Virological outcomes of boosted protease inhibitor-based first-line ART in subjects harbouring thymidine analogue-associated mutations as the sole form of transmitted drug resistance

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Objectives: In subjects with transmitted thymidine analogue mutations (TAMs), boosted PIs (PI/b) are often chosen to overcome possible resistance to the NRTI backbone. However, data to guide treatment selection are limited. Our aim was to obtain firmer guidance for clinical practice using real-world cohort data.

Methods: We analysed 1710 subjects who started a PI/b in combination with tenofovir or abacavir plus emtricitabine or lamivudine, and compared their virological outcomes with those of 4889 patients who started an NNRTI (predominantly efavirenz), according to the presence of ≥1 TAM as the sole form of transmitted drug resistance.

Results: Participants with ≥1 TAM comprised predominantly MSM (213 of 269, 79.2%), subjects of white ethnicity (206 of 269, 76.6%) and HIV-1 subtype B infections (234 of 269, 87.0%). Most (203 of 269, 75.5%) had single-tons TAMs, commonly a revertant of T215Y or T215F (112 of 269, 41.6%). Over a median of 2.5 years of follow-up, 834 of 6599 (12.6%) subjects experienced viraemia (HIV-1 RNA >50 copies/mL). The adjusted HR for viraemia was 2.17 with PI/b versus NNRTI-based therapy (95% CI 1.88–2.51; P < 0.001). Other independent predictors of viraemia included injecting drug use, black ethnicity, higher viral load and lower CD4 cell count at baseline, and receiving abacavir instead of tenofovir. Resistance showed no overall impact (adjusted HR 0.77 with ≥1 TAM versus no resistance; 95% CI 0.54–1.10; P = 0.15).

Conclusions: In this cohort, patients harbouring ≥1 TAM as the sole form of transmitted drug resistance gained no apparent virological advantage from starting first-line ART with a PI/b.

Introduction

In Europe and North America, >80% of ART-naive patients receive a baseline genotypic resistance test to inform treatment selection. In these regions, ~10% of patients show evidence of transmitted drug resistance (TDR), although prevalence rates and temporal trends vary by region, population and testing method. The most common TAM mutations are those affecting the NRTIs and the NNRTIs; resistance to protease and integrase inhibitors is less common, and multi-class resistance is rare. Thymidine analogue mutations (TAMs), particularly those at codon 215 of RT, remain one of the most frequent forms of TDR. Ongoing transmission of TAM-containing strains in Europe and North America is discordant with the diminished therapeutic role of thymidine analogues and the NRTI resistance patterns detected at treatment failure. It is proposed that a high proportion of cases of TDR in these regions originate from ART-naive patients with TDR.

It has traditionally been recommended that subjects with transmitted NRTI resistance receive a boosted PI (PI/b) as the third agent of triple combination regimens. In a previous study, the virological outcomes of various tenofovir-based first-line regimens were similar when comparing 17 patients with M41L and 248...
subjects with WT virus. More recently, investigators at Gilead Sciences merged data from a variety of clinical trials and reported that virological responses to 48 weeks of tenofovir-based first-line regimens were not diminished among 205 patients harbouring ≥1 TAM, including 76 subjects with revertants of T215Y or T215F (T215Yrev, e.g. T215C/D/E/L/S). 17

Using nationwide observational data, this study investigated the occurrence of viraemia in patients who started first-line ART with either a PI/b or an NNRTI in combination with tenofovir or abacavir plus emtricitabine or lamivudine according to the presence of ≥1 TAM as the sole form of TDR.

