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ORIGINAL RESEARCH

Immunological and virological response to antiretroviral treatment in migrant and native men and women in Western Europe; is benefit equal for all?

Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord*

Objectives

The aim of the study was to evaluate differences in immunovirological response to combination antiretroviral therapy (cART) in migrant and native men and women within a European collaboration of HIV cohorts Collaboration of Observational HIV Epidemiological Research in Europ (COHERE) in EuroCoord, 2004–2013.

Methods

Migrants were defined as those with geographical origin (GO) different from the reporting country and were grouped as originating from Western Europe and Western Countries (WEWC), Eastern Europe (EE), North Africa and the Middle East (NAME), sub-Saharan Africa (SSA), Latin America (LA), Caribbean (CRB) and Asia/Oceania (ASIA/OCE). Native (NAT) individuals were defined as those originating from the reporting country. CD4 cell counts were modelled using piecewise linear mixed-effects models with two slopes, whereas models to estimate subdistribution hazard ratios (sHRs) were used for time to virological response (VR) (i.e. time from cART initiation to the first of two successive HIV RNA measurements < 400 HIV-1 RNA copies/ml).

Results

Of 32 817 individuals, 25 799 (78.6%) were men. The percentage of migrants was higher in women (48.9%) than in men (21.2%) and migrants from SSA accounted for the largest migrant group (29.9% in men and 63.3% in women). Migrant men and women from SSA started at lower CD4 cell counts than NAT individuals, which remained lower over time. VR was ≥ 85% at 12 months for all groups except CRB women (77.7%). Compared with NAT men and women, lower VR was experienced by NAME [sHR 0.91; 95% confidence interval (CI) 0.86–0.97] and SSA (sHR 0.88; 95% CI 0.82–0.95) men and CRB (sHR 0.77; 85% CI 0.67–0.89) women, respectively.

Conclusions

Immunovirological response to cART in Western Europe varies by GO and sex of patients. ART benefits are not equal for all, underlining the point that efforts need to prioritize those most in need.

Keywords: HIV, combination antiretroviral therapy, immunovirological response, migrants, sex

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Introduction

Globally, migrants have higher rates of late HIV presentation than native populations [1,2] but, whereas those from high-income settings have similar proportions of late HIV presentation, migrants from middle- and low-income settings are more likely to present late [2]. Consequently, median CD4 cell count at combination antiretroviral therapy (cART) initiation is lower in most migrant groups [3]. Less is known about the immunological and virological responses to cART by specific geographical origin (GO). Available data largely refer to sub-Saharan Africans and Latin-Americans, with less data from other migrant groups [4–6]. Understanding the

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heterogeneity in immunovirological response to cART across HIV-positive populations in Europe is essential to improve the continuum of care, maximize the population impact of cART and minimize secondary HIV transmissions. We aimed to evaluate differences in immunological and virological response to cART in HIV-positive men and women according to GO within COHERE from 2004 to 2013.

Methods

Study population

Data were merged in COHERE (www.cohere.org) in EuroCoord (www.EuroCoord.net) in 2013, comprising 40 observational cohorts and cohort collaborations of HIV-positive individuals from 32 countries. We excluded cohorts and individuals with missing GO data and those infected through routes other than injecting drug use or sexual intercourse. Eligible individuals were antiretroviral-naïve patients recruited from 1 January 1997, who were 18–74 years old at enrolment and who initiated cART from 1 January 2004. Patients had to have both CD4 T-cell count and HIV RNA measurements within 6 months prior to cART initiation and at least two CD4 T-cell counts and HIV RNA measurements while on cART. Individuals with a viral load < 1000 HIV-1 RNA copies/ml at cART initiation were excluded.

Migrants were defined as having GO different from the reporting country and grouped in the following categories: Western Europe and Western Countries (WEWC), Eastern Europe (EE), North Africa and Middle East (NAME), sub-Saharan Africa (SSA), Latin America (LA), Caribbean (CRB) and Asia/Oceania (ASIA/OCE).

Statistical analysis

Trends in CD4 T-cell counts were modelled using piecewise linear mixed-effects models with two slopes and change point at month 6 based on exploratory analyses. We defined time to virological response (VR) as time from cART initiation to the first of two successive HIV RNA measurements < 400 copies/ml. We calculated the cumulative incidence of VR and used proportional hazards models on the subdistribution hazard to estimate subdistribution hazard ratios (sHRs) for VR by GO, treating deaths before VR as competing events.

