Neurological, visual and neurocognitive performance in perinatally HIV-1-infected patients as compared to healthy controls.*
NOVICE II Follow up study

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To increase insight in cerebral injury of perinatally HIV-infected children by comparing neurological, ophtalmological and neurocognitive outcomes to those of matched controls (with respect to age, sex, ethnic background, home environment and socio-...

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

Summary

ID

NL-OMON43220

Source
ToetsingOnline

Brief title
NOVICE II

Condition

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

Synonym
brain disease, neurologic and neurocognitive impairment

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: AIDSfonds

Intervention

Keyword: neurodevelopment, neurology, perinatally hiv infected patients

Outcome measures

Primary outcome

Main endpoints are alterations in neurocognitive performance over time, alterations in neuroimaging parameters and ophthalmological measurements over time, comparing HIV positive cases to healthy controls. CSF and blood parameters will be measured and correlated to the results of the above mentioned tests.

Secondary outcome

Not applicable

Study description

Background summary

Since HIV-infected children are being treated with cART, the incidence of HIV-encephalopathy has decreased while in the meantime neuro-imaging abnormalities shown by these conventional neuroimaging techniques have improved (Patel, 2007). Children can present with other neurologic disorders such as seizures, headaches and neurocognitive impairments (e.g. learning-, behavioural-, and motor deficits) (Chiriboga, 2005). The etiology of this neurocognitive impairment is complex and, most likely, not purely biologically determined. Environmental factors, such as home environment and socioeconomic status (SES), may play a confounding role in cognitive development. In our patient group, the SES is generally lower than in the average population.

As we have recently shown in the NOVICE case-control cohort in 2013, manifestations of HIV in the pediatric central nervous system (CNS) include reduced neurocognitive functioning (Cohen, CID, 2015), brain volume reduction and white matter lesions, as well as widespread microstructural changes, such as poorer white matter integrity (Cohen, Neurology, 2016) and alterations in cerebral metabolites (Blokhuis, Medicine 2016). Evidence implies significant roles for ongoing neuroinflammation, vascular dysfunction and hypercoagulability. Investigations combining neuropsychological assessment, multimodal neuroimaging and laboratory evaluation of inflammatory and neurodegenerative markers could greatly increase our understanding and improve treatment strategies. Longitudinal research will be crucial to observe and understand mechanisms underlying these long-term consequences of CNS exposure to HIV and cART as PHIV-infected survive into adulthood. In this study we will evaluate neurological and cognitive outcomes in the NOVICE case-control cohort which consists of PHIV infected children and sex, ethnicity and socioeconomic status matched healthy controls at an interval period of four years. We will investigate potential mechanisms and factors (such as inflammatory and neuronal biomarkers) that may influence these longitudinal CNS functions. There is an unmet need to longitudinally evaluate neurological, neuroimaging results with neuropsychological performances in the perinatally hiv infected (pediatric) hiv population as compared to matched healthy controls and to our knowledge this NOVICE follow up study is the first study that will address these issues.
With this study, we will compare for the first time neurological, neurocognitive outcomes with neuroradiological alterations and cART levels in CSF and blood while monitoring immune responses (i.e inflammatory, coagulation, endothelial cell activation and neural damage markers) in CSF and blood in perinatally HIV- infected children in a longitudinal setting after an interval of 4 years.
With this study we will be able to demonstrate alterations in the severity and nature of cerebral injury of perinatally HIV-infected children and alterations in underlying mechanisms. The results of this study may have direct implications on the pediatric hiv patient care. Guidelines advice on when to start with cART during childhood and what cART should be used based on international data of clinical data and systemic virological and immunological markers. The results of this proposed study may imply that we may need to start treating asymptomatic hiv-infected children at an earlier time point in life using those drug regimens that are most optimal for neurological and neurocognitive outcomes of perinatally HIV-infected children.
Additionally we may find that we need to investigate other compartments in the body (than blood alone) of the perinatally HIV- infected children in order to monitor optimal treatment of these children.

Study objective

To increase insight in cerebral injury of perinatally HIV-infected children by comparing neurological, ophtalmological and neurocognitive outcomes to those of matched controls (with respect to age, sex, ethnic background, home environment

and socio-economic status) in a longitudinal setting after an interval period of four years and to increase insight in underlying mechanisms associated with these cerebral insults.

Study design

An longitudinal observational case-control study in which all participants will undergo neuropsychological tests (NPA), advanced MRI techniques (MRS, DTI, ASL), and ophthalmological investigation (optical coherence tomography; OCT). In addition, several clinical and laboratory factors will be measured. This is a second assessment of the same battery of tests the same NOVICE case-control cohort will undergo after an interval of four years. The existing NOVICE case control cohort will be enlarged with new cases and controls that have reached the age of eight years.

Study burden and risks

This study is classified as an observational study in subjects that are competent (older than 18 years of age) and incompetent (younger than 18 years of age) to give informed consent. HIV positive study participants undergo NPA, MRI, LP and venous blood sampling as part of their normal treatment plan. For this study, HIV positive study participants will undergo one additional NPA, MRI and LP, and one ophthalmological examination. Any venous blood sampling will as much as possible be combined with standard blood sampling.
All patients are given extensive information on all tests and will be included on voluntary basis.
During all procedures we will guarantee guidance from research staff for all participants. Parents/guardians can join their child at all times except the NPA, which will be taken by an experienced pediatric neuropsychologist will guide the participant.
Our research question is group related. To understand the pathophysiology of neurocognitive deficits still found in HIV positive children (in the era of cART) we need to evaluate patients at an age as early as possible, without the confounding factors of general aging. We need the control group to minimize confounding effects of sex, age, ethnic background, home environment and socioeconomic status.
By accomplishing this study, we may be able to diagnose neurological and neurocognitive disorders at an early stage in HIV positive patients. The patients may benefit from close monitoring, and in the future early intervention could improve their general development. Former case-controlled pediatric neuro-imaging studies have obtained medical ethical approval and have produced satisfying results (Aukema, Int J Rad Onc 2009; Cohen, CID, 2015; Demirkaya , IOVS 2015; Cohen, AIDS Care. 2015; Cohen Neurology, 2016; van Dalen, Medicine, 2016; Blokhuis, IOVS 2016).
This NOVICE II follow up study is granted by the AIDSfonds, further indicating the importance of this study and the need for longitudinal observations of

perinatally HIV-infected children that grow (or have grown) into adulthood. The Dutch patient participation group HIV Vereniging Nederland fully supports this study.

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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)
Elderly (65 years and older)

Inclusion criteria

* Cases: Perinatally infected with hiv
* Age: older than 8 years of age

Exclusion criteria

* Intracranial malignancy, history of traumatic brain injury with loss of consciousness > 30 minutes
* Severe psychiatric disorders
* MRI contra-indications (e.g. implanted active devices such as pacemakers 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:	Recruitment stopped
Start date (anticipated):	24-04-2017
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	21-10-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2017
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	NL58216.018.16