J Antimicrob Chemother
doi:10.1093/jac/dky468

Journal of Antimicrobial Chemotherapy

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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Received 6 July 2018; returned 5 August 2018; revised 6 October 2018; accepted 13 October 2018

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 singleton 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.[1–4] In these regions, ~10% of patients show evidence of transmitted drug resistance (TDR),[1] although prevalence rates and temporal trends vary by region, population and testing method.[1,5–9] The most common TDR 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.[1] 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.[10] It is proposed that a high proportion of cases of TDR in these regions originate from ART-naive patients with TDR.[11–15]

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.[16] 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 (T215rev, 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;[18] 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,[20] 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 TDR 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 TDR 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 χ^2 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 viraemia, 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 viraemia 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 T215rev (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

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

Characteristic	Resistance profile		*P* value
	no resistance (*N* = 6330)	≥1 TAM (*N* = 269)	
Total number (%)	6330 (100)	269 (100)	—
Age at start of ART, years, median (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 group, *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[a]	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 subtype, *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, $\log_{10}$ copies/mL, median (IQR)	4.8 (4.3–5.3)	4.9 (4.3–5.3)	0.37
CD4 cell count, cells/mm^3, median (IQR)	230 (142–310)	234 (150–310)	0.57
ART regimen, *n* (%)			
NNRTI	4749 (75.0)	140 (52.0)	<0.001
PI/b	1581 (25.0)	129 (48.0)	<0.001
tenofovir	5117 (80.8)	221 (82.2)	0.59
abacavir	1213 (19.2)	48 (17.8)	0.59

FSM, females who have sex with males; MSF, males who have sex with females; IDU, injecting drug users.
[a]Other exposure groups comprised a history of receiving blood or blood products and vertical transmission.

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

Table 2. Resistance patterns of subjects showing ≥1 TAM as the sole form of TDR

Pattern	*N*	%
Any TAM	269	100.0
Singleton TAMs	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

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 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 T215rev 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 key determinant of HIV treatment outcomes in the UK.[21] There was also an effect of baseline viral load and CD4 cell count, and a marginal but significant effect of starting abacavir rather than tenofovir. In previous studies, a high baseline viral load predicted reduced responses to abacavir/lamivudine (versus tenofovir/emtricitabine) when used in combination with efavirenz or ritonavir-boosted atazanavir.[22,23] In our study, among 1261 abacavir recipients, 65% received efavirenz, 13% nevirapine and 15% ritonavir-boosted lopinavir; the effect of starting abacavir persisted after adjusting for the baseline viral load, suggesting that additional factors may contribute to a modest reduction in activity.

In the accepted model of HIV transmission, infection with a drug-resistant virus is followed by expansion of the founder strain in the absence of outcompeting WT virus, leading to long-term persistence of TDR variants despite the absence of drug-selective pressure.[24–26] Over time, the founder strain may undergo genetic evolution, with some resistance-associated mutations becoming undetectable, whereas others are replaced by fitter mutants. In this model, the full resistance spectrum may persist at low frequency in plasma and be archived in cellular HIV-1 DNA, retaining a potential impact on treatment outcomes. Emergence of T215Y and T215F from the WT virus (i.e. threonine to be replaced by tyrosine or phenylalanine) requires two nucleotide substitutions in RT. T215rev variants are molecular intermediates in reverse transition between T215Y or T215F and WT, and are generally taken to signal persistence of progenitor T215Y/T215F. However, in the UK as in other regions of Europe, various T215rev variants have become established as subtype B lineages circulating among MSM, and are often detected in linked transmission clusters.[10–15] In our national database, 55% of HIV-1 subtype B sequences harbouring TDR mutations including T215rev form transmission clusters.[12] In this epidemiological context, T215rev variants do not necessarily indicate the transmission of T215Y/T215F, thus diminishing clinical significance. Extrapolation to other epidemiological contexts is not warranted in the absence of supportive evidence.

Conventional (Sanger) sequencing has low sensitivity for variants that represent a minority (<20%) of strains within a patient's sample. It is possible to detect additional TDR mutations using ultrasensitive testing methods, although the enhancement varies by setting and is becoming less common in recent cohorts.[5] The question therefore remains as to the extent of undetected TDR in subjects with ≥1 TAM. In our population, additional, undetected mutations were either not present or had no appreciable clinical impact. In support of the former hypothesis, deep sequencing in an ART-naive Belgian population with T215rev failed to identify T215Y, T215F or other NRTI mutations.[27] Thus, in an epidemiological context in which the main source of TDR is ART-naive subjects harbouring TAM-containing subtype B lineages, the virus detected at diagnosis by population sequencing most likely represents the original infecting variant and ultrasensitive testing is unlikely to reveal hidden resistance.

