T-cell turnover during HIV infection; production and life span of T-cells in HIV infected individuals during cART

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON46926

Source
ToetsingOnline

Brief title
T-cell turnover during HAART: the CTRL-ALT-DEL study

Condition

- Viral infectious disorders

Synonym
AIDS, seropositive

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,Het AIDS fonds

Intervention

Keyword: AIDS, HAART, HIV-1, T-cell turnover

Outcome measures

Primary outcome

The most important study parameter is the lifespan of T-cells in HIV-1 infected individuals that reconstitute their CD4 T-cell numbers well, compared to HIV-1 infected individuals that do not.

Secondary outcome

A difference in T-cell origin between immunological responders and non-responders

A difference in source of the T-cells between immunological responders and non-responders

Study description

Background summary

It seems that depletion of naive T-cells during chronic HIV infection is caused by persistent activation of the immune system. This activation makes naive and memory T-cells differentiate continuously, thereby slowly exhausting the peripheral CD4 T-cell reservoir.
When HIV infected individuals have less than 200 CD4 T-cells per microliter blood or have an AIDS-indicator disease they are classified as having *acquired Immunodeficiency Syndrome * (AIDS). At this stage patients are more susceptible for other infections, due to a malfunctioning immune system.
In order not to reach this stage of the disease, HIV infected individuals start antiretroviral therapy (cART) when they have less than 350 CD4 T-cells per microliter blood. The goal of this therapy is to increase in CD4 T-cell numbers due to repression of the virus. Some patients respond very well to this therapy, whereas others hardly show an increase in CD4 T-cell numbers in spite of viral repression.

The generally accepted explanation is that this is due to different T-cell production rates in these individuals. In this study we would like to investigate whether death of newly produced CD4 T-cells also contributes to this process and hence to the difference between individuals.
We would like to measure the production and death (turnover) of CD4 T-cells in HIV infected individuals that reconstitute their CD4 T-cell number well during HAART and in individuals that do not. We would do this by labeling newly produced cells with deuterium, using deuterated water. By measuring different T-cell populations (recent thymic emigrants, naive- en memory T-cells), this technique allows us to follow the fate of newly produced naive T-cells. We are going to compare deuterated water labeling of HIV-1 infected individuals that reconstitute well with that of HIV-1 infected individuald that do not, together with Ki67 and CD31 staining and TREC analysis.
This way we measure the production rate of new T-cells in HIV infected individuals on cART as well as the rate at which these cells disappear again. With this information, we can determine whether the production rate or the lifespan (or both) of newly produced cells is reponsible for the degree of reconstitution.
Differences in the extent of T-cell production and/or death between the primary study group (immunological responders) and the control group (immunological non-responders) will tell us why there is a difference in reconstitution: in the immunological non-responders fewer cells are being produced or the cells are shorter lived. It has been assumed that there are two processes influencing the degree of reconstitution:
1) A homeostatic response to low cell numbers in the depleted pool, i.e., a lymphopenia-induced proliferation.
2) Immune activation, both directly, by the virus, through activation of Toll-like receptors on dendritic cells, and indirectly, resulting from increased permeability of the gut, through which bacterial translocation occurs and immunogenic products end up in the circulation.
The deepening research question can be formulated as: What are the relative contributions of (lymphopenia-induced) homeostasis and immune activation to the production and death rates of T cells? Answering this question is highly relevant, because insights in the relative contributions of homeostasis and immune activation during disease and recovery provide leads for the improvement of treatment for HIV infection.

Study objective

With this research we aim at gaining more insight into the reason for the fact that some individuals reconstitute well during cART whereas other do not. Also, we would like to investigate what mechanism is responsible for reconstituting the CD4 T-cell compartment.

Study design

Twenty five individuals will participate in this study. These are 15 HIV-1 infected individuals who reconstitute well during cART (= increase in CD4 T-cells to > 350/ul blood and an undetectable viral load) and 10 HIV infected individuals who are treated with cART and have undetectable viral load, but who's CD4 T-cell numbers are still below 350/ul blood. Theere are 5 HIV-1 infected individuals that do not reconstitute well during cART, who are participants in the deuterated water part of the MIRS study. They are also used as controls. The total duration of participation in this study is 24 weeks. The planning within these 24 weeks is as follows;

-Week 1-6:
Intake of deuterated water: On the first day of the study an amount of water has to be drunk that is equal to 10ml per kg bodywater (=60% of body weight) . This will be 350-550 ml for most individuals. Next, participants will be asked to drink 1/8 of this amount once daily from day 2 until day 42.
Blood and urine donation: During the first 6 weeks of the study, participants will donate 50ml blood and urine 4 times.
Questionnaire: At each study visit, the participants will fill in a questionnaire in order to check whether they have had conditions that might influence T-cell turnover, since the last visit. For instance, influenza.
-Week 7-24:
Intake of deuterated water: Participants do not have to take deuterated water anymore in this phase of the study.
Blood and urine donation: From week 7 until week 24, again participants will donate 50ml blood and urine 5 times.
Questionnaire: Again, at each visit a questionnaire will be filled in.

The start date of the study will be aimed June 1st 2010 and the end date will then be December 1st 2020.

Study burden and risks

The burden on the participants consists of a single intake of 10 ml deuterated water per kg bodywater. Thereafter 1,25 ml per kg body water will be taken once daily, for a duration of 42 days. The first intake of deuterated water will be a burden for the patient, because temporary dizziness and/or nausea can occur. Participants therefore have to be monitored for the first few hours after initial intake. We estimate the burden of the rest of the daily intakes, that take place at home, to be minimal. The amount of fluid are very small and also, there is no chance of dizziness and/or nausea.
Furthermore, during the period of heavy water intake, 50 ml of blood will be drawn and urine will be donated 4 times and in the 18 weeks after cessation of heavy water intake again 5 times. This will take place in the UMC Utrecht and we will try to plan these visits together with standard visits as much as possible, thereby minimizing the burden on the participant. The total volume of blood that is drawn (450 ml in 6 months) can be missed by adults, also HIV infected individuals.

The intake of above mentioned amounts of heavy water does not damage the health of participants. Therefore, to our knowledge, the risk of participation in this study is negligible.

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

All groups:
-All study subjects have to be adults (18 years of age, or older) and sound of mind and judgement.
Study group:
-They have to be HIV-1 infected and treated with cART.
-They have to have a long-term undetectable viral load (= HIV RNA , 50 copies/ml blood)
-The number of CD4 T-cells should have increased to at least 350 cells per microliter blood.

Control group low CD4 T-cells during cART:
-They have to be HIV-1 infected and treated with cART.
-They have to have a long-term undetectable viral load (= HIV RNA , 50 copies/ml blood)
-The number of CD4 T-cells should be less than 350 cells per microliter blood.
Control group HIV-1 infected, high CD4 T-cell numbers without cART
-They have to be HIV-1 infected.
-The number of CD4 T-cells should be more than 350 cells per microliter blood.

Exclusion criteria

-HIV-2 infection
-Participants may nog have an active infection for which anti microbial drugs are being used
-Participants may not have an active hepatitis B or C infection
-Chronic hepatisis B or C for which treatment with (peg)interferon and/or ribavirine (Note: patients with untreated chronic hepatitis B or C can be included)
-They may not use immune suppressive ot immune modulating medication
-Radiotherapy or chemotherapy in the past 2 years
-Pregnancy or breastfeeding an infant
-Participation in other studies

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):	17-05-2011
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	30-11-2010
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-12-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-07-2018
Application type:	Amendment
Review commission:	METC NedMec

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	NL24455.041.10