BIOMEDICAL RESEARCH PROTOCOL
RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

ANRS *12286 MOBIDIP*

Mono- or Dual therapy of the Protease Inhibitor

Evaluation of a maintenance therapy of protease inhibitors with or without lamivudine in patients with a controlled viral load under second-line antiretrovirals in Africa (Yaoundé, Bobo-Dioulasso, Dakar)

Version No. 1.2 of 15/07/2013

Registration number in clinicaltrials.gov: NCT01905059 Favourable opinion of Ethics Committee of *Cameroon, dated* Favourable opinion of Ethics Committee of *Senegal, 16/07/2013* Favourable opinion of Ethics Committee of *Burkina Faso, dated*

Sponsor:
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ANRS 12286 MOBIDIP

Mono- or Dual therapy with Protease Inhibitors

Evaluation of a maintenance therapy with protease inhibitors with or without lamivudine in patients with a controlled viral load under second-line antiretroviral in Africa (Yaoundé, Bobo-Dioulasso, Dakar)

Version no. 1.2 - of *15/07/2013*

SIGNATURE PAGE

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Summary

TABLE OF PROTOCOL VERSIONS

Version no.	Date	Amendment no.	Principal modifications
1.1	**16/04/2013**		
1.2	**15/07/2013**		**Clarifications on the secondary effects of Darunavir and Etravirine (paragraph 9.1.1)** **Change of Janssen Pharmaceutica NV representative** **Changes to the information notice**

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ANRS	Agence nationale de recherches sur le sida et les hépatites virales (National Agency for Research on AIDS and Viral Hepatitis)
bPI	Boosted protease inhibitor
CRF	Case Report Form
CSF	CerebroSpinal Fluid
DRV	Darunavir
DRV/r	Darunavir boosted with ritonavir
FDC	Fixed Dosed Combination
HAART	Highly active antiretroviral therapy
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IC	Independent Oversight Committee / Independent Committee
Inserm	Institut National de la Santé et de la Recherche Médicale (National Institute of Health of Medical Research)
ITT	Intention-to-treat
LPV	Lopinavir
LPV/r	Lopinavir boosted with ritonavir
MA	Marketing Authorisation
MMC	Methodology and Management Centre
MRC	Medical Research Council
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease inhibitor
RNA	Ribonucleic acid
RT	Retro-transcriptase
RT	Reference treatment
SAE	Serious Adverse Event
SC	Scientific Council
SPC	Summary of Product Characteristics
TUs	Treatment units
USAE	Unexpected Serious Adverse Event
V	Visit
VL	Viral Load
WHO	World Health Organization
3TC	Lamivudine

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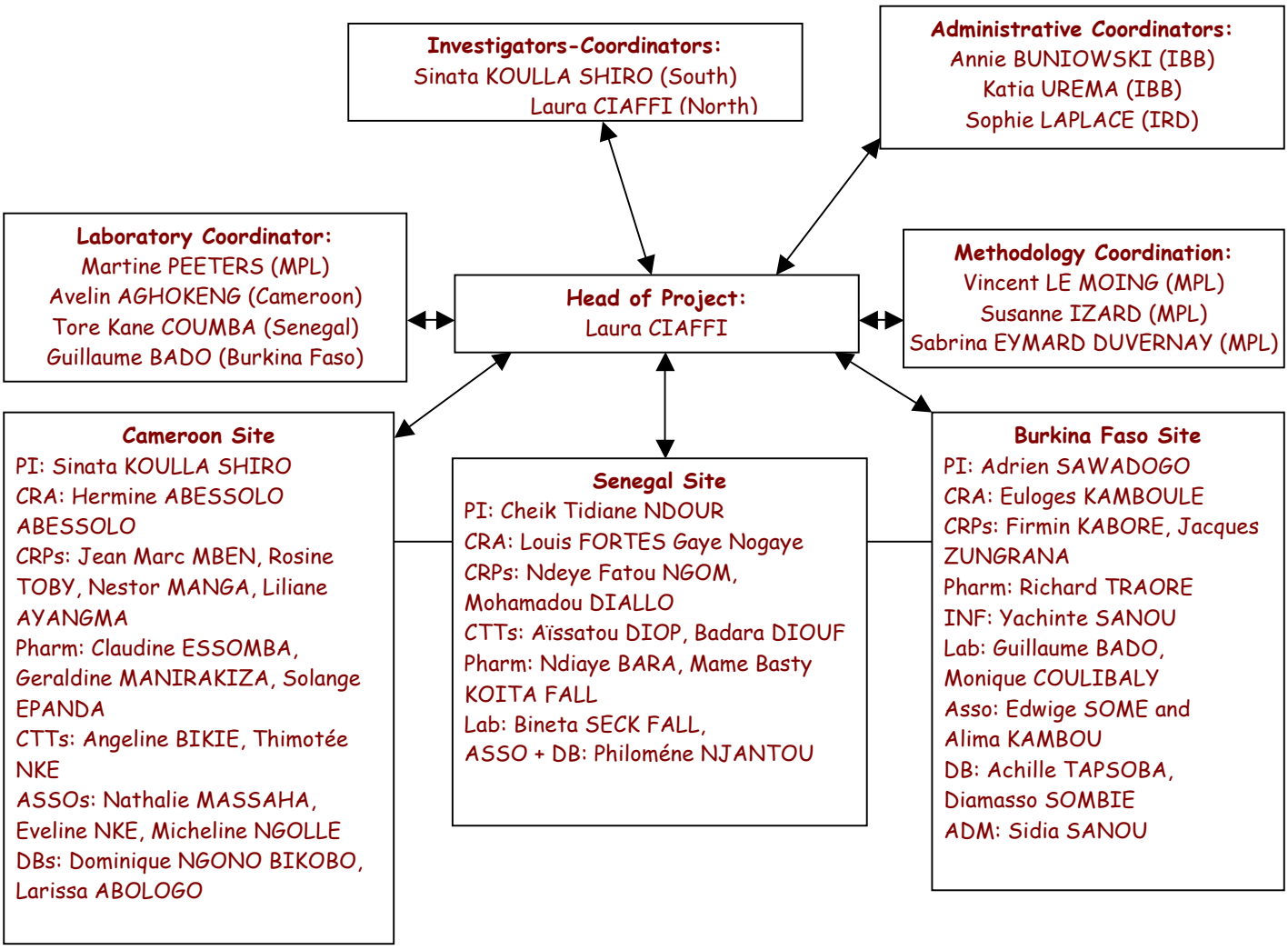
Pharmaceutical Laboratory

Janssen Pharmaceutica NV

1 Description of the operational team



PI: Principal Investigator
CRA: Clinical Research Associate (Monitor)
CRP: Clinical Research Physician (Co-investigator)
CTT: Clinical Trial Technician
Pharm: Pharmacy manager or assistant
Lab: Laboratory manager
ASSO: Associated mediator
DB: Data entry operator
IBB: Bouisson Bertrand Institute
IRD: Institute for Research and Development
MPL: Montpellier

2 TRIAL SUMMARY

Version *1.2 of 15/07/2013*

No.ClinicalTrials NCT01905059

Title - Evaluation of a maintenance strategy of protease inhibitors with or without lamivudine in patients with a controlled viral load under second line antiretrovirals in Africa (Yaoundé, Bobo-Dioulasso, Dakar)

Short title – ANRS 12286 MOBIDIP

Sponsor French National Institute of Health and Medical Research - French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)

Investigator(s)-Coordinator(s): South Prof. Sinata Koulla Shiro
North Dr Laura Ciaffi

Participating countries: Cameroon (Yaoundé Central Hospital and Yaoundé Military Hospital), Burkina Faso (Day Hospital Bobo-Dioulasso), Senegal (Clinical Research Centre and Treatment Centre of the Fann University Hospital, Dakar)

Objectives

Principal objective

To compare the failure rate (see definition) at 96 weeks of treatment with a boosted protease inhibitor in monotherapy versus dual therapy with a protease inhibitor boosted with lamivudine in HIV positive patients under second-line antiretroviral treatment (ART) for at least 48 weeks and with a viral load less than 200 copies/ml in Africa (Yaoundé, Bobo-Dioulasso, Dakar).

Secondary objectives

To describe the virological response at 48 and 96 weeks, the failure rate at 24 weeks after reintroduction of the NRTI, the clinical and immunological efficacy, the appearance of mutations, the tolerability and impact on the metabolic profile, the cognitive disorders and adherence.

Methodology

A phase III 1:1 randomised, international, multicentre, prospective, open label, comparative clinical trial of superiority comparing two second-line maintenance strategies in mono- or dual therapy based on boosted protease inhibitors (bPIs) with or without lamivudine.

Planned number of trial subjects 264 subjects in 3 countries: 132 per group
180 patients in Cameroon, 30 in Senegal and 54 in Burkina Faso

Evaluation criteria

Principal criterion:

Proportion of patients with a treatment failure at 96 weeks.
Treatment failure is defined as: 1) viral load ≥ 500 copies/ml confirmed in 2 samples with a 1-month interval, or 2) the reintroduction of the two NRTIs or 3) interruption of the PI/r.

Secondary criteria:

- the proportion of patients with plasmatic HIV RNA < 50, < 200, < 500 and <1000 copies/ml at 48 and 96 weeks, with or without reintroduction of the NRTIs.
- the frequency of resistance mutations in the case of treatment failure.
- The variation in the level of circulating CD4+ lymphocytes
- The number of deaths
- The frequency of stage 3 or 4 clinical events according to the WHO classification and of clinical events not classified as AIDS
- The incidence of bacterial infections leading to hospitalisation or prolongation of hospitalisation
- Cognitive disorders: appearance and / or development
- The frequency of adverse events

- The frequency of intolerance-related discontinuations of treatment
- Changes to the following biological parameters: blood count, glomerular filtration rate, blood transaminases, glycaemia, total cholesterol, HDL and LDL and triglycerides
- Changes to the following anthropometric measurements: waist circumference, hip circumference and thigh circumference
- Adherence

Study population

Inclusion criteria:

- HIV-1 infection in second-line treatment for at least 48 weeks in the trial ANRS 12169 2LADY
- VL ≤ 200 copies/ml for at least 6 months (verified in 2 consecutive samples with the most recent ≤ one month)
- No change in ART in the 3 months preceding recruitment
- CD4 ≥ 100 cells/ml at last check (which was less than 6 months previously)
- Signed informed consent
- Adherence ≥ 90% at the last visit in the 2LADY trial

Exclusion criteria:

- Previous viral failure (HIV RNA > 1000 copies/ml at least 2 consecutive times) while receiving PI
- Ongoing pregnancy or breast feeding mothers
- HBsAg positive patients
- Ongoing or treatment in the 3 months before recruitment of an opportunistic infection or of any serious or progressive disease
- Subject who, in the investigator's opinion, is unable to complete the study (relocation, transport difficulties, missed Vs, adherence difficulties)
- History or symptoms of HIV-related encephalitis

Treatment

Lopinavir/ritonavir

Pharmaceutical form: tablet of LPV 200 mg/RTV 50 mg

Dosage: 4 tablets/day, 2 in the morning, 2 in the evening

Lamivudine

Pharmaceutical form: tablet of 3TC 300 mg or 150 mg

Dosage: 1 x 300 mg tablet/day or 2 x 150 mg tablets/day

Darunavir/ritonavir

Pharmaceutical form: 400 mg darunavir tablet, 100 mg ritonavir tablet

Dosage: 2 tablets/day of darunavir + 1 tablet/day of ritonavir once a day with meals

Lopinavir/ritonavir and lamivudine will be provided by the national programmes while darunavir will be provided by Janssen Pharmaceutica NV for the duration of the trial. Ritonavir will be purchased by the trial if not available under the national programme.

Statistical analysis methods

The proportion of patients failing will be compared in each arm according to a procedure designed to deal with a significance level of 5%. No intermediate analysis is planned

Substudies in the submission process

Title: Medical/economic evaluation of four strategies for second-line antiretroviral treatment in mono- or dual therapy based on boosted protease inhibitors (PIs) with or without lamivudine – trial associated with the MOBIDIP-ANRS clinical trial (Cameroon, Burkina Faso, Senegal). Director: Dr Sylvie Boyer

Provisional calendar/timetable

Planned date for start of trial: 01/09/2013

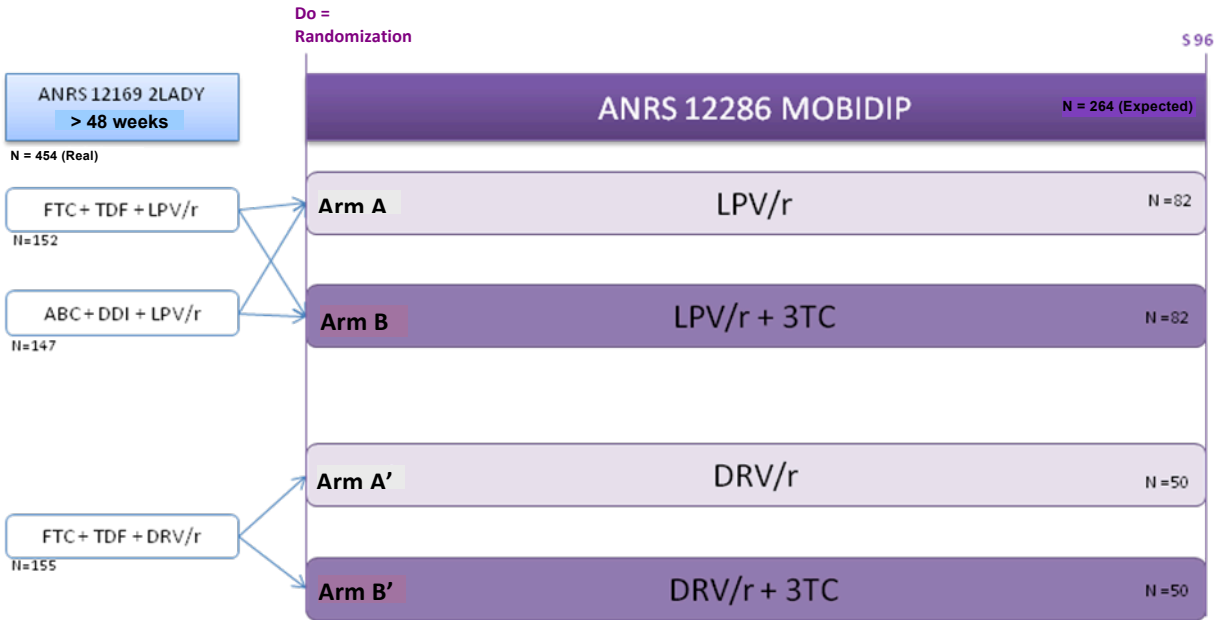
Duration of inclusion: 6 months

Duration of participation by subject: 2 years

Total scheduled duration of trial: 3 years

Scheduled date for end of trial: 30/09/2016

Trial design



Follow-up schedule for trial subjects

	Last visit in 2LADY	Randomisation	FOLLOW-UP									If VL > 500 copies/ml at V96	
	V-15	V0	V4	V12	V24	V36	V48	V60	V72	V84	V96	V108	V120
Informed Consent	X												
Signature of IC		X											
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg	X												
FBC	X			X	X	X	X	X	X	X	X	X	X
Creatinine	X				X		X		X		X		X
ALAT	X			X	X	X	X	X	X	X	X	X	X
Glycaemia	X				X		X		X		X		
Total Cholesterol, HDL, LDL, Triglycerides*	X						X				X		
Urine dipstick	X				X		X		X		X		X
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4/CD8	X				X		X		X		X		X
Plasma HIV RNA**	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma bank***	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence	X		X	X	X	X	X	X	X	X	X	X	X
Anthropometic measurements		X			X		X		X		X		

