

Mortality of treated HIV-1 positive individuals according to viral subtype in Europe and Canada: collaborative cohort analysis

The Antiretroviral Therapy Cohort Collaboration (ART-CC), Canadian Observational Cohort Collaboration (CANOC), The UK Collaborative HIV Cohort Study (UK CHIC), the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE)

Objectives: To estimate prognosis by viral subtype in HIV-1-infected individuals from start of antiretroviral therapy (ART) and after viral failure.

Design: Collaborative analysis of data from eight European and three Canadian cohorts.

Methods: Adults ($N > 20\,000$) who started triple ART between 1996 and 2012 and had data on viral subtype were followed for mortality. We estimated crude and adjusted (for age, sex, regimen, $CD4^+$ cell count, and AIDS at baseline, period of starting ART, stratified by cohort, region of origin and risk group) mortality hazard ratios (MHR) by subtype. We estimated MHR subsequent to viral failure defined as two HIV-RNA measurements greater than 500 copies/ml after achieving viral suppression.

Results: The most prevalent subtypes were B (15 419; 74%), C (2091; 10%), CRF02AG (1057; 5%), A (873; 4%), CRF01AE (506; 2.4%), G (359; 1.7%), and D (232; 1.1%). Subtypes were strongly patterned by region of origin and risk group. During 104 649 person-years of observation, 1172/20 784 patients died. Compared with subtype B, mortality was higher for subtype A, but similar for all other subtypes. MHR for A versus B were 1.13 (95% confidence interval 0.85, 1.50) when stratified by cohort, increased to 1.78 (1.27, 2.51) on stratification by region and risk, and attenuated to 1.59 (1.14, 2.23) on adjustment for covariates. MHR for A versus B was 2.65 (1.64, 4.28) and 0.95 (0.57, 1.57) for patients who started ART with $CD4^+$ cell count below, or more than, 100 cells/ μ l, respectively. There was no difference in mortality between subtypes A, B and C after viral failure.

Conclusion: Patients with subtype A had worse prognosis, an observation which may be confounded by socio-demographic factors.

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Introduction

HIV-1 is a highly diverse virus that is classified into four groups: M (major), O (outlier), N (nonmajor nonoutlier) [1], and group P, a recently discovered “proposed” new group [2]. The vast majority of HIV-1 infections are group M, which includes at least nine subtypes (clades) [3] and an increasing number of circulating recombinant forms (CRFs) [4]. The early spread of HIV-1 within Canada, the United States, and Western Europe was due to group M, subtype B infection, which occurred mainly among MSM and injection drug user (IDU) communities. Diagnostic and monitoring tests, as well as our understanding of the natural history, molecular biology and responses to antiretroviral therapy (ART), were established primarily for subtype B because this was dominant in Europe and North America. Worldwide however, subtype C, which is most often seen in heterosexuals, accounts for about half of currently infected individuals and the majority of new HIV-1 infections [5]. An increasing proportion of infections in Europe and Canada are non-B due to migration, particularly from Africa, with further secondary local transmission [6,7].

Monitoring viral diversity is important because differences between subtypes have been reported in transmissibility, disease pathogenesis [8], pretreatment progression [9], accuracy of viral load monitoring by conventional assays [10], genetic barriers to ART resistance [11,12], response to treatment [13–16], and rate of progression to AIDS [17–19]. The impact of these differences on prognosis in the ART era may be substantial and dependent on choice of ART regimen [20,21]. Published studies have been limited by small numbers of patients with individual subtypes, and short follow-up [13,22]. Several studies have compared subtype B with non-B subtypes grouped together [23,24], but there may be differences in prognosis between non-B subtypes. Large collaborations of cohorts are required to compare prognosis for clinical events between patients infected with different viral subtype [25].

The relationship of HIV subtype with prognosis may be confounded by social and demographic as well as clinical characteristics. In particular, subtypes cluster by geographic origin and transmission risk group. Therefore we compared mortality by subtype in patients starting ART accounting for their region of origin and risk group. Variation in outcomes would warrant further study of differences in response to specific ART regimens and development of viral resistance [21]. Our objectives were to characterize the frequencies of HIV subtypes in this population, compare demographic and clinical characteristics and estimate prognosis for mortality after starting ART and after viral failure by subtype or CRF.