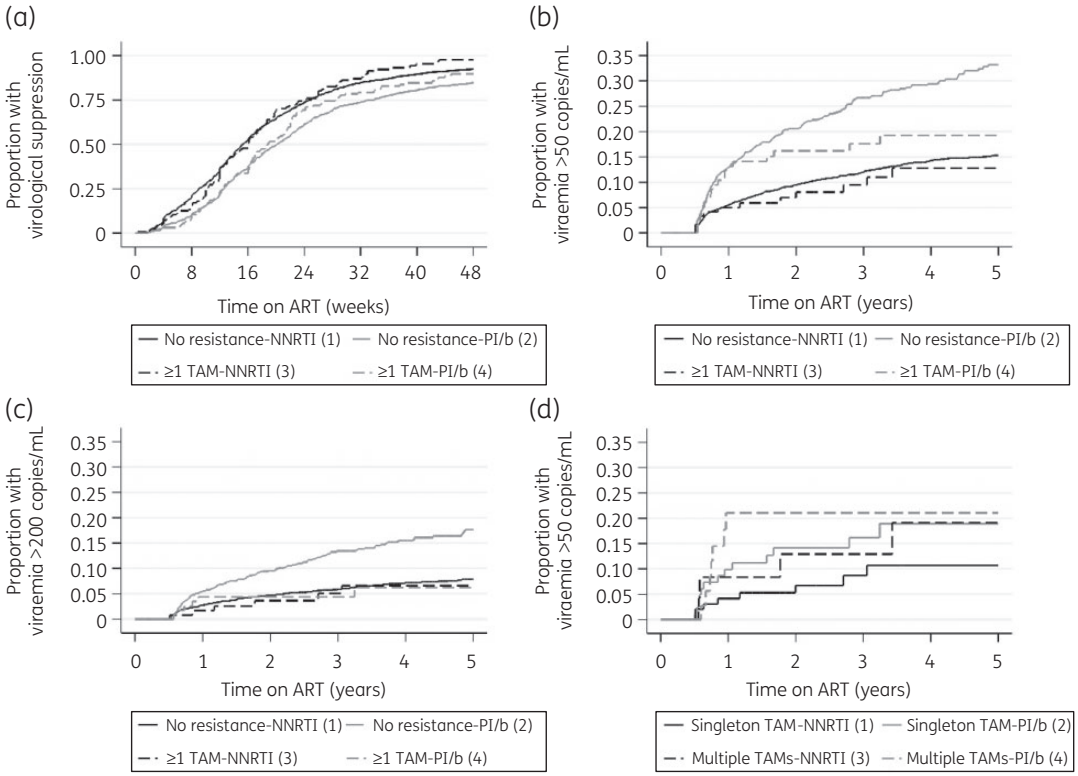

Figure 1. Kaplan–Meier analysis of virological responses to first-line ART by baseline resistance profile and treatment regimen. (a) Time to virological suppression (two consecutive viral load measurements ≤50 copies/mL). (b) Time to viraemia (two consecutive viral load measurements >50 copies/mL or a single measurement followed by a significant treatment change). (c) Time to viraemia using an HIV-1 RNA cut-off of >200 copies/mL. (d) Time to viraemia (>50 copies/mL) according to the presence of singleton TAMs or multiple TAMs. Number at risk in (a), (b) and (c) at the start of ART: group 1=4749; group 2=1581; group 3=140; and group 4=129. Number at risk in (d) at the start of ART: group 1=114; group 2=89; group 3=26; and group 4=40.

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[2] 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 preidentified 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.

Acknowledgements

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Coordinating centre: Institute for Global Health, UCL (David Dunn, Keith Fairbrother, Esther Fearnhill, Kholoud Porter, Anna Tostevin, Oliver Stirrup).

Table 3. Predictors of virological suppression (HIV-1 RNA ≤50 copies/mL) after starting first-line ART

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[a] (per 10 years older)	6599	0.97	1.01	0.98–1.04	0.44
Exposure group[b]					
MSM	4010	1.00	1.00	—	<0.001
FSM	1187	0.92	0.92	0.83–1.01	
MSF	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	
Ethnicity[b]					
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 (log_{10} 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/mm^3)					
<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.
[a]Age at start of ART.
[b]Unknown categories were included in the model but not in the global *P* values.

