CLINICAL TRIAL PROTOCOL WITH DRUGS

Virologic and immunological safety of a dose reduction strategy with the efavirenz/tenofovir/emtricitabine antiretroviral regimen

Protocol Code: A-TRI-WEEK

Version / Date: 1.0 Date: October 30, 2012
EudraCT number: **2012-004970-24**
NCT Number: NCT01778413

SPONSOR: Fundació Clínic per a la Recerca Biomèdica
Principal Investigator and coordinator of the study:
Dr. Esteban Martínez Chamorro.
Infectious Diseases Service. Hospital
Clínic de Barcelona.
Spain.
Phone: +34 932275400 [redacted]
[redacted]

CONFIDENTIAL

1. SUMMARY

1.0. Type of application:

Open-label, phase IV, randomized, pilot, prospective, single-center study.

1.1. Identification of the developer:

Fundació Clínic per a la Recerca Biomèdica
Manager: Ms. Pastora Martínez Samper
C. Roselló, 143
08036 Barcelona

1.2. Clinical Trial Title:

Virologic and immunological safety of a dose reduction strategy with the efavirenz/tenofovir/emtricitabine antiretroviral regimen

Version / Date: 1.0, dated October 30, 2012.

1.3. Protocol Code: A-TRI-WEEK

EudraCT number: 2012-004970-24

1.4. **Principal Investigator and Study Coordinator: Dr. Esteban Martínez Chamorro**

Collaborating researchers: Dr. Polyana Monteiro, Dr. Montserrat Loncá, Dr. Ana González.

1.5. Centres in which the trial is planned to be carried out:

The study will be a national Unicenter (Hospital Clínic de Barcelona).

1.6. Clinical Research Ethics Committees that have approved the trial:

The trial has been submitted to the corresponding CEIC of the Hospital Clínic de Barcelona as a reference CEIC.

1.7. Name and qualification of the person responsible for monitoring:

Dr. Anna Cruceta.
Clinical Trials Unit.
CTU Clinic. Clinical Pharmacology Service.
(Hospital Clínic de Barcelona).
Head of the CTU: Dr Joan Albert Arnaiz

1.8. Study Drug Information:

ATRIPLA® Atripla 600 mg/200 mg/245 mg film-coated tablets The drug has final approval from the Ministry of Health. As stated in its technical sheet (see annexes).

1.9. Clinical Trial Phase: Phase IV

1.10. Objectives:

1.10.1. Main objective:

The primary objective of this study is to determine the feasibility of maintaining virologic suppression on standard plasma viral load (limit of detection 37 copies/mL) of a once-daily dose reduction strategy of ATRIPLA® to three tablets per week in HIV-1-infected patients with sustained standard plasma viral load suppression for more than 2 years.

1.10.2. Secondary objectives:

- Virological study including: ultrasensitive viral load in plasma (limit of detection 1 copy/mL), and HIV-1 reservoir in peripheral blood mononucellar cells,
- Immunological study including: production of TRECs, immune profile of activation (CD38 and HLA-DR) and senescence (CD57 and CD28) in CD4 and CD8 lineages, apoptosis (annexin V staining), and ratios of naïve T cells and effectors and memory cells (CCR7 and CD45RA).
- Pharmacokinetic study, including baseline plasma levels of efavirenz at the beginning and end of the study.
- Safety study, which includes: test on sleep quality, vitamin D levels, estimated glomerular filtration rate and plasma lipids at the beginning and end of the study, as well as general tolerability.

1.11. Design:

Open-label, randomized, Phase IV, prospective, pilot, single-center study.

1.12. Disease under study:

HIV infection (acquired immunodeficiency virus)

1.13. Assessment variables:

1.13.1. Main

The primary endpoint of the study will be the proportion of patients who continue to have a viral load <37 copies/mL at 24 weeks using an intention-to-treat analysis.

1.13.2. Secondary

- Percentage of patients with virologic response viral load <1 copy/mL after 24 weeks.
- Change from baseline to 24 weeks in the viral reservoir of peripheral blood mononuclear cells
- Changes from baseline to 24 weeks in REBT production
- Changes in the immune profile of activation (CD38 and HLA-DR) and senescence (CD57 and CD28) in the CD4 and CD8 lineages, and in the proportions of naïve and effector and memory T cells (CCR7 and CD45RA).

- Changes in apoptosis levels in vitro by annexin V staining.
- Changes in plasma levels of efavirenz.
- Changes in sleep quality (Pittsburgh Sleep Quality Index), plasma levels of vitamin 25OH-D and lipids, and estimated glomerular filtration rate (CPK-EPI).
- Overall safety (reporting side effects, serious side effects, and discontinuation of treatment due to side effects)

1.14. Study population and total number of patients:

Adult patients with well-controlled chronic HIV infection and on treatment with ATRIPLA.® A total of 60 patients will be included.

1.15. Duration of treatment:

The approximate expected duration for the inclusion of patients is 12 months, and the duration of treatment and follow-up of the included patients will be extended by a maximum of 24 weeks.

1.16. Schedule and expected completion date:

The study is expected to begin, once the permits have been obtained, in March 2013. The recruitment period will be 48 weeks. The follow-up of the patients will last 24 weeks to start the study. The study is expected to be completed in October 2014.

2. INDEX

Annexes and documents:

3. Overview

3.1 Trial identification

Title:
Virologic and immunological safety of a dose reduction strategy with the efavirenz/tenofovir/emtricitabine antiretroviral regimen
Open-label study, Phase IV, randomized, prospective, pilot, single-center.

1.3. Protocol Code: A-TRI-WEEK

Version / Date: 1.0, dated October 30, 2012. EudraCT number: 2012-004970-24
.

