Received: 26 June 2018 | Revised: 13 May 2019 | Accepted: 14 May 2019

DOI: 10.1111/jvh.13146

SHORT COMMUNICATION

JOURNAL OF VIRAL HEPATITIS JVH WILEY

Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis

Sophie Willemse[1,2] | Colette Smit[2,3] | Philippe Sogni[4,5,6] | Mario Sarcletti[7,8] | Caterina Uberti-Foppa[9] | Linda Wittkop[6,10,11] | Dorthe Raben[12] | Antonella D'Arminio Monforte[13] | Francois Dabis[6,10,11] | Marc Van Der Valk[2,14] | Hepatocellular Carcinoma Screening Project Working Group for the Collaboration of Observational HIV on behalf of Epidemiological Research Europe (COHERE) In EuroCoord*

[1]Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]ATHENA, The Netherlands

[3]Stichting HIV-monitoring, The Netherlands

[4]INSERM U-1223, Pasteur Institute, Paris-Descartes University, Paris, France

[5]Department of Hepatology, Cochin Hospital, Paris, France

[6]ANRS CO13 HEPAVIH, France

[7]Department of Dermatology and Venereology, Medical University Innsbruck, Innsbruck, Austria

[8]AHIVCOS, Austria

[9]Department of Infectious Diseases, Scientific Institute San Raffaele Hospital (HSR), Milan, Italy

[10]Inserm, Bordeaux Population Health Research Center, Team MORPH3EUS, UMR 1219, Univ. Bordeaux, ISPED, Bordeaux, France

[11]CHU de Bordeaux, Pôle de santé publique, Service d'information médicale, Bordeaux, France

[12]Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[13]Department of Infectious and Tropical Diseases, S Paolo University Hospital, Milan, Italy

[14]Department of Internal Medicine, Division of Infectious Diseases, Amsterdam Infection and Immunity Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Sophie Willemse, Department of Gastroenterology and Hepatology, Amsterdam UMC, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: s.b.willemse@amc.uva.nl

Funding information
This work was supported by 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 no. 260694. A list of the funders of the participating cohorts can be found at www.cohere.org. The different funding sources of COHERE have all granted unrestricted funding to the COHERE collaboration. The funding sources did not interfere in the design of the project, edit or steer the results, receive drafts of the manuscript or interfere with writing the manuscript.

KEYWORDS: cancer screening, chronic viral hepatitis, co-infection, guideline adherence, hepatocellular carcinoma, hepatocellular carcinoma screening, human immunodeficiency virus, liver cirrhosis

Abbreviations: AHIVCOS, Austrian HIV cohort study; ATHENA, AIDS therapy evaluation in The Netherlands; cART, combination antiretroviral therapy; COHERE, Collaboration of Observational HIV Epidemiological Research in Europe; GEE, generalized estimating equation; HBV/HCV, hepatitis B or C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IDU, injecting drug use; MSM, men who have sex with men; NOS, not otherwise specified.

*See Appendix 1 for COHERE.

1 | INTRODUCTION

Chronic hepatitis B or C virus (HBV/HCV) infection is associated with the development of liver cirrhosis and hepatocellular carcinoma (HCC). In human immunodeficiency virus (HIV) co-infected patients, the risk for liver decompensation, liver-related death and development of HCC is increased.[1]

The incidence of HCC is rising in HIV/HCV co-infected individuals.[1] When ultrasonographic screening is performed every 6 months, HCC may be diagnosed in an earlier stage allowing curative treatment. Therefore, it is recommended in multiple international guidelines (AASLD, EASL and EACS) to screen individuals with cirrhosis twice a year with ultrasound for the presence of HCC.

Although an earlier survey showed that awareness of HCC screening guidelines in selected HIV treatment centres in the United States is high,[2] adherence to bi-annual HCC screening guidelines in viral hepatitis patients is low, varying from 13% to 51%.[3-7]

Our aim was to assess compliance with HCC screening guidelines in a large European cohort of HIV-infected patients with HBV and/or HCV co-infection and cirrhosis.

2 | PATIENTS AND METHODS

2.1 | Study population

Individuals included in this study were enrolled in observational HIV cohorts participating in the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). COHERE is a collaboration of 40 cohorts across Europe and is part of the EuroCoord network.[8] Our analyses were based on data pooled in the COHERE in EuroCoord merger in July 2015.

HBV and/or HCV co-infected HIV patients aged above 18 years at the time of HIV diagnosis were included. Only data from cohorts who routinely document ultrasound results were collected. Four cohorts from Austria (Austrian HIV Cohort Study [AHIVCOS]), the Netherlands (AIDS Therapy Evaluation in the Netherlands [ATHENA]), France (French national prospective cohort of patients co-infected with HIV and HCV [ANRS CO13 HEPAVIH]) and Italy (Hospital San Raffaele) provided data for our analysis.

Patients were followed up starting 1 January 2005 until 1 January 2015. HBV co-infection was defined as being HBsAg-positive and HCV co-infection as HCV antibody-positive. Assessment of liver cirrhosis was based on clinical diagnosis reported in the chart, liver biopsy or Fibroscan result (≥18.1 kPa for HBV infection[9] and ≥12.6 kPa for HCV infection[10]). The observation time started on the date of liver cirrhosis and continued until the earliest of the following: death, lost to follow-up, cohort censoring date or 1 January 2015. Compliance with HCC screening guidelines was defined as at least one ultrasound every 6 months after the diagnosis of cirrhosis, with a two-week grace period (6.5 months). Observation time started from the date of cirrhosis diagnosis and continued until the first ultrasound and "re-started" after each ultrasound. Patients were censored at the end of their last complete observation period of 6.5 months; in case, the last observation period was <6.5 months because of the database closure, death or lost to follow-up. Compliance was included as a time-varying outcome, and therefore, patients could switch between the compliance and noncompliance groups. Additionally, compliance with HCC screening guidelines was assessed in relation to frequency of outpatient visits and HIV-RNA measurements as a proxy for being linked to care (number of visits and HIV-RNA measurements per full year of follow-up, categorized as ≥2 or <2/year).

Validation of ultrasound data was performed by manually checking random samples of 10% of all data from each cohort; the data from the ATHENA cohort were manually checked in >75%.

2.2 | Statistical analysis

Predictors for low compliance were analysed within a logistic regression model using the generalized estimating equation (GEE) method with a logit link function and an exchangeable correlation structure to adjust for correlations between ultrasounds within the same individuals. Univariate GEE analyses were used to determine factors associated with compliance rate. Because age at baseline in our GEE model does not accurately reflect the effect of age on the odds of being screened, we used 'time-updated' age, increasing the age in accordance with the increase in follow-up time.

All variables with a *P*-value <0.2 were considered as potential independent determinants and were included in the multivariate model. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SAS v9.4. Additional sensitivity analyses were conducted, in which the allowed time to comply with HCC screening guidelines between ultrasound measurements was extended to 9 and 12 months, and the Fibroscan score for the diagnosis of cirrhosis in HCV patients was set to ≥14.6 kPa. Additionally, the effect of these analyses on outcome was assessed, using the multivariate GEE analyses.

3 | RESULTS

Data from 6431 HBV and HCV co-infected HIV patients were included. Of these patients, 1183 fulfilled the criteria of liver cirrhosis according to their clinical chart, liver biopsy or Fibroscan, of whom 537 were excluded due to lack of follow-up after the date of cirrhosis assessment, resulting in 646 individuals who were selected for analysis (Table 1). Of these patients, 518 (80%) were HCV co-infected, 85 (13%) HBV co-infected and 43 (7%) HCV and HBV co-infected.

The proportion of patients in whom HCC screening was performed according to screening guidelines varied between 5.4% in 2005, 18.4% in 2008 and 14.2% in 2014 (Figure 1).

Results from the univariate model showed that older age than 40 years (40-50 years: OR 2.02; 95% CI 1.45-2.80, ≥50 years: OR 2.59; 95% CI 1.80-3.70), being HIV infected by IDU compared with MSM (OR 3.16; 95% CI 2.18-4.48), longer duration of cART

TABLE 1 Demographic characteristics

Total	N	646
Cohort	AHIVCOS	115 (18%)
	ATHENA	243 (38%)
	HEPAVIH	242 (37%)
	Hospital San Raffaele	46 (7%)
Age at cirrhosis diagnosis	Years (median, IQR)	44 (40-49)
Gender	Male	514 (80%)
	Female	132 (20%)
Region of origin	Western	537 (83%)
	Sub Saharan Africa	34 (5%)
	Other	75 (12%)
Transmission route of HIV	IDU	371 (57%)
	MSM	137 (21%)
	Heterosexual	75 (12%)
	Other	40 (6%)
	Unknown	23 (4%)
Hepatitis co-infection	HCV	518 (80%)
	HBV	85 (13%)
	HCV & HBV	43 (7%)
Use of cART	N	603 (93%)
Follow-up time since diagnosis of cirrhosis (y)	Median (IQR)	5.33 (3.37-9.51)
Cirrhosis diagnosis	Fibroscan	368 (57%)
	Liver biopsy	15 (2%)
	Liver biopsy & Fibroscan	12 (2%)
	Clinical chart only[a]	251 (39%)
Mortality	Overall	138 (21%)
	Liver-related	76 (55%)
	HCC	9
	Decompensated cirrhosis	33
	HCV/HBV-related, NOS	34

Abbreviations: cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use; MSM, men who have sex with men; NOS, not otherwise specified.

[a]Clinical diagnosis based on clinical signs of cirrhosis such as ascites, hepatic encephalopathy, biochemical abnormalities (bilirubin, albumin, INR), signs of portal hypertension in the absence of portal vein thrombosis.

use (OR 1.44; 95% CI 1.30-1.60 per 5-year increase) and longer duration since cirrhosis diagnosis (OR 1.65; 95% CI 1.21-1.52 per 5-year increase) were all associated with being screened for HCC <6.5 months. Cirrhosis diagnosis based on liver biopsy or Fibroscan was also associated with higher compliance compared with diagnosis based on clinical events only (OR 1.82; 95% CI 1.28-2.56). In patients with HBV-HIV co-infection, the odds of being screened were lower (OR 0.44; 95% CI 0.31-0.65) compared to those with HCV-HIV co-infection. In the multivariate analysis, longer follow-up after cirrhosis diagnosis (OR 1.59; 95% CI 1.36-1.87) and cirrhosis diagnosis based on liver biopsy or Fibroscan (OR 1.68; 1.11-2.55) remained independently associated with a higher compliance. Lack of ALT measurements (OR 0.52; 95% CI 0.31-0.86 compared with normal ALT levels) was associated with a lower compliance. More recent calendar year of follow-up, included as a time-updated variable to the model, was not significantly associated with better compliance.

Of the patients with ≥2 clinic visits per year, 18% had HCC screening <6.5 months, compared to 3% among those with <2 clinic visits per year. Of the patients with ≥2 HIV-RNA measurements per year, 16% had HCC screening <6.5 months, compared to 12% among those with <2 HIV-RNA measurements per year.

Validation of the ultrasound data showed that for two cohorts' ultrasound data had been missed. In the random sample of these two cohorts, the missed ultrasound data had led to underreporting of HCC screening <6.5 months of 10% and 15%, respectively. When the analyses were repeated only for the cohorts with complete data, the rate of compliance did not change, and the results from GEE analyses showed the same associations as when data from all cohorts were included.

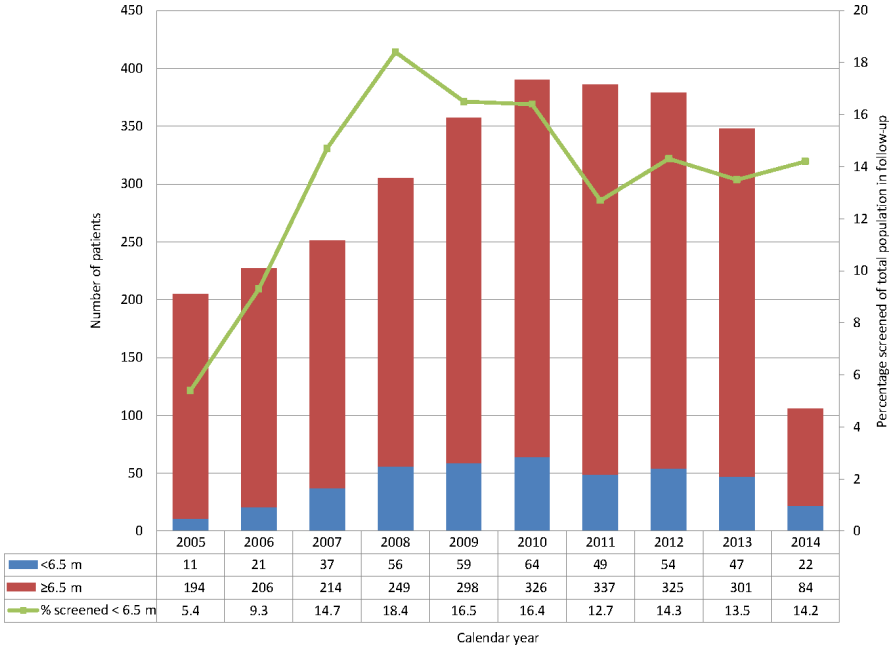
Sensitivity analyses in which the screening intervals between ultrasounds were increased to 9 and 12 months showed a varying compliance of 7% (2005), 12% (2006), 17%-18% (2007, 2011) to 20%-24% (2008-2010 and 2012-2014) for 9-month intervals, and of 7% (2005), 14% (2006), 20% (2007) to 26%-30% (2008-2014) for 12-month intervals.

Multivariate analysis performed after extending the permitted time between ultrasounds to 9 months showed comparable associations to those found with the 6.5-month interval. Additionally, longer duration of cART use was now associated with a higher compliance (per 5-year increase OR 1.19; 95% CI 1.05-1.34).

4 | DISCUSSION

We observed a strikingly low adherence of 5%-18% to HCC screening guidelines in a prospective European cohort of HIV/HBV, HIV/HCV and HIV/HCV/HBV co-infected patients with liver cirrhosis. Although low adherence to bi-annual HCC screening guidelines of 13%-51% has been reported previously in HBV and HCV mono-infected patients,[2-5] and of 24%-36% in HIV/HBV or HCV co-infected patients,[6,7] the compliance we report in HIV co-infected patients is even lower. Even though compliance with HCC screening guidelines increased slightly if the permitted time between ultrasounds was extended in our study, compliance rates remained very low at a maximum of 30% with an interval of 12 months between ultrasounds.

Multiple factors are likely to contribute to the low adherence to HCC screening guidelines in patients with cirrhosis. For example, healthcare providers may have insufficient knowledge about practice guidelines, and a standardized system for scheduling and



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
<6.5 m	11	21	37	56	59	64	49	54	47	22
≥6.5 m	194	206	214	249	298	326	337	325	301	84
% screened < 6.5 m	5.4	9.3	14.7	18.4	16.5	16.4	12.7	14.3	13.5	14.2

FIGURE 1 Absolute numbers and percentages of compliance with HCC screening guidelines ≤6 mo per calendar year. *6 mo is defined as a maximum interval of 6.5 mo between ultrasounds (a "grace period" of 2 wk)

following screening examinations geared towards HBV and/or HCV care may be missing,[7] leading to patients being lost to follow-up. The frequency of clinic visits has been positively correlated with adherence to HCC screening guidelines in earlier studies.[4,5] Our study seems to confirm this, as we found that frequency of clinical visits, ALT and HIV-RNA measurements, is positively correlated with better, but still low, compliance. Our finding that time since diagnosis of cirrhosis was associated with higher HCC screening rates could reflect a stable surveillance situation where both patient and healthcare provider are aware of the importance of regular follow-up and are attentive to the risks of concomitant co-morbidity.

In conclusion, our study in a prospective European cohort of HBV and/or HCV co-infected HIV patients with cirrhosis showed a very low rate of compliance to bi-annual HCC screening guidelines of only 14%-18%. In the context of an increasing incidence of HCC among ageing people living with HIV,[1] this finding warrants urgent action to ensure better implementation of HCC screening guidelines in this population.

CONFLICTS OF INTEREST

CS, PS, MS, CUF and FD have no conflicts of interest; AdAM has received grants from Gilead and MSD Advisory boards from Gilead, Janssen, BMS, MSD and ViiV; LW reports personal fees from Janssen and Gilead (lectures on methodological issues in clinical research – past) outside the submitted work; SW has received consultancy fees from Abbvie, BMS, Gilead, Janssen, MSD, Roche, and research support from AbbVie, Gilead, Janssen, MSD, Roche; MvV has received consultancy fees from Abbvie, BMS, Gilead, Johnson & Johnson, MSD, Viiv and research support from Gilead, Johnson & Johnson, MSD and Viiv.

AUTHORS' CONTRIBUTIONS

SW and CS performed the analyses and prepared and wrote the manuscript; PS provided data from cohort HEPAVIH; MS provided data from cohort AHIVCOS; CUF provided data from cohort HSR; CS and MvV provided data from cohort ATHENA; all authors were involved in designing and planning the research. All authors have reviewed and approved the manuscript.

ORCID

Sophie Willemse https://orcid.org/0000-0003-3165-4069

REFERENCES

1. Gjærde LI, Shepherd L, Jablonowska E, et al. Trends in incidences and risk factors for hepatocellular carcinoma and other liver events in HIV and hepatitis C Virus-coinfected individuals from 2001 to 2014: a Multicohort Study. *Clin Infect Dis*. 2016;63:821-829.
2. Gaglio PJ, Sterling R, Daniels E, Tedaldi E,Terry Beirn Community Programs for Clinical Research on AIDS Hepatitis Working Group. Hepatitis B virus and HIV coinfection: results of a survey on treatment practices and recommendations for therapy. *Clin Infect Dis*. 2007;45:618-623.
3. Tran SA, Le AN, Zhao C, et al. Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis. *BMJ Open Gastroenterol*. 2018;5:e000192.
4. Wang C, Chen V, Vu V, et al. Poor adherence and low persistency rates for hepatocellular carcinoma surveillance in patients with chronic hepatitis B. *Medicine*. 2016;95:e4744.
5. Wong CR, Garcia RT, Trinh HN, et al. Adherence to screening for hepatocellular carcinoma among patients with cirrhosis or chronic hepatitis B in a community setting. *Dig Dis Sci*. 2009;54:2712-2721.
6. Hearn B, Chasan R, Bichoupan K, et al. Low adherence of HIV providers to practice guidelines for hepatocellular carcinoma screening in HIV/hepatitis B coinfection. *Clin Infect Dis*. 2015;61:1742-1748.

7. Beauchamp E, Rollet K, Walmsley S, et al. Canadian co-infection cohort study (CTN222). Missed opportunities for hepatocellular carcinoma screening in an HIV/hepatitis C virus-coinfected cohort. *Clin Infect Dis*. 2013;57:1339-1342.
8. Chêne G, Phillips A, Costagliola D, et al. Cohort profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. *Int J Epidemiol*. 2016;45:1-15.
9. Marcellin P, Ziol M, Bedossa P, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int*. 2009;29:242-247.
10. de Lédinghen V, Vergniol J. Transient elastography (Fibroscan). *Gastroenterol Clin Biol*. 2008;32(6 Suppl 1):58-67.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Willemse S, Smit C, Sogni P, et al; Hepatocellular Carcinoma Screening Project Working Group for the Collaboration of Observational HIV on behalf of Epidemiological Research Europe (COHERE) In EuroCoord. Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis. *J Viral Hepat*. 2019;00:1–5. https://doi.org/10.1111/jvh.13146

APPENDIX 1

ADDITIONAL STUDY COHORTS AND PARTICIPANTS

COHERE in EuroCoord – HCC screening project working group: SB Willemse (ATHENA, the Netherlands), C. Smit (ATHENA, the Netherlands), PS Sogni (ANRS CO13 HEPAVIH, France), M. Sarcletti (AHIVCOS, Austria), C. Uberti-Foppa (HSR, Italy), L. Wittkop (Bordeaux RCC, France), D. Raben (Copenhagen RCC, Denmark), A. D'Arminio Monforte (S Paolo University Hospital, Milan, Italy), F. Dabis (Bordeaux RCC, France) and M. van der Valk (ATHENA, The Netherlands).

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.