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Cohort profile

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Cohort Profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

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Why was COHERE set up?

Widespread access to effective combination antiretroviral therapy (cART), beginning in 1996, dramatically reduced the number of AIDS-related events and deaths in people living with HIV (PLWH) in high-income settings.[1] The study of prognosis and specific clinical outcomes therefore requires larger populations. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) was founded in 2005 to continue to advance epidemiological research on the prognosis of PLWH in Europe. COHERE has expanded and strengthened collaborative efforts in Europe and facilitated those with other

Box 1: COHERE's Principles

- COHERE should neither threaten nor compete with the scientific agendas of participating cohorts/cohort collaborations.
- The individual contributing cohorts must express their interest in participating in COHERE.
- The scientific questions addressed by COHERE are determined by consensus according to both their scientific relevance and originality (not being addressed elsewhere).
- Individual cohorts may veto the use of their data in any new project.

regions by ensuring that longitudinal data, the product of early investments in clinic-based databases and observational studies, were compiled and harmonized. In 2011, COHERE joined three other European HIV collaborations, PENTA, EuroSIDA and CASCADE, to form 'EuroCoord', a network of excellence funded by the European Commission Seventh Framework Programme.[2] COHERE also collaborates with the ART Cohort Collaboration (ART-CC) and the International Epidemiologic Databases to Evaluate AIDS (IeDEA) global network.[3,4]

How does COHERE operate?

COHERE operates according to the principles set out in Box 1. Projects in COHERE provide added value by only addressing scientific questions that cannot be answered by participating cohorts.

Two regional coordinating centres (RCCs), based at the University of Bordeaux's Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED) in Bordeaux, France, and the Center for Health and Infectious Diseases Research (CHIP), Department of Infectious Diseases and Rheumatology, Rigshospitalet, in Copenhagen, Denmark, maintain COHERE's infrastructure. The COHERE steering committee (SC)–composed of representatives from the participating cohorts–oversees the COHERE Collaboration, ensuring compliance with its principles; it also elects the chair and the regional representatives to the COHERE executive committee (EC). The EC–composed of three representatives from each of the two regions, and the two RCC Heads)–acts as the functional link between the RCCs and the SC.

COHERE projects are organized by 'themes' (Prognosis and the effect of antiretroviral therapy (ART), Hepatitis, Opportunistic Infections, Malignancies, Late Presentation, and Socioeconomic Inequalities) to encourage collaboration and streamline the project proposal process. Theme leads stimulate scientific enquiry within their theme and develop projects. A detailed account of how COHERE operates is described in the Manual of Operations [www.cohere.org].

Who participates in COHERE?

COHERE has grown from 33 cohorts in 2005 to 40 in 2015. COHERE initially approached cohorts because of their proven ability to address scientific questions and collect good quality data at clinical sites. As COHERE is a project-based collaboration, the data pooled in annual mergers depend on the projects included. Western European countries with longstanding national cohorts contribute a large proportion of person-years of follow-up, but there is an increasing number of individuals in care in Eastern Europe, primarily via the EuroSIDA network.[5] Figure 1 presents the number of people living with HIV (excluding deaths) included in COHERE as of 31 December 2011 as a percentage of UNAIDS 2011 estimates of people living with HIV by country.

COHERE includes: clinic- hospital-based cohorts of HIV-infected individuals, where data are extracted primarily from medical records in the context of routine care; and interval cohorts of specific populations of HIV-infected people, where data are collected at regular intervals that are unrelated to participants' ongoing health care. Since people with HIV are seen regularly over a long period of time at a clinic/hospital, and are not just attending at times when they are symptomatic, the group of people seen at a given hospital naturally forms a cohort. Table 1a and b presents a complete list of the cohorts, their characteristics and funding sources. All COHERE cohorts follow local ethical standards.

The 2014 merger included data from 331 481 individuals, including 2808 children (aged less than 13 years), representing 2 135 896 person-years of follow-up. Table 2a highlights the demographic characteristics and prognostic markers of HIV in those aged 13 and older, enrolled in adult cohorts. Approximately a quarter of the COHERE sample is female (27%). The median age at inclusion is 35 years [interquartile range (IQR): 30, 43]. The primary mode of HIV transmission is sexual contact [homosexual/bisexual contact (38.7%), heterosexual contact (37%)], followed by injection drug use (IDU) (13.5%)]. Overall, 71.6% of the sample has never had a clinical AIDS diagnosis before, nor during enrolment. The median CD4 cell