Methods

We combined data from three Canadian and eight European cohorts: Montreal (Canada) [26], the UK Collaborative HIV Cohort (UK CHIC) [27], and those included in the ART Cohort Collaboration (ART-CC) which had more than 100 patients with data on viral subtype. Cohorts from USA were excluded as they do not exhibit large diversity in HIV subtypes. Details of ART-CC appear elsewhere (<http://www.art-cohort-collaboration.org>) [28]: Cohorts have been approved by their ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least every 6 months.

Included patients had confirmed HIV infection, were aged at least 16 years and started combination ART [at least two nucleoside reverse transcriptase inhibitors (NRTI) plus boosted protease inhibitor or nonnucleoside reverse transcriptase inhibitor (NNRTI)] between 1996 and 2012 and were without prior exposure to antiretroviral drugs. Eligible patients had data on viral subtype, region of origin, CD4⁺ and AIDS diagnosis at ART start. Patients were followed for mortality from ART start to cohort-specific database close date, which varied between cohorts from 31 December 2009 to 31 March 2012. Patients were considered lost to follow-up if there was a lag of more than 1 year between the dates the patient was last known to be alive and administrative censoring.

European cohorts recorded country of origin and/or ethnicity. Cohorts from mainland Europe had data on country of origin for migrants, but did not always record country of origin for those born in the home country. We assumed that patients treated in the United Kingdom who were identified as black Caribbean were from Europe as they were likely to have been born in the United Kingdom, whereas those who identified as black African were likely to be recent immigrants and were assumed to be from sub-Saharan Africa (SSA). We used a combination of ethnicity and country of origin to allocate patients to regions defined by the United Nations International Standard (unstats.un.org/unsd/methods/m49/m49.htm). Patients from west, east and southern Africa were grouped as SSA because some cohorts used the term “black African”. We used the following final classification of region of origin: Europe/SSA/N. Africa/Middle East/Asia/Australasia/N. America/Central and S. America/Canada First Nations.

We compared demographic and clinical characteristics at ART start by subtype. The Kaplan–Meier method was used to estimate cumulative mortality by subtype. We estimated crude mortality rates per 1000 person-years overall and by subtype. Because subtype was highly correlated with region of origin and transmission risk we

fitted a series of stratified Cox models to estimate crude and adjusted between-subtype mortality hazard ratios (MHR) from ART start, with subtype B as the comparator. We estimated MHR that were crude; stratified by cohort; additionally stratified by region of origin and risk group; additionally adjusting for age, sex, CD4⁺ and AIDS at baseline, period of starting ART (1996–2002, 2003–2009), and regimen (protease inhibitor-based, NNRTI-based, other). We did not adjust for viral load at ART start as it was not predictive in multivariable models and inclusion would have reduced sample size. We used Akaike Information Criteria (AIC) to compare model fit. Because IDUs have worse prognosis than other risk groups, comparisons excluding IDU were made. As subtype was strongly related to region of origin, we repeated analyses restricting to heterosexuals and MSM of European (EU) origin. We also estimated MHR comparing the most prevalent subtypes (A, B, and C) across the EU and SSA patient populations within the same model. In sensitivity analyses, we estimated adjusted MHR: restricting to white heterosexuals; excluding the UK CHIC cohort as it included black Caribbean patients; only including UK CHIC. To examine whether differences in mortality were mostly due to deaths soon after starting ART, we repeated analyses excluding the first 6 months of follow-up on ART. We examined whether CD4⁺ at ART start (<100 versus ≥100 cells/μl) modified effects of subtype on mortality by testing for interaction.

We investigated mortality subsequent to viral failure, because development of resistance has been found to vary by subtype [29]. For those experiencing viral failure (defined as two HIV RNA measurements >500 copies/ml after achieving viral suppression) we estimated crude and adjusted (for age, sex, CD4⁺ and AIDS at baseline, period of starting ART, and regimen) MHR stratified by cohort, region of origin, and risk. Follow-up was measured from date of first detectable viral load. We repeated analyses using unconfirmed viral failure, defined as a single viral load greater than 500 copies/ml. Statistical analyses were performed using Stata software (Version 12.0; College Station, Texas, USA).

