Low Viral Reservoir in Treated Subjects (LoViReT) - Phase II.
Predictors of Extremely Low HIV-1 DNA Reservoir in Subjects Initiating cART during Chronic Infection.

PROTOCOL SUMMARY

1. IDENTIFICATION OF THE PROTOCOL

Sponsor protocol code: LoViReT II
Version/Date: Version 5, 19/01/2017

2. TITLE OF THE STUDY

Low Viral Reservoir in Treated Subjects (LoViReT) - Phase II: Predictors of Extremely Low HIV-1 DNA Reservoir in Subjects Initiating cART during Chronic Infection

3. IDENTIFICATION OF THE SPONSOR

AIDS Research Institute IrsiCaixa
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4. PRINCIPAL INVESTIGADOR

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5. RESEARCH ETHICS COMMITTEE WITH DRUGS

The IRB at Univ. Hospital 'Germans Trias i Pujol'.

6. CENTER WHERE THE STUDY WILL BE CARRIED OUT

Univ. Hospital 'Germans Trias i Pujol'

7. JUSTIFICATION AND RELEVANCE OF THE STUDY

Antiretroviral therapy (ART) for HIV-1 significantly reduces the morbidity and mortality associated with AIDS events. However, it fails to eliminate the virus that persists in the form of latent infection in the cell reservoirs, which implies a rapid rebound of viral load if the treatment is interrupted[1]. Currently, there is a wide variety of strategies that aim to reduce the viral reservoir, with the ultimate goal of reducing it to undetectable levels[2-4].

To date, only two strategies have been successful in meeting this goal: the early start of antiretroviral treatment and allogeneic stem cell transplantation in the Berlin patient. However, despite having an undetectable latent reservoir, patients suffer a viral rebound within a few months after stopping treatment (except in the Berlin patient)[5-9]. These results show that an undetectable reservoir of HIV-1 does not mean a cure for the virus. Therefore, there is a need to understand the nature of HIV reservoirs that must be eliminated to achieve a cure[10].

Thus, LoViReT patients[11] are the perfect model to: I) discover the places where the virus persists in the body despite the apparent eradication of HIV in the blood; II) elucidate

the mechanisms by which a patient can maintain extremely low levels of HIV-1 DNA despite having started ART during chronic HIV-1 infection; and III) develop a predictive technique that can anticipate viral rebound before discontinuation of antiretroviral therapy.

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11. Salgado M , Gálvez C, Dalmau J, Carrillo J, Urrea V, Clotet B, Blanco J, M.-P. J. Low Viral Reservoir Treated patients (LoViReT): clinical predictors of low HIV-1 DNA (Abstract PP 3.10). Jounal Virus Erad. (Abstracts Seventh Int. Work. HIV Persistence Dur. Ther.1 suplem 1,

8. DESIGN

Unicentric, case-control, observational clinical study.

9. PRINCIPAL OBJECTIVE

The main objective of the LoViReT project is to identify and characterize the most relevant factors involved in maintaining an extremely low viral reservoir in an exceptional group of patients treated during the chronic phase of infection with antiretroviral therapy. Among these factors we would include both virological factors (viral tropism, complete genome, replicative capacity ...), immuno-genetic factors (HLA, CTL response, plasma neutralization capacity, phenotype of lymphocyte populations, cell activation, transcriptomics ...) and clinical factors (progression clinic, mode of transmission, age, therapeutic picture, sex ...).

10. EXPERIMENTAL DRUG AND CONTROL. DOSAGE, PHYSICAL FORM, ROUTE OF ADMINISTRATION, THERAPEUTIC GROUP

Does not apply

11. PRIMARY ENDPOINT

The primary endpoint is to study the cell-associated HIV DNA, the level of CD4 + T cells from both peripheral blood and associated lymphoid tissues (rectum and lymph node) plus clinical parameters, factors immuno-genetic and the virus itself.

12. STUDY POPULATION AND TOTAL NUMBER OF PATIENTS

12.1. Selection criteria:

Inclusion criteria

- ≥ 18 years of age;
- voluntarily signed informed consent;
- proven HIV-1 infection;
- on stable cART regimen for at least 3 years;
- HIV-RNA <50 copies/mL during the last 3 years prior to the study (blips under 200 copies/ml are permitted in 5% of determinations during last 3 years);
- proviral HIV-DNA <50 copies/million PBMCs by using the ultrasensitive BioRad residual ddPCR quantification platform.

Exclusion criteria

- In women, pregnancy or breastfeeding.
- cART discontinuation since the moment of the previous screening to the date of Visit #1.
- HIV-RNA above 200 copies/mL since the moment of the previous screening to the date of Visit #1

12.2. Total number of participants:

This study is expected to include a total of 86 HIV-infected patients of which 43 patients will come from the LoViReT I cohort, forming the experimental group and the other 43 patients will be shortlisted to form the control group.

The patients of the control group will be included according to the reason 1 control: 1 experimental, in a paired way by age, sex and clinical profile.

13. STATISTICAL ANALYSIS

The absence of previous data for the factors to be analyzed makes it impossible to make an accurate study of the statistical power and the required sample size. However, we can make a rough estimate of the power by reference to the use of non-parametric tests and the measurement of the Cohen effect size (d), defined as the difference between the means divided by the standard deviation of the data.

Although the size of the feasible sample does not allow us to achieve enough power to observe small effects (d = 0.2), with a sample size of 40 patients per group (a total N of 80) we reach a power of about 60% to average effects D = 0.5) and more than 90% for large effects (d = 0.8). With a sample size of 20 patients per group (N = 40) we reach a power of 70% for large effects. The calculations have been made considering a significance level of 0.05 and two tails.

14. ETHICAL CONSIDERATIONS

The study will be carried out in accordance with the principles contained in the Declaration of Helsinki and in accordance with the Law on Medical Research in Human Matters (WMO), Royal Decree 1090/2015, CREC and approval by the Director of the Institution.

The researcher undertakes to comply with the norms established in the applicable clinical trial regulations: Medicines Law 29/2006 (Official State Gazette No. 178, 07-27-06) and Royal Decree 1090/2015.

The protocol will be evaluated by, at a minimum, by a Research Ethics Committee with medications.

The participation of researchers in this study is free, voluntary and independent.

15. TREATMENT DURATION

Does not apply

16. TIMELINE AND EXPECTED FINALIZATION DATE

The expected duration of this study from the writing of the protocol to the final report is 1 year and 10 months (from January 2018 to November 2019). The estimated calendar is quoted below:

Presentation to IRB: February 2017
Inclusion and collection of samples: January 2018 - December 2018
Laboratory analysis: January 2018 – November 2019
Final report: November 2019