Timing of combined antiretroviral treatment initiation in male and female migrants living with HIV in Western Europe

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Background: We evaluate differences in timing of cART (combined antiretroviral treatment) initiation by geographical origin in male and female HIV-positive patients in the Collaboration of Observational HIV Epidemiological Research Europe, a large European Collaboration of HIV Cohorts.

Methods: We included individuals recruited in Western Europe between January 1997 and March 2013, with known geographical origin and at least 1 $CD4^+$ cell count measurement while cART-naive. Timing of cART was assessed through modified time-to-event methods, in which a scale of $CD4^+$ cell counts was used instead of time, with cART being the outcome. We estimated the median $CD4^+$ cell count at cART initiation (estimated $CD4^+$ levels at which the probability of having started cART is 50%) using Kaplan–Meier and adjusted hazard ratios of cART initiation using Cox regression.

Results: Of 151 674 individuals, 110 592 (72.9%) were men. Median (95% confidence interval) $CD4^+$ cell count falls far below 250 cells/μl in all groups and was lowest in sub-Saharan African [SSA: 161 (158–167)], Caribbean men [161 (150–174)] and in Asian women [Asian Continent and Oceania: 185 (165–197)]. Among men, the adjusted probability of cART initiation was lower in migrants compared with natives, but differences depended on initial $CD4^+$ cell count. For example, in the group with more than 500 $CD4^+$ at recruitment, they were 45% (36–53%), 30% (17–40%) and 25% (19–30%) lower for Caribbean, Eastern European and SSA men, respectively. In women, no meaningful differences were observed between natives and most migrant groups. However, SSA women had a 31% (24–38%) higher probability of cART initiation when recruited at a $CD4^+$ more than 500 cells/μl and 9% (4–14%) lower when recruited at $CD4^+$ less than 100 cells/μl.

Conclusion: Most migrant men initiate cART at lower $CD4^+$ cell count than natives, whereas this does not hold for migrant women.

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Introduction

Combined antiretroviral therapy (cART) has resulted in a drastic improvement in the prognosis of HIV infection. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) has shown that patients on cART with $CD4^+$ cell count greater than 500 cells/μl achieve death rates close to those of the general

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population [1]. However, available evidence demonstrates that the effectiveness of cART depends on the timing of treatment initiation, as those who initiate at lower $CD4^+$ cell count experience poorer responses to treatment, and higher rates of opportunistic diseases, non-AIDS events and mortality [2–5]. Early treatment initiation therefore represents the single most important intervention able to improve the quantity and quality of life for people living with HIV.

Individuals who achieve full control of HIV infection on cART, as characterized by an undetectable viral load, are now believed to be extremely unlikely to transmit HIV infection [6,7]. Thus, cART is now recognized to be a key aspect of HIV control at the community level for preventing new infections and controlling the HIV epidemic [6,8,9].

Migrants represent a considerable proportion of those living with HIV in Western Europe. Of the 137 983 persons diagnosed with HIV infection in this region between 2007 and 2012, 41% were migrants [10]. Migrants from countries with high HIV prevalence are a population of special focus for the European Centre for Disease Prevention and Control (ECDC) [11]. Literature suggests that adverse socioeconomic and living conditions, together with language, cultural and legal barriers, could result in later cART initiation largely through late diagnosis of HIV infection and difficulties in access to and retention in care [11–16]. Indeed, though in most European countries HIV testing is recommended for migrants originating from areas with high HIV prevalence [17], universal access to cART is not guaranteed for undocumented migrants in many European countries [11]. Delayed initiation of cART may place this group at a higher risk of suboptimal health outcomes [18,19] and could facilitate ongoing HIV transmission.

The objective of this work is to evaluate differences in timing of cART initiation, as measured by the $CD4^+$ cell count at cART initiation, by geographical origin, among HIV-positive men and women using data from a large European Collaboration of HIV Cohorts from 1997 to 2013.

Methods

Study population

Data were merged in 2013 in COHERE in EuroCoord (www.cohere.org), a collaboration of 40 observational cohorts of HIV-positive individuals in routine clinical care from 32 countries. A detailed description of COHERE has been previously published [20]. Each cohort submits data in a standardized format (www.hicdep.org) to coordinating centres at the Copenhagen HIV Program, Denmark or the Institut de Santé Publique, d'Epidémiologie et de Développement (Bordeaux School of Public Health), Bordeaux, France [21]. The two coordinating centres ensure adherence to strict quality assurance guidelines and perform data checks, including the removal of duplicate records. Ethics approval was granted by the ethics committees of each of the participating cohorts according to local regulations.

For this analysis, we included 24 cohorts systematically collecting geographical origin and/or ethnicity, representing 11 Western European countries (Austria, Belgium, Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, Switzerland and the United Kingdom). Individuals were eligible if enrolled in the cohort from January 1997 to March 2013, with known geographical origin and sex, aged between 18 and 75 years, not infected perinatally or following the receipt of clotting factor concentrates, and with at least one $CD4^+$ T-cell count measurement while naive to cART.