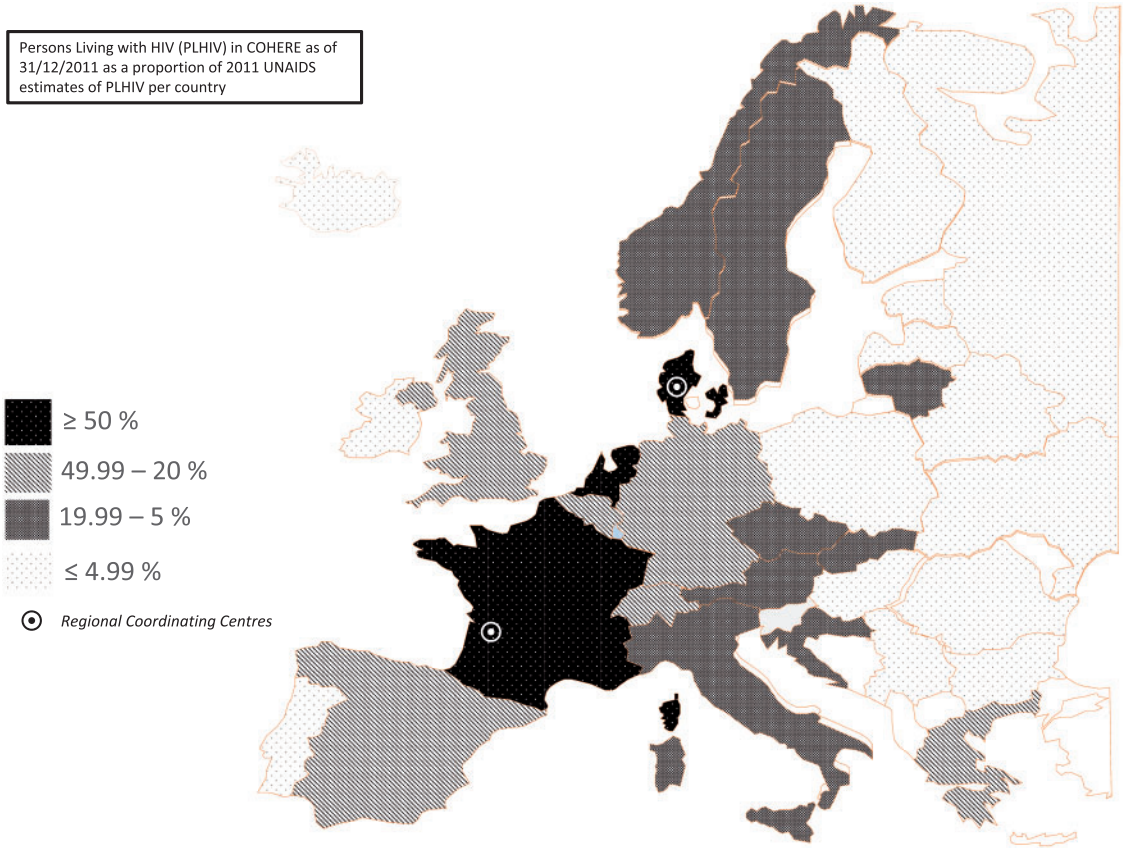

Figure 1. Persons Living with HIV (PLHIV) in COHERE as of 31/12/2011 as a proportion of 2011 UNAIDS estimates of PLHIV per country.

count at enrolment, defined as the period 6 months preceding and 1 month following the enrolment date, was 340 cells/mm^3 (IQR: 170, 530) in adults (Table 2a). Of those with available CD4 cell counts at enrolment, 29% had < 200 cells/mm^3, 22% had between 200 and 350 cells/mm^3 and 49% had > 350 cells/mm^3. Of those younger than age 13 ($N = 2808$, representing 23 458 persons), 93.7% were infected via vertical transmission and 73.4% had never had an AIDS diagnosis (Table 2b).

How often have they been followed up?

As a consortium of cohorts comprising clinic and interval cohorts, patient follow-up varies. For clinic or hospital-based cohorts, average patient follow-up reflects current standards of care in those countries. A derived measure of lost to follow-up (LTFU) was constructed by estimating the median last clinical encounter (defined as either the latest visit and/or the date of latest laboratory test) per active cohort. Those individuals who had not had a clinical encounter in the 18 months preceding this date were considered to be LTFU. Those who died during the same period were excluded. On average, 25% of the COHERE 2014 sample met this definition of LTFU, with variation between cohorts. LTFU in paediatric cohorts was estimated among those under age 17, as many cohorts discontinue follow-up at age 18. LTFU among paediatric patients youger than 17 ($N = 1960$) was 20% overall and ranged from 1.8% to 22% across cohorts.

What data are collected and how?

COHERE has benefited from dynamic data management processes, which have evolved to accommodate new projects and scientific questions. COHERE's data managers (DMs) work with project leads and statisticians to conduct preliminary surveys, feasibility studies and, occasionally, to collect additional data. COHERE collects data on basic clinical information including: date of first HIV-positive test, estimated date of seroconversion, cART and other medications, opportunistic infections and laboratory results (CD4, CD8, plasma viral load values, hepatitis B and C serological tests and HIV drug resistance tests), as well as socio-demographic data (see www.hicdep.org for more information about the definition of different variables). COHERE, via EuroCoord, conducts an inventory of data items and biological samples collected by participating cohorts. The submission of data to COHERE is facilitated by

Table 1a. Description of the cohort type, eligibility criteria, period of 'enrolment', and location of data collection of the adult or mixed (adult/paediatric) cohorts participating in COHERE (circa 2015)

Cohort	Cohort Type	Eligibility criteria	Beginning of Enrollment	End of Enrollment	Data Collection	N Sites/ Countries	Location of sites
AHIVCOS	Hospital-based, Surveillance System	All HIV + persons in care at 6/7 national centres	1/1/1996		Prospectively	6	Austria (National)
AMACS	Clinic-based, Hospital-based	All HIV-1 + persons in at affiliated sites for at least 1 year, alive on 1/1/1996	1/1/1996		Both prospectively and retrospectively	13	Greece (Regions : Attiki, Patras, Alexandroupolis)
ANRS CO2 SEROCO	Interval cohort	HIV diagnosis < 1 year before enrollment or a known date of infection identified by incomplete evokative Western-blot or an interval of less than 2 years between a negative and a positive ELISA	1/1/1988	12/31/2009	Prospectively	25	France (Paris area, Marseille, Nice)
ANRS CO3 AQUITAINE	Hospital-based	HIV-1 + > = age 13, seen at least once at a site & signed informed consent	1/1/1987		Prospectively	13	France (Region : Aquitaine)
ANRS CO4 FHDH	Hospital-based	HIV-1 or HIV-2 + individuals who have provided written informed consent	1/1/1989	12/31/2065	Prospectively	70	France (National, except Aquitaine)
ANRS CO6 PRIMO	Interval cohort	HIV 1 + patients presenting during primary infection in sites	1/1/1996		Prospectively	80	France (National)
ANRS CO8 APROCO-COPILOTE	Hospital-based	HIV-infected patients > = 18 years old, naive for protease inhibitors	1/4/1997	6/6/1999	Prospectively	49	France (National)
ANRS CO13 HEPAVIH	Hospital-based	Phase I : [12/2005, 12/2008]: HIV-1/HCV chronically infected > = age 18, Phase II : [9/2011, 3/2016]: HIV-1/HCV chronically infected > = age 18, beginning anti-HCV treatment comprising					

(Continued)

Table 1a. Continued

Cohort	Cohort Type	Eligibility criteria	Beginning of Enrollment	End of Enrollment	Data Collection	N Sites/ Countries	Location of sites
		'Telaprevir' or 'Boceprevir', or having cleared HCV spontaneously in the absence of anti-HCV treatment.					
		Phase III : [Q1/2014, Q1/2016] : Individuals who have received, are receiving, or will receive within the next 6 months combination therapy with new anti-HCV drugs, with or without peginterferon and/or ribavirin (temporary authorization, full marketing authorization, or within clinical trials) & individuals previously included in ANRS clinical trials evaluating new anti-HCV drugs	11/10/2005		Prospectively generally, and Prospective & Retrospective for Phase III	27	France (National)
ATHENA	Clinic-based	Any HIV + person entering care in one of the 27 adult (28 including Curacao) or 4 pediatric HIV treatment centers in 'the Netherlands' and who does not object to standardized collection of data obtained as part of routine care	1/1/1998		Both prospectively and retrospectively	31	'The Netherlands', Curacao (National)
Bonn-Cologne Cohort	Clinic-based, Hospital-based	HIV+	1/5/1988		Both prospectively and retrospectively	2	Germany (Bonn, Cologne)
CASCADE	Clinic-based, Hospital-based	HIV + with well estimated dates of HIV seroconversion	1/1/1979		Both prospectively and retrospectively	–	11 countries*

(Continued)

Table 1a. Continued

Cohort	Cohort Type	Eligibility criteria	Beginning of Enrollment	End of Enrollment	Data Collection	N Sites/ Countries	Location of sites
Clinserv	Clinic-based, Hospital-based	All patients HIV + presenting at the clinical sites after 0/0/ 1999	1/1/1999		Both prospectively and retrospectively	18	Germany
CoRIS	Clinic-based	Confirmed HIV +, cART-naive, attending partici-pating sitesl aged > 16 & signed informed consent	1/1/2004		Prospectively	37	Spain (Multi-region)
CoRIS-MD	Clinic-based	HIV+	1/1/1997	12/31/2003	Retrospectively	10	Spain (Multi-region)
DHK	Hospital-based	HIV+ & in care in HIV treatment centres	1/1/1995		Prospectively	8	Denmark (National)
ECS	Clinic-based, Hospital-based	Pregnant HIV+ women, diagnosed before or dur-ing pregnancy or as a re-sult of HIV testing intrapartum, delivering liveborn infant.	7/15/1985		Prospectively	10 countries	10 countries^
EuroSIDA	Clinic-based, Hospital-based, Interval cohort	Aged > 16 & prebooked hospital appointment	1/6/1994		Both prospectively and retrospectively	109 sites, 34 countries	34 countries^^
Frankfurt	Clinic-based	HIV + > age 16 in care at affiliated sites	1/1/1987		Prospectively	5	Germany (Frankfurt)
Gemes Haemo	Clinic-based, Surveillance System	HIV + haemophilics in-fected in early 1980s	5/26/1999	4/26/1999	Both prospectively and retrospectively	2	Spain (Madrid, Barcelona)
Georgian National HIV Cohort	Clinic-based, Hospital-based, Surveillance System	HIV + adults	1/1/2007		Both prospectively and retrospectively	1	Georgia
ICC (INMI Clinical Cohort)	Clinic-based, Hospital-based	HIV+ individuals in care at site	1/1/1995		Prospectively	1	Italy (Rome)
ICONA	Hospital-based	HIV+, ART-naive, > = age 18 & signed informed consent	1/1/1997		Prospectively	42	Italy
Infectious Disease Database (IDD) San Raffaele	Hospital-based	All HIV + patients in care at site	1/1/1991		Prospectively	1	Italy (Milan)
	Clinic-based		1/1/1997			8	Italy (multi-city)

(Continued)

Table 1a. Continued

Cohort	Cohort Type	Eligibility criteria	Beginning of Enrollment	End of Enrollment	Data Collection	N Sites/ Countries	Location of sites
Italian MASTER Cohort		HIV-1 or HIV-2+ (antibody test or positive HIV RNA) in care in participating sites			Both prospectively and retrospectively		
Modena	Clinic-based	All new HIV diagnosis in adult patients (>= 18 year) since 1985, inhabitant in Province of Modena and reffered to Regional Surveillance System. Data were retrospectively collected from 1992.	1/1/1992	12/31/2014	Retrospectively	1	Italy (Modena)
PISCIS	Clinic-based, Hospital-based	HIV+ > = age 16 in care at one of the sites after January 1st 1998, irrespective of the stage of disease or degree of immunosuppression.	1/1/1998		Both prospectively and retrospectively	11	Spain (Region : Catalonia)
SHCS	Clinic-based, Hospital-based	Any HIV+ persons > = age 18	1/1/1988		Prospectively	7	Switzerland (National)
St Pierre	Clinic-based, Hospital-based	HIV+ & at least one visit at affiliated sites	1/25/1980		Prospectively	1	Belgium (Brussels)
Swedish InfCare HIV cohort	Clinic-based, Hospital-based, Surveillance System	All HIV + persons in care in Sweden, opt out system	1/1/1983		Both prospectively and retrospectively	29	Sweden (National)
UK Collaborative HIV Cohort Study (UK CHIC)	Clinic-based	HIV + persons > age 16 & < = 1 visit at affilitated site after 1/1/1995	1/1/2001		Both prospectively and retrospectively	19	United Kingdom (National)
VACH	Hospital-based	HIV + persons > age 16 & 1st visit at affiliated site	1/1/1997		Prospectively	23	Spain

* Austria, France, Germany, Greece, Italy, Netherlands, Norway, Spain (Badalona, Barcelona, Madrid Valencia), Sweden, Switzerland, United Kingdom

^ Belgium, Denmark, Germany, Netherlands, Poland, Italy, Spain, Sweden, Ukraine, United Kingdom

^^ Argentina, Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Georgia, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg,Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom)

Table 1b. Description of the cohort type, eligibility criteria, period of 'enrolment', and location of data collection of 'paediatric' or adolescent cohorts participating in COHERE (circa 2015)

Name of Cohort	Cohort Type	Eligibility Criteria	Enrolment period	Data Collection	N Sites/ Countries	Location of sites
AALPHI	Clinic & community-based, Interval cohort	HIV + age 13–21 and in 'paediatric' care in UK, HIV-uninfected age 13–23, sibling of HIV-infected or has HIV + parent	06/01/2012–12/31/2014	Prospectively	–	United Kingdom (Region : England)
ANRS CO10 EPF	Interval cohort	HIV + children included at birth (born to HIV-pregnant women enrolled in the CO1-EPF cohort), or, since 2005, at time of first HIV care management in the clinical participating sites	09/07/1985 -	Prospectively	24	France
CHIPS	Clinic-based, Hospital-based, Surveillance System	All HIV + children living in the UK/Ireland	04/01/2000-	Prospectively	–	United Kingdom (National), Ireland (National)
CoRISPE-cat	Hospital-based	HIV + < 18 years at diagnosis	01/01/2008 -	Both prospectively and retrospectively	13	Spain (regions : Catalonia, Balearic Islands)
CoRISpeS-Madrid	Hospital-based	HIV +, infected before age 18	01/01/2002 -	Both prospectively and retrospectively	59	Spain (national)
KOMPNET Children Cohort	Clinic-based	HIV +, < 18 age	06/01/2005 -	Both prospectively and retrospectively	7	Germany (National)
Madrid PMTCT Cohort	Hospital-based	HIV-1 + women during pregnnacy and their HIV-exposed infants	1/2/0200	Prospectively	7	Spain (Madrid)
NENEXP	Hospital-based	HIV + pregnant women & HIV-exposed children, HAART-exposed children until 18 month-old age.	01/01/2000 -	Prospectively	12	Spain (region: Catalonia)

(Continued)

Table 1b. Continued

Name of Cohort	Cohort Type	Eligibility Criteria	Enrolment period	Data Collection	N Sites/ Countries	Location of sites
NSHPC	Surveillance System	All pregnancies in HIV+ women living in the UK or Ireland, their exposed infants, and all children with HIV infection	01/01/1990 -	Prospectively	230	United Kingdom & Ireland (National)
St Pierre 'Paediatric'	Hospital-based	All HIV + children/adolescents in care at site	01/01/2000 -	Both prospectively and retrospectively	1	Beligum (Brussels)

the use of the HIV Cohorts Data Exchange Protocol (HICDEP), a flexible data structure developed in 2004, to guide the mapping of individual cohort data into a standard format to facilitate data merging.[6]

For approved projects, COHERE DMs organize data collection by developing a standardized operating procedure (SOP) for individual cohort DMs. Data are submitted in two stages via the HIV-Distributed Data Management (HIV-DDM) Tool.[7] This implies that data submissions must therefore pass all format and edit checks, defined in HICDEP, before the submission can be completed. Additional inconsistencies are identified centrally. Cohorts are given an 8-week window to address said data inconsistencies before completing the second and final submission. Once data are merged, likely duplicate patient records between and within cohorts are identified using probability linkage. Data items used are gender, year of birth, treatment history, viral load measurements and CD4 cell counts. Duplicate records are reconciled based on previous agreements between participating cohorts. DMs identified and resolved 20 953 duplicate records in 2014. Cohorts resolve issues identified over time, ultimately improving data quality with each merger. To ensure transparency, the content of each merger together with cohort's QA check feedback is summarized in a report. DMs extract data for projects based on specified and agreed eligibility criteria. After signing a data protection agreement, project leads are sent data extractions in a secure format.

What has been found?

Projects within the COHERE collaboration have led to the publication of 28 articles in peer-reviewed journals as of April 2016, contributing high-quality evidence that has informed clinical and public health decision-making.

Prognosis and the effect of ART

The 'Prognosis and the effect of ART' group focuses on clinical outcomes in patients treated with cART. The effect of age on the response to cART was studied in around 50 000 antiretroviral-naive individuals. Older individuals were characterized by low pre-ART CD4 cell counts, and experienced poorer immunological responses but better virological responses, indicating those who are diagnosed or treated late are at increased risk of clinical events.[8]

Non-IDU HIV-infected individuals who achieved high CD4 cell counts after starting cART were found to have mortality patterns similar to those in the general population. Mortality was found to be persistently higher in individuals with a previous AIDS diagnosis,[9] whereas the incidence of AIDS events continued to decline until CD4

Table 2a. Number of individuals, person-years of follow-up, patient demographics, prior AIDS status, mode of infection, median CD4 cell count and logarithm viral load in individuals older than 13 years old, (COHERE, 2014 merger)

Cohort	'N'	Person-years	Female ['N' (%)]	Median Age (IQR)	No AIDS ['N', (%)] prior to/during follow-up	Mode of infection ['N' (%)]								HIV RNA (log10 cp/ml) assessment at 'enrolment'*, 'N' (%)		Median HIV RNA (log10 cp/ml) at 'enrolment'* (IQR)	CD4 cell count assessment at 'enrolment'*, 'N' (%)		Median CD4 cell count at 'enrolment'* (IQR)
						MSM**	Hetrosexual contact	IDU	Blood Products	Perinatal infected	Unknown								
AHIVCOS	4676	30505	1247 (27)	34(28; 42)	3232 (69.1)	1727 (36.9)	1673 (35.8)	1008 (21.6)	88 (1.9)	5 (0.1)	175 (3.7)			3296 (70.5)		4.7 (3.8; 5.3)	3865 (82.7)		354(175; 552)
AMACS	5359	35101	870 (16)	34(27; 42)	4377 (81.7)	2707 (50.5)	1399 (26.1)	351 (6.5)	101 (1.9)	9 (0.2)	792 (14.8)			3821 (71.3)		4.5 (3.7; 5.1)	4244 (79.2)		348(169; 548)
ANRS CO2 SEROCO	1543	15766	452 (29)	30(26; 36)	824 (53.4)	711 (46.1)	494 (32.0)	143 (9.3)	92 (6.0)		103 (6.7)			911 (59.0)		4.1 (3.6; 4.7)	1526 (98.9)		480(326; 669)
ANRS CO3 AQUITAINE	8457	63667	2202 (26)	35(29; 43)	5354 (63.3)	3268 (38.6)	2398 (28.4)	1969 (23.3)	390 (4.6)	29 (0.3)	403 (4.8)			2640 (31.2)		4.3 (3.0; 5.0)	6205 (73.4)		330(155; 516)
ANRS CO4 FHDH	87925	637178	28899 (33)	35(30; 43)	65261 (74.2)	28609 (32.5)	41088 (46.7)	9090 (10.3)	1560 (1.8)	298 (0.3)	7280 (8.3)			52143 (59.3)		4.4 (3.5; 5.1)	75154 (85.5)		337(175; 520)
ANRS CO6 PRIMO	1563	7997	219 (14)	35(29; 43)	1522 (97.4)	1101 (70.4)	366 (23.4)	4 (0.3)	1 (0.1)		91 (5.8)			1558 (99.8)		5.2 (4.5; 5.8)	1558 (99.7)		514(370; 666)
ANRS CO8 COPILOTE	1184	8761	280 (24)	36(32; 43)	873 (73.3)	464 (39.2)	405 (34.2)	194 (16.4)	30 (2.5)		91 (7.7)			1176 (99.3)		4.5 (3.7; 5.2)	1173 (99.1)		273(126; 424)
ANRS CO13 HEPAVIH	1146	4431	325 (28)	46(42; 49)	805 (70.2)	155 (13.5)	184 (16.1)	688 (60.0)	71 (6.2)	1 (0.1)	47 (4.1)			1076 (93.9)		1.6 (1.6; 1.9)	1071 (93.5)		450(312; 647)
ATHENA	21177	136563	4190 (20)	39(32; 46)	15667 (74.0)	12323 (58.2)	6434 (30.4)	749 (3.5)	233 (1.1)	32 (0.2)	1406 (6.6)			19806 (93.5)		4.4 (2.6; 4.9)	19736 (93.2)		360(190; 550)
Bonn***	1978	13125	377 (19)	36(30; 44)	1512 (76.4)	937 (47.4)	502 (25.4)	200 (10.1)	189 (9.6)	5 (0.3)	145 (7.3)			1270 (64.2)		4.1 (2.6; 4.9)	1653 (83.6)		365(191; 563)
Cologne***	1742	1951	221 (13)	37(30; 45)	926 (53.2)	1010 (58.0)	230 (13.2)	142 (8.2)	37 (2.1)		323 (18.5)			573 (32.9)		4.3 (3.1; 5.0)	946 (54.3)		250(50; 490)
CASCADE	9037	66196	1387 (15)	31(26; 38)	7288 (80.6)	5565 (61.6)	1467 (16.2)	1735 (19.2)			270 (3.0)			2655 (29.4)		4.9 (4.2; 5.6)	4223 (46.7)		514(368; 711)
ClinSurv	17599	98130	3467 (20)	38(32; 46)		9055 (51.5)	2581 (14.7)	1622 (9.2)	125 (0.7)	38 (0.2)	4178 (23.7)			13904 (79.0)		4.6 (3.8; 5.2)	14201 (80.7)		330(160; 520)
CoRIS***	6466	19589	1070 (17)	35(29; 43)	5432 (84.0)	3728 (57.7)	1893 (29.3)	621 (9.6)			224 (3.5)			5504 (85.1)		4.7 (4.0; 5.2)	5553 (85.9)		375(194; 538)
CoRIS-MD***	3493	14953	990 (28)	35(31; 39)	2334 (66.8)	492 (14.1)	755 (21.6)	1975 (56.5)	94 (2.7)		177 (5.1)			854 (24.4)		4.5 (3.0; 5.2)	1448 (41.5)		310(140; 527)
DHK	6367	49416	1573 (25)	38(31; 46)	4776 (75.0)	2894 (45.5)	2409 (37.8)	586 (9.2)	84 (1.3)	8 (0.1)	386 (6.1)			3704 (58.2)		4.6 (3.7; 5.1)	4772 (74.9)		300(120; 500)
ECS	5295	5453	5295 (100)	27(24; 31)	5074 (95.8)		4736 (89.4)	320 (6.0)	16 (0.3)		223 (4.2)			895 (16.9)		3.9 (2.8; 4.6)	1528 (28.9)		439(301; 604)
EuroSIDA	13384	85203	3854 (29)	36(30; 43)	8168 (61.0)	4645 (34.7)	4218 (31.5)	3665 (27.4)	169 (1.3)		687 (5.1)			7782 (58.1)		4.0 (2.8; 4.8)	12477 (93.2)		316(165; 486)
GEMES Haemo	94	2210	5 (5)	21(17; 24)	72 (76.6)				94 (100.0)					–		–	3 (3.2)		130(111; 748)
Infectious Disease Database (IDD) San Raffaele	2870	21618	485 (17)	36(31; 43)	2397 (83.5)	1257 (43.8)	620 (21.6)	274 (9.5)	8 (0.3)	4 (0.1)	707 (24.6)			2817 (98.15)		4.3 (3.3; 5.0)	2698 (94.0)		420(228; 620)
ICC (INMI Clinical Cohort)	2947	24752	823 (28)	37(31; 43)	2043 (69.3)	595 (20.2)	911 (30.9)	752 (25.5)	31 (1.1)	8 (0.3)	650 (22.1)			1795 (60.9)		4.5 (3.1; 5.2)	2696 (91.5)		315(135; 525)
ICONA	9894	50626	2586 (26)	36(31; 43)	8882 (89.8)	2913 (29.4)	3933 (39.8)	2436 (24.6)	44 (0.4)		568 (5.7)			8772 (88.7)		4.5 (3.8; 5.1)	9104 (92.0)		401(208; 593)
Italian MASTER Cohort	12728	74753	3458 (27)	37(31; 44)	9558 (75.1)	2250 (17.7)	5074 (39.9)	2583 (20.3)	62 (0.5)	5	2754 (21.6)			9723 (76.2)		4.6 (3.9; 5.2)	9927 (78.0)		304(122; 511)
Modena	1730	18239	560 (32)	33(27; 41)	1252 (72.4)	334 (19.3)	732 (42.3)	545 (31.5)	11 (0.6)	1 (0.1)	107 (6.2)			718 (41.5)		4.6 (3.8; 5.3)	907 (52.4)		321(133; 555)
PISCIS	14202	75297	3164 (22)	36(31; 43)	11054 (77.8)	5105 (35.9)	5340 (37.6)	2481 (17.5)	47 (0.3)	60 (0.4)	1169 (8.2)			9878 (69.6)		4.5 (3.4; 5.2)	10184 (71.7)		312(136; 516)
SHCS	10193	70179	2961 (29)	37(31; 44)	7957 (78.1)	4106 (40.3)	4197 (41.2)	1000 (9.8)	80 (0.8)	9 (0.1)	801 (7.9)			8028 (78.8)		4.4 (3.3; 5.1)	10147 (99.5)		349(179; 533)
St Pierre	6925	40047	2613 (38)	35(28; 42)	4909 (70.9)	2158 (31.2)	3834 (55.4)	429 (6.2)	128 (1.8)	53 (0.8)	323 (4.7)			3238 (46.8)		4.5 (3.4; 5.0)	4396 (63.5)		334(169; 528)
UK Collaborative HIV Cohort Study (UK CHIC)	47117	291082	12923 (27)	34(29; 40)	37616 (79.8)	23208 (49.3)	17178 (36.5)	1690 (3.6)		296 (0.6)	4745 (10.1)			21366 (45.3)		4.4 (3.1; 5.1)	25873 (54.9)		307(140; 488)
VACH	21582	149654	5020 (23)	35(30; 41)	16205 (75.1)	5914 (27.4)	6504 (30.1)	7089 (32.8)	76 (0.4)	14 (0.1)	1985 (9.2)			9344 (43.3)		4.8 (4.1; 5.3)	10000 (46.3)		308(129; 504)
TOTAL	**328,673**	**2112438**	**91,516 (28)**	**35(30; 43)**	**235,370 (71.6)**	**127,231 (38.7)**	**121,555 (37.0)**	**44341 (13.5)**	**3861 (1.2)**	**875 (0.3)**	**30,810 (9.4)**			**199,247 (60.6)**		**4.5 (3.5; 5.1)**	**247,268**	**75**	**340(170; 530)**

* Enrolment : measurements taken in the period six months prior to and one month after the variable "enrolment date"

** Includes a small proportion of MSM + IDU

*** Cohorts who have merged administratively but which represent 'one cohort' insofar as COHERE governance

Table 2b. Number of individuals, person-years of follow-up, patient demographics, prior AIDS status, mode of infection, median CD4 cell count and logarithm viral load in individuals enrolled in 'paediatric' cohorts or enrolled in mixed cohorts and younger than 13 years old, (COHERE, 2014 merger)

Cohort	'N'	Person-Years	Female ['N' (%)]		Median Age (IQR)		No AIDS ['N' (%)]		Mode of infection ['N' (%)]					HIV RNA (log10 cp/ml) assessment at 'enrolment'*, 'N' (%)		Median HIV RNA values (log10 cp/ml) at 'enrolment'* (IQR)		CD4 cell count assessment at 'enrolment'*, 'N' (%)		Median CD4 values (cells/μl) at 'enrolment'* (IQR)	
									Sexual Contact		Blood products		Perinatal infected	Unknown							
ANRS CO10 EPF	193	1583	112	(58.0)	0	(0; 3)	176	(91.2)			1	(0.5)	188	(97.4)	4	(2.1)	0	-	–	–	130	(67)	1535	(708;2349)
ATHENA**	254	1605	126	(49.6)	5	(3; 8)	204	(80.3)			5	(2.0)	235	(92.5)	14	(5.5)	241	(95)	2.5	(1.7; 4.8)	241	(95)	1000	(620; 1550)
CHIPS	1765	14793	914	(51.8)	4	(0.7; 8)	1281	(72.6)			33	(1.9)	1662	(94.2)	70	(4.0)	546	(30)	4.7	(4.0; 5.4)	618	(35)	553	(254; 1000)
CORISPE-cat	219	2834	129	(58.9)	1	(0.3; 3)	121	(55.3)			3	(1.4)	200	(91.3)	8	(3.7)	70	(32)	5.4	(4.9; 5.9)	79	(36)	1206	(464; 2185)
CoRISpeS-Madrid	318	2514	159	(50.0)	2	(0.3; 5)	237	(74.5)	3	0.9	5	(1.6)	294	(92.5)	16	(5.0)	235	(73)	5	(4.3; 5.6)	100	(31)	927	(358; 1977)
KOMPNET Children Cohort	59	129	28	(47.5)	8	(4;11)	49	(83.1)					53	(89.8)	6	(10.2)	44	(75)	1.7	(1.7; 2.5)	0	-	–	-
Total	**2808**	**23,458**	**1468**	**(52.3)**	**3**	**(0.5; 8)**	**1953**	**(73.4)**	**11**	**0.4**	**47**	**(1.7)**	**2632**	**(93.7)**	**118**	**(4.2)**	**1136**	**(40)**	**4.6**	**(3.3; 5.4)**	**1168**	**(42)**	**762**	**(366;1425)**

* Enrolment : measurements taken in the period six months prior to and one month after the variable "enrolment date"

** Mixed (adult/paediatric) cohorts

cell counts were greater than 750 cells/mm.[3,10] In patients with viral suppression, the risk of new AIDS events or death followed a CD4 cell count gradient, even benefiting those with a CD4 cell count $\geq$ 500 cells/mm^3.[11] Individuals who were virally suppressed on cART for more than 3 years, but had incomplete CD4 cell recovery, experienced substantially higher rates of mortality from both AIDS and non-AIDS causes, suggesting that these individuals should be monitored for diseases not conventionally considered HIV-related, especially non-AIDS defining cancers and liver diseases.[12] Future research will focus on new markers of the risk of morbidity and cause-specific mortality, outcomes in individuals treated for many years and outcomes in people ageing with HIV, particularly in the context of multi-morbidity and polypharmacy.

The COHERE's Pursuing Later Treatment Options (PLATO) II project looked at the rate of development of virological failure in adults, adolescents and children. When virological failure has occurred with at least two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a ritonavir-boosted protease inhibitor (PI), patients are said to have experienced triple-class virological failure (TCVF). Fewer than 9% of adult patients had experienced TCVF at year 9 after starting cART.[13] The risk of TCVF was somewhat higher in children and particularly higher in adolescents.[14] Virological suppression after TCVF was found to have increased from 20% in 2000 to 58% in 2009. Rates of AIDS and death also declined over time in people with TCVF.[15] The incidence of TCVF in people on cART declined after 2008, and prevalence stabilized at around 2.5%.[16] An approximately linear inverse relationship between $\log_{10}$ viral load and CD4 cell count in people with TCVF points to likely immunological benefits of reducing viral load, even by modest amounts, without necessarily resulting in an undetectable viral load.[17]

Late presentation

Late presentation is defined as an HIV diagnosis with a CD4 cell count < 350/mm^3 or an AIDS diagnosis, regardless of CD4 cell count, within 6 months of HIV diagnosis. This definition was applied to 84 524 PLWH presenting for care between 1 January 2000 and 30 June 2011 in Europe. Late presentation was present in over half (53.8%) of the sample. It decreased over time in both Central and Northern Europe among homosexual men and heterosexuals but, in contrast, increased over time in Southern Europe among female heterosexuals and male IDUs and in Eastern Europe among IDUs. Late presentation was associated with increased mortality, especially in the first year after diagnosis, with significant variation

across Europe.[18] Further analyses study changes in late presentation within different regions and demographic groups since 2010.[19] These findings have provided comprehensive evidence of patterns in late presentation in Europe and have informed discussions around earlier and more widespread testing for HIV and linkage to HIV care.[20]

Opportunistic infections

Of HIV-infected people, 30% either present late with an opportunistic infection (OI) or are at significant risk of an OI.[18] The COHERE OI group has described both the spectrum and the incidence of OIs in patients on cART with high CD4 cell counts.[10,11] By including viral suppression as a cofactor, it was found that *Pneumocystis jirovecii* prophylaxis could safely be stopped in an additional 40% of patients when compared with guidelines based exclusively on CD4 cell counts,[21] findings which informed both the American and the European treatment guidelines.[22,23] The group is conducting similar analyses for toxoplasmosis and other OIs and intends to reassess the guidelines on the timing for discontinuing secondary prophylaxes against specific OIs.

The early start of cART in the course of cryptococcal meningitis has been shown to be harmful in some clinical trials performed in resource-limited settings,[24,25] but in Western settings with advanced clinical monitoring this may not be the case.[26] Current COHERE projects are examining the effect on mortality of the time of cART initiation after a diagnosis of cryptococcal meningitis or *Toxoplasma gondii* encephalitis. Preliminary results from a COHERE, NA-ACCORD and CNICS collaboration have shown that early cART did not increase mortality in AIDS patients with cryptococcal meningitis in high-income countries, and overall mortality was lower than that reported by the clinical trials conducted in Africa.[27] Current analyses explore how specific OIs influence long-term immune reconstitution, morbidity and mortality in the most recent cART era.

Malignancy

The COHERE malignancy group has focused on defining the incidence, risk factors and prognosis of HIV-associated cancers in the cART era, with a focus on systemic non-Hodgkin lymphoma (NHL) and primary brain lymphoma (PBL), Hodgkin's lymphoma and, more recently, Kaposi's sarcoma.[28–30] The incidence of non-Hodgkin's lymphoma, primary brain lymphoma and Kaposi's sarcoma were substantially reduced in patients on cART, and timely initiation of therapy at high CD4 cell counts is important for preventing these malignancies.[28,30] In contrast, the incidence of Hodgkin's lymphoma was not reduced by cART. Patients whose CD4 cell counts declined despite suppression of HIV-1 replication on cART were at increased risk of Hodgkin's lymphoma.[29] Comparative analyses are planned in collaboration with the African regions of IeDEA.[4]

Hepatitis

The immunological changes over the course of HCV treatment and their effect on mortality were estimated in 6433 HIV-HCV co-infected adults (aged $\geq$ 16), 12% of whom had initiated HCV treatment ($n = 692$ interferon and ribavirin; $n = 88$ interferon alone).[31] CD4 cell counts decreased over the first 12 weeks but stabilized from week 24 onwards with no negative impact on mortality. The group is poised to monitor the effect of the introduction of direct-acting antiviral agents in co-infected patients.

Socioeconomic inequalities

The Socioeconomic Inequalities group studies differences in key outcomes by sex, race/ethnicity, migrant status and educational level as a proxy for socioeconomic position. Even in European countries with universal health care systems, it has been documented that individuals with lower educational level do not benefit equally from timely cART initiation and have a poorer response to cART.[32]

Mortality in migrants has been found to be lower compared with native populations, which has been attributed to the 'healthy migrant effect'. COHERE's larger sample size has allowed this group to study mortality in men and women from multiple geographical origins separately, highlighting heterogeneity among migrant groups and revealing how certain groups are at an increased risk of mortality,[33] work which was featured in the first issue of UNAIDS Science Now. The group plans to examine differences in cause-specific mortality by country of origin.

What are the main strengths and weaknesses?

COHERE in EuroCoord's infrastructure is a unique research platform which has prompted collaborations both within and beyond Europe. EuroCoord's cross-network work packages on data capture, HIV tuberculosis, migrant health and modelling and its interdisciplinary working groups (clinicians, virologists, epidemiologists, biostatisticians) have formalized this cross-network collaboration and fostered intra-European capacity building. COHERE's further investment in data harmonization (HICDEP) has

benefited other regional collaborations. Efforts to streamline data submission with the CASCADE and ART-CC cohort collaborations improved efficiency and reduced the workload of DMs. Finally, COHERE has provided excellent training opportunities for junior researchers (PhDs and Fellowships).

COHERE's greatest strength is its size, enabling stratification of subgroups of interest[8] (e.g. across 10 age groups and sex-stratification) and the study of uncommon outcomes.[28] The robustness of COHERE's findings transcends Europe, benefiting the global HIV-patient community. COHERE data are highly representative of those in care in countries with large regional and national cohorts. Such cohorts enable COHERE to monitor trends across countries. However, adequate representation of marginalized groups such as migrant populations has become a challenge as a consequence of informed consent requirements in some countries as well as barriers to accessing care.[34]

Although COHERE uses HICDEP, the heterogeneity in data quality remains an ongoing challenge. In collaboration with ART-CC,[3] COHERE has been an ideal platform for harmonizing the collection and validation of causes of deaths in HIV-1 infected individuals. With a growing proportion of deaths now caused by non-AIDS events, accurately monitoring causes of death is critical to identify trends and evaluate risk factors. The progressive implementation of the 'Coding Causes of Death in HIV' Protocol (CoDe), a uniform classification system for collecting and validating (via a centralized review process) data on causes of death and contributing factors in HIV-1 infected patients, developed by the D:A:D collaboration, has become a priority.[35]

Despite COHERE's demonstrated ability to evolve and adapt to respond to new research questions, it is now facing the challenge of expanding cohort and clinic-based databases to include clinical outcomes that were not initially of interest. As the cohort of PLWH in Europe ages, comorbidities such as cardiovascular, metabolic, neurocognitive and bone diseases have become increasingly relevant to the study of prognosis in the era of cART. If COHERE and its contributing cohorts were formed today, more emphasis would be placed on linking HIV databases with other health databases (e.g. cancer registries, hospital or other administrative databases, etc.).

COHERE has maintained close ties with the patient community via its patient representative on the COHERE SC. Data from COHERE helped to demonstrate the value of high-quality treatment strategies and enabled people living with HIV understand the evolving nature of the epidemic as well as face the ongoing challenges of growing older with HIV. Findings from COHERE have informed and guided the patient community's discussions with governments and authorities about treatment guidelines and standards of care.

COHERE is now a mature collaboration, which is unique in its size and coverage. It continues to produce new evidence on clinical outcomes, particularly AIDS-defining complications, late presentation and socioeconomic inequalities, which inform clinical guidelines and public health policy recommendations. As PLWH live longer with a chronic infection, comparisons between them and cohorts of uninfected individuals are needed to disentangle the role of HIV infection from its long-term treatment and comorbidities, especially those linked to ageing.

Can I get hold of the data? Where can I find out more?

COHERE welcomes applications from principal investigators (PIs) of European cohorts interested in joining the COHERE collaboration. Interested cohorts must be willing to transform their data to fit HICDEP codes and adhere to the data submission timeline laid out in the COHERE Data Management SOP. COHERE DMs hold several explanatory webinars covering the data submission process, to facilitate data transfer.

Those interested in using COHERE data to conduct a project can download a COHERE Project Proposal Form and a Data Specification Form from our website (www.cohere.org). Proposals from external investigators will undergo the same rigorous scrutiny as those from investigators within the study group; details are outlined in the COHERE Manual of Operations [www.cohere.org].

Profile in a nutshell

- The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) is a project-driven cohort consortium that was set up to address scientific questions that could not be addressed by single cohorts because of sample size requirements.
- COHERE has grown from 33 cohorts in 2005 to 40 in 2015. The 2014 merger, representing 14 projects, compiled data from 331 481 individuals from 34 European countries, including 2808 children (youger than 13 years), representing 2 135 896 person-years of follow-up.
- As a consortium of cohorts comprising clinic-/hospital-based and interval cohorts, the frequency of patient follow-up varies. For clinic- or hospital-based cohorts, average patient follow-up reflects current standards of care in those countries.

- COHERE compiles data on clinical characteristics, antiretroviral therapy and other medications, estimated date of HIV seroconversion, opportunistic infections, laboratory results and socio-demographic data according to the requirements of projects.
- External collaborators interested in conducting a project in COHERE should submit a project proposal to the regional coordinating centres in Bordeaux and Copenhagen for review by COHERE's governing bodies; see [www.cohere.org] for further information.

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Conflicts of interest: D.C. was a member of the French Gilead HIV board up until 2015, gave lectures for Janssen-Cilag, Merck-Sharp & Dohme-Chibret, ViiV and received travel/accommodation/meeting expenses from Gilead, ViiV, Janssen-Cilag. D.C. also conducted post-marketing studies for Janssen-Cilag, Merck-Sharp & Dohme-Chibret and ViiV. D.C. is currently a consultant at Innavirvax. H.F. has received grants from the Swiss National Science Foundation; his institution has received grants from ViiV, Abbvie, MSD, Janssen, Roche, BMS and Gilead. The other co-authors have no conflicts of interest to declare.

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