

# HIV-1 Drug Resistance Evolution During Persistent Near Target Viral Suppression

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# Background

- Persistent low-level viremia or near target viral suppression (NTVS, vRNA 50-1000 c/mL) while on treatment is associated with increased risks of overt virologic failure <sup>1,2</sup> immune activation <sup>2</sup> and perhaps mortality <sup>3</sup>.
- Major drug resistance mutations are common in treated patients with vRNA < 1,000 c/mL <sup>4</sup>. Less is known in the context of first-line antiretroviral therapy.
- Detection and management of drug resistance during NTVS remains a clinical challenge since conventional genotyping is validated for vRNA > 1,000 copies/mL.

1. Raboud JM, et al. AIDS 2002;16:1627-32

2. Karlsson AC, et al. AIDS 2004; 18:981-9

3. Hull M et al. CROI 2010, Abstract 504

4. Mackie NE et al. J Infect Dis 2010;201(9): 1303-7

# Study Objectives

- **Primary**

- To describe the evolution of resistance mutations in HIV-1 reverse transcriptase and protease in patients with NTVS while receiving first-line ART

- **Secondary**

- To determine predictors of new resistance emergence during NTVS while receiving first-line ART

# Study Design

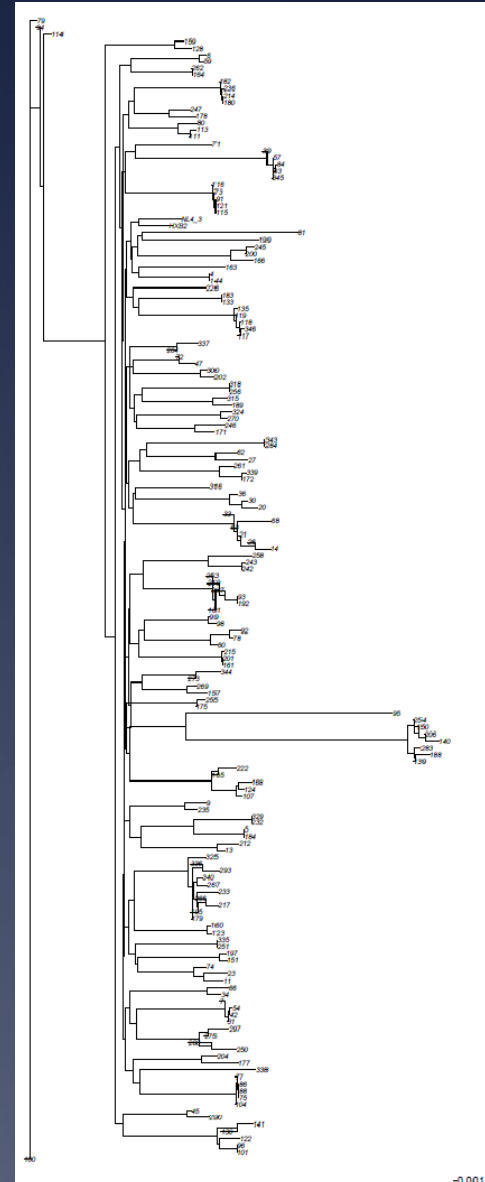
- Subjects were identified retrospectively from two ACTG clinical trials (A5142 and EFV arms of A5095)
- NTVS cases were defined as subjects with persistent vRNA levels between 50 and 1000 c/mL (2 or more determinations) after at least 24 weeks of initial randomized ART
  - One HIV-1 RNA  $< 50$  or  $> 1000$  c/mL was allowed if patient had  $\geq 3$  determinations in a 6 month period
- Plasma virus during NTVS was sequenced
- Pre-treatment reverse transcriptase (RT) and protease (PR) sequences were obtained from the parent study
  - Stored plasma was sequenced if these were not available

# Viral RNA Genotyping Methods

- RNA was extracted from 1.5 ml of plasma following ultracentrifugation
- PR-RT region of pol amplified by RT-PCR followed by nested PCR
- Population (“bulk”) sequencing performed on resulting amplicons by standard methods

# Methods

- Phylogenetic analysis (PhyML) confirmed specimen identity and the absence of cross-contamination
- Mutations considered of interest were:
  - \*Protease (PR): major protease mutations
  - Reverse transcriptase (RT): Any mutation present in  $\geq 3$  of the following 5 expert lists:
    1. ANRS drug interpretation algorithm (2008.07)
    2. Stanford HIVdb drug resistance algorithm (4.3.7)
    3. IAS-USA Mutations Associated with Drug Resistance (March/April 2008)
    4. Los Alamos National Laboratories HIV Database (2007)
    5. Rega Institute Drug Resistance Interpretation Algorithm (7.1.1)



