Protocol for CARE East Cohort

A study in the RESPOND Consortium

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CARE has received funding from the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement No 825673

1. PROTOCOL SUMMARY

Full title of proposal: CARE East Cohort Study in RESPOND

Acronym of proposal: CARE East Cohort

Summary:
The CARE East Cohort study in RESPOND is an observational cohort study with the overall objective to the clinical outcomes in HIV-1 infected and HIV/HCV co-infected persons and the uptake and clinical impact of anti-viral therapy in Eastern European patient populations. The study will include both HIV-1 mono-infected persons regardless of CD4 cell count and ART status; and HIV-1 infected persons who are positive for anti-HCV regardless of HCV-RNA, fibrosis stage and prior HCV therapy. Standardised clinical data based on local routine data collection will take place at enrolment and at a follow-up visit.

Background:
The CARE East Cohort study in RESPOND is developed within the framework of the Common Action against HIV/TB/HCV across Regions of Europe (CARE) project, which runs for two years (2019 and 2020) and is an EU supported H2020 research collaboration between investigators from clinics across EU, Georgia, Russian Federation and Ukraine. The set-up of the CARE East Cohort as a study in the RESPOND consortium is an important step towards sustainability of the collaborations beyond the duration of the CARE project.

The CARE East Cohort is a study in the RESPOND International Cohort Consortium of Infectious Diseases. The aim of RESPOND is to build an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV, as a generic structure for facilitating multi stakeholder involvement. Data collection in RESPOND is modular with a core data collection module onto which additional modules/studies can be added. Data can be entered on the patient level via an secure online platform or be transferred from existing local, regional or national data structures.

Study objective:
The overall objective of the CARE East Cohort is to study clinical outcomes in HIV-1 infected and HIV/HCV co-infected persons and the uptake and clinical impact of anti-viral therapy in Eastern European patient populations. The study will include both HIV-1 mono-infected persons regardless of CD4 cell count and ART status; and HIV-1 infected persons who are positive for anti-HCV antibodies regardless of HCV-RNA, fibrosis stage and prior HCV therapy. The following specific objectives will be addressed in the two populations:

Specific objectives for the HIV Outcomes sub-study (CARE Work Package 5):

1. Study the impact of host genetics on the risk of development of AIDS and serious non-AIDS events and adverse drug reactions in HIV-positive patients
2. Perform an initial assessment of the treatment-limiting toxicity for existing antiretroviral drugs by linking host genotypes and other factors to short and long-term adverse drug reactions.

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Specific objectives for the HIV/HCV Outcomes sub-study (CARE Work Package 6):

1. Monitor the uptake of hepatitis C therapy; to describe changes over time and country and use of specific DAA regimens
2. To monitor the rate of sustained virologic response (SVR) and determine factors associated with successful HCV therapy
3. To develop treatment algorithms for optimal use of DAAs in HCV infected patients
4. To study the influence of HCV treatment on long-term risk of development of liver disease and other clinical outcomes
5. To study the incidence of HCV re-infection after achieving SVR

Study visits: Enrolment + and 1-2 follow-up visits as feasible within the CARE study period 1 January 2019 to 31 December 2020.

Data collection: For all patients enrolled and under follow up, demographic, laboratory, therapeutic and clinical data on HIV, viral hepatitis and AIDS will be collected once a year. Data on serious non-AIDS clinical events will be collected in is real time or alternatively once a year.

Whole blood will be collected from HIV+ patients at the time of enrolment.

Study start date (date open for recruitment or date of first ptt enrolled)

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2. STUDY PURPOSE

2.1 The CARE Project

The CARE East Cohort study in RESPOND is developed within the framework of the Common Action against HIV/TB/HCV across Regions of Europe (CARE) project, which runs for two years (2019 and 2020) and aims to generate novel research findings based on existing biological material and data already collected by the consortium partners as well as on new samples and prospective data collection. CARE is an EU supported H2020 research project set up as a collaboration between investigators from clinics across EU, Georgia, Russian Federation and Ukraine.

The CARE project conducts research on HIV, tuberculosis (TB) and/or hepatitis C (HCV) in patients with mono-, co-infections and/or comorbidities in the context of fostering collaboration with the Russian Federation. The longer-term objective of the CARE project is to implement the necessary collaborative research infrastructure allowing the expansion of activities beyond the funding frame, sustaining the partners to share technology, protocols, structured data collections and knowledge to fuel and maintain cooperation and foster future research plans beyond the duration of CARE. The set-up of the CARE East Cohort as a study in the RESPOND consortium is an important step towards sustainability of the collaborations beyond the duration of the CARE project.

In the RESPOND Consortium all collected data is part of a common data repository or ‘data lake’, which is stored in a database. However, the data collection itself is project-based or modular, with specific studies consisting of targeted data collection for subgroups of participants. A participant can be part of several specific studies. All sites/centres will collect data to one or more specific studies depending on their participant inclusion. The common data repository allows for important cross-cutting research across modules and studies, with important synergies, and costs savings in terms of data collection. Core data is collected for most participants in the following categories: Demography and basic clinical information; Relevant virological and immunological information; Laboratory information regarding organ function and biomarkers for metabolic illness, genotype and relevant paraclinical information as well as information on treatment of HIV infection and related co-infections and co-morbidities.

2.2 Background and Rationale

Since immediate ARV treatment became the golden standard in HIV treatment guidelines globally, ART coverage has been rapidly scaled up across the world, including Russia and eastern Europe that are facing a growing HIV epidemic. To secure optimization and personalization of HIV treatment the host genomic’s influence on susceptibility to HIV, treatment tolerability and/or disease progression rates appears as a key area requiring further studies. Recent reviews have highlighted the progress in identifying genetic predictors of toxicity of antiretroviral treatment (ART) (Haas 2015, Mattevi 2017, Van Manen 2012). There remain many challenges to identifying genetic predictors of drug toxicities, and these challenges are similar to those identified in more general reviews that are not focused on HIV (Ma 2011, Nelson 2016). Larger studies that combine data from several trials or cohorts are needed to reliably assess genetic predictors of drug response, and ultimately clinical trials, like that carried out for abacavir (Mallal 2008), may be required to evaluate the utility of genotyping guided ART selection. Cohorts used for studying genetic predictors of drug toxicities should be geographically and racially diverse because previous studies indicate that adherence to ART varies by race, educational level and geographic

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region and drug toxicity is a frequent cause of non-adherence (Mannheimer 2002, Robinson 2008, O'Connor 2013). Also, important genetic variants may differ across different populations (Ioannidis 2004, Clark 2009, Ntzani 2012). A specific focus is due to the most frequently prescribed antiretroviral drugs worldwide: Efavirenz (EFV) and tenofovir disoproxil fumarate (TDF). EFV came off patent in November 2013 making generic versions of the drug more affordable; TDF came off patent in December 2017. Both drugs will likely be used for many years in many settings, and both have been associated with adverse events that can be treatment limiting: psychiatric toxicities for EFV (Arenas-Pinto 2018) and renal and bone toxicities for TDF (Mocroft 2016, Hoy 2017). Furthermore, the two drugs are often prescribed together, increasing the likelihood of having a genetic trait that predisposes an individual to at least one toxicity that leads to an ART regimen change. A protease inhibitor, typically used in combination with a pharmacological booster like ritonavir, is the key drug used in second line therapy, and has been associated with dyslipidaemia, diabetes and cardiovascular disease (Lundgren 2018).

In the eastern region of Europe, the size of the HCV-infected population is around 14 million, and in combination with excessive alcohol consumption is a major cause of excess morbidity and mortality. Chronic HCV infection is the leading cause of cirrhosis, hepatocellular carcinoma (HCC) and liver transplants in the developed world (El-Serag 1999, Poynard 2003, Thomas 2005). Effective and well-tolerated direct acting antivirals (DAAs) against hepatitis C virus (HCV) has been available since 2013, and communitywide eradication of HCV appears possible (Kattakuzhy 2017). Sustained virologic response (SVR) rates >95% have been reported in both HCV monoinfected persons and in those coinfected with HIV (Falade-Nwulia 2017). Despite these impressive results, the uptake of DAA therapy has been slow in many countries (Peters 2018), which is mainly explained by restrictions to their use because of the high cost of DAA therapy (Marshall 2018). Although the cost of DAAs has since decreased, a prioritization of patients in countries with a high case load is often necessary, but the exact criteria on which this can be based remain uncertain. Observational studies have shown that an SVR reduces but does not eliminate the risk of liver-related complications (Aleman 2013; van der Meer 2012). Risk factors for these complications after SVR are mainly age and stage of fibrosis at time of HCV treatment as well as alcohol abuse (Aleman 2013; van der Meer 2012). Whether HCV therapy also has any significant impact on lowering the risk of extra-hepatic morbidity and mortality such as cardiovascular disease and non-hepatic malignancies remains uncertain. Large well-designed studies are required to study this.