3 TRIAL SUMMARY

Version *1.2 of 17.05.13*

No.ClinicalTrials NCT01905059

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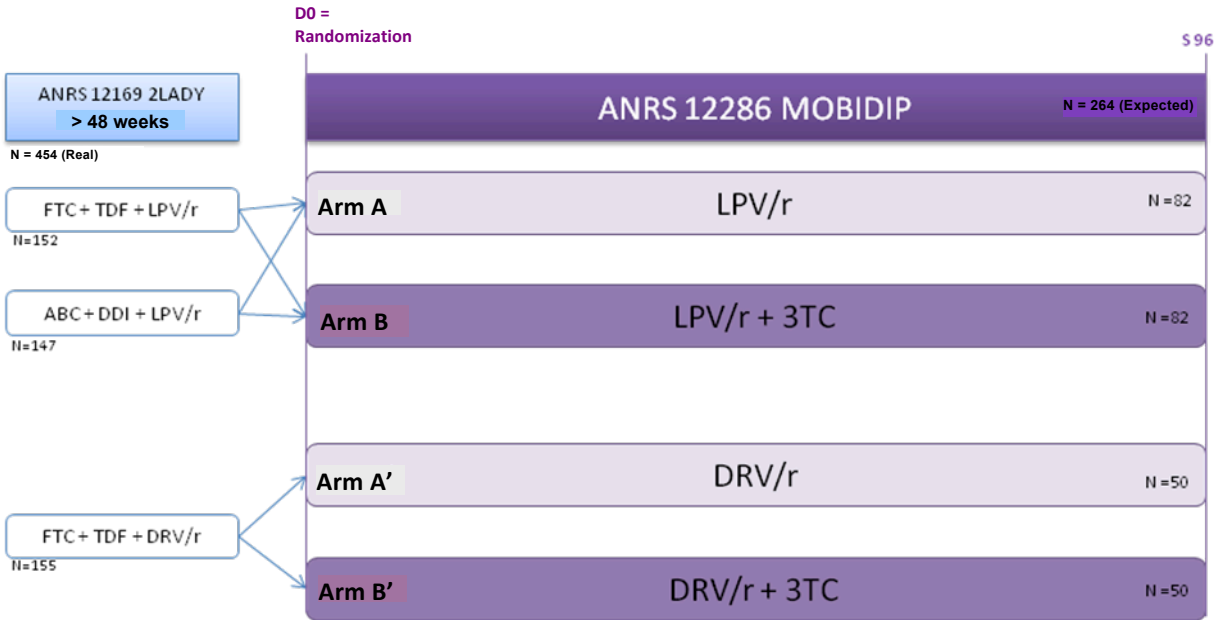


Schedule of assessments

	Last visit in 2LADY	Randomization	FOLLOW UP									If VL > 500 copies/ml	
	V-15	V0	V4	V12	V24	V36	V48	V60	V72	V84	V96	V108	V120
Patient Informed Consent	X												
Signature of IC		X											
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg	X												
FBC, platelets	X			X	X	X	X	X	X	X	X	X	X
Creatinine clearance	X				X		X		X		X		X
ALAT	X			X	X	X	X	X	X	X	X	X	X
Glycaemia	X				X		X		X		X		
Total Cholesterol, HDL, LDL, Triglycerides	X						X				X		
Urine dipstick	X				X		X		X		X		X
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4/CD8	X				X		X		X		X		X
Plasma HIV RNA**	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma bank***	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence	X		X	X	X	X	X	X	X	X	X	X	X
Antropometric measurements		X			X		X		X		X		

4 Scientific rationale and justification for the trial

4.1 Current state of knowledge of the pathology and reference treatments/strategies

Since the start of the era of Highly Active Antiretroviral Therapy (HAART), the possibility of a simplified treatment of HIV infection has attracted the interest of researchers, patients and governments. The first trials testing protocols involving less medicinal products were not very satisfactory due to the insufficient efficacy of simplified treatments. More recently, the availability of protease inhibitors (PIs), which have a raised genetic barrier, has allowed the development of clinical trials comparing the reference treatment (RT) by antiretroviral triple therapy with a monotherapy.

Lopinavir

One of the pioneering trials comparing a boosted PI monotherapy (bPI) with the RT is the OK pilot study (1). Forty-two patients were randomised, either to follow a triple therapy or to undergo monotherapy based on PI using lopinavir/ritonavir. The patients were included if they were undetectable (plasma HIV RNA < 50 copies/ml) for at least 6 months and without previous failures under PI. At week 48, 81% of patients under monotherapy compared with 95% (p=0.34) under the RT were still undetectable (at the threshold < 50 copies/ml). No resistance to the PI was observed and the detectable patients became undetectable again after the reintroduction of the two nucleotide reverse transcriptase inhibitors (NRTIs) of the RT. The trial follow-up was extended to a duration of 4 years (2): in the intention-to-treat analysis (ITT), 14 (67%) patients had a viral load (VL) which was undetectable after 4 years of monotherapy.

Subsequently, a larger trial was conducted (3) with 205 patients randomised with the same inclusion criteria for assessing the non-inferiority of a simplified strategy with boosted IPs. The efficacy was measured on the basis of the proportion of patients without treatment failure at 48 weeks. Treatment failure was defined by two successive measurements, with an interval of two weeks, of plasma HIV RNA greater than 500 copies/ml and not becoming undetectable again (< 50 copies/ml) after the introduction of two nucleosidic inhibitors. At 48 weeks, 94% compared with 90% of patients had not developed a treatment failure in the monotherapy group and in the RT group respectively. A CI of 95% would fulfil the criteria of non-inferiority. In applying an HIV RNA threshold of 50 copies/ml, 89% of the patients in the monotherapy group and 90% in the triple therapy group were virologically successful in the ITT analysis, while in the protocol analysis, the difference was statistically significant in favour of the triple therapy.

The comparison between the maintenance treatment with boosted lopinavir and the reference treatment based on efavirenz was performed in the induction-maintenance randomised trial MO3-613 (4). In this study, 155 ART-naive patients were randomised 2:1 to start triple therapy based on lopinavir/ritonavir or efavirenz combined with zidovudine/lamivudine. If the plasma viral load was < 50 copies/ml in three consecutive samples between weeks 24 and 48, the subjects in the bPI arm would discontinue the two NRTIs. The primary evaluation criterion, an HIV RNA < 50 copies/ml at week 96, was achieved by 60% of the patients in the lopinavir/ritonavir group and 63% of the patients in the efavirenz group in the ITT analysis: the difference was not significant. The virological failure in the monotherapy group generally occurred with a low viral load (50-500 copies/ml). Few of the patients developed PI resistance-associated mutations. No difference was reported concerning the secondary effects or the metabolic parameters, however, the average change in the fat/lipodystrophy level was favourable to the monotherapy group. The determinants of failure were identified in a subsequent analysis (5). In this study, better adherence and a raised initial CD4 level (> 200 cell/mm^3) were associated with an increased probability of maintenance of the virological suppression, independently of the lopinavir concentrations in the plasma.

Similar results were recently presented by Cahn (6) in a study in which patients stabilised with a viral load of < 50 copies/ml for at least 6 months with their first ARV therapy including a bPI-based triple therapy, were randomised in two groups i) continuation of treatment ii) simplification to monotherapy. The primary outcome was an HIV RNA of < 200 copies/ml at 360 days. Reintensification of treatment

due to viral rebound was not considered as a failure if the VL was again controlled. The sample size was not achieved in this trial due to the low level of recruitment: only 80 patients were included. In the ITT analysis, 95% in the RT group and 98% in the maintenance group had an HIV RNA of < 200 copies/ml at 360 days. Similar results were obtained in relation to an HIV RNA threshold of < 50 copies/ml: 10% of the patients in the monotherapy group had to be reintensified to obtain an undetectable VL. The safety and tolerability for the two groups were comparable.

Atazanavir

A question that is frequently raised in monotherapy trials is that of residual replication (presence of a low-level viraemia) and the persistence of the virus in compartmentalised reservoirs. This phenomenon has been highlighted in two trials using Atazanavir.

The results of ATARITMO (7), a 24-week non-comparative pilot study evaluating the efficacy of atazanavir boosted by ritonavir as maintenance treatment administered to patients who reached an undetectable VL (HIV RNA < 50 copies/ml) for at least three months, produced satisfactory results in terms of the suppression of the plasma viral load, but disappointing results in sperm, where viral replication persisted.

These results were confirmed in another trial (8), which was interrupted before completion. In the MOST trial, the principal evaluation criterion adopted was treatment failure defined as a plasma HIV RNA of > 400 copies/ml in the cerebrospinal fluid (CSF) and/or the genital tract. The trial was interrupted prematurely when six patients under monotherapy but none in the "continuation of the triple therapy" arm were found to have viraemia in the plasma. All the failures occurred in the first 24 weeks following randomisation and in the patients with a CD4 lowpoint of at least 200 cells/mm^3. The failed patients had a much higher viral load in the CSF and some of them had neurological symptoms. No viral resistance was reported.

Darunavir

The efficacy of another boosted PI under a maintenance regimen has been evaluated in two other studies: Darunavir, known for its raised genetic barrier and the possibility of a single daily dose.

The MONOI trial (9) evaluated the non-inferiority of boosted darunavir in comparison to a triple therapy including darunavir. Patients under antiretroviral treatment with an HIV RNA < 400 copies/ml at least 18 months were randomised, after an induction phase of 8 weeks of DRV/r (600/100 mg 2 times/day), to continue the triple therapy (2NRTI+ DRV/r) or switch to monotherapy (DRV/r) if their VL was < 50 copies/ml. Failure was defined by a VL of > 400 copies/ml or by interruption of the treatment. Two hundred and twenty five patients were randomised. At 48 weeks, 3 failures were reported in the monotherapy group. In the per-protocol analysis, the non-inferiority criteria were fulfilled, while in the ITT analysis, the results were contradictory.

The MONET trial (10), with a similar design, included 256 patients with an HIV RNA < 50 copies/ml while on triple antiretroviral therapy for more than the 24 weeks. The participants were switched to DRV/r 800/100 mg once a day, either to monotherapy (n=127), or with 2NRTI (n=129). Treatment failure was defined as 2 consecutive measurements of HIV RNA above 50 copies/ml at week 48 or the interruption of treatment in progress. With an HIV RNA criterion of < 50 copies/ml at week 48, non-inferiority was demonstrated, both in the ITT analysis with 84.3% against 85.3% success in the DRV/r arm and in the control arm, respectively, and in the per-protocol analysis with 86.2% against 87.8% success in each of the two arms.

In 2011, in a meta-analysis (11) on the efficacy of PI monotherapy as a maintenance strategy after having achieved a stable viral suppression with the reference triple therapy, 10 clinical trials comparing PI-based tritherapies and 3 different PIs in monotherapy in 1189 patients were identified. The selected trials applied different viral load thresholds to define virological failure: thresholds of 500, 400, 200, 80 and 50 copies/ml were applied. The authors analysed the ITT and per-protocol results with two thresholds of 50 and 500 copies/ml: the absolute increase of the virological failure risk under boosted PI monotherapy was between 2% and 13% in the ITT analysis and between 5%

and 10% in the per-protocol analysis. However, among the 44 failed patients in the monotherapy groups, 93% again obtained viral suppression after the reintroduction of the two NRTIs.

Resource-limited countries

In less-developed countries (LDCs), where boosted PIs are generally used in second-line treatment after a long period of failure (the VL not being routinely available), the validation of a maintenance treatment will have a major impact. It is likely that the NRTIs of the reference treatment would have already lost some of their efficacy (resistance to at least 3TC) in second-line patients, and there is a risk, in the case of total suppression, of accumulation of reverse transcriptase mutations. Interruption of the NRTIs may enable future treatment options to be spared. Moreover, it may be possible to reduce the treatment cost and toxicity and, and ultimately, the number of tablets.

A randomised trial has been conducted in Uganda and Zimbabwe (SARA) by the DART trial group in second-line patients on lopinavir boosted by ritonavir after at least 24 weeks. 196 patients were randomised to undergo either triple therapy or a monotherapy solely with boosted PI. The immunological and clinical parameters were evaluated: 24 weeks after randomisation, the immunological recovery was non-inferior in the monotherapy group in comparison with the triple therapy group, however the monotherapy was associated with a low-level increase in the viraemia, generally without resistance to the PIs (12).

Bartlett et al. (13) recently published results from an open-label pilot study performed in countries with limited resources, in which monotherapy with boosted lopinavir was administered as second-line treatment to patients who were refractory to a first-line treatment containing NNRTIs and with a VL of between 1,000 and 200,000 copies/ml. The patients were recruited in five African countries and in three Asian countries: 122/123 recruited patients were monitored for 24 weeks. The principal evaluation criterion was maintenance on boosted lopinavir without virological failure (defined as an HIV RNA level of > 400 copies/ml). At week 24, 87% of the patients receiving monotherapy did not have virological failure.

Another trial testing monotherapy with bPI in patients who were refractory to the first line treatment was conducted by the HIVNAT group (14). This was a randomised trial comparing a monotherapy with boosted lopinavir and a second-line treatment with LPV/r and 2 NRTIs in 200 patients in Thailand. The results at 48 weeks fulfil the non-inferiority criteria, but the proportion of patients with a VL of < 50 copies/ml was significantly reduced in the monotherapy with lopinavir/r arm.

EARNEST (The Europe-Africa Research Network for Evaluation of Second-line Therapy), a study of second-line treatments carried out in Uganda, Malawi, Zimbabwe, Kenya and Zambia included 1,277 patients whose first line treatment has failed.

In the protocol, one of the three arms specified is monotherapy with boosted lopinavir, started after 12 weeks of induction with raltegravir and boosted lopinavir. The primary evaluation criterion, defined as "good control of HIV" combines the following criteria: absence of stage events 4 according to the WHO definition, CD4 > 250 cells/mm3 and a VL < 10,000 copies/ml or > 10,000 copies/ml without PI resistance mutations. The results presented at the IAS conference (July 2013) showed an increased rate of virologic failure for the monotherapy arm (61% vs. 86% for a < 400 copies/ml), but the proportion of participants with undetectable VL just before switch to monotherapy is not yet made public.

Taken as a whole, the results of these clinical trials have produced satisfactory results and enable the identification of predictive factors for the success of monotherapy: the duration of treatment with an undetectable VL, adherence to the treatment, a lowpoint of CD4 before treatment (8) and probably chronic infection with HCV.

In spite of the results obtained, there are still a number of unanswered questions before maintenance monotherapy with bPIs can be used on a larger scale: the clinical significance of the residual viraemia, the efficacy of the monotherapy in the reservoirs, and the permanence of success. Thus other studies will be required.

Ongoing trials

The large number of clinical trials in developed or in wealthy or resource-limited countries underlines the interest in finding simplified maintenance strategies (clinicaltrial.gov).

ANRS is currently funding a trial in France comparing monotherapy with boosted lopinavir with the standard treatment based on triple therapy with tenofovir/emtricitabine/efavirenz (ANRS 140-DREAM) as maintenance treatment in patients with a VL of < 50 copies/ml. The evaluation criterion was successful treatment at 96 weeks.

In the UK, the MRC has ended recruitment for a randomised trial comparing monotherapy with bPIs with ongoing triple therapy (PIVOT) in 550 patients with a VL of < 50 copies/ml for at least 6 months and with CD4 of more than 100.

In Spain, boosted lopinavir was compared with boosted darunavir in a randomised trial with monotherapy as a maintenance strategy in patients with undetectable VLs on triple therapy with PI or NNRTIs. The outcome criterion is a VL at 48 weeks, virological failure being defined as a VL of > 50 copies/ml.

Janssen Pharmaceutica NV finances a trial (PROTEA) in 14 European countries comparing the efficacy, safety and tolerability of monotherapy with darunavir/ritonavir 800/100 mg compared with a triple therapy with darunavir/ritonavir 800/100 mg and 2 NRTIs in around 260 patients infected with the HIV-1 who have had a plasma VL of < 50 copies/ml for at least 48 weeks. Changes in neurocognitive functions will be compared throughout the trial. The primary outcome criterion is an undetectable VL of < 50 copies/ml at 48 weeks.