3.2 Developer Identification

Fundació Clinic per a la Recerca Biomèdica.
C/ Rossello 143
08036 Barcelona

3.3 Identification of the promoter's representative

Manager: Dr. Pastora Martínez Samper
Fundació Clinic per a la Recerca biomedica.
C/ Rossello 143
08036 Barcelona
e-mail: PMARTIN2@clinic.ub.es

3.4 Identification of researchers of the sponsoring entity

Hospital Clínic
Principal Investigator and Study Coordinator:
Dr. Esteban Martinez Chamorro
Infectious Diseases Service.
estebanm@clinic.ub.es

Collaborating researchers:
Dr Polyana Monteiro, Dr Montserrat Loncá, and Dr Ana González, from the Infectious Diseases Service

3.5 Identification of principal investigators from participating centers

The study is single-center. It will be held at the Hospital Clinic of Barcelona

3.6 Identification of researchers from other services involved

Virology Section of the Microbiology Laboratory: Marta Parera Pharmacy:
Anna Estafell and Begoña Gómez
Retrovirology and Viral Immunopathology Laboratory of the Infections Service: Alberto Crespo.
Carmen Alvarez and Sonsoles Sanchez-Palomino
Biostatistician: Jose Ignacio Pérez

Nurse: Merçé Poal
Laboratory Technician: Pilar Callau

3.7 Information on the laboratories or technical departments involved

Clinical evaluation of patients included in the study, routine blood/urine laboratory determinations and viral (HIV) determinations, will be performed at the Infections Day Hospital. And Retrovirology and Immunopathology Laboratory of the Infection Service:

3.8 Monitoring

CTU (Clinical Trial Unit).
Monitoring manager: Dr. Anna Cruceta. acruceta@clinic.ub.es
Tel 932275400 [redacted]

Head of the CTU:
Dr. Joan Albert Arnaiz.
Clinical Pharmacology Service.
Hospital Clínic de Barcelona

4. Justification

HIV-infected patients can live longer thanks to effective antiretroviral treatment. In addition, efforts are being made to diagnose people who may be infected with HIV as soon as possible, and the initiation of antiretroviral treatment is increasingly recommended and at earlier stages.

On the other hand, antiretroviral treatment must be administered indefinitely. All these factors have contributed to the incessant increase in the budget for antiretroviral treatment, in such a way that its provision free of cost represents a major challenge for public health systems even in developed countries such as Spain (1, 2).

The combination of efavirenz/tenofovir/emtricitabine has been the most frequently used contemporary treatment in clinical trials in people with no prior experience of antiretroviral treatment, and no other treatment regimen has shown superiority in efficacy against it
(3). This combination is available as a fixed-dose combination in a single pill (ATRIPLA),® which represents the simplest antiretroviral regimen in Spain today. In the short term, there may be tolerability problems, neuropsychological side effects that are usually of little intensity and that in many cases resolve after the first four weeks of treatment (4). In addition, a small proportion of patients with well-identified risk factors such as older age, low CD4, low weight weight, nephrotoxic drugs, and underlying kidney disease may experience a progressive risk of tenofovir-associated renal dysfunction (5) that usually improves with discontinuation of tenofovir. There is evidence to suggest an association between increased bioavailability of efavirenz or tenofovir and the risk of developing side effects due to these drugs. For most patients on chronically stable treatment with ATRIPLA®, serious long-term side effects are not expected. ATRIPLA® has shown a better cost-effectiveness balance than other antiretroviral regimens (6). For all these reasons, ATRIPLA® has become one of the most popular antiretroviral regimens. At the end of 2011, approximately 25% of active patients (n=4400) treated at the Hospital Clínic de Barcelona were treated with ATRIPLA,® making this regimen the most frequently prescribed antiretroviral treatment. Currently, more than 1000 patients are receiving virologically effective treatment with ATRIPLA® at the Hospital Clínic de Barcelona, of which 75% have been on this treatment for more than two years.

Since antiretroviral treatment has to be taken indefinitely, the search for strategies to simplify it has been an important element in the development of antiretroviral regimens. The simplification of antiretroviral treatment in patients with sustained virologic suppression represents a strategy accepted by most therapeutic recommendations (7). The longer the viral suppression lasts, the greater the probability of maintaining sustained virological success (8-11). In patients with sustained virologic suppression, the absolute risk of virologic failure is low, and regimens with non-nucleoside reverse transcriptase inhibitors have consistently shown better virologic outcomes than regimens with protease inhibitors. Strategies to simplify antiretroviral treatment have aimed to minimize the risk of toxicity, seek greater convenience, and more recently reduce the cost of antiretroviral.

Although ATRIPLA® is the simplest antiretroviral regimen at present, there is potential for further simplification. Each of the individual components of ATRIPLA® has the longest half-lives of all currently available antiretrovirals: 40-55 hours for plasma efavirenz (12), 39 hours for intracellular emtricitabine triphosphate, and 150 hours for intracellular tenofovir diphosphate (13). In a discontinuation study, efavirenz plasma levels were estimated to exceed the adjusted IC95 for protein concentration (46.7 ng/mL) for a median of 6.7 days (IQR 4.7-9.2) after the last dose of efavirenz (14). Clinical information is available on the dosing of efavirenz at dose intervals greater than once daily (PHOTO study). The FOTO study was a 48-week observational study in which 30 patients with virologic suppression (<50 copies/mL) for at least three months prior to the study switched their usual antiretroviral treatment from a daily dose to a weekly schedule of 5 consecutive days on treatment (usually Monday through Friday) followed by 2 days without treatment (usually on the weekend) (15). Overall, virologic suppression was maintained in 90% of patients. More interestingly, however, ten of the 30 patients included were taking efavirenz along with tenofovir and nucleoside reverse transcriptase inhibitors with long half-lives such as didanosine or lamivudine, and none of these showed virologic failure. Following these promising results, researchers in the FOTO pilot study designed a 24-week open-label randomized study in which treatment with ATRIPLA® for five days a week would be compared to the standard dose of ATRIPLA® once a day (NCT00414635). So far, we have no information that results of this study have been reported.

In our daily practice, we have detected at least two patients on chronic treatment with ATRIPLA® who, for personal reasons, different in each case, decided to take the dose every other day instead of the standard daily dosage for more than 6 and 12 months respectively, without the plasma viral load having become detectable in any of them. On the other hand, a small preliminary survey of a randomly selected sample of 36 consecutive patients treated with ATRIPLA® for more than 2 years, who claimed to have no tolerability problems and with a persistently undetectable viral load during that period of time, showed that 78% saw a dose reduction to three days per week as more favorable than the standard daily dose. 14% did not care, and only 8% did not want to change their dosage, their main reasons being the fact that they were already fine as they were and the fear that they could lose the undetectability of the plasma viral load.

We intend to evaluate the possibility of effective simplification by moving from the standard daily dose of ATRIPLA® to a three-day-weekly dose in patients with sustained virologic suppression. Although antiretroviral treatment regimens have not so far contemplated dosing with intervals greater than once a day, the dosing of three times a week in the same way as that proposed in this project has been used with a high degree of compliance in the prophylaxis of *P. jirovecii* pneumonia in HIV-infected patients (16, 17).