After achieving an SVR, reinfection is still possible in persons with ongoing risk behavior. Data presented so far have primarily been from the era of interferon-based therapies (Falade-Nwulia 2018). It remains unclear whether the high efficacy and tolerability of IFN-free therapy leads to increased risk behavior and increase the risk of reinfection of HCV in certain populations. Further studies are necessary to investigate HCV reinfection in the DAA era.

2.3 Aims and Objectives

The overall **aims of the CARE East Cohort in RESPOND** are to:

- Discover and validate variants in the host genome influencing susceptibility to contracting AIDS and serious non-AIDS clinical events and adverse reactions to antiretroviral medicines in HIV infected persons.

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- Compile experience for treating HCV infection by use of direct-acting antivirals from across Europe in order to inform best practice recommendations for how to use such medication in settings with current limited access and limited budgets.

Specific objectives for the HIV Outcomes sub-study:

1. Study the impact of host genetics on the risk of development of AIDS and serious non-AIDS events and adverse drug reactions in HIV-positive patients
2. Perform an initial assessment of the treatment-limiting toxicity for existing antiretroviral drugs by linking host genotypes and other factors to short and long-term adverse drug reactions.

Specific objectives for the HIV/HCV Outcomes sub-study:

1. Monitor the uptake of hepatitis C therapy; to describe changes over time and country and use of specific DAA regimens
2. To monitor the rate of SVR and determine factors associated with successful HCV therapy
3. To develop treatment algorithms for optimal use of DAAs in HCV infected patients
4. To study the influence of HCV treatment on long-term risk of development of liver disease and other clinical outcomes
5. To study the incidence of HCV re-infection after achieving SVR

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3 METHODOLOGY

3.1 Study design

The CARE East Cohort study in RESPOND is a retrospective and prospective observational cohort study that includes both HIV-1 mono-infected persons regardless of CD4 cell count and ART status; and HIV-1 infected persons who are positive for anti-HCV antibodies regardless of HCV-RNA, fibrosis stage and prior HCV therapy. Participants are seen at clinics in Georgia, the Russian Federation and Ukraine.

3.2 Expected number of participants

HIV outcome sub-study: The expected number of participants is 4500 (2500 enrolled from sites in the Russian Federation; 1000 from sites in Ukraine; and 1000 from sites in Georgia). Enrolled patients with HCV coinfection will also be counted in the HCV outcome sub-study.

HCV outcomes sub-study: The expected number of participants is 4000 (2000 enrolled from sites in the Russian Federation and 2000 from sites in Ukraine) – those with HIV-HCV coinfection will also be in counted in the HIV outcomes sub-study.

3.3 Inclusion criteria

Inclusion criteria for the HIV Outcomes sub-study:

1. Have a signed Informed consent for the CARE East Cohort study, if required by local authorities
2. Have a signed informed consent for the RESPOND consortium and data repository, if required by local/national legislation in order to have data in the common data repository.
3. Included persons are randomly selected HIV-1 positive persons regardless of CD4 cell count, ART status and co-infection status who are under active follow-up after 1/1/2016
4. Be of age 18 or above at baseline*

Inclusion criteria for the HIV/HCV Outcomes sub-study:

1. Have a signed Informed consent for the CARE East Cohort study, if required by local authorities
2. Have a signed informed consent for the RESPOND consortium and data repository, if required by local/national legislation in order to have data in the common data repository.
3. Randomly selected HIV-1 infected persons who are positive to anti-HCV antibodies regardless of HCV-RNA, fibrosis stage and prior HCV therapy who are under active follow-up after 1/1/2016
4. Be of age 18 or above at baseline*

**Baseline* is defined as the latest of HIV and/or anti-HCV diagnosis after 1/1/2016. For example, someone who was first diagnosed with HIV infection in 1/5/2017 and enrolled into the study will have a baseline of 1/5/2017. An HIV/HCV co-infected person enrolled in the HIV/HCV co-infected population who was first diagnosed with HIV infection in 1/5/2016 and tested anti-HCV positive 1/5/2017 will have a baseline of 1/5/2017.

3.4 Enrolment

Participants in the HIV Outcomes sub-study: a random selection from the local or national HIV database will be made among persons who fulfil the inclusion criteria. The selected persons will be enrolled by the treating physician/study nurse consecutively as they attend the outpatient

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clinic. Selected persons who are lost to follow-up or who died after 1/1/2016 should still be included in the study, provided they satisfy the other inclusion criteria.