4.2 Trial hypothesis

It is accepted that the introduction of a simplified maintenance regimen in patients under 2nd line antiretroviral treatment, who have a controlled viral load, has several recognised advantages (less toxicity, reduced treatment costs, therapeutic reserve for the future). This trial investigates the hypothesis that a bPI + lamivudine maintenance dual therapy is more effective than maintenance monotherapy with bPI only in maintaining therapeutic control and avoiding reintroduction of NRTIs.

4.3 Explanation of choices of methodology

This trial is designed to validate a maintenance strategy with mono- or dual therapy for patients in Africa infected with HIV in second-line treatment who have a controlled viral load.

Few studies of maintenance strategies have been conducted in countries with limited resources and none has evaluated the benefit of a dual therapy with boosted PI and lamivudine.

In clinical practice where the viral load is not routinely available, cases of late diagnosis of treatment failure are frequently encountered. These patients may have accumulated multiple mutations of the RT gene and as a consequence, obtain reduced benefit from the presence of NRTIs.

The virological and clinical impact of a low-level viral replication has been the object of much debate and research and for this reason, the therapeutic recommendations on the management of this situation vary according to the management guidelines. However, currently data suggest that a viral load of less than 400 copies/ml does not have an effect on the clinical and immunological course. This conclusion is supported by studies conducted for the evaluation of the monotherapies that did not show any significant difference at the end of follow-up in terms of CD4 in patients with a low-level viraemia. In contrast, controversy remains about the possible accumulation of mutations which seem to appear even in patients with a viraemia as low as 40 copies/ml.

The WHO recommendations for a public health strategy (15) define failure as a viral load greater than 5,000 copies/ml taking into account that replication above this threshold is associated with the clinical course and the decline in CD4 levels.

In the French recommendations (16), close monitoring of patients with a viral load between 50 and 200 copies/ml is recommended in order to decide either to change the treatment or to change over to a protocol based on one substance with a higher genetic barrier. The change in the viral load over

time, the substances used, the genotype on initiation and if possible, the genotype results during treatment should also be taken into account for decision-making.
In the US recommendations (17), it is also accepted that a persistent viral load of between 200 and 1000 copies/ml should be considered as a virological failure.
According to the UK recommendations (18), a viral load that is low but still detectable does not predict a conventional virological failure. A threshold of 400 copies/ml has been proposed for investigation of failure.
In the MOBIDIP study, a threshold of 200 copies/ml will be used for the switch to monotherapy, taking into account the low risk of progression of the disease with such a low viral load and the high genetic barrier of boosted PIs.
Moreover, patients with a viral load greater than 50 copies/ml but less than 200 will obtain an additional benefit (apart from the reduction of adverse events) due to the interruption of nucleosides and the switch to a monotherapy based on boosted PI, as they will avoid a possible accumulation of mutations of the RT gene, enabling this class to be held in reserve for future therapeutic options.
The M184V mutation of the HIV-1 RT develops rapidly following the failure of a treatment containing 3TC and provides a high level of resistance to this substance both in vitro and in vivo. The presence of the M184V mutation seems to be associated with an alteration of several mechanisms connected with RT function, which could translate into a reduced replicative capacity of the virus or a delay in the appearance of mutations in the RT or protease gene. Moreover, the M184V mutation may influence the viral transmission and the immunological response. Taken together, these factors could explain the residual antiviral effect and the clinical benefit observed with the continuous use of 3TC in conjunction with therapeutic protocols after the appearance of the M184V mutation. In fact, the results of several studies suggest that an improvement in the therapeutic results is associated with a use of 3TC and with maintenance of the M184V mutation. However, many of these trials did not have sufficient statistical power to demonstrate whether the continuation of 3TC would bring a real benefit, or were not specifically designed to test the hypothesis of the potential benefit of M184V. The study of these benefits is in progress in clinical trials conducted in less-developed countries in treatment-naive patients and in treatment-experienced patients.
A randomised clinical trial comparing the interruption of antiretroviral treatment with a treatment solely based on lamivudine in multi-resistant patients with a M184V mutation (19) showed the advantages of maintaining the mutation associated with lamivudine. In patients treated with lamivudine, the immunological and clinical failure was delayed. The average decrease in the CD4 percentage, the viral rebound and the recovery in the replicative capacity of HIV-1 were significantly lower in the lamivudine group.
It is highly likely that the patients whose first line treatment has failed over a prolonged period, as is the case in countries where the viral load is not easily available, have developed the M184 mutation of the RT with resistances to lamivudine and to emtricitabine. Lamivudine is a substance that is low in cost, available in generic form, and easily available in less-developed countries. If it is shown that this has benefited the maintenance of a controlled viral load while on monotherapy, it would be both practical and easy to integrate as part of a maintenance strategy.

The ANRS 12169 2LADY trial is an open label, randomised, non-inferiority, multicentre phase III trial comparing the virological efficacy and tolerability of three second-line antiretroviral treatment regimens at 48 weeks in patients infected with HIV-1 with failure of a 1st line antiretroviral treatment, in Yaoundé (Cameroon), Dakar (Senegal) and Bobo-Dioulasso (Burkina Faso). The trial compares the following second-line regimens: 1) tenofovir / emtricitabine combined with lopinavir / ritonavir, 2) abacavir, didanosine with the combination lopinavir/ritonavir and 3) tenofovir/emtricitabine with the combination darunavir/ritonavir. The primary outcome is a viral load of less than 50 copies/ml at 48 weeks.
In September 2012, the 2LADY trial ended recruitment (N=454). The patients who have more than 48 weeks of follow-up in the 2LADY trial and who fulfil the eligibility criteria will be offered inclusion in the MOBIDIP trial.

The characteristics at inclusion of the participants in the 2LADY trial were already known and at the end of October 2012, 297 patients had reached the week 48 visit. Of these, 262 (90%) had a viral load of less than 200 copies/ml, the principal inclusion criterion for MOBIDIP. Apart from patients with chronic hepatitis B (HBsAg positive), who accounted for almost 10% and taking into account several likely rejections, we believe that we will be able to obtain the sample planned for MOBIDIP.

We therefore propose to switch the 2LADY patients who fulfil the eligibility criteria, are in follow-up for more than 48 weeks, and agree to take part in the **MOBIDIP trial**, with a maintenance treatment with boosted PI +/- lamivudine. The NRTIs will be discontinued and the patients will continue the ongoing boosted PI.
They will thus receive either 2 tablets of lopinavir/ritonavir 200/50 twice daily or 2 x 400 mg darunavir tablets and a 100 mg ritonavir tablet in a single intake. The patients will be randomised 1:1 on the addition of lamivudine 150 mg, in 2 tablets per day or lamivudine 300 mg in 1 tablet per day according to availability in the national programmes. The randomisation will be stratified according to the inclusion centre and the level of plasma HIV RNA at the last 2LADY trial visit (≤ 50 copies/ml compared to 51-200 copies/ml).

5 OBJECTIVES

5.1 Principal objective

To compare the proportion of patients in treatment failure, after 96 weeks of treatment in two groups, one receiving monotherapy with a boosted PI (lopinavir/ritonavir or darunavir/ritonavir) and the other receiving dual therapy of a boosted PI with lamivudine, in HIV positive patients under second-line ART for at least 48 weeks and with a viral load less than 200 copies/ml.

The definition of treatment failure for this principal objective is: *1) the viral load ≥ 500 copies/ml confirmed in 2 samples with 1 month interval, or 2) the reintroduction of the two NRTIs or 3) discontinuation of the PI/ r.*

5.2 Secondary objectives

To describe the following parameters:

- Treatment failure defined by a viral load of ≥ 200, ≥ 500 and ≥ 1000 copies/ml in the 24 weeks following the reintroduction of the NRTI regime
- The virological response at 48 weeks
- The virological response at 96 weeks
- The appearance of mutations at failure
- The clinical course (AIDS-defining events, non-AIDS-defining events, fatality, adverse events)
- The immune response
- The tolerability, in particular modifications to the lipid profile, renal function and bone mineral density
- Changes in anthropometric measurements
- The neurocognitive functions (screening EACS 2012 (20) follow-up of specific NC tests in the case of positive screening)
- Compliance (measured by counting the tablets and questionnaire).

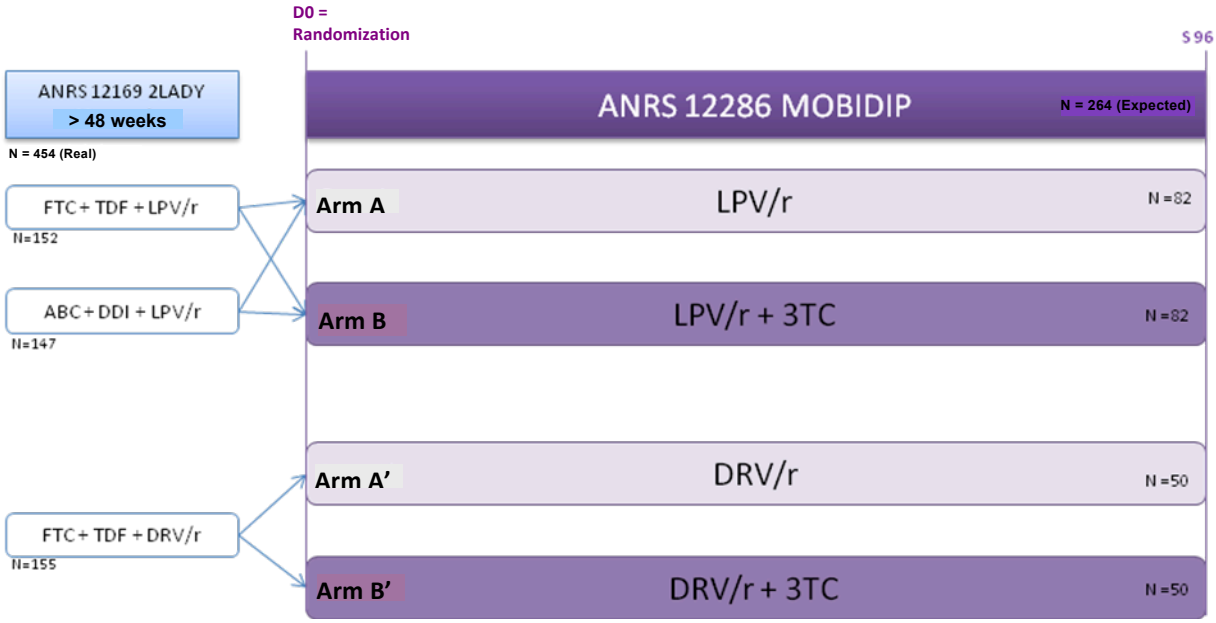
Identifying the factors associated with therapeutic success
Compare the virological response in the lopinavir group vs the darunavir group.

6 METHODOLOGY

6.1 Trial design

A phase III 1:1 randomised, international, multicentre, prospective, open label, comparative clinical trial of superiority comparing two second-line maintenance strategies in mono- or dual therapy based on boosted protease inhibitors (bPIs) with or without lamivudine in HIV+ patients under second-line treatment for at least 48 weeks and with a viral load of ≤ 200 copies/ml for at least 6 months in Dakar (Senegal), Bobo-Dioulasso (Burkina Faso) and Yaoundé (Cameroon).

The randomisation of eligible patients will be performed in a period of **6 months starting from September 2013**. We expect to include 180 patients in Cameroon, 30 in Senegal and 54 in Burkina Faso **(total: 264 participants).** With a follow-up over 96 weeks, we plan to end follow-up in March 2016 and the trial in September 2016 including the 6 months for following up patients whose treatment failed late in the trial.



The final results of the 2LADY trial (comparison of different second-line combinations) will make it possible to reconsider the relevance of the choice of the protease inhibitor in monotherapy or of the NRTIs to reintroduce in the case of viral load of ≥ 500 copies/ml. If the results of 2LADY could affect the MOBIDIP trial design and the management of participants, the trial Scientific Council will be urgently consulted to decide on the best choice for the participants in the MOBIDIP trial.

6.2 Randomisation

6.2.1 Drafting of randomisation lists

The randomisation lists will be created by the statistician from the Methodology and Management Centre (MMC) before the start of the trial. They will be kept in a strictly confidential manner. The numbers in the two treatment groups will be equal. **The randomisation is stratified** according to the **investigational centre** and the **level of plasma HIV RNA** (≤ 50 against 51-200 copies/ml) at the last 2LADY appointment which will correspond to the pre-inclusion appointment (V-15). A detailed document explaining the practical randomisation procedure will be provided to each investigational centre.

6.2.2 Practical arrangements

In each investigational centre, one person, independent of the clinical team, is designated as responsible for the randomisation. This person receives the predefined confidential randomisation lists and the randomisation procedure from the MMC.
The investigator notifies the person responsible for the randomisation of the date on which the patient will be randomised.
On the inclusion appointment day (V0) in MOBIDIP, the investigator verifies the inclusion criteria and if they are compliant, gets the patient to sign the informed consent and forwards the "Randomisation request form" to the person responsible for randomisation. On receiving the form, the person responsible checks the V-15 viral load result and assigns the 1st arm of treatment to the appropriate randomisation list according to the viral load level and enters the ID of the patient in the trial on the same line. The person responsible fills the "randomisation request" with the assigned treatment arm and immediately forwards a copy to the investigator and one to the pharmacist.
The new prescription for the treatment will be generated on the same day (V0).

6.3 Trial timetable

- Planned date for start of trial: 01/09/2013
- Planned duration of inclusion: 6 months
- Duration of follow-up per trial participant: 96 weeks
- Total duration of trial: 3 years (6 additional months for the follow-up of failed patients at the last visit).
- Planned date for end of trial: 30/09/2016

For each participant the duration of follow-up in the trial is 96 weeks after inclusion in the trial. Only participants with a viral load greater than 500 copies/ml at the last visit (V96) will receive an extended follow-up of 6 months for the VL to be checked after reintroduction of the NRTIs.

7 Study population

7.1 Inclusion criteria

- HIV-1 infection in second-line treatment for at least 48 weeks in the ANRS 12169 2LADY trial
- VL ≤ 200 copies/ml for at least 6 months (verified in 2 consecutive samples with the most recent ≤ one month)
- No change in ART in the 3 months preceding recruitment
- CD4 ≥ 100 cells/ml at last check (which was less than 6 months previously)
- Signed informed consent
- Adherence ≥ 90% at the last visit in the 2LADY trial

7.2 Exclusion criteria

- Previous viral failure (HIV RNA > 1000 copies/ml at least 2 consecutive times) while receiving PI
- Ongoing pregnancy or breastfeeding mothers
- HBsAg positive patients
- Ongoing or treatment in the 3 months before recruitment, of an opportunistic infection or of any serious or progressive disease
- Subject who, in the investigator's opinion, is unable to complete the study (relocation, transport difficulties, missed visits, adherence difficulties)
- History or symptoms of HIV-related encephalitis

8 Evaluation criteria

8.1 Principal evaluation criterion

The virological response

- Proportion of patients with a treatment failure at 96 weeks.

Definition of treatment failure: 1) viral load ≥ 500 copies/ml confirmed in 2 samples with 1 month interval, or 2) the reintroduction of the two NRTIs or 3) interruption of the PI/r.

The plasma HIV RNA is measured in the laboratory of each investigational centre using the ABBOTT technique. The virological laboratories must be registered and validated by an external quality control system for quantification of plasma HIV RNA before and during the trial.