Reducing the dosage of the most widely used antiretroviral treatment regimen as proposed in this project would reduce expenditure by 57%. In the case of the Hospital Clínic alone, this reduction in expenditure would mean going from 7.4 to 4.2 million euros per year. Since ATRIPLA® represents one of the most widely used regimens, the dose reduction strategy

could have a considerable impact on the budget for antiretroviral treatment within the policy of containing health expenditure promoted by the Spanish health authorities and more necessary today than ever in the current context of economic crisis (18). In addition, it can help reduce your already low risk of chronic toxicity. Finally, dose reduction is considered a popular measure and positively evaluated by a high proportion of treated patients. If our project obtains favorable results that support the dosage reduced to three days per week, the experimental regimen would become the simplest and cheapest among all the currently available regimens, including monotherapy with protease inhibitors.

Determination of plasma viral load and CD4 and CD8 cell counts have been key tools for clinical research and healthcare of HIV-positive patients until now. However, in patients with persistently undetectable viral load and relatively high CD4 counts, the simple determination of viral load and cell populations is unlikely to allow a fine distinction between the possible virological and immunological consequences of the dose reduction strategy to be evaluated. Therefore, viral reservoir analysis by determining proviral DNA and especially the proportion of that reservoir that produces viral particles can provide more detailed information on the virological safety of the new strategy (19). Similarly, the determination of plasma viral load using the most sensitive technique ("single copy assay" (limit of detection 1 copy/mL) (20) can discriminate whether this dose-reduction strategy produces any impact on viral replication that cannot be detected by the standard technique used in routine clinical practice. On the other hand, the extensive immunological study that is intended to be carried out (population analysis of the T lineage that includes its activation status and thymic production, among others) will allow us to exhaustively monitor the effects of any changes that may occur at this level on the study population (21-23). Therefore, we consider that the efficacy and safety of the dose reduction strategy of the efavirenz/tenofovir/emtricitabine regimen should be evaluated as consistently as possible with the previously mentioned virological and immunological tests.

Our study aims to conceptually confirm whether dose reduction of ATRIPLA® is feasible as a strategy and whether it entails any virological or immunological risk. If the results of this study are positive, they could form the basis for a randomized clinical trial of sufficient size to attempt to validate this strategy for future clinical use.

4.1 Investigational Drug Identification

Generic name: efavirenz, emtricitabine, and tenofovir disoproxil (as fumarate). 600 mg/200 mg/245 mg

Trade name: Atripla ®

Composition: Each tablet contains 600 mg efavirenz, 200 mg emtricitabine and 245 mg tenofovir disoproxil (as fumarate).

Pharmaceutical form: film-coated tablet.

4.2 Investigational Drug Information

The drug has been definitively approved by the Ministry of Health.

4.3 Treatment Regimen

Adults: The recommended dose of Atripla is one tablet, taken orally, once daily.

Description:

Atripla is a fixed-dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults 18 years of age or older with virologic suppression at HIV-1 RNA levels of < 50 copies/mL on their current combination antiretroviral therapy for more than three months.

Route of administration: oral

Storage: Keep in the original packaging to protect it from moisture. Keep the bottle tightly closed.

Dosage Schedule:

Atripla ® is given 1 tablet 1 time a day.

Study period and treatment:

Randomization to two treatment groups: A or B

GROUP A (control): ATRIPLA® at standard daily dose (1 tablet daily) for a period of 24 weeks
GROUP B (experimental): ATRIPLA® at a dose three days per week (1 tablet Monday, Wednesday, and Friday) for a period of 24 weeks

4.4 Compliance Statement

The study will be carried out in accordance with the principles emanating from the Declaration of Helsinki, and according to the legal regulations in force (Royal Decree 223/2004), and will not begin until the approval of the reference CEIC and the approval of the AEMPS have been obtained.

Patients will be informed orally and in writing and all relevant information tailored to their level of understanding will be communicated to participants.

(See Attachment III: Patient Information Sheet and Attachment III: Written Consent Sheet.)

The patient will be informed that their participation in the study will be treated with the same confidentiality as their clinical documentation and that only the people involved in the study will have access to their data. The patient's name will not appear in any publication or communication of the results of the study.

4.5 Population under study

Adults with HIV-1 infection controlled on an outpatient basis in the Infectious Diseases Service of the Hospital Clinic of Barcelona.

4.6 Relevant Bibliography

1. Mandalia S, Mandalia R, Lo G, et al. Rising population cost for treating people living with HIV in the UK, 1997-2013. PLoS ONE 2010; 5: e15677.
2. Stoll M, Kollan C, Bergmann F, et al. Calculation of direct antiretroviral treatment costs and potential cost savings by using generics in the German HIV ClinSurv cohort. PLoS ONE 2011; 6: E23946.
3. Boyd SD. Management of HIV infection in treatment-naive patients: a review of the most current recommendations. Am J Health Syst Pharm 2011; 68: 991-1001.