Results

Eleven cohorts supplied data on 29 248 patients with known HIV subtype who initiated ART in the study period. We excluded patients with data missing on region of origin (5536), CD4⁺ cell count (2482) and AIDS diagnosis (62) at ART start, leaving 21 168 eligible patients. A further 384 patients with rare subtypes (<100 cases, or equivalently <0.5% prevalence) were excluded as they were too few to analyse. We analysed 20 784 patients who experienced 1172 deaths during 104 649 person-years of follow-up for an overall mortality rate of

11.2 [95% confidence interval (CI), 10.6–11.9] per 1000 person-years. The mortality rate in those excluded due to missing data was higher at 19.5 (18.2–20.9) per 1000 person-years. Compared with included patients, a higher proportion of those excluded started ART before 2003, were IDU, came from SSA or America, and were infected with subtypes A, C, or D.

Demographic and clinical characteristics of the study population by subtype are shown in Table 1. Eighty-eight per cent of patients were from European and 12% from Canadian cohorts. Subtype B was most frequent [15 419/20 784 (74%)], whereas subtype C was predominant in those from SSA [1326/2091 (63%)]. Subtype CRF02_AG was common in those from SSA, and CRF01_AE was predominant in Asian patients. Subtype B included the highest proportion of MSM 10 347 of 15 419 (67%) and IDU 1563 of 15 419 (10%), whereas more than 50% of those with subtypes A, C, D, G and CRF02_AG were female. Supplementary Figure 1, <http://links.lww.com/QAD/A818>, shows the distribution of subtypes for all patients and separately for patients from SSA.

Older age, IDU and heterosexual (versus MSM) risk group, lower CD4⁺, AIDS diagnosis, starting ART pre 2003, and protease inhibitor-based (versus NNRTI-based) regimen were associated with increased mortality independently of viral subtype (supplementary Table 1, <http://links.lww.com/QAD/A818>). Compared with patients from EU, those from SSA, Australia and New Zealand had lower, and indigenous Canadians higher risk of mortality. Crude mortality was greatest for subtype B (Table 2). However, after stratification by cohort (which allows for between-cohort differences in mortality rates), the highest MHR [1.13 (95% CI 0.85–1.50)] was for subtype A. This was further increased to 1.78 (1.27–2.51) in the model stratified by cohort, region of origin and risk but was attenuated to 1.59 (1.13–2.23) after adjustment for age, sex, CD4⁺ and AIDS at baseline, regimen, and period of starting ART. There was little evidence that mortality rates for other subtypes differed from those for subtype B. AIC decreased substantially on stratification showing improved fit to the data (Table 2). Crude and adjusted MHR by subtype overall ($N=20\,784$) and restricted to heterosexual and MSM Europeans ($N=11\,038$) are compared in Fig. 1. Amongst European MSM and heterosexuals, the adjusted MHR comparing subtype A with B was greater 2.16 (1.43–3.26) than among all patients 1.59 (1.13, 2.23) (supplementary Table 2, <http://links.lww.com/QAD/A818>). In sensitivity analyses restricted to different patient groups, mortality for subtype A was consistently greater than for subtype B (supplementary Table 2, <http://links.lww.com/QAD/A818>). The MHR for subtype A compared with B was slightly reduced to 1.47 (95% CI, 1.01–2.13) when patients who died within 6 months of starting ART ($N=127$) were excluded (supplementary Table 3,

Table 1. Demographics and clinical characteristics at start of ART of the study population overall and by subtype.