Participants in the HIV/HCV Outcomes sub-study: a random selection from the local or national HIV database will be made among persons who fulfil the inclusion criteria. The selected persons will be enrolled by the treating physician/study nurse consecutively as they attend the outpatient clinic. Selected persons who are lost to follow-up or who died after 1/1/2016 should still be included in the study, provided they satisfy the other inclusion criteria.

3.3 Data collection

All centres collect data from their patients at the time of enrolment, and once a year hereafter. The data recorded in the Enrolment and follow up datasets are extracted from the patient records by staff at the participating sites/clinics by manual data keying or electronically. Manual data keying is performed by staff in a secure online browser-based platform called REDCap. Electronics data capture entails local extraction of data from clinical electronic databases and submission through the CHIP-developed web-based RESPOND Electronic submission tool (REST) to the RESPOND common data repository at CHIP - Rigshospitalet, RegionH. Sites reporting via REDCap have access to their own data and can draw reports with their own data (see also Appendix III on data handling and data protection).

Data on specific clinical events (cancer, stroke, myocardial infarction, invasive cardiac procedure, malignancies, renal failure, liver failure, bone fracture and cause of death) will preferably be captured in real-time using REDCap or alternatively reported once a year. The specific events are specified in the enrolment form.

4. DATA ANALYSIS METHODS

4.1 Analysis

Our objectives fall in two broad categories:

1. Discover and validate variants in the host genome influencing susceptibility to contracting AIDS and serious non-AIDS clinical events and adverse reactions to antiretroviral medicines in people living with HIV.
2. Monitor the rate of SVR and determine factors associated with successful HCV therapy and asses the influence of HCV treatment on long-term risk of development of liver disease and other clinical outcomes.

Regarding category 1:

Objectives in the HIV-outcomes sub-study is to investigate the host genomics' influence on susceptibility to contracting AIDS and serious non-AIDS clinical events and treatment tolerability and/or disease progression rates and to identify genetic predictors of toxicity of antiretroviral treatment (ART).

Regarding category 2:

Objectives in the HIV/HCV outcomes sub-study -co-infected subpopulation is to monitor the rate of SVR and determine factors associated with successful HCV therapy and asses the influence of HCV treatment on long-term risk of development of liver disease and other clinical outcomes.

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4.2 Possible Limitations

As for observational studies in general, possible limitations of the CARE in RESPOND study include unmeasured confounding and confounding by indication. Variables may be missing from some participants which may introduce bias and loss of statistical power

5. STUDY SUBJECTS

The study subjects are patients diagnosed after 1/1/2016 with HIV-1 infection, HIV/HCV co-infection or HCV mono-infection under follow up at the participating sites/clinics in Ukraine, Georgia and Russia. To secure the study subjects are representative of the broader patient population in care, we enrol a random sample of participants including those who have been lost-to-follow-up or who have died during the study period.

6. RISK FOR PARTICIPANTS

Participation in the CARE East Cohort study in RESPOND does not include any risk for participants. The study does not test any drugs and participation in this study does not interfere with the treatment/care participants may receive at the clinic.

There are no direct benefits to the participants. However, the benefit of conducting observational research including research includes advancing scientific understanding of HIV infection and other co-infections and co-morbidities and their complications; this knowledge guides international and European treatment recommendations to the benefit of people living with HIV.

7. BIOGICAL MATERIALS

7.1 Blood samples

Whole blood samples will be collected in the CARE East Cohort study in RESPOND from all HIV-1 positive patients regardless of ART status. The blood will be drawn simultaneously with samples collected for the routine clinical management of the patient, thus minimizing any patient discomfort.

Whole blood is drawn in 2 x 4.5mL tubes and distributed in 3 aliquots (approx. 1-1.5 mL each) in 2.0mL screw top cryovials transport vials for shipment for whole blood host genotype analysis. For detailed instructions regarding the collection, labelling, processing and shipment of these samples, please see the CARE Collection and Shipping of Whole Blood Samples – Instruction (Appendix V).

It is the responsibility of the investigator (to be assisted by the courier service and the coordinating centre) to ensure that all study samples for international transport are appropriately handled, packed and shipped.

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7.2 Repository/Biobank

Collected whole blood samples are shipped to the coordinating centre at Rigshospitalet, Denmark, and stored in secure holding facilities at - 80° Celsius. Access to these samples and any analysis performed are the responsibility of the CARE Management Board (MB). Samples will only be used for scientific research as described and will be stored in accordance with The Danish Data Protection Agency's approval. Samples will be destroyed the latest on 31st December 2045 in accordance with current legal and ethical requirements.

8. INFORMATION FROM PATIENT RECORDS

Staff at the sites in the CARE East Cohort in RESPOND will extract data from the patient records of enrolled patients and submit in the Enrolment and follow up datasets. Following data items are extracted:

Demography and basic information: Date of birth, gender, country of origin, ethnicity, height, weight, date of first HIV-1 positive test and mode of HIV-1 transmission.

Laboratory data: Relevant routine virological and immunological data for characterization of the HIV infection, hepatitis C and other relevant co-infections, as well as routine laboratory data that describe the function of the bone marrow, kidneys and liver. Biomarkers of metabolic disease will also be collected.

Medical treatment: Treatment naïve, or all HIV medicine, including start- and stop dates and reason for discontinuation. Medical treatment related to co-infections and co-morbidities.

Clinical events: AIDS, myocardial infarction, stroke, invasive cardiovascular procedures, kidney failure, liver failure, cancer, bone fractures, cause of death.

Additional: Alcohol abuse, smoking, active drug use

9. PERSONAL DATA HANDLING AND APPROVALS

9.1 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with the International Ethical Guidelines for Health-related Research Involving Humans (CIOMS 2016), Good Clinical Practice (GCP) as defined in current EU GCP Directive and all relevant national regulations.

Patients enrolled in the CARE East Cohort in RESPOND are provided with a unique PID number, which serves as the identification of the patient. A de-coding list is held in a safe location by the individual site only.

All study data is marked with the PID number. Date of birth is collected as date, month and year of birth, and no unique person identifiers are present on data submitted to the coordinating centre. If date of birth cannot be reported due to local regulations a standard date (01-07) can be used for all patients and the actual year of birth. All data (hardcopies, computerised and samples) at

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the coordinating centre are stored and protected in accordance with current regulatory laws and approved by The Danish Data Protection Agency (DK: Datatilsynet, approval no. 2012-58-0004, RH-2018-15, I-Suite nr.: 6140)

Every reasonable step will be taken to protect the privacy of participants health information and to prevent misuse of this information. The participants' records (paper/digital) may be seen by institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable and by research staff and study monitors, and their designees.

Data (information) will not be identified by name, or in any other way, in any publication about this study. The patient will be identified only by a code, and personal information from patient records will not be released without the patient's written permission.

9.2 Regulatory approval

Prior to the initiation of the study at each clinical research site, the protocol, all informed consent forms and the participant information materials will be submitted to and approved by the site's Ethics Committee (IRB or IEC). In addition, in case of any future amendments to the study protocol these will be submitted and approved by each site's Ethics Committee (IRB or IEC). After approval, sites must register for the protocol before screening potential participants and must also register for any protocol amendments. It is the responsibility of each participating site to ensure that all necessary documents and approvals are obtained according to local/national regulations.

9.3 Data handling

RegionH, the legal entity where CHIP is based, is the data protection officer (DPO) for the CARE East Cohort in RESPOND study and follows the General Data Protection Regulation (GDPR) in Europe. As CARE and RESPOND researchers physically are located at different European universities and hospitals, datasets containing information from the participants´ medical records and their biologic samples might be analysed at other locations than the coordinating centre provided that this remains within the appropriate ethics, regulatory and data protection approvals. All RESPOND data is annually sent to the Statistical Center at UCL, London, for statistical analysis.

Participants will in the Informed Consent forms be informed about the above conditions (see Appendix III).

10. ECONOMY AND STUDY ADMINISTRATION

10.1 Study sponsor

The CARE East Cohort in RESPOND is investigator-initiated and has been initiated by the partners in CARE. Sponsor and coordinator of the study is CHIP, which is an independent research institution at the Department of Infectious Diseases at Rigshospitalet under the legal entity REGION HOVEDSTADEN (REGIONH), established in Kongens Vaenge 2, DK-3400 Hillerod, Denmark.

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10.2 Funding and Collaborators

The CARE East Cohort in RESPOND is developed within the frame of the CARE project, which runs for 2-years (1 January 2019 to 31 December 2020). CARE has received funding from the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement No 825673. The CARE in RESPOND study is supervised by the CARE project's Scientific Management Board whose members provide support, including study design, study implementation, data analysis and drafting of publications.

10.3 Site reimbursement

Clinics participating in the study will be reimbursed for enrolment and follow up data collection for each participant. Site reimbursement will be done by the CARE partners to the participating staff or hospital/research account.

11. REMUNERATION OF STUDY PARTICIPANTS

No remuneration will be paid to the participants. There are no direct benefits to the participants. However, the benefit of conducting observational research including research on stored samples includes advancing scientific understanding of HIV infection and other co-infections and co-morbidities and their complications; this knowledge guides international and European treatment recommendations to the benefit of people living with HIV or AIDS.

12. RECRUITMENT OF STUDY PARTICIPANTS AND INFORMED CONSENT

Eligible patients will be informed verbally by a doctor or study nurse about the study and will receive written information about the study. The patient will be informed that participation is voluntary and that the patient can withdraw his/her consent at any time without any consequence for his/her treatment or future relationship to the clinic/hospital.

The patient will have the opportunity to ask questions. If participant wish to have time to consider their decision this will be arranged with staff at site.

The Patient Informed Consent form will be signed before any study related activities can begin (Sample form in Appendix II).

The local site PI or his/her designee will inform the patient of all aspects pertaining to his/her participation in the CARE East Cohort in RESPOND study and in the RESPOND consortium and data lake.

13. Publication

Findings from this study, positive, negative or inconclusive, are intended to be published as multi-centre publication(s) in accordance with the ICMJE- guidelines in peer-reviewed journals

and/or presented at medical conferences ('Publication'). CARE Management Board (MB) will review and approve abstracts and publications produced within the scope of the project.

All CARE MB members and all sites contributing data to the study will be acknowledged in all publications/presentations. Copyrights concerning Publication of the study remain with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.

All publications and presentations will be listed on the CARE webpage, www.careproject.eu

14. Ethical Considerations

The study will be conducted according to the Declaration of Helsinki in its current version. The requirements of Good Clinical Practice (GCP) as defined in current EU GCP Directive. Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever affords greater protection of human subjects.

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15. Reference List

Aleman S, Rahbin N, Weiland O, Davidsdottir L, Hedenstierna M, Rose N, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013; 57(2):230-236.

Arenas-Pinto A et al. Risk of Suicidal Behavior With Use of Efavirenz: Results from the Strategic Timing of Antiretroviral Treatment Trial. Clin Infect Dis. 2018 Jul 18;67(3):420-429

CIOMS: International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016. (Link: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf)

Clark R et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009 Dec 24;361(26):2518-28

El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999 Mar 11;340(10):745-50.

Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. J Viral Hepat 2018; 25(3):220-227.

Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. Ann Intern Med 2017; 166(9):637-648.

Haas DW, Taar PE. Perspectives on pharmacogenomics of antiretroviral medications and HIV-associated comorbidities. Curr Opin HIV AIDS. 2015 Mar;10(2):116-22

Hoy JF et al. Immediate Initiation of Antiretroviral Therapy for HIV Infection Accelerates Bone Loss Relative to Deferring Therapy: Findings from the START Bone Mineral Density Substudy, a Randomized Trial. J Bone Min Res 2017; 32(9):1945-1955

Ioannidis JP, Ntzani EE, Trikalinos TA. 'Racial' differences in genetic effects for complex diseases. Nat.Genet 2004 Dec;36(12):1312-8

Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, Silk R, Akoth E, Thomas A, Ahmed C, Espinosa M, Price A, Rosenthal E, Tang L, Wilson E, Bentzen S, Masur H, Kottilil S; and the ASCEND Providers. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. Ann Intern Med. 2017 Sep 5;167(5):311-318. doi: 10.7326/M17-0118.

Lundgren J, et al. Contemporary protease inhibitors and cardiovascular risk. Curr Opin Infect Dis. 2018 Feb;31(1):8-13

Ma Q, Lu AY. Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharmacol Rev. 2011 Jun;63(2):437-59. doi: 10.1124/pr.110.003533. Epub 2011 Mar

Mallal S et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008; 358:568-579

Mannheimer S et al. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis. 2002 Apr 15;34(8):1115-21

Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. Lancet Gastroenterol Hepatol 2018; 3(2):125-133.

Mattevi VS, Tagliari CG. Pharmacogenetic considerations in the treatment of HIV. Pharmacogenomics. 2017 Jan;18(1):85-98.

Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV 2016 Jan; 3(1):e23-e32.

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Nelson MR et al. The genetics of drug efficacy: opportunities and challenges. Nat Rev Genet. 2016 Apr;17(4):197-206

Ntzani EE et al. Consistency of genome-wide associations across major ancestral groups. Hum Genet. 2012 Jul;131(7):1057-71

O'Connor JL et al. Factors associated with adherence amongst 5295 people receiving antiretroviral therapy as part of an international trial. J Infect Dis. 2013 Jul;208(1):40-9.

Peters L, Laut K, Resnati C, Del CS, Leen C, Falconer K, et al. Uptake of hepatitis C virus treatment in HIV/hepatitis C virus-coinfected patients across Europe in the era of direct-acting antivirals. AIDS 2018; 32(14):1995-2004.

Poynard et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol. 2003 Mar;38(3):257-65

Robinson JH. Patient-centered care and adherence: Definitions and applications to improve outcomes. Journal of the American Academy of Nurse Practitioners20(2008) 600–607; 2008.

Thomas DL. Options for treatment of hepatitis C in HIV-infected persons. J Hepatol. 2006;44(1 Suppl):S40-3. Epub 2005 Nov 28

van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012; 308(24):2584-2593.

van Manen et al. Genome-wide association studies on HIV susceptibility, pathogenesis and pharmacogenomics. Retrovirology. 2012; 9: 70.

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Appendix IV Detailed list of data items collected

Section A - Demography and HIV-status

Gender
Mode of HIV infection
Country of origin
Date of HIV-1 confirmatory diagnosis
Is this patient currently an active injecting drug user (at least once within the last month)?
Is this patient currently receiving opiate maintenance therapy?

Section B - Laboratory values - immunology and virology

Most recent CD4 cell counts measured

Section C - Antiretroviral Treatment

Has the patient ever received antiretrovirals? If yes, please fill out the start date and composition of the first ART regimen received, as well as all antiretroviral drugs received in the last 12 months prior to enrolment
Reason for discontinuation

Section D – [HIV-Hep coinfected patients] Hepatitis Virology and fibrosis screening

Has a liver biopsy ever been performed?
Has FibroScan of the liver ever been performed?
Has Acoustic Radiation Force Impulse (ARFI) ever been performed

Section E - Treatment against hepatitis C and tuberculosis

Has HCV treatment ever been given?
Start and stop dates for HCV treatment
Was treatment interrupted before schedule?
Response
Has treatment against tuberculosis ever been given?
Start and stop dates for tuberculosis treatment
Drop down menu with different TB drugs
Was resistance of *Mycobacterium Tuberculosis* detected?
If yes, was it: monoresistance / MDR-TB / pre-XDR / XDR?

Section F - Severe Opportunistic Infections and sexually transmitted infections

Syphilis + date of diagnosis

Section G - Clinical Events

Has the patient had any of the following clinical events?
If yes, please complete the following section for all clinical events that have occurred since 1/1/2016.
- Bone fracture - Cancer, AIDS defining - Cancer, Non-AIDS defining - Diabetes - End Stage Liver Disease (acites, hepatic encephalitis, hepato-renal syndrome, oesophageal gastric-or varices or liver transplant)

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- End Stage Renal Disease (hemo or peritoneal dialysis > 3 months or renal transplant)
- Invasive cardiovascular procedure (ICP) (Coronary artery by-pass grafting, coronary angioplasty/stenting and/or carotic endarterectomy)
- Myocardial infarction (MI)
- Stroke

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Appendix V Lab Instructions

CARE Collection and Shipping of Whole Blood Samples –

Instruction, Version 1.0 dated 6 May 2019

Procedures:

Following consent to enrolment in the CARE cohort and Respond data repository, participants will be asked to sign an informed consent form to donate whole blood samples for future research. Consenting participants will have the following collected:

- 6mL of frozen whole blood collected and shipped as directed in this protocol.

Contact information (address for shipments):

CHIP (Centre for Health and Infectious Disease Research), Department of Infectious Diseases, Section 2100
Øster Alle 56, 5th floor
DK-2100 Copenhagen Ø
Denmark
Tel: +45 35 45 57 57
Fax: +45 35 45 57 58
Email: chip.rigshospitalet@regionh.dk
Web: www.regionh.dk www.chip.dk

Contact Person:
Bente Rosdahl Nykjær
Biomedical Laboratory Scientist
Direct phone: +45 35 45 57 78
Fax: +45 35 45 57 58
E-mail:bente.rosdahl.nykjaer@regionh.dk

Specimen Collection:
The following Table describes the specimen to be collected for CARE participants, the type of collection container to use, the amount of blood to draw, the number of transport vials required, and the specimen label to be used

Specimen	Frequency of Specimen collection	Type of collection container	Volume of Blood to draw	Number of transport vials 1-1.5 mL each vial	Label to be used

