Neurological, cardiovascular, visual and neurocognitive performance in pediatric HIV-1- infected patients as compared to healthy controls NOVICE - III a follow up study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Observational invasive

Summary

ID

NL-OMON53727

Source
ToetsingOnline

Brief title
NOVICE III

Condition

- Immunodeficiency syndromes
- Viral infectious disorders
- Central nervous system infections and inflammations

Synonym
Neurologic and neurocognitive impairment and brain injury

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Health Holland: Focus on Virus

Intervention

Keyword: Children with perinatally acquired HIV, Neurologic and cognitive development, Neurology

Outcome measures

Primary outcome

Main primary outcome measures and variables are first of all evaluating neurological, cognitive and psychosocial outcomes and change after a 10-year interval in children, adolescents and (if included in previous NOVICE studies) young adults with perinatally acquired HIV (PHIV) on adequate treatment as compared to HIV-negative controls matched for age, gender, ethnic background, and socioeconomic status. Outcome measures and variables are measured by neuropsychological assessment (NPA) and different MRI sequences.
Secondly, to find associations between structural neurological and cognitive outcomes, defined as MRI abnormalities, psychosocial and cognitive development, as well as associations between plasma biomarkers, faecal microbiome and structural neurological and cognitive outcomes in children, adolescents and young adults with PHIV compared to HIV negative controls.
Furthermore, identifying difference in biomarker expression between PHIV children and HIV-negative controls to further investigate and better understand the underlying pathophysiological mechanism and clinical course of

HIV-associated neurocognitive disorders despite adequate treatment.

Secondary outcome

Main secondary outcome measures are the examination of metabolic and cardiovascular risk profiles after a 10-year interval in children, adolescents and (if included in previous NOVICE studies) young adults with perinatally infected HIV (PHIV) on adequate treatment as compared to HIV-negative controls matched for age, gender, ethnic background, and socioeconomic status.
In addition, to identify associations between plasma biomarkers, fecal microbiome and cardiovascular/metabolic risk profile and combination antiretroviral therapy in children and adolescents with PHIV to further investigate the underlying pathophysiological mechanism and clinical course of HIV-associated neurocognitive disorders despite adequate treatment.

Study description

Background summary

The introduction of combination antiretroviral therapy (cART) against human immunodeficiency virus (HIV) improved the survival rates of effectively treated children and adolescents living with perinatally acquired HIV (PHIV). Simultaneously the incidence of severe HIV-associated complications, such as HIV-related encephalopathy decreased. Despite adequate viral suppression with cART, literature suggests structural neurologic and developmental cognitive impairment in PHIV children and adolescents. Longitudinal studies with long-term follow-up are scarce, but available studies report cerebral structure abnormalities such white matter hyperintensities (WMH) and lower white matter (WM) and gray matter (GM) volume on Magnetic Resonance Imaging (MRI) sequences and cognitive impairment in multiple cognitive domains and school performance. Longitudinal studies on cognitive impairment imply persistently lower intelligence quotient (IQ) and impaired executive functioning. In addition, the earlier NOVICE I and II studies (METC 2012_093 en METC 2016_173) looked at cardiovascular risk in children and young adults. In adults with HIV, HIV is an independent risk factor for the development of cardiovascular disease (CVD) and

is associated with a metabolic risk. Studies in children with PHIV may suggest a possible cardiovascular risk with cardiac abnormalities, endothelial dysfunction, subclinical vascular disease, increased carotid intima-media thickness, increased metabolic risk and insulin resistance despite adequate treatment.
The pathogenesis of comorbidities despite adequate viral suppression is not fully understood and several MRI, cerebrospinal fluid (CSF) and plasma biomarkers for immune activation, neuronal injury, endothelial activation and vascular inflammation have been studied in PHIV children. Hypotheses for HIV-associated neurological morbidities are HIV induced low-grade ongoing immune activation and inflammation, early neurological damage prior to treatment initiation, ongoing viral replication, possible toxic effects of early cART, endothelial systemic damage related to metabolic syndrome and possible confounding factors such as socio-economic factors. Hypotheses of increased CVD risk include vascular inflammation and some cART regimes are suggested as possible contributors to increased CVD or metabolic risk. Additionally, HIV related immunological activation and damage of the gastro-intestinal mucosa is hypothesized to result in an adverse change of the gut microbiome which could lead to systemic leukocyte activation, increased inflammatory proteins, ongoing inflammation and immune activation.

