

Switch from Enfuvirtide (E) to Raltegravir (R) in Highly Treatment-Experienced HIV-1 Infected Patients:

A Randomized Open-Label Non-Inferiority Trial (Easier - ANRS 138)

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ABSTRACT

BACKGROUND: Among patients (pts) with multidrug-resistant HIV-1 infection, E-based regimens (EBR) can durably suppress viral replication. However, due to the inconvenience of twice-daily subcutaneous injections and the high incidence of injection site reactions, alternatives to E are desirable.

METHODS: 170 pts with triple-class resistant HIV-1 infection and plasma HIV RNA < 400 cp/mL for at least 3 months under EBR, were randomized 1:1 to either the maintenance of EBR (M arm) or the switch to a R-based regimen (S arm). The primary endpoint was the cumulative proportion of pts with virologic failure, defined as a confirmed plasma HIV RNA \geq 400 cp/mL up to W24.

RESULTS: Baseline pts characteristics were well balanced across the two arms: median age: 47.9 years, male: 85%, CDC stage C: 52%, median HAART duration: 13.6 years, median EBR duration: 2.3 years, median baseline CD4 cell count: 393 cells/mm³, median nadir CD4 cell count: 50 cells/mm³. One patient withdrew his consent before being dosed and was excluded from the analysis. Through W24, virologic failure was observed in 1/85 (1.2%) pts in M arm and 1/84 pts (1.2%) in S arm in an ITT analysis (delta: 0.01%; 95% CI: -6.7; +6.8). In the per protocol analysis, 0/82 (0%) pts in M arm and 1/82 pts (1.2%) in S arm (delta: 1.22%; 95% CI: -5.6; +8.1) experienced virologic failure. At W24, 88% to 89% of pts in both arms had plasma HIV-1 RNA levels < 50 cp/mL. No significant CD4 changes occurred in either arm through W24. There was neither AIDS-defining event nor death during the study. Incidence of grade 3 to 4 adverse events was 8% and 13% in the M and S arms, respectively (p=0.13). Incidence of grade 3 to 4 laboratory abnormalities was 7% and 14% in the M and S arms, respectively (p=0.31).

CONCLUSION: In highly treatment-experienced pts with suppressed viral replication under EBR, a switch from enfuvirtide to raltegravir has non-inferior antiviral activity as compared to the maintenance of the EBR, with a similar safety profile.

RESULTS

Primary end point

Intention-to-treat analysis: The proportion of patients with virologic failure was 1.2% in each arm (one patient per arm). The difference (raltegravir minus enfuvirtide) was of 0.01% with a 95% CI = [-6.7%; +6.8%] (p<0.002)

On-treatment analysis: The proportion of patients with virologic failure was 1.2% in the raltegravir arm and 0% in the enfuvirtide arm. The difference (raltegravir minus enfuvirtide) was of 1.22% with a 95% CI = [-5.6%; +8.1%] (p<0.001)

Figure 1: Patients disposition

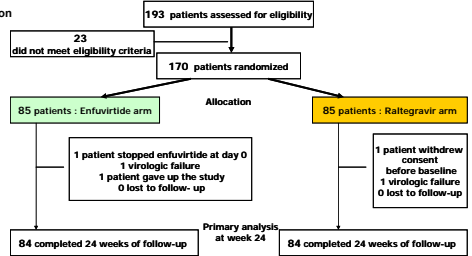


Figure 2: Proportion of patients with HIV RNA < 50 copies/mL over 24 weeks

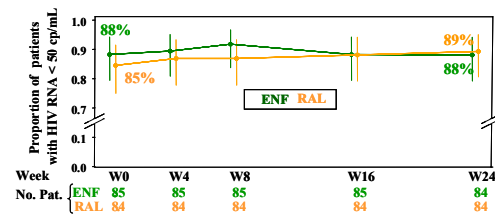


Figure 3: CD4 T-cell count changes over 24 weeks

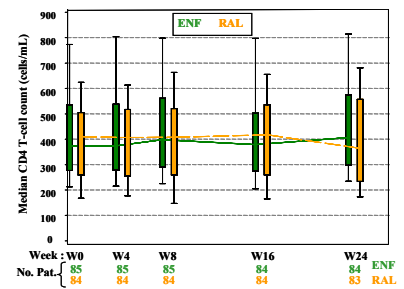


Table 2: Number of patients with one or more Grade 3 or 4 emerging Laboratory Abnormalities through 24 weeks

Laboratory abnormalities, no.	Enfuvirtide arm N=85	Raltegravir arm N=84	p-value
AST/ALT (\geq 5 ULN)	1	2	
GGT ($>$ 5 ULN)	2	6	
Alkaline Phosphatase ($>$ 5 ULN)	0	2	
Bilirubin (\geq 2 ULN)	0	0	
Hypertriglyceridaemia (\geq 8.6mmol/L)	0	2	
Creatinine phosphokinase ($>$ 5ULN)	3	2	
Hypolipasaemia (\leq 3ULN)	1	0	
Hypokalaemia (\leq 2.7 mEq/L)	1	0	
Total number of patients (%)	6 (7)	12 (14)	0.13
Total number of events	8	14	

No grade \geq 3 Creatinine or Hb levels; Neutrophils or Platelets counts

Table 3: Number of patients with one or more Grade 3 or 4 emerging Adverse Events through 24 weeks

Adverse events, no.	Enfuvirtide arm N=85	Raltegravir arm N=84	p-value
Coronary	2	2	
Gastrointestinal	1	1	
Respiratory	2	1	
Infections	0	3	
Nervous system	0	1	
Psychiatric	1	1	
Other	2	4	
Total number of patients (%)	7 (8)	11 (13)	0.31
Total number of events	8	13	

INTRODUCTION

Enfuvirtide (ENF) has demonstrated sustained antiviral and immunological efficacy in patients with multidrug-resistant HIV-infection and has therefore become a major antiretroviral drug for salvage regimens in these patients. However, the long-term use of enfuvirtide is inconvenient due to the twice-daily subcutaneous injections, and the high and sustained incidence of injections sites reactions with painful subcutaneous nodules in almost all patients. For these reasons, some patients may be willing to discontinue enfuvirtide, but this strategy carries a high risk of virologic failure and accumulation of more resistance mutations. Among the new drugs that have been recently available, raltegravir, the first HIV integrase inhibitor, seems to be a favorable candidate to replace enfuvirtide with a virologically suppressive salvage regimen.

A few pilot studies have been reported in which a switch from enfuvirtide to raltegravir in patients receiving a virologically suppressive regimen was successful [1-3]. However, these studies involved a limited number of patients, and did not use a randomized design.

The aim of our study was to determine, among patients with multidrug-resistant HIV-infection, virologically suppressed under an enfuvirtide-based antiretroviral regimen, whether a switch to raltegravir was as effective and well tolerated as the maintenance of enfuvirtide.

METHODS

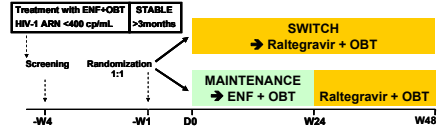
Study Design The study was a multicenter, randomized, comparative, 48-week open-label non-inferiority trial with a primary endpoint at 24 weeks, carried out at 39 ANRS sites in France.

Inclusion criteria

- HIV-1-infected adults \geq 18 years
- Past history of triple class (protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI)) failure or intolerance
- Enfuvirtide-based regimen, with no change in the previous 3 months
- Plasma HIV RNA levels < 400 copies/mL \geq 3 months
- No previous use of integrase inhibitor therapy.

Primary endpoint
 Cumulative proportion of patients with virologic failure throughout 24 weeks.
 Virologic failure was defined as

- confirmed plasma HIV-1 RNA \geq 400 copies/mL,
- patients with the last available plasma HIV-1 RNA \geq 400 copies/mL without confirmation
- patients who changed antiretroviral therapy following a single plasma HIV-1 RNA \geq 400 copies/mL



Statistical Analysis A sample size of 170 (85 patients per arm) was required to establish non-inferiority of the raltegravir arm as compared to the enfuvirtide arm, based on an expected virologic failure rate of 4% in the enfuvirtide arm [4], a margin of non-inferiority of 10%, with a alpha level of 0.05, and a statistical power of 80%.

Chi-Square tests or Fisher's exact tests were used to compare categorical variables among the arms. Differences in continuous variables between arms were analyzed with the use of non-parametric Wilcoxon rank-sum tests. Comparisons were made with use of a two-sided alpha level of 0.05. Statistical analyses were performed with the use of SAS software (SAS Institute Inc., Cary, NC). The primary efficacy analysis was to compare between the 2 arms the crude proportions of patients who reached the primary study endpoint through 24 weeks. This comparison was performed with a non-inferiority test using the Farrington-Manning method. Non-inferiority was established if the upper limit of the 95% two-tailed confidence interval (CI) of the difference in proportions between groups through week 24 (raltegravir arm minus enfuvirtide arm) was 10% or less.

CONCLUSION

- Switch from enfuvirtide to raltegravir within a virologically suppressive regimen in patients with multidrug-resistant HIV-1-infection, is effective and well tolerated, over 24 weeks.
- This regimen offers the advantage of simplicity and represents therefore an attractive therapeutic option for such patients.
- Long-term follow-up of these patients is required and will allow to address remaining issues relative to this strategy such as liver function tests profiles and pharmacokinetic interactions between PIs and raltegravir.

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