Study of the effect of atorvastatin for reducing "inflamaging" (aging-related complication) in HIV-infected patients older than 45 years receiving a protease inhibitor-based regimen versus a raltegravir-based regimen

Code: RALATOR

Version 4, 3rd May 2016

EudraCT: 2015-002682-30

Sponsor: *Lluita contra la SIDA Foundation*
Germans Trias i Pujol University Hospital
Carretera de Canyet s/n
08916 Badalona (Barcelona)

SIGNATURES

The coordinating investigator and the sponsor of the study:
Study of the effect of atorvastatin for reducing "inflamaging" (aging-related complication) in HIV-infected patients older than 45 years receiving a protease inhibitor-based regimen versus a raltegravir-based regimen

Declare that this study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) and the applicable regulatory requirements.

Modifications to this protocol must be submitted prior agreement of the principal investigator and sponsor.

Principal Investigator:

Signature and Date:

Sponsor:
Fundació Lluita contra la SIDA

Signature and Date:

1 GENERAL INFORMATION

1.1 TITLE

Study of the effect of atorvastatin for reducing "inflamaging" (aging-related complication) in HIV-infected patients older than 45 years receiving a protease inhibitor-based regimen versus a raltegravir-based regimen

1.2 CODE

RALATOR

1.3 PROTOCOL VERSION AND DATE

Version 4, 3 May 2016.

Any modification of the protocol must also bear the amendment number and date.

1.4 SPONSOR

Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Carretera de Canyet s/n
08916 Badalona (Barcelona)

1.5 MONITOR

FLS-Research Support
Germans Trias i Pujol University Hospital
Carretera de Canyet s/n
08916 Badalona (Barcelona)

1.6 PRINCIPAL INVESTIGATOR

HIV Unit, Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Carretera de Canyet s/n
08916 Badalona (Barcelona)

1.7 SITES AND INVESTIGATORS

HIV Unit, Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Carretera de Canyet s/n

08916 Badalona (Barcelona)

1.8 TECHNICAL SERVICES INVOLVED

Biochemistry, Haematology, HIV-1 RNA levels and CD4 counts will be performed in the laboratories of the Hospital Germans Trias i Pujol.

Bone densitometry (DEXAs) will be performed in DIGEST, C / Dels Arbres, 53, 08912 Badalona, Barcelona Tel. 93 389 00 22.

Bone turnover markers will be performed in the laboratory MDB. Duran Bellido Lab, C / Urgell, Baixos 161, 08036 Barcelona. Tel. 93 453 86 36.

Inflammation and coagulation markers, immune senescence and immune activation levels will be performed in the AIDS Research Institute –IrsiCaixa–.

TABLE OF CONTENTS

2 BACKGROUND INFORMATION

Physicians in charge of HIV-infected patients are increasingly being faced to previously unrecognized comorbid conditions such as atherosclerosis and cardiovascular events, loss of renal function, osteopenia/osteoporosis and bone fractures or non–AIDS-defining cancers (1-4).
The incidence of these conditions seems to be higher than in the general population but there are controversial data about if these diseases appear at a younger age in HIV-infected patients.
Different pathogenic mechanisms are involved in the increased risk of comorbidities. First, the increased life expectancy of the HIV-infected population. The number of elderly HIV+ individuals is dramatically increasing, and nowadays, approximately one-half of the people living with HIV in the United States are age 50 or older (5). In this sense, aging itself is a condition associated with a chronic inflammation and immune senescence, contributing to accelerate age-related morbidity. Second, the persistent inflammatory state and activation of the immune system also induced by the HIV-infection, *per se.* This condition amplifies the risk of age-related morbidity (6-9). Finally, antiretroviral-related toxicities contribute to accelerate the apparition of some of these diseases such as the dyslipidemia and cardiovascular events (mainly associated with the protease inhibitors use), renal damage or low bone mineral density (especially by tenofovir and probably also by protease inhibitors).

As a consequence, one of the current aims of HIV management is the management of chronic non-infectious co-morbidities in an increasingly older and more complex population. The use of the newest and more safety antiretroviral drugs is a mandatory strategy, especially in this elderly population, to achieve a maintained viral suppression. However, there are many published studies showing higher levels of inflammation even in patients under a viral suppression, in comparison with general population. Regarding this condition, we currently lack effective interventions to potently block this inflammatory status. Although some initial data are published about this regard, data in elderly HIV-infected people are lacking.

Based on these data, we propose a strategy for treatment of elderly HIV-infected patients with a double impact on systemic inflammation and age-related co-morbidities by switching the protease inhibitors by raltegravir, a integrase inhibitor with a neutral effect on lipid and bone metabolism, and adding an statin because of their anti-inflammatory effect. For safety reasons, only patients with maintained viral suppression (documented indetectable viral load for 1 year or more), and no history of virological failure to integrase inhibitors or suspected or documented resistance mutations to the integrase or retrotranscriptase will be candidates for the study.

Raltegravir is an antiretroviral drug that received approval by the U.S. Food and Drug Administration (FDA) in 2007. It was the first of a new class of HIV drugs, the integrase inhibitors, and exhibited rapid, potent and durable antiretroviral activity in antiretroviral naïve patients and in treatment-experienced patients with drug-resistant HIV-1 (10-12). Raltegravir has demonstrated a neutral effect on lipid and renal parameters, and a better impact on bone mineral density (13) and lipid profile than protease inhibitors (14).

Statins are lipid-lowering drugs that also exert anti-inflammatory effects, and have immune-modulatory properties. Recent studies in HIV-infected population have suggested that statins have an anti-inflammatory effect, evaluated by inflammatory markers (15-21), and that the statin use is associated with a lower risk of non-AIDS defining morbidities and malignancies and mortality (22-25). But limited data have been published, mainly based on retrospective studies, and no clinical recommendations are available. We propose the use of atorvastatin to study the anti-inflammatory effect measuring changes in inflammatory markers and some clinical conditions. Atorvastatin was chosen due to the low drug-drug interactions of this statin and ritonavir and the low cost. Since very few data are available about the effect of statins on inflammatory markers and clinical conditions, a intermediate dose (20 mg per day) was selected.

