Exhaustion of T cells in HIV-1 and HIV-2 infection

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1. Determine whether different classes of epigenetic modifiers affect HIV-1-specific T cell immunity.a. Investigate whether HIV-specific T cell exhaustion can be reversed by inhibitors of different classes of epigenetic modifiers.b. Examine whether...

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

Summary

ID

NL-OMON43390

Source
ToetsingOnline

Brief title
T cell Exhaustion in HIV

Condition

- Viral infectious disorders

Synonym
AIDS, HIV infection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: HIV-1, HIV-2, T cell Exhaustion, T cells

Outcome measures

Primary outcome

This is a discovery study aiming to examine exhaustion of HIV-specific CD8+ and CD4+ T cells in HIV-1 and HIV-2 infection and the role of epigenetic modifications in the exhaustion and function of these cells. The main study parameters are differences in a) phenotype (differentiation, activation, inhibitory receptor expression and transcription factors), b) effector functions (cytokine production, cytotoxicity), c) survival and d) proliferation of HIV-specific T cells; e) differentiation and activation phenotypes, and function of immune subpopulations (i.e. CD4+ and CD8+ T cells, B cells, NK cells, macrophages and DC). These differences will be measured directly ex vivo and after in vitro treatment with inhibitors of different classes of epigenetic modifiers

Secondary outcome

N/A

Study description

Background summary

HIV-1 and HIV-2 infection. The source virus for HIV-1 is SIVcp from chimpanzees whereas HIV-2 originates from sooty mangabey (SIVsm). Pathogenicity of HIV-2 is different from HIV-1, with the majority of HIV-2-infected patients presenting with undetectable viral loads, no progression and mortality comparable to uninfected individuals. This difference in pathogenesis can be due to viral factors or anti-viral immunity. When HIV-1 and HIV-2 replication

and infectivity was compared, it was shown that there is no differences in infectivity, however, HIV-2 replicates slower, therefore producing less virus per infected cells. This reduced replication is independent of CTL (1).
Pro-viral DNA load in HIV-1 and HIV-2 infected individuals is also comparable (2). Since HIV-1 and HIV-2 develop from different viral lineages, difference in sensitivity to host restriction factors may play a role. Indeed, HIV-2 is more susceptible to hTRIM5α-mediated restriction and this seems to be capsid-mediated (3).
Exhausted HIV-specific CTL. Antigen-specific cytotoxic CD8+ T lymphocyte (CTL) responses are considered to be major players in the protective immune response against acute and chronic viral infections. In HIV-1 infection a key role for CTL responses was indicated by several studies (4-9). CTL responses are also mounted against HIV-2. That CTL may have a direct impact on HIV-2 replication was indicated by the direct correlation between IFNγ+ HIV-2-specific CTL responses and viral loads (10). However, several studies indicate a comparable magnitude and breath of IFNγ-producing T cell response in HIV-1 and HIV-2 infection (11) indicating that it is not the numbers alone which explain control of progression in HIV-2 compared to the loss of control in HIV-1.
Although the immune response in HIV-infected individuals can control HIV replication for some time, ultimately, HIV-specific CTL in the majority of HIV-1-infected patients and in a minority of HIV-2-infected patients fail to clear or control HIV infection and AIDS develops. This failure of HIV-specific CTL to eradicate or control long-term HIV raises the question whether HIV-specific CTL become exhausted. Exhaustion of chronically antigen-stimulated T cells was first described in a mouse model of chronic viral infection (12) and is characterized by loss of proliferation, cytokine production and cytotoxicity and the upregulation of inhibitory receptors (reviewed in (13)). Similarly, CTL exhaustion has also been shown in HIV-1 infection (14-21). Although most HIV-2 infected patients have undetectable viral loads, a recent study indicated that even in aviremic HIV-2 infected patients viral replication is ongoing (22). This would suggest that HIV-2-specific T cells are chronically stimulated and this could lead to gradual exhaustion. Indeed, increased expression of inhibitory receptors is found on HIV-2-specific CTL but it is not clear whether they associate with viral loads (23, 24). The association of inhibitory receptors with exhaustion in humans has largely been based on HIV-1 infection, therefore HIV-2 may provide a unique opportunity to investigate the role of these receptors in a chronic infection that infrequently progresses. If HIV-2-specific T cells show indeed an upregulation of inhibitory receptors but are functionally not impaired, this would indicate that inhibitory receptors do not necessarily reflect exhaustion but serve to dampen immune activation and its detrimental effects. This also would suggest caution when equalizing immune exhaustion, inhibitory receptor expression and immune dysfunction in HIV-1 infection. This study of T cell exhaustion in HIV-1 and HIV-2-infected patients will allow to dissect the relation of inhibitory receptors and declining T cell immunity in HIV infection.
Epigenetics and the regulation of exhaustion and T cell function.
Epigenetics is a means of DNA-sequence independent and reversible regulation of

