Background

- In HIV treatment experienced patients, long term toxicity and quality of life are important challenges which may lead to switch to therapeutic regimens although at risk for virological failure in case of previous drug-resistance.
- The randomized EASIER-ANRS 138 trial showed that the switch from enfuvirtide to raltegravir was virologically non-inferior to the maintenance of enfuvirtide in highly treatment-experienced HIV-1-infected patients with suppressed viremia.
- Treatment regimens at baseline included enfuvirtide, at least 1 NRTI (95%), and 1 PI (99%), and 1 NNRTI (8%).

Methods

- With 3 months unchanged optimized background regimen (OBR) + plasma HIV-1 RNA throughout the course of previous antiretroviral regimens.
- Highly treatment-experienced HIV-1 infected pts with triple classes (NRTI, NNRTI and PI) failure or intolerance.
- Inclusion criteria:
  - Patients were heavily treatment experienced with a median duration of enfuvirtide of 2.3 years before randomization.
  - Plasma HIV RNA levels <400 cpy/mL for at least 3 months

EASIER Study Design

- a non-inferiority multicentric multicentric study

Pre-randomization

- Substitution
- RAL + OBR
- ENF + OBR
- ENF + OBR

Randomization 1/1

- W1
- W2
- W3
- W4

Post-randomization

- Substitution
- RAL + OBR
- ENF + OBR
- ENF + OBR

Inclusion criteria:

- Highly treatment-experienced HIV-1 infected pts with triple classes (NRTI, NNRTI and PI) failure or intolerance.
- With a 3 months unchanged optimized background regimen (OBR) + plasma HIV-1 RNA throughout the course of previous antiretroviral regimens.
- Plasma HIV-1 RNA levels <400 cpy/mL for at least 3 months

Objective

Our aim was to analyze whether a genotype performed in cellular HIV-1 DNA at the time of randomization could account for resistance mutations detected in previous plasma HIV RNA throughout the course of previous antiretroviral regimens.

Patients and Methods

- Patients: All 441 patients enrolled in the EASIER trial were three classes-experienced (NRTI, NNRTI and PI) and had plasma HIV RNA < 400 cpy/mL at baseline under an enfuvirtide-based regimen.
- Methods:
  - Resistance from plasma HIV-1 RNA: previous resistance genotypic tests performed from plasma were collected and drug resistance mutations were cumulated.
  - Resistance from cellular HIV-1 DNA: Centralized resistance genotype analyses were performed from HIV-1 DNA extracted from whole blood at the time of randomization.
  - Viral DNA was extracted from whole blood (MagnaPure, Roche).
  - RT and protease gene were analyzed according to the ANRS consensus methods.
  - Resistance mutations were considered according to the 2008 IAS-USA resistance list (www.iavusa.org) and ARV susceptibility interpreted according to the 2009 ANRS v18 algorithm (http://www.hivdrugresistance.org).

Resistance mutations (IAS List 2008)

- Plasma resistance
- Genotypic tests
- Drug-resistance (ANRS algorithm 2009)

- Plasma HIV RNA
  - Total of 214 for the 169 pts with a median (range) of 4 (3; 5) tests/patient
  - Among the 716 genotypes, 235 were informative for new mutations regarding resistance associated with NRTI, NNRTI and PI (excluding redundant resistance profile or wild-type genotype)
- Cellular HIV DNA
  - Positive amplification for RT or PR: 163 patients (96%)
  - No amplification for RT or PR: 6 patients (4%)
  - Positive amplification for RT and PR: 121 patients (72%)

Drug-resistance (ANRS algorithm 2009)

- No RNA resistance
- RNA resistance possible
- RNA resistance
- DNA resistance
- DNA resistance possible

Impact in a switch trial: example of EASIER

- Criteria of inclusion: triple class drug resistance
  - With previous genotypic(s) performed in plasma HIV RNA: 441 patients (95%)
  - With genotypic performed at the time of randomization on cellular HIV DNA: 42/121 patients (35%)
- Number of active drug according to the genotypic results (GSS) (excluding enfuvirtide)
  - GSS (n=121)
  - NC 0 6.0 ± 3.0
  - NC 0.0 ± 2.0

Conclusion

- In heavily treatment-experienced patients with controlled viremia, resistance testing performed on HIV-DNA lacks sensitivity compared to the cumulative drug-resistance from previous plasma genotypes and therefore can not be solely used to select an active antiretroviral regimen. These results have implications for the clinical management of patients, and the design of switch studies.

Class Drug resistance results of patients in EASIER trial.