Multivariable models were adjusted for age at cART initiation, risk group, $\log_{10}$ HIV RNA at cART initiation, pre-cART AIDS diagnosis, period of cART initiation and initial type of regimen. We also adjusted models for VR by pre-cART CD4 count. To adjust for clustering of patients within cohorts, robust methods were used to estimate standard errors. Wald tests were used to derive *P*-values. Statistical analyses were performed using STATA 14 (StataCorporation, College Station, Texas, USA).

Results

Study population characteristics

Of 32 817 individuals included, 78.6% (n = 25 799) were men. The percentage of migrants was higher in women (48.9%) than in men (21.2%) and migrants from SSA accounted for the largest migrant group (29.9% of men and 63.3% of women), followed by LA (29.0%) and WEWC (13.8%) in men and LA (10.8%) and CRB (6.6%) in women (Table 1).

Trends in CD4 T-cell count after cART

Compared with native (NAT) individuals, migrants from SSA started cART at lower CD4 T-cell counts. While men from this region experienced slower short-term (0–6 months) [adjusted difference in mean CD4 T-cell count increase/month (square root scale) −0.12; 95% CI −0.16, −0.09; $P < 0.001$] and long-term (> 6 months) (adjusted difference −0.01; 95% CI −0.01, −0.002; $P = 0.01$) rates of CD4 T-cell increase, rates of increase in women from SSA were significantly slower only over the short term (adjusted difference −0.10; 95% CI −0.13, −0.06; $P < 0.001$). Compared with NAT individuals, both migrant men and women from LA started cART at lower CD4 T-cell counts; while both men and women from LA exhibited a better short-term immunological response than NAT individuals, this was only significant in men (adjusted difference 0.05; 95% CI 0.02, 0.08; $P = 0.002$), but the small number of LA women may have prevented statistical significance being reached. Migrant men and women from EE experienced faster long-term CD4 T-cell increases compared with NAT individuals [adjusted difference 0.02 (95% CI 0.003, 0.03; $P = 0.02$) for men and adjusted difference 0.03 (95% CI 0.01, 0.05; $P = 0.001$) for women], although no significant differences were found in the CD4 T-cell count at which cART was started in men and women from this region (Supporting Information Table S1). Table S1, Figure S1 and Figure S2 were updated when paper was submitted. Please, ask for sending those again in case you do not have those.

Figure S1 depicts the predicted evolution of CD4 T-cell counts by GO, given the specific distributions of confounders in each GO group (univariable graphs) and assuming common characteristics (i.e. majority profile) in

Table 1 Sociodemographic and clinical characteristics at the start of combination antiretroviral therapy (cART) according to geographical origin, in (a) men (n = 25 799; 78.6%) and (b) women (n = 7018; 21.4%) in COHERE

