Influence of Geographical Origin and Ethnicity on Mortality in Patients on Antiretroviral Therapy in Canada, Europe, and the United States

The Antiretroviral Therapy Cohort Collaboration (ART-CC)[a]

(See the Editorial Commentary by Smith on pages 1810–1.)

Background. Our objective was to assess differences in all-cause mortality, as well as AIDS and non-AIDS death rates, among patients started on antiretroviral therapy (ART) according to their geographical origin and ethnicity/race in Europe, Canada, and the United States.

Methods. This was a collaboration of 19 cohort studies of human immunodeficiency virus–positive subjects who have initiated ART (ART Cohort Collaboration) between 1998 and 2009. Adjusted mortality hazard ratios (AHRs) were estimated using Cox regression. A competing risk framework was used to estimate adjusted subdistribution hazard ratios for AIDS and non-AIDS mortality.

Results. Of 46 648 European patients, 16.3% were from sub-Saharan Africa (SSA), 5.1% Caribbean and Latin America, 1.6% North Africa and Middle East, and 1.7% Asia/West; of 1371 patients from Canada, 14.9% were First Nations and 22.4% migrants, and of 7742 patients from North America, 55.5% were African American and 6.6% Hispanic. Migrants from SSA (AHR, 0.79; 95% confidence interval [CI], .68–.92) and Asia/West (AHR, 0.62; 95% CI, .41–.92) had lower mortality than Europeans; these differences appeared mainly attributable to lower non-AIDS mortality. Compared with white Canadians, mortality in Canadian First Nations people (AHR, 1.48; 95% CI, .96–2.29) was higher, both for AIDS and non-AIDS mortality rates. Among US patients, when compared with whites, African Americans had higher AIDS and non-AIDS mortality, and hazard ratios for all-cause mortality increased with time on ART.

Conclusions. The lower mortality observed in migrants suggests "healthy migrant" effects, whereas the higher mortality in First Nations people and African Americans in North America suggests social inequality gaps.

Keywords. HIV infection; migrants; ethnic minorities; antiretroviral therapy.

There is increasing heterogeneity in the geographical origin and ethnic backgrounds of human immunodeficiency virus (HIV)–positive patients in developed countries [1–3]. Because migrants and ethnic minorities differ from the general population in HIV-related health determinants and outcomes [3–12], they may also differ in uptake of and response to antiretroviral therapy (ART) and subsequent survival. While these groups may share economic disadvantage [13, 14], migrants are most often healthy and self-selected to be fit to work under market rules [15], whereas ethnic minorities may exhibit poorer health indicators than the general population [2, 3].

Migrants and ethnic minority populations are difficult to define; there are no good standardized definitions [16, 17]. Classifications, often derived from

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[a]The members of the Writing Committee are listed in the Notes section. The contributors to the ART-CC Collaboration are listed in the Supplementary Appendix.

Correspondence: Julia del Amo, PhD, National Center of Epidemiology, Instituto de Salud Carlos III, C/Sinesio Delgado 6, 28029 Madrid, Spain (jdamo@isciii.es).

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administrative categories, have been wrongly used for inferring racial causality [18, 19]. The International Organization for Migration defines an international migrant as anyone who changes his/her country of usual residence for longer than a year [20]. Some migrants become part of established ethnic minorities, which may include recent migratory waves such as Caribbean communities in the United Kingdom. Besides, there are established minorities such as Romani (gypsies) in Europe and African Americans in the United States. First Nations people in Australia, Canada, and the United States have become minorities within these countries.

Few data are available on all-cause and cause-specific mortality following ART initiation according to geographical origin (GO) and ethnicity/race (E/R). Although migrants and ethnic minorities are not equivalent, numerous studies have combined them together as "vulnerable populations." The large datasets available through multicohort collaborations provide an opportunity to explore these questions. The ART Cohort Collaboration (ART-CC) collects information on the geographical origin and the ethnicity of large numbers of HIV-positive people from cohorts in Europe, Canada, and the United States. In this work, we aim to assess differences in all-cause mortality, as well as AIDS and non-AIDS death rates, among patients started on ART according to their GO and E/R in Europe, Canada, and the United States.

SUBJECTS AND METHODS

Study Population

We combined data from 19 cohorts in Europe and North America. The ART-CC has been previously described [21]. In brief, it includes patients with confirmed HIV infection aged ≥16 years who started ART while antiretroviral naive from 1998 onward. For these analyses, patients had to have information either on GO or E/R. Contributing cohorts have been approved by ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least every 6 months. Access to healthcare and ART varied across cohorts; Europe and Canada have healthcare systems with universal access, whereas in the United States access to care and extent of healthcare coverage varies.

Variables and Definitions

Migrants were defined according to GO derived from information on country of birth and/or country of origin, nationality, and other surrogates. Information on GO was available for most (9/12) European, all Canadian (2/2), and 1 US (1/5) cohort.