Methods

Study population

Patients considered for inclusion started first-line ART with a PI/b or an NNRTI in combination with tenofovir disoproxil fumarate (henceforth referred to as tenofovir) or abacavir plus emtricitabine or lamivudine, had a genotypic drug resistance test prior to treatment initiation and underwent ≥2 viral load measurements after the first 12 months of ART. Eligible PI/b comprised atazanavir, darunavir, fosamprenavir and lopinavir, all combined with ritonavir; eligible NNRTIs comprised efavirenz, nevirapine and rilpivirine (Table S1, available as Supplementary data at JAC Online). Sanger RT and protease sequences were retrieved from the HIV Drug Resistance Database, clinical data were retrieved from the Collaborative HIV Cohort (CHIC) Study database. 19

Definitions of resistance

TAMs comprised the RT mutations M41L, D67N/G/E, K70R, L210W, T215Y/F/rev and K219Q/E/N/R; T215rev comprised any change from T215 other than T215Y and T215F. TDR mutations were defined according to the WHO 2009 surveillance list, with the addition of any unlisted change at position T215 and the non-polymorphic RT mutation E138K. Genotypic susceptibility scores (GSSs) were calculated using the Stanford Drug Resistance algorithm (version 8.2), assigning to each drug a score of 1 for susceptible/potential low-level resistance, 0.5 for low-level/intermediate-level resistance and 0 for high-level resistance.

Baseline resistance profiles

Among 6910 subjects initially considered for inclusion, those showing one of two baseline profiles were considered eligible. The reference group (n = 6330, 91.6%) had no TAM mutations and started a first-line regimen with a GSS of 3. The group with ≥1 TAM as the sole form of TDR (n = 269, 3.9%) showed ≥1 TAM in the absence of other TAM mutations and any other mutation that would reduce the GSS of the first-line regimen. The remaining 311 (4.5%) subjects were excluded owing to the presence of other forms of TDR, most commonly the NNRTI mutation K103N.

Virological responses

Virological suppression was defined as two consecutive viral load measurements ≤50 copies/mL. Viraemia was defined as: (i) two consecutive viral load measurements >50 copies/mL after ≥6 months of ART; or (ii) a single viral load measurement >50 copies/mL followed by a significant treatment change. A separate analysis used a viral load cut-off of >200 copies/mL. A significant treatment change was from NNRTI to PI/b or vice versa, or the use of a non-eligible regimen as defined above.

Statistical analysis

The baseline characteristics of subjects with ≥1 TAM were compared with those of subjects with no resistance using χ² tests for categorical variables and rank-sum tests for continuous variables. Virological responses were analysed using Kaplan–Meier plots and Cox regression models, with time to event calculated as the interval between ART initiation and the date of the first viral load measurement that fell above the predefined cut-off. The multivariable analysis included the baseline resistance profile, whether the first-line regimen was PI/b- or NNRTI-based and whether it included tenofovir or abacavir, age at the start of ART, exposure group, ethnicity, baseline viral load and CD4 cell count (measured in the 6 months prior to starting ART). Gender was categorized within the exposure groups in the main model and modelled separately. HIV-1 subtype was not included owing to the strong association with ethnicity, gender and exposure group. In the analysis of time to virological suppression, follow-up was censored at the occurrence of a significant treatment change (see above). In the analysis of time to virological follow-up was censored at the occurrence of a significant treatment change if the viral load was ≤50 copies/mL. An ITT analysis of time to virological suppression was conducted that ignored censoring owing to a significant treatment change. Additional analyses restricted the study population to subjects initiating efavirenz, ritonavir-boosted atazanavir or ritonavir-boosted darunavir, and evaluated responses according to whether singleton or multiple TAMs were detected.

Results

Study population at the start of first-line ART

The baseline characteristics of the study population according to the resistance profile are summarized in Table 1. The resistance patterns observed in the 269 participants harbouring ≥1 TAM are summarized in Table 2. There were 203 of 269 (75.5%) subjects with singleton TAMs, most commonly T215Yrev (112 of 269, 41.6%); a smaller subset harboured two (n = 52, 19.3%) or three (n = 14, 5.2%) TAMs. Relative to subjects without resistance, the group with ≥1 TAM was more likely to include MSM, subjects of white ethnicity and patients with HIV-1 subtype B infections (Table 1). Among the 6599 participants, 1710 (25.9%) started a PI/b and 4889 (74.1%) started an NNRTI in combination with tenofovir (n = 5338, 80.9%) or abacavir (n = 1261, 19.1%) plus emtricitabine or lamivudine. Subjects with ≥1 TAM were more likely to initiate a PI/b than those without resistance (Table 1), particularly if multiple TAMs were detected: 89 of 203 (43.8%) subjects with singleton TAMs versus 40 of 66 (60.6%) subjects with multiple TAMs started a PI/b (P = 0.02) (Table S1). Use of tenofovir rather than abacavir did not differ among subjects with ≥1 TAM versus those with no resistance (Table 1), and among subjects with singleton TAMs versus those with multiple TAMs (165 of 203, 81.3% versus 56 of 66, 84.8%; P = 0.51) (Table S1).