	HIV subtype N (%)								Overall 20784 (100%)	P value ^a
	A 873 (4%)	B 15 419 (74%)	C 2091 (10%)	D 232 (1.1%)	F 130 (0.6%)	G 359 (1.7%)	CRF01AE 506 (2.4%)	CRF02AG 1057 (5%)		
Sex										
Male	373 (43)	13 657 (89)	815 (39)	82 (35)	74 (57)	157 (44)	357 (71)	429 (41)	60 (51)	16 004 (77)
Risk group										
MSM	93 (11)	10 347 (67)	132 (6)	11 (5)	35 (27)	28 (8)	142 (28)	81 (8)	29 (25)	10 898 (52)
Het	671 (77)	2315 (15)	1723 (82)	199 (86)	82 (63)	285 (79)	314 (62)	873 (83)	68 (58)	6530 (31)
IDU	42 (5)	1563 (10)	22 (1)	5 (2)	5 (4)	15 (4)	13 (3)	9 (0.9)	7 (6)	1681 (8)
Other/Unknown	67 (8)	1194 (8)	214 (10)	17 (7)	8 (6)	31 (9)	37 (7)	94 (9)	13 (11)	1675 (8)
Region of origin										
Europe	284 (33)	11 221 (73)	464 (22)	43 (19)	69 (53)	107 (30)	297 (59)	261 (25)	48 (41)	12 794 (62)
Sub-Saharan Africa	510 (58)	291 (2)	1326 (63)	170 (73)	38 (29)	231 (64)	12 (2)	744 (70)	63 (54)	3385 (16)
N/Africa & Middle East	34 (4)	131 (0.9)	195 (9)	11 (5)	1 (0.8)	7 (2)	3 (0.6)	17 (2)	0 (0)	399 (2)
Asia	19 (2)	322 (2)	43 (2)	1 (0.4)	0 (0)	0 (0)	179 (35)	6 (0.6)	0 (0)	570 (3)
Australasia	4 (0.5)	173 (1)	3 (0.1)	0 (0)	0 (0)	1 (0.3)	3 (0.6)	2 (0.2)	2 (2)	188 (0.9)
North America	7 (0.8)	1675 (11)	18 (0.9)	1 (0.4)	0 (0)	1 (0.3)	5 (1)	6 (0.6)	0 (0)	1713 (8)
Central & S America	15 (2)	1386 (9)	42 (2)	6 (3)	22 (17)	12 (3)	7 (1)	21 (2)	4 (3)	1515 (7)
Canada 1st nations	0 (0)	220 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	220 (1)
Year of starting ART										
1996–2002	264 (30)	5232 (34)	405 (19)	93 (40)	32 (25)	46 (13)	96 (19)	151 (14)	14 (12)	6333 (30)
AIDS at start of ART										
Yes	182 (21)	3141 (20)	399 (19)	59 (25)	30 (23)	50 (14)	128 (25)	211 (20)	19 (16)	4219 (20)
Median age (years)	36 (30–44)	38 (32–44)	34 (29–41)	35 (29–40)	35 (29–43)	34 (29–40)	39 (31–47)	33 (28–40)	34 (29–39)	37 (31–44)
Median CD4 ⁺ cell count (cells/ μ l)	213 (110–313)	230 (130–325)	200 (110–290)	200 (70–290)	205 (130–314)	200 (110–283)	192 (60–292)	206 (110–310)	220 (138–319)	221 (121–320)
Median viral load (log copies/ml)	4.6 (3.9–5.1)	4.9 (4.4–5.4)	4.6 (3.9–5.1)	4.9 (4.1–5.3)	4.8 (4.2–5.3)	4.6 (3.8–5.1)	4.9 (4.4–5.4)	4.8 (4.0–5.4)	4.6 (4.1–5.2)	4.9 (4.3–5.3)
Median follow up (years)	4.1 (2.0–7.8)	4.1 (1.9–8.1)	3.7 (1.7–6.3)	5.6 (2.7–8.9)	3.6 (1.5–6.7)	2.9 (1.5–5.4)	3.7 (1.8–6.4)	3.1 (1.5–5.7)	3.2 (1.1–6.0)	4.0 (1.8–7.6)

Het, heterosexual risk group; IDU, injection drug user.

^aP value for difference in distribution of characteristics among subtypes.