	NAT	WEWC	EE	NAME	SSA	LA	CRB	ASIA/OCE
(a)								
n (%)	20 340 (78.8)	751 (2.9)	342 (1.3)	482 (1.9)	1632 (6.3)	1586 (6.1)	290 (1.1)	376 (1.5)
Age (years)								
[median (IQR)]	39 (33–46)	40 (32–46)	34 (29–40)	38 (33–44)	38 (32–44)	34 (29–41)	40 (34–47)	35 (30–43)
Transmission category [*n* (%)]								
Sex between men	14 623 (71.9)	549 (73.1)	210 (61.4)	195 (40.5)	180 (11.0)	1252 (78.9)	129 (44.5)	263 (69.9)
Sex between men and women	4260 (20.9)	142 (18.9)	60 (17.5)	231 (47.9)	1427 (87.4)	316 (19.9)	156 (53.8)	89 (23.7)
Injecting drug use	1457 (7.2)	60 (8.0)	72 (21.0)	56 (11.6)	25 (1.5)	18 (1.1)	5 (1.7)	24 (6.4)
CD4 T-cell count (cells/μl)								
[median (IQR)]	277 (180–364)	260 (140–350)	272 (190–355)	240 (136–334)	221 (117–314)	253 (148–336)	210 (90–295)	250 (150–345)
CD4 T-cell count category [*n* (%)]								
< 200 cells/μl	5895 (29.0)	255 (34.0)	94 (27.5)	186 (38.6)	698 (42.8)	555 (35.0)	130 (44.8)	130 (34.6)
200–350 cells/μl	8798 (43.2)	313 (41.7)	160 (46.8)	189 (39.2)	654 (40.1)	689 (43.4)	124 (42.8)	160 (42.5)
> 350 cells/μl	5647 (27.8)	183 (24.4)	88 (25.7)	107 (22.2)	280 (17.2)	342 (21.6)	36 (12.4)	86 (22.9)
Log_{10} HIV RNA (copies/ml)								
[median (IQR)]	4.9 (4.5–5.4)	4.9 (4.4–5.4)	4.8 (4.4–5.3)	4.9 (4.5–5.4)	4.9 (4.4–5.3)	4.8 (4.4–5.2)	4.9 (4.4–5.3)	4.8 (4.3–5.2)
HIV RNA category [*n* (%)]								
< 4 log_{10} copies/ml	2147 (10.6)	73 (9.7)	38 (11.1)	50 (10.4)	220 (13.5)	171 (10.8)	38 (13.1)	43 (11.4)
4–5 log_{10} copies/ml	9271 (45.6)	364 (48.5)	170 (49.7)	222 (46.1)	731 (44.8)	797 (50.2)	137 (47.2)	203 (54.0)
> 5 log_{10} copies/ml	8922 (43.9)	314 (41.8)	134 (39.2)	210 (43.6)	681 (41.7)	618 (39.0)	115 (39.7)	130 (34.6)
Pre-cART AIDS diagnosis [*n* (%)]								
No	15 552 (76.5)	516 (68.7)	250 (73.1)	336 (69.7)	1243 (76.2)	1295 (81.6)	229 (79.0)	280 (74.5)
Yes	2620 (12.9)	104 (13.8)	33 (9.6)	77 (16.0)	366 (22.4)	243 (15.3)	57 (19.7)	57 (15.2)
Unknown	2168 (10.7)	131 (17.4)	59 (17.2)	69 (14.3)	23 (1.4)	48 (3.0)	4 (1.4)	39 (10.4)
Period of cART initiation [*n* (%)]								
2004–2008	10 305 (50.7)	387 (51.5)	135 (39.5)	255 (52.9)	941 (57.7)	781 (49.2)	201 (69.3)	170 (45.2)
2009–2013	10 035 (49.3)	364 (48.5)	207 (60.5)	227 (47.1)	691 (42.3)	805 (50.8)	89 (30.7)	206 (54.8)
Type of cART regimen [*n* (%)]								
NNRTI-based	10 628 (52.2)	431 (57.4)	181 (52.9)	246 (51.0)	866 (53.1)	976 (61.5)	183 (63.1)	237 (63.0)
PI-based	6315 (31.0)	195 (26.0)	108 (31.6)	152 (31.5)	567 (34.7)	335 (21.1)	73 (25.2)	100 (26.6)
Other	3397 (16.7)	125 (16.6)	53 (15.5)	84 (17.4)	199 (12.2)	275 (17.3)	34 (11.7)	39 (10.4)
(b)								
n (%)	3586 (51.1)	141 (2.0)	193 (2.7)	149 (2.1)	2172 (30.9)	370 (5.3)	226 (3.2)	181 (2.6)
Age (years)								
[median (IQR)]	39 (31–47)	37 (30–46)	31 (27–38)	38 (29–46)	32 (27–39)	35 (29–42)	35 (29–45)	34 (30–41)
Transmission category [*n* (%)]								
Sex between men and women	3124 (87.1)	116 (82.3)	169 (87.6)	147 (98.7)	2164 (99.6)	366 (98.9)	225 (99.6)	178 (98.3)
Injecting drug use	462 (12.9)	25 (17.7)	24 (12.4)	2 (1.3)	8 (0.4)	4 (1.1)	1 (0.4)	3 (1.7)
CD4 T-cell count (cells/μl)								
[median (IQR)]	257 (158–339)	259 (120–344)	244 (155–337)	228 (137–340)	240 (145–320)	210 (100–305)	239 (146–321)	200 (56–315)
CD4 T-cell count category [*n* (%)]								
< 200 cells/μl	1225 (34.2)	53 (37.6)	76 (39.4)	68 (45.6)	809 (37.2)	170 (45.9)	89 (39.4)	90 (49.7)
200–350 cells/μl	1567 (43.7)	53 (37.6)	73 (37.8)	48 (32.2)	953 (43.9)	133 (36.0)	92 (40.7)	62 (34.2)
> 350 cells/μl	794 (22.1)	35 (24.8)	44 (22.8)	33 (22.1)	410 (18.9)	67 (18.1)	45 (19.9)	29 (16.0)
Log_{10} HIV RNA (copies/ml)								

Table 1 (*Continued*)

