow-up. Reasons for discontinuation were: virologic failure in 4, adverse events in 6 (5 CNS-adverse events and 1 rash) and non-compliance in 1 of 17 patients.

Of 14 patients who stopped PI-therapy and switched to EFV due to tolerability issues, 6 patients maintained EFV-therapy for more than 1 year. In 8/14 patients EFV-based HAART was discontinued during follow-up. Reasons for discontinuation were: virologic failure in 3, adverse events in 3 (2 CNS-adverse events and 1 patient had rash) and non-compliance in 2 of 14 patients.

In summary in this exploratory analysis of patients after instable switch to an EFV-based regimen due to virologic failure or toxicity reasons with a boosted or unboosted PI does not show significant differences but outcome was worse than had been described previously for stable switch settings, likely due to multiple prior virologic failures in many patients.

Our study has several limitations: There was no sample size calculation, this study is not powered for its´ primary or secondary endpoints. Results are only descriptive. As this is a pilot study the number of patients investigated is rather small. Data analysis was conducted retrospectively with all potentially undetected biases specified elsewhere. Patients had been treated with a wide range of antiretrovirals; the degree of pre-treatment might not be homogenous within groups of patients, which carries a risk of incorrect conclusions. We did not analyse the NRTI backbone and it is not calculated to what degree patients underwent a concurrent NRTI switch together with the substitution of PI with EFV.

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