Virological suppression

The Kaplan–Meier analysis of time to virological suppression is shown in Figure 1(a). By week 24, suppression rates were 62.1% (95% CI 59.7%–64.6%) versus 73.8% (95% CI 72.5%–75.1%) for PI/b- versus NNRTI-based ART, respectively. With NNRTI-based ART, suppression rates by week 24 were 75.2% (95% CI 67.4%–82.4%) with ≥1 TAM versus 73.8% (95% CI 72.4%–75.1%) without resistance. The respective rates with PI/b-based ART were 69.4% (95% CI 61.2%–77.3%) versus 61.4% (95% CI 58.8%–64.1%). The multivariable analysis confirmed that the presence of ≥1 TAM did not reduce the likelihood of virological suppression (Table 3). After adjustment, factors independently associated with a reduced likelihood of suppression comprised receiving PI/b-based ART and
showing a higher baseline viral load. In addition, there was an independent effect of exposure group and ethnicity, including a reduced likelihood of suppression in heterosexual males and injecting drug users.

Viraemia

In the primary analysis, which used a viral load cut-off of >50 copies/mL, 834 of 6599 (12.6%) subjects experienced viraemia over a median follow-up of 2.5 years (IQR 1.1–4.3). This comprised 359 (43.0%) subjects who did not achieve virological suppression and 475 (57.0%) who experienced virological rebound after initial suppression. The Kaplan–Meier analysis of time to viraemia is shown in Figure 1(b). Viraemia rates were 7.3% (95% CI 6.7%–8.1%) by 1 year, 15.1% (95% CI 14.1%–16.2%) by 3 years, and 19.0% (95% CI 17.8%–20.4%) by 5 years. The predicted probability of viraemia by 5 years was 31.8% (95% CI 28.5%–35.3%) with PI/b-based ART and 15.3% (95% CI 14.0%–16.7%) with NNRTI-based ART. Among subjects on an NNRTI, viraemia rates did not differ according to the presence of ≥1 TAM; among subjects on a PI/b, viraemia rates were lower in subjects with ≥1 TAM than in those with no resistance. The multivariable analysis confirmed that the presence of ≥1 TAM did not increase the likelihood of viraemia (Table 4). After adjustment, factors associated with an increased risk of viraemia comprised use of PI/b-based ART, higher viral load and lower CD4 cell count at baseline, and receiving abacavir rather than tenofovir. There was again an effect of exposure group and ethnicity, with injecting drug users and subjects of black ethnicity showing an increased risk of viraemia. A test for interaction between drug class and the presence of ≥1 TAM showed \( P = 0.43 \), indicating that the more favourable outcomes of NNRTI-based ART occurred regardless of the presence of ≥1 TAM.

Using a cut-off of >200 copies/mL reduced the cumulative risk of viraemia in all groups (Figure 1c). Rates of viraemia did not differ based on the use of a PI/b or an NNRTI among subjects with ≥1 TAM, indicating that excess viraemia on a PI/b occurred at levels between 50 and 200 copies/mL. Viraemia rates remained higher with PI/b- versus NNRTI-based ART among subjects with no resistance.

