# Impact of Transmitted Thymidine Analogue Mutations on Responses to First-Line ART

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## INTRODUCTION

- Thymidine analogue mutations (TAMs) remain a commonly reported form of transmitted drug resistance (TDR) *(Baxter et al. HIV Med 2015)*
- Guidelines recommend that subjects with transmitted TAMs start ART with a boosted protease inhibitor (bPI) in order to improve the barrier to resistance *(EACS 2015)*. The guidance substantially restricts treatment options

## AIM

- **To investigate the virological outcomes of first-line ART in HIV-1 positive adults harbouring ≥1 TAMs as the sole form of TDR compared with subjects who started ART in the absence of detectable resistance**

***Data source:*** Sanger sequences and clinical data retrieved from the UK HIV Drug Resistance and CHIC Study Databases

***Eligible patients:***

- Started tenofovir or abacavir and emtricitabine or lamivudine plus an NNRTI (efavirenz 91%; nevirapine 8.8%; rilpivirine 0.2%) or a bPI (atazanavir 35%; darunavir 18%; fosamprenavir 4%; lopinavir 43%; plus ritonavir)
- ≥1 resistance test prior to treatment initiation
- ≥2 viral load (VL) measures after the first 12 months of ART

***Resistance definitions:***

- **TAMs:** M41L, D67N/G/E, K70R, L210W, T215Y/F/rev, K219Q/E/N/R; **T215rev:** any T215 change other than T215Y/F
- **TDR mutations**: WHO 2009 list; T215rev; $_{RT}$E138K
- **GSS** (genotypic susceptibility score)**:** susceptible/potential low-level resistance=1; low-/intermediate-level resistance=0.5; high-level resistance=0 *(Stanford HIV Drug Resistance v7.0)*

**Table 1. Resistance patterns of subjects with isolated TAMs**

| Pattern | N | % |
|---|---|---|
| **Any TAM** | 269 | 100 |
| **Singleton TAM** | 203 | 75.5 |
| T215rev | 112 | 41.6 |
| K219Q/E/N/R | 58 | 21.6 |
| M41L | 21 | 7.8 |
| D67N/G/E | 6 | 2.2 |
| L210W | 4 | 1.5 |
| K70R | 1 | 0.4 |
| T215Y | 1 | 0.4 |
| **Two TAMs** | 52 | 19.3 |
| M41L T215rev | 40 | 14.9 |
| D67N K219Q/E | 5 | 1.9 |
| L210W T215rev | 3 | 1.1 |
| D67N/E T215rev | 2 | 0.7 |
| M41L T215Y/rev | 1 | 0.4 |
| K70R T215rev | 1 | 0.4 |
| **Three TAMs** | 14 | 5.2 |
| D67N T215rev K219Q/E | 7 | 2.6 |
| M41L L210W T215rev | 6 | 2.2 |
| D67N T215F K219E | 1 | 0.4 |

## BASELINE RESISTANCE

- **No resistance:** No TDR mutations; started an ART regimen with GSS=3 **(n=6330)**
- **Isolated TAMs:** ≥1 TAMs, no other TDR mutations, and no other mutation that would cause a reduction in the GSS of the initial ART regimen **(n=269)** **(Table 1)**
- Patients with isolated TAMs were more likely to be white MSM, to carry subtype B, and to initiate bPI-based ART **(Table 2)**

**Table 2. Characteristics of the study population at the start of ART**

| | | Resistance profile | | |
|---|---|---|---|---|
| | | No resistance N = 6330 | Isolated TAMs N = 269 | P[a] |
| Age, median years (IQR) | | 38 (32-44) | 38 (32-43) | 0.78 |
| Gender, n (%) | Male | 5064 (80.0) | 242 (90.0) | <0.001 |
| | Female | 1266 (20.0) | 27 (10.0) | |
| Exposure, n (%) | MSM | 3797 (60.0) | 213 (79.2) | <0.001 |
| | FSM | 1162 (18.4) | 25 (9.3) | |
| | MSF | 873 (13.8) | 17 (6.3) | |
| | IDU | 123 (1.9) | 0 (0.0) | |
| | Other | 302 (4.8) | 10 (3.7) | |
| | Unknown | 73 (1.2) | 4 (1.5) | |
| Ethnicity, n (%) | White | 3878 (61.3) | 206 (76.6) | <0.001 |
| | Black | 1783 (28.2) | 27 (10.0) | |
| | Asian | 215 (3.4) | 14 (5.2) | |
| | Other | 387 (6.1) | 18 (6.7) | |
| | Unknown | 67 (1.1) | 4 (1.5) | |
| HIV-1 clade, n (%) | B | 4003 (63.2) | 234 (87.0) | <0.001 |
| | C | 957 (15.1) | 11 (4.1) | |
| | Non-B/Non-C | 1370 (21.6) | 24 (8.9) | |
| HIV-1 RNA, median $\log_{10}$ cps/mL (IQR) | | 4.8 (4.3-5.3) | 4.9 (4.3-5.3) | 0.37 |
| CD4 count, median cells/mm³ (IQR) | | 230 (142-310) | 234 (150-310) | 0.57 |
| ART regimen, n (%) | NNRTI | 4749 (75.0) | 140 (52.0) | <0.001 |
| | bPI | 1581 (25.0) | 129 (48.0) | <0.001 |
| | TDF | 5117 (80.8) | 221 (82.2) | 0.59 |
| | ABC | 1213 (19.2) | 48 (17.8) | 0.59 |

*MSM= men who have sex with men; FSM= women who have sex with men; MSF= men who have sex with women; IDU= injecting drug users. [a]Chi-squared test or rank-sum test*

## VIROLOGICAL RESPONSES

- **Virological suppression** [2 consecutive VL ≤50 cps/mL] rates were higher for NNRTI-based ART whereas there was no effect of the baseline resistance profile ] **(Fig 1a)**
- **Virological failure** [2 consecutive VL >50 cps/mL after ≥6 months of ART or a single VL >50 cps/mL followed by a significant treatment change[a]] occurred in 834/6599 (12.6%) subjects over median 2.5 years (IQR 1.1-4.3) of follow-up. By 5 years, the predicted probability of virological failure was 15.3% (14.0-16.7) for NNRTI-based ART and 31.8% (28.5-35.3) for bPI-based ART **(Fig 1b)**
- With NNRTI-based ART, virological failure rates did not differ by the baseline resistance profile. With bPI-based ART virological failure rates were higher in subjects with no resistance
- Using a VL >200 cps/mL reduced the cumulative risk of failure for all groups, while continuing to show an increased risk with bPI-based ART among subjects with no resistance **(Fig 1c)**
- The multivariable model confirmed the effect of drug class on the likelihood of suppression and failure and the lack of effect of the baseline resistance profile **(Table 3)**

*[a]Significant treatment change = change from NNRTI to bPI or vice versa, or to a non-eligible ART regimen*

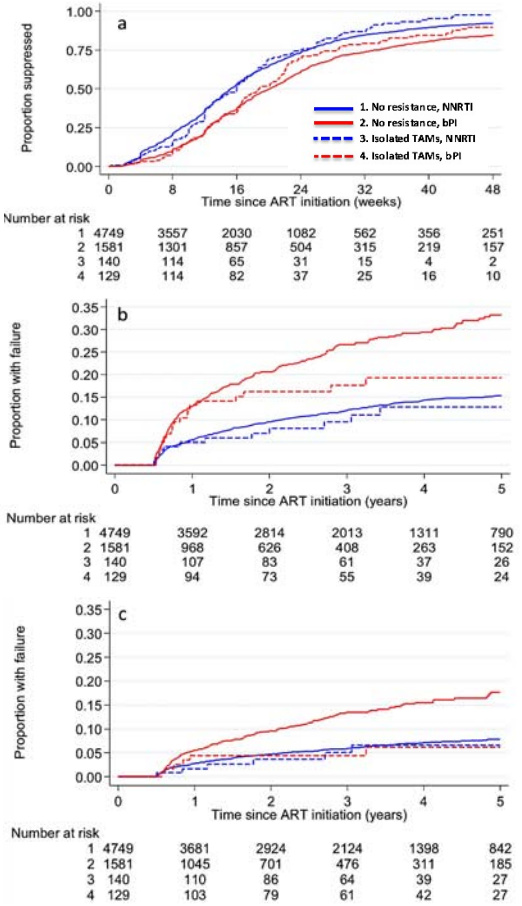
**Table 3. Predictors of virological suppression and virological failure**

| | | | Virological suppression | | | Virological failure | | |
|---|---|---|---|---|---|---|---|---|
| | | N | Adjusted HR | 95% CI | P | Adjusted HR | 95% CI | P |
| Resistance profile | No resistance | 6330 | 1.00 | --- | 0.62 | 1.00 | --- | 0.15 |
| | Isolated TAMs | 269 | 1.03 | 0.91-1.18 | | 0.77 | 0.54-1.10 | |
| ART regimen | NNRTI-based | 4889 | 1.00 | --- | <0.001 | 1.00 | --- | <0.001 |
| | bPI-based | 1710 | 0.70 | 0.65-0.74 | | 2.17 | 1.88-2.51 | |
| NRTI | TDF | 5338 | 1.00 | --- | 0.07 | 1.00 | --- | 0.02 |
| | ABC | 1261 | 0.94 | 0.87-1.01 | | 1.22 | 1.04-1.44 | |
| Age | Per 10 yrs older | 6599 | 1.01 | 0.98-1.04 | 0.44 | 0.97 | 0.90-1.04 | 0.39 |
| Exposure | MSM | 4010 | 1.00 | --- | <0.001 | 1.00 | --- | <0.001 |
| | FSM | 1187 | 0.92 | 0.83-1.01 | | 1.15 | 0.90-1.46 | |
| | MSF | 890 | 0.78 | 0.71-0.87 | | 1.24 | 0.98-1.57 | |
| | IDU | 123 | 0.60 | 0.48-0.74 | | 2.84 | 1.98-4.07 | |
| | Other | 312 | 0.99 | 0.87-1.12 | | 0.91 | 0.62-1.32 | |
| Ethnicity | White | 4084 | 1.00 | --- | 0.004 | 1.00 | --- | <0.001 |
| | Black | 1810 | 1.03 | 0.94-1.12 | | 1.43 | 1.15-1.77 | |
| | Asian | 229 | 1.17 | 1.00-1.36 | | 0.75 | 0.48-1.18 | |
| | Other | 405 | 1.20 | 1.07-1.34 | | 0.82 | 0.59-1.13 | |
| HIV-1 RNA ($\log_{10}$ cps/mL) | <4.0 | 1055 | 1.64 | 1.52-1.77 | <0.001 | 0.98 | 0.77-1.24 | <0.001 |
| | 4.0-5.0 | 2627 | 1.00 | --- | | 1.00 | --- | |
| | >5.0 | 2572 | 0.59 | 0.55-0.63 | | 1.91 | 1.63-2.25 | |
| CD4 count (cells/mm³) | <200 | 2447 | 0.94 | 0.88-1.00 | 0.08 | 1.23 | 1.05-1.45 | 0.04 |
| | 200-349 | 2800 | 1.00 | --- | | 1.00 | --- | |
| | 350-499 | 763 | 1.03 | 0.94-1.12 | | 1.14 | 0.88-1.47 | |
| | ≥500 | 259 | 0.91 | 0.79-1.05 | | 1.43 | 0.99-2.09 | |

## SUB-ANALYSES

- Subjects starting EFV, ATV/r, or DRV/r showed similar patterns of virological failure as seen in the total population
- Higher rates of virological failure observed with DRV/r than LPV/r or ATV/r
- Higher rates of virological failure observed with multiple vs. singleton TAMs within both the NNRTI and bPI treatment groups, although due to small numbers the difference was not statistically significant

**Figure 1. Kaplan-Meier analysis of virological responses by baseline resistance profile and treatment regimen. a) Time to virological suppression; b) Time to virological failure (VL >50 cps/mL); c) Time to virological failure (VL >200 cps/mL)**




## CONCLUSIONS

- Detection of isolated TAMs did not influence virological responses to NNRTI-based ART
- Virological responses were reduced with bPI-based ART. Subjects with no resistance showed an increased risk of failure regardless of whether the VL cut-off was set at 50 or 200 copies/mL. Subjects with TDR had similar failure rates as those on NNRTI-based ART when using a 200 copies/mL cut-off
- The results call into question current guidance on the management of subjects that by conventional sequencing show TAMs as the sole form of TDR, and pave the way to controlled studies
- The observations must be placed into the context of TAMs being detected most commonly as singleton mutations, and T215rev variants accounting for most cases

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