4. Gazzard B, Balkin A, Hill A. Analysis of neuropsychiatric adverse events during clinical trials of efavirenz in antiretroviral-naive patients: a systematic review. AIDS Rev 2010; 12: 67-75.
5. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis 2011; 57: 773-780.
6. Blasco AJ, Arribas JR, Clotet B, et al. Cost and cost/efficacy analyses of the preferred GESIDS regimens for initial antiretroviral therapy. Enferm Infecc Microbiol Clin 2011; 29: 721-730.
7. McKinnon JE, Mellors JW, Swindells S. Simplification strategies to reduce antiretroviral drug exposure: progress and prospects. Antivir Ther 2009; 14: 1-12.
8. Benzie AA, Bansi LK, Sabin CA, et al. Increased duration of viral suppression is associated with lower viral rebound rates in patients with previous treatment failures. AIDS 2007; 21: 1423-1430.
9. Geretti AM, Smith C, Haberl A, et al. Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. Antivir Ther 2008; 13: 927-936.
10. Rosenblum M, Deeks SG, van der Laan M, Bangsberg DR. The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy. PLoS ONE 2009; 4: E7196.
11. Reekie J, Mocroft A, Ledergerber B, et al. History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. HIV Med 2010; 11: 469-478.
12. Vrouenraets SM, Wit FW, van Tongeren J, Lange JM. Efavirenz: a review. Expert Opin Pharmacother 2007; 8: 851-871.
13. Anderson PL, Kiser JJ, Gardner EM, et al. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. J Antimicrob Chemother 2011; 66: 240-250.
14. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an adult AIDS Clinical Trials Group Study. Clin Infect Dis 2006; 42: 401-407
15. Cohen CJ, Colson AE, Sheble-Hall AG, McLaughlin KA, Morse GD. Pilot study of a novel short-cycle antiretroviral treatment interruption strategy: 48-week results of the Five-Days-On, Two-Days-Off (PHOTO) study. HIV Clin Trials 2007; 8: 19-23.
16. El-Sadr W.M., Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. Clin Infect Dis 1999; 29: 775-783.
17. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2009; 58: 1-207.
18. Rivero A. Does the cost of medicines influence the choice of antiretroviral treatment regimens? Enferm Infecc Microbiol Clin 2011; 29: 719-720.
19. Boulassel MR, Chomont N, Pai NP et al. CD4 T cell nadir independently predicts the magnitude of the HIV reservoir after prolonged suppressive antiretroviral therapy. J Clin Virol 2012; 53: 29-32.
20. Palmer S, Wiegand AP, Maldarelli F, et al. New real-time reverse transcriptase-initiated PCR assay with single-copy sensitivity for human immunodeficiency virus type 1 RNA in plasma. J Clin Microbiol 2003; 41: 4531-4536.
21. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of higly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis 2007; 44: 441-446.
22. Aiuti F, Mezzaroma I. Failure to reconstitute CD4+ T-cells despite suppression of HIV replication under HAART. AIDS Rev 2006; 8: 88-97.

5. Objective and Purpose of the Trial

Main:

The primary objective of this study is to determine the feasibility of maintaining virologic suppression on standard plasma viral load (limit of detection 37 copies/mL) of a once-daily dose reduction strategy of ATRIPLA® to three tablets per week in HIV-1-infected patients with sustained standard plasma viral load suppression for more than 2 years.

Side:

- Virological study including: ultrasensitive viral load in plasma (limit of detection 1 copy/mL), and HIV-1 reservoir in peripheral blood mononucellar cells,

- Immunological study including: production of TRECs, immune profile of activation (CD38 and HLA-DR) and senescence (CD57 and CD28) in CD4 and CD8 lineages, apoptosis (annexin V staining), and ratios of naïve T cells and effectors and memory cells (CCR7 and CD45RA).

- Pharmacokinetic study, including baseline plasma levels of efavirenz at the beginning and end of the study.

- Safety study, including: sleep quality test (Pittsburgh Sleep Quality Index), vitamin 25OH-D levels, estimated glomerular filtration rate (CPK-EPI) and plasma lipids (triglycerides, total cholesterol and HDL) at the beginning and end of the study, as well as general tolerability.

6. Trial Design

Open-label study, Phase IV, pilot, prospective single-center.

6.1 Primary and Secondary Endpoints

Primary Endpoint:

The primary endpoint of the study will be the proportion of patients who continue to have a standard plasma viral load (<37 copies/mL) at 24 weeks by intention-to-treat analysis.

Secondary endpoints:

1) The proportion of patients with ultrasensitive viral load (<1 copy/mL) after 24 weeks.

2) The change from baseline to 24 weeks in the viral reservoir of peripheral blood mononuclear cells

3) Changes from baseline to 24 weeks in TREC production, immune profile of activation (CD38 and HLA-DR) and senescence (CD57 and CD28) in CD4 and CD8 lineages, in naïve and effector and memory T cell ratios (CCR7 and CD45RA), and changes in apoptosis levels in vitro by annexin V staining.

4) Changes in plasma levels of efavirenz.

5) Changes in sleep quality (Pittsburgh Sleep Quality Index), plasma levels of vitamin D and lipids, and estimated glomerular filtration rate.

6) Overall safety (reporting side effects, serious side effects, and discontinuation of treatment due to side effects)

6.2 Design

Although the hypothesis of the study has been based on various congruent information that allow us to face with sufficient guarantee the feasibility of the study and the eventual demonstration of the virological and immunological efficacy of the ATRIPLA® dose reduction strategy, we are not absolutely certain that an unacceptably high virological failure rate (standard viral load ≥37 copies/mL on two consecutive occasions) can occur in the arm

experimental. We will consider a priori that the failure of at least 20% (n=6) of the patients in the experimental arm will represent an unacceptably high virological failure rate. In this case, its conclusion will be considered premature. In this extreme case, the data of the patients already included up to the time of the premature conclusion of the study would be analyzed.
The present study is proposed as a proof of concept to be able to formulate another study with a sufficiently large sample size to adequately demonstrate the non-inferiority of the strategy. The results of the present study can help to design the non-inferiority study and to estimate its sample size.

STUDY PROCEDURES

Selection Evaluations	
Clinical Evaluations	Selection
Informed consent	X
Inclusion and exclusion criteria	X
Assignment of the selection code	X
Vital signs	X
Weight Determination	X
Height determination	X
Demographics	X
Medical history	X
Physical examination	X
Concomitant medications	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X

Clinical Evaluations	Basal Day 0	S 1 (#)	S 2 (#)	S 4 (#)	S 6 (#)	S 8 (#)	S 12	S 24
Meet Inclusion and Exclusion Criteria	X							
Signed Informed Consent	X							
Vital signs	X							
Weight	X							X
Physical examination	X						X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Simplified Compliance Questionnaire		X	X	X	X	X	X	X
Test sobre calidad del sueño (Pittsburgh Sleep Quality Index)	X							X
Haematology	X							X
Blood biochemistry	X							X

Clinical Evaluations	Basal Day 0	S 1 (#)	S 2 (#)	S 4 (#)	S 6 (#)	S 8 (#)	S 12	S 24
Standard plasma viral load	X	X	X	X	X	X	X	X
Ultrasensitive plasma viral load ($)	X							X
HIV-1 reservoir of PBMCs	X							X
Immunology (CD4/CD8)	X						X	X
Immunology Sample	X							X
Pregnancy test (women only) Y(&)	X	X	X	X	X	X	X	X
Pharmacokinetics	X							X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.
(#) These visits will be made only to patients who are in the experimental treatment arm (3-day-per-week treatment)
& At baseline visit it is advised to perform a blood pregnancy test
* Genotypic resistance testing will be performed if the patient has virologic failure (defined by HIV-1 plasma viral load >50 copies/mL confirmed on two consecutive occasions)
Blood biochemistry: lipids (TG, total cholesterol and HDL), creatinine and estimated glomerular filtration rate (CPK-EPI), levels of 25OH vitamin D.
Hematology: Blood count

6.3 Guidelines for Dose Modification

Grade 1 and 2 AEs require close follow-up but no change in treatment.

