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

The Migrants Working Group on behalf of COHERE in EuroCoord

Running title: Immuno-virological response to cART in migrants.

Keywords: HIV; Combination Antiretroviral Therapy, Immuno-virological Response; Migrants; Sex.

Corresponding author: Inma Jarrin, PhD. National Center for Epidemiology, Institut of Health Carlos III, Avenida Monforte de Lemos, 5. 28029 Madrid, Spain. Telephone: (0034) 918222863. e-mail: ijarrin@isciii.es

ABSTRACT

Objective: To evaluate differences in immune-virological response to combination antiretroviral therapy (cART) in migrant and native men and women within a European collaboration of HIV cohorts (COHERE) in EuroCoord, 2004-2013.

Methods: Migrants were defined as those with geographical origin (GO) different to reporting country (NAT) and grouped as originating from Western Europe and Western Countries (WEWC), Eastern Europe (EE), North Africa & the Middle East (NAME), Sub-Saharan Africa (SSA), Latin America (LA), Caribbean (CRB) and Asia/Oceania (ASIA/OCE). CD4-cell counts were modelled using piecewise linear mixed-effects models with 2 slopes whereas models to estimate sub-distribution hazard ratios (sHR) were used for time to virological response (VR) (ie. time from cART initiation to the first of two successive HIV-RNA<400 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 which remained lower over time. VR was ≥85% at 12 months for all groups except CRB women (77.7%). Compared to NAT men and women, lower VR was experienced by NAME [sHR 0.91 (95% CI 0.86-0.97)] and SSA [0.88 (0.82-0.95)] men and CRB [0.77 (0.67-0.89)] women, respectively.

Conclusions: Immune-virological response to cART in Western Europe varies by GO and sex of patients. ART benefits are not equal for all, underlining that efforts need to prioritize those most in need.

INTRODUCTION

Globally, migrants have higher rates of late HIV presentation than native populations [1-2] but whereas those from high-income settings had similar proportions of late HIV presentation, migrants from middle and low-income settings were 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 heterogeneity in immune-virological response to cART across HIV-positive populations in Europe is essential to improve the continuum of care, maximize 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 infected through routes other than injecting drug use or sexual intercourse. Eligible individuals were antiretroviral-naïve patients recruited from 1st January 1997, 18-74 years old at enrolment who initiated cART from 1st January 2004. Patients had to have both $CD4^+$ T-cell count and HIV-RNA measurements within the last 6 months prior to cART initiation and at least two CD4+ T-cell counts and HIV-RNA measurements while on cART. Individuals with viral load <1,000 copies/mL at of cART initiation were excluded.

Migrants were defined by having GO different to the reporting country and grouped in 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 2 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<400 copies/mL. , We calculated cumulative incidence of VR and used proportional hazards models on the sub-distribution hazard to estimate sub-distribution hazard ratios (sHR) 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 levels 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 software (version 14, 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 counts after cART

Compared to NAT, 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-onwards) rates of CD4+ T-cell increases (-0.01, 95% CI: -0.01; -0.002, p=0.01), rates in women from SSA were significantly slower only over the short term (-0.10, 95% CI: -0.13; -0.06, p<0.001). Compared to NAT, both migrant men and women from LA started cART at lower CD4+ T-cell counts; whilst both men and women from LA exhibited better short-term immunological response than NAT, this was only significant in men (0.05; 95% CI: 0.02; 0.08, p=0.002) but the small number of LA women may preclude statistical significance. Migrant men and women from EE experienced faster long-term CD4+ T-cell increases compared to NAT (0.02, 95% CI: 0.003; 0.03, p=0.02 for men and 0.03, 95% CI: 0.01; 0.05, p=0.001 for women, respectively), although no significant differences were found in the CD4+ T-cell count at which cART was started in men and women from this region (Table 1 Appendix).

Figure 1 in de appendix 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 all GO groups (multivariable graphs). Migrant men and women from SSA and migrant women from LA, CRB and ASIA/OCE remain with a CD4+ T-cell count≤500 cells/μl during almost all the first 60 months 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, respectively. While in men, VR at 12 months was over 90% for all groups except for migrant men from SSA and CRB, in women, it was below 90% for

