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HIV-1 Genotypic Resistance Tests Performed in Cellular DNA are Less Informative than those Collected from Previous Plasma RNAs in Treatment Experienced Patients with Suppressed Viremia: a Sub-Study of EASIER-ANRS 138 Trial

Poster 573

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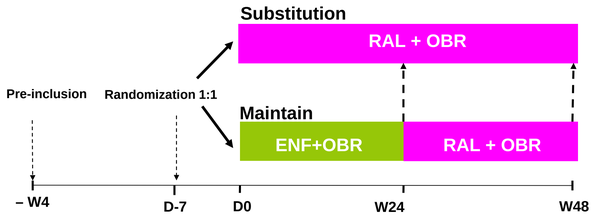
Background

- 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.

EASIER Study Design

a non-inferiority randomized multicentric study



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) + Enfuviritide
- ✓ Plasma HIV-1 RNA levels <400 cp/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-1 RNA throughout the course of previous antiretroviral regimens.

Patients and Methods

- **Patients**

  All 169 patients enrolled in the EASIER trial were three classes-experienced (NRTI, NNRTI and PI) and had plasma HIV RNA < 400 cp/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.iasusa.org) and ARV susceptibility interpreted according to the 2009 ANRS v18 algorithm (www.hivfrenchresistance.org).

Patients baseline characteristics

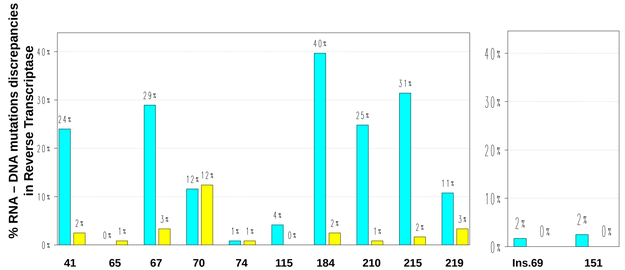
- Patients were mostly men (85%) with a median age of 48 years
- Patients were heavily treatment experienced with
  - a median duration of antiretroviral therapy of 13.6 years
  - a median duration of enfuvirtide of 2.3 years before randomization

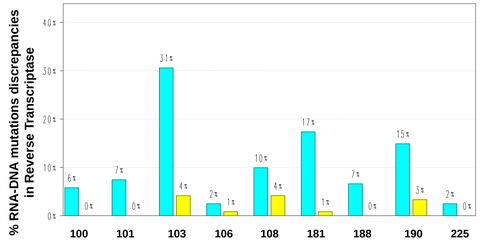
- Treatment regimens at baseline included enfuvirtide, at least 1 NRTI (95%), 1 or 2 PIs (99%), and 1 NNRTI (8%).

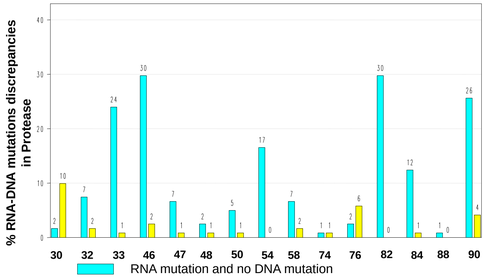
Resistance mutations (IAS List 2008)

	RNA (n=121)	DNA (n=121)	Diff. (n=121)	p* value
Nb RT+PR mutations #	17 [15 ; 19]	13 [8 ; 17]	+4 [0 ; 10]	0.001
Nb NRTI mutations	5 [5 ; 6]	4 [2 ; 5]	+1 [0 ; 3]	0.001
Nb NNRTI mutations	2 [1 ; 2]	1 [0 ; 2]	+1 [0 ; 2]	0.001
Nb PI min+MAJ mutations	10 [8 ; 12]	8 [3 ; 12]	+2 [-2 ; +5]	0.001

median [IQR], *p = Wilcoxon Signed-Rank Test







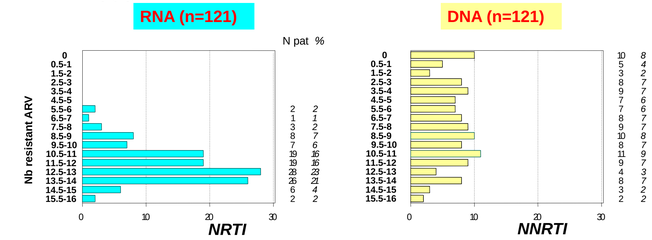
Genotypic tests

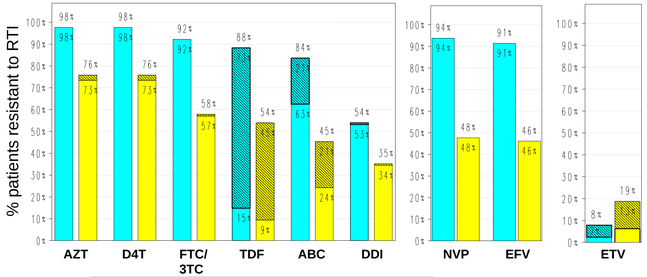
- Plasma HIV RNA
  - Total of 716 for the 169 pts with a median (range) of 4 (3 ; 5) tests/patient
  - Among the 716 genotypes, 235 were informative for new mutations regarding resistance associated with NRTI, NNRTI and PI (excluding redundant resistance profile or wild-type genotype)
- Cellular HIV 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%)

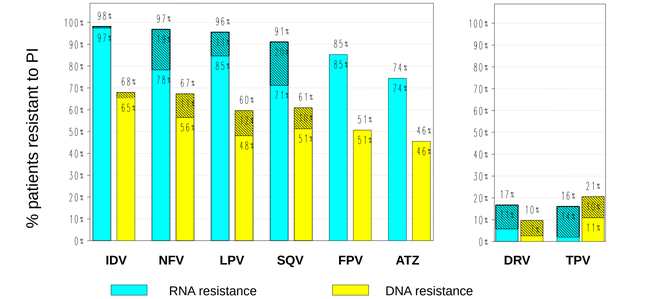
Drug-resistance (ANRS algorithm 2009)

	RNA (n=121)	DNA (n=121)	Diff. (n=121)	p* value
Nb ARV resistant #	12.5 [11.0 ; 13.5]	8.0 [4.0 ; 10.5]	4 [1 ; 8]	0.0001
Nb NRTI resistant	4.5 [4.0 ; 5.5]	3.0 [1.0 ; 4.5]	1 [0 ; 3]	0.0001
Nb NNRTI resistant	2.0 [2.0 ; 2.0]	0.0 [0.0 ; 2.0]	0 [0 ; 2]	0.0001
Nb PI resistant	6.0 [5.0 ; 6.0]	3.5 [0.0 ; 6.0]	1.5 [0 ; 5]	0.0001

median [IQR], *p = Wilcoxon Signed-Rank Test







Impact in a switch trial : example of EASIER

- Criteria of inclusion : triple class-drug resistance
  - With previous genotype(s) performed in plasma HIV RNA : **161/169 patients (95%)**
  - With genotype 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)	RNA	DNA
0	5 (4%)	2 (2%)
0.5	14 (12%)	5 (4%)
1	35 (29%)	22 (18%)
1.5	44 (36%)	22 (18%)
2	14 (12%)	20 (17%)
2.5	5 (4%)	9 (7%)
3	3 (2%)	30 (25%)
4	1 (1%)	3 (2%)
5	.	7 (6%)
Mean	1.3 (0.7)	2.1 (1.0)
Median-IQR	1.5 [1.0 ; 1.5]	2.0 [1.5 ; 3.0]

- HIV DNA Resistance genotypic tests at inclusion detected significantly less (~ 30%) drug resistance mutations than cumulative results from previous plasma HIV RNA resistance tests.
- This discrepancy was observed for all resistance associated mutations except for the RT mutation K70R and the PR mutations D30N and L76V. The mutation L76V has recently been documented.
- Percentage of patients with drug-resistance was higher in plasma HIV RNA than in cellular HIV DNA whatever the drugs except for the more recent ie. etravirine (ETV), tipranavir (TPV) and darunavir (DRV). For these more recent drugs, some resistance mutations were not documented in previous plasma genotypic tests.
- In this switch EASIER trial, triple class drug resistant inclusion criteria has been observed in only 35% according to DNA results of patients instead of 95% with previous plasma genotypic tests.
- In virologically controlled patients, the GSS was over estimated with tests performed in recent DNA compared to results collected in previous plasma RNA.

Conclusion

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