All grade 3 toxicities will be treated by the facility investigator as appropriate. Any grade 4 toxicity that, in the opinion of the investigator of the center, is directly related to the treatment of the study, will be treated with the permanent suspension of the study.

6.4 Trial Treatments

DRUG SUPPLY AND LABELLING

This study will use a drug already on the market and authorized for use in HIV-infected patients; The study drug is already taken regularly by these patients and will be distributed by the Pharmacy service of the Hospital Clínic. For clinical trials carried out in Spain, labelling in Spanish is mandatory in accordance with the regulations currently in force.

6.5 Trial duration

The approximate expected duration for the inclusion of patients is 12 months, and the duration of treatment and follow-up of the included patients will be extended by a maximum of 24 weeks

6.6 Termination and/or discontinuation criteria

The treatment will be **compulsorily** terminated during the study for any of the following reasons:

- Virologic failure, defined by two consecutive determinations of standard viral load >37 copies/mL separated by one week from each other.
- I express the patient's wish.
- Medical decision.
- Death.
- Pregnancy detection during the study.

Treatment **may** be terminated during the study for any of the following reasons:

- The medical investigator determines that a SAE is possibly or likely related to the study drug.
- Failure to administer, evaluate, or other study requirements.

If the confirmatory result is ≥37 copies/mL, a genotypic resistance detection study would be scheduled and the most appropriate attitude towards modifying their antiretroviral treatment would be discussed with the patient. In this case, unless he or she is against it, the patient would continue in the study.

All other virologic studies and immunological studies should be determined exclusively at baseline and 24 weeks (except if there is earlier virologic failure, in which case it would be performed at the time of confirmation of failure rather than at 24 weeks), and their determination should be deferred at the end of the study. To this end, plasma and peripheral blood mononuclear cell samples should be stored appropriately at -80°C until the planned determinations are made.

6.7 End of rehearsal

The end of the trial will be considered the time of the last visit of the last subject recruited.

7. Subject Selection

7.1 Inclusion criteria for subjects

A patient must meet ALL of the criteria listed below in order to participate:

1. Adults (≥18 years)
2. HIV-1 infection, clinical stability, and treatment with ATRIPLA® during the last two years.
3. Standard plasma viral load below the detection limit for at least the last 2 years.
4. CD4 count greater than 350/mm3 at the time of study consideration.

5. Negative pregnancy test in women of childbearing potential, and commitment to use acceptable contraceptive methods from at least 2 weeks before day 1 and until at least 6 months after the last dose of study drug.

6. Patients must have given written informed consent

7. In the opinion of the researcher, to be able to follow the design of the protocol visits.

7.2 Exclusion Criteria

Patients who meet ANY of the following criteria will be excluded from the study:

1. Patients who have had previous virologic failure with any antiretroviral regimen

2. Evidence of prior mutations against efavirenz, tenofovir, or emtricitabine

3. Use of any other chronic treatment besides ATRIPLA that has been introduced in the 6 months prior to the patient's entry into the study

4. Any co-indications to the study drug

5. Any condition that does not allow correct adherence to the study to be ensured at the discretion of the patient's attending physician

6. Uncontrolled pre-existing psychiatric illness

7. Any current signs of alcoholism or other drug use.

7.3 Withdrawal criteria (endpoints)

Treatment with the study drug will be terminated **immediately** during the study for any of the following reasons:

- Patient with virologic failure
- Pregnancy during the study.
- Express wish of the patient
- Medical criteria
- Exitus

Treatment with the study drug **may** be terminated during the study for any of the following reasons:

- The medical investigator determines that a SAE is possibly or likely related to the study drug.
- Failure to administer, evaluate, or other study requirements.

8. Treatment of Subjects

8.1 Treatment Branches

Randomization to two treatment groups: A or B

GROUP A (control): ATRIPLA® at standard daily dose (1 tablet daily) for a period of 24 weeks

GROUP B (experimental): ATRIPLA® at a dose three days per week (1 tablet Monday, Wednesday and Friday) for a period of 24 weeks

8.2 Concomitant and rescue medication

Any concomitant medication must be reflected in the CRF in an appropriate way (detailing the product, dosage, route, days of administration, reason for treatment, etc.).

Treatments not allowed:
The administration of treatments that are contraindicated with the study drugs will not be allowed. (see annex technical sheets)

8.3 Compliance monitoring

Adherence: to ensure the control and registration of medication, an adherence questionnaire will be added to the data collection notebook. At each visit, the investigator will ask the patient about treatment adherence.

Tablet count: The patient will be asked to bring any leftover medication or empty bottles with them to check whether or not they have taken all the capsules or tablets of the medication since the previous visit.

9. Effectiveness Assessment

9.1 Efficiency parameters

Virological tests

a. Determination of viral load

Standard determination of viral load (detection limit 37 copies/mL) Virologic failure will be defined as:
In case of detection of plasma viral load (≥37 copies/mL), the determination of plasma viral load should be repeated during the following week for confirmation. If the result of the confirmatory determination is ≥37 copies/mL

b. Methods of Analysis and Sensitivity

The standard HIV-1 viral load in the plasma sample will be previously performed using the commercial VERSANT HIV-1 RNA 1.0 Assay (kPCR) (SIEMENS HEALTHCARE DIAGNOSTICS) technique with a sensitivity of up to 37 copies/mL. The manufacturer's recommendations will be followed.

Ultrasensitive viral load (detection limit 1 copy/mL)

By ultracentrifugation (170000g, 30 minutes, 4ºC) the HIV-1 virions present in 7mL of plasma will be concentrated, a volume to which will have been added a known concentration of an RNA transcript used as a non-competitive internal control for the monitoring of ultracentrifugation, extraction and amplification processes. The supernatant will be removed leaving a residual volume of 200 L, from which the viral RNA will be extracted using the commercial QIAamp MinElute Virus Spin (QIAGEN) kit, following the manufacturer's recommendations. The RNA obtained will be aliquoted and frozen at -80ºC until use. The ultrasensitive quantification of the HIV-1 viral load will be performed by means of a one-step RT-PCR duplex in real time, using the STRATAGENE Mx3005P platform. For the amplification and detection of a conserved region of the HIV-1 gag gene, the primers and probes previously described by Palmer et al (2003) will be used. To detect the non-competitive internal control added to the sample, a set of specific primers and probe described above will be used (Almansa et al [PMID 21880131], Anton et al [PMID 20955912]). To carry out the quantification of the HIV-1 viral load and the internal control, two standard lines of serial dilutions from a known concentration of a standard will be amplified in parallel, one for the determination of the HIV-1 viral load and the other for internal control. Each quantification test will be performed in triplicate for each of the samples and for each of the dilutions of the standard line. In each of the tests, negative plasma samples will be used as a target to minimize the impact of possible contaminations in some of the steps of the process. For the quantification (copies/mL) of HIV-1 viral load, only those results within the linear range of the assay (R>0.95) will be considered. Initially, the result of the HIV-1 viral load will be validated in those samples where the recovery of internal control is greater than 55%, as described by Palmer et al (20), although this must be previously demonstrated in the process of optimizing our methodology.

The specific PCR product obtained with the primers specific for a conserved region of the gag gene previously described by Palmer et al (20) will be cloned into a pGEM-T Easy Vector (PROMEGA) plasmid that will be linearized by the restriction enzyme SpeI (NEW ENGLAND BIOLABS). This plasmid, which contains a T7 promoter for RNA polymerase, will be transcribed in vitro using the commercial MEGAscript Kit (AMBION). Purification of the RNA transcript obtained as a standard control for HIV-1 quantification will be performed using the commercial MEGAclear Kit (AMBION). The concentration and integrity of the RNA transcript obtained will be determined using the BioAnalyzer (AGILENT) platform. From a known concentration of this standard standard, a bank of dilutions will be generated to determine the efficiency, linearity range and lower limit of sensitivity.

The RNA transcript used as an internal control, based on a conserved region of the coding sequence of the M1 protein of the influenza A virus, has previously been used in the quantification of the influenza A (H1N1) pdm09 virus in our laboratory (Almansa et al [PMID 21880131], Anton et al [PMID 20955912]). For its synthesis, the methodology described in the previous section was followed. The percentage of internal control, added to the plasma sample prior to ultracentrifugation, which is recovered and from which we will consider the results of the HIV-1 viral load valid, will be validated in our laboratory, initially considering as good the 55% recovery previously described by Palmer et al (20).

B) HIV-1 viral reservoir study:

The study of the viral reservoir will be determined based on the methodology initially described by the group of Nicholas Chomont (19) modified by the Laboratory of Dr José Alcamí. It will be made from 50 X 10^6 frozen peripheral blood mononuclear cells. A purification of CD4+ T-cells by negative depletion will be performed. These purified cells will be activated in the presence of anti-CD3/CD28. The culture should be maintained for 9 days in the presence of a cocktail of antiretrovirals (zidovudine, efavirenz, and raltegravir) to prevent further rounds of infection and a reactivation of viral production. Finally, viral production will be quantified at 3, 6 and 9 days, from the supernatant of the cultures, by ultrasensitive RT-qPCR and p24 antigen assessment by capture ELISA.

C) Immunological studies:

The study of activation markers in the different CD4 and CD8 lymphocyte subpopulations will be carried out by extracellular staining with conjugated antibodies for subsequent analysis by flow cytometry.

The detection of cleaved circular DNA (TRECs) after genetic rearrangement of the T cell receptor (TCR) will be carried out by the usual methods (real-time PCR).
Determination of apoptosis will be performed using the annexin V staining method.

D) Pharmacokinetics

All patients will be proposed to be included in the pharmacokinetic substudy. At baseline, each of them should have their plasma levels determined in efavirenz in the morning before the next daily dose.

This determination will be repeated at week 24 of treatment. For patients who continue with the daily treatment, the extraction will be carried out any day in the morning; and for those randomized to receive ATRIPLA® on Monday, Wednesday and Friday, the extraction will be carried out on a Monday morning because it is the day of the week when the plasma concentration of efavirenz must be lower due to the maximum dose interval.

E) Safety
To evaluate sleep quality, the "Pittsburgh Sleep Quality Index" will be carried out, available in its validated Spanish version (http://www.medigraphic.com/pdfs/gaceta/gm-2008/gm086e.pdf).

The plasma concentration of vitamin 25OHD3 will be determined by immunoassay.

The estimated glomerular filtration rate will be calculated using the usual formula, available in http://www.nephron.com/MDRD_GFR.cgi .

10. Safety Rating

10.1 Detection and recording of Adverse Events

It is the investigator's responsibility to detect and document any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE) as set forth in this protocol. During the study, the existence of adverse events, whether serious or not, will be checked in accordance with the definition given in this section of the protocol.

a) Minimum information to be specified:

Description/definition:

Adverse event (AE) is any adverse health event in a patient or clinical trial subject treated with a medicine, even if it is not necessarily causally related to that treatment. Therefore, it can be any unfavorable and unintended signs (including an abnormal laboratory finding), symptom, or illness temporarily associated with the use of an investigational drug, whether or not related to the investigational drug.

Laboratory abnormalities of clinical importance that meet one or more of the following criteria are also considered AEs:

- It requires additional intervention or treatment.
- Requires a modification of the dose.

- It is accompanied by a clinical manifestation.

Any analytical anomaly that the investigating physician considers to be of clinical importance must be recorded as such in the printed copy of the laboratory report, indicating the physician's initials and the date of revision. An AA is also considered to be any event associated or observed in conjunction with an accidental or intentional overdose of the product, or with abuse or withdrawal of the product.

All AEs will be recorded in the subject's medical record and in the eCRDe. The start and end dates of each AA, the intensity and the relationship with the study drug will be recorded.

The criteria for subject treatment, dose discontinuation, dosage adjustment, withdrawal, or treatment changes will only apply to toxicities attributable to the study drugs (i.e., efavirenz, tenofovir, and emtricitabine).

The classification system for drug toxicity is set out in the DAIDS Table for Grading the Intensity of Adverse Events in Adults and Children, which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

In addition, for each AA, the measures taken or the outcome (e.g. hospitalization, discontinuation of treatment) will be recorded.

Adverse reaction (AR) is any harmful, unintended reaction to an investigational drug, regardless of the dose administered. In this case, there is a suspicion of a causal relationship between the investigational drug and the adverse event.

Serious adverse event (SAE) is any adverse event that, at any dose, results in death, threatens the life of the subject, makes hospitalization necessary or prolonged hospitalization, results in permanent or significant disability or disability, or results in a congenital anomaly or malformation. For the purposes of notification, suspected adverse events that are considered medically significant, even if they do not meet the above criteria, will also be treated as serious, including major medical events that require intervention to prevent one of the consequences described above from occurring. Likewise, all suspected transmission of an infectious agent through a drug will be reported as serious. Examples of these events include allergic bronchospasm requiring intensive treatment in an emergency department or at the individual's home, blood dyscrasia or seizures that do not require hospitalization, or the development of drug dependence or abuse.

Medical and scientific judgement should be used to decide whether other situations that have not resulted in the outcomes listed in the above definitions should be reported as SAGs.

A life-threatening term is defined as a situation where, in the opinion of the physician, the patient at the time of the adverse event or adverse reaction is at real risk of death.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AA to be serious. Only admission in which the patient spends the night in the hospital should be considered as hospitalization. The following situations will not meet the AAG criteria:

- if hospitalization or prolongation of hospitalization is necessary to perform a procedure required by the protocol (for example, if day or night visits will be made for biopsies or surgeries required by the protocol).

- if hospitalization or prolongation of hospitalization is part of the facility's routine procedure (e.g., removal of a stent after surgery)

- in case of scheduled hospitalization for a pre-existing process that has not worsened (e.g. scheduled hospitalization for the implantation of a knee prosthesis for a previous osteoarthritis process)

Grade IV laboratory alterations will be considered AAG.

DO NOT confuse the concept of "serious" with "severe" which refers to the intensity of the adverse event or adverse reaction.

Unexpected serious adverse reaction (RAGI) is a serious adverse reaction whose nature or severity does not correspond to the information regarding the product (for example, the investigator's manual in the case of an investigational medicinal product not authorised for marketing or the product label in the case of an authorised medicinal product).

b) Imputability criteria.

The causal relationship between the investigational product and the occurrence of AA/AAG shall be established on the basis of clinical judgment. To this end, other causes will be considered and studied, such as the natural history of the underlying diseases, concomitant treatment, other risk factors and the temporal relationship of the event with the investigational product. In addition, the technical data sheet of the products will be consulted.

In order to analyse the possible cause-effect relationship, the temporal relationship between the administration of the drug and the AA, possible alternative causes, the evolution (complete remission, partial recovery, death, sequelae, persistence), persistence or not after the suspension of administration, reappearance with the readministration of the product or the prior knowledge of said event coinciding with the known or expected response pattern of the drug under study will be considered.

The causal relationship of an AA with the medication under study will be established according to the following definitions:

Unlikely relationship: The adverse event does not occur after a plausible chronological sequence related to the administration of the product under study and/or is reasonably explainable by other factors, such as the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. In addition, it does not match the known or expected response pattern of the drug.

Possible relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, but can also be explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. It also matches the known or expected response pattern of the drug.

Probable relationship: The adverse event occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions, and after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence. It also matches the known or expected response pattern of the drug.

Very likely relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the clinical status of the patient or other concomitant therapeutic, toxic or environmental interventions, after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence and it is necessary that after the readministration of the suspicious drug the adverse event reappears. It also matches the known or expected response pattern of the drug.

Unrelated: Adverse event clearly due to causes unrelated to the medication under study and the criteria for another causal relationship are not met.

Non-assessable relationship: any notification that suggests an adverse effect, which cannot be judged because the information is insufficient or contradictory and which cannot be supplemented or verified.

10.2. Notification

The investigator or designee **must notify all AAGs, regardless of whether or not they are considered drug-related or planned,** to the head of the CTU. Dr. Anna Cruceta (acruceta@clinic.ub.es) tel 2275400 ext 4380 [redacted] in order to notify local and national health authorities **within one working day of becoming aware of the event**., so that the contact of the designated promoter can prepare the corresponding written report. AAGs occurring will be reported at any time from the subject's inclusion in the study and up to 30 days after the study has been completed or discontinued. In the specific case of selection failure, the AAGs will be recorded from the moment the consent is signed until the subject is considered a selection failure.

Regardless of the classification of adverse effects, the Investigator must collect all the AEs in the corresponding section of the study data collection notebook (CRD) and fill in all the information pertaining to them.

The sponsor must notify in an EXPEDITIOUS manner all relevant SAFETY INFORMATION, i.e. that could modify the risk/benefit ratio of the investigational medicine, or determine changes in its administration schedule or in the conduct of the trial, for example:
- a qualitative change or an increase in the percentage of occurrence of expected RAGs, which is considered clinically important.
- RAGIs that occur after the completion of a clinical trial and that are notified by the investigator to the sponsor.
-New developments related to the conduct of the trial or the development of the investigational medicinal product and likely to affect the safety of the subjects, such as:

- Serious adverse events that may be associated with the trial procedures and may modify the conduct of the trial
- A significant risk to subjects such as the lack of efficacy of an investigational drug used for the treatment of a life-threatening disease.
- Important new safety findings from new animal studies (such as cardiogenicity).
- Any premature termination or temporary halt of a clinical trial with the same investigational medicinal product for safety reasons, carried out in another country and by the same sponsor.
- GRAs related only to an MNI that are considered relevant as they are not subject to RAGI's general rules of expedited reporting of individual cases.

- Any recommendations from the data monitoring committee, which are relevant to the safety of the subjects.

This information must be notified as soon as possible and no later than 15 days after the promoter has become aware of it. In addition, if additional information that is relevant is obtained, it must be notified as quickly as possible.

10.3 Evaluation of toxicity parameters

The classification system for drug toxicity is set out in the DAIDS Table for Grading the Intensity of Adverse Events in Adults and Children, which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

Treatment of ATRIPLA side effects

The dose reduction levels of ATRIPLA® are indicated in the summary of product characteristics. (see annexes to the protocol)

10.4 COMMUNICATION TO RESEARCHERS

The sponsor shall communicate to investigators any information that may affect the safety of the trial subjects as soon as possible.

It is advisable when deemed appropriate that information on serious and unexpected adverse reactions (RAGI) be presented in a list together with a brief analysis of the data provided.

Researchers must also be informed of the safety aspects that impact the conduct of the clinical trial or the development of the product. Including disruption of the development program or security-related protocol modifications.