In Europe, information on GO was available for 46 648 (85.2%) patients and was classified as follows: European countries; sub-Saharan Africa (SSA); Caribbean and South and Central America (LA); Northern Africa and Middle East

Table 1. Sociodemographic and Clinical Characteristics at the Start of Antiretroviral Therapy Among 46 648 Patients in Europe, According to Geographical Origin

Characteristic	Europe, 35 113 (75.3)	SSA, 7592 (16.3)	LA, 2364 (5.1)	NAME, 781 (1.6)	ASIA/WEST, 798 (1.7)	*P* Value
Sex						<.001
Male	26 926 (76.7)	2968 (39.1)	1453 (61.5)	575 (73.6)	502 (62.9)	
Female	8187 (23.3)	4624 (60.9)	911 (38.5)	206 (26.4)	296 (37.1)	
Median (IQR) age, y	38 (32–45)	33 (28–40)	36 (30–43)	39 (33–49)	35 (29–41)	<.001
Transmission category						<.001
MSM	13 727 (39.1)	138 (1.8)	711 (30.1)	128 (16.4)	311 (39.0)	
IDU	5781 (16.5)	57 (0.8)	39 (1.7)	119 (15.2)	38 (4.8)	
Heterosexual	12 571 (35.8)	6670 (87.9)	1412 (59.7)	455 (58.3)	369 (46.2)	
Other/unknown	3034 (8.6)	727 (9.6)	202 (8.5)	79 (10.1)	80 (10.0)	
AIDS diagnosis						<.001
No	27 490 (78.3)	5928 (78.1)	1751 (74.1)	548 (70.2)	581 (72.8)	
Yes	7623 (21.7)	1664 (21.9)	613 (25.9)	233 (29.8)	217 (27.2)	
Median (IQR) CD4 count, cells/mL	225 (101–350)	200 (100–299)	190 (80–298)	171 (61–302)	180 (58–298)	<.001
Median (IQR) HIV load, copies/mL	67 900 (11 121–220 000)	44 203 (7140–158 559)	60 000 (12 350–180 000)	73 000 (10 800–265 562)	62 321 (15 000–180 000)	<.001
HIV load, copies/mL						<.001
<100 000	20 522 (58.5)	4983 (65.6)	1457 (61.6)	442 (56.6)	504 (63.2)	
≥100 000	14 591 (41.6)	2609 (34.4)	907 (38.4)	339 (43.4)	294 (36.8)	

Data are No. (%) unless otherwise specified.

Abbreviations: HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; LA, Caribbean and South and Central America; MSM, men who have sex with men; NAME, Northern Africa and Middle East; SSA, sub-Saharan Africa; WEST, non-European Western countries.

(NAME); Asia (ASIA); and non-European Western countries (WEST). (The 2 last categories are combined as ASIA/WEST.)

E/R data was available for some European (5/12), all Canadian (2/2), and all US (5/5) cohorts, and was classified as white, African American, Hispanic, First Nations, and Asian. We excluded patients whose E/R was "mixed" (n = 5) or "other" (n = 1053). In Canada, 1623 (54.2%) patients had information on GO, 1702 (56.8%) on E/R, and 1379 (46.1%) on both. Patients were classified according to E/R, (white, African American, First Nations, Asian, and Hispanic) and GO (Canadian and migrants). We excluded black (n = 4) and Asian Canadians (n = 4), because there were fewer than 5 deaths among these groups. In United States, valid data on E/R was available for 7759 patients (87.9%). Asians (n = 17) were excluded because there were fewer than 5 deaths.

Death and date of death were ascertained by cohorts through chart review and, in some, cross-checks with mortality registers. Cause of death was ascertained and classified centrally by ART-CC investigators in all but the Veterans Aging Cohort Study (VACS) cohorts and classified into AIDS deaths and non-AIDS deaths [22]. VACS obtained causes of death from the National Death Index using the *International Classification of Diseases, Tenth Revision* (*ICD-10*). Patients were considered lost to follow-up if there was a lag of >2 years between the last date the patient was known to be alive and the administrative censoring date, which varied between cohorts from 31 December 2006 to 31 December 2009. For the majority, the censoring date was 31 December 2009.

Statistical Analyses

Because of the different contexts, population composition, and healthcare delivery, we performed separate analyses for Europe, Canada, and the United States. Differences in demographic and clinical characteristics were assessed through Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. We used the Kaplan-Meier method to estimate the cumulative incidence of death by time since ART initiation. We calculated rates per 1000 person-years (py) with 95% confidence intervals (95% CIs). Mortality hazard ratios from ART initiation were estimated using Cox proportional hazards models. Individuals not known to have died during the follow-up period were censored on the date at which death was

Table 2. Sociodemographic and Clinical Characteristics at the Start of Antiretroviral Therapy Among Patients in Canada and the United States, According to Race/Ethnicity

