2000 HIV Human Functional Genomics Partnership Program

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Primary Objectives• Employ a systems biology approach to identify a set of candidate biomarkers (BM) in circulation and/or pathways & mechanisms that correlate with particular non-AIDS defining comorbidities (ie NASH, CVD) in HIV+ individuals...

Ethical review	Approved WMO
Status	Completed
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON52894

Source
ToetsingOnline

Brief title
2000-HIV study

Condition

- Immune disorders NEC
- Ancillary infectious topics
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ViiV Healthcare Inc.

Intervention

Keyword: HIV, immunology, microbioma, transcriptoma

Outcome measures

Primary outcome

Primary outcomes:

• Metadata: Lifestyle questionnaires, Neuropsychiatric questionnaire

• Clinical data: e.g. CD4 nadir, viral load, ART

• CVD Clinical events, metabolome, ECG IMT measurement

• DNA: Gene polymorphisms at DNA level, epigenetics

• Microbiome: Presence of groups of bacteria

• Phenotype: Specific populations of circulating cells

• Functional data: Cytokine production

• Virology Reservoir, resistance

• NAFLD Fibroscan/specialized ultrasound

Primary study endpoints:

• Generate a high quality, robust, cross-omics dataset complementary to clinical and immunological data within well-characterized clinical cohorts of HIV patients.

• Conduct systems biology analyses aligned with collaboration objectives, that will result in identifying novel biomarkers and pathways/mechanisms that determine susceptibility to non-AIDS complications such as NAFLD and CVD in PLHIV.

• Identify omics-based characteristics and biomarkers associated with extreme

HIV phenotypes.

• Describe potential relationship of host/immune profiles on efficacy, safety,

and tolerability of different standard of care regimens.

• Identify the contribution of aging, female gender, or genetic background on

host-immune profiles and non-AIDS complications in PLHIV.

Secondary outcome

NA

Study description

Background summary

Chronic HIV infection leads to a deregulated immune system, even if viral suppression is achieved by combination AntiRetroviral Therapy (cART). On the one hand, HIV causes persistent immune activation, which is related to an array of common non-AIDS related diseases such as cardiovascular disease (CVD) or non-alcoholic fatty liver disease (NAFLD). On the other hand, accelerated aging/depletion (senescence) of the immune system hinders effective immunity against infectious diseases and cancer. Likewise, this derailed inflammatory balance creates a niche for persisting viral replication and reservoir, and prevents cure or functional cure. Mechanisms behind this phenomenon are poorly understood. Restoring this balance has proven to be challenging and new targets for effectively restoring it are lacking. An integrative view on the functionality of different traits of the immune system is therefore warranted. Studies within the Human Functional Genomics Project (HFGP) have shown such integrative view in healthy subjects and certain disease cohorts. Also a limited HFGP study in 200 HIV patients provided first insights in immune dysregulation in these patients. Inclusion of a larger cohort of HIV infected patients in the discovery cohort, also with more extreme clinical phenotypes allows us a more precise assessment of the factors underlying the immune dysregulation, findings that need to be confirmed in a confirmation cohort. These studies may eventually result in new targeted treatments restoring the balance in immunity, reducing subsequent morbidity and mortality, and pave the way for effective strategies on viral elimination.

Study objective

Primary Objectives

• Employ a systems biology approach to identify a set of candidate biomarkers (BM) in circulation and/or pathways & mechanisms that correlate with particular non-AIDS defining comorbidities (ie NASH, CVD) in HIV+ individuals relative to healthy controls and well matched non-HIV chronic disease phenotypes; candidate BMs may be single or algorithm-based multi-parameter BM profile.
• Integrate diverse *omics* data to delineate biological processes (biomarkers, pathways, and/or mechanisms) associated with extreme HIV+ clinical phenotypes such as elite controllers, post-treatment controllers, immunological non-responders and rapid progressors.
• Prioritize therapeutic host targets of interest either for drug discovery to identify novel assets (ie screening and/or lead optimization) or for repurposing of clinical phase assets from other disease areas for HIV.

Secondary Objectives
• Evaluate potential relationship of host/immune profiles on efficacy, safety, and tolerability of different standard of care regimens.
• Evaluate the contribution of aging, female gender, and genetic background in host-immune profiles that are:
- distinct to HIV infection relative to well-matched healthy controls;
- associated with non-AIDS defining comorbidities in HIV infection relative to non-HIV chronic disease.

Study design

A multicenter study will performed, to build two cohorts with a total of 2000 HIV patients within the HFGP, consisting of a discovery cohort (n=1200) and confirmation cohort (n=800). We estimate a 2-year inclusion and 2-year follow-up period. We will strive for the inclusion of several clinical phenotypes such as long-term non-progressors (~2-3%), immunologic non-responders (~3%), and rapid progressors (~4-5%) and classical risk group patients such as men who have sex with men (MSM), females and subjects from Sub Sahara Africa. The samples size and patient selection will provide sufficient statistical power as well as representation of ethnic/genetic diversity to properly analyse patients with different HIV clinical outcomes as well as compare the data with well characterized cohorts of Healthy Controls and individuals with other disease(s).

We will use several approaches to characterize our study population:

At inclusion
1. Metadata will be collected from all the participants using questionnaires on lifestyle, health and clinical symptoms, including neuropsychiatric symptoms. Relevant data will also be collected from the patients records and the HIV Monitoring Foundation.
2. Co-pathology will be assesed:
- Cardiovascular risk scores (D:A:D risk score and Framingham CVD score) will be collected as well as intima-media thickness (IMT) in minimal

300 included patients.
- Non-Alcoholic Fatty Liver Disease (NAFLD) assessment through specific ultrasound and fibroscan will be performed in minimal 600 included patients.
3. Blood will be drawn (89 ml):
- DNA will be isolated for genetic analysis.
- The function of the immune system will be analysed at several levels using circulating cells from venous blood: immunophenotyping will be done using FCM analysis, circulating factors will be measured in plasma or serum, in-vitro stimulations of cells and analysis of mRNA and cytokine responses.
- Metabolism will be analysed by metabolome analysis.
- Virological analysis, characterizing the HIV reservoir, HIV resistance and viral sequences in circulating DNA and RNA
4. Microbiome analysis will be performed on stool and saliva.
5. Urine sample will be collected for metabolomics.

After 2 years (20-26 months) follow-up
1. Clinical data from last 2 years will be retrieved from electronic patient files.
2. Co-pathology will be assessed:
- Cardiovascular risk scores (Framingham CVD score) will be collected.
- Non-alcoholic fatty liver disease (NAFLD) assessment through specific ultrasound and fibroscan will be done in those subjects in whom a first assessment was performed 2 years before.
4. Blood samples (10ml) will be collected for biomarker and infection/inflammation parameter analysis. 6. For a subset of participants, we collect an additional 40 mL blood for extra in-depth analysis of virology and additional in-depth immunological analyses.This subset is defined as follows:
• The 2000HIV participants who have been registered to have the elite control clinical phenotype (n*70);
• And the 2000HIV participants identified as *normal progressors* who have also participated in the 2000HIV-trained substudy (NL76999.091.21/2021-7495, n*30).

Study burden and risks

No risks other than local hematoma related to a single venous puncture.
The burden for the patients consists mainly of time investment. Filling in the questionnaire will take approximately 30-40 minutes. The collection of feces, urine en swabs wil together take approximately 10 minutes. Patients also get two appointments with someone of the research team to perform non-invasive measurements and to draw blood. We will try to plan these appointments on the same day as their regular checkup in the hospital. Each visit for the study will take approximately 60 minutes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- HIV1 infection
- Age >/= 18
- cART >=6 months with an HIV-RNA load <200 copies/mL
- Elite controllers will be included as well:
Viremic elite controllers:
- HIV-positive >5 year without cART AND
- with always HIV-RNA >50-10.000 copies/ml AND
- always CD4> 500 cells/uL, OR
- on cART, but before start cART >5 year without cART AND
- with always HIV-RNA >50-10.000 copies/ml AND
- always CD4> 500 cells/uL

Non-viremic elite controllers:
- HIV-positive > 1 year without cART AND
- with >3 consecutive HIV-RNA < 75 copies/ml spanning >12 months
AND
- stable CD4> 350 cells/uL, OR
- on cART, but before start cART > 1 year without cART AND
- with >3 consecutive HIV-RNA < 75 copies/ml spanning >12 months
AND
- stable CD4> 350 cells/uL

- No active hepatitis B/C or signs of acute infections

Exclusion criteria

- Active hepatitic B/C or signs of acute infection
- Known malignancy
- Language barrier that limits effective communication
- Pregnancy

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-10-2019
Enrollment:	2000
Type:	Actual

Ethics review

Approved WMO Date:	09-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL68056.091.18