8.2 Secondary criteria

The virological response:

- the proportion of patients with plasma HIV RNA < 50 copies/ml at 48 weeks, with or without reintroduction of the NRTIs.
- the proportion of patients with plasma HIV RNA < 200 copies/ml at 48 weeks, with or without reintroduction of the NRTIs.
- the proportion of patients with plasma HIV RNA < 500 copies/ml at 48 weeks, with or without reintroduction of the NRTIs.
- the proportion of patients with plasma HIV RNA < 1000 copies/ml at 48 weeks, with or without reintroduction of the NRTIs.
- the proportion of patients with plasma HIV RNA < 50 copies /ml at 96 weeks, with or without reintroduction of the NRTIs.
- the proportion of patients with plasma HIV RNA < 1000 copies /ml at 96 weeks, with or without reintroduction of the NRTIs

The viral resistance:

- the frequency of resistance mutations in the case of treatment failure, defined as HIV RNA ≥ 500 copies/ml 24 weeks after the reintroduction of the combination of the two original NRTIs.

The immunological response:

- the variation in the level of circulating CD4+ lymphocytes

The lymphocyte count (CD4+ lymphocyte sub-populations) is conducted by the laboratories of the investigational centre by flow cytofluorometry in total blood with FITC-labelled monoclonal CD4 markers. The laboratories will be registered and must be validated by an external quality control system for measuring CD4s before and throughout the trial.

The clinical course of the HIV infection:

- number of deaths
- frequency of stage 3 or 4 clinical events according to the WHO classification (Revised WHO clinical staging and immunological classification of HIV for surveillance 2007)
- frequency of non-AIDS-defined clinical events (malaria, cardiovascular disorders, tumours, traumatic or non-traumatic fractures, etc.)
- incidence of bacterial infections leading to hospitalisation or prolongation of hospitalisation
- neurocognitive disorders: appearance and / or development

Tolerability:

- frequency of adverse events
- frequency of intolerance-related discontinuation of treatment

- changes to the following biological parameters: blood count, glomerular filtration rate, blood transaminases, glycaemia, total cholesterol, HDL and LDL and triglycerides
- changes to the following anthropometric measurements: waist circumference, hip circumference and thigh circumference

Adherence:
Adherence is considered high if consumption is greater than or equal to 95%, average if it is between 80 and 95% and low if it is less than 80%.
It is measured at each visit, by means of a questionnaire given to the participant by the person responsible for adherence monitoring and by the tablet count.

9 Treatment

9.1 Study treatment

9.1.1 Description of the products

Lopinavir/ritonavir
Pharmaceutical form: tablet of LPV 200 mg/RTV 50 mg
Dosage: 4 tablets/day, 2 in the morning, 2 in the evening
Lamivudine
Pharmaceutical form: tablet of 3TC 300 mg or 150 mg
Dosage: 1 x 300 mg tablet/day or 2 x 150 mg tablets/day
Darunavir/ritonavir
Pharmaceutical form: 400 mg darunavir tablet, 100 mg ritonavir tablet
Dosage: 2 darunavir tablets/day + 1 ritonavir tablet/day once a day with food

In the event of treatment failure, the therapeutic regimen will be determined on a case-by-case basis according to the available viral genotypes, by the trial clinicians with the MMC. The following substances will be available in connection with the trial:
Darunavir/ritonavir
Pharmaceutical form: 600 mg darunavir tablet, 100 mg ritonavir tablet
Dosage: 2 darunavir tablets/day, 1 in the morning, 1 in the evening with food
+ 2 ritonavir tablets/day, 1 tablet to accompany each 600 mg of darunavir
Etravirine
Pharmaceutical form: 100 mg etravirine tablet
Dosage: 4 tablets/day, 2 in the morning and 2 in the evening.
Raltegravir
Pharmaceutical form: 400 mg raltegravir tablets
Dosage: 2 tablets/day, 1 in the morning and 1 in the evening

Possible secondary effects:
Diarrhoea has been the adverse effect most frequently associated with treatment **with lopinavir/ritonavir**, generally of mild to moderate severity. Discontinuation of treatment as a result of adverse events occurred in 4.5% (of treatment-naive patients) and 9% (of pre-treated patients) in a period of 48 weeks.
It is important to note that cases of pancreatitis have been reported in patients treated by LPV/r, some of whom presented a hypertriglyceridaemia. Also, rare incidences of increases in the PR interval have been reported during the treatment.

The most frequent adverse events for **boosted darunavir** reported in clinical trials and in spontaneous notifications are: rashes, diarrhoea, nausea, vomiting, abdominal pains, headache, lipodystrophy,

changes in lipid metabolism and diabetes. The most frequent serious adverse events are: diarrhoea, hepatitis, immune reconstitution syndrome and severe rashes.

Etravirine has also been associated with rashes, sometimes severe, and with the increase in liver enzymes.

ARV therapy has been associated, in patients infected with HIV, with a redistribution of body fat mass (lipodystrophy), including a loss of peripheral and facial subcutaneous adipose, an increase in intra-abdominal and visceral fat mass, mammary hypertrophy and an accumulation of fat mass in the retrocervical area (buffalo hump).
Antiretroviral treatments with PIs have been associated with metabolic anomalies such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.
The data on the effects of bPIs on pregnant women are insufficient to conclude that they are totally safe. The results of cohort studies show a relationship, although controversial, between therapy with ARVs and an increase in premature births without consequences for the child. Registry studies do not show any increase in the risk of birth defect after exposure to antiretrovirals; nonetheless, their use during pregnancy is only advisable in cases of necessity. The combination lopinavir/ritonavir is the PI of choice in pregnant women.

9.1.2 Reference documents(s)

The reference documents for this trial are the Investigator's Brochure and the SPC (European countries or members of EC or other). Procedures for the use of trial drugs have been made available to guide the response in cases of adverse events.

9.2 Study treatment cycles

9.2.1 Provision of products

During the trial lopinavir/ritonavir and lamivudine will be provided via national programmes for combating AIDS.
Darunavir and etravirine will be provided by Janssen Pharmaceutica NV.
Ritonavir will be purchased for the trial via the Access initiative financed by Janssen Pharmacutica NV for patients receiving darunavir and for tuberculosis (unless rifabutine is available) for countries in which this drug is not provided under the national programmes. For countries in which ritonavir is available under the national programme, it will be provided by the latter.

In the case of second-line treatment failure during the trial, darunavir 600 mg and etravirine will be provided free of charge by Janssen Pharmaceutica NV. Raltegravir will be purchased by the trial, if necessary.
In the case of reintroduction of NRTIs, the latter will be provided by the national programmes.

9.2.2 Labelling of products

Labelling will be provided by the pharmacist or person responsible for the pharmacy under the supervision of the pharmacists responsible for the project. The label models will be validated by the Sponsor and the MMC. The MMC will ensure that the product is correctly labelled according to the provisions of the French Public Health Code (article R. 5121-16) and the decree of 24 May 2006 stipulating the content of labelling for experimental drugs.

9.2.3 Project management

Pharmaceutical coordination is provided by the pharmacist of the ANRS site in Yaoundé, Cameroon, by the pharmacist of the Day Hospital in Bobo-Dioulasso and by the pharmacy of the Clinical

Research Centre (CRCF) of the Fann University Hospital in Senegal. The pharmacy in each country is responsible for supplies, checking the WHO advance classification of drugs received by the National Programmes, storage, dispensing and management of the treatment units (TUs).

Ordering drugs:
Orders for products from the national programme will be placed by the pharmacists at each site, according to the project needs and the supply cycles of the programmes. To ensure the continuity of dispensation within the project, a buffer stock (of 2 months) will be purchased by the trial and kept in the pharmacies of sites that report difficulties in obtaining supplies.

For products provided by Janssen Pharmaceutica NV, orders will be sent by the MMC, in writing, to the laboratories. The timing of the orders/deliveries will be made as required and will be based on the timing of inclusions, the progress of the trial and the expiry dates of the products.
The shipping of darunavir and etravirine (products not issued with an MA in the country of importation) provided by Janssen Pharmaceutica NV is subject to import license in each country. The MMC is responsible for preparing the import license application in cooperation with the site pharmacists.

Management of medicinal products
In each country, the trial pharmacist will maintain up-to-date management documents for the medicinal products used (reception, stock records, consumption).

Storage arrangements
The pharmacies are required to observe the European Good Manufacturing Practices.
For the entire duration of the trial, the medicinal products will be stored under the required conditions, in the pharmacy of the research centre in each country, under the responsibility of the pharmacist of the establishment concerned.
In Cameroon, the central pharmacy of the ANRS coordination site stocks the medicinal products and supplies the dispensaries monthly, in the other countries the medicinal products will be stored directly in the pharmacy from which they are issued.

9.2.4 Dispensation, preparation and administration of the products

The treatment drugs will be dispensed from the pharmacy of the Clinical Research Centre (CRCF) of the Fann University Hospital (Senegal), from the pharmacy of the Day Hospital in Bobo-Dioulasso (Burkina Faso) and from the local pharmacies of the investigational centres in Yaoundé (Cameroon Central and Military Hospitals) on the basis of the assigned strategies and scheduled visits.
The dispensation of trial drugs to patients will be registered. It will be performed at the pharmacy of the investigational centre, under the direct supervision of the trial pharmacist, on presentation of a pre-printed prescription stating the patient's identity code issued on inclusion in the trial, the visit number and the duration of treatment. The treatment drugs will be dispensed in accordance with scheduled visits and will be accompanied by a reminder of usage and storage recommendations. The person responsible for dispensing the drugs will request the patient to return the drug cartons issued the last time, so that a tablet count can be performed.
On inclusion, the pharmacy concerned will receive the randomisation record and will be able to dispense the assigned treatment. An individual management sheet for treatments will be provided by the project director and must be kept up-to-date by the person responsible for dispensing the drugs. This sheet must state the quantity of treatment supplied to the patient, the batch and the expiry date, the quantity remaining per patient at each visit, with the corresponding dates.
All packaging issued, once empty, must be returned by the patient to the pharmacy; it will be documented on the individual management sheet and must be made available for each monitoring visit for monitoring. The empty packaging may be destroyed after monitoring.

9.2.5 Return and destruction of unused products

After monitoring and reconciliation, unused medicinal products at the end of the trial, or those that have passed their expiry data during the trial, will be destroyed at the project's own expense, according to the arrangements established in each country and under the responsibility of the trial pharmacist at each site.
A certificate of destruction will be provided to the Sponsor and to the partner pharmaceutical laboratory.

9.3 Associated treatments

Any concomitant treatment, including contraceptives, should be listed in the report form and will be provided by the study if it is related to HIV infection or side effects of the drugs, within financially reasonable limits.

In the case of tuberculosis:
Tuberculosis will be treated according to the WHO recommendations and national guidelines. The treatment must include rifampicin, given that rifabutin is not available in Africa.
For the interactions and safety of the participants:

- The NRTI will be reintroduced
- The treatment with darunavir may not be continued and will be replaced with boosted lopinavir
- The treatment lopinavir/ritonavir must be combined with high doses of ritonavir, 300 mg in the morning and in the evening

Given the potential hepatotoxicity of this combination (rifampicin and PI boosted with high dose of ritonavir), closer monitoring (at least once a month) of the liver function will be performed.
Patients who have had to change their therapeutic regimen will be monitored up to the end of the trial.
If rifabutin is not available, the international recommendations will be applied.

During the trial, the following concomitant treatments are not authorised:

- Any antiretroviral treatment other than the trial treatment
- Any medicinal product not prescribed by the study doctor (investigator)
- The following medicinal products or substances, of which the interactions with ritonavir may have serious consequences: astemizole, terfenadine, midazolam, triazolam, cisapride, pimozide, sertindole, amiodarone, ergot alkaloids, St Johns wort, simvastatin, lovastatin, atorvastatin and inhaled fluticasone.

In all cases, on the basis of interactions with ritonavir, precautions must be taken in administering a combined oral contraceptive of oestrogen-progesterone, vitamin K antagonists, of ketoconazole and itraconazole.
Standard clinical operational procedures with a list of interactions and precautions when using the treatments will be available to the study doctors.

10 Trial progression

10.1 Follow-up schedule for trial subjects

	Last visit in 2LADY	**Randomisation**	**FOLLOW-UP**									**If VL > 500 copies/ml at V96**	
	V-15	V0	V4	V12	V24	V36	V48	V60	V72	V84	V96	V108	V120
Informed Consent	X												
Eligibility criteria	X	X											
Signature of IC		X											
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg	X												

FBC	X			X	X	X	X	X	X	X	X	X	X
Creatinine clearance	X				X		X		X		X		X
ALAT	X			X	X	X	X	X	X	X	X	X	X
Glycaemia	X				X		X		X		X		
Total Cholesterol, HDL, LDL, Triglycerides*	X						X				X		
HBsAg	X												
Urine test strip	X				X		X		X		X		X
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4/CD8	X				X		X		X		X		X
Plasma HIV - RNA**	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma bank***	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence	X		X	X	X	X	X	X	X	X	X	X	X
Pharmaceutical dispensing		X	X	X	X	X	X	X	X	X	X	X	X
Anthropometric measurements		X			X		X		X		X		
Quantity of blood in mL	35	10	10	20	35	20	35	20	35	20	35	20	35

* sampling under fast conditions.
** the resistance genotypes will be carried out in case of treatment failure using tubes from the plasma bank.
*** indicate the date and time when the last dose of antiretroviral drug was taken.

10.2 Information and screening visit (last visit of 2LADY, at least week 48)

During the last visit of the 2LADY trial, the final 2LADY trial data will be collected following the protocol schedule. In addition, the study doctor will provide information concerning the MOBIDIP trial and discuss the study rationale with patients fulfilling the inclusion criteria. The participant information notice will be given to them, and they will be asked to carefully read this before the next visit (planned for 15 days afterwards).
A control of the hepatitis B HBs antigen will be carried out to assure the screening of the participants who may have been infected with HBV during the 2LADY trial.
If the last visit of the 2LADY protocol was more than one month ago, the patient may be recalled for a viral load control and to receive information (and the notice) concerning the MOBIDIP trial. A sample for the viral load, FBC, transaminase and creatinine may be carried out.

10.3 2LADY trial participants not included in MOBIDIP

Participants in the 2LADY trial who do not meet the eligibility criteria for inclusion in the MOBIDIP trial, or who do not wish to participate, will have the option of entering the "2LADY long term" trial.
2LADY long term is a 96-week extended monitoring to the 2LADY trial (as in the MOBIDIP trial). The monitoring will be that proposed in the 2LADY trial after week 48 (a visit every 6 months, same biological examinations.

Participation in 2LADY long term will be proposed to patients either during the last visit of 2LADY for participants who do not meet the inclusion criteria for MOBIDIP, or at the time of their refusal to participate in the MOBIDIP trial.

An amendment to the 2LADY trial protocol will be written to extend this to the last patient's exit from the trial. A new informed consent form will be signed by the participants wishing to continue the "2LADY long term" trial.

The medicinal products for the 2LADY long term participants will be supplied by the national programmes except for darunavir 400 mg and 600 mg and the etravirine which will be supplied by Janssen Pharmaceutica NV until March 2016. The trial will supply the ritonavir if it is not available in the national programmes. Raltegravir will be purchased by the trial, if necessary.

10.4 Collection of informed consent and randomisation (V0)

The criteria for patient eligibility will be checked again (based on the laboratory results of the screening visit and the clinical parameters of the patient at the time of the V0 consultation). After checking that the study information has been fully understood by the patient, the patient will be included and the study doctor will collect the signature on the informed consent form.
Randomisation will be done according to the procedure supplied to each site involved in the trial. The treatment corresponding to the arm assigned by the randomisation will be prescribed to the patient.

This visit corresponds to starting treatment in the trial and is the baseline for the statistical analyses.
During this visit, an additional review of the patient's clinical history will be carried out, noting the concomitant treatments.
A blood sample will be taken for the viral load and to store the plasma.
A urine pregnancy test will be performed to rule out an initial pregnancy.
Anthropometric measurements will also be taken as a screening for neurocognitive disorders.
A visit will be scheduled at 4 weeks to verify compliance.

