

## Background

- Emergence of drug resistance can hamper long-term success of antiretroviral therapy.
- Knowledge of emerging patterns of resistance upon virological failure of 1<sup>st</sup> line treatment is important for future treatment strategies.

## Objectives

- To assess virological failure and emergence of HIV-1 drug resistance for different 1<sup>st</sup> line combination antiretroviral therapy (cART) regimens containing either a non-nucleoside reverse transcriptase inhibitor (NNRTI group) or a ritonavir-boosted protease inhibitor (PI/r group).

## Methods

### Study population/inclusion criteria for on-treatment analysis:

- Patients enrolled in the Swiss HIV Cohort Study (SHCS)
- who have initiated 1<sup>st</sup> cART between 01/1999 and 12/2005 with  $\geq 2$  nucleoside reverse transcriptase inhibitor (NRTI) and 1 boosted PI or  $\geq 2$  NRTIs and 1 NNRTI and
- who either had one additional HIV RNA following viral suppression to  $< 50$  copies/mL or one HIV RNA measurement after 180 days of continuous treatment in patients where viral suppression was not achieved.

### Definition virological failure (one of the following):

- in patients with previous suppression of HIV RNA to undetectable:
  - viral rebound with two consecutive viral loads  $> 500$  copies/mL or
  - one value  $> 500$  copies/mL followed by a stop or a modification of the current therapy
- in patients without previous suppression of viral load to undetectable levels since ART initiation:
  - one viral load  $> 500$  copies/mL after at least 180 days of continuous treatment

### SHCS resistance database:

- Genotypic resistance tests from routine clinical practice and retrospective testing. Sequencing is performed on the entire protease gene and in minimum codons 28 to 225 of the reverse transcriptase gene using commercial assays (Viroseq Vs.1 PE Biosystems, Rotkreuz, Switzerland; Virsoeq Vs. 2, Abbott AG, Baar, Switzerland; vircoTYPE HIV-1 Assay, Virco Lab, Mechelen, Belgium) and in-house methods. Data is collected and stored in SMARTGENE's™ Integrated Database Network System (IDNS Version 3.3.0, SmartGene, Zug, Switzerland).
- All laboratories are regularly participating in the ANRS quality circle using "predefined" mixtures harboring specific mutations associated with drug resistance.

### Data analysis and statistics:

- Comparison of mutation patterns: Fisher's exact test, Mann-Whitney test.
- Survival analysis: Kaplan-Meier curves, logrank test, univariable and multivariable Cox regression models, competing risk analysis (Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. Jun 1995;51(2):524-532).
- Primary analysis was the on-treatment analysis, i.e. only patients fulfilling all inclusion criteria (n=1323). To verify our findings we also performed intent-to-treat analyses including all patients who initiated ART with PI/r or NNRTIs (n=1929).
- Mutations associated with drug resistance were determined using the International AIDS Society USA resistance mutation list (version Fall 2006). Minor PI mutations were not considered.
- Stanford Genotypic Sensitivity Scores (GSS), algorithm version 4.2.6. Viruses with a GSS  $< 15$  were considered susceptible, a GSS in the range of 15 to 59 indicated intermediate resistance and a GSS  $> 59$  indicated high resistance.
- Lamivudine (3TC) or emtricitabine (FTC) were considered a distinct drug class from other NRTIs.