Follow-up of subjects after adverse events will be performed by clinical and complementary examinations necessary for the duration of treatment and then on a monthly basis during follow-up and up to 30 days after the end of treatment. In the event of a possible pregnancy, the health status of both the mother and the newborn will be monitored during the trial, whether the person who has become pregnant is the one who is taking the investigational drug or if it has been taken by her partner.

No interim analyses are planned for the present study.

11. Statistics

11.1 Sample

The study will be carried out in 60 patients. This is a proof of concept and does not require an ad-hoc sample size calculation.

11.2 Sample size

11.3 Analysis

Comparison of patient proportions will be performed using Fisher's exact test and the 95% confidence interval will be calculated for the difference in proportions.

Quantitative data at baseline and after 24 weeks, as well as absolute and relative changes at 24 weeks, will be compared using the Wilcoxon rank sum test. The point estimate and 95% confidence interval of the difference in medians will be estimated using the Hodges-Lehman methodology using the Moses free distribution.

Correlations between continuous variables will be evaluated using Spearman's rank correlation test.

The study of baseline predictors of response will be carried out by means of a multivariate analysis of multiple logistic regression.

Limitations of the study:

Although the hypothesis of the study has been based on various congruent information that allow us to face with sufficient guarantee the feasibility of the study and the eventual demonstration of the virological and immunological efficacy of the ATRIPLA® dose reduction strategy, we are not absolutely certain that an unacceptably high virological failure rate (standard viral load ≥37 copies/mL on two consecutive occasions) may occur in the experimental arm. We will consider a priori that the failure of at least 20% (n=6) of the patients in the experimental arm will represent an unacceptably high virological failure rate. In this case, its conclusion will be considered premature. In this extreme case, the data of the patients already included would be analyzed.

This study, even with the most favorable virologic and immunological results, would not constitute definitive proof of the safety and efficacy of ATRIPLA'® s dose reduction strategy. The present study is only a proof of concept and another study with a sufficiently large sample size would be needed to adequately demonstrate the non-inferiority of the strategy. The results of the present study can help to design the non-inferiority study and to estimate its sample size.

11.4 Completion Criteria

The study will be considered to have been completed on the date of the last visit of the last subject recruited into the study.

11.5 Processing of lost data

Missing data imputation techniques will not be used. Only the available data will be analyzed.

11.6 Deviations from the statistical plan

Any deviation from the planned statistical analyses will be justified and detailed in the reports derived from the processing of the data.

11.7 Population under analysis

The population analyzed in the study will consist of all patients included in the study as detailed in the protocol and without major deviations from the protocol.

12. Direct Access to Source Data/Documents

The sponsor shall ensure that it is specified in the protocol or other written agreement that the investigator or institution shall allow direct access to the source data or documents for monitoring, auditing and review by the IRB as well as inspection of the trial by the competent health authorities.

13. Ethics

General considerations: The test will be carried out in accordance with the principles emanating from the Declaration of Helsinki *(See Annex VIII)* and according to the legal regulations in force (Royal Decree 223/2004) and will not be started until the approval of the reference IRB has been obtained, the

approval of the Management of all participating centres, and authorisation from the Spanish Agency for Medicines and Health Products.

Information to the subjects: Patients will be informed orally and in writing and all relevant information adapted to their level of understanding will be communicated to the participants.
(See Attachment III: Patient Information Sheet/Written Consent Sheet)

14. Data Management and Records Archiving

The patient will be informed that their participation in the trial will be treated with the same confidentiality as their clinical documentation.

In the data collection notebook, the patient will be identified only by their inclusion code in the study.

The patient's name will not appear in any publication or communication of the results of the study.

The patient's participation in the trial will be reflected in their medical history.

The investigator will complete a list that will include the names of the patients participating in the trial, their inclusion number in the trial and their medical history.

Only researchers and data quality assurance and data analysis personnel will have access to the participant's clinical documentation. Eventually, persons duly authorised by the Sponsor and the Health Authorities and the Clinical Research Ethics Committee may audit or inspect the trial. Personal information will not be available to the public, in compliance with the provisions of Organic Law 15/1999, of 13 December, on the Protection of Personal Data.

Prior to the start of treatment, a clinical examination, electrocardiogram and blood and urine sample will be taken *(SEE TABLE OF DAILY DETERMINATIONS).*

The data will be collected through an online electronic CRD.

15. Financing & Insurance

The promoter has taken out civil liability insurance in accordance with current regulations.

16. Publication Policy

The Promoter undertakes to publish the results, both positive and negative, of this study as stated in art. 39 of RD 223/2004.

17. Table of Examinations and treatment during follow-up

Selection Evaluations	
Clinical Evaluations	Selection
Informed consent	X
Inclusion and exclusion criteria	X
Assignment of the selection code	X
Vital signs	X
Weight Determination	X
Height determination	X
Demographics	X
Medical history	X
Physical examination	X
Concomitant medications	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X

Clinical Evaluations	Basal Day 0	S 1 (#)	S 2 (#)	S 4 (#)	S 6 (#)	S 8 (#)	S 12	S 24
Meet Inclusion and Exclusion Criteria	X							
Signed Informed Consent	X							
Vital signs	X							
Weight	X							X
Physical examination	X						X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Simplified Compliance Questionnaire		X	X	X	X	X	X	X
Test sobre calidad del sueño (Pittsburgh Sleep Quality Index)	X							X
Haematology	X							X
Blood biochemistry	X							X
Standard plasma viral load	X	X	X	X	X	X	X	X
Ultrasensitive plasma viral load ($)	X							X
HIV-1 reservoir of PBMCs	X							X
Immunology (CD4/CD8)	X						X	X
Immunology Sample	X							X

Clinical Evaluations	Basal Day 0	S 1 (#)	S 2 (#)	S 4 (#)	S 6 (#)	S 8 (#)	S 12	S 24
Pregnancy test (women only) Y(&)	X	X	X	X	X	X	X	X
Pharmacokinetics	X							X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.
(#) These visits will be made only to patients who are in the experimental treatment arm (3-day-per-week treatment)
& At baseline visit it is advised to perform a blood pregnancy test
* Genotypic resistance testing will be performed if the patient has virologic failure (defined by HIV-1 plasma viral load >50 copies/mL confirmed on two consecutive occasions)
Blood biochemistry: lipids (TG, total cholesterol and HDL), creatinine and estimated glomerular filtration rate (CPK-EPI), levels of 25OH vitamin D.
Hematology: Blood count