gene transcription, leading to changes in chromatin structure through methylation of DNA and modification of histones (25). Although T cell specific transcription factors (e.g. Blimp-1, BATF, Eomes and T-bet) are implemented in the regulation of T cell exhaustion and some factors like BATF may be directly induced by inhibitory PD-1 receptor signaling (26), another mechanism involved in exhaustion are epigenetic modifications. Several studies have demonstrated that epigenetic modifications play an important role in T cell immunity (27, 28). However, epigenetic-mediated gene silencing was recently also linked to CTL exhaustion by analyzing the epigenetic modifications of the inhibitory receptor PD-1 (29). Thus epigenetic modifications can affect the normal function of CTL but also potentially exhaustion. It is expected that different classes of epigenetic modifiers would impact differently normal CTL function and exhaustion. This is a question we will examine in this study.
HIV latency and epigenetics. Epigenetic modifications in the LTR region of HIV also inhibit downstream HIV gene transcription, and control HIV silencing in latency (30, 31). Since epigenetic modifications are reversible, a number of epigenetic modifications or proteins that interact with these are being targeted as therapeutic approaches to reactivate the latent HIV reservoir. According to the *shock and kill* concept proposed in the last years, reactivation of HIV provirus transcription by drugs would render the latent reservoir visible and susceptible to the immune system. Combined with cART this lead to the eradication of infection. Clinical trials are already testing the effect of inhibitors of epigenetic modifiers on the latent HIV reservoir. However, the effect epigenetic modifications have on the immune system and specifically anti-HIV immunity is not well understood. Since epigenetic modifications are genome-wide, their inhibition to reactivate the HIV latent reservoir will also affect many cell types and genes. Few clinical trials of epigenetic modifiers in HIV-infected patients analyzed the effect these drugs have on HIV-specific immune responses, and these findings are controversial (32). Our study will evaluate some of the most common inhibitors to determine whether some of these have fewer deleterious effects on HIV-specific CTL immunity or may even restore exhaustion.

Study objective

1. Determine whether different classes of epigenetic modifiers affect HIV-1-specific T cell immunity.
a. Investigate whether HIV-specific T cell exhaustion can be reversed by inhibitors of different classes of epigenetic modifiers.
b. Examine whether inhibition of epigenetic modifiers affects the function of HIV-specific T cells and other immune cells.
2. Determine whether HIV-specific T cell responses in HIV-2 infection are exhausted.
We will examine the association between T cell exhaustion phenotype, function and immune activation and test epigenetic inhibitors from objective 1 in HIV-2 infection.

Study design

This is an in vitro research study that uses peripheral blood received through venipuncture from HIV-infected individuals. In vitro experiments are carried out on isolated lymphocytes. Chronically HIV-1 or HIV-2-infected volunteers will be asked to donate blood (maximum 50 ml, 5 tubes) either during their scheduled physician visit or during a scheduled visit for the blood donation. PBMC will be isolated from peripheral blood and either analyzed immediately or cultured in vitro. For the epigenetic inhibitor studies PBMC will be treated with different epigenetic inhibitors and subsequently analyzed. In both ex vivo and in vitro studies, the phenotype of HIV-specific T cells (differentiation, activation, inhibitory receptor expression and transcription factors), effector function (cytotoxicity and cytokine production), proliferative capacity and survival will be determined. For the epigenetic inhibitor studies the phenotype and function of additional immune cell subsets (i.e. CD4+ and CD8+ T cells, B cells, NK cells, macrophages and DC) will be measured.

Study burden and risks

Participation involves at least one blood donation of max 50 ml blood (5 tubes). The only risk for the volunteers regarding this study is the risk connected to giving blood by using standard venipuncture. There is a rare, but possible risk of infection, pain or bruising at the site of the needle stick. Serious adverse events are extremely rare. Since this is an in vitro research study, no benefits will arise for blood donors from taking part in this study.

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. Age >18 years
2. Confirmed HIV-1 or HIV-2 infection
3. Fit description of study groups as outlined above

Exclusion criteria

1. Inability to donate 50 ml of blood
2. Pregnancy or breastfeeding
3. Major comorbidities

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-05-2016
Enrollment:	154
Type:	Actual

Ethics review

Approved WMO

Date:	04-05-2016
Application type:	First submission
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	NL55663.078.15