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# Impact of NRTI mutations on virological efficacy of antiretroviral regimens containing elvitegravir: an ARCA-ECCO cohort study

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## Background

Integrase inhibitor based-regimens are recommended by current guidelines as first-choice antiretroviral (ARV) therapy. ARV drug resistance mutations remain a major cause of treatment failure. Very recently, first results of GS-US-292-1824 study showed full virological suppression in experienced patients harboring M184V/I mutation, but results are pending for patients with M184V/I + TAM.

The **aim** of this **study** was to evaluate the effect of drug mutations on virological efficacy of elvitegravir-containing ARV regimens in naïve and treatment-experienced HIV-1 infected patients in a real life setting.

## Material and methods

From the **ARCA** and **ECCO databases** we selected naïve and treatment-experienced HIV-1 infected patients starting tenofovir disoproxil fumarate or tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat (from June 2012 to December 2017), with at least one pre-baseline PR/RT resistance genotype and at least 1 HIV-RNA during follow up. Patients with previous detection of mutation to INSTI (according to IAS-USA 2017), previous virological or treatment failure to INSTI or previous virological failure with a NRTI-including regimen without a following genotype were excluded.

NRTI resistance mutations were defined as the detection of at least one mutation among those included in IAS list (2017).

**Primary endopoint**:

- ✓ **virological failure** (VF, defined as an HIV-RNA > 1,000 copies/mL or 2 consecutive values of >50 cps/mL after week 24 for naive and treatment experienced with baseline VL >50 copies/mL and at any time for treatment experienced with baseline values of <50 copies/mL).

Secondary endopoint:

- ✓ predictors of virological failure

**Statistical analysis:**

- ✓ Kaplan-Meier curves to analyze time to VF
- ✓ Cox survival analysis to investigate predictors of VF

## Results

A total of 282 patients were included in the study: 46 (16%) naïve and 236 (84%) experienced (population characteristics in Table 1). Fourty-six (16%) patients presented at least one NRTI mutation (Table 2).

**Table 1: Population characteristics at baseline**

| | Naïve patients (n=46) | Experienced patients (n=236) |
|---|---|---|
| **Males, n (%)** | 39 (85%) | 157 (67%) |
| **Age, median (IQR)** | 38 (30-50) | 48 (41-54) |
| **Caucasian ethnicity, n (%)** | 24 (52%) | 161 (68%) |
| **Risk factor, n (%)** | | |
| **MSM** | 13 (28%) | 59 (25%) |
| **Heterosexual contacts** | 7 (15%) | 75 (32%) |
| **IDU** | 5 (11%) | 57 (24%) |
| **Other/Unknown** | 21 (46%) | 45 (19%) |
| **HBV coinfection, n (%)** | 1 (2%) | 18 (8%) |
| **HCV coinfection, n (%)** | 0 (0) | 47 (20%) |
| **Years from HIV diagnosis, median (IQR)** | 0.12 (0.05-1.11) | 11 (5-21) |
| **Years of ART, median (IQR)** | - | 8 (4-17) |
| **Nadir CD4⁺, cells/µL, median (IQR)** | 265 (138-453) | 158 (52-307) |
| **Baseline CD4⁺, cells/µL, median (IQR)** | 270 (206-473) | 557 (299-766) |
| **Baseline CD4⁺, cells/µL, n (%)** | | |
| **≤200** | 11 (24%) | 36 (15.3%) |
| **201-350** | 16 (35%) | 34 (14.4%) |
| **>350** | 19 (41%) | 166 (70.3%) |
| **Zenith HIV-RNA, $Log_{10}$ cps/mL, median (IQR)** | 4.96 (4.58-5.56) | 5.16 (4.59-5.70) |
| **Baseline HIV-RNA, $Log_{10}$ cps/mL, median (IQR)** | 4.87 (3.95-5.24) | 1.55 (0.95-1.79) |
| **Baseline HIV-RNA >100,000 cps/mL, n (%)** | 18 (39%) | 10 (4.2%) |
| **Baseline HIV-RNA >500,000 cps/mL, n (%)** | 4 (9%) | 3 (1.3%) |
| **Baseline HIV-RNA <50 cps/mL** | - | 174 (74%) |

Notes: IQR, interquartile range; ART, antiretroviral therapy

**Table 2: Population characteristics at baseline**

| NRTI mutation, n (%) | Overall (n=282) | Naïve pts (n=46) | Experienced pts (n=236) |
|---|---|---|---|
| M41L | 1 (0.3%) | 1 (2%) | 0 (0%) |
| D67N | 5 (1.8%) | 2 (4%) | 3 (1.3%) |
| K70R | 9 (3%) | 0 (0%) | 9 (3.8%) |
| L210W | 11 (4%) | 2 (4%) | 9 (3.8%) |
| T215Y/F | 14 (5%) | 0 (0%) | 14 (6%) |
| K219Q/E | 10 (4%) | 0 (0%) | 10 (4%) |
| L74V | 2 (0.7%) | 0 (0%) | 2 (0.8%) |
| Y115F | 3 (1%) | 0 (0%) | 3 (1.3%) |
| M184V/I | 32 (11%) | 1 (2%) | 31 (13%) |
| K65R | 1 (0.3%) | 0 (0%) | 1 (0.4%) |
| **M184+ K65R** | 1 (0.3%) | 0 (0%) | 1 (0.4%) |
| **Any TAM** | 28 (10%) | 2 (4%) | 26 (11%) |
| **Any mutation except M184V/I** | 31 (11%) | 2 (4%) | 29 (12%) |
| **At least one among M184V/I or K65R or TAM** | 45 (16%) | 3 (6.5%) | 42 (18%) |
| **Any mutation** | 46 (16%) | 3 (6.5%) | 43 (18%) |

During a median observation time of 8 months (4-17), 33 VF occurred (2 in naïve patients, 31 in experienced).