10.5 Follow-up visits

These visits allow information to be collected on the different evaluation criteria during follow-up. The first visit will take place 4 weeks after inclusion and every three months thereafter.
The visits include:

Collection of clinical and treatment data by the investigator (at each visit)

- Question the patient on clinical events that have taken place since the previous visit allowing detection of new stage 3 or 4 events of the WHO classification.
- Clinical examination (weight and blood pressure)
- Noting of any associated treatments (modifications since the last visit)
- Neurocognitive disorders (twice a year)

The anthropometric measurements (with the help of a tape measure) every 6 months:

- Waist circumference: measured with the subject standing, stomach relaxed, at the mid-point between the lower edge of the last rib and the iliac crest
- Hip circumference: measured, with the subject standing, level with the trochanters
- Thigh circumference: measured with the subject lying down, at a point on the right thigh, 15 cm from the upper edge of the patella

Compliance interview (at each visit)

This will be performed, face-to-face with a questionnaire, by the person in charge of compliance.
Every 3 months, alcohol consumption and mood disorders will be evaluated with the aid of a validated questionnaire: the AUDIT-C questionnaire for alcohol consumption and the PHQ9 for depression.
The pharmacist's assistant and/or trained person from the HIV+ association will be in charge of therapeutic education for treatment compliance.

Laboratory tests:

Carried out locally, they include:

- Pregnancy test (for women of childbearing age) at each visit
- FBC, platelets and liver function test (ALT) at each visit apart from week 4
- Creatinine, creatinine clearance (Cockcroft), urine dipstick and blood sugar level every 6 months
- Total cholesterol, HDL, LDL, triglycerides every 12 months
- Lymphocytes CD4/CD8 every 6 months
- Plasma HIV RNA at each visit
- Plasma bank every 6 months
- Search for HIV resistance mutations (Reverse Transcriptase and Protease Sequencing) if plasma HIV RNA measurements > 500 copies/ml

10.6 Last follow-up visit (Week 96)

At the penultimate follow-up visit, the participants will receive a letter informing them of the end of the trial, explaining the practical means put in place for their transfer to the national programme.
At the last visit, the participants will be directed towards their original support service or to a new one, if they so wish. A summary of the clinical and therapeutic history of the patient and laboratory results will be supplied by the study doctor to the doctor in charge of monitoring the patient in the national health structures.

10.7 What to do in case of insufficient virological response

An insufficient virological response is defined by the presence of plasma HIV RNA above 500 copies/ml, confirmed by 2 samples taken one month apart and after reinforcement of compliance.
Patients with treatment failure, with or without associated immunological or clinical failure criteria, will have the NRTI of the initial 2LADY treatment reintroduced. After reintroducing the NRTIs, patients will have a plasma HIV RNA measurement after 12 and 24 weeks. In the case of HIV RNA ≥ 500 copies/ml at 24 weeks after reintroducing the NRTIs, the viral genotype (if possible, depending on the amplification capacity of the local laboratory) for detecting resistance mutations will be carried out and the decision for 3rd line adapted therapy will be taken.
The 3rd line treatment will be chosen on a case-by-case basis by the doctors in charge of the patients and the MMC, taking into account the genotype done at the time of passing to the 2nd line (in 2LADY), as well as that carried out at the time of treatment failure.
When possible, depending on the genotype, patients in treatment failure taking boosted lopinavir may receive a treatment that includes darunavir 1200 mg/day (1 x 600 mg tablet twice daily) and ritonavir 200 mg/day (1 x 100 mg tablet twice daily) with food.

Patients with treatment failure taking boosted darunavir may take a combination including, among others, lopinavir/ritonavir and etravirine 400 mg/day (2 x 100 mg tablets twice daily).
Darunavir (600 mg tablet) and etravirine (100 mg tablet) will be supplied without any cost by Janssen Pharmaceutica NV for each patient in the trial who needs it, if the treatment is not available in the national programme until the end of the study (96 weeks for each patient; and 6 months for patients who failed in the last semester). Raltegravir will be purchased by the trial in case of need.
Clinical and laboratory monitoring will be continued following the schedule planned for MOBIDIP, whether or not the patient continues with the trial treatment.

10.8 End of trial

The end of the trial is planned for 96 weeks after inclusion for each patient. Only the participants with a viral load greater than 500 copies/ml at the last control at week 96 will benefit from an additional 6 months follow-up to allow their VL to be controlled after reintroduction of the NRTIs.

10.9 Therapeutic support at the end of the trial or on early interruption

After the end of the trial, all patients with therapy success will be put on 2nd line ARV therapy, as planned by the national programmes.
On a case-by-case basis and at the discretion of the health practitioner and the patient, it may be decided to continue the therapy in progress in the trial. Individual and trial results may help in the decision-making.
The investigational team will collaborate with the national authorities and international organisations to facilitate access to and support of participants in 3rd line, for whom the necessary substances are not, for the time being, available in the national programme.

10.10 Early and definitive interruption of the treatment

A person is considered to have *interrupted treatment* when they no longer follow - for whatever reason - the study strategy, but they do continue the planned follow-up within the protocol (visits, samples, additional examinations). Persons who have interrupted treatment should have the best possible support due to their state of health and the state of current knowledge. They will continue to be monitored, clinically and biologically, following the protocol schedule, and to benefit from the planned support until the end of the trial.

The patient may interrupt the study treatment at any time.
Early interruption of the treatment in the trial may occur in the following situations:

- a serious adverse event related to the treatment
- treatment failure as defined in the protocol
- at the patient's request
- any medical event requiring interruption for the patient's well-being
- non-compliance with the treatment, putting the patient's health at risk
- pregnancy (if VL > 50 copies/ml)
- tuberculosis
- HBV infection

In the case of tuberculosis, the first choice will be to reintroduce the original triple therapy (see above for what to do for bPI).
Concerning pregnancies, the original triple therapy will be reintroduced if the VL > 50 copies/ml with the objective of reducing the likelihood of transmission from mother to child as far as possible.
Reasons for stopping treatment in the trial, whether temporary or permanent, must be noted in the case report form and documented in the medical notes.

10.11 Participant lost to follow-up

A patient who does not return to the investigational centre for two consecutive protocol visits, despite efforts to contact him/her, is considered to be 'lost to follow-up'.

The teams in charge of monitoring patients must take all reasonable steps (telephone calls, home visit - if authorised by the patient when signing the consent form - contact with a partner if possible) to contact patients who miss their visits, in order to encourage them to return for an examination, and in case of refusal, to record their interrupted participation.
Notification of lost to follow-up patients must be sent as quickly as possible to the trial MMC.

10.12 Withdrawing consent

A person will be considered to have *withdrawn consent* if they no longer wish to continue the treatment and the follow-up as was assigned to them by the protocol. In this case, an "*end of trial sheet"* should be completed by the investigator. As from the date on which consent is withdrawn, no further data will be collected and no biological samples taken. The investigator will ask the patient, and note on the "*consent withdrawal form"*, whether the data collected and the samples taken before withdrawing consent may be used. The withdrawal date must be written in the source file. A summary of the patient's clinical and therapeutic history and laboratory results will be supplied by the study doctor to the doctor in charge of monitoring the patient in the national health structures. Consent may be withdrawn at any time.
Withdrawal of consent must be notified as quickly as possible to the MMC via the "*end of trial sheet"*. The date of consent withdrawal must be documented in the CRF and the source file and if possible, the reasons for withdrawal.

10.13 Deviations from the protocol

Deviations from the protocol must be documented and justified.
Deviations relating to the following are considered major violations:

- regulatory aspects,
- eligibility criteria,
- principal evaluation criterion,
- the treatment during the trial

other than those that have been the subject of a written deviation from the MMC and the investigator-coordinator.

Interruption of treatment, consent withdrawal, and protocol waiver will be presented at each meeting of the Scientific Council and the Independent Oversight Committee.

10.14 Questionnaires

The anticipated study data will be collected in each patient's own Case Report Form (CRF), identified by his/her anonymous number and code.
The data collected during each visit will be dated and signed by the investigator.
A compliance questionnaire (see appendix) will be completed at each visit by the person in charge of compliance support: questions relating to taking the medicinal products will be asked at each visit. An additional series of questions concerning alcohol consumption (AUDIT screening) and depression (WHO screening) will be asked every 6 months within the scope of compliance consultation because of the importance of these two factors on compliance.
Neurocognitive screening will be performed on all participants twice a year.

11 Sampling circuit

11.1 Samples for biological examinations planned for in the protocol

Blood samples are collected at the different visits (cf. trial schedule §9.1) to allow on-site biological examinations. Test tubes should be transferred according to the internal procedures of the investigational centre, controlled by the MMC team in charge of the trial management after the trials are put in place at the said sites.

11.2 Sample collection for storage

As specified in the informed consent form, two 5 cc tubes of plasma will be collected at each visit and stored at -20°C in the investigational centre laboratories of each country with the aim of carrying out secondary pharmacological analysis (antiretroviral doses), virological analysis (quality control, resistance study) or any other biological analysis related to the study, which will be subjected to and approved by the Scientific Council of the trial.
To interpret any pharmacological dose, the date and time of the sample for the plasma bank and the date and time of the last intake of the antiretroviral prior to the sample must be indicated on a specific sheet accompanying each sample.
Storage of the cells, in the same Laboratory, is also planned at each visit. Any examination carried out with the samples must be related to the study, validated by the Scientific Council and approved by the Ethics Committee.
The label on the samples must not contain any data by which the participants can be identified; only the identification code should appear.

12 Adverse events and in utero exposure

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is defined as: "any harmful medical occurrence with someone who presents themselves for biomedical research, whether or not this medical occurrence is linked to the research or to the product under investigation".
An adverse event is defined as "any harmful and undesired reaction to an experimental drug, regardless of administered dose".
An unexpected adverse event designates any adverse event of which the nature, severity or evolution do not match the information indicated in the documents relating to the product (Investigator's Brochure (IB) or the Summary of Product Characteristics (SPC).
Pregnancy is a specific case (cf. "pregnancy" paragraph below).

12.1.2 Serious adverse events (sae)

In this protocol, a serious adverse event (SAE) is considered as any event or undesirable effect, regardless of the administered dose that:

- leads to death,
- is life threatening to the person participating in the research,
- requires hospitalisation or causes prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- results in a congenital anomaly or birth defect, (including cases of spontaneous abortion or therapeutic interruption of pregnancy),
- requires medical intervention preventing the occurrence of the aforementioned,
- is judged by the investigator as potentially serious,
- is any grade 4 clinical or biological event.

EXCEPTIONS: SAE not requiring immediate notification to the Sponsor:

- Pre-existing or detected pathology prior to the first administration of the trial treatments and which does not worsen.
- Biological grade 1, 2 and 3 events (to be recorded in the "Adverse event" section of the CRF).
- Biological grade 4 events detected during the pre-inclusion visit prior to initiating any trial treatment or events proven to be pre-existing.
- Admission to day hospital; the patient is admitted for a period of less than 24 hours for a non-serious medical reason (cf. aforementioned severity criteria).

Moreover, events in which the only reason to be judged as such is the criterion of "hospitalisation" AND which fulfil one of the cases described in appendix 4, will be excluded from the list of serious adverse events to be declared.
The expression "life threatening" is reserved for immediate threat to life, at the time of the event, regardless of the consequences of corrective or palliative therapy
Certain circumstances requiring hospitalisation do not fall into the criteria of serious: "hospitalisation / prolongation of hospitalisation," such as:

- admission for social or administrative reasons
- hospitalisation pre-defined by the protocol
- hospitalisation for medical or surgical treatment planned before the investigation
- transfer to day hospital

12.1.3 Unexpected adverse event

Any adverse effect of the experimental drug, of which the nature, severity or evolution does not match with the information found in the reference document: Summary of Product Characteristics (SPC) or Investigator's Brochure (information notice for a medical device).

12.1.4 New safety facts

A new fact is defined as any new safety data that could lead to a re-evaluation of the trial's risk-benefit ratio, or which could be sufficient to consider modifications to the use of the experimental treatment, to the conduct of the trial, or to the trial documents.

12.2 Investigator's obligations

The investigator evaluates each adverse event with regard to its seriousness.

The investigator must notify the Sponsor, within 24 hours from the time he/she is made aware, of all serious adverse events occurring in the trial, with the exception of those listed in the protocol or in the Summary of Product Characteristics (SPC) as not requiring immediate notification. This initial notification requires a written report and must be followed, if necessary, by one or more written detailed report(s).

The investigator must fully document the event by giving, were possible, the medical diagnosis and establishing a causal link (cf. paragraph 12.5) between the serious adverse event and the experimental drug(s) and/or the associated treatments and/or investigation.

The investigator must assure that relevant follow-up information is passed to the Sponsor within 8 days of the first declaration.

The investigator must monitor the participant that has presented a SAE, until its resolution, stabilisation at a level judged to be acceptable by the investigator or return to the prior condition, even if the participant has left the trial.

12.3 Sponsor's obligations

The Sponsor must evaluate the causal link between the serious adverse event and the experimental drug (s) and the treatments associated with the research.

Evaluation of the expected or unexpected nature of an adverse event is generally carried out by the Sponsor, making use of the applicable reference documents (SPC). If the information on the expected or unexpected character has been made available by the investigator carrying out the notification, this should be taken into account by the Sponsor.

Within the regulatory period, all unexpected serious adverse events (USAE) must be declared to Eudravigilence (database of European pharmacovigilance), to the French Health Authority (ANSM) (according to the regulatory forms in force) and to the Committee for the Protection of Persons (CPP) and inform the investigators, according to a periodicity adapted to the research.

The regulatory declaration is made within a maximum period of:

- seven (7) calendar days for fatal or life-threatening unexpected serious adverse events. In this case, additional relevant information must be sought and transmitted within a new period of eight (8) days.
- fifteen (15) calendar days for any other unexpected serious adverse event. Similarly, additional relevant information must be sought and transmitted within a new period of eight (8) days.

In the case of a blind trial, as a general rule, the Sponsor declares the unexpected and serious adverse event to the Health Authorities and to the CPP after disclosure [unblinding] of the experimental drug.

12.4 Forms of declaration

12.4.1 Collection period for adverse events

Every adverse event is collected:

- As from the date of signing the consent form by the participant in the clinical trial
- Throughout the entire follow-up period for the participant as planned for in the trial

Furthermore, any serious adverse event is collected:

- Until 30 days after the planned end of monitoring of the trial when it is due to the research
- Without limitation of time after the end of the planned monitoring period when this is thought likely to be due to the experimental product.

12.4.2 Evaluation of an adverse event (AE)

When collecting an AE, the seriousness (immediate declaration cf. §10.4), the severity (grade) and the causality with the treatment under trial should be evaluated.

Severity

The severity of an adverse event must be evaluated on a scale of 1 to 4, on the "ANRS Scale to Evaluate the Severity of the Events in adults (version 6 of 9 September 2003)" (Appendix V).

Causal link between the event and the trial treatment

The investigator should endeavour to determine the causal link between the adverse event and the products of the trial. In the absence of information relating to a causal link from the investigator performing the notification, the sponsor should consult the investigator and encourage him/her to issue an opinion on this matter. The evaluation of the causality established by the investigator should not be minimized. If the sponsor disagrees with the assessment of causality provided by the investigator, both the investigator's and the sponsor's opinions should be attached to the report.
The causal link is classed as:

- Not related: the event is clearly related to other causes, such as the clinical state of the patient or a concomitant treatment without pharmacological interaction with the experimental drug
- Possibly related: clinical or biological event with relation to clinical signs and symptoms
- Relationship impossible to determine: potential causality between the experimental drug(s) and the event may exist, which is impossible at the time of declaration to either affirm or exclude due to a lack of clinical elements.

12.4.3 Notification of a serious adverse event (AE)

The investigator must notify, as soon as he/she is aware of, any Serious Adverse Event (SAE), whether or not there is a relationship with the treatment being studied (initial declaration form), to the Project Manager, via the local coordination centre for the project following the procedure in force for the trial:
After validating the declaration sheets, the Project Manager must declare the SAE within 24 hours:

- to the Methodology and Management Centre
- to the ANRS (Sponsor) pharmacovigilance department

The declaration to the partner pharmaceutical company will be made under the conditions described in the contract between the ANRS and said company.