Variables

Follow-up was performed according to routine clinical practice within the country where the individual was followed. Data were collected at each encounter and included information on age, sex, country of origin, ethnicity, mode of HIV acquisition, cART (defined as a combination of either $\geq$3 drugs from $\geq$2 classes, or $\geq$3 nucleoside reverse-transcriptase inhibitors, at least one of which was tenofovir or abacavir), $CD4^+$ cell counts, plasma HIV-RNA and various serological results and initial and subsequent AIDS-defining conditions.

The exposure variable geographical origin, as reported by cohorts, was classified based on the United Nations categories (available at http://unstats.un.org). We classified persons as either native, if they were originally from the country of enrolment [native population (NAT)] or from one of seven migrant populations based on region of origin: Western Europe and other Western countries, including North America, Australia and New Zealand (WEWC); Eastern Europe (EE); North Africa and The Middle East (NAME); sub-Saharan Africa (SSA); Latin America (LA): The Caribbean (CRB) and the rest of the Asian Continent and Oceania (ASIA/OC). The United Kingdom Collaborative HIV Cohort (UK CHIC) Study and the Swiss HIV Cohort Study (SHCS) only reported information on ethnicity to COHERE, which was mapped into geographical origin assigning 'Black Caribbean' to CRB, 'Hispanic' to LA, 'Asian' to ASIA/OC, 'White' to NAT and 'Black' to SSA.

Statistical analysis

All analyses were stratified by sex. Individuals were followed up until they either experienced the event of interest (cART initiation) or were right-censored because of loss to follow-up, death or administrative censoring (ranging from September 2009 to July 2013). To assess the

cumulative probability of cART initiation as the $CD4^+$ cell count decreased, we used the method proposed by Phillips *et al.* [22], using time-to-event analysis methods, but with the time scale substituted by a reversed scale of $CD4^+$ cell counts. In this framework, individuals are assumed to be at risk of initiating cART from the $CD4^+$ cell count origin, here set artificially to be 2000 cells/μl, down to the minimum recorded $CD4^+$ cell count during their follow-up, respecting the monotonically changing nature of time. As discussed by Phillips *et al.*, the method is insensitive to the choice of the $CD4^+$ cell count origin as long as it is higher than the highest recorded value.

Kaplan–Meier methods were used to estimate the median $CD4^+$ cell count at cART initiation, that is the $CD4^+$ levels at which the cummulative probability of starting cART is 50%, and 95% confidence intervals (95% CIs). Hazard ratios (95% CI) of cART initiation for migrants from each geographical origin compared with the native population were estimated using multivariable Cox regression. As the effect of each geographical origin on the probability of initiating cART may vary depending on the immunological status at entry into care, an interaction between geographical origin and first-recorded $CD4^+$ cell count after recruitment (<100, 100–250, 250–350, 350–500 and >500) was explored using the likelihood ratio test (LRT). Wald test was used to derive *P* values for hazard ratios.

All models were adjusted for the following potential confounders chosen *a priori* and measured at cohort entry: age (years: <25, 25–35, 35–50 and ≥50), HIV acquisition group [MSM, heterosexual transmission, persons who inject drugs or other (PWID/other), and unknown], HIV-RNA levels (log_{10} copies/ml: <4, 4–5, ≥5 and unknown), AIDS diagnosis at recruitment (no and yes), coinfection with hepatitis C virus (HCV RNA and/or antibody: positive and negative), hepatitis B virus (HBV DNA and/or any antibody excluding surface antibody: positive and negative) and calendar period (1997–1999, 2000–2003, 2004–2008, and 2009–2013). Due to the high proportion of individuals with unknown HCV and HBV status at baseline (over 60% for both viruses), in which this information was missing, data generated during follow-up were assumed to represent the status at baseline.

Sensitivity analyses were performed to assess the impact of the diverse assumptions: using last (instead of minimum) measured $CD4^+$ cell count for those initiating cART; accounting for left censoring, allowing individuals to enter the risk set at their first observed measure of $CD4^+$ cell count (only patients with more than one distinct $CD4^+$ cell count while being cART-naive could be included); modelling $CD4^+$ cell count trajectories using a piecewise linear mixed-effects model with random intercepts and random slopes for the square root transformation of the $CD4^+$ cell count, predicting the $CD4^+$ cell count at the date of cART initiation or right censoring [23]; excluding the three cohorts that only included HIV seroconverters (defined as patients with a negative test within 3 years of their first HIV-positive result and therefore less likely to have late diagnosis) – PRIMO, SEROCO and CASCADE; excluding UK CHIC and SHCS to assess the impact of possible misclassification in deriving geographical origin from ethnicity; restricting the analysis to individuals recruited in the cohort after 2004, when the recommendation to start cART with $CD4^+$ cell count below 350 cells/μl became widespread in Western Europe; excluding the HBV core antibody as a criteria for HBV coinfection; considering only known HBV status at maximum 1 month after cohort entry for classification of HBV coinfection; grouping transmission routes defined as 'other' with unknown (instead of PWID) to evaluate the impact of misclassification of this category.

Analyses were conducted using STATA (V12MP: Stata Corporation; College Station, Texas, USA).

Results

A total of 151 674 individuals were included in this analysis of which 110 592 (72.9%) were men and 45 412 (29.9%) were migrants. Among women, the proportion of migrants was higher ($n = 21\,490$; 52.3%) than among men ($n = 23\,922$; 21.6%). Migrants from SSA accounted for the largest migrant group (9.4% of men and 39.4% of women), followed by Latin America (3.8%) and WEWC (2.5%) in men and CRB (3.4%) and Latin America (2.7%) in women. Patient characteristics varied by geographical origin and sex (Table 1).

The cumulative probability of cART initiation and median $CD4^+$ cell counts at cART initiation are shown in Fig. 1. Median $CD4^+$ cell count falls far below 250 cells/μl in all groups, and with the exception of EE, it was lower in all migrant groups than in native population, especially in men. The lowest medians (95% CI) were estimated for men from SSA [161 (158–167) cells/μl] and CRB [161 (150–174) cells/μl], and for women from ASIA/OC [185 (165–197) cells/μl].

Adjusted hazard ratios (95% CI) for the effect of geographical origin on the probability of starting cART as compared with native population are shown in Table 2 and Fig. 2. In the case in which the LRT showed an interaction between geographical origin and $CD4^+$ cell count at recruitment, hazard ratios (95% CI) for geographical origin is shown stratified by $CD4^+$ cell count at recruitment.

Migrant men, with the exception of LA, had a lower probability of initiating cART compared with natives; the

Table 1. Sociodemographic and clinical characteristics of the study population ($n = 151\,674$) by geographical origin and sex at baseline and during follow-up.

Men 110 592 (72.9%)	NAT *n* (%)	WEWC *n* (%)	EE *n* (%)	NAME *n* (%)	SSA *n* (%)	LA *n* (%)	CRB *n* (%)	ASIA/OC *n* (%)
Number	86 670	2806	1119	1740	10 434	4185	1792	1846
% of men	(78.4)	(2.5)	(1.0)	(1.6)	(9.4)	(3.8)	(1.6)	(1.7)
% of migrant men	–	(11.7)	(4.7)	(7.3)	(43.6)	(17.5)	(7.5)	(7.7)
Baseline								
Age [years, Me(IQR)]	37.0 (31.0–44.1)	37.8 (31.7–44.4)	31.8 (27.2–37.4)	37.6 (31.5–45.1)	36.7 (31.2–42.6)	33.2 (28.2–39.3)	37.2 (30.5–44.4)	34.3 (29.1–40.9)
Transmission								
MSM	53 657 (61.9)	1637 (58.3)	536 (47.9)	542 (31.2)	1012 (9.7)	3172 (75.8)	703 (39.2)	1111 (60.2)
PWID/OTH	10 453 (12.1)	330 (11.8)	251 (22.4)	281 (16.2)	733 (7.0)	112 (2.7)	33 (1.8)	139 (7.5)
HTX	16 509 (19.1)	481 (17.1)	221 (19.8)	741 (42.6)	7951 (76.2)	715 (17.1)	927 (51.7)	426 (23.1)
UNK	6051 (7.0)	358 (12.8)	111 (9.9)	176 (10.1)	738 (7.1)	186 (4.4)	129 (7.2)	170 (9.2)
$CD4^+$ cell count [cells/μl, Me(IQR)]	382 (205–564)	365 (171–570)	397 (248–552)	297.5 (119–493.5)	254 (110–416)	368 (200–551)	319 (132–490)	335 (165–510)
Viral load [log_{10} copies/ml, Me(IQR)]	4.7 (4.0–5.2)	4.7 (4.0–5.2)	4.5 (3.9–5.0)	4.8 (4.1–5.3)	4.7 (3.9–5.2)	4.6 (4.0–5.1)	4.6 (3.9–5.1)	4.6 (3.9–5.1)
AIDS	8904 (10.3)	297 (10.6)	96 (8.6)	277 (15.9)	1496 (14.3)	465 (11.1)	217 (12.1)	214 (11.6)
HBV DNA and/or Ab (excluding sAB)								
Yes	18 298 (21.1)	763 (27.2)	397 (35.5)	357 (20.5)	3086 (29.6)	1380 (33.0)	371 (20.7)	515 (27.9)
No	48 782 (56.3)	1275 (45.4)	469 (41.9)	1078 (62.0)	5248 (50.3)	2394 (57.2)	1128 (63.0)	864 (46.8)
Unknown	19 590 (22.6)	768 (27.4)	253 (22.6)	305 (17.5)	2100 (20.1)	411 (9.8)	293 (16.4)	467 (25.3)
HCV RNA and/or Ab								
Yes	13 582 (15.7)	445 (15.9	300 (26.8)	299 (17.2)	476 (4.6)	294 (7.0)	71 (4.0)	185 (10.0)
No	53 793 (62.1)	1520 (54.2)	546 (48.8)	1115 (64.1)	7465 (71.5)	3400 (81.2)	1422 (79.4)	1186 (64.3)
Unknown	19 295 (22.3)	841 (30.0)	273 (24.4)	326 (18.7)	2493 (23.9)	491 (11.7)	299 (16.7)	475 (25.7)
Period								
1997–1999	16 826 (19.4)	311 (11.1)	38 (3.4)	282 (16.2)	1216 (11.7)	233 (5.6)	208 (11.6)	170 (9.2)
1999–2003	19 484 (22.5)	615 (21.9)	140 (12.5)	402 (23.1)	3150 (30.2)	617 (14.7)	537 (30.0)	354 (19.2)
2004–2008	31 128 (35.9)	1146 (40.8)	450 (40.2)	653 (37.5)	4103 (39.3)	1800 (43.0)	756 (42.2)	790 (48.2)
2009–2013	19 232 (22.2)	734 (26.2)	491 (43.9)	403 (23.2)	1965 (18.8)	1535 (36.7)	291 (16.2)	532 (28.8)
Follow-up								
Started cART	68 130 (78.6)	2063 (73.5)	726 (64.9)	1410 (81.0)	8128 (77.9)	2954 (70.6)	1265 (70.6)	1354 (73.4)
No. with only baseline $CD4^+$	29 904 (34.5)	987 (35.2)	363 (32.4)	708 (40.7)	4263 (40.9)	1401 (33.5)	553 (30.9)	576 (31.2)
No. $CD4^+$ cell count measurements [Me(IQR)]	2 (1–6)	2 (1–6)	3 (1–6)	2 (1–5)	2 (1–4)	2 (1–5)	2 (1–6)	2 (1–6)

Women 41 082 (27.1%)	NAT *n* (%)	WEWC *n* (%)	EE *n* (%)	NAME *n* (%)	SSA *n* (%)	LA *n* (%)	CRB *n* (%)	ASIA/OC *n* (%)
Number	19 592	633	624	616	16 197	1113	1379	928
% of women	(47.7)	(1.5)	(1.5)	(1.5)	(39.4)	(2.7)	(3.4)	(2.3)
% of migrant women	–	(2.9)	(2.9)	(2.9)	(75.4)	(5.2)	(6.4)	(4.3)
Baseline								
Age [years, Me(IQR)]	34.7 (28.7–42.2)	35.2 (29.3–43.0)	30.2 (25.6–36.0)	35.5 (28.4–44.7)	31.6 (27.0–37.5)	33.2 (27.6–40.1)	35.1 (28.5–43.3)	31.8 (27.5–37.9)
Transmission								
PWID/OTH	3554 (18.1)	133 (21.0)	91 (14.6)	40 (6.5)	1062 (6.6)	52 (4.7)	26 (1.9)	145 (15.6)
HTX	14 448 (73.7)	406 (64.1)	464 (74.4)	517 (83.9)	14 234 (87.9)	981 (88.1)	1225 (88.8)	718 (77.4)
UNK	1590 (8.1)	94 (14.9)	69 (11.1)	59 (9.6)	901 (5.6)	80 (7.2)	128 (9.3)	718 (7.0)

Table 1 (*continued*)

Women 41 082 (27.1%)	NAT *n* (%)	WEWC *n* (%)	EE *n* (%)	NAME *n* (%)	SSA *n* (%)	LA *n* (%)	CRB *n* (%)	ASIA/OC *n* (%)
$CD4^+$ cell count [cells/μl, Me(IQR)]	380 (199–577)	360 (194–550)	362.5 (217.5–546.5)	328.5 (159–532.5)	293 (157–456)	330 (160–522)	341 (169–527)	266.5 (86–453)
Viral load [log_{10} copies/ml, Me(IQR)]	4.3 (3.6–5.0)	4.4 (3.5–5.0)	4.2 (3.6–4.9)	4.4 (3.6–5.1)	4.3 (3.5–4.9)	4.4 (3.7–4.9)	4.2 (3.5–4.8)	4.5 (3.7–5.0)
AIDS	1949 (10.0)	63 (10.0)	62 (9.9)	70 (11.4)	1501 (9.3)	130 (11.7)	126 (9.1)	148 (16.0)
HBV DNA and/or Ab (excluding sAB)								
Yes	2342 (12.0)	112 (17.7)	144 (23.1)	97 (15.8)	3771 (23.3)	164 (14.7)	99 (7.2)	241 (26.0)
No	12 573 (64.2)	326 (51.5)	327 (52.4)	440 (71.4)	9004 (55.6)	809 (72.7)	1067 (77.4)	401 (43.2)
Unknown	4677 (23.9)	195 (30.8)	153 (24.5)	79 (12.8)	3422 (21.1)	140 (12.6)	213 (15.5)	286 (30.8)
HCV RNA and/or Ab								
Yes	4139 (21.1)	133 (21.0)	157 (25.2)	41 (6.7)	571 (3.5)	82 (7.4)	28 (2.0)	54 (5.8)
No	11 197 (57.2)	301 (47.6)	322 (51.6)	488 (79.2)	11 589 (71.6)	864 (77.6)	1108 (80.4)	536 (57.8)
Unknown	4256 (21.7)	199 (31.4)	145 (23.2)	87 (14.1)	4037 (24.9)	167 (15.0)	243 (17.6)	338 (36.4)
Period								
1997–1999	5097 (26.0)	90 (14.2)	20 (3.2)	96 (15.6)	1717 (10.6)	105 (9.4)	177 (12.8)	115 (12.4)
1999–2003	5679 (29.0)	191 (30.2)	92 (14.7)	157 (25.5)	5292 (32.7)	230 (20.7)	458 (33.2)	265 (28.6)
2004–2008	5998 (30.6)	215 (34.0)	244 (39.1)	239 (38.8)	6565 (40.5)	509 (45.7)	607 (44.0)	373 (40.2)
2009–2013	2818 (14.4)	137 (21.6)	268 (43.0)	124 (20.1)	2623 (16.2)	269 (24.2)	137 (9.9)	175 (18.9)
Follow-up								
Started cART	16 020 (81.8)	491 (77.6)	463 (74.2)	521 (84.6)	13 227 (81.7)	878 (78.9)	1136 (82.4)	811 (87.4)
No. with only baseline $CD4^+$	7602 (38.8)	265 (41.9)	252 (40.4)	276 (44.8)	6237 (38.5)	466 (41.9)	508 (36.8)	383 (41.3)
No. $CD4^+$ cell count measurements [Me(IQR)]	2 (1–5)	2 (1–5)	2 (1–4)	2 (1–5)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)

Ab, antibody; ASIA, the Asian Continent; CRB, The Caribbean; EE, Eastern Europe; HBV, hepatitis B virus; HCV, hepatitis C virus; HTX, heterosexual transmission; LA, Latin America; Me(IQR), median (interquartile range) ; NAME, North Africa and The Middle East; NAT, person originally from the country of enrolment; PWID/OTH, people who inject drugs or others; sAb, surface antibody; SSA, sub-Saharan Africa; Start cART, does patient start combined antiretroviral therapy during follow-up; UNK, unknown; WEWC, Western Europe and other Western countries, including North America, Australia and New Zealand.

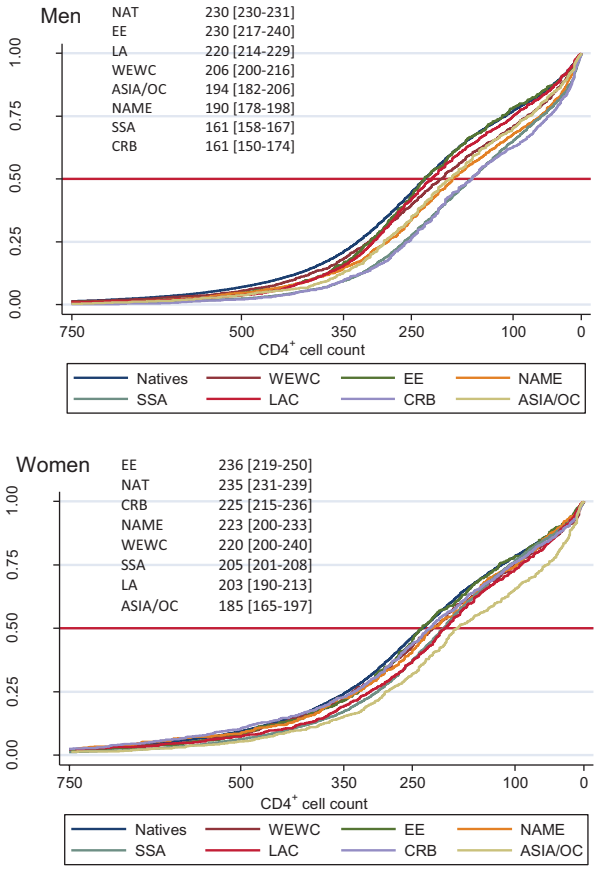

Fig. 1. Kaplan–Meier estimates of cumulative probability of combined antiretroviral treatment initiation at different CD4$^+$ cell counts (cells/μl) values and median CD4$^+$ cell count (cells/μl) at combined antiretroviral treatment initiation (95% confidence intervals) by geographical origin and sex. ASIA/OC, the rest of the Asian Continent and Oceania; CRB, The Caribbean; EE, Eastern Europe; LA, Latin America; NAME, North Africa and the Middle East; NAT, native population; SSA, sub-Saharan Africa; WEWC, Western Europe and other Western countries in North America, Australia and New Zealand.