***Experienced patients***

Virological outcome stratified by NRTI mutation is shown in Figure 1.

The estimated probability of being free from VF at 12 months was 89% (95% CI 77-101) in patients with any NRTI major mutation vs 89% (84-94) among those without (log rank 0.478). At multivariate analysis adjusting for any NRTI mutation and HCV serostatus, a longer duration of HIV infection, higher peak of viral load and VL>50 cps/mL at baseline showed a trend with higher risk of VF (Table 3).

**Figure 1: Virological outcome stratified by baseline NRTI mutation for experienced patients**

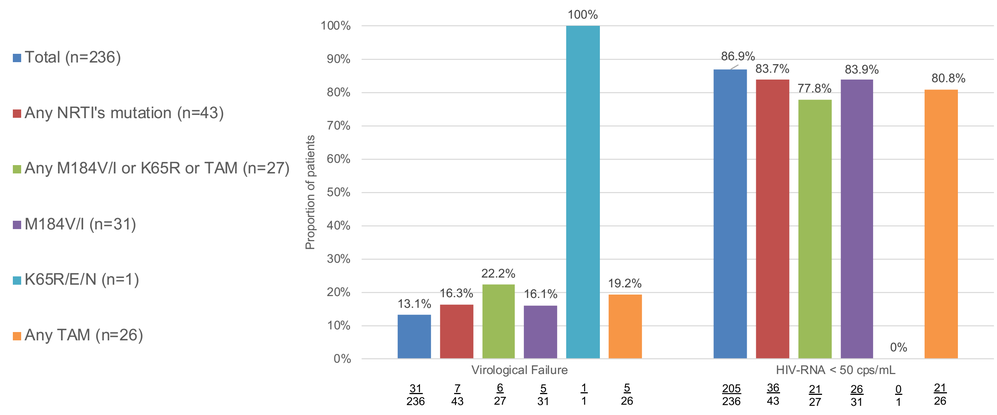


**Figure 2: Estimated probabilities of virological failure**

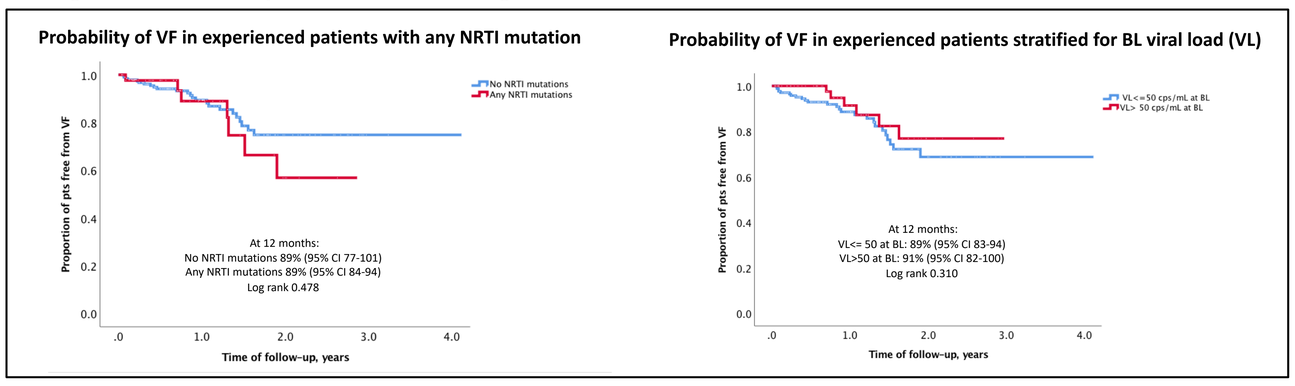


**Table 3: Predictors of virological failure in experienced patients**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| **Variables** | HR (95% CI) | P value | aHR (95% CI) | P value |
| **HCV coinfection (ref absent)** | | | | |
| **Present** | 2.51 (1.07; 5.87) | 0.034 | 1.17 (0.54; 5.20) | 0.376 |
| **Unknown** | 0.78 (0.31;1.98) | 0.605 | 0.85 (0.32; 2.30) | 0.752 |
| **Time from HIV diagnosis (+1 year)** | 1.06 (1.01; 1.10) | 0.007 | 1.05 (0.99; 1.09) | 0.063 |
| **Log Zenith HIV-RNA** | 1.89 (1.37; 2.63) | <0.001 | 1.42 (0.97; 2.08) | 0.069 |
| **Any NRTI mutation** | 1.36 (0.58; 3.15) | 0.480 | 1.15 (0.37; 3.58) | 0.804 |
| **HIV-RNA at BL >50 cps/mL** | 1.58 (0.65; 3.85) | 0.315 | 2.73 (0.95; 7.81) | 0.062 |

Notes: sex, ethnicity, risk factor, age, CD4 ad nadir and at BL, HBV coinfection did not show a significant association with VF, data not shown.

***Naive patients***

In the naïve group, 1/3 pts with any NRTI mutation versus 1/43 without NRTI mutation had virological failure (log rank p<0.001).

## Conclusions:

Elvitegravir-containing ARV regimens resulted in a good rate of virologic suppression, regardless the presence of pre-existing resistance mutations. In naïve patients it seems particularly prudent to consider the presence of transmitted NRTI resistance.

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