Study objective

This study is a follow-up study of the NOVICE I & NOVICE II (METC 2012_093 and METC 2016_173). The objective of the study is to both cross-sectionally and longitudinally, after an interval of 10 years, gain more insight into the presence, severity and development of cerebral damage, cognitive impairment and cardiovascular risks in children with perinatally acquired HIV (PHIV) with adequate treatment compared to HIV-negative controls (matched for age, sex, ethnicity and socio-economic status). In addition, the study aims to measure neurological, cognitive and cardiovascular outcomes and investigate associations using advanced MRI techniques, neurocognitive examination, faecal microbiome and plasma biomarkers in in children and adolescents with PHIV and HIV-negative controls. In order to identify HIV-associated comorbidities, in children and adolescents growing up with PHIV with adequate treatment, and to improve future monitoring or treatment directions and to further understand the underlying pathophysiological mechanisms.

Study design

The NOVICE III is a longitudinal observational cohort study and in accordance with previous cohorts of NOVICE I and II (METC 2012_093 en METC 2016_173), all participants will undergo neuropsychological assessment (NPA), advanced MRI techniques (MRI, MRS, DTI, ASL) and various clinical and laboratory factors are measured. In addition, a faecal sample will be obtained. This follow-up study repeats virtually the same battery of tests as the NOVICE studies cohort I and

II to compare longitudinal data with additional improvement or supplementations of NPO and MRI, laboratory studies, physical examination and analysis of the microbiome based on new insights and results of NOVICE I and II studies. CSF collection or ophthalmic examination will not be performed in this follow-up study. The current NOVICE case-control cohort will be expanded with new cases and controls aged 8 - 18 years, as carried out in accordance with the NOVICE I and II studies.

Study burden and risks

This study is a follow-up study and observational study in competent inidividuals both younger than 18 years and older than 18 years, who have been asked for permission to participate. Like previous NOVICE studies (METC 2012_093 en METC 2016_173), all study participants will undergo a neurocognitive assessment (NPA), MRI, and venipuncture. In addition, all study participants will collect fecal swab sample. The test battery consists of negligible or minimal risk. For the HIV-positive participants, an NPA, MRI and venipuncture are part of their normal treatment plan. HIV participants will undergo an additional NPO, MRI and venipuncture. Each blood sample is combined with regular blood collection as much as possible.
All patients will receive comprehensive information on all tests and will be enrolled on a voluntary basis. The burden mainly includes time consumption by children, adolescents and parents, and will be limited where possible by scheduling combination appointments with outpatient visits for cases. In addition, the examinations that take place per study participant will be scheduled for 1 day, in order to limit the load. There will be guidance for participants through each procedure, by an experienced nurse, researcher physician, pediatrician and pediatric neuropsychologist. Parents, guardians and friends or family are allowed to accompany participants at all times, with the exception of the NPA which is supervised by an experienced pediatric neuropsychologist. Some of the study participants, who have previously participated in one of the NOVICE studies, also have experience with the examinations. In addition, it was decided not to perform ophthalmic examination or lumbar puncture in this follow-up study (NOVICE III), with duration and risk being (further) limited.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Cases: Perinatally infected with HIV
Controls: HIV-unexposed and/or uninfected
Age: between 8-18 years old and furthermore adults >=18 years old can be included if previously included in NOVICE I or II cohort and matched according age, sex, SES and if possible adoption status

Exclusion criteria

Neurological disorders: intracranial malignancy, history of traumatic brain injury with loss of consciousness > 30 minutes Current severe psychiatric disorders (e.g. major depression) MRI contra-indications (e.g. implanted active devices such as cardiac pacemakers, implantable defibrillator or medication pumps, or metal splinters in eye, brain or lungs, claustrophobia, dental braces are allowed).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2022
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	31-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL81972.018.22