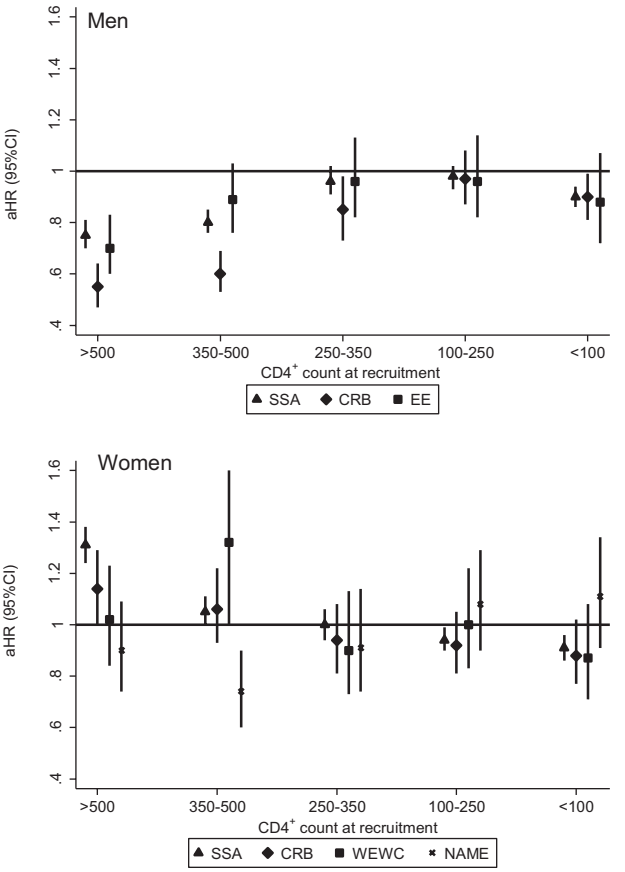

Fig. 2. Results from the multivariable Cox models: hazard ratios and 95% confidence intervals for the probability of initiating combined antiretroviral treatment for each geographical origin compared with natives, stratified by CD4$^+$ cell count (cells/μl) at recruitment, adjusted for baseline variables: calendar period, age, transmission category, viral load, AIDS stage and history of hepatitis B and hepatitis C infection. CRB, The Caribbean; EE, Eastern Europe; NAME, North Africa and the Middle East; SSA, sub-Saharan Africa; WEWC, Western Europe and other Western countries in North America, Australia and New Zealand.

effect was strongest for CRB men, who had a 23% (18–27%) lower probability of initiating cART. However, these hazard ratios varied depending on CD4$^+$ cell count at recruitment (overall interaction P value <0.01), with the effect of geographical origin being greater at higher CD4$^+$ cell count at recruitment (Fig. 2). The heterogeneity of strata was only statistically significant for EE, SSA and CRB men, so CD4$^+$ cell count strata-specific aHRs (95% CI) are provided in Table 2 for these groups. For men recruited at more than 500 cells/μl, the probability of initiating cART was 45% (36–53%) lower for CRB, 30% (17–40%) lower for EE and 25% (19–30%) lower for SSA compared with natives.

In women, overall, most migrant groups' CD4$^+$ cell count at cART initiation did not differ to those in native women except for SSA, whose probability was 3% (0–6%) higher, and Latin America, whose probability was 7% (0–13%) lower. Again, the effect was heterogeneous depending on the CD4$^+$ cell count at recruitment (overall interaction P value <0.01), specifically for SSA, CRB, WEWC and NAME women; CD4$^+$ cell count strata-specific aHRs (95% CI) are provided in Table 2 for these groups. For SSA and CRB women recruited at CD4$^+$ cell count more than 500 cells/μl, the probability of initiating cART compared with native women was 31% (24–38%) and 14% (0–29%) higher, respectively; in contrast, the effect was reversed or disappeared among women who entered into care at lower CD4$^+$ cell count, reaching a 9% (4–14%) lower probability for SSA women with CD4$^+$ cell count less than 100 cells/μl at recruitment.

In some of the sensitivity analyses (Appendix Table 1, http://links.lww.com/QAD/B41), the lower probability

Table 2. Probability of initiating combined antiretroviral treatment for migrant men and women of different geographical origins living in Western Europe compared with native men and women, respectively: results from multivariable Cox models.