Table 2. Crude mortality rates and crude and adjusted MHR by subtype (i) no stratification (ii) stratified by cohort (iii) additionally stratified by cohort (iii) additionally stratified by region of origin and risk (iv) additionally adjusted for age, sex, CD4⁺ cell count and AIDS at baseline, period of starting ART, and ART regimen.

Subtype	N patients	N deaths	Crude mortality Rate/1000 pyrs	Crude MHR (95% CI)		Stratified by cohort, region of origin and risk		Adjusted MHR (95% CI) P value
				No stratification	Stratified by cohort	Stratified by cohort, region of origin and risk	Additionally adjusted for covariates	
A	873	52	11.7 (8.9–15.3)	0.96 (0.72, 1.26)	1.13 (0.85, 1.50)	1.78 (1.27, 2.51)	1.59 (1.13, 2.23)	0.007
B	15 419	997	12.3 (11.6–13.1)	1	1	1	1	1
C	2091	51	5.6 (4.3–7.4)	0.47 (0.35, 0.62)	0.59 (0.44, 0.79)	0.95 (0.66, 1.35)	1.02 (0.71, 1.46)	0.76
D	232	10	7.2 (3.9–13.4)	0.58 (0.31, 1.09)	0.72 (0.39, 1.35)	0.97 (0.48, 1.97)	0.93 (0.46, 1.88)	0.84
F	130	4	7.1 (2.6–18.8)	0.59 (0.22, 1.56)	0.65 (0.24, 1.74)	0.94 (0.35, 2.54)	0.87 (0.32, 2.36)	0.78
G	359	7	5.2 (2.5–10.9)	0.43 (0.21, 0.91)	0.52 (0.25, 1.10)	0.68 (0.32, 1.46)	0.84 (0.39, 1.81)	0.66
CRF01AE	506	22	9.7 (6.4–14.8)	0.81 (0.53, 1.24)	0.87 (0.57, 1.34)	1.17 (0.74, 1.86)	1.06 (0.67, 1.68)	0.81
CRF02AG	1057	26	6.3 (4.3–9.3)	0.53 (0.36, 0.78)	0.64 (0.43, 0.95)	1.05 (0.67, 1.63)	1.19 (0.76, 1.85)	0.45
CRF06_cpx	117	3	6.7 (2.2–20.8)	0.56 (0.18, 1.74)	0.67 (0.22, 2.09)	0.82 (0.26, 2.60)	1.00 (0.31, 3.20)	1.00
TOTAL	20 784	1172	11.2 (10.6–11.9)	1	1	1	1	1
MODEL AIC				21 394	17 006	12 493	12 068	

AIC, Akaike Information Criterion; CI, confidence interval; MHR, mortality hazard ratio; pyrs, person years.

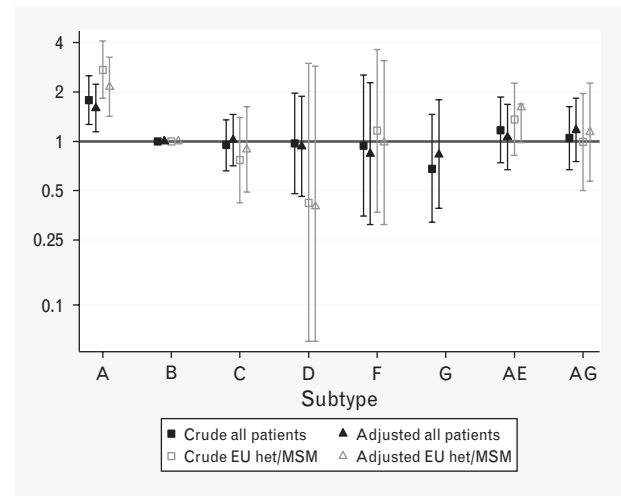


Fig. 1. Crude and adjusted mortality rate ratios by subtype for all patients and restricted to European heterosexuals and MSM. EU, European origin; het, heterosexual risk group. Subtype B is the comparator; bars show 95% confidence intervals. Crude model is stratified by cohort, region of origin, and risk. Adjusted model is adjusted for age, sex, CD4⁺ cell count and AIDS at baseline, period of starting ART, and stratified by cohort, region of origin, and risk.

