Tenofovir toxicity: association with Inosine Triphosphate Pyrophosphohydrolase activity and ITPA genotype

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To investigate the association of ITPA genotype and ITPase activity with nephrotoxicity, bone toxicity and recovery of nephrotoxicity and bone toxicity during and after anti-retroviral treatment with a tenofovir containing regimen for HIV.

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

Summary

ID

NL-OMON45178

Source
ToetsingOnline

Brief title
TenofoToxITP

Condition

- Other condition
- Viral infectious disorders

Synonym
Inosine triphosphate pyrophosphohydrolase deficiency

Health condition

Bijwerkingen medicatie

Research involving
Human

Sponsors and support

Primary sponsor: Inwendige geneeskunde, Sectie Infectieziekten
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: - Inosine triphosphatase, - Inosine triphosphate pyrophosphohydrolase, - ITPA, - ITPase, - Tenofovir

Outcome measures

Primary outcome

Association between ITPase activity and nephrotoxicity, bone toxicity and

recovery of nephrotoxicity and bone toxicity during and after tenofovir

containing antiretroviral treatment for HIV.

Secondary outcome

Association between ITPA genotype and nephrotoxicity, bone toxicity and

recovery of nephrotoxicity and bone toxicity during and after tenofovir

containing antiretroviral treatment for HIV.

Study description

Background summary

Anti-retroviral therapy (ART) for patients infected with the human immunodeficiency virus (HIV) has improved substantially over the last years. However, adverse events (AE) are common and can be severe. Measuring HLA-B*5701 can predict which patient will develop hypersensitivity for abacavir, a potent HIV-1-nucleoside-analogue reverse-transcriptase inhibitor (NRTI). However, no other genetic susceptibility traits are known to help guide the choice of ART regimen.
The enzyme Inosine 5*-triphosphate pyrophosphohydrolase (ITPase) is encoded by the ITPA gene and prevents intracellular accumulation of the inosine

nucleotides ITP (Inosine 5*-triphosphate) and dITP (deoxy-Inosine 5*-triphosphate). A substantial part of Western population carries one of the single nucleotide polymorphisms (SNPs) ITPA c.94 C>A and ITPA c.124+21 A>C. These polymorphisms result in a decreased ITPase activity compared to the wild type ITPA gene. ITPA population genetics were evenly distributed between HIV-infected and control populations. However, the majority of HIV-infected patients had decreased erythrocyte ITPase activity compared to healthy controls with the same ITPase genotype. Decreased ITPase activity is associated with a reduced risk to develop ribavirin-induced haemolytic anemia in patients on treatment for hepatitis, but with an increased risk of AEs in patients treated with thiopurines.
In the treatment of HIV-infected patients with ART the nucleoside analogues abacavir and didanosine and the nucleotide analogue tenofovir are purine analogues. Purine analogues are potential substrates for ITPase. To develop more tailor-made treatment for the patients with HIV, further investigation is warranted to the role of ITPase activity and ITPA genotype in the occurrence of adverse events during therapy with tenofovir.

Study objective

To investigate the association of ITPA genotype and ITPase activity with nephrotoxicity, bone toxicity and recovery of nephrotoxicity and bone toxicity during and after anti-retroviral treatment with a tenofovir containing regimen for HIV.

Study design

In a case-control study of HIV-infected patients who are using or have been using tenofovir in the antiretroviral treatment regimen, who had signs for nephrotoxicity during this treatment regimen, will be matched to control patients who are using or have been using tenofovir without nephrotoxicity. ITPA genotype and ITPase activity and the association of these parameters with adverse events will be determined.
Further, for the patients in which these data are available, the association between bone toxicity, determined by bone mineral density measurement, ITPA genotype and ITPase activity will be determined.

Study burden and risks

The burden of the patients participating will be minimal, while only two extra tubes of blood will be retrieved during venapuncture that is performed for their regular visit to the outpatient clinic. If the patients had already had his/her blood drawn for the regular outpatient visit, he will be asked if the two extra tubes of blood may be obtained by an extra vena puncture. Further cooperation will not be needed. The results of this investigation will possibly affect the prescription of antiretroviral therapy to them and other

HIV-infected patients, when an association will be found between ITPA genotype, ITPase activity and the occurrence of adverse events. In this way future adverse events caused by certain antiretroviral medication might reduced.

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

HIV-infected patients, aged over 18 years, who were or are still being treated with a anti-retroviral treatment containing tenofovir.

Exclusion criteria

Not applicable

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-04-2016
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	30-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL53795.078.15