	WEWC aHR (95% CI) *P* value	EE aHR (95% CI) *P* value	NAME aHR (95% CI) *P* value	SSA aHR (95% CI) *P* value	LA aHR (95% CI) *P* value	CRB aHR (95% CI) *P* value	ASIA/OC aHR (95% CI) *P* value
Men							
Effect of GO vs. NAT[a]	0.94 (0.90–0.99) $P=0.01$*	0.87 (0.80–0.93) $P<0.01$*	0.92 (0.88–0.97) $P<0.01$*	0.90 (0.87–0.92) $P<0.01$*	0.98 (0.95–1.02) $P=0.39$*	0.77 (0.73–0.82) $P<0.01$*	0.94 (0.89–1.00)[a] $P=0.04$*
Interaction test	$P=0.9603$**	$P=0.0362$**	$P=0.1845$**	$P=0.0000$**	$P=0.5615$**	$P=0.0000$**	$P=0.4654$**
Effect stratified by $CD4^+$ cell count at recruitment							
>500		0.70 (0.60–0.83) $P<0.01$*		0.75 (0.70–0.81) $P<0.01$*		0.55 (0.47–0.64) $P<0.01$*	
350–500		0.89 (0.76–1.03) $P=0.11$*		0.80 (0.76–0.85) $P<0.01$*		0.60 (0.53–0.69) $P<0.01$*	
250–350		0.96 (0.82–1.13) $P=0.65$*		0.96 (0.91–1.02) $P=0.20$*		0.85 (0.73–0.98) $P=0.02$*	
100–250		0.96 (0.82–1.14) $P=0.67$*		0.98 (0.93–1.02) $P=0.27$*		0.97 (0.87–1.08) $P=0.58$*	
<100		0.88 (0.72–1.07) $P=0.20$*		0.90 (0.86–0.94) $P<0.01$*		0.90 (0.81–0.99) $P=0.04$*	
Women							
Effect of GO vs. NAT[a]	1.01 (0.93–1.11) $P=0.79$*	1.01 (0.91–1.11) $P=0.91$*	0.94 (0.86–1.02) $P=0.14$*	1.03 (1.00–1.06) $P=0.03$*	0.93 (0.87–1.00) $P=0.05$*	0.99 (0.93–1.05) $P=0.63$*	0.98 (0.91–1.05) $P=0.60$*
Interaction test	$P=0.0471$**	$P=0.9905$**	$P=0.0269$**	$P=0.0000$**	$P=0.4689$**	$P=0.0473$**	$P=0.3215$**
Effect stratified by $CD4^+$ cell count at recruitment							
>500	1.02 (0.84–1.23) $P=0.87$*		0.90 (0.74–1.09) $P=0.28$*	1.31 (1.24–1.38) $P<0.01$*		1.14 (1.00–1.29) $P=0.05$*	
350–500	1.32 (1.09–1.60) $P<0.01$*		0.74 (0.60–0.90) $P<0.01$*	1.05 (1.00–1.11) $P=0.06$*		1.06 (0.93–1.22) $P=0.37$*	
250–350	0.90 (0.73–1.13) $P=0.38$*		0.91 (0.74–1.14) $P=0.42$*	1.00 (0.94–1.06) $P=0.99$*		0.94 (0.81–1.08) $P=0.36$*	
100–250	1.00 (0.83–1.22) $P=0.97$*		1.08 (0.90–1.29) $P=0.42$*	0.94 (0.90–0.99) $P=0.01$*		0.92 (0.81–1.05) $P=0.21$*	
<100	0.87 (0.71–1.08) $P=0.20$*		1.11 (0.91–1.34) $P=0.31$*	0.91 (0.86–0.96) $P<0.01$*		0.88 (0.77–1.02) $P=0.10$*	

Adjusted hazard ratios and 95% confidence intervals for combined antiretroviral treatment initiation are shown overall, and by $CD4^+$ cell count at recruitment where the test for interaction between geographical origin and $CD4^+$ cell count at recruitment was statistically significant. ASIA/OC, the rest of the Asian Continent and Oceania; CRB, The Caribbean; EE, Eastern Europe; LA, Latin America; NAME, North Africa and The Middle East; SSA, sub-Saharan Africa; WEWC, Western Europe and other Western countries in North America, Australia and New Zealand. All models are adjusted for baseline variables: calendar period, age, transmission category, viral load, AIDS stage and history of hepatitis B and hepatitis C infection.

[a]Models also adjusted by $CD4^+$ cell count at recruitment.

*P value for the Wald's test for the hazard ratio of each geographical origin compared with native population.

**P value for the likelihood ratio test for interaction between geographical origin and $CD4^+$ cell count.

of cART initiation in Latin America men reached statistical significance. Some other differences were found, especially when using the modelled instead of the observed $CD4^+$ cell count, and although the direction of the effect was preserved, some effects were no longer statistically significant, such as the previously described associations for EE and ASIA/OC men, and WEWC and NAME women.

Discussion

The current study is the first one to analyse the $CD4^+$ count at cART initiation in migrants from a wide range of geographical origins living with HIV in Western Europe. The $CD4^+$ cell counts at which the probability of having initiated treatment was 50% was below 250 cells/μl for all groups. Our results show that the majority of migrant men, particularly those from SSA and the CRB, initiate cART at lower $CD4^+$ cell count than native men, with the gap tending to be wider in men recruited at $CD4^+$ cell count at least 350 cells/μl. In contrast, women appeared to initiate cART at similar $CD4^+$ cell count compared with native women, most likely reflecting HIV testing and cART initiation to prevent mother-to-child transmission in the context of antenatal care. In SSA and CRB women, the probability of initiating cART was, in fact, higher than among natives when women were linked to care at $CD4^+$ cell count of at least 350 cells/μl, although the effect disappeared or was even reversed for those linked to care at very low $CD4^+$ cell count.

Later cART initiation in migrants can result in worse health outcomes [2–5,18,19,24], but is also of public health concern [8] as it facilitates ongoing transmission of HIV within the community, thus compromising the 90–90–90 target set by UNAIDS that relies on equitable access to cART for key populations worldwide [25]. Inequalities in timing of cART initiation may be explained by different factors associated with late diagnosis of HIV infection [12,26–30], impaired linkage and retention in clinical care [13–15,31,32] or to barriers to accessing antiretroviral drugs themselves [8,11,13]. Disentangling the contribution of each of these factors is difficult.