IL-6 and D-dimer are biomarkers that most strongly predict mortality in treated HIV infection and sCD14, sCD163 are soluble markers of monocyte activation that reflect a key source of inflammation and coagulation in HIV infection and predict mortality (26,27). For that reasons, these markers were chosen to determine changes on them after the introduction of the statin and the change of antiretrovirals.

2.1 STUDY HYPOTHESIS

1. Currently, there are new antiretroviral drugs with a neutral impact on renal parameters and lipid and bone metabolisms. The integrase inhibitor raltegravir has been associated with a neutral effect on these conditions and may help to prevent or delay the aging-related comorbidities.

- Hypothesis 1: Switching protease inhibitors by raltegravir in HIV-infected patients aged >60 years may be associated with an improvement of:
    - Metabolic parameters,
    - Bone mineral density,
    - Renal parameters.

2. Statins has a well-known anti-inflammatory and antithrombotic effect.

- Hypothesis 2: The addition of a statin may decrease levels of inflammation and coagulation markers, as well as the immune activation.

- Hypothesis 3: The improvement of systemic inflammation may be associated with an improvement of age-related conditions such as bone mineral density and renal parameters.

2.2 REFERENCES

1. Schouten J, Wit FW, Stolte IG, et al. Comorbidity and ageing in HIV-1 infection: the AGEhIV Cohort Study [Abstract #THAB0205]. Program and
Abstracts from the XIX International AIDS Conference; Washington, DC. 22–27 July, 2012.

2. Kendall CE, Wong J, Taljaard M, et al. A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. BMCPublic Health 2014; 14:161.

3. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. J Acquir Immune Defic Syndr 2012; 60 (Suppl 1):S1–S18.

4. Peter W. Hunt. HIV and aging: emerging research issues. Current Opinion HIV AIDS 2014;9:302-8.

5. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis. 2008;47:542–53.

6. French MA, King MS, Tschampa JM, et al. Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4þ T cells. J Infect Dis 2009; 200:1212–1215.

7. Boulware DR, Hullsiek KH, Puronen CE, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis 2011;203:1637–1646.

8. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One 2012;7:e44454.

9. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis 2010;201:1788–1795.

10. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, et al; STARTMRK investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet. 2009;374:796-806. Erratum in: Lancet. 2009 Dec 19-2010;374:2054.

11. Steigbigel RT, Cooper DA, Teppler H, Eron JJ, Gatell JM, Kumar PN, et al; BENCHMRK Study Team. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clin Infect Dis.2010;50:605-12.

12. Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, et al; Protocol 005 Team. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet. 2007;369:1261-9.

13. Brown T. Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir. 21th Conference on Retroviruses and Opportunistic Infections. March 3-6 2014. Abstract 779LB.

14. Ighovwerha Ofotokun. Darunavir or atazanavir vs raltegravir lipid changes are unlinked to ritonavir exposure: ACTG 5257. 21th Conference on Retroviruses and Opportunistic Infections. March 3-6 2014. Abstract 746.

15. Dubé MP. Will statins be an effective anti-inflammatory intervention for prevention of cardiovascular disease in patients with HIV? J Infect Dis. 2014;209:1149-50.

16. Calza L, Trapani F, Bartoletti M, Manfredi R, Colangeli V, Borderi M, et al. Statin therapy decreases serum levels of high-sensitivity C-reactive protein and tumor necrosis factor-α in HIV-infected patients treated with ritonavir-boosted protease inhibitors. HIV Clin Trials. 2012;13:153-61.

17. Calza L, Vanino E, Salvadori C, Manfredi R, Colangeli V, Cascavilla A, et al. Tenofovir/emtricitabine/efavirenz plus rosuvastatin decrease serum levels of inflammatory markers more than antiretroviral drugs alone in antiretroviral therapy-naive HIV-infected patients. HIV Clin Trials. 2014;15:1-13.

18. Funderburg NT, Jiang Y, Debanne SM, Labbato D, Juchnowski S, Ferrari B, et al. Rosuvastatin reduces vascular inflammation and T cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. J Acquir Immune Defic Syndr. 2014 Dec 13. [Epub ahead of print]

19. Funderburg NT, Jiang Y, Debanne SM, Storer N, Labbato D, Clagett B, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. Clin Infect Dis. 2014;58:588-95.

20. Auclair M, Afonso P, Capel E, Caron-Debarle M, Capeau J. Impact of darunavir, atazanavir and lopinavir boosted with ritonavir on cultured human endothelial cells: beneficial effect of pravastatin. Antivir Ther. 2014;19:773-82.

21. Eckard AR, Jiang Y, Debanne SM, Funderburg NT, McComsey GA. Effect of 24 weeks of statin therapy on systemic and vascular inflammation in HIV-infected subjects receiving antiretroviral therapy. J Infect Dis. 2014;209:1156-64.

22. Galli L, Spagnuolo V, Poli A, Salpietro S, Gianotti N, Cossarini F, et al. Use of statins and risk of AIDS-defining and non-AIDS-defining malignancies among HIV-1 infected patients on antiretroviral therapy. AIDS. 2014;28:2407-15.

23. Rasmussen LD(1), Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Obel N. Statin therapy and mortality in HIV-infected individuals; a Danish nationwide population-based cohort study. PLoS One. 2013;8:e52828.

24. Overton ET, Kitch D, Benson CA, Hunt PW, Stein JH, Smurzynski M, et al. Effect of statin therapy in reducing the risk of serious non-AIDS-defining events and nonaccidental death. Clin Infect Dis. 2013;56:1471-9.

25. Erlandson KM, Jiang Y, Debanne SM, McComsey GA. Effects of randomized rosuvastatin compared with placebo on bone and body composition among HIV-infected adults. AIDS. 2015;29:175-82.

