PROJECT FINAL REPORT

Grant Agreement number: 305522

Project acronym: COBRA

Project title: “Co-morbidity in relation to Aids”

Funding Scheme: HEALTH.2012.2.3.2-2

Period covered: **from** 1st March 2013 **to** 28th February 2017

Name of the scientific representative of the project's co-ordinator, Title and Organisation:

Prof P. Reiss, Professor of Medicine

Academisch Medisch Centrum bij de Universiteit van Amsterdam (AMC)

Tel: + 31 20 566 3321/6142

Fax: + 31 20 566 9557

E-mail: p.reiss@amc.uva.nl

Project website[7] address: http://fp7-cobra.eu/

Contents

PART I Final publishable summary report

1. Executive summary

The COBRA (Co-morbidity in relation to Aids) project (01/03/2013-28/02/2017) was implemented by a consortium of scientists from 12 institutions in 6 European countries. The project assessed whether living with treated HIV infection contributes to the development of age-associated non-communicable co-morbidity (AANCC), possibly by promoting an acceleration of the process of ageing. The study compared a group of HIV-positive people to a group of HIV-negative people with similar demographic characteristics and lifestyles. As all HIV-positive participants were on effective antiretroviral therapy (ART) and had an undetectable viral load, the results inform us about co-morbidity and ageing in the setting of treated HIV infection rather than about any effects of HIV among untreated people. COBRA also studied mice with a humanized immune system which allowed the investigators to separate the effects of HIV from those of ART on markers of co-morbidity and ageing; this also allowed the group to study the impact of starting ART earlier or later, something that is no longer possible to do reliably or ethically in human studies.

Several previous studies have suggested that HIV may increase the rate of ageing in people living with HIV. COBRA investigated whether ageing is more rapid in people living with HIV and, if so, whether this is due solely to HIV, or whether other factors also contribute. As a group, people living with HIV tend to differ from the general population in several ways (particularly lifestyle factors), and so the only way to reliably answer these questions is to compare a group of HIV-positive people to a group of people who are comparable to them in all respects other than HIV, and to follow them over time to see how they change. The two COBRA groups (one living with HIV and one not) were all aged over 45, included similar proportions of men and women, gay, bisexual and straight people, and smokers, regular drinkers, recreational drug users, etc. The groups were sufficiently similar to ensure that if there were any differences between them in the rate at which people aged, then it would be unlikely that the differences could be caused by these other factors. Unfortunately, there were only a few women in the study, so whilst the investigators did not find any evidence that the results differed in women and men, this possibility could not be ruled out. The small number of non-white people without HIV in the study also limits any conclusions around the role of HIV in the ageing process in this non-white group.

The COBRA results are reassuring for people living with treated HIV infection. Although there were differences in some age-related neuroimaging between the two groups, there was no evidence that treated HIV is associated with accelerated ageing based on cognitive testing, neuroimaging or ageing biomarkers. The group with treated HIV did not age any faster than those without HIV over the two years - they did not lose their mental abilities more quickly than those without HIV, nor did their brain scans appear to deteriorate more rapidly. Interestingly, the study did find differences in some of these ageing biomarkers when the people living with HIV were compared to a group of blood bank donors from the Dutch general population (the demographic and lifestyle characteristics of this group are likely to be very different from those of people living with HIV) but there were also some differences when this group of blood bank donors was compared to the group of COBRA participants without HIV. Of note, many of the people with HIV in COBRA had longstanding HIV infection with prolonged exposure to ART (including a subgroup with exposure to some of the older and more toxic regimens).

In a separate analysis conducted by study investigators on stored blood samples from a group of people with documented HIV seroconversion who were followed (without ART) over approximately 2 years, biological age based on epigenetic markers was already more advanced than expected compared to the general population even before HIV infection; there was little evidence that acquisition of HIV further affected this biological ageing. Together with the findings from COBRA, these results suggest that factors related to an individual's lifestyles (e.g. other acquired infections), as well as exposure to ART (particularly to older regimens), may be more important key drivers of how quickly the body ages than HIV.

2. A summary description of project context and objectives

Project context

Research conducted over the last 5-10 years has increasingly demonstrated that HIV infection, even when properly treated with combination antiretroviral therapy (cART), appears to be associated with more rapid aging. It has been proposed that HIV, through immune-mediated or other mechanisms, may induce widespread damage to tissues and organ systems, promoting the onset of a range of so-called non-AIDS clinical conditions, each of which are also associated with general ageing. Low-grade HIV-associated inflammation may persist in spite of cART, and this may be one contributing underlying mechanism. Realization that this inflammation may affect the process of ageing itself led researchers to propose the hypothesis that HIV and/or its treatment might be inducing an accelerated ageing phenotype.

Objectives

COBRA's main objectives and underlying sub-objectives were therefore:

1. To establish the link between HIV infection and age-associated non-communicable co-morbidities (AANCC)

1.1 To determine and compare the prevalence, incidence and outcomes of AANCC, including neurocognitive co-morbidity, in a cohort of middle-aged HIV-infected subjects with sustained HIV suppression on cART and similarly aged HIV-uninfected subjects, through comprehensive clinical and laboratory diagnostic means.

2. To elucidate and clarify this link by identifying its causative and underlying pathogenic mechanism(s)

2.1. To elucidate in the Humanized Immune System (HIS) mouse model the causative effect of HIV infection on metabolic changes which underlie certain AANCC in persons living with HIV;

2.2. To elucidate in the HIS mouse model the potential causative effect of cART on metabolic changes which underlie certain AANCC in persons living with HIV;

2.3. To clarify a number of possible pathogenic mechanisms, including the possible induction of an inflammation-associated accelerated ageing phenotype, underlying the causative link between HIV and AANCC through the use of a comprehensive range of biomarkers reflecting these mechanisms, in samples obtained from both the HIS mouse model and the clinical cohort.

The project was executed through 7 highly interactive and interdependent work packages.

3. Main S&T results/foregrounds

Management (COBRA Work Package 1)

Communication with the European Commission - The Project Office (AMC) has been the intermediary for any communication between the EC and partners during the project duration.

Administration of the financial contribution - The EC financial contribution was carefully managed regarding its allocation between partners and activities taken by the consortium. The Project Office ensured that all payments were made without delay.

Communication and Reporting - Communication within the consortium has been ensured through the normal means such as electronic mail, teleconferences and in-person meetings. The Project Office has developed a template for bi-monthly reporting which was completed by each WP leader. These reports helped monitor the progress of the project and successfully steered the discussions of the Project Management Board (PMB) during their bi-monthly teleconferences which were consistently held during the lifetime of the project.

Legal and administrative issues – The Project Office has, on behalf of the consortium, requested three grant amendments. All three amendments requests have been approved by the EC.

Installation of the Scientific Advisory Board – An independent Scientific Advisory Board (SAB) was set up prior to the start of the project; members included experts in ageing research, HIV policy, the HIS mouse model, HIV patient community representative and in HIV co-morbidity and ageing. The members provided guidance to the Steering Committee according to their expertise. The SAB were highly appreciative of the quality and execution of the project by the consortium.

Organization of project meetings – The Project Office organised multiple project meetings:
- Kick-off meeting in March 2013, in Amsterdam, the Netherlands
- First Steering Committee Meeting in March 2014, in Amsterdam, the Netherlands
- Second Steering Committee Meeting in March 2015, in Amsterdam, the Netherlands
- Mid-term stakeholder Meeting in March 2015, in Amsterdam, the Netherlands
- Third Steering Committee Meeting in March 2016, in Amsterdam, the Netherlands
- Final Symposium in January 2017, in Amsterdam, the Netherlands

The Project Management Board contributed to the agenda of all meetings and all partners have presented during these meetings.

Clinical Cohorts (COBRA Work Package 2)

A clinical cohort was established comprised of middle aged (45 years and above (Amsterdam)/50 years and above (London)) HIV-positive subjects with suppressed viraemia on cART and appropriately chosen and comparable HIV-negative controls across the two study sites. All subjects have undergone prospective comprehensive standardised assessment for a range of non-infectious comorbidities by clinical and laboratory diagnostic means, at study entry and again after approximately two years. Participants are a subset of participants in the larger AGEhIV (Amsterdam) and POPPY (London) cohorts.

HIV positive cohort (n=125)	HIV negative cohort (n=89)
• Aged >50 / 45 years • On effective cART with plasma HIV RNA undetectable	• Aged >50 / 45 years • Closely comparable to positive cohort for gender, ethnicity, country of origin, etc.

Assessments

Detailed information was captured on participant demographics, socioeconomic status, behavioural/lifestyle factors (including substance use), socio-economic factors (including questionnaires on work participation, depression symptoms and quality of life), and medical history including use of (non-ART) medication, anthropometric assessments, respiratory function (spirometry), cardiovascular function assessment (ECG and arterial stiffness assessment), spine and hip dual energy X-ray absorptiometry (DXA) scan for bone mineral density, an MRI scan and assessment of falls risk, fracture risk and a frailty assessment. Blood and urine samples have been taken for renal, liver and lipid profiles, glucose and HbA1c, thyroid function (TSH), full blood count, syphilis serology, hepatitis B and C serology, HIV serology (controls only), 25(OH) vitamin D and parathyroid hormone levels, D-dimer and hsCRP. In addition blood (serum, plasma, PBMCs, DNA) has been stored for biomarker analysis and stool and urine samples have been stored to allow analysis of gut microbiota and metabolomics. Both HIV-positive and HIV-negative subjects underwent a lumbar puncture assessment at baseline allowing assessment of routine parameters, CSF HIV RNA, biomarker analysis and CSF exposure of antiretroviral drugs; a follow-up lumbar puncture assessment was undertaken in the HIV-positive subgroup.

Detailed cognitive function assessment has been performed to assess all the major cognitive domains and included assessment of attention and working memory, speed of information processing, memory and learning, language, executive function and psychomotor performance. In addition, acquired impairment of everyday functioning has been assessed by self-report using questionnaires of cognitively related aspects/activities of daily living and depressive symptoms have been assessed.

Results

Overall cognitive performance was slightly lower in the group of people with HIV compared to the HIV-negative group, however the difference observed was lower than reported in many contemporary studies. Over the 2 year follow-up period, slight improvements in cognitive performance were observed in both groups (which may represent a learning effect) with the dynamics of these changes not differing between the study groups (table below).

	HIV positive		HIV negative		p-value interaction
	Mean (95% CI)	p	Mean (95% CI)	p	
Attention	0.67 (-0.66, 2.00)	0.319	-2.17 (-3.86, -0.48)	0.012	0.010
Executive Function	0.21 (-0.80, 1.22)	0.683	0.82 (-0.46, 2.10)	0.208	0.461
Language	0.19 (-0.85, 1.23)	0.719	0.48 (-0.83, 1.79)	0.473	0.735
Memory	2.21 (1.32, 3.11)	<.001	3.26 (2.13, 4.39)	<.001	0.154
Motor Function	0.49 (-0.55, 1.54)	0.353	0.19 (-1.14, 1.51)	0.782	0.719
Processing Speed	0.89 (0.15, 1.64)	0.019	0.20 (-0.75, 1.15)	0.676	0.259
Global T-score	0.79 (0.32, 1.27)	0.001	0.46 (-0.15, 1.06)	0.139	0.387

Neuroimaging (COBRA Work Package 3)

Outline

Advanced neuroimaging was used to test for subtle alterations to brain structure and function in the groups of people with and without HIV. This allowed the investigators to assess the neural correlates of cognitive impairment in the COBRA participants. Measures of brain structure and function were linked to the clinical parameters, captured through the clinical cohorts' workpackage, as well as to plasma and CSF biomarker parameters and antiretroviral drug exposure, measured through the Biomarker workpackage.

A state-of-the-art protocol of complementary neuroimaging modalities was employed amongst cohort participants, devised by experts on both study sites. The 3-Tesla MRI protocol was performed on all study participants at baseline and at the two-year follow-up visit. The protocol included:

1. T1-weighted MP-RAGE high-resolution structural scan: to determine grey and white matter volume and cerebral cortical thickness
2. T2-FLAIR imaging scan: to assess cerebral small vessel disease
3. Diffusion-weighted tensor imaging (DTI): to assess white matter microstructure and structural connectivity
4. Resting-state fMRI: to assess functional network connectivity
5. Magnetic Resonance Spectroscopy (MRS): to assess neuronal cell function and neuroinflammation
6. Arterial Spin Labelling (ASL): for the assessment of cerebral perfusion
7. Task fMRI using the Choice Reaction Time task (London only)

Pooling of datasets from the two sites required careful calibration of the MRI scanners at each site using identical physical phantoms and a selected group of humans to determine the level of between-scanner reliability. Advanced neuroimaging processing pipelines were developed and used to generate descriptive summary measures of global (i.e. whole brain) and local (i.e. specific brain regions) age-related brain health.

Results

Subtle alterations to a number of aspects of brain structure were seen in the HIV-positive participants at baseline. These included reduced grey matter and white matter volume, greater levels of white matter hyperintensities, abnormal white matter tract microstructure and perfusion of grey and white matter regions. Differences in functional connectivity were observed between the groups of people with and without HIV, though these only reached borderline statistical significance. Measures of brain structure correlated with indices of cognitive performance in a number of domains (executive function, motor function, memory, processing speed), though this was seen in both groups and was not specific to HIV-positive individuals. Longitudinally, both HIV-positive and HIV-negative groups exhibited changes in brain structure and function – these changes were of an expected size given that the study participants had aged by two years between visits. Importantly, the rate at which brain structure and function changed did not differ between the HIV-positive and HIV-negative groups.

HIS Mouse Studies (COBRA Work Package 4)

The mice studies

It is difficult in human studies to establish the causative mechanisms by which HIV and/or ART may affect the risk of co-morbidity and ageing. Similarly, dissecting any effects of HIV from those of ART is also difficult as it is unethical to withhold ART in those who need it. It is possible, however, to conduct some of these experiments in humanized immune system (HIS) mice.

Animal models that would allow investigators to study HIV in vivo are limited by the fact that the virus can only infect human cells. In order to overcome this limitation, Human Immune System (HIS) mice were developed. They are generated by injecting hHPCs (Human Hematopoietic Progenitor Cells) in

preconditioned NOD/scid-IL-2Rγc-/- (NSG) mice. This highly immunodeficient strain of mice allows the engraftment and the development of human hematopoietic cells including monocytes, B, NK and T cells. These human cells can then be infected by HIV and represents an accepted in vivo model to study HIV pathogenesis.

COBRA investigators generated several cohorts of HIS mice that were infected with HIV (JRCSF) at 12 weeks. Some of these animals were treated 2 or 4 weeks after their infection with a fully suppressive cART regimen of abacavir (ABC), lamivudine (3TC) and dolutegravir (DTG). These mice were then compared to control animals that were either non-infected (some of whom also received the cART regimen) or were infected but remained untreated. Investigators monitored the mice for up to 6 months after their infection by collecting blood regularly. This allowed the group to study 'long-term' changes in the mice as well as the process of ageing. At the time of sacrifice, several organs (spleen, bone marrow, brain, liver, fat, muscle, heart, etc.) were collected for further analysis.
Investigators analysed the evolution of the virus (viral load, residual viral replication), immunology (e.g. monocytes and T cells depletion, activation and senescence), the metabolic changes (e.g. glycaemia, triglyceridemia, leptin, insulin), ageing (e.g. GlycoAgeTest, ageing biomarkers), brain alterations (e.g. microglia activation) and drug concentration. Many of these tests were similar to those performed in the groups of people with and without HIV, allowing potential translation between the animal and human studies.

Although HIS mice are used widely to study HIV pathogenesis, no other study has reported the cumulative analysis of so many different parameters linked to immunology, ageing and metabolism. In addition, the long duration of the treatment in these mice, which meant that investigators could probe the ageing process, was unprecedented.

The study of these HIS mice did, however, result in specific challenges. Firstly, it was necessary for the investigators to find a suitable means by which the drugs could be administered to the mice in an effective manner for several months. Using pilot experiments, the group found that they were able to stably dissolve some but not all antiretroviral drugs in MediDrop (a liquid gel replacing drinking water) which would allow them to treat HIS mice in a stress-free manner for several months. Secondly, it was necessary to find an appropriate cART regimen which resulted in complete viral suppression for the whole duration of the experiment; after screening several regimens, the combination of ABC, 3TC and DTG was finally selected.

Preliminary results obtained during the project indicated that the brain microglia is activated upon untreated HIV infection. This state is, however, corrected by treatment with cART. A moderate bone mineral density decrease was observed in the treated mice even in the absence of infection. No effect of the infection or the treatment could be observed on the GlycoAgeTest. More sensitive analyses of ageing biomarkers are still ongoing.

CD4+ T cells decline during HIV infection. This is mainly due to loss of the CD4+ memory compartment, and expansion of CD8+ T cell population with a shift towards a more differentiated effector memory cell type. Upon initiation of cART, complete recovery of the CD4 and CD8 compartment is observed. Immune activation measured in the CD4 and CD8 compartment increased upon HIV infection, which normalized upon cART initiation. In contrast to what has been reported in humans, no effect of HIV infection could be observed in the levels of T cell senescence. In the monocyte compartment, a shift of classical monocytes towards intermediate/non-classical monocytes is observed in the blood and bone marrow upon HIV infection. The activation levels of the different monocyte populations as demonstrated by the expression of activation markers, adhesion molecules and costimulatory molecules, increased upon HIV infection. Incomplete recovery of the monocyte populations and activation levels were observed upon cART initiation.

Importantly, many samples were collected during the project and are now banked for future or ongoing analyses. Particularly interesting in this context will be the results of analyses of biomarkers of ageing at the tissue level (liver and brain) which are currently being generated.

Biomarkers (COBRA Work Package 5)

Biological material collected from HIS mice (blood, serum/plasma, various tissues) and cohort participants (PBMC, serum/plasma, CSF, urine, stool) was collected for use and has been stored for future ancillary studies. Selected biomarkers for metabolic changes, residual HIV transcription, immune activation and senescence, inflammation, coagulation activation, antiretroviral pharmacokinetics, neuronal damage and ageing (N-glycans) have been measured. Epigenetic and mRNA profiling has been performed in CD4+ T cells, CD8+ T cells and monocytes from cohort participants. Additionally, biomarkers comprising the MARK-AGE algorithm have been analysed in cohort participants.

Study investigators observed that people with HIV in COBRA still had higher levels of soluble markers of monocyte activation/inflammation and CD4 T cell activation than the people without HIV, even though they were receiving cART and had a suppressed viral load – this indicates ongoing immune activation possibly due to ongoing microbial translocation. Indeed, levels of intestinal fatty acid binding protein which is a biomarker of gastrointestinal barrier integrity and subsequent microbial translocation were also increased in the people with HIV.

Compared to the group of blood bank donors described earlier, T cell senescence and monocyte activation were higher in both groups of COBRA participants (HIV-positive and HIV-negative). The increased T cell senescence in COBRA participants was strongly associated with CMV (co-)infection. Furthermore, the study investigators observed that monocyte activation in the CSF was increased in the people with HIV, and that this was associated with cellular monocyte activation in the blood. Neuronal damage markers in CSF (tau, p-tau, amyloid-β1-42, neurofilament light protein) did not differ between the people with and without HIV.

Plasma protein glycosylation changes during human aging, and this has led to the development of the GlycoAgeTest (log(peak1/peak6)). In COBRA, the n-glycan profile was analysed in the plasma and CSF of all study participants - although there were significant differences between the people with and without HIV in the n-glycan profiles in both plasma and CSF, no differences in the GlycoAgeTest were observed between the two groups. Similarly, no differences were seen between the two groups in a measure of epigenetic aging (as expressed by the difference between the person's epigenetic age and their chronological age). Interestingly, the whole genome methylation analysis profile of CD4 T cells, CD8 T cells and monocytes was distinct between those with and without HIV; pathway analysis revealed that the pathways that were affected were shared between HIV and the aging process in CD4 and CD8 T cells.

Transcriptome analysis of CD4 T cells, CD8 T cells and monocytes revealed clear differences between the two groups in the CD4 T cell populations (495 genes) and CD8 T cell populations (697 genes), while no differences were observed in the monocytes. Interestingly, pathway analysis of the affected gene transcripts revealed again that most pathways were shared between HIV infection and the aging process.

The MARK-AGE algorithm is composed of a set of 10 biomarkers that have been shown to best predict biological age in the general population – the algorithm provides a value that denotes how far the body has aged in terms of age-related changes in body function or composition. Both the people with and those without HIV in COBRA had greater biological than chronological age, but the difference between the two measures of age was significantly larger in those living with HIV. Only weak associations between the rate of aging (the change in this 'difference' over the two-year follow-up period) and common socio-demographic factors were observed, while duration of infection or cART, time with CD4+ T cells below 200 cells/ul and a CD4:CD8 ratio below 1, were each associated with an increase in the difference between biological and chronical age.

Data Management and Statistical Analysis (COBRA Work Package 6)

This work package provided the framework within which to co-ordinate, manage and analyse data from the clinical cohort, HIS mouse model and biomarker studies.
The study group established a detailed Data Exchange Platform (DEP), which included information on the standardisation of data across the two clinical cohorts, data quality assurance checks, data protection, data preservation and sharing. In order to overcome typical problems of data from cohort studies (loss-to-follow-up, multiple testing and power issues, competing events and residual confounding), a detailed statistical analysis plan was then developed which was implemented at appropriate timepoints over the study, depending on when the different datasets were made available for analysis.

The investigators, working closely with those from the other workpackages, prepared a combined dataset that included all of the baseline clinical, bio-marker (including immune activation markers) and neuro-imaging data. Over the project itself, the group was able to support the various diverse analyses that were being undertaken through the other workpackages, or by members of the consortium through related studies. This support was through provision of both data and advice on the statistical methods, and through the undertaking of any additional analyses that were required. Investigators completed an analysis of the prevalence of AANCC at baseline and investigated the associations of the prevalence of these with age and HIV status. Summary statistics were produced for all biomarker and neuro-imaging data, and associations with age and HIV status were investigated. A detailed report of the associations of the baseline clinical, biomarker and neuro-imaging data with HIV status and age was produced which allowed strategic discussions around the precise nature of the follow-up assessments and analyses of these. Following the additional measurement of biomarkers included in the MARK-AGE algorithm, the group investigated associations of these markers with age and HIV status.

Analyses of follow up data mainly concerned the evaluation of changes in important clinical parameters (including cognitive function), biomarkers and neuro-imaging data over the two-year study period in those with and without HIV infection, and investigations into whether any observed changes differ between these two groups. Based on data obtained from the Modena HIV Metabolic Clinic, the group also developed a stochastic model to predict the burden of age-associated comorbidities in the next future in a population of people living with HIV.

Dissemination (COBRA Work Package 7)

Information on COBRA events, publications and results was disseminated through various means, such as the project website and presentations at various national and international scientific events. The Final COBRA symposium, organized in January 2017, ensured outreach to the wider scientific community and to a wide range of stakeholders.

4. Project Potential Impact

Socio-economic impact

Awareness regarding the increased risk of co-morbidity and to some extent "age-advancement" in people with HIV, with evidence for this risk to be stabilized by optimal HIV treatment, may help promote earlier diagnosis and treatment of HIV and adherence to healthier lifestyle. Thereby, it could contribute to ensure work participation and resilient aging of people living with HIV, resulting in sustained quality of life and economic productivity.

Wider social implications of the project so far

We show that optimally treated HIV-positive persons do not exhibit evidence of more rapid ageing than otherwise highly comparable HIV-negative persons over the period of 2 years during which we were able to study them. This observation should provide much reassurance to patients, and reinforces current global guidelines which advocate the importance for people to be aware of their HIV status, and when positive to start treatment immediately. Furthermore, some of our findings which show that our HIV-negative cohort with similar behaviour and lifestyle have higher than expected biological age, reinforces the importance of generally promoting a healthy lifestyle.

Main dissemination activities

Please refer to table A2.

Exploitations of results

Not applicable

Project website and contact details

Project website address: http://fp7-cobra.eu/

Project contact person from each beneficiary:

Beneficiary	Contact person	Email
Academisch Medisch Centrum bij de Universiteit van Amsterdam	Peter Reiss	p.reiss@amc.uva.nl
Imperial College of Science, Technology and Medicine	Alan Winston	a.winston@imperial.ac.uk
Goeteborgs Universitet	Magnus Gisslén	Magnus.gisslen@gu.se
University College London	Caroline Sabin	c.sabin@ucl.ac.uk
Stichting Katholieke Universiteit	David Burger	D.Burger@akf.umcn.nl
Alma Mater Studiorum-Universita di Bologna	Claudio Franceschi	Claudio.franceschi@unibo.it
Erasmus Universitair Medisch Centrum Rotterdam	Jan Hoeijmakers	j.hoeijmakers@erasmusmc.nl
VIB	Claude Libert	Claude.Libert@irc.vib-UGent.be
Gemeente Amsterdam	Maria Prins	MPrins@ggd.amsterdam.nl
Universita Degli Studi di Modena e Reggio Emilia	Giovanni Guaraldi	giovanni.guaraldi@unimore.it
Stichting HIV Monitoring	Sima Zaheri	s.zaheri@amc.uva.nl
Universität Konstanz	Alexander Bürkle	Alexander.buerkle@uni-konstanz.de

COBRA logo

COBRA consortium – Steering Committee meeting March 2016

COBRA Final Symposium, panel discussion, January 2017