	Canada (n = 1371)				United States (n = 7742)			
Characteristic	White Canadians, 859 (62.7)	First Nations, 205 (14.9)	Migrants, 307 (22.4)	*P* Value	White, 2934 (37.9)	African American, 4295 (55.5)	Hispanic, 513 (6.6)	*P* Value
Sex				<.001				<.001
Male	770 (89.6)	138 (67.3)	223 (72.6)		2747 (93.6)	3914 (91.1)	483 (94.1)	
Female	89 (10.4)	67 (32.7)	84 (27.4)		187 (6.4)	381 (8.9)	30 (5.9)	
Median (IQR) age, y	40 (35–47)	37 (31–42)	37 (30–44)	<.001	43 (36–51)	45 (38–51)	43 (35–50)	<.001
Transmission category				<.001				<.001
MSM	361 (42.0)	26 (12.7)	85 (27.7)		605 (20.6)	354 (8.2)	53 (10.3)	
IDU	263 (30.6)	141 (68.8)	28 (9.1)		530 (18.1)	1325 (30.9)	115 (22.4)	
Heterosexual	105 (12.2)	26 (12.7)	152 (49.5)		168 (5.7)	382 (8.9)	40 (7.8)	
Other/unknown	130 (15.1)	12 (5.8)	42 (13.7)		1,631 (55.6)	2234 (52.0)	305 (59.5)	
AIDS diagnosis				.069				.115
No	578 (67.3)	155 (75.6)	212 (69.1)		2116 (72.1)	3008 (70.0)	372 (72.5)	
Yes	281 (32.7)	50 (24.4)	95 (30.9)		818 (27.9)	1287 (30.0)	141 (27.5)	
Median (IQR) CD4 count, cells/mL	174 (68–300)	175 (80–290)	170 (70–2639)	.53	198 (67–340)	176 (46–306)	199 (59–311)	<.001
Median (IQR) HIV load, copies/mL	100 010 (37 000–210 000)	71 100 (19 700–151 000)	55 000 (12 000–170 000)	<.001	85 900 (23 834–197 484)	69 194 (19 328–208 717)	65 416 (15 977–242 000)	<.001
HIV load, copies/mL				<.001				<.001
<100 000	396 (46.1)	120 (58.5)	186 (60.6)		1557 (53.1)	2545 (59.2)	298 (58.1)	
≥100 000	463 (53.9)	85 (41.5)	121 (39.4)		1377 (46.9)	1750 (40.8)	215 (41.9)	

Data are No. (%) unless otherwise specified.

Abbreviations: HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men.

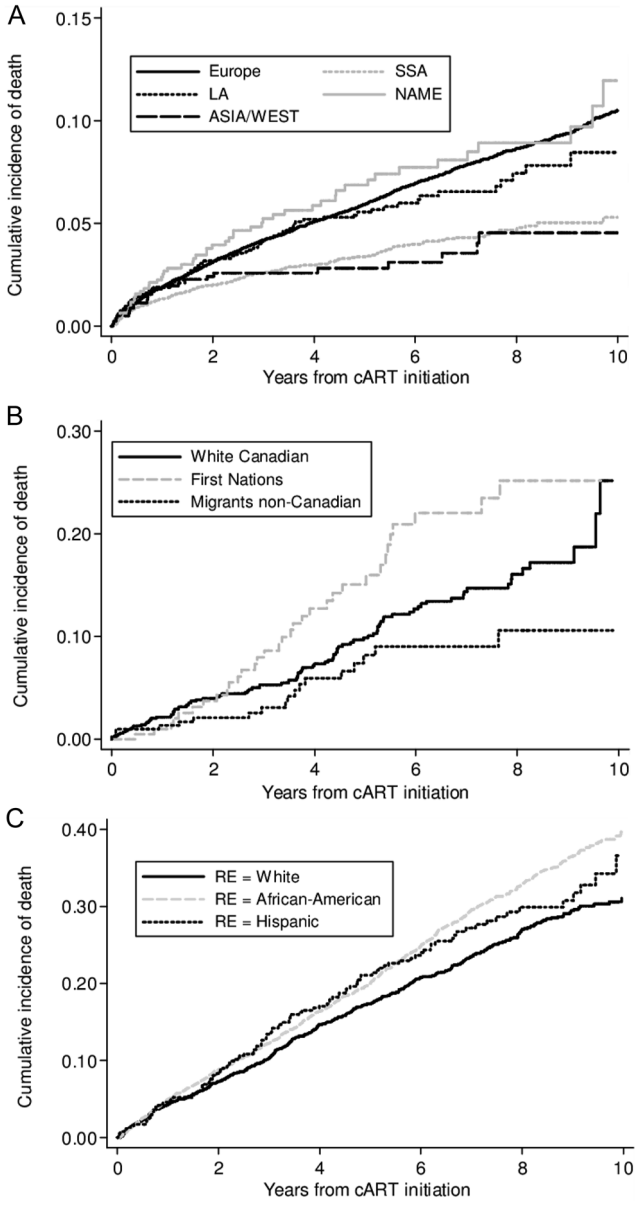


Figure 1. Cumulative incidence of death from antiretroviral initiation according to geographical origin and race/ethnicity in Europe (*A*), Canada (*B*), and the United States (*C*). Abbreviations: ASIA/WEST, Asia/non-European Western countries; cART, combination antiretroviral therapy; LA, Caribbean and South and Central America; NAME, Northern Africa and Middle East; RE, race/ethnicity; SSA, sub-Saharan Africa.

ascertained or on the cohort-specific date for which follow-up was assumed to be complete, whichever arose first. Proportional hazards models on the subdistribution hazard were used to estimate subdistribution hazard ratios (sHRs) [23] for associations of geographical origin with AIDS and non-AIDS mortality; non-AIDS mortality was treated as a competing event for AIDS mortality analyses, and vice versa. We used 2 methods to test the proportionality of hazards for overall mortality and subhazards for AIDS and non-AIDS mortality analyses: (1) tests based on Schoenfeld residuals and (2) including an interaction between exposure and time in the regression models. All models were stratified by cohort and adjusted for sex, transmission category (men who have sex with men [MSM], injection drug user [IDU], heterosexual, other/unknown), and age (16–29, 30–39, 40–49, ≥50 years), AIDS, CD4 count (0–24, 25–49, 50–99, 100–199, 200–349, 350–499, ≥500 cells/μL) and HIV load (<100 000, ≥100 000 copies/mL) at ART initiation. We explored interactions by sex, transmission category, and age at ART. Wald tests were used to derive *P* values. We examined immunological, virological, and clinical status of the patients lost to follow-up by GO and E/R. All statistical analyses were performed using Stata software (version 11.0, College Station, Texas).