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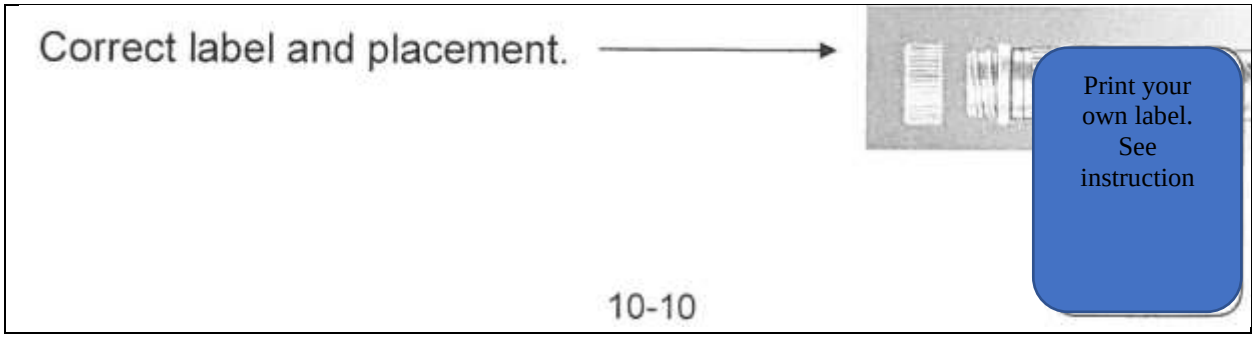
Whole blood	Enrolment	EDTA lavender top	Two 4.5mL tubes	3	Whole Blood CARE patient ID Date of blood collection

EDTA Whole Blood Specimens Processing:

1- Collect the CARE participant whole blood in two 4.5mL EDTA lavender-top EDTA tubes
2- Thoroughly mix the blood with additives by gently inverting the tube 4 or 5 times. Do not centrifuge
3- Before aliquoting, pre-label the transport vials with a label containing the following information: Whole Blood; CARE patient ID; and date of blood collection. Clearly label the tubes as illustrated below (Please print your own labels)



4- Collect blood using a sterile pipette
5- Distribute whole blood in 3 aliquots (approx. 1-1.5 mL each) in 2.0mL screw top cryovials. Glass vials are not permitted. If cryovials are not available to you, please contact CHIP.
6- Store blood samples at -70° Celsius or liquid nitrogen within 4 hours of blood collection. If -70° Celsius or liquid nitrogen is not available, whole blood specimens may be stored at a -20° Celsius freezer for up to 4 days but then must be transferred on dry ice to a -70°/80° freezer.
7- Keep a list of samples collected/stored available. Please ensure clear reference to CARE participant ID.
8- Describe the location in the grid box of each blood sample. The figure below depicts the order in which the samples should be placed in the grid box:

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1	2	3	4	5	6	7	8	9
10	11	12	13	14	15	16	17	18
19	20	21	22	23	24	25	26	27
28	29	30	31	32	33	34	35	36
37	38	39	40	41	42	43	44	45
46	47	48	49	50	51	52	53	54
55	56	57	58	59	60	61	62	63
64	65	66	67	68	69	70	71	72
73	74	75	76	77	78	79	80	81

Shipping:

Blood samples should be stored locally until shipped to the coordinating center at CHIP, Rigshospitalet. Blood samples should be sent annually or when a large volume of samples (more than 250 vials) is ready for shipment.

When ready to ship samples, please contact CHIP for precise instructions on handling, packaging and shipping.

Please identify a courier company in your country that can be used for international shipments. Normally, the courier provides sites with complete boxes when shipment is arranged.

CHIP will contact the courier to be used for practical arrangements regarding delivery.

Description on CARE sample ID.

Each CARE participant will have a 10-digit identification number like this: XXX-AAAAAAA, where XXX refers to the 3-digit center code and AAAAAA to the 7-digit patient code or sequence of enrolment.

- Ukrainian sites will be marked from 130 and onwards.
- Russian sites will be marked from 131 and onwards.
- Georgian sites will be marked from 106 and onwards.

Each site has to keep a record of all participations, connecting their personal ID to their CARE ID number.

The list following the samples to be shipped, should only contain the participants CARE ID number and the date of blood sampling, not the participants personal ID number or name.

The label on the samples to be shipped has to give information (in clear writing) on:

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Where the sample is taken-XXX

The participants patient code-AAAAAAA

The date the blood sample were taken.

Sample type: Whole blood, plasma ect.

Site 130 CARE ID: 130-0000001 Sample date: 12 March 2019 Whole Blood

This example shows that the sample is taken on site 130 in Ukraine – it is the first participant 0000001 and the blood sample is taken the 12th of March 2019.

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