26. Funderburg NT, Mayne E, Sieg SF, et al. Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation. Blood 2010; 115:161–167.

27. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 2011;203:780–790.

3 TRIAL OBJECTIVE AND PURPOSE

3.1 PRIMARY OBJECTIVE

To compare changes in IL-6 between patients that change from protease inhibitors to raltegravir, or to continue protease inhibitors, with or without atorvastatin.

3.2 SECONDARY OBJECTIVES

- To compare changes between protease inhibitors and raltegravir, with or without atorvastatin, in the following parameters:
  - Inflammation and coagulation markers, immune senescence and immune activation levels.
  - Lipid and lipoprotein parameters.
  - Lumbar spine (L2-L4) and femoral (total femur, trochanter, femoral neck) BMD and T-scores.
  - Bone turnover markers.
  - Renal parameters.
- To asses virological and immunological response.

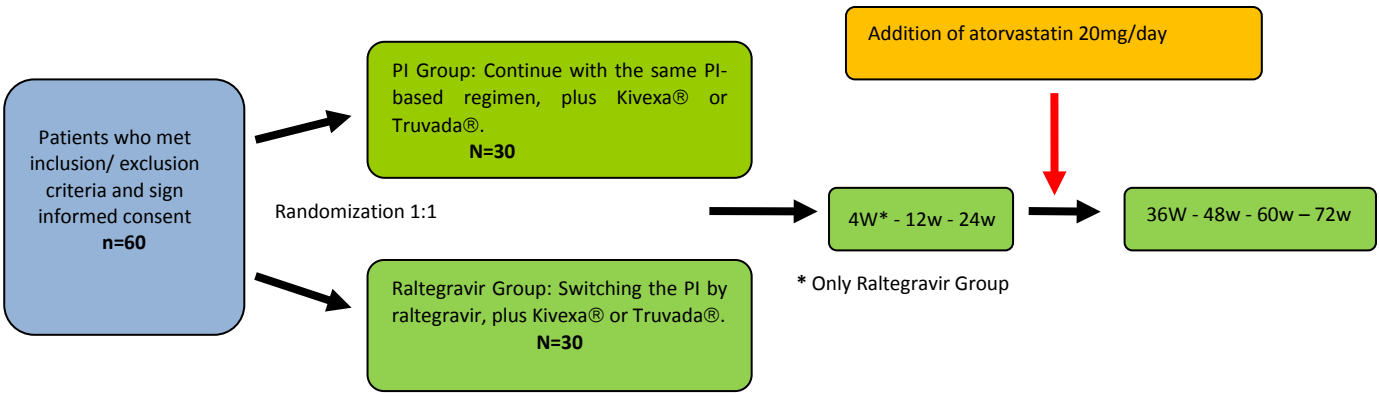
4 TRIAL DESIGN

4.1 TYPE OF TRIAL

This is a 72-week, active-controlled, randomized, open-label, pilot study in HIV-infected patients including investigational marketed products.

Clinical trial phase: IV

4.2 DESCRIPTION OF THE DESIGN



4.3 ENDPOINTS

4.3.1 Primary endpoint

Compare intergroup and intragroup changes at week 72 from week 24 to assess the effect of statin; at week 72 from baseline to assess the effect of PI or raltegravir plus statin and at week 24 from baseline to asses the effect of PI or raltegravir, in the following parameters:

- the inflammatory marker IL-6 *

4.3.2 Secundary endpoints

- Compare intergroup and intragroup changes at week 72 from week 24 to assess the effect of statin; at week 72 from baseline to assess the effect of PI or raltegravir plus statin and at week 24 from baseline to asses the effect of PI or raltegravir, in the following parameters:
  - the inflammatory, immune and coagulation *
  - lipid profile
  - lumbar and femoral BMD and *t*-score measured by DEXA
  - bone turnover markers
  - renal parameters
- Compare between groups the percentage of patients who maintain viral suppression at week 72.
- Compare between groups the percentage of patients who experienced virological failure throughout the study. Virological failure will be defined as an increase in HIV RNA >50 copies in 2 determinations within 1 month.

- Compare between groups the change in CD4+/CD8+ T lymphocytes at week 72 from baseline.
- Determination of antiretroviral resistance at the time of virological failure and comparison with baseline.

IL-6 and D-dimer are biomarkers that most strongly predict mortality in treated HIV infection and sCD14, sCD163 are soluble markers of monocyte activation that reflect a key source of inflammation and coagulation in HIV infection and predict mortality**.

- Funderburg NT, Mayne E, Sieg SF, et al. Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation. Blood 2010; 115:161–167.
- Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 2011;203:780–790.

4.4 MEASURES TO AVOID BIAS

To minimize or avoid bias patients will be randomized.

4.4.1 Randomization

Randomization table will be made by assigning a uniform distribution and a range of values to each of the groups. Patients will be randomly assigned in a 1:1 ratio to:

- Continue with the same PI-based regimen, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

- Switching the PI by raltegravir, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

All patients will be followed-up for 72 weeks in total.

The assignation will be performed by telephone and will be centralized. It will be impossible for the investigators to know which group will be assigned to a patient before his/her inclusion in the study.

4.4.2 Stratification

Patients will be stratified according to the baseline levels of LDL-cholesterol (LDL cholesterol > or < 160mg).
In addition, patients will be stratified according to the nucleoside drugs used, tenofovir/emtricitabine (Truvada®) or abacavir/lamivudine (Kivexa®).
In this way, the distribution of these parameters between the study groups will be balanced.

4.4.3 Blinding

Not applicable since it is an open clinical trial.

4.5 FORESEEN CALENDAR

- First patient first visit: October 2015
- Inclusion period: 24 weeks
- Follow-up period: 72 weeks
- Last patient last visit: October 2017

- Final report submission: October 2018

4.6 END OF TRIAL

The date of the end of the trial will be the last visit of the last patient.

The trial will be prematurely stopped if there are virological failures or withdrawals because of intolerance or toxicity more than 20%.

If the study must be interrupted prematurely, all non-used materials should be returned to the sponsor, at the *Lluita Contra la SIDA Foundation.* The principal investigator will keep the investigator file and the completed CRF.

In case there were no patients included in the study, the sponsor will take care of all materials.

4.7 SOURCE DATA

Source documents are the patient's medical records, the results obtained through blood tests as routine clinical and laboratory results obtained from blood samples collected on the same day that the blood test. Also the results of the DEXAs are source data.

Study data will be collected trough a Case Report Form (CRF).

5 TRIAL INVESTIGATIONAL PRODUCT(S)

5.1 EXPERIMENTAL AND CONTROL TREATMENTS

Two experimental treatments will be tested in this trial: raltegravir (Isentress®) and atorvastatin.

The control treatment is the PI boosted with ritonavir.

Study groups are:

- PI Group: Continue with the same PI-based regimen, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

- Raltegravir Group: Switching the PI by raltegravir, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

5.2 SUPPLY, PACKAGING, LABELING AND STORAGE

All treatments will be administered by the Pharmacy Service of the participating site in the marketed format.

Atorvastatin drug will be supplied on its marketed format by the sponsor.

To ensure traceability of investigational products, drug name, quantity and batch number will be obtained from Pharmacy Service. An actual inventory of all treatments administered and dispensed during the clinical study should be maintained.

No conditioning is required.

All study medication will be stored in a safe place during the study. Storage shall be in accordance with the conditions defined conservation in the summary of products characteristics. Being marketed medication, specific temperature control for the study will not be performed, but the usual procedures will be followed in the Pharmacy for the custody and traceability of medication.

5.3 DOSE, INTERVAL, ROUTE AND METHOD OF ADMINISTRATION

- PI Group: PI-based regimen, plus abacavir 600 mg/ lamivudina 300 mg (Kivexa®), 1 tablet every 24 hours or tenofovir 300mg/ emtricitabina 200mg (Truvada®) 1 tablet every 24 hours, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

- Raltegravir Group: Switching the PI by raltegravir, plus abacavir 600 mg/ lamivudina 300 mg (Kivexa®), 1 tablet every 24 hours or tenofovir 300mg/ emtricitabina 200mg (Truvada®) 1 tablet every 24 hours, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

The route of drug administration is oral.

5.4 DRUG ACCOUNTABILITY

No returned drug accountability will be performed.

To perform the drug accountability of the dispensed product, the records of the Pharmacy Service of the site will be used.

To ensure traceability of the investigational drug, trade name, quantity and batch number dispensed to each patient will be obtained from Pharmacy Service.

5.5 ARM DESCRIPTION

- IP Group: Continue with the same PI-based regimen, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.
- Raltegravir Group: Switching the PI by raltegravir, plus Kivexa® or Truvada®, for 24 weeks. After that, atorvastatin, 20mg/day, will be added for 48 weeks.

5.6 MODIFICATION OF THE TREATMENT REGIMEN

No changes in treatment regimes are foreseen during the study period.

In case of failure of one of the regimens, a new regimen will be decided using a resistance test.

In case adverse events to the medication occur, the investigator will decide if it is necessary to replace it.

At the end of the study, the change of treatment will be done at the discretion of the physician.

5.7 CONCOMITANT TREATMENTS

All other treatments apart from antiretroviral medication administered during the study period will be considered concomitant treatments and should be documented in the CRF.

It is remembered that the patients who participate in the study should not continue any concomitant treatment without the knowledge and permission of the investigator.

In the SmPC of each drug (appendix II), detail on pharmacological interacions and dose recomendations with other drugs are specified.

5.8 COMPLIANCE

Treatment adherence will be self-reported by the patient by answering the adapted SERAD questionnaire (included in the CRF).
The investigator is to ask the patient about treatment adherence to antiretroviral and concomitant treatment and this data is to be written in the clinical record. This data is to guarantee the compliance.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 INCLUSION CRITERIA

1. Patient having a diagnosis of HIV-1 infection.
2. Age ≥45 years old.
3. Current HAART including Truvada® or Kivexa® plus a ritonavir boosted PI started at least 3 months before.
4. Maintained undetectable plasma HIV-1 RNA (VL < 50 copies/mL) for at least 12 months.
5. Voluntary written informed consent.

6.2 EXCLUSION CRITERIA

1. History of virological failure to integrase inhibitors.
2. Suspected or documented resistance mutations to the integrase, as well as NRTI–related mutations that may impact nucleoside activity in current regimen.
3. Systemic concurrent process such as coinfection with hepatitis C or B, acute systemic infection within the last 4 months, neoplasm, chronic inflammatory process, etc.
4. Treatment with other drugs with anti-inflammatory, anticoagulant or antiplatelet effect (for instance corticosteroids, aspirin, etc…)
5. Therapy with statins within the last 6 months.

6.3 SUBJECT WITHDRAWAL CRITERIA

6.3.1 Early subject withdrawal

The patients will withdraw the clinical study in the following circumstances:

- Virological failure: it is defined as an increase in HIV RNA >50 copies on two consecutive visits within 4-6 weeks.
- Interruption of treatment due to adverse events, intolerance or poor adherence during the study.
- Concurrent process or illness which in the opinion of the investigator requires the withdrawal of the patient.
- The patient starts treatment with other drugs with anti-inflammatory, anticoagulant or antiplatelet effect such as aspirin, corticosteroids, etc…
- The patient does not wish to continue in the study.

6.3.2 Medical approach to withdrawal

In all cases, ‘end of study form’ is to be filled. Detailed information will be given about the date and reasons of the discontinuation to the sponsor. The investigator will facilitate the necessary medical support.

6.3.3 Follow-up after early withdrawal

That is, as a general rule, all patients who discontinue treatment prematurely will undergo a clinical examination and all tests specified in the visit.

In the presence of virological failure or change in the treatment due to toxicity, the new antiretroviral treatment regimen will be constructed based on the physicians' criteria.

6.3.4 Replacement of patients

Patients withdrawn by any reason will not be replaced.