RESULTS

Sociodemographic Characteristics

Of 46 648 patients from European cohorts, Europeans accounted for 35 113 (75.3%) of patients; 23.3% were women (Table 1). Among migrants, the commonest GO was SSA (n = 7592, 60.9% women); the second commonest GO was LA (n = 2364, 38.5% women); the third commonest GO was NAME (n = 781, 26.4% women); and the fourth commonest was ASIA/WEST (n = 798, of whom 698 were Asians and 46.7% women).

Of 1371 patients from Canadian cohorts, the majority were white Canadians (859 [62.7%]), followed by First Nations people (n = 205 [14.9%]) and migrants (n = 307 [22.4%]) (Table 2). Of 7742 patients from US cohorts, the commonest E/R was African American (n = 4295 [55.5%]), white (n = 2934 [37.9%]), and Hispanic (n = 513 [6.6%]; Table 2).

Mortality

Overall, 55 602 patients were followed for a median of 4 years (interquartile range [IQR], 2–7) after ART initiation, and 4270 died. In Europe, GO was associated with mortality in crude and adjusted analyses (Figure 1*A*, Table 3). Migrants from SSA and ASIA/WEST had lower mortality rates than Europeans (adjusted hazard ratio [AHR], 0.79 [95% CI, .68–.92] and 0.62 [95% CI, .41–.92], respectively). In Canada (Figure 1*B*, Table 3), mortality rates were higher in First Nations people compared to white Canadians (AHR, 1.48 [95% CI, .96–2.29]) and lower in migrants (AHR, 0.63 [95% CI, .37–1.07]), although differences were of borderline statistical significance. In the United States, there were associations between E/R and mortality in crude and adjusted analyses (Figures 1*C* and 2): mortality was higher in African Americans compared to whites. We found little evidence of nonproportional hazards comparing different groups in Europe or Canada ($P > .05$). However, in US patients, AHRs

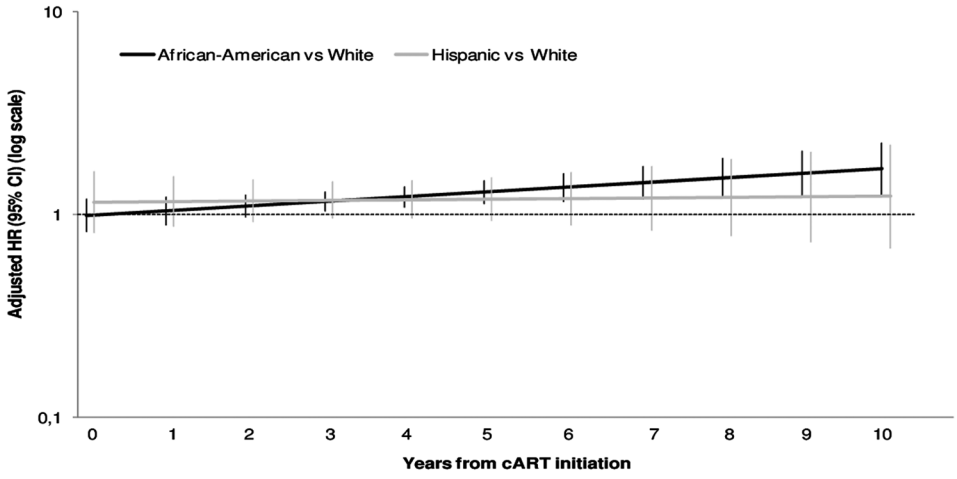
Table 3. Mortality From Antiretroviral Therapy Initiation According to Geographical Origin and Ethnicity/Race, in Europe, Canada, and the United States

Origin or Ethnicity/Race	No. of Deaths	Person-Years of Follow-up	Crude		Adjusted[a]	
			HR (95% CI)	*P* Value	AHR (95% CI)	*P* Value
Europe	2502	220 257		<.001		.004
EUROPE	2090	171 645	1.00		1.00	
SSA	230	32 129	.56 (.49–.64)		.79 (.68–.92)	
LA	106	9050	.83 (.68–1.01)		1.01 (.83–1.23)	
NAME	52	3748	1.11 (.84–1.46)		.85 (.64–1.12)	
ASIA/WEST	24	3685	.49 (.33–.73)		.62 (.41–.92)	
Canada	144	6634		.006		.024
White Canadian	93	4296	1.00		1.00	
First Nations	33	989	1.54 (1.04–2.29)		1.48 (.96–2.29)	
Migrants	18	1349	.61 (.37–1.01)		.63 (.37–1.07)	
United States	1709	38 416		<.001		.005
White	547	14 322	1.00		1.00	
African American	1045	21 502	1.21 (1.09–1.34)		1.19 (1.07–1.33)	
Hispanic	117	2593	1.13 (.93–1.38)		1.18 (.97–1.45)	

All models are stratified by cohort.

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; LA, Caribbean and South and Central America; NAME, Northern Africa and Middle East; SSA, sub-Saharan Africa; WEST, non-European Western countries.

[a] Adjusted for sex (male/female), age at antiretroviral therapy (ART) initiation (16–29, 30–39, 40–49, ≥50 years), transmission category (men who have sex with men, injection drug user, heterosexual, other/unknown), AIDS at ART initiation (yes/no), CD4 count at ART initiation (0–24, 25–49, 50–99, 100–199, 200–349, 350–499, ≥500 cells/μL) and human immunodeficiency virus load at ART initiation (<100 000, ≥100 000 copies/mL).