NAT and most migrant groups, and particularly low in those from CRB (77.7%) (Figure 2 Appendix). 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 geographical origin and sex. Among men, those from Sub-Saharan African had the poorest indicators in terms of CD4 cell count and viral load response. In contrast, male migrants from other Western countries and from Eastern Europe exhibited better immunological response to cART than natives. Virological suppression rates over 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; whilst the rates in most groups were around 90%, Caribbean women had particularly low rates 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 described poorer self-reported adherence in Sub-Saharan African migrants than in people from other origins [4]. Van Beckhoven et al have recently reported that viral load suppression on cART was also poorer in migrants from Sub-Saharan Africa compared to Belgian natives, the former group also having poorer retention in care [6]. Less data are available for HIV-positive migrants from Latin-America but our results are consistent with those reported by Monge et al of Latin-American migrants in Spain [5]. The worrying sub-optimal virological responses to cART observed in Caribbean

women suggest poor engagement to care as well as adherence to cART and is 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 reported that, compared to 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 [2]. This likely 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 [9, 8,14]. Migrants are thought to have poorer adherence secondary to socio-economic reasons [15]. Whereas this has previously been shown for some groups of migrants, our data illustrate that this cannot be generalized for all migrant groups..

We have not been able to adjust for socio-economic status. Data on administrative/legal status for migrants populations in COHERE are not collected. Viral clade and sub-type 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 by all-inclusive policies which scale up HIV testing and access to cART for all persons living with HIV in Europe.

Funding: The COHERE study group has received unrestricted funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found at www.COHERE.org.

Conflict of interest: None.

Acknowledgments

The Migrants Working Group

I Jarrin (CIBERESP, Spain; and National Centre of Epidemiology, Madrid, Spain), S Monge (CIBERESP, Spain; and University of Alcala, Alcala de Henares, Spain), A Mocroft (Research Department of Infection and Population Health, University College London, UK), C A Sabin (Research Department of Infection and Population Health, University College London, UK), G Touloumi (Athens University Medical School, Athens, Greece), A van Sighem (Stichting HIV Monitoring, Amsterdam, Netherlands), S Abgrall (AP-HP, Hopital

Antoine Beclere, Service de Medecine Interne, Clamart, Paris, France; and INSERM, Sorbonne Universites, UPMC Univ Paris 06, UMR_S 1136, Pierre Louis Institute of Epidemiology and Public Health, Department of Social Epidemiology, Paris, France), R Dray-Spira (INSERM, Sorbonne Universites, UPMC Univ Paris 06, UMR_S 1136, Pierre Louis

Institute of Epidemiology and Public Health, Department of Social Epidemiology, Paris, France), B Spire (INSERM, U912-SESSTIM; Aix-Marseille Universite, IRD, UMR-S912 ORS PACA; and Observatoire Regional de la Sante Provence Alpes Cote d'Azur, Marseille, France), A Castagna (Vita-Salute University, San Raff aele Scientifi c Institute, Italy), C Mussini (Division of Infectious Diseases, University Policlinic of Modena, Modena), R Zangerle (Department of Dermatology and Venereology, Medical University Innsbruck, Innsbruck, Austria), M Hessamfar (INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique & CIC1401-Epidemiologie Clinique, Bordeaux, France; Universite Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000, Bordeaux, France; and CHU Bordeaux, Service de Medecine Interne et Maladies Infectieuses, Bordeaux, France), J Anderson (Centre for the Study of Sexual Health and HIV, Homerton University Hospital NHS Foundation Trust, London, UK), O Hamouda (Robert Koch Institute, Department for Infectious Disease Epidemiology, Berlin, Germany), K Ehren (First Department of Internal Medicine, University Hospital of Cologne, Germany), N Obel (Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark), O Kirk (Copenhagen HIV programme, University of Copenhagen, Copenhagen, Denmark), L A de Monteynard (INSERM, Sorbonne Universites, UPMC Univ Paris 06, UMR_S 1136, Pierre Louis Institute of Epidemiology and Public Health, IPLESP UMRS 1136, F75013, Paris, France) A Antinori (National Institute for Infectious Diseases L. Spallanzani, Rome, Italy), E Girardi (National Institute for Infectious Diseases L. Spallanzani, Rome, Italy) A Saracino (Clinic of Infectious Diseases, University of Bari, Italy), A Calmy (Service de Infectious Diseases, HIV Unit, Geneva University Hospitals, Geneva, Switzerland), S De Wit (The Brussels Saint Pierre Cohort, University Hospital Saint Pierre, Universite Libre de Bruxelles, Brussels, Belgium), L Wittkop (INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique & CIC1401-Epidemiologie Clinique, F-33000, Bordeaux, France; Universite Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France; and CHU de Bordeaux, Pole de sante publique,