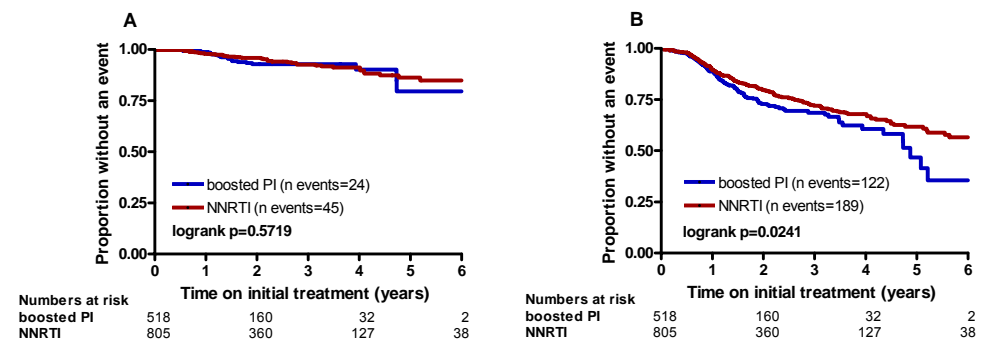
## Results

- 1929 patients initiated cART (792 on PI/r, 1137 on NNRTI). Of those, 606 (31.4%) were excluded because of short treatment duration or missing HIV RNA values (274/792 [34.6%] on PI/r, 332/1137 [29.2%] on NNRTI).
- Patient characteristics associated with the exclusion from the on-treatment analysis were being on a PI/r, IDUs, female or having higher CD4 counts (data not shown). Of the 274 excluded patients on PI/r, 127 (46.4%) stopped or modified treatment because of ART related toxicities. In the NNRTI group, the respective number was 169 (50.9%).
- Of the remaining 1323 patients, 518 were on therapy with boosted PI, 805 with NNRTI. Patients in the PI/r group tended to have a higher pre-treatment HIV viral load and lower CD4 counts (table 1).
- In total, 69 virological failure events occurred (24 in PI/r, 45 in NNRTI). Resistance tests were available for 20/24 (83%) in the PI/r group and 84% in the NNRTI group (table 2, figure 1).
- HIV subtypes could be evaluated for 94% of all virologically failing patients. 58% were infected with Subtype B (no difference between groups). The emergence of resistance was not associated with subtype (data not shown).

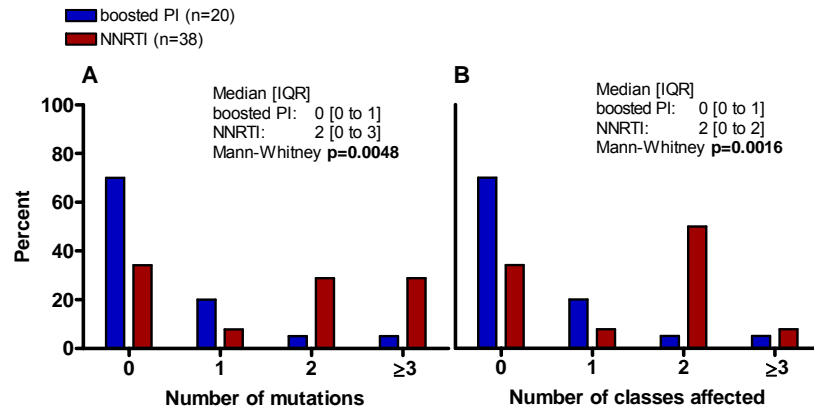
Table 1: Characteristics of patients initiating cART between 01/1999 and 12/2005 included in on-treatment analysis (n=1323).

|   | PI/r                | NNRTI               |
|---|---------------------|---------------------|
| n   | 518                 | 805                 |
| Median age [IQR]                                | 38 [32 to 45]       | 38 [32 to 44]       |
| Sex = male                                      | 371 (71.6%)         | 551 (68.4%)         |
| Transmission category                           |                     |                     |
| Homo-bisexual contact                           | 197 (38.0%)         | 269 (33.4%)         |
| Heterosexual contact                            | 222 (42.9%)         | 400 (49.7%)         |
| Injecting drug use                              | 69 (13.3%)          | 101 (12.5%)         |
| CDC stage C                                     | 120 (23.2%)         | 157 (19.5%)         |
| CD4 at cART initiation                          |                     |                     |
| Median [IQR]                                    | 182 [76.5 to 304]   | 209 [124 to 297]    |
| $< 200$ cells/ $\mu$ L                          | 233 (45.0%)         | 321 (39.9%)         |
| HIV RNA at cART initiation                      |                     |                     |
| Median log <sub>10</sub> [IQR]                  | 5.08 [4.58 to 5.59] | 4.90 [4.38 to 5.34] |
| $\geq 100^*000$ cps/mL                          | 234 (45.2%)         | 285 (35.4%)         |
| Frequency of 3TC or FTC containing combinations | 493 (95.2%)         | 762 (94.7%)         |
| Third drug (PI/r or NNRTI)                      |                     |                     |
| Indinavir                                       | 56 (10.8%)          | 0                   |
| Atazanavir                                      | 46 (8.9%)           | 0                   |
| Lopinavir                                       | 391 (75.5%)         | 0                   |
| Efavirenz                                       | 0                   | 736 (91.4%)         |

Figure 1: Kaplan-Meier curves for time to first-line therapy discontinuation due to virological failure (panel A) or virological failure and cART-related adverse events (panel B).



**Figure 2:** Drug resistance in patients experiencing virological failure on first-line cART. Resistance tests were available for 58/69 (84%). Panel A: Number of Fall 2006 IAS-USA mutations (excluding minor protease mutations). Panel B: Frequency of class resistance, defined as  $\geq 1$  drug with a Stanford (V4.2.6) Genotypic Sensitivity Score  $\geq 15$ . Note: 3TC or FTC were considered a distinct class from other NRTIs.



**Table 2: Summary of time-to-event analyses.**

The on-treatment analysis includes patients with  $\geq 1$  additional HIV RNA measurements after the attainment of undetectable HIV viral loads or, if not the case, patients with at least one HIV RNA measurement after  $\geq 180$  days of continuous treatment on first-line ART. The intent-to-treat analysis includes all patients who have initiated ART between 01/1999 and 12/2005 with a two-class therapy.

|   | PI/r                | NNRTI               | p                   |
|---|---------------------|---------------------|---------------------|
| <b>On treatment analysis (n=1323)</b>   | 518                 | 805                 |                     |
| Crude Incidence Rate of failures per 100 person years [95% CI]  | 2.7 [1.8 to 4.0]    | 2.4 [1.8 to 3.3]    | 0.5719 <sup>a</sup> |
| Crude Incidence Rate of adverse events per 100 person years [95% CI]  | 10.9 [9.0 to 13.3]  | 7.8 [6.6 to 9.2]    | 0.0244 <sup>a</sup> |
| Crude Incidence Rate of stopping because of virological failure or adverse events per 100 person years [95% CI]               | 13.6 [11.4 to 16.3] | 10.3 [8.9 to 11.8]  | 0.0241 <sup>a</sup> |
| Relative hazard of stopping ART because of adverse events/virological failure (competing risk analysis) [95% CI] <sup>b</sup> | 1.30 [1.02 to 1.65] | 1 (reference)       |                     |
| <b>On treatment analysis of patients on lopinavir and efavirenz (n=1154)</b>  | 391                 | 763                 |                     |
| Relative hazard of stopping ART because of adverse events/virological failure (competing risk analysis) [95% CI] <sup>b</sup> | 1.02 [0.77 to 1.37] | 1 (reference)       |                     |
| <b>Intent-to-treat analysis (n=1929)</b>  | 792 (28.8%)         | 1137 (41.3%)        |                     |
| Crude Incidence Rate of stopping because of virological failure or adverse events per 100 person years [95% CI]               | 25.9 [22.9 to 29.4] | 18.4 [16.5 to 20.4] | 0.0202 <sup>a</sup> |
| Relative hazard of stopping ART because of adverse events/virological failure (competing risk analysis) [95% CI] <sup>b</sup> | 1.23 [1.04 to 1.46] | 1 (reference)       |                     |

<sup>a</sup> Logrank test

<sup>b</sup> Cox model adjusted for age, sex, ethnicity, transmission category, CD4 count and HIV RNA at time of ART initiation.

**Table 3: Class resistance patterns in patients failing virologically on first-line cART (n=69).**

| n   | PI/r<br>24 | NNRTI<br>45 | p                    |
|---|------------|-------------|----------------------|
| Resistance test at baseline <sup>a</sup>  | 14 (58.3%) | 34 (75.6%)  |                      |
| Resistance test at failure  | 20 (83.3%) | 38 (84.4%)  |                      |
| Virus susceptible to all drugs in class according to Stanford algorithm                             |            |             |                      |
| NRTI  | 18 (90%)   | 30 (78.9%)  | 0.468 <sup>b</sup>   |
| 3TC/FTC   | 15 (75%)   | 16 (42.1%)  | 0.026 <sup>b</sup>   |
| Third drug  | 18 (90%)   | 20 (52.6%)  | <0.0001 <sup>b</sup> |
| Drug classes affected (high level resistance against $\geq 1$ drug according to Stanford algorithm) |            |             |                      |
| By class type   |            |             |                      |
| NRTI  | 0          | 2 (5.3%)    | 0.54 <sup>b</sup>    |
| 3TC/FTC   | 5 (25.0%)  | 22 (57.9%)  | 0.026 <sup>b</sup>   |
| Third drug  | 1 (5.0%)   | 18 (47.4%)  | 0.001 <sup>b</sup>   |
| By class combination  |            |             |                      |
| No resistance   | 15 (75.0%) | 13 (34.2%)  |                      |
| 3TC/FTC (1 class)   | 3 (15.0%)  | 6 (15.8%)   |                      |
| Third drug (1 class)  | 1 (5.0%)   | 3 (7.9%)    |                      |
| 3TC/FTC + NRTI (2 classes)  | 0          | 1 (2.6%)    |                      |
| 3TC/FTC + third drug (2 classes)  | 1 (5.0%)   | 14 (36.8%)  |                      |
| 3TC/FTC + NRTI + third drug (3 classes)   | 0          | 1 (2.6%)    |                      |

<sup>a</sup> The following baseline resistance mutations were observed:

PI/r group: 1 patient with RT 103N

NNRTI group: 1 patient with RT 103N.

<sup>b</sup> Fisher's exact test

## Conclusions

**While PI/r containing cART has similar potency like NNRTI regimens, they lead to less resistance in case of virological failure. This data demonstrates that in addition to drug potency, genetic barrier should also be considered when choosing first-line treatment.**

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