MISTRAL Study Protocol

An affiliated EuroSIDA study

Gut microbiome correlates of serious AIDS and non-AIDS events

Sponsor & Coordinating Centre:

Rigshospitalet – University of Copenhagen
CHIP, Section 2100
Blegdamsvej 9
DK-2100 Copenhagen Ø, Denmark
Tel: +45 35 45 57 57
Fax: +45 36 47 33 40

Web: www.regionh.dk, www.chip.dk
CHIP Email: chip.rigshospitalet@regionh.dk
MISTRAL Email: mistral.rigshospitalet@regionh.dk

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LIST OF ABBREVIATIONS AND DEFINITIONS

CHIP	Centre of Excellence for Health, Immunity and Infections
CVD	Cardiovascular diseases
DPO	Data Protection Officer
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
NAE	non-AIDS Event
rRNA	Ribosomal ribonucleic acid
RegionH	Capital Region of Copenhagen, Denmark
SNAE	serious non-AIDS event

1 STUDY BACKGROUND AND RATIONALE

1.1 Background and Rationale

The HIV/AIDS pandemic continues to be one of the major health challenges ever faced by mankind. Far from being resolved, HIV is soaring in Eastern Europe (60% increase in new infections and 27% increase in deaths since 2010) and other regions of the world despite increasing access to antiretroviral treatment[i]. There is emerging evidence that the human microbiome impacts some of the most important clinical aspects of HIV-1 infection, including immune disorders, chronic inflammation and accelerated aging[ii]. Work in other viral diseases and cancer immunotherapy suggest a critical role of the human microbiome also in the outcome of immune therapeutic interventions in HIV-1 infection[iii].

The Microbiome-based stratification of individuals at risk of HIV-1 acquisition, chronic clinical complications, antimicrobial drug resistance, and unresponsiveness to therapeutic HIV-1 vaccination (MISTRAL) is a European Union (EU) Horizon 2020 funded project that aims to explore the impact of the human microbiome on clinical outcomes in people living with HIV (PLWH). The MISTRAL project brings together a team of world-class HIV and microbiome researchers with ideal complementary knowledge and expertise. This team will work to discover and validate novel gut microbiome biomarkers to inform rationally designed, mechanistically-driven interventions on the gut microbiome to mitigate HIV-1 acquisition, systemic inflammation, chronic clinical complications, antimicrobial drug resistance, and boost the efficacy of HIV cure immunotherapies.

Within the MISTRAL project, the MISTRAL study will explore the impact of the microbiome on clinical outcomes in a large clinical cohort through the collection and analysis of stool and blood samples. The MISTRAL study will utilize the long-established network, clinical sites and expertise of the EuroSIDA study, a prospective, observational cohort study of PLWH that has been collecting observational data since 1994.

The stool samples collected in the MISTRAL study will configure a microbiome repository module. The microbiome data will be combined with those of other biomarkers obtainable from testing blood samples, which could result in increased efficiency and the possibility to use other biomarkers to test the relevance of specific hypothesized pathways. Ultimately, the expected outcome of the MISTRAL study is to have a better basic understanding of the pathophysiological factors of the interplay of HIV infection and the human microbiome.

If successful, MISTRAL, and the MISTRAL study, will benefit millions of human beings living with, or at risk of acquiring HIV-1 infection, and will produce novel concepts and technical innovations applicable to other human diseases. By doing that, MISTRAL will help to unlock the full clinical potential of the human microbiome to stratify patient outcomes and will irreversibly bring microbiome science closer to clinical practice.

1.2 Study Objectives

The primary objective of the MISTRAL study is to strengthen and evaluate the understanding of the association between the gut microbiome composition and the risk of developing serious AIDS and non-AIDS events (NAE), including cardiovascular events. The second objective is to evaluate the associations between the gut microbiome composition and function and pathologic increases in inflammation and coagulation mediators in PLWH. The third objective is to develop a risk score which makes use of information in the gut microbiome as well as other risk factors separately for the different endpoints.

2 METHODOLOGY

2.1 Study Design

The MISTRAL study is an observational protocol and requires the additional sampling of microbiome related clinical data as well as the collection of stool and blood from participants. The proposed study aims to include microbiome stool samples and blood samples from 1,000 individuals in established EuroSIDA sites, who will provide a sample at baseline and an additional follow-up sample between 10-24 months after baseline. These biological samples will be used to conduct pre-specified analyses into microbiome and immunological related factors, as well as forming the basis of an ongoing research biobank for future exploration of the impact on microbiome on clinical outcomes in PLWH. Clinical follow-up data from participants will be collected annually for two-four years after enrolment and may be extended based on the availability of project funding. For a subset of the cohort, analyses of host-genetic material will also be performed. A separate consent for the analysis of genetic material will be sought and consent for analysis of genetic material is not required for participation in the MISTRAL study.

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

- HIV-1 positive persons
- Age ≥50 years old
- Prospectively followed in a EuroSIDA site

Exclusion Criteria:

- Creatine Clearance <50
- Child-Pugh C end-stage liver disease
- Any ongoing severe life-threatening disease
- Experiencing any of the following events prior to inclusion: myocardial infarction, stroke, an invasive cardiovascular procedure, AIDS (diagnosed within 5 years of MISTRAL enrolment), and non-AIDS cancers (not including non-melanoma skin cancers)

2.3 Data Collection

MISTRAL study enrolment, participant information and follow-up data are captured electronically in electronic case report forms (e-CRFs) using the secure online browser-based Research Electronic Data Capture tool (REDCap). Electronic data capture includes extraction from local electronic databases and submission through an electronic submission tool (the RESPOND Electronic Submission Tool (REST)). Electronic data is submitted in the HICDEP (HIV Cohorts Data Exchange Protocol) format.

Data items collected in the MISTRAL study through enrolment and follow-up forms:

- Demography and basic information: Date of birth, gender, country of origin, race, 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 B+ 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; COVID-19 testing, hospitalization and vaccine status
- Medical treatment: 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, diabetes, bone fractures, cause of death

Additional data will be collected on a separate MISTRAL Questionnaire at baseline and follow-up visits. This data will be entered into REDCap by site staff. Data collected on the MISTRAL Questionnaire will include:

- Stool microbiome data such as time of defecation and average stool frequency
- Patient specific data about antibiotics usage, antifungal treatment, anti-inflammatory medication, hormonal birth control, hormone replacement therapy, gastrointestinal disease, gluten intolerance, international travel, pets, exercise, birth method
- Diet specific data such as dietary classification, portions of red meat, fruit/vegetables, diary/milk, fiber/whole grain, vitamins, alcohol.

Furthermore, there will be stool, plasma and whole blood sample collection at baseline and follow-up visits. An overview is shown in Table 1 below and further details regarding sample collection are described in Section 4.1.

Table 1: Overview of sample and data collection

	Baseline	Year 1 (10-24 months post baseline)	Year 2	Year 3	Year 4
Stool	x	x	X[a]		
Plasma	x	x	x[a]		
Whole Blood	x	x	x[a]		
MISTRAL enrolment form	x				
Follow-up form	x[b]	x	x	x	x
MISTRAL Questionnaire	x	x	x[a]		

[a]Only if not collected at year 1 visit

[b]If already part of EuroSIDA

2.4 Study Procedures and Follow-up

Enrolment:

Subjects eligible for the study will review and undergo informed consent. Once consented, subjects will receive a stool specimen collection kit to be used at home or on site which should be returned to the clinic within 48 hours. During the site visit within 48 hours, the participant will submit a stool sample and have a blood sample taken. Investigators from participating sites will complete the MISTRAL Questionnaire and enrolment form in the online secure data reporting system REDCap. Enrolments of individuals prospectively followed in the EuroSIDA sites will be conducted until reaching the target of 1,000 participants.

Follow-up:

Participants will provide a follow-up stool, plasma and whole blood sample between 10-24 months after enrolment. Investigators from participating sites will complete a second MISTRAL Questionnaire and follow-up form in REDCap. Hereafter participants will continue to be followed-up annually for two-four years after enrolment and may be extended based on the availability of project funding.

2.5 Study Duration

Data and sample collection for the MISTRAL study will begin in 2021. Final data and sample collection will be completed in 2025.

Following the closure of the MISTRAL study, the Principal Investigator (PI) at the EuroSIDA sites will maintain a copy of all site study records in a safe and secure location. The study coordinating centre, Centre of Excellence for Health, Immunity and Infections, (CHIP), at Rigshospitalet, Denmark will inform the investigator of the time period for retaining these records. Upon completion of the MISTRAL study, the following activities must be conducted by the PI, as appropriate:

- Return of all related study data to the coordinating centre
- Data clarifications and/or resolutions
- Review of site study records for completeness
- Shipment of stored samples to the repository at the coordinating centre.

3 RISKS AND BENEFITS TO PARTICIPANTS

No remuneration will be paid to the participants. Potential risks for participants regarding blood samples include slight pain, bleeding, bruising, light headedness, anxiousness, and in rare cases fainting or infection or a blood clot where the needle enters the body. There are no risks involved in delivering stool samples other than potential slight discomfort.

There are no immediate benefits to the participants. However, we expect that the information gained from this study will improve knowledge about HIV long-term prognosis leading to changes in the treatment guidelines and advance care and treatment for PLWH. In addition, the benefit of conducting observational research that includes analysis of biological samples will advance scientific understanding of HIV infection and other co-infections and co-morbidities as well as their complications.

The knowledge gained will guide international and European treatment recommendations for the benefit of PLWH and national health systems.

Potential benefits for PLWH may include decreased likelihood of cardiovascular and other AIDS and non-AIDS related morbidity and mortality. For national health systems, fewer follow-up visits as a result of reduced complications in patients' management will be cost saving. Additionally, results may improve risk prediction in PLWH.

4 BIOLOGICAL MATERIALS

4.1 Sample Collection

Stool Samples

Participants contribute a minimum of two ml of stool per sample. Stool samples are to be collected at baseline and at one follow-up visit (either the year 1 or year 2 visit).

Blood Samples

Participants contribute a blood sample of approximately 18 ml. Blood samples are to be collected at baseline and at one follow-up visit (either the year 1 or year 2 visit).

For detailed instructions regarding the collection, labelling, processing and shipment of stool and blood samples, please see the MISTRAL Lab Manual at www.chip.dk.

4.2 Sample Repository/Research Biobank

Collected stool, plasma and whole blood samples will initially be shipped to the coordinating centre at CHIP, Rigshospitalet, Denmark, and stored in secure holding facilities at - 80° Celsius. These samples will then be transferred to the MISTRAL biobank at IrsiCaixa, Hospital Germans Trias I Pujol, Barcelona Spain. Participants can at any time revoke their consent and have their samples destroyed. Samples will be used for scientific research as described below and will be stored for the duration of the study. Samples will be destroyed the latest on 31st December 2045 in accordance with current legal and ethical requirements.

Collection and analysis of biological samples using novel and established techniques is a key aspect of the MISTRAL study. Data generated from these analyses will be used as part of the three objectives of this study to better understand and predict the development of serious AIDS and non-AIDS events and their link to the microbiome. As part of the MISTRAL Consortium (see Appendix A), several analyses are planned for the collected samples. The data generated from these analyses and important data protection and General Data Protection Regulation (GDPR) concerns related to these data are addressed in Section 5, Data Management and Statistical Analysis. The planned analyses are outlined below, with a short explanation of their value for the MISTRAL study in parenthesis.

Planned analyses of stool samples include:

- **Shotgun metagenomic and 16S rRNA gene sequencing**
  (data from these analyses will include information regarding all bacterial species from the gut microbiome and their potential functions, allowing for associations between bacteria, bacterial diversity as well as functionality with clinical outcomes)
- **Faecal metabolomics, lipidomics and proteomics**
  (data from these analyses will add to the above data, with information of what the bacteria found in the previous analyses have produced in forms of metabolites (metabolics), fat-based compounds (lipidomics) and proteins (proteomics). This additional data will give an in-depth look at the bacterial ecosystem of the human gut, allowing the study to assess not only “who is there” in the bacterial ecosystem, but also “what are they doing/producing”? This information is essential for associations with the clinical outcomes of the study and will give a deeper understanding of the mechanisms behind potential associations.)

Planned analyses of plasma samples include:

- **Analyses of serious AIDS and non-AIDS biomarkers (IL-6, D-dimer and CRP)**
  (data from these analyses have been performed in earlier studies and are important for the present cohort to allow for comparisons between patients and for when assessing the less studied forms of data (e.g. shotgun metagenomic, 16S rRNA, metabolomics, etc.))
- **Analyses of other pro- and anti-inflammatory cytokines including plasma metabolomics, lipidomics and proteomics**
  (data from these analyses will allow for an understanding of how the processes in the gut (measured by the above-mentioned stool analyses) can potentially impact the blood system of patients by assessing blood metabolites (metabolomics), fat-based compounds (lipidomics) and proteins (proteomics). Again, these forms of data add to understanding the mechanisms of the gut microbiome and how they may influence clinical outcomes in HIV-positive individuals.

Planned analyses of whole blood samples include:

- **Transcriptomics**
  (data from these analyses will show the RNA transcripts in the blood, showing the stage before proteins or metabolites are made, adding to the understanding of plasma sample analyses detailed above).
- **Genomics** (for those who provide specific genomics consent)
  (data from these analyses will allow for a full halobiont perspective of each individual, enabling the study to assess if outcomes in individuals are driven by genetic or gut microbiome factors, or a potential combination of these factors)

These analyses will be performed by members of the MISTRAL Consortium. However, due to the expertise required, certain analyses will require collaborations or certain aspects of the analyses services to be performed outside the EU. All collaborators, subcontractors or service providers outside the EU are to abide by GDPR and EU requirements, and samples will not be sent outside the EU without data transfer agreements.

4.3 Genomics

Whether in the form of whole blood or blood products (e.g., extracted host DNA), the stored whole blood will be used for studies relevant to the aims of this protocol. Tests will include evaluating for genetic variants related to the gut microbiome composition and the risk of developing serious AIDS and non-AIDS events. The material will be used, via genotyping that may include target genes, for genome-wide single-nucleotide polymorphism (SNP) analysis, whole-genome resequencing or other analyses for appropriate control of population structures. These analyses may be merged with other studies that are carried out by other groups.

Due to the experimental nature of the assays involved and the inherent difficulty of interpreting their clinical significance in individual cases, individual test results will not be provided to participants, investigators, clinical site research staff or healthcare providers. Summaries of clinically relevant findings from pooled genetic tests conducted under research protocols approved by the MISTRAL and relevant ethics committees will be disseminated to all study participants through individual clinical units and the MISTRAL website. In extraordinary circumstances when knowledge generated from genetic tests may have profound and unequivocal implications for the health of study participants, every reasonable effort will be made to offer study participants a repeat of the genetic test done outside of the study. However, original study results cannot be provided to participants or clinicians under any circumstances.

4.4 Future Research Samples

As it is not possible to know all the analyses that may reveal crucial aspects of the relationship between the microbiome and clinical outcomes in this population, a proportion of the samples collected will also be stored for future, as yet unspecified research. All projects seeking access to future research samples must have ethical approval and agree to abide by GDPR regulation. Proposed research utilizing stored samples will be reviewed and approved by the protocol team, EuroSIDA Scientific Steering Committee and the MISTRAL Consortium. Samples will not be sold to third parties or used directly to produce commercial products.

If possible, samples with remaining material will be returned to the main research biobank after analysis. These samples will be marked indicating they have been used previously so that future researchers are aware of possible sample degradation due to freeze-thawing.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Data Collection and Transfer to the MISTRAL Database

Clinical data collected as part of this study will be collected initially into MISTRAL servers based at CHIP. At CHIP, the clinical data will undergo quality assurance procedures (outlined in Section 6, Quality Assurance) before being transferred to the MISTRAL data repository for storage. The MISTRAL data repository is contained within Amazon Web Services servers located within the EU and complies with EU data protection. Data contained within the MISTRAL data repository will be made available upon request to members of the MISTRAL Consortium for analyses related to the primary objectives of the study. Data will also be available for external researchers. Any external research projects will be assessed for scientific relevance by the MISTRAL Consortium and EuroSIDA Scientific Steering Committee and will require relevant ethics approval as well as a signed, EU approved, data transfer agreement. Only pseudonymized data will be sent to external researchers. Further details on the personal data handling for this study can be found in Section 8, Personal Data Handling and Approvals.

As stipulated by the conditions of the Horizon EU 2020 grant, the results of the MISTRAL project and the MISTRAL study will be uploaded to EU-based public repositories and shared through an interactive web-based repository, the MISTRAL project iVIHome portal. All data will be fully anonymised and compliant with GDPR-requirements prior to being uploaded into the repository.

5.2 Data Analysis Plan

Simple descriptive statistics will be used to describe all participants enrolled. Clinical data and data generated from the analysis of biological samples will be analysed using a variety of bioinformatics and biostatistical methods. Full details on these methodologies will depend on the data type and will be outlined in the statistical analysis plan for each objective. Survival analysis will be conducted using standard techniques such as Kaplan-Meier curves, log-rank test and univariable and multivariable Cox regression model. Unadjusted and adjusted estimates of the relative hazards with 95% confidence intervals will be tabulated. Standard linear models' approach as well as more sophisticated machine learning techniques such as logistic regression with LASSO estimation and Random Forests will be used to derive a predictive score for both endpoints. Because of the inclusion of participants from various regions of Europe, consideration will be given to potential confounding due to geographical location and population stratification.

5.3 Power Calculations for Clinically Relevant Endpoints

Sample size calculation is based on our experience to date of the events observed in the EuroSIDA cohort over the 5-year period 2013-2018 in the population aged 50 or older. In this target population, by 5 years of follow-up, the cumulative incidence was 5.5% for cardiovascular disease (CVD) events (a total of 196 expected events) and 15.6% for serious non-AIDS events (SNAE) (n=294). The assumption is that similar rates could be observed in the new prospective cohort of 1,000 patients.

Statistical considerations are summarized below. With 1,000 people, the incidence of events assumed above, at the 0.05 level of significance (2-sided), the tables below show the predicted power of the analysis for 50% prevalence of high gene richness, an expected 5-year rate of loss to follow-up of 10% and a range of magnitudes of the association between gene richness and outcomes:

CVD outcome

Expected 5-year hazard in low gene richness (reference group)	Hazard Ratio	Power
6%	1.5	21%
6%	2.0	56%
6%	2.5	84%

SNAE outcome

Expected 5-year hazard in low gene richness (reference group)	Hazard Ratio	Power
16%	1.5	50%
16%	2.0	95%

In summary, with 1,000 prospectively followed participants, in the CVD outcome analysis power is suitable for detecting relative risks of 2.5 or greater with 50% prevalence of the exposure. Power is greater for the analysis with SNAE as endpoint and suitable for detecting relative risks of 2.0 or greater.

6 QUALITY ASSURANCE

6.1 Study Monitoring of Data Quality

The proposed MISTRAL study will undergo extensive quality assurance procedures and has the following quality assurance (QA) processes in place:

1. Data quality checks/rules in REDCap that automatically detects and notifies when a user has entered in data erroneously, i.e. units measured beyond set limitations, etc.
2. The RESPOND Electronic Submission Tool (REST) for sites submitting data
   In a data dump, generates reports of errors during submission, making it possible to correct errors before submitting final data. REST does more than 200 data checks on submitted data
3. Generation of lists that detect missing data and/or data that need further clarification or correction are sent to sites for review and resolution
4. 100% QA review and validation of Event forms by Medical Personal
5. Extensive Data cleaning procedures once data has been downloaded to the database.

7 ETHICS

Participating sites will adhere to their appropriate local ethics approval procedures as required. Participants taking part in the MISTRAL study should provide informed consent prior to having clinical data and specimens collected. In addition to consent for participation in the MISTRAL study, participants will also be asked to consent for analysis of host genetic material.

Studies affiliated with EuroSIDA adhere to the Declaration of Helsinki[iv] and the requirements of Good Clinical Practice (GCP) as defined in the EU GCP Directive 2005/28/EC[v]. All data supplied to the MISTRAL study will follow local or national guidelines as appropriate, and enrolled participants are pseudonymized by assignment of a unique identifier, by the participating site before data transfer.

As data controller, the Coordinating Centre located within the Danish Capital Region of Copenhagen, Denmark, store, share and protects data in accordance with current legislation and under approval by The Danish Data Protection Agency (j.nr.: RH-2018-15), currently under the EU's GDPR (EU) 2016/679[vi].

EuroSIDA is registered at ClinicalTrials.gov (Identifier: NCT02699736).

8 PERSONAL DATA HANDLING AND APPROVALS

8.1 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

Participants in the MISTRAL study are de-identified and assigned a unique 7-digit Patient ID (PID) number at the sites where they are enrolled. The de-coding list is held by the individual site in a safe location.

All study data is marked with this 7-digit 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. All data (hardcopies, computerised and samples) at the coordinating centre are stored and protected in accordance with current regulatory laws and approved by The Danish Data Protection Agency (j.nr.: RH-2018-15). The MISTRAL data repository is stored and protected in accordance with current regulatory laws and approved by the Spanish Data Protection Authority.

The Principal Investigators and clinical site staff will keep any information and data related to the MISTRAL study provided by the coordinating centre, and all data and records generated in the course of conducting the study, confidential and will not use the information, data, or records for any purpose other than conducting the study.

Every reasonable step will be taken to protect the privacy of participant health information and to prevent misuse of this information. The participant 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.

8.2 Regulatory Approvals

It is the responsibility of each participating clinical research site to ensure that all necessary documents and approvals are obtained according to local and/or national regulations before any study related activities are performed.

The PI at each site is responsible for obtaining and maintaining this/these approval(s) at all times during the conduct of the study as stipulated in the site contract.

8.3 Data Handling

The Knowledge Center for Data Reviews within the Capital Region of Copenhagen, Denmark (RegionH), is the data controller for the MISTRAL study. The Knowledge Center for Data Reviews follows GDPR in Europe. The Data Protection Officer (DPO) for the MISTRAL study RegionH. The DPO for the MISTRAL project is IrsiCaixa in Barcelona, Spain. The contact details of the DPO in Denmark and Spain will be provided to study participants.

As MISTRAL researchers physically are located at different EU and non-EU universities and hospitals, datasets containing information from the participants´ medical records and their biologic samples from the MISTRAL study might be analysed at other locations than the coordinating centre provided that this remains within the appropriate ethics, regulatory and data protection approvals.

MISTRAL study participants will be informed about the above conditions in the informed consent process.

9 SAFETY CONSIDERATIONS

No ethical, safety or other issues have been identified within this study. Minor potential risks for participants when providing blood samples include slight pain, bleeding, bruising, light headedness, anxiousness, and in rare cases fainting or infection or a blood clot where the needle enters the body. There are no risks involved in delivering stool samples other than potential slight discomfort. The study does not intervene with the clinical management of the participants and it does not test or investigate any treatments. Participants remain under the guidance and treatment of their personal physician and treatment will not be influenced by the study.

10 ANTICIPATED PROBLEMS AND EXPECTED OUTCOMES

Anticipated Problems:

Collection of stool samples is a new process for many sites. Stool samples need to be collected within 48 hours of defecation. Furthermore, the study protocol requires two visits for participants. This will require the site to track the participants and contact them between 10-24 months after the baseline samples are collected.

Statistical power will likely be limited for investigating factors associated with cardiovascular disease (descriptive analysis only).

Expected Outcomes:

- A better basic understanding of the interplay between HIV infection and the human microbiome
- Identify the effect of the microbiome on the risk of clinical events
- Well powered to assess the impact on the risk of serious non-AIDS events[vii] in general
- Identify the effect of the microbiome on inflammation and coagulopathic pathways
- Determine if microbiome factors improve risk prediction of clinical events in PLWH

11 STUDY ADMINISTRATION AND ECONOMY

11.1 Sponsor and Coordinating Centre

The study sponsor and coordinator is CHIP, which is an independent research institution at Rigshospitalet, in the Capital Region of Copenhagen, Denmark, RegionH.

11.2 Funders

MISTRAL has received funding from the European Commission Directorate-General for Research and Innovation Horizon 2020 Grant Agreement number 847943 (9,994,383.75€).

11.3 Site Reimbursement

Sites participating in the MISTRAL study will be reimbursed for enrolment and follow up data collection for each participant, event forms and sending samples. Site reimbursement will be to the hospital/research account.

12 PUBLICATION

Findings from this study, positive, negative or inconclusive, are intended to be published as multi-centre publication(s) in accordance with the International Committee of Medical Journal Editors' guidelines in peer-reviewed journals and/or presented at medical conferences ('Publication'). Research proposals will be submitted and reviewed under the oversight of the MISTRAL Consortium and EuroSIDA Steering committee. Final approval of projects will be made by the MISTRAL Consortium and EuroSIDA Steering Committee.

The EuroSIDA study group will appear in an appendix in all published manuscripts. 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 CHIP webpage, www.chip.dk. A description of the MISTRAL study will be available at clinicaltrials.gov.

13 REFERENCES

[i] "UNAIDS announces nearly 21 million people living with HIV now on treatment." UNAIDS, 20 Nov. 2017, https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/november/20171121_righttohealth_report. Press release.

[ii] Li, S, Armstrong, A, et al. Complexities of gut microbiome dysbiosis in the context of HIV infection and antiretroviral therapy, 2016. Clin Pharmacol Ther. 2016; 99(6): 600-611.

[iii] Herrera, S, Martinez-Sanz, J, Serrano-Villar, S. HIV, Cancer, and the Microbiota: Common Pathways Influencing Different Diseases, 2019. Front Immunol. 2019; 10:1466.

[iv] World Medical Association, 2018, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[v] Journal of the European Union, 2005, https://eur-lex.europa.eu/eli/dir/2005/28/oj

[vi] Journal of the European Union, 2016, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679

[vii] Hsu, D, Sereti, I, Serious Non-AIDS events: Immunopathogenesis and interventional strategies, 2013. AIDS Research and Therapy, 2013; 10(1):29.

Appendix A: MISTRAL Consortium Members

Fundacio Privada Institut De Recerca De La Sida-Caixa
Carretera de Canyet, s/n, 08916 Barcelona, Spain

Universite D'Aix Marseille
Boulevard Charles Livon, 58, 13284 Marseille, France

Region Hovedstaden
Kongens Vænge, 2, 3400 Hillerød, Denmark

Case Western Reserve University – CWRU
Euclide Avenue 10900, Cleveland OH 44106-7037, United States of America

Karolinska Instituttet
17177 Stockholm, Sweden

Projecte Dels Noms-Hispanosida
Calle Comte Borrell, 164-166, Bajos, 08015 Barcelona, Spain

Consorci Institut D'Investigacions Biomediques August Pi I Sunyer
Calle Rossello, 149, Bajos, 08036 Barcelona, Spain

Fundaction Privada Instituo De Salud Global Barcelona
Calle Rossello, 132, Planta 5, 08036 Barcelona, Spain

Asphalion S.L.
Calle Tarragona, 151-157 PL, Barcelona (08014), Spain

Aelix Therapeutics S.L.
Calle Baldiri Reixac, 4-8, Barcelona (08028), Spain

Vendanta BioSciences, Inc.
19 Blackstone St., Floor 3, Cambridge MA 02139, United States of America