Service d'information medicale, F-33000 Bordeaux, France), H C Bucher (Basel Institute for Clinical Epidemiology & Biostatistics, University Hospital Basel, Basel, Switzerland), A Montoliu (CIBERESP, Spain; Centre for Epidemiological Studies on HIV/STI in Catalonia [CEEISCAT], Agencia de Salut Publica de Catalunya, Generalitat de Catalunya, Badalona, Spain; and Health Sciences Research Institute of the "Germans Trias i Pujol" Foundation, Badalona, Spain), D Raben (CHIP, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark), M Prins (Public Health Service of Amsterdam and Academic Medical Centre, Amsterdam, Netherlands), L Meyer (Institut National de la Sante et de la Recherche Medicale U1018, Universite Paris-Sud, le Kremlin-Bicetre, France), G Chene (INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique & CIC1401-Epidemiologie Clinique, F-33000, Bordeaux, France; Universite Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France; and CHU de Bordeaux, Pole de sante publique, Service d'information medicale, F-33000 Bordeaux, France), F Burns (Research Department of Infection and Population Health, University College London; and Royal Free London NHS Foundation Trust, London, UK), J Del Amo (CIBERESP, Spain; and National Centre of Epidemiology, Madrid, Spain).

Steering Committee - Contributing Cohorts: Ali Judd (AALPHI), Robert Zangerle (AHIVCOS),Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz

Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Roger Kouyos (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Deborah_Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti (The Italian Master Cohort), Caroline Sabin (UK CHIC), Ramon Teira (VACH), Myriam Garrido (VACH). David Haerry (European AIDS Treatment Group)

Executive Committee: Stéphane de Wit (Chair, St. Pierre University Hospital), Jose Mª Miró (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre). Paediatric Cohort Representatives: Ali Judd, Pablo Rojo Conejo.

Regional Coordinating Centres: Bordeaux RCC: Diana Barger, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Casper M. Frederiksen, Nina Friis-Møller, Jesper Kjaer, Dorthe Raben, Rikke Salbøl Brandt.

Project Leads and Statisticians: Juan Berenguer, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose Mª Miró, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Eliane Rohner, Michael Schomaker, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Marc van der Valk, Linda Wittkop.

References

1. The Gap Report, UNAIDS. Available at http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf. Accessed 10 December 2015.
2. Hernando V, Alvarez-Del Arco D, Alejos B, *et al*. HIV Infection in Migrant Populations in the European Union and European Economic Area in 2007-2012: An Epidemic on the Move. *J Acquir Immune Defic Syndr* 2015; **70**: 204-211.
3. Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Timing of cART initiation in male and female migrants living with HIV in Western Europe: an observational cohort study (1997 – 2013). AIDS 2017; doi: 10.197/QAD.0000000000001411. [Epub ahead of print]
4. Staehelin C, Rickenbach M, Low N, *et al*; Swiss HIV Cohort Study. Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: access to antiretroviral therapy, disease progression and survival. *AIDS* 2003; **17**: 2237-2244.
5. Monge S, Alejos B, Dronda F, *et al*; CoRIS. Inequalities in HIV disease management and progression in migrants from Latin America and sub-Saharan Africa living in Spain. *HIV Med* 2013; **14**: 273-283.
6. Van Beckhoven D, Florence E, Ruelle J, *et al*; BREACH (Belgian Research on AIDS and HIV Consortium). Good continuum of HIV care in Belgium despite weaknesses in retention and linkage to care among migrants. *BMC Infect Dis* 2015; **15**: 496.
7. Monge S, Jarrin I, Mocroft A, *et al*; Migrants Working Group on behalf of COHERE in EuroCoord. Mortality in migrants living with HIV in Western Europe (1997-2013): a collaborative cohort study. *Lancet HIV* 2015; **2**: e540-e549.

8. Deblonde J, Sasse A, Del Amo J, *et al*. Restricted access to antiretroviral treatment for undocumented migrants: a bottle neck to control the HIV epidemic in the EU/EEA. *BMC Public Health* 2015; **15**: 1228.
9. Alvarez-del Arco D, Monge S, Azcoaga A, *et al*. HIV testing and counselling for migrant populations living in high-income countries: a systematic review. *Eur J Public Health* 2013; **23**: 1039-1045.
10. European Centre for Disease Control and Prevention. HIV testing: increasing uptake and effectiveness in the European Union. Available at http://ecdc.europa.eu/en/publications/Publications/101129_GUI_HIV_testing.pdf. Accessed 10 December 2015.
11. European AIDS Clinical Society. Guidelines Version 8.0, October 2015. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8.0-english_rev-20151221.pdf. Accessed 10 December 2015.
12. INSIGHT Strategic Timing of AntiRetroviral Treatment (START) Study Group, Lundgren J, Babiker A, Gordin F, *et al*. Why START? Reflections that lead to the conduct of this large long-term strategic HIV trial. *HIV Med* 2015; **1**: 1-9.
13. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, *et al*. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808-822.
14. European Centre for Disease Control and Prevention. Thematic report: Migrants. Monitoring implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2012 progress. Available at: http://ecdc.europa.eu/en/publications/Publications/dublin-declaration-monitoring-report-migrants-september-2013.pdf. Accessed 10 December 2015.
15. Touloumi G, Pantazis N, Chaix ML, *et al*; for CASCADE Collaboration in EuroCoord. Virologic and immunologic response to cART by HIV-1 subtype in the CASCADE collaboration. *PLoS One* 2013; **8**: e71174.

Table 1. Socio-demographic and clinical characteristics at start of cART according to geographical origin, in men and in women in COHERE

Men: n=25,799 (78.6%)

	NAT	WEWC	EE	NAME	SSA	LA	CRB	ASIA/OCE
	20,340 (78.8)	**751 (2.9)**	**342 (1.3)**	**482 (1.9)**	**1,632 (6.3)**	**1,586 (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								
Sex between men	14,623 (71.9)	549 (73.1)	210 (61.4)	195 (40.5)	180 (11.0)	1,252 (78.9)	129 (44.5)	263 (69.9)
Sex between men and women	4,260 (20.9)	142 (18.9)	60 (17.5)	231 (47.9)	1,427 (87.4)	316 (19.9)	156 (53.8)	89 (23.7)
Injecting drug use	1,457 (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/ul)								
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)
<200	5,895 (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	8,798 (43.2)	313 (41.7)	160 (46.8)	189 (39.2)	654 (40.1)	689 (43.4)	124 (42.8)	160 (42.5)
>350	5,647 (27.8)	183 (24.4)	88 (25.7)	107 (22.2)	280 (17.2)	342 (21.6)	36 (12.4)	86 (22.9)
Log10 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)
<4	2,147 (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	9,271 (45.6)	364 (48.5)	170 (49.7)	222 (46.1)	731 (44.8)	797 (50.2)	137 (47.2)	203 (54.0)
>5	8,922 (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								
No	15,552 (76.5)	516 (68.7)	250 (73.1)	336 (69.7)	1,243 (76.2)	1,295 (81.6)	229 (79.0)	280 (74.5)
Yes	2,620 (12.9)	104 (13.8)	33 (9.6)	77 (16.0)	366 (22.4)	243 (15.3)	57 (19.7)	57 (15.2)
Unknown	2,168 (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								
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								
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	6,315 (31.0)	195 (26.0)	108 (31.6)	152 (31.5)	567 (34.7)	335 (21.1)	73 (25.2)	100 (26.6)
Other	3,397 (16.7)	125 (16.6)	53 (15.5)	84 (17.4)	199 (12.2)	275 (17.3)	34 (11.7)	39 (10.4)

Women: n=7,018 (21.4%)

	NAT	WEWC	EE	NAME	SSA	LA	CRB	ASIA/OCE
	3,586 (51.1)	**141 (2.0)**	**193 (2.7)**	**149 (2.1)**	**2,172 (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								
Sex between men and women	3,124 (87.1)	116 (82.3)	169 (87.6)	147 (98.7)	2,164 (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 (cell/ul)								
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)
<200	1,225 (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	1,567 (43.7)	53 (37.6)	73 (37.8)	48 (32.2)	953 (43.9)	133 (36.0)	92 (40.7)	62 (34.2)
>350	794 (22.1)	35 (24.8)	44 (22.8)	33 (22.1)	410 (18.9)	67 (18.1)	45 (19.9)	29 (16.0)
Log10 HIV-RNA (copies/ml)								
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)
<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	1,656 (46.2)	66 (46.8)	93 (48.2)	67 (45.0)	1,060 (48.8)	179 (48.4)	112 (49.6)	90 (49.7)
>5	1,219 (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								
No	2,729 (76.1)	99 (70.2)	117 (60.6)	110 (73.8)	1,822 (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								
2004-2008	2,185 (60.9)	75 (53.2)	86 (44.6)	89 (59.7)	1,401 (64.5)	230 (62.2)	190 (84.1)	103 (56.9)
2009-2013	1,401 (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								
NNRTI-based	1,564 (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	1,355 (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)

Table 2. Time to virological response from cART initiation according to geographical origin, in men and in women

	Men				Women			
	Univariable analysis		Multivariable analysis[1]		Univariable analysis		Multivariable analysis[1]	
	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

[1] Adjusted by transmission category (sex between men, IDU, sex between men and women), age at cART initiation, log10 HIV-RNA and CD4+ T cell count (<200, 200-350, >350) at cART, pre-cART AIDS diagnosis, period of cART initiation (2004-2008, 2009-2013) and type of cART regimen (NNRTI, PI, other)