Centres contributing data: Clinical Microbiology and Public Health Laboratory, Addenbrooke's Hospital, Cambridge (Justine Dawkins); Guy's and St Thomas' NHS Foundation Trust, London (Siobhan O'Shea, Jane Mullen); PHE—Public Health Laboratory, Birmingham Heartlands Hospital, Birmingham (Erasmus Smit); Antiviral Unit, National Infection Service, PHE, London (Tamyo Mbisa); Imperial College Health NHS Trust, London (Alison Cox); King's College Hospital, London (Richard Tandy); Medical Microbiology Laboratory, Leeds Teaching Hospitals NHS Trust (Tracy Fawcett); Specialist Virology Centre, Liverpool (Mark Hopkins); Department of Clinical Virology, Manchester Royal Infirmary, Manchester (Peter Tilston); Department of Virology, Royal Free Hospital, London (Clare Booth, Ana Garcia-Diaz); Edinburgh Specialist Virology Centre, Royal Infirmary of Edinburgh (Lynne Renwick); Department of Infection & Tropical Medicine, Royal Victoria Infirmary, Newcastle (Matthias L. Schmid, Brendan Payne); South Tees Hospitals NHS Trust, Middlesbrough (David Chadwick); Department of Virology, Barts Health NHS Trust, London (Jonathan Hubb); Molecular Diagnostic Unit, Imperial College, London (Simon Dustan); University College London Hospitals (Stuart Kirk); West of Scotland Specialist Virology Laboratory, Gartnavel, Glasgow (Rory Gunson, Amanda Bradley-Stewart).

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Funding

This study was supported by internal funding.

Transparency declarations

A. M. G. has received funding from Cepheid and Janssen for participation in advisory boards and educational workshops unconnected to the submitted work, and is currently employed as expert scientist at Roche Pharma Research & Early Development; Roche Pharma was not involved in the work. The University of Liverpool is the recipient of grant income from Gilead, Janssen and ViiV for research projects of which A. M. G. is the principal investigator. C. S. has received funding from Gilead, ViiV and Janssen for participation in advisory boards, membership of Data Safety and Monitoring Boards and speaker panels, and for preparation of educational materials

Table 4. Predictors of viraemia (HIV-1 RNA >50 copies/mL) after starting first-line ART

Variable	Total number	Number with viraemia (%)	HR	Adjusted HR	95% CI	*P* value
Resistance profile						
no resistance	6330	802 (12.7)	1.00	1.00	—	0.15
≥1 TAM	269	32 (11.9)	0.87	0.77	0.54–1.10	
Age[a] (per 10 years older)	6599	—	1.02	0.97	0.90–1.04	0.39
Exposure group[b,c]						
MSM	4010	446 (11.1)	1.00	1.00	—	<0.001
FSM	1187	167 (14.1)	1.62	1.15	0.90–1.46	
MSF	890	139 (15.6)	1.61	1.24	0.98–1.57	
IDU	123	33 (26.8)	3.65	2.84	1.98–4.07	
other	312	30 (9.6)	0.91	0.91	0.62–1.32	
Ethnicity[b]						
white	4084	481 (11.8)	1.00	1.00	—	<0.001
black	1810	283 (15.6)	1.58	1.43	1.15–1.77	
Asian	229	20 (8.7)	0.79	0.75	0.48–1.18	
other	405	41 (10.1)	0.81	0.82	0.59–1.13	
HIV-1 RNA (log_{10} copies/mL)						
<4.0	1055	93 (8.8)	0.99	0.98	0.77–1.24	<0.001
4.0–5.0	2627	246 (9.4)	1.00	1.00	—	
>5.0	2572	441 (17.1)	1.97	1.91	1.63–2.25	
CD4 count (cells/mm^3)						
<200	2447	387 (15.8)	1.69	1.23	1.05–1.45	0.04
200–349	2800	278 (9.9)	1.00	1.00	—	
350–499	763	76 (10.0)	1.13	1.14	0.88–1.47	
≥500	259	31 (12.0)	1.58	1.43	0.99–2.09	
ART regimen						
NNRTI	4889	513 (10.5)	1.00	1.00	—	<0.001
PI/b	1710	321 (18.8)	2.27	2.17	1.88–2.51	
tenofovir	5338	644 (12.1)	1.00	1.00	—	0.02
abacavir	1261	190 (15.1)	1.23	1.22	1.04–1.44	

FSM, females who have sex with males; MSF, males who have sex with females; IDU, injecting drug users.
[a]Age at start of ART.
[b]Unknown categories were included in the model but not in the global *P* values.
[c]In a separate model, the adjusted HR when comparing female versus male was 0.96 (95% CI 0.78–1.18; $P = 0.69$).

unconnected to the submitted work. D. T. D. and P. T. have received funding from Gilead and ViiV for participation in advisory boards and educational workshops unconnected to the submitted work. C. O. and C. L. have received funding from Abbvie, Gilead, Janssen, MSD and ViiV for participation in advisory boards and educational workshops unconnected to the submitted work. The remaining authors have none to declare.

Supplementary data

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

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