A sensitivity analysis restricted to subjects starting efavirenz, ritonavir-boosted atazanavir or ritonavir-boosted darunavir

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### Table 1. Characteristics of the study population at the start of first-line ART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resistance profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no resistance (N = 6330)</td>
</tr>
<tr>
<td>Total number (%)</td>
<td>6330 (100)</td>
</tr>
<tr>
<td>Age at start of ART, years, median (IQR)</td>
<td>38 (32–44)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>5064 (80.0)</td>
</tr>
<tr>
<td>female</td>
<td>1266 (20.0)</td>
</tr>
<tr>
<td>Exposure group, n (%)</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>3797 (60.0)</td>
</tr>
<tr>
<td>FSM</td>
<td>1162 (18.4)</td>
</tr>
<tr>
<td>MSF</td>
<td>873 (13.8)</td>
</tr>
<tr>
<td>IDU</td>
<td>123 (1.9)</td>
</tr>
<tr>
<td>othera</td>
<td>302 (4.8)</td>
</tr>
<tr>
<td>unknown</td>
<td>73 (1.2)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
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</tr>
<tr>
<td>white</td>
<td>3878 (61.3)</td>
</tr>
<tr>
<td>black</td>
<td>1783 (28.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>215 (3.4)</td>
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<tr>
<td>other</td>
<td>387 (6.1)</td>
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<tr>
<td>unknown</td>
<td>67 (1.1)</td>
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<tr>
<td>HIV-1 subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>4003 (63.2)</td>
</tr>
<tr>
<td>C</td>
<td>957 (15.1)</td>
</tr>
<tr>
<td>non-B/non-C</td>
<td>1370 (21.6)</td>
</tr>
<tr>
<td>HIV-1 RNA, log_{10} copies/mL, median (IQR)</td>
<td>4.8 (4.3–5.3)</td>
</tr>
<tr>
<td>CD4 cell count, cells/mm³, median (IQR)</td>
<td>230 (142–310)</td>
</tr>
<tr>
<td>ART regimen, n (%)</td>
<td></td>
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<tr>
<td>NNRTI</td>
<td>4749 (75.0)</td>
</tr>
<tr>
<td>PI/b</td>
<td>1581 (25.0)</td>
</tr>
<tr>
<td>tenofovir</td>
<td>5117 (80.8)</td>
</tr>
<tr>
<td>abacavir</td>
<td>1213 (19.2)</td>
</tr>
</tbody>
</table>

FSM, females who have sex with males; MSF, males who have sex with females; IDU, injecting drug users.

aOther exposure groups comprised a history of receiving blood or blood products and vertical transmission.
showed similar patterns of viraemia as seen in the total population (Figure S1a). The ITT analysis did not affect between-group comparisons (Figure S1b). Kaplan–Meier and Cox regression analyses were also applied to compare subjects with singleton or multiple TAMs. Higher rates of viraemia were observed in subjects with multiple TAMs who received either PI/b or NNRTI (Figure 1d); possibly because TAMs. Higher rates of viraemia were observed in subjects with multiple TAMs who received either PI/b or NNRTI (Figure 1d); possibly owing to the small numbers, the difference did not achieve statistical significance (unadjusted HR 1.56 for multiple versus singleton TAMs; 95% CI 0.75–3.25; P = 0.23).

**Discussion**

This study determined that patients with ≥1 TAM were more likely to initiate ART with a PI/b than patients without resistance, reflecting the understanding that a third agent with a high barrier to resistance should be preferred to compensate for a less active NRTI backbone. However, patients with ≥1 TAM did not gain virological benefit from starting a PI/b rather than an NNRTI.

The preference for PI/b-based ART in the presence of transmitted TAMs has been called into question.17 Our findings provide evidence from a real-world setting, although it is important to place them into context. Most subjects with ≥1 TAM had singleton mutations, with T215Srev accounting for a large proportion of cases. It cannot be excluded, and the data directly suggest, that co-occurrence of multiple TAMs, although less common, may have a more appreciable impact on virological responses in which the third agent has a low barrier to resistance. This remains a research need, particularly in the case of NRTI backbones containing abacavir plus lamivudine, for which published evidence is scarce and a greater impact of TAMs may be anticipated relative to tenofovir plus emtricitabine. Whether the findings also extend to combinations of two NRTIs with an integrase inhibitor remains to be conclusively demonstrated, and this may differ with first-wave versus second-wave integrase inhibitors and again by NRTI backbone. Although our clinical dataset on integrase inhibitors is growing, analyses are impacted by the limited use of integrase sequencing at baseline.

