A prospective open-label study to investigate the effects of switching to a darunavir based regimen on low level viremia, immune activation and neurocognitive performance in patients on antiviral therapy.

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To suppress low-level viremia to a level below 50cp/mL in patients using cART by switching their current non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI to DRV boosted with ritonavir (RTV) (DRV/r). Secondary objectives are to reduce the...

Ethical review	Not approved
Status	Will not start
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON38997

Source
ToetsingOnline

Brief title
LOWERIT

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
aids, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Janssen Cilag-BV,Janssen-Cilag

Intervention

Keyword: HIV, low level viremia, viral reservoirs

Outcome measures

Primary outcome

The proportion of subjects with virological response during intervention will

be compared to baseline and categorized according to responders (viral load <50

c/mL at 24 weeks) and non responders (viral load >50 cp/mL at 24 weeks).

Secondary outcome

Immunological markers, neurocognitive performance, periodontal inflammation,

HIV resistance associated mutations, HIV genetic variation (RNA and proviral

DNA). Genetic compartmentalization of HIV (CSF-plasma and saliva-plasma

comparison).

Study description

Background summary

HIV low-level viremia is a frequently observed clinical phenomenon and a possible risk for the development of drug resistance. The origin of low-level viremia is not known, but it is hypothesized that virus production or virus replication in cellular and anatomical reservoirs are involved. Low-level viremia may be associated with higher levels of immune activation, deterioration of neurocognitive performance and periodontitis. These are frequently observed problems in the HIV-infected population.
In clinical practice darunavir (DRV) is often chosen to prevent the development

of drug resistance in subjects who do not get virologically suppressed by combination antiretroviral therapy (cART). DRV is a potent HIV protease inhibitor (PI), with a high genetic barrier and might also be an adequate compound to reduce low-level viremia, immune activation and the development of comorbidities.

Study objective

To suppress low-level viremia to a level below 50cp/mL in patients using cART by switching their current non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI to DRV boosted with ritonavir (RTV) (DRV/r).
Secondary objectives are to reduce the risk for development of drug resistance, to decrease the level of immune activation, to improve neurocognitive performance and periodontal status and to investigate the source of low-level viremia in HIV-1 infected patients receiving cART.

Study design

A prospective multi-center cohort study of 24 weeks open-label treatment and an additional 24 weeks of observation, in which a non-randomised intervention is performed at baseline.

Intervention

The intervention includes DRV/r according to standard clinical practice.
Subjects pre-treated with PIs will receive twice daily DRV/r 600/100 mg.
Subjects not pre-treated with PI will receive once daily DRV/r 800/100 mg. The control group will continue with the cART already in use for the duration of study.

Study burden and risks

The study will include 6 hospital visits. To a great extent it includes normal clinical practice regarding clinical history taking, physical examination, viral load assessment, CD4 count measurements and safety controls in blood to monitor potential side-effects. The number of visits is to a great extent similar to patients with persistent low-level viremia. The additional burden lies in: 3 short questionnaires (about adherence, depression and self-reported impairment in daily functioning), 2-6 additional blood samples for virological and immunological analysis and 3 times a set of validated neurocognitive tests for 40 minutes.
Subjects will be informed about their personal neurocognitive test results after completion of the study at 48 weeks. Out of ethical considerations, subjects with cognitive impairment at the end of the study will be offered a thorough neurocognitive investigation by a clinical neuropsychologist and offered a revalidation programme to cope with the impairment if deemed

necessary or useful. DRV/r has several common side-effects of which gastro-intestinal problems (mainly diarrhoea) are most frequently observed. However, these are all common side-effects for HIV-therapy. Additionally, two facultative substudies are proposed in which subjects can approve that a lumbar puncture and/or periodontal examination at baseline and at week 24 will be used for scientific purposes.
Benefits of participation are that subjects have a lower risk for the selection of drug resistant variants. It is expected that subjects get an undetectable viral load, with potential benefits such as lower immune activation and neurocognitive improvement.

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

a. Using cART for at least 48 weeks, including 2 NRTIs + 1 NNRTI or 1 PI
b. Low level viremia (2 or more HIV viral loads between 50-1000 cp/mL in a year, without Target Not Detected (TND) in between
c. Viral load <200 cp/mL at at least one measurement since starting cART.

Exclusion criteria

a. Presence of known pol major IAS mutations for darunavir (I47V; I50V; I54M/L; L76V; I84V)
b. Signs of opportunistic infections
c. Major suspicion of inadequate therapy adherence
d. Severe depression at screening (BDI score >30)
e. Severe hepatic impairment (Child-Pugh Class C)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	65
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	norvir

Generic name:	ritonavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	prezista
Generic name:	darunavir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	25-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
EudraCT	EUCTR2013-003617-17-NL
CCMO	NL44789.041.13