<http://links.lww.com/QAD/A818>). Patients with subtype A had worse prognosis than those with subtype B for their CD4⁺ was less than 100 cells/ μ l [aMHR 2.65 (1.64–4.28)], but not if it was at least 100 cells/ μ l [0.95 (0.57–1.57)] at ART start (interaction *P*-value 0.0004, supplementary Table 3, <http://links.lww.com/QAD/A818>). In 40-year-old heterosexual males who started NNRTI-based ART after 2003, the estimated absolute 2-year mortality risk differences for subtype A compared with B were 6 and 5% for those from EU and SSA, respectively, in a high risk group (CD4⁺ 50 cells/ μ l and AIDS at ART start), with no difference in a low risk group (CD4⁺ 350 cells/ μ l and no AIDS diagnosis).

We further compared mortality in groups defined by both subtype (restricted to A, B and C) and region of origin (European MSM and heterosexuals compared with patients from SSA). The cumulative mortality for these six groups is shown in supplementary Figure 2, <http://links.lww.com/QAD/A818>. For both Europeans and those from SSA cumulative mortality was highest for patients with subtype A infection. However, within each subtype, the cumulative mortality was higher for patients from EU compared with SSA for all three subtypes. Table 3 shows the adjusted MHR for the six subtype-origin combinations with EU subtype B as the comparator. Adjusted MHR for all three subtypes were higher in EU compared with SSA patients, although CIs were wide (Table 3). In Europeans, those with subtype A had the worst, and subtype C the best prognosis, whereas within SSA, the order was A worst, and B best, although

Table 3. Crude and adjusted (for age, sex, CD4⁺ cell count and AIDS at baseline, period of starting ART, ART regimen) mortality hazard ratios (MHR) comparing subtypes A, B, and C in European MSM and heterosexuals, and people from sub-Saharan Africa; models are stratified by cohort and risk.

		Deaths/N	Crude MHR (95% CI)	P value	Adjusted MHR (95% CI)	P value
EU subtype	A	30/244	2.77 (1.85, 4.16)	<0.001	2.26 (1.50, 3.42)	<0.001
	B	403/9637	1		1	
	C	13/413	0.75 (0.41, 1.36)	0.34	0.90 (0.49, 1.63)	0.72
SSA subtype A	A	17/510	0.55 (0.31, 0.96)	0.13	0.75 (0.42, 1.33)	0.24
	B	6/291	0.50 (0.20, 1.23)	0.04	0.58 (0.24, 1.43)	0.32
	C	29/1326	0.51 (0.32, 0.82)	0.005	0.70 (0.43, 1.13)	0.14
TOTAL		498/12 421				

EU, European Union; CI, confidence interval; SSA, sub-Saharan Africa.

all three adjusted MHR in SSA were quite similar with overlapping CIs.

A total of 7865 patients experienced viral failure, of whom 6834 were infected with subtypes A, B and C and included in analyses. Of these, 736 died during 38 975 person-years of follow-up [mortality rate 18.9 (95% CI 17.6–20.3) per 1000 person-years]. Cumulative mortality after viral failure was highest for subtype B (Supplementary Figure 3, <http://links.lww.com/QAD/A818>). The adjusted MHR after confirmed or unconfirmed viral failure were similar for the three subtypes (Table 4).

Discussion

Patients treated with ART in Europe and Canada were infected with diverse HIV-1 viral subtypes. Although subtype B still constituted the majority of infections, over a quarter were other subtypes, including a significant number of infections with subtypes A and C, which are common in Africans, and the two recombinant forms CRF01AE and CRF02AG. We found a strong association of transmission risk with viral subtype, with MSM and IDU dominating subtype B, but heterosexual transmission dominating other subtypes. Crude mortality rates were highest for patients with subtype B, followed by A and CRF01AE, whereas patients infected with subtypes C, G and CRF02AG experienced lower mortality rates. However we found that MHR were highest for patients infected with subtype A after stratification on cohort, region of origin and transmission risk group, and adjustment for age, sex, CD4⁺ and AIDS at baseline, period of starting ART, and regimen. There was little difference in adjusted MHR between the other subtypes. These results indicated that there was strong confounding by region of origin in crude mortality rate comparisons. Our finding of worse prognosis for patients infected with subtype A compared with B was robust to all sensitivity analyses which estimated adjusted MHR in more homogeneous subgroups such as MSM and heterosexually infected Europeans, or white heterosexuals, but only applied to patients who started ART with CD4⁺ cell count less than 100 cells/ μ l. When we

compared mortality after viral failure, we found little evidence of a difference in survival between subtypes A, B, and C, but numbers of deaths after viral failure were few for subtypes A and C.

This is the largest study of mortality according to viral subtype to date: we analysed data on over 20 000 patients, of whom more than 1000 died. Our results should be generalizable to clinical settings in Europe and Canada where there are migrants with HIV-1 infections of diverse subtypes. Unlike many previous studies [23,24,30–32], we analysed mortality among patients infected with nine different subtypes or CRFs, rather than grouping non-B subtypes together. Previous studies have found that viral subtypes are compartmentalized by ethnicity and transmission group which convey epidemiological information [33–35], making it difficult to attribute differences in prognosis to the influence of viral subtype. We attempted to control for such confounding by stratifying analyses on region of origin and risk group, as well as by cohort. However, we had to use region of origin as a proxy for ethnicity and some patients will have been misclassified. We carried out sensitivity analyses which restricted comparisons to more homogeneous groups, such as MSM and heterosexuals of European origin, and only white heterosexuals. We could only compare the most frequently occurring subtypes (A, B and C) in some subgroup analyses and also in analyses of mortality subsequent to viral failure. We distinguished black Caribbean and black Africans in the United Kingdom, and white and black South Africans, and our main results were not substantially changed in these sensitivity analyses. There may have been misclassification of risk group, particularly amongst black patients who may be less likely to self-identify as MSM [36].

A limitation of our study was the exclusion of 8080 (28%) patients with missing data on region of origin, CD4⁺ and AIDS status at ART start. These patients had higher mortality than those included in analyses. Whilst it is likely that a higher proportion starting ART in earlier years and IDU partially account for the increased mortality, our results may be biased due to missing data. In particular, patients from SSA and both North and South America (compared with Europeans), and those

Table 4. Crude and adjusted [for age, sex, CD4⁺ cell count and AIDS at baseline, period of starting ART (1996–2002, 2003–2009), ART regimen] mortality hazard ratios (MHR) after viral failure stratified by cohort, region of origin, and risk; follow-up is measured from date of first detectable viral load (VL).

Subtype	Confirmed viral failure (2 VL > 500 copies/ml)				Unconfirmed viral failure (1 VL > 500 copies/ml)			
	Crude		Adjusted		Crude		Adjusted	
	Deaths/N	MHR (95% CI)	P value	MHR (95% CI)	P value	MHR (95% CI)	P value	
A	23/416	0.80 (0.42, 1.54)	0.51	1.07 (0.56, 2.04)	0.84	1.10 (0.63, 1.94)	0.74	1.43 (0.81, 2.51)
B	681/5598	0.85 (0.46, 1.56)	0.59	1.03 (0.53, 2.02)	0.93	1.03 (0.61, 1.74)	0.91	1.29 (0.73, 2.26)
C	32/820							
TOTAL	736/6834							

CI, confidence interval.