Several barriers have been postulated to explain these gaps, including factors at structural, healthcare and community levels. Social exclusion, racism and discrimination; economic instability; precarious working conditions; higher geographical mobility and administrative and legal frameworks, with fear of discrimination or deportation after a positive diagnosis, have all been reported as barriers [12–14,26,33–35]. Fear of disclosure, language barriers and cultural differences in settings in which translators and cultural mediators are not available may also contribute to higher disengagement from HIV care [14,36]. In addition, it is likely that personal choices and prescribing physicians' views are influenced by health literacy and socioeconomic status, which tend to be lower in most migrant groups [13]. The fact that migrants may already arrive to the destination country with HIV infection has also been discussed as contributing to late diagnosis and treatment. However, there is growing evidence that a significant proportion of HIV infections in migrants were acquired after their arrival into Western Europe [37–40].

Legal barriers deserve a special mention [8,14]. A recent ECDC report shows how 14 out of 29 EU/EEA countries denied access to cART for undocumented migrants in 2014 [11]. Furthermore, the austerity measures adopted following the economic crisis, with the reduction in the provision of essential services for migrants, have further contributed to widening the gap [33,41]. In some countries such as Spain, repeated changes in legislation have generated confusion and uncertainty, even among health providers, around who can access what services free of charge, acting as deterrents for the adequate use of available services or denials to people who should be entitled to them [32,42].

In our study, we tried to discriminate the effects of delay in diagnosis and delay in initiation of treatment allowing for a differential effect of geographical origin according to the $CD4^+$ cell count at which the person was recruited into the cohort, a surrogate for HIV diagnosis. Groups diagnosed later in the course of HIV infection (with $CD4^+$ cell count <350 cells/μl) tended to have similar probabilities of initiating cART than natives, whereas differences were indeed found for those diagnosed earlier. At higher $CD4^+$ cell count, guidelines did not consistently recommend initiation of cART, and we may observe higher clinical variability, with the decision influenced by a wider range of determinants. The abovementioned barriers may have a greater impact in this situation and probably result in the later cART initiation observed in migrant men in our study. Future analyses will need to evaluate whether the differences observed in this study remain in the current context in which guidelines recommend immediate cART, irrespective of $CD4^+$ cell count.

Women, however, seem to be protected to a certain degree by HIV testing and treatment to decrease mother-to-child transmission in the context of antenatal care. This is reinforced by the consolidated practice of universal screening in pregnant women in the European context [12] and by the widely known and accepted legal framework that recognizes the right to free and accessible healthcare for pregnant women independent of their administrative status [26]. The high acceptability of antenatal services among migrant women importantly contributes to the relatively high coverage, although gaps have been reported to persist for undocumented women

[43]. This results in some migrant women, such as those from SSA or the CRB, having an even higher probability than natives of initiating cART when diagnosed at a high $CD4^+$ cell count. The notable exception is Latin American women, who exhibit a globally lower initiation of treatment, something that has not been previously explored in the literature and which merits further investigations.

Consistent with our results, a recent study found the likelihood of cART initiation in migrant men from SSA living in France was 15% lower than in French population when diagnosed between 350 and 500 cells/μl, with the difference widening with earlier diagnosis; in contrast, no difference was found in other migrant groups [16]. Other studies have failed to find any evidence of delayed initiation of cART in migrants, although lack of stratification by sex or $CD4^+$ cell count at diagnosis [18,44] and restriction to individuals with known date of seroconversion [45] may partially explain the discrepancy of results.

A limitation of this study was that we were unable to control for the heterogeneity of cART initiation recommendations across participating countries and throughout the study period. The composition of the COHERE collaboration has been changing throughout the time, and the analysis of temporal trends may be biased by the incorporation or finalization of specific cohorts within the collaboration. However, between 2004 and 2013, the recommendation to start cART at a $CD4^+$ cell count of 350 cells/μl or below was widespread, and analysis restricted to years after 2004 led to similar conclusions.

Another limitation relates to the lack of information on the administrative and legal status, which could better identify the role of legal barriers and the risk of undocumented migrants, and on the socioeconomic status, which could lie on the pathway of the observed effects of geographical origin. Our results are based in ad-hoc cohort studies and have the advantage of achieving a large sample size. The composition of the migrant population and their characteristics in our study were similar to those reported by the ECDC HIV surveillance system [10]. The study is specific to the Western European region, and results are thus not generalizable to other geographical regions.

In summary, we have highlighted late initiation of cART in the migrant population in Western Europe and differences in timing of cART initiation for some groups within migrant communities, especially for men. Addressing existing barriers to access HIV testing and care and ensuring universal and free access to cART is important if we are to advance the elimination of inequities and in the control of the HIV epidemic in Western Europe.

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Conflicts of interest

There are no conflicts of interest.

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