# Study Population

1234 patients on first line ART for  $\geq 24$  weeks  
65 (5%) patients met NTVS definition

## Viral sequence availability

**Baseline**

**N=59**

- No sample available (N=4)
- Failed sequencing (N=2)

**During NTVS**

**N=59**

- No sample available (N=1)
- Failed sequencing (N=5)

**Baseline and  
during NTVS**

**N=54**

# Baseline Characteristics of NTVS Subjects

|   |                            | Total (N=65)     |
|---|----------------------------|------------------|
| <b>Age (yrs)</b>                            |                            | 38 (30 - 50)*    |
| <b>Sex (female)</b>                         |                            | 14%              |
| <b>Race/ethnicity</b>                       | <i>White, non-Hispanic</i> | 35%              |
|   | <i>Black, non-Hispanic</i> | 40%              |
|   | <i>Hispanic</i>            | 25%              |
| <b>Randomized ART</b>                       | <i>LPV/r +EFV</i>          | 14 (22%)         |
|   | <i>2NRTI +LPV/r</i>        | 20 (31%)         |
|   | <i>2NRTI + EFV</i>         | 20 (31%)         |
|   | <i>3NRTI + EFV</i>         | 11 (17%)         |
| <b>HIV RNA (log<sub>10</sub> copies/mL)</b> |                            | 5.1 (4.2 – 6.1)* |
| <b>History of IV drug use</b>               |                            | 6%               |
| <b>CD4 cell count (/mm<sup>3</sup>)</b>     |                            | 121 (22 - 340)*  |

\* Median (10th-90th percentile)

# Description of the NTVS period

|  |                          | Total (N=65)     |
|--|--------------------------|------------------|
| Length of NTVS period (weeks)            |                          | 38 (24 - 48)*    |
| Number of HIV-1 RNA determinations       |                          | 5 (4 - 8)        |
| First week of NTVS period                |                          | 39 (30 - 97)     |
| HIV-1 RNA during NTVS period (copies/ml) | <i>First value</i>       | 97 (59 - 368)    |
|  | <i>Minimum</i>           | <50 (<50 - 115)  |
|  | <i>Maximum</i>           | 260 (79 - 1,333) |
|  | <i>Time adjusted AUC</i> | 77 (49 - 470)    |
| ART discontinuation (>7 days)            | <i>Before</i>            | 8%               |
|  | <i>During</i>            | 6%               |

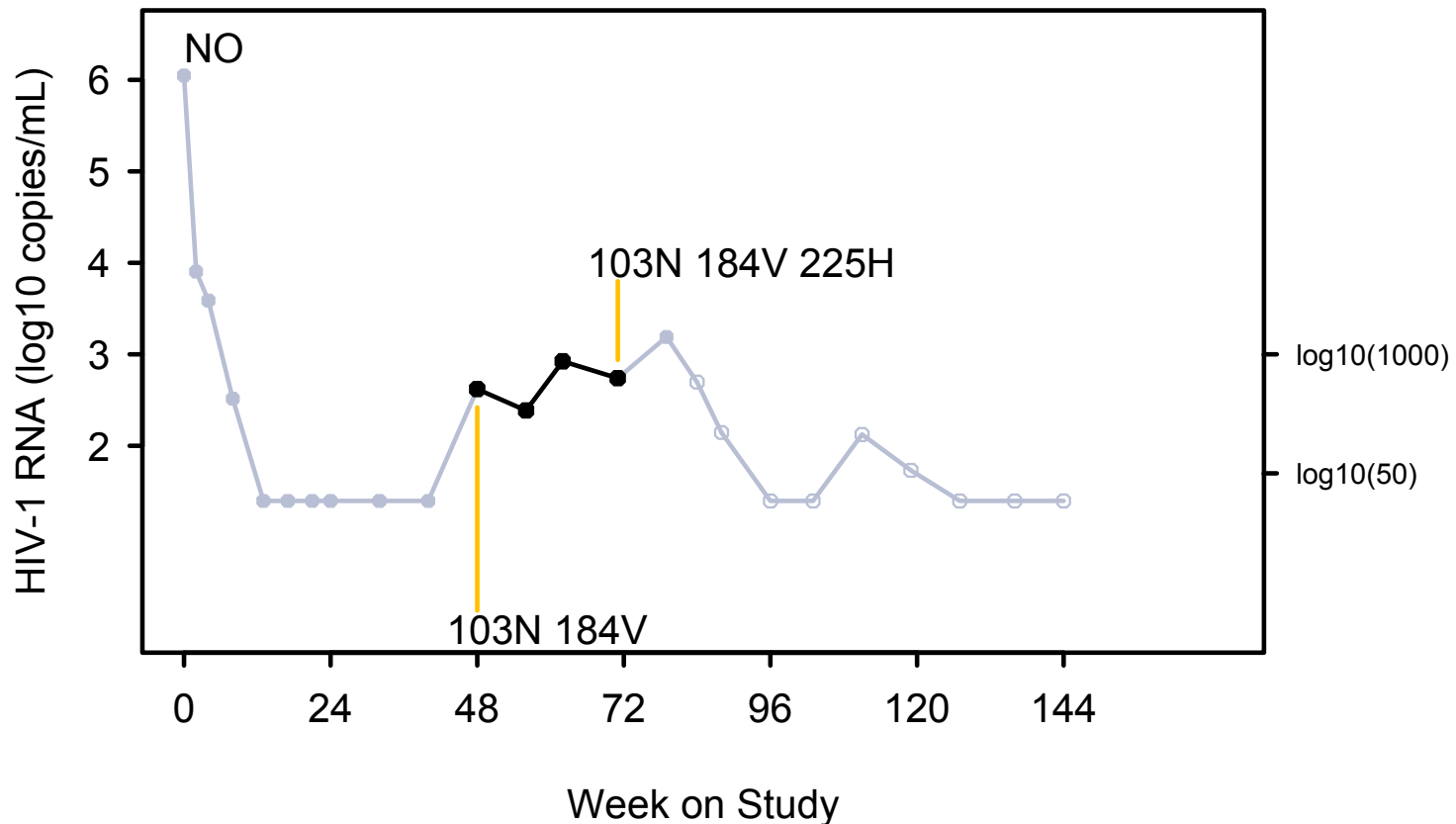
\* Median (10th-90th percentile)

# Baseline Resistance

|   | Total (N=59)    |
|---|-----------------|
| <b>Any RT mutation</b>  | <b>13 (22%)</b> |
| 69N   | 3               |
| 103R  | 3               |
| 69ST, 101Q, 103N, 106I, 108I, 118I, 179D,<br>179DV, 190A, 190EG, 215Y | 1*              |
| <b>Any PR mutation</b>  | <b>0</b>        |

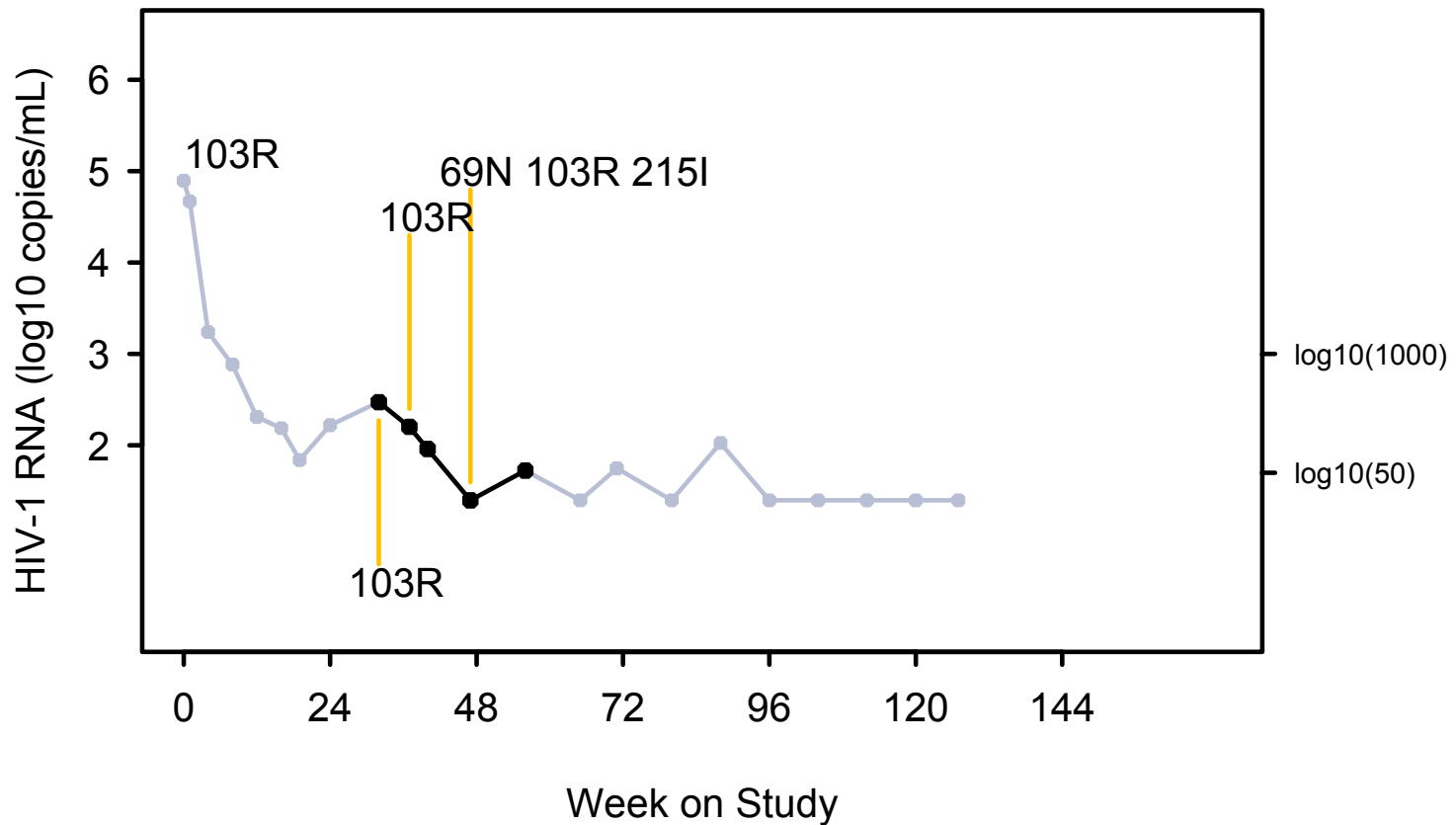
\* Observed once each (not necessarily in the same individual)

# Example of Resistance Evolution



Regimen: EFV + ZDV + 3TC + ABC

# Example of Resistance Evolution



Regimen: EFV + LPV/r

# New Mutations During NTVS

|  | Total (N=54)    |
|--|-----------------|
| <b>Any RT mutation</b>   | <b>23 (43%)</b> |
| 103N   | 9               |
| 103R   | 2               |
| 184IMV   | 2               |
| 184V   | 12              |
| 230L   | 2               |
| 69N, 74V, 75I, 101E, 106I, 106M, 108IV<br>115F, 118I, 138K, 181CY, 188CY, 190A,<br>190AG, 215I, 225H, 225HP, 230LM | 1*              |
| <b>Any PR mutation</b>   | <b>0</b>        |

\* Observed once each (not necessarily in the same individual)

# Factors Associated with New Resistance During NTVS

## Baseline/Demographics

|  | New Resistance  |                 | P      |
|--|-----------------|-----------------|--------|
|  | No (N=31)       | Yes (N=23)      |        |
| <b>Race/ethnicity</b>  |                 |                 |        |
| <i>White, non-Hispanic</i>   | 45%             | 17%             | 0.048* |
| <i>Black, non-Hispanic</i>   | 26%             | 57%             |        |
| <i>Hispanic</i>  | 29%             | 26%             |        |
| <b>Baseline HIV-1 RNA (log10 c/ml)*</b>  | 5.2 (4.5 – 6.0) | 4.9 (4.2 – 6.1) | 0.13** |
| <i>No evidence of an association with age, sex, randomized ART, baseline CD4, and history of IV drug use (P&gt;0.25)</i> |                 |                 |        |

\*Fisher's Exact Test

\*\* Exact Wilcoxon Test

\* Median (10th-90th percentile)

# Factors Associated with New Resistance During NTVS

## NTVS Period Characteristics

|                                     |        | New Resistance |                   | P       |
|-------------------------------------|--------|----------------|-------------------|---------|
|                                     |        | No (N=31)      | Yes (N=23)        |         |
| Length of NTVS period*              |        | 33 (24 – 56)   | 25 (23 – 48)      | 1.0**   |
| # of HIV-1 RNA determinations*      |        | 5 (4 – 8)      | 5 (3 – 7)         | 0.12*   |
| # of Outliers < 50 c/ml             | 1      | 61%            | 30%               | 0.05*   |
|                                     | 2      | 3%             | 4%                |         |
| # of Outliers >1,000 c/ml           | 1      | 6%             | 30%               | 0.03*   |
| HIV-1 RNA during NTVS period (c/ml) | Min.*  | <50 (<50 – 70) | 62 (<50 – 244)    | 0.003*  |
|                                     | Max.*  | 143 (86 – 592) | 368 (120 – 6,856) | 0.008*  |
|                                     | T-AUC* | 69 (52 – 135)  | 137 (63 – 758)    | <0.001* |

\* Median (10th-90th percentile)

\*Fisher's Exact Test

\*\* Exact Wilcoxon Test

# Conclusions

- NTVS was observed in 5% of our trial population
- Accumulation of resistance during NTVS occurred in 43% of evaluable cases (most commonly to 3TC and EFV)
  - No major PI mutations emerged
- A larger proportion of patients who accumulated resistance were Black non-Hispanic
- Accumulation of resistance was associated with higher HIV-1 RNA levels during the NTVS period
  - Although some mutations emerged at very low levels

# Acknowledgement

- Patients and study teams of the AIDS Clinical Trial Group (ACTG) studies A5142 and A5095