Thrombofilia, inflammation and markers of cardiovascular disease in HIV-1 infected patients

Published: 09-08-2010
Last updated: 30-04-2024

2.1 Primary Objective• Evaluation of the levels of thrombophilic factors in the blood of HIV-infected patients before starting with cART and the changes of these levels when on cART for the time of one year. 2.2 Secondary Objective• Evaluation of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational non invasive

Summary

ID

NL-OMON34363

Source
ToetsingOnline

Brief title
INF-BEAST

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Viral infectious disorders
- Embolism and thrombosis

Synonym
coagulation factors, venous thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cART, HIV, thrombofilia, venous thrombosis

Outcome measures

Primary outcome

Measurement of the levels of the following thrombophilic factors including:

anti-thrombin, protein C, protein S, free protein S, fibrinogen, lupus

anticoagulant, von Willebrand factor, factor VIII and D-dimer, at four moments

in time after starting with cART and comparing those levels with baseline to

determine changes.

Secondary outcome

Measurement of the levels of the following thrombophilic factors including:

CRP, hsCRP, Cholesterol, HDL- and LDL-cholesterol, triglycerides, at four

moments in time after starting with cART and comparing those levels with

baseline to determine changes.

Study description

Background summary

Mortality of HIV and HIV-related diseases has changed since the introduction of combined antiretroviral therapy (cART) in 1996. Although AIDS related deaths and unknown deaths decreased both over time when receiving cART, an increasing proportion of HIV-infected patients died of non-AIDS deaths [1]. The most frequently reported causes of death in the cART era are cardiovascular, pulmonary, hepatic disease and non-AIDS malignancies [1]. Thus, either through this prolonged survival or by the introduction of antiretroviral therapy, other underlying diseases or risks for such diseases could become clinically relevant.
Before highly active antiretroviral therapy was introduced in 1996, a

few reports indicated that HIV-infected patients were at increased risk of venous and arterial thrombosis [2]. Moreover, patients with AIDS have an almost 30-fold increased risk of venous thrombosis compared to patients without AIDS-defining illness [3]. In 1992, Bissuel et al [4] found free protein S levels were significantly lower in patients with full-blown AIDS (37.6% +/- 12.3) than in patients without AIDS (69.8% +/- 19.9, P<0.001). Low plasma free protein S levels correlated with low CD4+ T-cell counts (P<0.001). Similar results were found in a study of Stahl et al in 1993 [5]. Feffer et al [6] showed that protein C levels are also decreased in HIV-infected patients (n=52), while D-dimer and VWF levels were increased. Moreover, abnormal results correlated significantly with lower CD4+ cell counts. Recently, 109 consecutive HIV-infected patients in our university hospital were tested twice for currently known thrombophilic abnormalities at an interval of at least 3 months [7]. Repeated measurements established protein C deficiency in 9% of the patients, increased factor VIII levels in 41%, high fibrinogen levels in 22%, and free protein S deficiency in 60%. These frequencies are much higher than in the general population [8]. Median factor VIII levels were higher in patients with AIDS than in patients with a non-AIDS-defining illness (226% vs. 149%; P<0.001), whereas median free protein S levels were lower (45% vs. 58%; P<0.001). Developing AIDS was associated with increasing factor VIII levels and decreasing free protein S levels. Increasing factor VIII levels were correlated with increasing fibrinogen levels and decreasing free protein S levels. These findings all provide further evidence that HIV-infection itself contributes to the high prevalence of venous and arterial thrombosis in HIV-infected patients. However, there is little research available focusing on all thrombophilic markers in patients with HIV-infection but who are not on cART.
After the introduction of cART in the therapeutic regimen for HIV due their highly significant contribution to HIV suppression and reducing mortality [9], a new phenomenon was observed in which patients on protease inhibitors developed a syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance [10]. These findings were confirmed by others [11-13]. Wolf et al [14] found significantly higher levels of von Willebrand factor (VWF) in HIV-infected patients before they started with ART compared with healthy control subjects. After five months of treatment with ART, the levels of these markers decreased significantly. Also, there are large epidemiological studies suggesting a relationship between ART and increased risk of arterial and venous thrombosis [15-19], but not all [20, 21]. However, there are very few studies reporting on a cause by which this increased risk could be explained. Also, the effect of cART, especially non-nucleoside reverse transcriptase inhibitors (nNRTI*s), on the coagulation system has not been investigated systematically. This problem could be solved with the use of a randomized clinical trial, but would not be ethical to perform as ART is very effective in reducing mortality and morbidity in HIV-infected patients [1, 22]. Thus, in this study we want to determine the effect of starting cART in HIV-infected patients on the coagulation system, measuring all known thrombophilic factors and cardiovascular markers as well as inflammatory markers like (hs)C-reactive protein. This will provide us data about the status of the coagulation system

in HIV-infected patients who are not on cART yet, and about the changes in those markers after starting cART till one year of treatment.

Study objective

2.1 Primary Objective
• Evaluation of the levels of thrombophilic factors in the blood of HIV-infected patients before starting with cART and the changes of these levels when on cART for the time of one year.

2.2 Secondary Objective
• Evaluation of the levels of hs-CRP in the blood of HIV-infected patients before starting with cART, and of the changes of these levels when on cART for one year.
• Evaluation of the levels of total cholesterol, HDL cholesterol, LDL cholesterol and trigiclerids in the blood of HIV-infected patients before starting with cART, and of the changes of these levels when on cART for one year.

Study design

Longitudinal, prospective, observational case series.

Study burden and risks

After giving informed consent, blood samples will be taken from patients when visiting the hospital for a regular visit including regular blood sampling as determined by their primary HIV-treatment doctor, for a total of five times. Also, at start and after one year, a questionnaire will be needed to answer, taking 10 minutes of time. There are no direct benefits for patients, neither are there any risks. However, when the investigators detect clinical relevant findings, the primary doctor (infectiologist) will discuss these with the patient. Patients are informed about this and have to agree with it. Overall the burden is low for patients and adverse events are not expected.

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

Patients with active HIV-1 infection who have an indication for starting treatment with cART
18 years or older of age

Exclusion criteria

Patients with HIV-1 infection al ready on cART
HIV-2 infection
Pregnancy
Oral contraception
Not able to understand Dutch lor English anguage

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-08-2010
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	09-08-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL32622.042.10