6.4 PRE-RANDOMIZATION / PRE-BASELINE LOSSES

Data from patients that do not meet the selection criteria after completing the baseline visit will not be considered for the study. These data will not be collected.

7 TRIAL CONDUCTION AND RESPONSE EVALUATION

7.1 CRITERIA FOR RESPONSE EVALUATION

7.1.1 Primary parameter

The inflammatory marker IL-6.

7.1.2 Secundary parameters

- Inflammation marker: High-sensitivity C-reactive protein (hsCRP).
- Activation markers: CD38 i HLADR.
- Immune exhaustion marker: PD-1.
- Maturation markers: CCR7, CD45RA, CD27.
- Immunosenescence markers: CD38 i CD57.
- Coagulation: Fibrinogen and D Dimer.
- Lipid profile: total, HDL-, LDL-cholesterol and triglyceride levels.
- Lumbar spine (L2-L4) and femoral (total femur, trochanter, femoral neck) BMD and t-scores.
- Bone formation and resorption markers: CTX, Osteocalcin, N-terminal type I peptide (P1PN)
- Renal parameters: Serum creatinine and phosphatemia; estimated renal glomerular filtrate (CKD-EPI); albuminuria/creatinine and proteinuria/creatinine ratios; hematuria, glucosuria and phosphaturia.
- Plasma HIV-1 viral load.
- CD4+/CD8+ T lymphocyte count.
- Genotypic test if virological failure occurs.

7.2 TRIAL DEVELOPMENT

If patients meet the selection criteria, after accepting the participation, patients would be randomized and assessed the baseline visit. Study follow-up visits would be at weeks 4 (only raltegravir group), and every 3 months thereafter.

Blood specimens will be obtained and stored at the points specified in the flow chart of the study.

Plasma and serum samples and PBMC will be stored at –80ºC.

7.3 CLINICAL RECORD AND PHYSICAL EXAM

Demographic and HIV infection-related data will be collected in order to characterize the study population (sex, age, time since HIV diagnosis, risk factor and history of opportunistic infections or tumors).

A complete physical examination will be performed at the baseline visit, including weight and height. In the follow-up, a physical exam will be performed.

7.4 LABORATORY TESTS

Patients will fast for at least 8 hours prior to assessment, in the points specified in the flow chart of the study (section 7.5). The following parameters will be quantified, as needed:

- **Hematology:**
  Hematocrit
  Red blood cell count
  Hemoglobin
  Leucocytes
  Lymphocyte
  Platelet count
  Fibrinogen

- **Blood biochemistry:**
  Glucose
  Urea
  Creatinine
  Ionogramme: sodium, potassium
  Total Bilirubin
  Total protein
  Albumin
  Creatinin kinasa (CK)
  Liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-GT, alkaline phosphatase
  Lipid profile: total, HDL-, LDL-cholesterol and triglyceride levels.
  Renal parameters: Serum creatinine and phosphatemia; estimated renal glomerular filtrate (CKD-EPI); albuminuria/creatinine and proteinuria/creatinine ratios; hematuria, glucosuria and phosphaturia.

- **Immunology:**
  CD4+/CD8+ T lymphocyte count.

- **Virology**
  Plasma HIV-1 viral load.

- **Genotypic test if virological failure occurs.**

- **Bone formation and resorption markers:**
  CTX
  Osteocalcin
  N-terminal tipe I peptide (P1PN)

- **Specific Lab Procedures**
  Inflammatory marker IL-6.
  Inflammation marker: High-sensitivity C-reactive protein (hsCRP).
  Activation markers: CD38 i HLADR.
  Immune exhaustion marker: PD-1.
  Maturation markers: CCR7, CD45RA, CD27.
  Immunosenescence markers: CD38 i CD57.
  Coagulation: D Dimer.

- **DEXA**
  Lumbar spine (L2-L4) and femoral (total femur, trochanter, femoral neck) BMD and t-scores.

Note: Before the beginning of the study, all labs will facilitate to the sponsor and to the investigator a list of the reference normal values of the parameters assessed.

7.5 ASSESSMENTS FLOW-CHART

	BL	Wk 4	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 76 (security contact by phone)
Inclusion/ exclusión criteria	√								
Informed consent	√								
Clinical visit	√	√	√	√	√	√	√	√	
Inflammatory and immune markers	√			√				√	
Haematology and Biochemistry (including lipid and renal profiles)	√[a]	√[e]	√	√	√	√	√	√	
DEXA scan	√[b]			√				√	
Serum storage[c] for bone formation and resorption markers determination	√			√				√	
HIV1-1 Viral load	√[a]	√	√	√	√	√	√	√	
CD4 cell count	√[a]	√	√	√	√	√	√	√	
Adverse events		√	√	√	√	√	√	√	√
Plasma sample storage[d]	√	√	√	√	√	√	√	√	

[a] A blood test including HIV-1 RNA, CD4+ counts , biochemistry and haematology performed within 3 months previous to the baseline visit will be accepted as baseline.
[b] A DEXA scan performed within 6 months previous to the baseline visit will be accepted as baseline.
[c] Serum will be stored at -80ºC.
[d] Genotypic resistance testing will be performed to all participants experiencing virological failure during the study.
[E] Basic Haematology and biochemistry

8 ADVERSE EVENTS

The investigator is responsible for detecting and documenting any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE) per this protocol.
During the conduct of the study, the presence of adverse events, whether or nonserious, will be verified according to the adverse event definitions given in this section.

8.1 DEFINITION

An adverse event (AE) is any untoward occurrence to the health of a patient or clinical trial subject treated with a medicinal product and which does not necessarily have a causal relationship with this treatment.
It may be a new concomitant disease, a worsening of a concomitant disease, an injury, or any concomitant deterioration in the patient's health status, including laboratory values, regardless of etiology. Any medical condition that was present before the study treatment and that remains unchanged or improves should not be considered or recorded as an AE. A worsening of that medical condition will be considered as an AE.