	NAT	WEWC	EE	NAME	SSA	LA	CRB	ASIA/OCE
[median (IQR)]	4.7 (4.1–5.2)	4.9 (4.4–5.2)	4.7 (4.1–5.1)	4.7 (4.1–5.3)	4.6 (4.1–5.1)	4.7 (4.2–5.1)	4.4 (3.9–5.0)	4.8 (4.2–5.2)
HIV RNA category [*n* (%)]								
< 4	711 (19.8)	21 (14.9)	42 (21.8)	31 (20.8)	487 (22.4)	73 (19.7)	62 (27.4)	30 (16.6)
4–5	1656 (46.2)	66 (46.8)	93 (48.2)	67 (45.0)	1060 (48.8)	179 (48.4)	112 (49.6)	90 (49.7)
> 5	1219 (34.0)	54 (38.3)	58 (30.0)	51 (34.2)	625 (28.8)	118 (31.9)	52 (23.0)	61 (33.7)
Pre-cART AIDS diagnosis [*n* (%)]								
No	2729 (76.1)	99 (70.2)	117 (60.6)	110 (73.8)	1822 (83.9)	284 (76.8)	190 (84.1)	121 (66.8)
Yes	554 (15.4)	20 (14.2)	26 (13.5)	26 (17.4)	329 (15.1)	79 (21.3)	35 (15.5)	47 (26.0)
Unknown	303 (8.4)	22 (15.6)	50 (25.9)	13 (8.7)	21 (1.0)	21 (1.9)	1 (0.4)	13 (7.2)
Period of cART initiation [*n* (%)]								
2004–2008	2185 (60.9)	75 (53.2)	86 (44.6)	89 (59.7)	1401 (64.5)	230 (62.2)	190 (84.1)	103 (56.9)
2009–2013	1401 (39.1)	66 (46.8)	107 (55.4)	60 (40.3)	771 (35.5)	140 (37.8)	36 (15.9)	78 (43.1)
Type of cART regimen [*n* (%)]								
NNRTI-based	1564 (43.6)	66 (46.8)	89 (46.1)	71 (47.6)	953 (43.9)	196 (53.0)	104 (46.0)	110 (60.8)
PI-based	1355 (37.8)	53 (37.6)	74 (38.3)	61 (40.9)	960 (44.2)	105 (28.4)	111 (49.1)	51 (28.2)
Other	667 (18.6)	22 (15.6)	30 (15.5)	17 (11.4)	259 (11.9)	69 (18.6)	11 (4.9)	20 (11.0)

COHERE, Collaboration of Observational HIV Epidemiological Research Europe; WEWC, Western Europe and Western Countries; EE, Eastern Europe; NAME, North Africa and the Middle East; SSA, sub-Saharan Africa; LA, Latin America; CRB, Caribbean; ASIA/OCE, Asia/Oceania; cART, combination antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

all GO groups (multivariable graphs). Migrant men and women from SSA and migrant women from LA, CRB and ASIA/OCE maintained a CD4 T-cell count $\leq$ 500 cells/μl throughout almost the whole 60-month period after starting therapy. CD4 cell count differences persisted across groups as the baseline differences were not compensated for by differential immunological responses.

Virological response

VR was poorer in women than in men, with 89.0% of women and 93.3% of men achieving VR at 12 months from cART initiation. While in men, VR at 12 months was > 90% for all groups except for migrant men from SSA and CRB, in women, it was < 90% for NAT individuals and most migrant groups, and was particularly low in those from CRB (77.7%) (Figure S2). Results from adjusted analyses showed that migrant men from NAME (sHR 0.91; 95% CI 0.86–0.97) and SSA (sHR 0.88; 95% CI 0.82–0.95) experienced lower rates of response than NAT men, as also did migrant women from CRB (sHR 0.77; 95% CI 0.67–0.89) in comparison to their NAT counterparts (Table 2).

Discussion

Our study shows that, among HIV-positive patients linked to care and started on cART from 2004 to 2013 in Europe, immunological and virological responses varied significantly by GO and sex. Among men, those from sub-Saharan Africa had the poorest indicators in terms of CD4 cell count and VR. In contrast, male migrants from other Western countries and from Eastern Europe exhibited better immunological responses to cART than natives. Virological suppression rates > 90% at 12 months were achieved by all male migrants apart from those from sub-Saharan Africa and the Caribbean. Among women, viral load suppression rates at 12 months were poorer than those in men; while the rates in most groups were around 90%, Caribbean women had a particularly low rate of 77.7%.