											Overall	*P* value for interaction with time
African American												
HR	1.04	1.10	1.16	1.22	1.29	1.36	1.43	1.51	1.59	1.68	1.19	.013
95% CI	.90-1.21	.97-1.25	1.04-1.30	1.10-1.37	1.14-1.46	1.17-1.58	1.19-1.72	1.21-1.88	1.23-2.06	1.25-2.25	1.07-1.33	
Hispanic												
HR	1.16	1.17	1.18	1.19	1.19	1.20	1.21	1.22	1.23	1.23	1.18	.88
95% CI	.88-1.54	.93-1.48	.96-1.45	.96-1.46	.94-1.52	.90-1.61	.85-1.73	.79-1.87	.74-2.02	.69-2.19	.97-1.45	

** Adjusted for sex, transmission category (MSM, IDU, Heterosexual, Other/Unknown), and age (16-29, 30-39, 40-49, 50+), AIDS, CD4 count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, ≥500 cells/μL) and HIV load (<100 000, ≥100 000 copies/mL) at ART initiation. Stratified by cohort

Figure 2. Adjusted mortality hazard ratios (95% confidence interval) from combination antiretroviral therapy initiation according to race/ethnicity in the United States. Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug user; MSM, men who have sex with men.

Table 4. Number of AIDS-Related and Non-AIDS-Related Deaths and Rates per 1000 Person-Years, According to Geographical Origin and Ethnicity/Race, in Europe, Canada, and the United States

Origin or Ethnicity/Race	Person-Years of Follow-up	AIDS Related[a]		Non-AIDS Related[b]	
		No. of Deaths	Rate (95% CI)	No. of Deaths	Rate (95% CI)
Europe					
EUROPE	170 705	681	4.0 (3.7–4.3)	1101	6.4 (6.1–6.8)
SSA	32 046	109	3.4 (2.8–4.1)	80	2.5 (2.0–3.1)
LA	9002	44	4.9 (3.6–6.6)	40	4.4 (3.3–6.1)
NAME	3709	17	4.6 (2.8–7.4)	25	6.7 (4.6–10.0)
ASIA/WEST	3685	11	3.0 (1.7–5.4)	11	3.0 (1.7–5.4)
Canada					
White Canadian	4256	41	9.6 (7.1–13.1)	42	9.9 (7.3–13.4)
First Nations	983	12	12.2 (6.9–12.5)	20	20.3 (13.1–31.5)
Migrants	1339	8	6.0 (3.0–11.9)	8	6.0 (3.0–11.9)
United States					
White	14 161	277	19.6 (17.4–22.0)	225	15.9 (13.9–18.1)
African American	21 273	574	27.0 (24.9–29.3)	402	18.9 (17.1–20.8)
Hispanic	2551	65	25.5 (20.0–32.5)	42	16.5 (12.2–22.3)

Abbreviations: CI, confidence interval; LA, Caribbean and South and Central America; NAME, Northern Africa and Middle East; SSA, sub-Saharan Africa; WEST, non-European Western countries.

[a] AIDS-related mortality: AIDS, AIDS infection, AIDS malignancy.

[b] Non-AIDS-related mortality: liver related (hepatitis, gastrointestinal bleeding, liver failure), cardiovascular (myocardial infarction/ischemic heart disease, stroke, lung embolus, heart/vascular), pulmonary (pulmonary hypertension, chronic obstructive pulmonary disease, respiratory), external cause (accident/violence, suicide), other (diabetes, pancreatitis, lactic acidosis, renal failure, hematological, psychiatric, central nervous system, digestive, skin/motor system, other).

comparing African Americans with whites (though not Hispanics) increased with time since ART initiation (Figure 2).

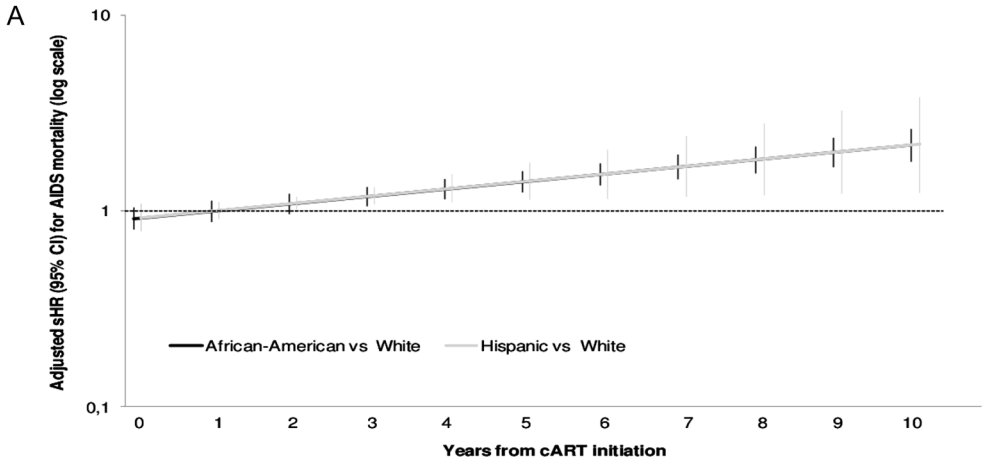
AIDS-Related and Non-AIDS-Related Causes of Death