Other predictive factors for viraemia included exposure group and ethnicity, which correlate with socio-economic status, a License Key Error: If you are a licensed user of this text, please contact your local support representative to resolve the issue. For more information, please visit: https://academic.oup.com/jac/advance-article-abstract/doi/10.1093/jac/dky468/5245309
There are limitations to this study. Cohort analyses are subject to potential confounding. Furthermore, one downside of pursuing large numbers is that available data repositories typically contain a limited number of more recent treatment regimens. The use of efavirenz and ritonavir-boosted lopinavir is becoming less common in Europe and North America, although it is still preferred in specific circumstances and highly prevalent on the global scale. Patients starting a PI/b in our study comprised subjects both with and without TDR, and the risk of viraemia differed between the two. In the UK, for many years NNRTIs were preferred in first-line ART, whereas PI/b-based regimens were reserved for selected circumstances, including presence of TDR but also a perceived increased risk of viraemia and treatment-emergent drug resistance, e.g. owing to suboptimal adherence. Thus, it may be proposed that patients who started PI/b-based ART in the absence of TDR had been pre-identified as being at risk of suboptimal responses. We lacked adherence data to confirm these assumptions.

Conclusions

Our study provides reassurance that in an epidemiological setting where singleton TAMs (predominantly T215rev) occur in MSM likely to have acquired HIV-1 subtype B infection from ART-naive patients, there is no virological benefit to starting ART with a PI/b rather than a third agent with a low barrier to resistance.

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Members of the UK HIV Drug Resistance Database

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Coordinating centre: Institute for Global Health, UCL (David Dunn, Keith Fairbrother, Esther Fearnhill, Kholoud Porter, Anna Tostevin, Oliver Starrup).
Variable | N | HR | Adjusted HR | 95% CI | P value
--- | --- | --- | --- | --- | ---
Resistance profile | | | | | |
no resistance | 6330 | 1.00 | 1.00 | — | 0.62 |
≥1 TAM | 269 | 1.00 | 1.03 | 0.91–1.18 | |
Age (per 10 years older) | 6599 | 0.97 | 1.01 | 0.98–1.04 | 0.44 |
Exposure group⁸ | | | | | |
MSM | 4010 | 1.00 | 1.00 | — | <0.001 |
FSM | 1187 | 0.92 | 0.92 | 0.83–1.01 | |
MF | 890 | 0.78 | 0.78 | 0.71–0.87 | |
IDU | 123 | 0.56 | 0.60 | 0.48–0.74 | |
other | 312 | 1.11 | 0.99 | 0.87–1.12 | |
Ethnicity⁹ | | | | | |
white | 4084 | 1.00 | 1.00 | — | 0.004 |
black | 1810 | 0.95 | 1.03 | 0.94–1.12 | |
Asian | 229 | 1.14 | 1.17 | 1.00–1.36 | |
other | 405 | 1.20 | 1.20 | 1.07–1.34 | |
HIV-1 RNA (log₁₀ copies/mL) | | | | | |
<4.0 | 1055 | 1.58 | 1.64 | 1.52–1.77 | <0.001 |
4.0–5.0 | 2627 | 1.00 | 1.00 | — | |
>5.0 | 2572 | 0.58 | 0.59 | 0.55–0.63 | |
CD4 cell count (cells/mm³) | | | | | |
<200 | 2447 | 0.77 | 0.94 | 0.88–1.00 | 0.08 |
200–349 | 2800 | 1.00 | 1.00 | — | |
350–499 | 763 | 1.05 | 1.03 | 0.94–1.12 | |
≥500 | 259 | 0.95 | 0.91 | 0.79–1.05 | |
ART regimen | | | | | |
NNRTI | 4889 | 1.00 | 1.00 | — | <0.001 |
PI/b | 1710 | 0.69 | 0.70 | 0.65–0.74 | |
tenofovir | 5338 | 1.00 | 1.00 | — | 0.07 |
abacavir | 1261 | 0.97 | 0.94 | 0.87–1.01 | |

FSM, females who have sex with males; MSF, males who have sex with females; IDU, injecting drug users.
⁸Age at start of ART.
⁹Unknown categories were included in the model but not in the global P values.

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Supplementary data

Table S1 and Figure S1 are available as Supplementary data at JAC Online.

References


