A phase IIa randomized, placebo controlled, double blinded study to evaluate the safety and immunogenicity of iHIVARNA-01 in chronically HIV-infected patients under stable combined antiretroviral therapy.

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To evaluate the safety and immunogenicity of iHIVARNA-01 as a new therapeutic vaccine in HIV infected patients.

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

Summary

ID

NL-OMON46133

Source
ToetsingOnline

Brief title
iHIVARNA phase IIa study

Condition

- Immunodeficiency syndromes
- 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: Europese unie

Intervention

Keyword: HIV, immunotherapy, intranodal, mRNA

Outcome measures

Primary outcome

* To evaluate the safety and tolerability of intranodal iHIVARNA-01 vaccination compared with placebo, focusing on the nature, frequency and severity of local adverse events (pain, cutaneous reactions including induration) and systemic adverse events (temperature, chills, headache, nausea, vomiting, malaise, and myalgia).

* To evaluate the immunogenicity of an immunization schedule with HIV-TriMix-mRNA (iHIVARNA-01) to increase the frequency of HIV-specific T-cell responses between baseline and 2 and 14 weeks after the last injection as compared to the control groups, immunized with TriMix-mRNA only or WFI only.

Secondary outcome

* To evaluate the magnitude and the kinetics of the HIV-specific CD4+ and CD8+ T cell responses generated by the immunization schedule in the 3 groups by two methods (ELISPOT, intra-cellular cytokine staining - ICS) at baseline and at weeks 6 and 30.

* To evaluate the ability of the immunization schedules to prolong time until viral rebound after discontinuation at W6.

* To evaluate the suppressive effect on plasma viral load in vivo after ATI from W6 to W18 compared to two control groups, receiving TriMix only or saline.

* To assess the proportion of patients with control of viral load below detectable level 12 and 24 weeks after start ATI (functional cure).

* To evaluate the percentage of patients who generate a primary immune response to previously not-recognized HIV peptides (as defined in 8.1.2)

* To analyze induction or enhancement of the CD8+ T-cell HIV suppressive capacity.

* To evaluate the effect on reservoir as measured by proviral DNA and the intracellular viral RNA (unspliced and multiple spliced viral RNA).

* To detect viral immune escape by sequencing of the HIV and conducting sieve effect analyses in rebounding virus after cART interruption.

* To evaluate host protein mRNA expression profiles in whole PBMC at baseline and W6 and W18.

* To store samples for future determination of gut microbiota composition and diversity in relation to HIV immune status

Study description

Background summary

The human immunodeficiency virus (HIV) is a single-stranded positive-sense RNA virus belonging to the lentivirus genus. It mainly infects human dendritic cells (DCs), macrophages and CD4+T cells where it integrates into the host genome after reverse transcription to double-stranded DNA. In the absence of antiretroviral therapy, infection progresses to acquired immunodeficiency syndrome (AIDS) as defined by progressive depletion of CD4+ T cells. Patients with advanced HIV infection have a CD4+ T-cell count below 50/mm3 and their median survival is between 12 to 18 months in the absence of antiretroviral

therapy.
The HIV pandemic has caused as much as 35 million deaths worldwide. As of December 2013, 35 million people were estimated to be infected with HIV, from which 23.5 million were living in Sub-Saharan regions.
Current therapy for HIV infection is based on combined anti-retroviral treatment (cART). HIV infected patients, which are currently treated with cART show a stabilized condition with no clinical progression. However, cART has to be maintained for life, since it is not able to eradicate the infection by itself. This represents very high costs for administrations together with difficulties for treatment adherence and widespread distribution, mainly in developing countries, but also in the developed world. Therefore, there is a clear unmet need regarding cost-effective and viable treatments for HIV-infected patients. Therapeutic vaccination has emerged as an attractive strategy aiming at achieving a *functional cure*, a situation in which the immune system is able to control viral replication without the need for cART. In this regard, several antigenic molecules, administration routes and strategies have been employed, so far with limited success. The most promising results to date were obtained by Garcia et al. (partner of the consortium iHIVARNA). In this clinical trial, HIV-infected patients were administered autologous dendritic cells pulsed with HIV viral particles, a strategy known as *ex vivo modification of DCs*. The results of this clinical trial indicate that DC-based vaccines offer a promising strategy for therapeutic vaccination. DC-based vaccines rely on the ability of DCs to uptake and present antigens to CD4+ and CD8+ T cells, eliciting an immune response that should ultimately control viral replication by lysing infected cells. In fact, in a small percentage of individuals who are known to efficiently suppress viral replication in the absence of cART (known as *elite controllers*), control of viral replication has been associated with effective CD8+T cell responses. Although results obtained by Garcia et al. demonstrated a reduction of 90-95% of pVL in HIV-infected patients, *functional cure* (a 100% reduction of pVL) was not achieved. In addition, the use of ex vivo modification of DCs is a technical challenge for widespread use and a very costly strategy.
For that reason, iHIVARNA-01, which is the current product under development, is based on the so-called *in vivo modification of DCs*, in which the product is directly administered to the patient without the need to modify DCs ex-vivo. The intended indication for iHIVARNA-01 is the therapeutic vaccination of HIV-infected patients. iHIVARNA-01 is a biological product that consists of naked mRNA to be administered through the intranodal route.
The product is a combination of mRNA sequences that fulfil two main objectives: 1) providing effective HIV antigens for specific T cell activation that will lead to protective immunity (HIVACAT mRNA sequence) and 2) providing adequate stimuli required for the activation of antigen presenting cells (APCs) (DCs) and co-activation of specific T cells (TriMix mRNA sequences).

Study objective

To evaluate the safety and immunogenicity of iHIVARNA-01 as a new therapeutic

vaccine in HIV infected patients.

Study design

Phase IIa, multicentre double-blind placebo controlled intervention study. Each patient will be followed for 30 weeks. The study duration will be 38 weeks from inclusion of the first patient.

Intervention

One group (n=40) receives the HIVACAT TriMix (300 microgram TriMix + 900 microgram HIVACAT-T) vaccine intranodally on three occasions with a two-week interval. One control group (n=15) receives TriMix only (300 microgram TriMix) and one group (n=15) receives saline intranodally on three occasions with a two-week interval. Two weeks after the last vaccination cART treatment will be interrupted. If plasma virus is detectable, cART will be re-initiated twelve weeks after treatment interruption. cART can always be re-initiated for medical reasons, as judged by the clinical investigator.

Study burden and risks

Participation to the trial will consist of 15 visits to the hospital for a estimated total of 11 hours for vaccinations and exams, during a 30-week period. During these visits blood will be drawn for various assays. A total of 926ml blood will be taken over a 30-week period.
Before inclusion a physical screening will be performed. The patient will be asked to fill in a diary card to record local and systemic adverse events during one week after vaccination.
Discomfort can be experienced as a result of intranodal vaccination including: local injection site reactions: pain, itching, redness/discoloration or fluid/blood filled blisters at the injection site. Hard swelling in skin surface at or close to site. General/ systemic reactions may include: temperature raise, chills/rigors, malaise, tiredness muscle aches, headache, nausea or vomiting.

As a result of treatment interruption a viral rebound syndrome may be experienced, with symptoms similar to those of acute HIV infection. Symptoms may include fever, fatigue, pharyngitis, lymphadenopathy, rash and/or weight loss.

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. * 18 years of age;
2. Voluntarily signed informed consent;
3. Proven HIV-1 infection (with documented antibodies against HIV-1 and a detectable plasma HIV-1 RNA before initiation of therapy);
4. On stable treatment with cART regimen (antiretroviral therapy consisting of at least three registered antiretroviral agents) for at least 3 years;
5. Nadir CD4+ * 350 cells/*l (up to 2 occasional determinations * 350 cells/*l are allowed);
6. Current CD4+ cell count * 450 cells/*l;
7. HIV-RNA below 50 copies/mL in the last 6 months prior to randomization, during at least two measurements (occasional so called *blips* * 500 copies/mL are permitted);
8. If sexually active, willing to use a reliable method of reducing the risk of transmission to their sexual partners during treatment interruption (including PrEP).
a. For heterosexually active female, using an effective method of contraception with partner (combined oral contraceptive pill; injectable or implanted contraceptive; IUD/IUS; consistent record with condoms; physiological or anatomical sterility (in self or partner) from 14 days prior to the first vaccination until 4 months after the last vaccination.
b. For heterosexually active male, using an effective method of contraception with their partner from the first day of vaccination until 4 months after the last vaccination.

Exclusion criteria

1. Treatment with non-cART regimen prior to cART regimen;
2. Previous failure to antiretroviral and/or mutations conferring genotypic resistance to antiretroviral therapy;
3. Non-subtype B HIV infection;
4. Active Hepatitis B virus and/or Hepatitis C virus co-infection;
5. History of a CDC class C event (see appendix A);
6. Pregnant female (screened with a positive pregnancy test), lactating or intending to become pregnant during the study;
7. History of malignancy * 30 days (extended period on the clinical assessment of the investigator) prior to screening;
8. Active infection with fever (38°C or above) * 10 days of screening and/or first vaccination;
9. Therapy with immunomodulatory agents (e.g. systemic corticosteroids), including cytokines (e.g. IL-2), immunoglobulins and/or cytostatic chemotherapy * 90 days prior to screening. This does not include seasonal influenza, hepatitis B and/or other travel related vaccines;
10. Congenital, acquired or induced coagulation disorders, such as thrombocytopenia (thrombocytes < 150x109/L) and/or current use of anti-coagulant medication (e.g. coumarins, inhibitors of Xa); Usage of NSAIDs (including acetylsalicylic acid) is allowed, however it is advised to interrupt therapy 10 days ahead of vaccination;
11. Usage of any investigational drug * 90 days prior to study entry;
12. An employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or is a family member of an employee or the investigator
13. Any other condition, which, in the opinion of the investigator, may interfere with the evaluation of the study objectives

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2017
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	iHIVARNA-01
Product type:	Medicine
Brand name:	TriMix

Ethics review

Approved WMO Date:	06-02-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2016-002724-83-NL
ClinicalTrials.gov	NCT02888756
CCMO	NL57593.000.16