Our results are consistent with the poorer virological and/or immunological responses in sub-Saharan African migrants reported by others [4–6]. This study demonstrates that this pattern is observed for both men and women. Staehelin *et al.* [4] described poorer self-reported adherence in sub-Saharan African migrants than in people of other origins. Van Beckhoven *et al.* [6] have recently reported that viral load suppression on cART was also poorer in migrants from sub-Saharan Africa compared with Belgian natives, the former group also having poorer retention in care. Fewer data are available for HIV-positive migrants from Latin America, but our results

Table 2 Time to virological response from combination antiretroviral therapy (cART) initiation according to geographical origin, in men and women

	Men				Women			
	Univariable analysis		Multivariable analysis*		Univariable analysis		Multivariable analysis*	
	sHR (95% CI)	*P*-value	sHR (95% CI)	*P*-value	sHR (95% CI)	*P*-value	sHR (95% CI)	*P*-value
NAT	1.00		1.00		1.00		1.00	
WEWC	0.98 (0.90; 1.06)	0.60	0.98 (0.87; 1.10)	0.71	0.90 (0.73; 1.11)	0.32	0.90 (0.0.74; 1.09)	0.29
EE	1.05 (0.96; 1.15)	0.31	1.06 (0.96; 1.17)	0.24	1.17 (1.00; 1.37)	0.055	1.17 (0.98; 1.39)	0.09
NAME	0.85 (0.76; 0.95)	0.005	0.91 (0.86; 0.97)	0.004	1.00 (0.86; 1.17)	0.98	1.00 (0.90; 1.11)	0.94
SSA	0.80 (0.76; 0.84)	<0.001	0.88 (0.82; 0.95)	0.001	1.05 (0.98; 1.12)	0.18	1.04 (0.96; 1.12)	0.30
LA	1.00 (0.90; 1.11)	0.98	0.95 (0.87; 1.03)	0.23	1.08 (0.95; 1.24)	0.23	1.08 (0.94; 1.25)	0.27
CRB	0.90 (0.61; 1.32)	0.58	0.95 (0.73; 1.24)	0.71	0.79 (0.65; 0.96)	0.02	0.77 (0.67; 0.89)	<0.001
ASIA/OCE	1.09 (0.94; 1.27)	0.24	1.07 (0.93; 1.23)	0.33	1.17 (0.95; 1.44)	0.14	1.14 (0.90; 1.45)	0.27
Overall *P*-value		<0.001		<0.001		<0.001		<0.001

*Adjusted by transmission category (sex between men, injecting drug use, and sex between men and women), age at cART initiation, $\log_{10}$ HIV RNA and CD4 T-cell count (< 200, 200–350 and > 350) at cART, pre-cART AIDS diagnosis, period of cART initiation (2004–2008 and 2009–2013) and type of cART regimen (nonnucleoside reverse transcriptase inhibitor, protease inhibitor and other).
CI, confidence interval; sHR, subdistribution hazard ratio; WEWC, Western Europe and Western Countries; EE, Eastern Europe; NAME, North Africa and the Middle East; SSA, sub-Saharan Africa; LA, Latin America; CRB, Caribbean; ASIA/OCE, Asia/Oceania.

are consistent with those reported by Monge *et al.* [5] for Latin-American migrants in Spain. The worrying suboptimal virological responses to cART observed in Caribbean women suggest poor engagement in care as well as adherence to cART and are consistent with previous COHERE findings highlighting a high rate of all-cause mortality in these women [7].

Although most migrant groups have difficulties accessing HIV-related services in European countries, not all of them face the same hardships [8,9]. Hernando *et al.* [2] reported that, compared with native populations, late HIV diagnosis in European surveillance data is not more common in those from Western, Eastern and Central Europe, nor in those from Australia, New Zealand or North America. This probably highlights how economic and social disadvantage shapes the type and number of barriers to accessing HIV testing and care. Legal barriers also exist despite all public health recommendations [10,11] and scientific evidence [12,13] supporting universal access to HIV testing and treatment; this is still denied to undocumented migrants in some European countries [8,9,14]. Migrants are thought to have poorer adherence secondary to socio-economic factors [15]. Whereas this has previously been shown for some groups of migrants, our data illustrate that this finding cannot be generalized to all migrant groups.

We were not able to adjust for socio-economic status. Data on administrative/legal status for migrant populations in COHERE are not collected. Viral clade and subtype data were not available for this analysis, but the CASCADE Collaboration in EuroCoord has found no clinically relevant differences in either immunological or virological response to cART by HIV-1 subtype [15].

Our results have important implications for clinical management and policy changes regarding earlier HIV testing and cART entitlement; they can help clinicians be alert to particular groups, especially women, who will require extra support with their treatments. Finally, many of the inequalities detected in this study are avoidable through all-inclusive policies which scale up HIV testing and access to cART for all persons living with HIV in Europe.

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Conflicts of interest: The authors have no conflicts of interest to declare.

Appendix: The Migrants Working Group

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