An adverse reaction (AR) is any noxious and unintended reaction to an investigational drug, regardless of the dose administered.

A serious adverse event (SAE) is any adverse event that, at any dose, results in death, is life-threatening, requires or prolongs hospitalization of the subject, causes persistent or significant disability or incapacity, or gives rise to a congenital anomaly or birth defect. Life-threatening is defined as the situation in which, in the opinion of physician, the patient would have died if it had not been for a timely therapeutic intervention.
For reporting purposes, any suspected adverse events considered medically important will be classified as serious even if they do not meet the above criteria.
Medically important events are defined as those events that may not be immediately life-threatening or cause death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias or convulsions not requiring hospitalization, or the development of drug dependency or drug abuse.
Medical and scientific judgment should be used to decide if other situations that have resulted in one of the outcomes listed in the above definitions should be reported as a SAE.
Hospitalization or prolongation of an existing hospitalization are a criterion for considering that an AE is serious. Only admission when the patient stays overnight in the hospital should be considered hospitalization.
The following situations do not meet the criteria for a SAE:

- if hospitalization or prolongation of hospitalization is required for completing a procedure required by the protocol (for instance day or night visits are performed for biopsies or surgery required by the protocol).

- if hospitalization or prolongation of hospitalization is part of the routine procedure at the site (such as withdrawal of a stent after surgery)

- if hospitalization was scheduled prior to patient entry in the study

- if hospitalization was scheduled for a preexisting condition that has not worsened

An unexpected adverse reaction (UAR) is defined as any adverse reaction whose nature or severity is not consistent with product information (e.g., Investigator’s Brochure for an unapproved investigational drug or the summary of product characteristics for an approved medicinal product).

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is both serious and unexpected.

8.2 ATTRIBUTABILITY CRITERIA

The causal relationship of the investigational product to the occurrence of the AE/SAE will be established based on a clinical judgment. For this, other causes will be considered and studied, such as the natural history of underlying diseases, concomitant treatment, other risk factors, and temporal relationship of the event to the investigational product. In addition, the summary of product characteristics of the products will be reviewed.

To analyze the possible cause-effect relationship, the temporal relationship between drug administration and the AE, possible alternative explanations, the outcome (complete remission, partial recovery, death, sequelae, persistence), persistence or not after discontinuation of the study drug, recurrence on drug rechallenge, or previous knowledge of the event consistent with the known or expected pattern of response to the study drug will be considered.

The causal relationship of an AE to the study drug will be described according to the following definitions:

Unlikely related: The adverse event does not occur after a plausible temporal sequence from administration of the study product and/or can be reasonably explained by other factors such as the patient's clinical state, toxic or environmental factors, or other concomitant therapies. In addition, it does not follow the known or expected pattern of response to the drug.

Possible relationship: The adverse event occurs after a plausible temporal sequence from administration of the study product, but can also be explained by the patient's clinical state, toxic or environmental factors, or other concomitant therapies. In addition, it does not follow the known or expected pattern of response to the drug.

Probable relationship: The adverse event occurs after a plausible temporal sequence from administration of the study product, cannot be reasonably explained by the patient's clinical state, toxic or environmental factors, or other concomitant therapies, and after withdrawal or dose reduction of the suspect drug, the event follows a logical clinical sequence. In addition, it follows the known or expected pattern of response to the drug.

Clear relationship: The adverse event occurs after a plausible temporal sequence from administration of study product, cannot be reasonably explained by the patient's clinical state, toxic or environmental factors or other concomitant therapies, after withdrawal or dose reduction of the suspect drug, the event follows a logical clinical sequence, and the adverse event recurs after reintroduction of the suspect drug. In addition, it follows the known or expected pattern of response to the drug.

No relationship: The adverse event is clearly due to causes unrelated to the study drug, and the criteria for another causal relationship are not met.

Nonassessable relationship: Any report suggesting an adverse effect which cannot be judged because the information is insufficient or contradictory, and which cannot be supplemented or verified.

8.3 ADVERSE EVENTS GRADING

The Division of AIDS (DAIDS) from the NIH from the United States of America has developped a graded scale to assess the intensity of the adverse events and laboratory test abnormalities with clinical IMPORTANCIA under the use of antiretroviral agents (http://rcc.tech-res.com/safetyandpharmacovigilance). When possible, the

investigator will use these definitions. In case of events or laboratory abnormalities not included in the table, the following scale will be used:

Grade 1 (mild): Symptoms causing no or minimal interference with usual social & functional activities

Grade 2 (moderate): Symptoms causing greater than minimal interference with usual social & functional activities

Grade 3 (severe): Symptoms causing inability to perform usual social & functional activities

Grade 4 (potentially life-threatening): Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Grade 5 (death): **A**ny AE where the outcome is death.

8.4 ADVERSE EVENTS DETECTION AND RECORDING

AEs will be recorded at each visit based on careful clinical observation of the patient, laboratory tests, spontaneous reports by the patient and also by open-ended questioning by the investigator.

All AEs (serious or not) occurring during the study must be noted in the medical history and recorded in the CRF. The investigator will also decide whether the adverse event is, based on his/her judgment, related or not to the study drug—this decision should also be noted in the medical history and CRF.

At each visit, all AEs experienced by the patient since the previous visit should be recorded in the specific adverse event form of the CRF.

The following will be recorded for each event: description, severity (grade 1, 2, 3, 4 and 5), duration (start and end dates), causal relationship with the drug (according to the previously attributability criteria) and study drug(s) for which this causal relationship is suspected, need for treatment (if applicable) or the actions taken, possible alternative explanations, predisposing factors, and outcome. For a preexisting AE that has worsened in terms of severity or frequency, the meaning of the change should be specified.

The degree of severity of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event elicited by the investigator or reported by the patient. Severity does not reflect the clinical seriousness of the event, only the grade or extent of the complaint or incidence.

The severity of an AE will be rated based on the Division of AIDS toxicity table.

8.5 PROCEDURES FOR EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR

The principal investigator will report immediately to the Sponsor all serious adverse events regardless of their degree of causal relationship with the study drug. All SAEs occurring from signing of informed consent and up to 30 days after receiving the last dose of the study drug should be reported.

The initial report of SAE should be written and as complete as possible including details of the current disease and SAE and assessment of the causal relationship between the AE and the investigational product. Reporting

will be made using the Serious Adverse Event Report Form within 24 hours from first knowledge by the investigator, completing all information on the form in the following two days.
The information missing at the time of the initial report must be reported in the SAE follow-up form.

For SAEs, the investigator will provide the Sponsor with all documentation related to the event (additional laboratory tests, discharge reports, etc.).

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

In the event of death, the investigator must provide the sponsor, the Ethics Committee (EC) involved, and the relevant regulatory authorities with all additional information requested by them.

8.6 PROCEDURES FOR EXPEDITED REPORTING OF SERIOUS AND UNEXPECTED ADVERSE REACTIONS BY THE SPONSOR

The study sponsor will report any events that are serious and unexpected that may be related to the investigational products (i.e., suspected unexpected serious adverse reactions, SUSARs) to the Spanish Regulatory Agency, the competent bodies of the Autonomous Communities involved (the communities in whose territory the trial is being conducted) and to the EC involved (EC of the site where the SUSAR occurred).

These reports will also be communicated simultaneously to the Pharmacovigilance responsibles at MSD within the 24 hr of uncknowledgement of the SAE in order to have the affiliate reporting it internally to its headquarters.

Reporting will be made using Suspected Adverse Reaction Report Form.
The maximum deadline for reporting will be 15 calendar days from the time the sponsor is aware of the SUSAR. For SUSARs causing death or that are life-threatening for the subject, the maximum reporting time will be 7 calendar days from the time the sponsor is aware of them. This information will be completed, when possible, in the following 8 days.

Information on adverse events that are not serious or unexpected and on those considered unrelated to the study treatment will be collected in tabular form at the end of the clinical trial or at the time of interim analyses when these are planned.

The Sponsor will keep a record of all AEs reported by investigators. These records will be submitted to the Spanish Regulatory Agency when requested.

8.7 ABNORMAL LABORATORY PARAMETERS

An abnormal laboratory parameter shall be considered an AE if the abnormality:

- results in withdrawal from the study
- requires treatment, dose modification or investigational drug interruption or any other therapeutical intervention
- is considered clinically important

Regardless of their severity, only laboratory abnormalities that meet criteria of seriosness should be recorded as SAE.

If the laboratory abnormality is part of a diagnosis or syndrome, only the syndrome or diagnosis will be included as AE or SAE. If the laboratory abnormality is not part of a diagnosis or syndrome, it shall be recorded as AA or AAG.

Clinically significant changes in safety parameters that are associated with the disease under study will not be rated as AE or SAE, unless the investigator judges that are more severe than expected given the patient's condition.

8.8 DOCUMENTATION RELATED TO AE AND SAE

Each AE and SAE to take place during the study should be documented in the medical records of the patient in accordance with standard clinical practice of the researcher, and in the CRF. For each SAE, an independent set of SAE form will be used independently. Only if there are multiple SAE at the time of the initial report and these are temporary and / or clinically interrelated can be registered on the same set of SAE form.

The researcher should try to make a diagnosis of the event based on the signs, symptoms and / or other clinical information. An AE diagnosis has to be recorded per line or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialed and dated by the investigator.

SAE pages found in the investigator's file shall be completed as precisely as possible, printed and shall be signed by the investigator before being sent to the sponsor. It is very important that the initial page SAE researcher provide its opinion in regard to the relationship of the event to the study drug.

8.9 SAE FOLLOW-UP

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

Although not considered an adverse event, it is the responsibility of the investigator and his/her coinvestigators to report immediately any pregnancy or suspected pregnancy (including positive pregnancy tests regardless of age) occurring during the study or within 28 days after the end of the study.

9 STATISTICS

A general descriptive analysis of all the variables of the study, overall and separately by groups of treatment is going to be done by means of mean, standard deviation, median, interquartile range, maximum and minimum values for the quantitative variables and absolute and relative frequencies of each category for categorical variables.

9.1 RESPONSE EVALUATION

The response evaluation is going to be done per-protocol, an interim analysis will be performed at the end of each phase, and when the interim analyses are planned.

The statistical significance of the longitudinal changes in the parameters of interest is going to be assessed by the calculation of the difference and compared using t-student, Wilcoxon or Mann-Whitney distinguishing between treatment groups and/or other relevant baseline factor. Comparisons concerning two categorical variables are going to be performed by means of Chi-square or Fisher's exact tests, regarding the nature of the variables.

Missing data treatment: The evidences that can show that the missing is explained by the value that it will have (missing non at random) are going to be described. When the missingness is produced at random or completely at random the distribution of the missing values is assumed to be the same that the observed or the same than the observed values conditioned to the value of the other covariates, respectively; for this reason any action is going to be carried out in the missingness treatment.

The significance level of the hypothesis testing is 5%. According to the assessed outcome one side or two sides testing are going to be performed.
If necessary, transformation of the data is going to be considered.

9.2 SECURITY ANALYSIS

The information about the safety of the treatment is going to be analyzed in a graphical and/or tabular descriptive form for all the patients included in the study. The clinical relevance of the values of each control as well as the changes happened between different controls is going to be evaluated.

All the adverse events are going to be tabulated and analyzed descriptively.

9.3 SAMPLE SIZE DESCRIPTION

We are planning to include in the study 60 patients, 30 in each group. This sample has been determined considering the possible number of candidates who could be enrolled in the study according to our patient's data base attended in our HIV Unit.

9.4 DEVIATION OF STATISTICAL PLAN

Any deviation from that presented statistical plan will be described and justified in the final report.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Researchers and institutions will allow the monitoring, and audits by the Health Authorities or the Sponsor giving direct access to data and original source documents.