Information on cause of death was available for 2119 patients in Europe, 131 in Canada, and 1585 in the United States (Table 4). This accounted for 85%, 91%, and 93% of all deaths, respectively. In Europe, patients of European origin had higher non-AIDS (6.4 per 1000 py) than AIDS (4.0 per 1000 py) mortality rates. AIDS mortality rates in patients from SSA were similar to those of Europeans (3.4 per 1000 py), but non-AIDS mortality rates were lower (2.5 per 1000 py). The highest rates of non-AIDS deaths in Europeans were non-AIDS malignancies (n = 284, 1.7 per 1000 py), liver disease (n = 163, 0.9 per 1000 py), cardiovascular disease (n = 161, 0.9 per 1000 py), and non-AIDS infections (n = 151, 0.9 per 1000 py). The corresponding number of events and rates in migrants from SSA were 19 (0.6 per 1000 py), 9 (0.3 per 1000 py), 19 (0.6 per 1000 py), and 20 (0.6 per 1000 py), respectively. Death rates due to external causes and drug abuse were also lower in migrants from SSA compared to Europeans.

Taking into account competing risks of death, migrants from SSA had similar AIDS mortality rates than Europeans (adjusted sHR, 0.97 [95% CI, .74–1.27]) but lower non-AIDS mortality (adjusted sHR, 0.64 [95% CI, .41–1.00]). Migrants from ASIA/WEST experienced lower AIDS and non-AIDS mortality rates (adjusted sHR, 0.70 [95% CI, .44–1.11] and 0.71 [95% CI, .52–.97], respectively). There was little evidence of nonproportional hazards for AIDS mortality ($P > .05$, Supplementary Figure 1*A*). However, for non-AIDS mortality there was evidence of nonproportional hazards as the adjusted sHR for non-Europeans decreased over time (Supplementary Figure 1*B*).

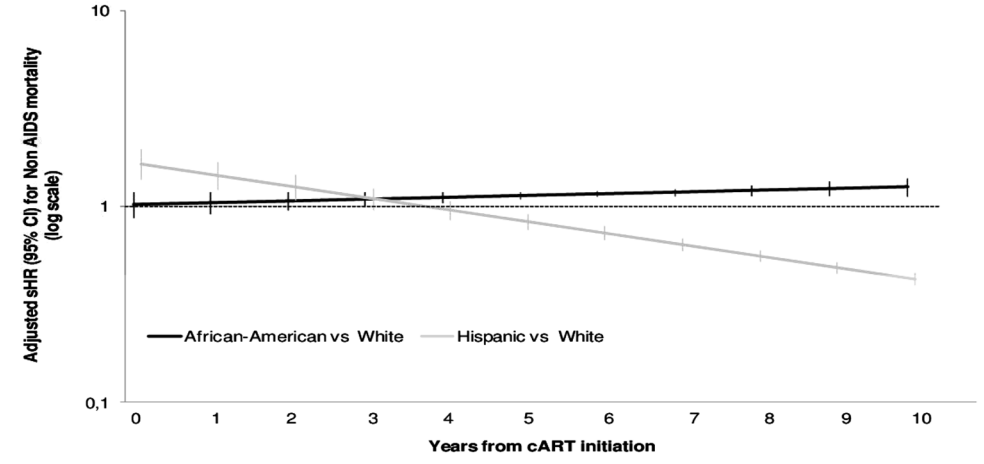
First Nations people had higher rates of AIDS and non-AIDS mortality than white Canadians (Table 4), and also had high rates of non-AIDS mortality (20.3 per 1000 py). The highest non-AIDS mortality rates in First Nations people were due to substance abuse (n = 6; 6.1 per 1000 py), cardiovascular disease (n = 4; 4.1 per 1000 py), non-AIDS-defining infections (n = 3; 3.1 per 1000 py), and external causes (n = 3; 3.1 per 1000 py).

In the United States, compared to whites, African Americans had higher AIDS (adjusted sHR, 1.22 [95% CI, 1.09–1.36]) and non-AIDS (adjusted sHR, 1.11 [95% CI, 1.04–1.18]) mortality. Hispanics also had higher AIDS mortality (adjusted sHR, 1.23 [95% CI, 1.11–1.37]) than whites. For both African Americans and Hispanics, sub–hazard ratios for AIDS mortality increased with increasing time since ART (Figure 3*A*). Sub–hazard ratios for non-AIDS mortality increased over time in



											Overall	*P* value for interaction with time
African-American												
sHR	1.00	1.09	1.19	1.30	1.41	1.54	1.68	1.83	2.00	2.18	1.22	<.001
95% CI	.89-1.12	.98-1.22	1.07-1.32	1.16-1.44	1.26-1.58	1.36-1.74	1.46-1.93	1.57-2.13	1.69-2.36	1.81-2.62	1.09-1.36	
Hispanic												
sHR	1.01	1.10	1.20	1.31	1.43	1.55	1.69	1.84	2.01	2.19	1.23	.013
95% CI	.92-1.11	1.03-1.18	1.09-1.33	1.12-1.53	1.15-1.77	1.17-2.06	1.19-2.40	1.22-2.79	1.24-3.25	1.26-3.79	1.11-1.37	

** Adjusted for sex, transmission category (MSM, IDU, Heterosexual, Other/Unknown), and age (16-29, 30-39, 40-49, 50+), AIDS, CD4 count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, ≥500 cells/μL) and HIV load (<100 000, ≥100 000 copies/mL) at ART initiation.



											Overall	*P* value for interaction with time
African-American												
sHR	1.04	1.06	1.09	1.11	1.13	1.16	1.18	1.21	1.23	1.26	1.11	.092
95% CI	.92-1.18	.96-1.18	1.01-1.17	1.05-1.17	1.09-1.17	1.12-1.19	1.14-1.23	1.14-1.28	1.14-1.33	1.13-.39	1.04-1.18	
Hispanic												
sHR	1.43	1.25	1.10	.96	.84	.73	.64	.56	.49	.43	1.05	<.001
95% CI	1.22-1.68	1.09-1.44	.97-1.24	.86-1.07	.76-.92	.68-.79	.60-.69	.52-.60	.46-.52	.40-.46	.95-1.15	

** Adjusted for sex, transmission category (MSM, IDU, Heterosexual, Other/Unknown), and age (16-29, 30-39, 40-49, 50+), AIDS, CD4 count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, ≥500 cells/μL) and HIV load (<100 000, ≥100 000 copies/mL) at ART initiation.

Figure 3. *A*, Adjusted subdistribution hazard ratios (sHRs) for AIDS mortality according to race/ethnicity in the United States. *B*, Adjusted sHRs for non-AIDS mortality according to race/ethnicity in the United States. Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug user; MSM, men who have sex with men; sHR, subdistribution hazard ratio.

African Americans but not in Hispanics (Figure 3*B*). The adjusted sHRs were higher in Hispanics than in whites in the first 2 years after ART to become lower after the fifth year after ART (Figure 3*B*).

Loss to Follow-up

Loss to follow-up (LTFU) differed between regions ($P < .001$): Europe 24.0%, Canada 8.9%, and United States 6.7%. In Europe, rates of LTFU differed by GO ($P < .001$): Europe

23.6%, SSA 26.5%, LA 23.7%, NAME 24.7%, ASIA/WEST 15.4%. Among patients lost to follow-up, there were significant differences by GO in the median CD4 cell counts (cells/mL) in the 6 months prior to the last date in which death was ascertained ($P < .001$): 410 (IQR, 252–600) in Europeans, 338 (IQR, 217–489) in SSA, 351 (IQR, 225–532) in LA, 358 (IQR, 210–523) in NAME, and 402 (IQR, 206–547) in ASIA/WEST.

In Canada, no significant differences in LTFU rates by E/R and GO were found ($P = .20$): white Canadian 8.3%, First Nations 12.2%, migrants 8.5%. Among patients lost to follow-up, no significant differences by E/R and GO in the median CD4 cell counts (cells/mL) in the 6 months prior to the last date in which death was ascertained were found ($P = .21$): 390 (IQR, 230–545) in white Canadians, 231 (IQR, 90–440) in First Nations people, and 361 (IQR, 200–691) in migrants.

In the United States, the percentage of LTFU differed by E/R ($P < .001$): whites 8.6%, African Americans 5.4%, and Hispanics 7.2%. Among patients lost to follow-up, no significant differences by E/R in the median CD4 cell counts in the 6 months prior to the last date in which death was ascertained were found ($P = .16$): 388 (IQR, 223–573) in whites, 318 (IQR, 184–531) in African Americans, and 326 (IQR, 264–516) in Hispanics.

DISCUSSION

We report striking differences in the associations between ethnicity and geographic origin with mortality after initiation of ART in Europe, the United States, and Canada. HIV-positive migrants from SSA and ASIA/WEST living in Europe had lower mortality following ART than HIV-positive, predominantly white Europeans, mainly attributable to lower non-AIDS mortality rates. By contrast, HIV-positive First Nations people in Canada, and African Americans in the United States, had higher mortality after ART than did white Canadians and Americans—although for First Nations in Canada, estimates were imprecise. In Canada, higher mortality was explained by higher non-AIDS mortality rates among First Nations people, probably attributable to substance use and underlying socioeconomic inequalities. Mortality rates also appeared to be lower in other migrant groups (North Africa and the Middle East in Europe and all migrants in Canada).

The lower mortality experienced by most migrant groups in Europe and Canada after ART initiation, compared to predominantly white nonmigrants, may have various explanations. Similar to the "healthy worker" effect, as the majority of migrants travel from developing to industrialized countries seeking work, they tend to have lower mortality rates than the general population [15]. This effect may be further exaggerated by the sickest migrants returning home to die ("unhealthy remigration" or "salmon bias"), prompted by their inability to remain in the country when they lose their jobs due to poor health and lack of social support networks [24]. It is unlikely that "salmon bias" played an important role in this study, because HIV care is more restricted and HIV-associated stigma high in most migrants' countries of origin [25], although we have no direct data to support this. In spite of lower incomes, migrants from developing countries tend to maintain, in their countries of destination, the healthier diet and lifestyles from less affluent societies [26], although length of residence has been described to be associated with increases in sedentary lifestyles and poorer eating habits [27, 28]. Although this is well established for general population migrants, it is hard to extrapolate these findings to HIV-positive migrants, the majority of whom are relatively young. Further, for those from SSA—although no firm data are available—length of stay in Europe is short [29], so exposure to acculturation processes is less likely to have had an impact. The lower non-AIDS mortality rates of migrants in Europe observed in our study support the hypothesis of lower background mortality. Migrants from SSA had lower rates of non-AIDS mortality, notably non-AIDS defining cancers, the commonest non-AIDS related death in Europeans in our study as well as in numerous others [24, 30, 31]. Arnold et al reviewed 37 studies from EU countries and report that migrants of unknown HIV status from non-Western countries were more likely to develop infectious disease-related cancers and less likely to develop those causally linked to lifestyles of affluent societies [31–33]. These findings are consistent with the variations in hepatitis B and C epidemiology of HIV-positive populations by geographic origin [34]. These nativity differentials have been also described in the United States by Singh and Hiatt for major cancers, cardiovascular diseases, diabetes, respiratory diseases, unintentional injuries, and suicide, with immigrants experiencing generally lower mortality than US-born people [35].

In our study, losses to follow-up in Europe were slightly higher in patients from SSA compared to Europeans and those lost to follow-up had lower CD4 cell counts; thus mortality rates in SSA may be underestimated. By contrast, migrants from Asia had better follow-up rates than Europeans. Although there may be some underestimation of mortality in migrants in Europe, this is unlikely to fully explain the differences in mortality rates that we observed.

HIV-positive migrants from SSA in Europe have lower mortality from date of seroconversion than native HIV-positive patients [7]. Previous studies have reported similar, or slightly better, HIV progression rates in migrants from SSA in Europe and lower CD4 cell count declines [36, 37]. Some of these studies have linked these better disease profiles to the higher prevalence of non-B subtypes but no firm data are available. Data from HIV-positive migrants other than those from SSA were scant. Here, we report also lower mortality of Asian

migrants in Europe and some evidence of lower mortality for those from North Africa and the Middle East. To our knowledge, no previous studies have reported mortality estimates in HIV-positive migrants of GO other than SSA.

The higher mortality of HIV-positive First Nations people in Canada and African Americans in the United States is likely to reflect social and health inequalities, including cultural discrimination, higher unemployment, lower incomes, higher rates of imprisonment, lack of access to adequate healthcare, and higher ART discontinuation rates [38–42]. Both populations have higher rates of HIV infection than the general population, but are less likely to reap the benefits of ART. First Nations people had slightly higher rates of LTFU, which occurred at lower CD4 counts. This may lead to underestimation of overall death rates in this population.

Misclassification of GO and E/R was inevitable. Providing that such misclassification is nondifferential (unrelated to underlying prognosis), resulting bias will be toward the null, such that true differences are likely to be larger than those we have observed. Both GO and E/R encompass biological, societal, and behavioral issues that cannot be separated, as we lack subtype and genetic data, smoking and health-seeking behaviors and socioeconomic status. Misclassification of cause of death was minimized by the ART-CC through an ad hoc committee [22, 43]. The *ICD-10* may overestimate HIV/AIDS-associated deaths at the expense of cirrhosis of viral cause or unknown etiology [44].

Finally, the inferences made from this study are applicable to patients who have already successfully accessed health services and are not representative of all HIV-infected patients. Participants in ART-CC cohorts are not fully representative of patients in their countries, and transmission category was unknown in half of US patients.

In conclusion, mortality rates following initiation of ART in HIV-positive migrants and established ethnic minorities in Europe and North America differ from those in predominantly white nonmigrants. The former have better survival, probably reflecting healthy migrant effects, whereas the latter fare worse, reflecting health and societal inequality.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Writing committee. Julia del Amo and Inma Jarrin* (National Centre of Epidemiology, Instituto de Salud Carlos III, Madrid, Spain), Margaret May (School of Social and Community Medicine, University of Bristol, United Kingdom), Francois Dabis (University of Bordeaux, France), Heidi Crane (School of Medicine, University of Washington, Seattle), Daniel Podzamczer (HIV Unit, Infectious Disease Service. IDIBELL-Hospital Universitari de Bellvitge, Barcelona. Spain), Timothy R. Sterling (Vanderbilt University School of Medicine, Nashville, Tennessee), Sophie Abgrall (INSERM U720, Paris, France), Fiona Lampe (Research Department of Infection and Population Health, University College London, United Kingdom), Amy Justice (Yale University School of Medicine, New Haven, and VA Connecticut Healthcare System, West Haven, Connecticut), Antonella Castagna (Infectious Diseases Department, San Raffaele Scientific Institute, Milan, Italy), Christoph Boesecke (Medizinische Klinik I, Universitätsklinikum Bonn, Germany), Cornelia Staehelin (University Hospital Berne, Switzerland), Frank De Wolf (HIV Monitoring Foundation, Academic Medical Centre, University of Amsterdam, The Netherlands), Jodie Guest (HIV Atlanta VA Cohort Study, Atlanta VA Medical Center, Decatur, Georgia), Michael J. Mugavero (Division of Infectious Disease, Department of Medicine, University of Alabama at Birmingham), Pavel Khaykin (Zentrum der Inneren Medizin, J.W. Goethe Universität, Frankfurt, Germany), Hasina Samji (Division of Epidemiology and Population Health, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada), Suzanne Ingle and Jonathan A. C. Sterne (School of Social and Community Medicine, University of Bristol, United Kingdom), and M. John Gill (Division of Infectious Diseases, University of Calgary, Alberta, Canada).

*Julia del Amo and Inma Jarrin contributed equally to this work.

Author contributions. All authors have contributed substantially to the conception of the study. J. d. A., M. J. G., I. J., and J. A. C. S. developed the idea and the analyses plan. Analyses were conducted by I. J. All authors were involved in the interpretation of data and the drafting or revision of the manuscript and have given the approval of the final version.

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