Declaration of death or a life-threatening event of a patient must be completed by an additional declaration within 8 days.

12.4.4 Follow-up of a serious adverse event after notification

After the initial notification, the SAE must be subject to a follow-up procedure until its resolution, stabilisation, or death of the patient.
The evolution and/or resolution of each event must be declared by the investigator as soon as he/she is aware of it, using the "additional declaration form" to the local coordination centre which then informs the same addressees as for the first declaration within 24 working hours.
Additional information relating to a SAE must be notified if:

- The investigator is aware of any significant additional information relating to a previous SAE declaration.
- The investigator makes a modified judgement on the causal relationship between the effect and the treatment of the trial.
- The ANRS has requested additional information.

The investigator must also send copies of the laboratory results and/or additional hospitalisation reports (anonymous reports showing only the patient identification number).
An SAE may be considered to be resolved when the clinical state is normalised, the biological values have returned to normal or the state prior to starting treatment, or the patient has returned to a stable clinical state judged satisfactory by the investigator.

12.4.5 Recommendations for support of patients with an SAE

Symptomatic treatment of the adverse event is put in place if necessary.
If the investigator wishes to reduce the dose or temporarily interrupt the trial treatment, he/she must first discuss this with the south investigator-coordinator of the country concerned (or with the north investigator if the latter is unable to be contacted or with the Project Manager). In case of permanent interruption of treatment, the patient remains in the study and is monitored according to the schedule as planned in the protocol. Every definitive interruption of treatment must be declared immediately to the management centre.

12.5 In utero exposure

During the trial, a contraceptive method other than condoms, will be proposed to all female participants of childbearing age. The contraception will be supplied free of charge for the trial.
The investigator in charge of monitoring the patient will notify any pregnancy to the Project Manager via the local project coordination centre as soon as he/she is aware of this, having completed the sheet "declaration of pregnancy" of the case report form.
The Project Manager must declare the pregnancy within 24 working hours.

- to the Sponsor
- to the Methodology and Management Centre

The declaration to the partner pharmaceutical company will be made under the conditions described in the contract between the ANRS and said company.

In the case of pregnancy, if the viral load is not less than 50 copies/ml, the antiretroviral treatment must be changed for a complete triple therapy that favours the NRTI combination that the patient used before passing to monotherapy with boosted PI or bPI + 3TC double therapy. This new treatment should be continued throughout pregnancy and while breastfeeding. A viral load will be carried out 8 weeks before giving birth. Formula feeding supplied free by the trial will be systematically offered.

At the end of the pregnancy, the trial co-investigator sends the obstetrician in charge of the patient a form "Collect of final pregnancy data," to be completed and returned. This form should be sent to the trial Project Manager, who will then send a copy to:

- the Sponsor
- the Methodology and Management Centre

The declaration to the partner pharmaceutical company will be made within the conditions described in the agreement between ANRS and the said company.

For women receiving third-line treatment and who become pregnant, if necessary, the therapy scheme will be modified on an individual basis depending on the patient history and expert advice.

Warning: any therapeutic interruption of the pregnancy or spontaneous abortion (linked to the detection of a congenital deformity or requiring hospitalisation) is a serious adverse event and should be declared as described in the aforementioned procedure.

12.6 Annual safety report

On the anniversary of the first trial authorisation issued by the first Health Authority, the safety report with the DSUR (Development Safety Update Report) format is completed by the pharmacovigilance department in collaboration with the MMC. It is then validated and signed by the coordinating investigator. It includes:

- The list of serious adverse events likely to be related to the experimental drug(s) in the trial including both expected and unexpected adverse effects.
- A summary table of the effects and the serious adverse events (SAEs), by organ and system, specifying the expected or unexpected characteristic of all the SAEs from the start of the investigation.
- A concise and critical analysis of the safety of participants who present themselves for research.

This preliminary report is sent to the investigator-coordinator for review and approval.

The final report is sent to the competent authority and to Janssen Pharmaceutica NV within the 60 days following the anniversary date of trial approval.

13 Monitoring the research

13.1 Scientific Council (SC)

13.1.1 Structure

The Scientific Council follows the rules described in the corresponding ANRS procedure. It is presided over by **Prof. J. Reynes** and includes all the members already involved in the 2LADY clinical trial. The structure of the scientific council will be validated by the Sponsor before taking office.

- *Members of the study:*
    - Sinata Koulla-Shiro
    - Cheik Tidiane Ndour
    - Adrien Sawadogo
    - Eric Delaporte
    - Alexandra Calmy
    - Vincent Le Moing
    - Jacques Reynes
    - Moussa Seydi
    - Charles Kouanfack
    - Ndeye Fatou Ngom
    - Laura Ciaffi
    - Pierre-Marie Girard

- *External experts*
    - Marie Laure Chaix (virologist)
    - Serge Eholié (clinician)
    - Jean-Baptiste Guiard Schmid (clinician)

Non-voting invited members (see ANRS procedure):

- *Representing the Sponsor*
    - Géraldine Colin, ANRS, Paris
    - Brigitte Bazin, ANRS, Paris
    - A representative of the ANRS Pharmacovigilance department

- *Representing the companies*
    - Maria Blanca Hadacek, Janssen Pharmaceutica NV

- *Representing the association of people living with HIV/AIDS*
    - Isaac Tita, RAP+, Cameroon

13.1.2 Frequency of meetings

The Scientific Council will meet before opening the clinical sites and at least once a year until closure of the trial.
An extraordinary meeting may be called at any time on the decision of the Scientific Council Chairperson, at the request of the Sponsor or of one or more members.

13.1.3 Role

The function of the Scientific Council of the trial is to supervise the correct conduct of the trial, as much from the scientific point of view, as for the ethical and logistical aspect, and it is answerable for this, vis-à-vis the Sponsor.

- It regularly assures the correct conduct of the trial and compliance to the protocol, in particular concerning the safety of the persons participating in the trial,
- It assures the information for all the investigators and other participants in the trial,
- It assures the scientific follow-up to the trial: continued relevance of trial research questions and the validity of methods used to obtain answers,
- It oversees application of the rules for data access from the trial and the communication and publication of the results,
- It maintains a permanent link with the Sponsor, the Independent Oversight Committee and the investigators.
- It decides on any relevant modification to the protocol necessary to continue the trial, in particular:
    - Measures to be taken that facilitate recruitment for the trial / research,
    - Amendments to the protocol before their presentation to the CPP and/or ANSM
    - The decision to open or close trial sites,

After each meeting, minutes of the session are written up by the Project Manager in collaboration with the Scientific Council Chairperson. The minutes are distributed to members of the Scientific Council, to people invited to the meetings, to ANRS supervisors of the investigation department of the LDC and the pharmacovigilance unit of the ANRS.

13.2 Independent Oversight Committee (IC)

The Independent Oversight Committee (IC) respects the rules laid down within the scope of the corresponding ANRS procedure. This committee plays a consultative role for the investigator-coordinators and the Scientific Council.

13.2.1 Members

- Dr Philippe FLANDRE (epidemiologist)
- Dr Christophe MICHON (Clinician)
- Dr Joseph DRABO (Clinician)
- Dr François SIMON (Virologist)

13.2.2 Frequency of meetings

The IC will meet before opening the clinical sites and at least once a year until closure of the trial.
Meetings should preferably take place in tandem with the trial SC meeting.
The IC may be asked, during the course of the trial and after agreement from the Scientific Council, at the instigation of the Sponsor, investigator-coordinator, Methodology and Management Centre, or other investigators, any question relating to the scientific or ethical integrity of the trial.

13.2.3 Role

This committee plays a consultative role for the investigator-coordinators and the Scientific Council. It gives general advice on the conduct of the trial / research. During the course of the trial / research, it may help in difficult decision making for which independent judgement is desirable. It may give advice in the following circumstances:

- advice on the early end to the trial / research (due to toxicity or because the trial / research is no longer feasible, or because the elements allowing its conclusion have already been gathered);

- advice concerning in-depth changes to the protocol that have become necessary due to recruitment or monitoring of the trials / research, or to take account of new scientific data;
- interim analysis: interpretation of the analytical results, request complementary analyses or data from the trial / research.

The advice from the IC is sent in writing to the Sponsor and to the Chairperson of the Scientific Council. A copy is also sent to the Project Manager at the Methodology and Management Centre for archiving.

13.3 Trial Management Centre, Project Manager and local coordination centres

The Management Centre is situated at the UMI233 of the IRD in Montpellier and includes the methodology coordinator, the data manager and the trial statistician.
The Project Manager will be based in Cameroon as of the end of 2013.

The Project Manager is responsible for the preparation and implementation of the trial and the logistical coordination of the trial. The Project Manager verifies the eligibility criteria and validates the randomisation request. He/She informs the Scientific Council of the trial progress, prepares meetings of the different committees and general meetings of the investigators.

The Project Manager coordinates the work of the clinical study monitors at the investigational centres.

The mission of the trial MMC is to prepare the case report forms, to establish the procedure and the list of randomisation. It is in charge of data management, statistical analyses and writing the final report. The mission of the MMC is also to prepare the dossiers facilitating decision-making by the Independent Oversight Committee of the summaries indicating trial progress and the files allowing data analysis for the Scientific Council.

The local coordination centres include, for each country, a minimum of one trained person responsible for managing the SAE declarations: collecting the declaration sheets from the investigators, checking the conformity of the declarations (essential items, treatments from the trial, etc.), checking the anonymity of the additional examination results, scanning and sending the declaration documents to the different addressees, checking the return receipts, monitoring the additional declarations, sending requests for additional information to the investigators, etc. The local coordination centres also group together all the data entry operators and the monitors (CRAs), who assure the monitoring of the trial operations.

14 Control and management of data

The data is collected and validated under the responsibility of the principal investigator of each centre.

14.1 Transfer of data to the MMC

The data is collected in a case report form under the responsibility of the principal investigator of each centre. A case report form is created for each person participating in the trial.
A set of instructions facilitating the completion of the sheets in the case report form, the management and logistics of the trial, is included in the case report form.
All the sheets must be completed from the medical source file by the investigating doctor.
After each monitoring, the case report form is sent to the data entry staff for registration of the data in a secure database developed by the MMC and installed locally at each investigational centre. The investigational centre receives a copy of each database each evening, in order to be able to follow the entry of information on a daily basis.
The MMC will provide the investigational centre with a user-handbook for the database.

The original copy of the case report form will be addressed to the MMC as well as photocopies of the chronological collection sheets, dated and signed at the end of the study, accompanied with anonymous copies of the clinical or biological examination results.

14.2 Control of data

14.2.1 Computer control of entered data

Data entered into the database will be subject to coherence controls. The forms of entry, coding, control, validation and data hold are described in the "data management" guide.

14.2.2 Checking data on-site

Before starting or at the latest on starting the trial, the MMC will establish a monitoring plan which will be made available to the ANRS. The monitoring plan may be modified during the course of the trial, depending on the frequency of inclusions.

14.2.3 Monitoring visits

Monitoring of the study is presented in detail in the trial procedures handbook and is assured by the Clinical Research Associate (CRA) or the MMC Project Manager approved by the Sponsor with respect to the regulations in force and recommendations of Good Clinical Practice.
Briefly speaking, the follow-up visits take place every week for the first 2 months of the trial then every 15 days.
They involve completing a dated and signed monitoring sheet by the clinical study monitor at each site involved in the trial.

The purpose of these visits is to:

- Assure the quality control of the data written in the case report form by comparison with source documents from the investigational centre,
- To search for additional information on the study data, to validate the modifications made and supervise the correction of any incoherent values,
- To inform the investigators of study progress and specific problems encountered during the study,
- To discuss the study approach in the centre (recruitment, data quality, transmission ...),
- To verify and recover copies of the consent forms,
- To verify notification of serious adverse events.

During these visits, access to the source documents will be given to personnel from the local coordination centre responsible for monitoring the trial depending on the monitoring needs and with respect to the standards of Good Clinical Practice.

At each visit, the clinical study monitor is required to check that the associated investigating doctor has sufficient material to carry out the study properly.

14.3 Audit - Inspection

The ANRS or the partner pharmaceutical company after agreement from the ANRS, as well as the Health Authorities in each country taking part in the trials, may ask for an audit of the data to verify the management according to Good Clinical Practice.
An audit may be carried out at any time by persons approved by the Sponsor and independent from the trial responsibilities. The purpose is to assure the quality of the trial, validity of results and respect for the law and regulations in force.
With the same aim, an inspection may be carried out by representatives of the competent Health Authorities.

15 STATISTICAL ASPECTS

15.1 Calculation of the number of subjects necessary

Given that in the boosted PI monotherapy group, the expected proportion of failed subjects is 20% (STAR trial), it is considered that the addition of lamivudine will be worthwhile if the proportion of failed subjects is reduced by more than 12%; the number of subjects required is 127 in each arm with a 5% bilateral risk of type 1 error and a 20% risk of type 2.

15.2 Statistical methods

15.2.1 Analysis strategy

Principal evaluation criterion

The analysis of the primary endpoint criterion will be carried out in the intention-to-treat (ITT) group. It will cover all the randomised subjects who will be analysed in the group in which they were initially randomised. Subjects who have died, lost to follow-up subjects or those who have abandoned the trial are included in the analysis up to the time of death / abandon /consent withdrawal / last news. They are considered as failed for the primary analysis.

The decision to exclude a subject from the analysis may be taken by the Scientific Council after blind documentation of the case by the MMC of the treatment group and evolution of the subject after inclusion.
Reasons that may lead to the exclusion of a subject from analysis are:

- Subject not having signed the consent form or who has withdrawn his/her consent before starting treatment.
- Subject incorrectly included for non-respect of major eligibility criteria, including regulatory criteria.
- Subject who continued triple antiretroviral therapy.

The causes of failure (HIV RNA > 500, reintroduction of NRTIs, interruption of the PI, value missing, lost to follow-up, death, abandon) will be carefully described in each arm. Interruption of treatment due to pregnancy is not considered to be a failure.

The secondary criteria will be stratified on the level of the viral load at inclusion (< 50 vs 50-200) and on the presence of a M184V mutation on the reverse transcriptase at inclusion in the ANRS 12169 2LADY trial.
For exploratory purposes, each protocol will be analyzed, excluding the patients with a missing value for week 96 or who have interrupted the assigned treatment for more than 15 days before week 96, other than those with virological failure.
The analysis will be carried out when all the subjects have reached week 96. The only risk for patients in the trial is to select resistance mutations, this should be low due to selected strategy (use of PI, and rapid reintroduction of NRTI). Any difference of frequency selection between the two arms should therefore not be detectable by statistical analysis. This is why we have decided not to carry out an interim statistical analysis during the trial, unless advised otherwise by the Independent Oversight Committee.

To determine which patients will benefit most from the relief strategy, an exploratory analysis of factors associated with failure will be carried out in each arm of randomisation using multivariate logistic regression models including the following factors: viral load at inclusion, CD4 at inclusion, presence of the 184 mutation, duration of viral load < 200 copies/ml, compliance, etc.

Secondary evaluation criteria
They will be described in each arm without statistical comparison unless expressly requested by the Scientific Council or the Independent Oversight Committee.
In case of statistical comparison, this will be performed in ITT and per-protocol.
The viral resistance analysis will be carried out under treatment.

15.2.2 Statistical methods

Comparison between treatment / strategy / intervention groups will be made
1) without adjustment
2) by adjusting the initial stratification variable and other initial characteristics, the distribution of which may, despite randomisation, be unbalanced between the treatment groups. These adjustments may necessitate the use of appropriate models of which the relevance of the choice is discussed, depending on the distribution and type of variables.
The tests will be carried out with type 1 error risk α=5% testing the hypothesis of superiority in the lamivudine + bPI arm over the bPI monotherapy arm.
The proportion of failure before week 96 in each arm will be described in terms of effective, percentage and confidence interval. Comparisons between groups will be made using the χ2 tests.
An analysis using the delay method until failure will also be used in ITT and using survival methods.
The quantitative variables will be described in terms of effective, percentage and confidence interval. Comparison between groups will be done by χ^2 or χ^2 corrected tests, or exact Fisher's test, depending on the expected effective values on the assumption of independence
The quantitative variables will be described in terms of effective, median, extended and interquartile extended or mean, deviation type, deviation type and mean confidence interval. The comparisons will preferably be carried out using non-parametric tests (Mann-Whitney or Wilcoxon tests) or else parametric tests such as the Student t test, according to the distribution of the variable under study.
The risk of first occurrence of an event being studied will be described in terms of probability of occurrence and confidence interval using the Kaplan-Meier method. The original date is the date of inclusion in the trial and the date of occurrence is the difference between the date of diagnosis of the event and the inclusion date. The different treatment groups will be compared using the log-rank test. Whenever possible a graph will be used to represent the analyses.

15.2.3 Procedure for imputation of missing values

Missing values for the viral load at week 96 for the primary endpoint will be considered as failure. An analysis of missing data sensitivity will be carried out using the maximum bias strategy.

15.2.4 Programmes used for statistical analyses

The analyses are carried out using the latest available version of the STATA program.

15.2.5 Analysis plan

A detailed statistical analysis plan will be prepared before carrying out the final analysis.

- Description of reasons for exclusion from the trial of patients having reached or passed the week 48 visit in the ANRS 12169 2LADY trial
- Description of the inclusions and follow-up (number of missed visits and reasons, deviation from protocol)
- Respect for eligibility criteria
- Characteristics of the included subjects (in particular CD4, viral load, therapy history, immunovirological evolution in the ANRS 12169 2LADY trial)
- Principal evaluation criterion
- Secondary evaluation criteria
- Adherence
- Clinical and biological adverse events

16 Deviation from the protocol

There should be no deviation from the protocol. However, if this does occur, the reason for the deviation should be documented and transmitted to the Sponsor as quickly as possible. Depending on the seriousness of the deviation (major deviation affecting participant safety or data integrity; minor deviations in other cases), the Sponsor, via the Methodology and Management Centre, will take the necessary measures.
Depending on the deviation, the participation of the participant concerned may be ended.

17 Scientific communications

The results of this study may not be published or communicated either orally or in writing without the agreement of the principal investigators and the trial Scientific Council. Analysis of the data supplied by the investigational centres is carried out by the Methodology and Management Centre. This analysis will give rise to a written report which is submitted to the Scientific Council for approval. This report will allow one or several publications to be prepared, the final version of which must be approved by the Scientific Council and the ANRS.

A results publication committee will be designated by the investigator-coordinators. The publication committee will respect the undertaking of the Sponsor vis-à-vis the pharmaceutical company associated with the trial concerning publication and disclosure of the results.
The principal results will be presented to the patients and authorities at the end of the trial, including the Ethics Committees (Burkina Faso, Cameroon, Senegal) and the Directors of national programmes for HIV support in these countries.
Presentation of the results should conform to the CONSORT recommendations in the updated version (Moher D et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91, http://www.consort-statement.org/).
In case of substudies, the results from these may only be published with the approval of the principal investigators and the Scientific Council, and only after publication of the results emanating from the principal study, which must be cited (ANRS no. 12286 MOBIDIP).

17.1 ETHICAL AND REGULATORY CONSIDERATIONS

17.2 Conformance to reference texts

The Sponsor and research teams undertake to conduct this study with respect to the national regulations in force in Cameroon, Burkina Faso and Senegal (Law No. 2009/17 of 9 March 2009, relating to the Code of Ethics for Health Research) concerning biomedical research procedures, as well as respecting:

- the French Law of 20 December 1988 (No. 88-1138) amended by the law of 23 January 1990 (No. 90-86) and by the law of 9 August 2004 (No. 2004-806);
- the Senegalese law No. 2008/12 dated 25 January 2008, relating to personal data protection and its application Decree No. 2008/721 (dated 30 June 2008);
- the regulations concerning Good Clinical Practice (GCP Version 4 of 1st May 1996);
- the Helsinki Declaration (October 2008);
- the ANRS ethical charter for less-developed countries (Version dated 8 October 2008).

The study is conducted in compliance with the present protocol, except for emergency situations necessitating specific treatment actions to be implemented, and the investigators give their agreement to respect all points of the protocol, in particular concerning the collection of consent, as well as the reporting and follow-up of serious adverse events.
The study protocol, as well as the patient information notice and the consent form must be approved by the principal investigators of the project and by the Sponsor and should receive approval from the Ethics Committees in Senegal, Burkina Faso and Cameroon.

The principal investigator in each country will submit a request for administrative authorisation to the competent Health Authorities, when this is necessary, and will inform the directors of the hospitals concerned, before starting implementation of the protocol.

17.3 Information and consent

The consent of the person participating in the trial will be signed before any clinical or para-clinical examination specific to the trial and after explanation by the investigator of the objective, the nature, the constraints and foreseen risks of the trial. The information notice consent forms are handed to the participant (cf. appendices *1 and 2*). The latter has time to think about it before making his/her decision. Each person will be informed that his/her participation is voluntary and that he/she is free, without having to give justification, to interrupt his/her participation at any time without there being any consequence to the quality of care that his/her doctor will continue to give.

If the person gives his/her consent to participate, the person and the investigator write their surnames and first names in full, date and sign the consent form.

The different copies of the forms for collecting the consent are as follows:

- The 1st copy is kept by the investigating doctor even if the participant relocates during the trial, in a safe place, for a period of fifteen (15) years after completion of the trial.
- The 2nd copy is given to the participant. If the person does not wish to take his/her copy, this will be noted in the CRF and in the source file and the participant's copy will be kept in the investigation file in an individual sealed envelope.

When judged necessary by the Sponsor or the Ethics Committee, in case of substantial modification having an impact on the protection of persons, in particular on their safety, a new consent form must be completed by each participant. The procedure for informing the person and collection of his/her consent is the same as described above.

Co-inclusion in substudies may be proposed to the MOBIDIP participants. Information and informed consent forms specific to this research will be supplied to the persons having given their consent.

The dates of the information and signature of the consent form should be indicated in the medical file of the participant, as well as the name of the investigator who informed the person and completed the consent form.

Any amendment to the protocol that modifies the support given to the subjects requires a new information note and a new consent form the collection of which the collection is the same as described above.

17.4 Amendment to the protocol

Any amendment to the protocol will be subject to a written amendment which will be submitted to the trial Scientific Committee, to the Sponsor, then to the Ethics Committees in each of the study countries. Before approval by the Ethics Committees and the competent Health Authorities, the amendment will be signed by the principal investigators and by the Sponsor (in the same manner as for the final version of the protocol).
Minor amendments that do not modify the protocol contents will be sent to the Ethics Committees for information only.
Any amendment to the protocol is sent to all the investigators participating in the study. The investigators undertake to respect the present text.

17.5 Data confidentiality

All information collected concerning the participants remains strictly confidential and anonymous. The patients will be identified with an identification number. Data concerning a patient included and required for the trial are indicated in a case report form by the investigator after each visit. No data allowing a patient to be identified other than by an anonymous identification number (as well as the sex and date of birth at the beginning of the file) appears in the case report form. The case report forms are kept apart from the patient medical files, in a safe place. The case report forms are subject to a double data entry system in the local coordination centres. The management centre knows only the anonymous identification numbers of the patients. Data is regularly entered into the database, and processed with a database management system and a programme developed specifically for the trial. In the database, each patient is identified only by his/her identification number. Access to this database is password protected. The actions possible with the data depend on the permission given to each user of the database.
Patients will be informed that any information concerning them will be entered into a computer, stored in a confidential manner, and that they have the right to consult and modify the information.
Data registered during this trial is subject to computer treatment under the "Data Protection" Law of 6 January 1978 completed by the law of 1st July 1994 and its application order dated 9 May 1995, as well as the law of 4 March 2002. When they exist, national laws of each country will be respected (see Senegalese Law No. 2004/21 dated 21 July 2004, concerning the organisation of statistical activities).
This treatment of data by computers will be communicated to the National Committee of Information and Liberty (CNIL) (Data Protection) by the Sponsor according to the information supplied by the management centre, in agreement with article 40 of the "Data Protection" Law.

The investigator must make available individual documents and data strictly necessary for monitoring, quality control (particularly monitoring) and the trial audit, to the persons having access to these documents and data (persons approved by the Sponsor to control quality and audit; representatives of the health authority). Any person having access to the data, including the investigator, is subject to professional secrecy.

17.6 Insurance

Before inclusion of the first patient, the ANRS will take out public liability insurance. A copy of the insurance certificate is attached in an appendix to the protocol.

17.7 Writing the final report

The MMC creates the final trial report as well as a summary of this final report.

The final report and its summary are created in agreement with to the recommendations from the International Conference for Harmonisation - ICH Topic E3 - Structure and Content of Clinical Study Reports CPMP/ICH/137/95. They are produced within a period of one year after the end of the trial and forwarded the ANRS, the Ethics Committees and the Health Authorities of the countries concerned.

17.8 Risk evaluation and ethical aspects

Despite its use in clinical practice in countries with high resources, the bPI based monotherapy is not yet a recommended strategy because of discordant results between clinical trials. The principal risks associated with the use of bPI in monotherapy are a low level of maintained viraemia with the appearance of mutations and the possible replication of HIV in compartmentalised reservoirs. In the MOBIDIP study, the viral load is controlled every three months and the VL threshold fixed for failure is lower than that in use in the countries concerned, in ongoing trials and in WHO recommendations. In case of failure, a genotype will be created to evaluate the eventual resistance and supply the most appropriate protocol. Persistence of the copy in the reservoirs cannot be evaluated, but selection of patients whose viral replication has been controlled for a long time and, again, the VL threshold

chosen for failure, is reassuring as to the possible replication in the reservoirs. Monitoring of neurocognitive function allows possible deficiencies to be detected and a final evaluation of their relationship with the viral control.
The side effects of the treatment used in the study are well known, but vigilance and supervision are put in place to assure participant safety.

The drawbacks linked to the research are principally linked to the time that patients have to consecrate to collecting data, and the importance of the blood samples compared with the standard practice of the national programme.

During the training and information sessions, the patients will be informed of all the terms of the study and the practices. Furthermore, two other aspects need to be taken into account:
- in a randomised clinical trial, it is important that the participants fully understand the objectives of the study in order to be able to adhere to the protocol while guaranteeing respect for their rights and safety.
- this study aims to deliver knowledge likely to improve the strategy for use of ARV drugs available in second-line. However, it is essential to put in place a strict supervision of eventual virological failure and possible appearance of mutations in order to avoid resistance development that will reduce the therapeutic options of future participants.

Throughout the study, it will be important to work in close collaboration with the national governments, the associations and the Health Authorities, as well as with the international organisations to assure the distribution and exploitation of the results, not only with the trial participants, but also with the general population.

In the MOBIDIP trial, several partners will be work together to guarantee better communication:
- The associations present in the countries where the study is conducted, who will be kept informed of the study progress and of its results;
- The national authorities and, in particular, the Ethics Committees to which the reports and notifications of serious adverse events will be communicated;
- The scientific and independent committees, who are not only in charge of monitoring the results of the study, but also of the distribution and questioning of the results;
- The presence in certain countries of "ethical mediators" who follow the trial progress and share the results and problems encountered during the course of the study with the community that they represent.

17.9 Availability of treatment after the trial

Second-line treatments are available in the three countries where the trial is being conducted. Patient access at the end of the trial is therefore guaranteed by the national programmes. If the boosted darunavir, second-line substance in one of the trial arms is not available at the end of the trial, the participants with a controlled viral load may be moved to the national protocol scheme.

The problem of access to treatment after the end of the trial is still there for the failed patients and therefore under third line, for whom the substances are not always available.
Numerous patients in the national programmes already need 3rd line treatment, and the competent authorities are already mobilised to facilitate access to this. The limited number of substances available and the financial restrictions of the national programmes do not allow for wider access to 3rd line treatment.

Despite the fact that we cannot guarantee continuity of supply after the end of the trials, we believe that within 2 to 3 years, the situation will have changed. We will continue to be active alongside the authorities and patients to support a coordinated action and facilitate progress of these negotiations (availability of generic drugs, registration and authorisation for marketing, knowledge of supervisory needs of toxicity, etc.).

17.10 Archiving

The documents and data relating to the trials constitute the essential documents that make up the permanent trial dossier. These documents serve to show that all personnel involved with the trial respect the standards of Good Clinical Practice as well as the legal and regulatory texts in force.

As such, all documents relating to the study will be archived for 15 years after completion of the study by the investigational centres, the MMC and the Sponsor. Examples of consent forms destined for the Sponsor will be kept in a sealed, inviolable envelope on which the corresponding centre identification and the name and signature of the principal investigator will be noted.
The investigators assure that the source files, and in particular the medical files, are available during this archive period of the trial.
No study document will be destroyed by an investigational centre after this period without the prior written approval of the Sponsor or his/her representative.

18 Access to data and the biological samples

In application of the protocol, all the material collected, i.e. trial data and biological samples, is placed from the beginning of the trial under the responsibility of the MMC who assures the methodology and management of the trial. It remains in his/her safekeeping throughout the trial and beyond for the trial data, after dissolution of the scientific council, unless contrary provisions are made by the ANRS. All use of biological material within the scope of the study not included in the protocol, its appendices and amendments should be the subject of a request according to the forms described in chapter 13.1 (Scientific Council).
The transfer of all or part of the database from the trial to manufacturers will be made, where necessary, according to the terms of the research collaboration contract signed between the partners and the ANRS on starting the trial.

19 Investigator's obligations

In agreement with the standards of Good Clinical Practice that aim to guarantee the quality of the trial, each investigator undertakes to:

- respect participants' rights and guarantee their safety and well-being,
- assure his/her availability and that of his/her team,
- assure that his/her possibilities of recruitment are compatible with carrying out the trial,
- take responsibility for organising the technical structures for putting in place the circuits specific to the trial (consultations, samples) and archiving the documents throughout the trial and for fifteen (15) years after the trial has finished,
- collect and archive the written consent of the participants in a safe place,
- assure respect for the protocol and supervise the quality of the data in the case report forms as well as their regular transmission to the Methodology and Management Centre in the allotted time: the monitoring sheets must be addressed by courier to the Methodology and Management Centre in a maximum of ten (10) days after the participant's visit,
- immediately inform the Methodology and Management Centre of any serious adverse event during the trial, according to the forms described in the protocol (cf. chapter on vigilance),
- allow the regular monitoring of the trial by a representative from the Methodology and Management Centre who must have access to the source documents of the participants to validate data reported in the case report forms. At any time, the Project Manager or investigator-coordinator may be contacted for any questions relating to the protocol, its practical application, or the action to take when faced with certain events,
- accept an eventual audit of the trial, either directly by the Sponsor or with his/her authorisation by another organisation,
- accept trial inspections by Health Authorities approved to do so.

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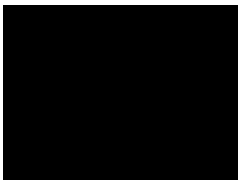
APPENDICES

20.1 Appendix 1: CPP approval

20.2 Appendix 2: Insurance

20.3 Appendix 3: Information letter and consent form



Patient information

ANRS 12286 MOBIDIP: Evaluation of a maintenance therapy of protease inhibitors with or without lamivudine in patients with a controlled viral load under second-line antiretrovirals in Africa (Yaoundé, Bobo-Dioulasso, Dakar)

Version No. 1.3 dated 15/07/2013 having received a favourable opinion from the Ethics committee on xx/xx/xxxx

Investigators
Dr Laura Ciaffi
Prof. Sinata Koulla Shiro
Prof. Cheikh Tidiane Ndour
Dr Adrien Sawadogo

Principal investigator for XXX
Add contact details local PI

Sponsor: National Institute of Health and Medical Research - National Agency for Research on AIDS and Viral Hepatitis (**INSERM-ANRS**) 101 rue de Tolbiac, 75013 Paris, France.

Please carefully read this information on the trial **"ANRS 12286 MOBIDIP"** that we are suggesting you participate in.
It is important for you to understand why this research is being undertaken and what it involves for you. We ask that you read the following information sheet carefully or have it read to you.
The whole study team is available to provide you with more information and to answer any questions you may have.
You are completely free to agree or refuse to participate in this trial. If you agree to participate in this trial, all you need to do is sign the consent form for participation. Should you refuse, this will have no effect on your relationships with your doctors or on the care that you will be given.

Dear Madam, Sir,

Your physician has invited you to participate in the ANRS 12286 MOBIDIP trial

This trial is a clinical research study that is intended to test a "maintenance treatment", i.e. a monotherapy (one drug) or dual therapy (two drugs) treatment with antiretroviral drugs instead of the usual triple therapy (three drugs) treatment. This trial involves you discontinuing some of your medicines to continue with just one or two.

1. What is the aim of this study?

The aim of the MOBIDIP trial is to show that HIV-infected patients who have had an undetectable viral load for several months are able to control the virus even with a reduced number of drugs.
Drugs from the family of "protease inhibitors" (including lopinavir and darunavir prescribed within the framework of the ANRS 12169 2LADY trial) despite the fact that they have not been registered for this use, have, in several studies, shown their efficacy as monotherapy for a "maintenance treatment", i.e. to maintain control over viral multiplication.
Furthermore, the MOBIDIP trial hypothesises that the addition of lamivudine (a drug that is not very toxic and is readily available) could, by preventing the emergence of resistances, improve the efficacy of a protease inhibitor monotherapy as "maintenance treatment".
Similar trials are also underway in Europe and in the United States and the results obtained to date are reassuring.

2. Who can participate in this study?

You are invited to participate in this trial because you are currently on an antiretroviral treatment, your treatment is effective, and you have the characteristics that suggest that you might benefit from a simpler treatment which would still continue to control virus multiplication.

To participate in this study, you must:

- be included in the 2LADY trial for at least 48 months
- be on antiretroviral therapy, unchanged for at least 3 months
- have had a viral load of less than 200 copies/ml for at least 6 months
- not be a carrier of the hepatitis B virus
- have more than 100 CD4
- be taking your current treatment regularly
- not have had any severe and progressive illnesses in the last 3 months

Your doctor will assess the results of the tests performed during your last 2LADY visit in order to verify these criteria.

Women of childbearing age must have a negative pregnancy test upon entering the study and cannot be breastfeeding.

3. Am I obliged to participate?

You are free to decide whether or not to participate in the MOBIDIP trial. If you agree to participate, you will be asked to sign the consent form at the end of this document, and a copy will then be provided to you.

You will be free to withdraw from the trial at any time without having to give a reason. You do not have to give a reason for withdrawing your consent or abandoning the trial.

Not participating in the trial or leaving the study early will entail no penalty for you. Your decision will have no repercussions on your access to medical care in the future. You will be referred to the department of your choice with a summary of your file, and you will have access to the second-line treatment available by the national program of your country.

In the event of withdrawal of your consent, the data and samples collected until then will, however, continue to be used, unless you object to it; then they will be destroyed.

If you withdraw your consent, you will undergo a final medical examination for your own safety.

4. What will happen if I participate in this study?

For this trial, we propose **that you discontinue the combination of tenofovir/emtricitabine (Truvada) or abacavir/didanosine and continue the boosted protease inhibitor (lopinavir/ritonavir or darunavir + ritonavir).**

Some of you, selected at random, will have an additional two tablets of lamivudine per day.

You will be followed up for 2 years (= 96 weeks) as part of the trial. It will take place in Cameroon, Senegal and Burkina Faso and will include a total of 264 participants.
During the study, you will be seen as an outpatient.

Study procedure:

- **During the D0 inclusion visit** (start of the study), after your inclusion criteria have been verified and you have signed the consent, **you will be assigned to one of the trial groups.**

Your assignment to group 1 or 2 will be determined by chance (randomisation). Group 1 will receive only the existing boosted protease inhibitor, group 2 will additionally receive lamivudine.

Group 1: darunavir + ritonavir or lopinavir/ritonavir (boosted protease inhibitor taken within the framework of 2LADY)

Group 2: darunavir + ritonavir plus lamivudine or lopinavir/ritonavir plus lamivudine

- **At each visit (D0, 4 weeks then every 3 months up to 96 weeks)** you will have:

- a medical visit with a clinical examination including anthropometric measurements (waistline measurement, etc.) at visits D0, V24, V48 and V96) and an interview about your health and your compliance.

- a blood test (maximum 40 ml = about 3 tablespoons) for biological analyses. These blood tests will include viral load for HIV and testing to verify that your kidneys, liver and other organs have not suffered side effects from the drugs. Women of child-bearing age will also undergo a urine pregnancy test. You will be informed of the results of your analyses.

- a visit to the pharmacy will be required to obtain your medication for the next 3 months.

During your participation in the MOBIDIP trial, it is very important that you ***take the medication exactly as it is prescribed to you and keep the study appointments without fail.*** We request your permission to contact you in the event that you do not attend one of your appointments: in fact, in order to obtain correct results, it is very important to know what happens to each participant.

You must report all side effects to your doctor or to the members of his team.

Do not change a dose and do not stop taking a drug without first discussing it with the members of the trial team looking after you. During your participation in this study, it is important that you do not take any other medication (over the counter, prescription or illegal) without your doctor's consent.

If you get sick and you need a drug, please contact the centre; you will be advised on the treatment that can be taken.

5. What are my alternatives if I do not want to participate?

In this case, you may continue your participation in the ANRS 12169 2LADY trial (after having signed a new consent form) for 96 weeks under the terms that you already know: follow-up by the project staff every 6 months and management of biological tests, medical visits and drugs for diseases related to HIV infection.

If you do not want to participate in the MOBIDIP trial or continue your follow-up in the 2LADY trial, you will be referred to a doctor at the centre of your choice who will continue your follow-up within the framework of the national programme.

6. What happens if I am pregnant or if I become pregnant during the study?

Pregnant women cannot participate in the MOBIDIP trial.

If you participate in the MOBIDIP trial, this is not the best time to start a pregnancy: there is an unpredictable risk of undesirable effects for the foetus. Additionally, because if the treatment is not completely effective and you are pregnant, the unborn baby could become infected. In fact, if you are pregnant it is best to have an undetectable viral load of less than 50 copies/ml to reduce the likelihood of the baby becoming infected as far as possible.

We will therefore provide you with the means to avoid pregnancy during the term of the trial (hormonal contraceptive and condoms) because common contraception techniques may be insufficient with some of the trial drugs.
If you think that you are pregnant during the trial, you should immediately speak to your doctor, who will adjust your treatment to allow for this condition.

7. Sample collection

Within the framework of this study, blood samples will be collected to perform your tests but also to be stored. The blood samples will be stored anonymously (identified only with a code) in the trial's partner laboratory. They could be used for further tests (for example: genotype to investigate for resistances in the case of treatment failure). The samples could be used for other trials, but only after approval by the trial's Scientific Council and a favourable opinion from your country's Ethics Committee.

8. What are the possible disadvantages and risks associated with participation in the MOBIDIP trial?

The withdrawal of one of the triple therapy drugs could cause a reduction in the efficacy of the treatment and lead to the resumption of viral replication with a risk of the appearance of resistance. This risk is reduced with the protease inhibitors, which are notably more robust (i.e. resistance appears less readily). The close control of the viral load (every 3 months) will allow us to quickly detect an increase in viral load and in the case of a viral load greater than 500 copies/ml to reintroduce the tablets that you had discontinued for the MOBIDIP trial. Then you will be monitored to ensure that the virus is once again well controlled.

Drugs: Boosted protease inhibitors are well known and you have already been taking them for a long time. They may cause liver problems (speak to your doctor if you experience lack of appetite or vomiting, if your urine becomes dark or your stools clear, if you have headaches, diarrhoea, an increase in blood lipids or diabetes). Lamivudine has been more frequently associated with general discomfort and fatigue, respiratory tract infections, throat problems, headache, abdominal pain or disorders, nausea, vomiting and diarrhoea. **Do not hesitate to contact your doctor if these symptoms or any other disorder appear.**

Blood tests: You may feel some discomfort during the blood collection intended to obtain a sample of your blood.

9. What are the potential benefits and advantages of participation?

During this trial you will take less medication and so you will be less exposed to the toxicity of certain drugs, including the risk of renal and nerve toxicity and of lipoatrophy. You will be carefully monitored and your complaints will be considered and managed if they are related to your HIV infection or the trial drug.
Clinical consultations, biological examinations, drugs for diseases related to the HIV infection and, if necessary, transportation (1,000 CFA Francs) to the consultation will be paid for during your participation in the study. You will also benefit from psychosocial support and compliance assistance provided by the trial staff.

10. What will happen in the event of the cessation of the clinical trial?

Your participation in this study may be terminated at any time. Your doctor may decide to have you withdrawn from the study for the following reasons:

- If continuing to participate in the study is not in your best interests, for example if it proves hazardous to your health
- In the event that the investigators terminate the study
- If you do not follow the drug dosing regimen, protocol procedures or the instructions of your investigating doctor or the study nurses.

If you are withdrawn from the study, you may have to undergo some of the examinations listed in the schedule of study visits. These tests are intended to protect your health and will be paid for by the study.

11. What will happen at the end of the study?

During the last visit of the MOBIDIP trial (at week 96) you will receive a summary of your file to present to the physician who will be treating you within the framework of your country's national programme after the trial. You will be assigned the national programme's standard treatment. According to your results and after discussion with your doctor, the continuation of the maintenance treatment may be considered. **Our project cannot guarantee treatment beyond the end of the trial**, but we will implement all possible strategies to facilitate your access to all necessary drugs through the national programme.

You will be informed of the study results.

12. What happens if new information becomes available?

During any research project, new information can be obtained on the treatment or drugs studied. In this case, the members of the team will discuss it with you and you will together discuss whether you want to continue to participate in the study.

13. What are my rights?

You have the right to ask questions at any time during the trial, to refuse to participate and to withdraw your consent at any time without this decision affecting your further medical care.

Within the framework of this trial, computerised processing of your personal and medical data will be used to permit the analysis of the results of this trial. You have the right to access and request the correction of your data.

Only persons authorised by the principal investigator will have access to information about you. The data about you that will have been obtained during your participation in the MOBIDIP trial, as well as associated medical records will be kept confidential and anonymous, i.e. encoded so that it is not possible to identify you. Your name cannot, under any circumstances, be published in reports or publications.

The sponsor's representative or representatives of the competent authorities can perform inspections and check the raw data about you. These people will be bound by a duty of confidentiality.

This study was approved by the Ethics Committee at their meeting of the XXX of the XXX.

The study sponsor (entrusted, among others things, with ensuring trial quality and safety and responsible for study monitoring and funding) has signed up to an insurance contract which guarantees compensation in the event of harm due to your participation in this trial.

14. What will happen with the results of the clinical trial?

The sponsor will use and disclose your information only for research purposes or for scientific publication after the end of the trial. Your name will never appear in forms, reports, databases, publications or any other future release.

You will be personally informed of the trial results by your doctor as soon as they become available.

Contacts for more information

The team that will be monitoring you within the framework of this trial remains at your disposal to answer any questions you may have. At your hospital, these people are:

Doctor ---------- Telephone: ----------

Mediator: ---------- Telephone: ----------

Contact of the Ethics Committee: _____

Thank you for agreeing to listen to our explanation of this trial.

Informed Consent Form

ANRS 12286 MOBIDIP: Evaluation of a maintenance therapy of protease inhibitors with or without lamivudine in patients with a controlled viral load under second-line antiretrovirals in Africa (Yaoundé, Bobo-Dioulasso, Dakar)
Version No. 1.3 dated 15/07/2013 having received a favourable opinion from the Ethics committee on xx/xx/xxxx

Sponsor: Inserm - ANRS
Coordinating Investigators: Dr. Laura Ciaffi, Prof. Sinata Koulla-Shiro
State contact according to country.

I, the undersigned: _____ declare that I have read the information sheet and/or had it explained to me; I have had the opportunity to ask Dr. _____ all of the questions that I wanted. I have had a period of time in which to reflect and hereby agree to participate in the ANRS 12286 MOBIDIP trial knowingly and freely by signing this form.

I understand the objectives, constraints, risks and benefits related to my participation in the MOBIDIP trial.

I have been informed that I will have to come to obtain my medication at the hospital pharmacy every three months.

I know that I will have to attend the hospital for my follow-up examinations in accordance with the schedule which will be provided to me, and that I will be provided with the results of those examinations.

I have been informed that approximately 3 tablespoons of blood will be collected from me every three months for the purpose of follow-up investigations, and that the physician will ask me about my health and any medication I am taking.

I have received a guarantee that clinical consultations, biological examinations, medicines and, if necessary, transportation costs will be paid for by the trial throughout my participation.

I have understood that at the end of the trial I will be referred to the treatment centre of my choice with my file summary (visits and results of laboratory tests) and I will resume the standard second-line antiretroviral therapy available through my country's national programme.

I agree that the non-identifying information collected on the occasion of this trial is subject to computer processing.

I accept that any physician or scientist involved in the conduct of this trial, as well as representatives of the health authorities and of the sponsor, have access to information under the strictest observance of confidentiality.

I can, at any time, if I so desire, discontinue my participation without having to give reasons for my decision, but I will do my best to inform Doctor _____. This interruption will not jeopardise the quality of my further care.

I have been informed that by signing this consent form, I am not waiving any of my rights and I am not in any way releasing the investigators, sponsors or the hospitals where the trial takes place from their legal and professional responsibilities.

I have been advised that I will be informed of the results of this trial.

I have been advised that I will receive a dated and signed copy of this form.

I have noted that the study sponsor has taken out an insurance policy.

Place: _____ Date: _____

Participant's last name and first name:…… Signature: _____

I the undersigned, doctor....., acting as investigator, certify that I have clearly explained the objective, the duration, the risks and benefits and advantages of this protocol to this participant.
Date: _____ Signature: _____

20.4 Appendix 4: List of adverse events with hospitalisation not subject to an obligatory declaration

Hospitalisations (not life-threatening or death) will not be subject to the procedure for declaration of serious adverse events if they are related to:

- a traumatic factor with the exception of fractures and osteonecrosis
- a disease of documented infectious origin (**iatrogenic cause excluded**):
    - acute infectious diarrhoea
    - infectious pneumonia
    - infectious pleurisy
    - a complicated urinary or genital infection
    - septic arthritis
    - infectious endophthalmitis
- a parasitic disease:
    - acute parasitic diarrhoea
    - malaria
    - dengue
- an infectious disease related to HIV that does not fall within the definition of an immune reconstitution syndrome:
    - HIV wasting syndrome,
    - Salmonella sepsis
    - histoplasmosis
    - isosporidiosis.
    - candidiasis
    - invasive cancer of the cervix
    - a lymphoma.
- a disease previously known or discovered upon inclusion, but unrelated to the HIV infection (e.g.: diabetes, high blood pressure, etc.) **provided it does not worsen** (for example, worsening of diabetes can potentially be linked to antiretrovirals)

20.5 Appendix 5: ANRS scale to evaluate the severity of the events

This rating scale is a working guide intended:

⇒ To avoid omitting a serious adverse event to be reported to the sponsor (ranked 4 in the rating scale)

⇒ To grade the severity of a clinical or biological symptom observed within the framework of a biomedical research protocol

⇒ To harmonise the symptomatology assessment practices and their rating in ANRS protocols

In practice, the criteria evaluated are grouped by device; this is a non-exhaustive table of symptoms (and not a classification of diseases). Our choice refers to the clinical and biological signs most commonly observed or whose monitoring is imperative to ensure the protection of research subjects.

Certain protocols may require additional criteria: to assess them, please refer to the table below: