The impact of cytotoxic T lymphocytes on the lifespan of productively infected cells in HIV infection

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

Summary

ID

NL-OMON39416

Source
ToetsingOnline

Brief title
THILIHT

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: AIDS fonds

Intervention

Keyword: Cytotoxic T cell, HIV, HLA

Outcome measures

Primary outcome

Primarily we will determine the average lifespan and dynamics of (productively) infected cells in different individuals and correlate this with parameters of the CTL-response (the height, breadth and quality of the T-cell response against HIV-gag epitopes) before HAART and/or the HLA background of the subjects.

Secondary outcome

NVT

Study description

Background summary

It is widely assumed that T-cell immunity is required to control HIV-infection, and current vaccines are developed based on that premise. This is supported by the fact that certain HLA-molecules are very clearly associated with relatively slow rates of HIV disease progression, suggesting that CTL (cytotoxic (CD8+) T lymphocyte) responses restricted by these HLA molecules successfully control virus replication. Nevertheless, recent studies in rhesus macaques have shown that the lifespan of productively infected cells is independent of the presence or absence of CD8+ T cells. These findings have seriously questioned the role of CTL in shortening the lifespan of HIV-infected cells in humans.
In this study, we aim to reconcile these contradicting findings about the role of CTL in HIV infection. We postulate that CTL*s are required to control HIV infection, but only a very distinct group of patients can generate a *protective CTL response* which is most likely restricted by HLA-alleles associated with slow progression to AIDS. There is increasing evidence that CTL responses targeting the HIV-gag protein play an important role in delay of disease progression. We hypothesize that in patients with such protective CTL responses the lifespan of productively infected cells is shortened.

Study objective

The primary objective of this study is to explore if (and which) HIV-specific CTL responses shorten the lifespan of productively infected cells in HIV-infected individuals. This will be accomplished by investigating the estimated life spans of productively infected cells in different HIV-infected individuals and correlating them with i) the characteristics of the specific CTL response against the gag protein of HIV, and ii) the presence or absence of at least one HLA-allele with a low relative hazard of HIV-disease progression (HLA-A31, B27 or B57).

Study design

It has previously been shown that the lifespan of productively infected cells in HIV-infected individuals can be estimated from the loss of viral load after successful viral treatment. The rationale of this approach is that during successful antiretroviral treatment, infection of new cells is prevented, such that the rate at which the viral load declines after start of antiretroviral treatment represents the lifespan of productively infected cells before treatment. We will closely monitor the decline of viral load in patients directly after the start of their first regimen of highly active antiretroviral therapy (HAART). In parallel, we will study the lifespan of productively infected cells by quantifying the number HIV infected cells in different CD4+ subsets over time. The measured lifespan of productively infected cells will be correlated to different characteristics of the CTL response in these individuals before start of HAART, and to their HLA-background. Because immune activation plays a dominant role in HIV infection, we will also measure different markers of T-cell proliferation and activation.

Study burden and risks

In total 350 mL of blood will be obtained from each study subject spread over 15 visits (12 months). 6 of these visits coincide with routine visits of the out-patient clinic during which 20 mL of blood is drawn routinely. 9 visits within the first 4 months are needed specifically for this study. During these visits a total of 230 mL blood will be drawn. To accommodate the patients, they will be offered the option of blood sampling at home. Because viral load is known to change rapidly after start of HAART, frequent sampling after start of HAART is necessary to make a reliable estimation of the lifespan of productively infected cells. We wish to stress that we have tried to keep the extra visits to an absolute minimum.

The main, group-related, benefit of this study is that the results could gain us important insights into the role for HIV-specific CTL in the control of HIV, which are a prerequisite for the successful development of HIV vaccines that aim to stimulate CTL responses. The insights gained from this project will

specifically help us understand
i) what can be expected from CTL-based HIV vaccines (will they only help individuals with protective HLA alleles or can the whole population benefit?),
ii) what the correlates of a protective CTL response are,
iii) what a vaccine should contain to boost such a response.
Participation in this study does not have direct advantages for the individual patient. However, the possibility to see the course of decrease in the HIV RNA viral load due to its frequent monitoring may provide extra motivation to keep a good adherence with the antiretroviral medication as it directly illustrates the effect of the antiretroviral drugs.

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

1. Written informed consent, including permission to store blood samples.
2. 18 years or older.
3. Diagnosis of HIV-1 infection: detectable plasma HIV-1 RNA load and/or serum p24 antigen
4. Infection with subtype B HIV-1
5. No prior antiretroviral treatment
6. Patient is scheduled to start the first HAART
7. A regimen including efavirenz or rilpivirine next to a backbone of two nucleot(s)ide reverse transcriptase inhibitors is to be administered

Exclusion criteria

1. CD4 count < 100 cells/mm3
2. Immunosuppressive medication
3. For female subjects: pregnancy (positive urine pregnancy test)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-04-2011
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	31-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-04-2013
Application type:	Amendment
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
CCMO	NL32689.041.10