infected with subtypes A, C, and D (compared with B), were more likely to have missing data. Therefore MHR for subtypes A, C and D compared with B may be underestimated. Our finding of worse prognosis in those with subtype A may be affected by residual confounding due to unmeasured social factors related to mortality rates. We were unable to control for time from diagnosis to treatment, and we lacked data on socio-economic status and lifestyle factors such as smoking, alcohol and drug abuse, which may be patterned by subtype and are related to mortality. The majority of subtype A infections in the United Kingdom were among Ugandans, categorized as black African heterosexual transmission risk, who may have had worse prognosis due to socio-economic disadvantage and late presentation. There is also a high prevalence of subtype A in Russia and Ukraine, where IDU is a strong transmission factor, and to a lesser extent in Greece and Cyprus. Only the EuroSIDA cohort included patients treated in these countries. However, it is likely that migrants from these countries were included in cohorts from Austria, Germany, Switzerland and the Netherlands as subtypes infecting immigrant patients living in Europe are mostly similar to those causing epidemics in their country of origin. We found that amongst white Europeans with subtype A in these cohorts, the prevalence of IDU was high. Such patients may be disadvantaged due to the effects of historic or ongoing substance abuse and/or socio-economic disadvantage. Among patients with subtypes A, B, and C, we found that compared with Europeans, those from SSA had lower mortality which may be due to a “healthy migrant” effect, or to a healthier life-style: in particular smoking prevalence may be lower in Africans than Europeans [37]. Alternatively, there may have been under-ascertainment of deaths in Africans or sicker patients may have returned home.

The documented increasing diversity in viral subtypes found in Canada and Europe [6,24,34] has been explained by travel and HIV acquisition abroad [38], immigration policy [39], and domestic transmission of non-B subtypes [7]. In the UK CHIC study, which includes a large immigrant population from SSA, diverse subtypes were increasingly represented across all demographic groups, which could be evidence of sexual mixing [34].

Several studies have considered the impact of viral subtype on untreated HIV disease progression. Data from a European seroconverter cohort showed that CD4⁺ at seroconversion was higher for CRF01 and lower for C, compared with B. Subsequent CD4⁺ decline was slower for A, C, and CRF02_AG compared with B [40], but viral load setpoint and time to AIDS or death did not differ by subtype [40]. Subtype D may progress more rapidly [9,19,41,42], whereas subtype A may have slower disease progression [41,43]. Better prognosis of patients from SSA compared with Europeans has been reported for untreated patients. A Swiss study found that Africans

had slower CD4⁺ decline than Europeans independently of viral subtype [44], which might be related to host factors allowing better tolerance of high levels of the virus in Africans. Differential prognosis by subtype before treatment with ART could have led to selection bias in our study of prognosis from ART start.

Several previous studies have examined whether response to ART differs by viral subtype [13,22,32]. A UK study found that viral load suppression occurred more rapidly in subtypes A and C compared with B, and that virologic rebound occurred more rapidly in patients with subtype C, but other subtypes were similar to B [13]. In the Greek cohort patients with subtype A had better viral load response than those with B [22]. A large collaboration of European cohorts found that risk of viral failure was higher in those with subtype C and CRF02_AG, and lower in A, compared with B [45]. In contrast, a Swiss study found that patients with non-B subtypes had a lower risk of viral failure than B, but their study was restricted to white patients and grouped all non-B subtypes together [32]. Taken together, these findings do not support the idea that worse prognosis in subtype A is a consequence of either slower viral suppression or higher risk of viral failure. The slow natural progression of subtype A may lead to longer duration of infection before treatment with accumulated risks for non-AIDS complications of HIV. Additional analyses of differences in causes of death between subtypes would be useful.

Patients with subtype A may have poorer immunological response to ART despite viral suppression. CD4⁺ recovery rate after starting ART was similar in all subtypes in a UK study,[13] and between A and B in a Greek study [35]. A French study found better CD4⁺ response in those with CRF02_AG compared with B. However, a Belgian study did find that patients with subtype A had the lowest CD4⁺ increase after starting ART [46].

In conclusion, patients infected with subtype A may be at a survival disadvantage compared with other subtypes when they present with low CD4⁺, although this may be due to other epidemiological factors rather than subtype per se. Although antiretroviral drugs have been designed primarily for subtype B infections, there is little evidence of disadvantage in those with non-B infection. Whilst ART can achieve excellent outcomes in all patients regardless of the infecting subtype, there remain many factors that potentially limit recovery such as late presentation to care, poor adherence to therapy, and lack of social care. Such factors are likely to be more important than viral subtype and, unlike subtype, are modifiable risk factors. However, it is also possible that real and important differences in prognosis between subtypes that are driven by drug resistance are obscured by such confounding factors

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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