Access to personal patient information will be restricted to the Study physician / staff. To allow monitorings, audits and inspections, access to data to Health Authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee and personnel authorized by the Sponsor, is guaranteed while maintaining the confidentiality thereof according to current legislation.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 STUDY MONITORING

In accordance with applicable regulations and Good Clinical Practice (GCP), the monitor will visit or contact the center on a regular basis. The duration, nature and frequency of visits / contacts depend on the monitoring plan.

During these contacts, the monitor shall:

- monitor and evaluate the progress of the study;
- examining the data collected;
- carry out a verification of the source documents;
- identify any problems and find solutions;

The goal of the monitoring activity is to verify that:

- the rights and welfare of subjects are respected;
- survey data are accurate, complete and verifiable with the help of original documents;
- the study is performed according to the protocol and any amendment adopted, GCPs and regulations.

The investigator must agree to:

- grant to monitor direct access to all relevant documentation;
- devote part of his/her time and staff time to the monitor in order to discuss the results of the monitoring, as well as any other possible aspect.

The monitor should also contact the center before starting the study with the aim to discuss with staff the Protocol and procedures for data collection.

11.2 AUDITS AND INSPECTIONS

Sponsor can carry out an audit of quality control at its sole discretion. In this case, the investigator should agree to grant the auditor direct access to all relevant documentation and devote part of his/her time and staff time to the auditor in order to discuss the results of the monitoring, as well as any other possible aspect.

Moreover, regulatory authorities may also inspect the study. In this case, the investigator should agree to give the inspector direct access to all relevant documentation and devote part of his/her time and staff time to the inspector in order to discuss the results of the supervision, as well as any other possible aspect.

11.3 CASE REPORT FORM

Data collection will be done through a CRF.

Accurate and reliable data collection is ensured by checking and cross checking the CRF front site records conducted by the study monitor (verification of source documents). The data collected will be added to a computer database which will be reviewed for possible inconsistencies to be resolved by the research team of the study in the site.

The content of the CRF is attached in Appendix I.

12 ETHICS

12.1 GENERAL CONSIDERATIONS

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brasil, octubre 2013.

This study will be conducted according to Spanish regulations and the required documentation prior to the start will be:

- Protocol acceptance by the sponsor and the principal investigator
- Protocol approval by the Ethics Committee.
- Protocol authorization from the Spanish Drug Agency (Ministry of Health)

All subjects will be guaranteed continued medical and nursing supervision throughout the duration of the study.

This study will conform to the standards of "Good Clinical Practice".

12.2 PATIENT INFORMATION SHEET AND INFORMED CONSENT

Informed consent will be obtained before including the patient in the trial (Appendix III). The investigator is to inform the patient of the nature, duration and purpose of the study, as well as of all the obstacles and inconveniences which – within reason – may be expected from it. Furthermore, the patient is to receive information in writing. The participating patients must be legally competent to give informed consent, with the possibility of taking decisions at his/her own free will. The patient has the right to leave the study at any time.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA HANDLING

The processing of the data to be compiled by the study sponsor during the trial will be subject to current legislation as regards data protection (LOPD, Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal). The patient will be identified in the records by the corresponding code number only. The patient is to be guaranteed anonymity, and is to be informed that all communication will take place between him/her and the investigator – not the sponsor of the trial.

Data transmitted to third countries and other countries will in no case contain personal data. In the event that such transfer occurs, it will be for the same purposes of the study described and ensuring confidentiality at least to the level of protection of the law in Spain.

13.2 RECORD KEEPING

13.2.1 Investigator file and document retention

The investigator must keep the investigator file with the proper and accurate records to enable the study to be fully documented and data subsequently verified.

The Investigator's study file will contain the protocol and its amendments, CRFs, questionnaires' forms, EC approval and authorization from the health authorities, samples of the patient information sheet and informed consent, staff curriculum, signatures' delegation log and listing of subjects, as well as other appropriate documents and correspondence.

Clinical source documents from subjects (usually predefined by the project to record key efficacy and safety parameters or documents that are not in the clinical record of the hospital) will be filed indicating the number of patient without personal data.

The investigator should retain these documents at least five years, according to SCO/ 256/2007, provided that the promoter does not express a greater period.

13.2.2 Source documents and basic data

The information contained in the CRF will be considered as primary data, except for patient filiation data and lab tests. Patient participation in the study will be collected on medical records, including assigned code number and identification of the different study visits that will take place throughout the study. At the end of the study, a copy of the CRF will be placed on the site.

14 FINANCING AND INSURANCE

14.1 SOURCE OF FINANCING

The funding source is the Lluita contra la SIDA Foundation.

14.2 INSURANCE POLICY

In accordance with Article 8 of Royal Decree 223/2004, of 6 February, the trial sponsor has a policy of liability insurance with Zurich Insurance Company PLC Branch in Spain established in Barcelona. The sponsor shall extend this policy or another with equivalent coverage until the end of the trial. The policy will cover the damages to the people that could be set as a result of the trial by an insured amount of 300,000 € per patient tested to a maximum of € 3,000,000 per year and clinical trial. This policy also covers the responsibilities of the sponsor, the principal and his/her collaborators, as well as the hospital or site where they carry out the clinical trial.

The sponsor agrees to pay the premiums to cover the liability pertaining to the trial. It is presumed, unless proven otherwise, that damage affecting the health of the person subject to testing during implementation and in the following year the completion of treatment, have occurred as a result of the trial. However, once the year ended, the test subject is required to prove the link between the trial and damage.

The site and the principal investigator undertake to inform the sponsor of any claim or legal, real or potential action if known, linkable to trial.

15 PUBLICATION POLICY

The publication of the trial results shall meet the requirements set out in Article 38 of Royal Decree 223/2004.

APPENDIX I: CASE REPORT FORM (CRF)

APPENDIX II: INVESTIGATOR'S BROCHURE

APPENDIX III: PATIENT INFORMATION AND WRITTEN INFORMED CONSENT

APPENDIX IV: INSURANCE

APPENDIX V: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS